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Cellulose-SO_3H catalyzed synthesis of bis(α-aminophosphonates) and their antioxidant activity

Nemallapudi Bakthavatchala Reddy,[1] Chereddy Syama Sundar,[1] Balam Satheesh Krishna[1], Sarva Santhisudha,[1] Poola Sreelakshmi,[1] Sandip Kumar Nayak[2] and Cirandur Suresh Reddy[1*]

[1]*Department of Chemistry, Sri Venkateswara University, Tirupati - 517 502, India*
[2]*Bio-Organic Division, Bhabha Atomic Research Centre, Mumbai 400 085, India*

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Abstract: A simple and efficient synthesis of bis(α-aminophosphonates) has been developed by the reaction of aromatic aldehydes, 1,4-phenylenediamine and diethylphosphite in the presence of cellulose-SO_3H as catalyst under neat conditions at room temperature for 10-30 minutes. The synthesized compounds were screened for their antioxidant activity against DPPH, NO and H_2O_2 scavenging methods. All the compounds exhibited good to moderate activity.

Keywords: Bis(α-aminophosphonates); 1,4-phenylenediamine; diethylphosphite; cellulose-SO_3H; antioxidant activity.

1. Introduction

Phosphorus-carbon bond formation reactions have attracted serious attention of chemistry researchers because of their application in the synthesis of α-functionalized phosphonic acids and their derivatives.[1-7] Since they are valuable intermediates for the preparation of bioactive compounds having good therapeutic values, a number of synthetic methods and routes for α-amino phosphonates have been developed.[8-9] Kabachnik-Fields and Pudovik reactions are the most general, straightforward and widely applied methods for the construction of C-P bonds.[10] Amongst them, acid/ base catalyzed nucleophilic addition reactions of phosphites to imines are well reported as it is the most convenient route. Specifically, Lewis acids such as $BF_3.OEt_2$, $ZnCl_2$ and $SnCl_4$ have been successfully employed in this transformation.[11-13] However, all these reactions were not succeed with one-pot single step reaction methodology as they are reversible due to the water liberated from the imine formation reaction will decomposes the product formed and hence deactivates the Lewis acid.[14]

This drawback has been limited up to certain extent by some of the recent synthetic methods for the synthesis of α-aminophosphonates by the addition of dialkyl/ diarylphosphites to schiff's bases,[15] *N*-α-naphthylimines prepared from terephthalic and isophthalic aldehydes to yield corresponding *N*-α-naphthylamino-phosphonates in good yields.[16] Lewkowski *et al.*,[17] synthesized bis(α-aminophosphonates) *via* the phosphite addition to *N*-(*o*-substituted phenyl) terephthalic schiff's bases. Bis(α-aminophosphonates) were synthesized by Rezaei *et al.*[18] using aldehydes, diethyl phosphite and diamines in the presence of $FeCl_3$ catalyst in moderate yields. Lewkowski et al.,[19] synthesized bis(α-aminophosphonates) *via* the phosphite addition to imine bearing (*R*,*R*) 1,2 diamino cyclohexane moiety whose reactions were diastereoselective.

* Corresponding Author: E-mail*: csrsvu@gmail.com;* Tel: (+) 91-9849694958; Fax: (+) 91877-2289555

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In recent, the significant focus on the green and sustainable resources is motivating the scientists and technologists. In such hierarchy, the two biopolymers such as cellulose and starch are using as most common solid supporting catalysts. In latest, the derivatives of cellulose and starch are receiving the significant attention and where their catalytic applications are under exploration.[20-22] Due to significant potential biological activity of *α*-aminophosphonates the emphasis was focused on the development of an efficient and at the same time bio-friendly sustainable synthesis for them. In this context the search for efficient and green catalyst arose. Efforts in this direction led to the discovery of Cellulose-SO_3H that was already proved as promising solid acid catalyst for the synthesis of some important class of organic compounds,[23] like *α*-amino nitriles, quinolines and imidazoazines. In continuation of our efforts in accomplishing new *α*-aminophosphonates from the simple synthetic procedures, we are herewith describing an efficient method for the synthesis of bis(*α*-aminophosphonates) *via* an one-pot, three-component neat reaction of aromatic aldehydes, 1,4-phenylenediamine and diethyl phosphite in the presence of cellulose-SO_3H catalyst.

2. Experimental

All the chemicals and reagents used in the study were obtained from Sigma-Aldrich & Alfa Aesar. Melting points of the synthesized compounds were recorded on Guna Digital Melting Point apparatus and IR spectral characterization was performed on Bruker Alpha-EcoATR-FTIR interferometer with single reflection sampling module equipped with ZnSe crystal. Similarly the ^{1}H, ^{13}C & ^{31}P NMR spectral analysis was performed on Bruker AMX 500 MHz NMR spectrometer and spectral patterns were recorded at an operating frequency of 400 MHz for ^{1}H, 100 MHz for ^{13}C and 160 MHz for ^{31}P NMR in $CDCl_3$ solvent and referenced to TMS (^{1}H and ^{13}C) and 85% H_3PO_4 (^{31}P) and the corresponding chemical shifts were reported in δ scale. Mass spectral studies were performed on a Jeol SX 102 DA/600 mass spectrometer and elemental analysis was performed on a Thermo Finnigan Instrument.

1.1. General procedure for the preparation of bis-aminophosphonates (4a-j)

2 mmol of Benzaldehyde **(1a)**, 1 mmol of 1,4-phenylenediamine **(2)** and 2.5 mmol of diethylphosphite **(3)** were taken in a round bottom flask along with 5mol% of cellulose-SO_3H catalyst and stirred the reaction mixture at room temperature under solvent-free conditions for a period of 25 min. Then the progress of the reaction was monitored by TLC analysis by using 3:1 hexane and ethyl acetate solution. After completion of the reaction crude tetraethyl ((1,4-phenylenebis(azanediyl))bis(phenylmethylene))bis (phosphonate) **(4a)** was purified by column chromatography by using 9:1 hexane and ethyl acetate as eluent and collected the desired product **4a**. The same procedure was followed for the synthesis of remaining compounds **4b-j** and all of them were characterized by spectral (IR, ^{1}H, ^{13}C, ^{31}P NMR, Mass) and elemental (C, H, N) analysis.

