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The nomenclature of 1-aminoalkylphosphonic acids and derivatives: evolution of the code system

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The approach for the unification of published proposals for the nomenclature and abbreviations of aminoalkylphosphonic acids and their derivatives is presented. Their modification was made on the basis of the IUPAC–IUB rules concerning the nomenclature and code system of proteinogenic amino acids. Our present proposal formulates the supplementary code and nomenclature system allowing unambiguous description of phosphonic analogs of proteinogenic amino acids, their analogs, homologs, metabolites, and derivatives including phosphonopeptides.

Key words: aminoalkylphosphonic acids, aminoalkylphosphonates, phosphonopeptides, nomenclature, code system

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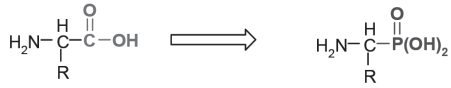
INTRODUCTION

Aminophosphonic acids (AA^P) as structural analogs of protein amino acids (AA^C) are extremely important antimetabolites which compete with their carboxylic counterparts for the active sites of enzymes and other cell receptors (Kafarski & Mastalerz, 1984; Kukhar & Hudson, 2000; Kafarski & Lejczak, 2001).

Rapid development of chemistry of 1-aminoalkylphosphonic acids (AA^P) which took place in the 1970–1980 period (Kafarski & Mastalerz, 1984; Kafarski *et al.*, 1985; Kukhar & Hudson, 2000; Kudzin 2005; Lejczak & Kafarski, 2009; Orsini *et al.*, 2010; Kudzin *et al.*, 2011) — AA^P were the subject of more than 6000 papers published until 2001 (Kafarski & Lejczak, 2001) — generated a need for an update of the IUPAC–IUB nomenclature and code system (IUPAC–IUB, 1976–8), elaborated in the years 1976–1978 for phosphono–organics of biochemical importance (Table 1).

The first attempt for codification of aminophosphonic acids and their *N*-aminoacyl derivatives, namely P-terminal phosphonopeptides, was made as early as 1978 [L-Ala(P); L-Ala-L-Ala(P) (Allen *et al.*, 1978)]. This attempt, based on the structural analogy of amino acids (2-aminoalkanoic acids; $AA^{(C)}$) and amino-phosphonic acids (1-aminoalkylphosphonic acids; AA^P), adapted the IUPAC rules for the nomenclature and code system of proteinogenic amino acids. The code, proposed by Allen *et al.* (1978), allows for the differentiation between an amino acid and aminophosphonic acid, both alone and also as constituents of phosphonopeptides, e.g. Ala *vs.* Ala(P) (Table 2).

As a matter of fact, the substitution of the carboxylic function in an amino acid structure by the phosphonic function ($AA^{(C)} \rightarrow AA^P$) affords its phosphonic analog (Renaud & Seebach, 1986; Seebach *et al.*, 1989; Zecchini *et al.,* 1989; Corcoran & Green, 1990; Gerber & Seebach, 1991; Kaname *et al.*, 2001; Osapay *et al.,* 1987).

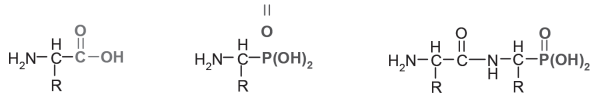


$AA^{(C)}$ AA^P

As a consequence of this fact, the substitution of long formal IUPAC names of 1-aminoalkylphosphonic acids, by short trivial names, derived from the amino acids nomenclature, was proposed. This approach expressed the structural analogy of aminophosphonic acids AA^P to their carboxylic analogs $AA^{(C)}$, and was achieved by the addition of the "*phosphono"* prefix to the trivial names of amino acids (e.g., the phosphonic analog of alanine was named *phosphono*-alanine).

Thus, in 1980–1981 names with the prefix "phosphono" — phosphonohomocystine $(Hcys^P)_2$, phosphono-*S*-alkyl-homocysteine ($RSHcys^P$), and phoshonocystine $(Cys^P)_2$ — appeared in the literature (Kudzin & Stec, 1980; Kudzin, 1981). After these reports, the names of aminoalkylphosphonic acids with the *phosphono* prefix became more frequently used. The illustration of the evolution in aminophosphonate code and nomenclature, which took place during the last decades, is presented in Tables 2–4.

Modification of these proposals according to the IUPAC–IUB rules (IUPAC–IUB, 1984) allowed for the



$AA^{(C)}$ AA^P $AA\text{-}AA^P$

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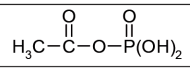
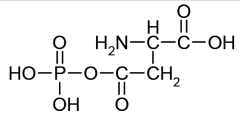
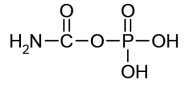
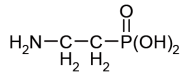
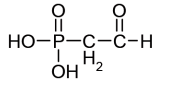
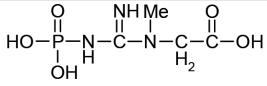
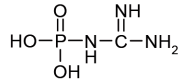
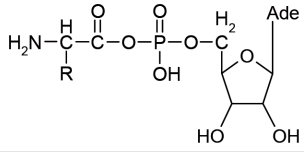
Abbreviations: AA^P, 1-aminoalkylphosphonic acids; AA^C, 2-aminoalkanoic acids

Table 1. Names and abbreviations of some phosphorus-containing compounds of biochemical importance according to IUPAC-IUB rules (IUPAC-IUB, 1978)

No.	Structure	Name	Abbrev.
1		Acetyl phosphate	Ac-P
2		β-Aspartyl phosphate	Asp(βP)
3		Carbamoyl phosphate	Cbm-P
4		(2-Aminoethyl)-phosphonic acid	
5		(2-Oxoethyl)-phosphonic acid	P-CH_2CHO
6		Phosphocreatine	P-creatine
7		Phospho-guanidine	P-guanidine
8		Aminoacyl adenylate [Jakubowski 1978, 1980, 1983, 1997]	AMP-Ser; Ser-P-Ado

formulation of the supplementary code and nomenclature system for phosphonic analogs of proteinogenic amino acids, and their analogs, homologs, metabolites, and derivatives, including phosphonopeptides. The guiding principles for this code and nomenclature system proposal are delineated in Tables 5–14.

PROPOSED NOMENCLATURE

Aliphatic Aminophosphonic Acids

Acyclic Aminophosphonic Acids

The fully systematic forms for acyclic aminophosphonic acids are derived from corresponding alkylphosphonic acids in which carbon linked to phosphorus atom is numbered as C1 or Cα (Table 5). A heteroatom has the same number as the carbon atom to which it is attached, e.g. N-1 is on C-1, N-5 is on C-5, etc.

Phosphonic Analog of Proline

The carbon atoms in prolines, both in carboxylic as well as phosphonic, are numbered as in pyrrolidine, the nitrogen atom being numbered N-1, and proceeding towards the carboxyl or the phosphonic group (Table 6).

