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Synthesis of novel phosphorylated peptidomimetics which contain ω-haloalkyl and ω-thiocyanoethyl residues

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The interaction of (2-aryl-5-(hydroxyalkylamino)-1,3-oxazol-4-yl)phosphonates with hydrogen chloride, hydrogen iodide and hydrogen thiocyanate in anhydrous medium led to formation of new phosphorylated peptidomimetics containing C-terminal ω-haloalkyl and ω-thiocyanoethyl residues.

1. Introduction

It is known that 1,3-oxazole derivatives are reactive compounds and can be converted to other five- and six-membered rings.[1-10] In addition, 1,3-oxazoles are unstable in an acidic medium and are cleaved by a water molecule to form acyclic products.[11,12] In the case of 4-functionalized 5-amino-1,3-oxazoles, this leads to formation of compounds of peptide nature. Particular attention is drawn to the derivatives of 5-amino-1,3-oxazol-4-ylphosphonic acids, which under conditions of acidic cleavage form peptidomimetics containing the residues of phosphorylated glycine.[13-19] High biological activity of phosphorus-containing peptides is known. For example, selective inhibitors of cellular cymase,[20] glutathione transferase,[21,22] HCV NS3/NS4A serine protease,[23] vasoactive compounds,[24-26] etc., were found among these compounds. Phosphorylated peptides are also valuable intermediates in the synthesis of some biologically active compounds. To illustrate, they enabled synthesis of iron and

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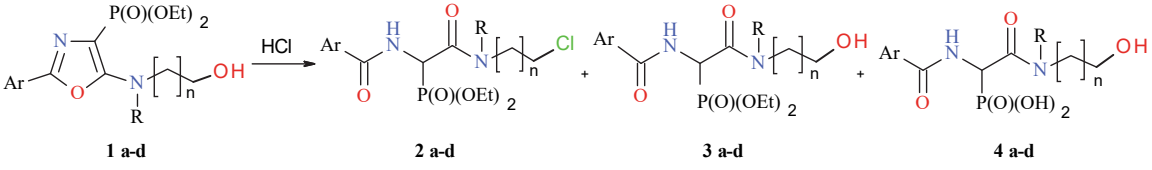
mollusk vanadium-containing blood pigment - Tunichromes Mm-1 and Mm-2,[27,28] peptide alkaloid Hexaacetylcelenamid A,[29,30] potential anticancer agents - Azinomycins A and B,[31,32] antibiotic Antrimycin D_V,[33] and others.

Thus, phosphorylated peptides and peptidomimetics not only display a variety of biological activities, but also are valuable reagents in the synthesis of bioactive products. Therefore, the study of approaches to the synthesis of phosphorylated peptidomimetics is of undoubted interest. It was previously shown that the 5-amino-1,3-oxazole derivatives containing the diethoxyphosphoryl group in position 4 are cleaved by water in the presence of various acidic agents such as acetic acid,[17,19] trifluoroacetic acid,[18,19] hydrochloric acid [34,35] and p-toluenesulfonic acid.[16] Also recently, we found that when diethyl ester (5-(2-hydroxyethyl)-N-methylamino)-2-phenyl-1,3-oxazol-4-ylphosphonic acid reacts with hydrogen chloride under anhydrous conditions, a phosphopeptidomimetic containing 2-chloroethyl fragment[18] is formed. The aim of the present work is to identify the scope of cleavage reaction of 4-phosphorylated 1,3-oxazole derivatives containing various aminoalkanol residues in position 5 in anhydrous medium in the presence of acidic reagents in order to obtain new phosphopeptidomimetics. For this, diethyl esters of 2-aryl-1,3-oxazole-4-ylphosphonic acids **1a-f**, containing in position 5 the residues 2-(methylamino)ethan-1-ol, 2-aminopropan-1-ol, piperidin-3-ol and piperidin-4-ol were synthesized according to the known procedure.[19]

2. Results and Discussion

At first, we investigated the interaction of these oxazoles with hydrogen chloride in anhydrous dioxane. The reaction was carried out by bubbling hydrogen chloride preliminarily dewatered above phosphorus pentoxide into saturated solution of one of the oxazoles **1a-f** (Scheme 1,2) in dioxane within 5-10 minutes. The temperature of the reaction mixture increased to 70-80°C. After that, the mixture was cooled to 20-25°C, the solvent was removed in vacuo and the residue was analyzed by LC/MS spectra. It turned out that the derivatives of 1,3-oxazole-4-ylphosphonic acids **1a-d** containing the residues of acyclic aminoalkanol in position 5 yield, as a rule, a mixture of products **2-4** (Scheme 1) with a significant predominance of diethyl (1-(aroylamino)-2-(chloroalkylamino)-2-oxoethyl)phosphonates **2a-d** (Table 1).



Ar = Ph, 4-$CH_3C_6H_4$; R = H, Me; n = 1, 2

Scheme 1. Interaction diethyl (2-aryl-(5-(hydroxyalkylamino)-1,3-oxazol-4-yl)phosphonates **1a-d** with hydrogen chloride.

Compounds **2a-d** were isolated from the reaction mixture by column chromatography. Minor products **3** and **4** could not be isolated in an individual state, but they can be obtained by other methods, which are described in paper.[18]

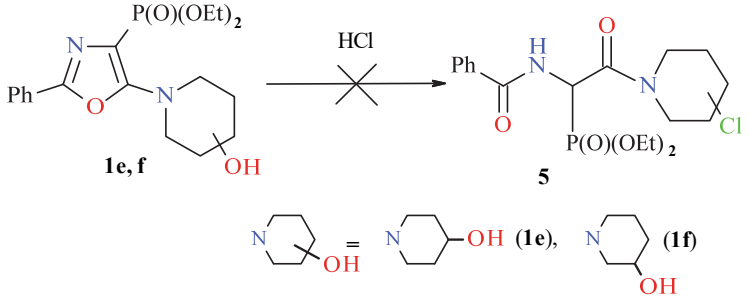
Table 1. The ratio of products **2**, **3** and **4** in the resulting mixture (see **Scheme 1**)

Substance	Ar	R	n	Yield, %		
				2	**3**	**4**
1a	Ph	H	2	75	15	10
1b	4-MeC_6H_4	H	2	79	14	7
1c	Ph	Me	1	92	8	0
1d	4-MeC_6H_4	Me	1	85	12	3

Chloroalkyl products **2a-d** are viscous colorless oils, poorly soluble in water and hexane, readily soluble in alcohols, benzene, methylene chloride, chloroform and dimethylsulfoxide. Their composition and structure are consistent with the data of elemental analysis, ^{1}H, ^{13}C, and ^{31}P NMR and IR spectroscopy, as well as chromatography-mass spectrometry. Thus, the data elemental analysis of compounds **2a-d** indicate that the atom of phosphorus and chlorine atom have correlation 1:1 in their molecules.

