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EC PHARMACOLOGY AND TOXICOLOGY
Review Article

Preparation of γ-(N·methoxy)-Amino-Phosphonic Acids Dimethyl Esters as Precursors to Biomimetic Peptides

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Received: February 20, 2019; **Published:** April 02, 2019

Abstract

Phosphono-1-N-methoxyamine acids may function in potential as useful biomimetic derivatives of natural amino acids and as a source for biomimetic peptides. A synthetic approach is presented herein for the preparation of y-phosphono N-methoxy amino acids 5 and a protected dipeptide namely benzyl (2-((2-(methoxy(3-(methoxy(oxo-l6-methyl)phosphoryl)-1-phenylpropyl)amino)-2-oxoethyl)amino)-2-oxoethyl)carbamate 9. γ-amino-phosphonates may be applied in folate (antibacterial, anticancer) research. The research effort on the subject of synthesis and biological value of g-amino phosphonates is being pursued in many places. The structure of our target molecule 9 has a Weinreb type amino acid amide moiety and a γ-amino-phosphonate unit as structural building block. Although Weinreb amides (see Drawing 1 and 2 below, red section) and γ- amino-phosphonates (green section) may operate in different molecular mechanisms, the synergy between the two moieties may introduce a remarkable antimicrobial effect in 8 and 9.

Keywords: *Synthesis; Biomimetic; Peptides; Precursors; Amino phosphonates*

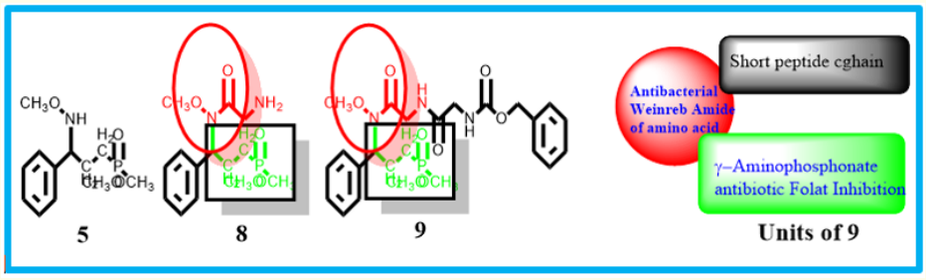

Figure 1: *Schematic design; Introducing N-Methoxy-γ-amino phosphonates into tripeptide mimics γ-amino-phosphonates (folic acid bio-synthesis inhibitor) and Weinreb amides of amino acids are antibacterial components.*

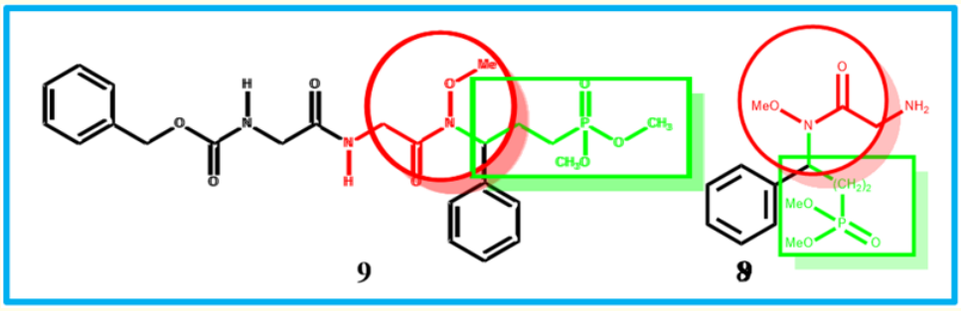

Figure 2: *The target molecules of this research.*

Introduction

The fatal nosocomial pandemic is the cause of hospital mortality mainly through incurable infections caused by new strands of bacteria that are resistant to contemporary antibiotic drugs. Peptides and their mimics have recently become one of the main topics of interest in chemistry and biochemistry, aiming at elucidating bioactive peptides and understanding their function and mode of action. Synthetic analogs, containing phosphorous and boron derivatives or organometallic units, for example, of the natural amino acids and peptide moieties are needed in the process of evaluating the structure-activity relationship (SAR) of peptides and of the corresponding peptidomimetic analogs [1-21]. Polypeptides of amphibian origin like South American tree frogs (*Cationic peptide isolated from skins of* American tropical frog Phyllomedusa Sauvage [22-25]*)* exhibit diverse biological activity and short fragments are a promising potential for novel very deserved antimicrobial drugs [26-32]. Approximately 40,000 harmful and/or lethal hospital errors occur each and every day in the US. The Hygiene at the healthcare facilities should be enhanced with more efficient antimicrobial agents, phosphonates [33-38] might be suitable materials.

However, a famous water pollutant is phosphate, water-softening mineral additives that were once widely used in laundry detergents and other cleaners. When phosphates enter waterways, they act as a fertilizer, spawning overgrowth of algae. This overabundance of aquatic plant life eventually depletes the water's oxygen supply, killing off fish and other organisms. Although many states have banned phosphates from laundry detergents and some other cleaners, they are still used in automatic dishwasher detergents. Phosphonates are similar to phosphates except that they have a carbon-phosphorous (C-P) bonding place of the carbon-oxygen-phosphorous (C-O-P) linkage. Due to their structural similarity to phosphate esters, phosphonates often act as inhibitors of enzymes due in part to the high stability of the C-P bond. In nature, bacteria play a major role in phosphonate biodegradation. The first phosphonate to be identified to occur naturally was 2-aminoethylphosphonic acid.

One of the promising approaches to combat this nosocomial pandemic is the utilizing of phosphonic acid moieties, present in many agricultural applicable agents. We have shown before that ultrashort fragments of Dermaseptin S4 are very potent antibacterial substances. The mono isopropyl-amine salt of *Glyphosate* is present as the active ingredient in the widely used herbicide Roundup®. Glyphosate and its natural product analog phosphinothricin *inhibit* the shikimate pathway of aromatic amino acid biosynthesis via the enzyme 5-enol-pyruvyl shikimate-3-phosphate (EPSP) synthase (3-phospho-shikimate-l-carboxyl vinyl-trans)- phrase [39-43]. It was reported that Interaction of the herbicide glyphosate with its target enzyme 5-enolpyruvylshikimate 3-phosphate synthase in atomic detail.

Although the phosphonic and carboxylic acid groups differ considerably with respect to shape, size, and acidity, amino phosphonic acids are considered to be structural analogs of the corresponding amino acids and the transition state [17,44-46] that mimics reversible peptide hydrolysis.

In this communication, we have pursued our effort of finding novel antibacterial agents in short peptide surrogates. For this we utilized oxime ethers, for the preparation of short peptide based on N-methoxy amide [44-48] combined with phosphonic acid moieties.

Some on the biological activity of synthetic amino phosphonates

Some phosphorous peptides display significant neurophysiological effects. Dipeptides containing phosphonic acid analogs of glycine and β-alanine are strongly antagonistic to NMDA, inhibiting NMDA-evoked responses in the pentapeptides**,** phosphonic analogs of enkephalins, exhibit analgesic activity comparable with, or stronger than, that of their opiate counterpart [49-51],to novel β-lactamase inhibitors (BLIs) bearing an electrophilic center (phosphonates, aldehydes, trifluoromethyl ketones, and boronic acids) that can covalently modify the nucleophilic catalytic serine is conceptually advancing our understanding in this field [52,53].

