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Novel Bisphosphonates Derived from 1*H*-Indazole, 1*H*-Pyrazolo[3,4-*b*]Pyridine, and 1*H*-Pyrazolo[3,4-*b*]Quinoline

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ABSTRACT: *Novel tetraethyl ethylene-1,1-bisphosphonate esters derived from 1H-indazole, 1H-pyrazolo[3,4-b]pyridine, and 1H-pyrazolo[3,4-b]quinoline were synthesized by a Michael addition reaction of tetraethyl ethylidene-1,1-bisphosphonate with the corresponding heterocycle, using conventional heating and microwave-assisted methods. The microwave-assisted method provides shorter reaction times and better yields. The hydrolysis of bisphosphonates afforded the corresponding bisphosphonic acids or salt, using concentrated hydrochloric acid or TMSBr/collidine, respectively. All new compounds were fully characterized, and their structures were assigned using ^{1}H, ^{31}P, and ^{13}C NMR and IR spectroscopies and mass spectrometry. The molecular structure of compound* **6** *was confirmed by X-ray diffraction studies.* © 2015 Wiley Periodicals, Inc. Heteroatom Chem. 27:3–11, 2016; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21282

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INTRODUCTION

Bisphosphonates are an important class of organophosphorus drugs known by their broad spectrum of therapeutic applications in the treatment of diseases characterized by abnormal calcium metabolism, due to their high affinity for calcium and target the bone mineral [1–5]. Bisphosphonates present other therapeutic applications against pathogenic agents due to their antiparasitic [6–8], herbicidal [9] and antibacterial activities [10]. Bisphosphonates were also studied as ligands for radioactive metal complexes [11, 12] and as chelating agents for the treatment of human metal intoxications [13].

The activity of bisphosphonates, in the treatment of bone disorders, is improved by the presence of a nitrogen containing group bonded to an alkyl moiety or to a heteroaromatic cycle [14–16]. Indazole, pyrazolo[3,4-*b*]pyridine, and pyrazolo[3,4-*b*]quinoline are heteroaromatic compounds with two or three nitrogen atoms in an aromatic moiety, resembling the heteroaromatic part of the most potent third-generation bisphosphonates, and are promising moieties for drug discovery.

Indazole, pyrazolo[3,4-*b*]pyridine and pyrazolo [3,4-*b*]quinoline have been studied, and a large

number of remarkable biological applications have been described, such as anticancer, antidepressant or antianxiety, antiinflammatory, and antiviral [17–20]. They also found applications as organic functional materials, including in fluorescent and optoelectronics materials, such as chemosensors and organic light emitting diodes [21–23].

Taking into account the potential of bisphosphonates and these heterocycles, it can be conceived that molecules bearing both moieties can provide compounds with high potential for applications in medicinal chemistry and also in materials chemistry.

Microwave-assisted heating is an invaluable methodology in organic synthesis, usually with some advantages over the standard heating techniques, such as the acceleration of the reaction, reduction of its time, high yields, and better selectivities [24, 25]. Microwave-assisted reactions were already used to prepare hydroxymethylene-1,1-bisphosphonates, from carboxylic acids, phosphorus trichloride and phosphorous acid [26], and aminomethylenebisphosphonates, from the reaction of amines with triethyl orthoformate and diethyl phosphite [27].

Following previous studies on bisphosphonates derived from indazole and condensed pyrazole [12, 28–30], the present investigation reports the synthesis of new tetraethyl ethylene-1,1-bisphosphonate esters derived from 1*H*-indazole, 1*H*-pyrazolo[3,4-*b*]pyridine, and 1*H*-pyrazolo[3,4-*b*]quinoline, and their hydrolysis to the corresponding bisphosphonic acids or salt, using conventional thermal or microwave irradiation conditions, to evaluate and compare reaction times, yields, and regioselectivity between both methods.

RESULTS AND DISCUSSION

Synthesis

The synthesis of 1*H*-pyrazolo[3,4-*b*]pyridine **2** and 1*H*-pyrazolo[3,4-*b*]quinoline **3** was performed in high yields, by a reaction of 2-chloro-3-formylpyridine or 2-chloro-3-formylquinoline and hydrazine with *p*-TsOH using a process reported in the literature [30, 31]. Tetraethyl ethylidene-1,1-bisphosphonate **4** was obtained from tetraethyl methylenebisphosphonate in two steps, according to a literature procedure [32].

The synthesis of new bisphosphonate esters derived from indazole and pyrazole-fused heterocycles was initially performed by conventional thermal conditions using a preheated oil bath. The formation of tetraethyl ethylidene-1,1-bisphosphonate esters **5–7** was carried out by a Michael addition reaction between the corresponding heterocycle **1–3** and tetraethyl ethylene-1,1-bisphosphonate **4**. The Michael addition reaction was carried out at reflux, in THF, during 16 h, to give the corresponding N-1 substituted bisphosphonate esters **5–7**, in good to very good yields (Table 1). This method presents complete regioselectivity, with formation of only the N-1 heterocyclic regioisomer.

