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Synthesis of novel pyrazolo[3,4-*b*]quinoline-bisphosphonic acids and an unexpected intramolecular cyclization and phosphonylation reaction†

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Novel pyrazolo[3,4-*b*]quinoline α-ketophosphonic and hydroxymethylenebisphosphonic acid compounds were synthesized using different methodologies, starting from 2-chloro-3-formylquinoline **1**. New phosphonic acid compounds were obtained as N-1 derivatives with a side chain with 1 or 3 (*n* = 1 or 3) methylene groups. All phosphonic acid compounds and their corresponding ester and carboxylic acid precursors were fully characterized, and their structures elucidated by spectroscopic data, using NMR techniques and infrared and high-resolution mass spectroscopy. During the process to obtain the N-1 substituted derivative with two methylene groups (*n* = 2) in the side chain, an unexpected addition–cyclization cascade reaction was observed, involving the phosphonylation of an aromatic ring and the formation of a new six-member lactam ring to afford a tetracyclic ring system. This was an unexpected result since other pyrazolo[3,4-*b*]quinoline derivatives and all corresponding pyrazolo[3,4-*b*]pyridine derivatives already prepared, under similar experimental conditions, did not undergo this reaction. This domino reaction occurs with different phosphite reagents but only affords the six-member ring. The spectroscopic data allowed the identification of the new synthesized tetracyclic compounds and the X-ray diffraction data of compound **11** enabled the confirmation of the proposed structures.

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Introduction

Pyrazolo[3,4-*b*]quinoline is a tricyclic ring system which, as its name suggests, is made up of a pyrazole ring, with two neighbouring nitrogen atoms, and a quinoline portion, with one more nitrogen atom. The positions of the nitrogen atoms in the ring system allow the relocation of a proton, with the formation of three regioisomers due to tautomerism (Fig. 1).[1,2]

Since its first synthesis,[3] pyrazolo[3,4-*b*]quinoline has been the subject of much interest and numerous studies. Pyrazolo[3,4-*b*]quinoline derivatives or intermediates containing this skeleton became inevitable moieties in several areas encompassing organic synthesis, medicinal chemistry and materials chemistry, due to their wide applications. In medicinal chemistry, pyrazolo[3,4-*b*]quinoline became an important heterocycle scaffold, since molecules with this moiety exhibit diverse biological activities, such as antimicrobial, antimalarial, antibacterial, anticancer, anti-inflammatory, anti-leishmaniasis and anti-Alzheimer's disease activities.[4–13] Also, pyrazolo[3,4-*b*]quinoline compounds have been deemed to be promising materials, especially for optoelectronics, due to their photophysical properties, such as fluorescence, phosphorescence, thermoluminescence and electroluminescence.[14–18]

Organophosphorus compounds encompass many structural scaffolds and have attracted increasing attention in recent decades due to their presence in a great variety of compounds, from natural products to molecules with diverse applications.[19] This multiplicity of applications keeps up with their structural diversity and spans from coordination chemistry,

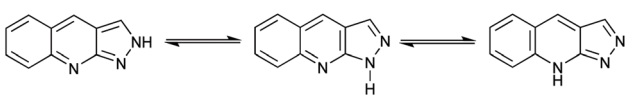

Fig. 1 Structure of pyrazolo[3,4-*b*]quinoline tautomers.

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organic synthesis to medicinal chemistry, as they have important roles as biologically active compounds or functional materials.[20–27] The achievement of new organophosphorus compounds, such as aryl- or heteroarylphosphonates, still relies on the development of improved methods for the formation of the C–P bond.[28–31] Among the organophosphorus compounds, phosphonates have received high interest due to the importance of their several applications. Their use ranges from coating agents, antistatic agents, emulsifiers, flame retardants, dyes for solar cells to drugs for the treatment of several bone diseases.[32–40]

Bisphosphonates (BPs) are an important group of organophosphorus compounds. Geminal bisphosphonates present P–C–P bonds but unlike P–O–P pyrophosphate bonds, these bonds are chemically stable and resistant to enzymatic hydrolysis. These compounds constitute an important class of drugs with a broad therapeutic application in the prevention and treatment of diseases of bone metabolism, due to their high affinity to calcium and bone material, where they are internalized in osteoclasts inducing their apoptosis. BPs were developed for bone therapy in the mid-1960s and had been used with success in diseases characterized by abnormal calcium metabolism such as osteoporosis, Paget's disease, osteolysis and hypercalcemia and in bone metastases of breast and prostate cancers, cell proliferation inhibition and invasion and adhesion to bone. BPs containing one or two nitrogen functional groups, especially in a heteroaromatic moiety, show higher therapeutic activity in primary and secondary bone disorders. The advantages of the therapeutic use of BPs include their minimal side effects and their specificity to bone tissue.[41–47]

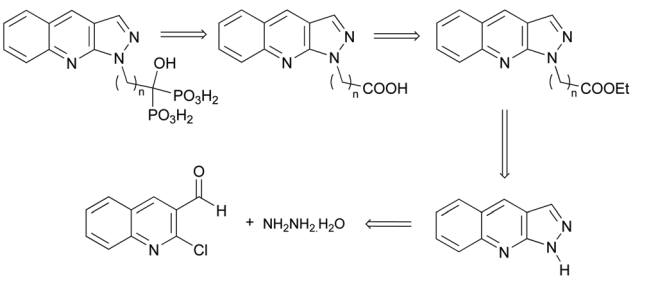
Studies on BP derivatives have also found biological applications as antibacterial, antiparasitic and anti-inflammatory agents, inhibitors of angiogenesis, and stimulators of γd-T cells of the immune system. Other studies dealt with the activities of these compounds regarding their affinity to metal cations, and they were studied as chelating agents for metal ions and radioactive metal complexes to be used in radiotherapy, scintigraphy and magnetic resonance imaging and imagiology.[48–53]

The usual approach for the synthesis of bisphosphonates involves the reaction of a carboxylic acid, usually accessible by conventional methods, with phosphorus chloride, phosphorus or phosphoric acid with or without solvents (such as chlorobenzene or methanesulfonic acid). Different conditions regarding reactants, solvents, temperature, reaction time or work-up have been used but purification, scale-up and reproducibility still constitute the major drawbacks of this methodology.[54–57] A second method involves the hydrolysis of dialkyl phosphonates prepared from the reaction of dialkyl phosphites with acyl chlorides. This methodology has, generally, several limitations due to the required basic conditions for the addition of dialkyl phosphites and needs strong acid conditions for their hydrolysis, including heating to reflux in aqueous hydrochloric or hydrobromic acids, which limits its application due to possible phosphono–phosphate rearrangements, degradation of compounds or the formation of products from partial hydrolysis.[56,58] An alternative methodology takes advantage of the soft conditions necessary for the nucleophilic addition of a tris(trialkylsilyl)phosphite to an acyl chloride, followed by a mild hydrolysis, usually using methanol, to afford the corresponding phosphonic acid.[59,60]

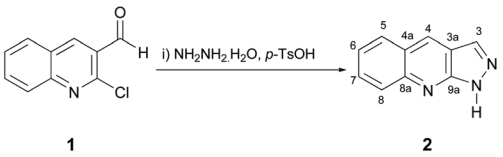
Taking into account the important applications that both BPs and pyrazolo[3,4-*b*]quinolines have, it is conceivable that molecules bearing both moieties could have interesting applications, including useful biological properties. Our group has longstanding interest in the development of N-heterocyclic phosphonates and their derivatives. The aim of this work is to extend the previous studies on benzimidazole- and benzotriazolebisphosphonates,[61] indazolebisphosphonates[62] and pyrazolopyridinebisphosphonates[63] to other condensed pyrazolephosphonate derivatives with potentially high activities. Herein, we report the synthesis and characterization of several pyrazolo[3,4-*b*]quinolinephosphonic acid derivatives substituted at N-1, with a side chain of 1 or 3 methylene groups. During these studies, a new and unexpected cascade reaction was observed, using different methods of synthesis and two different phosphite reactants. The new compounds show a six-member lactam ring, formed by the reaction between the acyl chloride side chain with two methylene groups ($n = 2$) and the aromatic N-9 of pyrazolo[3,4-*b*]quinolines, forming a tetracyclic ring system, and a non-catalyzed concurrent phosphonylation at the C4 position, with the change of the hybridization of this carbon atom from sp^2 to sp^3. The crystal structure of compound **11** confirmed the proposed structure.

Results and discussion

Our group has longstanding interest in phospho-azaheteroaromatic compounds. Following ongoing projects, we were interested in obtaining pyrazole–quinoline derivatives with phosphonate groups. To achieve this objective, we envisaged a strategy beginning with the synthesis of pyrazolo[3,4-*b*]quinoline **2**, to be used in the formation of ester derivatives, followed by their hydrolysis to afford the corresponding carboxylic acid derivatives, and the transformation of these compounds into the proposed pyrazolo[3,4-*b*]quinolinephosphonic acid compounds (Scheme 1).

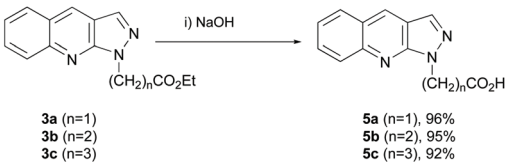


Scheme 1 Synthetic strategy to obtain pyrazolo[3,4-*b*]quinolinebisphosphonic acid compounds.



1 **2**

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



3a (n=1)
3b (n=2)
3c (n=3)

5a (n=1), 96%
5b (n=2), 95%
5c (n=3), 92%

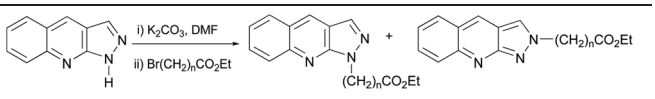
Scheme 3 Synthesis of pyrazolo[3,4-*b*]quinoline carboxylic acid derivatives **5**.

