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Article

New 1-Hydroxy-1,1-bisphosphonates Derived from 1*H*-Pyrazolo[3,4-*b*]pyridine: Synthesis and Characterization

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A partir da 2-cloro-3-formilpiridina, sintetizou-se uma série de compostos derivados da 1*H*-pirazolo[3,4-*b*]piridina de modo a obter os correspondentes 1-hidroxibisfosfonatos, uma classe de compostos com potencial interesse biológico. Os dados espectroscópicos foram utilizados na caracterização de todos os compostos e na identificação dos regioisômeros N-1 e N-2, e dos derivados mono- e bisfosfonatos. Estudos de difratometria de raios X do composto **7a** confirmaram a estrutura proposta.

A number of 1*H*-pyrazolo[3,4-*b*]pyridine derivatives, starting from 2-chloro-3-formyl pyridine, was synthesized to obtain new 1-hydroxybisphosphonates, a class of compounds with potential biological interest. Spectroscopic data were used to characterize all compounds and to identify N-1 and N-2 regioisomers, and mono- and bisphosphonates derivatives. X-ray diffractometry studies of compound **7a** confirmed the proposed structure.

Keywords: bisphosphonates, 1*H*-pyrazolo[3,4-*b*]pyridine, spectroscopic characterization, synthesis, X-ray diffractometry studies

Introduction

Bisphosphonates (BPs) are an important class of drugs known for their broad spectrum of therapeutical applications in the treatment and prevention of diseases of calcium metabolism.[1-3] These compounds have high affinity for calcium and therefore to target the bone mineral, where they appear to be internalized selectively by bone-reabsorbing osteoclasts inducing their apoptosis.[1-3] BPs were first developed in the mid 1960's and have been used as an effective treatment for Paget's disease.[4] Further applications of BPs have been proven to succeed in the treatment of diseases characterized by abnormal calcium metabolism including hypercalcemia, osteoporosis, osteolysis, heterotopic calcification and ossification, bone metastases secondary to breast cancer and prostate cancer, inhibition of cell proliferation, invasion and adhesion to bone.[2,5] BPs present several advantages in the treatment of bone diseases since they are bone-time specific, have minimal side effects, no known risk of carcinogenesis and antiresorptive efficacy equivalent or even greater than estrogens.[2,6]

The P–C–P bonds in BPs make them resistant to enzymatic hydrolysis and the nitrogen containing functional group of the alkyl moiety bound to the bisphosphonic structure improves their activity in the treatment of both primary and secondary bone disorders.[1-3,7] The most potent BPs contain one or two nitrogen atoms

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in a heteroaromatic moiety linked by a small side chain to the geminal bisphosphonate unit.[8]

BPs also have applications in the inhibition of angiogenesis,[9] as anti-inflammatory agents,[10] and showed antiparasitic activity towards some *Trypanosoma sp.*, such as *Trypanosoma cruzi* (agent of Chagas disease),[11] some *Leishmania sp.*,[12] and apicomplexans, such as *Toxoplasma gondii* (toxoplasmosis) and *Plasmodium falciparum* (malaria).[13] Also, herbicidal activity,[14] antibacterial[15] and anticancer properties,[16] as well as stimulation of γd-T cells of the immune system[17] have been described for some BPs.

Recently, BPs were studied as novel ligands in well-defined radioactive metal complexes that can be used in magnetic resonance imaging and imagiology, scintigraphy and radiotherapy applications,[18] and as chelating agents for the treatment of human metal intoxications.[19]

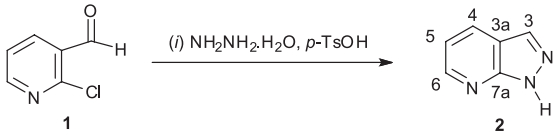
Pyrazole derivatives are pharmacologically important compounds and their ring systems form the basis of several drug molecules.[20] Pyrazolopyridine, a condensed pyrazole system, could be used as an isoster of indole or indazole, which are known to be pharmacophoric elements in numerous active compounds.[21]

The pyrazolopyridine system has attracted great interest in recent years due to the wide variety of biological and pharmacological properties associated with it. Among them, the biological applications range from anti-inflammatory,[22] antipyretic,[23] analgesic,[23] regulation of cardiovascular system,[24] hypoglycemic,[25] anti-tumor,[26] anxiolytic,[27] inhibitor of glycogen synthase kinase-3 (GSK-3)[28] and phosphodiesterase 4 (PDE4),[29] to antimicrobial,[30] antileishmanial[31] or antiviral activity.[32]

Taking these applications into account, it can be conceived that molecules bearing both the pyrazolopyridine and bisphosphonate units are prone to show biological properties. Following previous studies on bisphosphonates derived from indazole,[18,33] the present investigation reports the synthesis of new BPs derived from pyrazolo[3,4-*b*]pyridine, substituted at N-1 position of pyrazole rings, with a side chain bearing different methylenic lengths ($(CH_2)_n$ and n = 1, 2). The spectroscopic characterization, as well as the crystal structure determination of a BP to confirm the proposed molecular structure and to show its supramolecular arrangement in solid state, has also been performed. The aim of this work is to obtain new BPs derived from a condensed pyrazole with high potential biological/therapeutical activities.

Results and Discussion

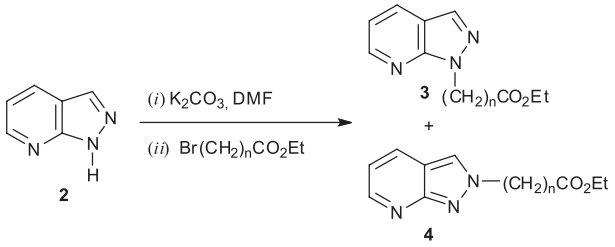
The synthesis of 1*H*-pyrazolo[3,4-*b*]pyridine **2** was performed in high yields (87%), using a process reported in the literature, by reaction of 2-chloro-3-formylpyridine **1** and hydrazine using *p*-TsOH[34,35] (Scheme 1). All spectrometric data are according to the literature.[34]



Scheme 1. Synthesis of 1*H*-pyrazolo[3,4-*b*]pyridine (**2**).

The pyrazolo[3,4-*b*]pyridine **2** was used to synthesize its side chain ester derivatives by nucleophilic substitution reactions of the corresponding bromo esters with different hydrocarbon methylene chain lengths (Table 1). 1*H*-pyrazolo[3,4-*b*]pyridine **2** reacted with a base, K_2CO_3, in *N*,*N*-dimethylformamide (DMF), followed by addition of the corresponding bromo esters with one or two methylene group chain length. Under these conditions, a mixture of N-1 or N-2 substituted regioisomers pyrazolo[3,4-*b*]pyridine ester derivatives **3** and **4** was obtained in different yields and ratios, as pale yellow oils (Table 1).

