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Green Synthesis and Antiviral Activity of Novel Triarylmethane Derivatives *via* Friedel-Crafts Alkylation by Polyethylene Glycol (PEG-400)

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A series of novel triarylmethane derivatives (**3a-j**) were synthesized by a one-pot, two-component method *via* Friedel-Crafts alkylation of various electron-rich arenes (**1a-j**) with a wide variety of aldehydes (**2a-j**) in presence of the polyethylene glycol (PEG-400) as a green solvent at 50-60 °C in good to excellent yields (76-96 %). Their structures were confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry and elemental analysis. All the triarylmethanes were tested and evaluated for their antiviral and antifungal activities. Compounds **3b**, **3f**, **3g** and **3i** exhibited highest antiviral activities against tobacco mosaic virus (TMV).

Keywords: Triarylmethanes, Friedel-Crafts alkylation, Green synthesis, Antiviral activity.

INTRODUCTION

Viral plant diseases can be found worldwide and are a serious threat to modern agriculture. Although, plant viruses are genetically rather simple, they are difficult to prevent or control and have devasting impact on crop growth. So plant virus is a type of plant disease, known as "plant cancer". In recent years, the impact of climate anomalies and the areas of crops affected by plant virus disease are on the rise resulting in tremendous economic losses in the world. The tobacco mosaic virus (TMV) is one of the most important classes of common diseases occurring in tobacco growing all over the world. This virus seriously affects the quality and yield of tobacco. It is estimated that each year an economic loss worth one billion U.S. dollars [1] is encountered worldwide only by the prevalence of tobacco mosaic virus disease in agricultural fields. As a result, development of efficient, environmentally friendly antiviral agents through chemical synthesis has become the core area of research for eradication of and/or prevention of attack by tobacco mosaic virus. Ningnanmycin can inhibit virus replication effectively and suppress virus symptoms.

Friedel-Crafts alkylation is one of the important C-C bond forming reactions in organic chemistry [2]. These reactions are usually assisted by either protic acids or Lewis acid catalysts. Triarylmethanes (TRAMs) have attracted considerable attention [3] due to their varied biological activity as antiviral [4], antitumour [5], antitubercular [6], antifungal [7], anti-inflammatory agents [7]. Moreover, these compounds have found widespread application in the chemical industry [8]. Methods for the synthesis of triarylmethanes have been developed [9,10] which centred mainly on Friedel-Crafts alkylation of electron-rich arenes with aldehydes using $AuCl_3$/AgOTf [11], $[Ir(COD)Cl]_2$-$SnCl_4$ [12], $Cu(OTf)_2$ and $Sc(OTf)_3$ [13] as the Lewis acids. However, the quest for low-cost, environmentally friendly catalysts and mild reaction conditions in which to synthesize these compounds remains a major challenge. Polyethylene glycol (PEG) is a biodegradable polymer used in several organic transformations as catalyst and medium. Polyethylene glycol has received growing attention in the field of green chemistry because of its excellent features such as non-toxic, inexpensive, easily recoverable and thermally stable [14].

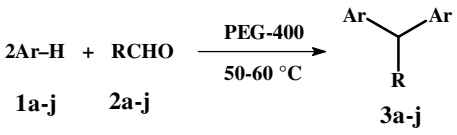
In this contribution, we disclose a highly efficient and practical synthesis of triarylmethanes (TRAMs) derivatives from aromatic aldehydes and electron-rich arenes by using polyethylene glycol (PEG-400) as a recyclable reaction medium *via* Friedel-Crafts alkylation. Mild reaction conditions and using an environmental-friendly solvent make this transformation an attractive option for the straight forward preparation of triarylmethanes. In addition, all the triarylmethanes were evaluated for antiviral activity.

EXPERIMENTAL

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. All reagents were from Sigma-Aldrich and were used without further purification.

Thin-layer chromatography (TLC) was performed using Merck aluminium-backed plates (Kieselgel 60 F_{254}) and visualization was achieved by UV light. Crude products were purified by column chromatography on silica gel of 60-120 mesh. The infrared spectra were recorded on a Perkin-Elmer FT-IR 240C spectrophotometer using KBr optics. NMR spectra were recorded in $CDCl_3$ on a Bruker 300 MHz spectrometer for ^1H NMR and ^{13}C NMR using tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are expressed in parts per million (ppm) and coupling constants (*J*) in hertz (Hz). Mass spectra were recorded on an ESI-MS mass spectrometer and elemental analysis was performed on a Thermo Finnegan instrument.

