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Synthesis, Spectroscopic Studies and Antimicrobial Activity of *Tetrakis*(4-bromo-2-formylphenoxy)cyclotriphosphazene and its Imino-Amino Derivatives

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Tetrakis(4-bromo-2-formylphenoxy)cyclotriphosphazene (**1**) derived from 5-bromo-2-hydroxybenzaldehyde and hexachloro cyclotriphosphazene have been synthesized. The condensation reactions of **1** with some amines in THF have been studied. A series of Schiff bases and amino containing phosphazenes (**2**, **3** and **4**) were isolated and characterized by elemental analysis, UV, IR, ^{1}H, ^{13}C, ^{31}P NMR and mass spectroscopy. The antimicrobial activities of these compounds have been screened *in vitro* against the organisms *Bacillus cereus* ATCC 7064, *Bacillus subtilis* ATCC 6633, *Escherichia coli* ATCC 11230, *Staphylococcus aureus* ATCC 6538P, *Staphylococcus epidermidis* ATCC NRRL 3284, *Enterobacter aerogenes* ATCC 13048, *Micrococcus luteus* LA 2971, *Proteus vulgaris* ATCC 8427, *Salmonella typhi* ATCC 19430, *Salmonella typhimurium* CCM 5445, *Pseudomonas aeruginosa* ATCC 27853, *Pseudomonas fluorescens* ATCC 17400, *Listeria monocytogenes* ATCC 19117, *Rhodotorula rubra* DSM 70403, *Debaryomyces hansenii* DSM 70238, *Hanseniaspora guilliermondii* DSM 3432, *Kluyveromyces fragilis* NRRL 2415, *Candida albicans* ATCC 10231, *Candida parapsilosis* ATCC 90018, *Candida tropicalis* ATCC 13803.

Key Words: Phosphazene, Schiff bases, Condensation reactions, Spectroscopic studies, Antimicrobial activities.

INTRODUCTION

The reactions of trimeric phosphazene, ($N_3P_3Cl_6$) with aryloxides[1-10] in different conditions have been studied. The phenoxy derivatives of trimeric phosphazene ($N_3P_3Cl_6$), have found applications in the synthesis of new, small-molecule organocyclophosphazenes[11] and polymeric phosphazene derivatives with inorganic backbones and aryloxy side groups which may be useful as high refractive index glasses[12], ferroelectric and non-linear optical polymers[13], liquid crystalline materials[14], biomedical materials[15] and small molecule models for the corresponding linear

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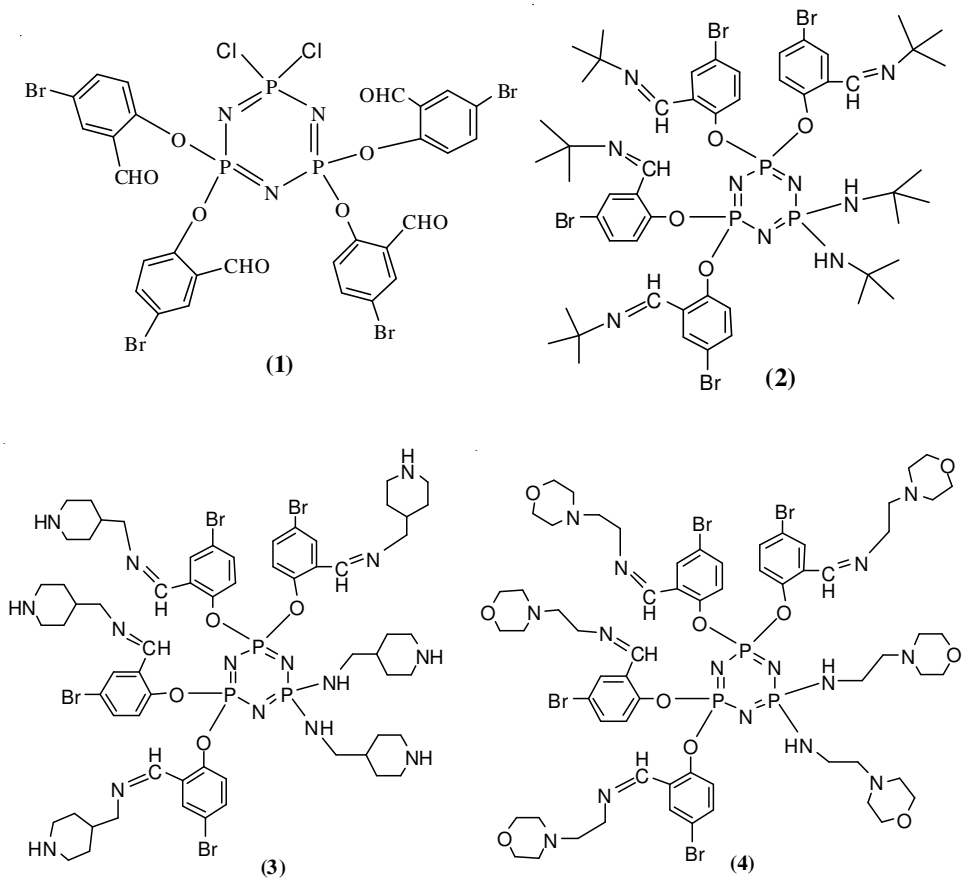
phosphazene macromolecules. The organic, inorganic or organometallic side groups are highly effective in determining the specific physical or chemical properties of phosphazene polymers[16-25]. They also possess a number of characteristics such as biomedical properties and applications due to their strong antitumor activity[26-30]. Their antimicrobial activities on bacterial and yeast cells have been studied[31-33]. Although the partial and complete phenolysis reaction of trimer ($N_3P_3Cl_6$) with hydroxyaldehyde have been studied[34-40], there are only a few reports about its Schiff base derivatives[34,35,37,41]. In this study, we synthesized partially substituted *tetrakis*(4-bromo-2-formylphenoxy)cyclotriphosphazene (**1**) from the reaction of hexachloro cyclotriphosphazene and 5-bromo-2-hydroxybenzaldehyde. The new phenoxyimino-amino phosphazene (**2**, **3** and **4**) derivatives have been isolated (**Scheme-I**). The structures of the compounds were characterized by elemental analysis, UV, IR, ^{1}H, ^{13}C, ^{31}P NMR and mass spectroscopy and then subjected to *in vitro* assays of antimicrobial activity.



