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Synthesis and Anti-microbial activity of a new class of α-Aminophosphonic acid esters by using TMG as Catalyst

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Abstract

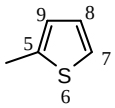
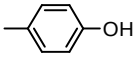
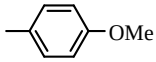
A new class of α-aminophoshonic acid esters (**3a-j**) has been synthesized by equimolar quantities of Schiff's bases, diethyl/dimethyl hydrogen phosphites in dry ethanol at refluxing conditions using TMG as a catalyst via Pudovik reaction in high yields (71-87%). The structures of the title compounds have been established by elemental analysis, IR, ^{1}H-, ^{13}C- & ^{31}P- NMR and Mass spectral analysis. They were found to possess significant anti-microbial activity.

Keywords: Aldimines, dialkyl hydrogen phosphites, α-aminophosphonates, Pudovik reaction, tetramethylguanidine (TMG),

Introduction

The α-aminophosphonic acids are considered to be one of the most important natural amino acids, mimetics, peptides and proteins key blocks building into the life chemistry. Because of their reduced toxicity and ability to substitute natural amino acids in the competition for the enzyme's active sites or other receptors the α-aminophosphonates (α-aminophosphonic acids and their derivatives) are used as enzyme inhibitors [1], natural amino acid mimetics [2], as well as medicine [3]. They are also used for metal complexing, anticancer activity [3], metals separation and concentration agents [4], antioxidants [5], pesticides [6], herbicide or plant growth regulators [7], ion matrix recognition [8], contrast agents in the nuclear magnetic resonance imagistic control of ill living human and animal bodies [9], pipe scale inhibition [10], radioprotecting agents [11], etc. α-Amino phosphonates are also chief substrates in the synthesis of phosphopeptides [12]. These biological activities of organophosphorus compounds are mostly associated with the tetrahedral structure of phosphonyl group acting as transition state analogue. Because of these numerous applications of α-aminophosphonates, a great variety of synthetic methods has been developed.

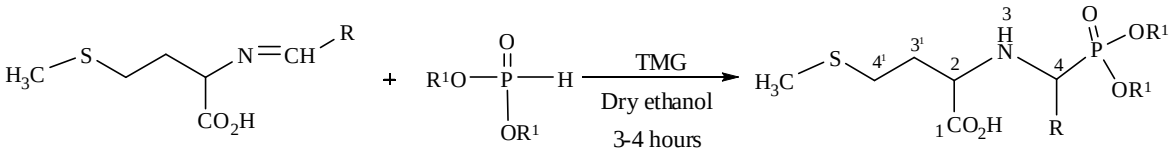
In this connection we prepared a new class of α-aminophoshonic acid esters (**3a-j**) has been synthesized by the addition of labile P-H to Schiff's bases in a one-pot Pudovik reaction. Previous results demonstrated that tetramethylguanidine (TMG) catalyzes the Michael addition of nitro methane to α, β-unsaturated ketones [13,14]. These results prompted us to take various aldimines as a starting compound for the synthesis of title compounds. Keeping in view the importance of α-aminophosphonates and several other possible applications, we report herein the synthesis, spectral characterization and antimicrobial activity.

Compd.	**3a & 3f**	**3b & 3g**	**3c & 3h**	**3d & 3i**	**3e & 3j**
R					

Compd.	**3a-e**	**3f-j**
R^1	$-CH_3$	$-C_2H_5$

Results and Discussion

A new class of α-aminophosphonates (**3a-j**) was conveniently synthesized by equimolar quantities of various aldemines (**1a-j**) and diethyl/dimethyl hydrogen phosphites (**2**) in dry ethanol with stirring at refluxing conditions using TMG as a catalyst via Pudovik reaction. The reaction proceeded smoothly, and completed in 3-4 h to afford the corresponding α-aminophosphonates in high yield (71-87%). This showed that TMG acts as an effective catalyst in this reaction. An important feature is that the TMG can be easily recovered from the reaction mixture after completion of the reaction and can be reused. The chemical structures of all the new compounds were confirmed by elemental analysis, IR, ^{1}H-, ^{13}C- and ^{31}P- NMR spectra.



