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Chemical Modification of Heptaene Macrolide Antibiotic Amphotericin B under Conditions of the Atherton–Todd Reaction

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Abstract—Chemical modification of heptaene macrolide antibiotic Amphotericin B with dialkyl(diaryl)-phosphites has been performed under conditions of the Atherton–Todd reaction. As a result, the corresponding dialkyl(aryl)amidophosphonate derivatives of Amphotericin B have been formed. The prepared derivatives have been characterized by their physicochemical properties, toxicity, and antifungal activity against a set of test cultures of pathogenic fungi and yeast-like fungi of the Candida species.

Keywords: polyene macrolide antibiotic, Amphotericin B, dialkyl(aryl)phosphite, dialkyl(aryl)amidophosphate derivative, toxicity, antifungal activity

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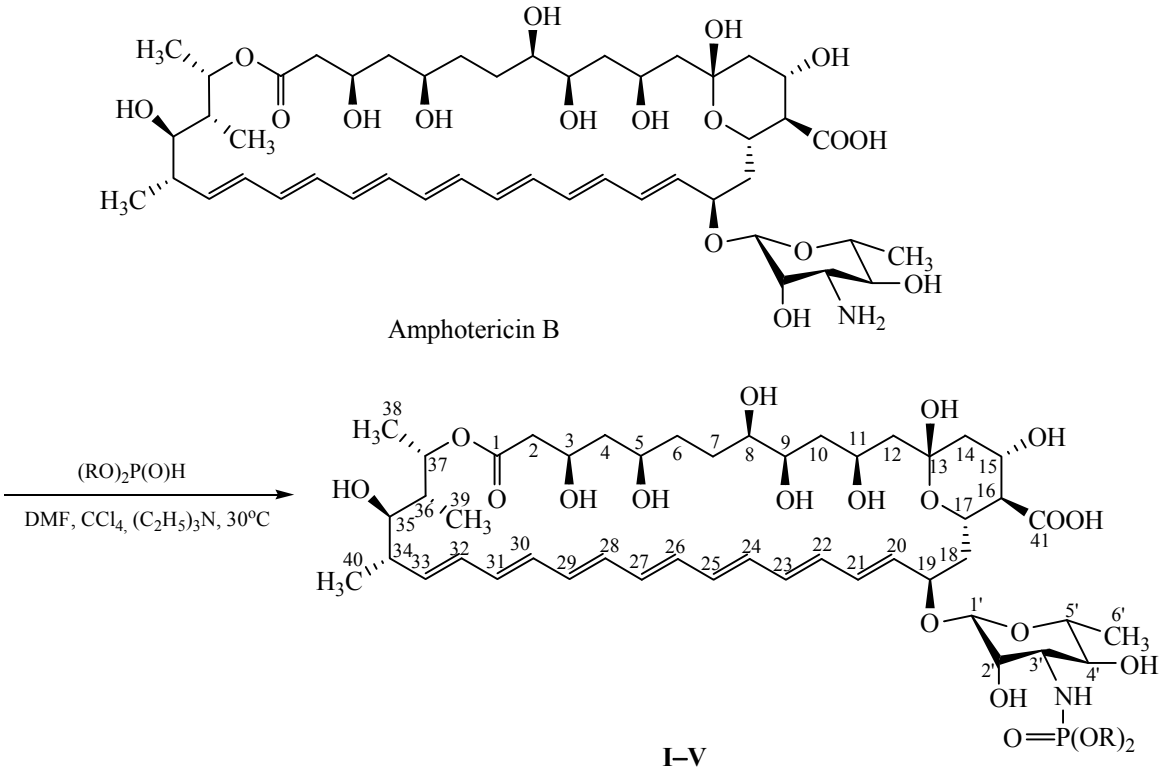
Polyene macrolide antibiotics (Amphotericin B, Levorin, Nystatin, Pimaricin, Candicidin, etc) are widely used in medical practice for the treatment of mycoses [1–3]. Polyene macrolide antibiotics are known for fungistatic as well as fungicide action that is due to binding these antimycotics with ergosterol component of a fungus membrane, disintegration of the latter, loss of cytoplasm, and finally the cell death [4, 5]. Heptaene macrolide antibiotic Amphotericin B has been clinically used for over fifty years, and is still considered the best option for antifungal therapeutics [6–8]. Its strong fungicide effect is both due to the direct action on the cell membrane permeability (formation of water channels) and to induction of active oxygen appearance in the cell [9, 10]. Systematic treatment with Amphotericin B is efficient against most of yeast-like, filamentous, and dimorphous fungi. In contrast to other polyene macrolide antibiotics, Amphotericin B is applied intravenously, therefore, its therapeutic efficiency against deep mycosis is significantly enhanced [11–13].

Growing prospects of Amphotericin B application are due to the possibility of its use in complex with synthetic antifungal drugs in mycotic infections treatment [14–16]; furthermore, to revealing the antiviral [17, 18] and antitumor [19, 20] activity on this antibiotic. On top of it, Amphotericin B is promising for treatment of leishmaniasis [21–23], as anti-inflammatoty drug [24], in genetic therapy [25], and for therapy of severe fungal sepsis (in combination with antibodies) [26, 27] as well as of AIDS-complicating fungal diseases [28–30]. However, Amphotericin B is known for high toxicity (mainly nephrotoxicity) [9, 11, 31], low gastroenteric absorptivity [32, 33], a number of side effects [3, 14], and a reduced resistance of certain pathogenic fungi to Amphotericin B action [34, 35]; therefore studies of various derivatives of this antibiotics have been emerging [36–39]. In earlier studies we prepared hydrophosphoryl [40], fluoroorganic [41], and *N*-benzyl derivatives of Amphotericin B [42].

