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Microwave-Assisted Synthesis and Anti-inflammatory Activity Evaluation of α-Aminophosphonates

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ABSTRACT

In the present report, an expeditious green synthetic approach was developed for the synthesis of α-aminophosphonates **5(a-j)** in good yields through one-pot three component reaction (Kabachnik-Fields reaction) in solvent-free conditions under microwave irradiation. The newly synthesized compounds were characterized by IR, NMR (^{1}H, ^{13}C and ^{31}P), mass and C, H, N analysis. The synthesized compounds were screened for their anti-inflammatory activity using rat paw edema method. Most of the compounds from the series showed significant ($p < 0.05$) anti-inflammatory activity.

KEYWORDS

α-Aminophosphonates, Microwave irradiation, Sulphadiazine, Antimicrobial activity.

INTRODUCTION

The area of drug discovery and drug development has experienced significant advances with the introduction of combinatorial chemistry approaches. This innovative technology of producing libraries of structurally related compounds is particularly beneficial in the step of lead optimization. Lead optimization involves structural modifications of a "lead" compound that has demonstrated desired biological or pharmacological activities and/or reduce unwanted side effects.

During the past few years, cyclooxygenases (COX-1 and COX-2) have been introduced as novel targets for anti-inflammatory and cancer treatment [1]. Currently, there is an increasing body of evidence stating that targeting COX enzymes, especially COX-2 isoform, is an effective approach for the prevention or treatment of inflammation and various types of cancers. Nimesulide is a relatively COX-2 selective, non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. But continuous use of nimesulide can cause diarrhea, vomiting, skin rash, dizziness and bitterness in mouth. Hence there is a need for developing superior anti-inflammatory with better safety profile.

The α-aminophosphonates, structural analogues of natural amino acids have received wide attention in medicinal, bioorganic and organic chemistry. They are reported to possess antitumor [2], anti-inflammatory [3] and antibiotic [4] activities.

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Their potential as good enzyme inhibitors [5], herbicides [6], peptide mimetics [7], fungicides [8], insecticides [9] plant growth regulators [10] *etc*. is also well documented. The assortment of possibilities of practical use of α-aminophosphonates has stimulated considerable interest toward α-aminophosphonate chemistry. Various synthetic protocols have been described for the synthesis of α-aminophosphonates. The nucleophilic addition of phosphites to imines (Kabachnik-Fields reaction) represents a convenient route for their preparation. A variety of Brønsted acid [11] or Lewis acids like $ZnCl_2$ [12], BF_3-Et_2O [13], CdI_2/benzene [14], CdI_2/microwave [15]. One-pot syntheses of α-aminophosphonates have been carried out in organic solvents using lanthanide triflate [16], $InCl_3$ [17], $ZrCl_4$ [18], $In(OTf)_3/MgSO_4$ [19], GaI_3 [20], $BiCl_3$ [21], $Cu(OTf)_2$ [22], $SbCl_3/Al_2O_3$ [23]. Moreover, water [24] and ionic liquid [25] turned to be a kind of promising medium for such three component syntheses of α-aminophosphonates. Solvent-free transformations of phosphite to α-aminophosphonates could be accomplished in the presence of $LiClO_4$_Et_2O [26,27], TFA [28], $LiClO_4$ [29], metal triflate [30], $Na_2CaP_2O_7$ [31], $ZrOCl_2{\cdot}8H_2O$, $ZrO(ClO_4)_2{\cdot}6H_2O$ [32] and TsCl [33].

Although, these approaches are satisfactory for three component, one-pot synthesis of α-aminophosphonates, nevertheless the utilization of toxic solvents, undesirable reaction conditions, expensive reagents, lengthened reaction times, costly catalysts and formation of side products limit the exercise of these approaches. The development of a simple and inexpensive procedure for one-pot synthesis of α-aminophosphonates is needed. Further, in recent years microwave irradiation [34-36] technique was playing a prominent role to promote one-pot synthesis of α-aminophosphonates and provide a number of advantages over the standard heating techniques such as improved reaction yield, shorten the reaction time and easy work-up procedure. For the most part, microwave assisted solvent-free reaction provides an opportunity to work with open vessels thus avoiding the development of high pressure and provide a possibility of up scaling the reaction on a preparative scale and helps the induction of the reaction under dry conditions. Overview of literature and to overcome the former drawbacks, we familiarized to explore the preparation of novel α-aminophosphonates under conventional as well as microwave assisted methods using solvent-free conditions.

