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Synthesis and photophysical properties of chiral dendrimers with quinoline surface group via click chemistry

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ABSTRACT

Synthesis of some novel chiral dendrimers containing quinoline as surface group and 1,2,3-triazole as branching unit is described. The chiroptical property exhibits the widening of the torsional angle in the BINOL core as the generation increases. The photophysical properties indicate an increase in the molar extinction coefficient and fluorescence intensity and a decrease in quantum yield and lifetime as the generation of the dendrimer increases.

Dendrimers are monodisperse macromolecular architectures with a high degree of surface functionality.[1] Dendrimers find applications in light harvesting systems,[2] catalysis,[3] drug delivery,[4] multivalent diagnostics for magnetic resonance imaging (MRI),[5] molecular encapsulation,[6] and bioconjugate chemistry.[7] Dendrimers are also used in organo electronic devices such as organic light-emitting diodes (OLEDs).[8] Quinoline is a bioactive residue present in various natural products and drugs and also used for the synthesis of electronics and optoelectronic devices due to its excellent mechanical properties.[9] Quinoline-based fluorophoric systems find applications in sensor,[10] OLEDs[11], and exhibit bactericidal, antitumor, antimalarial, anti-inflammatory, pro-apoptotic, and antiproliferative and also other biological activities.[12] Quinoline-based conjugated dendrimers exhibit photophysical, electroluminescence properties and function as electron transport materials for light-emitting diodes.[13] Further quinoline-based dendrimers have also been used in 'on–off' switchable luminescence[14] and for metal complexation.[15]

Click chemistry[16] refers to Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition of an azide to a terminal alkyne to yield triazole which can function as a possible ligand for metal ions and as a proton transport facilitator.[17] In the present study click chemistry approach is chosen as the best process for the synthesis of triazoles. The advantages of employing click chemistry are the excellent chemoselectivity, extraordinary reliability, high yield, atom-economy, no protection-deprotection protocol in addition to air and moisture tolerant reaction conditions. Studies of synthesis, DNA binding, and photonuclease activity of 1,2,3-triazole-fused quinoline-peptidomimetics have been reported.[18] Synthesis of dendrimers using click chemistry has received much attention during recent times.[19] Synthesis of water-soluble glycodendrimers and chalchone dendrimers through click chemistry has been reported from our laboratory.[20] Dendrimers with chiral *S*-(−)-BINOL core exhibit chiroptical, photophysical properties[21], and also used as enantioselective lewis acid catalysts.[22] Moreover, in the current context though optically inactive and cheap core molecules can be employed for the synthesis of dendrimer with quinoline surface group, we prefer to use *S*-(−)-BINOL core for many reasons. The chiral BINOL core-based dendrimer could be used as a chiral base and chiral auxiliary in organic synthesis,[22,23] further by increasing the dendrimer generation, the dendritic wedges would go farther apart which could increase the dihedral angle in the naphthyl unit, thereby making them chiral auxiliary with higher degree of molar rotation values. We report herein the versatile and highly efficient synthesis as well as chiroptical and photophysical properties of a new family of *S*-(−)-BINOL-based quinoline dendrimers **1–3** (Fig. 1) with 1,2,3-triazole as building unit through click chemistry by convergent approach.

The synthesis of 3-(azidomethyl)-2-methoxyquinoline **8** is outlined in Scheme 1. 2-Chloro-3-formylquinoline **4** was synthesized from acetanilide via Vilsmeier–Haack reaction.[24] The reaction of 2-chloro-3-formylquinoline **4** with methanol in the presence of KOH afforded 2-methoxy-3-formylquinoline **5**,[25] which was

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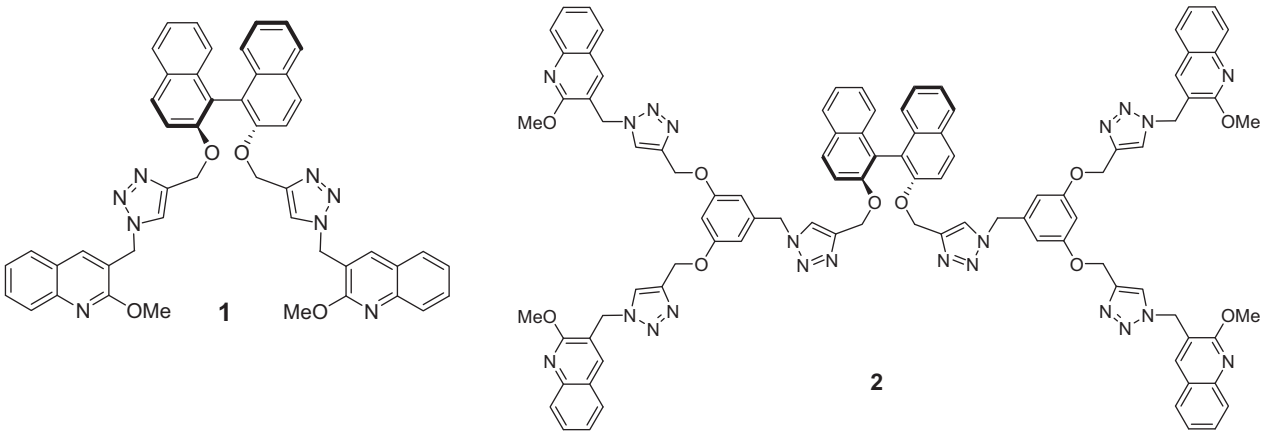