(**1a-j**) (**2**) (**3a-j**)

Scheme

The IR spectra of the title compounds (**3a-j**) showed absorption bands at 3338-3498 cm^{-1} (N-H), 1195-1245 cm^{-1} (P=O), 1607-1654 cm^{-1} (C=O) and 733-787 cm^{-1} (P-C $_{aliphatic}$) stretching frequencies [15]. Aromatic protons of the title compounds (**3a-j**) showed complex multiplets in the region δ 6.42-7.91. P-C-H protons appeared as a multiplet in the region δ 3.84-4.68, due to its coupling with phosphorus and neighboring N-H protons [15]. The N-H proton gave a broad

singlet peak in the range of δ 4.91-5.87. The methoxy protons of dimethyl phosphite moiety resonated as two distinct doublets in the range of δ 3.68 ($^3J_{CH}$ = 8.9 Hz) and 3.72 ($^3J_{CH}$ = 8.6 Hz) showing their non equivalence. The proton signal of PO$\underline{CH_2}CH_3$ showed a multiplet and $POCH_2\underline{CH_3}$ gave a triplet in the regions of δ 3.27-4.30 and δ 1.28-1.81 respectively [16]. The carbon chemical shifts for P-C-H appeared in the region δ 49.1- 51.8 ppm [16]. The diethyl carbons resonated as doublets, one at δ 63.1 (d, $^2J_{PC}$ = 6.9 Hz, P-OCH_2) and the other at δ 15.7 (d, $^2J_{PC}$ = 6.9 Hz, P-OCH_2). The chemical shift for methoxyl carbon of P-OCH_3 resonated as a doublet at 54.2 ppm (d, $^2J_{PC}$ = 7.4-8.2 Hz) [16].

In mass spectral data of the compounds exhibits their molecular ion peaks at their corresponding values. The ^{31}P NMR signal appeared as a singlet in the region 19.77-24.94 ppm in all the title compounds [16].

Materials and Methods

The melting points were determined in open capillary tubes on a Guna Digital Melting Point apparatus and are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded in KBr pellets on Nicolet 380FT-IR spectrophotometer at Environmental Engineering Laboratory, Sri Venkateswara University, Tirupati. The ^{1}H-, ^{13}C- and ^{31}P- NMR Spectra were recorded on Bruker AMX 400 MHz NMR Spectrometer operatining at 400 MHz for ^{1}H-, 100.57 MHz for ^{13}C- and 161.9 MHz for ^{31}P-NMR. All compounds were dissolved in $CDCl_3$ and chemical shifts were referenced to TMS (^{1}H- and ^{13}C- NMR) and 85% H_3PO_4 (^{31}P-NMR). Micro-analytical data were obtained from University of Hyderabad, Hyderabad, India.

General Procedure for the Synthesis of 2-[(methoxyphosphono)(4-hydroxyphenyl) methylamino]-4-(methylsulfanyl) butanoic acid **(3c).**
A mixture of 2-(4-hydroxybenzylideneamino)-4-(methylthio)butanoic acid (**1c**) (0.864 g, 0.005 mole) (generated *in situ* from methionine and *p*-hydroxy benzaldehyde), demethyl phosphite (0.458 mL, 0.005 mole) (2) and tetramethyl guanidine (TMG) catalyst (10 mol%) in dry ethanol (30 mL) was stirred at reflux temperature for an optimum time (4-5 h). Progress of the reaction was evaluated by running TLC (silica gel) at different intervals using ethyl acetate and *n*-hexane (2:8 by volume) as a mobile phase. After completion of reaction solvent was removed under reduced pressure in a rotary evaporator and the crude product obtained was washed with petroleum ether, water and purified by column chromatography on 60-120 mesh silica gel using ethyl acetate and *n*-hexane (2:8) as eluent to afford the pure brown-yellow **3c**, yield 0.61 g (87%), mp 218-220 °C. Other compounds (**3a-j**) were prepared by adopting the same procedure and were characterized by IR, ^{1}H-, ^{13}C-, ^{31}P- NMR and Mass spectral studies.

