Synthesis and Antimicrobial Activity of Novel 3-[1-(3-nitrophenyl)-ethyl]-1-(indole-1-yl) Substituted Aryl/alkyl-phosphinoyl/thiophosphinoyl/ selenophosphinoyl-1*H*-indole Derivatives

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Received 26 October 2007, revised 14 December 2007, accepted 21 January 2008.

ABSTRACT

Syntheses of novel 3-[1-(3-nitrophenyl)-ethyl]-1-(indole-1-yl) substituted aryl/alkyl phosphinoyl/thiophosphinoyl/ selenophosphinoyl-1*H*-indole derivatives were accomplished in two steps. The synthetic route involves the cyclisation of equimolar quantities of 3-[1*H*-3-indolyl(3-nitrophenyl)methyl]-1*H*-indole with dichlorophenyl phosphine/ethyldichlorophosphite in the presence of triethylamine in dry acetonitrile at room temperature. These compounds were further converted to the corresponding oxides, sulphides and selenides by reacting them with hydrogen peroxide, sulphur and selenium, respectively. The structures of the novel products were established by elemental analyses, IR, ^{1}H, ^{13}C and ^{31}P NMR and mass spectroscopy. They were screened for antibacterial and antifungal activity against *Staphylococcus aureus*/*Klebsiella pneumoniae* and *Pellicularia solmanicolor*/*Macrophomina phaseolina*, respectively.

KEYWORDS

Bisindolylalkanes, alkyl/aryl phosphorodichloridates, antimicrobial activity.

1. Introduction

Bisindolylalkanes and their derivatives constitute an important group of bioactive metabolites of terrestrial and marine origin.[1] Many of the indole alkaloids exhibit well-defined pharmacological activity[2] and several of them have found clinical use. Indeed the possibility of discovering new bisindolylalkane derivatives with useful pharmacological activity still provides the stimulus to investigation in this area as much as do the intellectual rewards of structure elucidation and synthesis. The most characteristic effect of these drugs is the arrest of cell division at metaphase, in a manner resembling the effect of colchicines. An increasing interest has been generated in the last twenty years in the chemistry of phosphorus heterocyclics due to their unique physicochemical properties[3] and potential biological activities.[4–7] Many classes of phosphorus heterocyclic systems bearing P-O and P-N moieties such as cyclophosphamide and its derivatives are also

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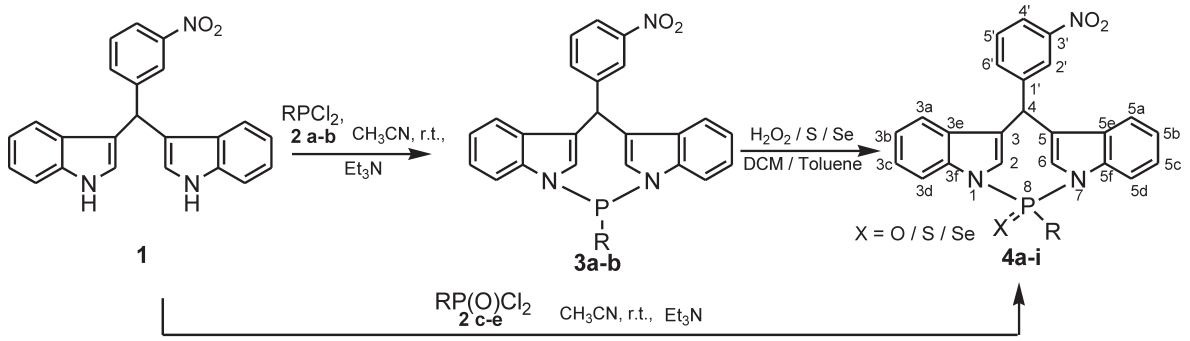

Compound	R	X	Compound	R	X	Compound	R	X
4a	C_6H_5	O	**4d**	OC_2H_5	O	**4g**	OC_6H_5	O
4b	C_6H_5	S	**4e**	OC_2H_5	S	**4h**	OC_6H_4-NO_2(4'')	O
4c	C_6H_5	Se	**4f**	OC_2H_5	Se	**4i**	$N(CH_2CH_2Cl)_2$	O

