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Short communication

Synthesis and antioxidant properties of enone core based dendrimers with carbazole as surface group

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ABSTRACT

Synthesis of enone core based dendrimers with carbazole as surface group has been achieved. All the synthesized dendrimers showed excellent antioxidant behavior with commercially available 1,1-diphenyl-2-picryl hydrazyl (DPPH).

1. Introduction

Dendrimers are monodisperse macromolecules possessing well-defined branched structure that can be precisely tailored into discrete and designated functionality to create multifunctional materials. Dendrimers are also often referred to as artificial proteins [1]. The size, shape, branching length and density and their surface functionality of dendrimers make them as ideal carriers in biomedical applications such as drug delivery [2], gene transfection [3], and imaging [4] and as catalyst in homogeneous as well as heterogeneous medium [5]. Some of the surface modified dendrimers themselves may act as nano-drugs [6,7] against cancer, tumors, bacteria and viruses. Recent successes in simplifying and optimizing the synthesis of dendrimers such as 'lego' [8] and 'click' [9] techniques, provide a large variety of structural variation while at the same time reducing the cost of their production. The surface of dendrimers provides as excellent platform for drug delivery. Very recently, PAMAM dendrimers have been successfully used as carriers of boron isotopes in boron neutron-capture treatment of cancer tumors [10] and in nonsteroidal anti-inflammatory drugs [11]. Hybrid dendrimers such as glycodendrimers exhibits potential application in medicinal field [12,13]. Synthesis of permanent fluorescence sensing hyper branched dendritic architecture [14] as well as bactericidal efficacy of novel dendrimers [15] and axially chiral enantiopure dendrimers [16] has been reported from our laboratory recently. Very recently the bio and pharmaceutical application of the dendrimers are well-defined in the literature [17–19]. The enone nucleus is present in various natural products [20] and known to be a very important organic residue in many potentially bioactive compounds [21]. However the synthesis and biological activity of hexanone core based bioactive carbazole [22] hyper branched dendritic architecture are yet to be investigated. To the best of our knowledge the antioxidant study of the carbazole based dendrimer is still a rare observation. Therefore, we report herein for the first time the synthesis of hexanone core based dendritic architecture **1a**, **1b**, **1c** and **1d** with carbazole as surface group and their antioxidant activity tested with commercially available DPPH.

2. Chemistry

Synthesis of bioactive enone based dendrimers (**1a**–**d**) up to third generation was achieved by simple *O*-alkylation method using convergent synthetic route which include LAH reduction, benzylic chlorination and NBS bromination starting from a bioactive carbazole moiety scheme (**1**–**4**). 2.1 Equiv. of dendritic bromide **3**,

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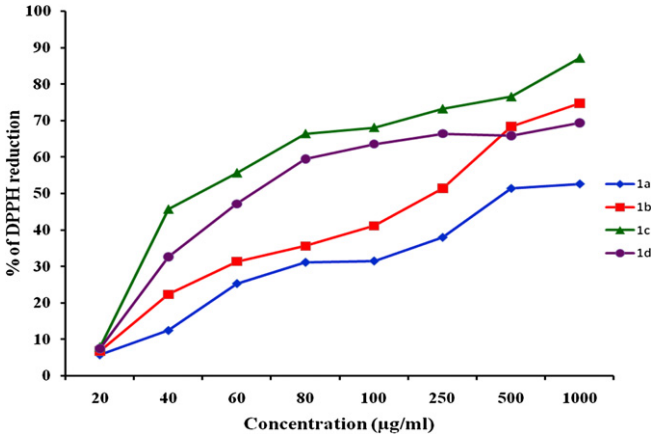


Fig. 1. DPPH scavenging activity spectrophotometric assay of various concentrations of the dendrimers **1a**, **1b**, **1c** and **1d**.

