

## Original Research Article

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## Application of *Lactobacillus* and *Streptococcus* from Yoghurt for Kabachnik - Field Synthesis of $\alpha$ -Aminophosphonates and Evaluation of their Catalytic Activity Using Molecular Docking

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### ABSTRACT

A simple, efficient and environmentally process for one pot three component synthesis of  $\alpha$ -aminophosphonates by the condensation reaction of diversity of substituted benzaldehyde, amine and triethyl phosphite in the presence of microorganisms and yoghurt as a catalyst at room temperature under solvent free condition is described. The reaction was carried out using bacterial strains viz. *Streptococcus thermophilus* and *Lactobacillus delbrueckii* ssp. *bulgaricus*. Both the bacterial strains were equally efficient for the synthesis of  $\alpha$ -aminophosphonates. Yoghurt containing both of these bacteria was found to be even more active as a catalyst in terms of reaction time. This green method provides  $\alpha$ -aminophosphonates in good to excellent yields with high purity in very short reaction time. Molecular docking study was also done in order to further understand the increased catalytic activity of yoghurt as a function of microorganisms present in it. Interaction of substrate i.e. substituted benzaldehyde with crystal structure of dehydrogenase from *Streptococcus thermophilus* (PDB: 3DZB) and *Lactobacillus delbrueckii* ssp. *bulgaricus* (PDB: 2YQ4) was done to obtain moldock energy (kcal/mol).

### Keywords

*Streptococcus thermophilus*,  
*Lactobacillus delbrueckii* ssp.  
*bulgaricus*, Yoghurt,  $\alpha$ -  
aminophosphonates,  
Molecular docking, Moldock  
energy (kcal/mol)

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### Introduction

Development of environmentally benign synthetic methodologies for organic synthesis is one of the challenges to chemists. In addition, the process should be economically viable. Application of green chemistry principles in the field of synthesis has open new vistas for organic chemists to develop innovative, non-hazardous and economically viable processes (Anastas and Warner, 1998; Dichiarante *et al.*, 2010; Horvath and Anastas, 2007; Galuszka *et al.*, 2013). Majority of

reactions use hazardous solvent or toxic catalyst. So, the reactions under solvent free condition employing natural catalyst are desirable. In literature a number of synthetic methods are reported in which natural catalysts like pineapple juice (Patil *et al.*, 2011), lemon juice (Patil *et al.*, 2012), clay (Habibi and Marvi, 2006; Ramesh and Raghunathan, 2009), phosphates (Zahouily *et al.*, 2006), animal bone (Riadi *et al.*, 2010) etc. has been employed.  $\alpha$ -Aminophosphonates are important compounds as they have wide applications as enzyme inhibitors (Allen *et al.*,

1989), antibiotics (Atherton *et al.*, 1986), herbicides, fungicides, insecticides (Maier and Spoerri, 1991) and plant growth regulators (Emsley and Hall, 1976). Nucleophilic addition of phosphite to imines catalyzed by oxalic acid (Vahdat *et al.*, 2008), Al(OTf)<sub>3</sub> (Sobhani and Tashrifi, 2009), FeCl<sub>3</sub> (Rezaei *et al.*, 2009), heteropoly acids (Heydari *et al.*, 2007), SbCl<sub>3</sub>/Al<sub>2</sub>O<sub>3</sub> (Ambica *et al.*, 2008), sulfamic acid (Mitragotri *et al.*, 2008), YbCl<sub>3</sub> (Xu *et al.*, 2006), silica sulfuric acid (Yang *et al.*, 2009), ZrOCl<sub>2</sub>.8H<sub>2</sub>O (Bhanushali *et al.*, 2009), ZnO (Kassaei *et al.*, 2009), BiCl<sub>3</sub> (Zhan and Li, 2005), Amberlite-IR 120 (Bhattacharya and Rana, 2008), PPh<sub>3</sub> (Tian *et al.*, 2009), TiO<sub>2</sub> (Hosseini-Sarvari, 2008), CAN (Kasthuraiah *et al.*, 2007) have been reported. However, some of the reported processes are associated with drawbacks like use of solvent, addition reagent, long reaction time, costly and moisture sensitive catalyst. In continuation to our program to develop environmentally benign synthetic methods (Agarwal *et al.*, 2014; Agarwal *et al.*, 2018; Agrwal *et al.*, 2014) we, herein, report the use of yoghurt as a catalyst, as a function of microorganisms present in it, for the synthesis of  $\alpha$ -aminophosphonates.