Table 1. Synthesis of pyrazolo[3,4-*b*]pyridine ester derivatives substituted at N-1 (**3**) and N-2 (**4**)



	n	**3** / %	**4** / %	(**3** + **4**) / %
a	1	87	–	87
b	2	31	18	49

The separation of these isomers and their correct identification were important since only the N-1 derivatives (**3**) were used in the subsequent synthesis. So, the mixture was separated by chromatography to provide the pure regioisomers, and the regioisomers substituted at N-1 (**3**) and N-2 (**4**) were identified by nuclear magnetic resonance (^{1}H and ^{13}C NMR spectroscopy, distortionless enhancement by polarization (DEPT) and two dimensional NMR techniques). The main resonances in the ^{1}H NMR spectra (in $CDCl_3$) (Table 2) of 1*H*-pyrazolo[3,4-*b*]pyridine ester derivatives **3a**-**b** are: (*i*) three resonances in the δ 7.13-8.55 ppm region, as one proton double doublet, corresponding to the 4-H, 5-H and 6-H protons, (*ii*) a singlet at δ 8.06 (n = 1) or 8.01 (n = 2) ppm corresponding to the 3-H proton, (*iii*) a singlet (n = 1) or a triplet (n = 2) for the

Table 2. ^{1}H NMR data of of pyrazolo[3,4-*b*]pyridine derivatives

Compound	Solvent	^{1}H NMR, δ / ppm					
		3-H	4-H	5-H	6-H	$N(CH_2)_n$	CH_2CH_3
2	$CDCl_3$	8.12	8.15	7.19	8.63	–	–
3a	$CDCl_3$	8.06	8.05	7.13	8.52	5.30	1.23, 4.20
3b	$CDCl_3$	8.01	8.06	7.14	8.55	3.01, 4.85	1.19, 4.13
4b	$CDCl_3$	8.04	8.02	7.04	8.68	3.12, 4.74	1.22, 4.12
5a	MeOD	8.13	8.23	7.24	8.52	5.29	–
5b	MeOD	8.06	8.19	7.20	8.52	2.96, 4.76	–
7a	DMSO-d_6	8.19	8.29	7.25	8.55	5.02	–
7b	DMSO-d_6	8.14	8.23	7.20	8.53	2.41, 4.75	–
8	DMSO-d_6	8.27	8.33	7.30	8.56	5.77	–

NCH_2 protons at δ 5.30 and 4.85 ppm, respectively, and (*iv*) resonances at δ 3.01 ppm for the remainder CH_2 protons. The ^{1}H NMR spectra of N-2 ester derivatives present similar chemical shifts and multiplicities.

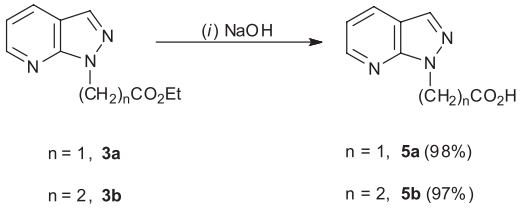
The ^{1}H NMR spectra of the two regioisomers do not shown significant differences, but ^{13}C NMR spectroscopy can be used to differentiate between the N-1 and N-2 substituted pyrazolo[3,4-*b*]pyridine derivatives as it was also shown for similar indazole derivatives.[36] In the ^{13}C NMR spectra, the C3 and C7a and NCH_2 atoms showed different chemical shifts between the N-1 and N-2 isomers (Table 3). In the N-1 substituted isomer spectrum, C3 was generally shifted downfield 8.7 ppm, and C7a and NCH_2 were shifted upfield, relatively to the corresponding carbon atoms in the N-2 substituted isomer.

The Fourier Transform Infrared (FTIR) spectra of esters **3a**-**b** and **4b** show ν (C=O) stretching bands in the range of 1727-1754 cm^{-1}. The ν (C=O) stretching band frequencies are similar for both N-1 and N-2 isomers. The absence of the NH stretching band confirmed the substitution on the nitrogen atom.

Compounds **3a**-**b** and **4b** were also characterized by electron impact (EI) mass spectrometry. The mass spectra of ester derivatives **3a**-**b** and **4b** are similar and their fragmentation pattern generally involves the formation of $[M–OEt]^+$, $[M–COOEt]^+$ and $[M–(CH_2)_nCOOEt]^+$ ions.

The ester N-1 isomers **3** were subject to basic hydrolysis to afford the corresponding N-1 pyrazolo[3,4-*b*]pyridine carboxylic acid derivatives (compounds **5**), as white crystalline solids, in excellent yields (Scheme 2). The carboxylic acids **5a**-**b** were fully characterized by ^{1}H and ^{13}C NMR spectroscopy, DEPT and two-dimensional NMR techniques, mass spectrometry and FTIR spectroscopy, and all data are in agreement with the proposed structures.

The main resonances in the ^{1}H NMR spectra (in MeOD) of carboxylic acid derivatives **5a**-**b** are similar in chemical shifts and multiplicity pattern to the corresponding ester



Scheme 2. Synthesis of pyrazolo[3,4-*b*]pyridine carboxylic acid derivatives substituted at N-1 (**5**).

Table 3. ^{13}C NMR data of pyrazolo[3,4-*b*]pyridine derivatives

Compound	Solvent	^{13}C NMR, δ / ppm									
		Ar:C3	Ar:C4	Ar:C5	Ar:C6	Ar:C3a	Ar:C7a	NCH_2	CH_2	OCH_2CH_3	*CO* or $C(OH)–(PO_3H_2)_2$
3a	$CDCl_3$	130.2	133.2	117.1	148.9	115.6	150.6	48.1	-	14.0, 61.6	167.9
3b	$CDCl_3$	132.3	130.1	116.9	148.7	115.6	150.1	42.7	34.3	14.1, 60.7	171.0
4b	$CDCl_3$	123.6	129.7	117.7	151.4	113.7	158.5	49.3	34.5	14.0, 65.8	170.8
5a	MeOD	134.4	132.3	118.5	150.1	117.4	151.7	48.9	–	–	171.3
5b	MeOD	133.7	132.1	118.2	149.9	117.3	151.0	43.8	34.7	–	174.4
7a	DMSO-d_6	132.6	131.4	117.2	148.2	115.6	150.1	50.7	–	–	73.6 (t)
7b	DMSO-d_6	133.1	131.6	118.0	149.6	116.2	150.4	43.4	34.3	–	72.2 (t)
8	DMSO-d_6	134.2	131.6	118.2	149.8	116.1	151.4	57.2 (d)	–	–	210.5 (d)

derivatives. Also, the ^{13}C NMR spectra present analogous chemical shifts and multiplicity pattern to the starting ester spectra.

The infrared analysis of compounds **5a** and **5b** also showed the presence of the carboxylic acid group with the strong C=O stretching band at 1728 and 1711 cm^{-1}, respectively, and O–H stretching broad band in the region of 3100-2300 cm^{-1}.

