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An Efficient and Controlled Synthesis of Persulfonylated G1 Dendrimers Via Click Reaction

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ABSTRACT: This work presented the first report on controlled synthesis of clickable dendrimers using aromatic and heteroaromatic cores and persulfonylated dendrons. Due to poor thermal stability of persulfonylated dendrons, CuAAC reaction condition was standardized at the room temperature. Click reactions went smoothly with $Cu(PPh_3)_3Br$ complex in the presence of tridentate chelating ligands and produced copper free G1 dendrimers in excellent yield. This methodology has now unveiled the peripheral decoration of high generation POPAM dendrimers with persulfonyl group in one step click reaction.

Introduction

Synthesis of bio-inspired molecules has fascinated the recent research activities. Among them synthesis of macromolecules with biologically active scaffold is of paramount interest.[1-3]

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Furthermore, recent year has witnessed unprecedented growth of research in the area of dendrimer synthesis for their application in the field of biomedical science[4,5] and nanoscience[6,7]. Consequently, development of dendrimers with well-defined size and shape is of eminent interest because macromolecular dendritic species generally suffer from structural imperfections and polydispersity.[9] However, the synthesis of dendritic molecules is an apparently straight forward iterative process,[10,11] yet, production of high generation dendrimers in good yield with high purity is challenging. To overcome this issue, click reactions are being used for the magnificent yield of dendrimers.[12,13] The azide and alkyne based click reactions incorporates 1,2,3-triazole ring in the branching positions of the dendrimers. Since triazoles are efficient ligand for Cu(I) complexation, therefore, selection of catalyst and ligand is a challenging task.[14-15] Moreover, functionalization of dendrimers at the perifery via N,N-bis-sulfonylation with various sulfonyl chlorides has been developed as a controlled and selective functionalization, but the difficulty arose with peripheral *p*-nitro benzenesulfonyl (*p*-Ns or nosyl) functional groups which convert back into corresponding amines.[16-18] No doubt, due to commercial availability of oligo-amines, POPAM and PAMAM dendrimers, these have often been decorated at their periphery with diverse groups aiming at the introduction of a specific function and consecutive dendrimer growth.[19] This was usually restricted to the complete functionalization at each of the peripheral amino groups. Therefore, such functionalization often lacks the selectivity and a monodisperse product.[9,16] Despite this, the groundwork on sulfone based clickable dendrimers is yet not reported in literature and its synthetic exploration is crucial.

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Results and Discussion

In this preliminary work we have synthesized alkyne functionalized aromatic and heteroaromatic cores (Scheme 1) and azide functionalized persulfonylated termini (Scheme 2). Subsequently, the obtained azide functionalized dendrons and alkyne functionalized cores were stitched together via Cu(I)-catalyzed Azide-Alkyne Cycloaddition (CuAAC) reaction. Since *p*-nosyl amines are thermally unstable, therefore, reaction condition for the click reaction has been standardized at the ambient temperature. Although, mere triethylamine is capable of stabilizing the copper(I) active species even in reactions carried out 'on water' yet the selection of appropriate ligand and solvent is consequential in the synthesis of macromolecues.[20,21] Table 1 shows the screening of copper catalyst and nitrogen containing ligands/bases. Inasmuch the triazole ring constructed in the click reaction itself have capability to form stable copper complex in the reaction media, therefore, use of nitrogen containing ligands/bases as an additive must be having the higher affinity towards stable copper complexation than the generated triazole ring in the reaction. It was observed that in the presence of CuI and monodentate ligands yield of **D2** was very low while **D6** was negligible. Lower yield of both the dendrimers revealed that generated dendrimers formed stable copper complexes than the DIPEA. Therefore, we checked the yield of dendrimers under same condition by adding CuI form 0.3 mole % to 10 mole % but yield was not improved satisfactorily. Subsequently, use of tridentate chelating ligands such as tris(benzyltriazolylmethyl)amine (TBTA), *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA), tris(2-benzimidazolylmethyl)amine $(BimH)_3$, Tris(2-pyridylmethyl)amine (TPMA) and tris[2-(dimethylamino)ethyl]amine **(**Me6TREN) produced up to 80-85 % yield with only 0.3 mole % of CuI.[22-23] It was observed that use of less hindered ligands lowered the yield of D8 while hindered ligands improved the yield as well as lowered the reaction time. After screening

