Diastereoselective synthesis of bis(α-aminophosphonates) by lipase catalytic promiscuity

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Rim Aissa,[a] Samia Guezane-Lakoud,[a,*] Emilie Kolodziej,[b] Martial Toffano,[b] and Louisa Aribi-Zouioueche.[a]

New bis(α-aminophosphonates) have been directly prepared with high diastereoselectivity by lipase catalytic promiscuity in the presence of immobilized *Candida Antarctica* lipase. We focused on the multi-component *Kabachnik-Fields* reaction using various aldehydes, benzidine and diethylphosphite in one pot. The reaction proceeds in short reaction times with good to excellent yields. The *CAL-B* was easily recovered and reused several times. A total diastereoselectivity was observed for bis(α-aminophosphonates) **4a**, **4c**, **4h**, **4i, 4k** and high for **4b**, **4f** and **4j.**

Introduction

The α-aminophosphonates are of great biochemical and pharmacological effects [1,2] due to the association of phosphonate and amine. These molecules are phosphorus structural analogues of amino acid [3] and they are interesting for medicinal chemistry.[4] The α-aminophosphonates derivatives have received much attention owing as enzyme inhibitors, pharmacogenic agents, haptens of catalytic antibodies, herbicidals, inhibitors of serine hydrolases, inhibitors of UDP-galactopyranose mutase and also as anticancer agents as reported in the literature. [5]

The *Kabachnik-Fields* reaction is the most efficient method for the synthesis of α-aminophosphonates. [6] We found various synthetic methodologies using different catalysts for the synthesis of α- aminophosphonates derivatives.[7] Recently, we have reported the synthesis of α-aminophosphonates by enzymatic catalytic promiscuity using *Candida antarctica* lipase B (*CAL-B*) by *Kabachnik-Fields* reaction.[8] This is the first example of C-P bond formation involving the principle of enzymatic promiscuity. These findings inspired us to seek lipase that could catalyze the formation of bis(α-aminophosphonates). These multidentate ligands are extremely interesting compounds that can be used in the extraction of metals or as monomers in the preparation of macrocyclic compounds or as polymers carrying phosphonate and amine.[9]

Bis(α-aminophosphonates) exhibit significant biological activities (**Figure 1**), compound **1** shows antifungal activity, compound **2** has

antioxidant activity,[10] and compound **3** shows optimal antiproliferative activity to human tumoral cells from colon carcinoma.[11]

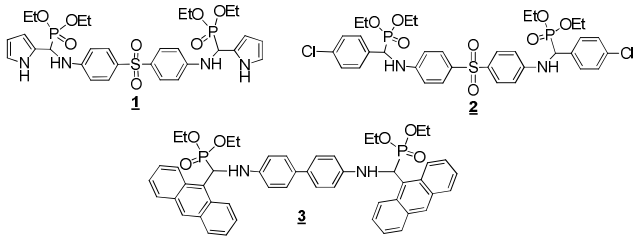


Figure 1. Bis(α-aminophosphonates) having biological activities

Bis(α-aminophosphonates) were synthesized from Schiff bases[12] or diamine [9, 13, 14] under microwave irradiation [10] or with Lewis acid.[9] However, most of these approaches involve longer reaction times, expensive reagents, high temperature, stoichiometric amount of catalysts, low diastereoisomers ratio and metallic contamination due to the use of metal catalyst or Lewis acid. Herein, we applied catalytic promiscuity with lipase as an efficient 'Green' method for the synthesis of new bis (α-aminophosphonates) with excellent diastereocontrol by *Kabachnik-Fields* multi-component condensation.

Enzymes are well-known for catalyzing specific reactions, and for their ability to perform highly regio-, chemo- and stereo-selective transformations, at high reaction rates in relatively mild conditions.[15] Enzymes have many benefits in the context of green and sustainable chemistry and are integrated to efficient and environmentally benign processes for chiral drug development by kinetic resolution or asymmetric synthesis.[16] Lipases especially, are the most used enzymes in synthetic organic chemistry.[17] They are known for their advantages such as providing products of high purity and good selectivity in one reaction step, fewer byproducts and simple separation, as shown in our previous works.[18]

Furthermore, the use of organic solvents in the enzymatic reaction instead of conventional media or aqueous-organic co-solvent mixtures,[19] allowed application of enzymes to expand in catalytic promiscuity, especially in multi-

component reaction. Exploiting enzymatic catalytic promiscuity might lead to improvements in existing catalysts and furnish judicious synthesis pathways. Enzymatic promiscuity is the ability of a single enzyme active site to catalyze multiple chemical transformations with different transition states, other than the reactions for which it has been specialized. This innovating approach is the starting point for a divergent evolution of new protein function which is explained by the creation of a new enzymatic activity depending on circumstances.[20, 21] *Hult* and *Berglund* [22] defined three types of promiscuity: (i)-condition promiscuity: catalysis of different reactions under different conditions from the native one, (ii)-substrate promiscuity: enzymes with broad substrate specificity and (iii)-catalytic promiscuity based on the ability of a single enzyme active site to catalyze several chemical transformations with different transition states. Recently, the product promiscuity was considered as a fourth kind, in which a single enzyme converts a single substrate to multiple products by different transition states.[20a] (**Figure 2**).

