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# Synthesis and Chemical Properties of New 3-Aryl Phosphacoumarin with Potential Biological Activity

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## Research Article

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**ABSTRACT**

A new member of 3-aryl phosphacoumarins family have been synthesized by the way of Knoevenagel condensation of 4-(diethylamino) salicylaldehyde and diethyl 4-nitrobenzylphosphonate with consequent cyclization. Chemical properties of obtained product were illustrated by reduction of nitro group. All synthesized compounds were fully characterized by NMR spectroscopy and high-resolution mass spectrometry.

## INTRODUCTION

Coumarins are members of the benzopyrone family and are of considerable synthetic and pharmacological interest because of their biological activity, such as antitumor, anti-HIV, antioxidation, vasorelaxant, tumor necrosis factor-R (TNF-R) inhibition, serine protease inhibition, antimicrobial and anticancer activity [1]. They are also widely used as fluorescent dyes or probes [2] due to their large Stokes shifts, high fluorescent quantum yields and high structural flexibility.

In recent years, organophosphorus compounds are widely spreading in organic and pharmaceutical chemistry, due to their ubiquity in biological systems and richness of phosphorus chemistry [3–6]. It was shown that in most cases phosphonic acids are bioisosteres of carboxylic acids and they show the same biological activity [7]. Based on these facts we can assume that replacement of ester fragment in coumarin with phosphonate fragment leads to phosphacoumarin with similar biological and physical properties. There are few examples of such compounds in literature [8–10]. Substituted 3-aryl phosphacoumarins were proposed [10] as inhibitors of one of protein tyrosine phosphatases-the enzyme SHP-1. Anomalous activity of these enzymes is often implicated in such diseases as diabetes, obesity, autoimmune diseases, infectious diseases, inflammation, cancer, osteoporosis, and neurodegeneration. Despite potential biological activity of these compounds, there is no information on the synthesis and applications of 3-aryl phosphacoumarins with free 4$^{th}$ position of benzooxaphosphinine cycle and existing methods of phosphacoumarins preparation have limited synthetic applicability.

Herein we describe a new efficient method of 3-aryl phosphacoumarins synthesis, preparation and some chemical transformations of 7-(diethylamino)-2-ethoxy-3-(4-nitrophenyl)-2*H*-benzo[e] [1,2]oxaphosphinin-2-oxide.

## RESULTS AND DISCUSSION

7-(Diethylamino)-2-ethoxy-3-(4-nitrophenyl)-2*H*-benzo[*e*][1,2]oxaphosphinin-2-oxide 3 was prepared according to slightly modified literature method of 3-aryl coumarins synthesis [2]. First step is Knoevenagel condensation of 4-(diethylamino) salicylic aldehyde 1 and 4-nitrobenzylphosphonate 2 in presence of catalytic quantity of piperidine **(Scheme 1).** Then, intramolecular

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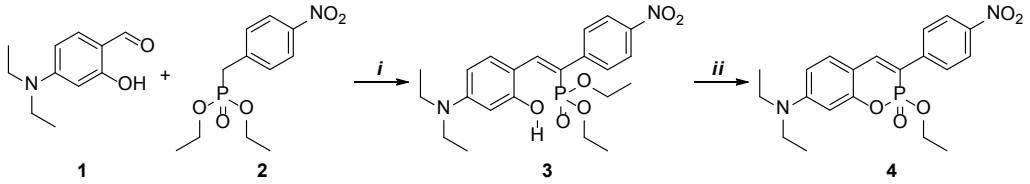
nucleophilic attack of hydroxyl on diethylphosphonate group in intermediate 3 leads to formation of desired phosphacoumarin 4. The main advantage of this approach is only one way of cyclisation in comparison with previously described syntheses [8,9].