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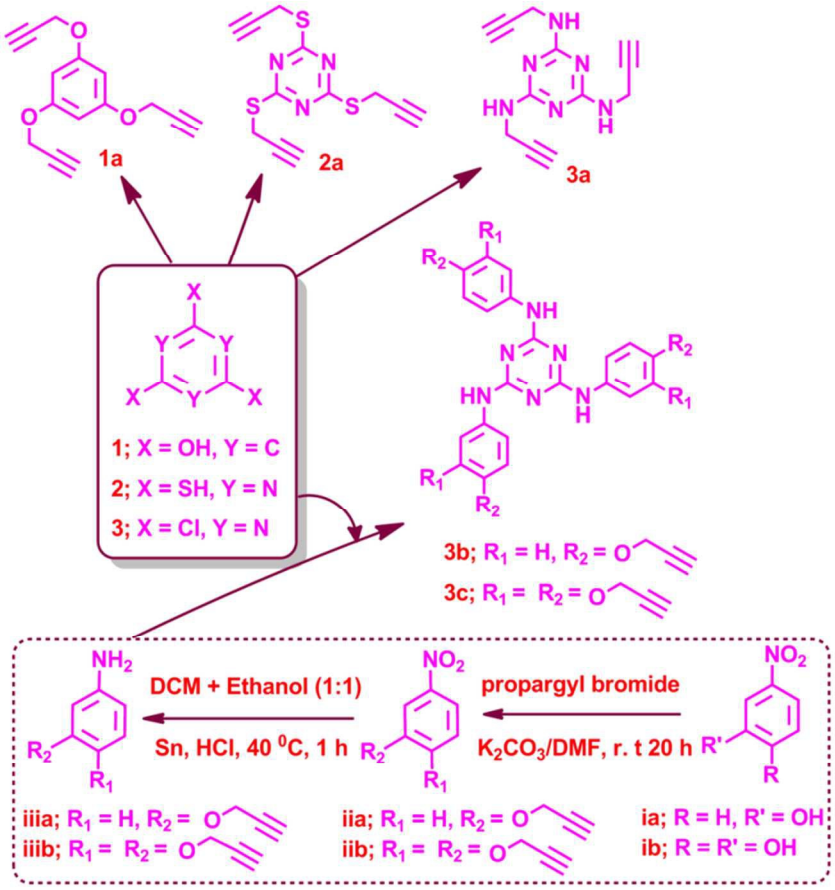
the ligands with CuI, click reaction was tested with $Cu(PPh_3)_3Br$. It is well known in the literature that PPh_3 improve the solubility of the catalyst in the reaction solvent (i.e. DCM) therefore it allowed for comparatively lower copper loadings. Consequently, dendrimers obtained with $Cu(PPh_3)_3Br$ / TPMA or Me_6TREN are highly pure and copper free.

Scheme 1. Synthesis of Alkyne Terminated Clickable Core Molecules 1a, 2a and 3a-c



Scheme 2. Synthesis of Azide Functionalized Persulfonylated Dendrons 5a-c

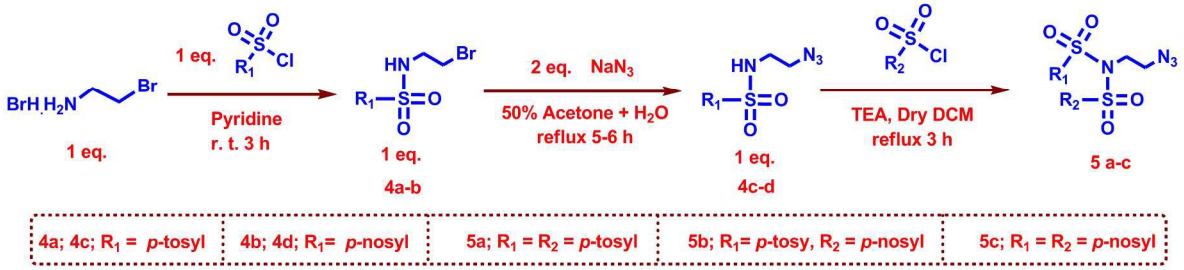


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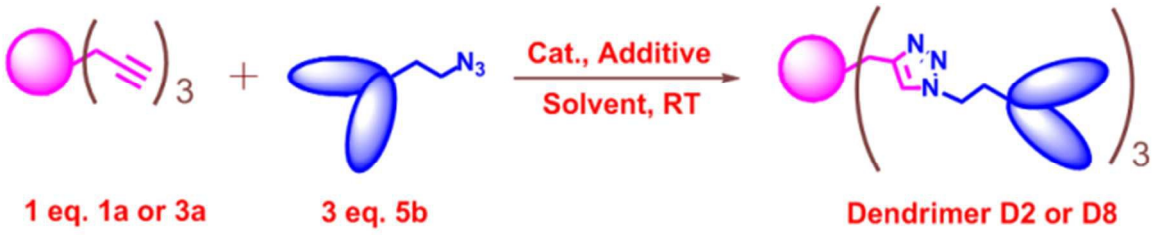
Table 1. Screening of Catalysts and Additives for CuAAC Reaction of Dendron and Core Molecules



S. No.	Catalyst (0.3 mol%)	Solvent	Additive (0.3 mol%)	Time (h)	Yield (%) [a] D2/D8
1.	$CuSO_4.5H_2O$	THF/H_2O	NaAsc	24	trace
2.	CuI	THF	DIPEA	24	10/trace
3.	CuI	DCM	DIPEA	24	30/5
4.	CuI	DCM	DBU	24	23/trace
5.	CuI	DCM	TBTA	8	55/20
6.	CuI	DCM	PMDTA	8	65/60
7.	CuI	DCM	$(BimH)_3$	8	50/32
8.	CuI	DCM	TPMA	3	85/82
9.	CuI	DCM	Me_6TREN	3	85/80
10.	$Cu(PPh_3)_3Br$	DCM	None	24	35/trace
11.	$Cu(PPh_3)_3Br$	DCM	DIPEA	8	50/30
12.	$Cu(PPh_3)_3Br$	DCM	PMDTA	4	90/88
13.	$Cu(PPh_3)_3Br$	DCM	TPMA	1	98/95
14.	$Cu(PPh_3)_3Br$	DCM	Me_6TREN	1	99/97

[a]Isolated yield has been reported. Since loss of sulfonyl group was common in these reactions therefore ^1H NMR did not predict the exact percent conversion of the products.