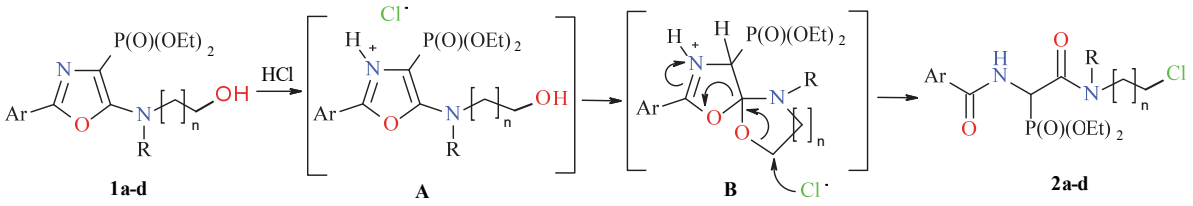
The IR spectra of compounds **2a-d** contained the vibrations of the C=O groups manifest themselves as wide intense bands in the range of 1649-1644 cm^{-1}. The absorption bands characteristic of the P=O group lie in the range of 1245-1235 cm^{-1}. In addition, their IR spectra contain intense signals in the range of 1017-1014 cm^{-1} and 975-969 cm^{-1}, corresponding to the P-O-C bond vibrations. In ^{1}H NMR spectra of compounds **2a-d**, it is possible to detect the signals of protons of the CHP group, which manifest themselves as a doublet in the range of 5.79-5.37 ppm with *J* 17.8-19.8 Hz (coupling with the nucleus of the phosphorus atom) and *J* 8.2- 8.8 Hz (with the proton NH). The signals of CH_2Cl protons are in the form of multiplets in the range of 3.82-3.56 ppm. For compounds **2a, b**, a double set of signals of the CHP, NHCHP, NCH_3 groups is observed in the ratio 1:2, which can be explained by rotation around the amide bond and the presence of a chiral carbon atom. In the ^{13}C NMR spectra, signals of the C=O group are in the range of 166.8-164.7 ppm as doublets with *J* 2.5-4.5 Hz (coupling of carbon nuclei with the nuclei of phosphorus atoms) for compounds **2a**, **b** and in the form of singlets for compounds **2c, d** were detected. Signals of the carbon nuclei of the CHP group are manifested in the form of doublets in the range of 50.5-47.9 ppm with the *J* 147.8-145.8 Hz.

A particular attention should be paid to ^{13}C NMR spectral data of these compounds. Interestingly, the diethyl (2-phenyl-1,3-oxazole-4-yl)phosphonates **1e, f** [19] containing in position 5 the residues of cyclic aminoalkanols –piperidin-3-ol and piperidin-4-ol, under the same conditions do not produce chlorine-containing peptidomimetics **5a, b** (Scheme 2).



Scheme 2. Interaction of the diethyl (1,3-oxazol-4-yl)phosphonates **1e, f** with hydrogen chloride.

Such difference in the reactivity of the products **1a-d** and **1e, f** can be explained by the probable mechanism of this reaction. That is, it is possible first to protonate the nitrogen atom of the oxazole ring to form intermediate **A**, the hydroxyl group of which attacks the carbon atom in C-5, which leads to the spiro-compound **B**. Further attack by the chloride anion on the carbon atom of the CH_2O group results in subsequent cleavage of the oxazole ring, leading to formation of peptidomimetics **2a-d** (Scheme 3).



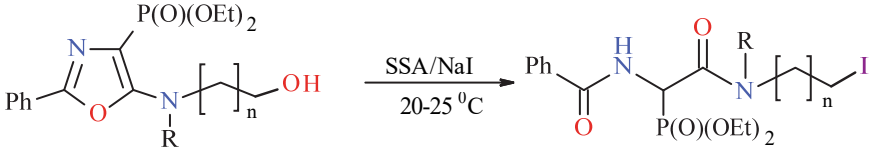
Ar = Ph, R = H, n = 2 (**1a**, **2a**);
Ar = 4-$CH_3C_6H_4$, R = H, n = 2 (**1b**, **2b**);
Ar = Ph, R = Me, n = 1 (**1c**, **2c**);
Ar = 4-$CH_3C_6H_4$, R = Me, n = 1 (**1d**, **2d**)

Scheme 3. Possible mechanism of the reaction of interaction of diethyl (1,3-oxazol-4-yl)phosphonates **1a-d** with hydrogen chloride.

In case of oxazoles **1e, f**, in which the hydroxyl group is rigidly fixed, it is impossible to form spirocompounds of type **B**; therefore, the products of substitution of the hydroxyl group by the chlorine atom, as well as the products of the oxazole ring cleavage, are not formed.

In order to broaden the scope of the reaction we have found, other acidic agents have also been used in which the anion has nucleophilic properties, in particular hydrogen iodide, since the insertion of an iodine atom into the alkylamide residue makes it possible to produce more reactive alkylating agents. However, the synthesis of pure anhydrous hydrogen iodide is a laborious process, so we decided to form it directly in the reaction medium. For this, it was necessary to fulfill a number of conditions: the formation of hydrogen iodide should occur in an anhydrous organic solvent and the cation acceptor should not react with substrates or solvents. The most appropriate was silicic acid (SSA),[36] the advantage of which is that it belongs to strong acids and is easily removed from the reaction mixture by filtration.

