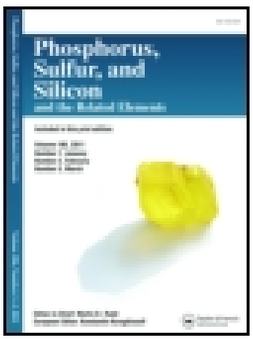

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Synthesis and bioactivity evaluation of some novel α-aminophosphonates

MICROWAVE-ASSISTED SYNTHESIS AND ANTI-INFLAMMATORY ACTIVITY EVALUATION OF SOME NOVEL α-AMINOPHOSPHONATES

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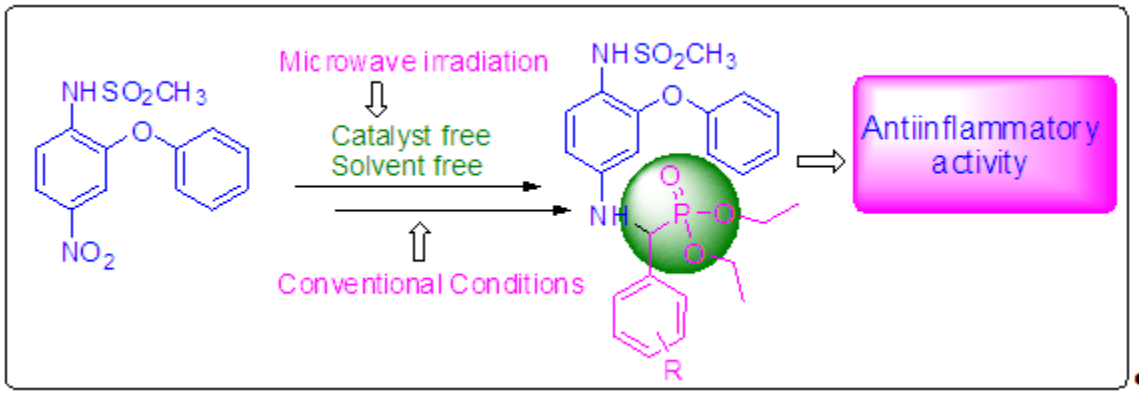
ABSTRACTS

An expeditious green synthetic approach was developed for the synthesis of α-aminophosphonates in good yields through one-pot three component reaction (Kabachnik-Fields reaction) of equimolar quantities of *N*-(4-amino-2-phenoxy phenyl)methanesulfonamide, diethylphosphite and various aldehydes under conventional as well as microwave irradiation methods. The newly synthesized compounds were characterized by NMR (^{31}P, ^{1}H and ^{13}C), Mass, IR and C, H, N analyses. The synthesized compounds were screened for their anti-inflammatory activity using rat paw edema method. Most of the compounds from the series showed good anti-inflammatory activity when compared with standard drug. Especially the compounds **5d** bearing 4-hydroxy-3-nitrophenyl moiety, **5e** bearing 3-bromo-4-fluorophenyl moiety, **5g** incorporated with 2,4-dichlorophenyl moiety and **5f** containing 4-chlorophenyl moiety exhibiting edema inhibition of 91.01 to 85.39% after 4 h of carrageenan injection while the other compounds displayed inhibition ≥75%.

Graphical Abstract



Keywords

α-aminophosphonates, Kabachnik-Fields reaction, microwave irradiation, anti-inflammatory activity.

INTRODUCTION

The area of drug discovery and drug development has experienced significant advances with the introduction of combinatorial chemistry approaches.[1] This innovative technology of producing libraries of structurally related compounds is particularly beneficial in the step of lead optimization. Lead optimizations involves structural modifications of a "lead" compound that has demonstrated desired biological or pharmacological activities and/or reduce unwanted side effects.[1]

Cyclooxygenases (COX-1 and COX-2) have been introduced as novel targets for anti-inflammatory and cancer treatment during the past few years.[2] At present, there is an increasing body of evidence stating that targeting COX enzymes, especially COX-2 isoform, is an effective move towards 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.[3] But the continuous use of nimesulide can cause diarrhea, vomiting, skin rash, dizziness and bitterness in the mouth.[3] Hence there is a need for developing superior anti-inflammatories with a better safety profile.

