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Graphical Abstract

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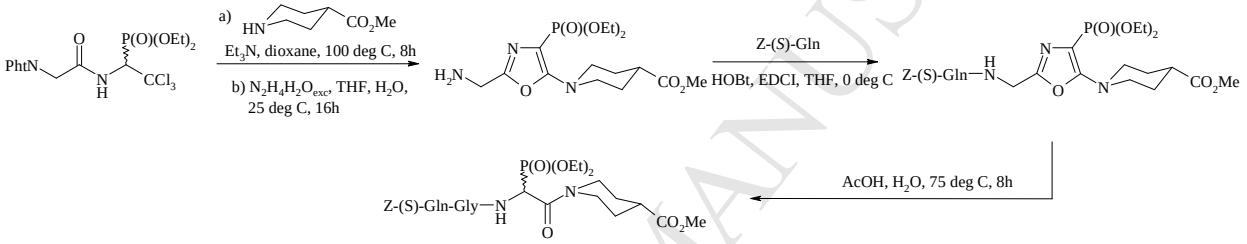
[a] *Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine, 1 Murmanska St., Kyiv 02660, Ukraine*

[b] *Research and Development Center for Chemistry and Biology, National Taras Shevchenko University, 62 Volodymyrska St., Kyiv 01033, Ukraine*



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ABSTRACT

Starting from phthalimidoalkanoylamines **1** (amino-protected derivatives of glycine, β-alanine, γ-amino butyric, δ-amino valeric, and ε-amino caproic acids), a facile synthetic method has been developed to obtain diethyl 5-alkyl(dialkyl)amino-2-aminoalkyl-1,3-oxazol-4-ylphosphonates **7** which have been further used in the preparation of phosphorylated peptidomimetics **10** and **12**.

1. Introduction

Currently aminophosphonic acids as structural analogues of the corresponding amino carboxylic derivatives, where the tetrahedral phosphonic acid functionality replaces the planar carboxylic group, have found a wide range of practical applications in the areas of biological, medicinal, and synthetic chemistry.[1] Phosphonic acids represent the "simplest" group of phosphate isosteres. These molecules with C-P bond in place of O-P bond are structurally similar to phosphate esters and anhydrides, but are quite stable under typical chemical and physiological conditions.[2] Because of the tetrahedral configuration at phosphorus, aminophosphonic acids mimic the tetrahedral transition state of peptide hydrolysis and therefore can act as inhibitors of peptidases or esterases. As a consequence, the biological properties of aminophosphonic acids have been studied extensively. However, limited cell permeability of highly polar aminophosphonic acids and their derivatives leads to intense search for new biologically active synthetic analogues of aminophosphorus compounds.

From the biochemical point of view, phosphorylated peptides and peptidomimetics are an area of special interest.[1e,3] As a rule, the phosphoryl residue in these compounds is inserted into the peptide chain or terminates it. Phosphono peptides containing the phosphoryl group in the side chain of peptides have been less studied due to their synthetic complexity.[4] To synthesize compounds with the phosphonoglycine residue, we have recently applied regioselective acid-assisted opening of the 4-phosphorylated oxazole ring.[5a] Though 4-phosphoryl-5-aminooxazole derivatives are easily accessible and well studied,[5] most of them bear only alkyl or aryl residues at position 2 of the oxazole ring. Here we focus on the synthesis of diethyl 5-amino-1,3-oxazol-4-ylphosphonates substituted at position 2 with aminoalkyl chains of varying length. Such compounds, when regioselectively ring-opened, may be particularly useful in the synthesis of phosphorylated peptidomimetics.

2. Results and discussions

We have synthesized 5-amino-2-aminoalkyl-1,3-oxazol-4-ylphosphonic acids by the reaction chain **1**→→**8** (see Schemes 1 and 2) starting from the condensation of ω,ω-phthalimidoalkanamides **1a-e** with chloral hydrate. Conversions **1**→**2**→**3** were studied previously[6] with phthalimidopropionamide (n=2) and phthalimidobutyramide (n=3), whereas

* Corresponding author. Tel.: +38-044-573-2561; fax: +38-044-573-2561; e-mail: brovarets@bpci.kiev.ua

phthalimidoacetamide (n=1), phthalimidovaleramide (n=4), and phthalimidohexanamide (n=5) have been reacted with chloral hydrate for the first time. Compounds **2a-e** were treated with thionyl chloride to produce highly reactive tetrachloroethyl-substituted amides which were then condensed with triethyl phosphite by the Arbuzov reaction thus affording hitherto unknown diethyl 1-(phthalimidoalkanoylamino)-2,2,2-trichloroethylphosphonates **4a-e**.

On treatment with triethylamine, products **4a-e** readily eliminate HCl to give 2,2-dichloro-1-(phthalimidoalkanoylamino)-ethenylphosphonates **5a-e** (see Scheme 2). Heating of trichloroethylphosphonates **4a-e** or dichloroethenylphosphonates **5a-e** with benzylamide or secondary amines in the presence of excess triethylamine leads to oxazole condensation[7] with the substitution of all chlorine atoms. As a result, we have synthesized a number of novel derivatives of diethyl 5-amino-2-phthalimidoalkyl-1,3-oxazol-4-ylphosphonates **6a-n**. Phthalimidoalkyloxazoles **6a-n** appear as crystals or viscous oils stable on prolonged storage, sparingly soluble in hexane, petroleum ether, and water, and highly soluble in alcohols, tetrahydrofuran, and dichloromethane. When treated with hydrazine hydrate in a THF-H_2O mixture at room temperature, these compounds are smoothly hydrazinolyzed to diethyl 5-amino-2-aminoalkyl-1,3-oxazol-4-ylphosphonates **7a-n** in high yields.

The primary aliphatic amino group of products **7a-n** is readily acylated with acyl chlorides to provide corresponding amides **8a-e**, as exemplified by the reaction of compounds **7f-j** with 4-tert-butylbenzoyl chloride (see Scheme 3).

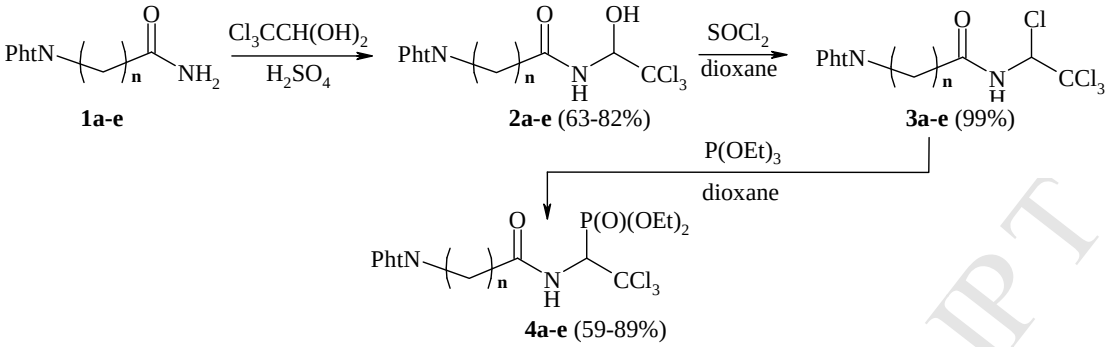
Acylation of oxazole **7k** with Z-(*S*)-Ala-OH under standard conditions of peptide synthesis, i.e. in a THF solution in the presence of 1-hydroxybenzotriazole (HOBt) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), also leads only to amide **(*S*)-9** (see Scheme 4). We used compound **(*S*)-9** to ascertain whether racemization at the chiral centre could occur during the oxazole ring opening. To this end, racemic amide **(*R,S*)-9** was prepared under similar conditions, followed by HPLC analysis of **(*S*)-9** and **(*R,S*)-9** on a chiral column (CHIRALPAK® IA). Phosphorylated peptidomimetics **10** resulting from the ring opening in **(*S*)-9** under mild conditions (in an AcOH-H_2O mixture at 75°C)[5a] were analyzed likewise. It is evident from HPLC data (see Experimental section) that no racemisation occurs during the oxazole ring opening as well as in peptide synthesis.

A phosphorylated peptidomimetic of more complex structure was obtained by the above procedure from oxazole **7m**. It was reacted with Z-protected optically active (*S*)-glutamine to give amide **(*S*)-11** (see Scheme 5) which yielded, on ring opening, peptidomimetic **(*S,R*),(*S,S*)-12** containing the residues of four amino acids ((*S*)-glutamine, glycine, phosphorylated glycine, and isonipecotic acid). Compounds of this type may be involved in biological studies on enzyme-dependent systems.

The structures of the compounds obtained (see Schemes 1-5) were established by elemental analysis as well as by IR and NMR (^{1}H, ^{13}C, ^{31}P) spectroscopy and LC/MS method. The latter is, however, uninformative for compounds **2a-e**, **3a-e**, **(*S*)-11**, and **(*S,R*),(*S,S*)-12**, since they decompose under the conditions of LC/MS analysis.

3. Conclusions

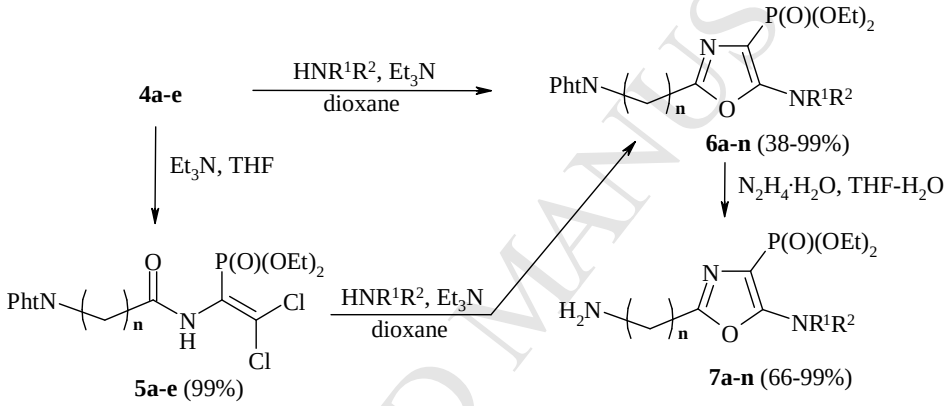
We have developed a preparative method to obtain diethyl 5-alkyl(dialkyl)amino-2-aminoalkyl-1,3-oxazol-4-ylphosphonates **7.** It implies the successive treatment of phthalimido amides **1** with chloral hydrate, thionyl chloride, triethyl phosphite, amines, and hydrazine hydrate. The resulting aminooxazoles have been further used in the preparation of optically active phosphorylated peptidomimetics **10** and **12** in which the introduced amino acid residues are not racemized.



1a-e **2a-e** (63-82%) **3a-e** (99%)

4a-e (59-89%)

Scheme 1. n = 1 (**a**), 2 (**b**), 3 (**c**), 4 (**d**), 5 (**e**).



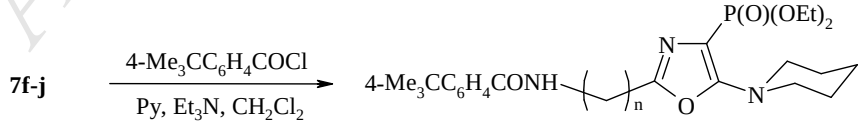
5a-e (99%)

6a-n (38-99%)

7a-n (66-99%)

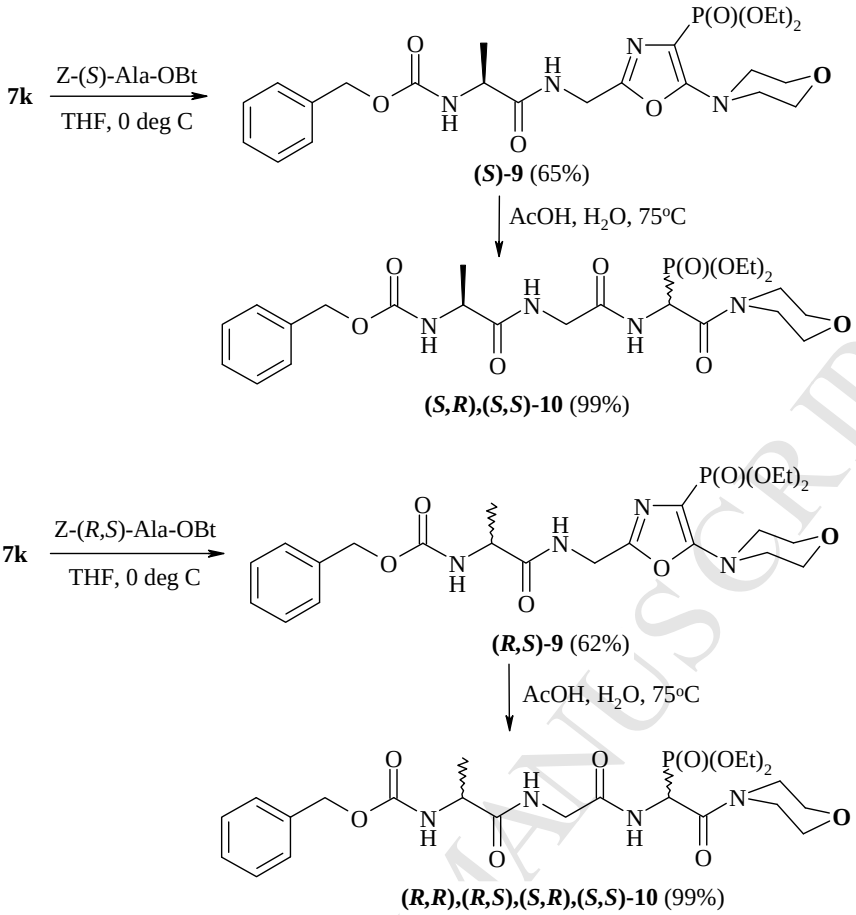
NR^1R^2	n	1	2	3	4	5
$NHCH_2Ph$		**6a, 7a**	**6b,7b**	**6c, 7c**	**6d, 7d**	**6e, 7e**
$N(CH_2)_5$		**6f, 7f**	**6g, 7g**	**6h, 7h**	**6i, 7i**	**6j, 7j**
$N(CH_2)_4O$		**6k, 7k**	**6l, 7l**			
$N(CH_2)_4CHCO_2Me$		**6m, 7m**	**6n, 7n**			

Scheme 2.