Pyrazolo[3,4-*b*]quinolone **2** was synthesized in a high yield, through a process reported in the literature, by the reaction of 2-chloro-3-formylquinoline **1** with hydrazine hydrate and *p*-TsOH as the catalyst (Scheme 2).[64]

1*H*-Pyrazolo[3,4-*b*]quinoline **2** reacted with K_2CO_3 (base), in *N*,*N*-dimethylformamide (DMF) as the solvent, followed by addition of bromo ester reagents with different hydrocarbon side chain lengths, with one to three methylene groups. The N-1 ester derivatives **3a** and **3c** (n = 1 and 3) were obtained by the nucleophilic substitution reaction of bromo esters (Br $(CH_2)_nCO_2Et$, n = 1 and 3) in excellent yields. In the case of n = 2 (*i.e.* two methylene groups), a mixture of N-1 and N-2 substituted pyrazolo[3,4-*b*]quinoline ester regioisomers **3b** and **4b** was obtained (Table 1). The separation and the correct identification of these isomers were important, since the N-1 derivative (**3b**) is to be used in the subsequent synthesis. This separation was performed by column chromatography to provide pure compounds. All compounds were identified by NMR, IR and MS techniques.

The identification of regioisomers substituted at N-1 and N-2 was performed by ^{1}H and ^{13}C NMR spectroscopy (including DEPT or APT, and two-dimensional HSQC and HMBC NMR techniques). As observed for similar azaheteroaromatic compounds, such as benzotriazole,[26] indazole[62,65] and pyrazolo[3,4-*b*]pyridine[63] derivatives, the ^{1}H NMR spectra of the two regioisomers do not allow their unequivocal identification, which was achieved by ^{13}C NMR spectral analysis. In the ^{13}C NMR spectra, the NCH_2, C9a and C3 atoms present different chemical shifts between the N-1 and N-2 regioisomers. In the spectrum of the N-1 substituted regioisomer, C3 is shifted downfield 9 ppm, and C9a and NCH_2 are shifted upfield approximately 8 ppm relative to the corresponding N-2 substituted regioisomer carbon atoms, easily enabling their identification.

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



2 **3a-c** **4a-c**

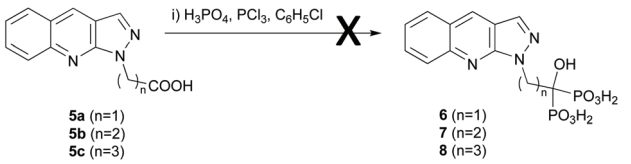
	Yield (%)		
n	**3**	**4**	**3** + **4**
1	99	—	99
2	67	17	84
3	93	—	93

The ester derivatives **3a–c** were subjected to basic hydrolysis to afford the corresponding carboxylic acids **5a–c**, as crystalline solids, in excellent yields (Scheme 3). The new compounds were fully characterized, and all spectroscopic data are in agreement with the proposed structures.

The new synthesized 1*H*-pyrazolo[3,4-*b*]quinolinecarboxylic acids **5** were used for the synthesis of the corresponding bisphosphonic acids. A method involving the reaction between the carboxylic acid derivative and phosphoric acid or phosphorous acid and phosphorus trichloride, followed by acid hydrolysis, is frequently used to obtain the bisphosphonic acid derivatives but, with the 1*H*-pyrazolo[3,4-*b*]quinolinecarboxylic acid compounds **5a–c** used in this study, this method did not work. The performed reactions always led to a mixture of compounds, with no indication of the presence of the intended bisphosphonic acid derivatives **6–8**, or led to a complex mixture that made it impossible to separate the compounds (Scheme 4).

A new attempt was made using a modified Arbuzov reaction method, involving the reaction of tris(trimethylsilyl)phosphite with an acyl chloride,[59] prepared from the corresponding carboxylic acids in $CHCl_3$ as the solvent or in neat thionyl chloride. Compound **5a** (n = 1) reacted with thionyl chloride in chloroform, according to method A, to afford the corresponding acyl chloride, followed by the addition of tris(trimethylsilyl)phosphite, to afford the monophosphonic acid derivative **9** in a moderate yield (Table 2). The spectroscopic data of compound **9** show m/z = 292 (MH^+, 100%), a carbonyl group stretching band ($\nu_{C=O}$) at 1696 cm^{-1}, a chemical shift of −3.89 ppm for the ^{31}P atom, a doublet at 56.3 ppm for the NCH_2 carbon atom, and another doublet at 210 ppm, attributed to a CO carbon atom bearing a phosphonic acid group, indicating the presence of an α-ketophosphonate structure, in agreement with the structure of monophosphonic acid derivative **9**.

A new attempt was made using method B. The reaction, using neat thionyl chloride, afforded the expected bisphospho-

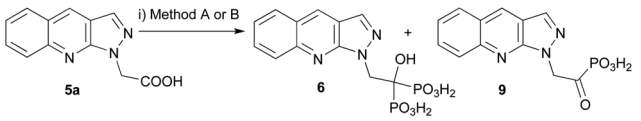


5a (n=1)
5b (n=2)
5c (n=3)

6 (n=1)
7 (n=2)
8 (n=3)

Scheme 4 Attempted syntheses of bisphosphonic acid derivatives by general procedure 3.

Table 2 Synthesis of bisphosphonic acid **6** and monophosphonic acid **9**



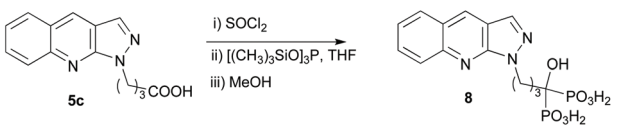
Method A: i) $SOCl_2$, $CHCl_3$; ii) $[(CH_3)_3SiO]_3P$, THF; iii) MeOH
Method B: i) $SOCl_2$; ii) $[(CH_3)_3SiO]_3P$, THF; iii) MeOH

Method	Yield of **6** (%)	Yield of **9** (%)
A	—	48
B	95	—

nic acid derivative **6** in a good yield (Table 2). The absence of the carbonyl stretching band and the chemical shift of 17.05 ppm for the ^{31}P atom and the triplet signal at 73.8 ppm for a CH–OH carbon atom confirm that the reaction product is different from the previous reaction and all spectroscopic data of the new compound are in agreement with the proposed bisphosphonic acid compound **6**.

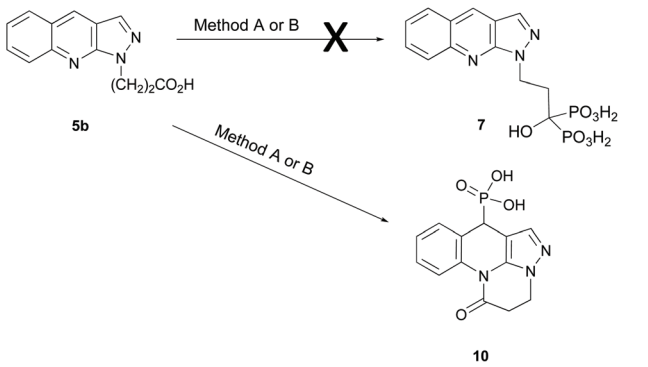
Compound **5c** (n = 3) was also subjected to a method B reaction to afford the corresponding bisphosphonic acid **8** in a moderate yield (Scheme 5). The spectroscopic data confirm the absence of the carboxylic acid or the α-ketophosphonic acid derivatives and are in agreement with a 1-hydroxy-1,1-bisphosphonate structure: the absence of $\nu_{C=O}$, and the characteristic singlet at 20.98 ppm in the ^{31}P NMR spectra, assigned to two chemically and magnetically equivalent phosphorus atoms.

In an attempt to synthesize compound **7** from compound **3b** (n = 2), using method A, the formation of the expected 1-hydroxy-1,1-bisphosphonic acid or the α-ketophosphonic acid derivatives was not observed. The reaction was repeated using method B, with the same result: the new and unexpected compound **10** was synthesized in an unusual cascade phosphonylation–intramolecular cyclization, with the formation of a tetracyclic ring system, due to the conjugate addition of tris (trimethylsilyl)phosphite at the C-4 position and the addition of N-9 to the acyl chloride of the side chain (Table 3). Despite the presence of $\nu_{C=O}$ at 1702 cm^{-1}, no multiplicity is observed for the CO signal in the ^{13}C NMR spectra, indicating that phosphite substitution did not occur at this carbon and the α-ketophosphonate derivative was not formed. Instead, using the NMR data, the formation of a P–C bond at the carbon C4‡ of the ring was identified, with a large upfield change of the chemical shift of this carbon atom, which moves from an aromatic ring signal to the aliphatic region of the spectra. Also, besides the usual multiplicity of proton atoms, several carbon



Scheme 5 Synthesis of bisphosphonic acid **8**.

Table 3 Attempted synthesis of bisphosphonic acid **7** and synthesis of compound **10**



Method A: i) $SOCl_2$, $CHCl_3$; ii) $[(CH_3)_3SiO]_3P$, THF; iii) MeOH
Method B: i) $SOCl_2$; ii) $[(CH_3)_3SiO]_3P$, THF; iii) MeOH

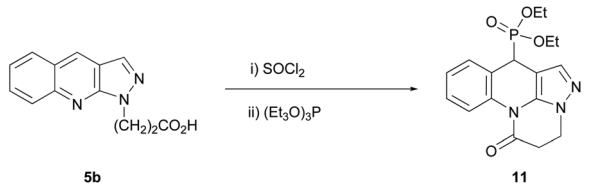
Method	Yield of **10** (%)
A	87
B	84

atoms, including all quaternary carbon atoms, appeared as doublets in the ^{13}C NMR spectrum, indicating that they are coupled with one phosphorus atom, which are at the central position of the pyrazolo[3,4-*b*]quinoline scaffold. Furthermore, the two protons of the methylene group bonded to the carbonyl group are magnetically inequivalent suggesting that the methylene group is subjected to stereochemical restraint, supporting the presence of the new ring as a result of the reaction. Only one regioisomer was observed.