Yoghurt is a one of the milk products of major importance in the Indian sub-continent. It is the most important fermented milk product used in India from times immemorial. The scale of production ranges from household level to industrial scale. To the best of our knowledge we are first to report the use of yoghurt as a catalyst for the synthesis of  $\alpha$ -aminophosphonates. In addition, molecular docking study was done to obtain moldock energy (kcal/mol), to achieve an insight into the interaction of substrate i.e. substituted benzaldehyde with crystal structure of dehydrogenase from *Streptococcus thermophilus* (PDB: 3DZB) and *Lactobacillus delbrueckii* ssp. *bulgaricus* (PDB: 2YQ4) as a receptor.

## Materials and Methods

### Culture of microorganism

Bacterial strains of *Streptococcus thermophilus* and *Lactobacillus delbrueckii* ssp. *bulgaricus* were obtained from Department of Microbiology, GB Pant University of Agriculture and Technology, Pantnagar. Strains were used individually as a catalyst for the synthesis of  $\alpha$ -aminophosphonates.

### General procedure for preparation of yoghurt

In the preparation of yoghurt, cow's milk was boiled in order to destroy viable organism, cooled to the body temperature and seeded with starter culture from an earlier batch. A starter culture contains combination of *Streptococcus thermophilus* and *Lactobacillus delbrueckii* ssp. *bulgaricus* organism.

Milk was then kept in undisturbed condition at ambient temperature for 4-6 hrs. A smooth homogeneous product having an acidity of 0.9 to 1.0 percent acid was formed. This homogenous product was then stirred to get thick porous yoghurt which was then used as catalyst.

### General procedure for the synthesis of $\alpha$ -aminophosphonates

A mixture of substituted benzaldehyde (5mmol), aniline (5mmol) and yoghurt/*Streptococcus thermophilus*/*Lactobacillus delbrueckii* ssp. *bulgaricus* (0.5g) was taken with triethyl phosphite (6mmol) in 100 ml round bottom flask and was stirred at room temperature (Scheme 1). After completion of the reaction as indicated by TLC, the reaction mixture was extracted with water and dichloromethane to give pure  $\alpha$ -aminophosphonate.

## Molecular docking

Molecular docking study was performed using software Molegro Virtual Docker (Version 2.3) (Bachwani and Kumar, 2011; Mahajan *et al.*, 2014; Thomsen and Christensen, 2006). The protein structure of target enzyme in PDB file and ligand (synthesized compound) in Mol file were imported in MVD, and bond orders, hybridization states, and angles were assigned if missing. Electrostatic type surface of protein was created. Potential binding sites of target protein were obtained by detecting maximum of 5 cavities setting parameters as molecular surface (expanded van der Waals), maximum number of cavities (n=5), minimum cavity volume (10), probe size (1.20), maximum number of ray checks (n=16), minimum number of ray hits (n=12), and grid resolution (0.80). Keeping all the parameters as default, docking wizard was used to obtain multiple poses and all docking calculations. The best one pose with lowest moldock score was selected manually. Using default parameters maximum 5 cavities were detected in the target protein for potential binding with selected best pose. Sphere center of center of protein with sphere radius 30-33 Å were selected for further docking studies. Moldock score or total energy (kcal/mol) was obtained for protein-ligand interaction (Ramathilagam *et al.*, 2013).

