Med Chem Res (2011) 20:962–967
DOI 10.1007/s00044-010-9425-z

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

# Synthesis, spectral, and antimicrobial evaluation of some new 8-membered phosphorus heterocyclic compounds

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Received: 10 December 2009 / Accepted: 2 September 2010 / Published online: 17 September 2010


**Abstract** Synthesis of 9-substituted-8, 9 10, 11-tetrahydro-7H-7, 11-diaza-9$\lambda^5$-phosphacycloocta [*d,e*] naphthalene-9-sulfides/selenides (**4–13**) was accomplished in three steps. 1,8-diamino naphthalene (**2**) was reacted with tris (bromomethyl) phosphine (**1**) in the presence of triethylamine in dry tetrahydrofuran (THF) under $N_2$ atmosphere to form the corresponding intermediate (**3**). It was converted to the corresponding sulfide (**4**) and selenide (**5**) by the reaction with sulfur and selenium, respectively. The intermediates **4** and **5** were reacted with two achiral alcohols and two achiral amines to obtain the title compounds (**6–13**). The structures of the title compounds were established by elemental analysis and spectral data (IR, $^1$H, $^{13}$C, $^{31}$P NMR, and FAB mass). The antimicrobial activity of these compounds was evaluated and they exhibited significant activity.

**Keywords** 1, 8-diamino naphthalene · Tris (bromomethyl) phosphine · Phosphocins · Antimicrobial activity

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## Introduction

Organophosphate moiety is an important pharmacophore in agricultural and pharmaceutical chemistry (Demir *et al.,* 1996). Phosphocin/phosphepin and their related derivatives containing this group represent an important class of pesticides, antibiotics, herbicides and antiviral agents (Vasu Goverdhana Reddy *et al.,* 2002). Some of them are well known for their insecticidal activities (Schrader, 1957) and are known to degrade hydrolytically and enzymatically to non-toxic residues. Discovery of their fungicidal properties also promotes developing chemically—the new chiral phosphorus ligands play vital role in asymmetric synthesis of—various intermediates in organic synthesis (Chi and Zhang, 2002; Reetz and Mehler, 2000; Ojima, 2000; Nayori, 1994; Li *et al.,* 2001). Keeping in view the importance of eight-membered organophosphorus heterocyclic compounds, we herein report the synthesis and spectral characterization and antimicrobial activity of the novel heterocyclic compounds containing achiral alcohols and achiral amines.

## Materials and methods

### General procedure

Melting points were determined in open capillary tubes on a Mel-temp apparatus and were uncorrected. Micro-analysis was performed on Heraeus Vario EL III Carlo Ebra 1108. IR Spectra were recorded in as KBr discs on a Nicolet 380 FT-IR spectrophotometer. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AMX 400 MHz spectrometer operating at 400 MHz for $^1$H, 100 MHz for $^{13}$C, and 161.9 MHz for $^{31}$P. The compounds were dissolved in

DMSO-$d_6$. The $^{1}H$ and $^{13}C$ and chemical shifts were referenced to tetramethylsilane and $^{31}P$ chemical shifts to 85% $H_3PO_4$. Mass spectra were recorded on a Jeol SX 102 DA/600 Mass spectrometer using Argon/Xenon (6 keV, 10 mA) as the FAB gas.