Although the phosphonylation of heteroaromatic rings is a known reaction, it is usually a catalyzed process in substitution reactions (see, for instance, ref. 30 and 31). The new product results from an unexpected cascade 1,4-phosphonylation and simultaneous cyclization reaction, with the formation of a new six-member ring, giving a tetracyclic ring system. This cascade reaction occurred under mild conditions and without any catalyst. There is also a clear reactivity selection for the formation of the six-member ring since no cyclization was observed for other n = 1 and n = 3 derivatives.

The new product **10** was also unexpected since in a previous work with pyrazolo[3,4-*b*]pyridine,[63] a similar molecule with the same substituents and same substitution pattern, with the same reagents and experimental conditions, afforded the bisphosphonic acid derivative, with no evidence of the cascade addition–cyclization reactions with the formation of a new C–P bond at C4 or a new cyclization at N-9. So, in this compound **10**, the presence of the 3rd aromatic ring seems to be important for this reaction to occur. Furthermore, after the reaction

‡ In this discussion, to be more easily identified in the structure of 1*H*-pyrazolo [3,4-*b*]quinoline rings, the same number was maintained for the hydrogen, nitrogen and carbon atoms of the 1*H*-pyrazolo[3,4-*b*]quinoline moiety in all derivatives, despite the atom numbering of the IUPAC nomenclature of compounds.



Scheme 6 Synthesis of compound **11**.

of carboxylic acid **5b** with thionyl chloride, the addition of methanol instead of a phosphite reagent to the acyl chloride derivative, gave the corresponding side chain ester, showing that an acyl chloride was formed and that it did not react with the quinoline N-9 atom. So, although the precise mechanism has not been elucidated, it seems that the presence of phosphite in the reaction is necessary for this cascade of reactions

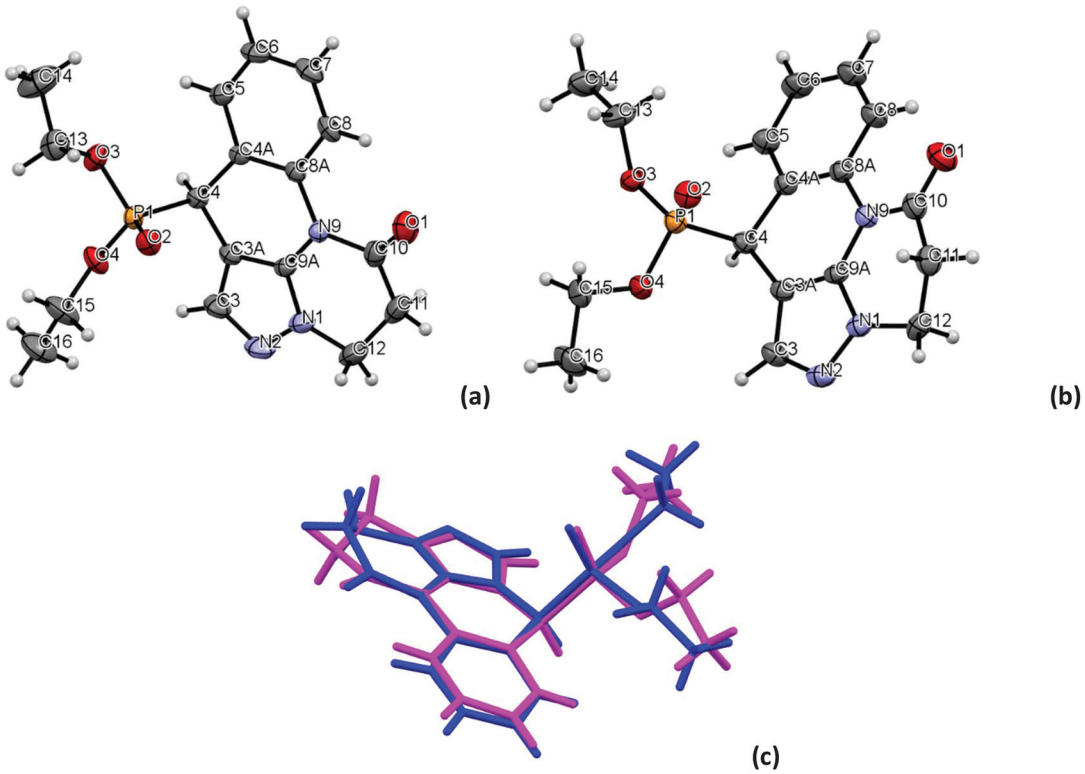


Fig. 2 Ellipsoid representation of the molecular structure of (a) **11-I** and (b) **11-II**, showing the atomic labelling scheme, with ellipsoids set at 50% probability; (c) overlap of **11-I** (pink) and **11-II** (blue) depicting the conformational differences.

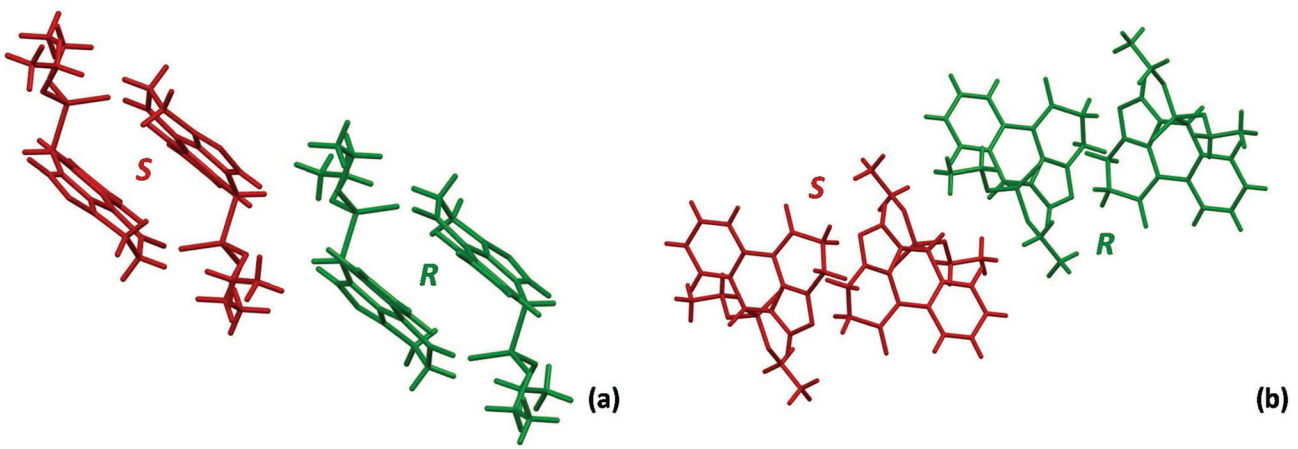


Fig. 3 Packing showing the alternance between 4*R* (green) and 4*S* (dark red) configuration molecules, in views along the *b*-axis, for (a) **11-I** and (b) **11-II**.

to occur, in the presence of a 3rd aromatic ring, to afford a new six-member ring.

Another attempt was made to obtain compound **7**. In this reaction, the strategy involved the use of triethyl phosphite as the reagent to form mono- or bisphosphonate esters that can be later hydrolyzed to the corresponding phosphonic acid **7**. The reaction was carried out under the same experimental conditions starting from the carboxylic acid **5b** (n = 2). Again, this reaction did not afford the intended compound. Instead it gave the product of a conjugate addition–cyclization reaction with the formation of a C–P bond, at C4, and a new lactam ring at N-9 (compound **11**, Scheme 6), a product analogous to compound **10** with similar spectroscopic data. The presence of $\nu_{C=O}$ at 1706 cm^{-1} was observed in this compound **11**, but the CO signal in the ^{13}C NMR spectrum was a singlet, excluding the formation of an α-ketophosphonate derivative. Also, NMR data are consistent with the formation of a P–C bond at carbon C4 of the ring, with a large coupling constant (J = 143.4 Hz) and a large upfield change of the chemical shift of this carbon atom to the aliphatic region of the spectra, from an aromatic ring signal at compound **5b**. Similar to compound **10**, several carbon atoms, including all quaternary carbon atoms, appeared as doublets in the ^{13}C NMR spectrum, indicating that they are coupled with one phosphorus atom, which are close to these atoms, at the central position of the pyrazolo [3,4-*b*]quinoline rings. Likewise, the two protons of the methylene group bonded to the carbonyl group are magnetically inequivalent suggesting that the methylene group is subjected to stereochemical restraint, supporting the formation of the new ring.

Recrystallization of phosphonate **11** under different conditions yielded two different types of crystals suitable for crystallographic studies. X-ray diffraction data allowed the structural characterization of two different polymorphs of compound **11** (**11-I** and **11-II**), both corresponding to the proposed formula based on its spectroscopic data. Both polymorphs crystallize in the monoclinic crystal system, space group $P2_1/n$, with one molecule of compound **11** per asymmetric unit. Fig. 2 shows the molecular structure for polymorphs **11-I** and **11-II**.

Due to the addition of phosphite, the C4 atom became chiral, and in the supramolecular arrangement of **11-I** and **11-II**, molecules with the 4*R* and 4*S* configurations alternate, turning the pyrazolo[3,4-*b*]quinoline ring to each other (Fig. 3).