EXPERIMENTAL

All the chemicals are procured from Sigma-Aldrich, Merck and Lancaster were used as such without further purification. All solvents used for spectroscopic and other physical studies were reagent grade and were further purified employing the reported methods. The melting points were determined in open capillary tubes on a Guna Digital melting point apparatus and are uncorrected. IR spectra (ν_{max}, cm^{-1}) were recorded as KBr pellets using Perkin-Elmer spectrophotometer at APL Research centre, Hyderabad. The ^1H NMR, ^{13}C NMR and ^{31}P NMR spectra were recorded on Bruker AMX 300 MHz NMR spectrometer operating at 300 MHz for ^1H NMR, 75.4 MHz for ^{13}C NMR and 161.9 MHz for ^{31}P NMR. All compounds were dissolved in DMSO-d_6 and chemical shifts were referenced to TMS (^1H NMR and ^{13}C NMR) and 85 % H_3PO_4 (^{31}P NMR) and mass spectra were recorded on API 2000 Perkin-Elmer PE-SCIEX Mass spectrometer. Micro-analytical data were obtained from University of Hyderabad, Hyderabad, India.

Preparation of *N*-(4-amino-2-phenoxy phenyl)methanesulfonamide (2): In the first step, to a mixture of nimesulide (5 g, 16.2 mmol) and tin (3.13 g) was added conc. HCl (20 mL) and the mixture was heated on a water bath at 90 °C for 3 h. After the completion of the reaction, the mixture was poured into ice water and the solid separated was filtered. After basification the crude product obtained was purified by re-crystallization from methanol and chloroform mixture to give the desired product as light brown solid; mp 198 °C; IR (KBr, ν_{max}, cm^{-1}): 3412, 1572, 1487, 1215 and 1154; ^1H NMR (200 MHz, DMSO-d_6) δ 9.2 (s, 1H), 7.4 (m, 2H), 7.3 (d, *J* 8.6 Hz, 1H), 7.2 (m, 2H), 6.8 (d, *J* 8.6 Hz, 1H), 6.5 (s, 1H), 3.5 (br s, 2H), 3.1 (s, 3H); Mass (*m/z*) 279.1 (M^+, 100 %); Elemental analysis found C, 56.25; H, 5.07; N, 10.26; $C_{13}H_{14}N_2O_3S$ requires C, 56.10; H, 5.07; N, 10.06 [37].

Procedure for the synthesis of a-aminophosphonates 5a-j

Conventional method: A mixture of N-(4-amino-2-phenoxy phenyl)methanesulfonamide (**2**, 0.005 mol) in ethanol, diethylphosphite (**3**, 0.005 mol) and 3-nitrobenzaldehyde (**4a**, 0.005 mol) were taken in flat-bottomed flask and stirred the reaction mixture vigorously at 40 °C for 4 h. The reaction progress was monitored by TLC on silica gel using ethyl acetate-hexane (7:3 v/v). After completion of the reaction, the solvent was removed under reduced pressure to get the crude product. The resulting crude product was purified by column chromatography on silica gel (100-200 mesh) using ethyl acetate-hexane (1:1) as eluent to afford pure diethyl (4-fluorophenyl)(4-(methylsulfonamido)-3-phenoxyphenylamino)methylphosphonate (**5a**). The other compounds **5b-j** were prepared by adapting to the above described procedure.

Microwave irradiation method: A mixture of N-(4-amino-2-phenoxy phenyl)methanesulfonamide (**2**, 0.005 mol), diethylphosphite (**3**, 0.005 mol) and 3-nitrobenzaldehyde (**4a**, 0.005 mol) were taken in flat-bottomed flask and irradiated with microwave radiations using catalyst systems (CATA-4R) at 490 Watts. The reaction mixture was heated successively twice for 2-3 min period each time followed by a 1 min cooling interval between irradiations. This method was intended to avoid continuous overheating of reactants. The reaction mixtures were kept under stirring to maintain the homogeneity of the irradiating field throughout the reaction. By monitoring with TLC, the reaction was stopped after 3-6 min. The obtained crude products were recrystallized from ethyl acetate to afford pure **5a-j** as solids with 80.9-90.6 % yield.