To develop a new methodology for the synthesis of bisphosphonate esters and to compare the behavior of these compounds in this reaction under other conditions, a Michael addition reaction was carried out using microwave-assisted conditions. In this method, the heteroaromatic derivative **1–3** and tetraethyl ethylidene-1,1-bisphosphonate **4** in THF was heated to 95°C, for 30 min, in a laboratory microwave reactor to afford, after purification, the ethylene-1,1-bisphosphonate derivative **5–7** in very good to excellent yields, with the yields decreasing with the extension of the aromatic system or the increase in the number of nitrogen atoms (Table 1). This methodology showed to be superior to the conventional thermal method, affording the same products in shorter times, with higher yields and fewer side products. Both methodologies showed complete regioselectivity, with the formation of only the same N-1 regioisomer.

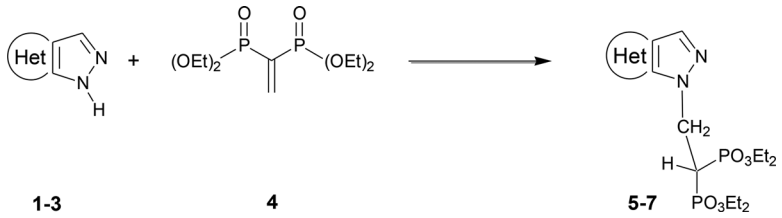
The bisphosphonate esters were submitted to acid hydrolysis with concentrated hydrochloric acid. The free bisphosphonic acids **8** and **9** were easily prepared and isolated in good yields, but the ^{31}P NMR spectra of the crude of the hydrolysis of bisphosphonate ester **7** showed a mixture of the corresponding bisphosphonic acid **10** and other unidentified phosphonated species (Table 2). All attempts to purify compound **10** by precipitation with acetone/methanol/water failed.

An alternative procedure to convert bisphosphonate esters to bisphosphonic acids is the McKenna procedure, using trimethylsilyl bromide, followed by methanolysis [33]. A first attempt to hydrolyze bisphosphonate ester **7** under McKenna conditions gave also a mixture of bisphosphonic acid **10** and other phosphonated species as revealed by ^{31}P NMR. Therefore, the current procedure by Wiemer et al. [34] was used, which involves the bisphosphonate ester **7** hydrolysis by treatment with trimethylsilyl bromide and 2,4,6-collidine, followed by a basic workup to afford quantitatively the corresponding bisphosphonic acid salt **11** (Scheme 1).

Spectroscopic Characterization

The structures of synthesized compounds **5–9** and **11** were determined from ^{1}H NMR, ^{31}P NMR, ^{13}C NMR, IR and mass spectra. The

TABLE 1 Synthesis of Bisphosphonates **5–7** by a Michael addition reaction



1-3 **4** **5-7**

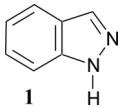
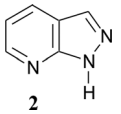
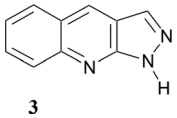
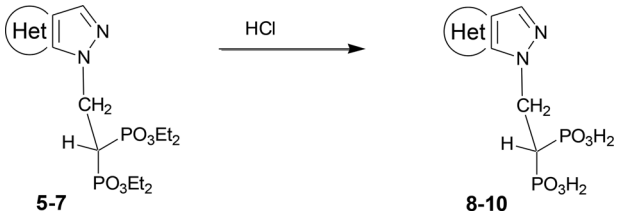
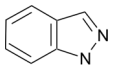
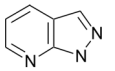
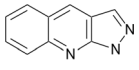
Het	*Heating Condition*	*Reaction Time (h)*	*Product*	*Yield (%)*
 **1**	Conventional	16	**5**	71
	Microwave	0.5		99
 **2**	Conventional	16	**6**	81
	Microwave	0.5		95
 **3**	Conventional	16	**7**	79
	Microwave	0.5		86

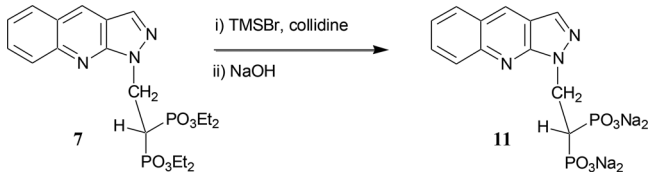
TABLE 2 Synthesis of Bisphosphonic Acids **8–10**



5-7 **8-10**

Het	*Reaction Time (h)*	*Product*	*Yield (%)*
 **5**	2	**8**	73
 **6**	4	**9**	76
 **7**	2	**10**	[a]

[a]A mixture of bisphosphonic acid **10** and unidentified phosphonated species was obtained.



7 **11**

SCHEME 1

structure of compound **6** was also confirmed by single crystal X-ray diffraction.

Several mass spectrometry (MS) techniques were used to show the characteristic fragment patterns of the lateral chain of the heterocycles containing phosphonate groups and to show the molecular ion, confirming the proposed formula of the new compounds [35].