These crystal structures show that the planarity of pyrazolo [3,4-*b*]quinoline rings was lost, the hydrocarbon aromatic ring and the pyrazole ring remaining planar, consistent with the loss of aromaticity of the pyridine ring due to the formation of an sp^3 C4 atom (Fig. 4). The new 4th ring of the compounds shows a half-chair conformation with N9, C9a and N1 at the same plane, and the methylene groups above (CH_2CO) and below (NCH_2) the plane of the half-chair conformation ring with the hydrogen atoms of these methylene groups in a staggered arrangement. The loss of aromaticity of the pyrazolo[3,4-*b*]quinoline ring is also inferred from the C3a–C4 and C4–C4a

Table 4 Selected bond lengths [Å] for polymorphs **11-I** and **11-II**

Bond lengths/Å		
	11-I	**11-II**
P(1)–O(2)	1.462(2)	1.455(3)
P(1)–O(4)	1.570(2)	1.571(3)
P(1)–O(3)	1.574(2)	1.576(3
P(1)–C(4)	1.822(2)	1.816(4)
O(4)–C(15)	1.438(4)	1.468(5)
O(3)–C(13)	1.440(4)	1.449(5)
N(9)–C(9A)	1.394(3)	1.393(5)
N(9)–C(10)	1.404(4)	1.387(6)
N(9)–C(8A)	1.445(3)	1.442(5)
O(1)–C(10)	1.202(4)	1.205(5)
N(1)–C(9A)	1.344(3)	1.352(5)
N(1)–N(2)	1.359(4)	1.360(5)
N(1)–C(12)	1.444(4)	1.440(6)
C(4)–C(3A)	1.489(3)	1.493(6)
C(4)–C(4A)	1.528(3)	1.539(5)
C(3A)–C(9A)	1.360(4)	1.353(6)
C(3A)–C(3)	1.405(4)	1.405(6)
C(4A)–C(5)	1.394(3)	1.379(6)
C(4A)–C(8A)	1.407(3)	1.400(6)
C(8A)–C(8)	1.406(3)	1.409(6)
N(2)–C(3)	1.317(4)	1.322(6)
C(8)–C(7)	1.364(4)	1.356(7)
C(5)–C(6)	1.379(4)	1.387(6)
C(6)–C(7)	1.384(5)	1.377(7)
C(10)–C(11)	1.491(5)	1.512(7)
C(12)–C(11)	1.473(6)	1.499(6)
C(13)–C(14)	1.440(6)	1.476(7)
C(15)–C(16)	1.436(5)	1.490(7)

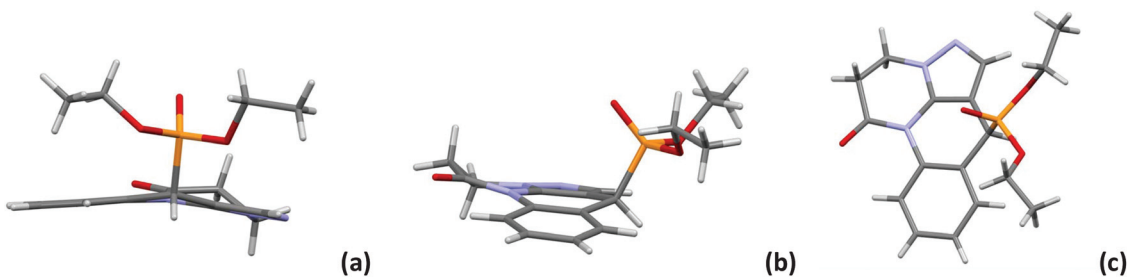


Fig. 4 (a) Conformation of the deformed pyrazolo[3,4-*b*]quinoline rings in a view along the plane of the ring (left-right), with the conformation of the phosphonic group above the plane of the ring; (b) conformation of the deformed pyrazolo[3,4-*b*]quinoline rings (proximal – carbon aromatic ring to distal – pyrazolo ring); (c) conformation of the phosphonic group in a view from the P–C4 bond. (Images from **11-I**, but similar for **11-II**.)

Table 5 Selected angles [°] for compound polymorphs **11-I** and **11-II**

Bond angles/°		
	11-I	**11-II**
O(2)–P(1)–O(4)	115.39(12)	116.33(19)
O(2)–P(1)–O(3)	114.36(12)	113.86(18)
O(4)–P(1)–O(3)	104.58(13)	103.16(17)
O(2)–P(1)–C(4)	115.62(11)	114.98(19)
O(4)–P(1)–C(4)	102.21(11)	99.62(17)
O(3)–P(1)–C(4)	103.04(11)	107.28(19)
C(13)–O(3)–P(1)	121.2(2)	120.7(3)
C(15)–O(4)–P(1)	122.2(2)	119.4(3)
C(10)–N(9)–C(9A)	118.1(2)	119.2(4)
C(10)–N(9)–C(8A)	126.4(2)	126.7(4)
C(9A)–N(9)–C(8A)	114.99(19)	114.0(3)
C(9A)–N(1)–N(2)	111.3(2)	110.9(4)
C(9A)–N(1)–C(12)	123.2(3)	123.1(4)
N(2)–N(1)–C(12)	124.9(3)	125.9(4)
C(3)–N(2)–N(1)	104.2(2)	104.1(4)
N(1)–C(9A)–C(3A)	108.5(2)	108.8(3)
N(1)–C(9A)–N(9)	123.6(2)	122.4(4)
C(3A)–C(9A)–N(9)	128.0(2)	128.7(4)
C(9A)–C(3A)–C(3)	103.3(2)	103.3(4)
C(9A)–C(3A)–C(4)	121.0(2)	120.6(3)
C(3)–C(3A)–C(4)	135.4(3)	136.0(4)
C(5)–C(4A)–C(8A)	117.9(2)	118.3(4)
C(5)–C(4A)–C(4)	118.0(2)	118.1(4)
C(8A)–C(4A)–C(4)	124.1(2)	123.6(4)
C(4A)–C(8A)–C(8)	119.3(2)	118.7(4)
C(4A)–C(8A)–N(9)	120.1(2)	120.8(3)
C(8)–C(8A)–N(9)	120.5(2)	120.5(4)
C(3A)–C(4)–C(4A)	109.9(2)	109.4(3)
C(3A)–C(4)–P(1)	108.41(16)	109.5(3)
C(4A)–C(4)–P(1)	110.37(15)	110.5(3)
N(2)–C(3)–C(3A)	112.8(3)	112.9(4)
C(4A)–C(5)–C(6)	122.3(3)	123.0(5)
O(1)–C(10)–N(9)	122.7(3)	123.6(5)
O(1)–C(10)–C(11)	121.1(3)	120.8(5)
N(9)–C(10)–C(11)	116.0(3)	115.5(4)
C(7)–C(8)–C(8A)	120.6(3)	120.8(5)
O(4)–C(15)–C(16)	111.4(4)	108.1(4)
N(1)–C(12)–C(11)	108.4(3)	106.8(4)
C(7)–C(6)–C(5)	118.8(3)	117.5(5)
C(12)–C(11)–C(10)	118.8(3)	117.4(4)
C(8)–C(7)–C(6)	120.9(3)	121.6(5)
O(3)–C(13)–C(14)	109.7(3)	110.7(4)

bond lengths and the tetrahedral geometry at C4, with approximately 109° angles, in agreement with single bonds and an sp^3 hybridized C4 atom and a torsion angle of about 16° around C4 (Tables 4 and 5).

N9 atoms shape a bridge between the pyrazolo and aromatic rings, forming three bonds, to C8a, C9a and CO atoms. These bonds are in the same plane, establishing a distorted trigonal planar geometry centred on N9, with angles between 114.99(19)° (C9a–N9–C8a) and 126.4(2)° (C10–N9–C8a) for **11-I** and 114.0(3)° (C9a–N9–C8a) and 126.7(4)° (C10–N9–C8a) for **11-II** (Fig. 4).

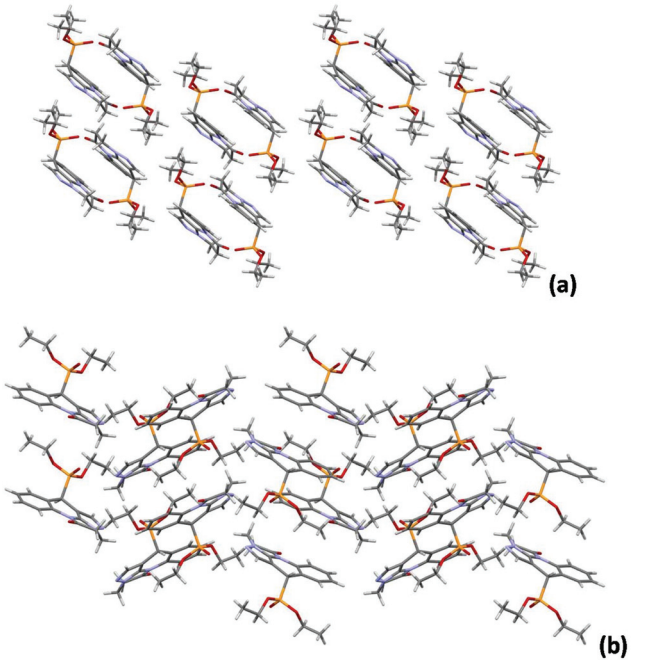


Fig. 5 Supramolecular arrangement of (a) **11-I** in a view along the *b* axis and (b) **11-II** in a view along the *a* axis.

Table 6 Details of non-classical hydrogen bonds and π···π interactions in **11-I** and **11-II**

Compound	Interaction	Symmetry operation	Cg–Cg or C–H distance/Å	X–H···Cg/°
11-I	Cg(1)···Cg(3)[a]	1/2 − *X*, −1/2 + *Y*, 1/2 − *Z*	2.7299(17)	n/a
	Cg(1)···Cg(4)[a]	1/2 − *X*, −1/2 + Y, 1/2 − *Z*	4.6153(19)	n/a
	Cg(3)···Cg(1)[a]	1/2 − *X*, 1/2 + *Y*, 1/2 − *Z*	5.7297(17)	n/a
	Cg(3)···Cg(4)[a]	1/2 − *X*, −1/2 + *Y*, 1/2 − *Z*	5.0025(17)	n/a
	Cg(4)···Cg(1)[a]	1/2 − *X*, 1/2 + *Y*, 1/2 − *Z*	4.6152(19)	n/a
	Cg(4)···Cg(3)[a]	1/2 − *X*, 1/2 + *Y*, 1/2 − *Z*	5.0026(17)	n/a
	C12–H12B···Cg(4)[a]	1/2 − *X*, −1/2 + *Y*, 1/2 − *Z*	3.648(4)	147
	C14–H14B···Cg(4)[a]	1 + *X*, *Y*, *Z*	3.740(5)	139
	C15–H15B···Cg(1)[a]	1 + *X*, *Y*, *Z*	3.732(5)	145
	C8–H8···O(1)	*X*, *Y*, *Z*	2.791(4)	126
	C11–H11A···O(2)	−1 + *x*, *y*, *z*	3.314(5)	154
	C15–H15A···O(1)	1/2 − *x*, −1/2 + *y*, 1/2 − *z*	3.449(5)	151
11-II	Cg(4)···Cg(4)[b]	−*X*, 1 − *Y*, 1 − *Z*	4.406(3)	n/a
	C8–H8···O(1)	*X*, *Y*, *Z*	2.811(7)	123
	C11–H11A···O(2)	*x*, 1 + *y*, *z*	3.307(6)	146
	C13–H13A···O(1)	−*x*, 1 − *y*, 1 − *z*	3.247(7)	135

[a] Cg(1) N1–C9A–N9–C10–C11–C12; Cg(3) N9–C8A–C4A–C4–C3A–C9A; Cg(4) C4A–C5–C6–C7–C8–C8A. [b] Cg(4) N1–N2–C3–C3A–C9A.