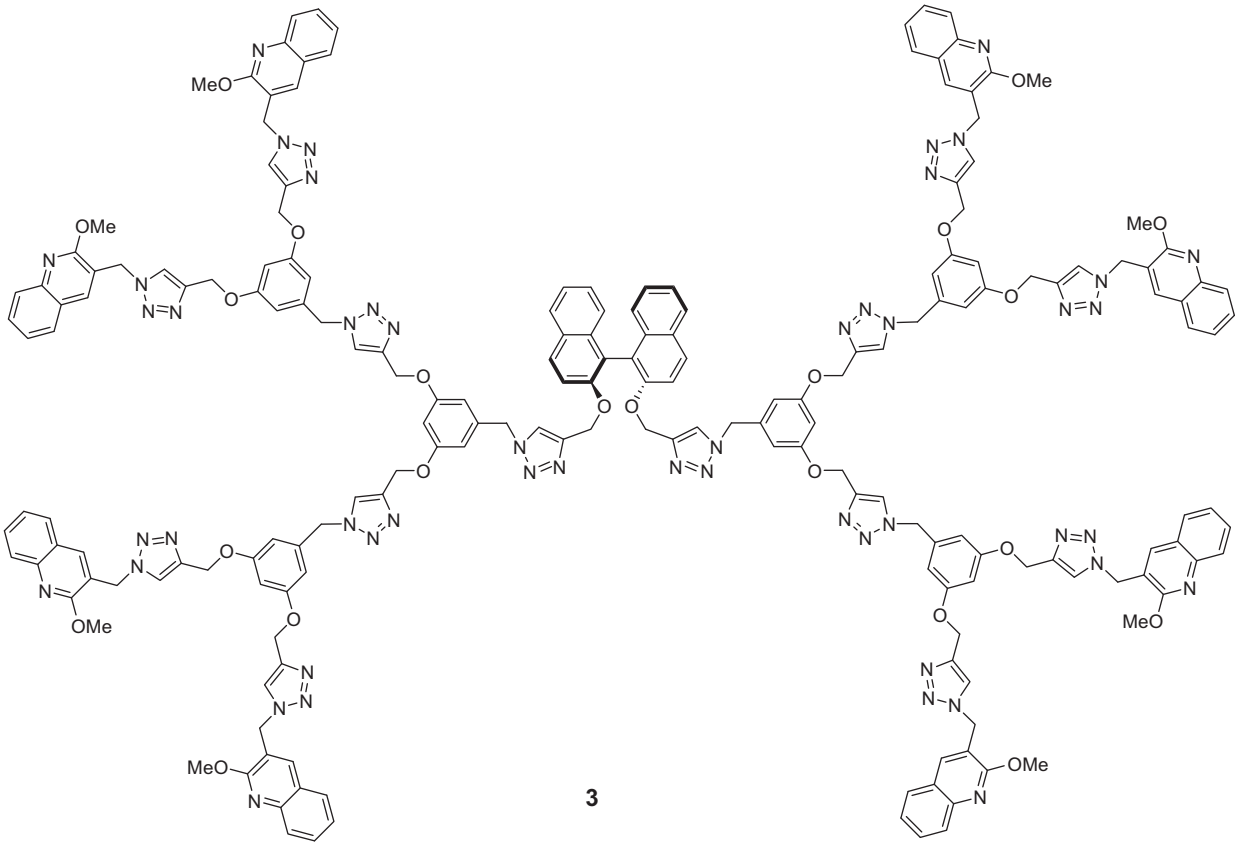
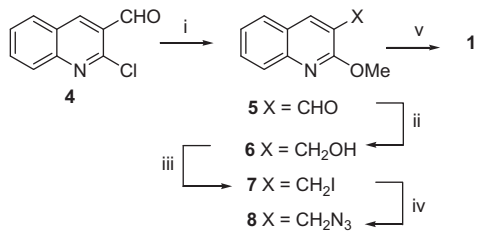


Figure 1. Molecular structure of dendrimers **1**–**3**.



Scheme 1. Synthesis of dendrimer **1**. Reagents and conditions: (i) MeOH, KOH, reflux, 3 h, **5**, 85%; (ii) $NaBH_4$, MeOH, 0 °C to rt, 6 h, **6**, 87%; (iii) PPh_3, I_2, imidazole, 0 °C, 5 h, **7**, 72%; (iv) NaN_3, DMF, 60 °C, 6 h, **8**, 81%; (v) 0.5 equiv bis(propargyloxy)-*S*-(−)-BINOL **9**, $CuSO_4{\cdot}5H_2O$ (5 mol %), sodium ascorbate (10 mol %), H_2O/THF (1:3), rt, 10 h, **1**, 84%.

reduced with $NaBH_4$ in MeOH to give the alcohol **6** which on further reaction with PPh_3 and I_2 in the presence of imidazole in dry CH_2Cl_2 gave 2-methoxy-3-(iodomethyl)quinoline **7** in 64% yield. The reaction of the iodide **7** with NaN_3 in DMF at 60 °C afforded 3-(azidomethyl)-2-methoxyquinoline **8** in 81% yield. The structure of the azide **8** has been confirmed from spectral and analytical data.[27]

