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To the 80th Anniversary of B.I. Ionin

Kabachnik–Fields Phosphorylation of Tetraene Macrolide Antibiotic Pimaricin

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Abstract—Polyene macrolide antibiotic pimaricin reacts with dialkyl(diaryl) phosphites and 4-bromobenzaldehyde to form 3'-*N*-α-[dialkoxy(diphenoxy)phosphinoyl]benzyl derivatives. Physicochemical and biological properties of the synthesized derivatives have been studied. According to the biological assay, the 3'-*N*-α-[dialkoxy(diphenoxy)phosphinoyl]benzyl derivatives are less toxic than the parent antibiotic and exhibit strong antifungal activity towards a wide range of *Candida* yeast-like fungi.

Keywords: polyene macrolide antibiotic, pimaricin, dialkyl(diaryl) phosphite, dialkyl(diphenyl) phosphonate, toxicity, antifungal activity

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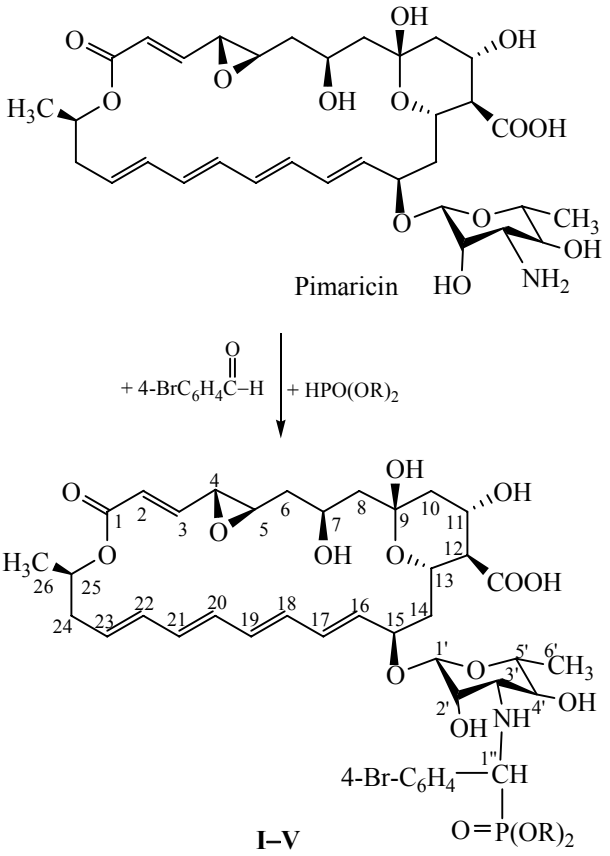
Pimaricin (natamycin), a polyene macrolide antibiotic, has been widely used in treatment of many clinical forms of candidiasis caused by *Candida* yeast-like fungi [1, 2]. However, the therapeutic efficiency of this antifungal antibiotic, as well as of other polyene macrolide antibiotics, is strongly limited by high toxicity, poor solubility in water, and growing resistance of pathogenic fungal microorganisms [3–5]. Therefore, preparation of new pimaricin derivatives with improved medical and biological properties is a topical issue.

A wide range of pimaricin derivatives have been described: esters [6–11], *N*-acyl derivatives [12, 13], *N*-glycosyl derivatives [14], enamine and amidine derivatives [15], amides [16], poly(trimethylsilyl) and polyacetyl derivatives [17], *N*,*N*-dialkyl derivatives [18], and water-soluble salts and complexes [19–22]. Special attention is at present drawn to liposomal [23–28] and other nanoscale derivatives [29, 30] of pimaricin revealing lower toxicity, improved pharmacokinetic characteristics, and enhanced stability. We earlier reported on synthesis of hydrophosphoryl [31], *N*-aryl [32], phosphorylated aldoketene imine [33], and *N*-benzyl derivatives [34] of pimaricin. Extending those studies, we applied reactions with dialkyl(diaryl) phosphites and *para*-substituted benzaldehydes to prepare the corresponding derivatives of the antibiotic and studied medical and biological properties of the products.

Pimaricin reacted with 4-bromobenzaldehyde and dialkyl(diaryl) phosphites to form dialkyl(diaryl) α-aminophosphonates **I**–**V**. The reaction could be considered as a specific version of the Kabachnik–Fields reaction [35–37] (for summary of mechanism, kinetics, and synthetic potential of the Kabachnik–Fields reaction see [38–42]). The first stage of the process involved addition of primary amino group of pimaricin carbohydrate fragment at carbonyl group of the aromatic aldehyde to form an azomethine intermediate. At the second stage dialkyl(diaryl) phosphite reacted with C=N bond of the azomethine intermediate to yield the corresponding pimaricin derivative **I**–**V**.

Compounds **I**–**V** were solid substances decomposing upon heating; the melting points were not clearly observed. They were readily soluble in DMSO and DMF, sparingly soluble in methanol, ethanol, pyridine, and water, and insoluble in acetone, chloroform, diethyl ether, and hexane.

Scheme 1.



I–V

R = CH_3 (**I**), C_2H_5 (**II**), $CH_3(CH_2)_3$ (**III**), C_6H_5 (**IV**), $[Si(CH_3)_3]_2$ (**V**).