In both polymorphs, a distortion was also observed from the ideal tetrahedral shape at the phosphorus atom with wider angles involving the P═O bond, which has a shorter bond length than other P–O bonds, due to its double character (Tables 4 and 5). This P═O bond is turned to the pyrazolo[3,4-*b*]quinoline ring, with $POCH_2CH_3$ groups turned outside the rings, in opposite directions alongside the ring.

The supramolecular arrangements of compounds **11-I** and **11-II** are based on non-classical hydrogen bonds (Table 6). In **11-I**, a total of six π···π, three C–H···π and three C–H···O interactions give rise to extensive networks (Fig. 5a), resulting in 67.8% of filled space. In **11-II**, the number of interactions is limited to one π···π and three C–H···O interactions, resulting in a supramolecular arrangement (Fig. 5b) with 68.4% of filled space.

Conclusions

New phosphonic acid compounds derived from pyrazolo[3,4-*b*]quinoline were synthesized and fully characterized. The synthetic methodologies started from 2-chloro-3-formylquinoline, to afford pyrazolo[3,4-*b*]quinoline. This compound reacted with bromo esters containing different numbers of methylene groups, through a nucleophilic substitution, to give N-1 esters, which were subjected to basic hydrolysis to achieve the corresponding carboxylic acid derivatives. When the bromo ester has two methylene groups, a mixture of N-1 and N-2 regioisomers was obtained which were separated and identified by NMR.

Since the usual method for the synthesis of bisphosphonic acids did not afford the desired compounds, other procedures were used to obtain those compounds. When the side chain had one or three methylene groups (n = 1 or 3), bisphosphonic or monophosphonic acids (when n = 1) were obtained. The reaction of compound **5b** (n = 2) gave an unexpected product, formed through a conjugated addition of the phosphite reagent at C4 and the simultaneous intramolecular cyclization of N-9 and the acyl chloride of the side chain. This compound **10** was obtained either in neat thionyl chloride or thionyl chloride in $CHCl_3$ in excellent yields. An analogous product (compound **11**) was afforded when a different phosphite, triethyl phosphite, was used. Crystals of two polymorphs of compound **11** were suitable for X-ray diffraction studies allowing the confirmation of the proposed structures for the new compounds.

Although the mechanism of this unexpected domino addition–intramolecular cyclization reaction has not been elucidated, the aryl ring of the quinoline moiety must play an important role in the process (since the corresponding pyrazolo[3,4-*b*]pyridine derivative does not undergo these unexpected reactions), in the presence of the phosphite reagent, so that the synchronised addition and cyclization reactions occur. But the most important aspect seems to be the formation of a six-member ring, due to its conformational restraints. With these requirements fulfilled, this method seems to be an easy procedure to afford new tetracyclic ring systems.

Experimental section

General remarks

Commercial reagents were purchased from Sigma-Aldrich and Acros and were used as received. All solvents were distilled under a nitrogen atmosphere. Reactions involving air-sensitive reagents were performed under an atmosphere of dry nitrogen. Chloroform was distilled from calcium hydride. THF was distilled from sodium benzophenone ketyl.

Column chromatography was performed on silica gel (230–400 mesh) under a positive pressure of nitrogen.

Infrared spectra were recorded on a PerkinElmer FT-IR system spectrum BX Fourier Transform spectrometer using a KBr film or discs. The wavenumbers of the bands are quoted in cm^{-1}.

NMR spectra were recorded, at the indicated frequencies, on Bruker AMX 300 or Bruker Avance II 300 (^{1}H 300 MHz, ^{13}C 75 MHz, ^{31}P 121 MHz) or Bruker Avance II 400 (^{1}H 400 MHz, ^{13}C 100 MHz, ^{31}P 162 MHz) spectrometers. Chemical shifts (δ) and coupling constants (J) are reported in ppm and in Hz, respectively. The assignment of ^{1}H and ^{13}C NMR chemical shifts was made by comparison of chemical shifts, peak multiplicities, and J values, with the invaluable contribution of DEPT and APT sequences, and bidimensional COSY, HETCOR, HSQC and HMBC techniques.

Low resolution and high resolution (HRMS) mass spectra analyses were performed on a VG AutoSpec M, MicroTOF (Bruker Daltonics) or APEX-Q (Bruker Daltonics) instrument, at the University of Vigo, Spain ('C.A.C.T.I. – Unidad de Espectrometria de Masas'). Melting points were determined on a Reichert Thermovar melting point apparatus and are not corrected.

Synthesis of 1*H*-pyrazolo[3,4-*b*]quinoline 2 [64]

Hydrazine hydrate (5.3 mL) was added to a mixture of 2-chloro-3-formylquinoline **1** (5.25 g, 27.4 mmol) and *p*-TsOH (2.74 g, 14.4 mmol). The reaction mixture was stirred for 3 h at 130 °C. A white precipitate was formed upon addition of cold water. After filtration, the solid was washed with ethyl acetate to give compound **2** (4.60 g, 99%) as a white solid; mp 190–192 °C (lit.[64] 203–204 °C), ^{1}H NMR (300 MHz, MeOD): δ 4.87 (s, 1H, N*H*), 7.48 (t, J = 7.2, 1H, Ar*H*, 6-H), 7.79 (m, 1H, Ar*H*, 7-H), 8.02 (d, J = 8.7, 1H, Ar*H*, 8-H), 8.08 (d, J = 8.4, 1H, Ar*H*, 5-H), 8.35 (s, 1H, Ar*H*, 3-H), 8.88 (s, 1H, Ar*H*, 4-H).

General procedure 1

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

Synthesis of ethyl 1*H*-pyrazolo[3,4-*b*]quinolin-1-ylacetate (3a)

Following general procedure 1, the reaction of 1*H*-pyrazolo[3,4-*b*]quinoline **2** (1.76 g, 10.00 mmol) in DMF (18 mL), K_2CO_3 (13.82 g, 100.0 mmol) and $BrCH_2CO_2Et$ (2.2 mL, 20.00 mmol) gave compound **3a** (2.54 g, 99%) as a yellow solid; mp 85–86 °C. ν_{max} (KBr) (cm^{-1}): 3054 (C–H Ar), 2988, 2935 (C–H), 1741 (C═O), 1614, 1575, 1499, 1470, 1449, 1439 (C═N, C═C), 1234 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, J = 7.2, 3H, OCH_2CH_3), 4.23 (q, J = 7.2, 2H, OCH_2CH_3), 5.42 (s, 2H, NCH_2), 7.45 (t, J = 7.4, 1H, Ar*H*, 6-H), 7.72–7.78 (m, 1H, Ar*H*, 7-H), 7.97 (d, J = 8.4, 1H, Ar*H*, 5-H), 8.10 (d, J = 8.7, 1H, Ar*H*, 8-H), 8.30 (s, 1H, Ar*H*, 3-H), 8.62 (s, 1H, Ar*H*, 4-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (OCH_2CH_3), 48.1 (NCH_2), 61.7 (OCH_2CH_3), 116.7 (Ar : C3a), 123.9 (Ar : C6), 124.5 (Ar : C4a), 128.1 (Ar : C8), 129.3 (Ar : C5), 130.8 (Ar : C7), 130.9 (Ar : C4), 134.0 (Ar : C3), 148.1 (Ar : C8a), 150.3 (Ar : C9a), 168.3 (C═O). MS (EI): m/z = 255 (M^+, 23%), 182 ($M^+ - CO_2Et$, 100%). HRMS (EI) m/z calcd for $C_{14}H_{13}N_3O_2$ 255.1008 $[M]^+$, found 255.1008.

Synthesis of ethyl 3-(1*H*-pyrazolo[3,4-*b*]quinolin-1-yl)-propanoate (3b) and ethyl 3-(2*H*-pyrazolo[3,4-*b*]quinolin-2-yl)-propanoate (4b)

Following general procedure 1, the reaction of 1*H*-pyrazolo[3,4-*b*]quinoline **2** (1.81 g, 10.70 mmol) in DMF (18 mL), K_2CO_3 (14.78 g, 107.0 mmol) and $Br(CH_2)_2CO_2Et$ (2.7 mL, 21.40 mmol) gave **3b** (1.94 g, 67%) and compound **4b** (500 mg, 17%), both as yellow-orange solids.

