

G. Chandra Sekhar Reddy, A. Uma Ravi Sankar, M. Veera Narayana Reddy, C. Radha Rani, and C. Suresh Reddy*

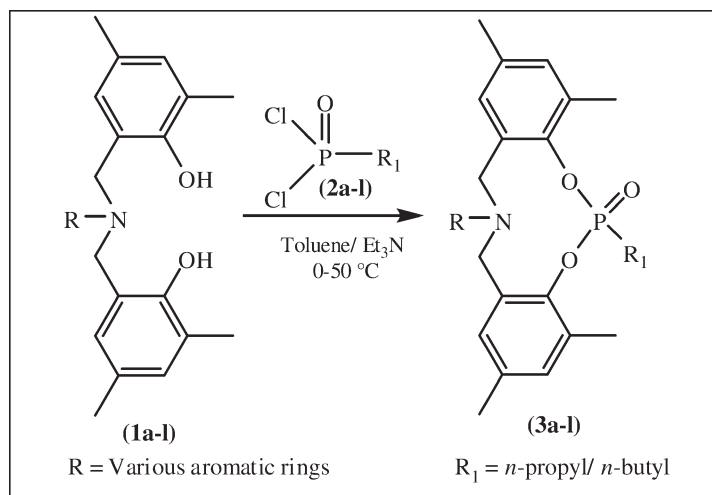
Department of Chemistry, Sri Venkateswara University, Tirupati, Andhra Pradesh 517 502, India

*E-mail: csrsvu@gmail.com

Received June 12, 2010

DOI 10.1002/jhet.727

Published online 30 June 2011 in Wiley Online Library (wileyonlinelibrary.com).



A series of a new class of phosphorus analogue macrocycles was accomplished by condensation of N-substituted-[bis(3,5-dimethyl-2-hydroxybenzyl)]-amines with various phosphorus dichlorides in dry toluene in the presence of triethylamine at 0–50 °C. All the title compounds were evaluated for antimicrobial activity to determine their efficacy and were effective in suppressing the growth of bacteria and fungi. The chemical structures of the title products were characterized by IR, ¹H, ¹³C, ³¹P-NMR, mass spectral studies, and elemental analysis.

J. Heterocyclic Chem., **48**, 1229 (2011).

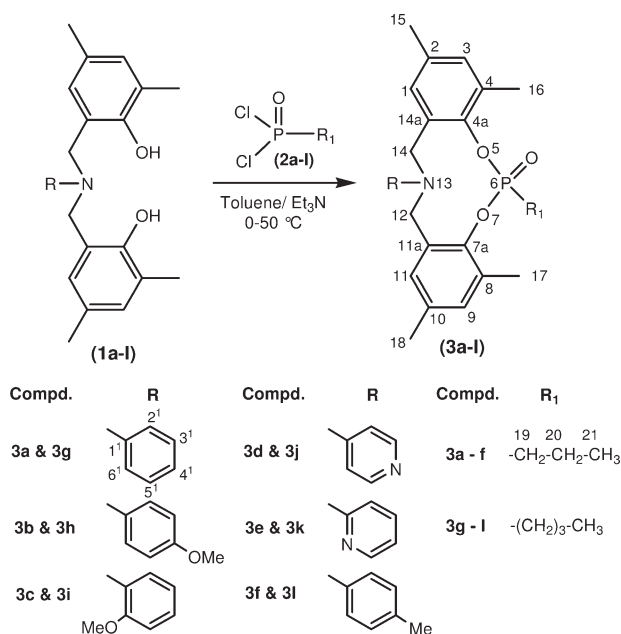
INTRODUCTION

Phosphorus, nitrogen, oxygen, and sulfur mixed donors containing macrocyclic systems have attracted increasing attention in recent years because of their interesting complexing abilities to form stable complexes with alkali and transition metal ions. These larger systems also have found that the ring size of the central ring system influence the chemical and physical properties of the compounds significantly. Another interest to synthesize the compounds arises from their potential application in coordination chemistry as recently illustrated with the characterization of palladium and silver complexes obtained from thiophosphonate as ligands [1].

As phosphorus analogues of crown ethers, they have important potential catalytic activity and ion-carrier properties in supramolecular and synthetic organic chemistry [2]. Therefore, mixed donor macrocycles have received much attention as receptors for a range of metal ions and other cations [3]. Phosphorus containing

macrocyclic compounds are expected to function as good “hosts” in the “host-guest” chemistry. This particular property enables them to carry the drug molecules to the required site in the living system, thus foreseeing great future for them in pharmaceutical industry. These macrocycles are also used in investigating the mechanism of cADPR-mediated Ca²⁺ signaling pathways and are also expected to be leads for the development of potential drug candidates [4]. Montesarchio and coworkers synthesized highly hydrophilic macrocycles for cation-scavenging in a wide range of solvents [5]. Recently, Chairuangsri and coworkers have been also used the sodium hexameta phosphate as additives in froth flotation of zinc metal by hydrometallurgy and electrometallurgy from silicate zinc ore [6]. Some of our past and present research has led to the construction of large preorganized macrocyclic cavities bearing concave functionalities [7]. Keeping in mind of these numerous applications of the phosphorus containing macrocycles with nitrogen and oxygen as donor atoms and novelty in

Scheme 1



“host-guest chemistry,” we have been synthesized, characterized, and evaluated their antimicrobial activity of a new class of macrocyclic phosphonates (Scheme 1).