**Scheme 1. Synthesis of phosphacoumarin 4. (i: toluene, 2 % (mol.) piperidine, 14 h; ii: toluene, reflux, 6 h).**

Structure of obtained product was confirmed by NMR spectroscopy and high-resolution mass spectrometry (HRMS). In general, $^{1}$H NMR spectrum **(Figure 1)** of phosphacoumarin 4 is very similar to spectrum of coumarin analogue [2], but there are some specific features related to introduction of phosphorus. First of all, due to inductive effect of phosphorus, chemical shifts of protons in 4, 5 and 7 positions of benzo[e] [1,2]oxaphosphinine fragment are shifted to stronger field for 0.15-0.3 ppm in comparison with benzopirone signals. Signal of hydrogen in 4$^{th}$ position is shifted for 0.8 ppm and appears as doublet with coupling constant $^{3}J_{P,H}$ = 38.9 Hz that is characteristic for oxaphosphinine cycle [11]. $^{13}$C{$^{1}$H} NMR spectrum **(Figure 2)** demonstrates the same tendencies. Additionally, carbon-phosphorus coupling constants provide valuable information for signal assignment. $^{31}$P NMR spectrum **(Figure 3)** contains doublet of triplets with chemical shift characteristic for phosphonate and coupling constants consistent with $^{1}$H NMR results. HRMS contains the signal of molecular ion with *m/z* value equal to theoretically predicted.

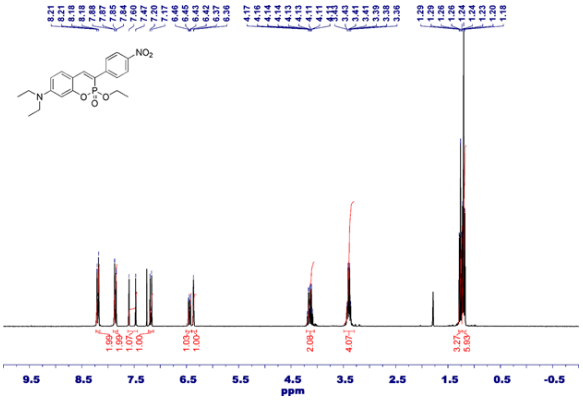



**Figure 1.** $^{1}$H NMR spectrum of 7-(diethylamino)-2-ethoxy-3-(4-nitrophenyl)-2H-benzo[e][1,2]oxaphosphinin-2-oxide 4.

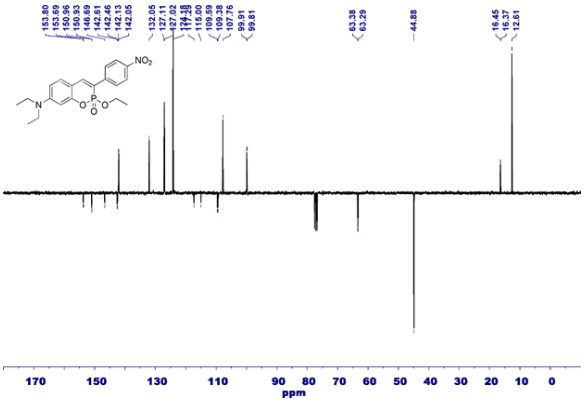



**Figure 2.** $^{13}$C{$^{1}$H} NMR spectrum of 7-(diethylamino)-2-ethoxy-3-(4-nitrophenyl)-2H-benzo[e][1,2]oxaphosphinin-2-oxide 4.

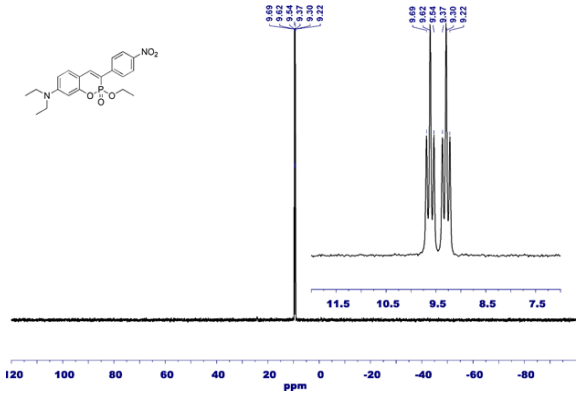



**Figure 3.** $^{31}$P NMR spectrum of 7-(diethylamino)-2-ethoxy-3-(4-nitrophenyl)-2H-benzo[e][1,2]oxaphosphinin-2-oxide 4.