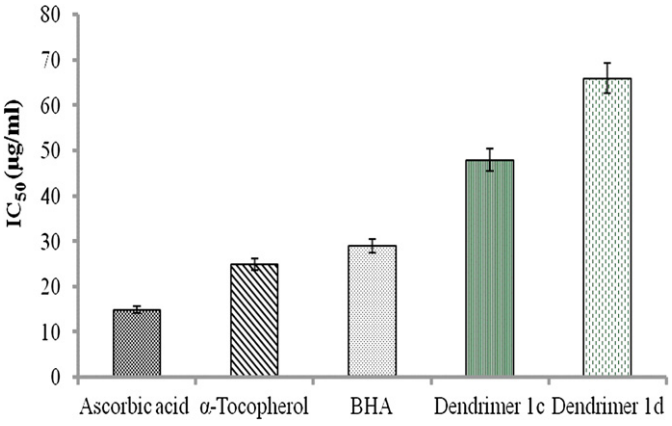


Fig. 2. DPPH scavenging capacities (IC_{50}) of dendrimer **1c** and **1d** with standard drugs.

chlorides **7**, **10**, and **13** react with 1 equiv. of 2,6-bis(4-hydroxy benzylidene)cyclohexanone **4** in the presence of K_2CO_3 to give the dendrimers **1a–d** in 65–80% yield and the rest of the yield contained mono alkylated product. All the new compounds gave satisfactory IR, ^1H and ^{13}C NMR, mass spectral and elemental analysis.

3. Biology

Antioxidant activity of all the dendrimers was tested by DPPH free radical scavenging activity by spectrometric assay method [23]. Samples at different concentration were prepared and tested for DPPH scavenging activity. The percentage of inhibition was calculated and the antioxidant activity of the dendrimers and standard antioxidants like Ascorbic acid, α-Tocopherol and Butylated Hydroxyanisole (BHA) were recorded and compared. The antioxidant activity and IC_{50} value of the dendrimers with standard drugs are shown in the Figs. 1 and 2 respectively.

4. Results and discussion

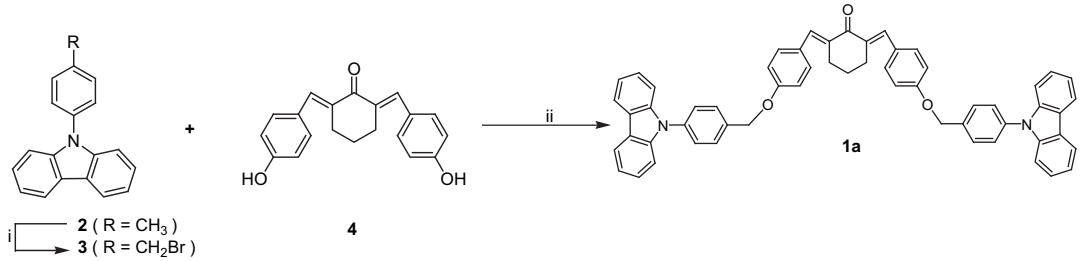
Synthesis of dendrimers **1a–d** was achieved by simple *O*-alkylation method using convergent synthetic route starting from a bioactive carbazole moiety. Alkylation of 2,6-bis(4-hydroxy benzylidene)cyclohexanone **4** with carbazole dendritic bromide **3** in the presence of K_2CO_3 and 18-crown-6 in DMF afforded the zeroth generation dendrimer **1a** in 80% yield. Dendritic bromide **3** was obtained in 84% yield by the radical bromination of 9-*p*-tolyl carbazole **2** which in turn was obtained by the known procedure [24] (Scheme 1).

In the ^1H NMR spectrum, **1a** displayed a quintet at δ 1.80 and a triplet at δ 2.95 for two type of methylene protons of hexanone moiety and a sharp singlet appeared at δ 5.21 integrating for four methylene protons in addition to the olefinic and aromatic protons and in ^{13}C NMR spectrum the two type of hexanone methylene, *O*-methylene carbons and the carbonyl carbon appeared at δ 23.1, δ 28.6, δ 69.6, and δ 190.2 respectively in addition to the olefinic and aromatic carbons. The structure of the dendrimer **1a** was further confirmed from mass spectrum and elemental analysis.