Structures of the synthesized pimaricin derivatives were confirmed by NMR (^1H, ^{13}C, and ^{31}P), IR, and UV spectroscopy. ^1H NMR spectra of compounds **I**–**V** contained pimaricin [43, 44] and phenyl proton signals along with a multiplet of the CH"P methane proton (δ 4.02–4.11 ppm). The *para*-substituted phenyl ring protons formed a system of two pairs of chemically equivalent but magnetically nonequivalent nuclei ABA^1B^1. The ^{13}C NMR spectra contained signals of pimaricin [45, 46] and phenyl groups; the carbon atom directly attached to phosphorus resonated as a doublet at δ_C 26.93–28.14 ppm (J_{CP} 132.1–134.3 Hz). ^{31}P signals of pimaricin derivatives **I**–**V** appeared at 21.57–21.85 ppm, being characteristic of dialkyl-(diaryl) α-aminophosphonates with four-coordinated phosphorus atom [47–49] (Scheme 1).

IR spectra of compounds **I**–**V** contained absorption bands characteristic of pimaricin [50, 51] as well as those assigned to P=O group (1230–1242 cm^{-1}), phenyl substituents (1577–1585 cm^{-1}), and the N–H bond (3410–3425 cm^{-1}).

Electronic absorption spectra of pimaricin derivatives **I**–**V** showed bands at 290, 303, and 318 nm with specific absorbances at λ_{max} ($E^{1\%}$ 1 cm) 710–713, 1100–1108, and 1020–1027, respectively, typical of the tetraene conjugated system [50]; another absorption band at 255–263 nm was assigned to phenyl.

In this work we used dimethyl phosphite, diethyl phosphite, dibutyl phosphite, diphenyl phosphite, and bis(trimethylsilyl) phosphite as the hydrophosphoryl component of the reaction. Dialkyl phosphites are widely used in organophosphorus synthesis [52, 53] as fairly mild hydrophosphorylating agents; this is especially important for modification of complex biologically active molecules [54, 55]. 4-Bromobenzaldehyde was chosen as the carbonyl component because polyene macrolide antibiotics modified with *para*-halogen-substituted aromatic aldehydes showed prominent antifungal activity [31, 56, 57]. We demonstrated that reactions of pimaricin with diakyl-(diaryl) phosphites and 4-bromobenzaldehyde were highly selectivity to yield the corresponding 3'-*N*-α-

Minimal fungistatic concentrations of pimaricin derivatives **I–V** (μg/mL)

Test culture	**I**	**II**	**III**	**IV**	**V**	Pimaricin
Candida albicans	1.56	1.56	3.12	1.56	6.25	1.56
Candida tropicalis	1.56	1.56	3.12	1.56	6.25	3.12
Candida parapsilosis	3.12	3.12	6.25	3.12	6.25	6.25
Candida glabrata	1.56	1.56	6.25	1.56	12.5	3.12
Candida krusei	3.12	3.12	6.25	3.12	12.5	6.25
Candida guillermondii	6.25	6.25	12.5	3.12	12.5	6.25
Candida lusitaniae	6.25	6.25	12.5	6.25	12.5	3.12
Candida kefyr	3.12	6.25	6.25	3.12	6.25	3.12
Candida utilis	1.56	3.12	3.12	1.56	6.25	1.56
Candida lypolytica	6.25	6.25	12.5	6.25	12.5	6.25
Candida norvegensis	6.25	6.25	12.5	6.25	12.5	6.25

[dialkoxy(diphenoxy)phosphinoyl]benzyl derivatives. Moreover, yields of pimaricin derivatives **I–V** were up to 80–85%, higher than the yield of the hydrophosphoryl derivatives obtained via the Kabachnik–Fields reaction with hypophosphorous acid (67–75%) [31]. The possible reason for the lower yields in the latter case was partial decay of pimaricin with hypophosphorous acid via protonation of the conjugated double bonds system.

Pharmacological tests showed that the acute toxicity of pimaricin derivatives **I–V** [490 to 520 mg/kg (white mice, intraperitoneal administration)] was four times lower compared to that of the parent antibiotic [58, 59].

As pimaricin is widely used in therapy of many clinical forms of candidiasis [1, 2, 60], special attention in the biological tests was paid to antifungal activity of compounds **I–V** against *Candida* yeast-like fungi. It was found that pimaricin derivatives **I–V** exhibited expressed antifungal activity against 11 test cultures of the *Candida* family. In particular, the activity of compounds **I**, **II**, and **IV** against *Candida albicans* was comparable to that of pimaricin, and their activity against *Candida tropicalis*, *Candida parapsilosis, Candida glabrata,* and *Candida krusei* exceeded that of the parent antibiotic (see table).

It should be stressed that *Candida albicans* has remained the most common cause of candidiasis (about 50% of cases) [61, 62]. At the same time, the ratio of fungal infections caused by *Candida tropicalis, Candida parapsilosis, Candida glabrata*, and *Candida krusei* has grown over the past 15–20 years [63–66]. In view of that, the high antifungal activity of the derivatives **I–V** against the listed *Candida* cultures along with the low toxicity of the pimaricin derivatives open up new possibilities development of antibiotics for candidiasis treatment.