Extending the studies on preparation of synthetic derivatives of Amphotericin B, we investigated its interaction with dialkylphosphites under conditions of the Atherton–Todd reaction. In particular, in the preliminary report we discussed Amphotericin B

Scheme 1.



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

reactions with dimethyl- and diethylphosphites [43]. This work aimed to chemically modify Amphotericin B via the Atherton-Todd reaction and to study toxicity and antifungal activity of the prepared derivatives.

We demonstrated that interaction of Amphotericin B with various dialkyl(diaryl)phosphites in the presence of organic base resulted in the corresponding dialkyl-(diaryl)amidophosphonate derivatives **I**–**V** (Scheme 1).

The following dialkyl(diaryl)phosphites were used: dimethylphosphite, diethylphosphite, dibutylphosphite, diphenylphosphite, and bis(trimethylsilyl)phosphite. The reaction of Amphotericin B with the said phosphites occurred in a 2 : 1 mixture of anhydrous dimethylformamide and tetrachloromethane (solvents) in the presence of triethylamine at 5–40°C. The described interaction can be regarded as a version of the Atherton–Todd method yielding dialkylamidophosphates [44–46] whose synthetic opportunities are comprehensively described in [47]. Chemical modification of Amphotericin B with dialkyl(diaryl)phosphites occurred with high selectivity to give the corresponding dialkyl(diaryl)amidophosphates; hence, the organophosphorus compounds reacted with the primary amino group of mycosamine (3-amino-3,6-dideoxy-D-mannose). Previously we studied the interaction of Amphotericin B with aromatic aldehydes and hypophosphorous acid under conditions of the Kabachnik–Fields reaction selectively yielding the corresponding hydrophosphoryl derivatives of the antibiotic [40]. Noteworthily, yield of compounds **I**–**V** was as low as 45–54%, evidently, due both to lability of the starting Amphotericin B under the reaction conditions and the instability of the derivatives in the course of their isolation and purification.

The prepared derivatives **I**–**V** were solid substances with no distinct melting point, decomposing upon heating. The compounds were readily soluble in DMSO and DMF, moderately soluble in methanol, ethanol, pyridine, and water, and insoluble in acetone, chloroform, diethyl ether, benzene, and hexane.

Structure of the dialkyl(diaryl)amidophosphate derivatives **I**–**V** was confirmed by NMR (^1H, ^{13}C, and ^{31}P), IR, and UV spectroscopy. ^1H NMR spectra of compounds **II** and **III** contained the signals of Amphotericin B protons [48, 49]. Methoxy groups protons resonated as doublets at 3.32–3.40 ppm, ethoxy groups

protons gave rise to triplet signals of the methyl groups at 1.10–1.13 ppm and quartet signals of methylene groups at 3.75–3.94 ppm, the coupling constant (with phosphorus atom) being 10.0–10.2 Hz. The broadened singlet at 5.12–5.23 ppm was assigned to a proton at the nitrogen atom.

^{13}C NMR spectra contained signals of carbon atoms of Amphotericin B [50, 51] and of ethoxy groups (16.34–17.45 ppm, J_{CP} 6.7–7.0 Hz; 61.57–62.73 ppm, J_{CP} 5.3–5.7 Hz) [52, 53]. Chemical shifts of phosphorus atom of the derivatives **I**–**V** were 11.40–11.78 ppm, typical of dialkyl(diaryl)amidophosphates with tetracoordinated phosphorus atom [52, 54].

IR spectra of compounds **I**–**V** contained, along with the absorption bands of Amphotericin B [55], the bands at 1230–1235 cm^{-1} (P=O) and 3955–3960 cm^{-1} (N–H); the spectrum of compound **IV** contained additional bands at 1577–1580 cm^{-1} assigned to phenyl groups. In the electron absorption spectra of compounds **I**–**V** bands appeared with maxima at 362, 383, and 405 nm confirming the presence of heptaene conjugated system; spectrum of compound **IV** additionally contained the band at 257 nm assigned to the absorption of phenyl fragments.

The high synthetic potential of the Atherton–Todd reaction affording various practically important amidophosphates [47, 56–59] has attracted considerable attention. Biological activity of the prepared amidophosphates is among the valuable properties of the derivatives. In particular, many of the substituted amidophosphates exhibited antifungal [60, 61], antibacterial [61], or antitumor [62–64] activity. The reported results and our earlier studies of phosphorylation of polyene macrolide antibiotics [40–43, 65–68] attracted our interest to investigation of medicinal and biological properties of the prepared derivatives **I**–**V**.

Acute toxicity (LD_{50}) of the studied derivatives I–V was four times lower than that of the starting antibiotic [69, 70]. In particular, the LD_{50} value of the studies derivatives was of 950 to 980 mg/kg (mice, intraperitoneal).