RESULTS AND DISCUSSION

Phosphorus, nitrogen, and oxygen containing 10-membered heterocyclic title compounds (**3a-l**) were synthesized by reacting equimolar quantities of *N*-substituted-[bis(3,5-dimethyl-2-hydroxybenzyl)]-amines (**1a-l**) with various phosphorous dichlorides (**2**) in toluene in the presence of triethylamine at 0–50°C.

The title compounds **3a-l**, exhibited characteristic bands [8] in their IR spectra, in the regions 1252–1260, 950–955, and 1213–1218 cm^{-1} for P=O, P–O, and C–O, respectively. Proton NMR spectral data of the title compounds **3a-l** showed a multiplet peak at δ 3.63–4.35 for methylene protons (C_{12} and C_{14}) [9] due to nonequivalency of the two protons couple to each

other (Fig. 1). The aromatic protons showed complex multiplet in the region δ 6.52–8.01. The entire methyl group protons on aromatic rings appears as singlet at δ 2.15–2.26 and the remaining all protons resonated at corresponding region. The ^{13}C -NMR spectral data of **3a**, **3b**, **3d**, and **3f-h** showed characteristic absorption peaks for aromatic carbons. The carbon chemical shift of methoxyl carbon of Ar-OCH₃ resonated as a singlet at 55.2 and 55.6 ppm. Methyne carbons presenting between nitrogen and aromatic ring appear as a singlet in an appropriate region and the entire methyl group carbons on aromatic rings appear as singlets at δ 15.1–21.2. ^{31}P -NMR resonance signals appeared within the region 12.10–13.80 ppm for the title compounds [9]. The compounds **3a**, **3b**, **3d**, **3g**, **3h**, and **3j** gave $\text{M}^{+\bullet}$ ion peaks in their LCMS at m/z 449, 479, 450, 463, 493, and 464, respectively.

EXPERIMENTAL

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. Elemental analyses were performed using Perkin Elmer 2400 instrument at the Central Drug Research Institute (CDRI), Lucknow, India. The IR spectra were recorded as KBr pellets on a Perkin-Elmer 1000 unit. The ^1H -, ^{13}C -, and ^{31}P -NMR spectra were recorded on AMX 400 MHz spectrometer operating at 400 MHz for ^1H -NMR, 100 MHz for ^{13}C -NMR, and 161.9 MHz for ^{31}P -NMR. The compound was dissolved in CD_3OD , and the chemical shifts were referenced to TMS (^1H - and ^{13}C -NMR) and 85% H_3PO_4 (^{31}P -NMR). LCMS and micro analytical data were obtained from Central Drug Research Institute, Lucknow, India.

General Procedures. *N*-Substituted-[bis(3,5-dimethyl-2-hydroxybenzyl)]-amines (**1a-l**) were prepared by condensation of 2 mol of 2,4-dimethyl-phenol, 2 mol of formaldehyde, and 1 mol of various 1°-amines according to the reported procedure [9].

Synthesis of 13-(4-methoxyphenyl)-2,4,8,10-tetramethyl-6-propyl-13,14-dihydro-12H-6 λ^5 -dibenzo[*d,i*][1,3,7,2]dioxazaphosphecin-6-one (3b). A solution of *n*-propylphosphorodichloridate (**2b**, 322 mg, 2 mmol) in 25 mL of dry toluene was added drop wise over a period of 20 min to a stirred solution of bis(3,5-dimethyl-2-hydroxybenzyl)(4-methoxyphenyl) amine (**1b**, 782 mg, 2 mmol) and triethylamine (404 mg, 4 mmol) in 20 mL of dry toluene at 0°C. After the addition, the temperature of the reaction mixture was raised to room

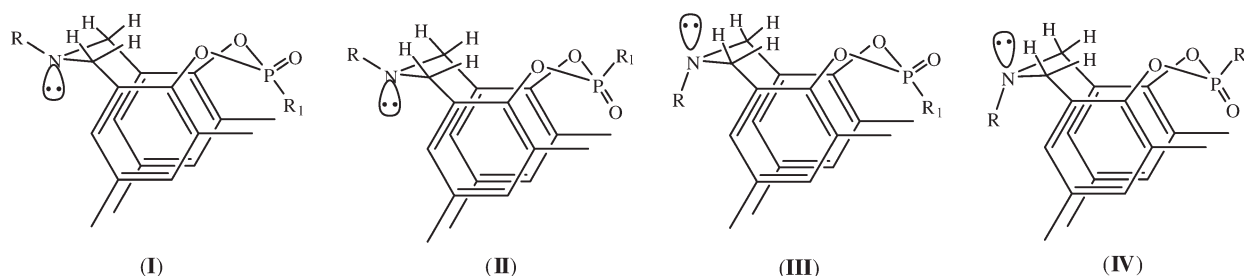


Figure 1. Conformational isomers of titled compounds.