*2.1.1. Tetraethyl ((1,4-phenylenebis(azanediyl))bis(phenylmethylene))bis(phosphonate) (**4a**):*[24-34] Yield: 83%, m.p.: 118-120ºC; IR (ZnSe) cm^{-1}: *ν* 3310 (-NH), 3047 (C-$H_{aromatic}$), 2854 (C-$H_{aliphatic}$), 1234 (P=O), 1020 (P-O-$C_{aliphatic}$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44-6.56 (14H, m, Ar-H), 5.08 (2H, d, *J*= 24 Hz, P-CH), 4.02-3.97 (4H, m, 2×-CH_2), 3.81-3.73 (2H, m, -CH_2CH_3), 3.70-3.61 (2H, m, -CH_2CH_3), 1.14 (6H, t, *J*= 6Hz, 2×-CH_3), 0.89 (6H, t, *J*= 6Hz, 2×CH_3);^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.6, 136.6, 130.4, 128.4, 127.2, 123.0, 63.4, 63.3, 56.2, 16.2, 16.1; ^{31}P NMR ($CDCl_3$, 160 MHz): δ 20.60; LC-MS: *m/z* (%): 560 ($M^{+\bullet}$). Anal. Calcd for $C_{28}H_{38}N_2O_6P_2$: % C, 59.99; H, 6.83; N, 5.00. Found: C, 59.91; H, 6.77; N, 4.96.

*2.1.2. Tetraethyl ((1,4-phenylenebis(azanediyl))bis((4-bromophenyl) methylene)) bis(phosphonate) (**4b**):*[33-34] Yield: 90%, m.p.: 124-126ºC; IR (ZnSe) cm^{-1}: *ν* 3302 (-NH), 3067 (C-$H_{aromatic}$), 2904 (C-$H_{aliphatic}$), 1231 (P=O), 1025 (P-O-$C_{aliphatic}$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43-6.54 (12H, m, Ar-H), 5.04 (2H, d, *J*= 24 Hz, P-CH), 3.98-3.93 (4H, m, 2×-CH_2), 3.80-3.73 (2H, m, -CH_2CH_3), 3.69-3.60 (2H, m, -CH_2CH_3), 1.01 (6H, t, *J*= 6 Hz, 2×-CH_3), 0.85 (6H, t, *J*= 6Hz, 2×-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.4, 137.0, 129.3, 128.9, 128.6, 128.1, 65.4, 65.1, 57.5, 18.8, 18.2; ^{31}P NMR ($CDCl_3$,

160 MHz): δ 21.65; LC-MS: *m/z* (%): 716 ($M^{+\bullet}$); Anal. Calcd for $C_{28}H_{36}Br_2N_2O_6P_2$: C, 46.82; H, 5.05; N, 3.90. Found: C, 46.79; H, 5.02; N, 3.88.

*2.1.3. Tetraethyl ((1,4-phenylenebis(azanediyl))bis((4-hydroxyphenyl) methylene)) bis(phosphonate) **(4c)**:*[33,36-38] Yield: 82%, m.p.: 120-123ºC; IR (ZnSe) cm^{-1}: *ν* 3298 (-NH), 3077 (C-$H_{aromatic}$), 2904 (C-$H_{aliphatic}$), 1218 (P=O), 1025 (P-O-$C_{aliphatic}$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39-6.75 (12H, s, Ar-H), 5.10 (2H, d, *J*= 24Hz, P-CH), 4.02-3.96 (4H, m, 2×-CH_2), 3.82-3.74 (2H, m, -CH_2CH_3), 3.72-3.68 (2H, m, -CH_2CH_3), 1.12 (6H, t, *J*= 6 Hz, 2×CH_3), 0.91 (6H, t, *J*= 6 Hz, 2×CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.2, 138.8, 138.2, 131.7, 129.5, 128.2, 62.9, 62.6, 58.3, 16.3, 16.0; ^{31}P NMR ($CDCl_3$, 160 MHz): δ 22.21; LC-MS: *m/z* (%): 592 ($M^{+\bullet}$); Anal. Calcd for $C_{28}H_{38}N_2O_8P_2$: C, 56.75; H, 6.46; N, 4.73. Found: C, 56.70; H, 6.42; N, 4.68.

*2.1.4. Tetraethyl ((1,4-phenylenebis(azanediyl))bis((4-methoxyphenyl) methylene)) bis(phosphonate) **(4d)**:*[33-35] Yield: 80%, m.p.: 125-127ºC; IR (ZnSe) cm^{-1}: *ν* 3300 (-NH), 3076 (C-$H_{aromatic}$), 2905 (C-$H_{aliphatic}$), 1226 (P=O), 1025 (P-O-$C_{aliphatic}$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38-6.73 (12H, m, Ar-H), 5.11 (2H, d, *J*= 24Hz, P-CH), 4.01 (6H, s, -OCH_3), 4.06-3.94 (4H, m, 2×-CH_2), 3.80-3.72 (2H, m, -CH_2CH_3), 3.70-3.65 (2H, m, -CH_2CH_3), 1.02-0.97 (6H, m, 2×CH_3), 0.95-0.84 (6H, m, 2×CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.6, 138.2, 137.8, 130.5, 129.3, 128.0, 63.1, 62.8, 58.2, 30.5, 18.6, 18.2; ^{31}P NMR ($CDCl_3$, 160 MHz): δ 22.12; LC-MS: *m/z* (%): 620 ($M^{+\bullet}$); Anal. Calcd for $C_{30}H_{42}N_2O_8P_2$: C, 58.06; H, 6.82; N, 4.51. Found: C, 58.00; H, 6.79; N, 4.48.