Scheme-I: Structures of compounds **1**-**4**

EXPERIMENTAL

^{1}H, ^{13}C NMR spectra were recorded on a Bruker DPX FT-NMR spectrometer operating at 400 and 101.6 MHz. Infrared absorption spectra were recorded on a Perkin-Elmer BX II spectrometer in KBr discs. UV-vis spectra were recorded on a Shimadzu 1201 series spectrometer. Carbon, hydrogen and nitrogen analyses were performed on a Leco CHNS-932 C-, H-, N- analyzer. LC mass spectra were obtained on a Agilent 1100 MSD spectrometer with an ion source temperature of 240 °C. Melting points were measured on a Electro Thermal IA 9100 apparatus using a capillary tube. Hexachloro cyclotriphosphazene was purchased from Aldrich. It was recrystallized from hexane and purified by fractional vacuum sublimation at 55 °C before use. Tetrahydrofuran was purchased from Merck, distilled over sodium/benzophenone and stored over molecular sieves. K_2CO_3 (Merck), *n*-hexane (Merck), $CHCl_3$ (Merck), CH_2Cl_2 (Merck), petroleum ether (50:70) (Merck), 5-bromo-2-hydroxybenzaldehyde (Merck), *t*-butylamine (Merck), 4-(aminomethyl)piperidine (Merck), 4-(2-aminomethyl)morpholine (Merck), silica gel (Aldrich, 70-230 mesh, 60 Å) were used as received and all reactions were monitored by using Kieselgel 60 F_{254} (silica gel) precoated TLC plates. All reactions and manipulations were carried out under an atmosphere of dry argon.

Synthesis of 2,2,4,4-*tetrakis*[4-bromo-2-formyl phenoxy]-6,6-dichlorocyclo-2λ^5,4λ^5,6λ^5-triphosphazatriene (1): Solution of 5-bromo-2-hydroxybenzaldehyde (13.065 g; 6.5×10^{-2} mol) in dry THF (50 mL) was added drop wise to a stirred solution of hexachloro cyclotriphosphazene (3.5 g; 1.0×10^{-2} mol) and K_2CO_3 (17.94 g; 1.3×10^{-1} mol), in dry THF (150 mL) in argon atmosphere. The mixture was stirred for 72 h at room temperature. It was boiled under reflux (12 h) using a condenser fitted with a $CaCl_2$ drying tube. The precipitated potassium chloride was filtered off and the solvent removed by rotary evaporation. The crude product was dried under *vacuo* and chromatographed (silica gel, 150 g, eluent; $CHCl_3$/hexane, 3:1) to give the compound **1**. It was recrystallized from CH_2Cl_2/petroleum ether (50:70) by the slow diffusion method yielding a white solid, m.p. 153-154 °C, 4.25 g (42 %) yields. IR (KBr, ν_{max}, cm^{-1}) (Ar-H) 3075 w, (C-H, aliphatic) 2872 m, (C=O) 1690 s, (C=C) 1590 s, (P-O-C) 1389, 1261, 1106 s, (P=N) 1171 s, (P-Cl) 618, 527 s. ^{31}P NMR ($CDCl_3$); δ ppm, 6.25 (d, 2P, $P(OArBrCH{=}N\text{-}R)_2$), 21.47 (t, 1P, PCl_2). MS (highest peak in multiplet, based on Cl^{35}): m/z; 1006 (M^+, 13 %).

