E-J.Chem
<http://www.e-journals.net>

ISSN: 0973-4945; CODEN ECJHAO
E-Journal of Chemistry
2008, 5(S1), 1025-1032

Synthesis and Biological Activity of Some new 2-Heterocyclic/acyclic amino/4'-acetamidophenoxy-3- (4-chloro-phenyl)-3, 4-dihydrobenzo[e]- [1,3,2]oxazaphosphinine 2-sulfides

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Received 1 September 2007; Accepted 1 November 2007

Abstract: 2-Heterocyclic/acyclicamino/4'-acetamidophenoxy-3-(4-chlorophenyl)-3,4-dihydrobenzo-[e][1,3,2]oxazaphosphinine 2-sulfides (4a-j) were synthesized through a two steps process. In the first step, 2-chloro-3-(4-chlorophenyl)-3, 4-dihydrobenzo[e] [1,3,2]-oxazaphosphinine 2-sulfide (2) was prepared by the reaction of 2-[(4-chlorophenylamino)methyl]phenol (1) with thiophosphoryl chloride in the presence of triethylamine in dry toluene-tetrahydrofuran. In the second step, 2 was treated with various heterocyclic/acyclicamines/4'-acetamidophenol in presence of triethylamine/sodium hydride in toluene-tetrahydrofuran at 45-50°C. All the synthesized compounds (4a-j) were characterized by elemental analysis, IR, NMR (¹H, ¹³C and ³¹P) and mass spectra and their biological activity was evaluated for antimicrobial activity.

Keywords: 2-[(4-Chlorophenylamino) methyl] phenol, Thiophosphoryl chloride, Benzoxazaphosphinine 2-sulfide, Triethylamine/sodium hydride, Antimicrobial activity.

Introduction

Organophosphorus compounds being ubiquitous in nature have found multifaceted applications. Oxazaphosphinine derivatives, cyclophosphamide and its analogues, isophosphamides are clinically useful anticancer drugs^{1, 2} organophosphorus esters are used as pesticides and insecticides³ Organophosphoramides are used as ligands in lewis based catalysed allylation and aldol addition reactions⁴ Some of the benzoxazaphosphinines posses

significant microbial activity^{5, 6}. Several organophosphorus fungicides such as iprobenfos and edifenphos are used for the control of fungal diseases in plants⁷. Application of pesticides in soil has become a necessity for the control of both soil-borne and foliar diseases. Modern agricultural practices depend on synthetic chemical to maintain insect pest population in economic threshold⁸. The results obtained in our present study indicated that some of the microorganisms are able to degrade the pesticide compounds which were synthesized. The ease with which they are able to degrade depends on the complexity of their structure. More complex structure degrade the required quantity more slowly either because fewer microorganisms in the soil to produce enzyme capable of degrading them or because of their inaccessibility to microbes⁹. Phosphorus being a part of important biomolecules plays a fundamental role in microbial cell physiology and biochemistry¹⁰. In view of this, a series of 2-heterocyclic/acyclic amino/4'-acetamidophenoxy-3-(4-chlorophenyl)-3, 4-dihydro-benzo[e][1,3,2]oxazaphosphinine 2-sulfides (4a-j) have been synthesized.