Scheme 1

Table 1 Physical, analytical, IR and ^{31}P NMR spectral data of **4a–i.**

Compound	M.p./°C	Yield [a] /%	Molecular formula	Elemental analysis Found (calculated)/%			$\bar{\nu}$ /cm^{-1}		δ(^{31}P)/ppm [b,c]
				C	H	N	P=O/S/Se	(P-C / P-O-C)$_{(aromatic)}$/ P-O-C$_{(aliphatic)}$	
4a	232–233	63	$C_{29}H_{20}N_3O_3P$	71.24 (71.16	4.11 4.08	8.54 8.58)	1271	938	16.69
4b	256–257	58	$C_{29}H_{20}N_3O_2PS$	68.97 (68.91	3.98 3.96	8.28 8.31)	779	940	68.38
4c	241–242	68	$C_{29}H_{20}N_3O_2PSe$	63.08 (63.04	3.67 3.62	7.64 7.60)	623	936	81.27
4d	226–254	61	$C_{25}H_{20}N_3O_4P$	65.69 (65.64	4.32 4.37	9.23 9.19)	1268	1128	24.37
4e	253–254	72	$C_{25}H_{20}N_3O_3PS$	63.48 (63.42	4.18 4.22	8.82 8.87)	784	1146	49.37
4f	238–239	63	$C_{25}H_{20}N_3O_3PSe$	57.76 (57.69	3.87 3.84	8.09 8.07)	632	1153	65.30
4g	246–247	57	$C_{29}H_{20}N_3O_4P$	68.98 (68.91	3.92 3.96	8.29 8.31)	1279	1172	19.41
4h	250–251	75	$C_{29}H_{19}N_4O_6P$	63.31 (63.27	3.41 3.45	10.14 10.18)	1273	1184	21.73
4i	221–222	64	$C_{27}H_{23}N_4O_3PCl_2$	61.18 (61.13	4.30 4.33	10.61 10.56)	1267	–	18.25

[a] Recrystallized from ethanol.
[b] Recorded in $CDCl_3$.
[c] Chemical shifts in ppm from 85% phosphoric acid.

antitumor agents.[8] In view of the exhibition of potential bioactivity of these molecular skeletons, their phosphorus structural analogues,[9] which are a rare class of heterocylces, have been synthesized. It is expected that they might possess a broad spectrum of biological activity with less toxicity in comparison with cyclophosphamides.

2. Results and Discussion

Syntheses of novel 3-[1-(3-nitrophenyl)-ethyl]-1-(indole-1-yl) substituted aryl/alkyl-phosphinoyl/thiophosphinoyl/selenophosphinoyl-1*H*-indole derivatives (**4a–f**) were accomplished in two steps. The synthetic route involves the cyclisation of equimolar quantities of 3-[1*H*-3-indolyl(3-nitrophenyl)methyl]-1*H*-indole (**1**) with dichlorophenyl phosphine/ethyldichlorophosphite (**2a–b**) in the presence of triethylamine in dry acetonitrile at room temperature. They were further converted to the corresponding oxides, sulphides and selenides by reacting them with hydrogen peroxide, sulphur and selenium, respectively (Scheme 1). The compounds (**4g–i**) were prepared by the direct cyclocondensation of equimolar quantities of **1** with various aryl phosphorodichloridates (**2c–d**) and bis-(2-chloroethyl)phosphoramidic dichloride (**2e**) in the presence of triethylamine in dry acetonitrile at room temperature. Purification of these products **4a–i** was achieved by filtering the reaction mixture to separate the triethylamine hydrochloride and evaporation of the filtrate in a rota-evaporator under vacuum to obtain a residue. It was washed with water and recrystallized from ethanol. Physical data along with IR absorption spectroscopy, elemental analysis and ^{31}P NMR spectroscopy of **4a–i** are given in Table 1.

All the compounds **4a–i** exhibited characteristic IR absorptions[10–12] for P=O/S/Se and (P-C/P-O-C)$_{(aromatic)}$ and P-O-C$_{(aliphatic)}$ groups (Table 1). The ^{1}H NMR spectra of **4a–i** (Table 2) showed[13] doublets for H-2 and 6, H-3a and 5a and H-3d and 5d at δ 6.54–6.64 (J = 2.0–2.4 Hz), 7.19–7.25 (J = 7.2–8.0 Hz) and 7.93–7.96 ppm (J = 7.8–8.2 Hz). The triplets at δ 7.01–7.05 and δ 6.78–6.85 ppm are attributed to H-3b and 5b and H-3c and 5c, respectively. The bridged methine proton (H-4) showed a singlet at δ 5.85–5.93 ppm.

The nitrosubstituted aryl protons H-2′ and 4′ and H-5′ and 6′ resonated as a doublet and a multiplet in the regions δ 8.00–8.05 and δ 7.31–7.45 ppm, respectively.