*2.1.5. Tetraethyl ((1,4-phenylenebis(azanediyl))bis((4-nitrophenyl) methylene)) bis(phosphonate) **(4e)**:*[34] Yield: 89%, m.p.: 128-130ºC; IR (ZnSe) cm^{-1}: *ν* 3305 (-NH), 3078 (C-$H_{aromatic}$), 2904 (C-$H_{aliphatic}$), 1238 (P=O), 1022 (P-O-$C_{aliphatic}$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35-6.72 (12H, m, Ar-H), 5.04 (2H, d, *J*= 24Hz, P-CH), 4.01-3.94 (4H, m, 2×-CH_2), 3.82-3.74 (2H, m, -CH_2CH_3), 3.72-3.68 (2H, m, -CH_2CH_3), 1.11 (6H, t, *J*= 6Hz, 2×-CH_3), 0.92 (6H, t, *J*= 6Hz, 2×-CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.5, 139.5, 138.2, 137.6, 131.2, 128.1, 62.7, 62.3, 58.1, 16.2, 16.0; ^{31}P NMR ($CDCl_3$, 160 MHz): δ 22.18; LCMS: *m/z* (%): 650 ($M^{+\bullet}$); Anal. Calcd for $C_{28}H_{36}N_4O_{10}P_2$: C, 51.69; H, 5.58; N, 8.61. Found: C, 51.60; H, 5.50; N, 8.58.

*2.1.6. Tetraethyl ((1,4-phenylenebis(azanediyl))bis(p-tolylmethylene))bis(phosphonate) **(4f)**:*[33-35] Yield: 85%, m.p.: 128-130ºC; IR (ZnSe) cm^{-1}: *ν* 3304 (-NH), 3079 (C-$H_{aromatic}$), 2901 (C-$H_{aliphatic}$), 1230 (P=O), 1023 (P-O-$C_{aliphatic}$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34-6.76 (12H, m, Ar-H), 5.12 (2H, d, *J*= 24 Hz, P-CH), 2.54 (6H, s, 2×-CH_3), 4.10-3.92 (4H, m, 2×-CH_2), 3.80-3.72 (2H, m, -CH_2CH_3), 3.70-3.66 (2H, m, -CH_2CH_3), 1.01-0.98 (6H, m, 2×-CH_3), 0.95-0.83 (6H, m, 2×-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.4, 144.2, 133.5, 130.3, 129.5, 127.8, 63.3, 62.4, 58.3, 30.7, 18.4, 18.5; ^{31}P NMR ($CDCl_3$, 160 MHz): δ 22.17. LC-MS: *m/z* (%): 588 ($M^{+\bullet}$); Anal. Calcd for $C_{30}H_{42}N_2O_6P_2$: C, 61.22; H, 7.19; N, 4.76. Found: C, 61.19; H, 7.14; N, 4.70.

*2.1.7. Tetraethyl ((1,4-phenylenebis(azanediyl))bis((3,4-dimethoxyphenyl) methylene)) bis(phosphonate) **(4g)**:* Yield: 84%, m.p.: 122-124ºC; IR (ZnSe) cm^{-1}: *ν* 3305 (-NH), 3075 (C-$H_{aromatic}$), 2907 (C-$H_{aliphatic}$), 1231 (P=O), 1020 (P-O-$C_{aliphatic}$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31-6.72 (10H, m, Ar-H), 5.03 (2H, d, *J*= 24 Hz, P-CH), 4.03 (12H, s, 4×-OCH_3), 4.09-3.91 (4H, m, 2×-CH_2), 3.79-3.72 (2H, m, -CH_2CH_3), 3.69-3.64 (2H, m, -CH_2CH_3), 1.10 (6H, t, *J*= 6 Hz, 2×CH_3), 0.89 (6H, t, *J*= 6 Hz, 2×CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.3, 144.7, 134.3, 130.5, 128.8, 127.5, 122.2, 119.8, 63.4, 68.7, 62.4, 57.6, 18.4; ^{31}P NMR ($CDCl_3$, 160 MHz): δ 21.78; LC-MS: *m/z* (%): 680 ($M^{+\bullet}$); Anal. Calcd for $C_{32}H_{46}N_2O_{10}P_2$: C, 56.47; H, 6.81; N, 4.12. Found: C, 56.40; H, 6.78; N, 4.09.

*2.1.8. Tetraethyl ((1,4-phenylenebis(azanediyl))bis((4-isopropylphenyl) methylene)) bis(phosphonate) **(4h)**:*[35] Yield: 79%, m.p.: 125-127ºC; IR (ZnSe) cm^{-1}: *ν* 3303 (-NH), 3078 (C-$H_{aromatic}$), 2905 (C-$H_{aliphatic}$), 1232 (P=O), 1023 (P-O-$C_{aliphatic}$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30-6.70 (12H, m, Ar-H), 5.05 (2H, d, *J*= 24 Hz, P-CH), 4.01-3.93 (4H, m, 2×-CH_2), 3.80-3.74 (2H, m, -CH_2CH_3), 3.67-3.63 (2H, m, -CH_2CH_3), 2.81-2.77 (2H, m, 2×-$CH(CH_3)_2$), 1.24 (12H, d, *J*= 5.3 Hz, 2×-$CH(CH_3)_2$), 1.11

(6H, t, *J*= 6Hz, 2×-CH_3), 0.90 (6H, t, *J*= 6Hz, 2×-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.5, 135.5, 133.2, 126.7, 125.9, 118.2, 71.3, 64.7, 34.2, 25.6, 16.8; ^{31}P NMR ($CDCl_3$, 160 MHz): δ 21.72; LC-MS: *m/z* (%): 644 ($M^{+\bullet}$); Anal. Calcd for $C_{34}H_{50}N_2O_6P_2$: C, 63.34; H, 7.82; N, 4.35. Found: C, 63.30; H, 7.79; N, 4.30.

*2.1.9. Tetraethyl ((1,4-phenylenebis(azanediyl))bis((4-(dimethylamino)phenyl) methylene))bis (phosphonate) (**4i**):*[32-35] Yield: 80%, m.p.: 119-122ºC; IR (ZnSe) cm^{-1}: *v* 3304 (-NH), 3080 (C-$H_{aromatic}$), 2902 (C-$H_{aliphatic}$), 1230 (P=O), 1020 (P-O-$C_{aliphatic}$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46-6.79 (12H, m, Ar-H), 5.15 (2H, d, *J*= 24Hz, P-CH), 4.10-4.01 (4H, m, 2×-CH_2), 3.89-3.81 (2H, m, -$\underline{CH_2}CH_3$), 3.66-3.62 (2H, m, -$\underline{CH_2}CH_3$), 3.10 (12H, s, 2×-N $(CH_3)_2$), 1.10 (6H, t, *J*= 6 Hz, 2×-CH_3), 0.89 (6H, t, *J*= 6Hz, 2×-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.4, 136.2, 127.5, 125.9, 119.6, 118.3, 72.5, 64.9, 41.5, 17.3; ^{31}P NMR ($CDCl_3$, 160 MHz): δ 22.32; LC-MS: *m/z* (%): 646 ($M^{+\bullet}$). Anal. Calcd. for $C_{32}H_{48}N_4O_6P_2$: C, 59.43; H, 7.48; N, 8.66. Found: C, 59.40; H, 7.43; N, 8.59.