Results and Discussion

The synthetic route involves preparation of the title compounds through a two-step process. The intermediate 2-chloro-3-(4-chlorophenyl)-3,4-dihydrobenzo[e][1,3,2]oxa-zaphosphinine 2-sulfide (2) was obtained from the cyclocondensation of 2-[(4-chlorophenylamino) methyl]phenol (1) with thiophosphoryl chloride in equimolar quantities in the presence of triethylamine in dry toluene-tetrahydrofuran at 35°C for 2 h. Subsequent nucleophilic substitution of heterocyclic/acyclic amines/4'-acetamidophenol (3a-j) on this monochloride (2) at 45-50 °C for 3h, yielded title compounds (4a-j). They were characterized by IR, ¹H, and ³¹P NMR spectroscopic data. ¹³C NMR data for 4a, 4b, 4d and 4f and mass spectral data for 4b, 4d, 4e and 4f are given in experimental section. Compounds 4a-j showed IR absorption bands at 803-825, 949-975, 1082-1101 and 1211-1234 cm⁻¹ for P=S, P-O, N-C and O-C_{arom} respectively^{3, 11}. Their aromatic protons show a multiplet in their ¹H NMR spectra at slightly downfield (δ 6.43-7.62) when compared with those of the starting compound 1 (δ 6.29-7.32) owing to the deshielding effect of the 2-thio-benzoxazaphosphinine ring. From ¹H NMR data of 4i, the amidic proton (-NH) signal amidic -NH proton is less reactive³ than phenolic group towards 2. The C-4 methylene protons resonated as two doublets of doublet at δ 4.32-4.48 (²J_{HH} = 10.6-11.2, ³J_{PH} = 5.2-5.3 Hz) and 4.78-4.98 (²J_{HH} = 10.6-11.2, ³J_{PH} = 11.1-12.8 Hz) indicating their non-equivalence and coupling with phosphorus in the six-membered chair conformation of the 2-thio-benzoxazaphosphinine system^{3, 12}. C-4 resonated at δ 44.5-46.0 in the ¹³C NMR spectra^{3, 6}. Other NMR data were also consistent for the substituents attached to the nitrogen, oxygen atom and aromatic protons and are presented in experimental section. The mass spectral data of 4a, 4d, 4e and 4f exhibited [M+2]⁺, M⁺ and daughter ions with substituted benzoxazaphosphinine and heterocyclic/acyclic moieties at appropriate m/z values. Their mass spectral behavior is in good agreement with that of similar organophosphorus compounds³. Thus the combined elemental analysis, IR, NMR and mass spectral data conclusively agree with the proposed structures for the title compounds.

Biological activity

Antimicrobial activity of the title compounds 4a-j revealed interesting information. Even though the starting compound 2-[(4-chlorophenylamino)-methyl]-phenol 1 has phenolic, chloro, N-alkyl and NH functions, it does not show any antimicrobial activity. But when this compound is cyclized with thiophosphoryl chloride and followed by nucleophilic substitution at phosphorus resulting the compounds, 4a-j containing substituted oxazaphosphonin-2-yl amine/ phenyl systems showed promising antimicrobial activity.

Compd.	-XR'R''	Compd.	-XR'R''
a		f	
b		g	
c		h	
d		i	
e		j	

Scheme 1

Antimicrobial activity

The antimicrobial activity of the compounds was comparable with that of the commercial antibiotics. The results indicated that compounds 4a-j exhibited significant antibacterial and antifungal activities. The compounds with nitrogen atom in the five membered aromatic rings showed the greatest inhibitory effect against one or more types of microorganisms (Table 1). The compound 4i showed the maximum zone of inhibition (25 mm) against *Staphylococcus aureus*.

Experimental

General synthetic procedures

All reactions were carried out in anhydrous conditions under nitrogen atmosphere. Melting points were determined with open capillary tubes using Mel-temp apparatus and were corrected. IR spectra ($\bar{\nu}_{\text{max}}$ cm⁻¹) were recorded on a Perkin Elmer 1600 instrument as KBr pellets. Mass spectra were recorded on a LC-MSD-Trap-SL instrument at 70 eV. The ³¹P, ¹H And ¹³C NMR spectra were taken on a Bruker AMX-300 MHz spectrometer operating at 121.5 MHz for ³¹P NMR, 300 MHz for ¹H NMR and 75 MHz for ¹³C NMR.

All the compounds were dissolved in CDCl_3 and chemical shifts were referenced to 85% H_3PO_4 (^{31}P NMR) or TMS (^1H NMR and ^{13}C NMR). Elemental analyses were performed using Perkin Elmer 2400 instrument at the Central Drug Research Institute (CDRI), Lucknow, India. 2-[(4-Chlorophenylamino) methyl] phenol (1) was prepared using a reported procedure¹³.

General procedure for the preparation of 2-(1-(N-methylpiperazinyl)-3-(4-chlorophenyl)-3, 4-dihydrobenzo[e][1,3,2]oxazaphosphinine 2-sulfide(4a).

The synthesis of the compound 4a was accomplished through a two-step process. A solution of thiophosphoryl chloride (0.003 mole) in dry toluene (20 mL) was added drop wise to a cooled (5-10 °C) solution of 2-(4-chlorophenylamino) methyl phenol (1, 0.003 mole) and triethylamine (0.006 mole) in dry toluene-tetrahydrofuran (40 mL, 1:1) under stirring. After the addition, the temperature of the reaction mixture was slowly raised to 35-40 °C and stirred for additional 4h. The formation of 2-chloro-3-(4-chlorophenyl)-3,4-dihydrobenzo[e][1,3,2]oxazaphosphinine 2-sulfide (2),¹⁴ was ascertained by TLC analysis and the product was used without further purification in the next following step.