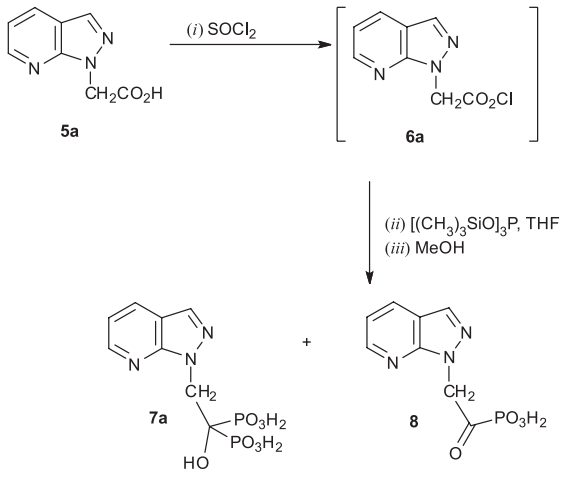
All data for compounds **5a** and **5b**, including a correct elemental analysis *m/z* 177 (M^+) and *m/z* 191 (M^+), respectively, were consistent with the proposed structures. Mass spectra of carboxylic acid derivatives **5a**-**b** also showed the formation of $[M–COOH]^+$ and $[M–(CH_2)_nCOOH]^+$ ions.

The carboxylic acids derived from 1*H*-pyrazolo[3,4-*b*] pyridine **5a**-**b** substituted at N-1 position were used as starting material for the synthesis of novel 1-hydroxy-1,1-bisphosphonates derived from 1*H*-pyrazolo[3,4-*b*] pyridine. Several methods for the synthesis of 1-hydroxy-1,1-bisphosphonates have been reported.[37] The most used method involves the reaction of a carboxylic acid with phosphorus trichloride and phosphorous acid or phosphoric acid, followed by acidic hydrolysis.[38,39] Recently, a modified Arbuzov reaction method[40] was proposed by Lecouvey *et al.*[41] This method involves the reaction of an acyl chloride with tris(trimethylsilyl)phosphite, followed by methanolysis.

In order to synthesize the 1-hydroxybisphosphonates **7a**-**b**, the classic method was used starting from the corresponding carboxylic acid **5a**-**b**, by treatment with a mixture of phosphoric acid and phosphorus trichloride, followed by acid hydrolysis. The ^1H NMR spectra of the crude mixture showed that the reaction afforded a complex mixture of products from which the separation and purification of BPs **7a**-**b** were not possible, by precipitation in acetone and methanol.

The next attempt was made using Lecouvey's method (Scheme 3). The acyl chloride **6a** was prepared *in situ*, by reaction of the carboxylic acid **5a** with 4 eq. of thionyl chloride, in $CHCl_3$. But, after reaction with 2 eq. of tris(trimethylsilyl)phosphite, followed by methanolysis, the only isolated pure product was the monophosphonate **8**, in 36% yield, and recovered starting material. Other attempt with 6 eq. of thionyl chloride, in $CHCl_3$, and 3 eq. of tris(trimethylsilyl)phosphite afforded a mixture of monophosphonate **8** and bisphosphonate **7a**. Purification by precipitation allowed the isolation the bisphosphonate **7a**.

The same methodology was tried once more but without any solvent. In neat thionyl chloride, from carboxylic acid **5a**, the acyl chloride **6a** was prepared *in situ*, and subsequently reacted with 3 eq. of tris(trimethylsilyl) phosphite, followed by methanolysis, to afford BP **7a** in 81% yield (Scheme 3) with traces of monophosphonate **8**. Repetition of both these reactions showed that to obtain the bisphosphonate **7a** as major product, the acyl chloride needs to be prepared without solvent, with excess thionyl chloride (Scheme 3).



Scheme 3. Synthesis of bisphosphonate **7a** and monophosphonate **8**.

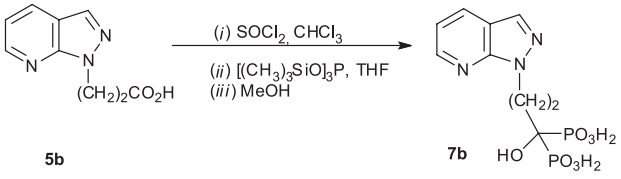
Both compounds were identified by NMR spectroscopy. By ^{31}P NMR spectroscopy, the monophosphonate **8** is clearly identified by its chemical shift at δ –4.1 ppm, in contrast to the bisphosphonate **7a**, which presents a more deshielded singlet with its chemical shift at δ 17.0 ppm, assigned to the two chemically and magnetically equivalent P atoms. The ^{13}C NMR spectrum of monophosphonate **8** shows a doublet at δ 210.5 (J_{CP} 169 Hz) for a carbonyl quaternary carbon atom (disappearing in DEPT 135 ^{13}C NMR mode), coupling with one phosphorus atom, consistent with the signal of a carbon bearing a phosphonate group, forming an α-ketophosphonate structure. Also, the methylene $NCH_2C(O)PO_3H_2$ carbon appears as a doublet at 57.2 (J_{CP} 64 Hz) while the ^{13}C NMR spectrum for the same carbon of bisphosphonate **7a** shows a triplet at δ 73.6 (J_{CP} 144 Hz) because of the coupling with two equivalent phosphorus atoms. The ^1H NMR spectroscopy also supports both proposed structures, with the ^1H NMR spectrum of BP **7a** showing a triplet at 5.02 ppm (J_{HP} 9 Hz) due to the coupling of NCH_2 protons with two phosphorus atoms of equivalent phosphonate groups attached to the same carbon, while the ^1H NMR spectrum of monophosphonate **8** shows a doublet at 5.77 ppm (J_{HP} 3 Hz) due to the coupling of NCH_2 protons with one phosphorus atom of the phosphonate group.

The structures of these two compounds are consistent with all the obtained spectrometric data. The IR spectra show the change of the strong C=O stretching band from the carboxylic **5a** at 1728 cm^{-1} to 1693 cm^{-1} of

monophosphonate **8**, and its disappearance in the IR spectrum of bisphosphonate **7a**, and the appearance of characteristic large and strong bands in the 1260-915 cm^{-1} region due to the ν (P=O), ν (P–OH) and δ (POH) bands of the bisphosphonate group. This one is with multiple maxima, whose number is increased due to the large number of hydrogen bonds (see below the crystal structure of compound **7a**).[42] Large and weak ν (PO–H) and δ (POH) bands were observed with maximum at 2619 and 2774 cm^{-1} for compounds **8** and **7a**, respectively.[42]

Both the monophosphonate **8** and bisphosphonate **7a** were also characterized by FAB (fast atom bombardment) mass spectrometry (low and high resolution) and their spectra are in agreement with the proposed structures.

These methods were extended to the carboxylic acid **5b**, with a side chain with two CH_2 groups. The first attempt using neat thionyl chloride afforded a complex mixture of compounds. The synthesis of bisphosphonate **7b** was performed from carboxylic acid **5b**, by reaction *in situ* using thionyl chloride in $CHCl_3$, to afford the corresponding acyl chloride, followed by reaction with 2 eq. of tris(trimethylsilyl)phosphate and methanolysis to obtain the expected compound **7b** in 41% yield (Scheme 4).



Scheme 4. Synthesis of bisphosphonate **7b**.

