ARTICLE

Microwave Mediated Michaelis-Arbuzov Reaction to Synthesize Bioactive Phenylphosphonate Derivatives Under Solvent Free Condition

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ABSTRACT

Microwave assisted easy, efficient, and environment friendly process has been devised for the synthesis of phosphonates within minutes *via* microwave-assisted Michaelis-Arbuzov reaction. The desired products were obtained in excellent yields and in high purity under solvent-free and catalyst-free conditions. The structure of all the synthesized compounds was confirmed by spectral and CHN analysis. *in vitro* Antibacterial and antifungal activity of these compounds was also analyzed. Majority of the title compounds showed good inhibition towards bacteria and fungi.

KEYWORDS

Microwave, Phosphonates, Michaelis-Arbuzov reaction, Antibacterial and Antifungal activities.

INTRODUCTION

Organophosphorus compounds particularly phosphonates have been played a key role in biologically active compounds [1]. Phosphonates feature tetrahedral phosphorus centers are structurally closely related to phosphorous acid [2]. Phosphonates and phosphonic acids are organophosphorus compounds containing C–PO(OH)$_2$ or C–PO(OR)$_2$ groups (where R = alkyl, aryl). Many commercially important phosphonates compounds includes glyphosate (1) (active molecule of herbicide "Roundup"), ethephon (2), a widely used plant growth regulator, tiludronate (3) as anti-inflammatory as well as anti-rheumatismal agent. Bisphosphonates are popular drugs for treatment of osteoporosis. In biology and medicinal chemistry, phosphonate groups are used as stable bioisoteres for phosphate, such as antiviral nucleotide analogue, tenofovir, one of the cornerstones of anti-HIV therapy [3]. Many synthetic phosphonates are now widely used as herbicides [4], stimulants for the latex production of *Hevea brasiliensis* [5], pesticides [6], detergents [7], reagents for Wittig-Horner reactions [8], antibacterial [9], antiviral [10] and anti-tumor agents [11,12].

Phosphonates have traditionally been accessed through the Arbuzov reaction [13-16]; a double SN^2 process between an alkyl halide and a trialkylphosphite, and this remains the most commonly employed route today. However, due to the resistance of aryl groups to nucleophilic attack, the classic

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Arbuzov reaction was essentially limited to the preparation of alkyl phosphonates. The synthesis of aryl phosphonates represents one early challenge. In this regard, transition-metal catalyzed Arbuzov reaction has gained remarkable success [17-21].

On the other hand, microwave-assisted organic synthesis has been given away to provide a number of advantages than the standard heating techniques such as clean reactions, improved reaction yields and shortened reaction times, easy work-ups and/or solvent free reaction conditions [22-25]. Keglevich *et al.* [26] also synthesized arylphosphonates by microwave-assisted Arbuzov reaction of triethylphosphite and aryl bromides in the presence of $NiCl_2$ as catalyst under solvent-free conditions.

As part of our research in the development of new methodologies for the synthesis of bioactive phosphonates, we synthesized a series of phenylphosphonate derivatives *via* Michaelis-Arbuzov reaction using microwave irradiation technique under solvent free condition. All the synthesized compounds were characterized by various spectrophotometric methods and screened for their antibacterial and antifungal activities. Majority of the compounds showed good inhibition towards bacteria and fungi.

EXPERIMENTAL

All the chemicals used in the present work were obtained from S.D. Fine Chem. Ltd., India; Qualigens, Mumbai and used after purifying them by following the established procedures.