To a cooled (0-5°C) solution of 2, N-methylpiperazine (3a, 0.003 moles) and triethylamine (0.003 moles) in dry toluene were added dropwise with stirring. After the addition, the temperature of the reaction mixture was slowly raised to 40-45 °C and stirring was continued for additional 3h. After filtration by suction pump, the solvent was removed from the filtrate under reduced pressure. The residue was washed with water followed by 2-propanol and recrystallised from 2-propanol to afford 4a.

Yield: 0.84 g (72%); White solid; m.p:118-121°C; IR $\bar{\nu}_{\text{max}}$ (KBr): 821 (P=S), 975 (P-O), 1226 (O-C), 1101 (N-C) cm^{-1} ; ^{31}P NMR (121.5 MHz, CDCl_3): 64.1 ppm; ^1H NMR (300 MHz, CDCl_3): δ 7.07-7.39 (8H, m, Ar-H), 4.48 (1H, dd, $^2J=10.6$, $^3J_{\text{P,H}}=5.2$ Hz, H_a -4), 4.85 (1H, dd, $^2J=10.6$, $^3J_{\text{P,H}}=11.1$, H_e -4), 3.27 (4H, t, $J=8.2$ Hz, H-2" and H-6"), 2.23 (4H, t, $J=8.2$ Hz, H-3" and H-5") and 1.98 (3H, s, N-CH₃); ^{13}C NMR: δ 46.0(C-4), 125.8 (C-5), 123.8 (C-6), 125.7 (C-7), 118.9 (C-8), 151.0 (C-9), 130.9(C-10), 142.4 (C-1'), 118.8 (C-2' and C-6'), 129.2 (C-3' and C-5'), 126.4(C-4'), 54.8 (C-2" and C-6"), 45.2 (C-3" and C-5") and 29.6 (N-CH₃); MS m/z (rel. int.): 396 [(MH+2)⁺, 39], 394 [(MH)⁺, 100], 337 [(MH-C₃H₇N)⁺, 8], 294 [(MH-C₅H₁₂N₂)⁺, 28], 259 [(MH-C₅H₁₂N₂Cl)⁺, 8], 232 [(MH-C₅H₁₁N₂PS)⁺, 6], 214 [(MH-C₅H₁₂N₂OPS)⁺, 3], 215 [(MH⁺-C₃H₁₃N₂OPS)⁺, 3], 187 [(MH-C₆H₁₄N₃OPS)⁺, 7]; Anal. Calcd for C₁₈H₂₁ClN₃OPS: C, 54.89, H 5.37 and N 10.60; Found: C 54.77, H 5.26 and N 10.52.

Compounds 4b-j were prepared by using corresponding amines (3b-j) in the above procedure.

2-Piperidinyl-3-(4-chlorophenyl)-3,4-dihydrobenzo[e][1,3,2]oxazaphosphinine 2-sulfide (4b)

Yield: 0.61 g (54%); Pale yellow solid; m.p:110-112°C; IR $\bar{\nu}_{\text{max}}$ (KBr): 826 (P=S), 955 (P-O), 1221 (O-C), 1092 (N-C) cm^{-1} ; ^{31}P NMR (121.5 MHz, CDCl_3): 64.4 ppm; ^1H NMR (300 MHz, CDCl_3): δ 7.06-7.52 (8H, m, Ar-H), 4.34 (1H, dd, $^2J=10.7$, $^3J_{\text{P,H}}=5.3$ Hz, H_a -4), 4.98 (1H, dd, $^2J=10.7$, $^3J_{\text{P,H}}=12.6$ Hz, H_e -4), 3.05 (4H, t, $J=7.9$ Hz, H-2" and H-6"), 1.64-1.75 (4H, m, H-3" and H-5"), and 1.19-1.30 (2H, m, H-4"); ^{13}C NMR (75 MHz, CDCl_3): δ 44.5 (C-4), 128.8 (C-5), 122.5 (C-6), 124.0 (C-7), 119.5 (C-8), 152.7 (C-9), 146.6 (C-1'), 115.8 (C-2' and 6'), 128.5 (C-3' and C-5'), 126.5 (C-4') and 40.3 (C-2" and C-6"), 29.71 (C-3" and C-5") and 29.3 (C-4"); Anal. Calcd for C₁₈H₂₀ClN₂OPS: C 57.07, H 5.32 and N 7.39; Found: C 57.19, H 5.37 and N 7.32.