The α-aminophosphonates, structural analogues of natural amino acids have received widespread attention in medicinal, bioorganic and organic chemistry. They have been reported to show a wide range of biological activity including antitumor,[4] anti-inflammatory[5] and antibiotic[6] activities. They also used as good enzyme inhibitors,[7] herbicides,[8] peptide mimetics,[9] fungicides,[10] insecticides[11] plant growth regulators.[12] The assortment of possibilities for the 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[13a] or Lewis acids like $ZnCl_2$,[13b] BF_3-Et_2O,[13c] CdI_2/benzene,[13d] CdI_2/microwave[13e] have been used for the synthesis of these compounds.

Recently, three-component one-pot syntheses of α-aminophosphonates have been carried out in organic solvents using lanthanide triflate,[14a] $InCl_3$,[14b] $ZrCl_4$,[14c] $In(OTf)_3/MgSO_4$,[14d] GaI_3,[14e] $BiCl_3$,[14f] $Cu(OTf)_2$,[14g] $SbCl_3/Al_2O_3$.[14h] Moreover, water[15] and ionic liquid[16] turned to be a kind of promising medium for such three component syntheses of α-aminophosphonates. Solvent-free transformations of diethylphosphite to α-aminophosphonates could be accomplished in the presence of $LiClO_4$-Et_2O,[17a,b] TFA,[17c] $LiClO_4$,[17d] metal triflate,[17e] $Na_2CaP_2O_7$ [17f], $ZrOCl_2.8H_2O$ or $ZrO(ClO_4)_2.6H_2O$,[17g] TsCl.[17h]

However, many of these catalysts are expensive, highly corrosive, and involve tedious separation procedures and also require prolonged reaction times. Therefore, the development of a simple, convenient and an efficient protocol using inexpensive and readily available reagents would extend the scope of the synthesis of α-amino phosphonates. Further, in recent years the use of a microwave irradiation technique[18a,b,c] has played a prominent role to promote one-pot synthesis of α-aminophosphonates and offer a number of advantages over the standard heating techniques such as enhanced reaction yield, shorten the reaction time and easy work-up procedure. To make this process more efficient, we herein describe the synthesis of some novel α-aminophosphonates with different species of aldehydes, *N*-(4-amino-2-phenoxy phenyl)methanesulfonamide and diethylphosphite under conventional as well as microwave assisted methods.

RESULTS AND DISCUSSION

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

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[19] 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 8.54-8.41, 5.33-5.29 and 4.56-4.49 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 triplet in the region δ 3.88-3.85 and δ 1.27-1.22 respectively. ^{13}C NMR chemical shift for P-$\underline{CH}$ and OCH_3 were observed in the region 56.1-55.4 and 38.2-37.6 ppm. ^{13}C NMR chemical shifts were observed in the regions, δ 64.5-64.4 and 16.8-16.3 ppm for P-O-$\underline{\mathbf{C}H_2}$-$CH_3$ and P-OCH_2-$\underline{\mathbf{C}H_3}$ respectively in the title compounds. IR absorptions in the regions 3399-3389, 3288-3279 and 1229-1222cm^{-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. Representative spectra (^{1}H, ^{13}C, ^{31}P) NMR, mass and IR spectra for the new compounds **5a, 5d**, **5f** and **5j** are presented in the Supplemental Materials (**Fig. S 1--S 20**).

Biology

Anti-inflammatory activity

In order to identify the potential anti-inflammatory agents among the newly synthesized compounds we evaluated them for their in vivo anti-inflammatory activity using carrageenan-induced paw edema method[20] in rats.