General procedure for the synthesis of triarylmethane derivatives (3a-j): To a 50 mL round bottomed flask, 1,3-dimethoxybenzene (**1a**, 2 mol), benzaldehyde (**2a**, 1 mol) and PEG-400 (15 mL) were successively added and then the mixture was magnetically stirred at 50-60 °C for the appropriate time specified in **Scheme-I**. The progress of the reaction was monitored by thin-layer chromatography (TLC) (ethyl acetate: hexane, 3:7). After completion of the reaction, the crude mixture was worked up in ice-cold water. The product that separated out was filtered and the filtrate was evaporated to remove water, leaving behind polyethylene glycol. The same polyethylene glycol was utilized to synthesize further triarylmethane derivatives. The resulting product, though seen as a single compound by TLC, was further purified by passing it over a column of silica gel (60-120 mesh) using ethyl acetate: hexane (3:7) as an eluent to afford the analytically pure compound, 4,4'-(phenylmethylene)*bis*(1,3-dimethoxy-benzene) (**3a**)**.** All other compounds **3b-j** were synthesized according to the same experimental procedure.



Scheme-I: Synthesis of novel triarylmethanes (**3a-j**)

4,4'-(Phenylmethylene)*bis*(1,3-dimethoxybenzene) (3a): White solid; yield 95 %; m.p. 142-144 °C; IR (KBr, ν_{max}, cm^{-1}): 3081, 2928, 1615, 1525, 1500, 1349, 1200, 830; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.49 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 7.0 Hz, 2H), 6.68 (d, *J* = 8.3 Hz, 1H), 6.45 (d, *J* = 2.4 Hz, 2H), 6.36 (dd, *J* = 2.4 Hz, 8.3 Hz, 2H), 6.01 (s, 1H), 3.77 (s, 6H), 3.67 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 159.0, 157.9, 144.5, 133.7, 130.3, 130.1, 129.0, 128.4, 127.7, 125.5, 125.2, 103.2, 98.6, 55.5, 55.1, 42.0; ESI-MS: (*m/z,* %): 387 (M+Na, 95); Anal. calcd. for $C_{23}H_{24}O_4$: C, 75.80; H, 6.64. Found: C, 75.69; H, 6.67.

4,4'-[(2-Methoxyphenyl)methylene]*bis*(1,3-dimethoxy-benzene) (3b): White solid; yield 76 %; m.p. 137-139 °C; IR (KBr, ν_{max}, cm^{-1}): 3087, 2931, 1618, 1520, 1504, 1353, 1206, 837; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.14-7.19 (m, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 7.4 Hz, 1H), 6.75 (dd, *J* = 1.6 Hz, 7.6 Hz, 2H), 6.64 (d, *J* = 8.3 Hz, 2H), 6.44 (d, *J* = 2.4 Hz, 2H), 6.33 (dd, *J* = 2.4, 8.3 Hz, 2H), 6.23 (s, 1H), 3.77 (s, 6H), 3.69 (s, 3H), 3.66 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 158.9, 157.9, 157.1, 133.0, 129.7, 129.3, 126.7, 125.0, 119.7, 110.5, 103.1, 98.5, 55.6, 55.5, 55.0, 35.7; ESI-MS: (*m/z*, %): 394 (M^+, 100); Anal. calcd. for $C_{24}H_{26}O_5$: C, 73.08; H, 6.64. Found: 73.19; H, 6.58.

4-[*Bis*(2,4-dimethoxyphenyl)methyl]phenol (3c): White solid; yield 79 %; m.p. 161-163 °C; IR (KBr, ν_{max}, cm^{-1}): 3089, 2923, 1618, 1522, 1507, 1340, 1210, 836; ^1H NMR ($CDCl_3$, 300 MHz): δ 9.86 (s, 1H), 7.81(d, *J* = 8.6 Hz, 2H), 6.96 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.3 Hz, 1H), 6.66-6.71 (m, 3H), 6.45 (d, *J* = 2.4 Hz, 1H), 6.36 (dd, *J* = 2.4 Hz, 1H), 5.94 (s, 1H), 3.78 (s, 6H), 3.67 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 162.3, 160.6, 158.9, 157.8, 153.4, 136.3, 132.6, 130.2, 130.1, 125.7, 116.0, 114.7, 106.1, 103.6, 98.9, 55.6, 55.2, 41.2; ESI-MS: (*m/z*, %): 403 (M+Na, 100); Anal. calcd. for $C_{23}H_{24}O_5$: C, 72.61; H, 6.36. Found: C, 72.55; H, 6.41.