The bisphosphonate structure of **7b** was readily identified through the analysis of the NMR data, including bidimensional techniques. The ^1H NMR spectrum shows a pair of multiplets at δ 2.41 and 4.75 ppm attributed to the CH_2 protons of the side chain. This does not allow the identification of the phosphorus atoms but ^{13}C NMR spectroscopy confirms the presence of the bisphosphonate group. The appearance of a quaternary carbon triplet (disappearing in DEPT 135 ^{13}C NMR spectra) at δ 72.2 ppm (with J_{CP} 143 Hz) supported the proposed structure with two phosphonate groups attached to the same carbon (P–C(OH)–P) (Tables 2 and 3). The proton-decoupled ^{31}P NMR spectra of BPs **7b** showed a single signal at 20.2 ppm confirming that two phosphorus atoms are magnetically equivalent. It is observed a lower chemical shift for BP **7b** relative to BP **7a**, which has a smaller aliphatic side chain, with the phosphorus atoms connected to a carbon atom directly bonded to the aromatic heteroatom ring. The chemical shift generally increases with the increasing number of methylene groups in the side chain.

The electrospray ionization (ESI) method was used to show the molecular ion of BP **7b**, which confirmed the proposed molecular formula. The MS spectrum showed the characteristic fragment ions corresponding to the loss of HPO_2 and H_3PO_3 fragments.[43]

The IR spectra of bisphophonate **7b** showed bands and intensities similar to the BP **7a** with the disappearance of the strong C=O stretching band from the carboxylic acid **5b** (starting material) and the appearance of multiple maxima at large and strong bands between 1261-919 cm^{-1} due to the phosphonate group vibrations ν (P=O), ν (P–OH) and δ (POH), whose number of maxima is increased due to the different influences of the hydrogen bonding system.[42] A large and weak ν (PO–H) and δ (POH) band was observed with a maximum at 2775 cm^{-1}.[42]

Bisphosphonate **7a** was recrystallized from a solution of acetone/water to afford crystals suitable for crystallographic studies. The X-ray analysis confirmed the structure of this compound proposed from the assignment of spectroscopic data. Compound **7a** crystallizes in the monoclinic crystal system, space group C2/c. The molecular structure of **7a**, with the atomic numbering scheme, is shown in Figure 1. The asymmetric unit cell contains one molecule of the compound **7a** and one water molecule.

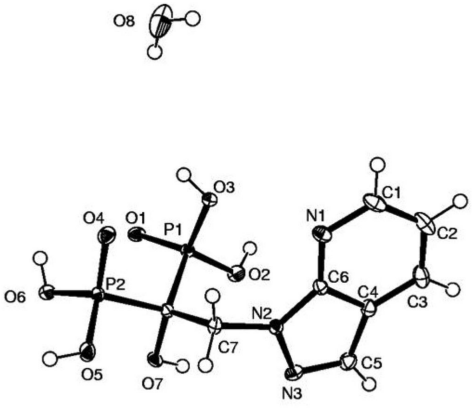


Figure 1. ORTEP[44] view of compound **7a** showing the atomic labelling scheme.

The crystal structure shows that the pyrazolo[3,4-*b*] pyridine ring is planar, and its bond lengths and angles are in agreement with its aromatic character (Table 4). The C7 atom, bonded to the ring, is also within the same plane. The C8 atom and both phosphonic groups are outside the plane of the ring (as shown in Figure 2), with one phosphonic acid moiety in a synclinal position (view from C8–C7) relative to the ring, displaying a torsion angle of –44.0(2)º between P1–C8–C7–N2.

The C8–O7, C8–C7 and C7–N2 bond distances correspond to single bonds. The P–C8 lengths fall

Table 4. Selected bond lengths (Å) and angles (degree) for compound **7a** (ORTEP numbering scheme)

Bond length / Å			
P1–C8	1.847(2)	P2–O4	1.507(2)
P1–O3	1.563(2)	P2–O5	1.528(2)
P1–O2	1.513(2)	C7–N2	1.454(3)
P1–O1	1.510(2)	C8–C7	1.548(3)
P2–C8	1.849(2)	C8–O7	1.429(3)
P2–O6	1.556(2)		
Bond angle / degree			
C8–P1–O3	105.59(9)	C8–P2–O5	103.9(1)
C8–P1–O2	104.9(1)	O4–P2–O5	115.5(1)
C8–P1–O1	108.91(9)	O6–P2–O4	113.95(9)
O2–P1–O1	115.83(9)	O6–P2–O5	106.97(9)
O3–P1–O2	108.89(9)	C8–C7–N2	116.0(2)
O3–P1–O1	111.99(9)	P1–C8–C7	114.0(1)
C8–P2–O6	108.16(9)	P1–C8–O7	108.5(1)
C8–P2–O4	107.68(9)	P2–C8–C7	104.4(1)

within the range observed for other alkylphosphonic acids (Table 4).[45] The C7 and C8 atoms present a slightly deformation from the ideal tetrahedral geometry with angles of C8–C7–N2 of 116.0(2)º, P1–C8–C7 of 114.0(1)º and P2–C8–C7 of 104.4(1)º probably due to the presence of the bulky phosphonic acid groups. This also causes similar deformation from the ideal tetrahedral shape at both phosphorus atoms with angles ranging from 115.83(9)-104.9(1)º for P1 and 115.5(1)-103.9(1)º for P2. The larger angles always involve the P=O and the P–OH bonds that present similar bond length: P1–O1 (1.510(2) Å), P1–O2(H) 7(1.513(2) Å), P2–O4 (1.506(2) Å) and P2–O5(H) (1.528(2) Å), as observed for other akylphosphonic acids.[45,46] The bond lengths and the wider angles could reflect the loss of pure double P=O or simple P–O bond to an intermediate character with electronic delocalization between these bonds.[47]

The supramolecular arrangement of compound **7a** results from the formation of an extended hydrogen bond network (see Table 5 and Figure 3) through the P=O and P–O–H groups in the phosphonic acids, water hydrogens and N3 atom that connect each BP molecule with four other molecules of BPs and with three water molecules. Two $R_2^2(8)$ and a $C_1^1(6)$ synthons are formed between the P=O and P–O–H groups in the phosphonic acids and an O–H···N interaction further connects the BP molecules (Figure 3a). The $R_2^2(8)$ synthons give rise to head-to-head dimers of BPs, while the $C_1^1(6)$ synthon and the O–H···N interactions connect these dimers with similar ones. Water molecules bridge two BP molecules (Figure 3b) originating extended chains of BP dimers along the *c* direction. Furthermore, the pyridyl rings are involved in short interactions (C–C 3.314(8) Å) connecting BP molecules.[47]

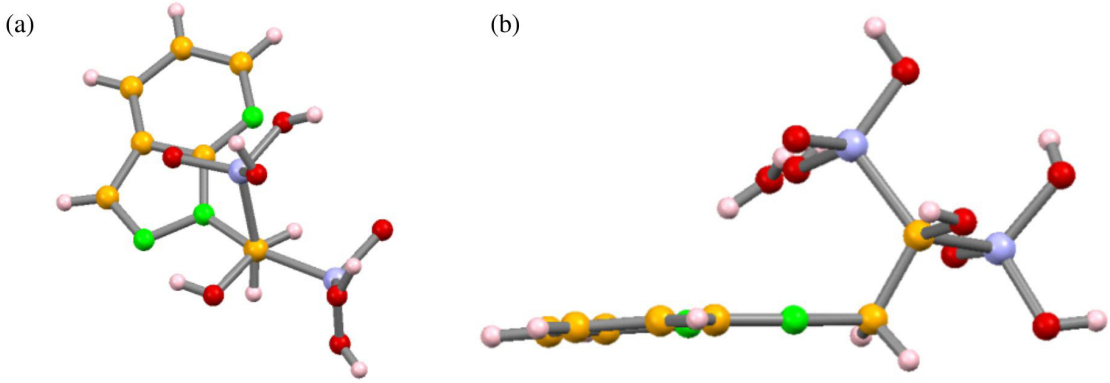


Figure 2. Conformation of phosphonic group relative to the aromatic ring (a) in a view along C7–C8 bond and (b) in a view along the plane of the ring.