Synthesis of 2,2,4,4-*tetrakis*[*N*-(5-bromo-2-oxybenzylidene)-2-methyl-propan-2-amine]-6,6-*bis*(*t*-butylamino)-2λ^5,4λ^5,6λ^5-triphosphazatriene (2): Solution of *t*-butylamine (0.293 g; 40.2×10^{-4} mol) in dry THF (10 mL) was added drop wise to a stirred solution of compound **1** (0.5 g; 4.9×10^{-4} mol), in dry THF (150 mL) in argon atmosphere. The mixture was stirred for 3 h at room temperature. It was boiled under reflux (12 h) using a condenser fitted with a $CaCl_2$ drying tube. The precipitated amine hydrochloride was filtered off and the solvent removed by rotary evaporation. The crude product was dried under *vacuo* and chromatographed

(silica gel, 60 g, eluent; $CHCl_3$/hexane, 3:1) to give the compound **2**. It was recrystallized from CH_2Cl_2/petroleum ether (50:70) by the slow diffusion method yielding a yellow solid, m.p. 85 °C, 0.575 g (89 %) yields. IR (KBr, ν_{max}, cm^{-1}): (N-H) 3432 m, (Ar-H) 3062 w, (C-H, aliphatic) 2970-2927 s, (C=N) 1633 s, (C=C) 1591 m, (P-O-C) 1390, 1254, 1178, 1108 s, (P=N) 1203 s. ^{31}P NMR ($CDCl_3$); δ ppm, 9.58 (d, 2P, P(OAr-BrCHO)$_2$), 2.88 (t, 1P, P(NH-R)$_2$). MS (highest peak in multiplet, based on Cl^{35}): m/z; 1299 (M^+, 21 %). 578 (M-*tert*-BuNH), 13 %), 270 (M- (OArBrCH)), 18 %).

Synthesis of 2,2,4,4-*tetrakis*[*N*-(5-bromo-2-oxybenzylidene)-1-(piperidin-4-yl)methanamine]-6,6-*bis*(4-(aminomethyl)piperidine)-2λ^5,4λ^5,6λ^5-triphosphazatriene (3): Solution of piperidin-4-ylmethanamine (0.45 g; 40.3×10^{-4} mol) in dry THF (10 cm^3) was added drop wise to a stirred solution of compound 1 (0.5 g; 4.9×10^{-4} mol), in dry THF (150 mL) under argon atmosphere. The mixture was stirred for 3 h at room temperature. It was boiled under reflux (12 h) using a condenser fitted with a $CaCl_2$ drying tube. Compound **3** was prepared and purified as compound **2**, yellow solid, m.p. 128-130 °C, 0.71 g (92 %) yields. IR (KBr, ν_{max}, cm^{-1}): (N-H) 3400 s, (Ar-H) 3070 w, (C-H, aliphatic) 2914, 2852 s, (C=N) 1638 s, (C=C) 1578 s, (P-O-C) 1347, 1262, 1162, 1110 s, (P=N) 1204 s. ^{31}P NMR ($CDCl_3$); δ ppm, 9.38 (d, 2P, P(OArBrCH=N-R)$_2$), -0.10 (t, 1P, P(NH-R)$_2$).