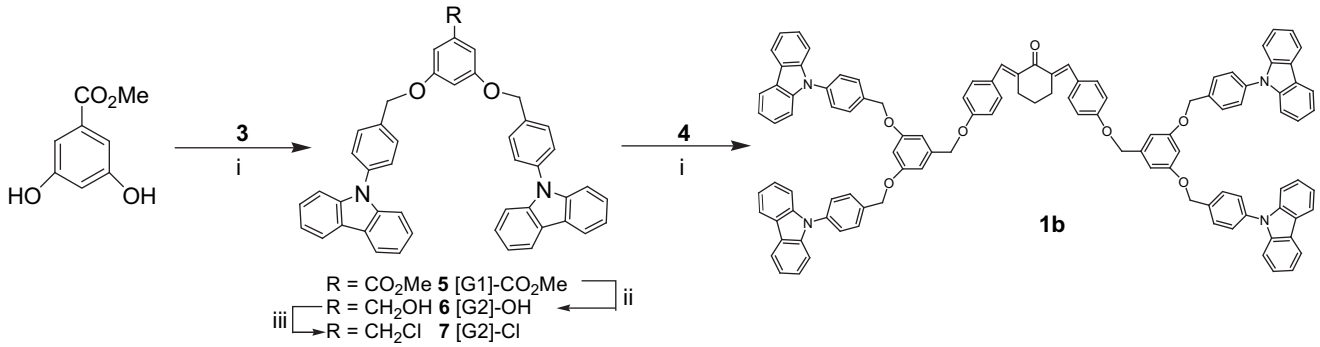
Similarly first generation dendrimer **1b** was obtained from the first generation dendritic chloride **7** [G1]-Cl. Reaction of methyl-3,5-dihydroxy benzoate with 2.1 equiv. of dendritic bromide **3** afforded methyl-carboxylate **5** in 72% yield. Reduction of **5** with lithium aluminum hydride in dry THF afforded the dendritic alcohol **6** [G1]-OH, which on further treatment with $SOCl_2$ in dry DCM at 0 °C, gave the dendritic chloride **7** [G1]-Cl in 83% yield. Reaction of 1.0 equiv. of hexanone **4** with 2.1 equiv. of the dendritic chloride **7** [G1]-Cl in dry DMF afforded the first generation dendrimer **1b** in 76% yield (Scheme 2).

In the ^1H NMR spectrum, dendrimer **1b** displayed two broad singlet each integrating for two and four proton at δ 1.72 and δ 2.84 for two types of methylene protons of hexanone unit and two sharp singlet at δ 5.09 and δ 5.17 each integrating for four and eight protons respectively for *O*-methylene protons in addition to the olefinic and the aromatic protons, and in ^{13}C NMR spectrum the two type of methylene carbon of hexanone and two type of *O*-methylene carbon and the carbonyl carbon appeared at δ 22.9, δ 28.5, δ 69.8, δ 70.0 and at δ 190.1 respectively in addition to the olefinic and the aromatic carbons. In the FAB – mass spectrum, the molecular ion peak appeared at *m*/*z* 1572 (M^+) and the structure of the dendrimer **1b** was further confirmed from satisfactory elemental analysis. Application of similar sequence afforded the second generation dendrimer **1c** in 65% yield from the second generation dendritic chloride **10** [G2]-Cl (Scheme 3).

In the ^1H NMR spectrum of dendrimer **1c** displayed two broad singlet at δ 1.68 and δ 2.79 integrating for two and four protons for methylene protons of hexanone moiety and three sharp singlet at



Scheme 1. Reagents and Conditions: (i) NBS, BZ_2O_2, CCl_4, reflux, 6 h, **3** (84%); (ii) K_2CO_3, 18-crown-6, DMF, 60 °C, 48 h, **1a** (80%).



