3-Hydroxypyridine and 3-(Hydroxymethyl)pyridine in the Synthesis of Salts of Aryldithiophosphonic Acids on the Basis of Monoterpenyl Alcohols

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Abstract: 3-Hydroxypyridinium and 3-(hydroxymethyl)pyridinium O-terpenyl arylidithiophosphonates were obtained by the reactions of 3-hydroxypyridine and 3-(hydroxymethyl)pyridine with O-terpenyl arylidithiophosphonic acids on the basis of (1R,2S,5R)-(−)-menthol, (1S)-endo-(–)-borneol, racemic isoborneol, and carvacrol. The obtained salts possess high antimicrobial activity against Bacillus cereus and Candida albicans.

Keywords: 3-Hydroxypyridine, 3-(hydroxymethyl)pyridine, dithiophosphonates, antimicrobial activity.


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1. INTRODUCTION

Among the pharmacophoric pyridine derivatives, 3-hydroxypyridine was found as a natural product in Paeonia lactiflora and Salvia divinorum (1). 3-Hydroxypyridine and its derivatives possess therapeutic properties (1-3) (Figure 1). The antihypoxic effect of 3-hydroxypyridine and succinic acid derivatives was established (2). 2-Ethyl-6-methyl-3-hydroxypyridinium N-acetyl-L-glutamate has acute hypoxia and a neuroprotective effect on rats (3). The decreasing of the anxiolytic effect of mexidol as a mixture of 3-hydroxypyridine cation and succinate anion was detected (4). Mexidol (2-ethyl-6-methyl-3-hydroxypyridinium succinate) was used for the solubilization of magnetite nanoparticles in hydrophilic medium (5). 3-Hydroxypyridine and erythropoietin had positive neuroprotective effects on rats as hemorrhagic stroke models (6). As pharmacological agents for the correction of ischemic brain injury after intracerebral hemorrhage, derivatives of 3-hydroxypyridine such as 3-hydroxy-2-ethyl-6-methylpyridinium, N-acetylmethylhexanoate, 4-aminobenzoate, N-acetylmancetate, and hydroxybutanedioic acid were used on rats (7, 8). Bacterial purulent meningitis of rats caused by Streptococcus pneumoniae leads to edema of the brain, which is reduced when 2-ethyl-6-methyl-3-hydroxypyridinium 2,6-dichlorophenyl (amino)phenylethanolic acid and bis(2-ethyl-6-methyl-3-hydroxypyridinium) 2,6-dichlorophenyl (amino)phenylethanoic acid are administered to rats (9). 3-Hydroxy-2-methylpyridine, 3-hydroxy-6-methylpyridine and 3-hydroxy-2,6-dimethylpyridine abolish lysozyme fibril formation that is associated with protein-misfolding disorders, including prevalent neurodegenerative diseases (10). Thus, no antimicrobial effects of 3-hydroxypyridine were detected.
On the other hand, less attention has been paid to the antimicrobial properties of pyridinium derivatives. Among them, we have chosen phosphorus dithioacids, which have a relatively low toxicity to warm-blooded animals compared to insects (11, 12). The use of phosphorus dithioacids in the reactions with pyridine alkaloids is likely to lead to low toxicity organosulfurphosphorus derivatives possessing ionic structures and promising as antimicrobials. Thus, the antimicrobial activity of pyridinium salts of dithiophosphoric acids on the basis of 3-hydroxypyridine and 3-pyridinemethanol, as well as the corresponding 3-hydroxypyridinium bisdithiophosphonic acids, was recently established (13, 14). In the development of research on synthesis of antimicrobial pyridinium salts of phosphorus dithioacids, we turned to chiral dithiophosphonic acids on the basis of 3-hydroxypyridine and 3-pyridinemethanol, as well as the corresponding 3-hydroxypyridinium bisdithiophosphonic acids, was recently established (13, 14). In the development of research on synthesis of antimicrobial pyridinium salts of phosphorus dithioacids, we turned to chiral dithiophosphonic acids on the basis of optically active monoterpenyl alcohols as well as racemic and aryl monoterpenyl alcohols. In this article, the reactions of O-terpenyl dithiophosphonic acids with 3-hydroxypyridine and 3-(hydroxymethyl)pyridine and their antimicrobial activity are presented.