## Results and Discussion

### Synthesis of $\alpha$ -aminophosphonates

Yoghurt is a product obtained by lactose fermentation of cow or buffalo milk or mixed milk through the action of single or mixed strains of lactic acid bacteria. The starter used in the manufacture of yoghurt includes *Streptococcus thermophilus* and *Lactobacillus delbrueckii* ssp. *bulgaricus*. The chemical composition of yoghurt has been reported as fat ranging from 5-9%, protein 3.3-3.4%, ash

0.75 – 0.79% and lactic acid 0.5-1.1%. The pH of commercial yoghurt is usually in the range of 3.5–4.3 (Bamise and Bamise, 2008; Shima *et al.*, 2012). Reaction of substituted benzaldehyde with amines results in the formation of imines intermediates which subsequently reacts with triethylphosphite to produce the corresponding  $\alpha$ -aminophosphonates. Further, to explore the possibility of catalytic activity of yoghurt as a function of microorganisms present in it, the individual reaction was carried out using *Streptococcus thermophilus*/*Lactobacillus delbrueckii* ssp. *bulgaricus* as catalyst. Percent (%) yield of  $\alpha$ -aminophosphonates obtained by multicomponent reaction of substituted benzaldehyde, aniline and triethyl phosphite using yoghurt/*Streptococcus thermophilus*/*Lactobacillus delbrueckii* ssp. *bulgaricus* are presented in table 1. Moreover, substituted benzaldehyde with either electron-donating or electron-withdrawing substituent reacted efficiently, giving excellent yield.

### Characterization data

IR spectra were recorded on Bruker FT-IR spectrophotometer using KBr pellets. <sup>1</sup>H NMR spectra were recorded on Bruker AVANCE II 400 MHz instrument using CDCl<sub>3</sub> with TMS as internal standard. <sup>1</sup>H NMR and IR spectra of synthesized compounds are as follows:

Table 1, Entry A1: Diethyl [1-(phenyl)-1phenylamino] methylphosphonate

IR (KBr): 3396, 3212, 1685, 1625, 1265, 763 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, TMS):  $\delta$  (ppm) 1.2 (3H, t, OCH<sub>2</sub>-CH<sub>3</sub>), 1.35 (3H, t, OCH<sub>2</sub>-CH<sub>3</sub>), 3.55 (1H, m, OCH<sub>2</sub>-CH<sub>3</sub>), 3.7 (1H, m, OCH<sub>2</sub>-CH<sub>3</sub>), 4.15 (2H, m, OCH<sub>2</sub>-CH<sub>3</sub>), 5.15 (1H, br s, N-H), 4.6-4.7 (1H, dd, NH-CH), 6.95-7.55 (10H, m, Ar-H).

Table 1, Entry A2: Diethyl [1-(3-nitrophenyl)-1phenylamino] methylphosphonate

IR (KBr): 3280, 1592, 1269, 1108, 811  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , TMS):  $\delta$  (ppm) 1.35 (3H, t,  $\text{OCH}_2\text{-CH}_3$ ), 1.6 (3H, t,  $\text{OCH}_2\text{-CH}_3$ ), 3.6-3.75 (1H, m,  $\text{OCH}_2\text{-CH}_3$ ),

4.25-4.35 (1H, m,  $\text{OCH}_2\text{-CH}_3$ ), 4.5-4.7 (2H, m,  $\text{OCH}_2\text{-CH}_3$ ), 5.25 (1H, br s, N-H), 5.4 (1H, dd, NH-CH-), 6.9-8.5 (9H, m, Ar-H).

Table 1, Entry A3: Diethyl [1-(4-chlorophenyl)-1phenylamino] methylphosphonate

IR (KBr): 3312, 3368, 1575, 1276, 1078, 767  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , TMS):  $\delta$  (ppm) 1.2 (3H, t,  $\text{OCH}_2\text{-CH}_3$ ), 1.4 (3H, t,  $\text{OCH}_2\text{-CH}_3$ ), 3.3-3.5 (1H, m,  $\text{OCH}_2\text{-CH}_3$ ), 3.6-3.7 (1H, m,  $\text{OCH}_2\text{-CH}_3$ ), 4.1 (3H, s,  $\text{OCH}_3$ ), 4.3-4.4 (2H, m,  $\text{OCH}_2\text{-CH}_3$ ), 4.7 (1H, br m, N-H), 5.1 (1H, dd, NH-CH-), 6.8-7.7 (9H, m, Ar-H).