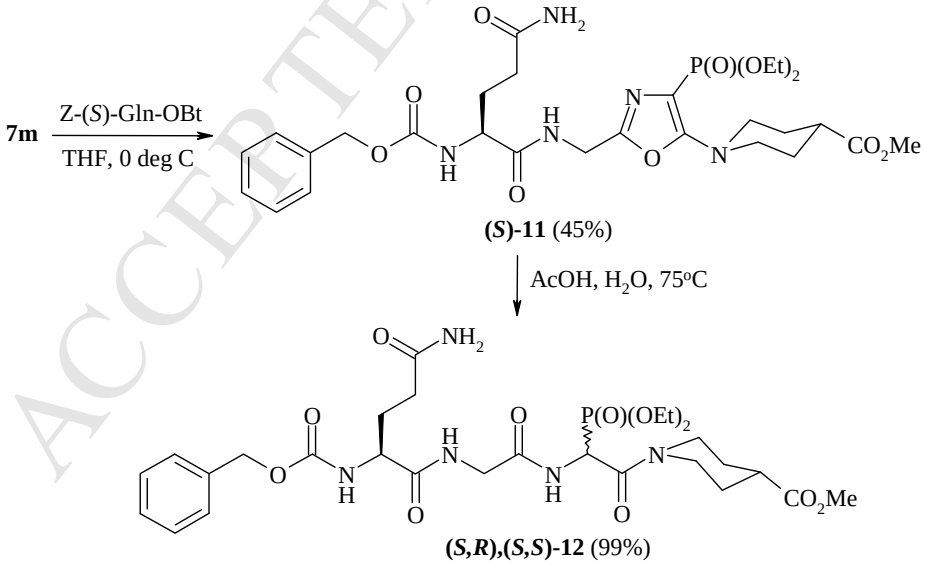


8a-e (88-95%)

Scheme 3. n = 1 (**a**), 2 (**b**), 3 (**c**), 4 (**d**), 5 (**e**).



Scheme 4.



Scheme 5.

4. Experimental section

4.1. General

The NMR spectra were obtained on a Bruker Avance DRX-500 instrument [^{1}H (500 MHz), ^{31}P (202 MHz), ^{13}C (125 MHz)] in a solution of DMSO-d_6, $CDCl_3$ relative to internal TMS or external 85% phosphoric acid. The IR spectra were recorded on a Vertex 70 spectrometer from KBr pellets, or dichloromethane solution, or adaptor ATR. The melting points were determined on a Fisher-Johns instrument. Elemental analysis was carried out in the analytical laboratory of IBOPC NASU. The LC/MS spectra were recorded on an Agilent 1100 Series high-performance liquid chromatograph equipped with a diode matrix with an Agilent LC\MSD SL mass selective detector allowing fast switching between positive and negative ionization modes. The LC/MS parameters were set as follows: column, Zorbax SBC18 1.8 μm, 4.6x15 mm (PN 821975-932); solvents A, acetonitrile–water mixture (95:5), 0.1% trifluoroacetic acid and B, 0.1% aqueous trifluoroacetic acid; eluent flow rate, 3 ml/min; injection volume, 1 μl; UV detection, 215, 254, 265 nm; atmospheric-pressure chemical ionization (APCI) was used; scanning range, *m*/*z* 80–1000. Optical purity was measured on the Agilent 1100 system with diode array detector on a CHIRALPAK® IA column (5 μm, 4.6x250 mm); mobile phase, hexane:2-propanol. The reaction progress was TLC-monitored on Silica gel 60 F_{254} (Merck).

4.2. Phthalimido amides

Commercially unavailable compounds **1a-c**,[8] and **1d**[9] were obtained by known methods.

*4.2.1. 6-(1,3-Dioxo-2,3-dihydro-1H-isoindol-2-yl)hexanamide (**1e**)*

A mixture of 6-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)hexanoic acid[10] (156.77 g, 0.60 mol), thionyl chloride (55 mL, 0.75 mol), and dry benzene (400 mL) was refluxed for 2 h and evaporated in vacuo; the residue was dissolved in dry dichloromethane (800 mL). Through the solution stirred and cooled at 20°C, a current of dry ammonia was passed to saturation, followed by washing with water (3x100 mL), drying over sodium sulfate, and evaporation to dryness *in vacuo* to give the analytically pure product (151.48 g, 97%) as a colorless crystals; mp 154-155°C; [Found: C, 64.49; H, 6.34; N, 11.24. $C_{13}H_{14}N_2O_3$ requires C, 64.60; H, 6.20; N, 11.38%]; ν_{max} (KBr) 3387, 3195, 2931, 2852, 1775, 1720, 1649 cm^{-1}; δ_H (DMSO-d_6) 7.85 (4H, m, aromatic), 7.21 (1H, br s, NH), 6.67 (1H, br s, NH), 3.56 (2H, m, CH_2), 2.03 (2H, m, CH_2), 1.59 (2H, m, CH_2), 1.50 (2H, m,CH_2), 1.25 (2H, m, CH_2); δ_C (DMSO-d_6) 175.0 (C=O), 168.4 (C=O), 134.9, 132.0, 123.4, 37.8, 35.4, 28.2, 26.4, 25.1; LCMS: found *m/z* 261.2, MH^+.

4.3. General procedure for the preparation of 2a-e. Condensation of amides 1a-e with chloral hydrate.

Compounds **2b,c** were obtained by known methods.[6]

A mixture of one of compounds **1a**, **1d**, or **1e** (0.50 mol), chloral hydrate (165.40 g, 1.00 mol), and conc. sulfuric acid (1 mL) was kept at a temperature of 95-100°C for 8h, cooled, and ground in water (500 mL). The crystalline precipitate was filtered, washed on the filter with water to pH 7, and recrystallized from 2-propanol.

*4.3.1. 2-(1,3-Dioxo-2,3-dihydro-1H-isoindol-2-yl)-N-(2,2,2-trichloro-1-hydroxyethyl)acetamide (**2a**).*

Yield 144.14 g, 82% as a colorless crystals; mp >180°C dec; [Found: C, 40.91; H, 2.67; Cl, 30.41; N, 7.89. $C_{12}H_{19}Cl_3N_2O_4$ requires C, 41.00; H, 2.58; Cl, 30.25; N, 11.38%]; ν_{max} (KBr) 3279, 3036, 2985, 2943, 1778, 1730, 1537, 1416 cm^{-1}; δ_H (DMSO-d_6) 9.24 (1H, d, *J* 8.8 Hz, NH), 7.95-7.85 (5H, m, aromatic, OH), 5.72 (1H, m, CH), 4.38 (1H, d, *J* 17.1 Hz, $CH_a\underline{H_b}$), 4.28 (1H, d, *J* 17.1 Hz, $C\underline{H_a}H_b$); δ_C (DMSO-d_6) 167.9 (C=O), 167.0 (C=O), 135.2, 132.0, 123.7, 102.7 (CCl_3), 81.3 (CH), 40.4 (CH_2).

*4.3.2. 5-(1,3-Dioxo-2,3-dihydro-1H-isoindol-2-yl)-N-(2,2,2-trichloro-1-hydroxyethyl)pentanamide (**2d**).*

Yield 123.98 g, 63% as colorless crystals; mp 109-110°C dec; [Found: C, 45.63; H, 3.97; Cl, 27.21; N, 7.01. $C_{15}H_{15}Cl_3N_2O_4$ requires C, 45.77; H, 3.84; Cl, 27.02; N, 7.12%]; ν_{max} (KBr) 3313, 1771, 1708, 1656 cm^{-1}; δ_H (DMSO-d_6) 8.65 (1H, d, *J* 9.1 Hz, NH), 7.86 (4H, m, aromatic), 7.61 (1H, d, *J* 5.7 Hz, OH), 5.73 (1H, dd, *J* 9.1, 5.7 Hz, CH), 3.57 (2H, m, CH_2), 2.24 (2H, m, CH_2), 1.59 (2H, m, CH_2), 1.52 (2H, m, CH_2); δ_C (DMSO-d_6) 172.9 (C=O), 168.4 (C=O), 134.9, 132.1, 123.5, 103.0 (CCl_3), 80.8 (CH), 37.7, 35.1, 28.1, 23.0.

*4.3.3. 6-(1,3-Dioxo-2,3-dihydro-1H-isoindol-2-yl)-N-(2,2,2-trichloro-1-hydroxyethyl)hexanamide (**2e**).*

Yield 130.46 g, 64% as a colorless crystals; mp 105-107°C dec; [Found: C, 47.03; H, 4.33; Cl, 26.24; N, 6.70. $C_{16}H_{17}Cl_3N_2O_4$ requires C, 47.14; H, 4.20; Cl, 26.09; N, 6.87%]; ν_{max} (KBr) 3256, 1771, 1711, 1665 cm^{-1}; δ_H (DMSO-d_6) 8.64 (1H, m, NH), 7.83 (4H, m, aromatic), 7.68 (1H, m, OH), 5.72 (1H, m, CH), 3.55 (2H, m, CH_2), 2.18 (2H, m, CH_2), 1.61 (2H, m, CH_2), 1.46 (2H, m, CH_2), 1.25 (2H, m, CH_2); δ_C (DMSO-d_6) 173.1 (C=O), 168.4 (C=O), 134.8, 132.0, 123.4, 103.0 (CCl_3), 80.8 (CH), 37.7, 35.4, 28.1, 26.2, 25.1.

4.4. General procedure for the preparation of 3a-e. Tetrachloroethylamides.

Compounds **3a**, **3d**, and **3e** were obtained similarly to previously described[6] **3b** and **3c**.

A mixture of one of compounds **2a-e** (0.30 mol), thionyl chloride (33 mL, 0.45 mol), and dry dioxane (150 mL) was refluxed with stirring until no more gas was evolved and another 30 min. After evaporation under reduced pressure to dryness, the resulting residue was heated to boiling with stirring in the minimum amount of dry benzene and cooled. The crystalline precipitate was filtered, washed on the filter with the minimum amount of dry benzene, and dried *in vacuo* to give the analytically pure product.

*4.4.1. 2-(1,3-Dioxo-2,3-dihydro-1H-isoindol-2-yl)-N-(1,2,2,2-tetrachloroethyl)acetamide (**3a**).*

Yield 104.41 g, 99% as a colorless crystals; mp 152-153°C; [Found: C, 38.88; H, 2.25; Cl, 38.51; N, 7.49. $C_{12}H_8Cl_4N_2O_3$ requires C, 38.95; H, 2.18; Cl, 38.33; N, 7.57%]; ν_{max} (KBr) 3278, 1730, 1692 cm^{-1}; δ_H ($CDCl_3$) 7.91 (2H, m, aromatic), 7.78 (2H, m, aromatic), 7.30 (1H, br s, NH), 6.53 (1H, d, *J* 10.5 Hz, CHN), 4.51 (2H, s, CH_2); δ_C ($CDCl_3$) 167.6 (C=O), 165.6 (C=O), 134.6, 131.8, 123.9, 99.2 (CCl_3), 73.6 (CHCl), 40.8**.**

*4.4.2. 5-(1,3-Dioxo-2,3-dihydro-1H-isoindol-2-yl)-N-(1,2,2,2-tetrachloroethyl)pentanamide (**3d**).*

Yield 122.39 g, 99% as a cream crystals; mp 96-97°C; [Found: C, 43.59; H, 3.53; Cl, 34.58; N, 6.69. $C_{15}H_{14}Cl_4N_2O_3$ requires C, 43.72; H, 3.42; Cl, 34.41; N, 6.80%]; ν_{max} (ATR) 3305, 1770, 1701 cm^{-1}; δ_H ($CDCl_3$) 7.84 (2H, m, aromatic), 7.73 (2H, m, aromatic), 6.89 (1H, d, *J* 10.4 Hz, NH), 6.55 (1H, d, *J* 10.4 Hz, CH), 3.74 (2H, m, CH_2), 2.44 (2H, m, CH_2), 1.67 (4H, m, $2CH_2$); δ_C ($CDCl_3$) 171.8 (C=O), 168.6 (C=O), 134.1, 132.0, 123.3, 99.5 (CCl_3), 73.8 (CHCl), 36.8, 35.4, 27.7, 22.3**.**

*4.4.2. 6-(1,3-Dioxo-2,3-dihydro-1H-isoindol-2-yl)-N-(1,2,2,2-tetrachloroethyl)hexanamide (**3e**).*

Yield 126.55 g, 99% as a yellowish crystals; mp 159-160°C; [Found: C, 45.02; H, 3.87; Cl, 33.46; N, 6.39. $C_{16}H_{16}Cl_4N_2O_3$ requires C, 45.10; H, 3.78; Cl, 33.28; N, 6.57%]; ν_{max} (KBr) 3257, 1771, 1712, 1666, 1529 cm^{-1}; δ_C ($CDCl_3$) 7.80 (2H, m, aromatic), 7.68 (2H, m, aromatic), 6.53 (2H, m, CHNH), 3.65 (2H, m, CH_2), 2.31 (2H, m, CH_2), 1.78-1.62 (4H, m, $2CH_2$), 1.37 (2H, m, CH_2); δ_C ($CDCl_3$) 171.7 (C=O), 134.0, 168.4 (C=O), 132.1, 123.2, 99.5 (CCl_3), 73.7 (CHCl), 37.6, 36.2, 28.2, 26.2, 24.5**.**

4.5. General procedure for the preparation of 4a-e. Arbuzov rearrangement.

A mixture of one of compounds **3a-e** (0.20 mol), triethyl phosphite (42 mL, 0.24 mol), and dry dioxane (200 mL) was refluxed for 3 h under argon and evaporated to dryness *in vacuo*; the residue was recrystallized from dioxane (**3a**, **3b**) or 2-propanol (**3c-e**).

*4.5.1. Diethyl [2,2,2-trichloro-1-[2-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)acetamido]ethyl]phosphonate (**4a**).*

Yield 83.95 g, 89% as a colorless crystals; mp 195-196°C; [Found: C, 40.63; H, 3.96; Cl, 22.71; N, 5.78; P, 6.73. $C_{16}H_{18}Cl_3N_2O_6P$ requires C, 40.74; H, 3.85; Cl, 22.55; N, 5.94; P, 6.57%]; ν_{max} (KBr) 3213, 1777, 1724, 1261, 1026 cm^{-1}; δ_H (DMSO-d_6) 9.68 (1H, d, *J* 10.2 Hz, NH), 7.92 (2H, m, aromatic), 7.89 (2H, m, aromatic), 5.19 (1H, dd, *J* 19.2, 10.2 Hz, CHP), 4.44 (2H, s, CH_2), 4.22-4.10 (4H, m, $2OCH_2$), 1.38-1.24 (6H, m, $2OCH_2\underline{CH_3}$); δ_C (DMSO-d_6) 167.8 (C=O), 167.6 (C=O), 135.2, 132.0, 123.8, 97.3 (d, *J* 14.0 Hz, CCl_3), 64.0 ($O\underline{C}H_2CH_3$), 61.8 (d, *J* 159.0 Hz, CP), 16.7 ($OCH_2\underline{C}H_3$); δ_P (DMSO-d_6) 14.2; LCMS: found *m/z* 471.0 M^+. $C_{16}H_{18}Cl_3N_2O_6P$ requires 471.7.