Compound **3b**: mp 53–54 °C. ν_{max} (KBr) (cm^{-1}): 3042 (C–H Ar), 2982, 2956, 2926 (C–H), 1727 (C═O), 1619, 1570, 1499, 1458, 1438 (C═N, C═C), 1188 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (t, J = 7.1, 3H, OCH_2CH_3), 3.07 (t, J = 7.2, 2H, NCH_2CH_2), 4.13 (q, J = 7.1, 2H, OCH_2CH_3), 4.95 (t, J = 7.2, 2H, NCH_2), 7.44 (t, J = 7.4, 1H, Ar*H*, 6-H), 7.75 (t, J = 7.2, 1H, Ar*H*, 7-H), 7.96 (d, J = 8.3, 1H, Ar*H*, 5-H), 8.11 (d, J = 8.7, 1H, Ar*H*, 8-H), 8.23 (s, 1H, Ar*H*, 3-H), 8.60 (s, 1H, Ar*H*, 4-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (OCH_2CH_3), 34.2 (NCH_2CH_2), 42.7 (NCH_2), 60.7 (OCH_2CH_3), 116.7 (Ar : C3a), 123.6 (Ar : C6), 124.4 (Ar : C4a), 128.2 (Ar : C8), 129.2 (Ar : C5), 130.4 (Ar : C4), 130.7 (Ar : C7), 132.8 (Ar : C3), 148.2 (Ar : C8a), 149.7 (Ar : C9a), 171.1 (C═O). MS (EI): m/z = 269 (M^+, 10%), 224 ($M^+ - OCH_2CH_3$, 6%), 196 ($M^+ - CO_2Et$, 8%), 182 ($M^+ - CH_2CO_2Et$, 100%), 168 ($M^+ - (CH_2)_2CO_2Et$, 5%). HRMS (EI) m/z calcd for $C_{15}H_{15}N_3O_2$ 269.1164 $[M]^+$, found 269.1166.

Compound **4b**: mp 72–73 °C. ν_{max} (KBr) (cm^{-1}): 3109, 3061 (C–H Ar), 2982, 2926 (C–H), 1727 (C═O), 1618, 1550, 1506, 1466, 1456 (C═N, C═C), 1190 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (t, J = 7.1, 3H, OCH_2CH_3), 3.22 (t, J = 6.4, 2H, NCH_2CH_2), 4.10 (q, J = 7.1, 2H, OCH_2CH_3), 4.87 (t, J = 6.4, 2H, NCH_2), 7.32 (t, J = 7.7, 1H, Ar*H*, 6-H), 7.63 (dt, J = 8.1 and 1.3, 1H, Ar*H*, 7-H), 7.85 (d, J = 8.5, 1H, Ar*H*, 5-H), 8.10 (d, J = 8.9, 1H, Ar*H*, 8-H), 8.35 (s, 1H, Ar*H*, 3-H), 8.69 (s, 1H, Ar*H*, 4-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (OCH_2CH_3), 34.3 (NCH_2CH_2), 50.2 (NCH_2), 61.0 (OCH_2CH_3), 115.0 (Ar : C3a), 123.4 (Ar : C6), 123.8 (Ar : C3), 124.9 (Ar : C4a), 128.8 (Ar : C5 or C8), 129.0 (Ar : C8 or C5), 130.3 (Ar : C7), 131.1 (Ar : C4), 150.4 (Ar : C8a), 158.0 (Ar : C9a), 170.8 (C═O). MS (EI): m/z = 269 (M^+, 7%), 224 ($M^+ - OCH_2CH_3$, 1%), 196 ($M^+ - CO_2Et$, 3%), 182 ($M^+ - CH_2CO_2Et$, 3%), 168 ($M^+ - (CH_2)_2CO_2Et$, 2%), 169 (100%). HRMS (EI) m/z calcd for $C_{15}H_{15}N_3O_2$ 269.1164 $[M]^+$, found 269.1165.

Synthesis of ethyl 4-(1*H*-pyrazolo[3,4-*b*]quinolin-1-yl)butanoate (3c)

Following general procedure 1, the reaction of 1*H*-pyrazolo[3,4-*b*]quinoline **2** (500 mg, 2.96 mmol) in DMF (5 mL), K_2CO_3 (4.09 g, 29.60 mmol) and $Br(CH_2)_3CO_2Et$ (0.85 mL, 5.92 mmol) gave compound **3c** (760 mg, 93%) as an orange oil. ν_{max} (film) (cm^{-1}): 3057 (C–H Ar), 2980, 2938 (C–H), 1732 (C═O), 1617, 1570, 1500, 1433 (C═N, C═C), 1182 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (t, J = 7.2, 3H, OCH_2CH_3), 2.32–2.38 (m, 4H, CH_2CH_2CO), 4.08 (q, J = 7.2, 2H, OCH_2CH_3), 4.73 (t, J = 6.0, 2H, NCH_2), 7.45 (t, J = 7.5, 1H, Ar*H*, 6-H), 7.76 (t, J = 7.4, 1H, Ar*H*, 7-H), 7.97 (d, J = 8.1, 1H, Ar*H*, 5-H), 8.14 (d, J = 8.7, 1H, Ar*H*, 8-H), 8.25 (s, 1H, Ar*H*, 3-H), 8.63 (s, 1H, Ar*H*, 4-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (OCH_2CH_3), 24.9, 31.5 (CH_2CH_2CO), 46.0 (NCH_2), 60.4 (OCH_2CH_3), 116.6 (Ar : C3a), 123.6 (Ar : C6), 124.4 (Ar : C4a), 128.3 (Ar : C8), 129.2 (Ar : C5), 130.3 (Ar : C7), 130.5 (Ar : C4), 132.6 (Ar : C3), 148.3 (Ar : C8a), 150.1 (Ar : C9a), 172.9 (C═O). MS (EI): m/z = 283 (M^+, 11%), 238 ($M^+ - OCH_2CH_3$, 11%), 210 ($M^+ - CO_2Et$, 7%), 196 ($M^+ - CH_2CO_2Et$, 3%), 182 ($M^+ - (CH_2)_2CO_2Et$, 100%), 168 ($M^+ - (CH_2)_3CO_2Et$, 5%). HRMS (EI) m/z calcd for $C_{16}H_{17}N_3O_2$ 283.1321 $[M]^+$, found 283.1315.

General procedure 2

1*H*-Pyrazolo[3,4-*b*]quinoline ester derivative (**3**) (1 eq.) was stirred at reflux for 1–2 h with an excess of aqueous NaOH solution (10 M). The mixture was cooled and acidified with 10% aqueous HCl solution. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed under vacuum to afford a solid which was purified by recrystallisation from ethyl acetate/petroleum ether to give the pure carboxylic acid derivatives **5**.

Synthesis of 1*H*-pyrazolo[3,4-*b*]quinolin-1-ylacetic acid (5a)

The reaction of compound **3a** (600 mg, 2.35 mmol) in aqueous NaOH solution (10 M, 4 mL) for 2 h gave compound **5a** (520 mg, 96%) as an orange solid; mp 188–190 °C. ν_{max} (KBr) (cm^{-1}): 3433, 3200–2300 (OH), 3059 (C–H Ar), 2976, 2936, 2870, 2721 (C–H), 1726 (C═O), 1617, 1573, 1500, 1441 (C═N, C═C). ^{1}H NMR (300 MHz, MeOD): δ 5.36 (s, 2H, NCH_2), 7.45 (t, J = 7.7, 1H, Ar*H*, 6-H), 7.76 (t, J = 7.7, 1H, Ar*H*, 7-H), 8.01 (d, J = 8.7, 2H, Ar*H*, 5-H and 8-H), 8.33 (s, 1H, Ar*H*, 3-H), 8.77 (s, 1H, Ar*H*, 4-H). ^{13}C NMR (75 MHz, MeOD): δ 48.9 (NCH_2), 118.4 (Ar : C3a), 125.1 (Ar : C6), 126.0 (Ar : C4a), 128.4 (Ar : C8), 130.8 (Ar : C5), 132.3 (Ar : C7), 133.1 (Ar : C4), 135.4 (Ar : C3), 149.4 (Ar : C8a), 151.5 (Ar : C9a), 171.6 (C═O). MS (EI): m/z = 227 (M^+, 17%), 182 ($M^+ - CO_2H$, 100%). HRMS (EI) m/z calcd for $C_{12}H_9N_3O_2$ 227.0695 $[M]^+$, found 227.0696.

Synthesis of 3-1*H*-pyrazolo[3,4-*b*]quinolin-1-ylpropionic acid (5b)

The reaction of compound **3b** (1.75 g, 6.52 mmol) in aqueous NaOH solution (10 M, 10.50 mL) for 1 h gave compound **5b** (1.49 g, 95%) as a yellow-orange solid; mp 180 °C. ν_{max} (KBr) (cm^{-1}): 3404, 3200–2300 (OH), 3106, 3058, 3044 (C–H Ar), 2972, 2924 (C–H), 1713 (C═O), 1621, 1576, 1505, 1496, 1443, 1427, 1418 (C═N, C═C). ^{1}H NMR (300 MHz, MeOD): δ 3.01 (t, J = 7.2, 2H, NCH_2CH_2), 4.86 (t, J = 7.2, 2H, NCH_2), 7.47 (t, J = 7.5, 1H, Ar*H*, 6-H), 7.77 (dt, J = 7.7 and 1.5, 1H, Ar*H*, 7-H), 8.05–8.08 (m, 2H, Ar*H*, 5-H and 8-H), 8.32 (s, 1H, Ar*H*, 3-H), 8.82 (s, 1H, Ar*H*, 4-H). ^{13}C NMR (100 MHz, MeOD): δ 34.8 (NCH_2CH_2), 43.8 (NCH_2), 118.2 (Ar : C3a), 125.0 (Ar : C6), 125.7 (Ar : C4a), 128.0 (Ar : C8), 130.7 (Ar : C5), 132.5 (Ar : C7), 133.5 (Ar : C4), 134.8 (Ar : C3), 149.1 (Ar : C8a), 150.6 (Ar : C9a), 175.2 (C═O). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.00 (t, J = 6.9, 2H, NCH_2CH_2), 4.80 (t, J = 7.2, 2H, NCH_2), 7.51–7.56 (m, 1H, Ar*H*, 6-H), 7.81–7.87 (m, 1H, Ar*H*, 7-H), 8.09 (d, J = 8.1, 1H, Ar*H*, 8-H), 8.18 (d, J = 8.4, 1H, Ar*H*, 5-H), 8.49 (s, 1H, Ar*H*, 3-H), 8.98 (s, 1H, Ar*H*, 4-H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 33.5 (NCH_2CH_2), 42.3 (NCH_2), 116.4 (Ar : C3a), 123.5 (Ar : C6), 124.1 (Ar : C4a), 127.8 (Ar : C8), 129.7 (Ar : C5), 130.8 (Ar : C7), 131.2 (Ar : C4), 133.2 (Ar : C3), 147.5 (Ar : C8a), 149.5 (Ar : C9a), 172.3 (C═O). MS (EI): m/z = 241 (M^+, 4%), 182 ($M^+ - CH_2CO_2H$, 19%), 168 ($M^+ - (CH_2)_2CO_2H$, 2%), 169 (100%). HRMS (EI) m/z calcd for $C_{13}H_{11}N_3O_2$ 241.0851 $[M]^+$, found 241.0852.