2. EXPERIMENTAL SECTION

2.1. Materials

3-Hydroxypyridine (purity 98%), 3-(hydroxymethyl)pyridine (purity 98%), (1R,2S,5R)-(-)-menthol (purity 99.5%), (1S)-endo-(-)-borneol (purity 97%), racemic isoborneol (purity 95%), carvacrol (purity 99%), Lawesson’s reagent (purity 97%), and tetraphosphorus decasulfide (purity 99%) were purchased from Sigma-Aldrich Co. (St. Louis, MO, USA). 2,6-Di-tert-butylphenol (purity 99%) was purchased from Acros Organics (New Jersey, USA). The organic solvents were dried prior to use. Test cultures of pathogenic and opportunistic microflora of museum strains of Bacillus cereus (ATCC 19637), Staphylococcus aureus (ATCC 29213) and Candida albicans (ATCC 885-653) were used from the Department of Microbiology of Kazan State Medical Academy.

2.2. Instrumentation

Fourier transform IR spectra were taken on a Bruker Tensor 27 infrared spectrophotometer (Bruker BioSpin AG, Fällanden, Switzerland) (400–4000 cm⁻¹) in liquid film or KBr pellet (δ = the deformation vibration, s – symmetric and as – asymmetric vibrations, gem – geminal, vst = very strong, st = strong, w = weak, v = very weak, m = medium, vbr = very broad, br = broad vibrations). The ¹H NMR spectra were obtained on a Bruker Avance-400 (400 MHz) (Bruker BioSpin AG, Fallanden, Switzerland) (400 MHz) or a Bruker Avance-600 (600 MHz) (Bruker BioSpin AG, Fallanden, Switzerland) in CD₃OD–CCl₄ (1:1). The ¹³C (¹H) and ¹⁵N (¹H) NMR spectra were recorded on a Bruker Avance-400 (Bruker BioSpin AG, Fallanden, Switzerland) (100.6 MHz) at ambient temperature (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet). Chemical shifts (δ) are measured relative to the residual resonance of solvents and given in parts per million (ppm). The ³¹P NMR spectra were run on a Bruker Avance-400 (Bruker BioSpin AG, Fallanden, Switzerland).
(161.98 MHz) with 85% H₃PO₄ as an external reference. The observed optical rotations were detected on a Perkin-Elmer 341 polarimeter at 20 °C (Norwalk, CT, USA) (D-line of sodium, 589 nm, a pathlength of 5.52 cm, concentration of 1%) and presented as specific rotations [α]D20. The determination of the carbon, hydrogen, nitrogen, and sulfur compositions was carried out on a EuroEA3000 CHNS-O Analyzer (EuroVector S.p.A., Milan, Italy). Phosphorus content was measured by thepyrrols method on a non-serial instrument.

2.3. Synthesis

2.3.1. Preparation of initial arylidiphosphonic acids 1a-d

O-(1R,2S,5R)-(−)-2-Isopropyl-5-methylcyclohex-1-yl 3,5-di-tert-butyldiphenylidiphosphonic acid (1d) was prepared by the reaction of 2,4-bis(3,5-di-tert-butyldiphenyl) 1,3,2,4-dithiodiphenosphate-2,4-disulfide with (1R,2S,5R)-(−)-menthol in the molar ratio 1:2 in chloroform at 50 °C for 1 h according to the literature method (15). [α]D19 = −33.2 (c = 1.00, C6H12). 31P{1H} NMR (161.98 MHz, CHCl₃, δ, ppm): 86.1. 2,4-Bis(3,5-di-tert-butyldiphenyl) 1,3,2,4-dithiodiphenosphate-2,4-disulfide was prepared by the reaction of tetraphosphorus decasulfide with 2,6-di-tert-butylenol according to the literary method (16).

O-(1R,2S,5R)-(−)-2-Isopropyl-5-methylcyclohex-1-yl 4-metoxypentylidiphosphonic acid (1a) was obtained similarly by the reaction of Lawesson’s reagent with (1R,2S,5R)-(−)-menthol in benzene at 50 °C for 2 h according to the literary method (15). [α]D19 = −44.5 (c = 1.00, C6H12). 31P{1H} NMR (161.98 MHz, C6H6, δ, ppm): 83.6.