A large variety of chemical modifications of peptides is commonly used in this regard, such as elimination and addition of one or more amino acid residues, isosteres [54-59] to the peptide bond etc.

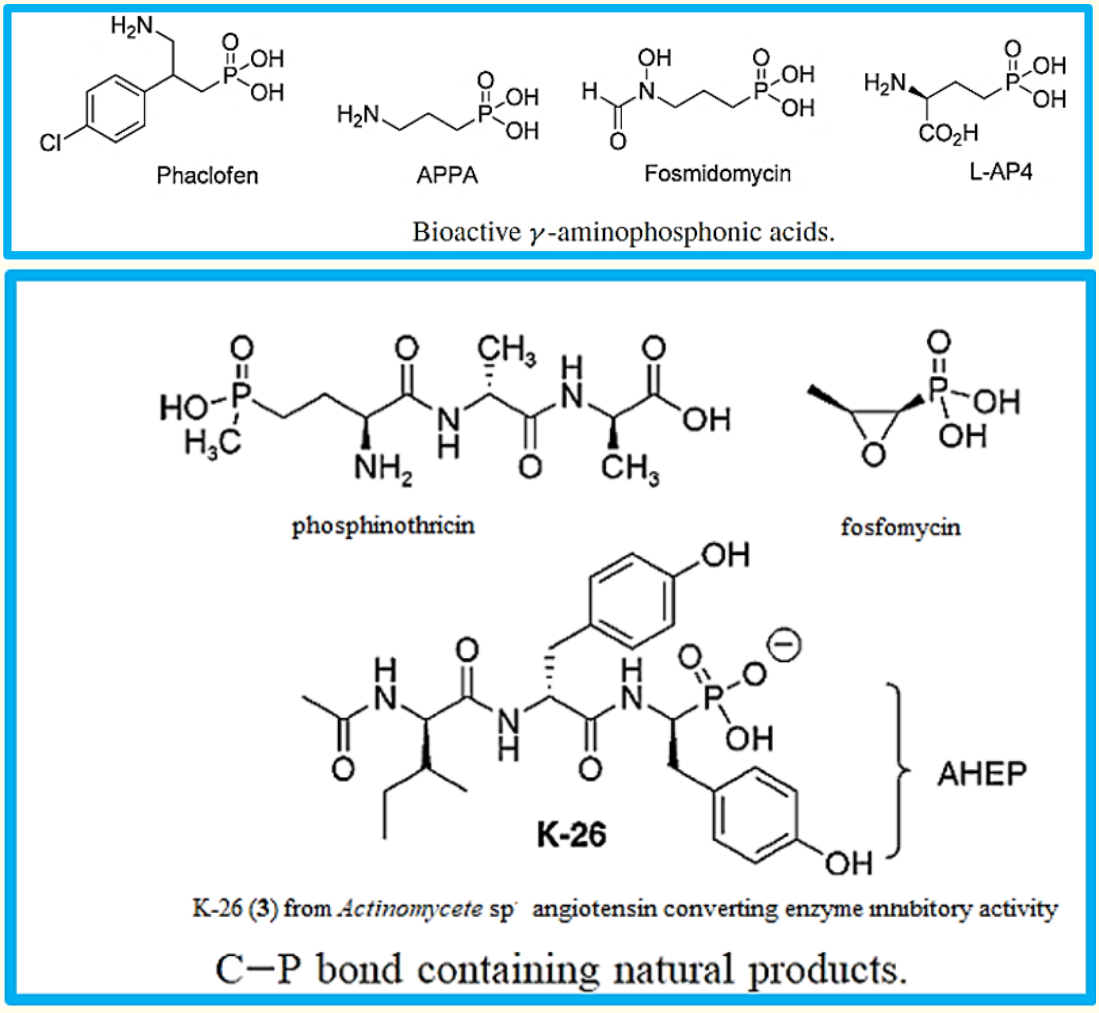

Figure 3: *Natural phosphorous based bioactive compounds.*

One significant modification that constrains peptides is the N-methylation of the nitrogen atom of the peptide amide. Many such N-methyl substituted natural peptides have been isolated from microorganisms and vegetables. Peptide-surrogates contain "unnatural" amino acids as building blocks. N-methyl peptides show antibiotic and antituhowevermor activities and immunosuppressive effects [60-63]. Such peptides were reported by Gilon and co-workers as analogs of Cholecystokinin and as N-methyl SP^3 analog. N-methylation causes a markable conformational change in the peptide mimics. It was shown that N-methylation might promote the eradiation of some bacteria [64-67]. Recent work from the Leibniz Institute of Plant Biochemistry, shows that a set of N-alkylated peptide derivatives were screened against *Aliivibrio fischeri*, but only the (*N*-methylated) natural product displayed noteworthy activity of ca. 40 μM IC50, independent of stereochemistry. The electron-donating property of the $-CH_3$ group might be considered. In such circumstance, the $-OCH_3$ unit might increase such electron donation to the amide bond [34,68-74]. N-Methoxy-N-methyl amide, popularly addressed as the Weinreb amide, has surfaced as an amide with a difference, they exhibit antimicrobial bio-activity. The Weinreb amides were subjected to in silico studies, to predict the preferred orientation and binding affinity between the molecules using scoring functions. s. Based on the minimum binding energies, antibacterial activities have been conducted for a number of the synthesized compounds. The antibacterial results of *Escherichia coli, Pseudomonas aeruginosa*, and *Staphylococcus aureus*. Based on the docking results the N-Fmoc-L-Ala-$N(OCH_3)CH_3$ and N-Fmoc-L-Phe-$N(OCH_3)CH_3$ were showing good activity in *in vitro* studies.

Herein, we report an efficient, one pot synthesis of Nα-protected amino acid/peptide acid-derived Weinreb amides employing N,N'-carbonyl diimidazole (CDI) as the activating agent. The prepared compounds were screened for in silico molecular docking studies and *in vitro* antibacterial activities. Antibacterial activity was screened by the Agar well diffusion method against three pathogenic bacterial strains, *Escherichia coli*, *Pseudomonas aeroginosa* and *Staphylococcus aureus* (one Gram +ve and two Gram -ve). This amide has served as an excellent acylating agent. Pakistani and Indian scientists report on the antibacterial activity of alanine and phenylalanine derived Weinreb amides against different bacterial strains.