Synthesis of 2,2,4,4-*tetrakis*[*N*-(5-bromo-2-oxybenzylidene)-2-morpholinoethanamine]-6,6-*bis*(2-morpholinoethanamino)-2λ^5,4λ^5,6λ^5-triphosphazatriene (4): Solution of 4-(2-aminomethyl)morpholine (0.52 g; 40.0×10^{-4} mol) in dry THF (10 mL) was added drop wise to a stirred solution of compound **1** (0.5 g; 4.9×10^{-4} mol), in dry THF (150 cm^3) in argon atmosphere. The mixture was stirred for 3 h at room temperature. It was boiled under reflux (12 h) using a condenser fitted with a $CaCl_2$ drying tube compound **4** was prepared and purified as compound **2**, orange solid, m.p. 78 °C, 0.64 g (79 %) yields. IR (KBr, ν_{max}, cm^{-1}): (N-H) 3434 s, (Ar-H) 3070 w, (C-H, aliphatic) 2926, 2848 s, (C=N) 1638, (C=C) 1474 s, (P-O-C) 1369 m, 1254, 1174, 1114 s, (P=N) 1200 s. ^{31}P NMR ($CDCl_3$); δ ppm, 10.11 (t, 1P, P(NH-R)$_2$), 9.65 (d, 1P, P(OArBrCH=N-R)$_2$).

Antimicrobial test: The compounds were dissolved in DMSO to a final concentration of 100 µg/mL. Empty sterilized antibiotic discs having a diameter of 6 mm (Schleicher and Schull No 2668, Germany) were each impregnated with 20 µL of solution. All the bacteria mentioned above were incubated at 30 ± 0.1 °C for 24 h by inoculution into Nutrient Broth (Difco) and the yeasts studied were incubated in Malt Extract Broth (Difco) for 48 h. An inoculum containing 106 bacterial cells or 10^8 yeast cells/mL was spread on Mueller-Minton Agar (Oxoid) plates (1 mL inoculum/plate). The discs injected with solutions were placed on the inoculated agar by pressing slightly and incubated at 35 °C (24 h) for bacteria and at 25 °C (72 h) for yeast. On each plate an appropriate reference antibiotic disc was applied depending on the test microorganisms[42,43].

RESULTS AND DISCUSSION

The reaction of trimer with exces of 5-bromo-2-hyroxybenzaldehyde in the presence of K_2CO_3 in THF gave *tetrakis*(4-bromo-2-formyl phenoxy)cyclotriphosphazene (**1**). Disubstituted amino-tetrasubstituted Schiff base compounds were obtained from the reactions of **1** with excess of *tert*-butyl amine, 4-(aminomethyl)-piperidine and 4-(2-aminomethyl)morpholine in THF. Although excess amount of 5-bromo-2-hyroxybenzaldehyde was used, only two P atoms was produced as geminal *tetrakis*-product in hexachloro cyclotriphosphazene. However, the other P atom was not reacted with 5-bromo-2-hydroxybenzaldehyde. On the other hand, the reaction of this P atom excess of amines in THF gave disubstituted-amino products (**2**, **3** and **4**).

The structures of the compounds were characterized by elemental analysis, UV, IR, ^{1}H, ^{13}C, ^{31}P NMR and mass spectroscopy. Analytical and experimental data are given in Table-1 for compounds **1**-**4**.

TABLE-1
ANALYTICAL AND EXPERIMENTAL DATA OF THE COMPOUNDS **1**-**4**

Compound	m.p. (°C)	Color	Yield (%)	C (%)		H (%)		N (%)	
				Calcd.	Exp.	Calcd.	Exp.	Calcd.	Exp.
1	153-154	white	42	33.40	33.39	1.59	1.59	4.17	4.17
2	85	yellow	89	48.03	47.98	5.54	5.53	9.69	9.69
3	128-130	yellow	92	49.70	49.69	5.83	5.82	13.59	13.59
4	78	orange	79	46.80	46.80	5.48	5.48	12.80	12.79

The IR spectra of the compounds are given in experimental section (Fig. 1). The characteristic ν(P=N) and ν(C=O) bands for **1** were observed at 1171 and 1690 cm^{-1}, respectively. The P=N and C=N stretching frequencies of compounds **2**-**4**