Aromatic Aminophosphonic Acids

The carbon atoms in aromatic rings of the phosphonic analogs of phenylalanine, tyrosine and/or tryptophan can be numbered as in systematic nomenclature, with 1' (or 3' for tryptophan), designating the carbon atom bearing the aliphatic chain. The carbon atoms of this chain can be designated with C1 or Cα (for the carbon atom attached to the amino and phosphonic groups) and C2 or Cβ for the adjacent atom (the atom attached to the ring system) (Table 7).

Use of the Prefix 'Homo' and 'Nor'

An α-amino acid that is similar to one of the common ones, but that contains one more methylene group in the carbon chain, may be named by adding prefix 'homo' to the name of that common amino acid. '*Homo*' in the sense of a higher homologue is commonly used for homoserine and homocysteine.

The prefix 'nor' in the names 'norvaline' and 'norleucine' presents amino acidic isomers with not branched (normal) carbon chain. Both of these prefixes can be easily adapted for the nomenclature of aminophosphonates (Table 8 and 9).

Configuration at the α-Carbon Atom

This is usually described using the Fischer–Rosanoff convention (D- and L-) or Cahn-Ingold-Prelog (*R*- and *S*-) convention, in which L-α-amino acids, both the carboxyl (IUPAC CNOC, 1976) as well as the phosphonic forms (Dhavan & Redmore, 1987), are represented by the structures illustrated in Table 10.

These illustrate that L-amino acids and L-aminophosphonic acids, due to the order of preference:
CO_2H<**N**H_2<**P**O_3H_2,

exhibit different RS configurations. Thus, the L-configuration of amino acids ($AA^{(C)}$), nearly always corresponds to *S* (with the exception of L-cysteine), whereas the L-configuration of aminophosphonic acids (AA^{P}), always correspond to *R*.

The nomenclature "*allo*" and "*threo*" and also *cis* and *trans* have been applied in a similar way for the diastereoisomers of amino acids (threonines or prolines) and aminophosphonic acids (phosphonic analogs of threonine) (Bongini *et al.*, 1996).

Optical Rotation

The indication of the direction of rotation of plane polarized light (specified wavelength in a specified solvent), can be done with a 'plus' or 'minus' sign in parenthesis, e.g. (+)-alanine or (+)-phosphonoalanine [D-(+)-1-Aminoethylphosphonic acid; (*S*)-(+)-1-aminoethylphosphonic acid]. Subsequently, a racemic amino acid may be indicated by (±), e.g. (±)-leucine or (±)-phosphonoleucine.

SYMBOLISM — GENERAL CONSIDERATIONS ON THE THREE-LETTER SYMBOLS

The trivial name for aminophosphonic acids can be derived from common names of their carboxylic analogs (e.g., aminomethylphosphonic acid *vs.* glycine), modified

Table 2. Applied names and abbreviations for phosphonic analogs of proteinogenic amino acids and their metabolites and/or homologs with phospho or related prefix (phosphono or phospha)

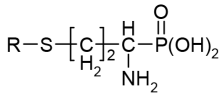
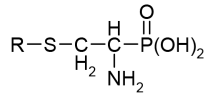
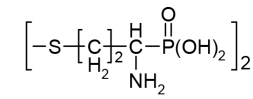
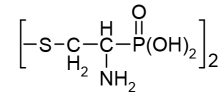
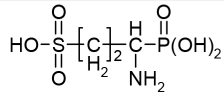
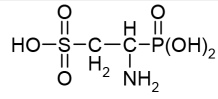
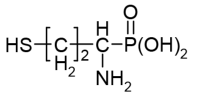
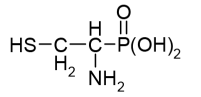
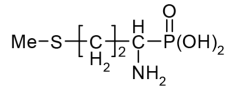
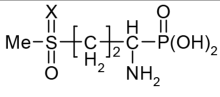
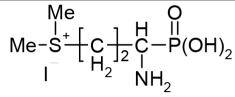
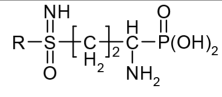
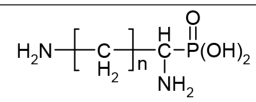
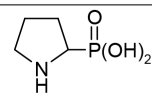
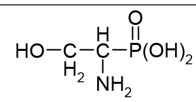
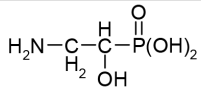
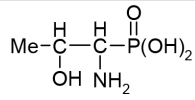
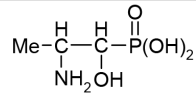
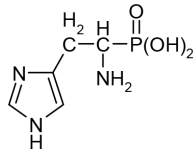
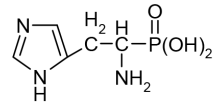
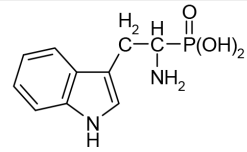
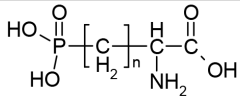
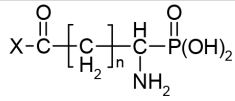
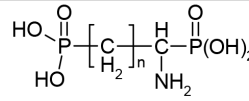
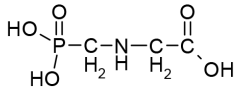
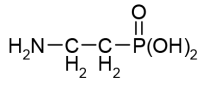
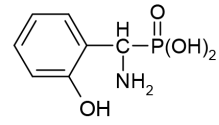
Structure			
Name	*Phosphohomocysteine derivatives* [Kudzin & Stec, 1980]	*Phosphocysteine derivatives* [Kudzin, 1981]	*Phosphohomocystine* [Kudzin & Stec, 1980; Tam *et al.*, 1982]
Abbrev.	RHcys^{P}: Met^{P}; Eth^{P} [Kudzin, 2005]	RCys^{P}: MCys^{P}; Etcys^{P} [Kudzin, 2005]	[Hcys^{P}]$_2$ [Kudzin, 2005]
Structure			
Name	*Phosphocystine* [Kudzin, 1981]	*Phosphonohomo-cysteic acid* [Kudzin *et al.*, 2005b]	*Phosphonocysteic acid* [Kudzin *et al.*, 2005b]
Abbrev.	[Cys^{P}]$_2$ [Kudzin, 2005]	Hcys^{P}A [Kudzin *et al.*, 2005b]	Cys^{P}A [Kudzin *et al.*, 2005b]
Structure			
Name	*Phosphohomocysteine* [Kudzin & Stec, 1983]; *Phosphonohomocysteine* [Kudzin *et al.*, 2005b; Beilstein base, 2005]	*Phosphocysteine* [Kudzin & Stec, 1983]; *Phosphonocysteine* [Kudzin *et al.*, 2005b; Beilstein base, 2005]	*Phosphomethionine* [Tam *et al.*, 1982]
Abbrev.	[Hcys^{P}]$_2$ [Kudzin *et al.*, 2005b]	[Cys^{P}]$_2$ [Kudzin *et al.*, 2005b]	Met^{P} [Kudzin, 2005]
Structure			
Name	*Phosphomethionine sulfoxide (X=el. pair) or sulfon (X=O)* [Tam *et al.*, 1982]	*Phosphomethionine methylsulfonium iodide* [Tam *et al.*, 1982]	*Phosphohomocysteine sulfoximides* [Nowakowski *et al.*, 1989]
Abbrev.			
Structure			
Name	L-*Phosphaornithine* (n=3); L-*Phosphalysine* (n=4) [Wuggenig *et al.*, 2011]	L-*Phosphaproline* [Wuggenig *et al.*, 2011]	L-*Phosphaserine* [Hammerschmidt *et al.*, 2000]
Abbrev.	Orn^{P}; Lys^{P} [Kudzin, 2005]	Pro^{P} [Kudzin, 2005]	L-Ser^{P} [Kudzin, 2005]