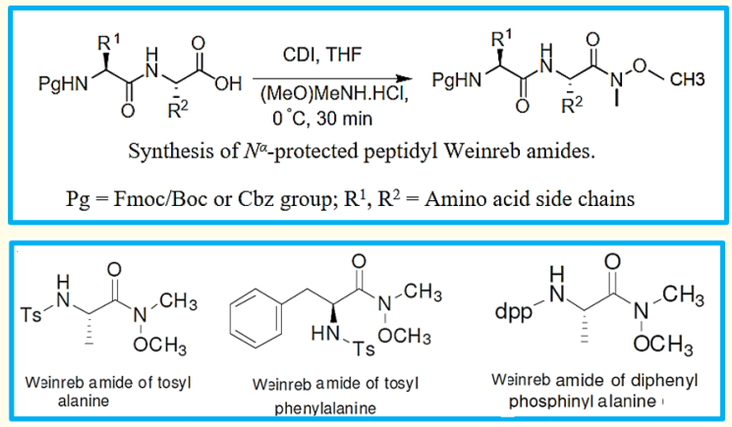

Figure 4: *Antibacterial Weinreb amides od some amino acids.*

Also, modification of peptides consists of changing the carboxylic group to its roster- a phosphonic acids [75-79] unit may enhance activity. (the α-N-substituted amino phosphonate can be prepared in a modified Kabachnik-Fields Reaction [80]). These compounds are structural analogs of amino acids in which a carboxylic moiety is replaced by phosphonic acid or related groups [81,82]. Acting as antagonists of amino acids, they inhibit enzymes involved in amino acid metabolism and thus affect the physiological activity of the cell. These effects may be extended as antibacterial agents, plant growth regulatory materials or neuromodulators. They can act as ligands, and heavy metal complexes with amino phosphonates have had medical applications investigated.

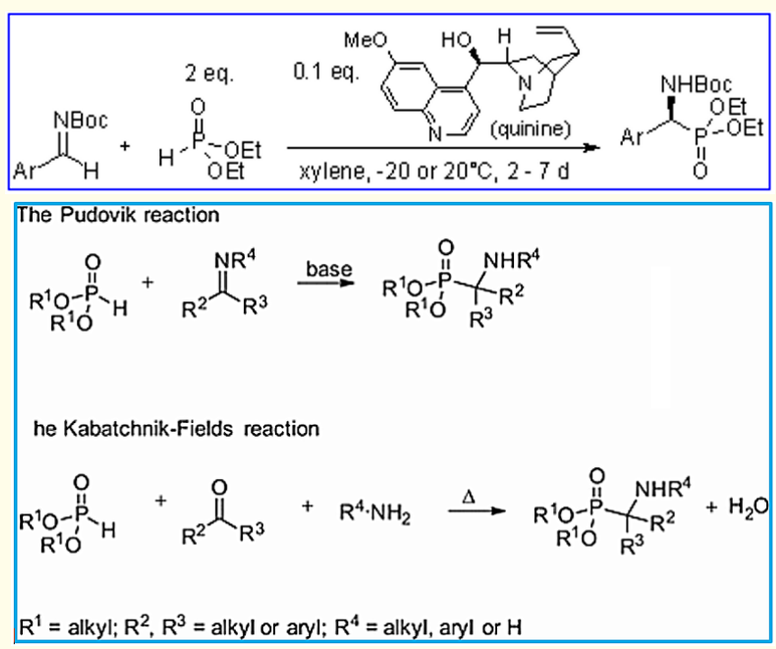

Figure 5: *Amino phosphonate synthesis by the Kabachnik-Fields and Pudovik Reactions.*

Synthesis of peptidomimetics based on γ-amino phosphonates

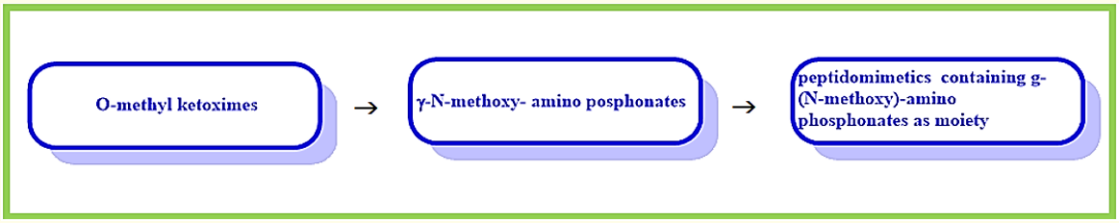

Figure 6: *Scheme 1: General strategy for the synthesis.*

Amino Phosphonic acids were used as bioactive materials [83-86] as well as analogs representing transition states of the group.

The biosynthesis of poly-γ-glutamyl peptide derivatives of folic acid and related anti-folate drugs such as the applied drug methotrexate (MTX) involves a non-ribosomal ATP-dependent reaction catalyzed by folylpolyglutamate synthetase (FPGS). Research has demonstrated that this reaction proceeds via a γ-glutamyl phosphate of reduced folate or MTX which then reacts with an incoming molecule of L-glutamate to form a new glutamyl- glutamate peptide bond.