Table 5. Hydrogen bonds lengths (Å) and angles (degree) for BP **7a** (ORTEP numbering scheme)

D–H····A	D–H / Å	H····A / Å	D····A / Å	D–H····A / degree	Symmetry code
O3–H3A····O1	0.82	1.74	2.533(2)	163	1–x, y, 3/2–z
O5–H5A····O2	0.82	1.66	2.450(2)	160	½–x, 1/–y, 1–z
O6–H6····O4	0.82	1.75	2.552(2)	167	1–x, y, 3/2–z
O7–H7····N3	0.82	2.08	2.833(2)	153	–x, y, 3/2–z
O8–H01····O4	0.81(4)	2.22(4)	2.974(3)	155(3)	1–x, –y, 1–z
O8–H02····O1	0.84(5)	1.94(5)	2.781(3)	174(3)	1–x, y, 3/2–z

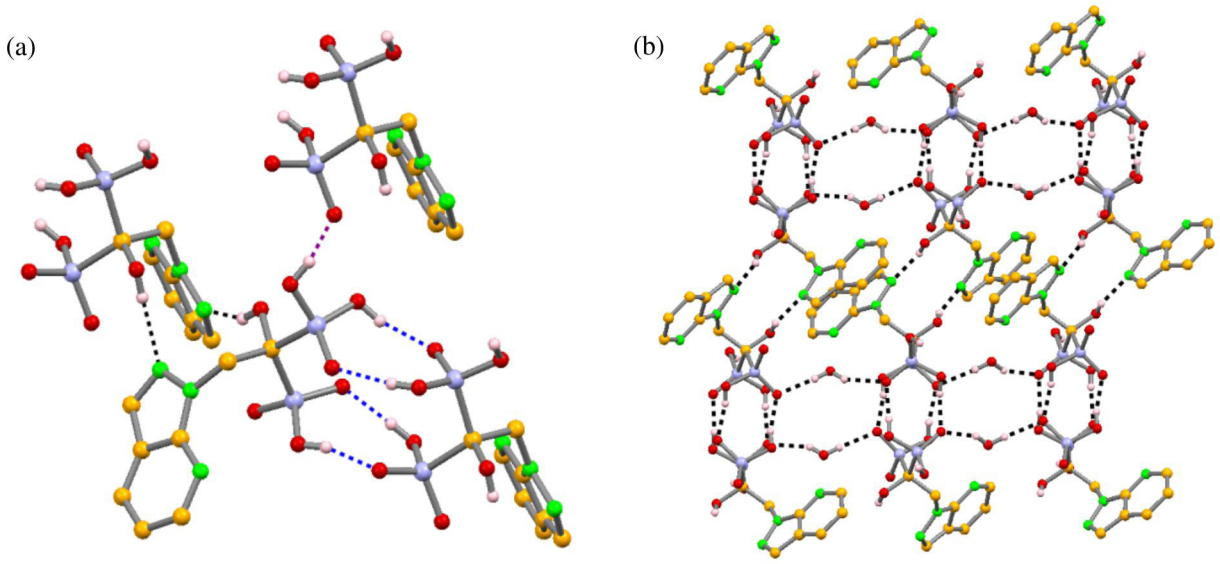


Figure 3. (a) Interactions between the BP molecules depicting the $R_2^2(8)$ synthons represented in blue, the $C_1^1(6)$ synthon in purple and the O–H···N hydrogen bonds in black; (b) supramolecular packing showing two sets of head-to-head dimers of BPs connected to the $R_2^2(8)$ synthons, linked by $C_1^1(6)$ synthons and O–H···N interactions, and the water molecules bridging two BP molecules (non-contact hydrogen atoms are omitted for clarity).

Conclusions

New bisphosphonates derived from pyrazolo[3,4-*b*] pyridine were obtained and characterized. All the syntheses, starting from 2-chloro-3-formylpyridine, were described and the products were fully characterized. Spectroscopic data were used to assign the substitution patterns and identify the regioisomers; ^{13}C NMR proved to be the best technique to identify the N-1 and N-2 ester regioisomers.

Following the hydrolysis of N-1 ester derivatives, the corresponding carboxylic acids were used as starting materials to synthesize the novel 1-hydroxy-1*H*-pyrazolo[3,4-*b*]pyridine bisphosphonates, in moderated to good yields. The formation of a monophosphonate compound was also reported. Bisphosphonates and monophosphonate were fully characterized using the usual spectroscopic methods, especially NMR spectroscopy, including two dimensional NMR techniques (correlation spectroscopy (COSY) and one-bond (HSQC) and long-range (HMBC) ^{1}H-^{13}C NMR). The recrystallization of BP **7a** (n = 1) yielded crystals suitable for single crystal X-ray diffraction analysis and its structure was determined, confirming the assignment of pyrazolo[3,4-*b*]pyridine derivatives.

Experimental

General remarks

NMR spectra were recorded on a Bruker AMX 300 and on a Bruker Avance II 300 (^{1}H 300 MHz, ^{13}C 75 MHz, ^{31}P 121 MHz) and on a Bruker Avance II 400 (^{1}H 400 MHz, ^{13}C 100 MHz, ^{31}P 162 MHz) spectrometers. Chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. ^{1}H and ^{13}C NMR chemical shifts were assigned using DEPT and APT (Attached Proton Test) sequences, and bidimensional COSY, HSQC and HMBC techniques. Assignments were made by comparison of chemical shifts, peak multiplicities and J values, and were supported by bidimensional heteronuclear HMBC and HSQC correlation techniques. Infrared spectra were recorded on a Perkin Elmer FTIR 1725xIR Fourier transform spectrophotometer using KBr discs or film. The bands are quoted in cm^{-1}. Low resolution and high resolution mass spectra (HRMS) analyses were performed at the 'C.A.C.T.I. - Unidad de Espectrometria de Masas' at the University of Vigo, Spain, on a VG AutoSpect M, MicroTOF (Bruker Daltonics) or APEX-Q (Bruker Daltonics) equipments. Elemental analysis were performed on a CE instrument EA 1110CHNSO and a Fisons EA-1108 elemental analyzer. Melting points were determined on a Reichert Thermovar melting point apparatus and are not corrected.