Table 2. Continued

Structure			
Name	L-*Phosphaisoserine* [Hammerschmidt *et al*., 2000]	*Phosphothreonine* [Bongini *et al*., 1994, 1996]	*Isothreonine-P* [Heisler *et al*., 1995]
Abbrev.	L-iSer^{P} [Kudzin, 2005]	Thr^{P} [Kudzin, 2005]	isoTHR-P [Heisler *et al*., 1995]
Structure			
Name	*Phosphonohistidine* [Merrett *et al*., 1988]	*Phosphonoisohistidine* [Merrett *et al.*, 1988]	*D,L-Phosphotryptophan* [Chen *et al.*, 1983; Beilstein base, 2005]
Abbrev.	His(P) [Merrett *et al*., 1988]; His^{P} [Kudzin, 2005]	isoHis(P) [Merrett *et al*., 1988]; iHis^{P} [Kudzin, 2005]	Trp^{P} [Kudzin, 2005]
Structure			
Name	n=1: Phosphonoalanine [Tan & Tan, 1989; Beilstein base, 2005]; n=2: γ-Phosphonoglutamic acid [Mastalerz, 1957]		
Abbrev.	n=1: Asp$^{\beta\text{-}P}$ [Kudzin, 2005] n=2: Glu$^{\gamma\text{-}P}$ [Kudzin, 2005]	X=OH, n=1: Asp$^{\alpha\text{-}P}$ [Kudzin, 2005] X=NH_2, n=1: Asn$^{\alpha\text{-}P}$ [Kudzin, 2005] X=HO, n=2: Glu$^{\alpha\text{-}P}$ [Kudzin, 2005] X=NH_2, n=2: Gln$^{\alpha\text{-}P}$ [Kudzin, 2005]	n=1: Asp^{P,P} [Kudzin, 2005; n=2: Glu^{P,P} [Kudzin, 2005]
Structure			
Name	*N*-Phosphono-glycine [Diel & Maier, 1984]; N-(Phosphonomethyl)-glycine [Aldrich, 2010; Beilstein base, 2010]		(o-hydroxyphenyl)-phosphonoglycine
Abbrev.	PMG	β-Ala^{P} [Kudzin, 2005]	OHPPG [Calvo, 1987]

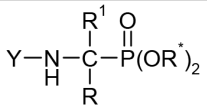
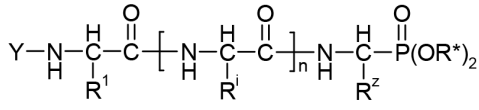
by the addition of the prefix "*phosphono*" (aminomethylphosphonic acid → phosphonoglycine).

Subsequently, the three–letter symbols of aminophosphonic acids (e.g., aminomethylphosphonic acid → phosphonoglycine) can be formed by the modification of their carboxylic analog symbols (e.g., Gly for glycine) by the addition to their right side the capital letter symbolizing the phosphono group in the superscript (Gly *vs.* Gly^{P}).

The comparison of nomenclature and symbolism for representative examples of amino acids and their phosphonic analogs is presented in Table 11.

Suggested nomenclature and symbolism for phosphonic analogs of the set of proteinogenic α–amino acids are listed in Table 12.

Table 3. Abbreviations for 1-aminophosphonic acids, phosphonopeptides, and derivatives

		Literature
Y=H; R^1=H; R*=HO Ala(P); L-Ala(P); D-Ala(P)	Gly-L-Ala(P); Ala-L-Ala(P); Ala-D-Ala(P); Val-L-Ala(P); Phe-L-Ala(P); Pro-L-Ala(P); Met-L-Ala(P); Glu-L-Ala(P); Lys-L-Ala(P); $(Ala)_n$-Ala(P) (n=0-4)	[Allen *et al*., 1978, 1979; Atherton *et al*., 1979]
Y=H; R^1=H; R*=HO GlyP; LeuP; MetP; PheP; YR^1=-$(CH_2)_3$-: ProP	Y=H; R*O=HO: Tyr-Gly-Gly-Phe-XP$(OR)_2$	[Kupczyk-Subotkowska & Mastalerz, 1983]
	ValAlaP; AlaValP; ValGluP; LeuGluP; ValAdiP; ValLeuP	[Lejczak *et al*., 1985]
	Z-Ala-"Ala"-OP$(OPh)_2$; Z-Leu-"Ala"-OP$(OPh)_2$; Z-Val-"Ala"-OP$(OMe)_2$;	[Gerber & Seebach, 1991]
	[R*O=HO, EtO, iPrO]: L-Ala-L,D-AlaP; L-Leu-D,L-PheP; L-Leu-D,L-PheP]; L-Phe-L,D-LeuP; [L-Phe-L,D-LeuP][1]; (Z)-L-Ala-L,D-AlaP$(OiPr)_2$; (Z)-L-Val-L,D-AlaP$(OiPr)_2$; (Z)-L-Phe-L,D-LeuP$(OEt)_2$	[Galushko *et al*., 1991, 1992]
Y=H; R^1=H; R*=HO Ala^P; D,L-Ala^P Y=PhAc; R^1=H; R*=HO D,L-PhAc-Ala^P		[Solodenko *et al*., 1993]
Y=H; R^1=H; R^*O=PhO $Val.^P(OPh)_2$; $Phe.^P(OPh)_2$	[Y=Boc; R*O=PhO]: Boc.Ala.$Phe.^P(OPh)_2$	[Hamilton *et al*., 1993]
	[Y=H; n=0]: L-Ala-L,D-Ala P; L-Leu-D,L-Phe P; L-Phe-L,D-Leu P	[Heisler *et al*., 1993]
Y=acyl (Ac, Prp, Btr, Piv, Bnz); R^1=H; R*=HO AA^P : Gly^P, Ala^P, $Hala^P$, Val^P, $Nval^P$, $Nleu^P$, Met^P, $Pgly^P$, Phe^P, $Hphe^P$		[Kudzin *et al*., 2005a]
(Y=TFA; R^1=H; R*=HO) TFA-AA^P [AA^P: Ala^P, Val^P, $Pgly^P$, Phe^P]		[Kudzin *et al*., 2007]
(Y= mca; R^1=H; R*=HO) mca-AA^P [AA^P: Ala^P, Val^P, $Pgly^P$, Phe^P]	Gly-AA^P [AA^P: Ala^P, Val^P, $Pgly^P$, Phe^P]; MeGly-AA^P [Ala^P, Val^P, $Pgly^P$, Phe^P]; Me_2Gly-AA^P [Ala^P, Val^P, $Pgly^P$, Phe^P]; H_2N-Gly-AA^P [Ala^P, Val^P, $Pgly^P$, Phe^P];	[Kudzin *et al*., 2008]
AA^P: full set of 24 amino acids	Atc-AA^P	[Kudzin *et al*., 2011]