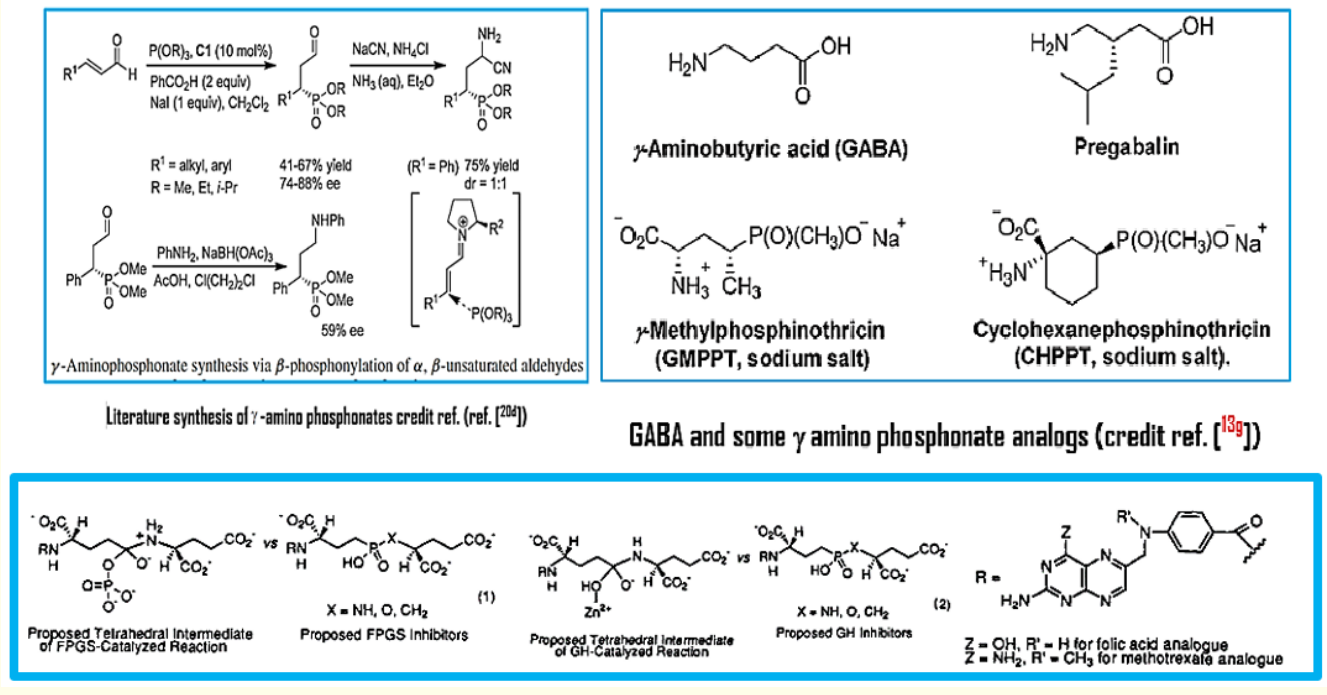

Figure 7*: γ-amino-phosphonates in research.*

Amino phosphonic acids (present in K-26, in Baclophen phosphonate analogs such as Phaclofen, CGP 54626, CGP 35348, and the alendronate, a bisphosphonate medication used to treat osteoporosis and Paget disease, bone diseases) and synthetic modifications show neurologic antibacterial, antibiotic and antitumor activities as well as the herbicides and fungicides activities [87,88]. Differential Inhibition by amino phosphonates was reported [89-91]. Gamma-amino phosphonates are reported to serve as the bio-isosteric analogs of gamma-aminobutyric acid (GABA). Gamma (γ)-Aminobutyric acid (GABA) has been shown to be an important central nervous system (CNS) neurotransmitter. The properties of amino phosphonates as transition state analogs of amino acids, and as anti-bacterial,

antifungal and anti-HIV agents, attracted considerable attention. γ-Amino phosphonic acid in particular is a bioisosteric analog of GABA (γ-aminobutyric acid). Acting as antagonists of amino acids, they inhibit enzymes involved in amino acid metabolism and thus affect the physiological activity of the cell. These effects may be extended as antibacterial, plant growth regulatory or neuromodulators, as well as analogs representing transition states of enzyme-substrate interactions. This was done with the purpose of understanding the mode of action of competitive inhibitors in biological systems. It was the purpose of the present research to synthesize γ-(N-methoxy)amino-γ-substituted phosphonic acids and to show the feasibility of using these acids as precursors for phosphonic acid-containing biomimetic peptides.

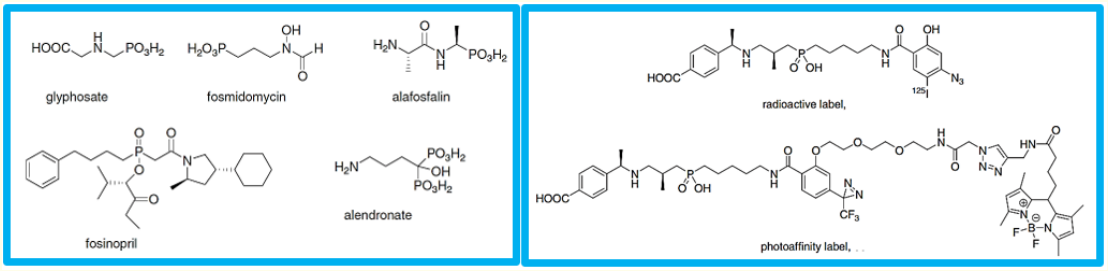

Figure 8: *Some aminophosphonated on medicinal applications.*

Results

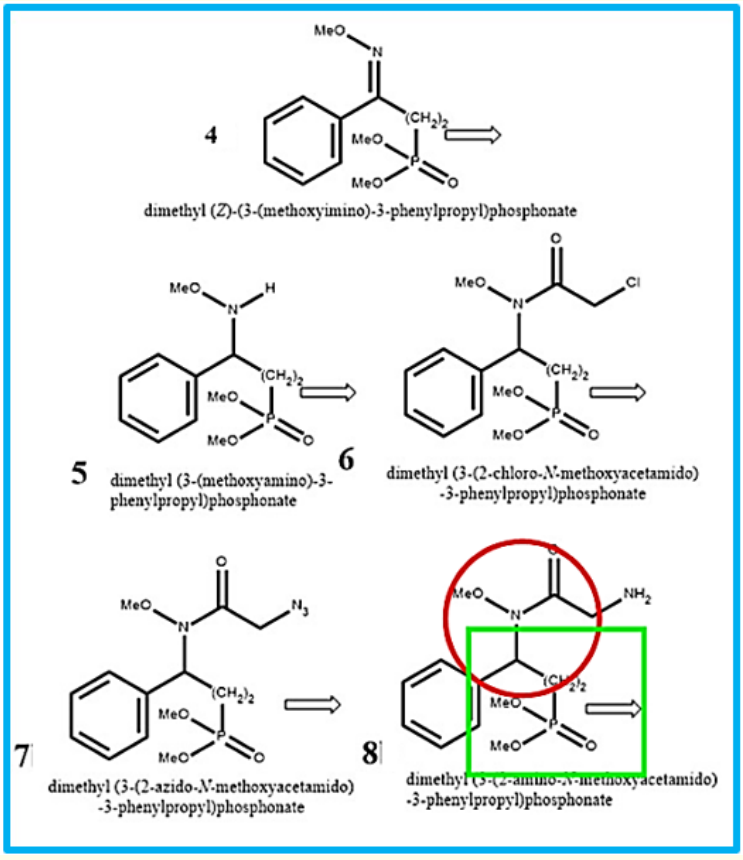

Figure 9: *Targets of synthesis and intermediates transformation of 4 to 8.*

Coupling of **8** with N-Cbz-glycine affected by DCC resulted in the derived biomimetic peptide **9**.

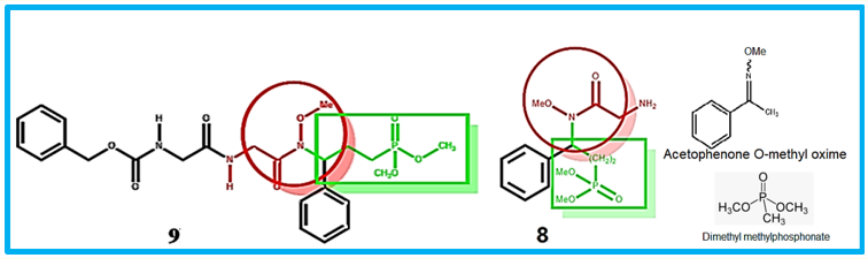

Figure 10: *Acetophenone O-methyl oxime and Dimethyl methyl phosphonate applied for the preparation of the bioactive Weinreb amides phosphonates 8 and 9.*

The synthesis of the target class of compounds, outlined in Drawing 9 is based on the chemistry of oxime ethers which was intensely studied in our laboratory [92]. The starting materials for the synthesis were oximes **l** and the ketones **la** which were converted to the corresponding oxime ethers **2** by either direct oximation using methyl hydroxylamine hydrochloride or by a two-step oximation reaction [93-95]. Subsequent α-bromination of these oxime ethers using N-Bromo succinimide [96-98].

Synthesis of 9

The starting materials for the synthesis were oxime **l** and the ketones **la** which were converted to the corresponding oxime ether **2** by either direct oximation using methyl hydroxylamine hydrochloride or by a two-step oximation reaction [99]. To yield the target class of compounds, namely the *dimethyl (3-(methoxamine)-3-arylpropyl)phosphonates* **5**.