2-(1-(Pyrolidinyl)-3-(4-chlorophenyl)-3,4-dihydrobenzo[e][1,3,2]oxazaphosphinine 2-sulfide (4c)

Pale yellow solid, Yield: 0.66 g (61%); m.p: 120-122°C; IR $\bar{\nu}_{\max}$ (KBr): 819 (P=S), 964 (P-O), 1230 (O-C), 1091 (N-C) cm^{-1} ; ^{31}P NMR (121.5 MHz, CDCl_3): 64.2 ppm; ^1H NMR (300 MHz, CDCl_3): δ 6.97-7.32 (8H, m, Ar-H), 4.34 (1H, dd, $^2J=11.1$, $^3J_{\text{P,H}}=5.3$ Hz, H_a -4), 4.85 (1H, dd, $^2J=11.1$ Hz, $^3J_{\text{P,H}}=12.3$ Hz, H_e -4), 3.24 (4H, t, $J=7.8$ Hz, H-2" and H-5"), and 2.24 (4H, t, $J=7.8$ Hz, H-3" and H-4"); Anal. Calcd for $\text{C}_{17}\text{H}_{18}\text{ClN}_2\text{OPS}$: C 55.97, H 4.97 and N 7.68; Found C 55.91, H 4.93 and N 7.65.

2-(Morpholinyl)-3-(4-chlorophenyl)-3,4-dihydrobenzo[e][1,3,2]oxazaphosphinine 2-sulfide (4d)

White solid, Yield: 0.85 g (75%); m.p:125-126°C; IR $\bar{\nu}_{\max}$ (KBr): 815 (P=S), 959 (P-O), 1211 (O-C), 1087 (N-C) cm^{-1} ; ^{31}P NMR (121.5 MHz, CDCl_3): 63.5 ppm; ^1H NMR (300 MHz, CDCl_3): δ 7.08-7.32 (8H, m, Ar-H) 4.38 (1H, dd, $^2J=11.2$, $^3J_{\text{P,H}}=5.3$ Hz, H_a -4), 4.98 (1H, dd, $^2J=11.2$, $^3J_{\text{P,H}}=12.1$ Hz, H_e -4), 3.54 (4H, t, $J=8.1$ Hz, H-3" and H-5"), and 3.22 (4H, t, $J=8.1$ Hz, H-2" and H-6"); ^{13}C NMR (75 MHz, CDCl_3): δ 44.2 (C-4), 126.4 (C-5), 123.5 (C-6), 129.8 (C-7), 121.6 (C-8), 148.7 (C-9), 129.6 (C-10), 144.4 (C-1'), 111.2 (C-2' and C-6'), 128.5 (C-3' and C-5'), 125.2 (C-4'), 42.9 (C-2" and C-6") and 64.3 (C-3" and C-5"); LC-MS m/z (rel. int.): 383 [(MH+2) $^+$, 38], 381 [(MH) $^+$, 100], 294 [(MH-C₄H₉NO) $^+$, 40], 270 [(MH-C₆H₄Cl) $^+$, 10], 259 [(MH-C₄H₉NOCl) $^+$, 14], 231 [(MH-C₄H₉NOPS) $^+$, 13], 214 [(MH-C₄H₁₀NO₂PS) $^+$, 1] and 187 [(MH-C₅H₁₁N₂O₂PS) $^+$, 8]; Anal. Calcd for: $\text{C}_{17}\text{H}_{18}\text{ClN}_2\text{O}_2\text{PS}$ (%): C, 53.62, H, 4.76 and N 7.36; Found: C, 53.53, H, 4.71, N, 7.30.