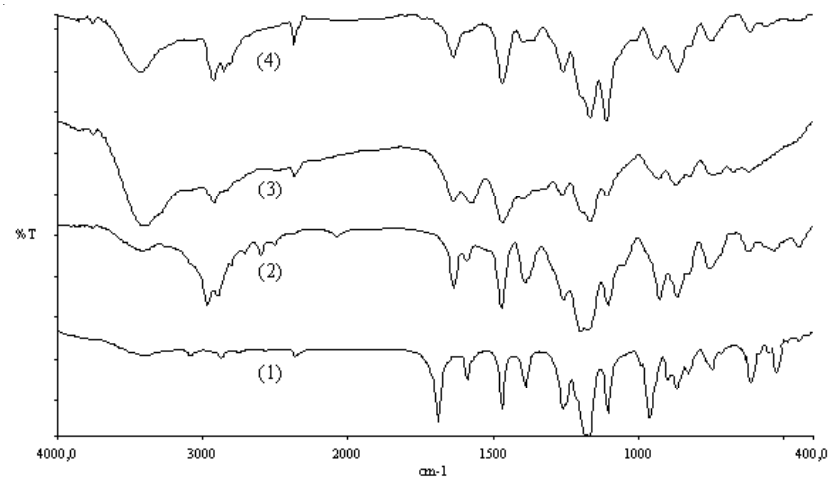


Fig. 1. FT-IR spectrum of the compounds **1**-**4**

were observed at 1203, 1204 and 1200 cm^{-1} ν(P=N) and 1633, 1636 and 1638 cm^{-1} ν(C=N), respectively. The P=N vibration bands of **1** observed in a lower frequency than the compounds **2**, **3** and **4**. The N-H bands for **2**-**4** were observed at 3432, 3400 and 3434 cm^{-1} ν(N-H), respectively. The P-Cl band was not observed for compounds **2**-**4**, while it is observed at 618-527 cm^{-1} for compound **1**.

In the ^1H NMR spectra, the formyl (O=C-H) proton is observed δ = 10.03 ppm doublet ($^5J_{PCH}$: 3.76 Hz) for compound **1**. The imine (N=C-H) protons are observed δ = 8.27 ppm singlet, δ = 4.70 ppm singlet and δ = 8.23 ppm singlet, respectively, for compounds **2**, **3** and **4**. The N-H protons are observed δ = 3.24 ppm doublet ($^2J_{PNH}$: 8.43 Hz) (**2**), δ = 3.80 ppm singlet, δ = 3.00 ppm doublet ($^2J_{PNH}$: 12.60 Hz) (**3**) and δ = 4.92 ppm broad-singlet (**4**). The phenyl protons resonate at δ = 7.96-6.98 ppm multiplet, δ = 7.39-6.83 ppm multiplet, δ = 7.72-6.80 ppm multiplet and δ = 7.47-6.74 ppm multiplet, respectively, for compounds **1**, **2**, **3** and **4**. The *tert*-Bu protons $C(C\underline{H}_3)_3$ in **2** also gave a singlet at δ = 1.36 and δ = 1.34, doublet δ = 1.20 ppm ($^4J_{PNCCH}$ = 2.80 Hz) and δ = 1.16 ppm ($^4J_{PNCCH}$ = 5.10 Hz). The $C(CH_3)_3$ protons are no equivalent for compound **2**. The $NC\underline{H}_2$ protons of **3** are observed at δ = 2.40-2.48 ppm multiplet. The $OC\underline{H}_2$ and $NC\underline{H}_2$ protons of the compound **4** gave a triplet at δ = 3.71 ppm ($^3J_{HH}$ = 5.19 Hz) and δ = 2.95 ppm ($^3J_{HH}$ = 5.19 Hz) and a multiplet at δ = 2.53 ppm, respectively.

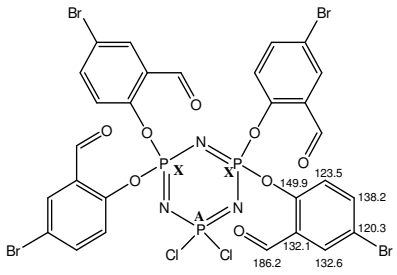
According to the ^{13}C NMR spectra compounds **1**, **2**, **3** and **4** have 7, 11, 15 and 15 signals. ^{13}C NMR data are given in Table-2.

The ^{31}P NMR spectra of compounds **1**, **2**, **3** and **4** were interpreted as the result of a simple AX_2 spin system. The ^{31}P NMR spectra showed, that fully substituted phosphazene compound was not found in a residue after the formylation process of trimer (only two signals at δ = 21.47 ppm and 6.25 ppm were observed for **1**) (Fig. 2). According to the proton coupled ^{31}P NMR spectrum, it can be concluded that compound **1** may have the partially substituted structure. Chemical shifts were, δ $P(OArBrCHO)_2$ = 6.25 and δ PCl_2 = 21.47 in **1**, δ $P(OArBrCH=N\text{-}R)_2$ = 9.58 and δ $P(NH\text{-}R)_2$ = 2.88 in **2**, δ $P(OArBrCH=N\text{-}R)_2$ = 9.38 and δ $P(NH\text{-}R)_2$ = -0.10 in **3** and δ $P(NH\text{-}R)_2$ = 10.11 and δ $P(OArBrCH=N\text{-}R)_2$ = 9.65 in **4**. Two bond coupling constants $^2J_{PNP}$ are 84.83, 78.09, 71.17 and 15.24 Hz for **1**, **2**, **3** and **4**, respectively.