Characterization: The reactions were carried out in a 100 mL round bottom flask holding condenser in nitrogen atmosphere. A magnetic agitator cum hot plate was used for stirring and heating the reaction mixtures. Rota evaporator was used for removing the solvent from the reaction mixture. All the chemicals were dehydrated before use by adopting the standard procedures and techniques. Thin layer chromatography (TLC) on aluminium sheet of silica gel was used to check the development of the reaction and purity of the compounds by iodine as visualizing agent. All microwave-assisted irradiation experiments were conducted using single-mode microwave synthesis apparatus. The ^{31}P (161.9 MHz), ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on Bruker AMX spectrometer. Chemical shifts were referenced to TMS (^{1}H and ^{13}C NMR) and 85 % H_3PO_4 (^{31}P NMR) and DMSO-d_6 was used to dissolve the samples. API 2000 Perkin-Elmer Mass spectrometer was used to record mass spectra. Bruker IFS 55 (Equinox) FTIR spectrometer in KBr was used to record IR spectra. Microanalytical data were obtained from University of Hyderabad, Hyderabad, India.

Synthesis of 4-chloro-*N*-(substituted) benzenesulfonamide (3a-i): To a stirred solution of 4-chlorobenzene-1-sulfonyl chloride (1) (0.2 mmol) and pyridin-3-amine (**2a**) (0.2 mmol) in dehydrated tetrahydrofuran (40 mL); triethylamine was added at 10 ºC with stirring for about 15 min. It was stirred further at ambient temperature for 4 h. TLC was used for monitoring the progress of the synthetic route and rota-evaporator on the way to eliminate the solvent to obtain crude product. By means of ethyl acetate- *n*-hexane (8:2) as eluent, the product was purified using column chromatography to afford 4-chloro-*N*-(pyridin-3-yl)benzenesulfonamide (**3a**). Similar experimental route was used to synthesize of left over compounds (**3b-i**).

Conventional synthesis of phenylphosphonate derivatives (5a-i): 4-Chloro-*N*-(substituted) benzenesulfonamide derivatives (**3a-i**) (0.01 mol) and trimethylphosphite (**4**) (0.02 mol) in THF were mixed together and stirred for 3-5 h at reflux temperature. TLC was used to check the progress of the process. After completion of the reaction, triethylamine hydrochloride salt was filtered off and the solvent was removed in a rota-evaporator. Finally column chromatography was used to get pure phenylphosphonate derivatives (**5a-i**) using ethyl acetate: *n*-hexane (6:4) as eluent.

Microwave assisted synthesis of phosphonates (5a-i): 4-Chloro-*N*-(substituted) benzenesulfonamide derivatives (**3a-i**) (0.01 mol) and trimethylphosphite (**4**) (0.02 mol) were mixed together and microwave radiated at 420 W under room temperature for about 12-30 min. TLC was used to check the progress of the reaction. After completion of the reaction, triethylamine hydrochloride salt was filtered off and the solvent was removed in a rota-evaporator. Finally, column chromatography was used to get pure phenylphosphonate derivatives (**5a-i**) by means of ethyl acetate:*n*-hexane (6:4) as eluent.

Spectral data

Dimethyl 4-(*N*-pyridin-3-ylsulfamoyl)phenylphosphonate (5a): Yield: 90 %; semi-solid. ^{31}P NMR spectrum (DMSO-d_6): δ 18.5 ppm; ^{1}H NMR spectrum (400 MHz, DMSO-d_6): δ 10.35 (s, 1H, NH), 8.35-7.20 (m, 8H, Ar-H), 3.65 (s, 6H, OCH_3); ^{13}C NMR spectrum (100 MHz, DMSO-d_6): δ 145.1 (C-1′), 141.5 (C-2), 141.2 (C-5), 138.8 (C-4′), 137.5 (C-2′), 131.4 (C-4, C-6), 126.8 (C-3, C-7), 124.7 (C-5′), 122.8 (C-6′), 52.5 (C-10, C-12); IR (KBr, ν_{max}, cm^{-1}): 3269 (NH), 1468 (P-car), 1332,1183 (SO_2), 1225 (P=O), 1018 (P-O-C aliph.), 905 (S-N). LC-MS (*m/z*, %): 343 ($M+H^+$,100); Anal. calcd (found) % for $C_{13}H_{15}N_2O_5PS$: C, 45.61 (45.69); H, 4.42 (4.48); N, 8.18 (8.12).

