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Synthesis and evaluation of novel tetrapropoxycalix[4]arene enones and cinnamates for protection from ultraviolet radiation

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ABSTRACT

A series of novel calix[4]arene enones (**5–7**) and cinnamates (**12–14**) have been synthesized and evaluated for ensuring protection from ultraviolet radiation (UVR). Spectroscopic analyses has revealed that compound **6** absorbs ultraviolet radiations between 280 and 350 nm with an absorption maximum at 312 nm. Its molar absorption coefficient (ε) (>5×10^4 M^{-1} cm^{-1}) and bandwidth are larger than those for the commercially used sun protectants (oxybenzone (OB), 2-ethylhexyl 4-methoxycinnamate (OMC) and avobenzone). The *in vitro* Sun Protection Factor (SPF) measurement revealed an SPF of 5.2 at 2% concentration of **6** in home made emulsion formulations while combination of 2% each of **6** and OMC gave an SPF of 8.8. Lower sun protection seems to be compensated by significant protection from more harmful UVA radiations (UVA/UVB absorbance ratio of 0.62).

1. Introduction

Calix[*n*]arenes (*n* = 4–20) are phenolic $[1]_n$-metacyclophanes in which phenolic units are interlinked through methylene bridges [1]. They have attracted considerable attention due to their utility in diverse areas [2,3], molecular separations [4,5] and sensing qualities [6–8]. These applications primarily result from their stable structure consisting of a distinct hydrophobic upper rim and a hydrophilic lower rim besides their ability to generate a number of structural and conformational isomers [9–11]. Calix[*n*]arenes can be functionally modified via derivatization of the upper-rim and the lower-rim [1,9]. Attaching substituents around the periphery of the upper rim of calix[4]arenes enhances the accommodative ability of these molecules [1,9,12]. With podand arms located close to the cavity, guest not only interact with the atoms at the periphery but possibly could also enter the cavity to make room for larger guest molecules and thus allowing opportunities for enhanced ionic and molecular recognition *via* utilization of external stimuli at the molecular level [1,9,12,13]. In this regard, calix[4]arenes appended with photosensitive moieties at their upper rim can provide light-triggered switches, ion-channel based biosensors and photomodulated devices [14–18]. For example, Vogtle et al. have reported the synthesis of photoresponsive doubly azobenzene chain substituted at the lower-rim of calix[4]arenes which undergo EZ photoisomerization and Z → E thermal isomerization [19]. Rojanathanes et al. [20] have reported photoswitchable calix[4]arene incorporating different regioisomers of stilbene and azobenzene. It has been observed that the stilbene bridged derivative isomerized only under UV irradiation while the azobenzene derivatives undergo thermal or photochemically induced isomerization [20].

Since calixarenes are high melting stable compounds with good chemical, radiation and thermal stability and relatively low toxicity, it was envisaged that suitable calixarene derivatives would either function as efficient sun-protectants to screen harmful ultraviolet radiations themselves or they can be used as carrier molecules to encapsulate established sun protectants.

As a part of above research objectives, we envisaged appropriate modification of the calix[4]arene aryl groups to ensure strong UVR absorption through introduction of the α,β-unsaturated ester and enone groups on the upper rim of calix[4]arene annulus as they are known to undergo light-induced reversible transformations. It was also anticipated that appropriate substitution at the upper rim of calix[4]arene annulus would not only provide a new class of UV-filters but would also promise a newer mechanism of protection from harmful ultraviolet radiations through the synergistic action of multiple chromophores and conformational motifs.

In this paper we present our preliminary results on novel sun protectants in the hope to eventually obtain sunscreen formulations with better efficacy, stability and compatibilities with or without other additives commonly employed for the intended application. They have a potential to be developed as designer sunscreens [21,22], since rapid conformational transformations in

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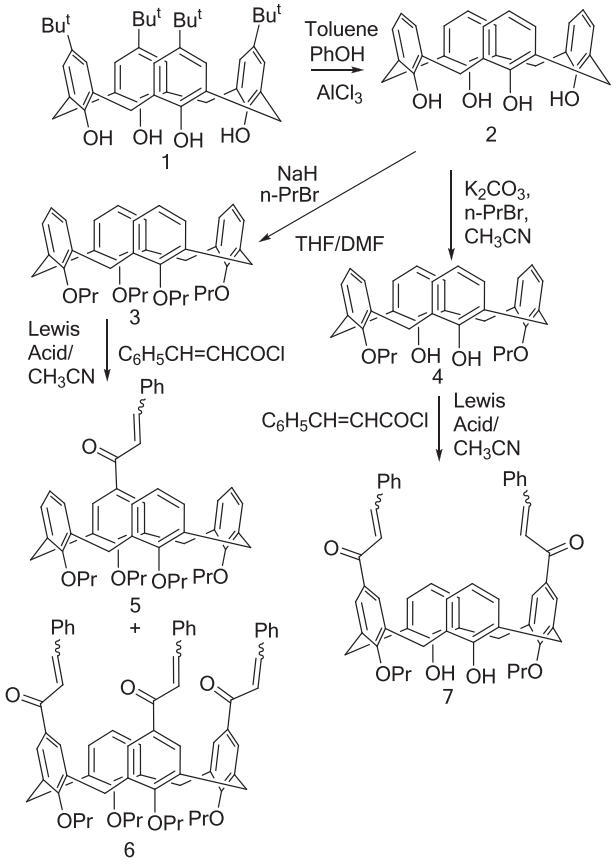
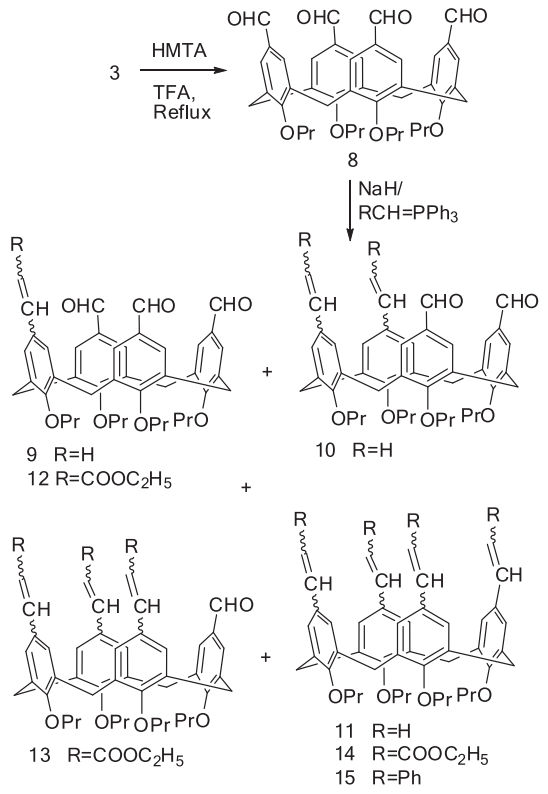
calix[*n*]arenes would allow dissipation of absorbed ultraviolet radiation.