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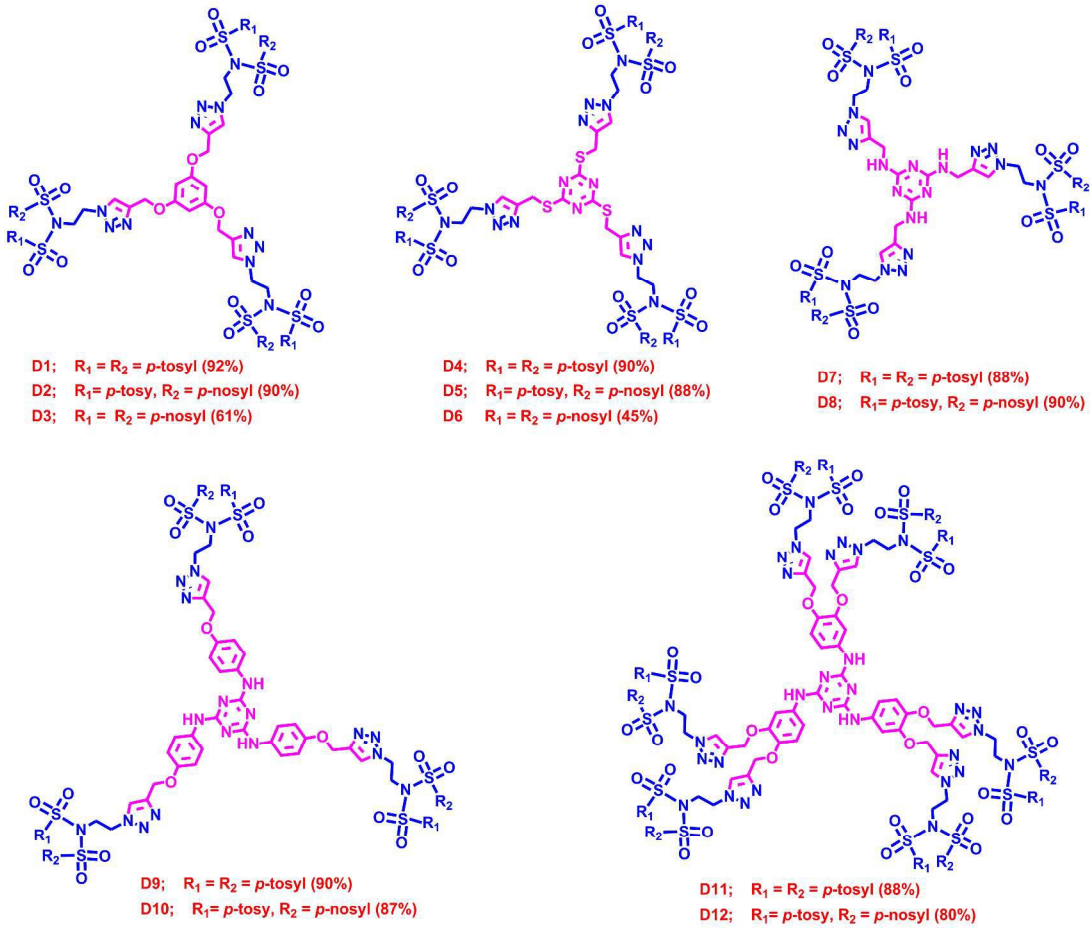
The scope of this reaction was then explored on various dendrons and cores (Scheme 3). The use of alkyne terminated simple cores (**1a**, **2a** and **3a**) and hypercores (**3b** and **3c**) did not affect the reaction rate, except bis-nosyl dendron (**5c**) which showed poor reactivity perhaps due to least stability under reaction condition. To our knowledge, this is the first time that a persulfonylated clickable dendrimers have been designed and structural purity of the G1-dendrimers were fully confirmed by means of NMR, GPC and MALDI-TOF spectrometry. From the ^{1}H and ^{13}C NMR spectra it is clear that all dendrimers possessed almost symmetrical structures in their solution phase (see in supporting information). Although dendrimers are often

Scheme 3. Synthesized Persulfonylated Dendrimers D1-12



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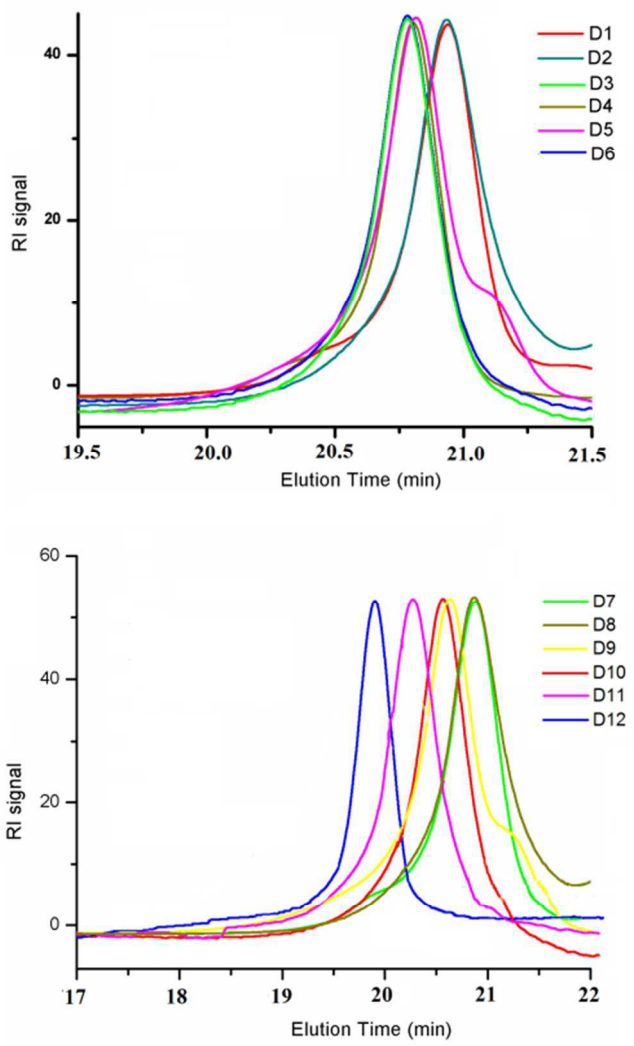