Substituted Amino Acids

Substitutions in the Amino and Phosphonic Groups

The substitutions used in the amino acid chemistry (*N*–acylation, esterification, amidation), **transplanted** into the aminophosphonate chemistry are described by abbreviations listed in Table 13 and Table 14 (phosphonopeptides).

Thus, such substitutions can concern the amino function (i), the phosphonic function (ii) as well as both functions (iii) of aminophosphonic acid (AA_P), which can be denoted as follows:

— (i) the hyphen removes H from the 1-amino group of the AA^P when it is placed on the left of the symbol (-AA^P);
— (ii) the hyphen removes OH from the 1-phosphonic group of the AAP (written in the conven-ional, not ion-ized form) when it is placed on the right of the symbol (AA^P-);
— (iii) both modifications can apply to one symbol (-AA^P-).

Table 4. Applied codes for representative phosphoramidate and phosphonamidate enzyme inhibitors

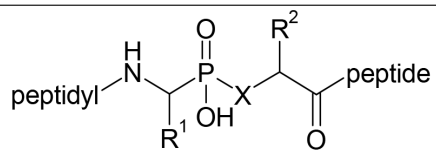
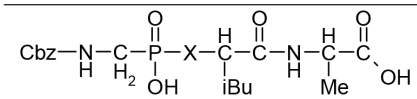
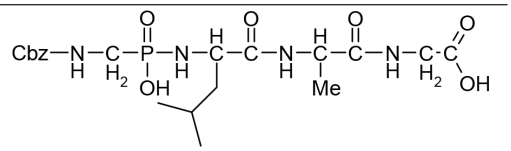
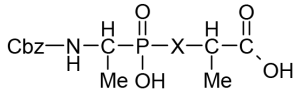
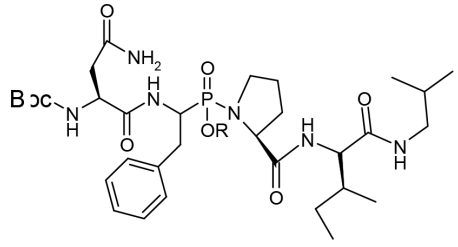
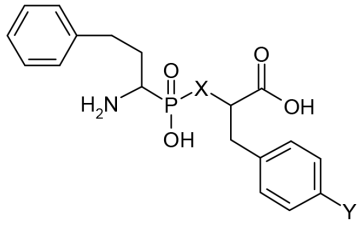
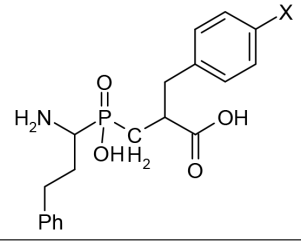
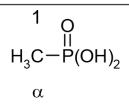
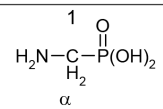
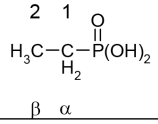
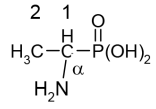
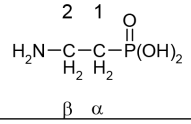
	
	
Thermolysin inhibitors [X=NH, CH_2, O] Cbz-Glyψ[P(O)(OH)X]Leu-Leu [Mucha *et al*., 2003]; Cbz–PheP[NH]Leu–Ala–OH [Mucha, 2006]	Matrix metalloproteinases inhibitors [MMP-8]: Cbz–GlyP[NH]Leu–Ala–Gly–OH [Mucha, 2006]
	
Carboxypeptydase A inhibitors [X=NH]: Cbz–Ala–AlaP[NH]Phe–OH [Mucha, 2006] [X=O]: Cbz–Ala–AlaP[O]Phe–OH [Mucha, 2006]	HIV protease inhibitor: (Boc-(2*S*)-Asn-Phe-'Ψ[P(OR)O-N]-(2*S*)-Pro-(2*S*)-Ile-NH-iBu) [R=Li, Me] [Camp *et al*., 1995]
	
LAP inhibitors: Y=H; X=NH: hPheP-Phe; [Mucha *et al*., 2003] Y=H; X=CH_2: hPheP[CH_2]Phe [Grembecka *et al*., 2003; Lejczak & Kafarski, 2009]; Y=OH; X=NH: hPheP-Tyr [Mucha *et al*., 2003]; Y=OH; X=CH_2: hPheP[CH_2]Tyr; [Grembecka *et al*., 2003; Lejczak & Kafarski, 2009]	LAP inhibitors: hPheP[CH_2]Phe (X=H); hPheP[CH_2]Tyr (X=OH) [Skinner-Adams *et al*., 2009; McGovan *et al*., 2010]

Table 5. Atom numbering in acyclic amino phosphonic acids

Parent Phosphonic Acid	Structure of Parent Phosphonic Acid	Structure of Derived Aminoalkylphosphonic Acid
Me-PO_3H_2		
Names	Methylphosphonic acid	1-Aminomethylphosphonic acid
Et-PO_3H_2		 

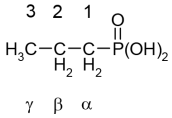
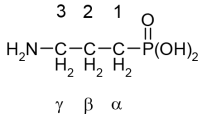
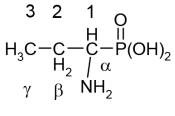
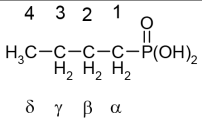
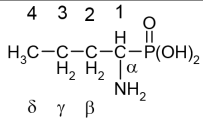
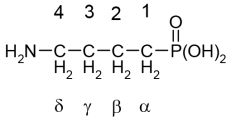
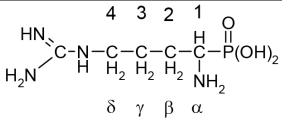
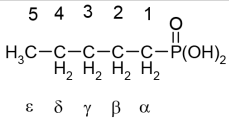
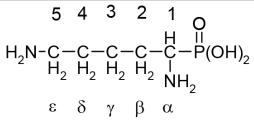
Names	Ethylphosphonic acid	1-Aminoethylphosphonic acid	2-Aminoethylphosphonic acid
Pr-PO_3H_2			
Names	Propylphosphonic acid	1-Aminopropylphosphonic acid (GABA P-Analog)	3-Aminopropylphosphonic acid
Bu-PO_3H_2 /Names			
	Butylphosphonic acid	1-Aminobutylphosphonic acid	
			