Physical, analytical and spectral data for the compounds (3a-j)
2-[(methoxyphosphono)(thiophen-2-yl)methylamino]-4-(methylsulfanyl) butanoic acid **(3a)**. Brown-yellow solid; yield: 72%; mp: 215-217 °C; IR (KBr)(ν_{max} cm^{-1}); 3404 (N-H), 1244 (P=O), 739 (P-$C_{aliphatic}$), 1653 (C=O); ^{1}H-NMR (δ ppm): 6.85-7.62 (m, 3H, Ar-H), 4.25-4.41 (m, 1H, P-CH), 5.03 (bs, 1H, NH), 2.72 (t, 2H, $^3J_{HH}$ = 7.6 Hz, SC$\underline{H_2}$-), 2.30 (m, 2H, S-CH_2-C$\underline{H_2}$), 3.51-3.86 (m, 1H, NC$\underline{H}$), 3.71 (d, 3H, $^2J_{PH}$ = 9.8 Hz, P-OCH_3), 3.65 (d, 3H, $^2J_{PH}$ = 9.1 Hz, P-OCH_3), 7.96 (s, 1H, CO_2H), 2.21 (s, 3H, S-CH_3); ^{13}C NMR (δ ppm): 168.3 (C-1), 57.5 (C-2), 56.2 (C-4),132.6 (C-5), 128.6 (C-7), 129.8 (C-8), 119.7 (C-9), 31.2 (C-3^1), 30.6 (C-4^1), 16.2 (-

SCH_3), 53.7 (d, $^2J_{PC}$ = 7.2 Hz, $POCH_3$); ^{31}P NMR (δ, ppm): 21.68; LCMS: (m/z) 353 ($M^{+\bullet}$, 30%), 309 (12%), 270 (25%), 244 (100%). Anal.calcd for $C_{12}H_{20}NO_5PS_2$: C, 40.78; H, 5.70; N, 3.96. Found: C, 40.21; H, 5.52; N, 3.85.

2-[(methoxyphosphono)(pyridin-4-yl)methylamino]-4-(methylsulfanyl) butanoic acid **(3b)**. Brown-yellow solid; yield: 78%; mp: 186-188 °C; IR (KBr)(ν_{max} cm^{-1}); 3338 (N-H), 1240 (P=O), 701 (P-$C_{aliphatic}$), 1620 (C=O); ^{1}H-NMR (δ ppm): 6.85-7.62 (m, 4H, Ar-H), 4.34-4.68 (m, 1H, P-CH), 4.83 (bs, 1H, NH), 2.51 (t, 2H, $^3J_{HH}$ = 7.5 Hz, SC<u>H</u>$_2$-), 1.98-2.06 (m, 2H, $SCH_2C\underline{H}_2$), 3.67-3.71 (m, 1H, NCH), 3.81 (d, 3H, $^3J_{PH}$ = 9.2 Hz, P-OCH_3), 3.62 (d, 3H, $^3J_{PH}$ = 8.8 Hz, P-OCH_3), 8.71 (s, 1H, CO_2H), 1.48 (*s*, 3H, S-CH_3); ^{13}C NMR (δ ppm): 169.5 (C-1), 58.5 (C-2), 59.4 (C-4),122.8 (C-5), 129.2 (C-6&10), 115.7 (C-7&9), 33.1 (C-3^1), 32.8 (C-4^1), 15.8 (-SCH_3), 54.4 (d, $^2J_{PC}$ = 7.3 Hz, $POCH_3$); ^{31}P NMR (δ,ppm): 19.77; LCMS: (m/z) 348 ($M^{+\bullet}$, 45%), 304 (17%), 270 (19%), 239 (100%). Anal.calcd for $C_{13}H_{21}N_2O_5PS$; C, 44.82; H, 6.08; N, 8.04. Found C, 44.15; H, 5.95; N, 7.96.