The reaction was carried out at temperature 20-25°C with a 5-fold excess of sodium iodide in an anhydrous acetonitrile medium. As a result, diethyl (1-(benzoylamino)-2-(iodoalkylamino)-2-oxoethyl)phosphonates **6a, b** were obtained with medium yields (Scheme 4).



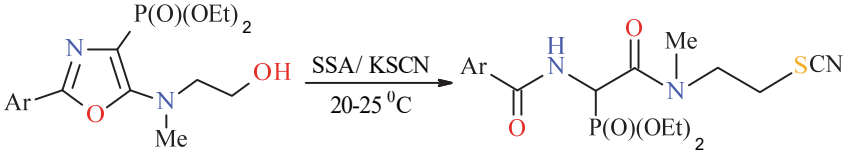
R = H, n = 2 (**1a**, **6a**);
R = Me, n = 1 (**1c**, **6b**);
SSA - silica-sulfuric acid

Scheme 4. Synthesis of the diethyl (1-(benzoylamino)-2-(iodoalkylamino)-2-oxoethyl)phosphonates **6a,b**.

Compounds **6a, b** are dark brown-colored oils, insoluble in water, hexane, readily soluble in most organic solvents. The structure of substances **6a, b** is confirmed by elemental analysis, IR and ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy, as well as chromatography-mass spectrometry. The ^{1}H NMR spectra of compounds **6a, b** contain a multiplet of NH group in the range of 8.01-7.86 ppm. The signals of CHP, NCH_3 and CH_2 groups are manifested as two sets of multiplets in the ratio 1:2. Thus, the signals of CHP protons are in the region of 5.75-5.63 ppm as a doublet of doublets with NH-CH coupling constant 8.0-8.5 Hz and *J* with a phosphorus atom 18.1-18.9 Hz. The protons of the CH_2I group are not equivalent and are fixed in the range of 3.36-3.16 ppm, and the group NCH_3 signals for compounds **6a, b** are in the range of 3.24-2.95 ppm.

It should be noted that the iodine atom in peptidomimetics **6b** is reactive and is quantitatively substituted by hydroxyl group in dimethylsulfoxide (DMSO) at room temperature due to the presence of water in it. Therefore, to study the structure of compound **6b** by physicochemical methods, it is not recommended to use its solution in DMSO.

We also studied the interaction of 4-phosphorylated oxazoles **1** with thiocyanic acid, which on one hand is a strong acid, while on the other - its anion is an ambident nucleophile that can lead to isothiocyanates or thiocyanates. It is known that thiocyanic acid is unstable and it is extremely difficult to obtain it in the free state. We managed to solve this problem using the same approach as in the case of hydrogen iodide. Indeed, treatment of oxazoles **1c, d** in anhydrous acetonitrile with a 5-fold excess of KSCN in the presence of SSA at 20-25°C leads to compounds **7a, b** containing the terminal SCN group, with good yields (*Scheme 5*).



1 c, d **7 a, b**

Ar = Ph (**1c**, **7a**), 4-$CH_3C_6H_4$ (**1d**, **7b**)

Scheme 5. Synthesis of the diethyl (1-(aroylamino)-2-((methyl)(2-thiocyanatoethyl)amino)-2-oxoethyl)phosphonates **7a, b**.

Compounds **7a, b** are yellowish oil. Their structure is in good agreement with the data of elemental analysis, ^{1}H, ^{13}C, ^{31}P NMR and IR spectroscopy, as well as chromatography-mass spectrometry. Thus, elemental analysis of compounds **7a, b** indicates that the atoms of phosphorus and sulfur have correlation 1:1 in their molecules. Thus, in the ^{1}H NMR spectra, a double set of signals of the groups CHP, CH_2SCN, NMe and 4-MeC_6H_4 in a ratio of 1:2 is observed. The signals of the NH groups manifest themselves in the region of 8.45-8.37 ppm as multiplets, and the CHR signals in the region of 5.78-5.63 ppm in the form of doublet of doublets with *J* 8.3-8.5 Hz and *J* with a phosphorus atom 19.2-19.3 Hz. The protons of the CH_2SCN group appear in the region of 3.72-3.31 ppm in the form of multiplets. The proton signals of the NCH_3 group are recorded in the form of singlets in the range of 3.16-2.93 ppm.

Compounds **7a, b** were also synthesized with yields 71-84% from compounds **6a, b** and potassium thiocyanate. The reaction was carried out in anhydrous acetonitrile at 20-25°C. The obtained products were identical with compounds **7a, b** according to physicochemical data.
In conclusion, it should be noted that substitution of the hydroxyl group in alkanols with an isocyanato group is the first example of reactions of this type that have not been previously described in the literature.

3. Conclusions

Thus, the interaction of 4-phosphorylated 2-R-5-(hydroxyalkyl)amino-1,3-oxazoles with hydrogen chloride, hydrogen iodide and hydrogen thiocyanate in an anhydrous medium was studied. As a result, peptidomimetics - derivatives of phosphorylated glycine, containing terminal haloalkyl and thiocyanalkyl substituents were obtained, which are potential bioregulators. The approach we have found is novel and scalable method for the preparation of this type of phosphonopeptidomimetics.

Acknowledgements

We would like to thank Enamine Ltd. for the material and technical support.