*2.1.10. Tetraethyl ((1,4-phenylenebis(azanediyl))bis((1H-indol-3-yl)methylene)) bis(phosphonate) (**4j**):* Yield: 78%, m.p.: 117-119ºC; IR (ZnSe) cm^{-1}: *v* 3302 (-NH), 3076 (C-$H_{aromatic}$), 2905 (C-$H_{aliphatic}$), 1227 (P=O), 1023 (P-O-$C_{aliphatic}$); ^{1}H NMR ($CDCl_3$, 400MHz): δ 7.45-6.78 (14H, m, Ar-H), 8.50 (2H, d, *J*= 7.5 Hz, Ar-NH), 5.14 (2H, d, *J*= 24 Hz, P-CH), 4.10-4.02 (4H, m, 2×-CH_2), 3.87-3.79 (2H, m, -CH_2CH_3), 1.80-1.75 (2H, m, -CH_2CH_3), 1.11 (6H, t, J = 6 Hz, 2×-CH_3), 0.91 (6H, t, *J*= 6Hz, 2×-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.5, 137.2, 129.6, 123.7, 125.5, 121.6, 119.8, 119.3, 118.9, 113.7, 111.4, 71.3, 64.5, 16.7; ^{31}P NMR ($CDCl_3$, 160MHz): δ 22.35; LC-MS: *m/z* (%): 638 ($M^{+\bullet}$); Anal. Calcd for $C_{32}H_{40}N_4O_6P_2$: C, 60.18; H, 6.31; N, 8.77. Found: C, 60.10; H, 6.29; N, 8.70.

In such, we are successful in employing the catalytic activity of cellulose-SO_3H for the synthesis of simple α-aminophosphonates[39] as well as the bis-α-aminophosphonates with good yields and simple operating procedures in comparison to the other reported methods.[24-38]

2.3. Antioxidant activity

2.3.1. DPPH Radical Scavenging Activity

The radical scavenging activity of bis(α-aminophosphonates) against DPPH radical was performed according to the Choi *et al* method.[40] A 85µM of DPPH solution was added to a medium containing different bis-aminophosphonic diesters. The medium was incubated for 30 min at room temperature. Then the absorbance values were recorded at 517 nm. A control sample without title compounds was also analyzed in the same procedure and the results were expressed as percentage of radical scavenging activity (%RSA), where ascorbic acid was used as standard reference. The DPPH radical scavenging activity was calculated by using the equation given below. All the experiments were conducted in triplicate and radical scavenging activity values are calculated from the absorbance values using the following formula;

$$\text{Radical Scavenging Activity}\,(\%) = \frac{[(A_{\text{control}} - A_{\text{sample}})]}{(A_{\text{control}})} \times 100$$

Where, $A_{control}$ = Absorbance of the control and A_{sample} = Absorbance of the sample

In the case of bis-aminophosphonic diesters **4a-j** (Fig. 1) derivatives, **4e** showed the highest DPPH radical scavenging activity with IC_{50} at 26.8 µg/mL in comparison to the other compounds. The order of remaining compounds exhibiting DPPH radical scavenging activity is as listed below: **4c** (IC_{50} 27.8 µg/mL), **4f** (IC_{50} 29.4 µg/mL), **4b** (IC_{50} 29.7 µg/mL), **4a** (IC_{50} 30.8 µg/mL), **4h** (IC_{50} 31.5 µg/mL),**4g** (IC_{50} 32.2 µg/mL), **4i** (IC_{50} 34.8 µg/mL), **4d** (IC_{50} 35.6 µg/mL), **4j** (IC_{50} 45.7 µg/mL), and ascorbic acid reference (IC_{50} 30.5 µg/mL).

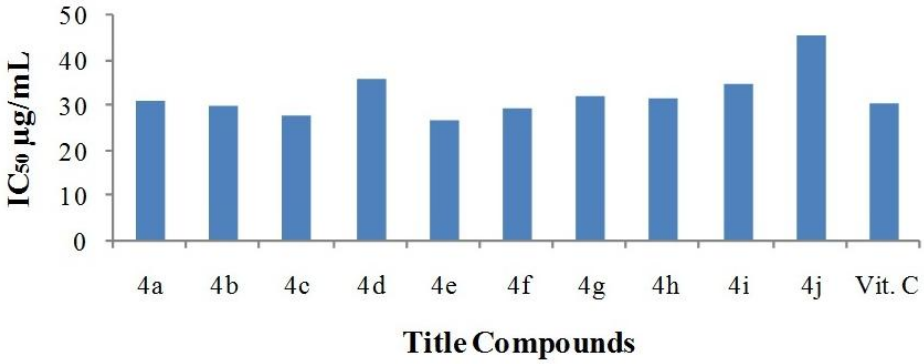


Figure 1. DPPH Radical Scavenging Activity of 4a-j

2.3.2. Nitric Oxide (NO) Scavenging Activity

The nitric oxide radical scavenging activity of bis-aminophosphonic diesters was performed according to the Shirwaiker *et al.* method.[41] In this method, NO radical was generated spontaneously from the sodium nitroprusside (SNP) buffer solution. The 3mL of reaction mixture containing 2mL of 10 mM sodium nitroprusside, 0.5mL saline phosphate buffer (SPB) and 0.5mL of extract (25-100µg/mL) were incubated at 25°C for a period of 150min. After 150 min of incubation, 0.5mL of the prepared reaction mixture was mixed with 1.5mL Griess reagent [1.0% sulphanilamide + 2.5% H_3PO_4 + 0.1% *N*- (1 naphtyl) ethylenediamine dihydrochloride]. Then the absorbance was measured at 546 nm by using UV-visible spectrophotometer and the results were expressed as a percentage of nitric oxide scavenging with respect to the control sample.