2-[(methoxyphosphono)(4-hydroxyphenyl)methylamino]-4-(methylsulfanyl) butanoic acid **(3c).** Brown-yellow solid; yield: 87%; mp: 218-220 °C; IR (KBr)(ν_{max} cm^{-1}); 3390 (N-H), 1245 (P=O), 780 (P-$C_{aliphatic}$), 1614 (C=O); ^{1}H-NMR (δ ppm): 6.54-7.53 (m, 4H, Ar-H), 3.84-4.21 (m, 1H, P-CH), 9.21 (bs, 1H, Ar-OH), 6.01 (bs, 1H, NH), 2.71 (t, 2H, $^3J_{HH}$ = 7.6 Hz, SC<u>H</u>$_2$-), 2.10-2.24 (m, 2H, $SCH_2C\underline{H}_2$), 3.54-3.78 (m, 1H, NCH), 3.64 (d, 3H, $^3J_{PH}$ = 9.4 Hz, P-OCH_3), 3.56 (d, 3H, $^3J_{PH}$ = 9.2 Hz, P-OCH_3), 8.41 (s, 1H, CO_2H), 1.35 (s, 3H, -SCH_3); ^{13}C NMR (δ ppm): 168.9 (C-1), 58.8 (C-2), 58.9 (C-4),118.8 (C-5), 136.7 (C-6&10), 115.9 (C-7&9), 158.9 (C-8), 31.4 (C-3^1), 30.7 (C-4^1), 16.7 (-SCH_3), 53.8 (d, $^2J_{PC}$ = 7.2 Hz, $POCH_3$); ^{31}P NMR (δ ppm): 22.05; LCMS: (m/z) 363 ($M^{+\bullet}$, 65%), 319 (20%), 270 (26%), 254 (100%). Anal.calcd for $C_{14}H_{22}NO_6PS$; C, 46.28, H, 6.10, N, 3.85. Found C, 46.12; H, 5.93; N, 3.64.

2-[(methoxyphosphono)(2-hydroxyphenyl)methylamino]-4-(methylsulfanyl) butanoic acid **(3d)**. Brown-yellow solid; yield: 74%: mp: 204-206 °C; $C_{14}H_{22}NO_6PS$; IR (KBr)(ν_{max} cm^{-1}); 3402 (N-H), 1195 (P=O), 740 (P-$C_{aliphatic}$), 1636 (C=O); ^{1}H-NMR (δ ppm): 6.42-7.71 (m, 3H, Ar-H), 3.88-4.29 (m, 1H, P-CH), 4.80 (bs, 1H, NH), 5.15 (bs, 1H, Ar-OH), 2.67 (t, 2H, $^3J_{HH}$ = 7.7 Hz, SC<u>H</u>$_2$), 1.92-2.12 (m, 2H, $SCH_2C\underline{H}_2$), 3.61-3.89 (m, 1H, NCH), 3.72 (d, 3H, $^3J_{PH}$ = 9.4 Hz, P-OCH_3), 3.64 (d, 3H, $^3J_{PH}$ = 9.2 Hz, P-OCH_3), 8.61 (s, 1H, CO_2H), 1.34 (s, 3H, -SCH_3); ^{13}C NMR (δ ppm): 169.7 (C-1), 59.3 (C-2), 57.8 (C-4),140.2 (C-5), 153.7 (C-6), 114.4 (C-7), 128.4 (C-8), 119.6 (C-9), 125.8 (C-10), 33.2 (C-3^1), 30.4 (C-4^1), 19.4 (-SCH_3), 53.8 (d, $^3J_{PC}$ = 7.3 Hz, $POCH_3$); ^{31}P NMR (δ ppm): 24.94. Anal.calcd for $C_{14}H_{22}NO_6PS$; C, 46.28, H, 6.10, N, 3.85. Found C, 46.12; H, 5.93; N, 3.64.