4. Experimental

4.1. Instruments, Reagents, and Methods

IR spectra were recorded on a Vertex 70 spectrometer in KBr pellets or films. The ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Varian Unityplus - 400 spectrometer (400, 125 and 202 MHz, respectively) in DMSO-d_6 or $CDCl_3$with TMS or 85% phosphoric acid as internal standard. The LC/MS spectra were recorded on an LC-MS system - HPLC Agilent 1100 Series equipped with a diode array detector Agilent LC\MSD SL. Parameters of GC-MS analysis: Zorbax SB - C18 column (1.8 μm, 4.6 × 15 mm, PN 821975-932), solvent water – acetonitrile mixture (95 : 5), 0.1% of aqueous trifluoroacetic acid; eluent flow 3 mL min–1; injection volume 1 μL; UV detecting at 215, 254, 265 nm; chemical ionization at atmospheric pressure (APCI), scan range m/z 80 - 1000. UV-Vis absorption spectra were recorded on Shimadzu UV-3100 spectrophotometer in toluene of spectral grade. Elemental analysis was carried out in the Analytical Laboratory of the Institute of Bioorganic and Petrochemistry of the National Academy of Sciences of Ukraine by manual methods. The carbon and hydrogen contents were determined using the Pregl gravimetric method, while nitrogen was determined using the Duma's gasometrical micromethod. Sulfur was determined by the Scheininger titrimetric method, chlorine content was determined by the mercurometric method, phosphorus content was determined by the colorimetric method.[37] M. P. were determined on a Fisher–Johns apparatus and are uncorrected. Reactions and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates using 9:1(v/v) chloroform–methanol as eluent. All reagents and solvents were purchased from Aldrich and used as received.

*4.2. Experimental procedure and physical data for compounds **1**, **2**, **6**, 7*

*General procedure for the preparation of the diethyl (2-aryl-(5-(hydroxyalkylamino)-1,3-oxazol-4-yl)phosphonates **1a-f***

Corresponding amine (2.52 g, 0.045 mol) was added to a solution of corresponding (3.0 g, 0.01 mol) of diethyl (1-acylamino-2,2,2-trichloroethyl)-phosphonate in methanol (50 ml). The mixture was stirred for 36–72 h at 18–25°C. The solvent was removed in a vacuum. The residue was treated with distilled water and extracted with tret-butyl methyl ether. The extract was dried over sodium sulfate. The solvent was removed in a vacuum, compounds **1b** and **1d** were analyzed without further purification.

*Diethyl (5-(3-hydroxypropyl)amino)-2-phenyl-1,3-oxazol-4-yl)-phosphonate (**1a)*** has been obtained as described previously.[19]

*Diethyl (5-(3-hydroxypropyl)amino)-2-(4-methylphenyl)-1,3-oxazol-4-yl)phosphonate **(1b).***

Colorless crystals (2.5 g, 91% yield), mp = 79 - 81ºC. IR (neat, cm^{-1}), ν: 3394 (N–H, O–H), 1620, 1426, 1392, 1224 (P=O), 1047, 1017 (P–O–C), 964 (P–O–C), 920, 815, 807, 615, 584. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.80 (d, J = 8.0 Hz, 2H, aromatic), 7.21 (d, J = 8.0 Hz, 2H, aromatic), 6.25 (t, J = 4.7 Hz, 1H, NH), 4.21-4.07 (m, 4H, $2OC\underline{H}_2CH_3$), 3.81 (t, J = 6.0 Hz, 2H, CH_2), 3.56-3.42 (m, 2H, CH_2), 2.38 (s, 3H, CH_3), 1.96-1.88 (m, 2H, CH_2), 1.35 (t, J = 7.1 Hz, 6H, $2OCH_2C\underline{H}_3$). ^{13}C NMR(125 MHz, $CDCl_3$), δ: 163.66 (d, J = 40.2 Hz, C-5 oxazole), 152.35 (d, J = 22.1 Hz, C-2 oxazole), 139.62, 129.31, 127.37, 125.47 (aromatic), 96.03 (d, J = 257.5 Hz, C-4 oxazole), 62.32 (d, J = 5.0 Hz, $O\underline{C}H_2CH_3$), 60.04 (CH_2OH), 40.77 (NCH_2), 32.42 (CH_2), 21.43 (CH_3), 16.25 (d, J = 6.0 Hz, $OCH_2\underline{C}H_3$).^{31}P NMR (202 MHz, $CDCl_3$), δ: 14.35. LCMS: $[M+H]^+$ = 369.2. $C_{17}H_{25}N_2O_5P$ (368.37): calcd. C 55.43, H 6.84, N 7.60, P 8.41; found C 55.35, H 6.91, N 7.83, P 8.29.

Diethyl (5-(2-hydroxyethyl)(methyl)amino)-2-phenyl-1,3-oxazol-4-yl)phosphonate ***(1c)*** has been obtained as described previously.[19]

Diethyl ester (5-(2-hydroxyethyl)(methyl)amino)-2-(4-methylphenyl)-1,3-oxazol-4-yl)phosphonate ***(1d)***.

Colorless crystals (2.63 g, 96% yield), mp = 61 - 63ºC. IR (neat, cm^{-1}), ν: 3373 (N–H, O–H), 2987, 2901, 1613, 1502, 1454, 1431, 1213 (P=O), 1022 (P–O–C), 974 (P–O–C), 826, 798, 646, 583. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.75 (d, *J* = 8.0 Hz, 2H, aromatic), 7.21 (d, *J* = 8.0 Hz, 2H, aromatic), 4.21-4.10 (m, 4H, $2OC\underline{H}_2CH_3$), 3.83 (t, *J* = 5.0 Hz, 2H, CH_2), 3.71 (t, *J* = 5.0 Hz, 2H, CH_2), 3.18 (s, 3H, NCH_3), 2.37 (s, 3H, CH_3), 1.36 (t, *J* = 6.9 Hz, 6H, $2OCH_2C\underline{H}_3$). ^{13}C NMR(125 MHz, $CDCl_3$), δ: 162.57 (d, *J* = 38.9 Hz, C-5 oxazole), 151.44 (d, *J* = 21.9 Hz, C-2 oxazole), 139.68, 129.32, 125.47, 124.32 (aromatic), 98.76 (d, *J* = 256.3 Hz, C-4 oxazole), 62.72 (d, *J* = 5.5 Hz, $O\underline{C}H_2CH_3$), 59.04, 55.03, 36.81 (CH_2, NCH_3), 21.45 (CH_3), 16.23 (d, *J* = 6.5 Hz, $OCH_2\underline{C}H_3$).^{31}P NMR (202 MHz, $CDCl_3$), δ: 15.61. LCMS: $[M+H]^+$ = 369.2. $C_{17}H_{25}N_2O_5P$ (368.37): calcd. C 55.43, H 6.84, N 7.60, P 8.41; found C 55.68, H 6.97, N 7.05, P 8.35.