The ^{13}C NMR spectra (Table 3) were recorded for a few members of the title compounds (**4a, 4e, 4g** and **4h**). The nitrogen-bearing aromatic carbons C-2 and 6, C-3e and 5e and C-3f and 5f resonated in the downfield region at δ 149.7–149.2, 147.6–147.2 and 151.9–151.2 ppm, respectively. The bridged chiral carbon in these compounds gave a signal in the region δ 31.7–31.2 ppm. The chemical shift values of the other aromatic carbons were observed in the expected region, δ 150.0–113.0 ppm.[9,17]

^{31}P NMR spectra of all the compounds **4a–i** showed only one phosphorus signal[14] in the range of δ 16.69–81.27 ppm depending on the atoms attached to phosphorus. Mass spectra for **4a, 4e** and **4g** were

Table 2. ^{1}H NMR spectral data [a,b] of **4a–i**.

4a	δ = 5.93 (s, 1H), 6.61 (d, 2H, J = 2.1 Hz), 6.81 (t, 2H, J = 7.9 Hz), 7.02 (t, 2H, J = 7.8 Hz), 7.23 (d, 2H, J = 7.9 Hz), 7.30 (d, 2H, J = 7.8 Hz), 7.40 (m, 2H), 7.96 (d, 2H, J = 7.8 Hz), 8.02–8.05 (d, 2H, J = 7.3 Hz), 7.16–7.21 (m, 5H)
4b	δ = 5.91 (s, 1H), 6.63 (d, 2H, J = 2.3 Hz), 6.80 (t, 2H, J = 7.8 Hz), 7.01 (t, 2H, J = 7.8 Hz), 7.23 (d, 2H, J = 7.8 Hz), 7.31 (d, 2H, J = 7.8 Hz), 7.43 (m, 2H), 7.93 (d, 2H, J = 8.1 Hz), 8.01–8.03 (d, 2H, J = 7.1 Hz), 7.16 7.20 (m, 5H)
4c	δ = 5.91 (s, 1H), 6.61 (d, 2H, J = 2.1 Hz), 6.84 (t, 2H, J = 7.9 Hz), 7.02 (t, 2H, J = 7.8 Hz), 7.25 (d, 2H, J = 7.9 Hz), 7.28 (d, 2H, J = 7.8 Hz), 7.38 (m, 2H), 7.94 (d, 2H, J = 7.8 Hz), 8.03–8.05 (d, 2H, J = 7.0 Hz), 7.16–7.20 (m, 5H)
4d	δ = 5.89 (s, 1H), 6.62 (d, 2H, J = 2.1 Hz), 6.83 (t, 2H, J = 7.8 Hz), 7.02 (t, 2H, J = 7.8 Hz), 7.21 (d, 2H, J = 7.9 Hz), 7.24 (d, 2H, J = 7.5 Hz), 7.35 (m, 2H), 7.95 (d, 2H, J = 7.8 Hz), 8.01–8.06 (d, 2H, J = 7.9 Hz), 3.71(q, 2H, OCH_2), 0.53 (t, 3H, CH_3)
4e	δ = 5.85 (s, 1H), 6.60 (d, 2H, J = 2.0 Hz), 6.78 (t, 2H, J = 7.2), 7.01 (t, 2H, J = 7.2 H), 7.19 (d, 2H, J = 7.2 Hz), 7.23 (d, 2H, J = 7.2 Hz), 7.31 (m, 2H), 7.94 (d, 2H, J = 7.8 Hz), 8.03–8.05 (d, 2H, J = 7.0 Hz), 3.68 (q, 2H, OCH_2), 0.51 (t, 3H, CH_3)
4f	δ = 5.86 (s, 1H), 6.64 (d, 2H, J = 2.1 Hz), 6.78 (t, 2H, J = 7.2 Hz), 7.02 (t, 2H, J = 7.4 Hz), 7.19 (d, 2H, J = 7.2 Hz), 7.21 (d, 2H, J = 7.2 Hz), 7.33 (m, 2H), 7.96 (d, 2H, J = 7.8 Hz), 8.00–8.04 (d, 2H, J = 7.4Hz), 3.70(q, 2H, OCH_2), 0.54 (t, 3H, CH_3)
4g [c]	δ = 5.93 (s, 1H), 6.61 (d, 2H, J = 2.4 Hz), 6.85 (t, 2H, J = 8.2 Hz), 7.05 (t, 2H, J = 8.21 Hz), 7.25 (d, 2H, J = 8.2 Hz), 7.30 (d, 2H, J = 8.2 Hz), 7.45 (m, 2H), 7.95 (d, 2H, J = 8.2 Hz), 8.00–8.05 (d, 2H, J = 7.9 Hz), 7.13–7.19 (m, 5H)
4h	δ = 5.91 (s, 1H), 6.61 (d, 2H, J = 2.4 Hz), 6.81 (t, 2H, J = 8.1 Hz), 7.04 (t, 2H, J = 8.2 Hz), 7.24 (d, 2H, J = 8.2 Hz), 7.32 (d, 2H, J = 8.1 Hz), 7.43 (m, 2H), 7.94 (d, 2H, J = 8.0 Hz), 8.01–8.05 (d, 2H, J = 7.8 Hz), 7.15–7.23 (m, 4H)
4i	δ = 5.90 (s, 1H), 6.54 (d, 2H, J = 2.1 Hz), 6.81 (t, 2H, J = 8.1 Hz), 7.02 (t, 2H, J = 8.1 Hz), 7.21 (d, 2H, J = 8.0 Hz), 7.28 (d, 2H, J = 7.9 Hz), 7.41 (m, 2H), 7.93 (d, 2H, J = 7.8 Hz), 8.02–8.05 (d, 2H, J = 7.3 Hz), 3.62–3.81 (m, 4H, N(CH_2)$_2$), 3.31–3.42 (m, 4H, (CH_2Cl)$_2$)