The IR spectra of the new compounds **5–9** and **11** present large and strong bands, usually with several maxima, characteristic of the bisphosphonate groups [36–38].

The structures of bisphosphonate esters and bisphosphonic acids and salt (compounds **5–9** and **11**) were readily identified by analysis of the NMR data, including bidimensional techniques. Analysis of these compounds by ^{1}H NMR shows signals with the expected and characteristic multiplicity due to the coupling of the methine and methylene protons of the side chain with the two phosphorus atoms attached to the same carbon.

^{13}C NMR spectroscopy confirms the presence of the bisphosphonate ester, acid and salt groups, with the presence of a carbon triplet at δ 36.9–37.3 ppm (J_{CP} = 130–133 Hz), at δ 39.3–40.4 ppm (J_{CP} = 121–123 Hz), and at δ 39.8 ppm (J_{CP} = 109 Hz),

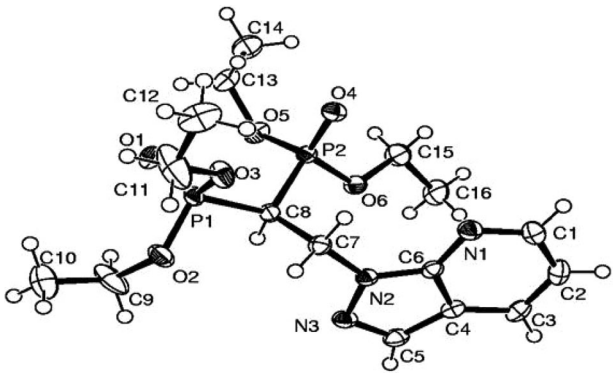


FIGURE 1 ORTEP view of bisphosphonate ester **6**, showing the atomic labelling scheme; ellipsoids are set at 50% probability [41].

respectively, supporting the proposed structure with two phosphonate or phosphonic groups attached to the same carbon (P–*C*H–P).

The proton-decoupled ^{31}P NMR spectra of bisphosphonate esters **5–7** and bisphosphonic acids **8–9** and salt **11** showed a single signal at 20.4–20.5 and 18.6–20.5 ppm, respectively, which is in agreement with the two phosphorus atoms magnetically equivalent attached to the same carbon atom, confirming the proposed structure.

Single Crystal X-Ray Diffraction Characterization

Bisphosphonate ester **6** was crystallized from an EtOAc/Et_2O/petroleum ether solution, yielding single crystals suitable for X-ray diffraction analysis that confirmed the assignment of spectroscopic data. The molecular structure of compound **6**, which crystallizes in the $P2_1/c$ monoclinic space group, is shown in Fig. 1.

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. The C atom bonded to the ring (C7) is also within the same plane (Fig. 2). The planarity, bond lengths and angles, and the positioning of C7 atom are similar to the previously reported 1-hydroxybisphosphonic acid derived from pyrazolo[3,4-*b*]pyridine [30].

The C8 carbon atom and both phosphonate ester groups are above the plane of the ring (as shown in Fig. 2), with one phosphonate ester moiety in a synclinal position relatively to the ring, displaying a torsion angle of –74.2(2)º between P2–C8–C7–N2, and the other phosphonate group in an antiperiplanar position, with a torsion angle of 157.8(2)º between P1–C8–C7–N2.

C8–C7 and C7–N2 bond distances correspond to usual single bond lengths. The P–C8 bond lengths are shorter than the corresponding 1-hydroxybisphosphonic acid bonds [30] but still fall within the range of other alkylphosphonic acids and esters [30, 38, 40, 41].

The P=O and P–O–C bond lengths are similar in both phosphonate ester groups, but P=O bonds are shorter and P–O–C bonds are longer than in the corresponding bisphosphonic acid [30]. This is observed due to the mesomeric structure of the phosphonic acid with no true double P=O or single P–O bonds.

C7 and C8 atoms present a slightly deformation from the ideal tetrahedral geometry (C8–C7–N2 113.3(1)°, P1–C8–C7 110.1(1)°, P2–C8–C7 112.0(1)°, and P1–C8–P2 114.0(1)°), due to the presence of the bulky phosphonate ester groups. This is also the cause of the deformation from the tetrahedral shape of both phosphorus atoms, which present angles ranging from 116.77(8)–101.63(8)° for P1, and 116.61(8)–100.02(8)° for P2, as observed for alkylphosphonic acids [30, 38, 40, 41]. In the phosphonate ester group, the P–O–C angles range between 120.1(1)° and 122.1(1)°, corresponding to oxygen atoms with sp^2 hybridization, and thus

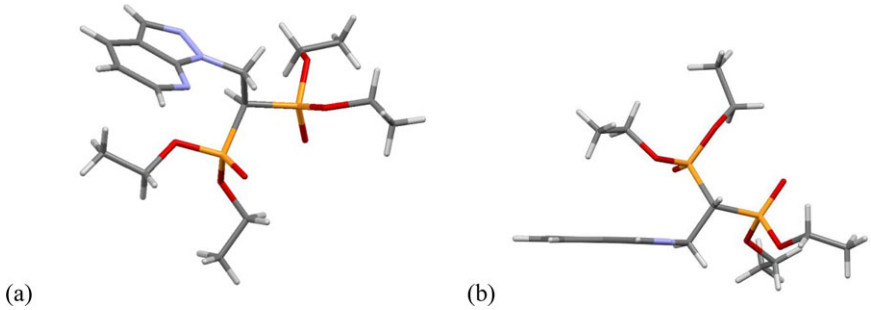


FIGURE 2 Conformation of phosphonate ester groups relatively to the aromatic ring (a) in the best view to depict the relative positioning of all the groups and (b) in a view along the plane of the ring.