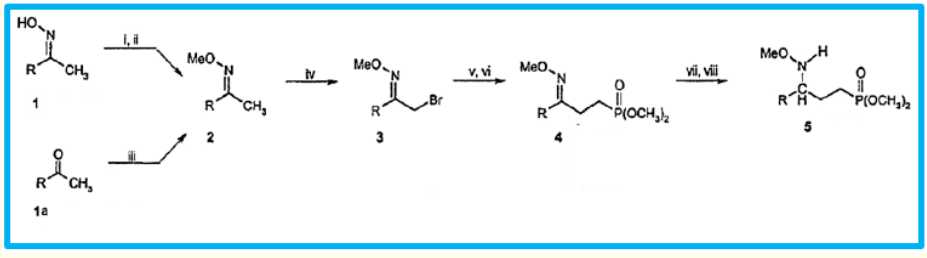

Figure 11: *Synthesis of dimethyl (3-(methoxyamino)-3-phenylpropyl)-phosphonate-arylpropyl)-phosphonates.*

The feasibility of using this new class of γ-(methoxy) amino phosphonic acids **5** as potential precursors for biomimetic peptides is demonstrated by the preparation of a derived biomimetic dipeptide - dimethyl.3-Phenyl-3(N-methoxy-N-aminoacetylation)-1-propyl phosphonate **5** (Figure 12). Attempts to affect the coupling of the substrate **6** with N-Cbz- glycine using the DCC-HOBT or BOP-Cl coupling agents were unsuccessful. This difficulty was bypassed by chloro-acetylation [100] of **6** to yield the chloro-acetyl derivative **6.** (recently this strategy was also applied to the preparation of as syn-bimane containing tripeptide surrogate agent that can cross the Blood Brain Barrier into the animal's brain from the bloodstream [101-103]. This was done by the use of the chloro-acetyl chloride and substitution of the chlorine to the azide **7** (**5 γ 6 γ 7** [104]). Reduction of the azide group of **7** with Pd-$CaC0_3$/H_2 [105] afforded the target amino derivative **8** [27,106].

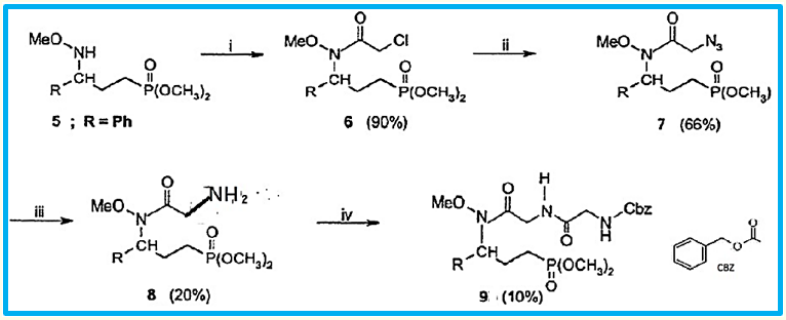

Figure 12: *Synthesis of benzyl (2-((2-((3-(dimethoxy-phosphoryl)-1-phenylpropyl) (methoxy)amino)-2-oxoethyl)amino)-2-oxoethyl) carbamate 9.*

Scheme legend: Reagents and conditions for the conversion of 5 to 8 and 9

6b, i 10% NaOH-H 0, 19% $NaCO_3$ -H 0, $ClCH_2CH_2Cl$, r.t., 30 minutes, extraction ($CH2Cl_2$); ii, NaN_3-DMF, 0°C, Sb-DMF, r.t., 3hr; iii, 7 CH_30H, $Pd/CaC0_3$ (cat.), H_2, 24 hr; iv, 8, HOBt, N-Cbz-glycine, THF, DCC, 0°C, 60 minutes, r.t., overnight.

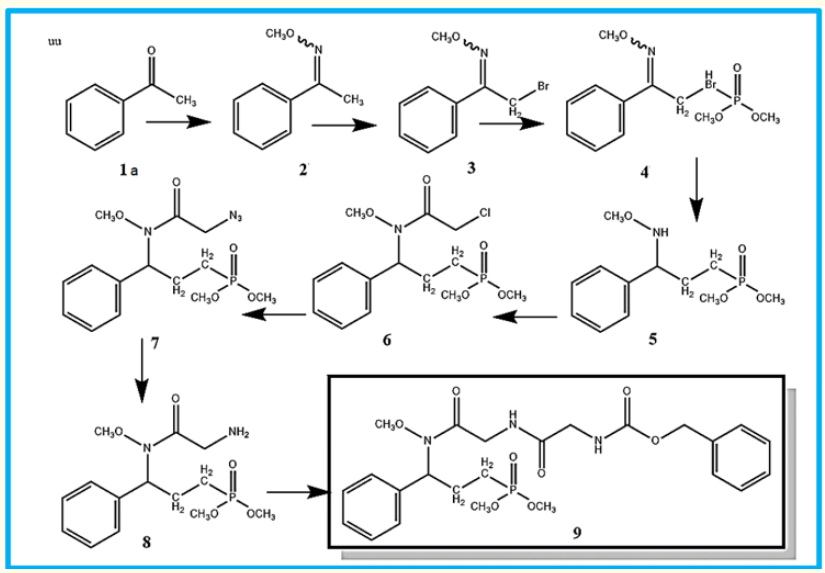

Figure 13: *Synthesis of 9 by the oxime ethers route.*

Conclusion

As our research program demanded, we continued our work towards examining a simple synthetic procedure to achieve a tripeptide surrogate for the testing of the biological feasibility for the eradication of bacteria. We have thus continued with the intermediate **4** aiming at **9** for the eradication test.

The C=N bond of the O-methyl-oxime group was reduced with various hydride agents, the best of those was sodium cyanoborohydride in acetic acid to yield **5**.

The reaction with chlorine acetyl-choline [107] afforded **6**. Reaction with NaN_3 in DMP gave the azide **7** and hydrogenation gave the amino compound **8**. Subsequently, the peptide bond formation afforded **9.**

Phosphonates are a class of compounds that are utilized in the agriculture-intensive farming methods as herbicides, fungicides as for example [3,4].

Biological activity

In our project we were on the quest for an antimicrobial agent. In preliminary testing, we examined our compounds towards the eradication of bacteria (E. Coli G- and Staph. Aureus G+) of the phosphonates **5**, **6** and **7,** but practically biological activity was observed in the eradication experiments only in very high molar concentrations.

In these compounds, the only moiety that is known as an antimicrobial entity is the phosphonate unit.

Although the compounds **8** as well as **9** contain two different antibacterial pharmacophores (see figure 1 above). The Weinreb amide (red) of the amino acid glycine and the γ-phosphonate moiety (green). The testing for antibacterial activity was carried out on *E. coli* (Gram-) and *Staph. aureus* (Gram+) bacteria are exhibiting only moderate (10^{-3} molar range activity) with similar MIC values [108] results that do not indicate selectivity.