Noteworthily, chemical modification of large bioorganic molecules such as polyene macrolide antibiotics via conventional methods of organic chemistry is complicated due to high lability of the substrate [67–73]. Therefore, alternative approaches to prepare derivatives of polyene macrolide antibiotics are required, such as genetic engineering of enzymes involved in their biosynthesis [74]. Pimaricin is produced by a gram-positive soil bacteria *Streptomyces natalensis* [75, 76]. Recently much effort has been focused on microbiological synthesis of pimaricin derivatives using modified gene clusters [77–83]. It has been shown that modification of biosynthetic gene clusters can yield the bacteria strains for targeted microbiological synthesis of pimaricin derivatives with improved biological properties. The examples include preparation of 4,5-deepoxypimaricin [84, 85], pimaricin amides [86], and 4,5-deepoxypimaricinolide aglycon [84, 85] using a genetically modified pimaricin gene *pimD*. Biological tests have revealed about four times higher antifungal activity of pimaricin amides as compared to the parent antibiotic [86]. However, antifungal activity of 4,5-deepoxypimaricin

and 4,5-deepoxypimaricinolide aglycon is low, as both epoxy group and mycosamine carbohydrate moiety are required [13, 50, 67, 73, 87]. Further development of biosynthetic approaches seems a promising direction in the search for new derivatives of pimaricin, which in many cases can be considered as an alternative of the chemical modification of this antifungal antibiotic.

EXPERIMENTAL

Pimaricin was purchased from Sigma (USA). Dialkyl(diaryl) phosphites and 4-bromobenzaldehyde purchased from Sigma−Aldrich (USA) or Fluka (Switzerland) were used as received. Organic solvents were purified as described in [88].

NMR spectra (^{1}H, ^{13}C, COSY, DEPT, and HMQC) of 15% solutions in MeOH-d_4 were registered with a Bruker Avance III spectrometer (Germany) at 600 MHz with TMS as internal reference. ^{31}P NMR spectra were measured with a Bruker AC-200 spectrometer (Germany) at 200 MHz referenced to external 85% H_3PO_4. MALDI−TOF mass spectra were obtained with a MALDI Micromass spectrometer (USA) in α-cyano-4-hydroxycinnamic acid matrix. IR spectra were recorded using a Bruker Vector 22 instrument (Germany) in KBr. UV spectra of 5 mg/mL solutions in methanol containing 0.1% of acetic acid were measured with an Ultrospec 2100pro spectrophotometer (Biochrom, Great Britain). Reaction progress and purity of pimaricin derivatives **I–V** were monitored by TLC on Silica Gel 60 F_{254} (0.25 mm, Merck, Germany) using a 8 : 1 : 1 methanol–acetone–acetic acid solvent system, the spots were developed via UV irradiation. Silica Gel 60 (63–200 μm, Merck, Germany) was used as sorbent. The melting (decomposition) points were determined with an Electrothermal IA9300 instrument (Great Britain).

3'-*N*-α-[Dialkoxy(diphenoxy)phosphinoyl]benzylpimaricins I–V *(general procedure).* 4-Bromobenzaldehyde, 0.02 mol, was added to a stirred solution of 0.01 mol of pimaricin in 25 mL of anhydrous DMF in the presence of a catalytic amount of triethylamine. The reaction was performed at 40°C during 3 h; 0.015 mol of the corresponding dialkyl(diaryl) phosphite was then added to the reaction mixture, and it was stirred at 40°C during 3–4 h. The reaction progress was monitored using TLC. After the reaction was complete, the mixture was cooled to 20°C and filtered; the filtrate was diluted with 400 mL of diethyl ether. 30 mL of methanol was added to the oily precipitate, the resulting suspension was filtered, and the filtrate was subject to column chromatography on silica gel using a 12 : 7 : 0.5 : 0.03 $CHCl_3$–MeOH–H_2O–NH_4OH mixture as eluent. The eluates containing the target product were combined and concentrated to about 30% of the initial volume in vacuum. The concentrate was diluted with 5-fold volume of diethyl ether; the formed precipitate was filtered off, washed with diethyl ether, and dried in vacuum at 30°C during 4–5 h to yield compounds **I–V** as white or cream-colored fine crystals.