Figure 1. GPC curves of D1-D6 (upper) and D7-D12 (below) after purification.

described as a polymer with excellent PDI (as low as 1.01), this is obtained only after extensive purification. The structural heterogeneity arose from undesired side-reactions during synthesis directly affect the weight-average (Mw) molecular weight, and PDI of the dendrimers. Therefore, GPC analysis was performed after purification by column chromatography. GPC analysis (Figure 1) determined the well-defined molecular structure for all the dendrimers with a low polydispersity ranging from 1.01 to 1.03. The Mw of the dendrimers increases from D1 = 1239 to D12 = 2880 and their retention time varies from 21.00 to 19.85 minutes.

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Matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry is frequently used for the dendrimer characterization due to the common coupling to time-of-flight analyzers that offer a broad mass range. Although, MALDI-MS may point to the presence of large amounts of defects, because they may be formed during laser irradiation.[24] The wavelength of the light required for photocleavage of sulfonamides falls in the UV range (i.e. 254 nm) which is far below the wavelength of the N_2 laser of MALDI instrument (i.e. 337 nm). But photochemical cleavage of the S−N bonds cannot be ignored at all because UV spectra of the dendrons show absorption around 330-336 nm and thus it has possibility to absorb light energy from the MALDI laser. To show the clear evidence for synthetic advantage of the catalysts, it has been tried to isolate the dendrimers with and without copper complex. To our great delight, purification of **D4** obtained by CuI catalyst delivered the **D4** with copper. The structurally perfect dendrimer appears with quite intense signals along with loss of SO_2 from parent ion with quite low intensity (Figure 2 left). Interestingly, the copper bounded **D4** shows intense signal at $[M+Cu+H]^+$ and second intense signal at $[M+2Cu+H]^+$ followed by low intense signals at $[M+Cu-Ts+H]^+$and $[M+2Cu-3Ts+H]^+$ (Figure 2 middle). The tentative mechanism for the loss of SO_2 and tosylsulfinic acid has been shown in Figure 2 (right). The most striking results came from MALDI is the photochemical cleavage of the S−N bonds. The copper free dendrimer losses only SO_2 keeping other parts of the molecule connected to each other through intramolecular ipso substitution in a concerted mechanism, while copper bounded dendrimer goes for detosylation through 1,2-elimination reactions.[17]

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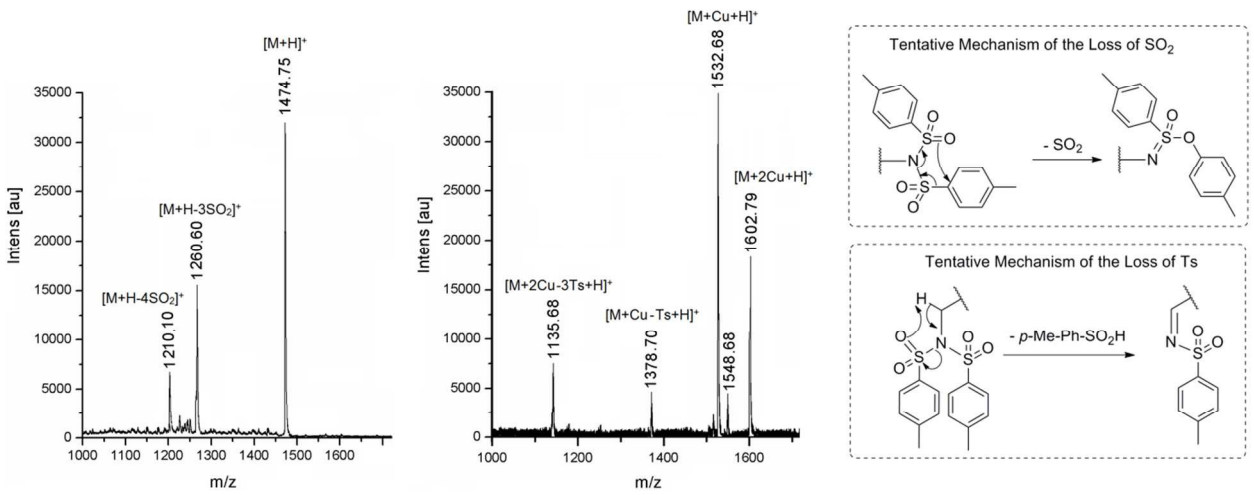

Figure 2. MALDI-TOF mass spectra of **D4** without copper complex (left) and with copper complex (middle) and tentative mechanism for the loss of SO_2 (right upper) and Ts (right lower).