temperature and stirred for 2 h, later the reaction mixture was stirred at 40–50°C for another 3 h. The progress of the reaction was monitored by TLC analysis (ethyl acetate:hexane, 1:3) on silicagel as adsorbent. The precipitated triethylamine hydrochloride was separated by filtration, and the filtrate was evaporated in a rotary-evaporator. The obtained crude product was washed repeatedly with petroleum ether, water and later purified by column chromatography on 60–120 mesh silica gel using ethyl acetate:hexane (1:3) as eluent to afford the pure 13-(4-methoxyphenyl)-2,4,8,10-tetramethyl-6-propyl-13,14-dihydro-12H-6 λ^5 -dibenzo[d,i][1,3,7,2]dioxazaphosphecin-6-one (3b), yield 0.801 g (70%); mp: 168–170°C. All the other compounds 3a, 3c–l was prepared by adopting the same procedure.

Spectral data. IR (KBr) ($\nu_{\max}$ cm⁻¹): 1255 (P=O), 954 (P–O), 1213 (O–C); ¹H-NMR (δ ppm): 6.65–7.97 (m, 8H, Ar–H), 3.70–4.26 (m, 4H, N–CH₂), 2.21 (s, 12H, Ar–CH₃), 3.50 (s, 3H, Ar–OCH₃), 1.59–1.61 (m, 2H, P–CH₂), 1.31–1.33 (m, 2H, –CH₂–), 0.96 (t, 3H, ³J_{HH} = 10.2, –CH₃); ¹³C-NMR (δ ppm): 127.1 (C₁ and C₁₁), 129.2 (C₂ and C₁₀), 123.6 (C₃ and C₉), 132.3 (C₄ and C₈), 146.2 (C_{4a} and C_{7a}), 53.3 (C₁₂ and C₁₄), 135.2 (C_{11a} and C_{14a}), 21.2 (C₁₅ and C₁₈), 15.2 (C₁₆ and C₁₇), 28.5 (C₁₉), 15.6 (C₂₀), 14.5 (C₂₁), 138.6 (C_{1'}), 124.3 (C_{2'} and C_{6'}), 112.8 (C_{3'} and C_{5'}), 156.4 (C_{4'}), 55.2 (OMe); ³¹P-NMR (δ ppm): 13.5; LCMS: (*m/z*) 479 (M⁺). Anal. calcd. for C₂₈H₃₄NO₄P: C, 70.13; H, 7.15; N, 2.92. Found: C, 70.05; H, 7.10; N, 2.85.

13-Phenyl-2,4,8,10-tetramethyl-6-propyl-13,14-dihydro-12H-6 λ^5 -dibenzo[d,i][1,3,7,2]dioxazaphosphecin-6-one (3a). Yield, 68%; mp: 158–160°C; IR (KBr) ($\nu_{\max}$ cm⁻¹): 1258 (P=O), 950 (P–O), 1215 (O–C); ¹H-NMR (δ ppm): 6.52–7.95 (m, 9H, Ar–H), 3.68–4.14 (m, 4H, N–CH₂), 2.17 (s, 12H, Ar–CH₃), 1.60–1.62 (m, 2H, P–CH₂), 1.30–1.32 (m, 2H, –CH₂–), 0.95 (t, 3H, ³J_{HH} = 10.2, –CH₃); ¹³C-NMR (δ ppm): 127.4 (C₁ and C₁₁), 129.6 (C₂ and C₁₀), 123.8 (C₃ and C₉), 132.1 (C₄ and C₈), 146.6 (C_{4a} and C_{7a}), 53.8 (C₁₂ and C₁₄), 135.2 (C_{11a} and C_{14a}), 21.1 (C₁₅ and C₁₈), 15.3 (C₁₆ and C₁₇), 28.7 (C₁₉), 15.6 (C₂₀), 14.5 (C₂₁), 152.6 (C_{1'}), 116.1 (C_{2'} and C_{6'}), 126.5 (C_{3'} and C_{5'}), 115.8 (C_{4'}); ³¹P-NMR (δ ppm): 12.1; LCMS: (*m/z*) 449 (M⁺). Anal. calcd. for C₂₇H₃₂NO₃P: C, 72.14; H, 7.18; N, 3.12. Found: C, 72.06; H, 7.10; N, 3.05.