TABLE 3 Details of the main short interactions responsible for the supramolecular arrangement for compound **6** (ORTEP numbering scheme)

D–H···A	*Sym. Op.*	*D–H (Å)*	*H···A (Å)*	*D···A (Å)*	*D-H···A (°)*
C3–H3···O4	*x*, –1 + *y*, *z*	0.93	2.39	3.315(2)	174
C5–H5···O1	*x*, –1 + *y*, *z*	0.88(3)	2.43(3)	3.278(3)	161(2)
C9–H9A···O1	*x*, *y*, *z*	0.97	2.60	3.006(3)	106
C9–H9B···N1	1 + *x*, *y*, *z*	0.97	2.59	3.442(3)	147
C13–H13A···O4	*x*, *y*, *z*	0.97	2.52	2.992(3)	110
C16–H16B···O4	1 – *x*, –1/2 + *y*, 3/2 – *z*	0.96	2.59	3.535(3)	168

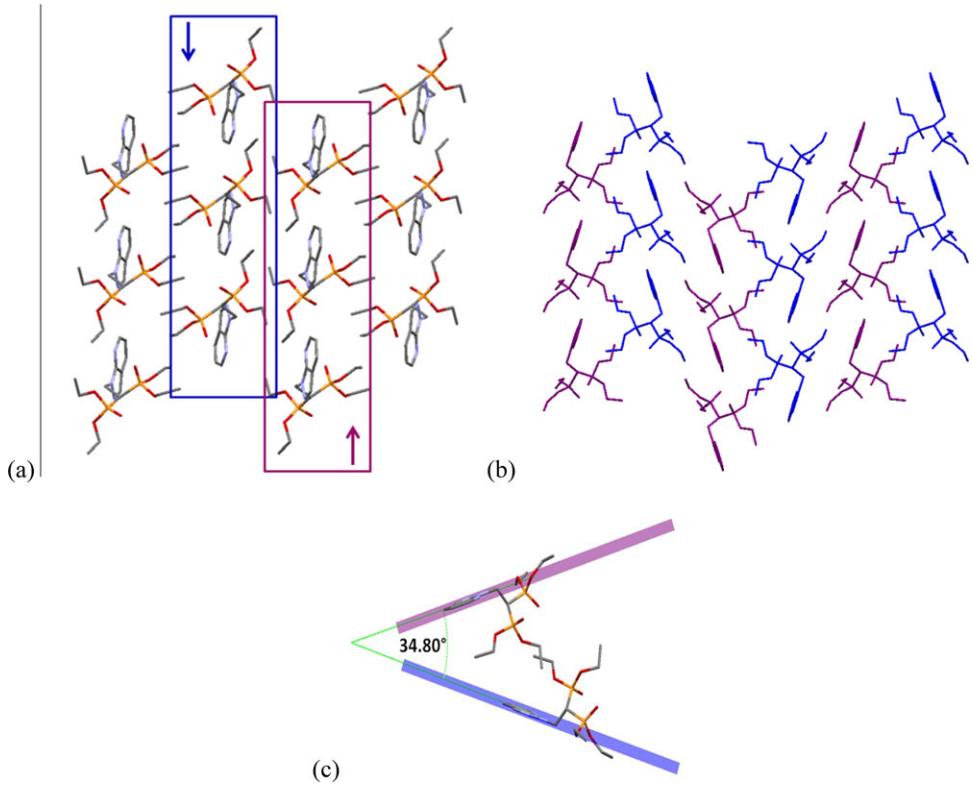


FIGURE 3 (a) Supramolecular arrangement of compound **6** in a view along the *b* axis, showing the formation of lines of molecules along *a*, with the pyrazolo rings oriented in a head-to-tail fashion within the same line, but with inverted orientation in consecutive lines. (b) Supramolecular arrangement of compound **6** in a view along the *a* axis, showing the formation of lines of molecules along *b*, with the pyrazolo rings oriented in a head-to-tail fashion within the same line, but with inverted orientation in consecutive lines (blue vs. purple). (c) Angle formed between the pyrazolo rings of consecutive lines.

reflecting their ability to lose the single P–O bond character to an intermediate stage with electronic delocalization between the P–O bonds of phosphonate groups.

Even though some C–H···O short interactions are present in the supramolecular arrangement of this compound (Table 3), no classic hydrogen bonds are observed.