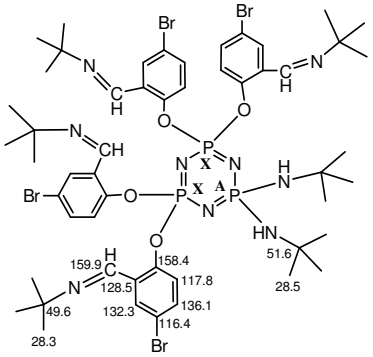
The electron impact MS spectrum of compounds (**1** and **2**) showed a well-defined parent ion at m/z 1006 and 1299 (13 and 21 %) with the expected isotope pattern. The peaks, at m/z values of 578 and 270, correspond to the loss of (M-*tert*-BuNH) and [M-(OArBrCH)] groups in **2**. N_3P_3 ring system in **1** and **2** is not stable (dominant ion was not observed: m/z 134) during the fragmentation that indicates the first loss of *tert*-butylamino and phenoxy fragments. The MS spectra of compounds **3** and **4** were not given because of their molecular weights that exceed the limitation of the spectrometer.

The UV-vis spectra of the compounds **1**-**4** were studied in $CHCl_3$. The absorptions are attributable to the π-π* transition of the phosphazene bonded organic groups[44]. Two absorption bands were observed for compounds **1**-**4** at 245, 245, 244, 243 and 307, 310, 326, 298 nm due to π-π* and ν-π* transitions, respectively (Fig. 3).

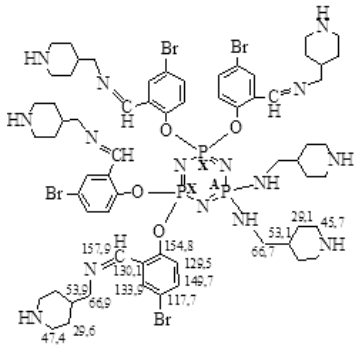
TABLE-2
^{13}C NMR DATA OF THE COMPOUNDS **1**-**4**



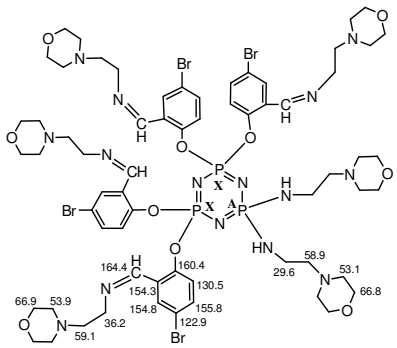
(**1**)



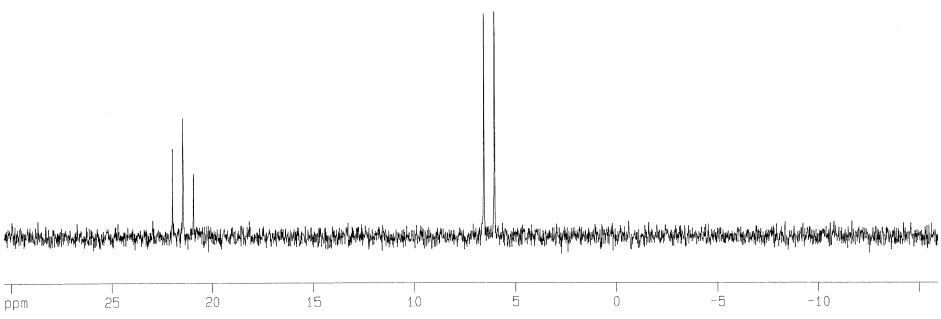
(**2**)



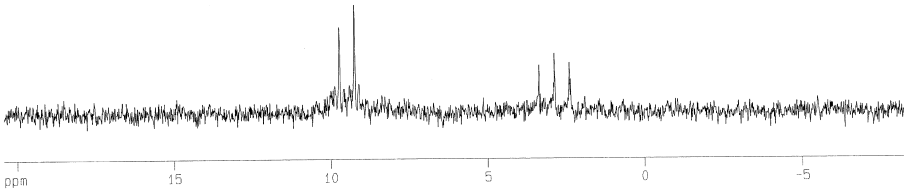
(**3**)