Dimethyl 4-(*N*-thiazol-2-ylsulfamoyl)phenylphosphonate (5b): Yield: 89 %; semi-solid. ^{31}P NMR spectrum (DMSO-d_6): δ 20.2 ppm; ^{1}H NMR spectrum (400 MHz, DMSO-d_6): δ 11.94 (s, 1H, NH), 8.36-6.70 (m, 6H, Ar-H), 3.65 (s, 6H, OCH_3); ^{13}C NMR spectrum (100 MHz, DMSO-d_6): δ 171.7 (C-2′), 141.5 (C-2), 141.2 (C-5), 137.0 (C-4′), 131.4 (C-4, C-6), 126.8 (C-3, C-7), 112.1 (C-5′), 52.5 (C-10, C-12). IR (KBr, ν_{max}, cm^{-1}): 3283 (NH), 1479 (P-car), 1338, 1186 (SO_2), 1228 (P=O), 1018 (P-O-C aliph.), 907 (S-N); LC-MS (*m/z*, %): 349 ($M+H^+$, 100). Anal. calcd. (found) % for $C_{11}H_{13}N_2O_5PS_2$: C, 37.93 (37.99); H, 3.76 (3.82); N, 8.04 (8.00).

Dimethyl 4-(*N*-(1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)sulfamoyl)phenylphosphonate (5c): Yield: 87 %; semi-solid. ^{31}P NMR spectrum (DMSO-d_6): δ 23.4 ppm; ^{1}H NMR spectrum (400 MHz, DMSO-d_6): δ 11.36 (s, 1H, urea-NH), 8.35 (d, 2H, Ar-H), 7.88 (d, 2H, Ar-H), 4.35 (d, 2H, ethylene-H), 3.69 (s, 6H, OCH_3), 3.24 (s, 3H, N-CH_3), 2.13 (s, 1H, NH); ^{13}C NMR spectrum (100 MHz, DMSO-d_6): δ 163.2 (C-2′), 142.9 (C-2), 142.1 (C-5), 162.3 (C-6′), 161.7 (C-4′), 131.4 (C-4, C-6), 126.8 (C-3, C-7), 75.5 (C-7'), 52.5 (C-10, C-12), 28.0 (C-8′). IR (KBr, ν_{max}, cm^{-1}): 3345, 3284 (NH), 1469 (P-car), 1338, 1181 (SO_2), 1232 (P=O), 1021 (P-O-C aliph.), 908 (S-N); LC-MS (*m/z*, %): 390 ($M+H^+$,100); Anal. calcd. (found) % for $C_{13}H_{16}N_3O_7PS$: C, 40.11 (40.19); H, 4.14 (4.18); N, 10.79 (10.85).

Dimethyl 4-(*N*-thiomorpholinosulfamoyl)phenylphosphonate (5d): Yield: 93 %; semi-solid. ^{31}P NMR spectrum (DMSO-d_6): δ 22.7 ppm; ^{1}H NMR spectrum (400 MHz, DMSO-d_6): δ 8.35 (d, 2H, Ar-H), 8.08 (d, 2H, Ar-H), 3.69 (s, 6H, OCH_3), 3.58 (t, 4H, methylene-H), 2.46 (t, 4H, methylene-H); ^{13}C NMR spectrum (100 MHz, DMSO-d_6): δ 142.9 (C-2), 142.1 (C-5), 131.4 (C-4, C-6), 126.8 (C-3, C-7),52.5 (C-10, C-12), 49.3 (C-2′, C-6′), 26.9 (C-3′, C-5′). IR (KBr, ν_{max}, cm^{-1}): 1464 (P-car), 1335, 1186 (SO_2), 1221 (P=O), 1018 (P-O-C aliph), 903 (S-N); LC-MS (*m/z*, %): 352 (M+H$^+$, 100). Anal. calcd. (found) % for $C_{12}H_{18}NO_5PS_2$: C, 41.02 (41.09); H, 5.16 (5.10); N, 3.99 (4.05).