3'-*N*-[(4-Bromophenyl)(dimethoxyphosphinoyl)-methyl]pimaricin (I). Yield 82%, mp 179–184°C (decomp.), R_f 0.53. ^{1}H NMR spectrum (MeOH-d_4), δ, ppm: 1.15 d (1H, $J_{6eq,7}$ 11.0 Hz, H^6_{eq}), 1.21 d.d (1H, H^0_{ax}, $J_{10ax,11}$ 11.2, $J_{10ax,10eq}$ 12.4 Hz), 1.25 s (3H, H$^{6'}$-CH_3), 1.29 s (3H, 26-CH_3), 1.53 d (1H, H^8_{ax}, $J_{8ax,8eq}$ 14.2 Hz), 1.59 d.d (1H, H^{14}_{ax}, $J_{14ax,14eq}$ 14.0, $J_{14eq,15}$ 2.0 Hz), 1.67 s (1H, H^8_{eq}), 1.92 d (H^{10}_{eq}, $J_{10eq,11}$ 4.8 Hz), 1.99 t (1H, H^{12}, $J_{12,13}$ 10.5 Hz), 2.09 d.d (1H, H^6_{ax}, $J_{6ax,6eq}$ 14.4, $J_{6ax,7}$ 0.9 Hz), 2.16 d.d (1H, H^4_{ax}, $J_{24ax,24eq}$ 13.5, $J_{24ax,25}$ 11.0 Hz), 2.24 d (1H, H^{14}_{eq}, $J_{14eq,15}$ 3.5 Hz), 2.33 d (1H, H^4_{eq}, $J_{24eq,25}$ 5.6 Hz), 2.74 d.d (1H, H^5, $J_{5,6ax}$ 1.8, $J_{5,6eq}$ 8.3 Hz), 3.10 d (1H, H^4, $J_{4,5}$ 1.5 Hz), 3.18 d (1H, H$^{3'}$, $J_{3',4'}$ 9.0 Hz), 3.24 d (1H, H$^{5'}$, $J_{5',6'Me}$ 6.5 Hz), 3.32 d [6H, (O)P(OCH_3)$_2$, J 11.2 Hz], 3.39 d (1H, H$^{4'}$, $J_{4',5'}$ 9.0 Hz), 4.02 m (1H, H$^{1''}$, CHP), 4.06 d (1H, H$^{2'}$, $J_{2',3'}$ 3.5 Hz), 4.22 d (1H, H^{11}, $J_{11,12}$ 10.5 Hz), 4.29 d.d (1H, H^7, $J_{7,8ax}$ 1.3, $J_{7,8eq}$ 10.2 Hz), 4.38 d.d (1H, H^{13}, $J_{13,14ax}$ 8.4, $J_{13,14eq}$ 1.2 Hz), 4.42 d (1H, H^{15}, $J_{15,16}$ 8.3 Hz), 4.53 d (1H, H$^{1'}$, $J_{1',2'}$ 1.0 Hz), 4.71 d (1H, H^{25}, $J_{25,26Me}$ 6.5 Hz), 5.51 d.d (1H, H^{23}, $J_{23,24ax}$ 8.8, $J_{23,24eq}$ 2.5 Hz), 5.90 d (1H, H^{16}, $J_{16,17}$ 15.2 Hz), 6.09 d.d (1H, H^2, $J_{2,3}$ 15.8, $J_{2,4}$ 0.6 Hz), 6.14 d (1H, H^{22}, $J_{22,23}$ 15.4 Hz), 6.17 d (1H, H^{17}, $J_{17,18}$ 10 Hz), 6.19 s (1H, H^{20}), 6.23 s (1H, H^{21}), 6.29 s (1H, H^{19}), 6.43 d (1H, H^3, $J_{3,4}$ 7.5 Hz), 6.47 s (1H, H^{18}), 6.70 d (2H, phenyl, J 8.2 Hz), 7.17 d (2H, phenyl, J 8.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 18.32 (C$^{6'}$), 20.60 (C^{26}), 26.93 d (C"HP, J_{CP} 132.1 Hz), 41.02 (C^6), 42.62 (C^{10}), 43.22 (C^{14}), 44.69 (C^{24}), 47.79 (C^8), 56.49 (C^4), 52.17 d [(O)P(OCH_3)$_2$, J_{CP} 6.2 Hz], 57.30 (C$^{3'}$), 60.35 (C^5), 61.19 (C^{12}), 65.95 (C$^{5'}$), 68.32 (C^{13}), 68.77 (C^{11}), 69.62 (C^7), 72.10 (C^{25}), 73.19 (C$^{2'}$), 74.88 (C$^{4'}$), 75.51 (C^5), 81.73 (C^{15}), 99.95 (C^9), 101.12 (C$^{1'}$), 126.44 (C^2), 115.87 (phenyl), 128.39 (phenyl), 130.83 (C^{16}), 133.19 (C^{17}), 133.40 (C^{18}), 134.08 (C^{19}), 134.47 (C^{20}), 134.79 (C^{21}), 135.29 (C^{22}), 136.41 (phenyl), 137.99 (C^{23}), 145.58 (C^3), 156.53 (phenyl), 168.13 (C^1), 178.30 (C^{27}). ^{31}P NMR spectrum: δ_P 21.57 ppm. Mass

spectrum (MALDI TOF): *m*/*z* 965.87 $[M + Na]^+$. $C_{42}H_{57}BrNO_{16}NaP$.