2-(1-Pyrrolyl)-3-(4-chlorophenyl)-3,4-dihydrobenzo[e][1,3,2]oxazaphosphinine 2-sulfide (4e)

Ash colour solid, Yield: 0.55 g (51%); m.p:137-140°C; IR $\bar{\nu}_{\max}$ (KBr): 815 (P=S), 957 (P-O), 1217 (O-C), 1082 (N-C) cm^{-1} ; ^{31}P NMR (121.5 MHz, CDCl_3): 52.4 ppm; ^1H NMR (300 MHz, CDCl_3): δ 6.85-7.48 (12H, m, Ar-H) and 4.47 (1H, dd, $^2J=10.7$, $^3J_{\text{P,H}}=5.2$ Hz, H_a -4), 4.79 (1H, dd, $^2J=10.7$, $^3J_{\text{P,H}}=11.3$ Hz, H_e -4); LC-MS m/z (rel. int.): 363 [(MH+2) $^+$, 23], 361 [(MH) $^+$, 54], 327 [(MH-SH) $^+$, 100], 316 [(MH-CH₃NO) $^+$, 49], 294 [(MH-C₄H₄N) $^+$, 9], 265 [(MH-C₅H₆NO) $^+$, 26], 211 [(MH-C₅H₇NOPS) $^+$, 63], 234 [(MH-C₄H₄NP) $^+$, 17], 202 [(MH-C₄H₄NPS) $^+$, 14]; Anal. Calcd for $\text{C}_{17}\text{H}_{14}\text{ClN}_2\text{OPS}$: C 56.59, H 3.93 and N 7.76; Found: C 56.73, H 4.02 and N 7.80.

2-(1-Indolyl)-3-(4-chlorophenyl)-3,4-dihydrobenzo[e][1,3,2]oxazaphosphinine 2-sulfide (4f)

Grey solid, Yield: 0.88 g (72%); m.p:130-132°C; IR $\bar{\nu}_{\max}$ (KBr): 817 (P=S), 956 (P-O), 1219 (O-C), 1094 (N-C) cm^{-1} ; ^{31}P NMR (121.5 MHz, CDCl_3): 51.1 ppm; ^1H NMR (300 MHz, CDCl_3): δ 6.48-7.49 (12H, m, Ar-H) and 4.32 (1H, dd, $^2J=10.9$, $^3J_{\text{P,H}}=5.3$ Hz, H_a -4), 4.78 (1H, dd, $^2J=10.9$, $^3J_{\text{P,H}}=12.5$ Hz, H_e -4); ^{13}C NMR (75 MHz, CDCl_3): δ 45.9 (C-4), 128.2 (C-5), 123.3 (C-6), 126.9 (C-7), 121.8 (C-8), 151.3 (C-9), 131.0 (C-10), 139.8 (C-1'), 118.3 (C-2' and C-6'), 129.6 (C-3' and C-5'), 125.8 (C-4'), 124.6 (C-2"), 128.9 (C-3"), 120.0 (C-4"), 122.0 (C-5"), 119.3 (C-6"), 111.2 (C-7") and 135.1 (C-8"). LC-MS m/z (rel. int.): 413 [(MH+2) $^+$, 17], 411 [(MH) $^+$, 44], 347 [(MH-C₄H₂N) $^+$, 100], 300 [(MH-C₆H₄Cl) $^+$, 13], 367 [(MH-CH₂NO) $^+$, 32], 301 [(MH-CH₃NOPS) $^+$, 46], 243 [(MH-C₇H₇NPS) $^+$, 44] and 187 [(C₁₂H₈Cl, 6) $^+$; Anal. Calcd for $\text{C}_{21}\text{H}_{16}\text{ClN}_2\text{OPS}$: C, 61.39, H 3.93 and N 6.82; Found: C61.24, H 4.03 and N 6.89.

2-(1-Imidazolyl)-3-(4-chlorophenyl)-3,4-dihydrobenzo[e][1,3,2]oxazaphosphinine 2-sulfide (4g)

Pale yellow solid, Yield: 0.62 (57%); m.p: 127-129°C; IR $\bar{\nu}_{\max}$ (KBr): 814 (P=S), 965 (P-O), 1231 (O-C), 1095 (N-C) cm^{-1} ; ^{31}P NMR (121.5 MHz, CDCl_3): 53.4 ppm; ^1H NMR (300 MHz, CDCl_3): δ 6.65-7.58 (11H, m, Ar-H) and 4.35 (1H, dd, $^2J=10.7$, $^3J_{\text{P,H}}=5.2$ Hz, $\text{H}_{\text{a-4}}$), 4.85 (1H, dd, $^2J=10.7$, $^3J_{\text{P,H}}=12.6$ Hz, $\text{H}_{\text{e-4}}$); Anal. Calcd for $\text{C}_{16}\text{H}_{13}\text{ClN}_3\text{OPS}$: C 53.12, H 3.62 and N 11.61; Found: C 53.24, H 3.58 and N 11.51.