Dimethyl 4-(4-Methylpiperazin-1-ylsulfonyl)phenylphosphonate (5e): Yield: 90 %; semi-solid. ^{31}P NMR spectrum (DMSO-d_6): δ 23.2 ppm; ^{1}H NMR spectrum (400 MHz, DMSO-d_6): δ 8.35 (d, 2H, Ar-H), 8.08 (d, 2H, Ar-H), 3.69 (s, 6H, OCH_3), 3.12 (t, 4H, methylene-H), 2.48 (t, 4H, methylene-H), 2.15 (s, 3H, N-CH_3); ^{13}C NMR spectrum (100 MHz, DMSO-d_6): δ 142.9 (C-2), 142.1 (C-5), 131.4 (C-4, C-6), 126.8 (C-3, C-7), 53.7 (C-3′, C-5′), 52.5 (C-10, C-12), 46.0 (C-2′, C-6′), 45.5 (C-7′). IR (KBr, ν_{max}, cm^{-1}): 1466 (P-car), 1332, 1183 (SO_2), 1226 (P=O), 1018 (P-O-C aliph.), 905 (S-N); LC-MS (*m/z*, %): 349 (M+H$^+$, 100). Anal. calcd. (found) % for $C_{13}H_{21}N_2O_5PS$: C, 44.82 (44.89); H, 6.08 (6.02); N, 8.04 (8.09).

Dimethyl 4-(*N*-(6-nitrobenzo[*d*]thiazol-2-yl)sulfamoyl)-phenylphosphonate (5f): Yield: 91 %; semi-solid. ^{31}P NMR spectrum (DMSO-d_6): δ 24.3 ppm; ^{1}H NMR spectrum (400 MHz, DMSO-d_6): δ 12.26 (s, 1H, NH), 8.58-8.08 (m, 7H, Ar-H), 3.69 (s, 6H, OCH_3); ^{13}C NMR spectrum (100 MHz, DMSO-d_6): δ 142.9 (C-2), 142.1 (C-5), 131.4 (C-4, C-6), 126.8 (C-3, C-7), 174.1 (C-2′), 131.3 (C-4′), 119.1 (C-5′), 144.3 (C-6′), 121.3 (C-7′), 117.3 (C-8′), 159.3 (C-9′), 52.5(C-10, C-12). IR (KBr, ν_{max}, cm^{-1}): 3292 (NH), 1477 (P-car), 1339, 1186 (SO_2), 1235 (P=O), 1024 (P-O-C aliph.), 909 (S-N); LC-MS (*m/z*, %): 444 (M+H$^+$, 100). Anal. calcd. (found) % for $C_{15}H_{14}N_3O_7PS_2$: C, 40.63 (40.69); H, 3.18 (3.11); N, 9.48 (9.54).

Dimethyl 4-(*N*-benzo[*d*]thiazol-2-ylsulfamoyl)phenylphosphonate (5g): Yield: 92 %; semi-solid. ^{31}P NMR spectrum (DMSO-d_6): δ 18.7 ppm; ^{1}H NMR spectrum (400 MHz, DMSO-d_6): δ 11.94 (s, 1H, NH), 8.58-7.50 (m, 8H, Ar-H), 3.69 (s, 6H, OCH3); ^{13}C NMR spectrum (100 MHz, DMSO-d_6): δ 142.9 (C-2), 142.1 (C-5), 131.4 (C-4, C-6), 126.8 (C-3, C-7),172.3 (C-2′), 131.3 (C-4′), 122.4 (C-5′), 124.9 (C-6′), 125.7 (C-7′), 117.7 (C-8′), 152.9 (C-9′), 52.5(C-10, C-12). IR (KBr, ν_{max}, cm^{-1}): 3274 (NH), 1465 (P-car), 1330, 1182 (SO_2), 1223 (P=O), 1018 (P-O-C aliph.), 902 (S-N); LC-MS (*m/z*, %): 399 (M+H$^+$, 100). Anal. calcd. (found) % for $C_{15}H_{15}N_2O_5PS_2$: C, 45.22 (45.28); H, 3.80 (3.74); N, 7.03 (7.08).