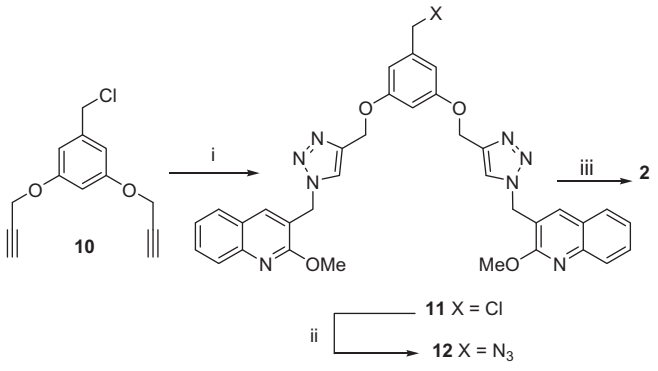
The core unit bis(propargyloxy)-*S*-(−)-BINOL **9** was obtained by the reaction of *S*-(−)-BINOL with propargyl bromide in the presence of K_2CO_3 in DMF as reported earlier.[20a] The reaction[26] of 0.5 equiv of bis(propargyloxy)-*S*-(−)-BINOL **9** with 1 equiv of quinoline azide **8** in the presence of $CuSO_4{\cdot}5H_2O$ (5 mol %) and sodium ascorbate (10 mol %) in a mixture of water and THF (1:3) at room temperature gave the bis-triazole chiral dendrimer **1** in 84% yield (Scheme 1). In ^1H NMR spectrum of dendrimer **1** showed a singlet at δ 3.99 for methoxy protons and two set of doublets at δ 5.06 and 5.15 for methylene protons attached to the *S*-(−)-BINOL and a singlet at δ 5.34 for the methylene protons attached to the triazole

ring in addition to aromatic protons. The ^{13}C NMR spectrum of dendrimer **1** displayed methoxy carbons at δ 49.4 and methylene carbons at δ 51.1, 63.9 respectively, in addition to the aromatic carbons. The structure of the dendrimer **1** was further confirmed from spectral and analytical data.[30]

In order to synthesize the first generation dendrimer **2**, the building unit viz. 3,5-bis(propargyloxy)benzyl chloride **10** was obtained as follows: the bis-propargyl derivative obtained by the reaction of methyl 3,5-dihydroxybenzoate with propargyl bromide in DMF in the presence of K_2CO_3 was treated with LAH followed by the reaction of $SOCl_2$/Py in DCM to give the chloride **10**. The reaction of 3,5-bis(propargyloxy)benzyl chloride **10** with 2 equiv of quinoline azide **8** under the Cu(I)-catalyzed Huisgen 'click reaction' conditions gave the first generation chloride G_1-Cl **11** in 91% yield (AB_2-type). The dendritic chloride **11** with NaN_3 in DMF at 60 °C afforded the first generation azide G_1-N_3 **12** in 83% yield.[28] The reaction of 0.5 equiv bis(propargyloxy)-*S*-(−)-BINOL core unit **9** with 1 equiv of dendritic azide G_1-N_3 **12** in the presence of the Cu(I)-catalyzed Huisgen 'click reaction' conditions generated the (AB_2-type) first generation dendrimer (G_1) **2** in 78% yield (Scheme 2).

The ^1H NMR spectrum of dendrimer **2** showed a singlet at δ 3.98 for methoxy proton and two sets of doublets at δ 4.93 and 5.01 for –CH_2– protons attached to *S*-(−)-BINOL unit and three singlets at δ 5.03, 5.04, and 5.59 for –N–CH_2– and –O–CH_2– protons, in addition to aromatic protons. The ^{13}C NMR spectrum of dendrimer **2** displayed methoxy carbons at δ 49.2 and –N–CH_2– carbons at δ 53.6, 53.8, and 61.9 and –O–CH_2– carbon at δ 63.8 in addition to aromatic carbons. In the MALDI-TOF mass spectrum, the molecular ion peak appeared at *m*/*z* 1723.31 $(M+Na)^+$ and the structure of the dendrimer **2** was further confirmed from spectral and analytical data.[31]

A similar synthetic strategy was adopted for the synthesis of second generation dendrimer **3** from the building block viz. 3,5-bis(propargyloxy)benzyl chloride **10** and dendritic azide G_1-N_3 **12** under Cu(I)-catalyzed Huisgen click reaction conditions to give second generation chloride (G_2-Cl) **13** in 75% yield. The use of NaN_3 in DMF at 60 °C allowed the conversion of the desired dendritic chloride **13** to the dendritic azide G_2-N_3 **14** in 79% yield.[29] The reaction of the bis(propargyloxy)-*S*-(−)-BINOL core unit **9** with 2 equiv of dendritic azide G_2-N_3 **14** in the presence of Cu(I)-catalyzed Huisgen click reaction conditions gave dendrimer **3** (AB_2-type) in 68% yield (Scheme 3). In the MALDI-TOF mass spectrum, the molecular ion peak appeared at *m*/*z* 3541.41 $(M+Na)^+$ and the structure of the dendrimer **3** was further confirmed from spectral and analytical data.[32]



