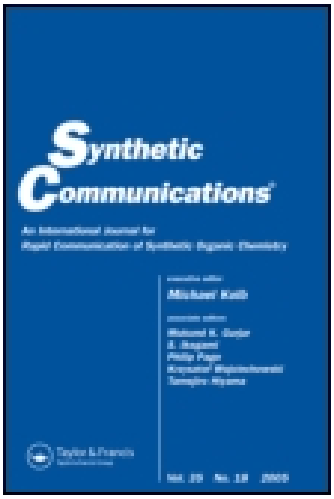

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SYNTHESIS AND BIOACTIVITY OF BENZOTHIAZAPHOSPHEPINES AND RELEVANT PHOSPHONATES AS ANTIOXIDANT/ANTIDIABETIC AGENTS

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GRAPHICAL ABSTRACT

Abstract *An efficient approach to a new series of benzothiazaphosphepines and their derived phosphonates in good yields (64–75%) was reported. The strategy relied on the reactions of the easily available 2-arylmethylene-aminobenzenethiols with different types of Wadsworth–Horner–Emmons (WHE) reagents in dimethylformamide (DMF)/lithium hydride (LiH) solution. All new compounds were bioscreened and showed, in vitro, moderate to good antioxidant and antidiabetic activities.*

Keywords Antioxidants/antidiabetics; *N,S,P*-heterocycles; phosphonates; phosphonyl carbanions; Schiff bases

INTRODUCTION

Phosphorus compounds play important roles in all living organisms, and there are many reports on the preparation and biochemistry of such compounds.[1,2] Phosphorus heterocyclic systems in particular continues to be some of most active areas; the introduction of the phosphor moiety into *N*- and/or *S*-heterocycles has attracted much attention in recent years because this system of heterocycles usually enhances the biological and pharmacological activities.[3–6]

In view of these observations, a series of *N,S,P*-heterocyclic systems, thiazaphosphepines, and relevant phosphonates were herein synthesized. The methodology

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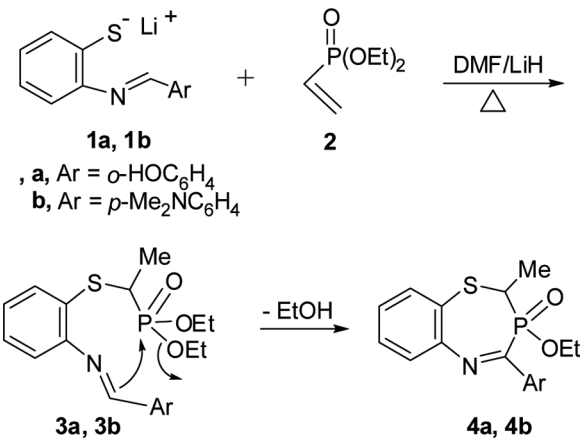
relied on addition–cyclization reactions of different types of Wadsworth–Horner–Emmons (WHE) reagents to α,β-bifunctional systems: arylideneaminothiophenols. Bioscreening of antioxidant and the antidiabetic properties of the products was also reported. This investigation is a continuation of our research program[7–10] for the application of phosphorus reagents to different systems of Schiff bases. Many of the synthesized materials showed significant analgesic/anti-inflammatory properties; particularly remarkable is their anticancer activity.[7–10]

RESULTS AND DISCUSSION

The substrates 2-[(2-mercaptophenyl)imino]methyl]phenol (**1a**) and 2-(4-(dimethylamino)-benzylideneamino)benzenethiol (**1b**) were synthesized according to the reported methods via the condensation of *o*-aminothiophenol with the proper aldehyde in ethanol.[11,12] Schiff bases **1a** or **1b** were added to 1.3 molar equiv of diethyl vinylphosphonate (**2**) in dimethylformamide (DMF) solution containing 3 molar equiv of LiH. Further heating of the reaction mixture under reflux for the proper time afforded 4-aryl-3-ethoxy-2-methyl-3-oxido-2,3-dihydro-1,5,3-benzothiaza-phosphepines **4a** or **4b** in ≈73% yield. Structure **4** was verified from the analytical and the spectroscopic data. Thiazaphosphepines **4a** and **4b** showed the lack of SH moiety in the infrared (IR) and ^{1}H NMR spectra, confirming the involvement of this moiety in the cycloaddition reaction. Bands for C=N, P=O, and P-O-C groups appeared in the IR spectra at ≈1574, 1241, 1078 cm^{-1}, whereas ^{1}H and ^{13}C NMR spectra confirmed the presence of [–HC–Me and EtOP] functionalities. The molecular weights (MS) and the relevant fragments were also in accordance with the assigned structure (see experimental section). The ^{31}P NMR spectra showed one singlet signal for each at upfield δp = 14.2 and 14.8 ppm for **4a** and **4b**, which is within the range expected for thiazaphosphenine-2--oxides.[13,14]