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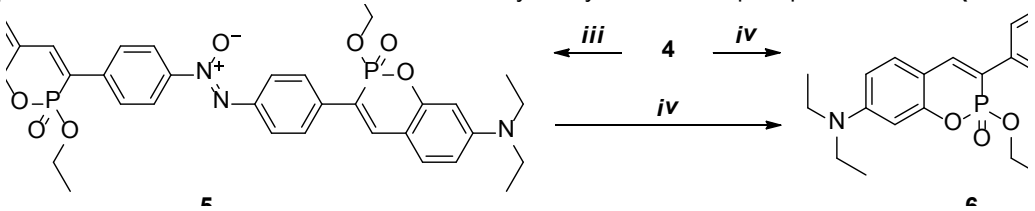
One of the most attractive ways of compound 4 modifications is reduction of nitro group. This transformation doesn't affect the integrity of phosphacoumarin system, but changes slightly the electron effect of phenyl group in 3rd position. Treatment of phosphacoumarin 4 with weak reducing agent (Zn dust and $NH_4Cl$ in water–ethanol mixture) [12] afforded azoxy compound 5 with a 60% yield **(Scheme 2).** Subsequent treatment with stronger reducing agent (tin(II) chloride dihydrate in ethanol) allowed us to obtain desired aminophenyl phosphacoumarin 6. Latter was obtained with a 70% yield by reduction of phosphacoumarin 4 **(Scheme 2).**




**Scheme 2.** Reduction of phosphacoumarin 4. (iii: Zn, $NH_4Cl$, water–ethanol, 14 h; iv: $SnCl_2{\cdot}2H_2O$, ethanol, 14 h).

$^1$H NMR spectra **(Figures 4)** of compounds 4 and 5 are almost identical; the only difference is nonequivalence of chemical shifts of 3-phenyl groups that is consistent to formation of azoxy-fragment. Reduction to amino group leads to dramatic displacement of nearly all signals in stronger field and appearance of signal of broad signal of amino group at 4.45 ppm **(Figure 5).** $^{31}$P NMR spectra **(Figures 6-9)** consist of two overlapping doublets of triplets for compound 5 and doublet of triplet for amine 6. Chemical shifts almost don't change during reduction that is connected to relatively low effect of phenyl group substitution on phosphorus atom of phosphacoumarin system. Finally, HRMS confirmed elemental constitution of both compounds.

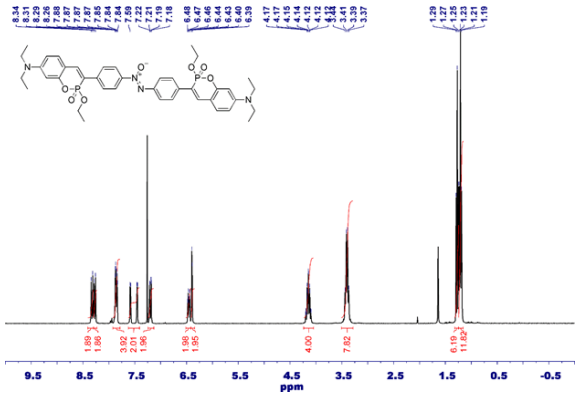


**Figure 4.** $^1$H NMR spectrum of 1,2-bis(4-(7-(diethylamino)-2-ethoxy-2-oxido-2H-benzo[e][1,2]oxaphosphinin-3-yl)phenyl)diazene oxide 5.