Physical, analytical and spectral data for the compounds (5a-j)

Diethyl (4-fluorophenyl)(4-(methylsulfonamido)-3-phenoxyphenylamino)methylphosphonate (5a): Yield: 91 %; semi solid. ^{31}P NMR spectrum (DMSO-d_6): δ 18.5 ppm; ^1H NMR spectrum (400 MHz, DMSO-d_6): δ 8.41 (s, 1H, SO_2-**NH**), 7.66-7.21 (m, 9H, Ar-H), 6.53 (d, 1H, Ar-H), 6.48 (d, *J* = 6.8 Hz, 1H, Ar-H), 6.33 (s, 1H, Ar-H), 5.32 (s, 1H, C-NH), 4.54 (d, 1H, P-CH), 3.86 (m, 4H, O-**CH_2**CH_3), 2.89 (s, 3H, SO_2**CH_3**), 1.25 (t, 6H, O-CH_2**CH_3**); ^{13}C NMR spectrum (100

MHz, DMSO-d_6): δ 161.9, 157.8, 141.5, 136.5, 132.8, 129.7, 127.6, 122.5, 121.5, 119.9, 118.3, 114.3, 113.6, 101.9, 64.4, 55.8, 37.9, 16.5; IR (KBr, ν_{max}, cm^{-1}): 3407 (-NH), 3296 (NH), 1227 (P=O); LCMS (*m/z*, %): 523 ($M+H^+$, 100); Anal. calcd. for $C_{24}H_{28}N_2O_6PSF$: C, 55.17; H, 5.40; N, 5.36 %; found: C, 55.54; H, 5.38; N, 5.42 %.

Diethyl (4-(methylsulfonamido)-3-phenoxyphenylamino)(3-nitrophenyl)methylphosphonate (5b): Yield: 91 %; semi solid. ^{31}P NMR spectrum (DMSO-d_6): δ 17.2 ppm; ^1H NMR spectrum (400 MHz, DMSO-d_6): δ 8.52 (s, 1H, SO_2-**NH**), 8.18-7.23 (m, 9H, Ar-H), 6.53 (d, 1H, Ar-H), 6.48 (d, *J* = 6.8 Hz, 1H, Ar-H), 6.33 (s, 1H, Ar-H), 5.31 (s, 1H, C-NH), 4.53 (d, 1H, P-CH), 3.86 (m, 4H, O-CH_2CH_3), 2.89 (s, 3H, SO_2**CH_3**), 1.24 (t, 6H, O-CH_2CH_3); ^{13}C NMR spectrum (100 MHz, DMSO-d_6): δ 157.8, 148.5, 141.5, 139.3, 136.5, 134.5, 130.4, 127.6, 122.6, 122.5, 121.5, 122.1, 119.9, 118.3, 113.6, 101.9, 64.4, 55.9, 37.9, 16.6; IR (KBr, ν_{max}, cm^{-1}): 3399 (NH), 3285 (NH), 1227 (P=O); LCMS (*m/z*, %): 550 ($M+H^+$, 100); Anal. calcd. for $C_{24}H_{28}N_3O_8PS$: C, 52.45; H, 5.14; N, 7.65 %; found: C, 52.52; H, 5.20; N, 7.62 %.

Diethyl (4-chloro-3-nitrophenyl)(4-(methylsulfonamido)-3-phenoxyphenylamino)methylphosphonate (5c): Yield: 90 %; semi solid. ^{31}P NMR spectrum (DMSO-d_6): δ 17.7 ppm; ^1H NMR spectrum (400 MHz, DMSO-d_6): δ 8.53 (s, 1H, SO_2-**NH**), 7.81-7.23 (m, 8H, Ar-H), 6.53 (d, 1H, Ar-H), 6.48 (d, *J* = 6.8 Hz, 1H, Ar-H), 6.33 (s, 1H, Ar-H), 5.32 (s, 1H, C-NH), 4.55 (d, 1H, P-CH), 3.86 (m, 4H, O-CH_2CH_3), 2.89 (s, 3H, SO_2**CH_3**), 1.23 (t, 6H, O-CH_2CH_3); ^{13}C NMR spectrum (100 MHz, DMSO-d_6): δ 157.8, 148.2, 141.5, 137.6, 136.5, 134.7, 131.5, 127.6, 124.1, 123.4, 122.5, 121.5, 119.9, 118.3, 113.6, 101.9, 64.4, 55.7, 37.9, 16.4; IR (KBr, ν_{max}, cm^{-1}): 3399 (NH), 3285 (NH), 1227 (P=O); LCMS (*m/z*, %): 584 ($M+H^+$, 100), 586 (M+1, 26.6 %), 586 (M+2, 36.8 %); Anal. calcd. for $C_{24}H_{27}N_3O_8PSCl$: C, 49.36; H, 4.66; N, 7.20 %; found: C, 49.42; H, 4.58; N, 7.24 %.