3'-*N*-[(4-Bromophenyl)(diethoxyphosphinoyl)-methyl]pimaricin (II). Yield 85%, mp 183–188°C (decomp.), R_f 0.50. ^{1}H NMR spectrum (MeOH-d_4), δ, ppm: 1.13 d.t [(6H, (O)P(OCH$_2$CH$_3$)$_2$], 1.16 d (1H, H^6_{eq}, $J_{6eq,7}$ 11.0 Hz), 1.20 d.d (1H, H^0_{ax}, $J_{10ax,11}$ 11.2, $J_{10ax,10eq}$ 12.4 Hz), 1.27 s (3H, H$^{6'}$-CH$_3$), 1.29 s (3H, 26-CH$_3$), 1.55 d (1H, H^8_{ax}, $J_{8ax,8eq}$ 14.2 Hz), 1.60 d.d (1H, H^{14}_{ax}, $J_{14ax,14eq}$ 14.0, $J_{14eq,15}$ 2.0 Hz), 1.69 s (1H, H^8_{eq}), 1.94 d (H^{10}_{eq}, $J_{10eq,11}$ 4.8 Hz), 2.02 t (1H, H^{12}, $J_{12,13}$ 10.5 Hz), 2.09 d.d (1H, H^6_{ax}, $J_{6ax,6eq}$ 14.4, $J_{6ax,7}$ 0.9 Hz), 2.14 d.d (1H, H^4_{ax}, $J_{24ax,24eq}$ 13.5, $J_{24ax,25}$ 11.0 Hz), 2.25 d (1H, H^{14}_{eq}, $J_{14eq,15}$ 3.5 Hz), 2.35 d (1H, H^4_{eq}, $J_{24eq,25}$ 5.6 Hz), 2.73 d.d (1H, H^5, $J_{5,6ax}$ 1.8, $J_{5,6eq}$ 8.3 Hz), 3.12 d (1H, $J_{4,5}$ 1.5 Hz, H-4), 3.20 d (1H, H$^{3'}$, $J_{3',4'}$ 9.0 Hz), 3.25 d (1H, H$^{5'}$, $J_{5',6'Me}$ 6.5 Hz), 3.36 d (1H, H$^{4'}$, $J_{4',5'}$ 9.0 Hz), 3.90 d. q [4H, (O)P(OCH$_2$CH$_3$)$_2$, J(CH$_2$OP) 10.0 Hz], 4.05 m (1H, H$^{1''}$, CHP), 4.09 d (1H, H$^{2'}$, $J_{2',3'}$ 3.5 Hz), 4.24 d (1H, H^{11}, $J_{11,12}$ 10.5 Hz), 4.31 d.d (1H, H^7, $J_{7,8ax}$ 1.3, $J_{7,8eq}$ 10.2 Hz), 4.36 d.d (1H, H^{13}, $J_{13,14ax}$ 8.4, $J_{13,14eq}$ 1.2 Hz), 4.44 d (1H, H^{15}, $J_{15,16}$ 8.3 Hz), 4.51 d (1H, H$^{1'}$, $J_{1',2'}$ 1.0 Hz), 4.73 d (1H, H^{25}, $J_{25,26Me}$ 6.5 Hz), 5.53 d.d (1H, H^{23}, $J_{23,24ax}$ 8.8, $J_{23,24eq}$ 2.5 Hz), 5.92 d (1H, H^{16}, $J_{16,17}$ 15.2 Hz), 6.07 d.d (1H, H^2, $J_{2,3}$ 15.8, $J_{2,4}$ 0.6 Hz), 6.13 d (1H, H^{22}, $J_{22,23}$ 15.4 Hz), 6.16 d (1H, H^{17}, $J_{17,18}$ 10 Hz), 6.20 s (1H, H^{20}), 6.24 s (1H, H^{21}), 6.31 s (1H, H^{19}), 6.41 d (1H, H^3, $J_{3,4}$ 7.5 Hz), 6.45 s (1H, H^{18}), 6.72 d (2H, phenyl, *J* 8.2 Hz), 7.19 d (2H, phenyl, *J* 8.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 16.37 d, [(O)P(OCH$_2$CH$_3$)$_2$, J_{CP} 6.7 Hz],18.34 (C$^{6'}$), 20.60 (C^{26}), 27.54 d (C"HP, J_{CP} 133.0 Hz), 41.05 (C^6), 42.60 (C^{10}), 43.24 (C^{14}), 44.72 (C^{24}), 47.82 (C^8), 52.19 d [(O)P(OCH$_3$)$_2$, J_{CP} 6.2 Hz], 57.33 (C$^{3'}$), 56.54 (C^4), 57.28 (C$^{3'}$), 60.38 (C^5), 61.22 (C^{12}), 61.59 d [(O)P(OCH$_2$CH$_3$)$_2$, J_{CP} 5.3 Hz], 68.30 (C^{13}), 68.74 (C^{11}), 69.64 (C^7), 72.13 (C^{25}), 73.21 (C$^{2'}$), 74.84 (C$^{4'}$), 75.53 (C^5), 81.70 (C^{15}), 99.98 (C^9), 101.09 (C$^{1'}$), 126.46 (C^2), 115.78 (phenyl), 128.43 (phenyl), 130.80 (C^{16}), 133.16 (C^{17}), 133.43 (C^{18}), 134.09 (C^{19}), 134.49 (C^{20}), 134.82 (C^{21}), 135.31 (C^{22}), 136.37 (phenyl), 138.08 (C^{23}), 145.62 (C^3), 156.59 (phenyl), 168.17 (C^1), 178.36 (C^{27}). ^{31}P NMR spectrum: δ_P 21.63 ppm. Mass spectrum (MALDI TOF): *m*/*z* 993.91 $[M + Na]^+$. $C_{44}H_{61}BrNO_{16}NaP$.