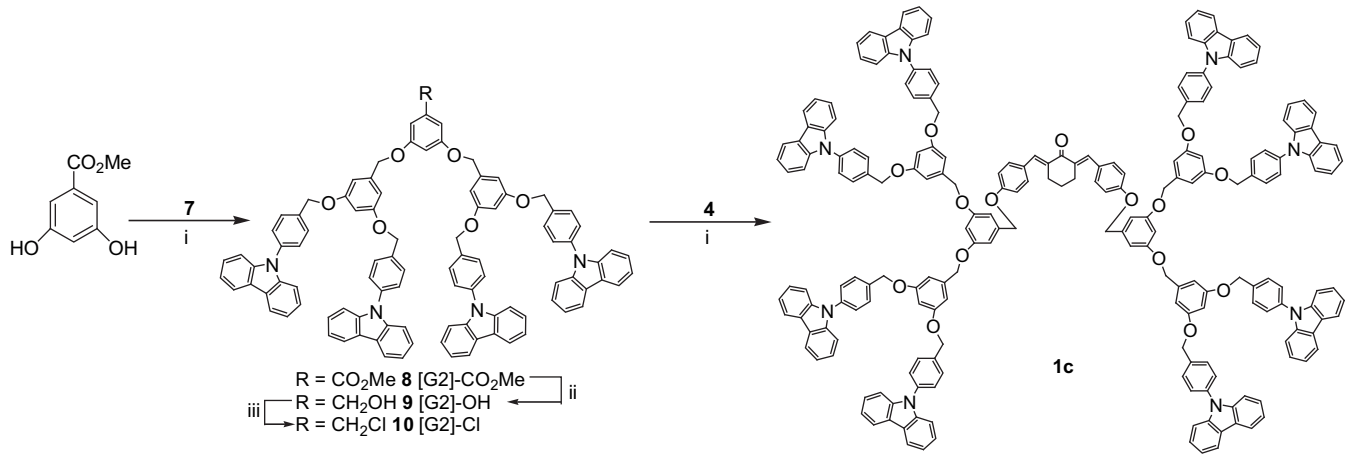
Scheme 2. Reagents and Conditions: (i) K_2CO_3, 18-crown-6, DMF, 60 °C, 48 h, **5** (72%), **1b** (76%); (ii) LAH, THF, reflux, 6 h, **6** (70%); (iii) $SOCl_2$, Py, DCM, 0 °C to rt, 3 h, **7** (83%).

δ 5.01, δ 5.05, δ 5.16 for *O*-methylene protons each integrating four, eight and sixteen protons in addition to the olefinic and aromatic protons. In the ^{13}C NMR spectrum, methylene carbon in hexanone moiety appeared at δ 22.7, δ 28.5, the three different *O*-methylene and carbonyl carbon appeared at δ 69.8, δ 69.9, δ 70.1 and δ 189.9 respectively in addition to the twenty one aromatic and olefinic carbon. In the mass spectrum, the molecular ion peak appeared at $m/z = 3105$ ($M + Na^+$) and the structure of dendrimer **1c** was further confirmed from satisfactory elemental analysis. Third generation dendrimer **1d** was obtained in 70% yield by similar methodology from the dendritic chloride **13** [G3]-Cl (Scheme 4).

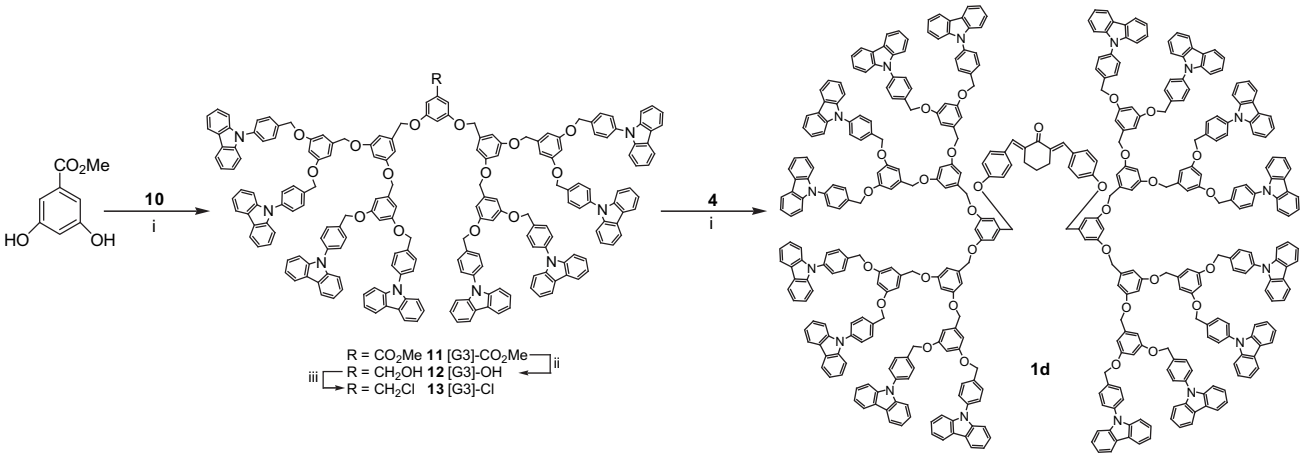
In the ^1H NMR spectrum, dendrimer **1d** showed two broad singlet at δ 1.67 and δ 2.78 for two type of methylene protons of hexanone moiety and four singlet at δ 4.94, δ 4.96, δ 5.00 and δ 5.10 for four different methylene proton integrating for four, eight, sixteen and thirty two protons in addition to the olefinic and aromatic protons. In the ^{13}C NMR spectrum, a set of methylene carbon present in hexanone moiety appeared at δ 21.9, δ 28.7, the *O*-methylene and carbonyl carbons appeared at δ 68.6, δ 68.8, δ 68.9 and δ 189.1 in addition to the olefinic and aromatic carbons. The structure of the dendrimer **1d** was further confirmed by the appearance of a molecular ion peak at $m/z = 6124$ ($M + Na^+$) in the MALDI-TOF mass spectrum as well as from elemental analysis.