Conclusions

Overall, it can be concluded that we have developed an efficient and highly controlled reaction condition for the synthesis of peripheral persulfonylated dendrimers via CuAAC reaction at room temperature. Yield of persulfonylated dendrimers in CuI catalyzed reactions were very low or in trace amount with DIPEA and DBU but addition of tridentate chelating ligands improved the yield to some extent as well as reduced the reaction time. Therefore, it can be estimated that the *in situ* generated dendrimers worked as competitive ligands for the copper center. Eventually we find $Cu(PPh_3)_3Br$ with TPMA or Me_6TREN as an excellent catalyst for the production of copper free dendrimers. Further, GPC analysis revealed that all dendrimers are monodisperse with PDI = 1.01 - 1.3. However, MALDI evinced the molecular perfection of the dendrimers with intense signals at $[M+H]^+$. After successful development of peripheral persulfonylated dendrimers with high molecular perfection, now decoration of higher generation POPAM dendrimer at periphery

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would be easy. Consequently, we are now developing the higher generation POPAM based persulfonylated clickble dendrimers using this methodology.

EXPERIMENTAL SECTION

General Considerations. All reagents and solvents used were of pure analytical grade. The glassware used in the experiments was carefully cleaned and oven dried. Completion of reaction was checked by commercially available thin layer chromatography (TLC) from Merck, made up of silica gel 60/Kieselguhr F_{254} precoated on Aluminum sheets (thickness 0.2 mm). Column chromatography was performed using Merck silica gel (100-200 mesh). Visualization of spots on TLC plate was accomplished with UV light. Products yield refer to either crude or isolated yield after column chromatography. ^{1}H and ^{13}C NMR spectra were recorded at 300 or 500 and 75 or 125 MHz spectrometers, respectively, using the internal standard tetramethylsilane (TMS). Chemical shifts are given in parts per million, and J values are in hertz. Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) was performed with Brukere ultraflextreme, equipped with smart beam technology and 2,5-dihydroxybenzoic acid (DHB) matrix. The number-average molecular weight (Mn) and polydispersity index (Mw/Mn) were determined in THF at 40 °C with a flow rate of 0.5 mL/min on two polystyrene gel columns. The columns were calibrated against seven polystyrene standard samples. Electronic absorption spectra were obtained in air-equilibrated solvents at room temperature.

Synthesis of core molecules: Compounds **1a**, **2a 3a, 3b, 3c iia** and **iib** were synthesized according to literature methods. [25-30]

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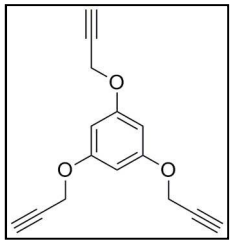
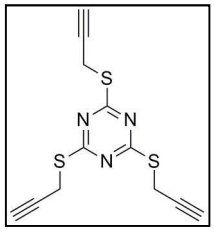
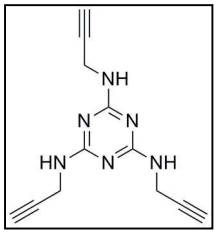


1,3,5-tris(prop-2-yn-1-yloxy)benzene (1a): In a 100 mL round bottomed flask phloroglucinol (1.0 g, 7.93 mmol) and K_2CO_3 (3.3 g, 23.79 mmol) were dissolved in DMF and stirred for 10 min at room temperature. Afterward, propargyl bromide (2.5 mL, 27.75 mmol) was added. and stirring was continued for further 24 h. Completion of reaction was checked with TLC. After completion of reaction, it was poured into a beaker containing ice cold water with continuous stirring and kept at 0-5 °C for precipitation. After getting a proper amount of precipitate, it was filtered and dried in air. White solid; Yield 1.90 g (99%); IR (ν_{max}/cm^{-1}) 3394, 3165, 2214, 1694, 1584; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.27 (s, 3 H, Ar-**H**), 4.64 (s, 6 H, -O-C**H**$_2$), 2.53 (s, 3 H, alkyne -C**H**); ^{13}C NMR (75 MHz, $CDCl_3$) 160.6, 94.30, 74.9, 48.2; **Chemical Formula: $C_{15}H_{12}O_3$**, **Elemental Analysis:** Calculated; C, 74.99; H, 5.03; Found; C, 74.94; H, 5.06.



2,4,6-tris(prop-2-yn-1-ylthio)-1,3,5-triazine (2a): It was synthesized according to the method used in the synthesis of **1a**. But phloroglucinol was replaced by thiocyanuric acid. Yellow solid; Yield 2.00 g (97%); IR (ν_{max}/cm^{-1}) 3447, 3176, 2208, 1698, 1583; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.98 (s, 6 H, -S-C**H**$_2$), 2.22 (s, alkyne -C**H**); ^{13}C NMR (75 MHz, $CDCl_3$) 178.3, 80.3, 71, 29.2; **Chemical Formula:** $C_{15}H_{12}S_3$, **Elemental Analysis:** Calculated; C, 49.46; H, 3.11; N, 14.42; S, 33.01 Found; C, 49.45; H, 3.10; N, 14.42; S, 33.00



N^2,N^4,N^6-tri(prop-2-yn-1-yl)-1,3,5-triazine-2,4,6-triamine (3a): In a round bottomed flask 1:1 mixture of THF and methanol (20/20 mL) was cooled down to 0-5 °C then cyanuric chloride (3.0 g, 16.27 mmol) was dissolved by slow addition so that temperature of the solution remain at 0-5 °C. In a conical flask containing THF at 0-5 °C, propargyl amine (3.30 mL, 16.27 mmol) was added.