Consequently, we have introduced photosensitive enones and cinnamates functionalities into the calixarene scaffold to yield derivatives which are structurally akin to commercially used sunscreen agent *trans*-2-ethylhexyl-4-methoxy cinnamate (*t*-EHMC). The parent *p-tert*-butylcalix[4]arene **1** was synthesized from *p-tert*-butyl phenol by a method reported by Gutsche et al. [23,24] followed by its debutylation by using $AlCl_3$/phenol under conditions reported by us and others [2,25–29]. Since propyl groups are known to immobilize the the calixarenes in a cone conformation, compound **2** was subjected to propylation under different conditions. Treatment of compound **2** with propyl bromide in the presence of K_2CO_3 gave the dipropyl calix[4]arene **4** while treatment with NaH in anhydrous THF/DMF gave the corresponding tetrapropyl derivative **3** (Scheme 1). The propyloxy calixarenes **3–4** were subjected to cinamoylation under different reaction conditions. For example, treatment of **3** with cinnamoyl chloride in the presence of stannic chloride afforded the di-cinnamoyl- and tri-cinnamoyl-tetrapropyloxycalix[4]arenes respectively. The treatment of **4** with cinnamoyl chloride and borontrifluoride diethyl etherate gave the mono-cinnamoyl dipropyloxycalix[4]arene **5**. Alkenylation of calix[4]arene tetraether (**3**) has been achieved *via* Wittig Olefination reaction which utilizes the tetraformyl calix[4]-arene derivatives **8** as the substrate. The significance and generality of the Wittig carbonyl olefination process in synthetic organic chemistry has prompted us to investigate it for obtaining alkenyl calix[4]arenes in their cone conformation (Scheme 2). Possible depropylation of tetrapropyloxy calix[4]arene was not observed during the reactions as determined by NMR experiments. The synthesized calix[4]arene alkene esters and enones were purified



Scheme 1. Synthetic route for the preparation of enone appended calix[4]arenes.



Scheme 2. Wittig Olefination reaction on formyl calix[4]arenes.

further by column chromatography and subjected to NMR analysis which revealed them to be present in their cone conformation (see experimental data).

2. Experimental

2.1. General

UV–visible spectra have been recorded on Lambda 35 UV/VIS spectrometer (Perkin Elmer, Inc. USA) with 10 mm quartz cells. The data was processed using UV WINLAB version 2.85.04 software. FT-IR spectra have been recorded on a [5-DX] Nicolet FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 300 MHz Bruker DPX 300 instrument at room temperature in deuterated solvents using tetramethylsilane (TMS) as an internal standard with the values of chemical shifts reported on a δ scale. FAB-mass spectra have been recorded on a JEOL SX 102/DA-6000 Mass Spectrometer. Melting points were recorded on an electric melting-point apparatus (Toshniwal, India) and are uncorrected. Analytical HPLC procedures were performed using a liquid chromatograph equipped with 2487 Dual λ absorbance detector and 600 Controller (Waters, Milford, MA, USA). The column used for the HPLC analysis was a 5 μ Spherisorb® ODS2 column (4.6 mm × 250 mm I.D., Waters Corp.) with an inline pre-filter. Data processing was accomplished by using a personal computer equipped with Empower™ personal software.

2-Ethylhexyl 4-methoxycinnamate (98%) and oxybenzone (⩾96%) were purchased from Aldrich and Fluka respectively. Sample of Arlacel P 135, Arlamol M812 were procured from ICI India Limited (Mumbai) and titanium dioxide from Whittaker Clark & Daniel (supplied by Colorcon). HPLC-grade tetrahydrofuran was purchased from E. Merck (India). Lewis acids ($TiCl_4$, $SnCl_4$, BBr_3), cinnamoyl chloride, sodium bicarbonate, potassium fluoride, sodium sulfate, citric acid, isopropyl palmitate and mineral oil were

obtained from Sigma Aldrich. Sunscreens (named in the text as A, B, C, D, E, F and G) were commercial samples purchased from the local markets. Other ingredients used in the preparation of emulsions were of high purity.

2.2. Synthesis

p-tert-Butylcalix[4]arene **1** and its debutylated analog **2** were synthesized by the method described in literature [23,24]. Calix[4]-arene formylated derivative **8** was synthesized according to the procedure reported by Chawla et al. [25,30]. The phosphonium salts were prepared by refluxing stoichiometric amounts of triphenylphosphine and alkyl halide in toluene for 30 min^{-1} h.

2.2.1. 25,26,27,28-Tetrapropoxycalix[4]arene (**3**)

To a suspension of 5.8 g of NaH (0.15 mol) in 150 mL of anhydrous DMF was added 3.0 g of tetrahydroxycalix[4]arene **2** (7.1 mmol). After the mixture was stirred for 15 min at 70 °C, alkyl halide (77 mmol) was added. The reaction mixture was stirred for an additional 1 h at 70 °C, cooled to room temperature and then quenched by dropwise addition of methanol. After removal of solvent under reduced pressure, 150 mL of water was added followed by stirring for 10 min. The crude product was washed with methanol and recrystallized from acetone or chloroform and methanol to give the calixarene **3,** m.p. 192 °C. FAB-MS: *m*/*z* 592.80; found = 593 [M^+, 100%]; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm): 0.96 (t, 12H, *J* = 7.6 Hz, C<u>H</u>$_3$), 1.85 (m, 8H, OCH$_2$C<u>H</u>$_2$), 3.02 (d, 4H, *J* = 13.3 Hz, ArC<u>H</u>$_2$Ar), 3.81 (t, 4H, *J* = 6.6 Hz, OC<u>H</u>$_2$), 4.42 (d, 4H, *J* = 13.1 Hz, ArC<u>H</u>$_2$Ar), 6.53 (m, 12H, Ar<u>H</u>).

2.2.2. 25,27-Bis-propyloxy-26,28-dihydroxy-calix[4]arene (**4**)

To a suspension of tetrahydroxycalix[4]arene **2** (3.0 g, 7.1 mmol) in CH_3CN (200 mL) were added 1-bromopropane (2.56 g, 28.2 mmol) and K_2CO_3 (3.9 g, 28.2 mmol) and the reaction mixture was refluxed with stirring for 24 h. The solvent was evaporated, the residue taken up with CH_2Cl_2 (100 mL), and the organic phase separated and washed twice with HCl (10%) and then with water. Evaporation of the organic phase afforded a solid which when recrystallized (CH_2Cl_2–MeOH) gave diether calixarene **4** as white crystals (87% yield). m.p. 268–270 °C. FAB-MS: *m*/*z* 508.65; found = 508 [M^+, 100%]; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm): 1.31 (t, 6H, *J* = 7.3 *Hz*, C<u>H</u>$_3$), 2.07 (quintet, 4H, OCH$_2$C<u>H</u>$_2$CH$_3$), 3.37 (d, 4H, *J* = 13.1 Hz, ArC<u>H</u>$_2$Ar), 3.97 (t, 4H, *J* = 6.5 Hz, OC<u>H</u>$_2$), 4.32 (d, 4H, *J* = 13.2 Hz, ArC<u>H</u>$_2$Ar), 6.74 (t, 2H, *J* = 7.1 Hz, Ar<u>H</u>), 6.64 (t, 2H, *J* = 7.0 Hz, Ar<u>H</u>), 6.92 (d, 4H, *J* = 7.2 Hz, Ar<u>H</u>), 7.05 (d, 4H, *J* = 7.7 Hz, Ar<u>H</u>), 8.61 (s, 2H, D_2O exch. O<u>H</u>), ^{13}C NMR ($CDCl_3$, δ): 153.3, 151.9, 133.4, 128.9, 128.4, 128.1, 125.2, 78.2, 31.4, 23.4, 10.8.