4,4'-[(3-Nitrophenyl)methylene]*bis*(1,3-dimethoxy-benzene) (3d): Yellow solid; yield 91 %; m.p. 153-155 °C; IR (KBr, $\nu_{max,}$ cm^{-1}): 3079, 2922, 1611, 1528, 1507, 1352, 1203, 827; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.14-8.16 (m, 4H), 7.06 (d, *J* = 7.1 Hz, 2H), 6.55 (s, 2H), 6.42 (s, 2H), 6.07 (s, 1H), 3.89 (s, 6H), 3.63 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 151.4, 147.8, 144.1, 142.5, 128.8, 127.8, 125.6, 124.3, 114.4, 98.1, 58.8, 55.8, 42.3; ESI-MS :*m/z*, %): 432 (M+Na, 95); Anal. calcd. for $C_{23}H_{23}NO_6$: C, 67.47; H, 5.66; N, 3.42. Found: C, 67.52; H, 5.57; N, 3.48.

4,4'-[(4-Methoxyphenyl)methylene]*bis*(1,3-dimethoxy-benzene) (3e): White solid; yield 81 %; m.p. 134-136 °C; IR (KBr, ν_{max}, cm^{-1}): 3085, 2921, 1622, 1523, 1505, 1346, 1206, 827; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.38-6.44 (m, 2H), 6.20-6.24 (m, 2H), 6.12-6.18 (m, 2H), 5.88-5.92 (m, 2H), 5.78-5.83 (m, 2H), 5.44 (s, 1H), 3.19 (s, 6H), 3.18 (s, 3H), 3.10 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 158.9, 157.6, 157.2, 136.2, 129.9, 129.7, 125.2, 112.9, 103.1, 98.3, 55.1, 54.7, 54.6, 41.0); ESI-MS: (*m/z*, %): 394 (M^+, 100); Anal. calcd. for $C_{24}H_{26}O_5$: C, 73.08; H, 6.64. Found: C, 73.11; H, 6.73.

4-[*Bis*(2,4-dimethoxyphenyl)methyl]benzonitrile (3f): White solid; yield 96 %; m.p. 169-171 °C; IR (KBr, ν_{max}, cm^{-1}): 3076, 2933, 1632, 1526, 1508, 1342, 1211, 834; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.51 (d, *J* = 8.3 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 2H), 6.62 (d, *J* = 8.3 Hz, 2H), 6.46 (d, *J* = 2.0 Hz, 2H), 6.37 (dd, *J* = 2.0 Hz, 8.3 Hz, 2H), 6.01 (s,1H), 3.78 (s, 6H), 3.67 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 159.4, 157.8, 159.8, 131.6, 130.2, 129.6, 123.4, 119.2, 109.2, 103.5, 98.6, 55.4, 55.1, 42.5; ESI-MS: (*m/z*, %): 389 (M^+, 100); Anal. calcd. for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95; N, 3.60. Found: C, 74.13; H, 5.85; N, 3.71.

2-[*Bis*(2,4-dimethoxyphenyl)methyl]naphthalene (3g): White solid; yield 90 %; m.p. 156-157 °C; IR (KBr, ν_{max}, cm^{-1}): 3077, 2932, 1640, 1528, 1506, 1354, 1206, 836; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.93-8.00 (m, 1H), 7.81 (t, *J* = 6.2 Hz, 1H), 7.69 (t, *J* = 7.1 Hz, 1H), 7.27-7.41 (m, 3H), 6.93 (s, 1H), 6.63-7.75 (m, 3H), 6.49 (d, *J* = 7.7 Hz, 2H), 6.28-6.34 (m, 2H), 3.75 (s, 6H), 3.68 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 159.1, 157.7, 140.9, 133.8, 131.9, 130.4, 128.3, 126.5, 125.5, 125.0, 124.7, 124.5, 103.3, 98.5, 55.5, 55.0, 38.1; ESI-MS: (*m/z*, %): 437 (M+Na, 90); Anal. calcd. for $C_{27}H_{26}O_4$: C, 78.24; H,6.32. Found: C, 78.33; H, 6.21.