Diethyl (5-(3-hydroxypiperidin-1-yl)-2-phenyl-1,3-oxazol-4-yl)phosphonate ***(1e)*** has been obtained as described previously.[19]

Diethyl (5-(4-hydroxypiperidin-1-yl)-2-phenyl-1,3-oxazol-4-yl)phosphonate ***(1f)*** has been obtained as described previously. [19]

General procedure for the preparation of the diethyl (1-(aroylamino)-2-(chloroalkylamino)-2-oxoethyl)phosphonates ***2a-d***.

To a solution corresponding diethyl 2-aryl-(5-(hydroxyalkylamino)-1,3-oxazol-4-yl)phosphonate **1a-d** (0.5 g, 0.0015 mol) in anhydrous dioxane (25 ml) saturated with dry hydrogen chloride. The temperature of the reaction mixture rose to 70-80°C. The mixture was cooled to 20-25°C and stirred for 3 h. The solvent was removed in a vacuum. Compounds **2a-d** were isolated from the mixture by column chromatography (with a dichloromethane-methanol, gradient eluent 98:2, 95:5, 90:10).

Diethyl (1-benzoylamino-2-(3-chloropropyl)amino)-2-oxoethyl)phosphonate ***(2a)***.

Colorless oil (0.41 g, 75% yield). IR (neat, cm^{-1}), ν: 3289 (N–H), 2982, 1646 (C=O), 1522, 1236 (P=O), 1017 (P–O–C), 973 (P–O–C), 698, 653, 522. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.84 (d, *J* = 8.0 Hz, 2H, aromatic), 7.55-7.49 (m, 1H, aromatic), 7.47-7.41 (m, 2H, aromatic), 7.40-7.31 (m, 2H, NH), 5.39 (dd, *J* = 8.2 Hz, *J* = 19.8 Hz, 1H, CHP), 4.33-4.20 (m, 2H, $OC\underline{H}_2CH_3$), 4.19-4.08 (m, 2H, $OC\underline{H}_2CH_3$), 3.58 (t, *J* = 6.3 Hz, 2H, CH_2Cl), 3.53-3.48 (m, 1H, CH), 3.43-3.36 (m, 1H, CH), 2.07-1.94 (m, 2H, CH_2), 1.38-1.26 (m, 6H, $2OCH_2C\underline{H}_3$). ^{13}C NMR(125 MHz, $CDCl_3$), δ: 166.70 (d, *J* = 4.5 Hz, C=O), 164.87 (d, *J* = 2.5 Hz, C=O), 132.94, 131.66, 128.21, 126.94 (aromatic), 63.78 (d, *J* = 6.0 Hz, $O\underline{C}H_2CH_3$), 63.30 (d, *J* = 7.0 Hz, $O\underline{C}H_2CH_3$), 50.45 (d, *J* = 147.8 Hz, CHP), 41.68, 36.89, 31.48 (CH), 15.98 (d, *J* = 5.5 Hz, $OCH_2\underline{C}H_3$), 15.88 (d, *J* = 6.5 Hz, $OCH_2\underline{C}H_3$).^{31}P NMR (202 MHz, DMSO-d_6), δ: 18.59. LCMS: $[M+H]^+$ = 391.2. $C_{16}H_{24}ClN_2O_5P$ (390.81): calcd. C 49.17, H 6.19, Cl 9.07, N 7.17, P 7.93; found C 49.34, H 6.01, Cl 9.25, N 7.40, P 7.85.

Diethyl (2-(3-chloropropylamino)-1-(4-methylbenzoyl)amino)-2-oxoethyl)phosphonate ***(2b)***.

Colorless oil (0.43 g, 79% yield). IR (neat, cm^{-1}), ν: 3287 (N–H), 1645 (C=O), 1530, 1497, 1235 (P=O), 1016 (P–O–C), 973 (P–O–C), 751, 520. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.67 (d, *J* = 7.8 Hz, 2H, aromatic), 7.47 (t, *J* = 5.3 Hz, 1H, NH), 7.35 (d, *J* = 8.3 Hz, 1H, NH), 7.15 (d, *J* = 7.8 Hz, 2H, aromatic), 5.38 (dd, *J* = 8.3 Hz, *J* = 20.1 Hz, 1H, CHP), 4.21-4.05 (m, 4H, $2OC\underline{H}_2CH_3$), 3.51 (t, *J* = 6.5

Hz, 2H, CH_2Cl), 3.46-3.38 (m, 1H, CH), 3.37-3.27 (m, 1H, CH), 2.31 (s, 3H, CH_3), 1.29-1.20 (m, 6H, $2OCH_2C\underline{H}_3$). ^{13}C NMR(125 MHz, $CDCl_3$), δ: 166.95 (d, *J* = 4.1 Hz, C=O), 165.29 (d, *J* = 2.5 Hz, C=O), 142.52, 130.54, 129.23, 127.34 (aromatic), 64.13 (d, *J* = 6.0 Hz, $O\underline{C}H_2CH_3$), 63.64 (d, *J* = 7.5 Hz, $O\underline{C}H_2CH_3$), 50.83 (d, *J* = 146.8 Hz, CHP), 42.08, 37.27, 31.92 (CH_2), 21.47 (CH_3), 16.38 (d, *J* = 6.0 Hz, $OCH_2\underline{C}H_3$), 16.28 (d, *J* = 6.6 Hz, $OCH_2\underline{C}H_3$).^{31}P NMR (202 MHz, DMSO-d_6), δ: 18.70. LCMS: $[M+H]^+$ = 405.2. $C_{17}H_{26}ClN_2O_5P$ (404.83): calcd. C 50.44, H 6.47, Cl 8.76, N 6.92, P 7.65; found C 50.57, H 6.40, Cl 8.90, N 7.18, P 7.78.