All reactions involving air sensitive reagents were performed under an atmosphere of dry nitrogen and all solvents were degassed before use. All solvents were distilled under a nitrogen atmosphere. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. $CHCl_3$ was distilled from calcium hydride. Column chromatography was performed on silica gel (230-400 mesh) under a positive pressure of nitrogen.

1*H*-Pyrazolo[3,4-*b*]pyridine (**2**)[34]

Hydrazine hydrate (10 mL) was added to a mixture of 2-chloro-3-formylpyridine **1** (5.00 g, 35 mmol) and *p*-TsOH (3.50 g, 18 mmol). The reaction mixture was stirred for 3 h at 130 °C. Upon cooling with cold water, the mixture was extracted with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuum and gave compound **2** (3.65 g, 87%) as a yellow solid; mp 88-90 °C (97-98 °C);[34] FTIR (KBr) ν_{max}/cm^{-1} 3450 (N–H), 3089, 3026 (C–H Ar), 2958, 2915 (C–H), 1606, 1588, 1509, 1470, 1429 (C=N, C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 1.69 (s, 1H, N–H), 7.19 (dd, 1H, *J* 4.7 and 7.5, Ar*H*, 5-H), 8.12 (s, 1H, Ar*H*, 3-H), 8.15 (d, 1H, *J* 8.1, Ar*H*, 4-H), 8.63 (d, 1H, *J* 4.5, Ar*H*, 6-H).

General procedure 1

A mixture of 1*H*-pyrazolo[3,4-*b*]pyridine **2** (1 eq.) and K_2CO_3 (10 eq.) in DMF was stirred at 80 °C. After 30 min, excess $Br(CH_2)_nCO_2Et$ was added and the reaction mixture was stirred for 1 h at 80 °C. Upon cooling, the mixture was acidified with 10% aqueous HCl solution and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuum and the resulting oil was purified by column chromatography (1:1 ethyl ether:petroleum ether).

Ethyl 2-(1*H*-pyrazolo[3,4-*b*]pyridin-1-yl)acetate (**3a**)

Following general procedure 1, reaction of 1*H*-pyrazolo[3,4-*b*]pyridine **2** (400 mg, 3.36 mmol) in DMF (4 mL), K_2CO_3 (4.64 g, 34.0 mmol) and $BrCH_2CO_2Et$ (0.75 mL, 6.76 mmol) gave compound **3a** (600 mg, 87%) as a pale yellow oil; FTIR (film) ν_{max}/cm^{-1} 3108, 3070 (C–H Ar), 2978, 2929 (C–H), 1754 (C=O), 1601, 1578, 1500, 1479, 1462, 1437 (C=N, C=C), 1201 (C–O); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 1.23 (t, 3H, *J* 7.1, OCH_2CH_3), 4.20 (q, 2H, *J* 7.2, OCH_2CH_3), 5.30 (s, 2H, NCH_2), 7.13 (dd, 1H, *J* 8.1 and 4.5, Ar*H*, 5-H), 8.05 (dd, 1H, *J* 7.8 and 1.5, Ar*H*, 4-H), 8.06 (s, 1H, Ar*H*, 3-H), 8.52 (dd, 1H, *J* 4.5 and 1.2, Ar*H*, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm 14.0 (OCH_2CH_3), 48.1 (NCH_2), 61.6 (OCH_2CH_3), 115.6 (Ar: C3a), 117.1 (Ar: C5), 130.2 (Ar: C3), 133.2 (Ar: C4), 148.9 (Ar: C6), 150.6 (Ar: C7a), 167.9 (C=O); MS (EI) *m/z* 205 (M^+, 18%), 132 (M^+–CO_2Et, 100%); HRMS (EI) *m/z* calcd. for $C_{10}H_{11}N_3O_2$ 205.0851 $[M]^+$, found 205.0855.

Ethyl 3-(1*H*-pyrazolo[3,4-*b*]pyridin-1-yl)propanoate (**3b**) and ethyl 3-(2*H*-pyrazolo[3,4-*b*]pyridin-2-yl)propanoate (**4b**)

Following general procedure 1, the reaction of 1*H*-pyrazolo[3,4-*b*]pyridine **2** (500 mg, 4.20 mmol) in DMF (5 mL), K_2CO_3 (5.80 g, 42.0 mmol) and $Br(CH_2)_2CO_2Et$ (1.0 mL, 8.40 mmol) gave compound **3b** (288 mg, 31%) and compound **4b** (167 mg, 18%) as pale yellow oils.

Compound **3b**: FTIR (film) ν_{max}/cm^{-1} 3099, 3062 (C–H Ar), 2982, 2937 (C–H), 1733 (C=O), 1600, 1572, 1499, 1458, 1436 (C=N, C=C), 1190 (C–O); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 1.19 (t, 3H, *J* 7.2, OCH_2CH_3), 3.01 (t, 2H, *J* 7.2, NCH_2CH_2), 4.13 (q, 2H, *J* 7.2, OCH_2CH_3), 4.85 (t, 2H, *J* 7.2, NCH_2), 7.14 (dd, 1H, *J* 8.1 and 4.5, Ar*H*, 5-H), 8.01 (s, 1H, Ar*H*, 3-H), 8.06 (dd, 1H, *J* 8.1 and 1.5, Ar*H*, 4-H), 8.55 (dd, 1H, *J* 4.5 and 1.2, Ar*H*, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm 14.1 (OCH_2CH_3), 34.3 (NCH_2CH_2), 42.7 (NCH_2), 60.7 (OCH_2CH_3), 115.6 (Ar: C3a), 116.9 (Ar: C5), 130.1 (Ar: C4), 132.3 (Ar: C3), 148.7 (Ar: C6), 150.1 (Ar: C7a), 171.0 (C=O); MS (EI) *m/z* 219 (M^+, 7.6%), 174 (M^+–OEt, 9.6%), 146 (M^+–CO_2Et, 10.7%), 132 (M^+–CH_2CO_2Et, 100%), 118 (M^+–$(CH_2)_2CO_2Et$, 6.6%); HRMS (EI) *m/z* calcd. for $C_{11}H_{13}N_3O_2$ 219.1008 $[M]^+$, found 219.1004.