Dimethyl 4-(*N*-(6-methoxybenzo[*d*]thiazol-2-yl)sulfamoyl)phenylphosphonate (5h): Yield: 93 %; semi-solid. ^{31}P NMR spectrum (DMSO-d_6): δ 21.6 ppm; ^{1}H NMR spectrum (400 MHz, DMSO-d_6): δ 11.92 (s, 1H, NH), 8.58-7.12 (m, 7H, Ar-H), 3.73 (s, 3H, OCH_3), 3.69 (s, 6H, OCH_3); ^{13}C NMR spectrum (100 MHz, DMSO-d_6): δ 172.3(C-2′), 154.7 (C-6′), 142.9 (C-2), 142.1 (C-5), 131.4 (C-4, C-6), 126.8 (C-3, C-7), 132.3 (C-4′), 113.8 (C-7′), 117.6 (C-8′), 105.8 (C-5′), 143.7 (C-9′), 54.8 (C-11′), 52.5 (C-10, C-12). IR (KBr, ν_{max}, cm^{-1}): 3263 (NH), 1461 (P-car), 1330, 1184 (SO_2), 1220 (P=O), 1017 (P-O-C aliph.), 904 (S-N); LC-MS (*m/z*, %): 429 (M+H$^+$, 100). Anal. calcd. (found) % for $C_{16}H_{17}N_2O_6PS_2$: C, 44.86 (44.91); H, 4.00 (3.94); N, 6.54 (6.59).

Dimethyl 4-(*N*-naphthalen-1-ylsulfamoyl)phenylphosphonate (5i): Yield: 95 %; semi-solid. ^{31}P NMR spectrum (DMSO-d_6): δ 23.8 ppm; ^{1}H NMR spectrum (400 MHz, DMSO-d_6): δ 10.53 (s, 1H, NH), 8.58-6.86 (m, 11H, Ar-H), 3.69 (s, 6H, OCH_3); ^{13}C NMR spectrum (100 MHz, DMSO-d_6): δ 142.9 (C-2), 142.1 (C-5), 131.4 (C-4, C-6), 126.8 (C-3, C-7), 141.5 (C-2′), 132.8 (C-8′), 128.9 (C-7′), 126.9 (C-10′), 126.2 (C-6′), 125.3 (C-5′), 124.9 (C-3′), 120.7 (C-4′), 119.5 (C-9′), 108.4 (C-11′), 52.5 (C-10, C-12). IR (KBr, ν_{max}, cm^{-1}): 3274 (NH), 1462 (P-car), 1328, 1180 (SO_2), 1215 (P=O), 1012 (P-O-C aliph.), 901 (S-N);LC-MS (*m/z*, %): 392 (M+H$^+$, 100). Anal. calcd. (found) % for $C_{18}H_{18}NO_5PS$: C, 55.24 (55.28); H, 4.64 (4.59); N, 3.58 (3.63).

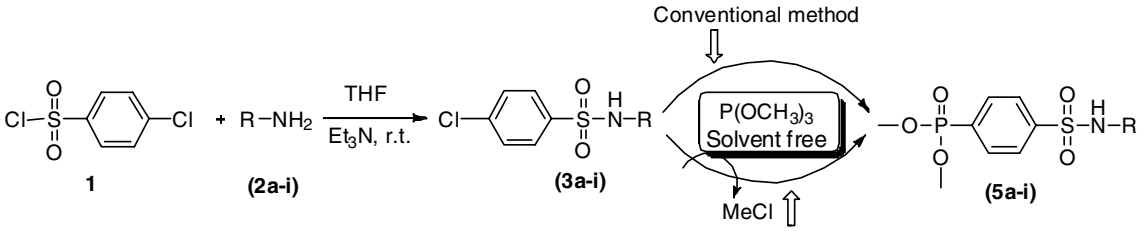
Antibacterial and antifungal assays: Antimicrobial activity of title compounds was tested by agar disc-diffusion method [27-29]. Sterile filter paper discs (6 mm diameter) moistened with the test compound solution in DMSO of specific concentrations 50 µg and 100 µg/disc were carefully placed on the agar culture plates that had been previously inoculated separately with the microorganisms. The plates were incubated at 37 ºC and the diameter of growth inhibition zones was measured after 24 h in case of bacteria and after 48 h in case of fungi. Penicillin was used as a reference antibacterial agent. Gresiofulvin was used as a reference antifungal agent. The test compounds, penicillin and gresiofulvin were dissolved in DMSO at concentrations of 50 and 100 µg/mL. Zone of inhibition is the area on an agar plate where growth of any microorganism is prevented by an antibiotic usually placed on the agar surface. If the test organism is susceptible to the antibiotic, the microorganisms will not grow.