[a] Recorded in $CDCl_3$.
[b] Chemical shifts in ppm.
[c] Recorded in DMSO.

recorded (Table 4). All three compounds exhibited [$M^{+\cdot}$] and [$M^{+\bullet}$ +1] ions in their mass spectra. Multinuclear NMR and mass spectral data conclusively confirm the structures of **4a–i**.

The compounds **4a–i** were screened for their antibacterial activity against *Staphylococcus aureus* and *Klebsiella pneumoniae* by comparing with standard penicillin and antifungal activity against *Pellicularia solmanicolor* and *Macrophomina phaseolina* with the standard fungicide griseofulvin. The highlight is that the title compounds exhibited very high activity against the standard griseofulvin. Similarly it is gratifying to observe that these compounds are more effective than the standard (griseofulvin) against both bacteria.

3. Experimental

The melting points were determined on a Mel-temp apparatus and were uncorrected. Elemental analyses were performed by the Central Drug Research Institute, Lucknow, India. All IR spectra were recorded as KBr pellets on a Perkin-Elmer 1430 unit, ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on an AMX 400 MHz spectrometer, operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C and 161.9 MHz for ^{31}P, as solutions in $CDCl_3$ and the chemical shifts were referenced to TMS (^{1}H and ^{13}C) and 85% H_3PO_4 (^{31}P). 3-[1*H*-3-indolyl(3-nitrophenyl)methyl]-1*H*-indole (**1**) was prepared by using the reported procedure.[17]

3.1. Preparation of 3-[1-(3-Nitrophenyl)-ethyl]-1-(indole-1-yl-phenylphosphinoyl)-1*H*-indole (4a)

To a cooled (0 °C) and stirred solution of 3-[1*H*-3-indolyl (3-nitrophenyl)methyl]-1*H*-indole (**1**, 0.367 g, 0.001 mol) and triethylamine (0.202 g, 0.002 mol) in 25 mL of dry acetonitrile under nitrogen gas, a solution of dichlorophenylphosphine (**2a**, 0.179 g, 0.001 mol) in 10 mL of dry acetonitrile was added over a period of 20 min at 5–10 °C. After completion of the addition, the temperature of the reaction mixture was raised to 45–50 °C and stirred for 1 h to form an intermediate (**3a**). The progress of the reaction was judged by TLC analysis of the reaction mixture.

Table 3. ^{13}C NMR chemical sthifts [a,b] of **4a, 4e, 4g** and **4h**.