Table 1, Entry A4: Diethyl [1-(4-hydroxyphenyl)-1phenylamino] methylphosphonate

IR (KBr): 3312, 3288, 1625, 1263, 1112, 764  $\text{cm}^{-1}$ .

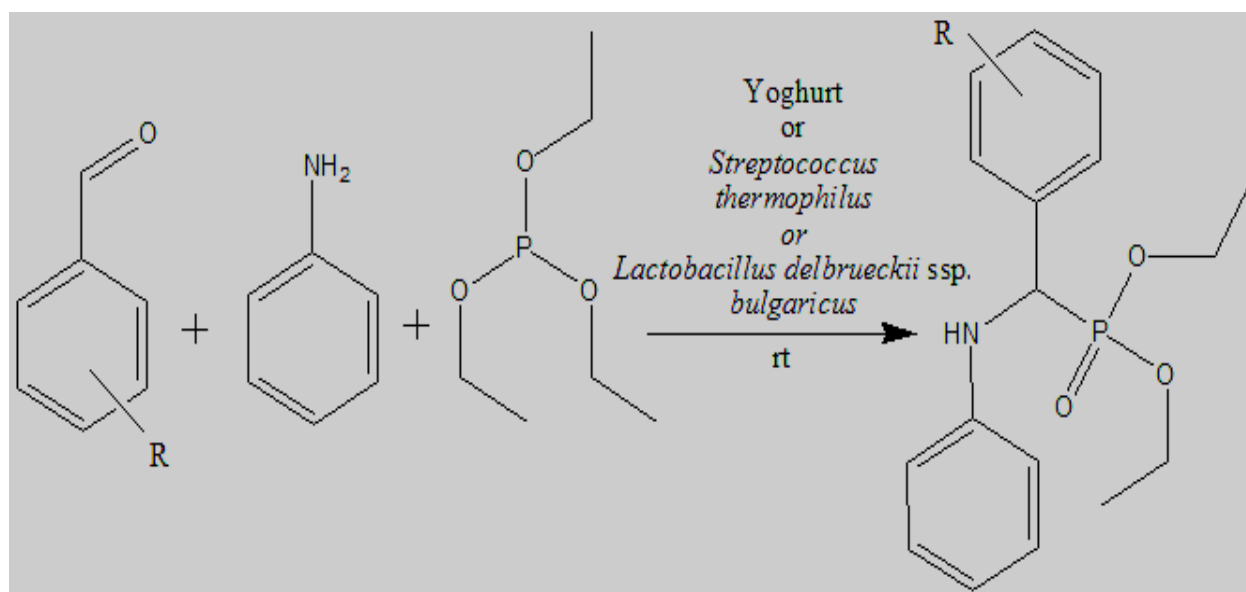
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , TMS):  $\delta$  (ppm) 1.3 (3H, t,  $\text{OCH}_2\text{-CH}_3$ ), 1.45 (3H, t,  $\text{OCH}_2\text{-CH}_3$ ), 3.35-3.5 (1H, m,  $\text{OCH}_2\text{-CH}_3$ ), 3.85-4.05 (1H, m,  $\text{OCH}_2\text{-CH}_3$ ), 4.2 (3H, s,  $\text{OCH}_3$ ), 4.45-4.6 (2H, m,  $\text{OCH}_2\text{-CH}_3$ ), 4.85 (1H, br m, N-H), 5.1 (1H, br s, -OH), 5.4 (1H, dd, NH-CH-), 6.95-7.85 (9H, m, Ar-H).