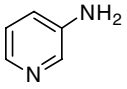
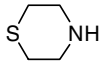
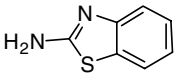
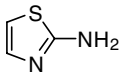
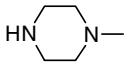
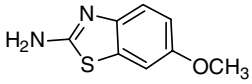
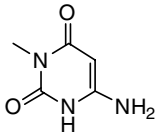
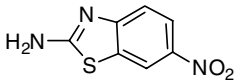
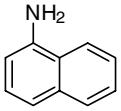
Minimum inhibitory concentration: Minimum inhibitory concentration (MIC) was evaluated using micro-broth-dilution method. MIC was determined by taking the minimum concentration at which there were observed no visually detectable bacteria/fungal growth. Specifically, 0.1 mL of standardized inoculum (1.2×10^7 c.f.u/mL) was added to each test tube. The tubes were incubated aerobically at 37 ºC for 24 h for bacterial activity and 48-72 h for fungal activity. Control was maintained for each test sample. The lowest concentration (highest dilution) of test compound that produced no visible signs of microbial growth (no turbidity) when compared with the control tubes were regarded as MICs.

RESULTS AND DISCUSSION

Synthesis of substituted phenylphosphonates (**5a-i**) was accomplished by reacting 4-chloro-*N*-(substituted) benzenesulfonamide derivatives (0.01 mmol) (**3a-i**) (which were synthesized by the reaction of 4-chlorobenzene-1-sulfonyl chloride (**1**) (0.2 mmol) and various amines (**2a-i**) (0.2 mmol) in THF in presence of triethylamine as base with trimethylphosphite (**4**) (0.02 mmol) using conventional and microwave irradiation techniques (**Scheme-I**) in high yields (73-95 %) in short period of time (12-30 min) under solvent free conditions (Table-1).

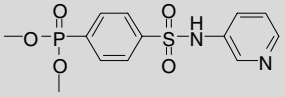
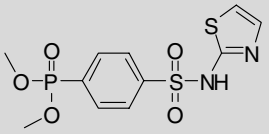
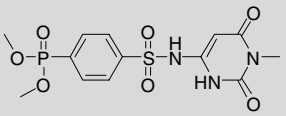
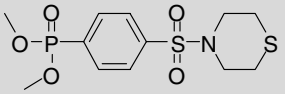
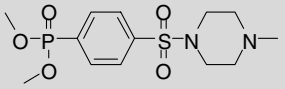
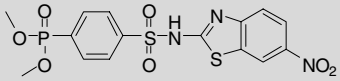
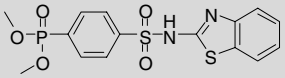
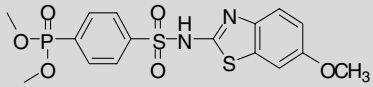
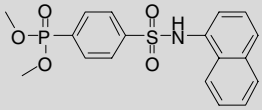
The structures of all the synthesized compounds were confirmed by NMR (^{31}P, ^{1}H, ^{13}C), IR, mass and CHN analysis. ^{31}P



Compd	R-NH$_2$	Compd	R-NH$_2$	Compd	R-NH$_2$
5a		**5d**		**5g**	
5b		**5e**		**5h**	
5c		**5f**		**5i**	