Compound **4b**: FTIR (film) ν_{max}/cm^{-1} 3075, 3050 (C–H Ar), 2959, 2926 (C–H), 1727 (C=O), 1610, 1550, 1511, 1458 (C=N, C=C), 1208 (C–O); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm 1.22 (t, 3H, *J* 7.2, OCH_2CH_3), 3.12 (t, 2H, *J* 6.3, NCH_2CH_2), 4.12 (q, 2H, *J* 7.2, OCH_2CH_3), 4.74 (t, 2H, *J* 6.5, NCH_2), 7.04 (dd, 1H, *J* 8.4 and 4.2, Ar*H*, 5-H), 8.02 (dd, 1H, *J* 8.4 and 1.5, Ar*H*, 4-H), 8.04 (s, 1H, Ar*H*, 3-H), 8.68 (dd, 1H, *J* 4.2 and 1.5, Ar*H*, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm 14.0 (OCH_2CH_3), 34.5 (NCH_2CH_2), 49.3 (NCH_2), 65.8 (OCH_2CH_3), 113.7 (Ar: C3a), 117.7 (Ar: C5), 123.6 (Ar: C3), 129.7 (Ar: C4), 151.4 (Ar: C6), 158.5 (Ar: C7a), 170.8 (C=O); MS (EI) *m/z* 219 (M^+, 21.9%), 174 (M^+–OEt, 9.4%), 146 (M^+–CO_2Et, 36.7%), 132 (M^+–CH_2CO_2Et, 21.4%), 118 (M^+–$(CH_2)_2CO_2Et$, 4.2%); HRMS (EI) *m/z* calcd. for $C_{11}H_{13}N_3O_2$ 219.1008 $[M]^+$, found 219.1008.

General procedure 2

1*H*-pyrazolo[3,4-*b*]pyridine ester derivative (**3**) (1 eq.) and excess aqueous NaOH solution (10 mol L^{-1}) were stirred at reflux for 1.5-2 h. After cooling, the mixture was acidified with 10% aqueous HCl solution and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent removed in vacuum. The resulting solid was purified by recrystallization from ethyl

acetate/petroleum ether. The following compounds were prepared by this procedure:

2-(1*H*-Pyrazolo[3,4-*b*]pyridin-1-yl)acetic acid (**5a**)

Reaction of compound **3a** (830 mg, 4.00 mmol) in aqueous NaOH solution (10 mol L^{-1}, 6 mL) for 2 h gave compound **5a** (690 mg, 97%) as pale yellow crystals; mp 180-182 °C; FTIR (KBr) ν_{max}/cm^{-1} 3100-2500 (OH), 3087 (C–H Ar), 2985, 2945 (C–H), 1728 (C=O), 1606, 1579, 1507, 1465 (C=N, C=C); ^{1}H NMR (300 MHz, MeOD) δ/ppm 4.92 (s, 1H, OH), 5.29 (s, 2H, NCH_2), 7.24 (dd, 1H, *J* 7.9 and 4.7, Ar*H*, 5-H), 8.13 (s, 1H, Ar*H*, 3-H), 8.23 (dd, 1H, *J* 8.1 and 1.5, Ar*H*, 4-H), 8.52 (dd, 1H, *J* 4.5 and 1.5, Ar*H*, 6-H); ^{13}C NMR (75 MHz, MeOD) δ/ppm 48.9 (N*C*H_2), 117.4 (Ar: C3a), 118.5 (Ar: C5), 132.3 (Ar: C4), 134.4 (Ar: C3), 150.1 (Ar: C6), 151.7 (Ar: C7a), 171.3 (C=O); MS (EI) *m/z* 177 (M^+, 5.6%), 132 (M^+–CH_2CO_2H, 100%); found C, 54.12, H, 3.98, N, 23.68; $C_8H_7N_3O_2$ requires: C, 54.24, H, 3.98, N, 23.72%.

3-(1*H*-Pyrazolo[3,4-*b*]pyridin-1-yl)propanoic acid (**5b**)

Reaction of compound **3b** (180 mg, 0.82 mmol) in aqueous NaOH solution (10 mol L^{-1}, 1.5 mL) for 1.5 h gave compound **5b** (150 mg, 98%) as yellow crystals; mp 83-84 °C; FTIR (KBr) ν_{max}/cm^{-1} 3100-2300 (OH), 3100, 3068 (C–H Ar), 2940, 2857 (C–H), 1711 (C=O), 1604, 1580, 1500, 1460, 1439, 1420 (C=N, C=C); ^{1}H NMR (300 MHz, MeOD) δ/ppm 2.96 (t, 2H, *J* 7.1, NCH_2C*H*$_2$), 4.76 (t, 2H, *J* 7.1, NCH_2), 7.20 (dd, 1H, *J* 7.8 and 4.5, Ar*H*, 5-H), 8.06 (s, 1H, Ar*H*, 3-H), 8.19 (d, 1H, *J* 8.1, Ar*H*, 4-H), 8.52 (d, 1H, *J* 4.5, Ar*H*, 6-H); ^{13}C NMR (75 MHz, MeOD) δ/ppm 34.7 (NCH_2*C*H_2), 43.8 (N*C*H_2), 117.3 (Ar: C3a), 118.2 (Ar: C5), 132.1 (Ar: C4), 133.7 (Ar: C3), 149.9 (Ar: C6), 151.0 (Ar: C7a), 174.4 (C=O); MS (EI) *m/z* 191 (M^+, 5.2%), 146 (M^+–CO_2H, 5.2%), 132 (M^+–CH_2CO_2H, 100%), 118 (M^+–$(CH_2)_2CO_2H$, 4.5 %); found C, 56.64, H, 4.82, N, 21.87; $C_9H_9N_3O_2$ requires: C, 56.54, H, 4.74, N, 21.98%.

1-Hydroxy-2-(1*H*-pyrazolo[3,4-*b*]pyridin-1-yl)ethane-1,1-diylbis(phosphonic acid) (**7a**) and 2-(1*H*-pyrazolo[3,4-*b*]pyridin-1-yl)acetylphosphonic acid (**8**)

Thionyl chloride (0.49 mL, 6.76 mmol) was added to a solution of a carboxylic acid **5a** (300 mg, 1.69 mmol) in $CHCl_3$ (6 mL) at 0 °C, then it was kept under reflux for 2 h. Solvents were removed under reduced pressure to give the corresponding acyl chloride, which was immediately used without further purification. The crude acyl chloride was dissolved in dry THF (6 mL) and tris(trimethylsilyl) phosphite (1.13 mL, 3.38 mmol) was added. Then, the mixture was stirred at room temperature for 1 h. The excess solvent was removed under reduced pressure, methanol (1.5 mL) was added and the mixture was stirred for 1 h. After solvent removal under reduced pressure, the residue was washed with ethyl ether and precipitated with acetone and methanol. Compound **8** (150 mg, 36%) was isolated as a white powder; mp 229 °C (decomp.); FTIR (KBr) ν_{max}/cm^{-1} 3455 (OH), 3123, 3099 (C–H Ar), 2970, 2938 (C–H), 2619 (PO–H), 1693 (C=O), 1560, 1508, 1438 (C=N and C=C), 1239, 1155, 1101, 1066, 1008, 946, 920 (P=O, P–OH, POH); ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm 5.77 (d, 2H, J_{HP} 3.2, NCH_2), 7.30 (dd, 1H, *J* 8.0 and 4.8, Ar*H*, 5-H), 8.27 (s, 1H, Ar*H*, 3-H), 8.33 (dd, 1H, *J* 8.0 and 1.2, Ar*H*, 4-H), 8.56 (dd, 1H, *J* 4.4 and 1.2, Ar*H*, 6-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm 57.2 (d, J_{CP} 64.3, N*C*H_2), 116.1 (Ar: C3a), 118.2 (Ar: C5), 131.6 (Ar: C4), 134.2 (Ar: C3), 149.8 (Ar: C6), 151.4 (Ar: C7a), 210.5 (d, J_{CP} 169.2, C=O); ^{31}P NMR (121 MHz, H_3PO_4/DMSO-d_6) δ/ppm –4.1 (s); MS (FAB) *m/z* 242 ([M + H]$^+$, 60.8%), 154 (100%); HRMS (FAB) *m/z* calcd. for $C_8H_8N_3O_7P$ 242.0331 [M + H]$^+$, found 242.0328.