## Chemistry

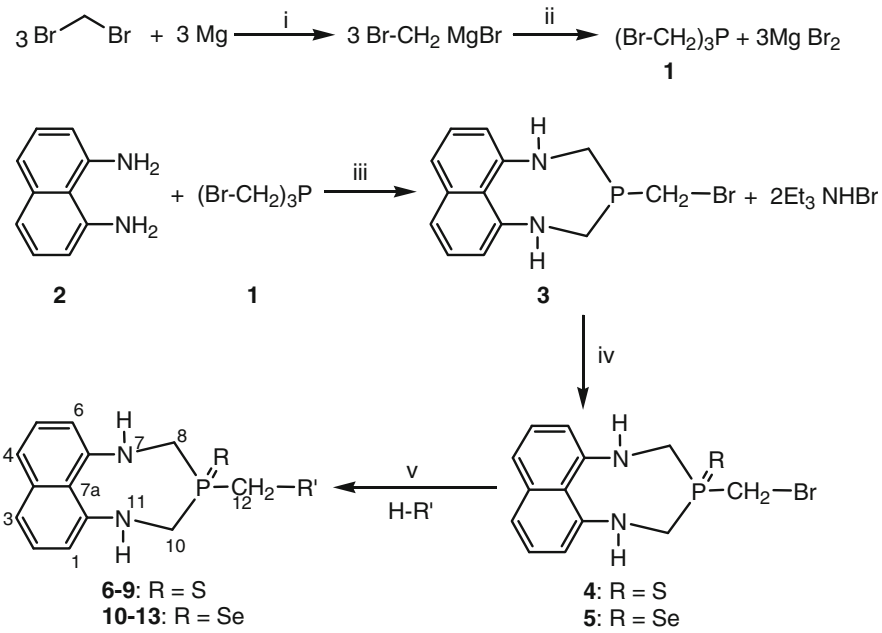
The preparation of tris (bromomethyl) phosphine (**1**), compounds **3–5** and synthetic route for the preparation of the title compounds **6–13** is depicted in Scheme 1.

Preparation of tris (bromomethyl) phosphine (**1**)

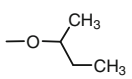
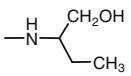
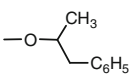
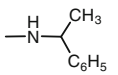
Because of the sensitivity of the reagents and products to moisture and oxygen, all manipulations were performed in an anhydrous inert nitrogen atmosphere. In a dry 100 ml three necked round bottomed flask fitted with dropping funnel, a reflux condenser attached to a calcium chloride tube, an inlet for dry nitrogen and a thermometer reaching close to the bottom in the flask were placed magnesium turnings (0.12 g, 0.005 mol) and dry THF (5.0 ml). The reaction mixture was kept under stirring and dibromo methane (0.78 g, 0.005 mol) in 10 ml of dry THF was added drop wise at 10–15°C after completion of the addition, the reaction temperature raised to room temperature and continued stirring until the magnesium metal was dissolved to form bromo methyl magnesium bromide. It is further reacted with $PBr_3$ to form tris (bromo methyl) phosphine and magnesium bromide salt. The magnesium bromide salt was separated by filtration under $N_2$ atmosphere and the solvent was distilled off to get tris (bromomethyl) phosphine (**1**) (Chance *et al.,* 1967).

Synthesis of 9-bromomethyl-7, 8, 10, 11-tetrahydro-7, 11, diaza-9$\lambda^5$-9-phospha-cycloocta [d, e] naphthalene-9-oxide (**3**)

To a cooled (5°C) and stirred solution of 1, 8-diaminonaphthalene (**2**, 0.69 g, 0.005 mol) and triethyl amine (1.01 g, 0.01 mol) in 10 ml of dry THF under nitrogen gas, a solution of tris (bromomethyl) phosphine (**1**, 1.35 g, 0.005 mol) in 10 ml of dry THF was added over a period of 20 min. After completion of the addition, the temperature of the reaction mixture was raised to room temperature and stirred for 1 h to form the intermediate **3**. The progress of the reaction was judged by the TLC analysis. After




**Scheme 1** Reagents and conditions: (i) $N_2$/THF, 10–15°C; (ii) $PBr_3$, rt; (iii) $N_2$ atm/THF, $Et_3N$, rt; (iv) S/Se, THF, reflux, 2 h; (v) THF, $Et_3N$, 30–35°C

| Compd. | R' | Compd. | R' |
|---|---|---|---|
| 6/10 |  | 8/12 |  |
| 7/11 |  | 9/13 |  |

completion of the reaction, the triethylamine HBr salt was removed by filtration and the concentration of filtrate yielded the crude product which was subjected to the next reaction without further purification.

Synthesis of 9-bromomethyl-8, 9, 10, 11-tetrahydro-7H-7, 11-diaza-9$\lambda^5$-phospha-cycloocta [d,e] naphthalene 9-sulfide/selenide (**4/5**)

The intermediate **3** in THF was cooled to 5°C, sulfur powder/selenium metal was added to it and heated slowly up to gentle reflux with stirring and continued for 2 h for the completion of the reaction as indicated by TLC analysis. The solvent was removed in a rota-evaporator and the residue was extracted with ethyl acetate. The extract after drying over anhydrous $MgSO_4$ was removed in a rota-evaporator. The obtained crude products (**4** and **5**) were purified by column chromatography (hexane-ethylacetate 2:1) to yield **4** (59%) and **5** (70%) with m.p. 180–182°C and 156–158°C, respectively.