Compound	C–2 and C–6	C–3 and C–5	C–4	C–3a and C–5a	C–3b and C–5b	C–3c and C–5c	C–3d and C–5d	C–3e and C–5e	C–3f and C–5f	C–1″	C–2″ and C–6″	C–3″ and C–5″	C–4″
4a	149.5	121.7	31.6	119.3	123.5	125.3	113.2	147.2	151.9	134.4	132.1	126.4	126.9
4e	149.2	121.1	31.2	119.0	123.2	125.8	113.0	147.6	151.4	61.4	17.2	–	–
4g	149.6	121.3	31.5	119.3	123.6	125.6	113.2	147.4	151.2	150.0 (d, 6.9)	120.1 (d, 4.6)	129.3	125.4
4h	149.7	121.6	31.7	119.7	123.8	125.7	113.4	147.6	151.6	153.1 (d, 7.2)	121.9 (d, 4.6)	129.5	145.4

Compound	C–1′	C–2′	C–3′	C–4′	C–5′	C–6′
4a	143.2	124.7	142.6	120.7	127.3	131.7
4e	143.5	124.2	142.3	120.2	127.5	131.0
4g	143.1	124.8	142.7	120.9	127.6	131.5
4h	143.3	124.9	142.7	120.8	127.8	131.7

[a] Recorded in $CDCl_3$.
[b] Chemical shifts in ppm and *J* (Hz) in brackets.

Table 4. Mass spectral data of **4a, 4e** and **4g**.

Compound	m/z (% relative abundance)
4a	490 ($M^{+\bullet}$ +1, 36), 489 ($M^{+\bullet}$ 23), 481 (3), 471 (8), 470 (30), 469 (100), 460 (13), 447 (2), 424 (1), 423 (4), 422 (38), 404 (19), 390 (12), 376 (16), 373 (11), 353 (2), 343 (8), 342 (12), 341 (54), 329 (11), 315 (4), 299 (6), 295 (14), 285 (4), 272 (14), 250 (3), 249 (18)
4e	474 ($M^{+\bullet}$ +1, 24), 473 ($M^{+\bullet}$, 17), 470 (3), 469 (13), 461 (2), 418 (2), 404 (4), 390 (12), 379 (3), 367 (8), 366 (34), 357 (4), 351 (2), 337 (2), 330 (4), 329 (19), 323 (2), 313 (6), 301 (8), 282 (2), 268 (8), 267 (9), 252 (2), 251 (10), 240 (26), 239 (100), 234 (4), 194 (4), 184 (3), 160 (3), 149 (2), 116 (2)
4g	506 ($M^{+\bullet}$ + 1, 40), 505 ($M^{+\bullet}$, 32), 500 (35), 484 (24), 460 (23), 439 (8), 438 (6), 408 (4), 391 (5), 367 (32), 366 (5), 337 (4), 323 (4), 307 (41), 289 (26), 273 (4), 251 (48), 239 (46), 235 (2), 204 (4), 203 (5), 178 (2), 154 (100), 137 (46), 136 (58), 120 (4), 102 (62), 89 (10)

After completion of the reaction, it was filtered under nitrogen atmosphere and triethylamine hydrochloride and the solvent removed from the filtrate in a rota-evaporator. The crude product **3a** obtained was dissolved in dichloromethane (30 mL) and hydrogen peroxide (30% H_2O_2, 0.04 mL, 0.001 mol) was added to it dropwise at 0–5 °C. The reaction mixture was brought to 45–50 °C and kept with stirring for 2 h for the completion of oxidation as indicated by TLC analysis. The solvent was evaporated from the filtrate in a rota-evaporator. The resulting crude product was recrystallized from ethanol to yield 0.23 g (63%) of **4a**, m.p. 232–233 °C. The compound **4d** was prepared by adopting the above procedure using **2b**.

3.2. Preparation of 3-[1-(3-Nitrophenyl)-ethyl]-1-(indole-1-yl)phenylthio/seleno-phosphinoyl-1*H*-indole (4b and 4c)

A solution of dichlorophenylphosphine (**2a**, 0.179 g, 0.001 mol) in 20 mL of dry acetonitrile was added slowly to a solution of 3-[1*H*-3-indolyl(3-nitrophenyl)methyl]-1*H*-indole (**1,** 0.367 g, 0.001 mol) and triethylamine (0.202 g, 0.002 mol) in 30 mL of dry acetonitrile under nitrogen gas at 0 °C. After completion of the addition, the temperature of the reaction mixture was raised to 50–55 °C and stirred for 3 h to form the trivalent P(III) intermediate, **3b**. The progress of the reaction was judged by the TLC analysis of the reaction mixture using n-hexane and ethylacetate (7:3) and silica gel as adsorbent. The precipitated triethylamine hydrochloride was separated by filtration under nitrogen atmosphere. Sulphur/selenium (0.001 mol) in 20 mL of dichloromethane was added dropwise at 5–10 °C. The reaction mixture was brought to reflux and kept with stirring for 2 h to completion of reaction as indicated by TLC analysis. The solvent was evaporated by means of a rota-evaporator. The resulting crude product (**4b**/**4c**) obtained was recrystallized from ethanol. Synthesis of the other compounds **4e** and **4f** was achieved by adopting the above procedure using **2b**.