Diethyl(4-hydroxy-3-nitrophenyl)(4-(methylsulfonamido)-3-phenoxyphenylamino)methylphosphonate (5d): Yield: 87 %; semi solid. ^{31}P NMR spectrum (DMSO-d_6): δ 18.1 ppm; ^1H NMR spectrum (400 MHz, DMSO-d_6): δ 10.12 (s, 1H, -OH), 8.50 (s, 1H, SO_2-**NH**), 7.85-7.20 (m, 8H, Ar-H), 6.52 (d, 1H, Ar-H), 6.43 (d, *J* = 6.8 Hz, 1H, Ar-H), 6.35 (s, 1H, Ar-H), 5.30 (s, 1H, C-NH), 4.53 (d, 1H, P-CH), 3.85 (m, 4H, O-CH_2CH_3), 2.87 (s, 3H, SO_2**CH_3**), 1.23 (t, 6H, O-CH_2CH_3); ^{13}C NMR spectrum (100 MHz, DMSO-d_6): δ 157.8, 156.2, 141.5, 138.4, 136.5, 135.8, 130.7 127.6,, 123.5, 122.5, 122.1, 121.5, 119.9, 118.3, 113.6, 101.9, 64.4, 55.6, 37.7, 16.4; IR (KBr, ν_{max}, cm^{-1}): 3399 (NH), 3285 (NH), 1227 (P=O); LCMS (*m/z*, %): 566 ($M+H^+$, 100); Anal. calcd. for $C_{24}H_{28}N_3O_9PS$: C, 50.97; H, 4.99; N, 7.43 %; found: C, 50.92; H, 4.95; N, 7.48 %.

Diethyl (3-bromo-4-fluorophenyl)(4-(methylsulfonamido)-3-phenoxyphenylamino)methylphosphonate (5e): Yield: 92 %; semi solid. ^{31}P NMR spectrum (DMSO-d_6): δ 17.9 ppm; ^1H NMR spectrum (400 MHz, DMSO-d_6): δ 8.52 (s, 1H, SO_2-**NH**), 7.65-7.21 (m, 8H, Ar-H), 6.53 (d, 1H, Ar-H), 6.48 (d, *J* = 6.8 Hz, 1H, Ar-H), 6.33 (s, 1H, Ar-H), 5.31 (s, 1H, C-NH), 4.51 (d, 1H, P-CH), 3.86 (m, 4H, O-CH_2CH_3), 2.88 (s, 3H, SO_2**CH_3**), 1.22 (t, 6H, O-CH_2CH_3); ^{13}C NMR spectrum (100 MHz, DMSO-d_6): δ 166.3, 157.8, 141.5, 136.5, 134.6, 132.5, 128.4, 127.6, 122.5, 121.5, 119.9, 119.2, 118.3, 113.6, 110.7, 101.9, 64.4, 55.7, 37.9, 16.5; IR (KBr, ν_{max}, cm^{-1}): 3399 (NH), 3285 (NH), 1227 (P=O); LCMS (*m/z*, %): 601 ($M+H^+$, 100), 599 (M-2, 96.7 %), 602 (M+1, 26.9 %); Anal. calcd. for $C_{24}H_{27}N_2O_6PSBrF$: C, 47.93; H, 4.53; N, 4.66 %; found: C, 47.89; H, 4.57; N, 4.62 %.

Diethyl (4-chlorophenyl)(4-(methylsulfonamido)-3-phenoxyphenylamino)methylphosphonate (5f): Yield: 90 %; semi solid. ^{31}P NMR spectrum (DMSO-d_6): δ 17.6 ppm; ^1H NMR spectrum (400 MHz, DMSO-d_6): δ 8.51 (s, 1H, SO_2-**NH**), 7.66-7.21 (m, 9H, Ar-H), 6.53 (d, 1H, Ar-H), 6.48 (d, *J* = 6.8 Hz, 1H, Ar-H), 6.33 (s, 1H, Ar-H), 5.33 (s, 1H, C-NH), 4.54 (d, 1H, P-CH), 3.86 (m, 4H, O-CH_2CH_3), 2.87 (s, 3H, SO_2**CH_3**), 1.23 (t, 6H, O-CH_2CH_3); ^{13}C NMR spectrum (100 MHz, DMSO-d_6): δ 157.8, 141.5, 136.5, 135.1, 134.2, 129.9, 129.4, 127.6, 122.5, 121.5, 119.9, 118.3, 113.6, 101.9, 64.4, 55.7, 37.6, 16.4; IR (KBr, ν_{max}, cm^{-1}): 3399 (NH), 3285 (NH), 1227 (P=O); LCMS (*m/z*, %): 539 ($M+H^+$, 100), 541 (M+2, 38); Anal. calcd. for $C_{24}H_{28}N_2O_6PSCl$: C, 53.48; H, 5.24; N, 5.20 %; found: C, 53.52; H, 5.20; N, 5.15 %.