4.1. Antioxidant studies of the dendrimers *1a–d*

Free radical scavenging assay methodology has been employed to study the antioxidant property of the dendrimers **1a–d**. DPPH (1,1-diphenyl-2-picryl hydrazyl) known as stable free radical source has been used for the determination of antioxidant property. DPPH has violet colour and has absorption band at 517 nm in ethanol. When DPPH is mixed with the dendrimers which can donate free electron, DPPH looses its colour and undergoes reduction to give diphenyl picryl hydrazine [25]. Dendrimers **1a–d** were dissolved in $CHCl_3$ with concentration of 20, 40, 60, 80, 100, 250, 500 and 1000 μg/ml and used for the study. The test solution of the dendrimers **1a–d** (0.1 ml) in $CHCl_3$ was added to DPPH solution (0.5 ml) in ethanol and absorption was measured at 517 nm. Percentage activity was calculated from the following equation. Percentage Activity = [As − Ab/Ac − Ab] × 100, where As = absorbance of DPPH test solution. Ab = absorption of DPPH solution with blank without DPPH and dendrimers and Ac = control with DPPH solution without adding the dendrimer. Fig. 1 shows the percentage of DPPH reduction with change in the concentration of the dendrimers **1a–d**. The second generation dendrimer **1c** showed the excellent activity at all the concentration ranging from 20 to 1000 μg/ml and hence dendrimer **1c** has the efficient antioxidant property. However the antioxidant property of first and third generation dendrimer **1b** and **1d** alters depending on the concentration of the dendrimers in the test solution. In fact zeroth generation dendrimer **1a** has the lowest antioxidant property. The antioxidant property gradually increases with increasing the generation of dendrimers and hence **1c** shows better antioxidant property than **1b** and **1a**, which could be due to more number of carbazole groups on the surface generally termed as multivalent effect [13]. Based on similar trend **1d** should show much greater antioxidant property. However, high carbazole loading will cause serious steric hindrance due to crowding effect which in turn decrease the availability of



Scheme 3. Reagents and Conditions: (i) K_2CO_3, 18-crown-6, DMF, 60 °C, 48 h, **8** (74%), **1c** (65%); (ii) LAH, THF, reflux, 6 h, **9** (67%); (iii) $SOCl_2$, Py, DCM, 0 °C to rt, 3 h, **10** (80%).



Scheme 4. Reagents and Conditions: (i) K_2CO_3, 18-crown-6, DMF, 60 °C, 48 h, **11** (72%), **1d** (70%); (ii) LAH, THF, reflux, 6 h, **12** (68%); (iii) $SOCl_2$, Py, DCM, 0 °C to rt, 3 h, **13** (78%).

carbazole to exhibit antioxidant property. IC_{50} values were determined in order to confirm the reducing activity of the dendrimers synthesized. All the dendrimers exhibited variation of free radical scavenging activity with respect to the variation of concentration. Scavenging activity of 50% was observed at 48 μg/ml and 66 μg/ml for dendrimers **1c** and **1d** respectively (Fig. 2). The activity is significant when compared with the standard antioxidant drugs [26] like Ascorbic acid, α-Tocopherol and BHA (with IC_{50} as 48 μg/ml, 25 μg/ml and 29 μg/ml respectively). The antioxidant property of the dendrimers derived from syringaldehyde [27] is due to the presence of phenolic unit where as the antioxidant effect of the dendrimers reported herein is due to the presence of the bioactive carbazole functionality. Though the antioxidant property of syringaldehyde dendrimer reported is comparable to that of carbazole dendrimer, the acidic and corrosive nature of phenolic group could prevent their use in biological system and hence the dendrimer reported in the current investigation will have more applicability. In general some of the dendrimers have good water-solubility, bioavailability and biocompatibility, and hence they can be administrated by intravenous, oral, transdermal, and ocular delivery systems [28]. Hence, in conclusion the carbazole based dendrimers reported herein may have good biocompatibility, cytotoxicity and bioavailability.