Diethyl (1-(benzoylamino)-2-((2-chloroethyl)(methyl)amino)-2-oxoethyl)phosphonate ***(2c)***.

Colorless oil (0.5 g, 92% yield). IR (neat, cm^{-1}), ν: 2982 (N–H), 1644 (C=O), 1523, 1244 (P=O), 1014 (P–O–C), 969 (P–O–C), 710, 520. ^1H NMR (400 MHz, $CDCl_3$), δ: 7.82 (d, *J* = 7.4 Hz, 2H, aromatic), 7.56-7.50 (m, 1H, aromatic), 7.49-7.41 (m, 2H, aromatic), 7.34-7.24 (m, 1H, NH), 5.79 (dd, *J* = 8.8 Hz, *J* = 17.8 Hz, 1/3H, CHP), 5.72 (dd, *J* = 8.8 Hz, *J* = 17.8 Hz, 2/3H, CHP), 4.27-4.14 (m, 4H, $2OC\underline{H}_2CH_3$), 3.87-3.61 (m, 4H, $2CH_2$), 3.36 (s, 2H, CH_3), 3.06 (s, 1H, CH_3), 1.40-1.28 (m, 6H, $2OCH_2C\underline{H}_3$). ^{13}C NMR(125 MHz, $CDCl_3$), δ: 166.07, 166.03,165.99, 165.87 (C=O), 132.98, 131.66, 128.28, 126.84 (aromatic), 63.49 (d, *J* = 6.0 Hz, $O\underline{C}H_2CH_3$), 63.28 (d, *J* = 6.0 Hz, $O\underline{C}H_2CH_3$), 51.19, 50.87 (CH_2), 48.10 (d, *J* = 146.6 Hz, CHP), 47.93 (d, *J* = 146.6 Hz, CHP), 40.54, 40.42, 37.44, 34.38 (CH_2, CH_3), 16.08 (d, *J* = 5.5 Hz, $OCH_2\underline{C}H_3$), 15.96 (d, *J* = 5.5 Hz, $OCH_2\underline{C}H_3$).^{31}P NMR (202 MHz, DMSO-d_6), δ: 16.93, 16.82. LCMS: $[M+H]^+$ = 391.2. $C_{16}H_{24}ClN_2O_5P$ (390.81): calcd. C 49.17, H 6.19, Cl 9.07, N 7.17, P 7.93; found C 49.41, H 6.33, Cl 8.90, N 7.39, P 7.87.

Diethyl (2-(2-chloroethyl)(methyl)amino)-1-(4-methylbenzoyl)amino)-2-oxoethyl)phosphonate ***(2d)***.

Colorless oil (0.47 g, 85% yield). IR (neat, cm^{-1}), ν: 3362 (N–H), 1642 (C=O), 1533, 1498, 1321, 1187, 1159, 1017 (P–O–C), 951, 751, 512, 475. ^1H NMR (400 MHz, $CDCl_3$), δ: 7.72 (d, *J* = 8.1 Hz, 2H, aromatic), 7.28-7.19 (m, 1H, NH, 2H, aromatic), 5.78 (dd, *J* = 8.7 Hz, *J* = 17.9 Hz, 1/3H, CHP), 5.72 (dd, *J* = 8.4 Hz, *J* = 17.9 Hz, 2/3H, CHP), 4.28-4.12 (m, 4H, $2OC\underline{H}_2CH_3$), 3.83-3.74 (m, 1H, CH), 3.72-3.61 (m, 3H, CH, CH_2), 3.36 (s, 2H, CH_3), 3.06 (s, 1H, CH_3), 2.39 (s, 3H, CH_3), 1.37-1.27 (m, 6H, $2OCH_2C\underline{H}_3$). ^{13}C NMR(125 MHz, $CDCl_3$), δ: 165.96-165.80 (m, 2C=O), 142.10, 142.08, 130.04, 130.00, 128.83, 128.80, 126.79, 126.76 (aromatic), 63.47-63.16 (m, $O\underline{C}H_2CH_3$), 51.11, 50.77 (CH_2Cl), 48.00 (d, *J* = 147.1 Hz, CHP), 47.82 (d, *J* = 147.1 Hz, CHP), 40.46, 40.32 (CH_2), 37.33, 34.31(NCH_3), 21.02 (CH_3), 15.98 (d, *J* = 6.0 Hz, $OCH_2\underline{C}H_3$), 15.85 (d, *J* = 6.0 Hz, $OCH_2\underline{C}H_3$).^{31}P NMR (202 MHz, DMSO-d_6), δ: 17.07, 16.95. LCMS: $[M+H]^+$ = 405.2. $C_{17}H_{26}ClN_2O_5P$ (404.83): calcd. C 50.44, H 6.47, Cl 8.76, N 6.92, P 7.65; found C 50.60, H 6.68, Cl 9.00, N 7.11, P 7.53.

General procedure for the preparation of the diethyl (1-(benzoylamino)-2-(iodoalkylamino)-2-oxoethyl)phosphonates ***6a, b***

To a solution corresponding diethyl 2-aryl-(5-(hydroxyalkylamino)-1,3-oxazol-4-yl)phosphonate **1a, c** (0.5 g, 0.0015 mol) in anhydrous acetonitrile (25 ml) added (1.5 g, 0.01 mol) dry sodium iodide and (0.5 g) silica-sulfuric acid (SSA), the color of the mixture gradually became yellow. The mixture was stirred at 20-25°C for 24 h, then SSA was filtered, the solvent was removed in a vacuum. Compounds **6a**, **b** were isolated from the mixture by column chromatography (with a dichloromethane-methanol, gradient eluent 98:2, 95:5, 90:10).

Diethyl (1-benzoylamino-2-(3-iodopropyl)amino)-2-oxoethyl)phosphonate ***(6a)***.