O-endo-(1S)-(−)-Trimethylbicyclo[2.2.1]hept-2-yl 4-metoxypentylidiphosphonic acid (1b) was obtained similarly by the reaction of Lawesson’s reagent with (1S)-endo-(−)-borneol in benzene at 50 °C for 3 h according to the literary method (17). [α]D19 = −25.4 (c = 0.99, C6H12). 31P{1H} NMR (161.98 MHz, C6H6, δ, ppm): 84.7.

O-(R,S)-(±)-Trimethylbicyclo[2.2.1]hept-2-yl 4-metoxypentylidiphosphonic acid (1c) was obtained similarly by the reaction of Lawesson’s reagent with racemic borneol in benzene at 50 °C for 3.5 h. 31P{1H} NMR (161.98 MHz, C6H6, δ, ppm): 84.3.

O-2-Isopropyl-5-methylcyclohex-6-yl-phenyl 4-metoxypentylidiphosphonic acid (1e) was obtained similarly by the reaction of Lawesson’s reagent with carvacrol in benzene at 50 °C for 5 h according to the literary method as likely thymol (18). 31P{1H} NMR (161.98 MHz, C6DCl₃, δ, ppm): 85.3.

2.3.2. Synthesis of 3-hydroxyxypyrindinum arylidiphosphonates 3a-d and 3-(hydroxymethyl)pyridinium arylidiphosphonates 4a-c

3-Hydroxyxypyrindinum O-(1R,2S,5R)-(−)-2-isopropyl-5-methylcyclohex-1-yl 4-metoxypentylidiphosphonate (3a)

3-Hydroxyxypyrindine 2 (0.1 g, 1.1 mmol) was added portionwise under dry argon with stirring at 20 °C to the solution of acid 1a (0.4 g, 1.1 mmol) in anhydrous ethanol (10 mL). The mixture was stirred at 20 °C for 2 h, stored at 20 °C for 12 h, evaporated at reduced pressure (0.5 mm Hg) at 40 °C for 1 h, and then in vacuum (0.02 mm Hg) for 1 h to give 3a (0.5 g, 80%) as a colorless semisolid that was isolated as crystalline solid when washed with acetone, [α]D19 = −29.5 (c = 1.00, EtOH).

31P{1H} NMR (161.98 MHz, EtOH, δ, ppm): 108.7. Microelemental analysis: found C 58.56; H 7.03; N 2.76; P 6.64; S 14.43 %. C22H30NO3PS2, calcd. C 58.25; H 7.11; N 3.09; P 6.83; S 14.14 %. Salts 3b-d and 4a-c were obtained similarly as semisolids and then isolated as crystalline solids when washed with acetone. These salts melt below 30–40 °C.

3-Hydroxyxypyrindinum O-endo-(1S)-(−)-trimethylbicyclo[2.2.1]hept-2-yl 4-metoxypentylidiphosphonate (3b): yield 76 %, [α]D19 = −13.5 (c = 1.00, EtOH). 31P{1H} NMR (161.98 MHz, EtOH, δ, ppm): 105.6. Microelemental analysis: found C 58.51; H 6.70; N 3.10; P 6.86; S 14.20 %. C22H30NO3PS2, calcd. C 58.51; H 6.70; N 3.10; P 6.86; S 14.20 %.

3-Hydroxyxypyrindinum O-(R,S)-(±)-trimethylbicyclo[2.2.1]hept-2-yl 4-metoxypentylidiphosphonate (3c): yield 88%, 31P{1H} NMR (161.98 MHz, EtOH, δ, ppm): 104.7 and 106.8 (1:0.14). Microelemental analysis: found C 58.45; H 6.43; N 3.05; P 6.73; S 14.56 %. C22H30NO3PS2, calcd. C 58.51; H 6.70; N 3.10; P 6.86; S 14.20 %.

3-Hydroxyxypyrindinum O-(1R,2S,5R)-(−)-2-isopropyl-5-methylcyclohex-1-yl 3,5-di-tert-butyldiphenylidiphosphonate (3d): yield 80%, 31P{1H} NMR (161.98 MHz, EtOH, δ, ppm): 109.1. Microelemental analysis: found C 63.34; H 8.22; N 2.43; P 5.34; S 11.89 %. C22H30NO3PS2, calcd. C 63.12; H 8.40; N 2.54; P 5.61; S 11.62 %.