2-[(methoxyphosphono)(4-methoxyphenyl)methylamino]-4-(methylsulfanyl) butanoic acid **(3e)**. Brown-yellow solid; yield: 72%; mp: 221-223 °C; IR (KBr) (ν_{max} cm^{-1}); 3380 (N-H), 1230 (P=O), 746 (P-$C_{aliphatic}$), 1616 (C=O); ^{1}H-NMR (δ ppm): 6.91-7.85 (m, 4H, Ar-H), 4.21-4.36 (m, 1H, P-CH), 5.21 (bs, 1H, NH), 2.68 (t, 2H, $^3J_{HH}$ = 7.5 Hz, SC<u>H</u>$_2$-), 2.16-2.39 (m, 2H, $SCH_2C\underline{H}_2$), 3.58-3.61 (m, 1H, NCH), 3.65 (d, 3H, $^3J_{PH}$ = 9.6 Hz, P-OCH_3), 3.58 (d, 3H, $^3J_{PH}$ = 8.9 Hz, P-OCH_3), 3.95-4.12 (m, 3H, Ar-OCH_3), 7.94 (s, 1H, CO_2H), 1.84 (s, 3H, -SCH_3); ^{31}P NMR (δ ppm): 23.27. Anal.calcd for $C_{15}H_{24}NO_6PS$: C, 47.74; H, 6.41; N, 3.71. Found C, 47.16; H, 6.25; N, 3.34.

2-[(ethoxyphosphono)(thiophen-2-yl)methylamino]-4-(methylsulfanyl) butanoic acid **(3f)**. Brown-yellow solid; yield: 71%; mp: 198-200 °C; IR (KBr)(ν_{max} cm^{-1}); 3402 (N-H), 1212 (P=O), 770 (P-$C_{aliphatic}$), 1654 (C=O); ^{1}H-NMR (δ ppm): 7.02-7.84 (m, 3H, Ar-H), 4.16-4.34 (m, 1H, P-CH), 5.11 (bs, 1H, NH), 2.52 (t, 2H, $^3J_{HH}$ = 7.6 Hz, SC$\underline{H}_2$-), 1.96-2.24 (m, 2H, $SCH_2C\underline{H}_2$), 3.64-3.76 (m, 1H, NCH), 3.71-3.86 (m, 4H, P-OC$\underline{H}_2CH_3$), 1.63 (t, 6H, $^3J_{HH}$ = 7.5 Hz, P-OCH_2-C$\underline{H}_3$), 8.14 (s, 1H, CO_2H), 2.13 (s, 3H, -SCH_3); ^{31}P NMR (δ ppm): 24.03. Anal.calcd for formula: $C_{14}H_{24}NO_5PS_2$: C, 44.08; H, 6.34; N, 3.67. Found C, 44.01; H, 6.25; N, 3.54.

2-[(ethoxyphosphono)(pyridin-4-yl) methylamino]-4-(methylsulfanyl) butanoic acid **(3g)**. Brown-yellow solid; yield: 71%; mp: 220-222 °C; IR (KBr)(ν_{max} cm^{-1}); 3396 (N-H), 1236 (P=O), 739 (P-$C_{aliphatic}$), 1643 (C=O); ^{1}H-NMR (δ ppm): 6.83-7.56 (m, 4H, Ar-H), 4.01-4.22 (m, 1H, P-CH), 4.92 (bs, 1H, NH), 2.65 (t, 2H, $^3J_{HH}$ = 7.8 Hz, SC$\underline{H}_2$-), 1.91-2.21 (m, 2H, $SCH_2C\underline{H}_2$), 3.42-3.61 (m, 1H, NCH), 3.68-3.84 (m, 4H, P-OC$\underline{H}_2CH_3$), 1.81 (t, 6H, $^3J_{HH}$ = 7.5 Hz, P-OCH_2-C$\underline{H}_3$), 8.62 (s, 1H, CO_2H), 1.35 (s, 3H, -SCH_3); ^{31}P NMR (δ ppm): 22.98. Anal.calcd for formula: $C_{15}H_{25}N_2O_5PS$: C, 47.86; H, 6.69; N, 7.44. Found C, 47.76; H, 6.45; N, 7.38.