In the case of bis-aminophosphonic diesters **4a-j** (Fig. 2) derivatives, **4e** showed the highest nitric oxide scavenging with IC_{50} of 33.8 µg/mL when compared with other compounds. The remaining compounds exhibited NO scavenging activity in the following order: **4a** (IC_{50} 34.3 µg/mL), **4b** (IC_{50} 35.6 µg/mL), **4h** (IC_{50} 39.8 µg/mL), **4c** (IC_{50} 40.2 µg/mL), **4i** (IC_{50} 41.5 µg/mL), **4d** (IC_{50} 42.6 µg/mL), **4f** (IC_{50} 47.7 µg/mL), **4g** (IC_{50} 48.7 µg/mL), **4j** (IC_{50} 50.6 µg/mL) and when compared with standard ascorbic acid reference (IC_{50} 42.4 µg/mL).

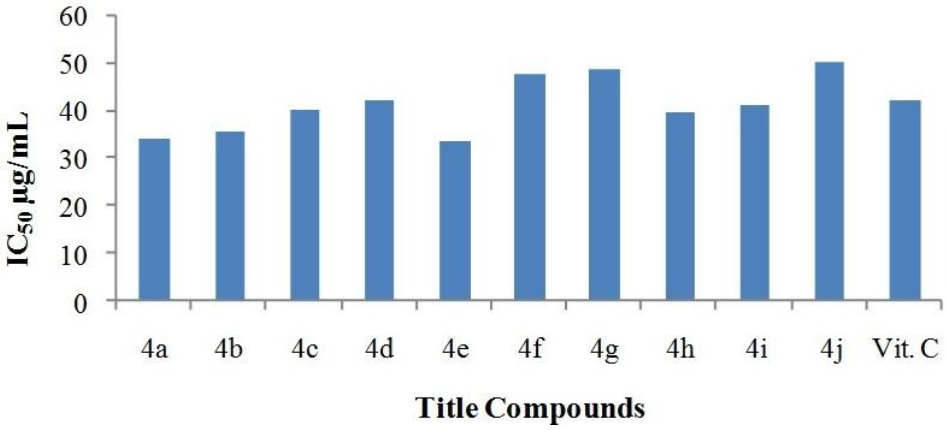


Figure 2. NO Scavenging Activity of 4a-j

2.3.3. Hydrogen Peroxide (H_2O_2) Scavenging Activity

Hydrogen peroxide scavenging activity was determined by using a Gow-Chin Yen and Hui-Yin Chen modified method.[42] Initially a solution of hydrogen peroxide (40 mM) was prepared in

phosphate buffer (pH 7.4) and spectrophotometrically quantified at 230 nm. Then the aqueous extracts (25 - 100µg/mL) in distilled water was added to this hydrogen peroxide solution (0.6 mL, 40 mM) and the absorbance of hydrogen peroxide at 230 nm was determined after 20 min against a blank solution. The percentages of peroxide radical scavenging capacity of title compounds were calculated.

Among all the bis-aminophosphonic diester derivatives **4a-j** (Fig 3), **4c** showed the highest H_2O_2 scavenging activity with IC_{50} of 40.5 µg/mL when compared with other compounds. The remaining compounds exhibited H_2O_2 scavenging activity in the following order: **4e** (IC_{50} 42.5 µg/mL), **4b** (IC_{50} 43.5 µg/mL), **4f** (IC_{50} 43.7 µg/mL), **4a** (IC_{50} 44.3 µg/mL), **4d** (IC_{50} 48.4 µg/mL), **4h** (IC_{50} 48.9 µg/mL), **4g** (IC_{50} 51.6 µg/mL), **4i** (IC_{50} 55.8 µg/mL), **4j** (IC_{50} 61.5 µg/mL), and when compared with ascorbic acid (IC_{50} 60.2 µg/mL).

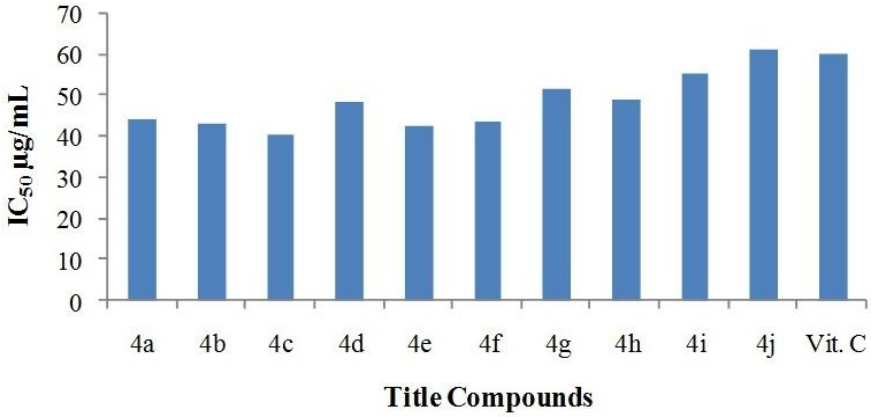
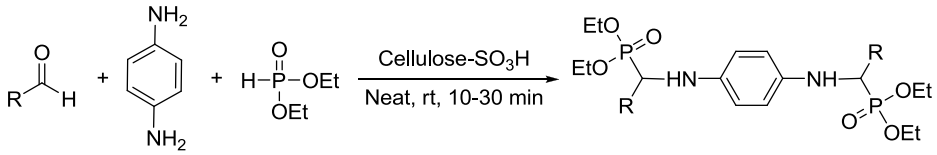


Figure 3. H_2O_2 Scavenging Activity of 4a-j

3. Results and discussion

3.1. Chemistry

In this accomplishment, we are herewith reporting the synthesis of a series of bis(*α*-aminophosphonates) from the reaction of various aromatic aldehydes, 1,4-phenylenediamine and diethyl phosphite in the presence of cellulose-SO_3H catalyst in an one-pot, three-component procedure at room temperature under solvent free conditions (Scheme 1).