2.2.3. 5-Mono(3-phenyl-2-propenoyl)-25,26,27,28-tetrapropoxycalix[4]arene (**5**)

Calix[4]arene **4** (0.1 g, 0.169 mmol) was dissolved in 50 mL of dry $CHCl_3$. $BF_3{\cdot}Et_2O$ (0.42 mL, 3.37 mmol) and cinnamoyl chloride (0.31 g, 1.86 mmol) were diluted with 5 mL of $CHCl_3$ and the solution was added to the calixarene solution at room temperature. Reaction mixture was stirred further for 72 h at room temperature. A saturated solution of $NaHCO_3$ and KF was added and the mixture was stirred for 30 min. The biphasic mixture was decanted into a separatory funnel and the organic layer was separated. The organic layer was washed with saturated mixture of $NaHCO_3$ and KF thrice followed by washing with distilled water. The solution was dried over Na_2SO_4 and the solvent was removed *in vacuo* to obtain the oily product. Precipitation with $CHCl_3$–MeOH allowed the isolation of a pale yellow precipitate of calixarene **5** (63% yield). m.p. 165 °C. FAB-MS: *m*/*z* calcd. 722.95; found 723 [M^+]; Anal. calcd. for $C_{49}H_{54}O_5$: C 81.41, H 7.53; found: C 81.43, H 7.57; IR (KBr, cm^{-1}): 1690 cm^{-1} ($\nu_{c=o}$), 1634 ($\nu_{c=c}$); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm): 0.87 (m, 12H, C<u>H</u>$_3$), 1.82 (m, 8H, C<u>H</u>$_2$), 3.06 (dd, 4H, *J* = 13.3 Hz, ArC<u>H</u>$_2$Ar), 3.69 (m, 8H, OC<u>H</u>$_2$), 4.32 (t, 4H, *J* = 10.3 Hz, ArC<u>H</u>$_2$Ar), 6.24 (d, *J* = 6.99 Hz, 2H, CH=C<u>H</u> + Ar<u>H</u>), 6.53 (m, 7H, Ar<u>H</u> + CH=C<u>H</u>), 7.03 (s, 2H, Ar<u>H</u>), 7.34 (m, 3H, Ar<u>H</u>), 7.44 (m, 4H, Ar<u>H</u>). ^{13}C NMR: (300 MHz, $CDCl_3$): δ 10.16, 10.41, 23.27, 29.67, 30.93, 77.42, 117.13, 121.79, 122.09, 122.03, 127.30, 127.85, 128.14, 128.65, 128.89, 129.48, 130.67, 133.71, 134.61, 135.27, 135.69, 137.96, 143.01, 146.90, 156.0.

2.2.4. 5,11,17-tris(3-phenyl-2-propenoyl)-25,26,27,28-tetrapropoxycalix[4]arene (**6**)

Calix[4]arene **3** (0.10 g, 0.17 mmol) was dissolved in 50 mL of dry $CHCl_3$. $SnCl_4$ (0.31 mL, 1.689 mmol) and cinnamoyl chloride (0.32 g, 1.94 mmol) were diluted with 5 mL of $CHCl_3$ and the solution was added to the calixarene solution at room temperature. Reaction mixture was stirred further for 15 h at room temperature following which the product was obtained as above by precipitation with $CHCl_3$–MeOH to give a yellow precipitate of calixarene **6** (25% yield). m.p. 125 °C. FAB-MS *m*/*z* calcd. 982.48; found 982 [M^+, 100%]; Anal. calcd. for $C_{67}H_{66}O_7$: C 81.84, H 6.77; found: C 81.80, H 6.67; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm): 0.87 (m, 12H, C<u>H</u>$_3$), 1.82 (m, 8H, C<u>H</u>$_2$), 3.06 (dd, 4H, *J* = 13.3 Hz, ArC<u>H</u>$_2$Ar), 3.69 (m, 8H, OC<u>H</u>$_2$), 4.32 (t, 4H, *J* = 10.3 Hz, ArC<u>H</u>$_2$Ar), 6.13–7.44 (m, 30H, Ar<u>H</u> + CH=C<u>H</u>). ^{13}C NMR: (300 MHz, $CDCl_3$): δ 10.83, 10.91, 23.43, 29.77, 31.28, 78.45, 121.69, 122.26, 122.52, 125.56, 127.48, 128.11, 128.24, 128.31, 128.65, 128.90, 128.94, 129.44, 130.49, 132.53, 134.99, 136.13, 136.47, 137.10, 144.26.

2.2.5. 5,17-Bis(3-phenyl-2-propenoyl)-25,27-dipropoxy calix[4]arene (**7**)

Calix[4]arene **4** (0.10 g, 0.17 mmol) was dissolved in 50 mL of dry $CHCl_3$. $SnCl_4$ (0.31 mL, 1.69 mmol) and cinnamoyl chloride (0.28 g, 1.69 mmol) were diluted with 5 mL of $CHCl_3$ and the solution was added to the calixarene solution at room temperature. Reaction mixture was stirred further for 15 h at room temperature following which the product was obtained as above by precipitation with $CHCl_3$–MeOH to give a yellow precipitate of calixarene **7** (45% yield). m.p. 120 °C. FAB-MS: *m*/*z* calcd. 768.93; found 769 [M^+, 100%]; Anal. calcd. for $C_{52}H_{48}O_6$: C 81.22, H 6.29; found: C 81.21, H 6.30; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm): 1.32 (t, 6H, *J* = 7.41 Hz, C<u>H</u>$_3$), 2.06 (m, 4H, C<u>H</u>$_2$), 3.50 (d, 4H, *J* = 13 Hz, ArC<u>H</u>$_2$Ar), 4.01 (t, 4H, *J* = 5.88 Hz, OC<u>H</u>$_2$), 4.31 (d, 4H, *J* = 13.02 Hz, ArC<u>H</u>$_2$Ar), 6.81 (d, 2H, *J* = 7.5 Hz, C<u>H</u>=CH), 6.99 (d, 2H, *J* = 7.5 Hz, CH=C<u>H</u>), 7.41 (m, 10H, Ar*H* (enone ring)), 7.57 (m, 2H, Ar<u>H</u>), 7.65 (m, 4H, Ar<u>H</u>), 7.85 (s, 4H, Ar<u>H</u>), 9.12 (s, 4H, O<u>H</u>). ^{13}C NMR: (300 MHz, $CDCl_3$): δ 10.86, 23.45, 29.77, 31.39, 78.48, 1222.23, 125.535, 128.28, 128.85, 129.81, 130.14, 132.60, 143.52, 146.74, 151.70, 158.38.

2.2.6. General procedure for Wittig Olefination reaction

A mixture of phosphonium salt (stoichiometric amount) and NaH (6.99 mmol) in 20 mL of CH_2Cl_2 was refluxed for 30 min. This was followed by addition of 25,26,27,28-tetrapropoxycalix[4]arene (0.1 g, 0.17 mmol) in THF (50 mL) to the above mixture. The reaction mixture was refluxed and monitored by TLC. On completion of the reaction, the reaction was quenched with 20 mL of 1% HCl solution in water and stirred for 1 h. The organic layer was extracted with CH_2Cl_2 (2 × 50 mL) and washed with water thrice. The combined CH_2Cl_2 layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to yield an oily residue which was subjected to purification by column chromatography on silica gel.