2,2'-(Phenylmethylene)*bis*(1,3,5-trimethoxybenzene) (3h): White solid; yield 92 %; m.p. 165-137 °C; IR (KBr, ν_{max}, cm^{-1}): 3087, 2921, 1610, 1528, 1506, 1352, 1203, 828; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.12 (d, *J* = 7.7 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.05 (d, *J* = 6.7 Hz, 2H), 6.11 (s, 1H), 6.09 (s, 1H), 3.78 (s, 6H), 3.49 (s, 12H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 171.9, 159.9, 159.7, 159.0, 145.5, 133.6, 130.0, 129.2, 128.3, 127.6, 126.8, 124.4, 114.1, 92.7, 91.7, 55.9, 55.1, 54.9, 36.9; ESI-MS: (*m/z*, %): 424 (M^+, 95); Anal. calcd. for $C_{25}H_{28}O_6$: C, 70.74; H, 6.65. Found: C, 70.78; H, 6.71.

5,5'-[(3-Nitrophenyl)methylene]*bis*(1,2,4-trimethoxybenzene) (3i): Yellow solid; yield 95 %; m.p. 148-150 °C; IR (KBr, ν_{max}, cm^{-1}): 3078, 2929, 1616, 1522, 1507, 1344, 1205, 833; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.14-7.26 (m, 4H), 6.55 (s, 2H), 6.42 (s, 2H), 6.07 (s, 1H), 3.89 (s, 6H), 3.66 (s, 6H), 3.63 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 151.4, 147.8, 144.1, 142.5, 128.8, 127.8, 125.6, 124.3, 114.4, 98.1, 58.8, 55.8, 42.3; ESI-MS: (*m/z*, %): 492 (M+Na, 95); Anal. calcd. for $C_{25}H_{27}NO_8$: C, 63.96; H, 5.80; N, 2.80. Found: C, 63.92; H, 5.72; N, 2.84.

2,2'-[(3-Chlorophenyl)methylene]*bis*(1,3,5-trimethoxybenzene) (3j): White solid; yield 84 %; m.p. 159-162 °C; IR (KBr, ν_{max}, cm^{-1}): 2933, 2832, 1593, 1461, 1379, 1348, 1211, 1174, 1039, 955, 817; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.10-7.06 (m, 2H), 7.03-6.94 (m, 2H), 6.18 (s, 1H), 6.11 (s, 4H), 3.79 (s, 6H), 3.53 (s, 12H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 159.6, 159.4, 148.2, 131.9, 127.8, 127.1, 125.4, 124.0, 113.0, 91.4, 55.8, 55.2, 36.7; ESI-MS: (*m/z*, %): 492 (M+Na, 95); Anal. calcd. for $C_{25}H_{27}O_6Cl$: C, 65.43; H, 5.93. Found: C, 65.53; H, 5.81.

Antiviral bioassay

Purification of tobacco mosaic virus (TMV): Using Gooding's method [15], upper leaves of *Nicotiana tabacum L* inoculated with tobacco mosaic virus were selected and ground in phosphate buffer, then filtered through a double-layer pledget. The filtrate was centrifuged at 10,000 g, treated with polyethylene glycol and centrifuged again. The whole experiment was carried out at 4 °C. Absorbance values were measured at 260 nm using an ultraviolet spectrophotometer.

$$\text{Virus concentration} = \frac{(A_{260} \times \text{Dilution ratio})}{E_{1cm}(0.1\,\%, 260\text{ nm})} \times 100$$

Curative effect of compounds against tobacco mosaic virus *in vivo*: Growing leaves of *Nicotiana tabacum L* of the same age was selected. Tobacco mosaic virus (concentration of 6×10^{-3} mg/mL) was dipped and inoculated on the whole leaves, which were then washed with water and dried. The compound solution was smeared on the left side and the solvent was smeared on the right side for control. The local lesion numbers were counted and recorded 3-4 days after inoculation [16]. For each compound, three repetitions were measured. The rates of inhibition for the compounds **3a-i** are shown in Table-1. The inhibition rates of the compounds were then calculated according to the following formula:

$$\text{Inhibition rate } (\%) = \frac{A - B}{A} \times 100$$

where, A = Average local lesion numbers of control (not treated with compound; B = Average local lesion numbers smeared with drugs.

RESULTS AND DISCUSSION

The reaction of various electron-rich arenes **1a-j** with a wide variety of aldehydes **2a-j** in the presence of PEG-400 by one-pot, two-component method *via* Friedel-Crafts alkylation at 50-60 °C led to the formation of triarylmethane derivatives **3a-j** in good to excellent yields (**Scheme-I**).