Further biological tests showed the pronounced antifungal activity of derivatives **I**–**V** against 6 test-cultures of yeast-like *Candida* fungi. The activity of compounds **I** and **IV** against *Candida albicans*, *Candida utilis*, *Candida tropicalis*, and *Candida krusei* was enhanced as compared to that of the parent antibiotic, and the activity against *Candida parapsilosis* and *Candida guillermondii* was comparable to that of Amphotericin B (see table). The antifungal activity of derivative **II** against the same cultures was similar to that of the parent antibiotic, whereas compounds **III** and **V** were less active as compared to Amphotericin B. The derivatives containing methoxy (**I**) or phenoxy (**IV**) groups at phosphorus atom revealed the antifungal activity against blastomycosis agent (*Blastomyces dermatitidis*) close to that of the parent antibiotic, whereas other derivatives **II**, **III**, and **V** were less active. Of all the studied derivatives, only compounds **IV** and **V** showed the activity against trichomycosis (*Trichophyton tonsurans* and *Trichophyton violaceum*) and histoplasmosis (*Histoplasma capsulatum*) agents comparable to that of Amphotericin B, the other derivatives were less active. The antifungal activity of compounds **I**, **II**, and **IV** against aspergillosis (*Aspergillus fumigatus, Aspergillus flavus*) and mold mycosis (*Penicillium granulatum*) agents was higher than that of Amphotericin B, and the other derivatives were less active. The following fungi were of low sensitivity to the studied derivatives **I**–**V**: chromomycosis (*Cladosporium carrionii*), sporotrichosis (*Sporotrichum schenkii*), and phycomycosis (*Rhizopus nigricans*, *Mucor mucedo*).

The test revealed a high antifungal activity of some of the studied derivatives against yeast-like *Candida* fungi and the *Aspergillus* fungi (see Table). The result is of primary importance, because the increased resistivity of these hospital cultures to Amphotericin B has been recently marked [5, 34, 35, 71–73]. The *Candida* and *Aspergillus* fungi are known to induce severe invasive mycoses (*candidiasis* and *aspergillosis*) as well as highly lethal opportunist mycoses accompanying AIDS [2–5, 30, 74].

Amphotericin B is known for fairly low water solubility of 1.5–2.0 mg/L [7, 75–77]; that significantly reduces its efficiency against various mycoses. Therefore, it is important to mention that the studied derivatives **I**–**V** showed higher solubility, of 35–45 mg/L. The over 20-fold increase of solubility due to introduction of phosphoryl group coincided with similar results on the hydrophosphoryl derivatives reported in [40]. The increased water solubility of antibiotics can potentially enhance the biopharmaceutical efficiency of these antifungal agents [3, 74].

To conclude, the application of conventional Atherton–Todd phosphorylation method afforded the amidophosphate derivatives of Amphotericin B. The prepared derivatives showed the improved pharma-

Minimal fungistatic concentration (μg/mL) of dialkyl(diaryl)amidophosphate derivatives of Amphotericin B (**I–V**)

Testing culture	**I**	**II**	**III**	**IV**	**V**	Amphotericin B
Candida albicans	0.04	0.05	1.56	0.40	3.12	0.05
Candida utilis	0.70	0.85	1.56	0.75	1.56	0.85
Candida tropicalis	0.10	0.15	3.12	0.10	3.12	0.15
Candida krusei	0.45	0.60	6.25	0.50	6.25	0.60
Candida parapsilosis	0.75	0.75	6.25	0.75	3.12	0.75
Candida guillermondii	1.25	1.25	3.12	1.25	6.25	1.25
Blastomyces dermatitidis	0.45	6.25	6.25	0.45	12.0	0.45
Histoplasma capsulatum	6.25	6.25	12.5	0.30	0.30	0.30
Trichophyton tonsurans	12.5	25.0	12.5	3.75	3.75	3.75
Trichophyton violaceum	12.5	25.0	25.0	4.40	4.40	4.40
Cladosporium carrionii	12.5	25.0	50.0	12.5	50.0	2.50
Aspergillus fumigatus	1.56	2.50	12.5	2.50	25.0	3.75
Aspergillus flavus	2.50	3.75	12.5	2.50	25.0	4.60
Penicillium granulatum	0.85	1.20	6.25	0.85	12.5	1.25
Sporotrichum schenkii	25.0	50.0	5.02	25.0	50.0	12.5
Rhizopus nigricans	50.0	50.0	100.0	50.0	100.0	6.15
Mucor mucedo	50.0	100.0	100.0	50.0	100.0	5.40

ceutical and biological properties as compared to those of the parent antibiotic.

EXPERIMENTAL

Amphotericin B (Sigma) had the biological activity of 740 UN/mg and specific absorbance ($E^{1\%}_{1cm}$) of 782 (362 nm), 1373 (383 nm), and 1564 (405 nm). Dialkyl-(diaryl)phoaphites (Sigma-Aldrich) were used as received. Organic solvents were purified as described elsewhere [78].

NMR spectra (^1H, ^{13}C, COSY, DEPT, and HMQC) were recorded using a Bruker Avance III instrument (600 MHz, DMSO-d_6 as solvent, and TMS as internal reference). ^{31}P NMR spectra were recorded using a Bruker AC-200 instrument (200 MHz, 85% H_3PO_4 as external standard). MALDI-TOF mass spectra were recorded using a MALDI Micromass spectrometer with α-cyano-4-hydroxycinnamic acid as a matrix. IR spectra were recorded using a Bruker Vector 22 instrument (KBr pellets). UV spectra of the solutions in methanol containing 0.1% of acetic acid were recorded with an Ultrospec 2100pro spectrophotometer (Biochrom) at the studied compound concentration of 5 mg/mL. The reaction course and the purity of prepared derivatives was monitored with TLC on Silica Gel 60 F_{254} plates (0.25 mm, Merck) using a 3 : 2 : 2 : 1 $CHCl_3$–MeOH–1-propanol–borate buffer (pH 8.14) solvent and developing with UV irradiation. Silica Gel 60 (63–200 μm, Merck) was used as sorbent.