In a view along the *b* axis, it is clear that the pyrazolo[3,4-*b*]pyridine rings are parallel among them and align along *a* with the molecules oriented in a head-to-tail fashion in the same line while assuming opposite directions in consecutive lines (Fig. 3a). Each line is based on C–H···O (3.315(2), and 3.278(3) Å) and C–H···N 3.442(3) Å) short contacts established between the pyrazolo ring and two other molecules and reinforced by another C–H···O (3.006(3) and 2.992(3) Å). Consecutive lines are connected by C–H···O (3.535(3) Å) interactions involving the phosphonate moiety. Also in a view along the *a* axis, a similar packing is observed with lines growing along the *b* axis. (Fig. 3b). The pyrazolo rings in consecutive lines form a 34.80(20)° angle among them (Fig 3c).

CONCLUSIONS

Novel tetraethylethylene-1,1-bisphosphonate esters derived from 1*H*-indazole, 1*H*-pyrazolo[3,4-*b*]pyridine, and 1*H*-pyrazolo[3,4-*b*]quinoline were synthesized using conventional heating and microwave-assisted methods by a Michael addition reaction of tetraethyl ethylidene-1,1-bisphosphonate with the corresponding heterocycle, with good to excellent yields. Both methods present complete regioselectivity, with formation of only the N-1 heterocyclic derivative. The microwave-assisted method has the advantages of short reaction times and better yields, while achieving the same regioselectivity.

The bisphosphonate esters **5–7** were hydrolyzed to afford the corresponding bisphosphonic acids **8–9** or salt **11**.

All new compounds were fully characterized using their mass, infrared, and ^{1}H NMR, ^{31}P NMR, and ^{13}C NMR data. Compound **6** gave crystals suitable for X-ray diffraction studies, and its molecular and crystalline structure was presented and confirmed the proposed structure based on the assignment of spectroscopic data.

EXPERIMENTAL

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 Distortionless Enhancement by Polarization Transfer (DEPT) and Attached Proton Test (APT) sequences, and bidimensional 2D Correlation Spectroscopy (COSY), Heteronuclear Single Quantum Correlation (HSQC), and Heteronuclear Multiple-Bond Correlation (HMBC) techniques. Infrared spectra were recorded on a Perkin Elmer FT-IR 1725xIR Fourier transform spectrophotometer using KBr disks or film. The bands are quoted in cm^{-1}. Low-resolution and high-resolution (HRMS) mass spectra analyses were obtained by electron impact ionization (EI), fast atom bombardment (FAB), or electrospray ionization (ESI). Mass spectrometry (MS) techniques 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) instrument. Melting points were determined on a Reichert Thermovar melting point apparatus and are not corrected.

All solvents were distilled under a nitrogen atmosphere and were degassed before use. THF was distilled from sodium benzophenone ketyl. CH_2Cl_2 was distilled from calcium hydride. Column chromatography was performed on silica gel (230-400 mesh) under a positive pressure of nitrogen.

Microwave-assisted reactions were carried out using a Milestone's MicroSYNTH–Microwave Labstation for the Synthesis with power supply 1600 W.

1*H*-Indazole **1** is commercially available (Aldrich, Sintra, Portugal) and was used as received. 1*H*-Pyrazolo[3,4-*b*]pyridine **2** [30], 1*H*-pyrazolo[3,4-*b*]quinoline **3** [31] and tetraethyl ethenylidene-1,1-bisphosphonate **4** [32] were prepared according to literature procedures.

General Procedure 1 (Thermal Conditions)

A mixture of azole **1–3** (1 mmol) and tetraethyl ethenylidene-1,1-bisphosphonate **4** (1 mmol) in THF was stirred under reflux for 16 h. The solvent was evaporated in vacuum, and the crude material was purified by column chromatography (silica, 1:1 ethyl acetate/acetone) to give the corresponding ethylidene-1,1-bisphosphonate derivative.

General Procedure 2 (Microwave-Assisted Conditions)

In the microwave reactor, a mixture of azole **1–3** (1 mmol) and tetraethyl ethenylidene-1,1-bisphosphonate **4** (1 mmol) in THF was heated for 30 min at 95°C under microwave irradiation, with a power of 300 W. Upon removal of the solvent, the crude material was purified by column chromatography (silica, 1:1 ethyl acetate/acetone) to give the corresponding ethylidene-1,1-bisphosphonate derivative.

*Tetraethyl (2-(1H-indazol-1-yl)ethane-1,1-diyl) bisphosphonate (**5**).* Compound **5** was prepared from 1*H*-indazole **1** (0.500 g, 4.23 mmol), during 16 h, following general procedure 1 (1.25 g, 71%), as a colorless oil.

Compound **5** was prepared from 1*H*-indazole **1** (100 mg, 0.85 mmol), following general procedure 2 (350 mg, 99%) as a colorless oil.