General procedure for the preparation of (**6–13**)

To the intermediate **4** in dry THF, two chiral alcohols ((±)sec-butanol, (±)1-phenyl ethanol) and two chiral amines ((±)1-phenylethyl amine, (±)2-amino-1-butanol) were added in the presence of triethylamine at 10–15°C over a period of half an hour. After the addition, temperature of the reaction mixture was slowly raised to 30–35°C and continued stirring. The progress of the reaction was monitored by the TLC analysis. After completion of the reaction, solvent was removed, and the resulting crude products were recrystallized from 2-propanol to obtain pure sulfur-based compounds of **6–9**. The same procedure was adopted for the preparation of selenium-based phosphorus compounds **10–13.**

Antimicrobial activity

The compounds **4–13** were screened by disc diffusion method (Umamaheswari Devi *et al.,* 2000; Colle *et al.,* 1989) for their antimicrobial activity against the fungi, *Aspergillus niger* and *Helminthosporium oryzae* and bacteria, *Escherichia coli* and *Staphylococcus aureus* by comparing with standard fungicide Griseofulvin and standard bactericide penicillin at three different concentrations (100, 50, and 25 ppm) and the results are presented in Tables 5 and 6.

## Results and discussion

Preparation of a few eight-membered phosphonate heterocyclic compounds such as 9-substituted-8, 9, 10, 11-tetrahydro-7*H*-7,11-diaza-9$\lambda^5$-phosphacycloocta [*d,e*] naphthalene-9-sulfides/selenides (**6–13**) was accomplished in three steps. The synthetic route (Scheme 1) involves the cyclization of equimolar quantities of 1,8-diamino naphthalene (**2**) with tris (bromomethyl) phosphine (**1**) in the presence of triethylamine in dry tetrahydrofuran (THF) under $N_2$ atmosphere to form the corresponding $P_{III}$ intermediate 9-bromomethyl-8,9,10,11-tetrahydro-7*H*-7,11-diaza-9-phospha-cycloocta [*d,e*] naphthalene (**3**). It was converted to the corresponding sulfide (**4**) and selenide (**5**) by the reaction with hydrogen peroxide, sulfur, and selenium, respectively. The compounds **4** and **5** further reacted with two achiral alcohols and two chiral amines in the presence of triethylamine in dry tetrahydrofuran to form the corresponding title compounds (**6–13**) (Scheme 1).

The physical, elemental analyses, IR, and $^{31}$P NMR data of the compounds **4–13** are given in Table 1. Compounds **4–13** exhibited characteristic P=S/Se stretching frequencies in the region 757–780 (P=S) and 617–635 (P=Se) cm$^{-1}$. Characteristic absorption bands for P–$C_{(aliphatic)}$ and N–H