	4-Aminobutylphosphonic acid	1-Amino-4-guanidinobutylphosphonic acid	
Am-PO_3H_2			
Names	Pentylphosphonic acid	1,5-Diaminopentylphosphonic acid	

Table 6. Atom numbering in prolines

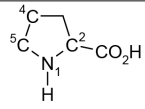
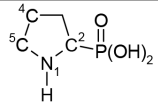
	
Pyrrolidine-2-carboxylic acid	Pyrrolidine-2-phosphonic acid

Table 7. Aromatic amino phosphonic acids

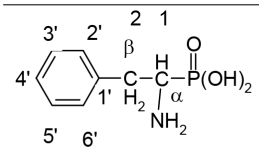
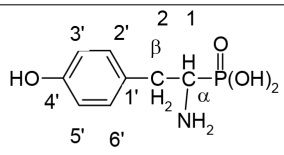
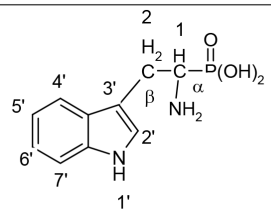
		
1-Amino-2-phenylethyl-phosphonic acid	1-Amino-2-(4'-hydroxyphenyl)ethyl-phosphonic acid	Amino-2-(1*H*-indol-3-yl)ethyl-phosphonic acid

Table 8. Amino acids names with prefix "homo"

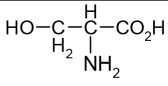
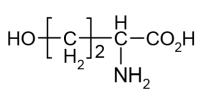
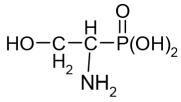
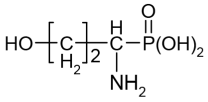
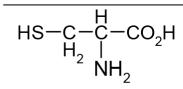
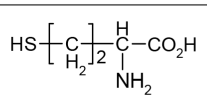
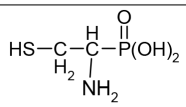
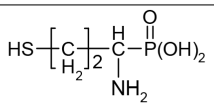
			
Serine	Homoserine	PhosphonoSerine	Phosphono-Homoserine
			
Cysteine	Homocysteine	PhosphonoCysteine	Phosphono-Homocysteine

Table 9. Amino acid names with prefix "Nor"

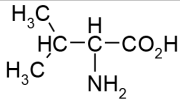
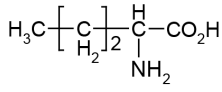
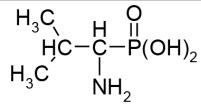
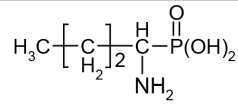
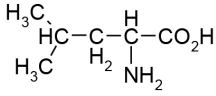
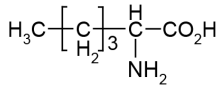
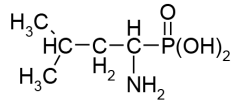
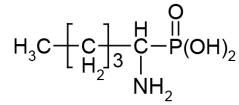
			
Valine	Norvaline	PhosphonoValine	PhosphonoNorvaline
			
Leucine	Norleucine	PhosphonoLeucine	PhosphonoNorleucine

Table 10. Configuration comparison of proteinogenic amino acids and their phosphonic analogs

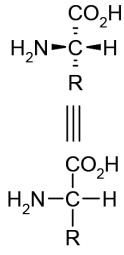
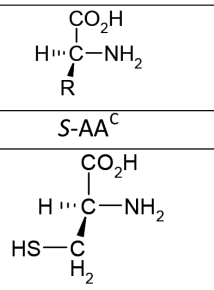
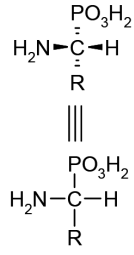
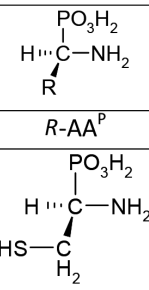
			
L-AA^{C}	*R*-Cys	L-AA^{P}	*R*-Cys^{P}

Table 11. Nomenclature and symbolism of amino acids and their phosphonic analogs

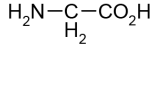
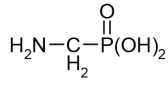
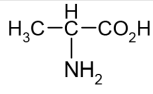
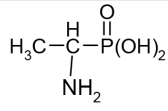
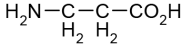
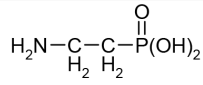
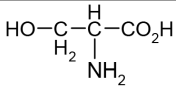
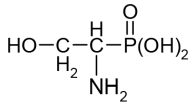
Amino Acid			Phosphonic analog		
Structure	Name	Symbol	Structure	Name	Symbol
	Glycine	Gly		Phosphono-Glycine	Gly^{P}
	Alanine	Ala		Phosphono-Alanine	Ala^{P}
	2-Alanine; β-Alanine	2-Ala; β-Ala		Phosphono-2-Alanine; Phosphono-β-Alanine	2-Ala^{P}; β-Ala^{P}
	Serine	Ser		Phosphono-Serine	Ser^{P}

Table 12. Proposed nomenclature and symbolism for phosphonic analogs of proteinogenic α-amino acids