13-(2-Methoxyphenyl)-2,4,8,10-tetramethyl-6-propyl-13,14-dihydro-12H-6 λ^5 -dibenzo[d,i][1,3,7,2]dioxazaphosphecin-6-one (3c). Yield, 65%; mp: 162–164°C; IR (KBr) ($\nu_{\max}$ cm⁻¹): 1255 (P=O), 955 (P–O), 1216 (O–C); ¹H-NMR (δ ppm): 6.65–7.95 (m, 8H, Ar–H), 3.87–4.24 (m, 4H, N–CH₂), 2.20 (s, 12H, Ar–CH₃), 3.45 (s, 3H, Ar–OCH₃), 1.60–1.61 (m, 2H, P–CH₂), 1.31–1.33 (m, 2H, –CH₂–), 0.95 (t, 3H, ³J_{HH} = 10.2, –CH₃); ¹³C-NMR (δ ppm): 127.3 (C₁ and C₁₁), 129.1 (C₂ and C₁₀), 123.5 (C₃ and C₉), 132.1 (C₄ and C₈), 146.2 (C_{4a} and C_{7a}), 53.5 (C₁₂ and C₁₄), 135.3 (C_{11a} and C_{14a}), 21.0 (C₁₅ and C₁₈), 14.5 (C₁₆ and C₁₇), 28.8 (C₁₉), 15.2 (C₂₀), 14.5 (C₂₁), 139.0 (C_{1'}), 124.6 (C_{2'}), 120.8 (C_{3'}), 111.6 (C_{4'}), 158.7 (C_{5'}), 121.1 (C_{6'}), 55.4 (OMe); ³¹P-NMR (δ ppm): 13.3. Anal. calcd. for C₂₈H₃₄NO₄P: C, 70.13; H, 7.15; N, 2.92. Found: C, 70.05; H, 7.10; N, 2.85.

13-(4-Pyridyl)-2,4,8,10-tetramethyl-6-propyl-13,14-dihydro-12H-6 λ^5 -dibenzo[d,i][1,3,7,2]dioxazaphosphecin-6-one (3d). Yield, 68%; mp: 164–166°C; IR (KBr) ($\nu_{\max}$ cm⁻¹): 1257 (P=O), 951 (P–O), 1214 (O–C); ¹H-NMR (δ ppm): 6.68–8.01 (m, 8H, Ar–H), 3.69–4.20 (m, 4H, N–CH₂), 2.18 (s, 12H, Ar–CH₃), 1.58–1.60 (m, 2H, P–CH₂), 1.30–1.32 (m, 2H,

–CH₂–), 0.95 (t, 3H, ³J_{HH} = 10.2, –CH₃); ¹³C-NMR (δ ppm): 128.2 (C₁ and C₁₁), 132.2 (C₂ and C₁₀), 131.8 (C₃ and C₉), 130.2 (C₄ and C₈), 146.8 (C_{4a} and C_{7a}), 53.3 (C₁₂ and C₁₄), 135.2 (C_{11a} and C_{14a}), 21.2 (C₁₅ and C₁₈), 15.1 (C₁₆ and C₁₇), 28.5 (C₁₉), 15.6 (C₂₀), 14.5 (C₂₁), 155.8 (C_{1'}), 109.2 (C_{2'} and C_{6'}), 151.4 (C_{3'} and C_{5'}), 154.5 (C_{4'}); ³¹P-NMR (δ ppm): 13.8; LCMS: (*m/z*) 450 (M⁺). Anal. calcd. for C₂₆H₃₁N₂O₃P: C, 69.32; H, 6.94; N, 6.22. Found: C, 69.28; H, 6.88; N, 6.17.

13-(2-pyridyl)-2,4,8,10-tetramethyl-6-propyl-13,14-dihydro-12H-6 λ^5 -dibenzo[d,i][1,3,7,2]dioxazaphosphecin-6-one (3e). Yield, 65%; mp: 162–164°C; IR (KBr) ($\nu_{\max}$ cm⁻¹): 1260 (P=O), 954 (P–O), 1214 (O–C); ¹H-NMR (δ ppm): 6.67–8.00 (m, 8H, Ar–H), 3.78–3.87 (m, 4H, N–CH₂), 2.20 (s, 12H, Ar–CH₃), 1.58–1.60 (m, 2H, P–CH₂), 1.30–1.32 (m, 2H, –CH₂–), 0.95 (t, 3H, ³J_{HH} = 10.2, –CH₃); ¹³C-NMR (δ ppm): 127.4 (C₁ and C₁₁), 131.3 (C₂ and C₁₀), 131.5 (C₃ and C₉), 130.4 (C₄ and C₈), 146.1 (C_{4a} and C_{7a}), 53.7 (C₁₂ and C₁₄), 135.5 (C_{11a} and C_{14a}), 21.4 (C₁₅ and C₁₈), 15.6 (C₁₆ and C₁₇), 28.2 (C₁₉), 15.9 (C₂₀), 14.4 (C₂₁), 155.6 (C_{1'}), 106.5 (C_{2'}), 153.8 (C_{3'}), 151.1 (C_{4'}), 154.8 (C_{5'}); ³¹P-NMR (δ ppm): 13.5. Anal. calcd. for C₂₆H₃₁N₂O₃P: C, 69.32; H, 6.94; N, 6.22. Found: C, 69.28; H, 6.88; N, 6.17.