Table 1, Entry A5: Diethyl [1-(4-methylphenyl)-1phenylamino] methylphosphonate

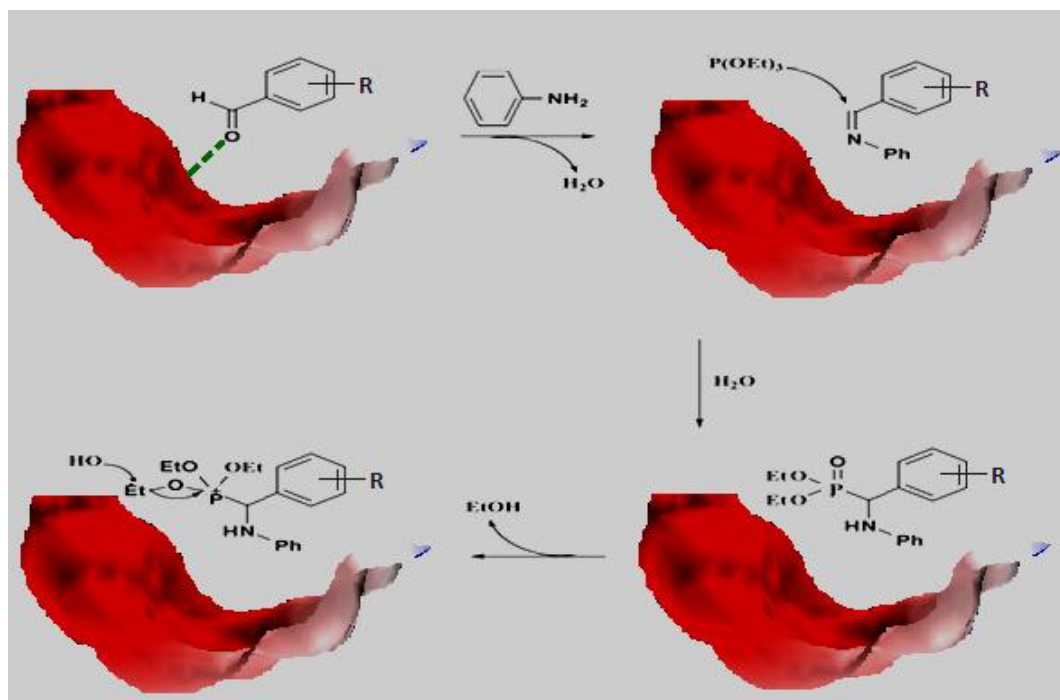
IR (KBr): 3383, 1265, 1047, 784  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , TMS):  $\delta$  (ppm) 1.25 (3H, t,  $\text{OCH}_2\text{-CH}_3$ ), 1.45 (3H, t,  $\text{OCH}_2\text{-CH}_3$ ), 2.35 (3H, s,  $\text{CH}_3$ ), 3.65 (2H, q,  $\text{OCH}_2\text{-CH}_3$ ), 4.25 (2H, q,  $\text{OCH}_2\text{-CH}_3$ ), 4.4 (1H, br m, N-H), 4.65 (1H, dd, NH-CH), 6.8-7.5 (9H, m, Ar-H).

**Scheme.1** Synthesis of  $\alpha$ -aminophosphonates in the presences of yoghurt/ *Streptococcus thermophilus*/ *Lactobacillus delbrueckii* ssp. *bulgaricus*