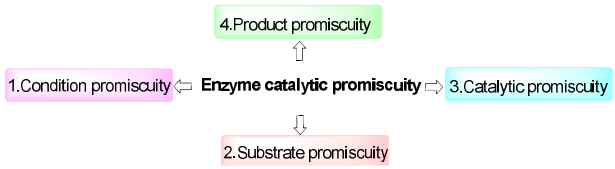


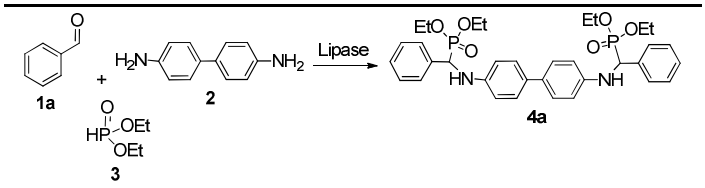
Figure 2. Different kinds of promiscuity

Catalytic promiscuity is described by several reactions for the C-C and C-N bond formation in the presence of different enzymes[23] such as: Knoevenagel reaction,[24] Biginelli reaction,[25] Mannich reaction,[26] Morita-Baylis-Hillman reaction,[27] Henry reaction,[28] Michael reaction,[29] Aldolisation reaction[30] and others.[31,32,33] In organophosphorus chemistry, utilization of lipases is also described for the resolution of racemic hydroxyphosphonates by acylation[34] or hydrolysis.[35] To the best of our knowledge, the use of lipase catalytic promiscuity in a diastereoselective synthesis including the simultaneous formation of two P-C bond is novel and has never been reported yet (c est une proposition de modification.

Results and discussion

The multi-component reactions (MCRs) are realized by lipase catalytic promiscuity for the bis(*α*-aminophosphonates) synthesis. This new benign and clean protocol implies the condensation in one pot of two equivalents of benzaldehyde **1a**, one equivalent of benzidine **2** and two equivalents of diethylphosphite **3** which is used as model reaction with lipase in 2 mL of organic solvent. Several parameters have been studied such as: lipases, solvents, temperature and the reaction time. The reactions were monitored by TLC analysis. The products were obtained in two diastereoisomers mixture, and then separated by extraction or by flash chromatography in ethyl acetate and hexane (70/30). All results are summarized in **Table 1**.

Table 1. Optimization reaction of the bis (*α*-aminophosphonates).



Entry [a]	Lipase (mg)	Solvent	T °C	Time /h	Yield(%)[c]
1[b]	--	THF	70	24	--
2	*CAL-B*(100)	THF	40	24	80
3	*PCL* (80)	THF	40	24	29
4	CCL(100)	THF	40	24	22
5	*PPL* (100)	THF	40	24	16

6	*RGL* (100)	THF	40	24	20
7	*CAL-B*(100)	THF	50	24	90
8 [d]	***CAL-B* (50)** [e]	**THF**	**50**	**24**	**90**
9	*CAL-B* (50)	TBME	50	24	Traces
10	*CAL-B* (50)	PhMe	50	24	Traces
11	*CAL-B* (50)	Et_2O	50	24	26
12	*CAL-B* (50)	AcOEt	50	24	62
13	CAL-B (50)	THF	50	3	90
14	CAL-B (50)	THF	50	1	90
15	**CAL-B (50)**	**THF**	**50**	**30 min**	**90**

[a] Reaction conditions: benzaldehyde (2 mmol), benzidine (1 mmol) and diethylphosphite (2.4 mmol) were stirred with lipase and solvent.
[b] Reaction conditions: benzaldehyde (2 mmol), benzidine (1 mmol) and diethylphosphite (2.4 mmol) were stirred without lipase in solvent (2 mL), at 70°C. No reaction observed at 25°C and at 50°C.
[c] Yield of the pure product purified by column chromatography.
[d] No reaction was observed by less 50 mg of *CAL-B* and with 50 mg of *CAL-B* at room temperature. No reaction also with denatured *CAL-B* lipase.

In all cases the bis (α-aminophosphonates) **4a** were obtained with high yield by catalytic promiscuity using *CAL-B*. Firstly, the multi-component reaction was performed without lipase in THF during 24 hours, the results show that no reaction was observed even by increasing the temperature up to 70°C (Table 1, entry 1).
The denatured CAL-B has been tested, there is no advancement. The nature of the lipase has a significant effect on reaction, five lipases were examined (two animals and three microbial): *Rabbit gastric Lipase* (*RGL*) lipase,[36] *Porcine pancreatic lipase* (*PPL*) and: *Candida cylindracea lipase* (*CCL*), *Pseudomonas cepacia lipase* (*PCL*) which are free lipases and *Candida antarctica B lipase* immobilized on acrylic resin (*CAL-B*). Under these conditions, only *CAL-B* can promote catalytic promiscuity and allows obtaining **4a** compound with 80% yield (Table 1, entry 2), compared with the use of *PCL, CCL, PPL* and *RGL* lipases which lead to the bis(*α*-aminophosphonates) with low yields (< 29%) (Table 1, entries 3, 4, 5 and 6). For a better performance, the temperature was increased to 50°C with *CAL-B* and the product **4a** was obtained in 90% yield (Table 1, entry 7). Product **4a** was obtained in a similar yield at the same temperature by decreasing the amount of *CAL-B* lipase from 100 mg to 50 mg (Table 1, entry 8) but no reaction by less than 50 mg of *CAL-B* or at room temperature. Subsequently, the hydrophobicity solvent effect has been studied, we found that the THF is the best solvent (Table 1, entry 8 *vs* entries 9, 10, 11 and 12). No progress of the reaction was observed in TBME and toluene (Table 1, entry 9 and 10) and a moderate yield was obtained in Et_2O (26%) (Table 1, entry 11), whereas in AcOEt 62% of **4a** was isolated (Table 1, entry 12). A study of the time was also carried out; we found that at the 30th minute, a total disappearance of benzidine was observed (90% yield) (Table 1, entry 15).