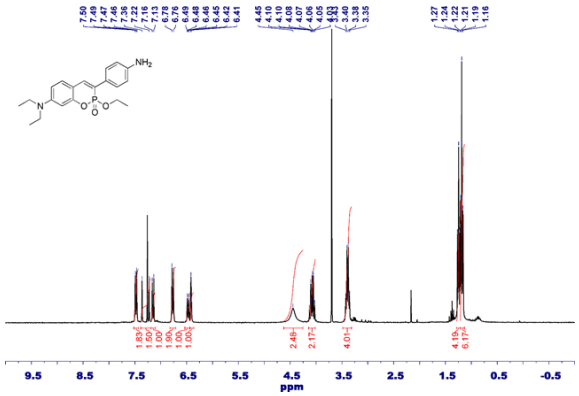


**Figure 5.** $^1$H NMR spectrum of 7-(diethylamino)-2-ethoxy-3-(4-aminophenyl)-2H-benzo[e][1,2]oxaphosphinin-2-oxide 6.

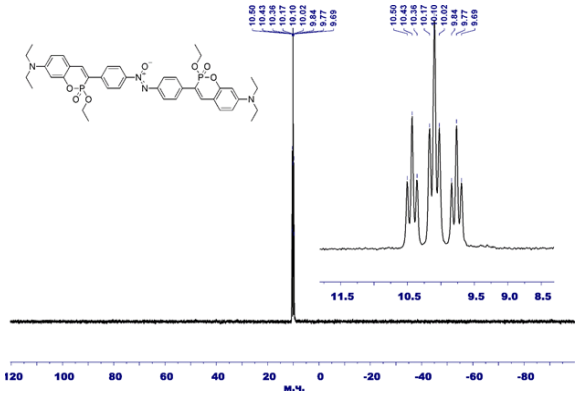


**Figure 6.** $^{31}$P NMR spectrum of 1,2-bis(4-(7-(diethylamino)-2-ethoxy-2-oxido-2H-benzo[e][1,2]oxaphosphinin-3-yl)phenyl)diazene oxide 5.

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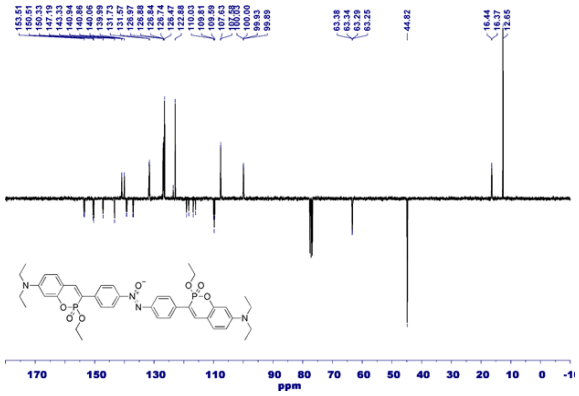

**Figure 7.** $^{13}C\{^{1}H\}$ NMR spectrum of 1,2-bis(4-(7-(diethylamino)-2-ethoxy-2-oxido-2H-benzo[e][1,2]oxaphosphinin-3-yl)phenyl)diazene oxide 5.

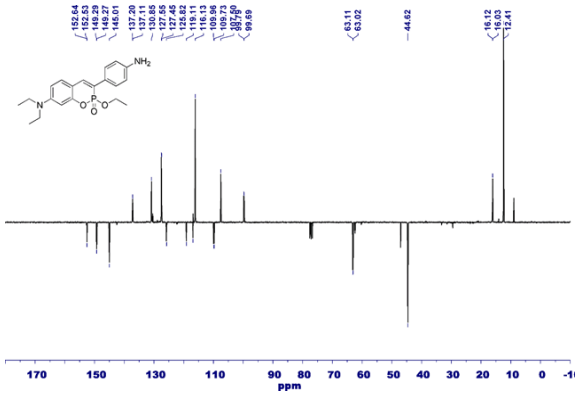

**Figure 8.** $^{13}C$ $\{^{1}H\}$ NMR spectrum of 7-(diethylamino)-2-ethoxy-3-(4-aminophenyl)-2H-benzo[e][1,2]oxaphosphinin-2-oxide 6.

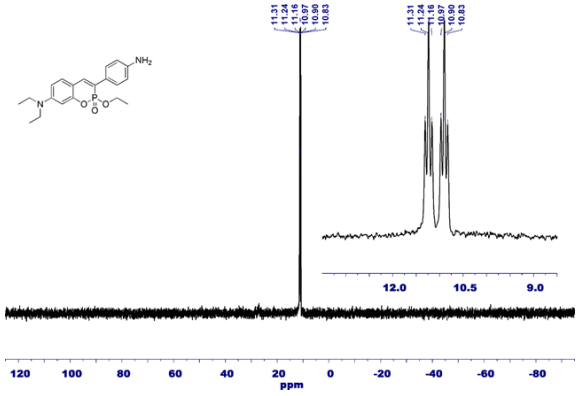

**Figure 9.** $^{31}P$ NMR spectrum of 7-(diethylamino)-2-ethoxy-3-(4-aminophenyl)-2H-benzo[e][1,2]oxaphosphinin-2-oxide 6.