[3'-*N*-Dialkoxy(diphenoxy)phosphoryl]amphotericin B (I–V). 20 mL of tetrachloromethane and 0.22 g (0.31 mL, 2.2 mmol) of triethylamine were added to 1.0 g (1.1 mmol) of Amphotericin B in 40 mL of anhydrous dimethylformamide under stirring. After cooling the reaction mixture to 5°C, 2.2 mmol of a corresponding dialkyl(diaryl)phosphite was added at vigorous stirring under an argon atmosphere. After addition of the phosphite, the reaction mixture was heated to 40°C, and the reaction was continued for

4–5 h. After the reaction was complete, the reaction mixture was cooled to 10°C, filtered, and 400 mL of diethyl ether was added to the filtrate. 40 mL of methanol was added to the separated oily liquid, the so formed suspension was filtered, and the filtrate was passed through a silica gel column. A 15 : 7 : 0.5 : 0.03 $CHCl_3$–MeOH–H_2O–NH_4OH mixture was used as eluent. The eluted fractions containing the target product were combined and concentrated under a reduced pressure; the residue was dried in a vacuum at 20°C during 4 h. The isolated compounds **I**–**V** were yellow crystalline solids.

(3'-*N*-Dimethoxyphosphoryl)amphotericin B (I). Yield 52%, mp 143–148°C (decomp.), R_f 0.52. ^{1}H NMR spectrum, δ, ppm. (*J*, Hz): 0.92 d (3H, H^{39}, *J* 7.0), 1.04 d (3H, H^{40}, *J* 6.5), 1.11 d (3H, H^{38}, *J* 6.5), 1.13 m (1H, $H^{14}{}_{ax}$), 1.17 d (3H, $H^{6'}$, *J* 6.5), 1.27–1.40 m (6H, H^4, H^6, H^{12}), 1.45–1.53 m (4H, H^7, H^{10}), 1.59 m (1H, H^{18b}), 1.71 m (1H, H^{36}), 1.88 d.d (1H, H^{18a}, *J* 5.5, 16.0), 1.92 d.d (1H, $H^{14}{}_{eq}$, *J* 5.0, 12.0), 2.09 m (1H, H^{16}), 2.14 d.d (1H, H^{2b}, *J* 3.0, 16.5), 2.21 d.d (1H, H^{2a}, *J* 9.0, 16.5), 2.28 m (2H, $H^{3'}$, H^{34}), 2.86 m (1H, $H^{4'}$), 3.07 m (1H, $H^{5'}$), 3.10 m (1H, H^8), 3.14 m (1H, H^{35}), 3.32 d [6H, (O)P(OC$\underline{H}_3$)$_2$, *J* 11.2], 3.45 m (1H, H^9), 3.52 s (1H, $H^{2'}$), 3.57 m (1H, H^5), 4.01 m (1H, H^{15}), 4.07 m (1H, H^3), 4.24 m (2H, H^{11}, H^{17}), 4.29 s (1H, $H^{1'}$), 4.37 m (1H, H^{19}), 5.12 s (1H, NH), 5.18 m (1H, H^{37}), 5.53 d.d (1H, H^{33}, *J* 9.5, 15.5), 5.75 d.d (1H, H^{29}, *J* 11.0, 34.0), 5.97 d.d (1H, H^{20}, *J* 9.0, 15.5), 6.10 d.d (1H, H^{21}, *J* 10.5, 15.5), 6.13 d.d (1H, H^{32}, *J* 10.5, 15.5), 6.18 d.d (1H, H^{27}, *J* 15.5, 28.0), 6.24 d.d (1H, H^{31}, *J* 10.5, 15.0), 6.29 d.d (1H, H^{23}, *J* 12.0, 15.0), 6.32 d.d (1H, H^{30}, *J* 11.0, 15.0), 6.34 d.d (1H, H^{25}, *J* 11.0, 14.5), 6.36 d.d (1H, H^{28}, *J* 10.5, 15.0), 6.42 d.d (1H, H^{22}, *J* 11.0, 15.0), 6.57 d.d (1H, H^{26}, *J* 11.0, 15.0), 6.61 d.d (1H, H^{24}, *J* 12.0, 14.5). ^{13}C NMR spectrum, δ_C, ppm: 11.95 (C^{39}), 16.97 (C^{38}), 17.80 ($C^{6'}$), 18.47 (C^{40}), 29.02 (C^7), 35.07 (C^6), 36.33 (C^{18}), 39.67 (C^{10}), 39.82 (C^{36}), 41.94 (C^2), 42.41 (C^{34}), 44.36 (C^4), 44.65 (C^{14}), 46.39 (C^{12}), 56.12 ($C^{3'}$), 52.17 d [(O)P(OCH$_3$)$_2$, J_{CP} 6.2], 58.44 (C^{16}), 65.21 (C^{17}), 65.48 (C^{15}), 66.15 (C^3), 67.70 (C^{11}), 68.74 ($C^{2'}$), 69.09 (C^{37}), 69.74 (C^5), 70.54 ($C^{4'}$), 72.54 ($C^{5'}$), 73.49 (C^8), 73.86 (C^9), 74.13 (C^{19}), 77.12 (C^{35}), 95.56 ($C^{1'}$), 97.08 (C^{13}), 129.74 (C^{26}), 130.68 (C^{23}), 130.77 (C^{30}), 131.36 (C^{24}), 131.55 (C^{32}), 131.67 (C^{28}), 132.35 (C^{21}), 132.43 (C^{25}), 134.51 (C^{22}), 136.31 (C^{20}), 136.72 (C^{27}), 137.03 (C^{29}), 137.16 (C^{33}), 137.22 (C^{31}), 170.47 (C^1), 176.82 (C^{41}). ^{31}P NMR spectrum, δ_P, ppm: 11.40. Mass spectrum (MALDI TOF): *m*/*z* 1055.17 $[M + Na]^+$ (calculated for $C_{49}H_{78}NO_{20}NaP$ 1055.12).