2S-(Ethylcarboxyindolyl)-3-(4-chlorophenyl)-3,4-dihydrobenzo[e][1,3,2]oxazaphosphinine 2-sulfide, (4h)

Brown solid, Yield: 0.78 g (54%); m.p: 127-129°C; IR $\bar{\nu}_{\max}$ (KBr): 814 (P=S), 958 (P-O), 1217 (O-C), 1092 (N-C) cm^{-1} ; ^{31}P NMR (121.5 MHz, CDCl_3): 56.4 ppm; ^1H NMR (300 MHz, CDCl_3): δ 6.93-7.62 (12H, m, Ar-H), 4.32 (1H, dd, $^2J=11.1$, $^3J_{\text{P,H}}=5.3$ Hz, $\text{H}_{\text{a-4}}$), 4.82 (1H, dd, $^2J=11.2$, $^3J_{\text{P,H}}=12.8$ Hz, $\text{H}_{\text{e-4}}$), 3.60 (2H, s, $\text{H-3}''$), 2.82 (1H, s, $\text{H-2}''$), 3.27 (2H, q, $J=7.8$ Hz, CO_2CH_2), and 1.56 (3H, t, $J=7.8$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$); Anal. Calcd for $\text{C}_{24}\text{H}_{22}\text{ClN}_2\text{O}_3\text{PS}$: C 59.44, H 4.57 and N 5.78; Found: C 59.54, H 4.64 and N 5.67.

2-(4'-Acetamidophenoxy)-3-(4-chlorophenyl)-3,4-dihydro-2H-benzo[e][1,3,2]oxazaphosphinine 2-sulfide (4i)

Pale yellow solid, Yield: 0.87 g (68%); m.p: 120-123°C; IR $\bar{\nu}_{\max}$ (KBr): 830 (P=S), 949 (P-O), 1223 (O-C), 1093 (N-C) cm^{-1} ; ^{31}P NMR (121.5 MHz, CDCl_3): 62.7 ppm; ^1H NMR (300 MHz, CDCl_3): δ 6.43-7.55 (12H, m, Ar-H), 4.35 (1H, dd, $^2J=10.8$, $^3J_{\text{P,H}}=5.2$ Hz, $\text{H}_{\text{a-4}}$), 4.97 (1H, dd, $^2J=10.8$, $^3J_{\text{P,H}}=11.2$ Hz, $\text{H}_{\text{e-4}}$), 2.18 (s, 3H), and 6.44 (1H, s, N-H); Anal. Calcd for $\text{C}_{21}\text{H}_{18}\text{ClN}_2\text{O}_3\text{PS}$: C 54.89, H 5.37 and N 10.67; Found: C 54.77, H 5.26 and N 10.52.

2-[1-(1,1,1,3,3,3-Hexamethyl)disilazanyl]-3-(4-chlorophenyl)-3,4-dihydrobenzo[e][1,3,2]oxazaphosphinine 2-sulfide, (4j)

Pale brown solid, Yield: 0.91 g (67%); m.p: 126-128°C; IR $\bar{\nu}_{\max}$ (KBr): 815 (P=S), 959 (P-O), 1211 (O-C), 1087 (N-C) cm^{-1} ; ^{31}P NMR (121.5 MHz, CDCl_3): 63.8 ppm; ^1H NMR (300 MHz, CDCl_3): δ 6.83-7.52 (8H, m, Ar-H), 4.34 (1H, dd, $^2J=10.6$, $^3J_{\text{P,H}}=5.2$ Hz, $\text{H}_{\text{a-4}}$), 4.90 (1H, dd, $^2J=10.6$, $^3J_{\text{P,H}}=11.2$ Hz, $\text{H}_{\text{e-4}}$), and 0.12 (18H, s, Si-CH_3). Anal. Calcd for $\text{C}_{19}\text{H}_{28}\text{ClN}_2\text{OPSSi}_2$: C 50.14, H 6.20 and N 6.16; Found: C 50.18, H 6.25 and N 6.06.