## CONCLUSION

New efficient method of 3-aryl phospacoumarins preparation starting from corresponding salicylic aldehydes and benzyl phosphonates was described. It allowed us to synthesize 7-(diethylamino)-2-ethoxy-3-(4-nitrophenyl)-*2H*-benzo[e][1,2] oxaphosphinin-2-oxide with moderate yield and high purity. Proposed approach can be extended in future to preparation of biologically active phosphacoumarins. Additionally, reduction of nitro group led to formation of 7-(diethylamino)-2-ethoxy-3-(4-aminophenyl)-2*H*-benzo[e][1,2]oxaphosphinin-2-oxide that can be proposed as potential fluorescent label [13].

## EXPERIMENTAL

Solvents were purified by conventional methods before use. 4-(Diethylamino)salicylaldehyde (Alfa Aesar, 99%), 4-nitrobenzyl bromide (Sigma Aldrich, 98%), triethylphosphite (Sigma Aldrich, 98%), piperidine (Alfa Aesar, 99%), zinc (Sigma Aldrich, dust <10 μm, ≥ 98%), ammonium chloride (Sigma Aldrich, ≥99.5%), tin(II) chloride dihydrate (Alfa Aesar, 98%), triethylamine (Sigma Aldrich, ≥ 99.5%) and 2-bromopropionyl bromide (Alfa Aesar, 97%) were used as received. Diethyl 4-nitrobenzylphosphonate 2 was synthesized according to the literature method [14] starting from triethylphosphite and 4-nitrobenzyl bromide.

NMR spectra were recorded using a Bruker AMX 300 spectrometer at 298 K. Chemical shifts are expressed in parts per million with residual solvent signals as internal reference ($^{1}H$, $^{13}C$ NMR). The external chemical shift reference for $^{31}P$ NMR is 40% aqueous solution of $H_3PO_4$ (0 ppm). High-resolution mass spectra (HRMS) were measured on Waters GCT Premier CAB109 TOF

detector in ESI mode. All syntheses were carried out using standard Schlenk and high vacuum line techniques under an argon atmosphere.