**Table 1** Physical, IR, and $^{31}$P NMR spectral data of the compounds **4–13**

| Compounds | Molecular formula | m.p. °C | Yield % | Elemental analysis % found (Calcd.) | | | IR cm$^{-1}$ | | | $^{31}$P NMR ppm |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | C | H | N | NH | P=S/Se | P–$C_{alip}$ | |
| **4** | $C_{13}H_{14}BrN_2PS$ | 180–182 | 59 | 45.72 (45.80) | 4.14 (4.18) | 8.20 (8.25) | 3,315 | 776 | 734 | 42.18 |
| **5** | $C_{13}H_{14}BrN_2PSe$ | 156–158 | 70 | 40.23 (40.31) | 3.64 (3.70) | 7.20 (7.25) | 3,348 | 624 | 739 | 82.45 |
| **6** | $C_{17}H_{23}N_2OPS$ | 172–174 | 65 | 61.03 (61.10) | 6.90 (6.95) | 8.35 (8.41) | 3,379 | 769 | 745 | 41.06 |
| **7** | $C_{21}H_{23}N_2OPS$ | 154–156 | 55 | 65.90 (65.98) | 6.04 (6.08) | 7.30 (7.35) | 3,388 | 780 | 710 | 45.54 |
| **8** | $C_{21}H_{24}N_3PS$ | 145–147 | 60 | 66.10 (66.15) | 6.34 (6.37) | 11.01 (11.05) | 3,399 | 765 | 714 | 46.21 |
| **9** | $C_{16}H_{22}N_3OPS$ | 154–156 | 52 | 57.28 (57.35) | 6.61 (6.65) | 12.50 (12.56) | 3,382 | 757 | 716 | 44.82 |
| **10** | $C_{17}H_{23}N_2OPSe$ | 142–144 | 62 | 53.55 (53.60) | 6.06 (6.10) | 7.33 (7.38) | 3,404 | 628 | 758 | 83.17 |
| **11** | $C_{21}H_{23}N_2OPSe$ | 175–177 | 59 | 58.70 (58.80) | 5.40 (5.45) | 6.52 (6.56) | 3,359 | 621 | 747 | 86.29 |
| **12** | $C_{21}H_{24}N_3PSe$ | 162–164 | 62 | 58.84 (58.90) | 5.64 (5.68) | 9.80 (9.85) | 3,312 | 617 | 756 | 84.94 |
| **13** | $C_{16}H_{22}N_3OPSe$ | 182–184 | 65 | 50.23 (50.30) | 5.80 (5.84) | 10.96 (11.02) | 3,406 | 635 | 736 | 87.16 |

stretching vibrations were observed in the region 710–758 and 3,275–3,406 $cm^{-1}$, respectively (Thomas, 1974). $^{1}H$ NMR chemical shifts for, aromatic protons of the naphthyl ring of the **6–13** complex multiplets in the region 6.12–7.76 ppm (Silverstein and Webster, 1998). The N–H proton resonated as a broad singlet at $\delta$ 4.85–5.30. The other aliphatic protons of **6–13** were observed in the expected region (Table 2). $^{13}C$ NMR chemical shifts for aromatic carbons were observed in the expected region (Table 3). C-1 & C-6 were observed in the range of 109.4–110.1 ppm. Chemical shifts for C-2 & C-5 and C-3 & C-4 were observed in the regions 124.6–124.9 and 119.6–119.9 ppm, respectively. C-3a & C-7a carbons resonated in the region 136.2–136.7 and 113.19–113.10 ppm, respectively. C-6a & C-11a which are present in similar chemical and magnetically same environment resonated in the region 135.5–135.8 ppm. C-8 & C-10 which are directly linked to phosphorus experienced coupling with it and appeared as doublet in the region $\delta$ 54.21–55.26 ($J$ = 126–132 Hz). All the carbons of achiral alcohols and amines resonated in the expected region (Quin and Verkade, 1994). The $^{31}P$ NMR chemical shifts of the title compounds (**4–13**) appeared in the range of 41.06–87.16 ppm as expected (Quin and Verkade, 1994), further mass spectral data of the compounds **6** and **10** were represented as typical examples (Table 4, Scheme 2).

## Biological activity

The Whatman No.1 filter paper disc method (Umamaheswari Devi *et al.,* 2000; Colle *et al.,* 1989) was employed for