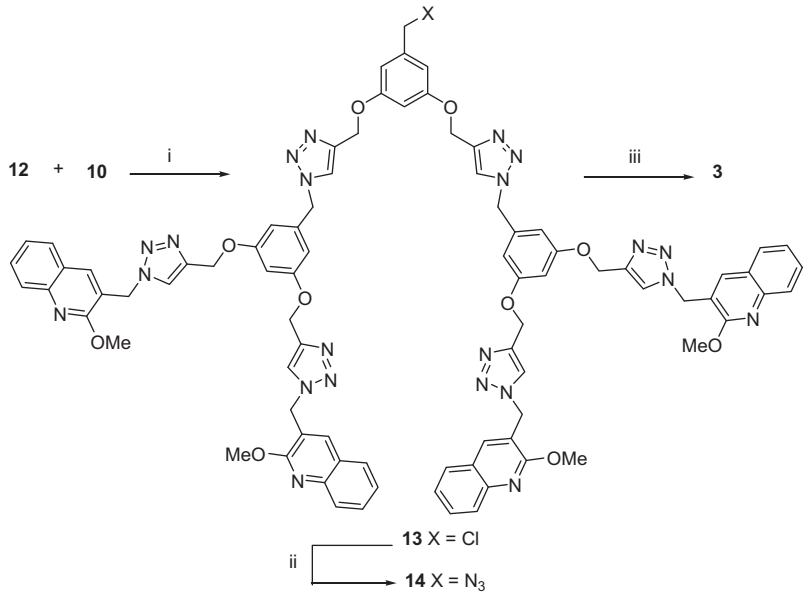
Scheme 2. Synthesis of dendrimer **2**. Reagents and conditions: (i) 2 equiv 2-methoxy-3-azidomethylquinoline **8**, $CuSO_4{\cdot}5H_2O$ (5 mol %), sodium ascorbate (10 mol %), H_2O/THF (1:3), rt, 10 h, **11**, 80%; (ii) 1.5 equiv NaN_3, DMF, 60 °C, 6 h, **12**, 83%; (iii) 0.5 equiv bis(propargyloxy)-*S*-(−)-BINOL **9**, $CuSO_4{\cdot}5H_2O$ (5 mol %), sodium ascorbate (10 mol %), H_2O/THF (1:3), rt, 10 h, **2**, 78%.

Chiroptical studies of enantiopure chiral dendrimers **1–3**: The molar specific rotation values were determined for the chiral dendrimers **1–3** in $CHCl_3$ at 589 nm. The specific rotation $[\alpha]_D^{25}$ and molar rotation data are given in Table 1. The specific rotation value decreases with an increase in the dendrimer generation G_0 to G_2. The molar rotation values are due to the presence of chiral *S*-(−)-BINOL unit which makes the dendrimer as an auxiliary chiral molecule with dendritic wedges. The dihedral angle between the naphthyl units in the BINOL core increases as the generation of the dendrimer increases, which leads to a greater steric repulsion between the dendritic wedges and hence increases to negative values of specific rotation. In our earlier observation with respect to chiral glycodendrimers,[20] the specific rotation of the dendrimer was due to the presence of both the glucose unit and binaphthyl unit and hence the overall rotation values could switch over from negative to positive values as the generation increases. However, in the present study the molar rotation changes to large negative values on passing over from zero to second generation, because of the increase in the dihedral angle at the naphthyl moiety and the dendritic wedges broaden out to a maximum value due to steric hindrance. Similar observation has also been reported by Meijer and co-workers,[33] Chen et al.[34] and Gibson and Rendell[35] in various chiral dendrimer with binaphthyl core unit. However the molar rotation values do not switch over to the positive side, which indicate that broadening of the dihedral angle occurs without exceeding the critical angle of 110°. The enhancement of molar rotation value of the dendrimers, which have the same molar content of the element, upon the addition of large dendritic fragments turns out to be the most interesting result.

Photophysical properties of chiral dendrimers **1–3**: The photophysical data for chiral dendrimers **1–3** are listed in Table 2. Figure 2 shows the absorption spectra of compounds **1–3** in DMSO. There are three major absorption bands at 272, 312, and 324 nm and three shoulder peaks at 282, 298, and 339 nm due to the BINOL and quinoline units, respectively. Molar extinction coefficients of the absorption bands increase significantly as the generation of the dendrimer increases. Also, it should be noted that there is no spectral broadening or spectral shift with increase in generation (Fig. 2) which reflects the perfection of the synthesized quinoline dendrimers. The absorbance in UV spectrum increases relatively to a small extent while passing from zero to first generation due to slight increase in the number of quinoline units from 2 to 4. However, on passing from first to second generation the absorbance probably increases enormously due to the presence of a large number of quinoline units viz. 8.

Figure 3 shows fluorescence spectra of dendrimers **1–3** in DMSO and the fluorescence parameters for these compounds are collected in Table 2. As shown in Figure 3, on excitation at 324 nm, the dendrimers **1–3** give emission bands at 374 nm due to the quinoline units. It is clear from Figure 3, the fluorescence intensity of the chiral dendrimers increases as the generation grows, which is consistent with the increased number of fluorophoric quinoline units, otherwise known as multivalency effect[36] in dendrimer chemistry. The fluorescence quantum yields Φ_f of dendrimers **1–3** have been measured in DMSO using anthracene as the standard. The quantum yields of dendrimers **1–3** are listed in Table 2. As the generation increases, the quantum yield decreases consistently.

To further prove the observed decrease in the quantum yield we have carried out fluorescence lifetime measurement by exciting the sample at 295 nm using time correlation single photon counting method. Lifetime of all the three dendrimers shows biexponential decay as shown in Figure 4. Lifetime values with their relative amplitudes are given in Table 3. The average lifetime of the dendrimers is found to be lower with increasing length of the dendritic arm, which is in good agreement with the observed decrease in fluorescence quantum yield of dendrimers **1–3**. The observed biexponential



Scheme 3. Syntheis of dendrimer **3**. Reagents and conditions: (i) $CuSO_4{\cdot}5H_2O$ (5 mol %), sodium ascorbate (10 mol %), H_2O/THF (1:3), rt, 10 h, **13**, 75%; (ii) 1.5 equiv NaN_3, DMF, 60 °C, 6 h, **14**, 79%; (iii) **9**, $CuSO_4{\cdot}5H_2O$ (5 mol %), sodium ascorbate (10 mol %), H_2O/THF (1:3), rt, 10 h, **3**, 72%.