*4.5.2. Diethyl [2,2,2-trichloro-1-[3-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)propanamido]ethyl]phosphonate (**4b**).*

Yield 68.96 g, 71% as a colorless crystals; mp 166-167°C; [Found: C, 41.95; H, 4.26; Cl, 22.02; N, 5.63; P, 6.49. $C_{17}H_{20}Cl_3N_2O_6P$ requires C, 42.04; H, 4.15; Cl, 21.90; N, 5.77; P, 6.38%]; ν_{max} (KBr) 3234, 1774, 1719, 1676, 1263, 1130 cm^{-1}; δ_H (DMSO-d_6) 9.32 (1H, d, *J* 10.3 Hz, NH), 7.85 (4H, m, aromatic), 5.23 (1H, dd, *J* 19.3, 10.3 Hz, CHP), 4.14-4.00 (4H, m, $2OCH_2$), 3.83 (2H, m, CH_2), 2.79 (2H, m, CH_2), 1.21 (6H, m, $2OCH_2\underline{CH_3}$); δ_C (DMSO-d_6) 170.8 (C=O), 168.0 (C=O), 134.9, 132.1, 123.4, 97.6 (d, *J* 14.5 Hz, CCl_3), 63.7 ($O\underline{C}H_2CH_3$), 61.3 (d, *J* 159.0 Hz, CP), 34.4, 33.3, 16.6 ($OCH_2\underline{C}H_3$); δ_P (DMSO-d_6) 14.7; LCMS: found *m/z* 487.0 MH^+. $C_{17}H_{20}Cl_3N_2O_6P$ requires 485.7.

*4.5.3. Diethyl [2,2,2-trichloro-1-[4-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)butanamido]ethyl]phosphonate (**4c**).*

Yield 65.96 g, 66% as a colorless crystals; mp 133-134°C; [Found: C, 43.18; H, 4.54; Cl, 21.33; N, 5.51; P, 6.38. $C_{18}H_{22}Cl_3N_2O_6P$ requires C, 43.26; H, 4.44; Cl, 21.25; N, 5.61; P, 6.20%]; ν_{max} (KBr) 3240, 1769, 1710, 1680, 1246, 1019 cm^{-1}; δ_H (DMSO-d_6) 9.13 (1H, d, *J* 10.2 Hz, NH), 7.85 (m, 4H, aromatic), 5.24 (1H, dd, *J* 19.31, 10.2 Hz, CHP), 4.18-4.01 (4H, m, $2OCH_2$), 3.62 (2H, m, CH_2), 2.38 (2H, m, CH_2), 1.87 (2H, m, CH_2), 1.24 (6H, m, $2OCH_2\underline{CH_3}$); δ_C (DMSO-d_6) 172.6 (C=O), 168.4 (C=O), 134.8, 132.2, 123.5, 97.7 (d, *J* 14.9 Hz, CCl_3), 63.6 ($O\underline{C}H_2CH_3$), 61.3 (d, *J* 159.0 Hz, CP), 37.7, 32.9, 24.8, 16.6 ($OCH_2\underline{C}H_3$); δ_P (DMSO-d_6) 14.9; LCMS: found *m/z* 501.0 MH^+. $C_{18}H_{22}Cl_3N_2O_6P$ requires 499.7.

*4.5.4. Diethyl [2,2,2-trichloro-1-[5-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)pentanamido]ethyl]phosphonate (**4d**).*

Yield 63.70 g, 62% as a colorless crystals; mp 132-133°C; [Found: C, 44.34; H, 4.82; Cl, 20.84; N, 5.26; P, 6.25. $C_{19}H_{24}Cl_3N_2O_6P$ requires C, 44.42; H, 4.71; Cl, 20.70; N, 5.45; P, 6.03%]; ν_{max} (KBr) 3248, 1769, 1715, 1677, 1236, 1032 cm^{-1}; δ_H (DMSO-d_6) 9.07 (1H, d, *J* 10.1 Hz, NH), 7.85 (4H, m, aromatic), 5.24 (1H, dd, *J* 19.5, 10.1 Hz, CHP), 4.16-3.99 (4H, m, $2OCH_2$), 3.58 (2H, m, CH_2), 2.36 (2H, m, CH_2), 1.68-1.49 (4H, m, $2CH_2$), 1.23 (6H, m, $2OCH_2\underline{CH_3}$); δ_C (DMSO-d_6) 172.6 (C=O), 168.4 (C=O), 134.8, 132.2, 123.5, 97.7 (d, *J* 14.9 Hz, CCl_3), 63.6 ($O\underline{C}H_2CH_3$), 61.3 (d, *J* 159.0 Hz, CP), 37.7, 32.9, 24.8, 16.6 ($OCH_2\underline{C}H_3$); δ_P (DMSO-d_6) 15.0; LCMS: found *m/z* 515.0 MH^+. $C_{19}H_{24}Cl_3N_2O_6P$ requires 513.7.

*4.5.5. Diethyl [2,2,2-trichloro-1-[6-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)hexanamido]ethyl]phosphonate (**4e**).*

Yield 62.27 g, 59% as a colorless crystals; mp 152-153°C; [Found: C, 46.46; H, 5.33; Cl, 20.34; N, 5.18; P, 6.03. $C_{20}H_{26}Cl_3N_2O_6P$ requires C, 46.55; H, 5.21; Cl, 20.15; N, 5.31; P, 5.87%]; ν_{max} (KBr) 3248, 1773, 1685, 1241, 1030 cm^{-1}; δ_H (DMSO-d_6) 9.05 (1H, d, *J* 10.4 Hz, NH), 7.85 (4H, m, aromatic), 5.24 (1H, dd, *J* 19.3, 10.4 Hz, CHP), 4.16-4.02 (4H, m, $2OCH_2$), 3.56 (2H, m, CH_2), 2.32 (2H, m, CH_2), 1.58 (4H, m, $2CH_2$), 1.32-1.19 (8H, m, CH_2, $2OCH_2\underline{CH_3}$); δ_C (DMSO-d_6) 173.2 (C=O), 168.4 (C=O), 134.9, 132.1, 123.5, 97.8 (d, *J* 14.5 Hz, CCl_3), 63.6 ($O\underline{C}H_2CH_3$), 61.3 (d, *J* 159.0 Hz, CP), 37.8, 34.9, 28.2, 26.3, 25.2, 16.7 ($OCH_2\underline{C}H_3$); δ_P (DMSO-d_6) 15.0; LCMS: found *m/z* 527.0 M^+. $C_{20}H_{26}Cl_3N_2O_6P$ requires 527.8.

4.6. General procedure for the preparation of 5a-e. Dichloroenamides.

A mixture of one of compounds **4a-e** (0.01 mol), Et_3N (4.2 mL, 0.03 mol), and dry THF (50 mL) was stirred at 20-25°C for 18 h. The precipitate was filtered and washed on the filter with dry THF, and the combined filtrates were evaporated to dryness *in vacuo* to give the analytically pure product.

*4.6.1. Diethyl [2,2-dichloro-1-[2-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)acetamido]ethenyl]phosphonate (**5a**).*

Yield 4.31 g, 99% as a colorless crystals; mp 159-160°C; [Found: C, 44.08; H, 4.05; Cl, 16.44; N, 6.27; P, 7.25. $C_{16}H_{17}Cl_2N_2O_6P$ requires C, 44.16; H, 3.94; Cl, 16.29; N, 6.44; P, 7.12%]; ν_{max} (KBr) 3198, 1775, 1724, 1261, 1023, 984 cm^{-1}; δ_H ($CDCl_3$) 8.32 (1H, br s, NH), 7.88 (2H, m, aromatic), 7.75 (2H, m, aromatic), 4.52 (2H, s, CH_2), 4.16 (4H, m, $2OCH_2$), 1.36 (6H, m, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 167.6 (C=O), 164.8 (C=O), 136.5 (d, *J* 33.7 Hz, CCl_2), 134.0, 132.2, 124.8 (d, *J* 217.8 Hz, CP), 123.5, 63.8 ($O\underline{C}H_2CH_3$), 40.5, 16.1 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 8.7; LCMS: found *m/z* 435.0 M^+. $C_{16}H_{17}Cl_2N_2O_6P$ requires 435.2.

*4.6.2. Diethyl [2,2-dichloro-1-[3-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)propanamido]ethenyl]phosphonate (**5b**).*

Yield 4.44 g, 99% as a colorless crystals; mp 148-149°C; [Found: C, 45.37; H, 4.39; Cl, 15.91; N, 6.05; P, 6.98. $C_{17}H_{19}Cl_2N_2O_6P$ requires C, 45.45; H, 4.26; Cl, 15.78; N, 6.24; P, 6.89%]; ν_{max} (KBr) 3234, 1773, 1721, 1683, 1246, 1037, 1001 cm^{-1}; δ_H ($CDCl_3$) 8.20 (1H, br s, NH), 7.74 (2H, m, aromatic), 7.64 (2H, m, aromatic), 4.08 (4H, m, $2OCH_2$), 3.97 (2H, m, CH_2), 2.74 (2H, m, CH_2), 1.26 (6H, t, *J* 7.0 Hz, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 168.0 (C=O), 135.5 (d, *J* 27.3 Hz, CCl_2), 134.0, 132.1, 125.0 (d, *J* 208.5 Hz, CP), 123.2, 63.5 ($O\underline{C}H_2CH_3$), 34.1 ($2CH_2$), 16.1 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 9.1; LCMS: found *m/z* 449.0 M^+. $C_{17}H_{19}Cl_2N_2O_6P$ requires 449.2.

*4.6.3. Diethyl [2,2-dichloro-1-[4-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)butanamido]ethenyl]phosphonate (**5c**).*

Yield 4.58 g, 99% as a colorless crystals; mp 69-70°C; [Found: C, 46.59; H, 4.68; Cl, 15.50; N, 5.88; P, 6.82. $C_{18}H_{21}Cl_2N_2O_6P$ requires C, 46.67; H, 4.57; Cl, 15.31; N, 6.05; P, 6.69%]; ν_{max} (KBr) 3208, 1775, 1722, 1665, 1242, 1011, 964 cm^{-1}; δ_H ($CDCl_3$) 7.94 (1H, br, NH), 7.79 (2H, m, aromatic), 7.68 (2H, m, aromatic), 4.13 (4H, m, $2OCH_2$), 3.76 (2H, t, *J* 7.0 Hz, CH_2), 2.32 (2H, t, *J* 7.5 Hz, CH_2), 2.01 (2H, m, CH_2), 1.30 (6H, t, *J* 7.0 Hz, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 170.1 (C=O), 168.6 (C=O), 135.3 (d, *J* 29.6 Hz, CCl_2), 134.1, 132.0, 125.2 (d, *J* 213.6 Hz, CP), 123.3, 63.5 ($O\underline{C}H_2CH_3$), 37.1, 33.5, 25.0, 16.2 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 9.3; LCMS: found *m/z* 463.0 M^+. $C_{18}H_{21}Cl_2N_2O_6P$ requires 463.3.

*4.6.4. Diethyl [2,2-dichloro-1-[5-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)pentanamido]ethenyl]phosphonate (**5d**).*

Yield 4.73 g, 99% as a colorless crystals; mp 108-109°C; [Found: C, 47.72; H, 4.96; Cl, 14.99; N, 5.69; P, 6.65. $C_{19}H_{23}Cl_2N_2O_6P$ requires C, 47.81; H, 4.86; Cl, 14.86; N, 5.87; P, 6.49%]; ν_{max} (KBr) 3206, 1769, 1705, 1675, 1574, 1243, 1008, 972 cm^{-1}; δ_H ($CDCl_3$) 7.81 (2H, m, aromatic), 7.70 (2H, m, aromatic), 7.64 (1H, br, NH), 4.16 (4H, m, $2OCH_2$), 3.70 (2H, m, CH_2), 2.37 (2H, m, CH_2), 1.73 (4H, m, $2CH_2$), 1.34 (6H, m, $2OCH_2\underline{CH_3}$); δ_C NMR ($CDCl_3$) 170.6 (C=O), 168.3 (C=O), 135.4 (d, *J* 28.7 Hz, CCl_2), 133.9, 132.1, 125.1 (d, *J* 210.4 Hz, CP), 123.2, 63.5 ($O\underline{C}H_2CH_3$), 37.3, 35.4, 27.9, 22.6, 16.2 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 9.3; LCMS: found *m/z* 477.0 M^+. $C_{19}H_{23}Cl_2N_2O_6P$ requires 477.3.

*4.6.5. Diethyl [2,2-dichloro-1-[6-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)hexanamido]ethenyl]phosphonate (**5e**).*

Yield 4.86 g, 99% as a colorless crystals; mp 119-120°C; [Found: C, 48.80; H, 5.24; Cl, 14.56; N, 5.52; P, 6.45. $C_{20}H_{25}Cl_2N_2O_6P$ requires C, 48.89; H, 5.13; Cl, 14.43; N, 5.70; P, 6.30%]; ν_{max} (KBr) 3170, 1770, 1708, 1678, 1245, 1016, 973 cm^{-1}; δ_H ($CDCl_3$) 7.84 (2H, m, aromatic), 7.71 (2H, m, aromatic), 7.27 (1H, br, NH), 4.17 (4H, m, $2OCH_2$), 3.69 (2H, t, *J* 7.0 Hz, CH_2), 2.32 (2H, t, *J* 7.5 Hz, CH_2), 1.72 (4H, m, $2CH_2$), 1.41 (2H, m, CH_2), 1.35 (6H, t, *J* 7.0 Hz, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 170.4 (C=O), 168.3 (C=O), 134.5 (d, *J* 29.4 Hz, CCl_2), 133.8, 132.1, 124.8 (d, *J* 209.4 Hz, CP), 123.1, 63.5 ($O\underline{C}H_2CH_3$), 37.7, 36.1, 28.6, 26.3, 24.8, 16.2 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 9.4; LCMS: found *m/z* 491.0 M^+. $C_{20}H_{25}Cl_2N_2O_6P$ requires 491.3.