(3'-*N*-Diethoxyphosphoryl)amphotericin B (II). Yield 54%, mp 152–157°C (decomp.), R_f 0.50. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.91 d (3H, H^{39}, *J* 7.0), 1.03 d (3H, H^{40}, *J* 6.5), 1.07 d, (3H, H^{38}, *J* 6.5), 1.10 and 1.13 m [(6H, (O)P(OCH$_2$C$\underline{H}_3$)$_2$], 1.15 m (1H, $H^{14}{}_{ax}$), 1.19 d (3H, $H^{6'}$, *J* 6.0), 1.29–1.39 m (6H, H^4, H^6, H^{12}), 1.44–1.55 m (4H, H^7, H^{10}), 1.58 m (1H, H^{18b}), 1.70 m (1H, H^{36}), 1.86 d.d (1H, H^{18a}, *J* 5.5, 16.0), 1.90 d.d (1H, $H^{14}{}_{eq}$, *J* 5.0, 12.0), 2.12 m (1H, H^{16}), 2.16 d.d (1H, H^{2b}, *J* 3.0, 16.5), 2.23 d.d (1H, H^{2a}, *J* 9.0, 16.5), 2.30 m (2H, $H^{3'}$, H^{34}), 2.89 m (1H, $H^{4'}$), 3.08 m (1H, $H^{5'}$), 3.10 m (1H, H^8), 3.16 m (1H, H^{35}), 3.43 m (1H, H^9), 3.50 s (1H, $H^{2'}$), 3.56 m (1H, H^5), 3.75 and 3.90 d. q [4H, (O)P(OC$\underline{H}_2$CH$_3$)$_2$, *J* 10.0], 4.03 m (1H, H^{15}), 4.08 m (1H, H^3), 4.25 m (2H, H^{11}, H^{17}), 4.29 s (1H, $H^{1'}$), 4.39 m (1H, H^{19}), 5.15 s (1H, NH), 5.20 m (1H, H^{37}), 5.55 d.d (1H, H^{33}, *J* 9.5, 15.5), 5.73 d.d (1H, H^{29}, *J* 11.0, 34.0), 5.94 d.d (1H, H^{20}, *J* 9.0, 15.5), 6.10 d.d (1H, H^{21}, *J* 10.5, 15.5), 6.13 d.d (1H, H^{32}, *J* 10.5, 15.5), 6.19 d.d (1H, H^{27}, *J* 15.5, 28.0), 6.25 d.d (1H, H^{31}, *J* 10.5, 15.0), 6.27 d.d (1H, H^{23}, *J* 12.0, 15.0), 6.32 d.d (1H, H^{30}, *J* 11.0, 5.0), 6.34 d.d (1H, H^{25}, *J* 11.0, 14.5), 6.37 d.d (1H, H^{28}, *J* 10.5, 15.0), 6.42 d.d (1H, H^{22}, *J* 11.0, 15.0), 6.56 d.d (1H, H^{26}, *J* 11.0, 15.0), 6.63 d.d (1H, H^{24}, *J* 12.0, 14.5). ^{13}C NMR spectrum, δ_C, ppm (*J*, Hz): 11.93 (C^{39}), 16.34 d [(O)P(OCH$_2$CH$_3$)$_2$, J_{CP} 6.7], 16.92 (C^{38}), 17.75 ($C^{6'}$), 18.44 (C^{40}), 29.05 (C^7), 35.06 (C^6), 36.31 (C^{18}), 39.68 (C^{10}), 39.80 (C^{36}), 41.96 (C^2), 42.41 (C^{34}), 44.34 (C^4), 44.67 (C^{14}), 46.37 (C^{12}), 56.11 ($C^{3'}$), 58.42 (C^{16}), 61.57 d [(O)P(OCH$_2$CH$_3$)$_2$, J_{CP} 5.3], 65.23 (C^{17}), 65.50 (C^{15}), 66.17 (C^3), 67.72 (C^{11}), 68.76 ($C^{2'}$), 69.09 (C^{37}), 69.78 (C^5), 70.55 ($C^{4'}$), 72.58 ($C^{5'}$), 73.49 (C^8), 73.84 (C^9), 74.15 (C^{19}), 77.14 (C^{35}), 95.59 ($C^{1'}$), 97.11 (C^{13}), 129.78 (C^{26}), 130.71 (C^{23}), 130.82 (C^{30}), 131.39 (C^{24}), 131.53 (C^{32}), 131.63 (C^{28}), 132.33 (C^{21}), 132.46 (C^{25}), 134.53 (C^{22}), 136.30 (C^{20}), 136.70 (C^{27}), 137.09 (C^{29}), 137.18 (C^{33}), 137.24 (C^{31}), 170.51 (C^1), 176.87 (C^{41}). ^{31}P NMR spectrum: δ_P 11.52 ppm Mass spectrum (MALDI TOF): *m*/*z* 1083.21 $[M + Na]^+$ (calculated for $C_{51}H_{82}NO_{20}NaP$ 1083.17).