In addition, a recycling of *CAL-B* was examined on the model reaction, it showed that the lipase lost its catalytic performance from the fourth cycle (**Fig 3**). So, in optimized conditions, the bis(α-aminophosphonate) **4a** was obtained with high yield using *CAL-B* (50mg) in THF at 50°C.

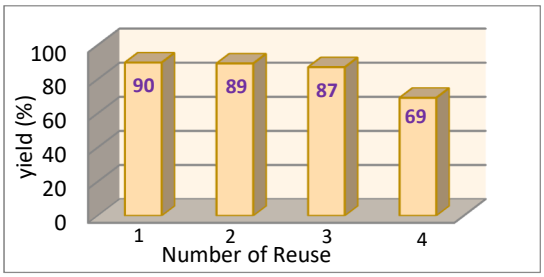
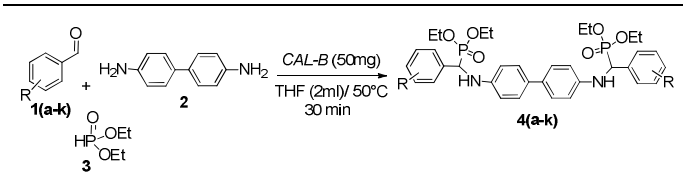


Figure 3 Reusing of the *CAL-B catalyst*

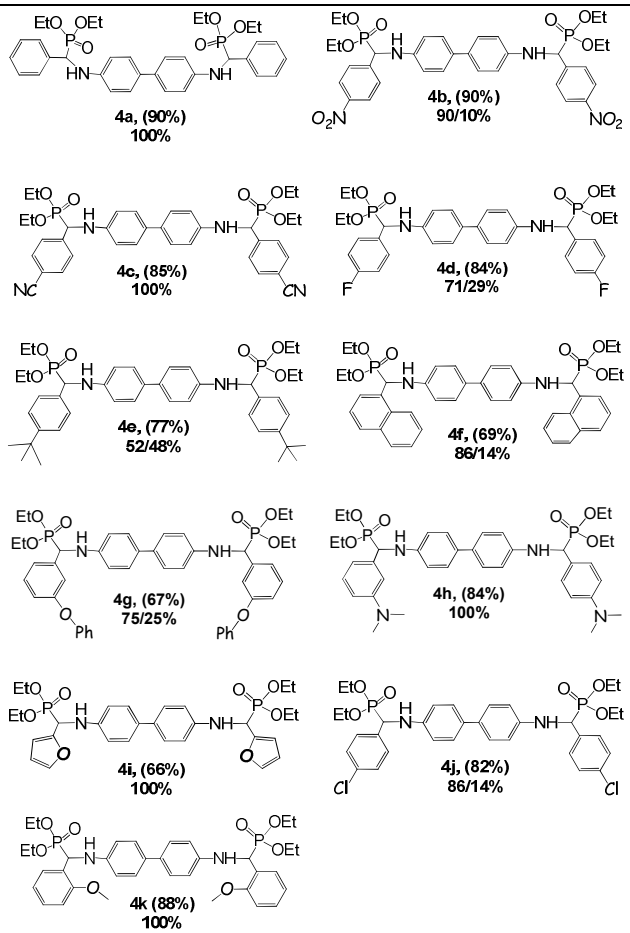
In order to explore the effectiveness and limitations of the MCRs by biocatalytic promiscuity with *CAL-B*, we applied optimized reaction conditions on a series of variously substituted aldehydes with electron-withdrawing and electron-donating groups (**Table 2**).

The molecular structure of all bis (*α*-aminophosphonates) was confirmed by NMR ^{1}H, ^{13}C and ^{31}P spectroscopy and HRMS analysis. ^{1}H NMR and ^{31}P NMR experiments were used for diastereomers (meso/dl ratio) quantification in the crude reaction.

Table 2 Lipase-catalyzed bis (*α*-aminophosphonates) synthesis [a]



Product **4** (yield)[b], *dr%*



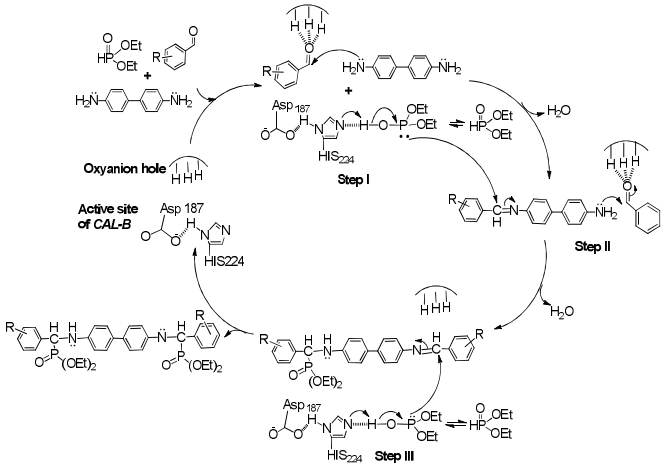
[a] Reaction conditions: benzaldehyde (2 mmol), benzidine (1 mmol) and diethylphosphite (2.4 mmol), *CAL-B* (50 mg), room temperature, 30min.