4.7. General procedure for the preparation of 6a-n. Oxazole cyclization.

Method A. A mixture of one of compounds **4a-e** (20 mmol), the corresponding amine (21 mmol), and Et_3N (16.7 mL, 120 mmol) in dry dioxane (100 mL) was refluxed for 24 h and cooled. The precipitate was filtered and washed on the filter with dry dioxane; the combined filtrates were evaporated *in vacuo* to dryness. Compounds **6f-n** were thus obtained in the analytically pure state without further purification. To purify compounds **6a-e**, the residue after evaporation was recrystallized from the minimum amount of 2-propanol. If necessary, the reaction products can be purified by extraction with boiling petroleum ether (bp 80-110°C), followed by evaporation of the combined extracts *in vacuo*.

Method B. The above procedure was performed starting from compounds **5a-e** and using less Et_3N (13.9 mL, 100 mmol).

Compounds **6a-n** produced by methods A and B provided identical characterization data.

*4.7.1. Diethyl [5-(benzylamino)-2-[(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)methyl]-1,3-oxazol-4-yl]phosphonate (**6a**).*

Yield 3.755 g, 40% (by method A), 4.037 g, 43% (by method B) as a yellowish crystals; mp 174-175°C; [Found: C, 58.76; H, 5.24; N, 8.76; P, 6.77. $C_{23}H_{24}N_3O_6P$ requires C, 58.85; H, 5.15; N, 8.95; P, 6.60%]; ν_{max} (KBr) 3302, 1722, 1639, 1600, 1224, 1031, 972 cm^{-1}; δ_H ($CDCl_3$) 7.89 (2H, m, aromatic), 7.77 (2H, m, aromatic), 7.26-7.15 (5H, m, C_6H_5), 6.39 (1H, t, *J* 6.2 Hz, $CH_2\underline{NH}$), 4.85 (2H, s, CH_2), 4.39 (2H, d, *J* 6.2 Hz, $\underline{CH_2}NH$), 4.11-3.95 (4H, m, $2OCH_2$), 1.28 (6H, t, *J* 7.0 Hz, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 167.1 (C=O), 163.9 (d, *J* 39.4 Hz, O-$\underline{C}$=C-P), 148.1 (d, *J* 21.9 Hz, O-C=N), 137.9, 134.3, 132.0, 128.6, 127.5, 127.4, 123.6, 95.9 (d, *J* 255.3 Hz, CP), 62.3 ($O\underline{C}H_2CH_3$), 47.4, 34.5,16.2 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 13.9; LCMS: found *m/z* 470.0 MH^+. $C_{23}H_{24}N_3O_6P$ requires 469.4.

*4.7.2. Diethyl [5-(benzylamino)-2-[2-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)ethyl]-1,3-oxazol-4-yl]phosphonate (**6b**).*

Yield 3.674 g, 38% (by method A), 3.964 g, 41% (by method B) as a colorless crystals; mp 133-134°C; [Found: C, 59.52; H, 5.54; N, 8.53; P, 6.55. $C_{24}H_{26}N_3O_6P$ requires C, 59.62; H, 5.42; N, 8.69; P, 6.41%]; ν_{max} (KBr) 3393, 1713, 1641, 1597, 1222, 1024, 957 cm^{-1}; δ_H ($CDCl_3$) 7.81 (2H, m, aromatic), 7.70 (2H, m, aromatic), 7.34-7.23 (5H, m, C_6H_5), 6.28 (1H, t, *J* 6.5 Hz, $CH_2\underline{NH}$), 4.38 (2H, d, *J* 6.5 Hz, $\underline{CH_2}NH$), 4.07-3.90 (6H, m, $2OCH_2$, CH_2), 3.02 (2H, t, *J* 6.7 Hz, CH_2), 1.25 (6H, t, *J* 7.0 Hz, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 167.7 (C=O), 164.0 (d, *J* 39.4 Hz, O-$\underline{C}$=C-P), 151.3 (d, *J* 21.9 Hz, O-C=N), 138.1, 134.0, 132.0, 128.6, 127.5, 127.3, 123.3, 95.4 (d, *J* 254.8 Hz, CP), 62.1 ($O\underline{C}H_2CH_3$), 47.3, 35.4, 27.1, 16.2 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 14.4; LCMS: found *m/z* 484.0 MH^+. $C_{24}H_{26}N_3O_6P$ requires 483.5.

*4.7.3. Diethyl [5-(benzylamino)-2-[3-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)propyl]-1,3-oxazol-4-yl]phosphonate (**6c**).*

Yield 4.577 g, 46% (by method A), 4.875 g, 49% (by method B) as a colorless crystals; mp 104-105°C; [Found: C, 60.25; H, 5.79; N, 8.29; P, 6.39. $C_{25}H_{28}N_3O_6P$ requires C, 60.36; H, 5.67; N, 8.45; P, 6.23%]; ν_{max} (KBr) 3331, 1773, 1720, 1650, 1599, 1222, 1250, 964 cm^{-1}; δ_H ($CDCl_3$) 7.84 (2H, m, aromatic), 7.71 (2H, m, aromatic), 7.34-7.22 (5H, m, C_6H_5), 6.28 (1H, t, *J* 6.5 Hz, NH), 4.44 (2H, d, *J* 6.5Hz, $\underline{CH_2}NH$), 4.04 (4H, m, $2OCH_2$), 3.75 (2H, t, *J* 7.0 Hz, CH_2), 2.69 (2H, t, *J* 7.7 Hz, CH_2), 2.10 (2H, m, CH_2), 1.30 (6H, t, *J* 7.0 Hz, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 168.2 (C=O), 163.5 (d, *J* 39.4 Hz, O-$\underline{C}$=C-P), 153.8 (d, *J* 22.4 Hz, O-C=N), 138.3, 134.0, 128.6, 127.5, 127.4, 127.3, 123.2, 95.5 (d, *J* 254.8 Hz, CP), 62.1 ($O\underline{C}H_2CH_3$), 47.4, 37.2, 25.8, 25.4, 16.2 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 14.5; LCMS: found *m/z* 498.2 MH^+. $C_{25}H_{28}N_3O_6P$ requires 497.5.

*4.7.4. Diethyl [5-(benzylamino)-2-[4-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)butyl]-1,3-oxazol-4-yl]phosphonate (**6d**).*

Yield 4.706 g, 46% (by method A), 5.013 g, 49% (by method B) as a yellow crystals; mp 99-100°C; [Found: C, 60.96; H, 6.02; N, 8.02; P, 6.21. $C_{26}H_{30}N_3O_6P$ requires C, 61.05; H, 5.91; N, 8.21; P, 6.06%]; ν_{max} (KBr) 3303, 1770, 1720, 1707, 1636, 1238, 1016, 968 cm^{-1}; δ_H ($CDCl_3$) 7.85 (2H, m, aromatic), 7.73 (2H, m, aromatic), 7.34-7.23 (5H, m, C_6H_5), 6.29 (1H, t, *J* 6.5 Hz, NH), 4.44 (2H, d, *J* 6.5 Hz, $\underline{CH_2}NH$), 4.05 (4H, m, $2OCH_2$), 3.70 (2H, m, CH_2), 2.68 (2H, m, CH_2), 1.73 (4H, m, $2CH_2$), 1.31 (6H, t, *J* 7.0 Hz, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 168.2 (C=O), 163.6 (d, *J* 38.9 Hz, O-$\underline{C}$=C-P), 154.5 (d, *J* 21.4 Hz, O-$\underline{C}$=N), 138.4, 133.9, 132.1, 128.6, 127.3, 123.2, 95.4 (d, *J* 255.8 Hz, CP), 62.2 ($O\underline{C}H_2CH_3$), 47.4, 37.4, 27.9, 27.2, 24.1, 16.2 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 14.5; LCMS: found *m/z* 512.4 MH^+. $C_{26}H_{30}N_3O_6P$ requires 511.5.

*4.7.5. Diethyl [5-(benzylamino)-2-[5-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)pentyl]-1,3-oxazol-4-yl]phosphonate (**6e**).*

Yield 4.414 g, 42% (by method A), 4.625 g, 44% (by method B) as a yellow crystals; mp 96-97°C; [Found: C, 61.60; H, 6.23; N, 7.84; P, 6.03. $C_{27}H_{32}N_3O_6P$ requires C, 61.71; H, 6.14; N, 8.00; P, 5.89%]; ν_{max} (KBr) 3293, 1773, 1715, 1644, 1594, 1228, 1024, 961 cm^{-1}; δ_H ($CDCl_3$) 7.83 (2H, m, aromatic), 7.71 (2H, m, aromatic), 7.35-7.23 (5H, m, C_6H_5), 6.29 (1H, t, *J* 6.5 Hz, NH), 4.44 (2H, d, *J* 6.5 Hz, $\underline{CH_2}NH$), 4.12-3.97 (4H, m, $2OCH_2$), 3.66 (2H, t, *J* 7.3 Hz, CH_2), 2.62 (2H, t, *J* 7.5 Hz, CH_2), 1.71 (4H, m, $2CH_2$), 1.36 (2H, m, CH_2), 1.30 (6H, t, *J* 7.0 Hz, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 168.4 (C=O), 163.6 (d, *J* 38.9 Hz, O-$\underline{C}$=C-P), 154.9 (d, *J* 21.9 Hz, O-$\underline{C}$=N), 138.4, 133.9, 132.1, 128.6, 127.5, 127.3, 123.2, 95.3 (d, *J* 255.8 Hz, CP), 62.2 ($O\underline{C}H_2CH_3$), 47.5, 37.5, 28.2, 27.7, 26.4, 26.2, 16.2 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 14.7; LCMS: found *m/z* 526.2 MH^+. $C_{27}H_{32}N_3O_6P$ requires 525.5.

*4.7.6. Diethyl [2-[(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)methyl]-5-(piperidin-1-yl)-1,3-oxazol-4-yl]phosphonate (**6f**).*

Yield 8.769 g, 98% (by method A), 8.859 g, 99% (by method B) as a yellowish crystals mp 57-60°C; [Found: C, 56.28; H, 5.97; N, 9.22; P, 7.10. $C_{21}H_{26}N_3O_6P$ requires C, 56.37; H, 5.86; N, 9.39; P, 6.92%]; ν_{max} (CH_2Cl_2) 1777, 1724, 1620, 1284, 1025, 961 cm^{-1}; δ_H ($CDCl_3$) 7.89 (2H, m, aromatic), 7.76 (2H, m, aromatic), 4.84 (2H, s, CH_2), 4.08 (4H, m, $2OCH_2$), 3.46 (4H, m, $2CH_2$), 1.61 (6H, m, $3CH_2$), 1.29 (6H, m, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 167.2 (C=O), 162.2 (d, *J* 36.9 Hz, O-$\underline{C}$=C-P), 147.4 (d, *J* 21.9 Hz, O-C=N), 134.2, 132.0, 123.6, 100.1 (d, *J* 255.8 Hz, CP), 62.3 ($O\underline{C}H_2CH_3$), 49.4, 34.5, 25.3, 23.9, 16.2 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 13.7; LCMS: found *m/z* 448.2 MH^+. $C_{21}H_{26}N_3O_6P$ requires 447.4.

*4.7.7. Diethyl [2-[2-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)ethyl]-5-(piperidin-1-yl)-1,3-oxazol-4-yl]phosphonate (**6g**).*

Yield 9.044 g, 98% (by method A), 9.137 g, 99% (by method B) as a yellowish crystals mp 76-77°C; [Found: C, 57.15; H, 6.23; N, 8.95; P, 6.84. $C_{22}H_{28}N_3O_6P$ requires C, 57.26; H, 6.12; N, 9.11; P, 6.71%]; ν_{max} (CH_2Cl_2) 1774, 1717, 1620, 1240, 1027, 967 cm^{-1}; δ_H ($CDCl_3$) 7.81 (2H, m, aromatic), 7.70 (2H, m, aromatic), 4.08-3.93 (6H, m, $2OCH_2$, CH_2), 3.41 (4H, m, $2CH_2$), 3.00 (2H, t, *J* 6.6 Hz, CH_2), 1.58 (6H, m, $3CH_2$), 1.24 (6H, t, *J* 7.0 Hz, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 167.7 (C=O), 162.3 (d, *J* 36.9 Hz, O-$\underline{C}$=C-P), 150.9 (d, *J* 22.4 Hz, O-$\underline{C}$=N), 134.0, 132.1, 123.3, 100.1 (d, *J* 255.8 Hz, CP), 62.1 ($O\underline{C}H_2CH_3$), 49.6, 35.4, 27.1, 25.4, 24.0,16.2 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 14.0; LCMS: found *m/z* 462.2 MH^+. $C_{22}H_{28}N_3O_6P$ requires 461.5.

*4.7.8. Diethyl [2-[3-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)propyl]-5-(piperidin-1-yl)-1,3-oxazol-4-yl]phosphonate (**6h**).*

Yield 8.654 g, 91% (by method A), 9.034 g, 95% (by method B) as a brown viscous oil; [Found: C, 58.02; H, 6.47; N, 8.69; P, 6.67. $C_{23}H_{30}N_3O_6P$ requires C, 58.10; H, 6.36; N, 8.84; P, 6.51%]; ν_{max} (CH_2Cl_2) 1772, 1709, 1618, 1572, 1257, 1019, 956 cm^{-1}; δ_H ($CDCl_3$) 7.80 (2H, m, aromatic), 7.69 (2H, m, aromatic), 4.08 (4H, m, $2OCH_2$), 3.73 (2H, t, *J* 7.0 Hz, CH_2), 3.43 (4H, m, $2CH_2$), 2.65 (2H, t, *J* 7.5 Hz, CH_2), 2.07 (2H, m, CH_2), 1.60 (6H, m, $3CH_2$), 1.29 (6H, t, *J* 7.0 Hz, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 168.2 (C=O), 161.9 (d, *J* 36.9 Hz, O-$\underline{C}$=C-P), 153.1 (d, *J* 21.9 Hz, O-$\underline{C}$=N), 134.0, 132.0, 123.2, 99.7 (d, *J* 255.8 Hz, CP), 62.1 ($O\underline{C}H_2CH_3$), 49.5, 37.3, 25.8, 25.4, 25.3, 24.0, 16.3 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 14.3; LCMS: found *m/z* 476.2 MH^+. $C_{23}H_{30}N_3O_6P$ requires 475.5.