5. Conclusion

In conclusion, enone core based dendrimers with carbazole as surface group up to third generation were synthesized and all of which showed better antioxidant activity. Among the dendrimers, dendrimer **1c** exhibited better antioxidant property and IC_{50} values are significant for the second and third generation dendrimers **1c** and **1d** when compared with the standard antioxidant drugs. The second generation dendrimer **1c** may be developed as antioxidant drug as it showed better activity compared with commercial available drugs. The cytotoxicity, biocompatibility and bioavailability and *in-vivo* studies of the dendrimers synthesized are under investigation and will be communicated latter as a full paper.

6. Experimental

6.1. Chemistry

All the reagents and solvents employed were of the best grade available and were used without further purification. The melting points were determined using a Toshniwal melting point apparatus by open capillary tube method and are uncorrected. Spectroscopic data were recorded by the following instruments IR: FTIR-8300 spectrometer; NMR Bruker 300 MHz; MS: FAB-MS spectra Jeol SX 102/DA-600 mass spectrometer and MALDI-TOF mass recorded using Voyager DE-PRO Biospectrometry workstation (applied Biosystems) MALDI-TOF-MS instruments. The elemental analysis of the dendrimers was carried out using the Perkin–Elmer 240B elemental analyzer.

6.2. General procedure for the synthesis of dendrimers (*1a–d*)

A mixture of the corresponding dendritic bromide (or) chloride (2.1 equiv.), 2,6-bis(4-hydroxy benzylidene)cyclohexanone (1.0 equiv.), 18-crown-6 (0.1 equiv.) and potassium carbonate (5.0 equiv.) in dry DMF (25 ml) was heated at 60 °C with stirring for 48 h under nitrogen. The reaction mixture was then allowed to cool to room temperature and poured into ice water. The resulting precipitate was filtered, washed thoroughly with water and dissolved in $CHCl_3$ (150 ml). The filtrate was evaporated under vacuum and the residue was extracted with $CHCl_3$ (2×50 ml), washed with brine (1×50 ml) and then dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave the dendrimer as a crude material, which was purified by column chromatography (SiO_2).

6.2.1. Dendrimer *1a*

Yield 80%; mp 222 °C; IR (KBr, cm^{-1}):1644 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.80 (quin, 2H, $J = 5.4$ Hz), 2.95 (t, 4H, $J = 4.8$ Hz), 5.21 (s, 4H), 7.08 (d, 4H, $J = 9.0$ Hz), 7.27–7.34 (m, 4H), 7.41–7.44 (m, 8H), 7.50 (d, 4H, $J = 8.7$ Hz), 7.60 (d, 4H, $J = 6.6$ Hz), 7.67 (d, 4H, $J = 8.4$ Hz), 7.80 (s, 2H), 8.15 (d, 4H, $J = 7.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.1, 28.6, 69.6, 109.7, 114.8, 120.1, 120.4, 123.5, 126.0, 127.3, 129.0, 129.3, 132.3, 134.6, 135.8, 136.5, 137.6, 140.8, 159.0, 190.2; *m/z* (FAB-MS): 817 (M^+). Elemental Anal. Calcd for $C_{58}H_{44}N_2O_3$: C, 85.27; H, 5.43; N, 3.43. Found: C, 85.19; H, 5.52; N, 3.36.