3'-*N*-[(4-Bromophenyl)(dibutoxyphosphinoyl)-methyl]pimaricin (III). Yield 81%, mp 190–195°C (decomp.), R_f 0.47. ^{1}H NMR spectrum (MeOH-d_4), δ, ppm: 0.93 t [3H, (O)P(OCH$_2$CH$_2$CH$_2$CH$_3$)$_2$], 1.13 d (1H, H^6_{eq}, $J_{6eq,7}$ 11.0 Hz), 1.22 d.d (1H, H^0_{ax}, $J_{10ax,11}$ 11.2, $J_{10ax,10eq}$ 12.4 Hz), 1.28 s (3H, H$^{6'}$-CH$_3$), 1.32 s (3H, 26-CH$_3$), 1.53 d (1H, H^8_{ax}, $J_{8ax,8eq}$ 14.2 Hz), 1.59–1.63 m [8H, (O)P[(OCH$_2$CH$_2$CH$_2$CH$_3$)$_2$], 1.68 d.d (1H, H^{14}_{ax}, $J_{14ax,14eq}$ 14.0, $J_{14eq,15}$ 2.0 Hz), 1.75 s (1H, H^8_{eq}), 1.96 d (H^{10}_{eq}, $J_{10eq,11}$ 4.8 Hz), 2.05 t (1H, H^{12}, $J_{12,13}$ 10.5 Hz), 2.10 d.d (1H, H^6_{ax}, $J_{6ax,6eq}$ 14.4, $J_{6ax,7}$ 0.9 Hz), 2.16 d.d (1H, H^4_{ax}, $J_{24ax,24eq}$ 13.5, $J_{24ax,25}$ 11.0 Hz), 2.27 d (1H, H^{14}_{eq}, $J_{14eq,15}$ 3.5 Hz), 2.39 d (1H, H^4_{eq}, $J_{24eq,25}$ 5.6 Hz), 2.76 d.d (1H, H^5, $J_{5,6ax}$ 1.8, $J_{5,6eq}$ 8.3 Hz), 3.14 d (1H, H^4, $J_{4,5}$ 1.5 Hz), 3.19 d (1H, H$^{3'}$, $J_{3',4'}$ 9.0 Hz), 3.27 d (1H, H$^{5'}$, $J_{5',6'Me}$ 6.5 Hz), 3.38 d (1H, H$^{4'}$, $J_{4',5'}$ 9.0 Hz), 3.99 d. q [4H, (O)P(OCH$_2$CH$_2$CH$_2$CH$_3$)$_2$, J(CH$_2$OP) 10.2 Hz], 4.07 m (1H, H$^{1''}$, CHP), 4.11 d (1H, H$^{2'}$, $J_{2',3'}$ 3.5 Hz), 4.26 d (1H, H^{11}, $J_{11,12}$ 10.5 Hz), 4.33 d.d (1H, H^7, $J_{7,8ax}$ 1.3, $J_{7,8eq}$ 10.2 Hz), 4.37 d.d (1H, H^{13}, $J_{13,14ax}$ 8.4, $J_{13,14eq}$ 1.2 Hz), 4.43 d (1H, H^{15}, $J_{15,16}$ 8.3 Hz), 4.54 d (1H, H$^{1'}$, $J_{1',2'}$ 1.0 Hz), 4.70 d (1H, H^{25}, $J_{25,26Me}$ 6.5 Hz), 5.55 d.d (1H, H^{23}, $J_{23,24ax}$ 8.8, $J_{23,24eq}$ 2.5 Hz), 5.96 d (1H, H^{16}, $J_{16,17}$ 15.2 Hz), 6.09 d.d (1H, H^2, $J_{2,3}$ 15.8, $J_{2,4}$ 0.6 Hz), 6.14 d (1H, H^{22}, $J_{22,23}$ 15.4 Hz), 6.18 d (1H, H^{17}, $J_{17,18}$ 10 Hz), 6.21s (1H, H^{20}), 6.26 s (1H, H^{21}), 6.33 s (1H, H^{19}), 6.42 d (1H, H^3, $J_{3,4}$ 7.5 Hz), 6.46 s (1H, H^{18}), 6.74 d (2H, phenyl, *J* 8.2 Hz), 7.17 d (2H, phenyl, *J* 8.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 17.44 d [(O)P(OCH$_2$CH$_2$·CH$_2$CH$_3$)$_2$, J_{CP} 7.0 Hz], 18.36 (C$^{6'}$), 19.11 [(O)P(OCH$_2$CH$_2$CH$_2$CH$_3$)$_2$], 20.63 (C^{26}), 28.02 d (C"HP, J_{CP} 132.5 Hz), 41.07 (C^6), 42.63 (C^{10}), 43.24 (C^{14}), 44.75 (C^{24}), 47.87 (C^8), 52.16 d [(O)P(OCH$_3$)$_2$, J_{CP} 6.2 Hz], 57.33 (C$^{3'}$), 56.50 (C^4), 57.28 (C$^{3'}$), 60.41 (C^5), 61.22 (C^{12}), 62.73 d [(O)P(OCH$_2$CH$_3$)$_2$, J_{CP} 5.7 Hz], 68.33 (C^{13}), 68.72 (C^{11}), 69.63 (C^7), 72.15 (C^{25}), 73.24 (C$^{2'}$), 74.81 (C$^{4'}$), 75.56 (C^5), 81.73 (C^{15}), 99.95 (C^9), 101.07 (C$^{1'}$), 126.45 (C^2), 115.72 (phenyl), 128.37 (phenyl), 130.74 (C^{16}), 133.22 (C^{17}), 133.49 (C^{18}),134.02 (C^{19}), 134.54 (C^{20}), 134.88 (C^{21}), 135.35 (C^{22}), 136.43 (phenyl), 138.13 (C^{23}), 145.69 (C^3), 156.66 (phenyl), 168.23 (C^1), 178.42 (C^{27}). ^{31}P NMR spectrum: δ_P 21.70 ppm Mass spectrum (MALDI TOF): *m*/*z* 1059.68 $[M + Na]^+$. $C_{48}H_{79}BrNO_{16}NaP$.