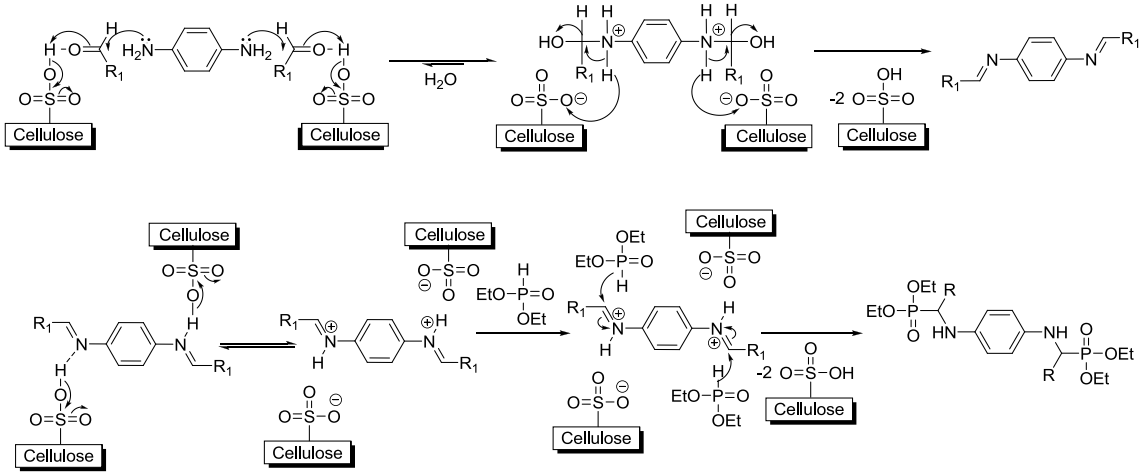
(1a-j) (2) (3) (4a-j)

Compound	R	rt (min)	Compound	R	rt (min)
4a		25	4f	H_3C	30
4b	Br	10	4g	H_3CO, H_3CO	25
4c	HO	30	4h		25
4d	H_3CO	30	4i	N	30
4e	O_2N	25	4j	N H	30

Scheme 1. Synthesis of bis(*α*-aminophosphonates)

Initially in optimizing the reaction conditions we have selected a model reaction for the synthesis of **4b** from 4-bromo benzaldehyde **(1b)**, 1,4-phenylenediamine **(2)**, and diethylphosphite **(3)**. Initially the model reaction has been performed in different solvents such as methanol, toluene, tetrahydrofuran, dioxane, chloroform, dichloromethane, diethyl ether and acrylonitrile in the presence of cellulose-SO_3H at room temperature and obtained the compound **4b** in low yields. Use of higher catalyst concentrations and elevated temperatures has not given any significant improvement in the reaction yields. Remarkably the solvent free room temperature reaction has given 90% yield of **4b** with 5mol% of cellulose-SO_3H catalyst in 10 min and adopted these optimized conditions as valid. The reaction progress was monitored by TLC analysis by using hexane and ethyl acetate (3:1) as eluent. After successful completion of the reaction, the obtained crude product was purified by silica gel column chromatography by using hexane and ethyl acetate (9:1) as eluent and collected the desired product **4b**. By following the same reaction procedure the other products of the series (**4b-j)** were synthesized.

The interaction of 1,4-phenylenediamine and an aldehyde has been accelerated by the use of cellulose-SO_3H in the due course of the reaction, at initiation itself. This interaction helps to remove the water formed during the generation of imine intermediate. Here the key role of the cellulose-SO_3H catalyst i.e., able to form the quaternary ammonium salt of cellulose sulfate and hence arresting the backward reaction to form substrates again. The formed imine will interact again with cellulose-SO_3H catalyst and generates the iminium salt of cellulose sulfate and abstracts a proton from the diethyl phosphite and enhances the nucleophilicity on the phosphorus atom and makes it to add to the electrophilic carbon atom in imine and ultimately forms the required bis(α-aminophosphonates). In overall view, the cellulose-SO_3H catalyst successfully catalyzes the two steps of the Kabachnik-Fields reaction. The advantage of the cellulose-SO_3H catalyst is it is recoverable and reusable as it just transfers a proton and chemically remains stable. This operational simplicity may finds to use this as a choice of industrial applications for the synthesis of α-aminophosphonates and their derivatives.



Scheme 2. Mechanistic pathway for the synthesis of bis(α-aminophosphonates)

3.2. Antioxidant activity

The antioxidant activity of the title compounds **4a-j** having substituted with 4-bromo, 4-hydroxy, 4-methoxy, 4-nitro, 4-methyl, 3,4dimethoxy, 4-iso-propyl, 4-di-methylamino groups and 3-indolyl moiety has been screened against DPPH, NO and Hydrogen peroxide scavenging methods. The successful screening revealed that all the synthesized compounds have shown good activity and specifically compounds **4e** (substituted with 4-nitro group) and **4c** (substituted with 4-hydroxy group) have exhibited high antioxidant activity in comparison to the other compounds of the series. This is due to the fact that the compounds **4c** & **4e** having nitro and hydroxy groups respectively on them are able to generate free radicals easily and hence easily binds with the other free radical that are

generated in the test solutions. The antioxidant activity of the compounds was referenced to the standard ascorbic acid (Vitamin C) and hence detailed their comparative results in this study.

4. Conclusion

In conclusion, Cellulose-SO_3H was found and herewith reporting that it is an efficient catalyst for the synthesis of corresponding bis(*α*-aminophosphonates) and affording them in good to excellent yields. All the title compounds **(4a-j)** were tested for their antioxidant activity against the three methods *viz*., DPPH, NO and H_2O_2 radical scavenging methods. In result, it is noticed that compounds **4e** and **4c** have exhibited high antioxidant activity and remaining compounds have showed moderate activity. The main advantages of the present method are use of eco-friendly catalyst, mild reaction conditions, simple reaction work-up procedures and good product yields.

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References

[1] Amin, R.; Bahareh, A.; Darush, M. Synthesis, characterization and catalytic properties of magnetic nanoparticle supported guanidine in base catalyzed synthesis of *α*-hydroxyphosphonates and *α*-acetoxyphosphonates. *Appl. Catal., A*, **2013**, *467*, 7-16.