[b] Yield of the pure product, purified by column chromatography or recrystallization from hexane.

The results of **Table 2** show the efficiency of the MCRs catalyzed by *CAL-B* for the preparation of bis(*α*-aminophosphonates) giving a 66-90% yield with high diastereoselectivity control depending on the electronic effect of aldehydes. The best results

yields (> 80%) are obtained for: **4a**, **4b, 4c, 4d, 4h, 4j** and **4k,** and with average yields (66-77%) for **4e, 4f, 4g,** and **4i** compounds. In addition, five derivatives of bis (*α*-aminophosphonates) **4a**, **4c**, **4h**, **4i** and **4k** are obtained with a total diastereoselectivity (100% dr). A high diastereoselectivity is obtained for **4b** (96/4% dr), even for **4f** and **4j** which is obtained with (80/20% and 86/14% dr) respectively, it also remains good for **4d** (71/29% dr). On the other hand, the diastereoselectivity decreases sharply for the **4g** and **4e,** this is probably be due to the high steric hindrance of aldehydes. To the best of our knowledge, all these bis(*α*-aminophosphonates) derivatives, except the **4h** compound, have never been reported in the literature yet.[37] We completed this works by a multi-gram scale reaction. Thus, a scaling up of the procedure was carried out from 0,636 g (6 mmol) of aromatic aldehyde, 0,636 g (3 mmol) benzidine, (0,828 g, 6 mmol) diethylphosphite in THF and an appropriate amount of *CAL-B* lipase. The quantitative yields were obtained regardless of the scale and the remaining product was isolated with (up on 92%).

In order to be able to propose a reaction mechanism, we proceeded to several experiments. When the multi-component reaction is carried out with an equimolar quantity of starting materials (1/1/1 ratio of aldehyde / benzidine / diethylphosphite), the results show that the bis(α-aminophosphonates) is the sole and only compound obtained in these reaction conditions. No trace of mono-phosphonated compound is observed. This suggests that the formation of the C-P bond is performed on both sides simultaneously of benzidine or that the second addition of diethylphosphonate is extremely rapid and efficient which is probably favored by the proximity of the monophosphonate/enzyme pair. Anyway, at this stage, we suppose that the enzyme plays a crucial role in the privileged selectivity for the bis-phosphonate compounds formation. Combining the viewpoints developed by Per Berglund *et al* [22] and on the basis of our observations described above, we proposed the mechanism of the reaction, summarized in **Scheme 1.** We propose a mechanism involving the coordination to the oxyanion hole by the carbonyl and simultaneous activation of nucleophile by histidine and aspartate from the active site.



Scheme 1. Proposed mechanism of *CAL-B*-catalyzed bis(*α*-aminophosphonates) synthesis

The oxyanion hole activates the carbonyl of aldehyde substrate and renders it susceptible to nucleophilic attack by one amine of benzidine to form an imine (**Step I**). The active-site histidine with aspartate as a base that activates the diethylphosphite as nucleophile for attack of the imine to form the corresponding product (**Step II**). In a concomitant manner in the same active site of lipase, the oxyanion hole activates the carbonyl of aldehyde which promotes the attack of the second amine of benzidine to form the corresponding imine (**Step III**). The following nucleophilic attack of the diethylphosphite activated by histidine / aspartate couple, leads to the formation of the bis(*α*-aminophosphonate) **4**.

Conclusion

In conclusion, we describe the first simultaneous formation of two Carbon–Phosphore bonds by catalytic promiscuity using acrylic resin-immobilized lipase *CAL-B* in a one pot multi-component reaction. This original strategy gives access to a novel series of bis(*α*-aminophosphonates) with high diastereoselectivity and very satisfactory yields, in a short reaction time and under mild and green chemistry conditions. The lipase-catalyzed *Kabachnik-Fields* reaction provides a new case of catalytic promiscuity and might be a useful synthetic method for bioorganic synthesis. The *CAL-B* was easily recovered and reused several times. We have also, devised a multi-gram scale reaction for the preparation of

bis(α-aminophosphonates) 4a with replicable quantitative yields . The development of this new easy route opens up very interesting perspectives to easily recoverable applications.
We design a straightforward, efficient and utile protocol to create double Carbon–Phosphore bond formation using *CAL-B* in non-conventional media and metal-free access. These results suggest a new synthetic route toward biological derivatives under mild and green conditions.