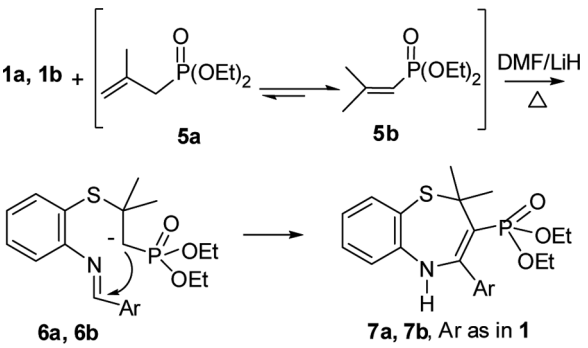
Scheme 1. Preparation of thiazaphosphepine-3-oxides **4a** and **4b**.

Compounds **4** may be formed via an initial [2 + 2] addition of **2** to **1** to give the intermediate **3**, which underwent intramolecular cyclization to give the target compounds **4**, under partial collapse of the phosphonate moiety, and extrusion of ethyl alcohol molecule as depicted in Scheme 1. The latter step was previously reported in similar occasions.[13,15]

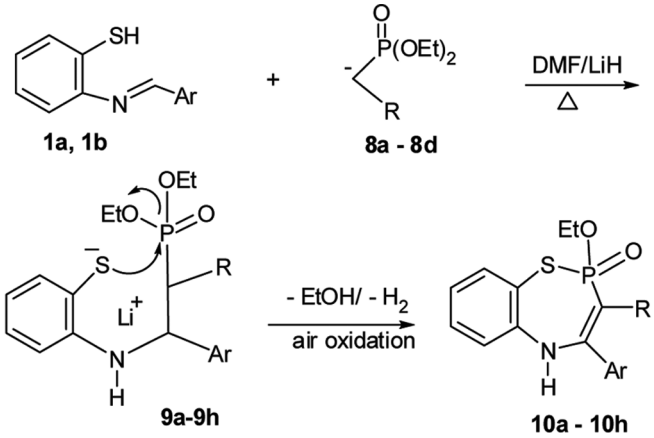
In a systematic study, diethyl 4-aryl-2,2-dimethyl-2,5-dihydro-benzo[b][1,4]-thiazepin-3-yl-phosphonates **7a, 7b** (≈66%) were isolated from the reactions of the imines **1a** and **1b** with diethyl 2-methallylphosphonate **5** (Scheme 2). We assumed the initial formation of the vinyl phosphonate **5b** via the rearrangement **5a** to **5b**. Addition of **5b** to **1a** and **1b** afforded intermediates **6a** and **6b**, followed by intramolecular cyclization, giving rise to the phosphonates **7a** and **7b,** as described in the previous reaction.

Chemical structure of **7** ($\delta_P \approx 27$ ppm) was delineated from the elemental analysis and spectral data (IR, ^{1}H, ^{13}C, ^{31}P NMR, and MS). The distinguishing features of ^{13}C NMR of **7** were the presence of signals around $\delta \approx 110$ (d, $^1J_{p\text{-}c} \approx$ 82 Hz, *C*-P), ≈47 (d, $^2J_{p\text{-}c} \approx 16$ Hz, *C*-Me$_2$), and ≈154 (d, $^2J_{p\text{-}c} \approx 32$ Hz, *C*-4) ppm. The magnitudes of the phosphorus coupling with *C*-2, *C*-3, and *C*-4 were in accord with the suggested structures. The mass spectrum of compound **7a** recorded the molecular ion peak at $m/z = 418$ (17%) [M$^+$– 1], and the base peak was displayed at 234 (100).