**Synthesis of 7-(diethylamino)-2-ethoxy-3-(4-nitrophenyl)-2H-benzo[e][1,2]oxaphosphinin-2-oxide 4.**

A solution of 4-(diethylamino) salicylaldehyde (0.97 g, 5 mmol), diethyl 4-nitrobenzylphosphonate (1.37 g, 5 mmol) and piperidine (0.01 mL, 0.1 mmol) in 25 mL of dry toluene was stirred at ambient temperature for 14 h and refluxed with Dean-Stark distilling trap for 6 h. Then reaction mixture was concentrated under reduced pressure and purified using flash-chromatography (silica gel, pentane-ethyl acetate (7:3)). After crystallization from ethyl acetate, product was obtained in form of violet crystals. Yield: 1.4 g (70%). $^{1}$H NMR (300.13 MHz, $CDCl_3$, 298 K, δ, ppm): 1.20 (t, $^{3}J_{H,H}$ = 7.1 Hz, 6H; $C\underline{H}_3CH_2N$), 1.26 (td, $^{3}J_{H,H}$ = 7.1 Hz, $^{4}J_{P,H}$ = 0.4 Hz, 3H; $CH_3CH_2O$), 3.40 (q, $^{3}J_{H,H}$ = 7.5 Hz, 4H; $CH_3C\underline{H}_2N$), 4.12 (qd, $^{3}J_{P,H}$ = 8.7 Hz, $^{3}J_{H,H}$ = 7.1 Hz, 1H; $CH_3C\underline{H}_2O$), 4.15 (qd., $^{3}J_{P,H}$ = 8.7 Hz, $^{3}J_{H,H}$ = 7.1 Hz, 1H; $CH_3C\underline{H}_2O$), 6.36 (d, $^{4}J_{H,H}$ = 2.5 Hz, 1H; 8-H), 6.44 (dd, $^{3}J_{H,H}$ = 8.8 Hz, $^{4}J_{H,H}$ = 2.5 Hz, 1H; 6-H), 7.18 (d, $^{3}J_{H,H}$ = 8.8 Hz, 1H; 5-H), 7.53 (d, $^{3}J_{P,H}$ = 38.9 Hz, 1H; 4-H), 7.83–7.89 (m, 2H; 2-H, 4-$NO_2C_6H_4$), 8.16–8.22 (m, 2H; 3-H, 4-$NO_2C_6H_4$); $^{13}$C{$^{1}$H} NMR (75.47 MHz, $CDCl_3$, 298 K, δ, ppm): 12.6 (s; $C\underline{H}_3CH_2N$), 16.4 (d, $^{3}J_{P,C}$ = 6.3 Hz; $\underline{C}H_3CH_2O$), 44.9 (s.; $CH_3\underline{C}H_2N$), 63.3 (d, $^{2}J_{P,C}$ = 6.9 Hz; $CH_3\underline{C}H_2O$), 99.9 (d, $^{3}J_{P,C}$ = 7.7 Hz; 8-C), 107.8 (s; 6-C), 109.5 (d, $^{3}J_{P,C}$ = 16.3 Hz; 4'-C), 116.1 (d, $^{1}J_{P,C}$ = 172.9 Hz; 3-C), 124.2 (s; 2-C, $C_6H_4NO_2$), 127.1 (d, $^{4}J_{P,C}$ = 7.3 Hz; 3-C, $C_6H_4NO_2$), 132.1 (d, $^{3}J_{P,C}$ = 1.4 Hz; 5-C), 142.1 (d, $^{2}J_{P,C}$ = 5.5 Hz; 4-C), 142.5 (d, $^{2}J_{P,C}$ = 11.4 Hz; 1-C, $C_6H_4NO_2$), 146.7 (s; C-$NO_2$), 150.9 (d, $^{4}J_{P,C}$ = 1.9 Hz; 7-C), 153.7 (d, $^{2}J_{P,C}$ = 8.6 Hz; 8'-C); $^{31}$P NMR (121.49 MHz, $CDCl_3$, 298 K, δ, ppm): 9.5 (dt, $^{3}J_{H,P}$ = 38.9 Hz, $^{3}J_{H,P}$ = 9.0 Hz). HRMS: found — 403.1423, calculated for $C_{20}H_{24}N_2O_5P$ — 403.1423.