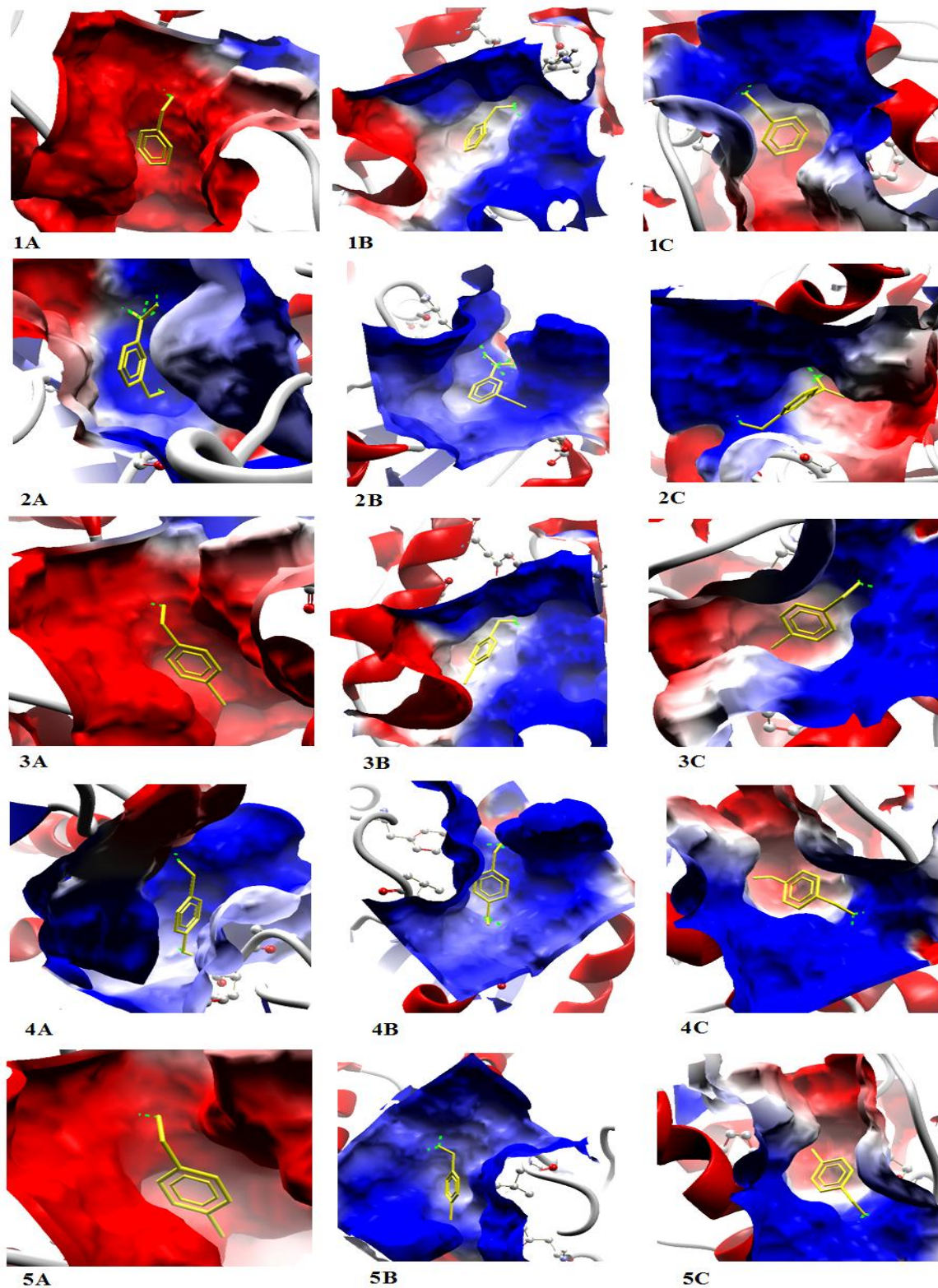
**Scheme.2** Plausible mechanism of synthesis of  $\alpha$ -aminophosphonates