13-(4-Methylphenyl)-2,4,8,10-tetramethyl-6-propyl-13,14-dihydro-12H-6 λ^5 -dibenzo[d,i][1,3,7,2]dioxazaphosphecin-6-one (3f). Yield, 64%; mp: 150–152°C; IR (KBr) ($\nu_{\max}$ cm⁻¹): 1252 (P=O), 952 (P–O), 1216 (O–C); ¹H-NMR (δ ppm): 6.65–7.95 (m, 8H, Ar–H), 3.72–4.35 (m, 4H, N–CH₂), 2.20 (s, 15H, Ar–CH₃), 1.58–1.60 (m, 2H, P–CH₂), 1.30–1.32 (m, 2H, –CH₂–), 0.95 (t, 3H, ³J_{HH} = 10.2, –CH₃); ¹³C-NMR (δ ppm): 127.1 (C₁ and C₁₁), 128.8 (C₂ and C₁₀), 124.1 (C₃ and C₉), 131.4 (C₄ and C₈), 146.4 (C_{4a} and C_{7a}), 53.8 (C₁₂ and C₁₄), 135.2 (C_{11a} and C_{14a}), 21.2 (C₁₅ and C₁₈), 15.2 (C₁₆ and C₁₇), 28.5 (C₁₉), 15.5 (C₂₀), 19.5 (C₂₁), 15.1 (C₂₂), 21.7 (Ar–CH₃), 148.3 (C_{1'}), 113.8 (C_{2'} and C_{6'}), 128.8 (C_{3'} and C_{5'}), 131.2 (C_{4'}), 154.5 (C_{4'}); ³¹P-NMR (δ ppm): 13.2. Anal. calcd. for C₂₈H₃₄NO₃P: C, 72.55; H, 7.39; N, 3.02. Found: C, 72.50; H, 7.34; N, 2.97.

13-Phenyl-2,4,8,10-tetramethyl-6-butyl-13,14-dihydro-12H-6 λ^5 -dibenzo[d,i][1,3,7,2]dioxazaphosphecin-6-one (3g). Yield, 67%; mp: 149–151°C; IR (KBr) ($\nu_{\max}$ cm⁻¹): 1257 (P=O), 950 (P–O), 1216 (O–C); ¹H-NMR (δ ppm): 6.52–7.95 (m, 8H, Ar–H), 3.68–3.98 (m, 4H, N–CH₂), 2.15 (s, 12H, Ar–CH₃), 1.55–1.57 (m, 2H, P–CH₂), 1.25–1.41 (m, 4H, –CH₂–CH₂–), 0.95 (t, 3H, ³J_{HH} = 10.2, –CH₃); ¹³C-NMR (δ ppm): 127.1 (C₁ and C₁₁), 128.7 (C₂ and C₁₀), 122.7 (C₃ and C₉), 131.6 (C₄ and C₈), 143.6 (C_{4a} and C_{7a}), 52.4 (C₁₂ and C₁₄), 135.2 (C_{11a} and C_{14a}), 21.1 (C₁₅ and C₁₈), 15.3 (C₁₆ and C₁₇), 27.3 (C₁₉), 16.5 (C₂₀), 15.7 (C₂₁), 12.8 (C₂₂), 151.4 (C_{1'}), 115.3 (C_{2'} and C_{6'}), 125.8 (C_{3'} and C_{5'}), 114.7 (C_{4'}); ³¹P-NMR (δ ppm): 12.9; LCMS: (*m/z*) 463 (M⁺). Anal. calcd. for C₂₈H₃₄NO₃P: C, 72.55; H, 7.39; N, 3.02. Found: C, 72.50; H, 7.34; N, 2.97.

13-(4-Methoxyphenyl)-2,4,8,10-tetramethyl-6-butyl-13,14-dihydro-12H-6 λ^5 -dibenzo[d,i][1,3,7,2]dioxazaphosphecin-6-one (3h). Yield, 68%; mp: 158–160°C; IR (KBr) ($\nu_{\max}$ cm⁻¹): 1255 (P=O), 955 (P–O), 1218 (O–C); ¹H-NMR (δ ppm): 6.65–7.97 (m, 8H, Ar–H), 3.64–3.95 (m, 4H, N–CH₂), 2.18 (s, 12H, Ar–CH₃), 3.50 (s, 3H, Ar–OCH₃), 1.54–1.56 (m, 2H, P–CH₂), 1.25–1.41 (m, 4H, –CH₂–CH₂–), 0.95 (t, 3H, ³J_{HH} = 10.2, –CH₃); ¹³C-NMR (δ ppm): 127.3 (C₁ and C₁₁), 129.1 (C₂ and C₁₀), 128.6 (C₃ and C₉), 129.3 (C₄ and C₈),

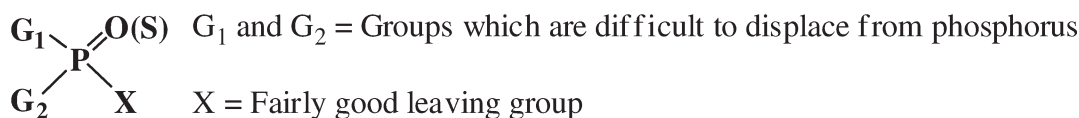


Figure 2. The main pharmacophoric structure unit of organophosphorus compounds.