Diethyl (2,4-dichlorophenyl)(4-(methylsulfonamido)-3-phenoxyphenylamino)methylphosphonate (5g): Yield: 91 %; semi solid. ^{31}P NMR spectrum (DMSO-d_6): δ 18.4 ppm; ^1H NMR spectrum (400 MHz, DMSO-d_6): δ 8.54 (s, 1H, SO_2-**NH**), 7.75-7.23 (m, 8H, Ar-H), 6.53 (d, 1H, Ar-H), 6.48 (d, *J* = 6.8 Hz, 1H, Ar-H), 6.33 (s, 1H, Ar-H), 5.33 (s, 1H, C-NH), 4.56 (d, 1H, P-CH), 3.86 (m, 4H, O-CH_2CH_3), 2.88 (s, 3H, SO_2**CH_3**), 1.24 (t, 6H, O-CH_2CH_3); ^{13}C NMR spectrum (100 MHz, DMSO-d_6): δ 157.8, 141.5, 140.6, 136.5, 134.7, 132.6, 131.3, 129.5, 128.4, 127.6, 125.3, 122.5, 121.5, 119.9, 118.3, 113.6, 101.9, 64.4, 56.1, 38.2, 16.8; IR (KBr, ν_{max}, cm^{-1}): 3399 (NH), 3285 (NH), 1227 (P=O); LCMS (*m/z*, %): 573 ($M+H^+$, 100), 573 (M+2, 70); Anal. calcd. for $C_{24}H_{27}N_2O_6PSCl_2$: C, 50.27; H, 4.75; N, 4.89 %; found: C, 50.35; H, 4.84; N, 4.95 %.

Diethyl (2-hydroxyphenyl)(4-(methylsulfonamido)-3-phenoxyphenylamino)methylphosphonate (5h): Yield: 87 %; semi solid. ^{31}P NMR spectrum (DMSO-d_6): δ 18.0 ppm; ^1H NMR spectrum (400 MHz, DMSO-d_6): δ 10.15 (s, 1H, -OH), 8.45 (s, 1H, SO_2-**NH**), 7.63-6.95 (m, 9H, Ar-H), 6.53 (d, 1H, Ar-H), 6.48 (d, *J* = 6.8 Hz, 1H, Ar-H), 6.33 (s, 1H, Ar-H), 5.29 (s, 1H, C-NH), 4.49 (d, 1H, P-CH), 3.87 (m, 4H, O-CH_2CH_3), 2.88 (s, 3H, SO_2**CH_3**), 1.22 (t, 6H, O-CH_2CH_3); ^{13}C NMR spectrum (100 MHz, DMSO-d_6): δ 158.4, 157.8, 141.5, 136.5, 129.5, 129.2, 127.6, 124.2, 122.7, 122.5, 121.5, 119.9, 118.4, 118.3, 113.6, 101.9, 64.4, 55.4, 37.7, 16.3; IR (KBr, ν_{max}, cm^{-1}): 3399 (NH), 3285 (NH), 1227 (P=O); LCMS (*m/z*, %): 521 ($M+H^+$, 100); Anal. calcd. for $C_{24}H_{28}N_3O_8PS$: C, 55.38; H, 5.62; N, 5.38 %; found: C, 55.45; H, 5.70; N, 5.32 %.

Diethyl (4-(methylsulfonamido)-3-phenoxyphenylamino)(thiophen-2-yl)methylphosphonate (5i): Yield: 90 %; semi solid. ^{31}P NMR spectrum (DMSO-d_6): δ 16.8 ppm; ^1H NMR spectrum (400 MHz, DMSO-d_6): δ 8.52 (s, 1H, SO_2-**NH**), 7.66-6.92 (m, 8H, Ar-H), 6.53 (d, 1H, Ar-H), 6.48 (d, *J* = 6.8 Hz, 1H, Ar-H), 6.33 (s, 1H, Ar-H), 5.31 (s, 1H, C-NH), 4.50 (d, 1H, P-CH), 3.86 (m, 4H, O-CH_2CH_3), 2.89 (s, 3H, SO_2**CH_3**), 1.24 (t, 6H, O-CH_2CH_3); ^{13}C NMR spectrum (100

MHz, DMSO-d_6): δ 157.8, 141.5, 140.3, 136.5, 129.3, 128.3, 127.6, 126.3, 122.5, 121.5, 119.9, 118.3, 113.6, 101.9, 64.4, 55.8, 37.7, 16.4; IR (KBr, ν_{max}, cm^{-1}): 3399 (NH), 3285 (NH), 1227 (P=O); LCMS (*m/z*, %): 511 ($M+H^+$, 100); Anal. calcd. for $C_{22}H_{27}N_2O_6PS_2$: C, 51.75; H, 5.33; N, 5.49 %; found: C, 51.82; H, 5.27; N, 5.56 %.