Next, another series of seven-membered phosphorus heterocycles, benzothiazaphosphepine derivatives **10a**–**10h,** were obtained in ≈70% yield, by applying the saturated WHE reagents **8a**–**8d** to the Schiff bases **1a/1b** in dimethylformamide (DMF)/LiH solution (Scheme 3). Obviously, compounds **10a**–**10h** formed through the intermediates **9a**–**9h** initially formed via the nucleophilic attack of the phosphonyl carbanions on the imino-C in **1**. Further intramolecular cyclization and auto-oxidation resulted in the formation of **10** in tandem loss of ethanol and hydrogen molecules. The latter step was promoted by the thermal energy, the alkaline medium, and the aromatization of the final products.[15] Furthermore, the process of homo-oxidation was previously observed in similar occasions.[15,16] New compounds were clearly verified by studying their elemental analyses and spectral data (IR; ^{1}H, ^{13}C, and ^{31}P NMR; and MS).



Scheme 2. Preparation of benzothiazapinephosphonates **7a** and **7b**.



Compd.	Ar	R	Compd.	Ar	R
10a	*o*-HOC_6H_4	CO_2Me	**10e**	*p*-$(Me)_2NC_6H_4$	CO_2Me
10b	*o*-HOC_6H_4	CO_2Et	**10f**	*p*-$(Me)_2NC_6H_4$	CO_2Et
10c	*o*-HOC_6H_4	SMe	**10g**	*p*-$(Me)_2NC_6H_4$	SMe
10d	*o*-HOC_6H_4	$C(S)NH_2$	**10h**	*p*-$(Me)_2NC_6H_4$	$C(S)NH_2$

Scheme 3. Preparation of thiazaphosphepine-2-oxides **10a**–**10h**.

PHARMACOLOGY

Antioxidant Activity

Organophosphorus compounds[17,18] and *P*-heterocycles in particular[18] have been recognized as antioxidant drugs. Furthermore, their mechanism of action and the structure–activity relationships (SAR) were extensively studied.[18,19] Therefore, the antioxidant activity of the new synthesized benzothiazaphosphepines **4a, 4b, 10a**–**10h** and relevant phosphonates **7a** and **7b** were in vitro evaluated using lipid peroxidation (LPO) by two methods: 2,2′-azobis-(2-amidino-propane)dihydrochloride (AAPH), and 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS). The activity expresses their ability to inhibit LPO in rat's brain homogenate and the rate of erythrocyte hemolysis. Pro-oxidant activities of the formed compounds were also assayed for their effect on bleomycin-induced DNA damage. Vitamin C (**Y**) was used as a positive standard for the antioxidant activity in all experiments. The results of antioxidant assay by erythrocyte hemolysis ($1 - A/B \times 100$), antioxidant assay by ABST method [Abs (control) – Abs (test)/Abs (control) $\times$ 100], and the assay for protection of bleomycin/DNA damage were presented in Tables 1–3 in the Supplementary Material.

The data presented in Tables 1–3 showed that all new synthesized compounds showed good to moderate antioxidative activity. Nevertheless, *N,S,P*- heterocycles **4a, 4b,** and **10a**–**10h** exhibited good radical scavenging ability (96. 65%) as compared to standard ascorbic acid (95.16%), whereas compounds **7a** and **7b** displayed moderate radical scavenging activity (~60%). However, the starting compound **1b** showed minimum activity (26.6%). Furthermore, it is obvious that compounds **4a, 4b,** and **10a**–**10h** have greater antioxidative activity in the lipid per-oxidation assay

and inhibitory effect in the hemolysis assay than thiazapinephosphonates **7a** and **7b**. On the other hand, **7a, 7b**, and **10d** and **10h**, indicated better protection for DNA from the damage induced by bleomycin. Furthermore, other phosphepines **10a, 10b, 10c**, and **10e**–**10g** exhibited moderate protective activity.