Table 1
Specific rotation of chiral quinoline dendrimers **1–3**

Compound	Mass calculated	$[\alpha]_D^{25}$	Molar rotation
1	790.03	−41.40	−327.07
2	1700.64	−24.97	−424.64
3	3521.33	−16.65	−586.30

Table 2
Photophysical properties data for chiral dendrimers **1–3** in DMSO (1×10^{-5} mol/L)

Compound	λ_{abs} max (nm)	ε (mol/L) ($\times 10^4$)	λ_{em} max (nm)	Φ_F
1	272	1.74	374	0.65
	312	1.12		
	324	1.33		
2	272	2.64	374	0.60
	312	1.62		
	324	1.85		
3	272	4.94	374	0.49
	312	3.02		
	324	3.39		

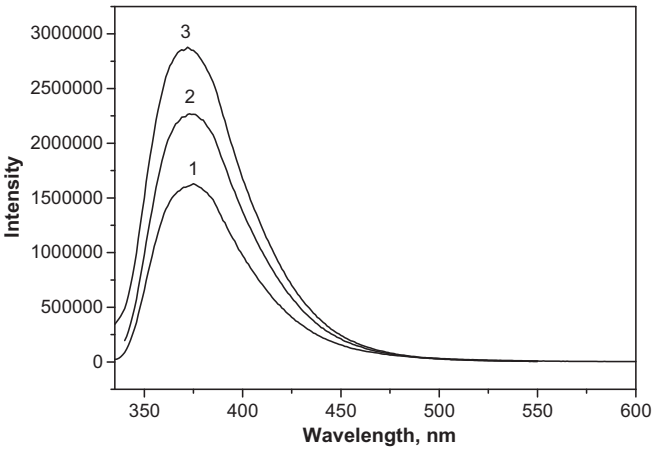


Figure 3. Fluorescence spectra of the chiral dendrimers **1–3** in DMSO (1×10^{-5} mol/L).

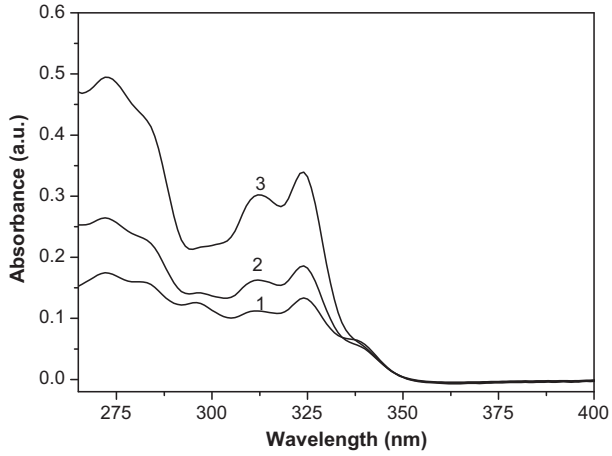


Figure 2. Absorption spectra of chiral dendrimers **1–3** in DMSO (1×10^{-5} mol/L).

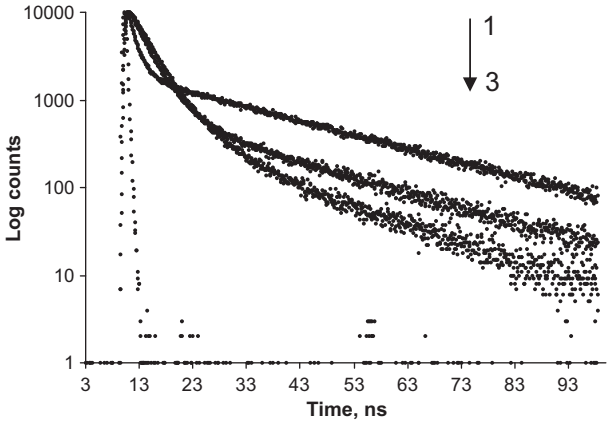


Figure 4. Fluorescence decay curve for the dendrimers **1–3** in DMSO. The excitation wavelength is 295 nm.

Table 3
Fit parameters for fluorescence decay curves shows in Figure 4 in DMSO (1×10^{-5} mol/L)

Compound	τ_1 (ns)	B_1	τ_2 (ns)	B_2	χ^2	τ_{avg} (ns)
1	1.48	29.27	26.27	70.73	1.09	19.01
2	3.24	67.78	21.27	32.22	1.18	9.05
3	3.82	79.45	16.32	20.55	1.11	6.39

fluorescence decay is probably due to the presence of two fluorophoric units viz. BINOL and quinoline and τ_1 decay time is due to the quinoline moiety, which increases together with their relative amplitude as the number of quinoline unit increases from zero to second generation. The τ_2 decay time could be due to BINOL unit and the decay time and its amplitude has decreased because of excess crowding in G_2 generation. The number of BINOL unit remains the same in all the dendrimers. Only when the generation increases the crowding increases from G_0 to G_2 and hence biexponential decay is observed. Therefore, the decreased quantum yield and lifetime are attributed to self-quenching effect and the enhancement of nonradiative transition in the higher generation dendrimers compared to the lower generations.