**Table.1** Synthesis of  $\alpha$ -aminophosphonates in the presence of microorganisms

Entry	Compound (R= Substituted Benzaldehyde)	Yoghurt containing both <i>Streptococcus thermophilus</i> (3DZB) and <i>Lactobacillus delbrueckii</i> <i>ssp. bulgaricus</i> (2YQ4)			<i>Streptococcus thermophilus</i> (3DZB)			<i>Lactobacillus delbrueckii</i> <i>ssp. bulgaricus</i> (2YQ4)		
		% Yield	Time (min)	MolDock Energy (kcal/mol)	% Yield	Time (min)	MolDock Energy (kcal/mol)	% Yield	Time (min)	MolDock Energy (kcal/mol)
A1.	R= H	89	4	-69.6	87	35	-53.8	85	30	-58.3
A2.	R= 3-NO <sub>2</sub>	90	2	-84.3	86	20	-68.8	85	15	-67.7
A3.	R= 4-Cl	88	3	-79.1	82	25	-59.6	87	20	-61.1
A4.	R= 4-OH	85	3	-79.1	86	20	-62.6	84	30	-61.9
A5.	R= 4-CH <sub>3</sub>	88	3	-79.6	87	30	-56.8	84	35	-61.8
A1: Diethyl [1-(phenyl)-1phenylamino] methylphosphonate					A2: Diethyl [1-(3-nitrophenyl)-1phenylamino] methylphosphonate					
A3: Diethyl [1-(4-chlorophenyl)-1phenylamino] methylphosphonate					A4: Diethyl [1-(4-hydroxyphenyl)-1phenylamino] methylphosphonate					
A5: Diethyl [1-(4-methylphenyl)-1phenylamino] methylphosphonate										

**Fig.1** Interaction of substrate i.e. substituted benzaldehyde in the binding site of (1A-5A) - 2YQ4, (1B-5B) - 3DZB and (1C-5C) - both, 2YQ4 and 3DZB



## Molecular docking

Interactions of substituted benzaldehyde with X-ray crystal structure of dehydrogenase from *Streptococcus thermophilus* (PDB: 3DZB), *Lactobacillus delbrueckii* ssp. *bulgaricus* (PDB: 2YQ4) obtained by molecular docking are presented in figure 1. In figure 1, images 1A-5A represents docking of substituted benzaldehyde with PDB: 2YQ4, images 1B-5B with PDB: 3DZB and images 1C-5C with both, PDB: 2YQ4 and PDB: 3DZB. Higher catalytic activity of yoghurt as compared to *Streptococcus thermophilus* and *Lactobacillus delbrueckii* ssp. *bulgaricus* can be explained on the basis of moldock energy (kcal/mol). Binding of substituted banzaldehyde with both crystal structures PDB: 2YQ4 and PDB: 3DZB gave rise to higher negative moldock energy as compared to *Streptococcus thermophilus* and *Lactobacillus delbrueckii* ssp. *bulgaricus* (Table 1), explaining increased catalytic activity of yoghurt.

The role of microorganisms (*Streptococcus thermophilus* and *Lactobacillus delbrueckii* ssp. *bulgaricus*) present in yoghurt as a catalyst has been proposed to increase the polarity of carbonyl group by binding with carbonyl oxygen which enhances the electrophilicity of the carbonyl carbon consequently increasing the reaction rate (leading high negative moldock energy (kcal/mol) (Table 1). The plausible mechanism of this reaction is believed to involve condensation between a carbonyl compound and an amine leading to *in situ* formation of the activated imine so that addition of phosphite is facilitated to afford phosphonium intermediate, which then undergoes reaction with water generated during the formation of imine to give  $\alpha$ -aminophosphonates and ethanol (Scheme 2).

Thus, this article describes a simple and efficient method for the green synthesis of  $\alpha$ -

aminophosphonates derivatives through multicomponent one-pot protocol at room temperature under solvent-free condition using *Streptococcus thermophilus*, *Lactobacillus delbrueckii* ssp. *bulgaricus* and yoghurt as a function of microorganisms present in it. This method is found to be more advantageous as yoghurt offers the convenient, environmentally benign and inexpensive green approach for one pot synthesis of  $\alpha$ -aminophosphonates within very short reaction time. Molecular docking on the basis of higher negative moldock energy (kcal/mol) described higher catalytic activity of yoghurt in comparison to *Streptococcus thermophilus*, *Lactobacillus delbrueckii* ssp. *bulgaricus* in terms of reaction time.

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