(3'-*N*-Dibutoxyphosphoryl)amphotericin B (III). Yield 50%, mp 159–164°C (decomp.), R_f 0.43. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.90 d (3H, H^{39}, *J* 7.0), 0.96 t [3H, (O)P(OCH$_2$CH$_2$CH$_2$C$\underline{H}_3$)$_2$], 1.08 d (3H, H^{40}, *J* 6.5), 1.11 d (3H, H^{38}, *J* 6.5), 1.14 m (1H, $H^{14}{}_{ax}$), 1.21 d (3H, $H^{6'}$, *J* 6.0), 1.31–1.42 m (6H, H^4, H^6, H^{12}), 1.46–1.56 m (4H, H^7, H^{10}), 1.59–1.64 m [8H, (O)P[(OCH$_2$C$\underline{H}_2$C$\underline{H}_2$CH$_3$)$_2$], 1.70 m (1H, H^{18b}), 1.76 m (1H, H^{36}), 1.83 d.d (1H, H^{18a}, *J* 5.5, 16.0), 1.95 d.d (1H, $H^{14}{}_{eq}$, *J* 5.0, 12.0), 2.03 m (1H, H^{16}), 2.11 d.d (1H,

H^{2b}, *J* 3.0, 16.5), 2.18 d.d (1H, H^{2a}, *J* 9.0, 16.5), 2.25 m (2H, $H^{3'}$, H^{34}), 2.89 m (1H, $H^{4'}$), 3.03 m (1H, $H^{5'}$), 3.09 m (1H, H^{8}), 3.17 m (1H, H^{35}), 3.42 m (1H, H^{9}), 3.50 s (1H, $H^{2'}$), 3.59 m (1H, H^{5}), 4.06 m (1H, H^{15}), 3.81 and 3.94 d. q [4H, (O)P(OC$\underline{H}_2$$CH_2CH_2CH_3)_2$, *J* 10.2], 4.11 m (1H, H^{3}), 4.21 m (2H, H^{11}, H^{17}), 4.28 s (1H, $H^{1'}$), 4.38 m (1H, H^{19}), 5.23 s (1H, NH), 5.29 m (1H, H^{37}), 5.59 d.d (1H, H^{33}, *J* 9.5, 15.5), 5.73 d.d (1H, H^{29}, *J* 11.0, 34.0), 6.01 d.d (1H, H^{20}, *J* 9.0, 15.5), 6.09 d.d (1H, H^{21}, *J* 10.5, 15.5), 6.15 d.d (1H, H^{32}, *J* 10.5, 15.5), 6.20 d.d (1H, H^{27}, *J* 15.5, 28.0), 6.26 d.d (1H, H^{31}, *J* 10.5, 15.0), 6.29 d.d (1H, H^{23}, *J* 12.0, 15.0), 6.32 d.d (1H, H^{30}, *J* 11.0, 15.0), 6.34 d.d (1H, H^{25}, *J* 11.0, 14.5), 6.37 d.d (1H, H^{28}, *J* 10.5, 15.0), 6.42 d.d (1H, H^{22}, *J* 11.0, 15.0), 6.54 d.d (1H, H^{26}, *J* 11.0, 15.0), 6.68 d.d (1H, H^{24}, *J* 12.0, 14.5). ^{13}C NMR spectrum, δ_C, ppm (*J*, Hz): 12.05 (C^{39}), 17.06 (C^{38}), 17.45 d [(O)P($OCH_2CH_2CH_2\underline{C}H_3)_2$, J_{CP} 7.0], 17.84 ($C^{6'}$), 18.49 (C^{40}), 19.08 [(O)P($OCH_2CH_2\underline{C}H_2CH_3)_2$], 29.07 ($C^{7}$), 31.94 [(O)P($OCH_2\underline{C}H_2CH_2CH_3)_2$], 35.11 ($C^{6}$), 36.39 ($C^{18}$), 39.71 ($C^{10}$), 39.85 ($C^{36}$), 42.00 ($C^{2}$), 42.47 ($C^{34}$), 44.42 ($C^{4}$), 44.69 ($C^{14}$), 46.42 ($C^{12}$), 56.16 ($C^{3'}$), 58.47 ($C^{16}$), 62.73 d [(O)P(O$\underline{C}H_2CH_3)_2$, J_{CP} 5.7], 65.25 (C^{17}), 65.51 (C^{15}), 66.18 (C^{3}), 67.77 (C^{11}), 68.79 ($C^{2'}$), 69.12 (C^{37}), 69.81 (C^{5}), 70.48 ($C^{4'}$), 72.52 ($C^{5'}$), 73.55 (C^{8}), 73.90 (C^{9}), 74.19 (C^{19}), 77.08 (C^{35}), 95.62 ($C^{1'}$), 97.13 (C^{13}), 129.80 (C^{26}), 130.61 (C^{23}), 130.79 (C^{30}), 131.41 (C^{24}), 131.58 (C^{32}), 131.72 (C^{28}), 132.35 (C^{21}), 132.49 (C^{25}), 134.59 (C^{22}), 136.37 (C^{20}), 136.77 (C^{27}), 137.09 (C^{29}), 137.21 (C^{33}), 137.27 (C^{31}), 170.50 (C^{1}), 176.91 (C^{41}). ^{31}P NMR spectrum: δ_P 11.67 ppm. Mass spectrum (MALDI TOF): *m*/*z* 1139.19 $[M + Na]^+$ (calculated for $C_{55}H_{90}NO_{20}NaP$ 1139.28).