[2] Reddy, C.B.; Kumar, K.S.; Kumar, M.A.; Reddy, M.V.; Krishna, B.S.; Naveen, M.; Arunasree, M.K.; Reddy, C.S.; Raju C.N.; Reddy, C.D., PEG-SO_3H catalyzed synthesis and cytotoxicity of *α*-aminophosphonates. *Eur. J. Med. Chem.*, **2012,** *47*, 553-559.

[3] Prasad, S.S.; Jayaprakash, S.H.; Syamasundar, Ch.; Sreelakshmi, P.; Bhuvaneswar, C.; Bhaskar, B.V.; Rajendra, W.; Nayak S.K., Reddy, C.S. Tween 20/H_2O Promoted green synthesis, computational and antibacterial activity of amino acid substituted methylene bisphosphonates. *Phosphorus, Sulfur Silicon Relat. Elem.* **2015,** *190*, 2040-2050.

[4] Iwona, E.G.; Jan, B.; Graciela, A.; Robert, S.; Dominique, S.;, Dorota G.P. Design, synthesis, antiviral and cytostatic activity of ω-(1*H*-1,2,3-triazol-1-yl)(polyhydroxy)alkylphosphonates as acyclic nucleotide analogues. *Bioorg. Med. Chem.*, **2014**, *22*, 3629-3641.

[5] Kim, S.H.; Kim, K.H.; Lim, J.W.; Kim, J.N. An expedient synthesis of pyrrole-2-phosphonates via direct oxidative phosphorylation and γ-hydroxy-γ-butyrolactams from pyrroles. *Tetrahedron Lett.* **2014,** *55*, 531-534.

[6] Shafeek, A.R.M.; Mohsinkhan, Y.P.; Santosh, S.C.; Suwara, P.G. Dhiman Sarkar,Highly efficient one-pot multi-component synthesis of α-aminophosphonates and bis-*α*-aminophosphonates catalyzed by heterogeneous reusable silica supported dodecatungstophosphoric acid (DTP/SiO_2) at ambient temperature and their antitubercular evaluation against Mycobactrium Tuberculosis. *RSC Adv.* **2014**, *4*, 7666-7672.

[7] Samuele, S.; Alessandro, D.; Alberto, M. Metal-free synthesis of *E*-vinylphosphonates *via* photoinduced alkyne hydrophosphonylation and thiol promoted isomerization sequence. *Tetrahedron Lett.* **2015,** *56*, 374-377.

[8] Kukhar, V.P.; Solodenko, V.A. The Phosphorus Analogues of Aminocarboxylic Acids. *Russ. Chem. Rev*., **1987,** 56, 859-874.

[9] Yokomatsu, T.; Yoshida, Y.; Shibuya, S.; Stereoselective Synthesis of *β*-Oxygenated *α*-Hydroxy phosphonates by Lewis Acid-Mediated Stereoselective Hydrophosphonylation of *α*-Benzyloxy Aldehydes: An Application to the Synthesis of Phosphonic Acid Analogs of Oxyamino Acids. *J. Org. Chem.*, **1994,** *59*, 7930-7933.

[10] Merino, P.; Lopez, E.M.; Herrera, R.P. Catalytic Enantioselective Hydrophosphonylation of Aldehydes and Imines. *Adv. Synth. Catal.* **2008**, *350*, 1195-1208.

[11] Laschat, S.; Kunz, H.; Carbohydrates as Chiral Templates: Stereoselective Synthesis of (R)- and (S)- *α*-Aminophosphonic Acid Derivatives. *Synthesis* **1992**, *1992*, 90-95.

[12] Ha, H.J.; Nam, G.S. An Efficient Synthesis of Anilinobenzylphosphonates. *Synth. Commun.* **1992**, *22*, 1143-1148.

[13] Yadav, J.S.; Reddy, B.V.S.; Raj, S.; Reddy, K.B.; Prasad, A.R. Zr^{4+}-Catalyzed Efficient Synthesis of α-Aminophosphonates. *Synthesis* **2001**, *2001*, 2277-2280.

[14] Atherton, F.R.; Hassal, C.H.; Lambert, R.W. Synthesis and structure-activity relationships of antibacterial phosphonopeptides incorporating (1-aminoethyl)phosphonic acid and (aminomethyl) phosphonic acid. *J. Med. Chem.* **1986,** 29, 29-40.

[15] Lewkowski, J.; Rzezniczak, M.; Skowronski, R.; Synthesis of 1,4-Phenylene-bisaminomethane phosphonates: The Stereochemical Aspect. *Heteroatom Chem.* **2000**, *11*, 144-151.

[16] Lewkowski, J.; Skowronski, R. The unusual stereochemical behavior in the addition of phosphites to *N*-1-naphthyl terephthalic and isophthalic Schiff bases. *Heteroatom Chem.* **2001**, *12*, 27-32.

[17] Lewkowski, J.; Lewkowska, E.S. Addition of Dialkyl and Diaryl Phosphites to *N*-(ortho-Substituted Phenyl) Terephthalic Schiff Bases: The Stereochemical Behavior. *Phosphorus, Sulfur Silicon Relat. Elem.* **2006**, *181*, 1323-1330.

[18] Rezaei, Z.; Firouzabadi, H.; Iranpoor, N.; Ghaderi, A.; Jafari, M.R.; Jafari, A.A.; Zare, H.R.; Design and one-pot synthesis of α-aminophosphonates and bis(α-aminophosphonates) by iron(III) chloride and cytotoxic activity. *Eur. J. Med. Chem.* **2009**, *44*, 4266-4275.

[19] Lewkowski, J.; Tokarz, P.; Lis, T.; Slepokura, K. Synthesis and resolution of diastereomers of (R,R)-1,2-cyclohexylenediamino-di-phenylmethylphosphonates. *Tetrahedron: Asymm.*, **2012**, 23, 482-488.

[20] Lancaster, M. in *Hand Book of Green Chemistry and Technology*. Eds. Clark, J.H.; Macquarrie D.J. Blackwell, Abingdon, 2002.