Experimental section

General information: All starting materials, reagents and enzymes used in this study were purchase from Sigma-Aldrich or Acros company and were used without purification. Various commercially available lipases were screened: lipase from *Porcine pancreas* type II (*PPL*; LA = 100-500 U/mg), Rabbit Gastric Lipase (*RGL;* LA > 1170 U/mg**),** *Candida Cylindracea* lipase (*CCL*, LA = 3.85 U/mg), *Pseudomonas Cepacia* lipase (*PCL*; LA > 30 000 U/mg), and the *Candida antarctica* lipase fraction B immobilized on acrylic resin (*CAL-B*; LA > 5 000 U/mg). All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25-mm Merck silica gel plates (60F-254) using ultraviolet light (254 nm) as the visualizing agent and $KMnO_4$ solution as developing agents. ^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker spectrometers (360MHz, 300 MHz and 250 MHz for 1H, 90 MHz, 75 MHz or 63 MHz for ^{13}C and 101 MHz or 121 MHz for ^{31}P). Chemical shifts were reported downfield from $CDCl_3$ (δ = 7.26 ppm). For ^{13}C NMR, chemical shifts were reported in the scale relative to the solvent of $CDCl_3$ (δ = 77 ppm) used as internal reference. Coupling constants (J) are given in hertz. Following abbreviations classify the multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal. Melting points were measured using Buchi Melting Point B-545. Mass spectra were recorded with a MicrOTOF-Q Bruker spectrometer using electrospray ionization (ESI) analysis.

General procedure for synthesis of bis(α-aminophosphonates) 4a-4k.
To the stirred mixture of aromatic aldehyde (2 mmol), benzidine (184 mg, 1 mmol) and diethylphosphite (331.2 mg, 2.4 mmol) in THF (2ml), the CAL-B (50 mg) was added. The reaction was stirred at 50°C for 30 minutes. After the reaction proceeded to completion, the lipase was removed by filtration. The two diastereoismer mixtures were separated by column chromatography using ethyl acetate /hexane: 90/10 as eluent. Complete experimental data have been provided (NMR spectra and HRMS). These compounds do not have rotatory power, it means that the diastereomers obtained exist as meso (RS/SR) or racemic (RR/SS) forms mixtures.
Tetraethyl [(4,1-phenylene) bis(azanediyl)] bis[(phenyl) methylene] bisphosphonate **(4a).** Yellow solid, Yield: 90%, mp 210°C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 5.6, 3.8 Hz, 4H, H-Ar), 7.38 – 7.17 (m, 10H, H-Ar), 6.61 (d, *J* = 8.6 Hz, 4H, H-Ar), 4.78 (d, *J* = 24.3 Hz, HCP), 4.24 – 4.02 (m, 4H, O-CH_2-CH_3), 4.02 – 3.82 (m, 2H, O-CH_2-CH_3), 3.74 – 3.57 (m, 2H, O-CH_2-CH_3), 1.28 (t, *J* = 7.1 Hz, 6H, O-CH_2-CH_3), 1.11 (t, *J* = 7.1 Hz, 6H, O-CH_2-CH_3). ^{13}C NMR (91 MHz, $CDCl_3$) δ 144.89 (d, *J* = 14.7 Hz), 135.92 (s), 131.42 (s), 128.62 (s), 127.90 (dd, *J* = 9.5, 4.0 Hz), 127.10 (s), 114.10 (s), 63.31 (d, *J* = 6.0 Hz), 56.96 (s), 55.30 (s), 16.32 (dd, *J* = 22.2, 5.9 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, 25°C): δ 22.63 ppm. HRMS (ESI) *m/z* calcd for $C_{34}H_{42}N_2O_6NaP_2$ [*M* +Na^+]: 659.2410; Found 659.2406.

Tetraethyl [(4,1-phenylene)bis(azanediyl)] bis[(4-nitrophenyl) methylene]bisphosphonate **(4b).** Orange solid, 90% Yield, mp: 219.5°C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.3 Hz, 4H), 7.66 (dd, *J* = 8.9, 2.3 Hz, 4H), 7.27 – 7.18 (m, 4H), 6.54 (d, J = 8.6 Hz, 4H), 4.86 (d, *J* = 25.1 Hz, 2H), 4.22 – 3.96 (m, 8H), 3.93 – 3.81 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 6H), 1.18 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 144.21 (dd, *J* = 20.4, 8.9 Hz), 132.16 – 131.84 (m), 128.63 (d, *J* = 4.7 Hz), 127.31 (s), 123.78 (s), 114.12 (s), 63.63 (dd, *J* = 15.8, 7.0 Hz), 57.33 (s), 54.98 (s), 16.33 (dd, *J* = 10.9, 5.7 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, 25°C): δ 20.70 ppm. HRMS (ESI) *m/z* calcd for $C_{34}H_{40}N_4O_{10}NaP_2$ [M+Na^+]: 749.2111; Found 749.2129.

Tetraethyl [(4,1-phenylene)bis(azanediyl)] bis[(4-cyano-phenyl) methylene] bisphosphonate **(4c)**. Yellow solid, 85% Yield, mp: 203.7°C. NMR ^{1}H (250 MHz, $CDCl_3$, 25°C) :δ 7.71 – 7.58 (m, 8H, H-Ar), 7.31 – 7.18 (m, 4H, H-Ar), 6.57 (d, *J* = 11.0 Hz, 4H, H-Ar), 4.84 (d, *J* = 22.0 Hz, 4H, HCP+NH), 4.24 – 4.10 (m, 4H, O-CH_2-CH_3), 4.09 – 3.96 (m, 2H, O-CH_2-CH_3), 3.95 – 3.75 (m, 2H, O-CH_2-CH_3), 1.31 (t, *J* = 7.1 Hz, 6H , O-CH_2-CH_3), 1.19 (t, *J* = 7.1 Hz, 6H, O-CH_2-CH_3). NMR ^{13}C (63 MHz, $CDCl_3$, 25°C): δ 144.42 (d, $J^3_{C\text{-}P}$ = 14.2 Hz), 142.00, 139.17 (s), 132.38 (s), 131.78 (s), 128.55 (d, $J^2_{C\text{-}P}$ = 5.1 Hz), 127.27 (s), 114.09 (s), 111.79 (d, *J* = 3.4 Hz), 111.13 (s), 63.66 (d, $J_{C\text{-}P}$ = 14.8Hz, C-O), 63.42 (d, $J_{C\text{-}P}$ = 6.7 Hz, C-O), 57.38(s, C-N), 55.02(s, C-P), 16.43 (d, $J^3_{C\text{-}P}$ = 5.7 Hz, $\underline{C}H_3$-CH_2-O-P), 16.24 (d, $J^3_{C\text{-}P}$ = 5.5 Hz, $\underline{C}H_3$-CH_2-O-P). ^{31}P NMR (121 MHz, CDCl3, 25°C): δ 22.05 ppm. HRMS (ESI) *m/z* calcd for $C_{36}H_{40}N_4NaO_6P_2$ [*M* +Na^+]: 709.2135; Found 709.2344.