**Table 2** $^{1}H$ NMR spectral data of the compounds **4–13**

| Compounds | Ar–H | NH | P–$CH_2$–R |
|---|---|---|---|
| **4** | 6.48–7.35 (m, 6H) | 4.93 (br s) | 3.7 (m, 4H, $CH_2$–P(S)), 3.3 (s, 2H, $CH_2$ Br) |
| **5** | 6.12–7.49 (m, 6H) | 5.02 (br s) | 3.9 (m, 4H, $CH_2$–P(Se)), 3.28 (s, 2H, $CH_2$ Br) |
| **6** | 6.24–7.53 (m, 6H) | 4.95 (br s) | 3.4 (m, 4H, $CH_2$–P(S)), 3.8 (s, 2H, $CH_2$–O), 3.1 (m, 1H, OCH), 1.42 (m, 2H, CH ($CH_3$) $\underline{CH_2}CH_3$), 1.22 (m, 3H, CH($\underline{CH_3}$) $CH_2$ $CH_3$), 0.91 (m, 3H, CH($CH_3$) $CH_2\underline{CH_3}$) |
| **7** | 6.32–7.76 (m, 11H) | 5.13 (s) | 3.48 (m, 4H, $CH_2$P(S)), 3.98 (m, 1H, O$\underline{CH}$ ($CH_3$) Ph), 1.27 (s, 3H, OCH ($\underline{CH_3}$) Ph) |
| **8** | 6.42–7.35 (m, 11H) | 5.25 (s) | 3.38 (m, 4H, $CH_2$P(S)), 3.31 (m, 2H, –$\underline{CH_2}$–NH–), 4.2 br s, 1H N$\underline{H}$–CH ($CH_3$) Ph), 2.59 (m, 1H NH–C$\underline{H}$ ($CH_3$) Ph), 1.19 (s, 3$\underline{H}$, NH–CH($C\underline{H_3}$) Ph) |
| **9** | 6.49–7.49 (m, 6H) | 5.17 (s) | 5.21 (s, 1H, $CH_2O\underline{H}$), 3.35 (m, 4H, $CH_2$P(S)), 4.16 br, s, 1H, N$\underline{H}$–CH ($CH_2OH$), $CH_2CH_3$), 2.70 (m, 1H, NH–C$\underline{H}$($CH_2OH$), $CH_2$ $CH_3$), 3.59 (m, 2H, CH ($\underline{CH_2}OH$) $CH_2CH_3$), 1.21 (m, 2H, CH ($\underline{CH_2}OH$), $\underline{CH_2}CH_3$), 0.92 (m, 3H, CH($CH_2OH$) $CH_2\underline{CH_3}$ |
| **10** | 6.26–7.59 (m, 6H) | 5.05 (br s) | 3.3 (m, 4H, $CH_2$P(Se)), 3.6 (s, 2H–$CH_2$–O), 3.1 (m, 1H, O–CH), 1.45 (m, 2H,CH ($CH_3$) $\underline{CH_2}$ $CH_3$), 1.21 (m, 3H, –CH($\underline{CH_3}$) $CH_2CH_3$), 0.92 (m, 3H, CH ($CH_3$) $CH_2$ $\underline{CH_3}$) |
| **11** | 6.45–7.73 (m, 11H) | 4.98 (br s) | 3.49 (m, 4H, $CH_2$P(Se)), 3.5 (s, 2H, $CH_2$–O), 3.96 (m, 1H, O–C$\underline{H}$($CH_3$) Ph), 1.28 (s, 3H, O–CH– ($C\underline{H_3}$) Ph) |
| **12** | 6.43–7.65 (m, 11H) | 5.30 (br s) | 3.39 (m, 4H, $CH_2$ P(Se)), 3.31 (m, 2H–$CH_2$–NH–), 4.3 (br, s, 1H, NH–CH($CH_3$) Ph) 2.57 (m, 1H, NH–C$\underline{H}$ ($CH_3$) Ph), 1.19 (s, 3H, NH–CH ($\underline{CH_3}$) Ph) |
| **13** | 6.52–7.64 (m, 6H) | 4.85 (br s) | 5.22 (s, 1H, $CH_2O\underline{H}$), 3.34 (m, 4H, $CH_2$P(Se)), 4.16 (br, s, 1H, N$\underline{H}$–CH($CH_2OH$) $CH_2CH_3$), 2.71 (m, 1H, NH–C$\underline{H}$($CH_2OH$) $CH_2CH_3$), 3.58 (m, 2$\underline{H}$, CH($\underline{CH_2}OH$) $CH_2CH_3$), 1.21 (m, 2H, CH($CH_2OH$) $\underline{CH_2}$–$CH_3$), 0.94 (m, 3H, CH, $CH_2OH$ $CH_2\underline{CH_3}$) |