Diethyl (4-(methylsulfonamido)-3-phenoxyphenyl-amino)(5-nitrothiophen-2-yl)methylphosphonate (5j): Yield: 91 %; semi solid. ^{31}P NMR spectrum (DMSO-d_6): δ 17.1 ppm; ^{1}H NMR spectrum (400 MHz, DMSO-d_6): δ 8.53 (s, 1H, SO_2-**NH**), 7.95-6.96 (m, 7H, Ar-H), 6.53 (d, 1H, Ar-H), 6.48 (d, *J* = 6.8 Hz, 1H, Ar-H), 6.33 (s, 1H, Ar-H), 5.33 (s, 1H, C-NH), 4.54 (d, 1H, P-CH), 3.86 (m, 4H, O-CH_2CH_3), 2.86 (s, 3H, SO_2**CH_3**), 1.22 (t, 6H, O-CH_2CH_3); ^{13}C NMR spectrum (100 MHz, DMSO-d_6): δ 157.8, 152.1, 149.9, 141.5, 136.5, 129.3, 128.4, 127.6, 122.5, 121.5, 119.9, 118.3, 113.6, 101.9, 64.4, 55.8, 37.8, 16.5; IR (KBr, ν_{max}, cm^{-1}): 3399 (NH), 3285 (NH), 1227 (P=O); LCMS (*m/z*, %): 556 ($M+H^+$, 100); Anal. calcd. for $C_{22}H_{26}N_3O_8PS_2$: C, 47.56; H, 4.72; N, 7.56 %; found: C, 47.52; H, 4.78; N, 7.62 %.

Anti-inflammatory activity: Anti-inflammatory activity was determined by carrageenan induced paw edema method. A either sex of rats weighing 150-200 g were divided into 6 groups (n = 6) and they were fasted with free access to water at least 16 h. Group-I received 1 % sodium CMC (negative control), Group-II received diclofenac sodium and nimesulide at a dose of 40 mg/kg (positive control) and Group-III to VI were given the compounds **5a-j** (40 mg/kg). All the compounds **5a-j** were given in oral route. After 30 min, 0.1 mL of 1 % carrageenan suspension in normal saline was injected into the subplantar region of the left hind paw of each rat to induce edema. The edema volumes of the injected paw measured with the help of plethysmograph at the interval of 1, 2, 3 and 4 h. The difference between the paw volumes of treated animals were compared with that of the control group and the mean edema volume was calculated. Percentage inhibition was calculated as per the formula,

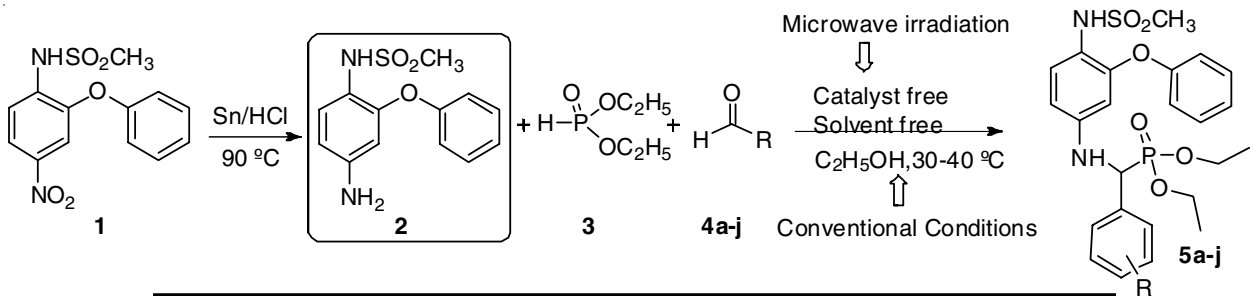
$$\text{Inhibition } (\%) = \left(\frac{V_o - V_t}{V_o} \right) \times 100$$

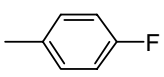
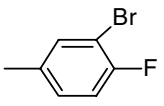
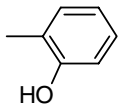
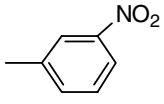
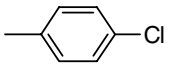
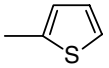
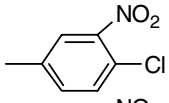
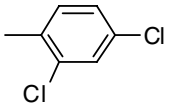
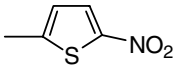
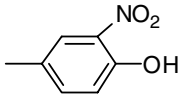
where V_o = volume of the paw control at time t, V_t = volume of the paw of drug treated at time t.