2.2.7. Synthesis of 5-ethenyl-11,17,23-triformyl-25,26,27,28-tetrapropoxy calix[4]arene (**9**)

The reaction procedure described above was followed by using calix[4]arene **8** (0.10 g, 0.17 mmol) and methylidenetriphenyl phosphorane ylide (0.07 g, 0.17 mmol) affording a white solid

(0.046 g, 44% yield); m.p. 163–164 °C; Anal. calcd. for $C_{45}H_{50}O_7$: C 76.90, H 7.17; Found: C 76.91, H 7.18; FAB-MS: *m*/*z* calcd. 702.87; Found 703 [M^+, 100%]; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm): 0.99 (m, 12H, *J* = 3.5 Hz, C$\underline{H}_3$), 1.87 (m, 8H, *J* = 6.78 Hz, —C$\underline{H}_2$CH$_3$), 3.12 (m, 4H, ArC$\underline{H}_2$Ar), 3.89 (m, 8H, —OC$\underline{H}_2$), 4.37 (m, 4H, ArC$\underline{H}_2$Ar), 4.98 (d, H, *J* = 17.5 Hz, =C$\underline{H}_2$), 5.30 (d, H, *J* = 17.5 Hz, =C$\underline{H}_2$), 6.28 (m, H, C$\underline{H}$=CH$_2$), 6.61, 6.65, 7.15, 7.19 (s, 8H, Ar$\underline{H}$), 9.61 (s, 3H, C$\underline{H}$O). ^{13}C NMR: (300 MHz, $CDCl_3$): δ 10.16, 10.41, 23.27, 29.67, 30.93, 77.42, 117.13, 121.79, 122.09, 122.03, 127.30, 127.85, 128.14, 128.65, 128.89, 129.48, 130.67, 133.71, 134.61, 135.27, 135.69, 137.96, 143.01, 146.90, 156.0.

2.2.8. Synthesis of 5,11-bisethenyl-17,23,-diformyl-25,26,27,28-tetrapropoxy calix[4]arene (**10**)

The reaction procedure described above was followed by using calix[4]arene **8** (0.10 g, 0.17 mmol) and methylidenetriphenyl phosphorane ylide (0.20 g, 0.51 mmol) affording a white solid (0.04 g, 35% yield); m.p. 178 °C; Anal. calcd. for $C_{46}H_{52}O_6$: C 78.83, H 7.48; found: C 78.89, H 7.50; FAB-MS: *m*/*z* calcd. 700.90; Found 701 [M^+, 100%]; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm): 0.99 (m, 12H, C$\underline{H}_3$), 1.87 (m, 8H, —C$\underline{H}_2$CH$_3$), 3.12 (m, 4H, ArC$\underline{H}_2$Ar), 3.8 (m, 8H, —OC$\underline{H}_2$), 4.37 (m, 4H, ArC$\underline{H}_2$Ar), 4.98 (d, 2H, *J* = 10.7 Hz, =C$\underline{H}_2$), 5.5 (d, 2H, *J* = 17.7 Hz, =C$\underline{H}_2$), 6.28 (m, 2H, C$\underline{H}$=CH$_2$), 6.61, 6.65, 7.15, 7.19 (s, 8H, Ar$\underline{H}$), 9.56 and 9.61 (s, 2H, C$\underline{H}$O).

2.2.9. Synthesis of 5,11,17,23-tetrakis(ethenyl)-25,26,27,28-tetrapropoxy calix[4]arene (**11**)

The reaction procedure described above was followed by using calix[4]arene **8** (0.10 g, 0.17 mmol) and methylidenetriphenyl phosphorane ylide (0.68 g, 1.69 mmol) affording a white solid (0.059 g, 53% yield); m.p. 350 °C (decomp.); Anal. calcd. for $C_{48}H_{56}O_4$: C 82.72, H 8.10; found: C 82.73, H 8.09; FAB-MS: *m*/*z* calcd. 696.96; found 697 [M^+, 100%]; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm): 0.95 (m, 12H, *J* = 7.0 Hz, C$\underline{H}_3$), 1.86 (m, 8H, —C$\underline{H}_2$CH$_3$), 3.1 (m, 4H, ArC$\underline{H}_2$Ar), 3.81 (t, 8H, *J* = 6.8 Hz, —OC$\underline{H}_2$), 4.38 (m, 4H, ArC$\underline{H}_2$Ar), 4.93 (d, 2H, *J* = 10.7 Hz, =C$\underline{H}_2$), 5.32 (d, 2H, *J* = 17.4 Hz, =C$\underline{H}_2$), 6.34 (m, 4H, C$\underline{H}$=CH$_2$), 7.25 (s, 8H, Ar$\underline{H}$). ^{13}C NMR (75 MHz, $CDCl_3$): 10.3, 23.1, 31.0, 76.7, 111.3, 126.1, 131.6, 134.8, 137.0, 156.5.

2.2.10. Synthesis of 5-(2-ethoxycarbonyl)ethenyl-11,17,23-triformyl-25,26,27,28-tetrapropoxy calix[4]arene (**12**)

The reaction procedure described above was followed by using calix[4]arene **8** (0.10 g, 0.17 mmol) and (ethoxycarbonylmethyl)-triphenylphosphonium bromide (0.07 g, 0.169 mmol) affording a white solid (0.02 g, 18% yield); m.p. 232–236 °C; Anal. calcd. for $C_{48}H_{54}O_9$: C 74.39, H 7.02; found: C 74.40, H 7.0; FAB-MS: *m*/*z* calcd. 774.94; found 775 [M^+, 100%]; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm): 0.78 (m, 12H, C$\underline{H}_3$), 0.92 (m, 3H, OCH$_2$C$\underline{H}_3$), 1.82 (m, 8H, —C$\underline{H}_2$CH$_3$), 3.17 (m, 4H, ArC$\underline{H}_2$Ar), 3.84 (m, 2H, —COOC$\underline{H}_2$), 4.19 (m, 8H, —OC$\underline{H}_2$), 4.37 (m, 4H, ArC$\underline{H}_2$Ar), 6.02 (m, H, =C$\underline{H}$), 6.69 (d, H, *J* = 15.9 Hz, C$\underline{H}$=), 7.02, 7.09 and 7.15 (s, 8H, Ar$\underline{H}$), 9.48 and 9.55 (s, 3H, C$\underline{H}$O).

2.2.11. Synthesis of 5,11,17-tris(2-ethoxycarbonyl)ethenyl-23-formyl-25,26,27,28-tetrapropoxy calix[4]arene (**13**)

The reaction procedure described above was followed by using calix[4]arene **8** (0.10 g, 0.17 mmol) and (ethoxycarbonylmethyl)-triphenylphosphonium bromide (0.29 g, 0.67 mmol) affording a white solid (0.034 g, 23% yield); m.p. 140–142 °C; Anal. calcd. for $C_{56}H_{66}O_{11}$: C 73.5, H 7.27; found: C 73.52, H 7.25; FAB-MS: *m*/*z* calcd. 915.12; Found 915 [M^+, 100%]; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm): 0.78 (m, 12H, C$\underline{H}_3$), 0.92 (m, 9H, OCH$_2$C$\underline{H}_3$), 1.81 (m, 8H, —C$\underline{H}_2$CH$_3$), 3.15 (m, 4H, ArC$\underline{H}_2$Ar), 3.80 (m, 6H, —COOC$\underline{H}_2$), 4.16 (m, 8H, —OC$\underline{H}_2$), 4.37 (m, 4H, ArC$\underline{H}_2$Ar), 6.05 (m, 3H, =C$\underline{H}$), 6.55–7.38 (m, 12H, Ar$\underline{H}$ + C$\underline{H}$=), 9.43 (s, H, C$\underline{H}$O).