**Synthesis of 1,2-bis(4-(7-(diethylamino)-2-ethoxy-2-oxido-2H-benzo[e][1,2]oxaphosphinin-3-yl)phenyl)diazene oxide 5.**

A suspension of 7-(diethylamino)-2-ethoxy-3-(4-nitrophenyl)-2H-benzo[e][1,2]oxaphosphinin-2-oxide (0.4 g, 1 mmol), ammonium chloride (0.11 g, 2 mmol) and zinc dust (0.13 g, 2 mmol) in 25 mL of aqueous ethanol was stirred at ambient temperature for 14 h. Then reaction mixture was diluted with 25 mL of ethyl acetate and filtered through celite. After concentration under reduced pressure, product was obtained as amorphous red-brown solid. Yield: 0.23 g (60%). $^{1}$H NMR (300.13 MHz, $CDCl_3$, 298 K, δ, ppm): 1.21 (t, $^{3}J_{H,H}$ = 7.0 Hz, 12H; $C\underline{H}_3CH_2N$), 1.27 (t, $^{3}J_{H,H}$ = 7.1 Hz, 6H; $C\underline{H}_3CH_2O$), 3.40 (q, $^{3}J_{H,H}$ = 7.2 Hz, 8H; $CH_3C\underline{H}_2N$), 4.08–4.21 (m, 4H; $CH_3C\underline{H}_2O$), 6.39 (d, $^{4}J_{H,H}$ = 2.4 Hz, 2H; 8-H), 6.42–6.48 (m, 2H; 6-H), 7.19 (d, $^{3}J_{H,H}$ = 8.8 Hz, 1H; 5-H), 7.20 (d, $^{3}J_{H,H}$ = 8.8 Hz, 1H; 5-H'), 7.51 (d, $^{3}J_{P,H}$ = 39.4 Hz, 1H; 4-H), 7.52 (d, $^{3}J_{P,H}$ = 39.7 Hz, 1H; 4-H'), 7.86 (m, 4H; 2-H, $C_6H_4$), 8.27 (d, $^{3}J_{H,H}$ = 8.1 Hz 2H; 3-H, $C_6H_4$); 8.33 (d, $^{3}J_{H,H}$ = 8.2 Hz 2H; 3-H, $C_6H_4$'); $^{13}$C{$^{1}$H} NMR (75.47 MHz, $CDCl_3$, 298 K, δ, ppm): 12.7 (s; $C\underline{H}_3CH_2N$), 16.4 (d, $^{3}J_{P,C}$ = 6.4 Hz; $\underline{C}H_3CH_2O$), 44.8 (s.; $CH_3\underline{C}H_2N$), 63.3 (d, $^{2}J_{P,C}$ = 6.9 Hz; $CH_3\underline{C}H_2O$), 100.0 (d, $^{3}J_{P,C}$ = 7.7 Hz; 8-C), 107.6 (s; 6-C), 109.8 (d, $^{3}J_{P,C}$ = 16.5 Hz; 4'-C), 117.2 (d, $^{1}J_{P,C}$ = 171.3 Hz; 3-C), 118.0 (d, $^{1}J_{P,C}$ = 170.0 Hz; 3-C'), 122.9 (s; 2-C, $C_6H_4$), 126.5 (s; 2-C, $C_6H_4$'), 126.8 (d, $^{4}J_{P,C}$ = 7.5 Hz; 3-C, $C_6H_4$), 126.9 (d, $^{4}J_{P,C}$ = 7.3 Hz; 3-C, $C_6H_4$), 131.6 (d, $^{3}J_{P,C}$ = 1.0 Hz; 5-C), 131.7 (d, $^{3}J_{P,C}$ = 1.2 Hz; 5-C'), 137.0 (d, $^{2}J_{P,C}$ = 11.1 Hz; 1-C, $C_6H_4$), 139.2 (d, $^{2}J_{P,C}$ = 11.2 Hz; 1-C, $C_6H_4$'), 140.0 (d, $^{2}J_{P,C}$ = 5.7 Hz; 4-C), 140.9 (d, $^{2}J_{P,C}$ = 5.6 Hz; 4-C'), 143.3 (s; 4-C, $C_6H_4$), 147.2 (s; 4-C, $C_6H_4$'), 150.3 (d, $^{4}J_{P,C}$ = 1.7 Hz; 7-C), 150.5 (d, $^{4}J_{P,C}$ = 1.7 Hz; 7-C), 153.4 (d, $^{2}J_{P,C}$ = 8.5 Hz; 8'-C), 153.5 (d, $^{2}J_{P,C}$ = 8.5 Hz; 8'-C'); $^{31}$P NMR (121.49 MHz, $CDCl_3$, 298 K, δ, ppm): 9.9 (dt, $^{3}J_{H,P}$ = 40.2 Hz, $^{3}J_{H,P}$ = 8.8 Hz), 10.3 (dt, $^{3}J_{H,P}$ = 40.5 Hz, $^{3}J_{H,P}$ = 8.9 Hz). HRMS: found-757.1590, calculated for $C_{40}H_{47}N_4O_7P_2$-757.2920.