Previously, toxic solvents such as chloroform, dichloromethane and benzene have been used in the synthesis of triarylmethanes (TRAMs). Polyethylene glycol has gained importance as a 'green' reaction medium in view of environmental perception [17]. In this perspective, polyethylene glycol has become a 'green' solvent as an alternative reaction medium to perform organic synthesis due to its inherent advantages over toxic solvents. Furthermore, polyethylene glycol is inexpensive, easy to handle, thermally stable, non-toxic and recyclable. As depicted in **Scheme-I**, the nature of substituents on the aromatic aldehyde molecules has a significant effect on the yields and time of the reactions. In the presence of PEG-400, various electron-rich arenes reacted with a number of aromatic aldehydes. The aromatic aldehydes with electron-withdrawing groups such as NO_2, CN and CHO increased the yields and reduced the reaction times (**Scheme-I**), whereas electron-donating substituents such as the OH and OCH_3 groups behaved differently in the synthesis of triarylmethanes (**Scheme-I**).

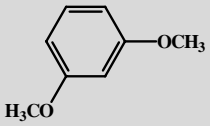
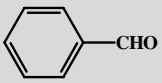
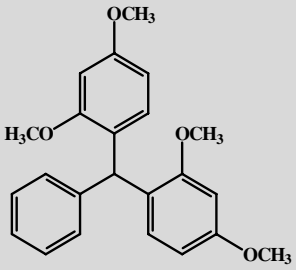
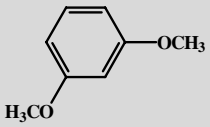
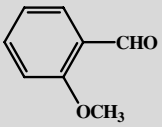
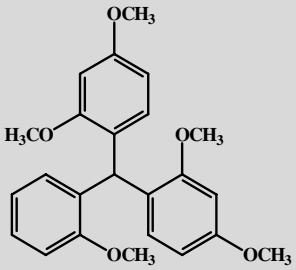
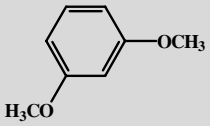
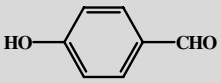
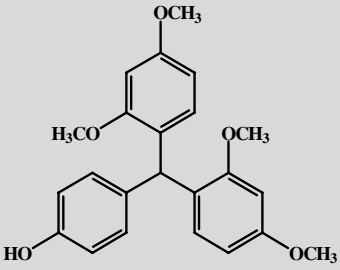
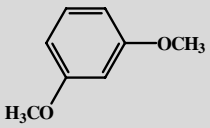
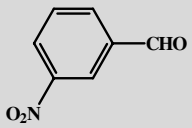
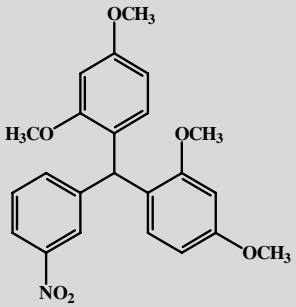
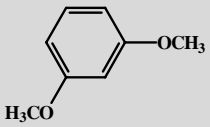
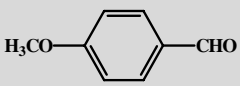
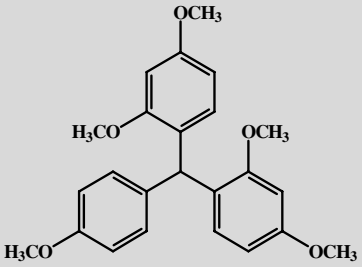
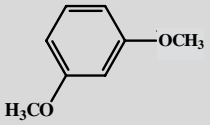
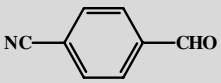
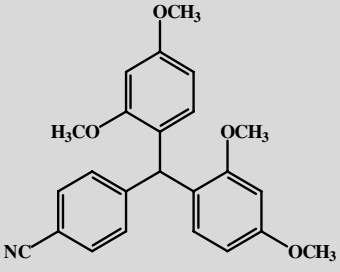
The chemical structures of all the triarylmethanes **3a-j** were confirmed by elemental analysis, IR, ^1H NMR, ^{13}C NMR and mass spectral data. All the compounds displayed characteristic IR stretching absorptions at 3089, 2931, 1618, 1522 and 1504 cm^{-1} respectively. The ^1H and ^{13}C NMR spectral data for all compounds **3a-j** showed characteristic chemical shifts in the expected region. The ESI mass spectra of **3a-j** agreed with the proposed structures.