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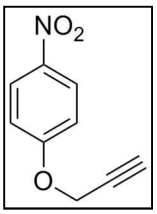
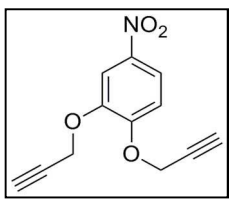
Then solution of propargyl amine in THF was added to the cyanuric chloride solution in drop wise fashion. The obtained reaction mixture was treated with solution of $NaHCO_3$ (4.10 g, 16.27 mmol) in THF (10 mL) at 0-5 °C to neutralize the solution. Then it was stirred at room temperature for 1 hour with subsequent refluxing for 1.5 hours. After conformation of the completion of the reaction with TLC, solvent was evaporated in reduced pressure. The obtained crude solid was re-dissolved in THF and undissolved impurities were filtered out. Afterward, THF was evaporated from the filtrate and pure compound (**3a**) was obtained. Yellow solid; Yield 3.9 g (99%); m.p. 147-149 °C; IR (ν_{max}/cm^{-1}) 3426, 3338, 2853, 1586, 1475; ^1H NMR (300 MHz, $DMSO_{d6}$) δ_H 8.25 (s, 3 H, -N**H**) 3.98 (s, 6 H, -N-C**H**$_2$), 2.49, (s, 3 H, alkyne -C**H**); ^{13}C NMR (75 MHz, $DMSO_{d6}$) 165.4, 82.3, 72.1, 29.2; **Chemical Formula:** $C_{15}H_{15}N_3$, **Elemental Analysis:** Calculated; C, 59.99; H, 5.03; N, 34.98;. Found; C, 59.92; H, 5.05; N, 34.97.



1-nitro-4-(prop-2-yn-1-yloxy)benzene (iia): 4-nitrophenol (2.0 g, 12.89 mmol) was reacted with propargylbromide (1.9 mL, 21.57 mmol), and K_2CO_3(2.17 g, 25.79 mmol) in DMF (20 mL) according to synthetic procedure of **1a**. Pure compound **iia** was isolated as a crystalline light yellow solid; Yield 2.5 g (98%); IR (ν_{max}/cm^{-1}) 3290, 2980, 2112, 1524, 1330; ^1H NMR (300 MHz, $CDCl_3$) δ_H 8.23 (d, 2 H, J = 9.3 Hz, Ar–**H**), 7.15 (d, 2 H, J = 9 Hz, Ar–**H**), 4.82 (s, 2 H, -C**H**$_2$), 2.58, (s, 1 H, alkyne -C**H**); ^{13}C NMR (75 MHz, $CDCl_3$) 150.8, 139.2, 136.1, 125.2, 119.0, 115.6, 74.5, 72.5, 57.0; **Chemical Formula:** $C_9H_7NO_3$, **Elemental Analysis:** Calculated; C, 61.10; H, 3.95; N, 7.90; Found; C, 61.02; H, 3.98; N, 7.91.



4-nitro-1,2-bis(prop-2-yn-1-yloxy)benzene (iib). 3, 4-dihydroxycatachol (2 g, 12.89 mmol) was reacted with propargylbromide (3.5 mL, 28.37 mmol),

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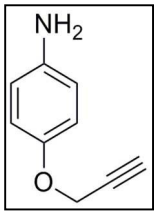
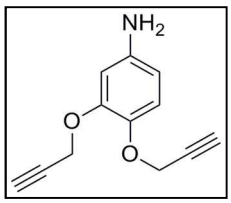
and K_2CO_3 (2.17 g, 25.79 mmol) in DMF (20 mL) according to synthetic procedure of **1a**. Pure compound **iib** was isolated as a light yellow solid; Yield 2.8 g (98 %); Mp.= 107°C; IR (ν_{max}/cm^{-1}) 3298, 2986, 2118, 1521, 1335; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.98 (d, 1 H, J = 9 Hz, Ar–**H**), 7.28 (s, 1 H, Ar–**H**), 7.15 (d, 1 H, J = 8.6 Hz, Ar–**H**), 4.90 (s, 4 H, **C**$\mathbf{H_2}$), 2.62, (s, 2 H, alkyne **C**$\mathbf{H}$); ^{13}C NMR (75 MHz, $CDCl_3$) 152.7, 139.2, 136.1, 135.1,128.2, 119.0, 118.3, 112.6, 109.6 105.8, 72.5, 59.2, 57.0; **Chemical Formula:** $C_{12}H_9NO_4$, **Elemental Analysis:** Calculated; C, 62.34; H, 3.92; N, 6.06; Found; C, 62.31; H, 3.91; N, 6.04.