[21] Guibal, E.; Heterogeneous catalysis on chitosan-based materials: a review. *Prog. Polym. Sci.* **2005**, *30*, 71-109.

[22] Klemm, D.; Heublein, B.; Fink, H.P.; Bohn, A. Cellulose: Fascinating biopolymer and sustainable raw material. *Angew. Chem. Int. Ed.* **2005**, *44*, 3358-3393.

[23] Shaabani, A.; Rahmati, A.; Badri, Z. Sulfonated cellulose and starch: New biodegradable and renewable solid acid catalysts for efficient synthesis of quinolones. *Catal. Commun.* **2008**, 9, 13-16.

[24] Pudovik, A.N.; Pudovik, M.A. Atomic refraction of phosphorus in esters of alkylarylphosphinic acids and arylphosphonous acids and addition reactions of unsaturated compounds. *Zh. Obshch. Khim.*, **1966**, *36*, 1467-72.

[25] Nastopoulos, V.; Germain, G.; Kallitsis, J.; Voliotis, S., Structures of five N,N'-bis[(dialkoxyphosphinoyl)methyl]-1,4-benzenediamines. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, **1987**, *C43*, 245-249.

[26] Hoerhold, H.H.; Klee, J. Preparation of fire-resistant epoxide-amino phosphonate copolymers. Patent: DD 293357A5.

[27] Failla, S.; Finocchiaro, P.; Hagele, G.; Rapisardi, R. Synthesis, NMR investigation and fast-atom-bombardment mass spectra characterization of 1-amino-2-arylmethyl-diphosphonate esters. *Phosphorus, Sulfur Silicon Relat. Elem.*, **1993**, *82*, 79-89.

[28] Rezaei, Z.; Firouzabadi, H.; Iranpoor, N.; Ghaderi, A.; Jafari, M.R.; Jafari, A.A; Zare, H.R. Design and one-pot synthesis of α-aminophosphonates and bis(α-aminophosphonates) by iron(III) chloride and cytotoxic activity. *Eur. J. Med. Chem.*, **2009**, *44*, 4266-4275.

[29] Banik, A.; Batta, S.; Bandyopadhyay, D.; Banik, B.K. A highly efficient bismuth salts-catalyzed route for the synthesis of α-aminophosphonates. *Mole*cules, **2010**, *15*, 8205-8213.

[30] Hou, J.T.; Gao, J.W.; Zhang, Z.H. $NbCl_5$: An efficient catalyst for one-pot synthesis of α-aminophosphonates under solvent-free conditions. *Appl. Organomet. Chem.*, **2011**, *25*, 47-53.

[31] Mulla, S.A.R.; Pathan, M.Y.; Chavan, S.S.; Gample, S.P.; Sarkar, D. Highly efficient one-pot multi-component synthesis of α-aminophosphonates and bis-α-aminophosphonates catalyzed by heterogeneous reusable silica supported dodecatungstophosphoric acid (DTP/SiO_2) at ambient temperature and their antitubercular evaluation against Mycobacterium tuberculosis. *RSC Adv.* **2014**, 4, 7666-7672.

[32] Pudovik, A.N.; Pudovik, M.A. Synthesis of esters of phosphonic and thiophosphonic acids. XL. Addition of acid phosphites, diphosphites, and phenylphosphine to unsaturated electrophilic reagents containing one or two double bonds. *Zh. Obshch. Khim.*, **1963**, *33*, 3353-3358.

[33] Li, J.; Li, H.; Liu, G.; Qiu, J.; Guo, H.; Zhang, Y. Green synthesis and antimicrobial activity of 1,4-phenyl bis(aminophosphonates). *Huaxue Tongbao*, **2011**, *74*, 159-163.

[34] Milen, M.; Abranyi, B.P.; Kangyal, R.; Dancso, A.; Frigyes, D.; Keglevich, G., T3P-Mediated One-Pot Synthesis of Bis(α-aminophosphonates). *Heteroat. Chem.* **2014**, *25*, 245-255.

[35] Eshghi, H.; Mirzaei, M.; Hasanpour, M.; Mokaber, E.M. Benzimidazolium dicationic ionic liquid as an efficient and reusable catalyst for the synthesis of α-aminophosphonates and bis (α-aminophosphonates) under solvent-free condition. *Phosphorus, Sulfur Silicon Relat. Elem.* **2015**, *190*, 1606-1620.

[36] Fang, Z.; Liu, Y.; Zhang, Y.; Cao, Z. Polyphosphonate intumescent flame retardant and its manufacture method. Patent: CN103073727A
[37] Xu, K.; Liu, H.; Chen, M.; Su, J.; Cai, H. Method for preparing phosphorus-containing hydroquinone derivative and phosphorus-containing fire-resistant epoxy resin. Patent: CN101830929A
[38] Failla, S.; Finocchiaro, P.; Hagele, G.; Kalchenko, V.I., *α*-Aminophosphonates bearing free hydroxyl groups in the aromatic rings. Synthesis and NMR characterization. *Phosphorus, Sulfur Silicon Relat. Elem.*, **1997**, 128, 63-77.
[39] Krishnammagari Suresh Kumar, Balam Satheesh Krishna, Chinnapareddy Bhupendra Reddy, Mudumala Veeranarayana Reddy, Cirandur Suresh Reddy, Solvent-free synthesis of α-aminophosphonates: Cellulose-SO_3H as an efficient catalyst. (Published online, 10.1016/j.arabjc.2012.09.009)
[40] Choi, C.W.; Kim, S.C.; Hwang, S.S.; Choi, B.K.; Ahn, H.J.; Lee, M.Y.; Park, S.H.; Kim, S.K.; Antioxidant activity and free radical scavenging capacity between Korean medicinal plants and flavonoids by assay-guided comparison. *Plant Sci.* **2002**, *163*, 1161-1168.
[41] Shirwaiker, A.; Rajendran, K.; Kumar, C.D. *In vitro* antioxidant studies of *Annona squaosa* Linn. leaves. *Indian J. Expl. Biol.* **2004**, *42*, 803-807.
[42] Yen, G.C.; Chen, H.Y. Antioxidant Activity of Various Tea Extracts in Relation to Their Antimutagenicity. *J. Agr. Food Chem.*, **1995**, *43*, 27-32.