145.6 (C_{4a} and C_{7a}), 53.1 (C₁₂ and C₁₄), 135.2 (C_{11a} and C_{14a}), 21.1 (C₁₅ and C₁₈), 15.3 (C₁₆ and C₁₇), 27.3 (C₁₉), 16.5 (C₂₀), 15.7 (C₂₁), 12.8 (C₂₂), 146.8 (C₁^j), 124.8 (C₂^j and C₆^j), 112.8 (C₃^j and C₅^j), 155.7 (C₄^j), 55.2 (OMe); ³¹P-NMR (δ ppm): 12.6; LCMS: (m/z) 493 (M⁺•). Anal. calcd. for C₂₉H₃₆NO₄P: C, 70.57; H, 7.35; N, 2.84. Found: C, 70.52; H, 7.30; N, 2.79.

13-(2-Methoxyphenyl)-2,4,8,10-tetramethyl-6-butyl-13,14-dihydro-12H-6λ⁵-dibenzo[d,i][1,3,7,2]dioxazaphosphecin-6-one (3i). Yield, 65%; mp: 157–159°C; IR (KBr) (ν_{max} cm⁻¹): 1256 (P=O), 954 (P–O), 1218 (O–C); ¹H-NMR (δ ppm): 6.65–7.95 (m, 8H, Ar–H), 3.63–3.95 (m, 4H, N–CH₂), 2.18 (s, 15H, Ar–CH₃), 3.50 (s, 3H, Ar–OCH₃), 1.54–1.56 (m, 2H, P–CH₂), 1.25–1.41 (m, 4H, –CH₂–CH₂–), 0.95 (t, 3H, ³J_{HH} = 10.2, –CH₃); ¹³C-NMR (δ ppm): 127.2 (C₁ and C₁₁), 129.4 (C₂ and C₁₀), 123.0 (C₃ and C₉), 131.7 (C₄ and C₈), 146.4 (C_{4a} and C_{7a}), 54.4 (C₁₂ and C₁₄), 135.5 (C_{11a} and C_{14a}), 21.4 (C₁₅ and C₁₈), 15.2 (C₁₆ and C₁₇), 29.3 (C₁₉), 15.8 (C₂₀), 15.7 (C₂₁), 14.7 (C₂₂), 139.2 (C₁^j), 124.1 (C₂^j), 120.5 (C₃^j), 111.7 (C₄^j), 158.4 (C₅^j), 121.5 (C₆^j), 55.6 (OMe); ³¹P-NMR (δ ppm): 12.9. Anal. calcd. for C₂₉H₃₆NO₄P: C, 70.57; H, 7.35; N, 2.84. Found: C, 70.52; H, 7.30; N, 2.79.

13-(4-Pyridyl)-2,4,8,10-tetramethyl-6-butyl-13,14-dihydro-12H-6λ⁵-dibenzo[d,i][1,3,7,2]dioxazaphosphecin-6-one (3j). Yield, 65%; mp: 155–157°C; IR (KBr) (ν_{max} cm⁻¹): 1257 (P=O), 950 (P–O), 1215 (O–C); ¹H-NMR (δ ppm): 6.68–8.01 (m, 8H, Ar–H), 3.66–3.95 (m, 4H, N–CH₂), 2.20 (s, 12H, Ar–CH₃), 1.56–1.58 (m, 2H, P–CH₂), 1.26–1.42 (m, 4H, –CH₂–CH₂–), 0.96 (t, 3H, ³J_{HH} = 10.2, –CH₃); ¹³C-NMR

(δ ppm): 127.8 (C₁ and C₁₁), 131.4 (C₂ and C₁₀), 130.6 (C₃ and C₉), 130.0 (C₄ and C₈), 147.1 (C_{4a} and C_{7a}), 53.5 (C₁₂ and C₁₄), 135.8 (C_{11a} and C_{14a}), 21.6 (C₁₅ and C₁₈), 15.2 (C₁₆ and C₁₇), 28.8 (C₁₉), 15.2 (C₂₀), 15.5 (C₂₁), 14.2 (C₂₂), 155.7 (C₁^j), 109.3 (C₂^j and C₆^j), 151.2 (C₃^j and C₅^j), 154.8 (C₄^j); ³¹P-NMR (δ ppm): 13.3; LCMS: (m/z) 464 (M⁺•). Anal. calcd. for C₂₇H₃₃N₂O₃P: C, 69.81; H, 7.16; N, 6.03. Found: C, 69.77; H, 7.12; N, 5.97.