Antidiabetic Evaluation

Diabetes mellitus II is a metabolic disorder characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion or insulin action, or both.[20,21] Heterocyclic phosphor esters are known to serve as both hyperglycemic and hypoglycemic agents in different concentrations.[22,23] In addition, earlier literature on the effect of organophosphorus compounds (OPC) on carbohydrate metabolism showed an increase in blood glucose and decrease in glycogen in various constituents of brain rats after treatment with malathion.[22] Nevertheless, glycogen levels were decreased in rat liver when treated with dichlorovos.[23] Several drugs such as biguanides, sulfonylureas (glibenclamide), and others are presently available to reduce hyperglycemia in diabetes mellitus. Despite their widespread use, none of the presently available agents is ideal; each has its shortcomings,[24] and therefore search for a new class of compounds is essential to overcome these problems. The antidiabetic activity of cyclic *P*-heterocycles **4a, 4b,** and **10a**–**10h**, phosphonates **7a** and **7b**, glibenclamide (**Z**, standard) and also the substrate **1b** has been studied at the same dose (50 mg/kg), and the results of blood glucose levels of diabetic rats treated with thiaphosphepines **4a, 4b,** and **10a**–**10h,** phosphonates **7a** and **7b**, substrate **1b,** and **Z** (glibenclamide) are displayed in Table 4 in the Supplemental Material.

Other than the substrate **1b**, all tested compounds **4a, 4b, 7a, 7b**, and **10a**–**10h** showed hypoglycemia effect that can decrease the blood glucose levels in diabetic rats. The screening showed that after 7 days, supplementation of EtOH solutions of the tested compounds resulted in a significant diminution of fasting blood glucose level in respect to diabetic rat, but no significant alteration of fasting blood glucose level to the control, which further strengthens the antidiabetogenic action of these compounds. Fasting blood glucose level of all animals before treatment was within the normal range (Table 4). Fasting blood glucose level was significantly elevated after 24 h of streptozotocin injection in respect to the control level. From the observed data it has been noticed that the tested compounds reflect moderate or no activity at all on decreasing the blood glucose levels in diabetic rats in relative to the control data (520.26) and comparable to the positive reference (140.74). However, few compounds (**10g** and **10h**) showed good antidiabetic potency (~145) compared to the positive control glibenclamide.

EXPERIMENTAL

Melting points were determined with an open capillary tube on an Electrothermal (variable heater) melting-point apparatus. Later, the thermometer was calibrated by using standard compounds of known mps and the melting points of the new compounds were corrected exclusively. IR spectra were recorded on a Jasco FT-IR 6100 using KBr the bromide disc. NMR spectra were measured using Jeol

E.C.A. 500-MHz (^{1}H: 500.7 MHz,^{13}C: 125.4 MHz, ^{31}P: 200.7 MHz) spectrometer. The mass spectra were performed at 70 eV on an MS-50 Kratos (A.E.I.) spectrometer provided with a data system. Elemental analysis of the products was carried out at the Microanalysis Laboratory, Cairo University, Cairo, Egypt, using an elemental C, H, N analyzer (Vario EL II I, Germany). The purity of all new samples was verified by microchemical analysis (C/H/N/P/S) and spectroscopy. Thin-layer chromatography (TLC) used Merck 0.2-mm silica-gel 60 F254 analytic aluminum plates.

Synthesis

The substrates 2-[(2-mercaptophenyl)imino]methyl]phenol (**1a**) and 2-(4-(dimethylamino) benzylideneamino)benzenethiol (**1b**) were synthesized according to the reported methods from the condensation of *o*-aminothiophenol with the proper aldehyde in ethanol.[11,12]

Reaction of 1a and 1b with Wadsworth–Horner–Emmons (WHE) reagents 2, 5, and 8a–8d: Synthesis of 4a, 4b, 7a, 7b, and 10a–10h. A solution of dry DMF (20 mL) containing 3.9 mmol of LiH and 1.3 mmol of diethyl vinylphosphonate (**2**), diethyl 2-methallyl-phosphonate (**5**), methyl diethyl phosphonoacetate (**8a**), triethyl phosphonoacetate (**8b**), diethyl methylthiomethyl- (**8c**), or diethyl 2-amino-2-thioxoethyl-phosphonate (**8d**) was treated, under stirring, with 1 mmol of **1a** or **1b** in DMF (15 mL) in one portion at rt. The suspension was further heated under reflux for the proper time (18–25 h, TLC). The reaction mixture was poured into distilled water (100 mL), acidified with HCl (1*N*), and extracted with AcOEt. The organic phase was washed and dried over anhydrous sodium sulfate, followed by removal of the solvents under reduced pressure. The resulting residue was collected and crystallized from the proper solvent to give the benzothiazaphosphepines **4a, 4b, 10a**–**10h** or the phosphonates **7a** and **7b**.