**Table 3** $^{13}C$ NMR spectral data of the compounds **6**, **9**, **10**, and **13**

| Compounds | C-1 & C-6 | C-2 & C-5 | C-3 & C-4 | C-3a | C-7a | C-6a & C-11a | C-10 & C-8 | P–$CH_2$–NH/O | OCH/–NH–$\underline{CH}$ | CH–$\underline{CH_2}$–$CH_3$ | –CH–$\underline{CH_3}$ | CH–$\underline{CH_2}$–$\underline{CH_3}$ | CH–$\underline{CH_2}$–OH |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **6** | 109.9 | 124.6 | 119.9 | 136.1 | 113.1 | 135.6 | 55.2 (d, $^{1}J_{P-C}$ = 132 Hz) | 69.5 | 75.9 | 33.0 | 19.7 | 9.7 | – |
| **9** | 110.1 | 124.7 | 119.8 | 136.4 | 113.1 | 135.7 | 54.2 (d, $^{1}J_{P-C}$ = 126 Hz) | 54.5 | 59.2 | 33.7 | – | 9.5 | 72.5 |
| **10** | 110.1 | 124.6 | 119.6 | 136.2 | 113.1 | 135.5 | 55.1 (d, $^{1}J_{P-C}$ = 130 Hz) | 69.3 | 75.9 | 33.5 | 21.1 | 9.4 | – |
| **13** | 110.1 | 124.9 | 119.6 | 136.7 | 113.1 | 135.8 | 54.7 (d, $^{1}J_{P-C}$ = 128 Hz) | 54.7 | 59.8 | 33.9 | – | 9.8 | 72.9 |

Chemical shifts in ppm $J$ (Hz) given in parenthesis

**Table 4** Mass spectral data of the compounds **6** and **10**

| Compounds | *m/z* (% relative abundance) |
|---|---|
| **6** | 334[$M^{\bullet+}$, 17], 277 (41), 261 (21), 247 (14), 219 (100), 184 (11), 155 (31), 126 (28), 73 (36) |
| **10** | 381[$M^{\bullet+}$, 19], 324 (31), 308 (33), 294 (29), 266 (100), 184 (13), 155 (19), 126 (30) |

the in vitro study of antibacterial and antifungal effects against *Escherichia coli, Staphylococcus aureus, Aspergillus niger*, and *Helminthosporium oryzae*. The inhibitory effects of compounds **4–13** against these organisms are given in Tables 5 and 6.

## Antibacterial activity

Antibacterial activity of all the title compounds **4–13** was assayed (Umamaheswari Devi *et al.,* 2000) against the growth of *Staphylococcus aureus* (gram +ve) and *Escherichia coli* (gram −ve) at concentrations (100, 50, and 25 ppm) (Table 5). Highlight is that majority of the compounds exhibited high activity against both the bacteria,

**Table 5** Antibacterial activity of compounds **4–13**

| Compounds | Zone of inhibition (%) | | | | | |
|---|---|---|---|---|---|---|
| | *Escherichia coli* | | | *Staphylococcus aureus* | | |
| | 100 | 50 | 25 | 100 | 50 | 25 |
| **4** | 10 | 5 | 3 | 13 | 11 | 9 |
| **5** | 12 | 6 | 4 | 9 | 8 | – |
| **6** | 14 | 10 | 9 | 13 | 12 | 8 |
| **7** | 8 | 9 | 8 | 10 | 9 | 7 |
| **8** | 10 | 10 | 8 | 11 | 9 | 5 |
| **9** | 11 | 7 | 6 | 12 | 7 | 8 |
| **10** | 13 | 10 | 8 | 14 | 10 | 7 |
| **11** | 10 | 8 | 7 | 12 | 10 | 7 |
| **12** | 19 | 6 | 7 | 10 | 6 | 8 |
| **13** | 10 | 5 | 3 | 11 | 9 | 5 |
| Penicillin[a] | 12 | 8 | - | 12 | 8 | – |

[a] Standard antibacterial compound

and the compounds **6** and **12** were more effective than that of the standard compound. Penicillin was tested as a standard reference compound to compare the activity of these compounds.