Synthesis of 4-1*H*-pyrazolo[3,4-*b*]quinolin-1-ylbutyric acid (5c)

The reaction of compound **3c** (720 mg, 2.56 mmol) in aqueous NaOH solution (10 M, 4.36 mL) for 1.5 h gave compound **5c** (600 mg, 92%) as a yellow-orange solid; mp 147 °C. ν_{max} (KBr) (cm^{-1}): 3447, 3100–2400 (OH), 3109, 3056, 3037 (C–H Ar), 2977, 2915, 2869 (C–H), 1709 (C═O), 1618, 1573, 1500, 1438, 1429 (C═N, C═C). ^{1}H NMR (300 MHz, MeOD): δ 2.21–2.38 (m, 4H, CH_2CH_2CO), 4.64 (t, J = 6.6, 2H, NCH_2), 7.45 (t, J = 7.9, 1H, Ar*H*, 6-H), 7.76 (dt, J = 7.5 and 1.5, 1H, Ar*H*, 7-H), 8.03 (d, J = 9.3, 2H, Ar*H*, 5-H and 8-H), 8.31 (s, 1H, Ar*H*, 3-H), 8.79 (s, 1H, Ar*H*, 4-H). ^{13}C NMR (75 MHz, MeOD): δ 26.1 and 32.0 (CH_2CH_2CO), 47.1 (NCH_2), 118.2 (Ar : C3a), 124.8 (Ar : C6), 125.8 (Ar : C4a), 128.5 (Ar : C8), 130.6 (Ar : C5), 132.0 (Ar : C7), 132.8 (Ar : C4), 134.3 (Ar : C3), 149.3 (Ar : C8a), 150.9 (Ar : C9a), 176.5 (C═O). MS (EI): m/z = 255 (M^+, 12%), 210 ($M^+ - CO_2H$, 10%), 182 ($M^+ - (CH_2)_2CO_2H$, 100%), 168 ($M^+ - (CH_2)_3CO_2H$, 6%). HRMS (EI) m/z calcd for $C_{14}H_{13}N_3O_2$ 255.1008 $[M]^+$, found 255.1009.

General procedure 3 (method A)

A mixture of carboxylic acid **5** (1 eq.) and thionyl chloride (4 eq.), in $CHCl_3$, was kept under reflux for 2 h. Removal of the solvents afforded the corresponding acyl chloride. The acyl chloride derivative was immediately dissolved in dry THF without further purification, and the mixture was cooled to 0 °C. Then tris(trimethylsilyl)phosphite was added, and the mixture was stirred for 2 h at room temperature. The solvent was removed under reduced pressure, methanol was added to the residue and the mixture was stirred for 1 h. After solvent removal, the residue was washed with ethyl ether. Acetone and methanol were added to obtain the pure product.

General procedure 4 (method B)

A mixture of carboxylic acid **5** (1 eq.) and neat thionyl chloride was kept under reflux for 2 h. The mixture was brought to dryness under reduced pressure to give the crude product containing the corresponding acyl chloride, which was immediately used without further purification. The crude acyl chloride was dissolved in dry THF, cooled to 0 °C and tris(trimethylsilyl)phosphite was added. The remaining procedure was similar to method A.

Synthesis of (1*H*-pyrazolo[3,4-*b*]quinolin-1-yl)acetylphosphonic acid (9)

Following general procedure 3 (method A), the reaction of compound **5a** (100 mg, 0.44 mmol) in $CHCl_3$ (2 mL), thionyl chloride (0.13 mL, 1.76 mmol) and tris(trimethylsilyl)phosphite (0.29 mL, 0.88 mmol) gave monophosphonic acid **9** (62 mg, 48%) as a cream-white solid; mp 195 °C (decomp.). ν_{max} (KBr) (cm^{-1}): 3448 (OH), 3108 (C–H Ar), 2982, 2925, 2853 (C–H), 1696 (C═O), 1654, 1636, 1498, 1439 (C═N, C═C), 1206, 1146, 1121, 1105, 1072, 1042, 1013, 940 (P═O, P–OH, POH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.82 (d, J_{HP} = 3.6, 2H, NCH_2), 7.53 (dt, J = 7.6 and 1.2, 1H, Ar*H*, 6-H), 7.81 (dt, J = 7.6 and 1.2, 1H, Ar*H*, 7-H), 8.00 (d, J = 8.4, 1H, Ar*H*, 8-H), 8.19 (d, J = 8.0, 1H, Ar*H*, 5-H), 8.54 (s, 1H, Ar*H*, 3-H), 9.02 (s, 1H, Ar*H*, 4-H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 56.3 (d, J_{CP} = 63.7, NCH_2), 116.4 (Ar : C3a), 123.7 (Ar : C6), 124.2 (Ar : C4a), 127.6 (Ar : C8), 129.8 (Ar : C5), 131.0 (Ar : C7), 131.6 (Ar : C4), 134.4 (Ar : C3), 147.5 (Ar : C8a), 150.3 (Ar : C9a), 210.0 (d, J_{CP} = 168.4, C═O). ^{31}P NMR (162 MHz, DMSO-d_6): δ −3.89 (s). MS (ESI): m/z = 314 (MNa^+, 15%), 292 (MH^+, 100%), 228 ($MH^+ - HPO_2$, 6%). HRMS (ESI) m/z calcd for $C_{12}H_{11}N_3O_4P$ 292.0482 $[MH]^+$, found 292.0477.

Synthesis of [1-hydroxy-2-(1*H*-pyrazolo[3,4-*b*]quinolin-1-yl)-ethane-1,1-diyl]bis(phosphonic acid) (6)

Following general procedure 4 (method B), the reaction of compound **5a** (50 mg, 0.22 mmol), thionyl chloride (1 mL) and tris(trimethylsilyl)phosphite (0.22 mL, 0.66 mmol) gave bisphosphonic acid **6** (78 mg, 95%) as a cream-white solid; mp 250 °C (decomp.). ν_{max} (KBr) (cm^{-1}): 3431, 3200–2600 (OH), 3107, 3050 (C–H Ar), 2993, 2925, 2854 (C–H), 2757 (PO–H), 1648, 1500, 1439 (C═N, C═C), 1260, 1228, 1174, 1106, 1074, 1055, 997, 957, 926 (P═O, P–OH, POH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.09 (t, J_{HP} = 9.6, 2H, NCH_2), 7.54 (t, J = 7.5, 1H, Ar*H*, 6-H), 7.86 (t, J = 7.7, 1H, Ar*H*, 7-H), 7.98 (d, J = 8.7, 1H, Ar*H*, 8-H), 8.20 (d, J = 8.1, 1H, Ar*H*, 5-H), 8.48 (s, 1H, Ar*H*, 3-H), 9.04 (s, 1H, Ar*H*, 4-H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 52.1 (NCH_2), 73.8 (t, J_{CP} = 141.6, $C(OH)(PO_3H_2)_2$), 117.2 (Ar : C3a), 123.9 (Ar : C6), 124.0 (Ar : C4a), 126.8 (Ar : C8), 129.9 (Ar : C5), 131.4 (Ar : C7), 132.5 (Ar : C4), 133.6 (Ar : C3), 146.1 (Ar : C8a), 150.0 (Ar : C9a). ^{31}P NMR (121 MHz, DMSO-d_6): δ 17.05 (s). MS

(FAB): m/z = 374 (MH^+, 7%), 154 (100%). HRMS (FAB) m/z calcd for $C_{12}H_{14}N_3O_7P_2$ 374.0307 $[MH]^+$, found 374.0309.

Synthesis of [1-hydroxy-4-(1*H*-pyrazolo[3,4-*b*]quinolin-1-yl)-butane-1,1-diyl]bis(phosphonic acid) (8)

Following general procedure 4 (method B), the reaction of compound **5c** (50 mg, 0.196 mmol), thionyl chloride (1 mL) and tris(trimethylsilyl)phosphite (0.20 mL, 0.598 mmol) gave bisphosphonic acid **8** (51 mg, 65%) as a cream-white solid; mp 265 °C (decomp.). ν_{max} (KBr) (cm^{-1}): 3448, 3500–2300 (OH), 3100 (C–H Ar), 2963, 2924 (C–H), 2673 (PO–H), 1570, 1560, 1498, 1474 (C=N, C=C), 1245, 1223, 1153, 1126, 1092, 1021, 994, 970, 946, 930 (P=O, P–OH, POH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.94–1.98 (m, 2H, $NCH_2CH_2CH_2$), 2.17–2.23 (m, 2H, $NCH_2CH_2CH_2$), 4.52 (t, J = 7.2, 2H, NCH_2), 7.50 (t, J = 7.2, 1H, Ar*H*, 6-H), 7.80 (t, J = 7.6, 1H, Ar*H*, 7-H), 8.05 (d, J = 8.8, 1H, Ar*H*, 8-H), 8.16 (d, J = 8.0, 1H, Ar*H*, 5-H), 8.46 (s, 1H, Ar*H*, 3-H), 8.97 (s, 1H, Ar*H*, 4-H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.0 ($NCH_2CH_2CH_2$), 30.5 ($NCH_2CH_2CH_2$), 47.0 (NCH_2), 72.1 ($C(OH)(PO_3H_2)_2$), 116.5 (Ar : C3a), 123.6 (Ar : C6), 124.1 (Ar : C4a), 127.8 (Ar : C8), 129.8 (Ar : C5), 130.9 (Ar : C7), 131.4 (Ar : C4), 133.0 (Ar : C3), 147.5 (Ar : C8a), 149.5 (Ar : C9a). ^{31}P NMR (121 MHz, DMSO-d_6): δ 20.98 (s). MS (ESI): m/z = 402 (MH^+, 13%), 320 ($MH^+ - H_3PO_3$, 26%), 276 (320-HPO_2, 59%), 238 (100%). HRMS (ESI) m/z calcd for $C_{14}H_{18}N_3O_7P_2$ 402.0615 $[M + H]^+$, found 402.0615.