2.2.12. Synthesis of 5,11,17,23-tetrakis(2-ethoxycarbonyl)ethenyl-25,26,27,28-tetrapropoxy calix[4]arene (**14**)

The reaction procedure described above was followed by using calix[4]arene **8** (0.10 g, 0.17 mmol) and (ethoxycarbonylmethyl)-triphenylphosphonium bromide (0.29 g, 0.67 mmol) affording a white solid (0.06 g, 35% yield); m.p. 165–166 °C; Anal. calcd. for $C_{60}H_{72}O_{12}$: C 73.15, H 7.37; found: C 73.35, H 7.18; FAB-MS: *m*/*z* calcd. 985.21; found 986 [M^+, 100%]; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm): 0.99 (m, 12H, C$\underline{H}_3$), 1.32 (m, 12H, —OCH$_2$C$\underline{H}_3$), 1.89 (m, 8H, —C$\underline{H}_2$CH$_3$), 3.14 (d, 4H, *J* = 13.3 Hz, ArC$\underline{H}_2$Ar), 3.87 (m, 8H, —COOC$\underline{H}_2$CH$_3$), 4.23 (m, 8H, —OC$\underline{H}_2$), 4.40 (d, 4H, *J* = 12.9 Hz, ArC$\underline{H}_2$Ar), 6.05 (d, 4H, *J* = 15.96 Hz, =C$\underline{H}$), 6.80 (s, 8H, Ar$\underline{H}$), 7.32 (d, 4H, *J* = 15.93 Hz, C$\underline{H}$=).

2.2.13. Synthesis of 5,11,17,23-tetrakis(2-phenyl)ethenyl-25,26,27,28-tetrapropoxy calix[4]arene (**15**)

The reaction procedure described above was followed by using calix[4]arene **8** (0.10 g, 0.17 mmol) and benzylidenetriphenyl phosphorane ylide (0.29 g, 0.675 mmol) affording a white solid mixture of cis and trans isomer (44% yield); m.p. >250 °C; Anal. calcd. for $C_{72}H_{72}O_4$: C 86.36, H 7.25; Found: C 86.45, H 7.23; FAB-MS *m*/*z* calcd. 1001.34, Found 1002 [M^+, 100%]; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm): 1.12 (t, 6H, *J* = 7.4 Hz), 2.05–1.70 (m, 8H), 3.15 (d, 4H, *J* = 13.3 Hz), 3.66 (t, 4H, *J* = 7.0 Hz), 4.02 (t, 4H, *J* = 7.9 Hz), 6.95 (d, 4H, *J* = 16.3 Hz), 7.13 (d, 4H, *J* = 16.3 Hz), 7.15–7.35 (m, 20H, ArH), 7.43 (s, 8H, *J* = 7.0 Hz, ArH), ^{13}C NMR δ 10.8, 23.4, 31.1, 77.6, 122.2, 126.2, 126.9, 127.7, 128.6, 129.0, 133.6, 136.6, 137.8, 155.6, 157.7.

2.3. UV spectroscopy

λ_{max}, ε and UV specific extinction values of synthesized calixarenes and reference UV filters were determined as follows: three solutions of **5, 6, 7, 12, 13** and **14** in the concentration range 10^{-4}–10^{-5} M were prepared in chloroform. Similarly, three different molar concentrations of reference UV filters (OMC, OB and avobenzone) were also prepared in this range and their absorbance (*A*) was recorded at respective peak wavelengths (λ_{max}) using quartz cuvettes of 1 cm path length (*L*). A plot of *A* versus molar concentration at λ_{max} was prepared and ε value was obtained from the slope of straight line. The UV specific extinction ($E_{1\%,1cm}$) was evaluated by using stock solutions of 1 mg mL^{-1} which were prepared for the reference and calixarene UV filters by appropriate dilution to obtain a 10 ppm solution. Absorbance of all the solutions was recorded at their λ_{max} using quartz cuvettes of 1 cm path length to give $E_{1\%,\ 1cm}$ values.

To obtain the absorption in the UVA to UVB regions for OMC, OB, avobenzone and **6**, UV specific extinction spectrum obtained above in chloroform were used and the mean absorbance values were calculated separately in the UVB (290–320 nm) and UVA (320–400 nm) regions of the spectrum. The total area under the curve in individual UVB and UVA regions was also obtained arithmetically by using the UVWINLAB software. These were then used to calculate the UVA/UVB ratio in terms of absorbance as well area under the curve.

2.4. HPLC analysis

HPLC analysis of **6** was done on a reverse-phase ODS2 column by using THF (100% v/v) as mobile phase at a constant flow-rate of 1.0 mL min^{-1} in isocratic mode at ambient temperature with the detector wavelength set at 312 nm. Stock solution (250 μg mL^{-1}) was prepared by dissolving accurately weighed **6** in chloroform. Three working standards were made by dilution of stock solutions with chloroform and subsequent dilutions were done to prepare standard solutions of concentration 1.0–10 μg mL^{-1} which were

injected (20 μL) onto the HPLC system in triplicates and chromatograms were recorded. All the samples were filtered through 0.45 μm membrane filter before injection for HPLC profiling.

2.5. Preparation of O/W emulsion-based formulations

Several oil in water (O/W) emulsions were made in the laboratory by using varying proportions of **6** and OMC. Arlacel P 135 (2%) was used as a polymeric emulsifier while isopropyl palmitate (9.5%) and mineral oil (7.0%) were used as primary emollients. Arlamol M812 (4%) was used as the solubilizer for **6**. Citric acid was used for final adjustment of pH of the formulation. The formulation samples were stored in airtight glass containers until used. pH of the formulated emulsions was determined at room temperature.

2.6. Procedure used for determination of in vitro Sun Protection Factor (SPF)

Of the various *in vitro* techniques that have been developed for evaluation of Sun Protection Factor (SPF) [31–36], the SPF values of calixarene analog **6** in emulsion was determined by using the method proposed by Walters et al. that assumes a simplified relationship between absorbance and SPF [37].

$$A = -\log_{10}\left(\frac{1}{\mathrm{SPF}}\right) = log_{10}\mathrm{SPF}$$

A standard calibration plot using different sunscreen products with labeled SPF ranging from 5 to 34 was prepared as follows: about 0.050 ± 0.005 g of each of the formulated sunscreens was weighed and 50.0 mL of distilled water was added to it and stirred until the formulation was uniformly suspended in water. To 1.00 mL of the resultant mixture, 9.00 mL of 1-propanol was added and stirred to produce a clear solution. A maximum in absorbance was determined at 312 nm for the sunscreen solutions [38]. The absorbance at 312 nm by a sample of 0.05 g was plotted versus $\log_{10}$(SPF) on a semilog paper. *In vitro* SPF of eight different formulations (F1–F8) prepared that (contained **6** in combination with OMC and TiO_2) were determined by interpolation from the calibration plot after preparation of sample solutions from different O/W emulsion formulations.

2.7. Procedure for photo-irradiation

Irradiation experiments on **6** were performed by using LZC-4 (Dual irradiation model) photo reactor (Luzchem Research, Inc. Canada) equipped with 14 lamps located at the top and sides. Solutions of calixarene **6** were prepared in the concentration range of 5–100 μg mL^{-1} in chloroform and the samples were placed in quartz tubes. All the experiments were carried out at room temperature (25–28 °C). The temperature in the irradiation chamber was determined to be approximately 3–4 °C above room temperature. Separate UV-B and UV-A lamps were used for irradiation with specific UV-B and UV-A incident radiations. The energy distribution at the target sample was 35,337 and 52,670 mW m^{-2} (Technical bulletin, Luzchem, Canada) in UV-B (281–315 nm) and UV-A (316–400 nm) regions respectively in case of individual [39] as against irradiance of about 60,000 mW m^{-2} for natural sunlight on a sunny day and 10 mW m^{-2} on a cloudy day [40]. Out of the total 14 lamps, eight of them on the side walls of the chamber were switched on during each experiment. Solutions of **6** were subjected to photo irradiation for following time points: 0 min, 1 min, 5 min, 10 min, 15 min, 20 min, 25 min, 30 min and 1 h. UV spectrum was recorded after each exposure using chloroform as the blank.