Scheme-I: Synthesis of phenylphosphonate derivatives (**5a-i**)

TABLE-1
SYNTHESIS OF COMPOUNDS (**5a-i**) UNDER VARIOUS CONDITIONS

Compd.	Structure	Conventional method[a]		Microwave irradiation method[b]	
		Time (h)	Yield[c] (%)	Time (h)	Yield[c] (%)
5a		5	58	30	73
5b		4	61	20	77
5c		5	63	26	79
5d		4.5	65	24	80
5e		3	62	12	86
5f		3.5	68	16	74
5g		4.5	71	27	88
5h		4	80	19	95
5i		4	69	18	82

[a]Reaction of 4-chloro-N-(substituted)benzenesulfonamide derivatives and trimethylphosphite in THF at reflux temperature; [b]Reaction of 4-chloro-N-(substituted)benzenesulfonamide derivatives and trimethylphosphite without solvent under microwave irradiation at optimum temperature; [c]Isolated yield.

NMR signals appeared in the region δ 24.3-18.5 ppm for all the compounds (**5a-i**). ^{1}H NMR spectra of the compounds (**5a-i**) gave signals for aromatic protons in the range of 8.58-6.70 ppm. The methyl protons of P-O-CH_3 showed singlet in the region δ 3.69-3.65 ppm for the compounds (**5a-i**). In ^{13}C NMR spectra of compounds (**5a-i**), P-O-CH_3 was resonated at δ 52.5 ppm for the compounds (**5a-i**). In IR spectra, the bands in the region 1479-1461, 1235-1215 and 1024-1012 cm^{-1} for P-car, P=O and P-O-C aliph. stretching frequencies. In mass spectra of the compounds, molecular ions were found in the accepted *m/z* values.

Antibacterial activity: All the synthesized compounds were assayed for their antibacterial activity against the growth of two Gram positive bacteria namely *Staphylococcus aureus*, *Bacillus subtilis* and two Gram negative bacteria such as *Escherichia coli*, *K. pneumoniae* at two different concentrations 50 and 100 μg/mL by agar well diffusion method. The standard drug, penicillin was used as reference for the comparison of the antibacterial activity. The diameter of zone of inhibition (mm) are represented in Table-1. Some analogues of this series were found to equipotent with the standard drug while some of them have comparable potency.

Especially, compound **5f**, bearing with 6-nitrobenzothiazolyl moiety and compound **5b** bearing with thiazol-2-yl group and compound **5c** incorporated with 1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl moiety were found to be most potent among all the title compounds. Zone of inhibition (ZOI) of compound **5f** is in the range 7.2-15.3 mm against Gram positive bacteria and 8.1-14.2 mm against Gram negative bacteria. The compound **5b** exhibited ZOI in the range 6.8-14.9 mm against Gram positive bacteria and 7.9-14.1 mm against Gram negative bacteria. The compound **5c** exhibited ZOI in the range 7.1-14.3 mm against Gram positive bacteria and 7.7-13.6 mm against Gram negative bacteria.The standard drug exhibited ZOI in the range 7.4-16.2 mm and 8.7-15.3 mm, respectively against Gram positive and Gram negative bacteria. The remaining compound exhibited modest activity. The results are shown in Table-2.

Antifungal activity: Two pathogenic fungi such as *Curvularia lunata* and *Aspergillus niger* were used to study the antifungal activity of synthesized compounds at two different concentrations 50 and 100 μg/mL using poison plate technique. Standard fungicide, gresiofulvin was used for the comparison of antifungal activity. All the compounds showed moderate to good antifungal activity.