A careful study of the results shown in **Table S 2** revealed that most of the compounds showed significant anti-inflammatory activity 3 h and 4 h after carrageenan injection. A total of 5 compounds showing more than 80% inhibition after 3 h (as compared to the reference drugs 88.34 & 85.88%) and 7 compounds showing more than 80% inhibition after 4 h (as compared to the references drug 91.57% & 88.20%). Compounds **5d** (R = 4-OH, 3-NO_2), **5e** (R = 3-Br, 4-F), **5g** (R = 2,4-Cl), **5f** (R = 4-Cl), and **5b** (R = 3-NO_2) showed remarkable anti-inflammatory activity ranging from 87.73% to 84.04% which is 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 = 4-F), **5i** (R = thiophen-2-yl), **5c** (R = 3-NO_2, 4-Cl) and **5h** (R = 2-OH) showed appreciable anti-inflammatory activity ranging from 79.75% to 74.84%, 3 h after carrageenan injection. Similarly compounds **5d** (R = 4-OH, 3-NO_2), **5e** (R = 3-Br, 4-F), **5g** (R = 2,4-Cl), **5f** (R = 4-Cl), and **5b** (R = 3-NO_2), **5a** (R = 4-F) and **5j** (5-nitrothiophen-2-yl) showed anti-Inflammatory activity ranging from 91.01% to 80.33% inhibition, 4 h after carrageenan injection. The remaining compounds showed anti-Inflammatory activity ranging from 78.08% to 75.84% inhibition, 4 h after carrageenan injection (**Fig. S 21)**. 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. Overall majority of the title compounds exhibited good anti-inflammatory activity when compared with the reference drugs (**Table S 2**).

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} in cm^{-1}) were recorded as KBr pellets using Perkin-Elmer spectrophotometer at University of Hyderabad, Hyderabad. The ^{1}H, ^{13}C and ^{31}P NMR Spectra were recorded on Bruker AMX spectrometer operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C and 161.9 MHz for ^{31}P NMR. All compounds were dissolved in DMSO-d_6 and chemical shifts were referenced to TMS (^{1}H 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[21] (2).

In the first step, to a mixture of nimesulide (5.00 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 3h. 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; ^{1}H NMR (400 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.

Procedure for the synthesis of α-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 4-fluorobenzaldehyde (**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 4-fluorobenzaldehyde (**4a**, 0.005 mol) were taken in flat-bottomed flask and irradiated with microwave radiations in a microwave oven at 490 W. 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 the 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)methanephosphonate* (5a):**

Yield: 90%; solid. ^{31}P NMR spectrum (DMSO-d_6): δ 18.5 ppm; ^{1}H NMR spectrum (DMSO-d_6)**:** δ 8.41 (s, 1H, SO_2-**NH**), 7.68-7.23 (m, 9H, Ar-H), 6.54 (d, J = 8.0 Hz, 1H, Ar-H), 6.49 (d, J = 6.8 Hz, 1H, Ar-H), 6.33 (s, 1H, Ar-H), 5.33 (s, 1H, C-NH), 4.55 (d, 1H, P-CH), 3.88 (m, 4H, O-**CH$_2$**CH_3), 2.89 (s, 3H, SO_2**CH$_3$**), 1.27 (t, J = 5.6 Hz, 6H, O-CH_2**CH$_3$**); ^{13}C NMR spectrum (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 (SO_2-**NH**), 3296 (NH), 1227 (P = O); LCMS (m/z, %): 523 ($M+H^+$, 100); Anal. Calcd for $C_{24}H_{28}FN_2O_6PS$: C, 55.17; H, 5.40; N, 5.36%; found: C, 55.54; H, 5.38; N, 5.42%.