3. Results and discussion

3.1. Characterization of calixarene derivatives

The synthesized calix[4]arenes were characterized by IR, NMR and mass spectrometry. For example, **5** revealed strong absorptions at 1690 cm^{-1} and 1634 cm^{-1} which could be ascribed to the carbonyl and the C=C functions. The appearance of a doublet of doublet at δ 3.06 and a triplet at δ 4.32 for the CH_2 protons was also consistent with its cone conformation (Fig. 1). The aromatic protons appeared as three multiplets (δ 6.24, 6.53 and 7.34), a singlet and a doublet at δ 7.03 and 6.24 respectively. Integration for 18 protons revealed that the 3-phenyl-2-propenoyl unit (cinnamoyl group) has been introduced at one of the *para* aromatic positions in **5**. The doublets at δ 6.24 and δ 6.53 could be attributed to the olefinic protons. However, it was determined that the aromatic signals merged with the protons of the olefinic moiety thereby making elucidation of the exact stereochemistry little more difficult by conventional techniques. 2D NMR experiments (COSY and NOESY) were thus performed to understand the exact stereochemistry around the olefinic double bond (Fig. 2). These techniques were able to confirm the identification of olefinic protons. Compound **5** showed a molecular ion peak at m/z 723 [M^+] in its FAB-MS spectrum thereby confirming the introduction of one enone moiety.

The ^{1}H NMR spectrum of **6** (Fig. 1) revealed the appearance of a doublet of doublet at δ 3.06 and a triplet at δ 4.32 in the methylene bridge región again consistent with a cone conformation. The aromatic region of the spectrum revealed a complex pattern of resonances integrating for 30 protons indicating the introduction of three cinnamoyl groups at the upper rim. While NMR spectrum for compound **6** was similar to the other compounds of the series, the FAB-MS spectrum of **6** showed the appearance of a molecular ion peak at m/z 982 [M^+] to confirm that it is a tricinnamoyl derivative.

It was also observed that compound **6** readily got photoisomerized around the double bond on exposure to UV radiations. Such quick isomerization gave credence to the anticipated utility of the calixarene enone system for development of novel materials for protection from UVR.

The ^{1}H NMR spectrum of **7** revealed the introduction of two cinnamoyl groups at the *para* positions of the phenolic rings and not para to the propyl ether aromatic rings.

In order to assess the UV-protection properties of the synthesized calixarenes, they were purified by using high performance liquid chromatography and the purified derivatives were subjected to irradiation by UVA and UVB light. Rigorous purification and isomerization experiments and the broad band width (280–350 nm) reveal that compound **6** was suitable for further investigations for sun-screen formulations and was therefore further work was done on **6**.

The ^{1}H NMR spectrum of **11** obtained by the reaction of methyl phosphonium bromide ylide and tetraformyl calix[4]arene **8** revealed the disappearance of aldehydic protons and appearance of a pair of doublets at δ 4.93 (4H) and 5.32 (4H) and a multiplet at δ 6.34 (4H) in its ^{1}H NMR. These signals could be ascribed to vinylic protons revealing that the ethenyl groups had been introduced at all the four *para* positions of the calix[4]arene annulus. ^{1}H NMR characterization of **9** and **10** revealed the introduction of olefinic group at one and two *para* positions respectively. The calix[4]arene derivative **10** revealed the presence of multiplets at δ 3.1 and 4.38 for methylene bridge protons in its ^{1}H NMR spectrum that indicated that two ethenyl groups in **10** are introduced on proximal aromatic rings at the upper rim of calix[4]arenes (Fig. S1, Supplementary information).

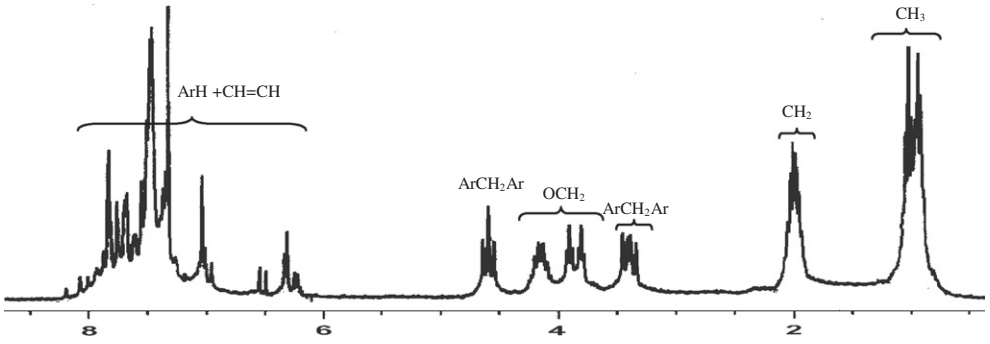


Fig. 1. ^{1}H NMR spectra of 5,11,17-tris(3-phenyl-2-propenoyl)-25,26,27,28-tetrapropoxycalix[4]arene (**6**).

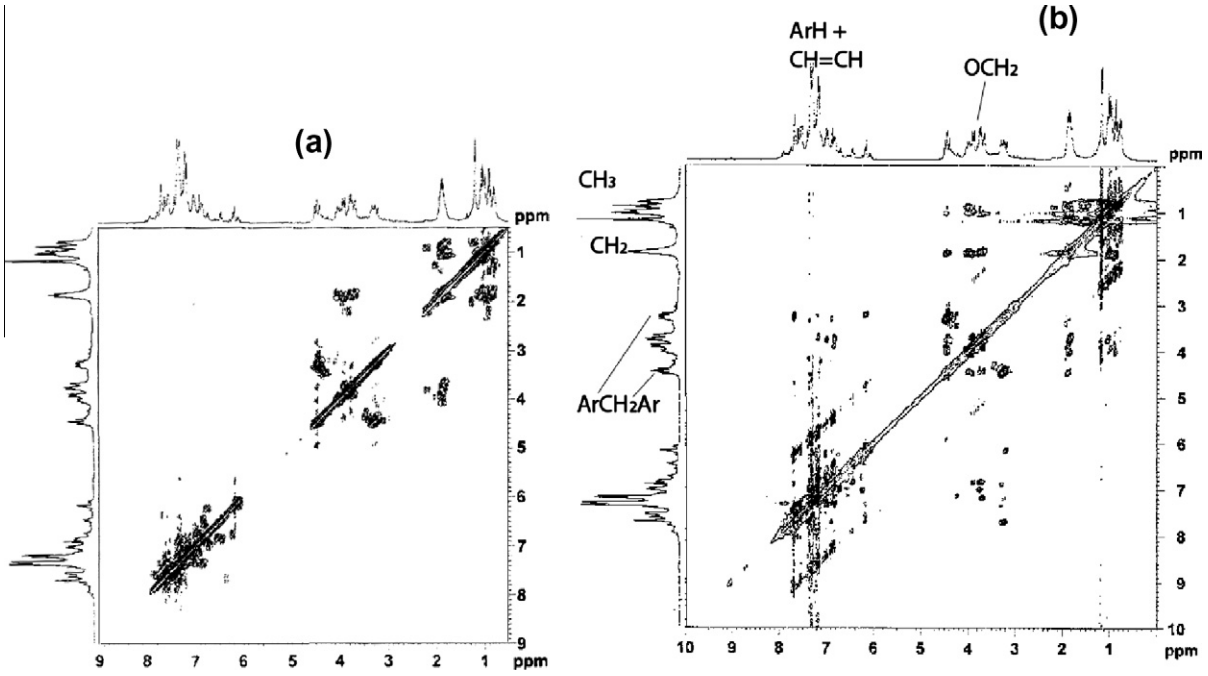


Fig. 2. (a) COSY and (b) NOESY spectra of 5,11,17-tris(3-phenyl-2-propenoyl)-25,26,27,28-tetrapropoxycalix[4]arene (**6**).