4-(3-Ethoxy-2-methyl-3-oxido-2,3-dihydro-1,5,3-benzothiazaphosphepin-4-yl)phenol (4a). Compound **4a** was obtained as yellow crystals (0.25 g, 72%); mp 138 °C (EtOH); ν_{max}/cm^{-1} 3417, 1574, 1241, 1078; δ_H (500.7 MHz, $CDCl_3$) 1.17 (dt, $J_{H\text{-}H} = 6.6$ Hz, $^4J_{P\text{-}H} = 4.6$ Hz, 3H, *Me*CO), 1.29 (dd, $J_{HH} = 8.7$ Hz, $J_{P\text{-}H} = 8.9$ Hz, 3H, *Me*), 4.19 (dq, $J_{H\text{-}H} = 6.6$ Hz, $^3J_{P\text{-}H} = 5.7$ Hz, 2H, H_2C), 5.05 (dq, $J_{H\text{-}H} = 8.7$ Hz, $^2J_{P\text{-}H} = 14.7$ Hz, 1H, *H*C), 7.02-7.96 (m, 8H, *H*-Ar) 12.5 (s, 1H, *H*O); δ_C (125.4 MHz, $CDCl_3$) 191.4 (d, $J_{P\text{-}C} = 78.5$ Hz, *C*-4), 160.9, 152.2, 134.8, 133.2, 129.7, 127.0, 126.3, 126.0, 125.2, 121.7, 117.9, 112.0 (*C*-Ar), 62.4 (d, $^2J_{P\text{-}C} = 10.5$ Hz, CH_2OP), 32.4 (d, $^1J_{P\text{-}C} = 68.8$ Hz, *C*HMe), 16.7 (d, $^3J_{P\text{-}C} = 6.9$ Hz, *Me*COP), 15.7 (d, $^2J_{P\text{-}C} = 11.8$ Hz, C-2-*Me*); δ_P (200.7 MHz, $CDCl_3$) δ_P 14.2; *m*/*z* (%) 346 (11) [M^+– 1], 238 (100). Anal. calcd. for $C_{17}H_{18}NO_3PS$ (347.3): C, 58.78; H, 5.22; N, 4.03; P, 8.92; S, 9.23. Found: C, 58.86; H, 5.13; N, 3.98; P, 8.98; S, 9.38.

Methyl 2-ethoxy-4-(4-hydroxyphenyl)-2,5-dihydro-1,5,2-benzothiazaphosphepine-3-carboxylate 2-oxide (10a). Compound **10a** was obtained as yellow crystals (0.27 g, 69%); mp 150 °C (CH_2Cl_2); ν_{max}/cm^{-1} 3434, 1697, 1256, 1087; δ_H (500.7 MHz, $CDCl_3$) 1.24 (dt, $^3J_{H\text{-}H} = 6.7$ Hz,$^4J_{P\text{-}H} = 4.3$ Hz, 3H, *Me*COP), 3.61 (s, 3H, H_3C, ester), 4.39 (dq, $J_{H\text{-}H} = 6.7$ Hz, $^3J_{P\text{-}H} = 6.7$ Hz, 2H, H_2COP),

6.91–8.01 (m, 8H, *H*-Ar), 9.56 (s, 1H, *H*N), 12.56 (br, 1H, *H*O); δ_C (125.4 MHz, $CDCl_3$) 166.6 (d, $J_{P\text{-}C} = 11.4$ Hz, *C*-4), 160.4 (d, $^2J_{P\text{-}C} = 7.6$ Hz, *C*=O), 156.6, 141.3, 130.8, 130.3, 129.1, 126.9, 126.3, 123.9, 119.7, 118.9, 118.7 (*C*-Ar), 91.3 (d, $^1J_{P\text{-}C} = 123.1$ Hz, *C*-P), 61.5 (d, $^2J_{P\text{-}C} = 10.4$ Hz, CH_2), 52.2 (*Me*), 15.8 (d, $J_{PC} = 7.5$ Hz, *Me*COP); δ_P (200.7 MHz, $CDCl_3$) 13.2; m/z (%) 390 (9) [$M^+ - 1$], 282 (100). Anal. calcd. for $C_{18}H_{18}NO_5PS$ (391.3): C, 55.24; H, 4.64; N, 3.58; P, 7.91; S, 8.19. Found: C, 55.33; H, 4.52; N, 3.46; P, 7.82; S, 8.06.