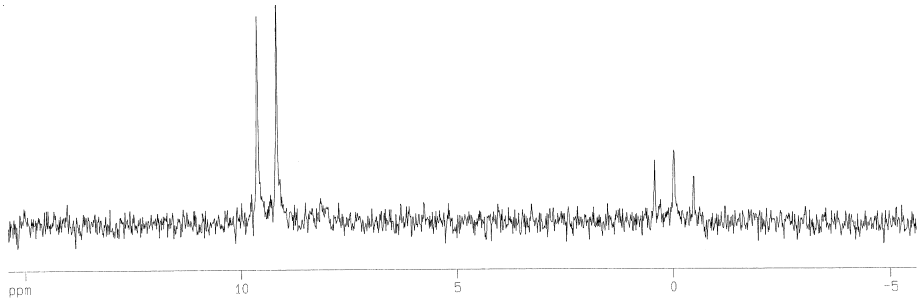
(**4**)



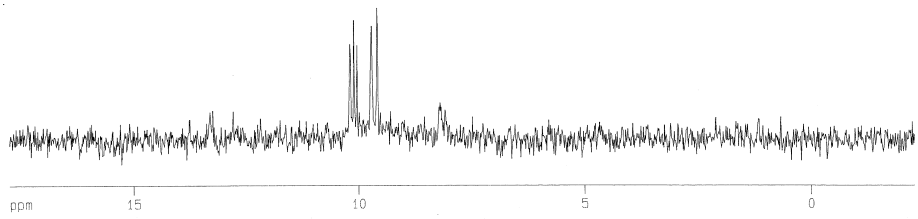
(**1**)



(**2**)



(**3**)



(**4**)