3'-*N*-[(4-Bromophenyl)(diphenoxyphosphinoyl)-methyl]pimaricin (IV). Yield 83%, mp 203–208°C (decomp.), R_f 0.44. NMR spectrum ^{1}H (MeOH-d_4), δ, ppm: 1.16 d (1H, H^6_{eq}, $J_{6eq,7}$ 11.0 Hz), 1.20 d.d (1H, H^0_{ax}, $J_{10ax,11}$ 11.2, $J_{10ax,10eq}$ 12.4 Hz), 1.26 s (3H, H$^{6'}$-CH$_3$), 1.32 s (3H, 26-CH$_3$), 1.57 d (1H, H^8_{ax}, $J_{8ax,8eq}$ 14.2 Hz), 1.63 d.d (1H, H^{14}_{ax}, $J_{14ax,14eq}$ 14.0, $J_{14eq,15}$ 2.0 Hz), 1.71 s (1H, H^8_{eq}), 1.97 d (H^{10}_{eq}, $J_{10eq,11}$ 4.8 Hz), 2.03 t (1H, H^{12}, $J_{12,13}$ 10.5 Hz), 2.10 d.d (1H, H^6_{ax}, $J_{6ax,6eq}$ 14.4, $J_{6ax,7}$ 0.9 Hz), 2.18 d.d (1H, H^4_{ax}, $J_{24ax,24eq}$

13.5, $J_{24ax,25}$ 11.0 Hz), 2.26 d (1H, H^{14}_{eq}, $J_{14eq,15}$ 3.5 Hz), 2.35 d (1H, H^{4}_{eq}, $J_{24eq,25}$ 5.6 Hz), 2.76 d.d (1H, H^5, $J_{5,6ax}$ 1.8, $J_{5,6eq}$ 8.3 Hz), 3.12 d (1H, H^4, $J_{4,5}$ 1.5 Hz), 3.19 d (1H, $H^{3'}$, $J_{3',4'}$ 9.0 Hz), 3.26 d (1H, $H^{5'}$, $J_{5',6'Me}$ 6.5 Hz), 3.42 d (1H, $H^{4'}$, $J_{4',5'}$ 9.0 Hz), 4.09 m (1H, $H^{1''}$, CHP), 4.11 d (1H, $H^{2'}$, $J_{2',3'}$ 3.5 Hz), 4.25 d (1H, H11, $J_{11,12}$ 10.5 Hz), 4.30 d.d (1H, H^7, $J_{7,8ax}$ 1.3, $J_{7,8eq}$ 10.2 Hz), 4.39 d.d (1H, H^{13}, $J_{13,14ax}$ 8.4, $J_{13,14eq}$ 1.2 Hz), 4.47 d (1H, H^{15}, $J_{15,16}$ 8.3 Hz), 4.53 d (1H, $H^{1'}$, $J_{1',2'}$ 1.0 Hz), 4.70 d (1H, H^{25}, $J_{25,26Me}$ 6.5 Hz), 5.55 dd (1H, H^{23}, $J_{23,24ax}$ 8.8, $J_{23,24eq}$ 2.5 Hz), 5.95 d (1H, H^{16}, $J_{16,17}$ 15.2 Hz), 6.07 d.d (1H, H^2, $J_{2,3}$ 15.8, $J_{2,4}$ 0.6 Hz), 6.11 d (1H, H^{22}, $J_{22,23}$ 15.4 Hz), 6.16 d (1H, H^{17}, $J_{17,18}$ 10 Hz), 6.20 s (1H, H^{20}), 6.27 s (1H, H^{21}), 6.32 s (1H, H^{19}), 6.40 d (1H, H^3, $J_{3,4}$ 7.5 Hz), 6.49 s (1H, H^{18}), 6.73 d (2H, phenyl, *J* 8.2 Hz), 7.19 d (2H, phenyl, *J* 8.2 Hz), 7.23–7.33 m [10H, $(O)P(OC_6H_5)_2$]. ^{13}C NMR spectrum, δ_C, ppm: 18.34 ($C^{6'}$), 20.63 (C^{26}), 27.97 d (C"HP, J_{CP} 133.6 Hz), 41.07 (C^6), 42.69 (C^{10}), 43.21 (C^{14}), 44.72 (C^{24}), 47.74 (C^8), 56.55 (C^4), 57.37 ($C^{3'}$), 60.30 (C^5), 61.23 (C^{12}), 65.91 ($C^{5'}$), 68.39 (C^{13}), 68.82 (C^{11}), 69.68 (C^7), 72.15 (C^{25}), 73.22 ($C^{2'}$), 74.83 ($C^{4'}$), 75.56 (C^5), 81.77 (C^{15}), 100.05 (C^9), 101.19 ($C^{1'}$), 126.50 (C^2), 115.82 (phenyl), 120.37, 121.59, 130.21, 150.33 [$(O)P(OC_6H_5)_2$], 128.43 (phenyl), 130.89 (C^{16}), 133.11 (C^{17}), 133.34 (C^{18}),134.12 (C^{19}), 134.52 (C^{20}), 134.70 (C^{21}), 135.33 (C^{22}), 136.45 (phenyl), 138.09 (C^{23}), 145.66 (C^3), 156.59 (phenyl), 168.21 (C^1), 178.39 (C^{27}). ^{31}P NMR spectrum: δ_P 21.85 ppm. Mass spectrum (MALDI TOF): *m*/*z* 1089.90 $[M + Na]^+$. $C_{52}H_{61}BrNO_{16}NaP$.