*4.7.9. Diethyl [2-[4-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)butyl]-5-(piperidin-1-yl)-1,3-oxazol-4-yl]phosphonate (**6i**).*

Yield 9.105 g, 93% (by method A), 9.301 g, 95% (by method B) as a brown viscous oil; [Found: C, 58.78; H, 6.70; N, 8.39; P, 6.51. $C_{24}H_{32}N_3O_6P$ requires C, 58.89; H, 6.59; N, 8.58; P, 6.33%]; ν_{max} (CH_2Cl_2) 1771, 1708, 1617, 1572, 1257, 1020, 958 cm^{-1}; δ_H ($CDCl_3$) 7.83 (2H, m, aromatic), 7.71 (2H, m, aromatic), 4.10 (4H, m, $2OCH_2$), 3.70 (2H, m, CH_2), 3.45 (4H, m, $2CH_2$), 2.65 (2H, m, CH_2), 1.74 (4H, m, $2CH_2$), 1.62 (6H, m, $3CH_2$), 1.32 (6H, t, *J* 7.0 Hz, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 168.3 (C=O), 161.9 (d, *J* 36.9 Hz, O-$\underline{C}$=C-P), 153.9 (d, *J* 21.9 Hz, O-$\underline{C}$=N), 133.9, 132.1, 123.2, 99.8 (d, *J* 256.8 Hz, CP), 62.1 ($O\underline{C}H_2CH_3$), 49.5, 37.5, 28.0, 27.3, 25.4, 24.3, 24.0, 16.3 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 14.5; LCMS: found *m/z* 490.4 MH^+. $C_{24}H_{32}N_3O_6P$ requires 489.5.

*4.7.10. Diethyl [2-[5-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)pentyl]-5-(piperidin-1-yl)-1,3-oxazol-4-yl]phosphonate (**6j**).*

Yield 8.560 g, 85% (by method A), 9.064 g, 90% (by method B) as a brown viscous oil; [Found: C, 59.54; H, 6.92; N, 8.17; P, 6.31. $C_{25}H_{34}N_3O_6P$ requires C, 59.63; H, 6.81; N, 8.35; P, 6.15%]. ν_{max} (CH_2Cl_2) 1772, 1709, 1617, 1571, 1256, 1021, 953 cm^{-1}; δ_H ($CDCl_3$) 7.82 (2H, m, aromatic), 7.70 (2H, m, aromatic), 4.10 (4H, m, $2OCH_2$), 3.66 (2H, t, *J* 7.3 Hz, CH_2), 3.45 (4H, m, $2CH_2$), 2.59 (2H, t, *J* 7.5 Hz, CH_2), 1.77-1.55 (10H, m, $5CH_2$), 1.40 (2H, m, CH_2), 1.31 (6H, m, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 168.4 (C=O), 161.8 (d, *J* 36.9 Hz, O-$\underline{C}$=C-P), 154.3 (d, *J* 21.9 Hz, O-$\underline{C}$=N), 133.9, 132.1, 123.2, 99.7 (d, *J* 257.3 Hz, CP), 62.1 ($O\underline{C}H_2CH_3$), 49.6, 37.8, 28.2, 27.7, 26.5, 26.3, 25.4, 24.0,16.3 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 14.5; LCMS: found *m/z* 504.2 MH^+. $C_{25}H_{34}N_3O_6P$ requires 503.5.

*4.7.11. Diethyl [2-[(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)methyl]-5-(morpholin-4-yl)-1,3-oxazol-4-yl]phosphonate (**6k**).*

Yield 8.808 g, 98% (by method A), 8.898 g, 99% (by method B) as a yellow viscous oil; [Found: C, 53.37; H, 5.48; N, 9.18; P, 6.98. $C_{20}H_{24}N_3O_7P$ requires C, 53.45; H, 5.38; N, 9.35; P, 6.89%]. ν_{max} (CH_2Cl_2) 1777, 1724, 1618, 1280, 1026, 969 cm^{-1}; δ_H ($CDCl_3$) 7.85 (2H, m, aromatic), 7.73 (2H, m, aromatic), 4.81 (2H, s, $2CH_2$), 4.05 (4H, m, $2OCH_2$), 3.72 (4H, m, $2CH_2$), 3.49 (4H, m, $2CH_2$), 1.25 (6H, t, *J* 7.0 Hz, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 167.2 (C=O), 161.6 (d, *J* 36.9 Hz, O-$\underline{C}$=C-P), 148.2 (d, *J* 21.9 Hz, O-$\underline{C}$=N), 134.3, 131.9, 123.6, 101.6 (d, *J* 252.3 Hz, CP), 66.2, 62.5 ($O\underline{C}H_2CH_3$), 48.3, 34.5, 16.2 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 12.5; LCMS: found *m/z* 450.2 MH^+. $C_{20}H_{24}N_3O_7P$ requires 449.4.

*4.7.12. Diethyl [2-[2-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)ethyl]-5-(morpholin-4-yl)-1,3-oxazol-4-yl]phosphonate (**6l**).*

Yield 9.083 g, 98% (by method A), 9.176 g, 99% (by method B) as a yellow viscous oil; [Found: C, 54.35; H, 5.76; N, 8.92; P, 6.74. $C_{21}H_{26}N_3O_7P$ requires C, 54.43; H, 5.65; N, 9.07; P, 6.68%]; ν_{max} (CH_2Cl_2) 1774, 1717, 1618, 1284, 1026, 969 cm^{-1}; δ_H ($CDCl_3$) 7.79 (2H, m, aromatic), 7.69 (2H, m, aromatic), 4.09-3.90 (6H, m, $2OCH_2$, CH_2), 3.71 (4H, m, $2CH_2$), 3.46 (4H, m, $2CH_2$), 3.00 (2H, t, *J* 6.6 Hz, CH_2), 1.22 (6H, t, *J* 7.0 Hz, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 167.7 (C=O), 161.8 (d, *J* 36.9 Hz, O-$\underline{C}$=C-P), 151.7 (d, *J* 21.9 Hz, O-$\underline{C}$=N), 134.1, 132.0, 123.3, 101.7 (d, *J* 253.3 Hz, CP), 66.3, 62.3 ($O\underline{C}H_2CH_3$), 48.5, 35.3, 27.0, 16.2 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 12.8; LCMS: found *m/z* 464.2 MH^+. $C_{21}H_{26}N_3O_7P$ requires 463.4.

*4.7.13. Methyl 1-[4-(diethoxyphosphoryl)-2-[(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)methyl]-1,3-oxazol-5-yl]piperidine-4-carboxylate (**6m**).*

Yield 9.806 g, 97% (by method A), 10.008 g, 99% (by method B) as a yellow viscous oil; [Found: C, 54.57; H, 5.67; N, 8.13; P, 6.23. $C_{23}H_{28}N_3O_8P$ requires C, 54.65; H, 5.58; N, 8.31; P, 6.13%]; ν_{max} (KBr) 1774, 1731, 1620, 1257, 1019, 970 cm^{-1}; δ_H ($CDCl_3$) 7.88 (2H, m, aromatic), 7.75 (2H, m, aromatic), 4.83 (2H, m, CH_2), 4.08 (4H, m, $2OCH_2$), 3.94 (2H, m, CH_2), 3.67

(3H, s, OCH_3), 3.11 (2H, m, CH_2), 2.47 (1H, m, CH), 1.94 (2H, m, CH_2), 1.78 (2H, m, CH_2), 1.28 (6H, m, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 174.6 (C=O), 167.2 (C=O), 161.7 (d, *J* 36.9 Hz, O-<u>C</u>=C-P), 147.9 (d, *J* 21.9 Hz, O-C=N), 134.3, 132.0, 123.6, 101.2 (d, *J* 258.8 Hz, CP), 62.4 ($O\underline{C}H_2CH_3$), 51.8, 47.9, 40.4, 34.5, 27.5, 16.2 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 13.0; LCMS: found *m/z* 506.2 MH^+. $C_{23}H_{28}N_3O_8P$ requires 505.5.

*4.7.14. Methyl 1-[4-(diethoxyphosphoryl)-2-[2-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)ethyl]-1,3-oxazol-5-yl]piperidine-4-carboxylate (**6n**).*

Yield 10.182 g, 98% (by method A), 10.286 g, 99% (by method B) as a yellow viscous oil; [Found: C, 55.40; H, 5.94; N, 7.91; P, 6.08. $C_{24}H_{30}N_3O_8P$ requires C, 55.49; H, 5.82; N, 8.09; P, 5.96%]; ν_{max} (CH_2Cl_2) 1774, 1717, 1620, 1234, 1028, 968 cm^{-1}; δ_H ($CDCl_3$) 7.82 (2H, m, aromatic), 7.72 (2H, m, aromatic), 4.03-3.92 (6H, m, $2OCH_2$, CH_2), 3.91 (2H, m, CH_2), 3.70 (3H, s, OCH_3), 3.08 (2H, m, CH_2), 3.03 (2H, t, *J* 6.7 Hz, CH_2), 2.48 (1H, m, CH), 1.94 (2H, m, CH_2), 1.78 (2H, m, CH_2), 1.26 (6H, m, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 174.7 (C=O), 167.7 (C=O), 161.9 (d, *J* 36.9Hz, O-<u>C</u>=C-P), 151.4 (d, *J* 21.9 Hz, O-<u>C</u>=N), 134.0, 132.0, 123.3, 101.3 (d, *J* 254.8 Hz, CP), 62.2 ($O\underline{C}H_2CH_3$), 51.8, 48.1, 40.5, 35.4, 27.6, 27.1, 16.2 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 13.3; LCMS: found *m/z* 520.2 MH^+. $C_{24}H_{30}N_3O_8P$ requires 519.5.

4.8. General procedure for the preparation of 7a-n. Removal of the phthalimido protecting group by hydrazinolysis.

A mixture of one of compounds **7a-n** (10 mmol), hydrazine hydrate (2.5 mL, 50 mmol), THF (60 mL), and water (20 mL) was stirred at 20-25°C for 48 h with TLC monitoring. After addition of EtOAc (100 mL) to the reaction mixture, it was washed with saturated aqueous K_2CO_3 (5x10 ml) and dried over K_2CO_3; the resulting precipitate was filtered and washed on the filter with EtOAc. The combined filtrates were evaporated to dryness *in vacuo* at a temperature above 35°C and the residue was dissolved in absolute CH_2Cl_2 (50 mL). The solution was filtered through activated carbon and evaporated *in vacuo* to dryness to give the analytically pure product.

*4.8.1. Diethyl [2-(aminomethyl)-5-(benzylamino)-1,3-oxazol-4-yl]phosphonate (**7a**).*

Yield 2.749 g, 81% as a yellow viscous oil; [Found: C, 52.99; H, 6.60; N, 12.20; P, 9.22. $C_{15}H_{22}N_3O_4P$ requires C, 53.09; H, 6.53; N, 12.38; P, 9.13%]; ν_{max} (KBr) 2982, 1647, 1591, 1209, 1025, 964 cm^{-1}; δ_H ($CDCl_3$) 7.37-7.24 (5H, m, C_6H_5), 6.35 (1H, t, *J* 6.5 Hz, NH), 4.47 (2H, d, *J* 6.5 Hz, CH_2), 4.15-3.99 (4H, m, $2OCH_2$), 3.80 (2H, s, CH_2), 1.65 (2H, br, NH_2), 1.32 (6H, t, *J* 7.0 Hz, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 163.7 (d, *J* 39.4 Hz, O-<u>C</u>=C-P), 155.3 (d, *J* 20.9 Hz, O-<u>C</u>=N), 138.2, 128.7, 127.6, 127.3, 95.5 (d, *J* 256.8 Hz, CP), 62.2 ($O\underline{C}H_2CH_3$), 47.4, 39.3, 16.2 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 14.5; LCMS: found *m/z* 338.2 $M\text{-}H^-$. $C_{15}H_{22}N_3O_4P$ requires 339.3.

*4.8.2. Diethyl [2-(2-aminoethyl)-5-(benzylamino)-1,3-oxazol-4-yl]phosphonate (**7b**).*

Yield 2.473 g, 70% as a yellow viscous oil; [Found: C, 54.29; H, 6.93; N, 11.78; P, 8.87. $C_{16}H_{24}N_3O_4P$ requires C, 54.38; H, 6.85; N, 11.89; P, 8.77%]; ν_{max} (ATR) 2926, 1632, 1218, 1019, 959 cm^{-1}; δ_H ($CDCl_3$) 7.35-7.20 (5H, m, C_6H_5), 6.33 (1H, t, *J* 6.5 Hz, NH), 4.43 (2H, d, *J* 6.5 Hz, CH_2), 4.04 (4H, m, $2OCH_2$), 3.00 (2H, t, *J* 6.5 Hz, CH_2), 2.73 (2H, t, *J* 6.5 Hz, CH_2), 1.66 (2H, br, NH_2), 1.28 (6H, t, *J* 7.0 Hz, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 163.6 (d, *J* 39.4 Hz, O-<u>C</u>=C-P), 153.5 (d, *J* 21.9 Hz, O-<u>C</u>=N), 138.3, 128.6, 127.5, 127.2, 95.7 (d, *J* 256.8 Hz, CP), 62.1 ($O\underline{C}H_2CH_3$), 47.5, 39.4, 32.1, 16.2 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 14.5; LCMS: found *m/z* 354.2 MH^+. $C_{16}H_{24}N_3O_4P$ requires 353.4.

*4.8.3. Diethyl [2-(3-aminopropyl)-5-(benzylamino)-1,3-oxazol-4-yl]phosphonate (**7c**).*

Yield 2.461 g, 67% as a yellow viscous oil; [Found: C, 55.49; H, 7.24; N, 11.29; P, 8.51. $C_{17}H_{26}N_3O_4P$ requires C, 55.58; H, 7.13; N, 11.44; P, 8.43%]. ν_{max} (ATR) 2931, 1633, 1589, 1216, 1019, 961 cm^{-1}; δ_H ($CDCl_3$) 7.35-7.23 (5H, m, C_6H_5), 6.31 (1H, t, *J* 6.3 Hz, NH), 4.44 (2H, d, *J* 6.3 Hz, CH_2), 4.13-3.96 (4H, m, $2OCH_2$), 2.68 (4H, m, $2CH_2$), 1.80 (2H, m, CH_2), 1.56 (2H, br, NH_2), 1.30 (6H, t, *J* 7.0 Hz, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 163.5 (d, *J* 39.4 Hz, O-<u>C</u>=C-P), 154.8 (d, *J* 21.9 Hz, O-<u>C</u>=N), 138.3, 128.6, 127.4, 127.2, 95.4 (d, *J* 256.3 Hz, CP), 62.1 ($O\underline{C}H_2CH_3$), 47.5, 41.3, 30.7, 25.3,16.2 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 14.5; LCMS: found *m/z* 368.2 MH^+. $C_{17}H_{26}N_3O_4P$ requires 367.4.