3-(Hydroxymethyl)pyridinium O-(1R,2S,5R)-(−)-2-isopropyl-5-methylcyclohex-1-yl 4-metoxypentylidiphosphonate (4a): yield 92%, 31P{1H} NMR (161.98 MHz, EtOH, δ, ppm): 103.8. Microelemental analysis: found C 59.34; H 7.01; N 2.79; P 6.32; S 13.98 %. C22H30NO3PS2, calcd. C 59.07; H 7.33; N 3.00; P 6.62; S 13.71 %.

3-(Hydroxymethyl)pyridinium O-(R,S)-(±)-trimethylbicyclo[2.2.1]hept-2-yl 4-metoxypentylidiphosphonate (4b): yield 85%, 31P{1H} NMR (161.98 MHz, EtOH, δ, ppm): 104.6 and 106.8 (7.3:2). Microelemental analysis: found C 59.12; H 6.78; N 3.32; P 6.39; S 13.94 %. C22H30NO3PS2, calcd. C 59.33; H 6.93; N 3.01; P 6.65; S 13.77 %.
3-(Hydroxymethyl)pyridinium O-2-isopropyl-5-methylcyclohex-6-yl-phenyl 4-metoxyphenylidithiophosphonate (4c): yield 96%, \( ^{31}\text{P} (\text{H}) \) NMR (161.98 MHz, EtOH, \( \delta \)) ppm: 106.8. Microelemental analysis: found C 59.64; H 6.19; N 3.28; P 6.43; S 14.16 %. \( C_{28}H_{30}NO_3PS_2 \), calc. C 59.85; H 6.11; N 3.03; P 6.71; S 13.89 %.

2.4. Bioactivity Tests

24 h cultures of bacteria and fungi were washed with physiological solution from beef nutrient agar and standardized according to the turbidity standard up to 0.5 by McFarland (1.5 \times 108 CFU mL\(^{-1}\)). Bacterial and fungal cultures (0.4 mL) were added to melted and then cooled (at 45 °C) Mueller-Hinton agar (10 mL). The mixture was stirred, poured on sterile Petri dishes (90 mm), and allowed to solidify. Agar plates were punched with a sterile borer with a 6 mm diameter, and holes were filled with the test compounds. Petri dishes were incubated at 35 °C for 24–48 h in an incubator. After the incubation period, the diameter of the growth inhibition zones was measured with an accuracy of 0.1 mm.

3. RESULTS AND DISCUSSION

3.1. Synthesis and characterization of 3-hydroxypyridinium aryldithiophosphonates

Thus, ethanol appears to be the most suitable organic solvent and promotes the formation of ionic compounds 3a-d. In contrast to this, in nonpolar organic solvents, e.g., benzene, these reactions practically do not occur. Salts 3a-d formed as colorless or yellow semisolids purified by recrystallization from acetone. Compounds 3a, 3b, and 3d on the basis of \((1R,2S,5R)-(\text{−})\)-menthol and \((1S)-(\text{−})\)-borneol possess optical activity (see Experimental). In contrast, 3c obtained from racemic borneol as well as 4c obtained on the basis of carvacrol are optically inactive.

In general, aryldithiophosphonlic acids possess a strong P-C bond and a prochiral tetracoordinated phosphorus atom. The presence of asymmetric carbon atoms in O-terpenyl substituents at the phosphorus atom in the aryldithiophosphonic acids can serve as the basis for the creation of new selective antimicrobial drugs. 3-Hydroxypyridine as well as other pyridine derivatives have an unshared electron pair and exhibit basic properties in reactions with strong acids to form pyridinium salts (19). As rather strong organic acids, O-terpenyl aryldithiophosphonic acids can be used in reactions with 3-hydroxy pyridine. For these reactions, it was necessary to find a suitable organic solvent. 3-Hydroxypyridine is known to exist in a tautomeric equilibrium between the enol and zwitterion forms in neutral aqueous solution (16). The protonated form at the nitrogen atom of 3-hydroxy pyridine cannot accept a proton from the sulfhydryl group of the aryldithiophosphonic acids. Ethanol, as a protic polar organic solvent, seems to shift equilibrium towards the hydroxy form of 3-hydroxy pyridine. That is why we have managed to carry out the reactions of chiral O-terpenyl aryldithiophosphonic acids 1a-d with 3-hydroxy pyridine 2a in ethanol under mild conditions (20 °C, 1–2 h) to give 3-hydroxypyridinium dithiophosphonates 3a-d in 76-88% yields (Scheme 1).