**Synthesis of 7-(diethylamino)-2-ethoxy-3-(4-aminophenyl)-2H-benzo[e][1,2]oxaphosphinin-2-oxide 6.**

A suspension of 7-(diethylamino)-2-ethoxy-3-(4-nitrophenyl)-2H-benzo[e][1,2]oxaphosphinin-2-oxide (0.4 g, 1 mmol) and SnCl2·2H20 (0.97 g, 4.25 mmol) in 25 mL of ethanol was stirred at ambient temperature for 14 h. Then reaction mixture was neutralized with concentrated solution of NaOH, concentrated under reduced pressure and extracted with hot ethyl acetate. After purification with flash chromatography (silica gel, DCM–methanol (8:2)), product was obtained as amorphous orange solid. Yield: 0.26 g (70%). $^{1}$H NMR (300.13 MHz, $CDCl_3$, 298 K, δ, ppm): 1.19 (t, $^{3}J_{H,H}$ = 7.1 Hz, 6H; $CH_3C\underline{H}_2N$), 1.24 (t, $^{3}J_{H,H}$ = 7.1 Hz, 3H; $C\underline{H}_3CH_2O$), 3.39 (q, $^{3}J_{H,H}$ = 7.2 Hz, 4H; $CH_3C\underline{H}_2N$), 4.08 (qd., $^{3}J_{P,H}$ = 8.8 Hz, $^{3}J_{H,H}$ = 7.1 Hz, 2H; $CH_3C\underline{H}_2O$), 4.31–4.59 (broad, 2H; $N\underline{H}_2$), 6.41 (d, $^{4}J_{H,H}$ = 2.4 Hz, 1H; 8-H), 6.47 (dd, $^{3}J_{H,H}$ = 8.6 Hz, $^{4}J_{H,H}$ = 2.4 Hz, 1H; 6-H), 6.77 (d, $^{3}J_{H,H}$ = 8.0 Hz, 2H; 3-H, 4-$NH_2C_6H_4$), 7.15 (d, $^{3}J_{H,H}$ = 8.7 Hz, 1H; 5-H), 7.29 (d, $^{3}J_{P,H}$ = 40.8 Hz, 1H; 4-H), 7.48 (d, $^{3}J_{H,H}$ = 8.6 Hz, $^{4}J_{P,H}$ = 1.3 Hz, 2H; 2-H, 4-$NH_2C_6H_4$); $^{13}$C{$^{1}$H} NMR (75.47 MHz, $CDCl_3$, 298 K, δ, ppm): 12.4 (s; $C\underline{H}_3CH_2N$), 16.1 (d, $^{3}J_{P,C}$ = 6.6 Hz; $\underline{C}H_3CH_2O$), 44.6 (s; $CH_3\underline{C}H_2N$), 63.1 (d, $^{2}J_{P,C}$ = 6.8 Hz; $CH_3\underline{C}H_2O$), 99.7 (d, $^{3}J_{P,C}$ = 7.6 Hz; 8-C), 107.5 (s; 6-C), 109.9 (d, $^{3}J_{P,C}$ = 16.8 Hz; 4'-C), 116.1 (s; 3-C, $C_6H_4NH_2$), 118.0 (d, $^{1}J_{P,C}$ = 166.9 Hz; 3-C), 127.5 (d, $^{3}J_{P,C}$ = 7.5 Hz; 2-C, $C_6H_4NH_2$), 125.8 (d, $^{2}J_{P,C}$ = 11.1 Hz; 1-C, $C_6H_4NO_2$), 130.9 (s; 5-C), 137.2 (d, $^{2}J_{P,C}$ = 6.3 Hz; 4-C), 145.0 (s; C-$NH_2$), 149.3 (d, $^{4}J_{P,C}$ = 1.6 Hz; 7-C), 152.6 (d, $^{2}J_{P,C}$ = 8.4 Hz; 8'-C); $^{31}$P NMR (121.49 MHz, $CDCl_3$, 298 K, δ, ppm): 11.1 (dt, $^{3}J_{H,P}$ = 40.7 Hz, $^{3}J_{H,P}$ = 8.7 Hz). HRMS: found-373.1678, calculated for $C_{20}H_{24}N_2O_5P$- 373.1681.

## RELATED CONTENT

$^{1}$H, $^{13}$C and $^{31}$P NMR spectra of compounds 4-6 can be found in electronic supplementary information **(Figures 1-9).**

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