Antiviral activity: The newly synthesized derivatives **3a-j** were evaluated for their antiviral activity against tobacco mosaic virus (TMV) by Gooding and Hebert method [15]. It is clear that the compounds **3a-j** showed a certain degree of antiviral activity against tobacco mosaic virus (TMV). The structural modification caused by changing the substituents (R) on the aromatic aldehydes has a wide impact on antiviral activity of the final synthesized compounds. Among the compounds screened, **3b**, **3f**, **3g** and **3i** displayed high antiviral activities against the virus. The other compounds showed reasonably moderate to good antiviral activity (Table-2).

Conclusion

We have developed a mild and highly efficient one-pot protocol for the 'green' synthesis of triarylmethanes (TRAMs) from aromatic aldehydes and electron-rich arenes by using PEG-400 as a recyclable reaction medium and as a catalyst *via* Friedel-Crafts alkylation in good to excellent yields (76-96 %). Moreover, the compounds **3b**, **3f**, **3g** and **3i** displayed high antiviral activity against tobacco mosaic virus. Environmental acceptability, excellent yields, simple work-up procedure,

TABLE-1
SYNTHESIS OF NOVEL TRIARYLMETHANES (**3a-j**)

Compound	Ar-H	RCHO	Product	Time (h)	Yield (%)
3a				2	95
3b				3	76
3c				3	79
3d				2	91
3e				3	81
3f				2	96

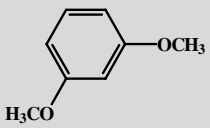
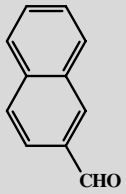
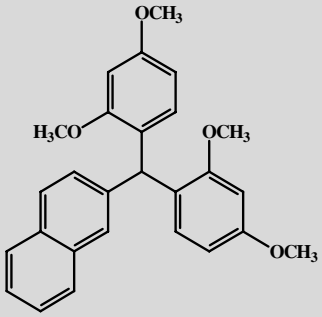
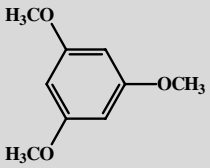
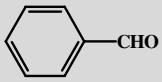
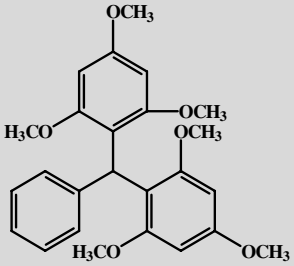
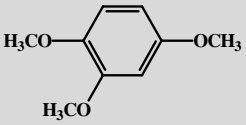
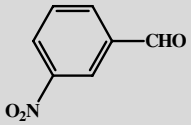
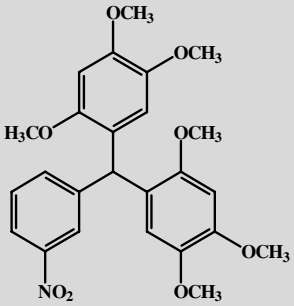
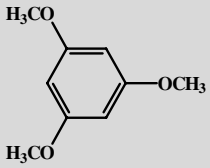
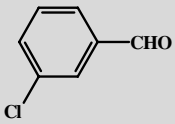
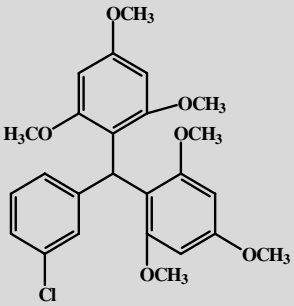
3g				2	90
3h				2	92
3i				2	95
3j				3	84

TABLE-2
ANTIVIRAL INHIBITORY ACTIVITY OF NOVEL TRIARYLMETHANES (**3a-j**) AGAINST TOBACCO MOSAIC VIRUS

Compound	Concentration (μg/mL)	Inhibition rate (%)
3a	0.5	37.21
3b	0.5	43.12
3c	0.5	35.67
3d	0.5	31.00
3e	0.5	36.22
3f	0.5	42.40
3g	0.5	44.08
3h	0.5	34.65
3i	0.5	41.19
3j	0.5	38.11
Ningnanmycin[a]	0.5	54.51

[a]Ningnanmycin was used a standard.

cleaner reaction profiles, eco-friendly solvent, shorter reaction time, inexpensive and recyclable non-ionic solvent are the additional notable features of this protocol to synthesize potentially useful antiviral products.

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