In conclusion, synthesis of 1,2,3-triazole-linked chiral quinoline dendrimers has been achieved by click reaction. Though, UV absorption and emission spectra did not show the changes in absorption and emission bands, the molar extinction coefficients and fluorescence intensity increased with increase in dendrimer generation due to increase in the number of quinoline surface group. Fluorescence quantum yield and lifetime were found to be lower for the higher generations due to self-quenching effect and the enhancement of nonradiative transitions. The detailed biological activities and the use of such dendrimers for the cleavage of DNA are underway.

Acknowledgments

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References and notes

1. (a) Frechet, J. M. J. *Science* **1994**, *263*, 1710; (b) Tomalia, D. A. *Adv. Mater.* **1994**, *6*, 529.
2. (a) Adronov, A.; Frechet, J. M. J. *Chem. Commun.* **2000**, 1701; (b) Gilat, S. L.; Adronov, A.; Frechet, J. M. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 1422.
3. (a) Kleiji, A. W.; Gossage, R. A.; Gebbink, R. J. M. K.; Brinkmann, N.; Reijerse, E. J.; Kragl, U.; Lutz, M.; Speck, A. L.; Koten, V. G. *J. Am. Chem. Soc.* **2000**, *122*, 12112; (b) Mager, M.; Becke, S.; Windisch, H.; Denninger, U. *Angew. Chem., Int. Ed.* **2001**, *40*, 1898.
4. (a) Svenson, S.; Tomalia, D. A. *Adv. Drug Delivery Rev.* **2005**, *57*, 2106; (b) Majoros, I. J.; Myc, A.; Thomas, T.; Mehta, C. B.; Baker, J. R., Jr. *Biomacromolecules* **2006**, *7*, 572.
5. Wiener, E. C.; Brechbiel, M. W.; Brothers, H.; Magin, R. L.; Tomalia, D. A.; Lauterbur, P. C. *Magn. Reson. Med.* **1994**, *3*, 1.
6. Kleiji, A. W.; Gossage, R. A.; Gebbink, R. J. M. K.; Brinkmann, N.; Reijerse, E.; Vogtle, F.; Vicinelli, V.; Ceroni, P.; Maestri, M.; Balzani, V. *Angew. Chem., Int. Ed.* **2002**, *41*, 3595.
7. (a) Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 3192; (b) Burley, G. A.; Gierlich, J.; Mofid, M. R.; Nir, H.; Tal, S.; Eichen, Y.; Carell, T. *J. Am. Chem. Soc.* **2006**, *128*, 1398.
8. (a) Jiuyan, Li.; Liu, Di. *J. Mater. Chem.* **2009**, *19*, 7584; (b) Shih-Chen, Lo.; Burn, P. L. *Chem. Rev.* **2007**, *107*, 1097.
9. (a) Chaudhuri, M. K.; Hussain, S. *J. Chem. Sci.* **2006**, *118*, 199; (b) Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 605; (c) Jegou, G.; Jenekhe, S. A. *Macromolecules* **2001**, *34*, 7926.
10. (a) Hu, H.-Y.; Chen, C.-F. *Tetrahedron Lett.* **2006**, *47*, 175; (b) Ghosh, K.; Adhikari, S. *Tetrahedron Lett.* **2008**, *49*, 658.
11. (a) Liang, F.; Xie, Z.; Wang, L.; Jing, X.; Wang, F. *Tetrahedron Lett.* **2002**, *43*, 3427; (b) Jiang, P.; Zhu, W.; Gan, Z.; Huang, W.; Li, J.; Zeng, H.; Shi, J. *J. Mater. Chem.* **2009**, *19*, 4551.
12. (a) Musiol, R.; Jampilek, J.; Kralova, K.; Richardson, D. R.; Kalinowski, D.; Podeszwa, B.; Finster, J.; Niedbala, H.; Palka, A.; Polanski, J. *Bioorg. Med. Chem.* **2007**, *15*, 1280; (b) Moret, V.; Laras, Y.; Cresteil, T.; Aubert, G.; Ping, D. Q.; Di, C.; Barthelemy-Requin, M.; Beclin, C.; Peyrot, V.; Allegro, D.; Rolland, A.; Angelis, F. D.; Gatti, E.; Pierre, P.; Pasquini, L.; Petrucci, E.; Testa, U.; Kraus, J. *Eur. J. Med. Chem.* **2009**, *44*, 558.
13. Kwon, T. W.; Alam, M. M.; Jenekhe, S. A. *Chem. Mater.* **2004**, *16*, 4657.
14. Tsukube, H.; Suzuki, Y.; Paul, D.; Kataoka, Y.; Shinoda, S. *Chem. Commun.* **2007**, 2533.
15. (a) Shen, L.; Li, F.; Sha, Y.; Hong, X.; Huaung, C. *Tetrahedron Lett.* **2004**, *45*, 3961; (b) Kikkeri, R.; Hossain, L. H.; Seeberger, P. H. *Chem. Commun.* **2008**, 2127.
16. (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004; (b) Tornoe, C. M.; Christensen, C.; Maldal, M. J. *J. Org. Chem.* **2002**, *67*, 3057.
17. (a) Subbaraman, R.; Ghassemi, H.; Zawodzinski, T. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 2238; (b) Martwiseta, S.; Woudenberga, R. C.; Granados-Focila, S.; Yavuzcetinb, O.; Yuominenb, M. T.; Coughlin, E. B. *Solid State Ionics* **2007**, *178*, 1398.
18. Aravinda, T.; Bhojya Naik, H. S.; Prakash Naik, H. R. *Int. J. Pept. Res. Ther.* **2009**, *15*, 273.
19. (a) Lee, J. W.; Kim, B. K.; Hen, S. C.; Kim, J. H. *Bull. Korean Chem. Soc.* **2009**, *30*, 157; (b) Li, Z.; Yu, G.; Wu, W.; Liu, Y.; Ye, C.; Qin, L. Z. *Macromolecules* **2009**, *42*, 3864; (c) Shen, X.; Liu, H.; Li, Y.; Liu, S. *Macromolecules* **2008**, *41*, 2421; (d) Elmer, S. L.; Man, S.; Zimmerman, S. C. *Eur. J. Org. Chem.* **2008**, 3845.
20. (a) Rajakumar, P.; Ananthan, R.; Kalpana, V. *Synlett* **2009**, 1417; (b) Rajakumar, P.; Raja, S. *Synth. Commun.* **2009**, *39*, 3888.
21. Ma, L.; Lee, S. J.; Lin, W. *Macromolecules* **2002**, *35*, 6178.
22. Liu, G.-H.; Fan, Q.-H.; Yang, X.-Q.; Chen, X.-M. *ARKIVOC* **2003**, *ii*, 123.
23. (a) Bandyopadhyaya, A. K.; Sangeetha, N. M.; Maitra, U. *J. Org. Chem.* **2000**, *65*, 8239; (b) Pu, L. *Chem. Rev.* **1998**, *98*, 2405.