**Scheme 2** Mass fragmentation of compound **6**

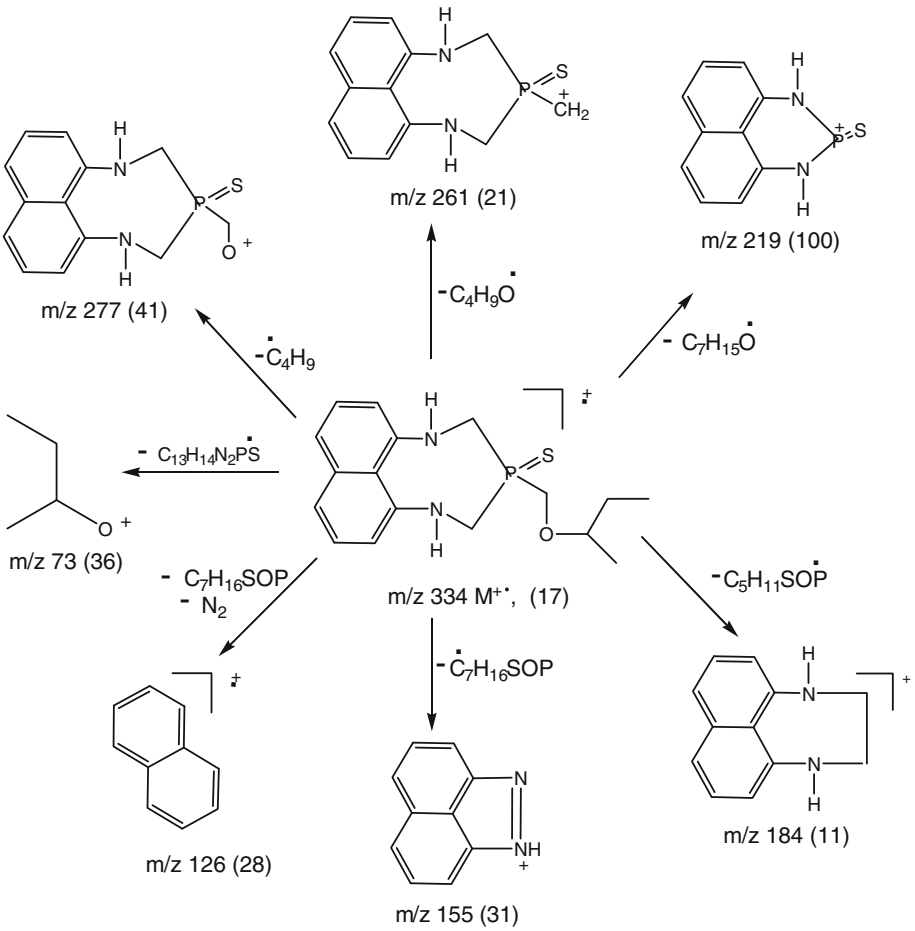


**Table 6** Antifungal activity of compounds **4–13**

| Compounds | Zone of inhibition (%) | | | | | |
|---|---|---|---|---|---|---|
| | *Aspergillus niger* | | | *Helminthosporium oryzae* | | |
| | 100 | 50 | 25 | 100 | 50 | 25 |
| **4** | 9 | 5 | 3 | 13 | 11 | 9 |
| **5** | 10 | 6 | 4 | 9 | 8 | – |
| **6** | 14 | 10 | 9 | 13 | 12 | 8 |
| **7** | 13 | 9 | 8 | 10 | 9 | 7 |
| **8** | 10 | 10 | 8 | 11 | 9 | 5 |
| **9** | 9 | 7 | 6 | 12 | 7 | 8 |
| **10** | 13 | 10 | 8 | 14 | 10 | 7 |
| **11** | 10 | 8 | 7 | 12 | 10 | 7 |
| **12** | 9 | 6 | 4 | 10 | 9 | 6 |
| **13** | 12 | 9 | 6 | 9 | 8 | 5 |
| Griseofulvin[a] | 10 | 7 | – | 10 | 7 | – |

[a] Standard antifungal compound

## Antifungal activity

The compounds **4–13** (Table 6) were screened for their antifungal activity against *Aspergillus niger* and *Helminthosporium oryzae* species along with standard fungicide Griseofulvin. Disc diffusion method (Colle *et al.,* 1989) was followed for screening the compounds at three different concentrations (100, 50, and 25 ppm).

It is gratifying to observe that all the compounds **4–13** were exhibited higher antifungal activity when compared with that of reference compound. The highlight is that all the compounds exhibited very high activity against fungi and the compounds **6**, **7**, and **10** were more effective than the standard Griseofulvin.

## Conclusion

In summary, we have successfully synthesized new class of phosphorus-based heterocyclic compounds by employing simple three step synthetic protocol. Many of these novel analogs showed comparable to better inhibitory activity than the standard drugs.

**Acknowledgments** The authors express their thanks to Prof. C. Devendranath Reddy and Dr. C. Suresh Reddy, Department of Chemistry, Sri Venkateswara University, Tirupati, India for encouragement and helpful discussion and the Directors, I.I.Sc. Bangalore and CDRI, Lucknow, India, for the analytical and spectral data.

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