3'-*N*-{[Bis(trimethylsilyloxy)phosphinoyl)](4-bromophenyl)methyl}pimaricin (V). Yield 80%, mp 175–180°C (decomp.), R_f 0.55. ^1H NMR spectrum (MeOH-d_4), δ, ppm: 0.25 s {18H, $(O)P[OSi(CH_3)_3]_2$}, 1.15 d (1H, H^6_{eq}, $J_{6eq,7}$ 11.0 Hz), 1.21 d.d (1H, H^0_{ax}, $J_{10ax,11}$ 11.2, $J_{10ax,10eq}$ 12.4 Hz), 1.25 s (3H, $H^{6'}$-CH_3), 1.29 s (3H, 26-CH_3), 1.53 d (1H, H^8_{ax}, $J_{8ax,8eq}$ 14.2 Hz), 1.59 d.d (1H, H^{14}_{ax}, $J_{14ax,14eq}$ 14.0, $J_{14eq,15}$ 2.0 Hz), 1.67 s (1H, H^8_{eq}), 1.92 d (H^{10}_{eq}, $J_{10eq,11}$ 4.8 Hz), 1.99 t (1H, H^{12}, $J_{12,13}$ 10.5 Hz), 2.09 dd (1H, H^6_{ax}, $J_{6ax,6eq}$ 14.4, $J_{6ax,7}$ 0.9 Hz), 2.16 d.d (1H, H^4_{ax}, $J_{24ax,24eq}$ 13.5, $J_{24ax,25}$ 11.0 Hz), 2.24 d (1H, H^{14}_{eq}, $J_{14eq,15}$ 3.5 Hz), 2.33 d (1H, H^4_{eq}, $J_{24eq,25}$ 5.6 Hz), 2.74 d.d (1H, H^5, $J_{5,6ax}$ 1.8, $J_{5,6eq}$ 8.3 Hz), 3.10 d (1H, H^4, $J_{4,5}$ 1.5 Hz), 3.18 d (1H, $H^{3'}$, $J_{3',4'}$ 9.0 Hz), 3.24 d (1H, $H^{5'}$, $J_{5',6'Me}$ 6.5 Hz), 3.39 d (1H, $H^{4'}$, $J_{4',5'}$ 9.0 Hz), 4.11 m (1H, $H^{1''}$,CHP), 4.06 d (1H, $H^{2'}$, $J_{2',3'}$ 3.5 Hz), 4.22 d (1H, H^{11}, $J_{11,12}$ 10.5 Hz), 4.29 d.d (1H, H^7, $J_{7,8ax}$ 1.3, $J_{7,8eq}$ 10.2 Hz), 4.38 d.d (1H, H^{13}, $J_{13,14ax}$ 8.4, $J_{13,14eq}$ 1.2 Hz), 4.42 d (1H, H^{15}, $J_{15,16}$ 8.3 Hz), 4.53 d (1H, $H^{1'}$, $J_{1',2'}$ 1.0 Hz), 4.71 d (1H, H^{25}, $J_{25,26Me}$ 6.5 Hz), 5.51 d.d (1H, H^{23}, $J_{23,24ax}$ 8.8, $J_{23,24eq}$ 2.5 Hz), 5.90 d (1H, H^{16}, $J_{16,17}$ 15.2 Hz), 6.09 d.d (1H, H^2, $J_{2,3}$ 15.8, $J_{2,4}$ 0.6 Hz), 6.14 d (1H, H^{22}, $J_{22,23}$ 15.4 Hz), 6.17 d (1H, H^{17}, $J_{17,18}$ 10 Hz), 6.19 s (1H, H^{20}), 6.23 s (1H, H^{21}), 6.29 s (1H, H^{19}), 6.43 d (1H, H^3, $J_{3,4}$ 7.5 Hz), 6.47 s (1H, H^{18}), 6.70 d (2H, phenyl, *J* 8.2 Hz), 7.17 d (2H, phenyl, *J* 8.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 4.90 {$(O)P[OSi(CH_3)_3]_2$}, 18.32 ($C^{6'}$), 20.60 (C^{26}), 28.14 d (C"HP, J_{CP} 134.3 Hz), 41.02 (C^6), 42.62 (C^{10}), 43.22 (C^{14}), 44.69 (C^{24}), 47.79 (C^8), 56.49 (C^4), 57.30 ($C^{3'}$), 60.35 (C^5), 61.19 (C^{12}), 65.95 ($C^{5'}$), 68.32 (C^{13}), 68.77 (C^{11}), 69.62 (C^7), 72.10 (C^{25}), 73.19 ($C^{2'}$), 74.88 ($C^{4'}$), 75.51 (C^5), 81.73 (C^{15}), 99.95 (C^9), 101.12 ($C^{1'}$), 126.44 (C^2), 115.87 (phenyl), 128.39 (phenyl), 130.83 (C^{16}), 133.19 (C^{17}), 133.40 (C^{18}), 134.08 (C^{19}), 134.47 (C^{20}), 134.79 (C^{21}), 135.29 (C^{22}), 136.41 (phenyl), 137.99 (C^{23}), 145.58 (C^3), 156.53 (phenyl), 168.13 (C^1), 178.30 (C^{27}). ^{31}P NMR spectrum, δ_P 21.79 ppm. Mass spectrum (MALDI TOF): *m*/*z* 1053.84 $[M + Na]^+$. $C_{46}H_{69}BrNO_{16}NaPSi$.

Acute toxicity (LD_{50}) of pimaricin derivatives **I–V** was studied on mongrel white male mices weighting 18–20 g. Suspensions of the compounds in a 0.5% aqueous solution of carboxymethylcellulose were prepared and injected intraperitoneally. The LD_{50} values were calculated by the Kerber method [89, 90].

The antifungal activity assay of compounds **I–V** was performed via the serial dilutions procedure in broth. The minimum fungistatic concentration (MFsC) was determined by visual assessment of the intensity of growth of the culture in the test and reference tubes; all test runs were performed in triplicate. Pimaricin was used as reference in all medical biological experiments.

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