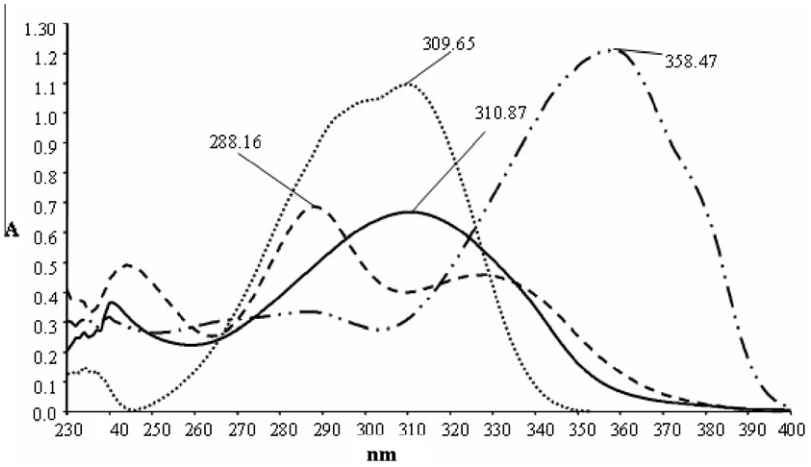


Fig. 3. Extinction curves of (——) **6**, (·····) OMC, (– – –) OB and (— · ·) avobenzone in chloroform.

The ^{1}H NMR spectrum of the calix[4]arene **14** derived from the reaction of ethyl bromoacetate ylide and formyl calix[4]arene (**10**), exhibited two well resolved doublets. One of the doublets centered at δ 7.32 (J = 15.96 Hz; 4H) to the left of phenyl resonance (at δ

Table 1
UV spectral analysis of calix[4]arenes (**5–7**) and reference UV filters.

Compound	λ_{max}[a]	$E_{1\%,1cm}$[a]	ε[a] (M^{-1} cm^{-1})	Absorbance
5	312	584.50	19,187	UVB, UVA II
6	312	666.10	59,541	UVB, UVA II
7	300	612.50	23,125	UVB
12	273	–	–	–
13	295	508.50	14,256	UVB
14	294	541.00	19,141	UVB
OB	287	686.45	15,150	UVB, UVA II
Avobenzone	356	1213.70	39,470	UVA I
OMC	310	1058.90	31,670	UVB

[a] Chloroform.

Table 2
Absorbance in the UVA/UVB regions of **6**, OMC, OB and avobenzone.

UV filter	Mean absorbance (5 nm interval)		Total area		UVA/UVB ratio	
	UVB region (280–320 nm)	UVA region (320–400 nm)	UVB region (280–320 nm)	UVA region (320–400 nm)	Absorbance	Area
6	0.5722	0.1903	23.2571	14.5743	0.33	0.62
OB	0.5151	0.1943	20.7463	15.4336	0.37	0.74
OMC	0.9431	0.1328	38.7465	9.0016	0.14	0.23
Avobenzone	0.3349	0.7350	13.0260	61.3280	2.19	4.70

6.80) and other at δ 6.05 (J = 15.93 Hz; 4H) to the right of the phenyl resonance in the aromatic region. These signals were attributed to the ethylenic protons of the *trans* isomer. Vinyl proton attached to the carbon bearing the phenyl ring could be assigned to the larger chemical shift as it would be in the deshielding area of the anisotropic field of the aromatic ring (Fig. S2, Supplementary information). All the products obtained were identified as cone conformers through the analysis of its ^{13}C NMR spectra.

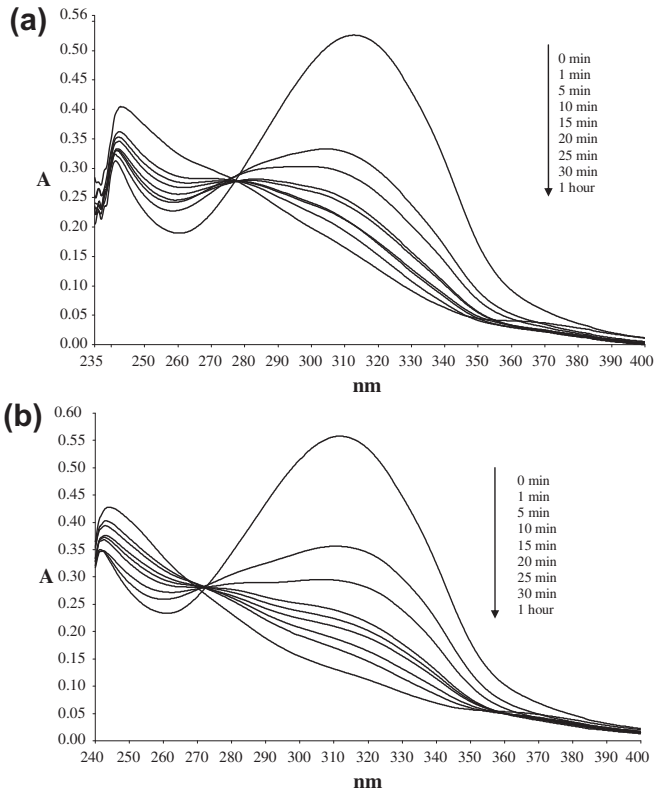


Fig. 4. Time-dependent absorption spectra of **6** in chloroform (8 μg mL^{-1}) after exposure to (a) UVB and (b) UVA range of radiations on UV photo reactor.

Table 3
In vitro SPF analysis of formulation batches (F1–F8) prepared during the study.

Emulsion formulation	Active components	Calculated SPF[a]
F1	2% **6**	5.2 ± 0.25
F2	2% OMC	6.4 ± 0.18
F3	2% **6** + 2% OMC	8.8 ± 0.45
F4	4% OMC	8.4 ± 0.19
F5	2% **6** + 4% OMC	10.8 ± 0.54
F6	4% TiO_2	5.2 ± 0.40
F7	2% **6** + 4% TiO_2	5.6 ± 0.49
F8	2% OMC + 4% TiO_2	6.8 ± 0.51

[a] Each value is mean ± SD of three determinations.

3.2. Comparison of UV spectra of calixarenes (*5–7* and *12–14*), OMC, OB and avobenzone

The UV spectral behavior in relation to the absorption maximum and absorption range in the UV region from 280 to 400 nm was examined for all the calix[4]arene analogs selected for the study. The enone-appended calixarenes **5–7** and unsaturated ester appended calixarenes **12–14** were found to absorb between 280–350 nm in the UV region (Figs. 3 and S3). For example, **7** showed an absorption maximum at 300 nm while **5** and **6** exhibited absorption máxima at 312 nm. A comparison of the extinction curves of **6** and reference UV filters (Fig. 3) in chloroform indicated that **6** showed $E_{1\%,1cm}$ of 666 compared to 686 for OB, 1058 for OMC and 1213 for avobenzone. The results obtained indicated that although the UV specific extinction coefficient of **6** was lower than OMC and avobenzone, it was comparable to that of OB.