Bioassay

The experiments were carried out on the cultures *Escherichia coli*, *Bacillus subtilis*, *Salmonella enteritidis*, *Staphylococcus aureus* and fungal cultures *Aspergillus niger* and *Candida albicans*.

Microbial testing

The filter paper disc method^{14,15} was followed using Sabouraud dextrose broth and Mueller Hinton broth. These agar media were inoculated with 0.5 mL of the 24h liquid cultures containing 10^7 microorganisms/mL. Whatman No. 1 filter paper discs containing 10 μg , 20 μg and 30 μg of test compounds were placed on the nutrient agar already plated with test bacteria. The incubation time was 24h at 37°C for bacteria and

48 h at 30°C for fungal species. Discs with only Gentamycin and Nystatin were used as control for bacterial and fungal species respectively. Inhibitory activity was measured in mm as the diameter of the observed inhibition zones. The tests were repeated to confirm the findings and the average of three readings was taken into consideration. (Table 1).

Table 1. Antimicrobial activity of 1, 4a-j -inhibition zones (mm) - no activity

Compd.	Concentration mg/mL	<i>Escherichia coli</i>	<i>Bacillus subtilis</i>	<i>Salmonel laenteritidis</i>	<i>Staphilococcus aureus</i>	<i>Aspergillus niger</i>	<i>Candida albicans</i>
1	1	-	-	-	-	-	-
	5	-	-	-	-	-	-
	10	-	-	-	-	-	-
4a	1	13.0	12.1	13.5	13.2	13.1	12.0
	5	15.0	14.3	15.0	15.0	14.4	14.0
	10	16.0	16.0	16.3	16.0	15.5	15.5
4b	1	15.3	14.0	15.5	15.0	14.0	13.2
	5	16.7	15.0	17.0	17.0	16.5	14.7
	10	18.0	16.5	19.0	19.0	18.0	15.5
4c	1	14.0	13.0	13.0	15.5	14.0	14.0
	5	14.0	13.0	13.0	17.0	16.0	15.5
	10	17.0	15.5	15.0	19.0	17.0	16.5
4d	1	15.0	16.0	14.0	15.0	14.5	16.0
	5	17.0	17.5	16.5	16.5	16.0	17.5
	10	19.0	18.5	18.5	17.5	18.0	20.0
4e	1	14.0	14.0	16.0	16.0	15.0	15.0
	5	15.0	16.0	17.0	18.5	17.3	17.0
	10	16.5	18.0	19.0	22.0	19.0	18.7
4f	1	15.0	14.4	13.0	16.0	16.0	15.5
	5	17.0	15.5	14.5	18.5	17.5	17.0
	10	18.0	17.0	16.0	21.0	19.0	18.5
4g	1	16.0	16.0	17.0	20.0	18.0	17.0
	5	17.0	18.0	20.0	22.0	20.0	18.0
	10	20.0	20.0	21.5	24.0	22.0	19.0
4h	1	10.0	9.0	10.0	10.0	10.0	10.0
	5	13.0	12.0	12.0	12.0	13.0	12.5
	10	15.0	14.0	13.0	15.5	16.5	14.5
4i	1	16.0	14.0	16.0	20.0	12.5	14.5
	5	18.0	15.5	17.0	22.5	14.5	15.5
	10	19.0	17.0	19.0	25.0	16.5	17.0
4j	1	9.0	15.0	10.0	9.0	10.0	14.0
	5	12.0	16.0	12.0	10.5	12.5	15.5
	10	14.0	18.0	15.0	12.0	15.5	16.0
Gentamycin	10	16.0	13.0	17.0	15.0	-	-
Nystatin	10	-	-	-	-	11.0	12.0

Conclusions

A simple synthesis of novel 2-heterocyclic /acyclicamino/4'-Acetamidophenyl 3-(4-chlorophenyl)-3, 4-dihydrobenzo [e] [1,3,2]oxazaphosphinine 2-sulfides (4a-j) is presented. The title compounds were exhibited promising antibacterial and fungicidal activity.

Acknowledgement

The authors are thankful to Prof. C. Devendranath Reddy, Dept. of Chemistry, S.V. University, Tirupati, India for helpful discussion and to The Director, CDRI, Lucknow for spectral and analytical data.

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