υ_{max} (film) (cm^{-1}): 2984, 2933, 2908 (C–H), 1617, 1501, 1467, 1444 (C=N, C=C), 1392, 1369, 1252 (P=O), 1164, 1023, 975 (P–OC). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.18 (12H, m, OCH_2CH_3), 3.44 (1H, tt, J_{HP} 23.0 and J 6.6, $CH(PO_3Et_2)_2$), 4.06 (8H, m, OCH_2CH_3), 4.93 (2H, td, J_{HP} 13.7 and J 6.6, NCH_2), 7.13 (1H, t, J 7.5, Ar*H*, 5-H), 7.38 (1H, t, J 7.7, Ar*H*, 6-H), 7.55 (1H, d, J 8.4, Ar*H*, 7-H), 7.69 (1H, d, J 8.1, Ar*H*, 4-H), 8.02 (1H, s, Ar*H*, 3-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 15.7 (d, J_{CP} = 6.4, CH_3), 37.3 (t,

J_{CP} = 130.5, *C*H(PO_3Et_2)$_2$), 44.3 (t, J_{CP} = 3.1, NCH_2), 62.4 (dd, J_{CP} = 26.6 and 6.6, OCH_2), 109.3 (Ar: C7), 120.2 (Ar: C5), 120.4 (Ar: C4), 123.3 (Ar: C3a), 125.9 (Ar: C6), 133.3 (Ar: C3), 139.7 (Ar: C7a).^{31}P NMR (121 MHz, H_3PO_4/ $CDCl_3$): δ (ppm) = 20.5. MS (FAB): *m/z* = 419 (MH^+, 90%), 373 (M^+ – OEt , 9%), 301 (M^+ – Indz, 100%), 281 (M^+ – PO_3Et_2, 16%). HRMS (FAB) *m/z* calcd for $C_{17}H_{29}N_2O_6P_2$ 419.1501 $[MH]^+$, found 419.1500.

*Tetraethyl (2-(1H-pyrazolo[3,4-b]pyridin-1-yl) ethane-1,1-diyl)bisphosphonate (**6**).* Compound **6** was prepared from 1*H*-pyrazolo[3,4-*b*]pyridine **2** (500 mg, 4.17 mmol), during 16 h, following general procedure 1 (1.42 g, 81%), as a pale yellow solid.

Compound **6** was prepared from 1*H*-pyrazolo[3,4-*b*]pyridine **2** (100 mg, 0.84 mmol), following general procedure 2 (335 mg, 95%) as a pale yellow solid.

mp 50–51°C. υ_{max} (film) (cm^{-1}): 3095, 3053 (C–H Ar), 2984, 2905 (C–H), 1597, 1574, 1502, 1461, 1445 (C=N, C=C), 1249 (P=O), 1017, 972 (P–OC). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.13 (6H, t, *J* 7.0, OCH_2CH_3), 1.99 (6H, t, *J* 7.1, OCH_2CH_3), 3.66 (1H, tt, J_{HP} 23.0 and *J* 7.8, C*H*(PO_3Et_2)$_2$), 4.06 (8H, m, CH_2CH_3), 5.05 (2H, td, J_{HP} 13.4 and *J* 6.9, NCH_2), 7.10 (1H, dd, *J* 7.8 and 4.6, Ar*H*, 5-H), 8.00 (1H, s, Ar*H*, 3-H), 8.03 (1H, dd, *J* 8.1 and 1.4, Ar*H*, 4-H), 8.51 (1H, dd, *J* 4.5 and 1.4, Ar*H*, 6-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 16.1 (d, J_{CP} 4.0, OCH_2CH_3), 16.2 (d, J_{CP} 4.0, OCH_2CH_3), 36.9 (t, J_{CP} 132.5, *C*H(PO_3Et_2)$_2$), 43.2 (m, NCH_2), 62.7 (m, OCH_2), 115.6 (Ar: C3a), 116.8 (Ar: C5), 129.8 (Ar: C4), 132.1 (Ar: C3), 148.5 (Ar: C6), 150.4 (Ar: C7a).^{31}P NMR (121 MHz, H_3PO_4/ $CDCl_3$): δ (ppm) = 20.4. MS (EI): *m/z* = 419 (M^+, 12%), 282 (M^+ – PO_3Et_2, 100%), 145 (M^+ – (PO_3Et_2)$_2$,14%), 132 (M^+ – CH(PO_3Et_2)$_2$, 27%), 118 (M^+ – CH_2CH(PO_3Et_2)$_2$, 15%). HRMS (EI) *m/z* calcd for $C_{16}H_{27}N_3O_6P_2$ 419.1375 $[M]^+$, found 419.1377.

*Tetraethyl (2-(1H-pyrazolo[3,4-b]quinolin-1-yl) ethane-1,1-diyl)bisphosphonate (**7**).* Compound **7** was prepared from 1*H*-pyrazolo[3,4-*b*]quinoline **3** (500 mg, 2.96 mmol), during 16 h, following general procedure 1 (1.10 g, 79%), as a pale yellow solid.