Our preliminary tests show that **8** and **9** exhibits very similar antibacterial activity, hinting that the combination of the two pharmacophores might be needed to eradicate the microbes. That may suggest that the additional CBZ- protected glycine unit in **9** might become superfluous regarding the antimicrobial activity. In addition, some amino phosphonates [109,110], for instance benzothiazole phosphonate derivatives, also possess the ability to cross the blood-brain barrier *in vivo* mice studies and thus hold great potential for inner brain therapy. It is reported that antibiotic-induced perturbations in gut microbial diversity influences neuro-inflammation and amyloidosis in a murine model of Alzheimer's disease [111-114]. The combat with the into the brain infiltrating Gut Microbes might be a new focus for Alzheimer's therapy.

However, the Weinreb amide and the γ-amino- phosphonate units are needed for the eradication of the bacteria. Although a weak antibacterial activity was detected, we concluded our project with this result.

Experimental Section

General

^{1}H-NMR and 13C-NMR spectra were recorded, unless otherwise stated, with a Bruker WH 360 instrument in $CDCI_3$; the chemical shifts are reported in δ values relative to TMS (tetramethylsilane) as an internal standard. - Infrared spectra were recorded with a Perkin-Elmer 251 instruments.

Quadrupole mass spectrometers Varian MAT 44 (ionization energy 63 eV) and a double focus mass spectrometer Varian 311 A (ionization energy 100 eV) were used for mass spectrometry.

The solvents were purified by distillation over potassium or P_2O_5.

Liquid materials were distilled in a "kugelrohr" apparatus. Simple multi-bore columns for superior fractionation [115] were used for the separation of products mixtures.

Kieselgel60 (Merck; no. 1097) was used for column chromatography. HP-1100 HPLC model was used with a diode array detector. The level of purity of the materials at each stage was established on the device. Reverse phase application of Hypersil, of C-8 is Kelowna column. The mobile phase was automatically mixed water gradient (O% - 70%) in acetonitrile.

Synthesis of the O-methyl oximes 2

A generalp for the preparation of O-alkyloximes from ketones or their oximes (Methods A and B)

Method A

0.1 M solution of the ketone in 50 ml ethanol/water (1:1) is combined with an equimolar amount of O-alkyl hydroxylamine hydrochloride and an equimolar amount of Na_2C0_3 and refluxed for 3h. The product is extracted with dichloromethane and dried over $MgS0_4$. The oxime ethers are distilled or chromatographed [34]. The O-methyl oximes of acetophenone **3** were prepared and were comparable with the literature data.

Method B

0.1 M of a ketoxime was dissolved in 100 ml water free THF containing an equimolar amount of NaOH. The solution is kept at 25°C and an equimolar amount of the alkylating agent (dimethyl sulfate) is added dropwise over 1h. The solution is brought to pH 10 with a few drops of aqueous NaOH, extracted with ether, and dried over $MgS0_4$. Evaporation of the solvent furnishes the crude products, which are distilled or chromatographed [34].

A general procedure for the bromination of the O-alkyl oximes 3

Use of N-Bromo succinimide

The procedure for the preparation of α-Bromo-acetophenone oxime O-methyl ether is a representative one. A mixture of oxime O-methyl ether (0.2 mol) and 35.6g (0.2 mol) of N-Bromo succinimide in 80 ml of carbon tetrachloride was heated at reflux with occasional shaking and irradiated with a 275-W sunlamp (about 10 cm. away). Vigorous boiling ensued with the development of - In about 15 minutes, an intense reddish-brown color and, after an additional 10 minutes, the color suddenly disappeared and the boiling subsided.

The reaction mixture was cooled and filtered with suction, and the residue was washed with a small amount of carbon tetrachloride. The filtrate was combined with the washings and then shaken with 50 ml of a saturated solution of sodium bicarbonate. The organic layer was dried (Na_2S0_4) and distilled under diminished pressure to remove the solvent. The residual yellow liquid was then distilled twice under reduced pressure to yield 26.2g (72.8%) of **3**.

Bromination of the O-alkyloxime 2 *via* the lithim salt

Use of n-BuLi and molecular bromine

Bromination of methyl-aryl ketoxime ethers, general procedure

A cold (-65°C) solution of n-Butyllithium in n-hexane (10 ml, 1.2 M) was added over one min. under a dry nitrogen atmosphere to a stirred solution of the *methyl-aryl ketoxime ethers* (10 mmol.) in tetrahydrofuran (THF) (20 ml) and dry n-hexane (15 ml) at -65°C and the temperature was then held for 10 minutes. The initiated O-methyl oxime derivative was added over 30 minutes to Bromine (20 mmol) dissolved in THF (30 ml) at -65^{0}C and the temperature was then held for 5 more minutes. The solution was discolored by adding water (20 ml) and a saturated sodium thiosulfate solution (10 ml), extracted with ether and the combined organic solutions were washed again with sodium thiosulfate, dried over $MgS0_4$ and concentrated under vacuum. The α-bromo-O-methyl oxime **2** was isolated by "kugelrohr" distillation to give a colorless oil of **3**; yield 78-85%, bp 75°C/0.5 mmHg.

The reaction of the lithium salt of dimethyl methylphosphonate with a-bromo O-methyl oximes-Procedure for the Preparation of dimethyl (Z)-(3-(methoxy imino)-3 -aryl propyl)phosphonate 4

A precooled (-78°C) solution of n-BuLi in n-hexane (1.6 M, 30 mL. 48mmol.) was added under dry nitrogen to a stirred solution of an equivalent amount of dimethyl methyl phosphonate (48 mmol, 5.2 gr) in 80 ml dry tetrahydrofuran (THF) at -78°C during 15 minutes. After an additional 5 minutes at -78°C, a solution of the α-Bromo-O-methyl-oximes **3** (48 mmol, 10.8 gr.) respectively, in 20 mL dry THF was introduced dropwise over 15 minutes, and the reaction was allowed to continue for another 30 minutes at -78°C and then another 30 minutes at room temp. 20 ml of water was added, and the mixture was extracted with three 20-ml portions of diethyl ether, then with 20

ml of CH_2Cl_2. The combined extracts were dried with anhydrous $MgS0_4$, and the residue which was obtained after removal of the solvent was chromatographed [34] using ligroin-chloroform (9: 1) to give the dimethyl (Z)-(3-(methoxy-imino)-3-arylpropyl) phosphonate **4,** 8.12gr, (60%) yield as a colorless liquid.

Reduction [116-118] of the C=N bond - Synthesis of the amino compounds 5 from the O-alkyloximes 4

The O-alkyl oxime ethers **4** (0.01 Mol) were dissolved in acetic acid (195 ml) and cooled to -10°C. Sodium cyanoborohydride (1.25g, 2 eq) was added to the yellow solution in one portion. After stirring for 15 minutes at -10°C, the mixture was diluted with H_2O (200 ml), made basic with saturated Na_2CO_3 (aq.), and extracted with EtOAc (2 × 480 ml). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and evaporated to dryness in vacuo. The residue was chromatographed [34] (7:3 petroleum ether: EtOAc) to provide **5** (3.5g, 98% yield) as white crystalline solid. HPLC: λ260-98.8% purity.