Fawn oil (0.40 g, 60% yield). IR (neat, cm^{-1}), ν: 3424 (N–H), 1641 (C=O), 1524, 1323, 1208 (P=O), 1160, 1020 (P–O–C), 954 (P–O–C), 709, 517. ^1H NMR (400 MHz, $CDCl_3$), δ: 7.83 (d, *J* = 6.9 Hz, 2H, aromatic), 7.53 (t, *J* = 7.0 Hz, 1H, aromatic), 7.45 (d, *J* = 6.9 Hz, 2H, aromatic), 7.26-7.15 (m, 2H, 2NH), 5.76 (dd, *J* = 7.1 Hz, *J* = 19.4 Hz, 1H, CHP), 4.35-4.23 (m, 2H, $OC\underline{H}_2CH_3$), 4.21- 4.11 (m, 2H,

OC$\underline{H}_2$CH$_3$), 3.57-3.43 (m, 1H, CH$_2$), 3.42-3.30 (m, 1H, CH$_2$), 3.29-3.17 (m, 2H, CH$_2$), 2.20-1.93 (m, 2H, CH$_2$), 1.46-1.23 (m, 6H, 2OCH$_2$C$\underline{H}_3$). ^{13}C NMR(125 MHz, CDCl$_3$), δ: 166.52 (d, *J* =3.5 Hz, C=O), 164.47 (d, *J* = 2.5 Hz, C=O), 132.98, 131.58, 128.19, 126.79 (aromatic), 63.86 (d, *J* = 6.0 Hz, O$\underline{C}$H$_2$ CH$_3$), 63.08 (d, *J* = 7.0 Hz, O$\underline{C}$H$_2$CH$_3$), 50.00 (d, *J* = 147.1 Hz, CHP), 40.14 (CH$_2$), 32.33 (CH$_2$), 15.98 (d, *J* = 5.0 Hz, OCH$_2\underline{C}$H$_3$), 15.82 (d, *J* = 6.5 Hz, OCH$_2\underline{C}$H$_3$), 2.10 (CH$_2$J).^{31}P NMR (202 MHz, CDCl$_3$), δ: 18.97.. LCMS: [M+H]$^+$ = 483.0. $C_{16}H_{24}JN_2O_5P$ (482.26): calcd. C 39.85, H 5.02, N 5.81, P 6.42; found C 40.09, H 4.99, N 6.02, P 6.30.

Diethyl (1-(benzoylamino)-2-[(2-iodoethyl)(methyl)amino)-2-oxoethyl)-phosphonate ***(6b)***.

Brown oil (0.45 g, 66% yield). IR (neat, cm^{-1}), ν: 3416 (N–H), 2980, 1650 (C=O), 1522, 1482, 1213 (P=O), 1157, 1014 (P–O–C), 951 (P–O–C), 710, 512. ^{1}H NMR (400 MHz, CDCl$_3$), δ: 8.03-7.92 (m, 1H, NH), 7.82 (d, *J* = 7.3 Hz, 2H, aromatic), 7.52-7.44 (m, 1H, aromatic), 7.40-7.33 (m, 2H, aromatic), 5.75 (dd, *J* = 8.8 Hz, *J* = 18.6 Hz, 1/3H, CHP), 5.68 (dd, *J* = 8.8 Hz, *J* = 18.6 Hz, 2/3H, CHP), 4.23-4.06 (m, 4H, 2OC$\underline{H}_2$CH$_3$), 3.99-3.90 (m, 1/3H, CH), 3.85-3.72 (m, 1H, CH), 3.68-3.59 (m, 2/3H, CH), 3.36-3.29 (m, 2/3H, CH$_2$), 3.24 (s, 2H, CH$_3$), 3.22-3.16 (m, 4/3H, CH$_2$), 2.95 (s, 1H, CH$_3$), 1.33-1.21 (m, 6H, 2OCH$_2$C$\underline{H}_3$). ^{13}C NMR(125 MHz, CDCl$_3$), δ: 167.36 (d, *J* = 4.5 Hz, C=O), 167.06 (d, *J* = 1.5 Hz, C=O), 132.77, 132.73, 132.39, 128.70, 128.67, 127.66, 127.62 (aromatic), 64.59 (d, *J* = 6.6 Hz, O$\underline{C}$H$_2$ CH$_3$), 64.43 (d, *J* = 7.3 Hz, O$\underline{C}$H$_2$CH$_3$), 64.34 (d, *J* = 6.6 Hz, O$\underline{C}$H$_2$CH$_3$), 64.24 (d, *J* = 7.3 Hz, O$\underline{C}$H$_2$CH$_3$), 52.20, 51.72 (CH$_2$), 48.78 (d, *J* = 153.3 Hz, CHP), 48.61 (d, *J* = 153.3 Hz, CHP), 37.23, 30.98 (CH$_3$), 16.69-16.11 (m, OCH$_2\underline{C}$H$_3$), 0.88, -0.73 (CH$_2$J). LCMS: [M+OH-J]$^+$ = 373.0. $C_{16}H_{24}JN_2O_5P$ (482.26): calcd. C 39.85, H 5.02, N 5.81, P 6.42; found C 40.00, H 5.10, N 6.03, P 6.50.

General procedure for the preparation of the diethyl (1-(aroylamino)-2-((methyl)(2-thiocyanatoethyl)amino)-2-oxoethyl)phosphonates ***7a, b***.

To a solution corresponding diethyl (2-aryl-(5-(2-hydroxyalkyl)(methyl)amino)-1,3-oxazol-4-yl)phosphonates **1c, d** (0.5 g, 0.0015 mol) in anhydrous acetonitrile (25 ml) added (1.0 g, 0.012 mol) a dry KSCN and (0.5 g) silica-sulfuric acid (SSA), the color of the mixture gradually changed from light yellow to dark brown. The mixture was stirred at 20-25°C for 24 h, then SSA was filtered, the solvent was removed in a vacuum. Compounds **7a**, **b** were isolated from the mixture by column chromatography (with a dichloromethane-methanol, gradient eluent 98:2, 95:5, 90:10).

Diethyl (1-(benzoylamino)-2-[(methyl)(2-thiocyanoethyl)amino)-2-oxoethyl)phosphonate ***(7a)***.