*4.8.4. Diethyl [2-(4-aminobutyl)-5-(benzylamino)-1,3-oxazol-4-yl]phosphonate (**7d**).*

Yield 2.517 g, 66% as a yellow viscous oil; [Found: C, 56.59; H, 7.51; N, 10.89; P, 8.26. $C_{18}H_{28}N_3O_4P$ requires C, 56.68; H, 7.40; N, 11.02; P, 8.12%]; ν_{max} (ATR) 2931, 1630, 1589, 1220, 1020, 959 cm^{-1}; δ_H ($CDCl_3$) 7.35-7.23 (5H, m, C_6H_5), 6.33 (1H, t, *J* 6.3 Hz, NH), 4.45 (2H, d, *J* 6.3 Hz, CH_2), 4.13-3.97 (4H, m, $2OCH_2$), 2.67 (2H, m, CH_2), 2.63 (2H, m, CH_2), 1.70 (2H, m, CH_2), 1.56 (2H, br, NH_2), 1.45 (2H, m, CH_2), 1.30 (6H, t, *J* 7.0 Hz, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 163.5 (d, *J* 39.4 Hz, O-<u>C</u>=C-P), 154.8 (d, *J* 21.9 Hz, O-C=N), 138.3, 128.6, 127.4, 127.2, 95.4 (d, *J* 256.3 Hz, CP), 62.1 ($O\underline{C}H_2CH_3$), 47.4, 41.7, 33.0, 27.7, 24.2, 16.2 (OCH_2CH_3); δ_P ($CDCl_3$) 14.7; LCMS: found *m/z* 382.2 MH^+. $C_{18}H_{28}N_3O_4P$ requires 381.4.

*4.8.5. Diethyl [2-(5-aminopentyl)-5-(benzylamino)-1,3-oxazol-4-yl]phosphonate (**7e**).*

Yield 2.610 g, 66% as a yellow viscous oil; [Found: C, 57.63; H, 7.76; N, 10.47; P, 7.99. $C_{19}H_{30}N_3O_4P$ requires C, 57.71; H, 7.65; N, 10.63; P, 7.83%]; ν_{max} (ATR) 2930, 1632, 1589, 1223, 1021, 960 cm^{-1}; δ_H ($CDCl_3$) 7.30-7.18 (5H, m, C_6H_5), 6.26 (1H, br, NH), 4.40 (2H, m, CH_2), 4.09-3.91 (4H, m, $2OCH_2$), 3.33 (2H, br, NH_2), 2.64 (2H, m, CH_2), 2.57 (2H, m, CH_2), 1.64 (2H, m, $2CH_2$), 1.45 (2H, m, CH_2), 1.26 (8H, m, $2OCH_2\underline{CH_3}$, CH_2); δ_C ($CDCl_3$) 163.5 (d, *J* 39.4 Hz, O-<u>C</u>=C-P), 155.1 (d, *J* 22.4 Hz, O-<u>C</u>=N), 138.4, 128.6, 127.5, 127.3, 95.4 (d, *J* 256.3 Hz, CP), 62.1 ($O\underline{C}H_2CH_3$), 47.5, 42.40, 33.3, 27.8, 26.7, 26.3, 16.2 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 14.8; LCMS: found *m/z* 396.2 MH^+. $C_{19}H_{30}N_3O_4P$ requires 395.4.

*4.8.6. Diethyl [2-(aminomethyl)-5-(piperidin-1-yl)-1,3-oxazol-4-yl]phosphonate (**7f**).*

Yield 3.141 g, 99% as a yellow viscous oil; [Found: C, 49.12; H, 7.71; N, 13.05; P, 9.87. $C_{13}H_{24}N_3O_4P$ requires C, 49.21; H, 7.62; N, 13.24; P, 9.76%]; ν_{max} (ATR) 2926, 1615, 1572, 1222, 1017, 951 cm^{-1}; δ_H ($CDCl_3$) 4.10 (4H, m, $2OCH_2$), 3.76 (2H, s, CH_2), 3.46 (4H, m, $2CH_2$), 2.07 (2H, br, NH_2), 1.62 (6H, m, $3CH_2$), 1.31 (6H, m, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 161.8 (d, *J* 36.9 Hz, O-<u>C</u>=C-P), 154.7 (d, *J* 20.9 Hz, O-<u>C</u>=N), 100.0 (d, *J* 256.8 Hz, CP), 62.1 ($O\underline{C}H_2CH_3$), 49.5, 39.2, 25.4, 23.9, 16.3 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 13.6; LCMS: found *m/z* 318.2 MH^+. $C_{13}H_{24}N_3O_4P$ requires 317.3.

*4.8.7. Diethyl [2-(2-aminoethyl)-5-(piperidin-1-yl)-1,3-oxazol-4-yl]phosphonate (**7g**).*

Yield 3.280 g, 99% as a yellow viscous oil; [Found: C, 50.64; H, 8.00; N, 12.56; P, 9.43. $C_{14}H_{26}N_3O_4P$ requires C, 50.75; H, 7.91; N, 12.68; P, 9.35%]; ν_{max} (ATR) 2926, 1618, 1572, 1256,

1019, 954 cm^{-1}; δ_H ($CDCl_3$) 4.09 (4H, m, $2OCH_2$), 3.43 (4H, m, $2CH_2$), 3.01 (2H, m, CH_2), 2.71 (2H, m, CH_2), 1.60 (8H, m, $3CH_2$, NH_2), 1.30 (6H, m, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 161.8 (d, *J* 36.0 Hz, O-<u>C</u>=C-P), 152.8 (d, *J* 21.9 Hz, O-<u>C</u>=N), 100.0 (d, *J* 256.8 Hz, CP), 62.1 ($O\underline{C}H_2CH_3$), 49.5, 39.5, 32.0, 25.4, 23.9, 16.2 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 13.6; LCMS: found *m/z* 332.2 MH^+. $C_{14}H_{26}N_3O_4P$ requires 331.4.

*4.8.8. Diethyl [2-(3-aminopropyl)-5-(piperidin-1-yl)-1,3-oxazol-4-yl]phosphonate (**7h**).*

Yield 3.212 g, 93% as a yellow viscous oil; [Found: C, 52.02; H, 8.25; N, 12.01; P, 9.11. $C_{15}H_{28}N_3O_4P$ requires C, 52.16; H, 8.17; N, 12.17; P, 8.97%]; ν_{max} (ATR) 2977, 1620, 1572, 1256, 1019, 956 cm^{-1}; δ_H ($CDCl_3$) 4.08 (4H, m, $2OCH_2$), 3.43 (4H, m, $2CH_2$), 2.71 (2H, m, CH_2), 2.63 (2H, m, CH_2), 1.79 (2H, m, CH_2), 1.60 (8H, m, $3CH_2$, NH_2), 1.30 (6H, m, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 161.8 (d, *J* 36.9 Hz, O-<u>C</u>=C-P), 154.1 (d, *J* 21.9 Hz, O-<u>C</u>=N), 99.8 (d, *J* 256.8 Hz, CP), 62.1 ($O\underline{C}H_2CH_3$), 49.5, 41.4, 30.8, 25.4, 25.2, 24.0, 16.3 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 14.5; LCMS: found *m/z* 346.2 MH^+. $C_{15}H_{28}N_3O_4P$ requires 345.4.

*4.8.9. Diethyl [2-(4-aminobutyl)-5-(piperidin-1-yl)-1,3-oxazol-4-yl]phosphonate (**7i**).*

Yield 3.306 g, 92% as a yellow viscous oil; [Found: C, 53.39; H, 8.50; N, 11.52; P, 8.76. $C_{16}H_{30}N_3O_4P$ requires C, 53.47; H, 8.41; N, 11.69; P, 8.62%]; ν_{max} (ATR) 2934, 1619, 1573, 1258, 1018, 963 cm^{-1}; δ_H ($CDCl_3$) 4.11 (4H, m, $2OCH_2$), 3.46 (4H, m, $2CH_2$), 2.71 (2H, m, CH_2), 2.62 (2H, m, CH_2), 1.73 (2H, m, CH_2), 1.64 (8H, m, $3CH_2$, NH_2), 1.50 (2H, m, CH_2), 1.33 (6H, m, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 161.8 (d, *J* 36.9 Hz, O-<u>C</u>=C-P), 154.4 (d, *J* 21.9 Hz, O-<u>C</u>=N), 99.8 (d, *J* 256.8 Hz, CP), 62.1 ($O\underline{C}H_2CH_3$), 49.6, 41.7, 33.1, 27.7, 25.4, 24.3, 24.0, 16.3 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 14.6; LCMS: found *m/z* 360.2 MH^+. $C_{16}H_{30}N_3O_4P$ requires 359.4.

*4.8.10. Diethyl [2-(5-aminopentyl)-5-(piperidin-1-yl)-1,3-oxazol-4-yl]phosphonate (**7j**).*

Yield 3.585 g, 96% as a yellow viscous oil; [Found: C, 54.60; H, 8.72; N, 11.08; P, 8.38. $C_{17}H_{32}N_3O_4P$ requires C, 54.68; H, 8.64; N, 11.25; P, 8.29%]; ν_{max} (ATR) 2933, 1619, 1571, 1256, 1019, 955 cm^{-1}; δ_H ($CDCl_3$) 4.32 (2H, br, NH_2), 4.08 (4H, m, $2OCH_2$), 3.42 (4H, m, $2CH_2$), 2.71 (2H, m, CH_2), 2.55 (2H, m, CH_2), 1.61 (8H, m, $4CH_2$), 1.49 (2H, m, CH_2), 1.30 (8H, m, $2OCH_2\underline{CH_3}$, CH_2); δ_C ($CDCl_3$) 161.7 (d, *J* 36.9 Hz, O-<u>C</u>=C-P), 154.5 (d, *J* 21.9 Hz, O-C=N), 99.7 (d, *J* 256.8 Hz, CP), 62.1 ($O\underline{C}H_2CH_3$), 49.5, 41.4, 32.1, 27.7, 26.6, 26.4, 25.4, 24.0, 16.3 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 14.7; LCMS: found *m/z* 374.2 MH^+. $C_{17}H_{32}N_3O_4P$ requires 373.4.

*4.8.11. Diethyl [2-(aminomethyl)-5-(morpholin-4-yl)-1,3-oxazol-4-yl]phosphonate (**7k**).*

Yield 3.033 g, 95% as a yellow viscous oil; [Found: C, 45.03; H, 7.02; N, 13.00; P, 9.85. $C_{12}H_{22}N_3O_5P$ requires C, 45.14; H, 6.94; N, 13.16; P, 9.70%]; ν_{max} (ATR) 2975, 1610, 1571, 1263, 1016, 955 cm^{-1}; δ_H ($CDCl_3$) 4.12 (4H, m, $2OCH_2$), 3.79 (2H, s, CH_2), 3.77 (2H, m, CH_2), 3.54 (2H, m, CH_2), 1.71 (2H, br s, NH_2), 1.33 (6H, m, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 161.4 (d, *J* 36.9 Hz, O-<u>C</u>=C-P), 155.5 (d, *J* 20.9 Hz, O-<u>C</u>=N), 101.5 (d, *J* 255.8 Hz, CP), 66.3, 62.3 ($O\underline{C}H_2CH_3$), 48.5, 39.2, 16.3 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 13.2; LCMS: found *m/z* 320.0 MH^+. $C_{12}H_{22}N_3O_5P$ requires 319.3.

*4.8.12. Diethyl [2-(2-aminoethyl)-5-(morpholin-4-yl)-1,3-oxazol-4-yl]phosphonate (**7l**).*

Yield 3.167 g, 95% as a yellow viscous oil; [Found: C, 46.73; H, 7.35; N, 12.43; P, 9.41. $C_{13}H_{24}N_3O_5P$ requires C, 46.84; H, 7.26; N, 12.61; P, 9.29%]; ν_{max} (ATR) 2972, 1615, 1570, 1233, 1017, 948 cm^{-1}; δ_H ($CDCl_3$) 4.11 (4H, m, $2OCH_2$), 3.76 (4H, m, $2CH_2$), 3.51 (4H, m, $2CH_2$), 3.29 (2H, br, NH_2), 3.08 (2H, m, CH_2), 2.79 (2H, m, CH_2), 1.32 (6H, m, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 161.3 (d, *J* 36.9 Hz, O-<u>C</u>=C-P), 153.4 (d, *J* 21.9 Hz, O-<u>C</u>=N), 101.0 (d, *J* 255.8 Hz, CP), 66.3, 62.3 ($O\underline{C}H_2CH_3$), 48.5, 39.1, 31.3, 16.3 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 13.3; LCMS: found *m/z* 334.0 MH^+. $C_{13}H_{24}N_3O_5P$ requires 333.3.

*4.8.13. Methyl 1-[2-(aminomethyl)-4-(diethoxyphosphoryl)-1,3-oxazol-5-yl]piperidine-4-carboxylate (**7m**).*

Yield 2.590 g, 69% as a yellow viscous oil; [Found: C, 47.93; H, 7.10; N, 11.03; P, 8.38. $C_{15}H_{26}N_3O_6P$ requires C, 48.00; H, 6.98; N, 11.19; P, 8.25%]; ν_{max} (ATR) 2953, 1731, 1635, 1255, 1018, 958 cm^{-1}; δ_H ($CDCl_3$) 4.14 (4H, m, $2OCH_2$), 4.01 (2H, m, CH_2), 3.96 (2H, br, NH_2), 3.81 (2H, s, CH_2), 3.70 (3H, s, OCH_3), 3.14 (2H, m, CH_2), 2.52 (1H, m, CH), 1.99 (2H, m, CH_2), 1.82 (2H, m, CH_2), 1.35 (6H, m, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 174.6 (C=O), 161.4 (d, *J* 36.9 Hz, O-<u>C</u>=C-P), 155.3 (d, *J* 20.9 Hz, O-<u>C</u>=N), 101.0 (d, *J* 255.8 Hz, CP), 62.2 ($O\underline{C}H_2CH_3$), 51.8, 40.2, 39.3, 27.6, 16.3 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 13.7; LCMS: found *m/z* 376.2 MH^+. $C_{15}H_{26}N_3O_6P$ requires 375.4.