2-[(ethoxyphosphono)(4-hydroxyphenyl)methylamino]-4-(methylsulfanyl) butanoic acid **(3h)**. Pale-yellow solid; yield: 72%; mp: 224-226 °C; Molecular formula: $C_{16}H_{26}NO_6PS$; IR (KBr)(ν_{max} cm^{-1}); 3498 (N-H), 1214 (P=O), 768 (P-$C_{aliphatic}$) 1607 (C=O); ^{1}H-NMR (δ ppm): 6.42-6.91 (m, 4H, Ar-H), 3.91-4.16 (m, 1H, P-CH), 4.91 (bs, 1H, NH), 9.23 (bs, 1H, Ar-OH), 2.69 (t, 2H, $^3J_{HH}$ = 7.4 Hz, SC$\underline{H}_2$-), 2.01-2.19 (m, 2H, $SCH_2C\underline{H}_2$), 3.61-3.84 (m, 1H, NCH), 3.91-4.30 (m, 4H, P-OC$\underline{H}_2CH_3$), 1.28 (t, 6H, $^3J_{HH}$ = 7.5 Hz, P-$OCH_2C\underline{H}_3$), 7.81 (s, 1H, CO_2H), 2.09 (s, 3H, -SCH_3); ^{31}P NMR (δ ppm): 24.05.

2-[(ethoxyphosphono)(2-hydroxyphenyl)methylamino]-4-(methylsulfanyl) butanoic acid **(3i)**. Brown-yellow solid; yield: 73%; mp: 210-212 °C; Molecular formula: $C_{16}H_{26}NO_6PS$; IR (KBr) (ν_{max} cm^{-1}); 3401 (N-H), 1222 (P=O), 757 (P-$C_{aliphatic}$), 1643 (C=O); ^{1}H-NMR (δ ppm): 6.80-7.51 (m, 3H, Ar-H), 4.10-4.21 (m, 1H, P-CH), 5.17 (bs, 1H, NH), 5.12 (bs, 1H, Ar-OH), 2.64 (t, 2H, $^3J_{HH}$ = 7.7 Hz, SC$\underline{H}_2$-), 2.04-2.24 (m, 2H, $SCH_2C\underline{H}_2$), 3.47-3.66 (m, 1H, NCH), 3.71-3.80 (m, 4H, P-OC$\underline{H}_2CH_3$), 1.67 (t, 6H, $^3J_{HH}$ = 7.5 Hz, P-$OCH_2C\underline{H}_3$), 8.73 (s, 1H, CO_2H), 1.46 (s, 3H, S-CH_3); ^{31}P NMR (δ ppm): 23.89.