RESULTS AND DISCUSSION

A series of α-aminophosphonates (**5a-j**) were conveniently synthesized by equimolar quantities of *N*-(4-amino-2-phenoxy phenyl)methanesulfonamide (**2**) which is previously prepared from nimesulide (**1**, 0.005 mol) on reduction, diethylphosphite (**3**, 0.005 mol) and various aldehydes (**4a-j**) (0.005 mol) through Kabachinic-Field reaction under conventional and microwave irradiation methods using neat reaction conditions was depicted in **Scheme-I**. The physical data of the title compounds are given in Table-1.

The chemical structure of the title compounds **5a-j** are supported by spectral data (^{31}P, ^{1}H and ^{13}C NMR, IR and LC-MS), elemental analysis and the results are presented in Experimental section. ^{31}P NMR signals were observed in the region 18.5-16.8 ppm [38] for all the compounds **5a-j**. The ^{1}H NMR spectra gave signals due to Ar-H in the range of δ 8.18-6.33 ppm. The proton signals in the range of 8.53-8.41, 5.32-5.30 and 4.55-4.53 ppm were due to SO_2-NH, C-NH and P-CH respectively. The methylene protons of P-O-$\underline{CH_2}CH_3$ gave a multiplet and methyl protons of P-O-$CH_2\underline{CH_3}$ resonated as a



Compd	R	Compd	R	Compd	R
5a		5e		5h	
5b		5f		5i	
5c		5g		5j	
5d					

Scheme-I: Microwave assisted synthesis of α-aminophosphonates (**5a-j**)

TABLE-1
COMPARISON OF CONVENTIONAL/MICROWAVE CONDITIONS OF THE SYNTHESIZED COMPOUNDS **5a-j**

Compd.	Conventional conditions		Microwave conditions	
	Time (h)	Yield (%)	Time (min)	Yield (%)
5a	4	80.2	7	90.6
5b	3	78.3	5	86.2
5c	5	75.6	9	89.7
5d	3	81.2	6	85.5
5e	6	77.3	12	89.1
5f	4	70.3	8	80.9
5g	3	75.2	5	85.2
5h	4	80.5	7	87.2
5i	3	84.2	6	88.5
5j	6	78.9	10	85.9

triplet in the region δ 3.86-3.84 and δ 1.25-1.22 respectively. ^{13}C NMR chemical shift for P-CH was observed in the region 56.1-55.4 ppm. IR absorptions in the regions 3399-3380, 3285-3256 and 1227-1220 cm^{-1} were assigned to SO_2-NH, NH and P=O stretching vibrations respectively for the compounds **5a-j**. In their mass spectra, $M^{+\cdot}$ ions were observed in the expected *m/z* values.

Anti-inflammatory activity: In order to identify the potential anti-inflammatory agents among the newly synthesized compounds was evaluated for their *in vivo* anti-inflammatory activity using carrageenan-induced paw edema method [39] in rats. Considering the fact that carrageenan-induced paw edema assay is a biphasic event involving the release of histamine and serotonin as the mediators of inflammation in the first phase which normally lasts for about 2 h after the carrageenan injection followed by the second phase which generally operates between 2 and 4 h after the carrageenan injection and involves prostaglandins as the mediators for the inflammation, thus any anti-inflammatory activity in the second phase of this biphasic event can be attributed to the inhibition of prostaglandin synthesis.