The \(^{31}\text{P} (\text{H}) \) NMR spectra of 3a-d in ethanol reveal signals in the range of \( \delta = 104–109 \) ppm like those of other salts of phosphorus dithioacids (20). These resonances are shifted toward low field in comparison with the \(^{31}\text{P} (\text{H}) \) data of the initial acids 1a-d (\( \delta = 83–86 \) ppm in benzene or chloroform). It is noteworthy that, as a mixture of isomers, 3c reveals two signals at \( \delta = 104.7 \) and 106.8 ppm in the ratio 1:0.14 in the \(^{31}\text{P} (\text{H}) \) NMR spectrum in ethanol. In the FTIR spectra of 3a-d, a medium broad band in the range of \( \nu = 3279–3632 \) cm\(^{-1}\) is attributed to the O-H stretching vibrations of 3-hydroxypyridinium cation, similarly to monograph

![Scheme 1: Synthesis of 3-hydroxypyridinium aryldithiophosphonates 3a-d.](image-url)
(18). The FTIR spectra of 3a-d confirmed the absence of the bands in the range of ν = 2400–2550 cm⁻¹ of the stretching vibrations of the S–H bonds attributed to acids 1a-b (21). The ¹H NMR spectrum of 3b in CD₂OD–CCl₄ solution (1:1) exhibits a doublet at δ = 0.82 ppm ( JHH = 7.0 Hz) due to the methyl protons of the fragment C₃H₃CH of O-methyl substituent. A doublet at δ = 8.21 ppm ( JHH = 4.0 Hz) and a singlet at δ = 8.27 ppm are assigned to the aromatic protons of the fragments C₃H and C₄H respectively, of the cation. In the ¹³C{¹H} NMR spectra in CD₂OD–CCl₄ solution (1:1), 3b and 3c are characterized by a singlet in the low field region (154–155 ppm), that is attributed to the carbon atom of the C₃-OH group of cation. The proton of the C₄-OH fragment of racemic 3c resonates as two singlets at 154.8 and 154.9 ppm. Thus, the aromatic hydroxyl group of 3-hydroxypridine is not involved in reactions with aryldithiophosphonic acids. The reactions proceed with the protonation of the pyridine nitrogen atom by the action of dithiophosphonic acids.

3.2. Synthesis and characterization of 3-(hydroxymethyl)pyridinium aryldithiophosphonates

In continuation of a study of the reactivity of the pyridine derivatives towards phosphorus dithioacids, we have tried to extend the salt formation reactions to 3-(hydroxymethyl)pyridine. It should be emphasized that 3-(hydroxymethyl)pyridine contains a more active aliphatic hydroxyl group compared to the aromatic O-H bond of 3-hydroxypridine. It could be expected that 3-(hydroxymethyl)pyridine would react with aryldithiophosphonic acids with the participation of the O–H bond under severe conditions, which would lead to S-ester aryldithiophosphonates. However, under mild conditions (20 °C, 1–2 h), the reaction of acids 1a,c,e with 3-(hydroxymethyl)pyridine 2b has been found to brought about the formation of 3-(hydroxymethyl)pyridinium aryldithiophosphonates 4a-c in 85–96% yields (Scheme 2).