Bioscreening Assays

All international principles and local regulations concerning the care and use of laboratory animals were considered during the pharmacological screening.

Antioxidant evaluation.

Assay for erythrocyte hemolysis. Erythrocyte hemolysis was proceeded using the proxyl radicals as mediator in this assay system.[25] A 10% suspension of erythrocyte in pH 7.4 phosphate-buffered saline (PBS) was added to the same volume of 200 mM 2,2′-azobis-(2-amidino-propane)dihydrochloride (AAPH) containing samples to be tested: **1b, 4a, 4b, 7a, 7b, 10a–10h**, or vitamin C (**Y**) (2 mM). The absorbance A of the supernatant was read at 540 nm. Similarly, the absorbance B of the supernatant was measured after complete hemolysis and measured at 540 nm. Data were expressed as mean standard deviation and the percentage of hemolysis was calculated using the equation $[(1 - A/B) \times 100]$. The results are displayed in Table 1.

Antioxidant activity screening assay-, ABTS method. For each of the tested compounds **1b, 4a, 4b, 7a, 7b**, and **10a–10h**, 2 mL of 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS, pH 7.0) solution containing MnO_2 solution was processed in the usual manner. The absorbance ($A_{control}$) of the resulting green-blue solution was adjusted at ca. 0.5 at λ 734 nm. Then 50 mL of (2 mM) solution of each of the tested compound in EtOH/PBS was added. The absorbance (A_{test}) was measured and the reduction in color intensity was expressed as percent of inhibition. The percent of inhibition for each compound is calculated from the following equation:[26]

$$\%\text{Inhibition} = \{[A_{control} - A_{test}]/A_{control}\} \times 100$$

The results are displayed in Table 2.

Bleomycin-dependent DNA damage. The assay for protection of bleomycin/DNA damage by the selected samples to be tested **Y, 4b, 7a, 7b, 10a, 10b, 10g,** and **10h** (2 mM) was done according to the reported method.[27] The extent of DNA damage was measured by the increase in absorbance at 532 nm. The resulting data are displayed in Table 3.

Antidiabetic evaluation. Diabetes was induced in rats (five groups, eight rats in each group) by the intraperitoneally (i.p.) injection of streptozocin (STZ) dissolved in freshly prepared phosphate buffer saline (PBS). The antidiabetic activity

of new compounds **4a, 4b, 7a, 7b, 10a–10h**, glibenclamide (**Z**, standard), and the substrate **1b** has been studied at the same dose (50 mg/kg).[28] The results of blood glucose levels of diabetic rats treated with the tested samples **4a, 4b, 10a-10h, 7a, 7b**, and **Z** are displayed in Table 4.

CONCLUSION

In this investigation, an efficient and simple method for the synthesis of a series of new benzothiazaphosphepines and their relevant phosphonates is accomplished. Antioxidant evaluation revealed the ability of benzothiazaphosphepines and relevant phosphonates to inhibit LPO in rat's brain homogenate and the rate of erythrocyte hemolysis. In parallel, the data of our study indicated that ethanolic solutions of benzothiazaphosphepines have beneficial effects on diabetes mellitus II, suggesting new generation of antidiabetogenic drugs. Comprehensive chemical and pharmacological research is, however, required to find out the exact mechanism of these OPC for the antidiabetogenic effect and to identify the active constituents responsible for the effect.

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SUPPORTING INFORMATION

Full experimental details, complete characterization of the synthesized compounds, and copies of ^{1}H, ^{13}C, and ^{31}P NMR spectral data as well as the methods and results of the biological testing for this article can be accessed on the publisher's website.

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