The results shown in Table-2 revealed that most of the compounds showed significant anti-inflammatory activity 3 h and 4 h after carrageenan injection with as many as 5 compounds showing more than 80 % inhibition after 3 h (as compared to the reference drugs 88.34 and 85.88 %) and 7 compounds showing more than 80 % inhibition after 4 h (as compared to the references drug 91.57 and 88.20 %). The compounds **5d** (R = 4-F), 5e (R = 3-Br, 4-F), **5g** (R = 3,4-Cl), **5f** (R = 4-Cl) and **5b** (R = 3-NO_2, 4-Cl) showed remarkable anti-inflammatory activity ranging from 87.73 to 84.04 % comparable to the reference drug diclofenac sodium (88.34 %) and nimesulide (85.88 %) 3 h after carrageenan injection. The compounds **5j** (R = 5-nitrothiophen-2-yl), **5a** (R = 3-NO_2), **5i** (R = 5-nitrothiophen-2-yl), **5c** (R = 3-NO_2, 4-OH) and **5h** (R = 4-OH) showed appreciable anti-inflammatory activity ranging from 79.75 to 74.84 % 3 h after carrageenan injection. After 4 h of carrageenan injection, the compounds **5d** (R = 4-F), **5e** (R = 3-Br, 4-F), **5g** (R = 3,4-Cl), **5f** (R = 4-Cl), **5b** (R = 3-NO_2, 4-Cl), **5a** (R = 3-NO_2) and **5j** (5-nitrothiophen-2-yl) showed anti-inflammatory activity ranging from 91.01 to 80.33 % inhibition comparable to diclofenac sodium (91.57 %) and nimesulide (88.20 %). The remaining compounds showed anti-inflammatory activity ranging from 78.08 to 75.84 % inhibition 4 h after carrageenan injection. It is difficult to draw a correlation between the anti-inflammatory activity and the substituents present on the aromatic rings in 1 or 2 as the anti-inflammatory activity seems to be independent of the nature of substituents. The excellent anti-inflammatory inhibition exhibited by these compounds, 4 h after carrageenan injection suggested that these compounds do not get easily metabolized in the body.

Conclusion

In conclusion, a new series of α-aminophosphonates has been prepared and fully assigned by analytical and spectral data. The present investigation showed significant anti-inflammatory action to all compound of the series when compared against vehicle treated control. The results were found to be equipotent with diclofenac. The anti-inflammatory effect was found to be most significant at 3 and 4 h. Overall looking at duration of action and percent inhibition, the sustained and momentous action was reported with **5d**, **5e**, **5g**, **5f**, **5b**, **5a** and **5j**. Hence the present series could be developed as a novel class of anti-inflammatory agents.

TABLE-2
MEAN PAW VOLUME (mL) AND % INHIBITION OF COMPOUNDS **5a-j**

Compd.	Mean paw volume (mL) ± SEM				Inhibition of edema (%)			
	1 h	2 h	3 h	4 h	1 h	2 h	3 h	4 h
Control	1.03 ± 0.12	1.32 ± 0.16	1.63 ± 0.09	1.78 ± 0.20	–	–	–	–
Diclofenac	0.08 ± 0.02*	0.17 ± 0.05*	0.19 ± 0.03*	0.15 ± 0.05*	92.23	87.12	88.34	91.57
Nimesulide	0.12 ± 0.02*	0.26 ± 0.06*	0.23 ± 0.06*	0.21 ± 0.06*	88.34	80.30	85.88	88.20
5a	0.29 ± 0.10*	0.34 ± 0.10*	0.35 ± 0.08*	0.35 ± 0.10*	71.84	74.24	78.52	80.33
5b	0.20 ± 0.10*	0.25 ± 0.06*	0.26 ± 0.06*	0.25 ± 0.06*	80.58	81.06	84.04	85.95
5c	0.24 ± 0.10*	0.35 ± 0.06*	0.39 ± 0.07*	0.39 ± 0.06*	76.69	73.48	76.07	78.08
5d	0.10± 0.03*	0.22 ± 0.06*	0.20 ± 0.01*	0.16 ± 0.06*	90.29	83.33	87.73	91.01
5e	0.11 ± 0.03*	0.20 ± 0.06*	0.21 ± 0.06*	0.18 ± 0.06*	89.32	84.84	87.11	89.88
5f	0.17 ± 0.04*	0.22 ± 0.08*	0.24 ± 0.09*	0.26 ± 0.05*	83.49	83.33	85.27	85.39
5g	0.16 ± 0.06*	0.19± 0.14*	0.22 ± 0.10*	0.22 ± 0.07*	84.46	85.60	86.50	87.64
5h	0.28 ± 0.08*	0.39 ± 0.07*	0.41 ± 0.09*	0.43 ± 0.09*	72.81	70.45	74.84	75.84
5i	0.23 ± 0.10*	0.37 ± 0.05*	0.39 ± 0.07*	0.40 ± 0.08*	77.66	71.96	76.07	77.52
5j	0.26 ± 0.08*	0.28 ± 0.10*	0.33 ± 0.08*	0.35 ± 0.07*	74.75	78.78	79.75	80.33

Test compounds = 40 mg/kg. reference standard, diclofenac sodium = 40 mg/kg.
*Significantly different compared to respective control values, $P < 0.01$.
[a]Values are expressed as mean ± SEM (number of animals = 6) and analyzed by ANOVA.
[b]Values in parentheses (percentage anti-inflammatory activity, %).

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