Compound **7** was prepared from 1*H*-pyrazolo[3,4-*b*]quinoline **3** (145 mg, 0.86 mmol), following general procedure 2 (347 mg, 86%) as a pale yellow solid.

mp 81–82°C. υ_{max} (KBr) (cm^{-1}): 3099, 3035 (C–H Ar), 2984, 2905 (C–H), 1618, 1570, 1498, 1455, 1438 (C=N, C=C), 1257, 1246 (P=O), 1046, 1028, 971, 946 (P–OC). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.17 (6H, t, *J* 7.0, OCH_2CH_3), 1.23 (6H, t, *J* 7.0, OCH_2CH_3), 3.77 (1H, tt, J_{HP} 23.0 and *J* 7.0, C*H*(PO_3Et_2)$_2$), 4.11 (8H, m, OCH_2CH_3), 5.22 (2H, td, J_{HP} 13.6 and *J* 7.3, NCH_2), 7.45 (1H, dt, *J* 7.6 and 0.8, Ar*H*, 6-H), 7.76 (1H, dt, *J* 7.8 and 1.6, Ar*H*, 7-H), 7.97 (1H, d, *J* 8.0, Ar*H*, 5-H), 8.17 (1H, d, *J* 8.4, Ar*H*, 8-H), 8.25 (1H, s, Ar*H*, 3-H), 8.63 (1H, s, Ar*H*, 4-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 16.47 (d, J_{CP} 5.1, CH_2CH_3), 16.53 (d, J_{CP} 5.2, CH_2CH_3), 37.1 (t, J_{CP} 130.7, *C*H(PO_3Et_2)$_2$), 44.2 (NCH_2), 63.1 (t, J_{CP} 6.4, OCH_2), 117.5 (Ar: C3a), 124.2 (Ar: C6), 124.5 (Ar: C4a), 128.0 (Ar: C8), 129.6 (Ar: C5), 131.3 (Ar: C4 and C7), 133.4 (Ar: C3), 147.5 (Ar: C8a), 149.7 (Ar: C9a). ^{31}P NMR (121 MHz, H_3PO_4/ $CDCl_3$): δ (ppm) = 20.5. MS (EI): *m/z* = 469 (M^+, 3%), 332 (M^+ – PO_3Et_2, 10%), 195 (M^+ – (PO_3Et_2)$_2$, 3%), 182 (M^+ – CH(PO_3Et_2)$_2$, 9%), 169 ($C_{10}H_7N_3^+$, 100%), 168 (M^+ – CH_2CH(PO_3Et_2)$_2$, 6%). HRMS (EI) *m/z* calcd for $C_{20}H_{29}N_3O_6P_2$ 469.1532 $[M]^+$, found 469.1527.

*(2-(1H-Indazol-1-yl)ethane-1,1-diyl)bisphosphonic Acid (**8**).* A solution of compound **5** (100 mg, 0.24 mmol) in concentrated HCl (1 mL) was refluxed for 2 h. After solvent removal under reduced pressure, the residue was precipitated with acetone and methanol. Compound **8** (53 mg, 73%) was isolated as a white solid. mp 245°C. υ_{max} (KBr) (cm^{-1}): 3500–2200 (O–H), 3123, 3018 (C–H Ar), 2987, 2891 (C–H), 2632 (PO–H), 1628, 1575, 1520, 1457 (C=N, C=C), 1234 (P=O), 1195, 1164, 1125, 1056, 998, 988 (P–OC). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 2.99 (1H, tt, J_{HP} 22.2 and *J* 6.2, C*H*(PO_3H_2)$_2$), 4.80 (2H, td, J_{HP} 13.8 and *J* 6.4, NCH_2), 7.14 (1H, t, *J* 7.4, Ar*H*, 5-H), 7.40 (1H, t, *J* 7.6, Ar*H*, 6-H), 7.64 (1H, d, *J* 8.8, Ar*H*, 7-H), 7.76 (1H, d, *J* 8.0, Ar*H*, 4-H), 8.10 (1H, s, Ar*H*, 3-H). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) = 40.4 (t, J_{CP} 121.6, *C*H(PO_3H_2)$_2$), 45.8 (NCH_2), 111.1 (Ar: C7), 121.1 (Ar: C5), 121.6 (Ar: C4), 124.4 (Ar: C3a), 126.7 (Ar: C6), 133.8 (Ar: C3), 140.5 (Ar: C7a).^{31}P NMR (121 MHz, H_3PO_4/ DMSO-d_6): δ (ppm) = 18.8. MS (ESI): *m/z* = 307 (MH^+, 100%). HRMS (ESI) *m/z* calcd for $C_9H_{13}N_2O_6P_2$ 307.0243 $[MH]^+$, found 307.0250.