3.3. Preparation of 3-[1-3-(Nitrophenyl)-ethyl]-1-(indole-1-yl-phosphonic acid) phenyl ester (4g)

A solution of phenyl phosphorodichloridate (**2c**, 0.2 g, 0.001 mol) in 20 mL of dry acetonitrile was added over a period of 20 min at 0–5 °C to a stirred solution of **1** (0.367 g, 0.001 mol) and triethylamine (0.20 g, 0.002 mol) in 50 mL of dry acetonitrile. After completion of the addition the temperature of the reaction mixture was raised to 45–50 °C and kept for 3–4 h with stirring. The progress of the reaction mixture was monitored by TLC analysis using n-hexane and ethylacetate (4:1) on silica gel as adsorbent. The precipitated triethylamine hydrochloride was filtered off and the filtrate was evaporated in a rota-evaporator. The residue obtained was washed with water, then with chilled ethanol. Colourless crystals were obtained after recrystallization of the product from ethanol, to yield 0.29 g (57%) of **4g**, m.p. 246–247 °C. The compounds **4h** and **4i** were prepared by adopting the above procedure using **2d** and **2e**.

3.4. Antimicrobial Activity

The compounds were diluted in dimethylformamide (DMF) for bioassay. Solvent control was included although no antimicrobial activity has been noted in the solvent employed. All samples were tested in triplicate and average results were recorded. The compounds were assayed for antibacterial activity against six registered bacterial isolates which were obtained from the National Collection of Industrial Microorganisms (NCIM), National Chemical Laboratories, Pune, India.

The compounds **4a–i** (Table 5) were screened for their antifungal activity against *Pellicularia solmanicolor* and *Macrophomina phaseolina* (ATCC 97556) along with the standard fungicide griseofulvin. The disc diffusion method[15,16] was followed for screening the compounds at three different concentrations (25, 50 and 100 μg disc^{-1}). Their antibacterial activity was also evaluated according to the disc diffusion method at three different concentrations against *Staphylococcus aureus* (ATCC 6538) and

Table 5. Antibacterial and antifungal activities of compounds **4a–i**.

Compound	Zone of inhibition/mm						Zone of inhibition/mm					
	Staphylococcus aureus μg disc^{-1}			*Klebsiella pneumoniae* μg disc^{-1}			*Pellicularia solmanicolor* μg disc^{-1}			*Macrophomina phaseolina* μg disc^{-1}		
	100	50	25	100	50	25	100	50	25	100	50	25
4a	11	7	4	9	7	2	10	6	2	10	4	–
4b	10	6	2	12	9	3	7	2	–	11	5	1
4c	11	8	3	10	6	4	9	4	1	10	6	3
4d	8	6	2	7	5	3	7	2	–	8	–	–
4e	10	8	2	10	6	2	12	5	1	11	6	1
4f	9	5	–	11	7	3	9	5	1	8	–	–
4g	7	3	–	8	5	–	–	–	–	8	5	–
4h	11	7	3	13	9	5	11	4	–	9	5	2
4i	13	9	4	14	10	4	14	9	3	11	7	3
Penicillin	11	7	2	10	7	2	–	–	–	–	–	–
Griseofulvin	–	–	–	–	–	–	10	6	–	9	7	–

Klebsiella pneumoniae (ATCC 31488) by comparing with standard penicillin.

It is interesting to observe that all the compounds **4a–i** exhibited higher antifungal and antibacterial activity than standard griseofulvin. The highlight is that all the compounds exhibited very high activity against the standard. Similarly it is gratifying to observe that these compounds are considerably more effective against both the bacteria *Staphylococcus aureus* and *Klebsiella pneumoniae*.

4. Conclusions

In conclusion, we have developed a convenient method for the synthesis of novel 3-[1-(3-nitrophenyl)-ethyl]-1-(indole-1-yl) substituted aryl/alkyl-phosphinoyl/thiophosphinoyl/selenophosphinoyl-1*H*-indole derivatives. These compounds exhibited significant activity against the growth of both bacteria and fungi.

Acknowledgements

The authors express thanks to Prof. C. Devendranath Reddy and Dr C. Suresh Reddy, Department of Chemistry, Sri Venkateswara University, Tirupati, India, for encouragement, and the Director, Indian Institute of Sciences, Bangalore, India, for recording spectral data.

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