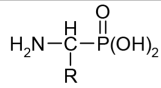
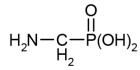
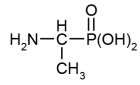
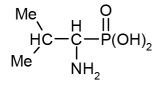
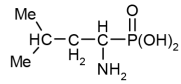
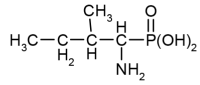
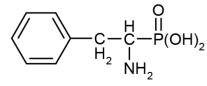
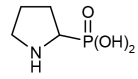
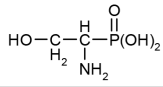
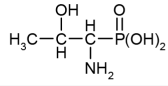
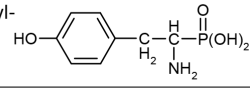
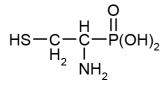
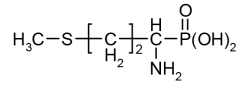
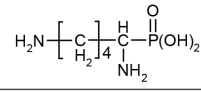
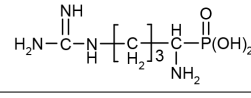
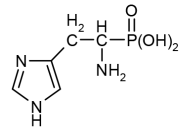
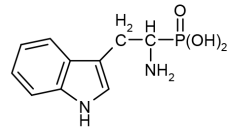
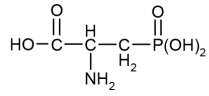
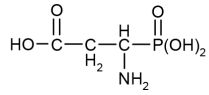
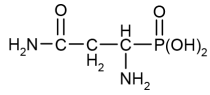
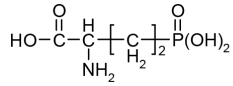
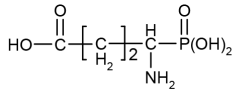
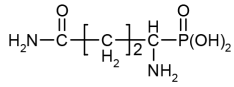
Trivial name[a]	Symb.	One-letter symb.[b]	Systematic name[c]	Formula[c]
Phosphono-Amino Acid	AA^P	X^P	1-Aminoalkylphosphonic acid	
Phosphono-Glycine	Gly^P	G^P	Aminomethylphosphonic acid	
Phosphono-Alanine	Ala^P	A^P	1-Aminoethylphosphonic acid	
Phosphono-Valine	Val^P	V^P	1-Amino-2-methylpropyl-phosphonic acid	
Phosphono-Leucine	Leu^P	L^P	1-Amino-3-methylbutyl-phosphonic acid	
Phosphono-Isoleucine	Ile^P	I^P	1-Amino-2-methylbutyl-phosphonic acid	
Phosphono-Phenylalanine	Phe^P	F^P	1-Amino-2-phenylethyl-phosphonic acid	
Phosphono-Proline	Pro^P	P^P	Pyrrolidin-2-yl-phosphonic acid	
Phosphono-Serine	Ser^P	S^P	1-Amino-2-hydroxyethyl-phosphonic acid	
Phosphono-Threonine	Thr^P	T^P	1-Amino-2-hydroxypropyl-phosphonic acid	
Phosphono-Tyrosine	Tyr^P	Y^P	1-Amino-2-(4′-hydroxyphenyl)ethyl-phosphonic acid	
Phosphono-Cysteine	Ala^P	A^P	1-Amino-2-mercaptoethyl-phosphonic acid	
Phosphono-Methionine	Met^P	M^P	1-Amino-3-(methylthio)propyl-phosphonic acid (1-amino-3-methylsulfanyl-propylphosphonic acid)	
Phosphono-Lysine	Lys^P	K^P	1,5-Diaminobutylphosphonic acid	
Phosphono-Arginine	Arg^P	R^P	1-Amino-4-guanidinobutyl-phosphonic acid	
Phosphono-Histidine	His^P	H^P	1-Amino-2-(1H-imidazol-4-yl)-ethylphosphonic acid)	
Phosphono-Tryptophan	Trp^P	W^P	1-Amino-2-(1*H*-indol-3-yl)ethyl-phosphonic acid	

Table 12. Continued

β-Phosphono-Aspartic Acid	$Asp^{\beta P}$	$D^{\beta P}$	2-Amino-3-phosphono-propionic acid	
α-Phosphono-Aspartic Acid	$Asp^{\alpha P}$	$D^{\alpha P}$	3-Amino-3-phosphono-propionic acid	
Phosphono-Aspargine	$Asn^{\alpha P}$	$N^{\alpha P}$	3-Amino-3-phosphono-propionamide (1-amino-2-carbamoyl-ethyl)-phosphonic acid	
α-Phosphono-Glutamic Acid	$Glu^{\gamma P}$	$E^{\gamma P}$	2-Amino-4-phosphono-butyric acid	
α-Phosphono-Glutamic Acid	$Glu^{\alpha P}$	$E^{\alpha P}$	4-Amino-4-phosphono-butyric acid	
Phosphono-Glutamine	$Gln^{\alpha P}$	$Q^{\alpha P}$	4-Amino-4-phosphono-butyramide (1-amino-3-carbamoyl-propyl)-phosphonic acid	

[a]The trivial name refers to the L or D or DL-amino acid. [b]Use of the one-letter symbols should be restricted to the comparison of long sequences (3-20 residues). [c]The systematic names and formulas given refer to hypothetical forms in which amino groups are not protonated and phosphonic groups are not dissociated.

Table 13. Proposed abbreviations for phosphonic amino acids and derivatives

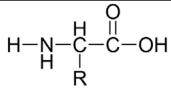
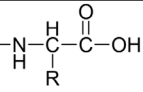
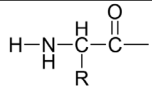
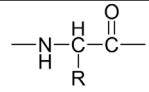
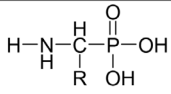
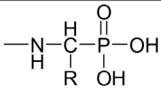
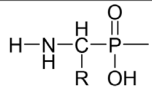
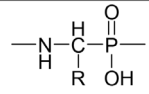
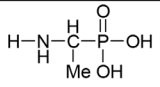
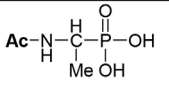
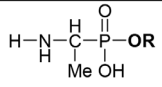
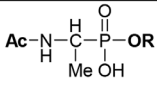
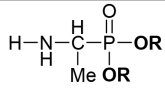
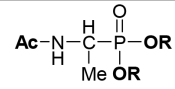
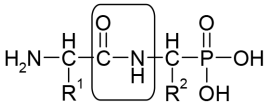
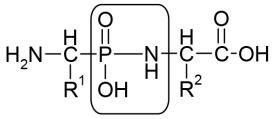
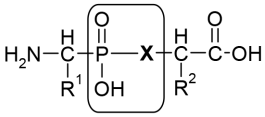
Proteinogenic amino acids			
			
AA^C	**-AA^C**	**AA^C-**	**-AA^C-**
Phosphonic analogs of amino acids			
			
AA^P	**-AA^P**	**AA^P-**	**-AA^P-**
			
Ala^P	**Ac-Ala^P**	**Ala^P(OR)**	**Ac-Ala^P(OR)**
			
		$Ala^P(OR)_2$	**Ac-$Ala^P(OR)_2$**
R – alkyl, aryl, aralkyl			

Table 14. Proposed abbreviations for phosphonopeptides

		
AA^C-AA^P	**AA^P-AA^C**	**AA^P[X]AA^C**
R^1=R^2=Me: Ala-Ala^P	R^1=R^2=Me: Ala^P-Ala	R^1=R^2=Me: Ala^P[X]Ala

CONCLUSIONS

We believe that the implementation of the nomenclature and abbreviations proposed here will remove the ambiguity and will simplify the description of phosponate analogs of amino acids and their derivatives, including phosphonopeptides. Acceptance of these rules will facilitate unambiguous communication of research involving these classes of compounds.