A mixture of a carboxylic acid **5a** (200 mg, 1.13 mmol) and thionyl chloride (3.7 mL, excess) was kept under reflux for 2 h. Solvents were removed under reduced pressure to give the corresponding acyl chloride **6a**, which was immediately used without further purification. The crude acyl chloride was dissolved in dry THF (1.9 mL), cooled to 0 °C and tris(trimethylsilyl)phosphite (1.13 mL, 3.38 mmol) was added. Then, the mixture was stirred at room temperature for 10 min. The excess solvent was removed under reduced pressure, methanol was added and the mixture was stirred for 1 h. After solvent removal under reduced pressure, the residue was washed with ethyl ether and precipitated with acetone to afford bisphosphonate **7a** (290 mg, 81%) as white powder; mp 224-227 °C; FTIR (KBr) ν_{max}/cm^{-1} 3368, 3125-2566 (OH), 3115, 3079, 3044 (C–H Ar), 2817 (C–H), 2774 (PO–H), 1619, 1522, 1503, 1469 (C=N, C=C), 1257, 1235, 1160, 1137, 1109, 1091, 1055, 1036, 1009, 982, 915 (P=O, P–OH, POH); ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm 5.02 (t, 2H, *J* 9.0, NCH_2), 6.87 (br s, 1H, OH), 7.25 (m, 1H, Ar*H*, 5-H), 8.19 (s, 1H, Ar*H*, 3-H), 8.29 (d, 1H, *J* 6.0, Ar*H*, 4-H), 8.55 (d, 1H, *J* 3.0, Ar*H*, 6-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm 50.7 (N*C*H_2), 73.6 (t, J_{CP} 144.0, *C*(OH)$(PO_3H_2)_2$), 115.6 (Ar: C3a), 117.2 (Ar: C5), 131.4 (Ar: C4), 132.6 (Ar: C3), 148.2 (Ar: C6), 150.1 (Ar: C4a); ^{31}P NMR (121 MHz, H_3PO_4/DMSO-d_6) δ/ppm 17.0 (s); MS (FAB) *m/z* 324 ([M + H]$^+$, 14.4%), 157 (100%); HRMS (FAB) *m/z* calcd. for $C_8H_{12}N_3O_7P_2$ 324.0151 [M + H]$^+$, found 324.0152.

1-Hydroxy-3-(1H-pyrazolo[3,4-*b*]pyridin-1-yl)propane-1,1-diylbis(phosphonic acid) (**7b**)

Thionyl chloride (0.08 mL, 1.05 mmol) was added to a solution of a carboxylic acid **5b** (50 mg, 0.26 mmol) in $CHCl_3$

(1 mL), then it was kept under reflux for 2 h. Solvents were removed under reduced pressure to give the corresponding acyl chloride, which was immediately used without further purification. The crude acyl chloride was dissolved in dry THF (1 mL), cooled to 0 °C and tris(trimethylsilyl) phosphite (0.18 mL) was added. Then, the mixture was stirred at room temperature for 1 h. The excess solvent was removed under reduced pressure, methanol (1 mL, 0.524 mmol) was added and the mixture was stirred for 1 h. After solvent removal under reduced pressure, the residue was washed with ethyl ether and precipitated with acetone and methanol. Bisphosphonate **7b** (36 mg, 41%) was isolated as a white powder; mp 130 °C (decomp.); FTIR (KBr) ν_{max}/cm^{-1} 3393, 3150-2500 (OH), 3121 (C–H Ar), 2940 (C–H), 2775 (PO–H), 1629, 1618, 1508, 1475, 1458 (C=N, C=C), 1261, 1153, 1107, 1065, 996, 976, 938, 919 (P=O, P–OH, POH); ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm 2.41 (m, 2H, NCH_2CH_2), 4.75 (m, 2H, NCH_2), 7.20 (dd, 1H, *J* 8.0 and 4.4, Ar*H*, 5-H), 8.14 (s, 1H, Ar*H*, 3-H), 8.23 (dd, 1H, *J* 8.0 and 1.6, Ar*H*, 4-H), 8.53 (dd, 1H, *J* 8.0 and 1.4, Ar*H*, 6-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm 34.3 (NCH_2CH_2), 43.4 (NCH_2), 72.2 (t, J_{CP} 143.5, $C(OH)(PO_3H_2)_2$), 116.2 (Ar: C3a), 118.0 (Ar: C5), 131.6 (Ar: C4), 133.1 (Ar: C3), 149.6 (Ar: C6), 150.4 (Ar: C7a); ^{31}P NMR (121 MHz, H_3PO_4/DMSO-d_6) δ/ppm 20.2 (s); MS (ESI) *m/z* 338 ($[M + H]^+$, 100%), 256 ($[M + H]^+ – H_3PO_3$, 29,9%), 192 (256-HPO_2, 12,8%); HRMS (ESI) *m/z* calcd. for $C_9H_{14}N_3O_7P_2$ 338.0301 $[M + H]^+$, found 338.0287.

Crystal structure determination of 1-hydroxy-2-(1*H*-pyrazolo[3,4-*b*]pyridin-1-yl)ethane-1,1-diylbis(phosphonic acid) (**7a**)

Crystal data for the BP **7a** were collected at 150 K on a Bruker AXS-KAPPA APEX II diffractometer using graphite-monochromated Mo K_α radiation ($\lambda = 0.71069$ Å) at room temperature. The X-ray generator was operated at 50 kV and 30 mA. X-ray data collection was monitored by the SMART program (Bruker).[48] All data were corrected for Lorentzian, polarization and absorption effects using the SAINT and SADABS programs (Bruker).[48] All non-hydrogen atoms were refined by full matrix least squares on F2 with anisotropic thermal motion parameters whereas H-atoms were placed in idealized positions and allowed to refine isotropically riding on the parent C atom. The structure was solved by direct methods with SIR97[49] program and refined by full matrix least-squares on F2 with SHELXL-97 program,[50] both included in the package of programs WINGX version 1.70.01.[51] Graphical representations were prepared using ORTEP35[44] and Mercury 36 programs.[52]

A summary of the crystal data, structure solution and refinement parameters are given in the Supplementary Information (SI) section. Cambridge Crystallographic Data Centre 912669 contains all crystallographic details of this publication.

Supplementary Information

Supplementary data (NMR data ^{1}H, ^{13}C and ^{31}P NMR spectra) of new compounds and crystal data and structure refinement for compound **7a** are available free of charge at http://jbcs.sbq.org.br as PDF file.

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