*(2-(1H-Pyrazolo[3,4-b]pyridin-1-yl)ethane-1,1-diyl)bisphosphonic Acid (**9**).* A solution of compound **7** (100 mg, 0.24 mmol) in concentrated HCl (1 mL) was refluxed for 4 h. After solvent removal under reduced pressure, the residue was precipitated with acetone and methanol. Bisphosphonate **9** (56 mg, 76%) was isolated as a white solid. mp 245°C (decomp.). υ_{max} (KBr) (cm^{-1}): 3500–2300 (O–H), 3102, 3096 (C–H Ar), 2927 (C–H), 2718 (PO–H), 1649, 1544, 1459 (C=N, C=C), 1241 (P=O), 1150, 1114, 1066, 1051, 998, 973, 954 (P-OC). ^{1}H

NMR (400 MHz, DMSO-d_6): δ (ppm) = 3.27 (1H, tt, J_{HP} 22.0 and J 6.4, C*H*$(PO_3H_2)_2$), 4.92 (2H, td, J_{HP} 13.6 and J 6.8, NCH_2), 7.23 (1H, dd, J 8.0 and 4.4, Ar*H*, 5-H), 8.17 (1H, s, Ar*H*, 3-H), 8.25 (1H, dd, J 8.0 and 1.2, Ar*H*, 4-H), 8.57 (1H, d, J 3.2, Ar*H*, 6-H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 39.3 (t, J_{CP} 123.4, *C*H$(PO_3H_2)_2$), 44.1 (N*C*H_2), 116.3 (Ar: C3a), 117.7 (Ar: C5), 131.3 (Ar: C4), 132.9 (Ar: C3), 149.2 (Ar: C6), 150.8 (Ar: C7a).^{31}P NMR (121 MHz, H_3PO_4/ DMSO-d_6): δ (ppm) = 18.6. MS (ESI): m/z = 308 ([M + H]$^+$, 100%). HRMS (ESI) m/z calcd for $C_9H_{12}N_3O_6P_2$ 308.0195 [MH]$^+$, found 308.0210.

*(2-(1H-Pyrazolo[3,4-b]quinolin-1-yl)ethane-1,1-diyl)bisphosphonic Acid Tetrasodium Salt (**11**).* To a solution of bisphosphonate ester **9** (50 mg, 0.107 mmol) in dry CH_2Cl_2 at 0°C, collidine (0.15 mL, 1.07 mmol) and TMSBr (0.15 mL, 1.07 mmol) were added. After 2 h at 0ºC, the reaction mixture was allowed to warm to room temperature and was stirred for 18 h. To the mixture, toluene was added and the solvents were removed in vacuum to obtain a white solid. To the solid, an aqueous NaOH solution (1 M) (5 mL) was added. After 24 h, the mixture was poured into acetone and stored at 0ºC for 24 h. The mixture was decanted, and the residue was washed with cold hexane and dried in vacuum to afford bisphosphonate **11** (48 mg, quantitative) as a white solid.

mp >350°C. υ_{max} (KBr) (cm^{-1}): 3600–2900 (O–H), 1688, 1624, 1458 (C=N, C=C), 1219 (P=O), 1083, 954 (P–OC). ^{1}H NMR (300 MHz, D_2O): δ (ppm) = 2.85 (1H, tt, J_{HP} 20.0 and J 7.6, C*H*$(PO_3H_2)_2$), 4.76 (2H, m, NCH_2), 7.39 (1H, t, J 7.4, Ar*H*, 6-H), 7.73 (1H, t, J 7.6, Ar*H*, 7-H), 7.83 (1H, d, J 8.8, Ar*H*, 5-H), 7.87 (1H, d, J 8.4, Ar*H*, 8-H), 8.21 (1H, s, Ar*H*, 3-H), 8.58 (1H, s, Ar*H*, 4-H). ^{13}C NMR (100 MHz, D_2O): δ (ppm) = 39.8 (t, J_{CP} 109.2, *C*H$(PO_3Na_2)_2$), 45.1 (N*C*H_2), 117.2 (Ar: C3a), 123.6 (Ar: C6), 125.8 (Ar: C4a), 129.6 (Ar: C8), 131.5 (Ar: C5), 133.0 (Ar: C4 and C7), 133.6 (Ar: C3), 146.9 (Ar: C8a), 148.7 (Ar: C9a). ^{31}P NMR (121 MHz, D_2O): δ (ppm) = 20.5. MS (ESI): m/z = 424 ([M – Na + 2H]$^+$). MS (negative ion - ESI): m/z = 356 ([M – 4Na + 3H]). HRMS (ESI) m/z calcd for $C_{12}H_{11}N_3O_6P_2Na_3$ 423.9811 [M – Na + 2H]$^+$, found 423.9812.

*Crystal Structure Determination of Tetraethyl(2-(1H-pirazolo[3,4-b]piridin-1-yl)ethane-1,1-diyl)bisphosphonate (**6**).* Crystal data for the bisphosphonate **6** were collected at 150 K on a Bruker AXS-KAPPA APEX II diffractometer using graphite-monochromated Mo-Kα radiation (l = 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, 2003) [42]. All the data were corrected for Lorentzian, polarization, and absorption effects using the SAINT and SADABS programs (Bruker, 2003) [42]. 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 [43] and refined by full matrix least squares on F2 with SHELXL97 [44], both included in the package of programs WINGX-VERSION 1.70.01 [45]. Graphical representations were prepared using ORTEP3.5 [39] and Mercury 3.3 programs [46].

CCDC 1050362 contains all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ; UK, fax: +44-(0)1223-336033; or deposit@ccdc.cam.ac.uk.

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