4-(prop-2-yn-1-yloxy)aniline (iiia): In a 100 mL round bottomed flask compound **iia** (2 g, 11.29 mmol) was dissolved in 20 mL DCM/Ethanol (1:1) mixture. Then a solution of $SnCl_2.H_2O$ (3.52 g, 16.93 mmol) in 37% HCl was added and reaction mixture was stirred at 40 °C for 4 h. After completion of the reaction it was poured into 300 mL of deionized water and extracted with CH_2Cl_2 (2 × 200 mL). The combined organic layers were washed with water followed by saturated $NaHCO_3$. The isolated organic layer was dried over anhydrous Na_2SO_4. Then solvent was removed under reduced pressure and the resulting solid residue was dried in air. A viscous yellow product was obtained; Yield 1.32g (79%); IR (ν_{max}/cm^{-1}) 3490, 2880, 2115, 1330, 1208; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.85 (d, 2 H, J = 8.6 Hz, Ar–**H**), 6.64 (d, 2 H, J = 8.9 Hz, Ar–**H**), 5.62 (br, 2 H, N$\mathbf{H_2}$), 4.65 (s, 2 H, -**C**$\mathbf{H_2}$), 2.49, (s, 1 H, alkyne -**C**$\mathbf{H}$); ^{13}C NMR (75 MHz, $CDCl_3$) 139.0, 137.1, 115.2, 112.6, 72.5, 70.1, 56.2; **Chemical Formula:** C_9H_9NO, **Elemental Analysis:** Calculated; C, 73.45; H, 6.16; N, 9.52; Found; C, 73.40; H, 6.18; N, 9.60.



3,4-bis(prop-2-yn-1-yloxy)aniline (iiib): It was also synthesized in the same procedure as given in synthesis of compound (iiia). It is a brown viscous

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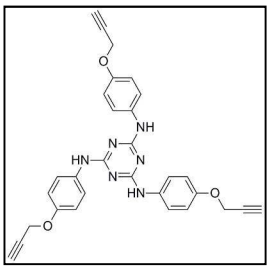
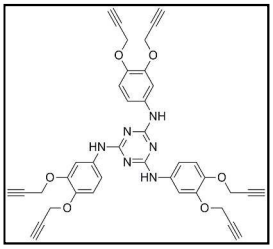
product; Yield 1.8g (98%); IR (ν_{max}/cm^{-1}) 3543, 3459, 3291, 2919, 1614, 1266; ^{1}H NMR (300 MHz, $DMSO_{d6}$) δ_H 10.10 (s, 2H, **N<u>H</u>$_2$**), 7.21 (d, 1 H, J = 7.2 Hz, Ar–**<u>H</u>**), 7.04 (s,1 H, Ar–**<u>H</u>**), 6.96 (d,1 H, Ar–**<u>H</u>**), 4.87 (s, 4 H, **-C<u>H</u>$_2$**), 3.62 (s, 6 H, alkyne **-C<u>H</u>**); ^{13}C NMR (75 MHz, $DMSO_{d6}$) 148.2, 147.3, 146.2, 125.4, 115.8, 114.9, 109.4, 56.3; **Chemical Formula:** $C_{12}H_{11}NO_2$, **Elemental Analysis:** Calculated; C, 71.63; H, 5.51; N, 6.96; Found; C, 71.65; H, 5.48; N, 6.98.



N^2,N^4,N^6-tris(4-(prop-2-yn-1-yloxy)phenyl)-1,3,5-triazine-2,4,6-triamine (3b): Synthetic procedure was same as in **3a**. But the refluxing time was 10-12 h. The reactants and product stoichiometry was as follows; Compound **iiia** (2.25 g, 16.27 mmol) in THF (20mL), cyanuric chloride (1.0 g, 5.42 mmol) in THF/methanol (10/10 mL) mixture and $NaHCO_3$ (2.25 g, 16.27 mmol). The solid product was obtained. Light brown solid; Yield 2.7 g (96%); IR (ν_{max}/cm^{-1}) 3282, 3250, 2925, 2119, 1592; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.50 (d, 6 H, J = 8.4 Hz, Ar–**<u>H</u>**), 7.44 (s, 3 H, **N<u>H</u>**) 7.32 (d, 6 H, J = 8.1 Hz, Ar–**<u>H</u>**), 4.70 (s, 6 H, **C<u>H</u>$_2$**), 2.51 (s, 3 H, alkyne **-C<u>H</u>**); ^{13}C NMR (75 MHz, $CDCl_3$) 165.5, 148.2, 147.6, 146.2, 135.2, 121.9, 115.2, 79.4, 78.5, 56.0; **Chemical Formula:** $C_{30}H_{24}N_6O_3$, **Elemental Analysis:** Calculated; C, 69.76; H, 4.68; N, 16.27; Found; C, 69.78; H, 4.65; N, 16.22.



Compound 3c: Cyanuric chloride (1.0 g, 5.42 mmol) was reacted with compound **iiib** (3.27 g, 16.27 mmol) and $NaHCO_3$ (3.0 g, 16.27 mmol) in THF/ methanol (2:1) mixture according to synthetic procedure of compound **3b**. Pure compound **3c** was isolated as a brown solid; Yield 3.0 g (81.5%); IR (ν_{max}/cm^{-1}) 3382, 3286, 2923, 2852, 1586, 1391; ^{1}H NMR (300 MHz, $DMSO_{d6}$) δ_H 9.95 (s, 3 H, **N<u>H</u>**), 7.20 (d, 3 H, J = 8.7 Hz), 7.15 (s, 3 H), 7.04 (d, 3 H, J = 8.7 Hz, Ar–**<u>H</u>**), 4.75 (s, 6 H, **C<u>H</u>$_2$**), 4.54 (s, 6 H, **C<u>H</u>$_2$**), 3.75 (s, 3 H, **C<u>H</u>**), 3.51(s, 3 H, alkyne **C<u>H</u>**); ^{13}C

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NMR (75 MHz, $DMSO_{d6}$) 163.8, 146.8, 143.4, 132.4, 114.8, 109.0, 104.8, 79.8, 78.9, 56.4; **Chemical Formula:** $C_{39}H_{30}N_6O_6$, **Elemental Analysis:** Calculated; C, 69.02; H, 4.46; N, 12.38; Found; C, 69.04; H, 4.50; N, 12.40.