![Scheme 2: Synthesis of 3-(hydroxymethyl)pyridinium aryldithiophosphonates 4a-c.](image)

The ³²P{¹H} NMR spectral signals of 4a-c with 3-(hydroxymethyl)pyridinium cation (δ = 104–109 ppm in ethanol) show no significant change compared to 3a-d. In the case of racemic isoborneol derivative 4b, its ³²P{¹H} NMR spectrum exhibits two singlets at δ = 104.6 and 106.8 ppm in the ratio 7:3:2 that is assigned to the formation of the mixture of isomers. The FTIR spectra of the hydroxymethyl containing salts 4a-c reveal a strong broad band in the range of ν = 3313–3329 cm⁻¹ due to the stretching vibrations of the O–H bond of the cation. In the ¹H NMR spectrum of 4a in CD₂OD–CCl₄ (1:1), the methylene protons of the C₃H₃OH fragment of 3-(hydroxymethyl)pyridinium cation appear as a singlet at δ = 4.77 ppm. Similar singlets are also observed in the ¹H NMR spectra of 4b and 4c in CD₂OD–CCl₄ (1:1) (δ = 4.59 ppm for 4b and 4.78 ppm for 4c). In the ¹³C NMR spectrum of 4a in CD₂OD–CCl₄ (1:1), the carbon atom of the C₃H₃OH fragment of cation resonates as a triplet at δ = 60.5 ppm ( JCH = 143.4 Hz), whereas in the ¹³C{¹H} NMR spectrum the same carbon atom appears as a singlet. Thus, under mild conditions, 3-(hydroxymethyl)pyridine reacts with aryldithiophosphonic acids with an increase in the coordination number of the pyridine nitrogen atom and the formation of 3-(hydroxymethyl)pyridinium aryldithiophosphonates.

3.3. Biological evaluation

Bacteria and fungi cause significant damage by affecting food and feed, causing various diseases in humans and animals (22, 23). So, the creation of new bactericidal and fungicidal drugs is an urgent problem. To develop the scientific basis for novel selective antimicrobials, the synthesized pyridinium salts 3a-d and 4a-c were screened for bactericidal and fungicidal activities against Bacillus cereus (ATCC 19637), Staphylococcus aureus (ATCC 29213), and Candida albicans (ATCC 885-653) (Table 1) using gel diffusion test on
Mueller-Hinton agar in 1% solutions of test compounds in dimethyl sulfoxide (DMSO). Antibiotic cefazolin (1% in DMSO) and fungicide triticonazole (1% in DMSO) were used as controls.

<table>
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<th>Compound</th>
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<th>C. albicans</th>
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<tr>
<td>3a</td>
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<td>3b</td>
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<td>3c</td>
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<tr>
<td>Triticonazole</td>
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aInhibition zone in mm in DMSO
b1% in DMSO

Salts 3c and 4b containing a racemic O-isoborneolyl substituent show the most bactericidal activity against B. cereus (growth inhibition zone of 29–27 mm) as compared to cefazolin (25 mm). Salt 4c bearing a pharmacophoric O-aryl substituent (on the basis of carvacrol) exhibits remarkable antifungal activity toward the tested C. albicans (20 mm) and approaches triticonazole (22 mm). Thus, substituted pyridinium salts of dithiophosphonic acids prepared from racemic monoterpenyl alcohols possess more antifungal activity as compared to salts on the basis of enantiomerically pure monoterpenyl alcohols.

4. CONCLUSION

The synthesis of 3-hydroxy pyridinium and 3-(hydroxymethyl) pyridinium O-terpenyl aryl dithiophosphonates has been successfully carried out. These salts were obtained by reacting O-terpenyl aryl dithiophosphonic acids with 3-hydroxy pyridine and 3-(hydroxymethyl) pyridine under mild conditions. Ethanol is the best organic solvent for these reactions and promotes the formation of ionic products. Pyridinium aryl dithiophosphonates on the basis of (1R,2S,5S)-(-)-menthol and (15)-endo-(−)-borneol possess optical activity. The reactions proceed with the protonation of the pyridine nitrogen atom by the action of dithiophosphonic acids. The synthesized salts have been tested for their antimicrobial activity. 3-Hydroxy pyridinium and 3-(hydroxymethyl) pyridinium aryl dithiophosphonates containing a racemic O-isoborneolyl substituent show the most bactericidal activity against Bacillus cereus. 3-(Hydroxymethyl)pyridinium aryl dithiophosphate bearing O-carvacrolyl substituent exhibits remarkable antifungal activity toward Candida albicans. The obtained results seem promising for carrying out the next steps in the antimicrobial activity study.

5. CONFLICT OF INTEREST

The authors declare no conflicts of interest.

6. ACKNOWLEDGMENTS

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