13-(2-Pyridyl)-2,4,8,10-tetramethyl-6-butyl-13,14-dihydro-12H-6λ⁵-dibenzo[d,i][1,3,7,2]dioxazaphosphecin-6-one (3k). Yield, 64%; mp: 153–155°C; IR (KBr) (ν_{max} cm⁻¹): 1257 (P=O), 950 (P–O), 1215 (O–C); ¹H-NMR (δ ppm): 6.67–8.00 (m, 8H, Ar–H), 3.63–3.95 (m, 4H, N–CH₂), 2.20 (s, 12H, Ar–CH₃), 1.55–1.57 (m, 2H, P–CH₂), 1.25–1.41 (m, 4H, –CH₂–CH₂–), 0.95 (t, 3H, ³J_{HH} = 10.2, –CH₃); ¹³C-NMR (δ ppm): 127.1 (C₁ and C₁₁), 131.5 (C₂ and C₁₀), 132.1 (C₃ and C₉), 130.3 (C₄ and C₈), 146.3 (C_{4a} and C_{7a}), 53.2 (C₁₂ and C₁₄), 135.2 (C_{11a} and C_{14a}), 21.7 (C₁₅ and C₁₈), 15.4 (C₁₆ and C₁₇), 28.7 (C₁₉), 15.3 (C₂₀), 16.2 (C₂₁), 14.6 (C₂₂), 155.6 (C₁^j), 106.5 (C₂^j), 153.8 (C₃^j), 151.1 (C₄^j), 154.8 (C₅^j); ³¹P-NMR (δ ppm): 12.8. Anal. calcd. for C₂₇H₃₃N₂O₃P: C, 69.81; H, 7.16; N, 6.03. Found: C, 69.77; H, 7.12; N, 5.97.

13-(4-Methylphenyl)-2,4,8,10-tetramethyl-6-butyl-13,14-dihydro-12H-6λ⁵-dibenzo[d,i][1,3,7,2]dioxazaphosphecin-6-one (3l). Yield, 63%; mp: 153–155°C; IR (KBr) (ν_{max} cm⁻¹): 1252 (P=O), 952 (P–O), 1216 (O–C); ¹H-NMR (δ ppm): 6.65–7.95 (m, 8H, Ar–H), 3.72–4.04 (m, 4H, N–CH₂), 2.26 (s, 15H, Ar–CH₃), 2.12 (s, 3H, Ar–CH₃), 1.55–1.57 (m, 2H, P–CH₂), 1.25–1.41 (m, 4H, –CH₂–CH₂–), 0.95 (t, 3H, ³J_{HH} = 10.2, –CH₃); ¹³C-NMR (δ ppm): 126.6 (C₁ and C₁₁), 128.4

Table 1

Antibacterial Activity of Title Compounds (3a–l).

Compounds	Zone of inhibition (mm)			
	<i>Staphylococcus aureus</i>		<i>Escherichia coli</i>	
	250 (mg/disk)	500 (mg/disk)	250 (mg/disk)	500 (mg/disk)
3a	17.3	20.3	17.2	20.5
3b	18.8	22.6	19.2	21.7
3c	18.7	22.4	18.9	21.9
3d	17.8	19.4	18.3	20.4
3e	17.6	19.2	18.2	20.2
3f	18.2	19.8	18.8	20.9
3g	17.2	19.6	17.3	20.7
3h	18.9	22.9	18.8	22.4
3i	18.8	22.6	18.6	22.2
3j	17.9	19.6	18.2	22.1
3k	18.0	19.2	18.4	22.3
3l	17.6	19.8	17.8	20.1
Penicillin ^a	22.0	–	21.0	–

^a Reference compound.

Table 2

Antifungal Activity of Title Compounds (3a–l).

Compounds	Zone of inhibition (mm)			
	<i>Aspergillus niger</i>		<i>Fusarium solani</i>	
	250 (mg/disk)	500 (mg/disk)	250 (mg/disk)	500 (mg/disk)
3a	16.4	20.8	15.2	19.8
3b	15.8	19.7	14.7	19.2
3c	15.6	19.5	15.2	19.3
3d	14.9	18.7	14.8	18.9
3e	14.7	18.8	14.5	18.7
3f	17.2	21.2	15.5	20.1
3g	17.1	20.8	14.3	19.6
3h	18.1	21.7	16.5	21.5
3i	17.8	19.8	15.6	18.7
3j	16.7	18.2	14.8	17.9
3k	16.6	18.1	14.6	16.7
3l	15.2	18.5	13.8	16.8
Griseofulvin ^a	18.0	–	18.0	–

^a Reference compound.

(C₂ and C₁₀), 124.5 (C₃ and C₉), 131.7 (C₄ and C₈), 146.3 (C_{4a} and C_{7a}), 54.3 (C₁₂ and C₁₄), 135.7 (C_{11a} and C_{14a}), 21.6 (C₁₅ and C₁₈), 15.5 (C₁₆ and C₁₇), 28.9 (C₁₉), 15.2 (C₂₀), 17.1 (C₂₁), 15.2 (C₂₂), 22.3 (Ar—CH₃), 148.6 (C₁^I), 113.5 (C₂^I and C₆^I), 128.4 (C₃^I and C₅^I), 131.1 (C₄^I), 154.1 (C₄^I); ³¹P-NMR (δ ppm): 13.2. Anal. calcd. for C₂₉H₃₆NO₃P: C, 72.93; H, 7.60; N, 2.93. Found: C, 72.88; H, 7.55; N, 2.89.