Light yellow oil (0.4 g, 70% yield). IR (neat, cm^{-1}), ν: 3412 (N–H), 2984, 2156 (C≡N), 1637 (C=O), 1515, 1482, 1404, 1234 (P=O), 1137, 1013 (P–O–C), 976 (P–O–C), 711, 520, 453. ^{1}H NMR (400 MHz, DMSO-d$_6$), δ: 8.65-8.44 (m, 1H, NH), 7.87 (d, *J* = 6.6 Hz, 2H, aromatic), 7.61-7.54 (m, 1H, aromatic), 7.51-7.42 (m, 2H, aromatic), 5.72 (dd, *J* = 8.5 Hz, *J* = 19.2 Hz, 1/3H, CHP), 5.66 (dd, *J* = 8.5 Hz, *J* = 19.2 Hz, 2/3H, CHP), 4.18-4.03 (m, 4H, 2OC$\underline{H}_2$CH$_3$), 3.78-3.60 (m, 2H, CH$_2$), 3.49-3.35 (m, 1H, CH), 3.28-3.21 (m, 1H, CH), 3.18 (s, 2H, 2/3CH$_3$), 2.94 (s, 1H, 1/3CH$_3$), 1.29-1.13 (m, 6H, 2OCH$_2$C$\underline{H}_3$). ^{13}C NMR(125 MHz, DMSO-d$_6$), δ: 166.82 (C=O), 166.58 (d, *J* = 4.5 Hz, C=O), 166.28 (d, *J* = 1.5 Hz, C=O), 134.88, 133.86, 132.36, 131.79, 128.98, 128.78, 128.24, 128.04 (aromatic), 113.48, 113.34 (SCN), 63.80 (d, *J* = 6.0 Hz, O$\underline{C}$H$_2$ CH$_3$), 63.66 (d, *J* = 6.0 Hz, O$\underline{C}$H$_2$CH$_3$), 63.49 (d, *J* = 6.0 Hz, O$\underline{C}$H$_2$ CH$_3$), 63.40 (d, *J* = 6.0 Hz, O$\underline{C}$H$_2$ CH$_3$), 49.90 (CH$_2$), 49.17 (d, *J* = 149.1 Hz, CHP), 48.94 (d, *J* = 149.1 Hz, CHP), 48.21, 36.56, 34.54, 31.58, 30.89 (CH$_2$, NCH$_3$), 16.90 (d, *J* = 5.0 Hz, OCH$_2\underline{C}$H$_3$), 16.79 (d, *J* = 5.0 Hz, OCH$_2\underline{C}$H$_3$).^{31}P NMR (202 MHz, DMSO-d$_6$), δ: 17.63(2/3), 17.56 (1/3). LCMS: [M+H]$^+$ = 414.2. $C_{17}H_{24}N_3O_5PS$ (413.44): calcd. C 49.39, H 5.85, N 10.16, P 7.49, S 7.76; found C 49.61, H 5.85, N 10.38, P 7.30, S 7.59.

Diethyl (1-(4-methylbenzoylamino)-2-[(methyl)(2-thiocyanoethyl)amino)-2-oxoethyl)-phosphonate ***(7b)***.

Colorless oil (0.35 g, 60% yield). IR (neat, cm^{-1}), ν: 2983, 2155 (C≡N), 1643 (C=O), 1483, 1243 (P=O), 1014 (P–O–C), 969 (P–O–C), 750, 523. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 8.45-8.36 (m, 1H, NH), 7.81-7.78 (m, 2H, aromatic), 7.31-7.28 (m, 2H, aromatic), 5.70 (dd, *J* = 8.8 Hz, *J* = 19.3 Hz, 1/3H, CHP), 5.64 (dd, *J* = 8.3 Hz, *J* = 19.3 Hz, 2/3H, CHP), 4.15-4.04 (m, 4H, 2OC$\underline{H}_2$CH$_3$), 3.71-3.66 (m, 2H, CH_2), 3.45-3.38 (m, 1H, CH_2), 3.26-3.21 (m, 1H, CH_2), 3.16 (s, 2H, CH_3), 2.93 (s, 1H, CH_3), 2.36 (s, 1H, CH_3), 2.35 (s, 2H, CH_3), 1.24-1.17 (m, 6H, 2OCH$_2$C$\underline{H}_3$). ^{13}C NMR(125 MHz, DMSO-d_6), δ: 166.75 (d, *J* = 3.0 Hz, C=O), 166.52 (d, *J* = 5.0 Hz, C=O), 166.25 (d, *J* = 5.0 Hz, C=O), 165.57 (d, *J* = 3.0 Hz, C=O), 142.69, 142.29, 130.89, 130.65, 129.53, 129.41, 128.21, 128.15 (aromatic), 113.39, 113.24 (SCN), 63.65 (d, *J* = 6.0 Hz, O$\underline{C}$H$_2$ CH$_3$), 63.51 (d, *J* = 6.0 Hz, O$\underline{C}$H$_2$CH$_3$), 63.36 (d, *J* = 6.0 Hz, O$\underline{C}$H$_2$ CH$_3$), 63.26 (d, *J* = 6.0 Hz, O$\underline{C}$H$_2$ CH$_3$), 49.77 (CH_2), 48.95 (d, *J* = 149.1 Hz, CHP), 48.76 (d, *J* = 149.1 Hz, CHP), 48.07, 36.42, 34.40, 31.41, 30.75 (CH_2, NCH_3), 21.52, 21.48 (CH_3), 16.95-16.48 (m, OCH$_2$$\underline{C}H_3$). ^{31}P NMR (202 MHz, DMSO-d_6), δ: 17.65(2/3), 17.59 (1/3). LCMS: $[M+H]^+$ = 428.2. $C_{18}H_{26}N_3O_5PS$ (427.46): calcd. C 50.58, H 6.13, N 9.83, P 7.25, S 7.50; found C 50.73, H 5.85, N 10.00, P 7.38, S 7.75.

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