Tetraethyl [(4,1-phenylene)bis(azanediyl)] bis[(4-fluoro-phenyl)methylene] bisphosphonate **(4d)**. Green solid, 84% Yield, mp: 172.3°C. ^{1}H NMR (250 MHz, $CDCl_3$, 25°C) δ 7.56 – 7.40 (m, 4H, H-Ar), 7.27 (d, *J* = 8.5 Hz, 4H, H-Ar), 7.06 (t, *J* = 8.6 Hz, 4H, H-Ar), 6.62 (d, *J* = 8.4 Hz, 4H, H-Ar), 4.79 (d, *J* = 24.2 Hz, 3H, HCP+NH), 4.25 – 4.07 (m, 4H, O-CH_2-CH_3), 4.07 – 3.84 (m, 2H, O-CH_2-CH_3), 3.86 – 3.63 (m, 2H, O-CH_2-CH_3), 1.31 (t, *J* = 7.1 Hz, 6H, O-CH_2-CH_3), 1.17 (t, *J* = 7.0 Hz, 6H, O-CH_2-CH_3). ^{13}C NMR (63 MHz, $CDCl_3$): δ 164.44 (s), 160.47 (s), 144.79 (d, *J* = 15.0 Hz), 131.64 (d, *J* = 13.2 Hz), 130.13 – 128.79 (m), 127.14 (s), 115.76

(s), 115.42 (s), 114.13 (s), 63.33 (t, $J_{C\text{-}P}$ = 5.7 Hz, C-O), 56.69 (s), 54.29 (s), 16.44 (d, $J^{3}_{C\text{-}P}$ = 5.4 Hz), 16.24 (d, $J^{3}_{C\text{-}P}$ = 5.6 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, 25°C): δ 21.95 ppm. HRMS (ESI) *m/z* calcd for $C_{34}H_{40}N_2O_6NaP_2F_2$ [*M* + Na^+]: 695.2221; Found 695.2208.

Tetraethyl [(4,1-phenylene)bis(azanediyl)] bis[4-(tert-butyl)phenyl)methylene] bisphosphonate (**4e**). Green solid, 77 % Yield, mp: 220°C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.41 – 7.30 (m, 8H, H-Ar), 7.27 – 7.21 (m, 4H, H-Ar), 6.61 (d, J = 8.5 Hz, 4H, H-Ar), 4.75 (d, *J* = 24.0 Hz, 2H, HCP), 4.17 – 4.03 (m, 4H, O-CH_2-CH_3), 3.92 (m, 3H, O-CH_2-CH_3+NH), 3.66 (m, 3H, O-CH_2-CH_3+NH), 1.35 – 1.23 (m, 25 H, O-CH_2-CH_3), 1.08 (t, *J* = 7.0 Hz, 6H, O-CH_2-CH_3). ^{13}C NMR (63 MHz, $CDCl_3$) δ 150.87 (d, *J* = 2.7 Hz), 145.02 (d, *J* = 14.5 Hz), 139.17 (s), 132.69 (s), 131.34 (s), 127.46 (d, *J* = 5.4 Hz), 127.06 (s), 125.47 – 124.98 (m), 114.09 (s), 63.21 (d, $J_{C\text{-}P}$ = 6.8 Hz), 56.94 (s), 54.54 (s), 34.52 (s), 31.32 (s), 16.44 (d, $J^{3}_{C\text{-}P}$ = 5.5 Hz), 16.12 (d, $J^{3}_{C\text{-}P}$= 5.7 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, 25°C): δ 22.93 ppm. HRMS (ESI) *m/z* calcd for $C_{42}H_{58}O_6NaN_2P_2$ [*M* + Na^+]: 771.3662; Found 771.3696.