The synthesis of bioactive compounds **8** and **9** applying the amino phosphonate **5**.

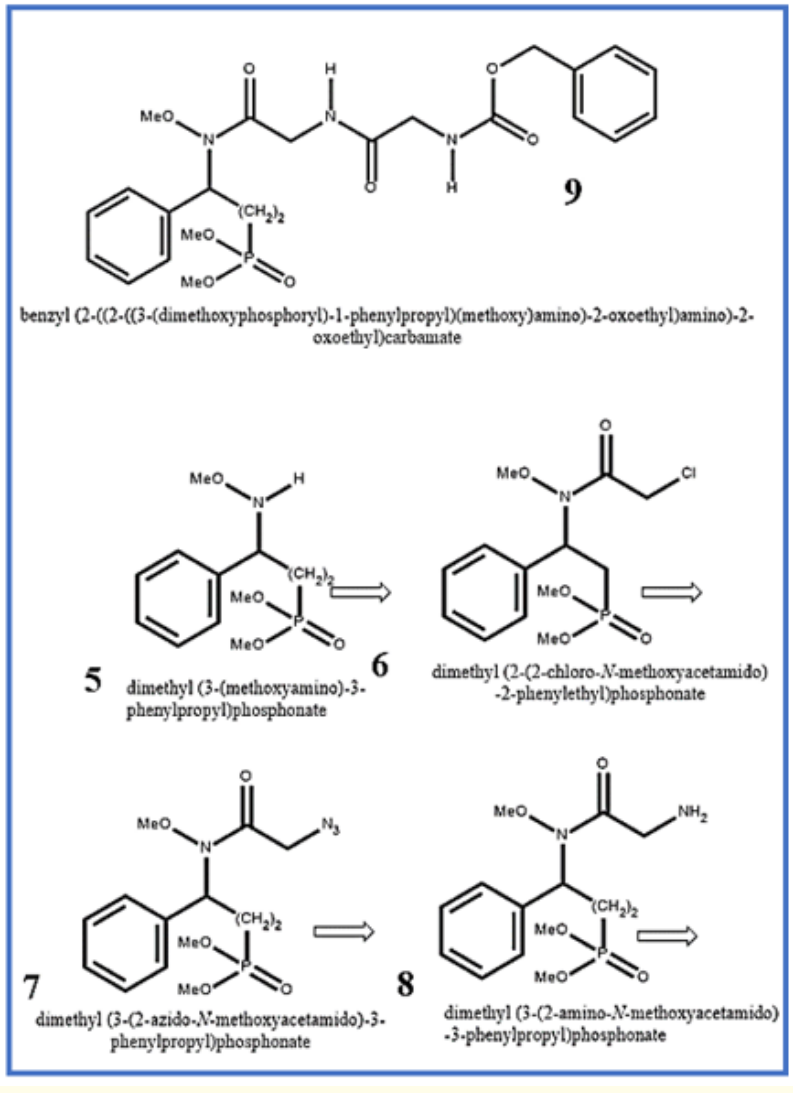

Figure 14: *Synthesis of 8 from 5.*

Synthesis of 6

A solution of chloro-acetyl chloride (8.4 ml, 11.93g, 1.06 eq) in toluene (20 ml) was added dropwise at 10°C during 30 minutes to a solution of 270 mg (1 mM) 2- dimethyl (3-(methoxyamine)-3-phenyl-propyl) phosphonate **5** in dry toluene (200 ml). The reaction mixture was then stirred at room temperature for 3h. The resulting mixture was evaporated to dryness. The crude product was crystallized by stirring in 96% ethanol (100 ml) at room temperature for 20h. The crystals were separated by filtration, washed with 96% ethanol (3 × 10 ml), and dried at 50°C for 20h to yield **6** (230 mg 66% yield) as colorless crystals. HPLC: λ260-99%purity. M.p: 120°C. for physical data see table 1 below

compound#	IR (KBr)	^{1}H-NMR	^{13}C-NMR, δ^{31}P	Analysis	MASS
4	1050, 1170, 1250, 1620 and 2950 cm·';	δH: 2.02 (2H, m), 2.97 (2H, m), 3.72-3.78 (6H, d,J=10.8), 3.99 (3H, s), 7.37 (3H, m), 7.62 (2H, m);	δc: 19.3, 19.9-22.8, 52.15, 61.9, 125.9, 128.4, 129.1, 134.5, 156.2; δp: 33.49;	Calcd for: $C_{12}H_{18}NO_4P$ C, 53.14; H, 6.69; N, 5.16; O, 23.59; P, 11.42 Found C 53.45; H,6.87; N, 5,50, P, 11.24	m/z: 271
5	3600,2203,1603, 1475,1405,1380, 1170,1065,910	δH: L57 (2H, m), 3.47 (3H, s), 3.7 (6H, d, J=10.8), 3.69 (2H, m), 3.9 (lH, m), 7.28 (5H, m);	δc: 21.9, 26.47, 52.2, 62.56, 65.7, 127.6, 127.9, 128.6; dp: 34.17	Calcd for: $C_{12}H_{20}NO_4P$ C, 52.74; H, 7.38; N, 5.13; O, 23.42; P, 11.33 Found C, 52.55; H7.54; N 5.45, P11.07	m/z: 274
6	1050, 1200, 1700 and 3000 cm·	δH 1.79 (2H, m), 2.41 (2H, m), 3.49 {3H, s), 3.76 (6H, d, J=8.I), 4.08 (2H, s), 5.46 (1 H, m), 7.327.43 (5H, m);	δc: 22.34, 30.36, 41.63, 53.44, 61.59, 65.89, 127.0, 128.9, 129.4, 169.0; δp: 34.615	Calcd for: $C_{14}H_{21}ClNO_5P$ C, 48.08; H, 6.05; Cl, 10.14; N, 4.00; O, 22.87; P, 8.86 Found C, 48.23; H, 5.98; Cl, 10,45, N, 3.76; P8.65	m/z: 318;
7	3250-2203,1050, 1700, 2200, 3000 and 3400	δH: 1.49 (2H, m), 2.52 (2H, m), 3.46 (3H, s), 3.77 (6H, d, J=8.2), 5.46 (l H, m), 6.46 (2H, s), 7.44-7.66 (5H, rn);	δc: 22.2, 30.5, 53.2, 61.6, 65.7, 128.1, 129.1, 129.4, 130.1, 139.5, 168; δp: 34.56;	Calcd for: $C_{14}H_{21}N_4O_5P$ C, 50.91; H, 7.02; N, 8.48; O, 24.22; P, 9.38 Found: C, 51.o3; H, 7.34; N, 8.40; P9/17	m/z 356
8	3250-2203 1050, 1750 and 3200-4000 cm·	H 1.48 (2H, m), 2.52 (2H, m), 3.43 (3H, s), 2.78 (6H, d, J=8.1), 5.43 (lH, m), 6.45 (2H, s), 7.43-7.65 (5H, m);	δc: 22.2, 30.45, 53.1, 61.6, 65.7, 128.1, 129.1, 129.3, 130.0, 139.4, 168; /δp: 34.6.	Calcd for:$C_{14}H_{23}N_2O_5P$ C, 50.91; H, 7.02; N, 8.48; O, 24.22; P, 9.38 Found: C, 51.09.; H,6.78; N, 8.32; P, 9.45	m/z=330
9	3250-2203,1600, 1575,1400,1210, 1160,1055,915	δH. 1.08-1.90 (4H, m), 3.32-3.47 (2H, m), 4.06-4.16 (12H, m), 5.13 (2H, d), 5.44-5.67 (4H, m), 7.18-7.84 (lOH, m);	δc: 23.9, 41.3, 48.24, 54.9, 64.05, 7C 110.01, 116.45, 124.6, 125.3, 126.57, 126.9, 127.3, 128.9, 131.1, 173.95; δx: 34.6	Calcd for $C_{24}H_{32}N_3O_8P$: C, 55.28; H, 6.19; N, 8.06; O, 24.54; P, 5.94 Found:C, 55.03, H, 6.42, N, 8.33, P, 6.23	m/z=521