***Diethyl (4-chlorophenyl)(4-(methylsulfonamido)-3-phenoxyphenylamino) methanephosphonate* (5f):**

Yield: 81%; solid. ^{31}P NMR spectrum (DMSO-d_6): δ 17.6 ppm; ^{1}H NMR spectrum (DMSO-d_6)**:** δ 8.41 (s, 1H, SO_2-**NH**), 7.68-7.22 (m, 9H, Ar-H), 6.54 (d, J = 8.0 Hz, 1H, Ar-H), 6.49 (d, J = 6.8 Hz, 1H, Ar-H), 6.33 (s, 1H, Ar-H), 5.33 (s, 1H, C-NH), 4.55 (d, 1H, P-CH), 3.88 (m, 4H, O-**CH$_2$**CH_3), 2.89 (s, 3H, SO_2**CH$_3$**), 1.27 (t, J = 5.6 Hz, 6H, O-CH_2**CH$_3$**); ^{13}C NMR spectrum (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 (SO_2-**NH**), 3285 (NH), 1227 (P

= O); LCMS (m/z, %): 539 ($M+H^+$, 100), 541 (M+2, 38); Anal. Calcd for $C_{24}H_{28}ClN_2O_6PS$: C, 53.48; H, 5.24; N, 5.20%; found: C, 53.52; H, 5.20; N, 5.15%.

Anti-inflammatory activity

Anti-inflammatory activity of newly synthesized compounds was evaluated *in vivo* using carrageenan-induced paw edema method[19] in rats. Majority of the title compounds exhibited good anti-inflammatory activity when compared to the standard drugs (**Table S 2**).

CONCLUSION

In conclusion, in an attempt of developing a new class of anti-inflammatory agents, a new series of α-aminophosphonates has been prepared using a green and an efficient solvent-free procedure under conventional and microwave irradiation methods. The excellent yields of α-aminophosphonates were obtained in microwave irradiation method in short reaction times. Anti-inflammatory screening results of **5a-j** showed that most of the derivatives markedly reduced the paw edema volume in the immediate one hour of administration and the inhibitory effect was regularly increasing from the administration time to the end of 4th hour. It was found to be most significant at 3 h and 4h. 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.

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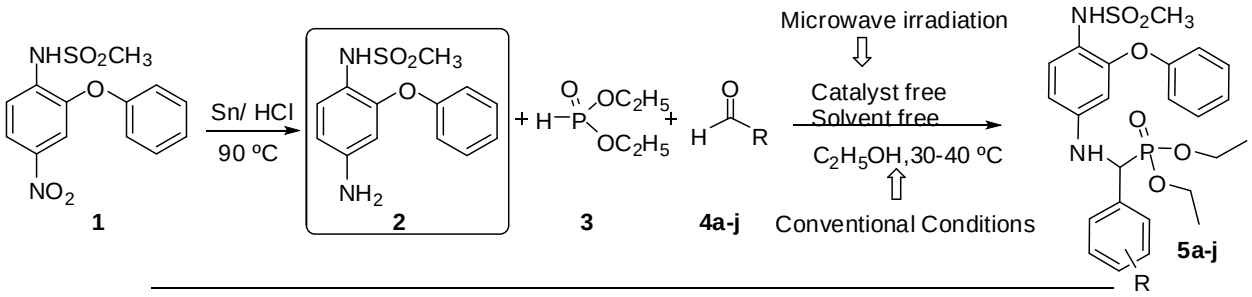

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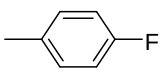
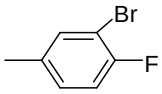
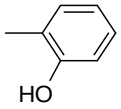
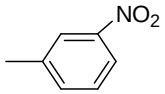
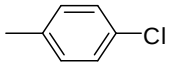
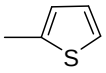
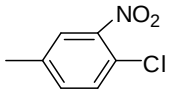
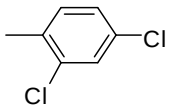
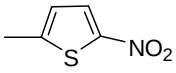
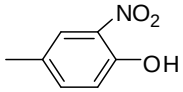
5a		**5e**		**5h**	
5b		**5f**		**5i**	
5c		**5g**		**5j**	
5d					

Scheme 1: Microwave assisted synthesis of some novel α-aminophosphonates (**5a-j**)