It was determined that **6** had a very high molar extinction coefficient ($\varepsilon > 5 \times 10^4$) than those of **5** and **7** as well as commercial UV filters like OMC, OB and avobenzone when examined under identical conditions (Table 1). Therefore **6** was subjected to detailed evaluation.

Amongst the olefinic calixarene analogs studied, **14** showed a good extinction in the UVB region but was not subjected to further studies due to its susceptibility to degradation in solution on exposure to UV light (Fig. S4, Supplementary information). Calixarene analog **12** did not absorb in the desirable UV region and therefore not studied further.

3.3. Comparison of UVA/UVB protection ratio of *6* with OMC, OB and avobenzone

A comparison of the extinction spectrum of **6** in the UVA and UVB regions with those of OMC, OB and avobenzone was done

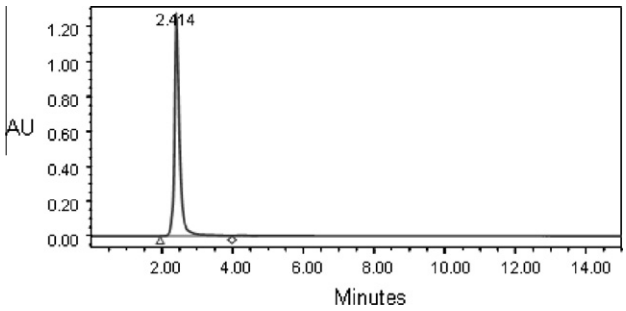


Fig. 5. HPLC analysis of 100 μg mL^{-1} solution of calixarene **6**.

Table 4
Quantitative results for HPLC assay of calix[4]arene **6**.

Retention time (min)	Linear range ($\mu g\ mL^{-1}$)	Intercept ($\times 10^2$)	r^2	Slope (log plot)	Sensitivity* ($L\ mg^{-} \times 10^4$)	LOD** ($mg\ L^{-1} \times 10^{-4}$)	LOQ*** zzz($mg\ L^{-1} \times 10^{-4}$)
2.93 (0.004)	1.0–10.0	0.0 (0.0)	0.9993 (0.001)	1.04 (0.019)	10.70 (0.015)	17.36 (0.471)	52.63 (0.284)

* Slope of the calibration curve.
** Calculated as per equation; LOD = $3.3S_{x/y}/b$; where $S_{x/y}$ is the standard deviation and b is the slope of the unweigted least square calibrated plot.
*** Calculated as per equation; LQD = $10S_{x/y}/b$; $S_{x/y}$ and b are defined above.

by determining their UVA/UVB ratios which was calculated arithmetically from the mean absorbance and total areas under the absorption curves in individual UVB and UVA regions. It has been determined that the UVA/UVB ratio was 0.62 for **6** (Table 2) indicating that it is predominantly a UVB absorber with sufficient efficiency for offering pretection from UVA.

3.4. Spectral changes in *6*, OB and OMC on photo-irradiation with UVB and UVA light

The photostability of **6** was examined for both UVB and UVA light by recording the temporal changes in the UV absorption spectrum in neat chloroform due to the insolubility of calix[4]arenes in water. It was found that when **6** was subjected to UV-B radiations, there was nearly 65% loss of absorption of **6** after 30 min of exposure as indicated by a time-dependant spectrum showing shift in the spectral band position with an isosbestic point at 278 nm. When subjected to UVA radiations, about 70% loss of UV absorption after 30 min of exposure was noted with the time-dependant spectrum showing a shift in the spectral band position with an isosbestic point appearing at 272 nm (Fig. 4).

These results indicated that **6** undergoes a change in its absorption profile on exposure to both UVA and UVB light. Both octylmethoxycinnamate (OMC) and oxybenzone (OB) were also quantitatively analyzed simultaneously in the mixture with other excipients in the commercial sunscreen formulation through second order derivative spectrophotometry allowed their determination without matrix interferences (Fig. S5, Supplementary information). While zero-order calibration methods provided a higher content for both the UV filters, second-order calibration (D2 values; derivative mode for OB and derivative + peak mode for OMC) resulted in values that were in agreement with the labeled content of commercial sunscreens, reported earlier for OMC by us [41] and others [42,43].

3.5. Evaluation of in vitro Sun Protection Factor of *6* in combination with OMC and TiO_2

To test the protection offered by **6** in the UVB region, its *in vitro* Sun Protection Factor was determined for different formulations made from **6**, OMC and OB. Accordingly, several formulations (F1–F8) were made by combining **6** with UVB absorber (OMC) and physical sunscreen (titanium dioxide). Absorbance of sunscreen formulations available in the market was determined at 312 nm and corrected to a weight of 0.050 g. A calibration plot was prepared between the corrected absorbance and the labeled SPF value and the following equation was determined.

$$\log_{10}\mathrm{SPF} = 0.980(\mathrm{Abs}) + 0.5051$$

SPF represents the Sun Protection Factor and Abs denotes the absorbance of diluted sunscreen solution. The slope of least-squares line fitted to the data was 0.980 and the intercept was 0.5051. The SPFs of **6**, OMC and TiO_2 were determined after sample preparation from the formulations (F1–F8) and recording the absorbance at 312 nm (Table 3).

The *in vitro* SPF analysis of F1–F8 indicated that **6** has a synergistic effect on boosting the SPF of OMC. For example, 2% of **6** and 2% of OMC combined in the formulation (F3) has a higher SPF than 4% OMC alone (formulation F4). On the other hand, there was no boosting effect on the SPF of TiO_2 because 4% titanium dioxide when combined with 2% **6**, showed insignificant increment in the SPF of **6** from 5.2 to 5.6.

3.6. HPLC analysis of *6*

Compound **6** was purified by column chromatography to give a sample which gave a sharp peak at a retention time of 2.414 min in its chromatogram when examined by high performance liquid chromatography on a reverse-phase ODS2 column using THF (100%) as the mobile phase and UV detection at 312 nm (Fig. 5).

A calibration curve of concentration of **6** versus the peak area could be prepared in the concentration range of 1.0–10.0 $\mu g\ mL^{-1}$ to derive an equation through linear unweighted regression analysis. The linearity of the concentration versus the peak area plot was ensured by a log area versus log C diagram where the slope was determined to be one throughout the whole concentration range examined. The quantitative results for HPLC assay of **6** are summarized in Table 4.

The HPLC analysis of **13** and **14** was also examined by high performance liquid chromatography on a reverse-phase ODS2 column using THF:acetonitrile:triethylamine (89:10:1) as the mobile phase at flow rate 0.4 mL min^{-1} and UV detection at 295 nm. The chromatogram revealed that **13** eluted at a characterstic sharp peak at 6.06 min (Fig. S6) while **14** eluted at 6.07 min (Fig. S7).

4. Conclusion

In conclusion, we have observed that of the three synthesized calix[4]arene enones, **6** effectively assimilate the properties of photosensitive cinnamates and show a significant absorption ($\varepsilon > 5 \times 10^4$) in the UVB (280–320 nm) and UVA II (320–340 nm) region of the ultraviolet spectrum. The calix[4]arene enone **6** has specific extinction coefficient and the ratio of absorbance in the UVA to UVB regions similar to commercially used mixed UV filter oxybenzone. **6** exhibits an SPF boosting effect to OMC in emulsion formulations.

Acknowledgements

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jphotobiol.2011.06.007.

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