Tetraethyl [(4,1-phenylene)bis(azanediyl)] bis[(napht-1-ylmethylene] bisphosphonate ***(4f).*** Brown solid, 69% Yield, mp: 222.7°C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.4 Hz, 2 H-Ar), 7.92 (d, *J* = 7.9 Hz, 2H-Ar), 7.87 – 7.74 (m, 4H-Ar), 7.60 (m, *J* = 20.6, 6.9 Hz, 4H-Ar), 7.46 (t, *J* = 7.7 Hz, 2H-Ar), 7.15 (d, *J* = 8.5 Hz, 4H-Ar), 6.56 (d, *J* = 8.5 Hz, 4H), 5.68 (d, *J* = 24.0 Hz, 2H), 4.29 – 4.13 (m, 4H, O-CH_2-CH_3), 3.82 – 3.66 (m, 2H, O-CH_2-CH_3), 3.29 – 3.12 (m, 2H, O-CH_2-CH_3), 1.35 (t, *J* = 7.1 Hz, 6H, O-CH_2-CH_3), 0.75 (t, *J* = 7.1 Hz, 6H, O-CH_2-CH_3). ^{13}C NMR (63 MHz, $CDCl_3$) δ 144.70 (d, *J* = 14.7 Hz), 139.16 (s), 133.83 (s), 131.54 (dd, *J* = 16.8, 12.3 Hz), 129.43 – 129.10 (m), 128.78 (d, *J* = 32.5 Hz), 127.09 (s), 126.30 (s), 125.87 – 124.10 (m), 122.99 (s), 113.84 (s), 63.30 (dd, *J* = 10.3, 7.5 Hz), 52.80 (s), 50.37 (s), 16.49 (d, $J^{3}_{C\text{-}P}$ = 5.5 Hz), 15.78 (d, $J^{3}_{C\text{-}P}$ = 5.6 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, 25°C): δ 22.92 ppm. HRMS (ESI) *m/z* calcd for $C_{30}H_{38}N_2O_8NaP_2$ [*M* + Na^+]: 759.2723; Found 759.2702.

Tetraethyl[(4,1-phenylene)bis(azanediyl)] bis[(3-phenoxy-phenyl) methylene]bisphosphonate **(4g).** Beige solid, 67% Yield, mp: 184.6°C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.43 – 7.23 (m, 13H, H-Ar), 7.19 – 7.05 (m, 3H, H-Ar), 7.01 – 6.90 (m, 6H, H-Ar), 6.64 (d, J = 8.6 Hz, 4H, H-Ar), 4.79 (d, *J* = 24.6 Hz, 4H, HCP+NH), 4.26 – 4.09 (m, 4H, O-CH_2-CH_3), 4.10 – 3.95 (m, 2H, O-CH_2-CH_3), 3.81 (m, 2H, O-CH_2-CH_3), 1.32 (t, *J* = 7.1 Hz, 6H, O-CH_2-CH_3), 1.20 (t, *J* = 7.1 Hz, 6H, O-CH_2-CH_3). ^{13}C NMR (63 MHz, $CDCl_3$) δ 157.21 (d, *J* = 22.3 Hz), 144.77 (d, *J* = 8.8 Hz), 139.18 (s), 138.19 (s), 131.57 (s), 129.85 (d, *J* = 14.1 Hz), 127.11 (s), 123.28 (s), 122.76 (d, *J* = 5.0 Hz), 119.33 – 117.56 (m), 114.29 (s), 63.39 (d, $J_{C\text{-}P}$ = 4.5 Hz), 57.24 (s), 54.84 (s), 16.36 (dd, $J^{3}_{C\text{-}P}$ = 11.7, 5.8 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, 25°C): δ 22.22 ppm. HRMS (ESI) *m/z* calcd for $C_{46}H_{50}N_2O_8NaP_2$ [*M*+Na^+]: 843.2934; Found 843.2938.

Tetraethyl[(4,1-phenylene)bis(azanediyl)] bis[(4-dimethyl-aminophenyl)methylene] bisphosphonate (**4h)**. Orange solid, 84% Yield, mp: 199.3°C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 8.8, 2.3 Hz, 4H, H-Ar), 7.25 (d, *J* = 8.5 Hz, 4H, H-Ar), 6.71 (d, *J* = 8.7 Hz, 4H, H-Ar), 6.65 (d, *J* = 8.6 Hz, 4H, H-Ar), 4.71 (d, *J* = 20.5 Hz, 4H, HCP+NH), 4.23 – 4.02 (m, 4H, O-CH_2-CH_3), 4.04 – 3.86 (m, 2H, O-CH_2-CH_3), 3.78 – 3.58 (m, 2H, O-CH_2-CH_3), 2.94 (s, 12H, $N(CH_3)_2$), 1.31 (t, *J* = 7.1 Hz, 6H, , O-CH_2-CH_3), 1.17 (t, *J* = 7.1 Hz, 6H , O-CH_2-CH_3). ^{13}C NMR (63 MHz, $CDCl_3$) δ 150.20 (s), 145.16 (d, *J* = 14.7 Hz), 131.30 (s), 128.63 (d, *J* = 5.3 Hz), 127.03 (s), 123.03 (s), 114.17 (s), 112.57 (s), 63.12 (t, $J_{C\text{-}P}$ = 6.4 Hz), 56.70 (s), 54.26 (s), 40.51 (s), 16.42 (dd, $J^{3}_{C\text{-}P}$ = 9.8, 5.7 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, 25°C): δ 23.51 ppm. HRMS (ESI) *m/z* calcd for $C_{38}H_{52}N_4O_6NaP_2$ [*M* + Na^+]: 745.3254; Found 745.33256.