24. Meth-Cohn, O.; Narine, B.; Tarnowski, B. *Tetrahedron Lett.* **1979**, *33*, 3111.
25. Kuethe, J. T.; Wong, A.; Qu, C.; Smitrovich, J.; Davies, I. W.; Hughes, D. L. *J. Org. Chem.* **2005**, *70*, 2555.
26. *General procedure for the Cu-catalyzed Huisgen click reaction*: acetylenic derivative (1.0 mmol) was added to dendritic azide (2.0 mmol) in a mixture of THF and water (3:1) solution. Solid sodium ascorbate (10 mol %) was added to the reaction mixture, followed by the addition of $CuSO_4{\cdot}5H_2O$ (5 mol %). The reaction mixture was stirred overnight at rt. The solvent was evaporated under reduced pressure and the crude product was dissolved in EtOAc (100 mL), washed with NH_4Cl solution (50 mL), brine solution (50 mL), H_2O (100 mL), dried (Na_2SO_4), and concentrated. Evaporation of the solvent afforded the residue which was purified by column chromatography (silica gel) with $CHCl_3$/MeOH (99.7:0.3) as eluent to give the corresponding triazole.
27. *Azide [G_0]–CH_2–N_3* **8**: pale yellow liquid; yield: 81%; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 4.05 (s, 3H); 4.14 (s, 2H); 7.33 (t, 1H, J = 7.5 Hz); 7.56 (t, 1H, J = 7.7 Hz); 7.66 (d, 1H, J = 7.8 Hz); 7.79 (t, 1H, J = 8.1 Hz); 7.88 (s, 1H). ^{13}C NMR: (75 MHz, $CDCl_3$) δ 50.1, 53.6, 120.1, 124.3, 124.9, 127.0, 127.4, 129.7, 137.2, 146.2, 160.1. MS (ESI): m/z = 215.1 [M+1]. Anal. Calcd for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.15. Found: C, 61.56; H, 4.79; N, 26.24.
28. *First generation dendritic azide [G_1]–CH_2–N_3* **12**: white solid; yield: 83%; mp: 158 °C; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 4.11 (s, 6H); 4.23 (s, 2H); 5.18 (s, 4H); 5.64 (s, 4H), 6.56 (s, 2H); 6.60 (s, 1H); 7.39 (t, 2H, J = 7.5 Hz); 7.61–7.68 (m, 4H); 7.71 (s, 2H), 7.81 (s, 2H); 7.85 (d, 2H). ^{13}C NMR: (75 MHz, $CDCl_3$) δ 49.2, 53.8, 54.6, 62.1, 101.7, 107.5, 119.1, 123.3, 124.6, 124.8, 127.1, 127.6, 130.2, 137.8, 138.3, 143.9, 146.6, 159.5, 159.6. MS (ESI): m/z = 670.3 [M+1]. Anal. Calcd for $C_{35}H_{31}N_{11}O_4$: C, 62.77; H, 4.67; N, 23.01. Found: C, 62.86; H, 4.61; N, 23.13.
29. *Second generation dendritic azide [G_2]–CH_2–N_3* **14**: white solid; yield: 79%; mp: 118 °C; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 4.10 (s, 12H); 4.17 (s, 2H); 5.09 (s, 12H); 5.53 (s, 4H), 6.60 (s, 8H); 6.48 (s, 6H); 6.55 (s, 1H); 6.59 (s, 2H); 7.36 (t, 4H, J = 7.1 Hz); 7.58 (d, 2H, J = 6.6 Hz); 7.63 (d, 8H, J = 7.5 Hz); 7.71 (s, 4H); 7.78 (s, 4H); 7.87 (d, 4H, J = 8.4 Hz). ^{13}C NMR: (125 MHz, $CDCl_3$) δ 49.3, 53.9, 54.1, 54.6, 61.9, 70.0, 101.6, 102.0, 107.4, 107.5, 119.1, 123.1, 123.6, 124.6, 124.8, 126.9, 127.6, 130.2, 136.8, 137.7, 138.3, 143.6, 144.1, 146.5, 159.4, 159.5, 159.8. MS (ESI): m/z = 1580.5 [M+1]. Anal. Calcd for $C_{83}H_{73}N_{25}O_{10}$: C, 63.07; H, 4.66; N, 22.15. Found: C, 62.93; H, 4.59; N, 22.27.
30. *Dendrimer* **1**: white solid; yield: 84%; mp: 88 °C; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 3.99 (s, 6H); 5.06 (d, 2H, J = 12.6 Hz); 5.15 (d, 2H, J = 12.6 Hz); 5.34 (s, 4H); 6.58 (s, 2H); 7.05 (d, 4H, J = 3.6 Hz); 7.14–7.19 (m, 2H); 7.35–7.40 (m, 4H); 7.45 (s, 2H); 7.53 (d, 2H, J = 8.1 Hz); 7.62–7.67 (m, 4H); 7.71 (s, 2H); 7.87 (d, 2H, J = 8.4). ^{13}C NMR: (125 MHz, $CDCl_3$) δ 48.9, 53.7, 63.9, 115.8, 119.1, 120.6, 122.9, 123.9, 124.6, 124.8, 125.3, 126.3, 127.1, 127.6, 127.8, 129.4, 129.4, 130.2, 133.8, 137.8, 144.8, 146.5, 153.5, 159.4.. MS (ESI): m/z = 791.2 [M+1]. Anal. Calcd for $C_{48}H_{38}N_8O_4$: C, 72.90; H, 4.84; N, 14.17. Found: C, 72.75; H, 4.90; N, 14.24.
31. *Dendrimer* **2**: white solid; yield 78%; mp: 106 °C; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 3.99 (s, 12H); 4.93 (d, 2H, J = 12.6 Hz); 5.01 (d, 2H, J = 11.4); 5.03 (s, 4H); 5.04 (s, 8H); 5.59 (s, 8H); 6.34 (s, 4H); 6.51 (s, 2H); 6.59 (s, 2H); 7.07–7.12 (m, 4H); 7.18–7.23 (m, 2H); 7.31–7.36 (m, 6H); 7.57–7.61 (m, 8H), 7.73 (s, 10H, J = 9.9 Hz); 7.80 (d, 6H, J = 8.7 Hz). ^{13}C NMR: (75 MHz,$CDCl_3$) δ 49.2, 53.6, 53.8, 61.9, 63.8, 101.7, 107.4, 115.9, 119.1, 120.6, 122.5, 123.6, 123.9, 124.6, 124.8, 125.3, 126.4, 127.1, 127.6, 127.9, 129.5, 130.2, 133.9, 136.9, 138.3, 143.6, 145.1, 146.5, 153.6, 159.4, 159.7. MS (MALDI-TOF): m/z = 1723.31 $[M+Na]^+$. Anal. Calcd For $C_{96}H_{80}N_{22}O_{10}$: C, 67.75; H, 4.74; N, 18.11. Found: C, 67.87; H, 4.83; N, 18.13.
32. *Dendrimer* **3**: white solid; yield 72%; mp: 106 °C; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 4.04 (s, 24H); 4.81 (d, 4H, J = 12.9 Hz); 4.90 (d, 4H, J = 7.9 Hz); 4.94 (s, 8H); 5.01 (s, 16H); 5.30 (s, 8H); 5.53 (s, 16H), 6.17 (s, 4H); 6.45 (s, 10H); 6.48 (s, 2H); 6.52 (s, 4H); 7.02 (s, 4H); 7.13–7.21 (m, 2H); 7.32 (t, 8H, J = 7.3 Hz); 7.55–7.60 (m, 20H); 7.64 (s, 8H); 7.67–7.73 (m, 14H); 7.79 (d, 8H,