2-[(methoxyphosphono)(2-methoxyphenyl)methylamino]-4-(methylsulfanyl) butanoic acid **(3j)**. Brown-yellow solid; yield: 78%; mp: 227-229 °C; Molecular formula: $C_{17}H_{28}NO_6PS$; IR (KBr)(ν_{max} cm^{-1}); 3394 (N-H), 1216 (P=O), 751 (P-$C_{aliphatic}$), 1651 (C=O); ^{1}H-NMR (δ ppm): 6.92-7.84 (m, 4H, Ar-H), 3.96-4.13 (m, 1H, P-CH), 5.34 (bs, 1H, NH), 2.56 (t, 2H, $^3J_{HH}$ = 7.6 Hz, SC$\underline{H}_2$-), 2.19-2.31 (m, 2H, $SCH_2C\underline{H}_2$), 3.56-3.62 (m, 1H, NCH), 3.84-3.92 (m, 4H, P-OC$\underline{H}_2CH_3$), 1.73 (t, 6H, $^3J_{HH}$ = 7.5 Hz, P-$OCH_2C\underline{H}_3$), 3.96-4.13 (m, 3H, Ar-OCH_3), 8.34 (s, 1H, CO_2H), 1.95 (s, 3H, S-CH_3); ^{31}P NMR (δ ppm): 23.45.

Antibacterial Activity

All the title compounds **3a-j** were screened for their antibacterial activity against the growth of *Staphylococcus aureus* ATCC-25923 (Gram positive) and *Escherichia coli* ATCC-25922 (Gram negative) at two concentrations 250 and 100 µg/disc [17,18] in DMF (**Table 1**). The compounds were diluted in DMF for bioassay. Solvent control was included although no antibacterial activity has been noted in the solvent employed. They where showed moderate antibacterial

activity against both bacteria when compared with that of the standard compound. All samples were tested in triplicate and average results were recorded.

Table 1: Antibacterial activity of the title compounds 3a-j

Compd.	Zone of inhibition (mm)			
	Staphylococcus aureus		*Escherichia coli*	
	250 µg/disc	100 µg/disc	250 µg/disc	100 µg/disc
3a	10	5	12	6
3b	11	4	11	5
3c	9	5	9	4
3d	11	7	13	7
3e	10	5	10	5
3f	8	5	9	6
3g	9	6	8	4
3h	11	5	10	5
3i	10	4	9	6
3j	11	5	11	5
[b]*Penicillin*	12	8	14	8

[a]Concentration in ppm; [b]Reference Compound.

Antifungal Activity

All the title compounds **3a-j** were tested for their antifungal activity against the growth of *Aspergillus niger* and *Helminthosporium oryzae* at two concentrations 250 and 100 µg/disc [19] in DMF (**Table 2**).

Table 2: Antifungal activity[a] of α-aminophosphonates 3a-j

Compd.	Zone of inhibition (mm)			
	Aspergillus niger		*Helminthosporium oryzae*	
	250 µg/disc	100 µg/disc	250 µg/disc	100 µg/disc
3a	11	5	10	5
3b	9	4	8	4
3c	12	6	11	5
3d	10	5	9	4
3e	12	6	12	5
3f	14	7	13	7
3g	13	6	12	6
3h	9	5	11	5
3i	8	4	10	6
3j	10	5	9	4
[b]*Griseofulvin*	16	8	16	8

[a]Concentration in ppm; [b]Reference Compound.

When compared with the reference compound *Griseofulvin*, all the compounds showed moderate to high antifungal activity against the growth of both the fungi. The majority of the compounds exhibited high activity against fungi. The compound **3f** showed higher activity against *Aspergillus niger* and *Helminthosporium oryzae*, when compared with that of the standard and warrants further testing to determine their minimum inhibitory concentrations as well as their cytotoxicity.

Conclusion

From the above discussion, we concluded that the TMG is a best catalyst for synthesis of a new class of α-aminophosphonic acid esters in high yields (71-87%) by the addition of labile P-H to Schiff's bases in a one-pot Pudovik reaction. The anti-microbial activity of the all titled compounds shown moderate to high activity, and the compounds **3b**, **3d**, **3h** and **3j** are have significantly antibacterial activity, however the compounds; **3c**, **3e**, **3f** and **3g** showed moderate to considerable antifungal activities against all the employed organisms at conc. 250 µg/disc, 100 µg/disc in ppm and are comparable to that of standard drugs (*Penicillin* and *Griseofulvin*).

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