Tetraethyl [(4,1-phenylene)bis(azanediyl)] bis[(furan-2 ylmethylene]bisphosphonate **(4i).** Brown solid, 66% Yield: mp: 218.9°C. ^{11}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 0.4 Hz, 2H, H-furan), 7.31 (t, *J* = 8.2 Hz, 4H, H-Ar), 6.71 (d, *J* = 8.6 Hz, 4H, H-Ar), 6.41 (t, *J* = 3.3 Hz, 2H, H-furan), 6.35 (d, *J* = 1.8 Hz, 2H, H-furan), 4.93 (d, *J* = 23.8 Hz, 2H, HCP), 4.26 – 4.14 (m, 4H, O-CH_2-CH_3, O-CH_2-CH_3), 4.12 – 4.00 (m, 3H, O-CH_2-CH_3+NH), 3.89 (m, 3H, O-CH_2-CH_3+NH), 1.31 (t, *J* = 7.1 Hz, 6H, O-CH_2-CH_3), 1.22 (t, *J* = 7.1 Hz, 6H, O-CH_2-CH_3). ^{13}C NMR (91 MHz, $CDCl_3$) δ 149.37 (s), 144.71 (d, *J* = 13.6 Hz), 142.53 (d, *J* = 2.4 Hz), 131.87 (s), 127.17 (s), 114.23 (s), 110.84 (s), 108.83 (d, *J* = 6.9 Hz), 63.48 (dd, $J_{C\text{-}P}$ = 18.5, 6.7 Hz), 51.19 (s), 49.43 (s), 16.46 (d, $J^{3}_{C\text{-}P}$ = 5.3 Hz), 16.30 (d, $J^{3}_{C\text{-}P}$ = 5.7 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, 25°C): δ 20.13 ppm. HRMS (ESI) *m/z* calcd for $C_{30}H_{38}O_8NaN_2P_2$ [*M* + Na^+]: 639.1996; Found 639.2006.

Tetraethyl [(4,1-phenylene)bis(azanediyl)] bis[4-chlorophenyl)methylene] bis phosphonate **(4j)**. Green oil, 82 % Yield. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.43 (m, 4H), 7.31 (d, *J* = 8.4 Hz, 4H, H-Ar), 7.27 – 7.19 (m, 4H, H-Ar), 6.58 (d, *J* = 8.6 Hz, 4H, H-Ar), 4.75 (d, *J* = 24.4 Hz, 2H, HCP), 4.23 – 4.03 (m, 5H, O-CH_2-CH_3+NH), 3.96 (m, 2H, O-CH_2-CH_3), 3.84 – 3.67 (m, 2H, O-CH_2-CH_3), 1.28 (t, *J* = 7.1 Hz, 6H, O-CH_2-CH_3), 1.16 (t, *J* = 7.1 Hz, 6H, O-CH_2-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.72 (d, *J* = 14.6 Hz), 134.66 (d, *J* = 2.8 Hz), 133.74 (d, *J* = 3.9 Hz), 131.60 (s), 129.19 (d, *J* = 5.3 Hz), 128.81 (d, *J* = 2.5 Hz), 127.16 (s), 114.14 (s), 63.43 (dd, $J_{C\text{-}P}$ = 9.2, 7.1 Hz), 56.64 (s), 54.64 (s), 16.44 (d, $J^{3}_{C\text{-}P}$ = 5.7 Hz), 16.25 (d, $J^{3}_{C\text{-}P}$ = 5.7 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, 25°C): δ 21.68 ppm. HRMS (ESI) *m/z* calcd for $C_{34}H_{40}O_6N_2P_2Cl_2$ [*M* + H^+]: 727.1630; Found 727.1610.

Tetraethyl [(4,1-phenylene)bis(azanediyl)] bis[2-methoxy-phenyl)methylene] bisphosphonate (**4k).** Orange solid, 88 % Yield, mp: 165.6°C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.46 (d, *J* = 9.7 Hz, 2H, H-Ar), 7.27 – 7.18 (m, 6H, H-Ar), 6.90 (dd, *J* = 12.6, 5.5 Hz, 4H, H-Ar), 6.61 (d, *J* = 8.6 Hz, 4H, H-Ar), 5.39 (d, *J* = 24.6 Hz, 2H, HCP), 4.25 – 4.09 (m, 4H, O-CH_2-CH_3), 3.97 – 3.80 (m, 8H, O-CH_2-CH_3), 3.68 – 3.51 (m, 2H, O-CH_2-CH_3), 1.30 (t, *J* = 7.1 Hz, 6H, O-CH_2-CH_3), 1.03 (t, *J* = 7.1 Hz, 6H, O-CH_2-CH_3). ^{13}C NMR (75 MHz,

$CDCl_3$) δ 157.26 (d, *J* = 6.1 Hz), 144.93 (s), 131.30 (s), 128.94 (d, *J* = 2.9 Hz), 128.24 (d, *J* = 4.6 Hz), 127.02 (s), 124.60 (s), 121.05 (d, *J* = 2.9 Hz), 113.81 (s), 110.47 (s), 63.09 (dd, $J_{C\text{-}P}$ = 6.7, 4.5 Hz), 55.74 (s), 49.16 (s), 47.11 (s), 16.45 (d, $J^3_{C\text{-}P}$ = 5.8 Hz), 16.11 (d, $J\ ^3_{C\text{-}P}$ = 5.9 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, 25°C): δ 23.53 ppm. HRMS (ESI) m/z calcd for $C_{36}H_{46}O_8N_2NaP_2$ [M + Na^+]: 719.2621; Found 719.2617.

Conflicts of interest

There are no conflicts to declare.

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