Synthesis of (1-oxo-2,3-dihydro-1*H*,6*H*-3*a*,4,10*b*-triazaacephenanthrylen-6-yl)phosphonic acid (10)

1. Following general procedure 3 (method A), the reaction of compound **5b** (50 mg, 0.21 mmol) in $CHCl_3$ (1 mL), thionyl chloride (0.06 mL, 0.84 mmol) and tris(trimethylsilyl)phosphite (0.14 mL, 0.42 mmol) gave compound **10** (56 mg, 87%) as a yellow solid; mp 173–175 °C. ν_{max} (KBr) (cm^{-1}): 3386, 3450–2300 (OH), 3124, 3086 (C–H Ar), 2958, 2928, 2879 (C–H), 2629 (PO–H), 1702 (C=O), 1605, 1570, 1484, 1466, 1447 (C=N, C=C), 1254, 1233, 1188, 1148, 1107, 1040, 1011, 961 (P=O, P–OH, POH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.89–2.94 (m, 1H, CHCO), 3.14–3.21 (m, 1H, CHCO), 4.32–4.38 (m, 2H, NCH_2), 4.34 (d, J_{HP} = 23.2, 1H, $CHPO_3H_2$, 4-H), 7.19 (t, J = 7.4, 1H, Ar*H*, 6-H), 7.29–7.32 (m, 2H, Ar*H*, 7-H and 3-H), 7.46 (d, J = 7.6, 1H, Ar*H*, 5-H), 7.70 (br s, 4H, OH), 8.65 (d, J = 8.4, 1H, Ar*H*, 8-H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 33.7 (CH_2CO), 37.6 (d, J_{CP} = 135.0, $CHPO_3H_2$: C4), 42.2 (NCH_2), 98.1 (d, J_{CP} = 8.0, Ar : C3a), 120.3 (d, J_{CP} = 2.6, Ar : C8), 123.7 (d, J_{CP} = 6.8 Ar : C4a), 124.9 (d, J_{CP} = 2.8, Ar : C6), 127.1 (d, J_{CP} = 2.9, Ar : C7), 131.6 (d, J_{CP} = 4.0, Ar : C5), 134.9 (d, J_{CP} = 4.9, Ar : C8a), 136.4 (d, J_{CP} = 4.9, Ar : C9a), 136.7 (Ar : C3), 164.1 (C=O). ^{31}P NMR (121 MHz, DMSO-d_6): δ 22.32 (s). MS (ESI): m/z = 306 (MH^+, 100%), 242 ($MH^+ - HPO_2$, 60%). HRMS (ESI) m/z calcd for $C_{13}H_{13}N_3O_4P$ 306.06382 $[M + H]^+$, found 306.06476.

2. Following general procedure 4 (method B), the reaction of compound **5b** (200 mg, 0.83 mmol), thionyl chloride (1 mL) and tris(trimethylsilyl)phosphite (0.83 mL, 2.48 mmol) gave compound **10** (213 mg, 84%) as a white solid, identical to the product from general procedure 3 above.

Synthesis of diethyl (1-oxo-2,3-dihydro-1*H*,6*H*-3a,4,10b-triazaacephenanthrylen-6-yl)phosphonate (11)

A mixture of carboxylic acid **5b** (100 mg, 0.414 mmol) and thionyl chloride (1 mL) was kept under reflux for 2 h. The solvent was removed under vacuum to give the corresponding acyl chloride. The obtained acyl chloride was suspended in dry THF, and triethyl phosphite (0.14 mL, 0.828 mmol) was added and the mixture was stirred for 1 h at room temperature. Then, the solvent was removed and methanol was added and the mixture was stirred for 1 h. After solvent removal under reduced pressure, the residue was washed with ethyl ether to afford a yellow solid. This solid was recrystallized from ethyl ether and petroleum ether to afford compound **11** (117 mg, 78%) as white crystals; mp 137–139 °C. ν_{max} (KBr) (cm^{-1}): 3133, 3078 (C–H Ar), 2980, 2913, 2900 (C–H), 1706 (C=O), 1621, 1558, 1508, 1478, 1435 (C=N, C=C), 1247 (P=O), 1039, 1036, 961 (P–OC). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (t, J = 7.2, 3H, CH_3), 1.26 (t, J = 7.2, 3H, CH_3), 3.02–3.08 (m, 1H, CHCO), 3.21–3.31 (m, 1H, CHCO), 3.80–3.93 (m, 2H, OCH_2CH_3), 3.97–4.05 (m, 2H, OCH_2CH_3), 4.32–4.46 (m, 2H, NCH_2), 4.50 (d, J_{HP} = 22.8, 1H, $CHPO_3Et_2$), 7.24 (t, J = 7.4, 1H, Ar*H*, 6-H), 7.36 (tt, J = 8.0 and 2.0, 1H, Ar*H*, 7-H), 7.43 (d, J = 1.2, 1H, Ar*H*, 3-H), 7.53 (dt, J = 8.0 and 2.0, 1H, Ar*H*, 5-H), 8.81 (d, J = 8.8, 1H, Ar*H*, 8-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.3 (t, J_{CP} = 7.4, $PO(OCH_2CH_3)_2$), 34.1 (CH_2CO), 36.9 (d, J_{CP} = 143.4, $CHPO_3Et_2$), 42.7 (NCH_2), 62.7 (d, J_{CP} = 7.4, $PO(OCH_2CH_3)$, 63.2 (d, J_{CP} = 7.3, $PO(OCH_2CH_3)$, 97.1 (d, J_{CP} = 9.1, Ar : C3a), 120.7 (d, J_{CP} = 6.8, Ar : C4a), 121.2 (d, J_{CP} = 3.0, Ar : C8), 125.7 (d, J_{CP} = 3.0, Ar : C6), 128.4 (d, J_{CP} = 3.0, Ar : C7), 131.5 (d, J_{CP} = 4.5, Ar : C5), 135.0 (d, J_{CP} = 5.3, Ar : C8a), 136.9 (d, J_{CP} = 5.3, Ar : C7a), 137.6 (Ar : C3), 163.5 (C=O). ^{31}P NMR (121 MHz, $CDCl_3$): δ 21.20 (s). MS (EI): m/z = 361 (M^+, 1%), 224 ($M^+ - PO(OEt)_3$, 100%), 196 (224-CO, 3%), 182 (224-$COCH_2$, 48%). HRMS (ESI) m/z calcd for $C_{17}H_{20}N_3O_4P$ 361.1191 $[M + H]^+$, found 361.1187.

Crystal structure determination of the two polymorphs of diethyl (1-oxo-2,3-dihydro-1*H*,6*H*-3a,4,10b-triazaacephenanthrylen-6-yl)phosphonate (11-I and 11-II)

X-ray crystallography. Crystals of **11-I** and **11-II** suitable for X-ray diffraction studies were mounted with Fomblin© in a cryoloop. Data were collected on a Bruker AXS-KAPPA APEX II diffractometer with graphite-monochromated radiation (Mo Kα, λ = 0.71073 Å) at 296 K. The X-ray generator was operated at 50 kV and 30 mA and the X-ray data collection was monitored using the APEX2[66] program. All data were corrected for Lorentzian, polarization and absorption effects using SAINT[66] and SADABS[66] programs. SHELXT 2014/4[67] was used for structure solution and SHELXL 2014/7[68] was used for full matrix least-squares refinement on F^2. These programs are included in the package of the program WINGX-Version 2014.1.[69] Non-hydrogen atoms were refined anisotropically. A full-matrix least-squares refinement was used for the non-hydrogen atoms with anisotropic thermal parameters. All the hydrogen atoms were inserted in idealized positions and allowed to refine in the parent carbon atom. MERCURY 4.3.1[70] was used for

Table 7 Crystal data and structure refinement details for **11-I** and **11-II**

	11-I	**11-II**
Formula	$C_{17}H_{20}N_3O_4P$	$C_{17}H_{20}N_3O_4P$
fw	361.33	361.33
Crystal form, colour	Block, colourless	Block, colourless
Crystal size (mm)	0.13 × 0.06 × 0.06	0.15 × 0.05 × 0.40
Cryst. syst.	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/n$
a, Å	7.8318(10)	11.592(3)
b, Å	10.2797(13)	7.7150(15)
c, Å	21.689(3)	19.848(5)
α, °	90.0	90.0
β, °	98.470(6)	105.237(7)
γ, °	90.0	90.0
Z	4	4
V, Å^3	1727.1(4)	1712.7(7)
T, K	296(2)	296(2)
D_c, g cm^{-3}	1.390	1.401
μ(Mo Kα), mm^{-1}	0.187	0.188
θ range (°)	2.744–29.605	2.846–25.361
Refl. collected	30 838	8322
Independent refl.	4838	3108
R_{int}	0.1115	0.1102
R_1 [a], wR_2 [b] [$I \geq 2\sigma(I)$]	0.0825, 0.2171	0.0817, 0.1960
GOF on F^2	1.040	0.96

[a] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $wR_2 = [\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]]^{1/2}$.

packing diagrams. PLATON[71] was used for the determination of hydrogen bond interactions. The crystal data and details of data collection for **11-I** and **11-II** are reported in Table 7. Crystallographic data of compounds **11-I** and **11-II** were deposited at the Cambridge Crystallographic Data Centre (CCDC 2054058 and 2054059†).

Conflicts of interest

There are no conflicts to declare.

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