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REFERENCES

Allen JG, Atherton FR, Hall MJ, Hassal CH, Holmes SW, Lambert RW, Nisbet LJ, Ringrose PS (1978) Phosphonopeptides, a new class of synthetic antibacterial agents. *Nature* **272**: 56–58.

Atherton FR, Hall MJ, Hassall CH, Lambert RW, Ringrose PS (1979) Phosphonopeptides as antibacterial agents: rationale, chemistry, and structure–activity relationships. *Antimicrob Agents Chemother* **15**: 677–683.

Bongini A, Camerini R, Hoffmann S, Panuzio M (1994) Synthesis of (1S, 2S)-phosphonothreonine *via* N-TMS-silylamine of lactic aldehyde. *Tetrahedron Lett* **35**: 8045–8049.

Bongini A, Camerini R, Panuzio M (1996) Synthesis of the four diastereoisomers of phosphothreonine from lactic aldehyde. *Tetrahedron: Asymmetry* **7**: 1467–1476.

Calvo KC (1987) Pyridoxal-mediated dephosphonylation of 1–aminophosphono acids. *J Org Chem* **52**: 3654–3658.

Camp NP, Perrey DA, Kinchington D, Hawkins PCD, Gani D (1995) Synthesis of peptide analogues containing phosphonamidate methyl ester functionality: HIV-1 proteinase inhibitors possessing inique cell uptake properties. *Bioorg Med Chem Lett* **3**: 297–212.

Chen SF, Kumar S, Tishler M (1983) Synthesis of D,L–phosphotryptophan. *Tetrahedron Lett* **24**: 5461–5465.

Corcoran RC, Green JM (1990) Conversion of α-aminocarboxylic acids to α-aminophosphonic acids. *Tetrahedron Lett* **31**: 6827–6830.

Dhavan B, Redmore D (1987) Optically active 1-aminoalkylphosphonic acids. *Phosphorus & Sulfur* **32**: 119–144.

Diel PJ, and Maier L (1984) Synthesis and properties of N-phospho–glycine derivatives. *Phosphorus & Sulfur* **20**: 313–330.

Galushko S, Belyk M, Solodenko V, Kasheva T, Kukhar V (1991) Normal- and reversed-phase high-performance liquid chromatography of some phosphonodipeptides. *J Chromatogr* **553**: 143–147.

Galushko S. Belyk M, Solodenko V, Kasheva T, Kukhar V. (1992) Ion-exchange high-performance liquid chromatography of diastereoisomers of some phosphonodipeptides *J Chromatogr* **600**: 79–81.

Gerber C, Seebach D (1991) Dipeptide derivatives with a phosphonate instead of carboxylate terminus by *C*-alkylation of protected (decarboxy-dipeptidyl)-phosphonates. *Helv Chim Acta* **74**: 1373–1385.

Grembecka J, Mucha A, Cierpicki T, Kafarski P (2003) The most potent organophosphorus inhibitors of leucine aminopeptidase. Structure–based design, chemistry, and activity. *J Med Chem* **46**: 2641–2655.

Hamilton R, Kay G, Schute R, Travers J, Walker B, Walker JB (1993) The synthesis of phosphonate analogs of amino acids and peptides. *Phosphorus & Sulfur* **76**: 127–130.

Hammerschmidt F, Lindner W, Wuggenig F, Zarb E (2000) Enzymes in organic chemistry. Part 10: Chemo-enzymatic synthesis of L-phosphaserine and L-phosphaisoserine and enantioseparation of amino-hydroxyethylphosphonic acids by non-aqueous capillary electrophoresis with quinine carbamate; as chiral ion pair agent. *Tetrahedron Asymmetry* **11**: 2955–2964.

Heisler A, Rabiller C, Douillard R, Goalou N, Hagele G, and Levayer F (1993) Enzyme catalyzed resolution of 1-aminophosphonic acids. Serin and Isoserin analogues. *Tetrahedron: Asymmetry* **4**: 959–960.

Heisler A, Rabiller C, Haegele G (1995) Enzyme catalyzed transesterification of aminophosphonic acids. II. Isothreonine-P analogs. *Phosphorus, Sulfur & Silicon* **101**: 273–280.

IUPAC Commission on Nomenclature of Organic C hemistry (CNOC). Nomeniclature of Organiic Chemistry. Section E: Stereochemnistry. Recommendations 1974 (1976) *Pure Appl Chem* **45**: 11–30.

IUPAC–IUB Commission on Biochemical Nomenclature. Nomenclature of Phosphorus-Containing Compounds of Biochemical Importance. Recommendations 1976. (1978) *Biochem J* **171**: 1–19.

IUPAC–IUB Joint Commission on Biochemical Nomenclature (JCBN) (1984). Nomenclature and Symbolism for Amino Acids and Peptides. Recommendations 1983. *Eur J Biochem* **138**: 9–37.

Jakubowski H (1978) Yellow lupin (*Lupinus luteus*) aminoacyl-tRNA synthetases. Isolation and some properties of enzyme-bound valyl adenylate and seryl adenylate. *Biochim Biophys Acta* **521**: 584–96.

Jakubowski H (1980) Valyl-tRNA synthetase form yellow lupin seeds: hydrolysis of the enzyme-bound noncognate aminoacyl adenylate as a possible mechanism of increasing specificity of the aminoacyl-tRNA synthetase. *Biochemistry* **19**: 5071–5078.

Jakubowski H (1983) Synthesis of diadenosine 5',5'''-P1,P4-tetraphosphate and related compounds by plant (Lupinus luteus) seryl-tRNA and phenylalanyl-tRNA synthetases. *Acta Biochim Pol* **30**: 51–69.

Jakubowski H (1997) Aminoacyl thioester chemistry of class II aminoacyl-tRNA synthetases. *Biochemistry* **36**: 11077–11085.

Kafarski P, Lejczak B (2001) Aminophosphonic acids of potential medical importance. *Curr Med Chem; Anti-Cancer Agents* **1**: 301–312.

Kafarski P Mastalerz P (1984) Aminoalkanephosphonates: natural occurence, biochemistry and biological properties. *Beitr Wirkst Forsch* **24**: 1–110.

Kafarski P, Lejczak B, Mastalerz P (1985) Phosphonopeptides. Synthesis and biological activity. *Beitr Wirkst Forsch* **25**: 1–77.

Kaname M, Mashige H, Yoshifuji S (2001) Chemical conversion of cyclic amino acids to cyclic α-aminophosphonic acids. *Chem Pharm Bull* **49**: 531–536.

Kudzin MH, Kudzin ZH, Drabowicz J (2011) Thioureidoalkylphosphonates in the synthesis of 1-amino-alkylphosphonic acids. The Ptc-aminophosphonate method. *Arkivoc* **vi**: 227–269.

Kudzin ZH (1981) Phosphocysteine derivatives. Thioureidoalkanephosphonates *via* acetals. *Synthesis:* 643–645.