(3'-*N*-Diphenoxyphosphoryl)amphotericin B (IV). Yield 45%, mp 163–168°C (decomp.), R_f 0.39. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.92 d (3H, H^{39}, *J* 7.0), 1.08 d (3H, H^{40}, *J* 6.5), 1.10 d (3H, H^{38}, *J* 6.5), 1.14 m (1H, $H^{14}{}_{ax}$), 1.21 d (3H, $H^{6'}$, *J* 6.0), 1.20–1.40 m (6H, H^{4}, H^{6}, H^{12}), 1.44–1.54 m (4H, H^{7}, H^{10}), 1.59 m (1H, H^{18b}), 1.74 m (1H, H^{36}), 1.86 d.d (1H, H^{18a}, *J* 5.5, *J* 16.0), 1.95 d.d (1H, $H^{14}{}_{eq}$, *J* 5.0, *J* 12.0), 2.11 m (1H, H^{16}), 2.17 d.d (1H, H^{2b}, *J* 3.0, *J* 16.5), 2.24 d.d (1H, H^{2a}, *J* 9.0, *J* 16.5), 2.31 m (2H, $H^{3'}$, H^{34}), 2.91 m (1H, $H^{4'}$), 3.09 m (1H, $H^{5'}$), 3.12 m (1H, H^{8}), 3.18 m (1H, H^{35}), 3.41 m (1H, H^{9}), 3.50 s (1H, $H^{2'}$), 3.59 m (1H, H^{5}), 4.00 m (1H, H^{15}), 4.11 m (1H, H^{3}), 4.20 m (2H, H^{11}, H^{17}), 4.25 s (1H, $H^{1'}$), 4.41 m (1H, H^{19}), 5.17 s (1H, NH), 5.21 m (1H, H^{37}), 5.59 d.d (1H, H^{33}, *J* 9.5, *J* 15.5), 5.70 d.d (1H, H^{29}, *J* 11.0, *J* 34.0), 5.91 d.d (1H, H^{20}, *J* 9.0, *J* 15.5), 6.07 d.d (1H, H^{21}, *J* 10.5, *J* 15.5), 6.13 d.d (1H, H^{32}, *J* 10.5, *J* 15.5), 6.19 d.d (1H, H^{27}, *J* 15.5, *J* 28.0), 6.25 d.d (1H, H^{31}, *J* 10.5, *J* 15.0), 6.29 d.d (1H, H^{23}, *J* 12.0, *J* 15.0), 6.32 d.d (1H, H^{30}, *J* 11.0, *J* 15.0), 6.34 d.d (1H, H^{25}, *J* 11.0, *J* 14.5), 6.36 d.d (1H, H^{28}, *J* 10.5, *J* 15.0), 6.48 d.d (1H, H^{22}, *J* 11.0, *J* 15.0), 6.53 d.d (1H, H^{26}, *J* 11.0, *J* 15.0), 6.68 d.d (1H, H^{24}, *J* 12.0, *J* 14.5), 7.17–7.28 m [10H, (O)P($OC_6\underline{H}_5)_2$]. ^{13}C NMR spectrum, δ_C, ppm (*J*, Hz): 12.09 (C^{39}), 17.05 (C^{38}), 17.89 ($C^{6'}$), 18.55 (C^{40}), 29.12 (C^{7}), 35.11 (C^{6}), 36.41 (C^{18}), 39.60 (C^{10}), 39.76 (C^{36}), 41.90 (C^{2}), 42.38 (C^{34}), 44.30 (C^{4}), 44.71 (C^{14}), 46.43 (C^{12}), 56.17 ($C^{3'}$), 58.49 (C^{16}), 65.28 (C^{17}), 65.52 (C^{15}), 66.15 (C^{3}), 67.76 (C^{11}), 68.79 ($C^{2'}$), 69.14 (C^{37}), 69.71 (C^{5}), 70.59 ($C^{4'}$), 72.61 ($C^{5'}$), 73.54 (C^{8}), 73.91 (C^{9}), 74.13 (C^{19}), 77.20 (C^{35}), 95.66 ($C^{1'}$), 97.13 (C^{13}); 120.34, 121.56, 130.17, 150.29 [(O)P($OC_6H_5)_2$], 129.80 (C^{26}), 130.57 (C^{23}), 130.88 (C^{30}), 131.39 (C^{24}), 131.58 (C^{32}), 131.71 (C^{28}), 132.40 (C^{21}), 132.49 (C^{25}), 134.60 (C^{22}), 136.22 (C^{20}), 136.65 (C^{27}), 137.09 (C^{29}), 137.17 (C^{33}), 137.26 (C^{31}), 170.55 (C^{1}), 176.92 (C^{41}). ^{31}P NMR spectrum: δ_P 11.78 ppm. Mass spectrum (MALDI TOF): *m*/*z* 1179.30 $[M + Na]^+$ (calculated for $C_{59}H_{82}NO_{20}NaP$ 1179.26).