Fig. 2. ^{31}P NMR spectrum of the compounds **1**-**4**

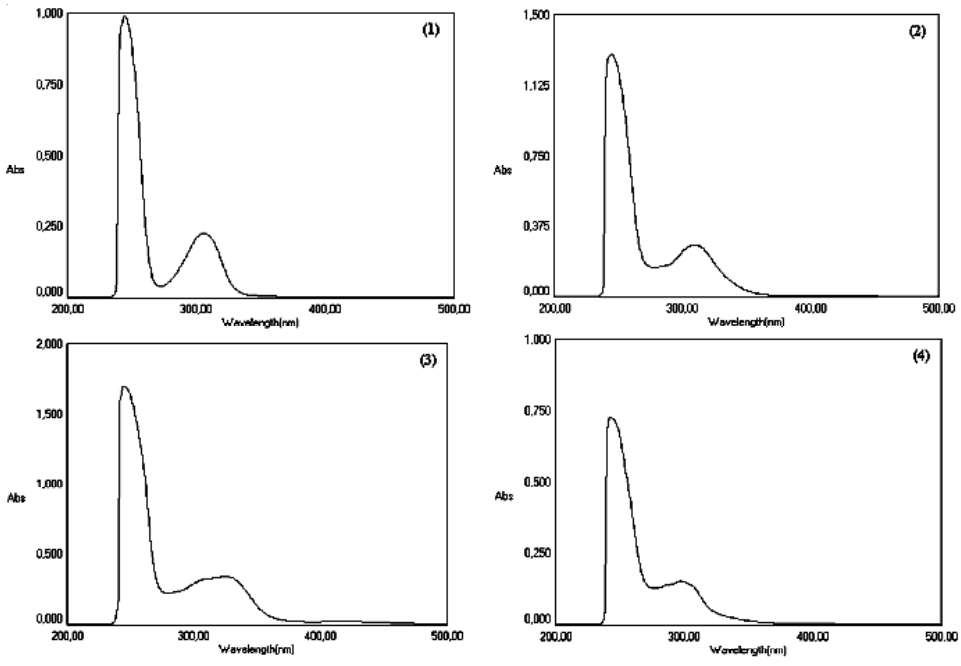


Fig. 3. UV-Vis spectrum of the compounds **1**-**4**

All the bacterias, *Bacillus cereus* ATCC 7064, *Bacillus subtilis* ATCC 6633, *Escherichia coli* ATCC 11230, *Staphylococcus aureus* ATCC 6538P, *Staphylococcus epidermidis* ATCC NRRL 3284, *Enterobacter aerogenes* ATCC 13048, *Micrococcus luteus* LA 2971, *Proteus vulgaris* ATCC 8427, *Salmonella typhi* ATCC 19430, *Salmonella typhimurium* CCM 5445, *Pseudomonas aeruginosa* ATCC 27853, *Pseudomonas fluorescens* ATCC 17400, *Listeria monocytogenes* ATCC 19117 and, the yeast cultures *Rhodotorula rubra* DSM 70403, *Debaryomyces hansenii* DSM 70238, *Hanseniaspora guilliermondii* DSM 3432, *Kluyveromyces fragilis* NRRL 2415, *Candida albicans* ATCC 10231, *Candida parapsilosis* ATCC 90018, *Candida tropicalis* ATCC 13803 were used in this study as the test microorganisms. The data reported in Table-3 are the average data of three experiments.

TABLE-3
ANTIMICROBIAL ACTIVITIES OF THE COMPOUNDS
(**1**-**4**) AND SOME STANDARD ANTIBIOTICS

Microorganisms	Inhibition zone (mm)										
	Compounds				Antibiotics						
	1	2	3	4	AK30	SAM20	CTX30	VA30	NY100	KETO20	CLT10
B. subtilis	12	12	12	12	20	14	16	20	–	–	–
B. cereus	14	12	14	18	16	12	14	18	–	–	–
Escherichia coli	11	9	11	12	17	12	10	22	–	–	–
S. aureus	9	10	9	10	24	16	12	13	–	–	–
S. epidermidis	11	12	12	13	23	18	15	15	–	–	–
E. aerogenes	11	10	10	12	18	15	14	18	–	–	–
S. typhimurium	10	10	10	10	20	20	18	16	–	–	–
S. typhi	12	11	12	13	19	18	18	18	–	–	–
L. monocytogenes	11	12	12	13	20	12	16	26	–	–	–
Micrococcus luteus	10	10	8	9	24	32	32	34	–	–	–
Proteus vulgaris	10	10	10	9	18	16	18	20	–	–	–
P. aeruginosa	12	13	14	16	19	10	54	10	–	–	–
P. fluorescens	12	14	14	16	18	16	36	16	–	–	–
H. guilliermondii	10	12	10	10	–	–	–	–	21	24	22
K. fragilis	10	10	10	10	–	–	–	–	18	16	18
C. albicans	10	11	10	15	–	–	–	–	20	21	15
C. parapsilosis	12	11	11	16	–	–	–	–	22	20	16
C. tropicalis	11	13	13	16	–	–	–	–	18	18	16
Rhodotorula rubra	9	10	12	12	–	–	–	–	18	22	16
Debaryomyces hansenii	10	11	11	10	–	–	–	–	16	14	18

AK30: Amikacin 30 µg, SAM20: Ampicillin 10 µg, CTX30: Cefotaxime 30 µg, V30: Vancomycin 30 µg, NY100: Nystatin 100 µg, KETO20: Ketaconazole 20 µg: CLT10: Clotrimazole 10 µg.

Table-3 shows antimicrobial activities of the compounds and standard antibacterial and antifungal antibiotic discs. The compounds showed antibacterial activity against both gram-positive and gram-negative bacteria and the yeast cultures in this study. In classifying the antibacterial activity as gram-positive or gram-negative, it would generally expected that more number would be active against gram-positive than gram-negative bacteria[45,46]. However, in this study, the compounds are active against

both types of the bacteria and as well as active against yeasts, which may indicate broad-spectrum properties.

Compound **4** against *Bacillus* and *Pseudomonas* species has stronger antibacterial effect than those of some standard antibacterial antibiotics. Similarly, The same compound has higher antifungal activity against species of *Candida* species than those of the standard antifungal antibiotic clotrimazole.

Fungi used in this study were chosen primarily on the basis of their importance as oppurtunictic pathogens of humans. According to findings from the National Nosocomial Infection Surveillance System (NNIS), 61 % of reported nosocomial fungal infections were due to *Candida albicans*, followed by other *Candida* spp.[47]. *Candida albicans*, while naturally occurring in the intestinal flora, can cause oral thrush and systemic infections.

The results of our study indicate that the compounds especially the compound **4** have the potential to generate novel metabolites. Their strong effect on many tested organisms, particularly their lethal anticandidal activity could result in the discovery of novel anticandidal agents, demonstrating broad-spectrum characteristic. These compounds could be selected for further pharmacological tests to be evaluated as potential drugs against many infectious diseases.

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