Kudzin ZH (2005) 1-Aminoalkanephosphonic acids: six decades of exploration. *Sci Issues Acad J Długosza, Częstochowa* **IX**: 29–76.

Kudzin ZH, Stec WJ (1980) Phosphohomocysteine derivatives. *Synthesis* 1032–1034.

Kudzin ZH, Stec WJ (1983) Phosphocysteine and phosphohomocysteine. Synthesis and isolation. *Synthesis* 812–814.

Kudzin ZH, Depczyński R, Andrijewski G, Drabowicz J (2005a) Aminoalkanephosphonates. IV. 1-(*N*-acylamino)alkanephosphonates. The synthesis *via N*-acylation of 1-aminoalkanephosphonic acids. *Pol J Chem* **79**: 499–513.

Kudzin ZH, Saganiak M, Andrijewski G, Drabowicz J (2005b) Oxidation of phosphonocysteine and phosphonohomocysteine. Synthesis of phosphonocysteic and phosphonohomocysteic acids. *Pol J Chem* **79**: 529–539.

Kudzin ZH, Depczyński R, Kudzin MH, Drabowicz J, Łuczak J (2007) 1-(*N*-Trifluoroacetylamino)alkylphosphonic acids. Synthesis and properties. *Amino Acids* **33**: 663–667.

Kudzin ZH, Depczyński R, Kudzin MH, Drabowicz J (2008) 1-(*N*-Chloroacetylamino)-alkylphosphonic acids — synthetic precursors of glycylophosphono-peptides and related compounds. *Amino Acids* **34**: 163–168.

Kudzin ZH, Kudzin MH, Drabowicz J, Stevens C (2011) Aminophosphonic acids — phosphorus analogues of natural amino acids. Part 1: Syntheses of α-aminophosphonic acids. *Curr Org Chem* **15**: 2015–2071.

Kukhar VP, Hudson HR (2000) *Aminophosphonic and aminophosphinic acids. Chemistry and biological activity.* Wiley & Sons Ltd, Chichester, London, Toronto.

Kupczyk-Subotkowska L, Mastalerz P (1983) Synthesis of phosphonic analogs of enkephalins. Pentapeptides with COOH replaced by PO3H2 group. *Int J Peptide Protein Res* **21**: 485–490.

Lejczak B, Kafarski P (2009) Biological activity of aminophosphonic acids and their short peptides. *Top Heterocycl Chem* **20**: 31–63.

Lejczak B, Kafarski P, Mastalerz P (1985) Chromatographic assignment of the configuration of 1-aminoalkanephosphonic acid. *J Chromatogr* **324**: 455–461.

Mastalerz P (1957) Synthesis of γ-phosphonoglutamic acid. *Acta Biochim Pol* **4**: 19–21.

McGowan S, Oellig CA, Birru WA, Caradoc-Davies TT, Stack CM, Lowthere J, Skinner-Adams T, Mucha A, Kafarski P, Grembecka J, Trenholme KR, Ashley M, Buckle AM, Gardiner DL, Dalton JP, Whisstock JC (2010) Structure of the Plasmodium falciparum M17 aminopeptidase and significance for the design of drugs targeting the neutral exopeptidases. *Proc Natl Acad Sci* **107**: 2449–2454.

Merrett JH, Spurden WC, Thomas WA, Tong BP, Whitecombe IWA (1988) The synthesis and rotational isomerism of 1-amino-2-(imidazol-4yl)ethylphosphonic [phosphonohistidine, His(P)] and 1-amino-2-(imidazol-2-yl)ethylphosphonic [phosphono-isohistidine, iso-His(P)]. *J Chem Soc, Perkin Trans* **I**: 61–75.

Mucha A (2006) Phosphonamidate and phosphinate inhibitors of metalloproteases. *Sci Issues Chem Fac Wroclaw Tech Univ* **1**: 1–106 (in Polish).

Mucha A, Grembecka J, Cierpicki T, Kafarski P (2003) Hydrolysis of the phosphonamidate bond in phosphono dipeptide analogues — the influence of the nature of the N-terminal functional group. *Eur J Org Chem* 4797–4803.

Nowakowski M, Tishler M, Domeyko AM (1989) The Synthesis and biological activity of *S*-alkyl phosphonohomocysteine sulfoximides. *Phosphorus & Sulfur* **45**: 183–188.

Orsini F, Sello G, Sisti M (2010) Aminophosphonic acids and derivatives. Synthesis and biological applications. *Curr Med Chem* **17**: 264–289.

Osapay G, Szilagyi I, Seres J (1987) Conversion of amino acids and dipeptides into their phosphonic analogues. *Tetrahedron* **43**: 2977–2983.

Renaud P, Seebach D (1986) Preparation of chiral building blocks from amino acids and peptides via electrolytic decarboxylation and TiCl4-induced aminoalkylation. *Angew Chem Int Ed* **25**: 843–844.

Seebach D, Charczuk R, Gerber C, Renaud P, Berner H, Schneider H (1989) Electrochemical decarboxylation of L-threonine and oligopeptide derivatives with formation of *N*-acyl-*N,O*-acetals: preparation of oligopeptides with amide or phosphonate C-terminus. *Helv Chim Acta* **72**: 401–425.

Skinner-Adams TS, Lowther J, Teuscher F, Stack CM, Grembecka J, Mucha A, Kafarski, P, Trenholme KR, Dalton JP, Gardiner DL (2007) Identification of phosphinate dipeptide analog inhibitors directed against the Plasmodium falciparum M17 leucine aminopeptidase as lead antimalarial compounds. *J Med Chem* **50**: 6024–6031.

Solodenko VA, Belik MV, Galushko SV, Kukhar VP, Kozlova EV, Mironernko DA, Svedas VK (1993) Enzymatic preparation of both L- and D-enantiomers of phosphonic and phosphonous analogues of alanine using penniciilin acylase. *Tetrahedron: Asymmetry* **4**: 1965–1968.

Tam CC, Mattocks KL, Tishler M (1982) Synthesis of phosphonomethionine and related compounds. *Synthesis* 188–191.

Tan SA, Tan LG (1989) Distribution of ciliatine (2-aminoethylphosphonic acid) and phosphonoalanine (2-amino-3-phosphonopropionic acid) in human tissues. *Clin Physiol Bio-Chem* **7**: 303–309.

Wuggenig F, Schweifer A, Mereiter K, Hammerschmidt F (2011) Chemoenzymatic synthesis of phosphonic acid analogues of L-lysine, L-proline, L-ornithine, and L-pipecolic acid of 99% ee — assignment of absolute configuration to (–)-proline. *Eur J Org Chem:* 1870–1879.

Zecchini GP, Paradisi MP, Torrini ILG (1989) A convenient route to pyrrolidine-2-phosphonic acid dipeptides. *Int J Peptide Protein Res* **34**: 133–136.