*4.8.14. Methyl 1-[2-(2-aminoethyl)-4-(diethoxyphosphoryl)-1,3-oxazol-5-yl]piperidine-4-carboxylate (**7n**).*

Yield 2.609 g, 67% as a yellow viscous oil; [Found: C, 49.26; H, 7.36; N, 10.62; P, 8.12. $C_{16}H_{28}N_3O_6P$ requires C, 49.35; H, 7.25; N, 10.79; P, 7.95%]; ν_{max} (ATR) 2949, 1732, 1619, 1568, 1290, 1018, 958 cm^{-1}; δ_H ($CDCl_3$) 4.11 (4H, m, $2OCH_2$), 3.95 (2H, m, CH_2), 3.68 (3H, s, OCH_3), 3.11 (2H, m, CH_2), 3.04 (2H, t, *J* 7.5 Hz, CH_2), 2.74 (2H, t, *J* 7.5 Hz, CH_2), 2.49 (1H, m, CH), 1.97 (2H, m, CH_2), 1.80 (2H, m, CH_2), 1.53 (2H, br, NH_2), 1.32 (6H, m, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 174.7 (C=O), 161.5 (d, *J* 36.9 Hz, O-<u>C</u>=C-P), 153.3 (d, *J* 21.9 Hz, O-<u>C</u>=N), 101.1 (d, *J*=256.3 Hz, CP), 62.2 ($O\underline{C}H_2CH_3$), 51.8, 48.1, 40.5, 39.4, 32.0, 27.6, 16.3 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 13.8; LCMS: found *m/z* 390.2 MH^+. $C_{16}H_{28}N_3O_6P$ requires 389.4.

4.9. General procedure for the preparation of 8a-e.

To a mixture of one of compounds **7f-j** (1.0 mmol), pyridine (1 mL), and dry CH_2Cl_2 (20 mL), a solution of 4-*tert*-butylbenzoylchloride (216 mg, 1.1 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise at 0°C. After stirring at 20-25°C for 1 h and addition of Et_3N (1 mL), the reaction mixture was left overnight and then washed successively with water, saturated aqueous $NaHCO_3$, 5% aqueous citric acid, and brine. Further drying over anhydrous Na_2SO_4 followed by evaporation of the solvent *in vacuo* provided the analytically pure product.

*4.9.1. Diethyl (2-[[(4-tert-butylphenyl)formamido]methyl]-5-(piperidin-1-yl)-1,3-oxazol-4-yl)phosphonate (**8a**).*

Yield 420 mg, 88% as a yellow viscous oil; [Found: C, 60.23; H, 7.69; N, 8.61; P, 6.61. $C_{24}H_{36}N_3O_5P$ requires C, 60.36; H, 7.60; N, 8.80; P, 6.49%]; ν_{max} (ATR) 3288, 1615, 1574, 1265, 1020, 961 cm^{-1}; δ_H ($CDCl_3$) 7.71 (2H, d, *J* 8.3 Hz, aromatic), 7.41 (2H, d, *J* 8.3 Hz, aromatic), 6.78 (1H, br, NH), 4.60 (2H, d, *J* 5.2 Hz, $NHCH_2$), 4.10 (4H, m, $2OCH_2$), 3.46 (4H, m, $2CH_2$), 1.60 (6H, m, $3CH_2$), 1.30 (15H, m, $2OCH_2\underline{CH_3}$, $C(\underline{CH_3})_3$); δ_C ($CDCl_3$) 167.2 (C=O), 161.6 (d, *J* 36.9 Hz, O-<u>C</u>=C-P), 155.3, 150.4 (d, *J* 21.9 Hz, O-<u>C</u>=N), 130.9, 127.0, 125.5, 100.0 (d, *J* 256.8 Hz, CP), 62.2 ($O\underline{C}H_2CH_3$), 49.4, 36.8, 34.9 ($\underline{C}(CH_3)_3$), 31.1 ($C(\underline{C}H_3)_3$), 25.3, 23.9, 16.2 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 14.1; LCMS: found *m/z* 478.4 MH^+. $C_{24}H_{36}N_3O_5P$ requires 477.5.

*4.9.2. Diethyl (2-[2-[(4-tert-butylphenyl)formamido]ethyl]-5-(piperidin-1-yl)-1,3-oxazol-4-yl)phosphonate (**8b**).*

Yield 452 mg, 92% as a yellow viscous oil; [Found: C, 61.00; H, 7.88; N, 8.37; P, 6.48. $C_{25}H_{38}N_3O_5P$: C, 61.08; H, 7.79; N, 8.55; P, 6.30%]; ν_{max} (ATR) 3309, 1616, 1573, 1259, 1021, 963 cm^{-1}; δ_H ($CDCl_3$) 7.70 (2H, d, *J* 8.3 Hz, aromatic), 7.36 (3H, m, NH, aromatic), 4.05 (4H, m, $2OCH_2$), 3.77 (2H, m, CH_2), 3.41 (4H, m, $2CH_2$), 2.88 (2H, m, CH_2), 1.56 (6H, m, $3CH_2$), 1.27 (15H, m, $2OCH_2\underline{CH_3}$, $C(\underline{CH_3})_3$); δ_C ($CDCl_3$) 167.2 (C=O), 161.8 (d, *J* 36.5 Hz, O-<u>C</u>=C-P), 154.8, 152.6 (d, *J* 21.7 Hz, O-<u>C</u>=N), 131.6, 126.8, 125.3, 100.0 (d, *J*=256.8 Hz, CP), 62.1 ($O\underline{C}H_2CH_3$), 49.5, 36.5, 34.8 ($\underline{C}(CH_3)_3$), 31.1 ($C(\underline{C}H_3)_3$), 27.7, 25.3, 23.9, 16.2 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 14.3; LCMS: found *m/z* 492.2 MH^+. $C_{25}H_{38}N_3O_5P$ requires 491.6.

*4.9.3. Diethyl (2-[3-[(4-tert-butylphenyl)formamido]propyl]-5-(piperidin-1-yl)-1,3-oxazol-4-yl)phosphonate (**8c**).*

Yield 460 mg, 91% as a yellow viscous oil; [Found: C, 61.69; H, 8.09; N, 8.14; P, 6.31. $C_{26}H_{40}N_3O_5P$ requires C, 61.77; H, 7.97; N, 8.31; P, 6.13%]; ν_{max} (ATR) 3309, 1618, 1572, 1259, 1021, 961 cm^{-1}; δ_H ($CDCl_3$) 7.70 (2H, d, *J* 8.3 Hz, aromatic), 7.32 (2H, d, *J* 8.3 Hz, aromatic), 7.25 (1H, br, NH), 4.02 (4H, m, $2OCH_2$), 3.42 (2H, m, CH_2), 3.34 (4H, m, $2CH_2$), 2.63 (2H, m, CH_2), 1.95 (2H, m, CH_2), 1.50 (6H, m, $3CH_2$), 1.23 (15H, m, $2OCH_2\underline{CH_3}$, $C(\underline{CH_3})_3$); δ_C ($CDCl_3$) 167.4 (C=O), 161.7 (d, *J* 36.5 Hz, O-<u>C</u>=C-P), 154.6, 154.0 (d, *J* 21.7 Hz, O-<u>C</u>=N), 131.5, 126.9, 125.2, 99.8 (d, *J* 256.8 Hz, CP), 62.0 ($O\underline{C}H_2CH_3$), 49.4 (CH_2), 39.3, 34.7 ($\underline{C}(CH_3)_3$), 31.1 ($C(\underline{C}H_3)_3$), 26.4, 25.5, 25.3, 23.8, 16.2 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 14.5; LCMS: found *m/z* 506.2 MH^+. $C_{26}H_{40}N_3O_5P$ requires 505.6.

*4.9.4. Diethyl (2-[4-[(4-tert-butylphenyl)formamido]butyl]-5-(piperidin-1-yl)-1,3-oxazol-4-yl)phosphonate (**8d**).*

Yield 483 mg, 93% as a yellow viscous oil; [Found: C 62.33, H 8.26, N 7.91, P 6.12. $C_{27}H_{42}N_3O_5P$ requires C 62.41, H 8.15, N 8.09, P 5.96%]; ν_{max} (ATR) 3316, 1618, 1572, 1260, 1022, 962 cm^{-1}; δ_H ($CDCl_3$) 7.73 (2H, d, *J* 8.3 Hz, aromatic), 7.36 (2H, d, *J* 8.3 Hz, aromatic), 6.94 (1H, br, NH), 4.05 (4H, m, $2OCH_2$), 3.40 (6H, m, $3CH_2$), 2.60 (2H, m, CH_2), 1.73 (2H, m, CH_2), 1.67-1.52 (8H, m, $4CH_2$), 1.27 (15H, m, $2OCH_2\underline{CH_3}$, $C(\underline{CH_3})_3$); δ_C ($CDCl_3$) 167.5 (C=O), 161.8 (d, *J* 37.0 Hz, O-<u>C</u>=C-P), 154.6, 154.2 (d, *J* 21.7 Hz, O-<u>C</u>=N), 131.8, 126.9, 125.2, 99.8 (d, *J* 256.8 Hz, CP), 62.0 ($O\underline{C}H_2CH_3$), 49.6, 39.3, 34.8 ($\underline{C}(CH_3)_3$), 31.1 ($C(\underline{C}H_3)_3$), 30.3, 29.4, 29.0, 27.4, 25.4, 24.0, 23.9, 16.2 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 14.5; LCMS: found *m/z* 520.4 MH^+. $C_{27}H_{42}N_3O_5P$ requires 519.6.

*4.9.5. Diethyl (2-[5-[(4-tert-butylphenyl)formamido]pentyl]-5-(piperidin-1-yl)-1,3-oxazol-4-yl)phosphonate (**8e**).*

Yield 507 mg, 95% as a yellow viscous oil; [Found: C, 62.95; H, 8.42; N, 7.69; P, 5.96. $C_{28}H_{44}N_3O_5P$ requires C, 63.02; H, 8.31; N, 7.87; P, 5.80%]; ν_{max} (ATR) 3315, 1619, 1572, 1260, 1023, 960 cm^{-1}; δ_H ($CDCl_3$) 7.70 (2H, d, *J* 8.3 Hz, aromatic), 7.38 (2H, d, *J* 8.3 Hz, aromatic), 6.60 (1H, br, NH), 4.07 (4H, m, $2OCH_2$), 3.40 (6H, m, $3CH_2$), 2.57 (2H, m, CH_2), 1.69 (2H, m, CH_2), 1.59 (8H, m, $4CH_2$), 1.39 (2H, m, CH_2), 1.28 (15H, m, $2OCH_2\underline{CH_3}$, $C(\underline{CH_3})_3$); δ_C ($CDCl_3$) 167.4 (C=O), 161.8 (d, *J* 37.0 Hz, O-<u>C</u>=C-P), 154.6, 154.4 (d, *J* 21.7 Hz, O-<u>C</u>=N), 131.9, 126.8, 125.3, 99.7 (d, *J* 256.8 Hz, CP), 62.1 ($O\underline{C}H_2CH_3$), 49.5, 39.7, 34.8 ($\underline{C}(CH_3)_3$), 31.2 ($C(\underline{C}H_3)_3$), 29.3, 27.7, 26.5, 25.4, 23.9, 16.2 ($OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 14.6; LCMS: found *m/z* 534.4 MH^+. $C_{28}H_{44}N_3O_5P$ requires 533.6.

4.10. General procedure for the preparation of (*S*)-9, (*R,S*)-9, and (*S*)-11.

To a solution of the appropriate protected amino acid [Z-(*S*)-alanine, or Z-(*R,S*)-alanine, or Z-(*S*)-glutamine] (5 mmol) and HOBt (675 mg, 5 mmol) in dry THF (20 mL), EDCI (846 mg, 5 mmol) was added at -20°C and the mixture was stirred at this temperature for 12 h. After addition of the appropriate aminomethyloxazole (**7k** or **7m**) (5 mmol), stirring continued for another 12h at 0°C, followed by addition of EtOAc (50 mL) and successive washing with 20 ml of brine, 10% AcOH, brine, and saturated aqueous K_2CO_3. Further drying over $MgSO_4$ and evaporation of the solvent *in vacuo* provided the analytically pure product.

*4.10.1. Benzyl N-[(1S)-1-([[4-(diethoxyphosphoryl)-5-(morpholin-4-yl)-1,3-oxazol-2-yl]methyl]carbamoyl)ethyl]carbamate [**(S)-9**].*

Obtained from Z-(*S*)-Ala and oxazole **7k**. Yield 1.704 g, 65% as a yellow viscous oil; [Found: C, 52.60; H, 6.44; N, 10.55; P, 6.06. $C_{23}H_{33}N_4O_8P$ requires C, 52.67; H, 6.34; N, 10.68; P, 5.91%]; $[a]_D^{20}$ -6.7 (*c* 1.5, EtOH); ν_{max} (ATR) 3282, 1718, 1675, 1617, 1574, 1528, 1230, 1018, 962 cm^{-1}; δ_H ($CDCl_3$) 7.30 (6H, m, NH, aromatic), 5.78 (1H, br, NH), 5.08 (1H, d, *J* 11.9 Hz, $C\underline{H_a}H_bOPh$), 5.03 (1H, d, *J* 11.9 Hz, $CH_a\underline{H_b}OPh$), 4.40 (2H, m, $\underline{CH_2}NH$), 4.30 (1H, m, $\underline{CH}CH_3$), 4.08 (4H, m, $2O\underline{CH_2}CH_3$), 3.73 (4H, m, $2CH_2$), 3.48 (4H, m, $2CH_2$), 1.37 (3H, d, *J* 7.0 Hz, $CH\underline{CH_3}$), 1.30 (6H, t, *J* 7.0 Hz, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 172.7 (C=O), 161.3 (d, *J* 37.0 Hz, O-<u>C</u>=C-P), 156.0 (C=O), 150.9 (d, *J*=21.7 Hz, O-<u>C</u>=N), 136.2, 128.5, 128.2, 128.0, 101.2 (d, *J* 254.8 Hz, CP), 67.0 ($O\underline{CH_2}Ph$), 66.2, 62.4 ($O\underline{CH_2}CH_3$), 50.6 ($\underline{CH}CH_3$), 48.3 ($NHCH_2$), 36.3, 18.6 ($CH\underline{CH_3}$), 16.3 ($OCH_2\underline{CH_3}$); δ_P ($CDCl_3$) 13.0; LCMS: found m/z 525.2 MH^+. $C_{23}H_{33}N_4O_8P$ requires 524.5. Chiral HPLC: 100%, eluent: hexane-2-propanol (80:20, v:v), flow rate 0.6 ml/min.