[3'-*N*-Bis(trimethylsilyl)phosphoryl]amphotericin B (V). Yield 47%, mp 140–145°C (decomp.), R_f 0.47. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.21 s {18H, (O)P[$OSi(CH_3)_3]_2$}, 0.90 d (3H, H^{39}, *J* 7.0), 1.01 d (3H, H^{40}, *J* 6.5), 1.10 d (3H, H^{38}, *J* 6.5), 1.14 m (1H, $H^{14}{}_{ax}$), 1.20 d (3H, $H^{6'}$, *J* 6.0), 1.25–1.41 m (6H, H^{4}, H^{6}, H^{12}), 1.47–1.57 m (4H, H^{7}, H^{10}), 1.62 m (1H, H^{18b}), 1.78 m (1H, H^{36}), 1.89 d.d (1H, H^{18a}, *J* 5.5, *J* 16.0), 1.95 d.d (1H, $H^{14}{}_{eq}$, *J* 5.0, *J* 12.0), 2.10 m (1H, H^{16}), 2.14 d.d (1H, H^{2b}, *J* 3.0, *J* 16.5), 2.20 d.d (1H, H^{2a}, *J* 9.0, *J* 16.5), 2.31 m (2H, $H^{3'}$, H^{34}), 2.89 m (1H, $H^{4'}$), 3.08 m (1H, $H^{5'}$), 3.12 m (1H, H^{8}), 3.17 m (1H, H^{35}), 3.42 m (1H, H^{9}), 3.50 s (1H, $H^{2'}$), 3.61 m (1H, H^{5}), 4.00 m (1H, H^{15}), 4.11 m (1H, H^{3}), 4.23 m (2H, H^{11}, H^{17}), 4.28 s (1H, $H^{1'}$), 4.39 m (1H, H^{19}), 5.19 s (1H, NH), 5.21 m (1H, H^{37}), 5.59 d.d (1H, H^{33}, *J* 9.5, *J* 15.5), 5.79 d.d (1H, H^{29}, *J* 11.0, *J* 34.0), 5.94 d.d (1H, H^{20}, *J* 9.0, *J* 15.5), 6.10 d.d (1H, H^{21}, *J* 10.5, *J* 15.5), 6.13 d.d (1H, H^{32}, *J* 10.5, *J* 15.5), 6.19 d.d (1H, H^{27}, *J* 15.5, *J* 28.0), 6.26 d.d (1H, H^{31}, *J* 10.5, *J* 15.0), 6.29 d.d (1H, H^{23}, *J* 12.0, *J* 15.0), 6.32 d.d (1H, H^{30}, *J* 11.0, *J* 15.0), 6.34 d.d (1H, H^{25}, *J* 11.0, *J* 14.5), 6.38 d.d (1H, H^{28}, *J* 10.5, *J* 15.0), 6.46 d.d (1H, H^{22}, *J* 11.0, *J* 15.0), 6.53 d.d (1H, H^{26}, *J* 11.0, *J* 15.0), 6.67 d.d (1H, H^{24}, *J* 12.0, *J* 14.5). ^{13}C NMR spectrum, δ_C, ppm (*J*, Hz): 4.83 {(O)P[$OSi(CH_3)_3]_2$}, 11.92 (C^{39}), 16.92 (C^{38}), 17.77 ($C^{6'}$), 18.50 (C^{40}), 29.08 (C^{7}), 35.02 (C^{6}),

36.38 (C^{18}), 39.60 (C^{10}), 39.75 (C^{36}), 41.99 (C^{2}), 42.46 (C^{34}), 44.30 (C^{4}), 44.61 (C^{14}), 46.47 (C^{12}), 56.19 ($C^{3'}$), 58.46 (C^{16}), 65.28 (C^{17}), 65.53 (C^{15}), 66.22 (C^{3}), 67.76 (C^{11}), 68.74 ($C^{2'}$), 69.13 (C^{37}), 69.81 (C^{5}), 70.59 ($C^{4'}$), 72.52 ($C^{5'}$), 73.41 (C^{8}), 73.89 (C^{9}), 74.10 (C^{19}), 77.19 (C^{35}), 95.62 ($C^{1'}$), 97.12 (C^{13}), 129.79 (C^{26}), 130.72 (C^{23}), 130.81 (C^{30}), 131.30 (C^{24}), 131.53 (C^{32}), 131.67 (C^{28}), 132.33 (C^{21}), 132.49 (C^{25}), 134.50 (C^{22}), 136.37 (C^{20}), 136.76 (C^{27}), 136.95 (C^{29}), 137.11 (C^{33}), 137.24 (C^{31}), 170.42 (C^{1}), 176.89 (C^{41}). ^{31}P NMR spectrum: δ_P 11.45 ppm. Mass spectrum (MALDI TOF): *m*/*z* 1143.29 $[M + Na]^+$ (calculated for $C_{53}H_{90}NO_{20}NaPSi$ 1143.34).

Biological tests. In all biological tests, Amphotericin B was used as a reference.

Acute toxicity of the studied derivatives was studied using outbred white male mice with body mass of 18–20 g. The compounds to be tested were diluted with 0.5% aqueous solution of carboxymethylcellulose, and the prepared suspension was used for intraperitoneal introduction. The LD_{50} values were calculated using the Kerber's method [79, 80].

Antifungal activity of the studied derivatives against various pathogenic fungi was determined using the serial dilution in liquid nutrient medium. The lowest fungistatic concentration was determined after visual inspection of the test-culture growth intensity in the test and the control specimens; the experiments were performed in triplicate.

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