BIOACTIVITY

Structure–function relationships of organophosphorus compounds (OPC). Schrader [10] proposed that organophosphorus compounds containing the main pharmacophoric structure unit (Fig. 2) may have significant biological activity. Slight variation in pharmacophoric structure (Fig. 2) can have very drastic effects on the bioactive efficiency of organophosphorus compounds (OPC) due to the fact that an OPC substrate is very sensitive to the size, shape and polarity. These chemically and biologically variable parameters which are hard to estimate are involved in deciding “structure-activity” relationship of these compounds.

Antibacterial activity. All the title compounds (**3a–l**) were tested for their antibacterial activity [11] (Table 1) against *Staphylococcus aureus* (gram positive) and *Escherichia coli* (Gram negative) by the Kirby-Bauer's disk-diffusion method in Mueller-Hinton agar medium, at various concentrations (250, 500 mg/disk) in dimethyl formamide (DMF). These solutions were added to each filter disk and DMF was used as control. The plates were incubated at 35°C and examined for zone of inhibition around each disk after 12 h. The results were compared with the activity of the standard antibiotic penicillin (250 mg/disk). Triplicates were used for each observation.

Antifungal activity. The antifungal bioassay [12] for all the title compounds (**3a–l**) were evaluated against *Curvularia lunata* and *Fusarium oxysporium* (Table 2) at different concentrations (250 and 500 mg/disk). Griseofulvin was used as the reference compound. Fungal cultures were grown on potato dextrose broth at 25°C, and finally, spore suspension was adjusted to 10⁵ spore/mL. Most of the compounds showed moderate to high activity against both bacteria and fungi.

CONCLUSIONS

Simple and efficient method for synthesis of a new class of macrocyclic phosphonates (**3a–l**) was accomplished by reacting equimolar quantities of various *N*-substituted amines (**1a–l**) with different phosphorous dichlorides (**2**) in toluene in the presence of triethylamine at 0–50°C. This method is simple and also significant route to synthesis macrocyclic compounds. All the titled compounds showed moderate to high antibacterial activity toward *Staphylococcus aureus* (Gram positive) and *Escherichia coli* (Gram negative) and antifungal bioassay toward *Curvularia lunata* and *Fusarium oxysporium* organisms at different concentrations.

Acknowledgments. The authors thank Prof. C. Devendranath Reddy, Department of Chemistry, S.V. University, Tirupati for his valuable advice and CSIR, Human Resources Development Group, Govt. of India, New Delhi for providing financial assistance ((01/2347)/09/EMR-II).

REFERENCES AND NOTES

- [1] Aurore, F.; Martin, L.; Anthony, S. L.; Klein Gebbink, R. J. M.; Koten, G. V.; Salaún, J. Y.; Jaffrès, P. A. Dalton Trans 2010, 39, 2942.
- [2] Caminade, A. M.; Majoral, J. P. Chem Rev 1994, 94, 1183.
- [3] Zhao, B.; Wang, F. Q.; Tian, L. J. J Heterocycl Chem 2001, 38, 78.
- [4] Kudoh, T.; Weber, K.; Guse, A. H.; Potter, B. V. L.; Hashii, M.; Higashida, H.; Arisawa, M.; Matsuda, A.; Shuto, S. Tetrahedron Lett 2008, 49, 3976.
- [5] D'Onofrio, J.; Coppola, C.; Fabio, G. D.; De Napoli, L.; Montesarchio, D. Eur J Org Chem 2007, 3849.
- [6] Pomjaturad, J.; Rattanakawin, C.; Sriprang, N.; Tongteeka, S.; Chairuangsi, T.; Mai, C. J Sci 2007, 34, 191.
- [7] Kasthuraiah, M.; Reddy, M. V. N.; Sankar, A. U. R., Kumar, B. S.; Reddy, C. S. Bulg Chem Commun 2009, 41, 248.
- [8] Hari Babu, B.; Syam Prasad, G.; Stephen Babu, M. F.; Hara-nath, P.; Hemadri Reddy, S.; Naga Raju, C. Heterocycles 2008, 75, 611.
- [9] Sankar, A. U. R.; Kumar, B. S.; Reddy, M. V. N.; Reddy, S. S.; Reddy, C. S.; Raju, C. N. Bulg Chem Commun 2009, 41, 59.
- [10] Schrader, G. World Rev Pest Control 1965, 4, 140.
- [11] Vincent, J. C.; Vincent, H. W. Proc Soc Exp Biol Med 1994, 55, 162.
- [12] Benson, H. J. Microbiological Applications, 5th ed.; W.C. Brown Publications: Boston, MA, USA, 1990; pp 156–159.