*4.10.2. Benzyl N-[1-([[4-(diethoxyphosphoryl)-5-(morpholin-4-yl)-1,3-oxazol-2-yl]methyl]carbamoyl)ethyl]carbamate [**(R,S)-9**].*

Obtained from Z-(*R,S*)-Ala and oxazole **7k**. Yield 1.626 g, 62% as a yellow viscous oil. All spectral and analytical data for compound **(*R,S*)-9** are identical to those for **(*S*)-9**. Chiral HPLC, 2 peaks of equal intensity; eluent, hexane-2-propanol (80:20, v:v); flow rate, 0.6 ml/min.

*4.10.3. Methyl 1-(2-[[(2S)-2-[[(benzyloxy)carbonyl]amino]-4-carbamoylbutanamido]methyl]-4-(diethoxyphosphoryl)-1,3-oxazol-5-yl)piperidine-4-carboxylate [**(S)-11**].*

Obtained from Z-(*S*)-Gln and oxazole **7m**. Yield 1.435 g, 45% as a yellow viscous oil; [Found: C, 52.62; H, 6.49; N, 10.81; P, 4.99. $C_{28}H_{40}N_5O_{10}P$ requires C, 52.74; H, 6.32; N, 10.98; P, 4.86%]; ν_{max} (CH_2Cl_2) 3423-3305, 1727, 1679, 1624, 1580, 1233, 1029, 970 cm^{-1}; δ_H ($CDCl_3$) 7.71 (1H, br, NH), 7.38 (5H, m, aromatic), 7.13 (1H, br, NH), 6.31 (1H, br, NH), 5.89 (1H, br, NH), 5.10 (1H, d, *J* 12.2 Hz, $C\underline{H_a}H_bOPh$), 5.06 (1H, d, *J* 12.2 Hz, $CH_a\underline{H_b}OPh$), 4.41 (2H, m, $\underline{CH_2}NH$), 4.31 (1H, m, CH), 4.08 (4H, m, $2O\underline{CH_2}CH_3$), 3.90 (2H, m, CH_2), 3.70 (3H, s, OCH_3), 3.10 (2H, m, CH_2), 2.51 (2H, m, CH_2), 2.38 (1H, m, CH), 2.09 (2H, m, CH_2), 1.97 (2H, m, CH_2), 1.79 (2H, m, CH_2), 1.31 (6H, t, *J* 7.0 Hz, $2OCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 175.7 (C=O), 174.6 (C=O), 171.9 (C=O), 161.2 (d, *J* 36.0 Hz, O-<u>C</u>=C-P), 155.7 (C=O), 151.0 (d, *J* 21.7 Hz, O-<u>C</u>=N), 136.3, 128.5, 128.1, 128.0, 100.9 (d, *J* 256.2 Hz, CP), 67.0 ($O\underline{CH_2}Ph$), 62.3 ($O\underline{CH_2}CH_3$), 51.8 ($\underline{CH}CO_2Me$), 48.0 ($N(CH_2)_2$), 40.3 (OCH_3), 36.3 (CH_2NH), 31.2, 31.0, 27.6 [$(\underline{CH_2})_2CHCO_2Me$], 16.3 (d, *J* 6.9 Hz, $OCH_2\underline{CH_3}$); δ_P ($CDCl_3$) 12.8.

4.11. General procedure for the preparation of peptidomimetics. Oxazole ring opening.

The compounds were obtained as described in the literature.[5a] Heating one of oxazoles [**(*S*)-9, (*R,S*)-9** or **(*S*)-11**] (1 mmol) in a 5:1 AcOH-H_2O mixture (20 mL) for 8 h at 75°C followed by evaporation to dryness *in vacuo* yielded analytically pure products.

*4.11.1. Benzyl N-[(1S)-1-[N-([N-[1-(diethoxyphosphoryl)-2-(morpholin-4-yl)-2-oxoethyl]carbamoyl]methyl)carbamoyl]-ethyl]carbamate [**(S,R),(S,S)-10**]*

Obtained from **(*S*)-9**. Yield 537 mg, 99% as a yellow viscous oil; [Found: C, 50.81; H, 6.66; N, 10.21; P, 5.89. $C_{23}H_{35}N_4O_9P$ requires C, 50.92; H, 6.50; N, 10.33; P, 5.71%]; $[a]_D^{20}$ -12.1 (*c* 1.5, EtOH); ν_{max} (ATR) 3295, 1637, 1518, 1238, 1013, 975 cm^{-1}; δ_H ($CDCl_3$) 7.64 (1H, br, NH), 7.38 (5H, m, Ph), 7.18 (1H, br, NH), 5.88 (1H, br, NH), 5.48 (1H, dd, *J* 17.9, 7.8 Hz, CHP), 5.14 (1H, d, *J* 11.9 Hz, $C\underline{H}_aH_bOPh$), 5.07 (1H, d, *J* 11.9 Hz, $CH_a\underline{H}_bOPh$), 4.36 (1H, m, $\underline{CH}CH_3$), 4.22-3.99 (6H, m, $3CH_2$), 3.81-3.42 (8H, m, $4CH_2$), 1.41 (3H, m, $CH\underline{CH}_3$), 1.30 (6H, m, $2OCH_2\underline{CH}_3$); δ_C ($CDCl_3$) 173.0 (C=O), 168.3 (C=O), 164.1 (C=O), 156.1 (C=O), 136.3, 128.5, 128.2, 128.0, 67.0 ($O\underline{CH}_2Ph$), 66.5 (OCH_2), 63.8 ($O\underline{CH}_2CH_3$), 50.5 ($\underline{CH}CH_3$), 47.8 (d, *J* 147.5 Hz, CP), 46,8 (NCH_2), 43.1 (NCH_2), 42.9 (NCH_2), 18.7 ($CH\underline{CH}_3$), 16.4 ($OCH_2\underline{CH}_3$); δ_P ($CDCl_3$) 17.1; LCMS: found *m/z* 543.2 MH^+. $C_{23}H_{35}N_4O_9P$ requires 542.5. Chiral HPLC: 2 peaks with equal intensivity, eluent: hexane-2-propanol (60:40, v:v), flow rate 0.5 ml/min.

*4.11.2 Benzyl N-[1-[N-([N-[1-(diethoxyphosphoryl)-2-(morpholin-4-yl)-2-oxoethyl]carbamoyl]methyl)carbamoyl]-ethyl]carbamate [**(R,R),(R,S),(S,R),(S,S)-10**].*

Obtained from **(*R,S*)-9**. Yield 537 mg, 99% as a yellow viscous oil. All spectral and analytical data for the mixture of diastereomers **(*R,R*),(*R,S*),(*S,R*),(*S,S*)-10** are identical to those for **(*S,R*),(*S,S*)-10**. Chiral HPLC, 4 peaks with equivalent intensity; eluent, hexane-2-propanol (60:40, v:v); flow rate, 0.5 ml/min.

*4.11.3. Methyl 1-(2-[2-[(2S)-2-[[(benzyloxy)carbonyl]amino]-4-carbamoylbutanamido]acetamido]-2-(diethoxyphosphoryl)-acetyl)piperidine-4-carboxylate [**(S,R),(S,S)-12**].*

Obtained from **(*S*)-11**. Yield 649 mg, 99% as a yellow viscous oil; [Found: C, 51.18; H, 6.57; N, 10.52; P, 4.88. $C_{28}H_{42}N_5O_{11}P$ requires C, 51.29; H, 6.46; N, 10.68; P, 4.72%]; ν_{max} (CH_2Cl_2) 3303, 1725, 1682, 1645, 1506, 1250, 1023, 980 cm^{-1}; δ_H (DMSO-d_6) 8.38 (1H, br, NH), 8.16 (1H, br, NH), 7.47 (1H, br, NH), 7.42-7.28 (5H, m, Ph), 7.25 (1H, br, NH), 6.76 (1H, br, NH), 5.48 (dd, 1H, *J* 19.5, 8.3 Hz, CHP), 5.05 (2H, m, $O\underline{CH}_2Ph$), 4.33 and 4.23 (1H, m, CH), 4.05 (4H, m, $2O\underline{CH}_2CH_3$), 3.90 (1H, m, CH), 3.79 (1H, m, CH), 3.62 (2H, m, CH_2), 3.36 (3H, s, OCH_3), 3.19 (1H, m, CH), 2.82 (1H, m, CH), 2.65 (1H, m, CH), 2.14 (2H, m, CH_2), 1.89 (2H, m, CH_2), 1.73 (2H, m, CH_2), 1.50 (1H, m, CH), 1.40 (1H, m, CH), 1.22 (6H, m, $2OCH_2\underline{CH}_3$); δ_C ($CDCl_3$) 174.8, 174.3, 173.4, 172.5, 169.0, 164.2, 156.4, 137.5, 128.3, 128.2, 128.1, 66.9, 66.0, 65.9, 63.6, 63.3, 54.9, 52.0, 51.4, 48.2, 47.7 (d, *J* 147.1 Hz, CP), 45.9, 45.4, 42.3, 41.9, 41.6, 41.0, 40.7, 33.8, 32.0, 31.4, 28.7, 28.3, 28.2, 27.9, 25.8, 24.9, 24.8, 21.5, 16.7 (dd, *J* 12.0, 5.0 Hz, $OCH_2\underline{CH}_3$); δ_P (DMSO-d_6) 18.3.

References and notes

1. (a) *Aminophosphonic and Aminophosphinic Acids*; Kukhar, V. P., Hudson, H. R., Eds.; John Wiley & Sons: Chichester, 2000; (b) Kukhar, V. P.; Soloshonok, V. A.; Solodenko, V. A. *Phosphorus, Sulfur, and Silicon* **1994**, *92*, 239-264; (c) Palacios, F.; Alonso, C.; de los Santos, M. *Chem. Rev.* **2005**, *105*, 899–931; (d) Wardle, N. J.; Bligh, S. W. A.; Hudson, H. R. *Curr. Org. Chem.* **2007**, *11*, 1635–1651; (e) Lejczak, B.; Kafarski, P. *Top. Heterocycl. Chem.* **2009**, *20*, 31–63; (g) Ordonez, M.; Rojas-Cabrera, H.; Cativiela, C. *Tetrahedron* **2009**, *65*, 17–49; (f) Orsini, F.; Sello, G.; Sisti, M. *Curr. Med. Chem.* **2010**, *17*, 264–289; (h) Mucha, A.; Kafarski, P.; Berlicki, L. *J. Med. Chem.* **2011**, *54*, 5955–5980; (i) Seto, H.; Kuzuyama, T. *Nat. Prod. Rep.* **1999**, *16*, 589–596.
2. (a) Bowler, M. W.; Cliff, M. J.; Waltho, J. P.; Blackburn, G. M. *New J. Chem.* **2010**, *34*, 784–794; (b) Metcalf, W. W.; van der Donk, W. A. *Annu Rev Biochem.* **2009**, *78*, 65–94; (c) Naydenova, E. D.; Petar, T.; Todorov P. T.; Kolio D.; Troev K. D. *Amino Acids* **2010**, *38*, 23–30; (d) Tadeusiak, E. J. *Bioorg. Chem.* **2004**, *32*, 473–482; (e) Fields, S. *Tetrahedron* **1999**, *55*, 12237-12273.
3. (a) Lejczak, B.; Kafarski, P. In *Aminophosphonic and Aminophosphinic Acids*; Kukhar, V. P., Hudson, H. R., Eds.; John Wiley & Sons: Chichester, 2000. pp 173-196; (b) Kafarski, P.; Lejczak, B. *Curr. Med. Chem. – Anti-Cancer Agents* **2001**, *1*, 301-312; (c) Palacios, F.; Alonso, C.; de los Santos, J. M. *Curr. Org. Chem.* **2004**, *8*, 1481-1496.
4. (a) Lall, S., Engel, R. In *Aminophosphonic and Aminophosphinic Acids*; Kukhar, V. P., Hudson, H. R., Eds.; John Wiley & Sons: Chichester, 2000. pp 103-122; (b) Han, L.; Hiratake, J.; Tachi, N.; Suzuki, H.; Kumagai, H.; Sakata, K. *Bioorg. Med. Chem.* **2006**, *14*, 6043-6054; (c) van Zutphen, S.; Margarit, V. J.; Mora, G.; Le Floch, P. *Tetrahedron Lett.* **2007**, *48*, 2857-2859; (d) Kukhar, V. P., Romanenko, V. D. In *Amino Acids, Peptides and Proteins in Organic Chemistry*; Hughes, A. B., Ed.; Wiley-VCH: Weinheim, Germany, 2009; Vol.2, pp 189-260; (e) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53; (g) Köhler, B.; Schöllkopf, U. *Lieb. Ann. Chem.* **1987**, 267-269.
5. (a) Kondratyuk, K. M.; Lukashuk, E. I.; Golovchenko, A. V.; Rusanov, E. B.; Brovarets, V. S. *Rus. J. Gen. Chem.* **2012**, *82*, 643-651; (b) Kondratyuk, K. M.; Golovchenko, A. V.; Osadchuk, T. V.; Brovarets, V. S. *Rus. J. Gen. Chem.* **2011**, *81*, 1470-1476; (c) Prokopenko, V. M.; Pil'o, S. G.; Vasilenko, A. N.; Brovarets, V. S. *Rus. J. Gen. Chem.* **2010**, *80*, 2358-2365; (d) *Oxazoles: synthesis, reactions, and spectroscopy. Part A*; Palmer D.C., Ed.; John Wiley & Sons, Inc.: Hoboken, New Jersey, 2003.
6. Chumachenko, S. A.; Shablykin, O. V.; Vasilenko, A. N.; Brovarets, V. S. *Chem. Heterocycl. Compd. (N.Y.)* **2011**, *47*, 1020-1028.
7. Drach, B. S.; Sviridov, E. P.; Shatursky, Ya. P. *J. Gen. Chem. USSR (Engl. Transl.)* **1974**, 44, 1712-1715.
8. Usifoh, C. O.; Lambert, D. M.; Wouters, J.; Scriba, G. K. E. *Arch. Pharm. (Weinheim, Germany)* **2001**, *334*, 323-331.
9. Crook, L. R.; Jansen, A. B. A.; Spencer, K. E. V.; Watson, D. H. G.B. Patent 1 036 694, 1966; *Chem. Abstr.* **1966**, *65*, 16910h.
10. Guenin, E.; Monteil, M.; Bouchemal, N.; Prange, T.; Lecouvey, M. *Eur. J. Org. Chem.* **2007**, *20*, 3380-3391.