J = 8.7 Hz). ^{13}C NMR: (125 MHz, $CDCl_3$) δ 49.2, 53.5, 53.8, 53.9, 61.7, 61.7, 61.9, 63.7, 101.6, 101.9, 107.3, 107.4, 115.8, 119.1, 120.5, 122.7, 123.4, 123.6, 123.9, 124.6, 124.6, 127.9, 129.4, 130.2, 133.8, 136.9, 138.2, 143.5, 143.7, 146.5, 153.5, 159.4, 159.6, 159.7. MS (MALDI-TOF): m/z = 3541.41 $[M+Na]^+$. Anal. Calcd for $C_{192}H_{164}N_{50}O_{22}$: C, 65.44; H, 4.69; N, 19.88. Found: C, 65.56; H, 4.75; N, 20.01.

33. (a) Peerling, H. W. I.; Meijer, E. W. *Eur. J. Org. Chem.* **1998**, 573; (b) Rosini, C.; Superchi, S.; Peerlings, H. W. I.; Meijer, E. W. *Eur. J. Org. Chem.* **2000**, 61.
34. Chen, Y.-M.; Chen, C.-F.; Xi, F. *Chirality* **1998**, *10*, 661.
35. Gibson, S. E.; Rendell, J. T. *Chem. Commun.* **2008**, 922.
36. Galeazzi, S.; Hermans, T. M.; Paolino, M.; Anzini, M.; Mennuni, L.; Giordani, A.; Caselli, G.; Makovee, F. *Biomacromolecules* **2010**, *11*, 182.