Especially, compounds **5c** bearing with 1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl moiety and **5f**, bearing with 6-nitrobenzothiazolyl moiety, **5d** bearing with thiomorpholine group were found to be most potent among all the title compounds. Zone of inhibition (ZOI) was found in the range 9.9-20.3 mm

TABLE-2
ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY OF PHOSPHONATE DERIVATIVES (**5a-i**)

Compd.	Zone of inhibition (mm)											
	Antibacterial Activity								Antifungal activity			
	S. aureus		*B. subtilis*		*E. coli*		*K. pneumoniae*		*C. lunata*		*A. niger*	
	50 μg/mL	100 μg/mL	50 μg/mL	100 μg/mL	50 μg/mL	100 μg/mL	50 μg/mL	100 μg/mL	50 μg/mL	100 μg/mL	50 μg/mL	100 μg/mL
5a	10.1	12.4	6.8	8.3	7.4	10.2	9.6	11.5	10.7	17.3	7.2	16.9
5b	11.9	14.9	6.8	8.8	7.9	11.8	10.5	14.1	9.5	15.2	8.4	16.1
5c	11.5	14.3	7.1	8.4	7.7	11.1	10.8	13.6	12.4	20.3	9.9	18.7
5d	9.2	11.8	6.1	8.2	7.0	9.8	8.6	11.9	11.2	18.0	8.6	17.1
5e	10.3	13.5	6.4	8.6	7.2	10.8	9.5	12.3	8.4	13.6	7.2	15.3
5f	12.1	15.3	7.2	9.2	8.1	11.8	11.0	14.2	11.8	18.7	8.9	17.9
5g	7.4	10.3	5.1	8.0	5.4	7.9	8.8	11.9	5.8	12.5	6.2	11.3
5h	6.9	9.1	4.5	5.6	6.0	7.7	8.4	10.7	6.0	13.1	7.0	12.1
5i	7.9	11.0	6.3	8.5	6.3	8.5	9.7	12.4	7.3	13.5	7.6	15.2
Penicillin	12.3	16.2	7.4	10.5	8.7	12.6	12.3	15.3	–	–	–	–
Gresiofulvin	–	–	–	–	–	–	–	–	12.8	21.2	10.2	18.9

TABLE-3
MIC VALUES OF THE SYNTHESIZED SULFONAMIDE DERIVATIVES (**5a-i**)

Compd.	Minimum inhibitory concentration (μg/mL)					
	Bacterial strains				Fungal strains	
	S. aureus	*B. subtilis*	*E. coli*	*K. pneumoniae*	*C. lunata*	*A. niger*
5a	75	60	45	55	60	55
5b	20	25	40	35	40	25
5c	25	30	45	35	20	15
5d	59	64	59	44	20	30
5e	25	45	30	35	55	60
5f	15	20	25	15	15	20
5g	85	90	75	70	70	80
5h	75	80	65	70	85	60
5i	90	75	55	65	25	35
Penicillin	5	10	10	10	–	–
Gresiofulvin	–	–	–	–	5	10

for **5c**, 8.9-18.7 mm for **5f** and 8.6-18.0 for compound **5d** against the fungal strains where as the standard drug exhibited ZOI in the range 10.2-21.2 mm. The remaining compound exhibited moderate activity against all fungal strains. The results are presented in Table-2.

Minimum inhibitory concentration (MIC) was evaluated using micro-broth-dilution method [21]. The compounds **5f**, **5b** and **5c** exhibited the lower MIC values in the range of 15-45 µg/mL against bacteria and compounds **5c**, **5f** and **5d** showed lower MIC values in the range of 15-30 µg/mL against fungal strains (Table-3).

Conclusion

In outline, we have demonstrated the synthesis of substituted phenylphosphonates (**5a-i**) by the reactions of 4-chloro-*N*-(substituted)benzene sulfonamide derivatives (**3a-i**) with trimethylphosphite under solvent free condition using microwave irradiation. Mild, non-hazardous and environment friendly reaction conditions, excellent yield in short reaction time are major advantages of this technique. The compounds **5f**, **5c** and **5b** showed promising antibacterial activity when compared with the remaining title compounds and were closer to standard drug. The compounds **5c**, **5f** and **5d** showed potent antifungal activity against the two tested fungal strains when compared with the remaining compounds. The remaining compounds exhibited reasonable activity against both bacterial and fungal strains.

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