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# Microwave-assisted synthesis and anti-inflammatory activity evaluation of some novel α-aminophosphonates

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ABSTRACT

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 95.29% after 4 h of carrageenan injection while the other compounds displayed inhibition ≥75%.

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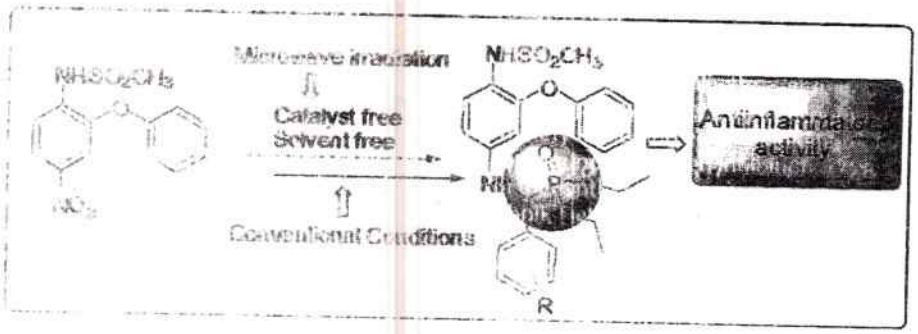
α-Aminophosphonates; Kabachnik-Fields reaction; microwave irradiation; anti-inflammatory activity

GRAPHICAL ABSTRACT




## 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.[2]

Cyclooxygenases (COX-1 and COX-2) have been introduced as novel targets for anti-inflammatory and cancer treatment during the past few years.[3] 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, nonsteroidal 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

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