Table 1: *Physical Data for the sequence of compounds 4 γ 9.*

^{1}H-NMR, ^{13}C-NMR, ^{31}P-NMR, IR

MS spectra and elemental analysis.

Synthesis of 7

A solution of **6** (0.567gr, 1.62 mmol) in dry DMF (80 ml) was added to a heterogeneous mixture of sodium azide (0.316gr, 4.86 mmol) in dry DMF (22 ml) at 0°C. The mixture was stirred for 3 hr and water was added to it. The aqueous phase was extracted with ether, the ether extracts were washed with an aqueous sodium chloride solution. The product - the N-acetylazido derivative **7** was recovered from the ethereal extracts as a solid in a yield of 0.38lgr (66%). For physical data see table 1 below.

Synthesis of 8

A mixture of Pd/$CaCO_3$ (catalytic amount) and a solution of **7** in methanol (5 ml) was hydrogenated for 2 hr at room temperature and atmospheric pressure using Pd over $CaCO_3$ 5% as a catalyst. The reaction mixture was filtered through celite. The product - the corresponding N-acetyl-amine derivative, *dimethyl (3-(2-amino-N-methoxy acetamido)-3-phenylpropyl)phosphonate,* **8**. Was recovered from the filtrate, was obtained as a yellow oil (2 gr, 20%). All new compounds gave satisfactorily. For physical data see table 1 below.

Synthesis of 9

Mixed Anhydride Coupling [119-126] benzyl (2-((2-((3-(dimethoxyphosphoryl)-1-phenylpropyl)(methoxy)amino)-2-oxoethyl) amino)-2-oxoethyl)carbamate **9.**

Procedure a: Peptide bond formation by the Mixed anhydride [121,122] procedure

A solution of N-CBZ glycine (1.25 mmol) in CH_2Cl_2 (5 mL) was added to ethyl chloroformate (142 mg, 1.31 mmol) at-5°C, then triethylamine (132 mg, 1.31 mmol) was added. The reaction mixture was stirred for 15 minutes at -5°C, a solution of 10 (300 mg, 1.14 mmol) in CH_2Cl_2 (5 mL) was then added. The mixture was stirred overnight at ambient temperature, then ethyl ether (75 mL) was added, the organic solution washed with saturated Na_2CO_3 (25 mL · 2), saturated NaCl (25 mL), and dried over Na_2SO_4. After evaporation of the solvent in vaccuo, the remaining crude product was purified by chromatography with ether-MeOH (10:2) to afford 229 mg (49%) of product **9**.

Preparation of a solution of ((benzyloxy)carbonyl)glycine

Glycine (1.25 mmol) in CH_2Cl_2 (5 mL) was added to ethyl chloroformate (142 mg, 1.31 mmol) at -5°C, then triethylamine (132 mg, 1.31 mmol) was added. The reaction mixture was stirred for 15min at -5°C, then a solution of CBZ-Cl (1.14 mmol) in (5 mL) was added. The mixture was stirred overnight at ambient temperature, then ethyl ether (75 mL) was added, washed with saturated Na_2CO_3 (25 mL), saturated NaCl (25 mL), and dried over Na_2SO_4. After evaporation of the solvent in vacuo, the crude product was purified by chromatography with ether-MeOH (10:2) to afford after chromatography [28] 229 mg (49%) of **9** as a colorless oil.

Coupling of 8 with CBZ glycine using isobutyl-chloroformate as coupling agent

Preparation of benzyl (2-((2-((3-(dimethoxyphosphoryl)-1-phenylpropyl)(methoxy)amino)-2-oxoethyl)amino)-2-oxoethyl) carbamate. Mixed anhydride procedure. Using CBZ glycine.

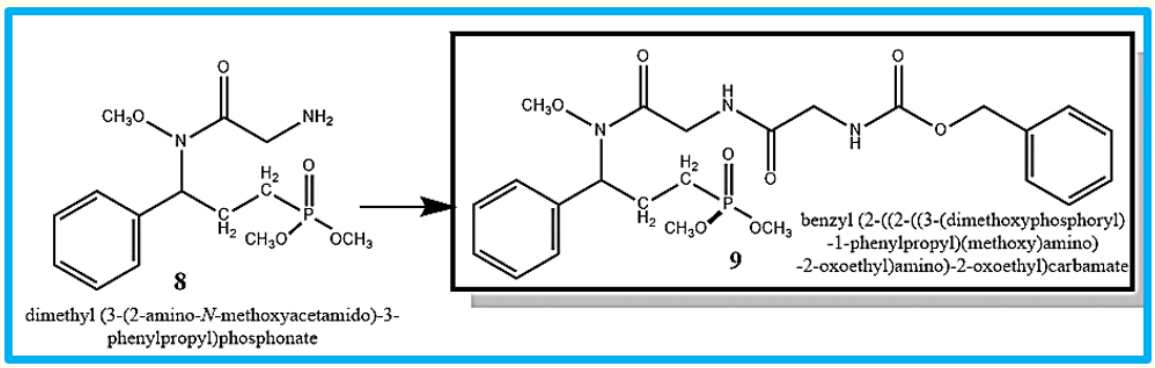

Figure 15

Procedure 2

To a stirred -12°C solution of CBZ glycine (0.25 mmol) in anhydrous tetrahydrofuran (3 mL) were added N-methyl morpholine (28 µ, 0.25 mmol) and isobutyl-chloroformate (32 µL, 0.25 mmol) sequentially. After 3 min, a -12 °C solution of **8** in anhydrous tetrahydrofuran (3 mL) was added. Ten minutes later, the mixture was allowed to warm to room temperature for 2 h, at which time the solvent was evaporated, and the resulting residue was partitioned between ethyl acetate (20 mL) and saturated $NaHCO_3$ (5 mL). The organic phase was washed sequentially with 0.1 M H_3P0_4 (5 mL) and brine (5 mL). Drying (Na_2S0_4) and evaporating provided crude material, which was chromatographed on silica gel (dichloromethane/methanol, 98:2) [28] to give 51 mg (39%) of the desired compound **9** as a gum: see data in following table 1.

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