6.2.2. Dendrimer *1b*

Yield 76%; mp 148 °C; IR (KBr, cm^{-1}):1643 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.72 (bs, 2H), 2.84 (bs, 4H), 5.09 (s, 4H), 5.17 (s, 8H), 6.71 (s, 2H), 6.79 (s, 4H), 7.26 (t, 8H, $J = 7.5$ Hz), 7.36–7.45 (m, 24H), 7.58 (d, 8H, $J = 8.1$ Hz), 7.66 (d, 8H, $J = 8.1$ Hz), 7.74 (s, 2H), 8.13 (d, 8H, $J = 7.8$ Hz), ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.9, 28.5, 69.8, 70.0, 101.8, 106.6, 109.7, 114.2, 114.9, 120.1, 120.4, 123.5, 126.0, 127.3, 129.1, 132.3, 134.5, 135.9, 136.4, 137.6, 139.5, 140.8, 159.0, 160.3, 190.1; *m/z* (FAB-MS):1572 (M^+). Elemental Anal. Calcd for $C_{110}H_{82}N_4O_7$: C, 84.05; H, 5.26; N, 3.56. Found: C, 83.91; H, 5.35; N, 3.43.

*6.2.3. Dendrimer **1c***

Yield 65%; mp 154 °C; IR (KBr, cm^{-1}): 1646 (C═O); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.68 (bs, 2H), 2.79 (bs, 4H), 5.01 (s, 4H), 5.05 (s, 8H), 5.16 (s, 16H), 6.65(s, 2H), 6.70–6.78 (m, 16H), 6.92 (d, 4H, $J = 8.7$ Hz), 7.25–7.28 (m, 12H), 7.34–7.39 (m, 36H), 7.56–7.58 (m, 20H), 7.65 (d, 16H, $J = 8.1$ Hz), 7.71 (s, 2H), 8.11 (d, 16H, $J = 7.5$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.7, 28.5, 69.8, 69.9, 70.1, 101.8, 106.8, 109.8, 114.6, 114.8, 120.1, 120.4, 123.5, 126.0, 127.2, 128.5, 129.1, 132.3, 134.4, 135.9, 136.4, 137.6, 139.5, 14 0.8, 158.9, 160.2, 189.9; *m/z* (MALDI-TOF-MS): 3105 ($M + Na^+$). Elemental Anal. Calcd for $C_{214}H_{158}N_8O_{15}$: C, 83.41; H, 5.17; N, 3.64. Found: C, 83.27; H, 5.04; N, 3.78.

*6.2.4. Dendrimer **1d***

Yield 70%; mp 156–158 °C; IR (KBr, cm^{-1}): 1648 (C═O); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.67 (bs, 2H), 2.78 (bs, 4H), 4.94 (s, 4H), 4.96 (s, 8H), 5.00 (s, 16H), 5.10 (s, 32H), 6.63–6.66 (m, 20H), 6.70–6.75 (m, 24H), 7.22–7.26 (m, 39H), 7.30–7.38 (m, 60H), 7.51–7.53 (m, 31H), 7.58–7.69 (m, 35H), 8.07 (s, 6H), 8.08–8.11 (m, 29H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.9, 28.7, 68.6, 68.8, 68.9, 100.6, 105.5, 108.6, 113.1, 113.7, 114.4, 118.9, 119.3, 122.3, 124.9, 126.1, 127.3, 128.0, 130.4, 131.2, 131.4, 132.9, 133.4, 134.8, 135.2, 136.4, 138.3, 138.4, 139.7, 155.8, 157.8, 159.1, 161.5, 189.1; *m/z* (MALDI-TOF-MS): 6124 ($M + Na^+$). Elemental Anal. Calcd for $C_{422}H_{310}N_{16}O_{31}$: C, 83.06; H, 5.12; N, 3.67. Found: C, 83.19; H, 5.22; N, 3.54.

6.3. Biological activity

6.3.1. Antioxidant studies

Antioxidant activity of all the dendrimers studied by the method used to determine the free radical scavenging activity. Samples were prepared at various concentrations of 20, 40, 60, 80, 100, 250, 500, 750 and 1000 μg/ml and 0.1 ml of this solution is mixed with 0.5 ml of DPPH solution in ethanol. After 30 min the absorption was measured at the wavelength 517 nm on Beckman UV–vis spectrometer. Every measurement was repeated three times. From the absorption value, percentage of activity was calculated using the formula. Percentage Activity = [As − Ab/Ac − Ab] × 100, where As – absorbance of DPPH solution with a tested solution (test), Ab – absorbance of a DPPH solution with a blank without sample and DPPH, Ac – Control with DPPH solution without sample solution. The antiradical activity was defined as the concentration of a sample showing the DPPH radical scavenging activity and determined from the graph (Fig. 1) in which concentration and reduction activity were plotted against each other.

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