Synthesis of Dendrons: Mono/bis-sulfonylation and azidation have been done according to literature methods.[31-33] Dendrons **5a-c** were synthesized in three steps as shown in Scheme 2.

Step-1: Nosyl/tosylchloride (1 eq.) was added to a stirred solution of 2-bromoethylaminehydrobromide (1 eq.) in pyridine and stirring was continued for next 2-3 h at room temperature. After completion of the reaction ice cold water was added until precipitation was completed. Then obtained precipitate was filtered and dried at room temperature.

Step-2: In this step azidation of mono nosyl/tosyl products (**4b/4a**)[34,35] were done. For this purpose, **4b/4a** (1 eq.) were dissolved in water/acetone mixture (1:4) and to it NaN_3 (1.5 eq.) was added. Reaction mixture was stirred at 60 °C for 6-7 h. After completion of the reaction excess amount of water was added at room temperature then kept at 0 °C for 4 h. Thereupon crystalline precipitate was filtered and air dried.

Step-3: In this step persulfonylation was done. For this purpose azide derivative of mono nosyl/tosyl products (1 eq.) and TEA (4 eq.) were dissolved in dry DCM. In another beaker sulfonyl chloride derivatives (4 eq.) were dissolved in DCM and added to the previous solution by stirring under argon atmosphere. After complete addition, reaction mixture was refluxed for 3-4 h. After completion of the reaction solvent was removed under reduced pressure and desired products were purified by column chromatography.

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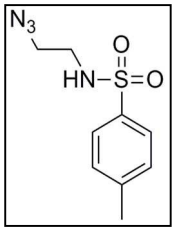
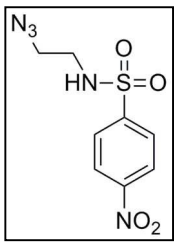
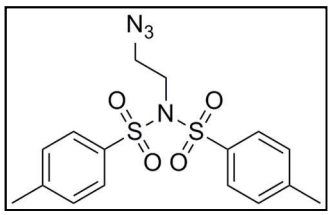


Compound 4c: Compound **4a** (2.5 g, 8.99 mmol) was reacted with sodium azide (1.8 g, 17.97 mmol) according to step 2. White crystalline solid; Yield 2.0 g (92%); m.p. 180-185 °C; IR (ν_{max}/cm^{-1}) 3441, 3346, 2244, 1693, 1602, 1509, 1344; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.77 (s, 2 H, J = 8.6 Hz, Ar-**H**), 7.34 (d, 1 H, J = 8.8 Hz, Ar-**H**), 4.87 (s, 1 H, -N**H**), 3.41 (t, 2 H, J = 6.0 Hz, -C**H**$_2$), 3.11 (t, 2 H, J = 6 Hz, -C**H**$_2$), 2.43 (s, 3 H, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 143.8, 136.6, 129.8, 127.0, 50.8, 42.2, 21.5; **Chemical Formula:** $C_{10}H_7N_3O_3$, **Elemental Analysis:** Calculated; C, 55.30; H, 3.25; N, 19.35;. Found; C, 55.28; H, 3.26; N, 19.36.



Compound 4d: Compound **4b** (2.5 g, 8.09 mmol) was reacted with sodium azide (1.8 g, 16.17 mmol) according to step 2. Yellow crystalline solid; Yield 2.0 g (91%); m.p. 136-140 °C; IR (ν_{max}/cm^{-1}) 3449, 2952, 2107, 1594, 1363; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.36 (d, 2 H, J = 8.4 HZ, Ar-**H**), 7.86 (d, 4 H, J = 8.6 HZ, **Ar-H**), 5.04 (s, 1 H, -N**H**), 3.55 (t, 2 H, J = 6.0Hz, **-CH**$_2$), 3.38 (t, 2 H, J = 6 Hz, **-CH**$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) 150.2, 144.4, 128.4, 124.5, 51.1, 41.80; **Chemical Formula:** $C_8H_9N_5O_4S$, **Elemental Analysis:** Calculated; C, 35.42; H, 3.34; N, 25.82; S, 11.82 Found; C, 35.45; H, 3.35; N, 25.80; S, 11.80.



Dendron 5a: Azide derivative **4a** (2.0 g , 8.32 mmol) was allowed to react with TEA (4.21 mL, 38.23 mmol) and p-touluene sulfonylchloride (6.35 g, 33.29 mmol) in dry DCM (40 mL) according to step 3 of persulfonylation . White crystalline product was isolated; Yield 3.0 g (92%); m.p. 93-98 °C; IR (ν_{max}/cm^{-1}) 2955.30, 2105.89, 1597.44, 1383.48; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.93 (d, 4 H, J = 8.4 Hz, Ar-**H**), 7.36 (d, 4 H, J = 8.1 Hz, Ar-**H**), 3.81 (t, 2 H, J = 6.6, 6.5 Hz, -C**H**$_2$), 3.52 (t, 2 H, J = 6.5, 6.9 Hz, -C**H**$_2$), 2.45 (s, 6 H,

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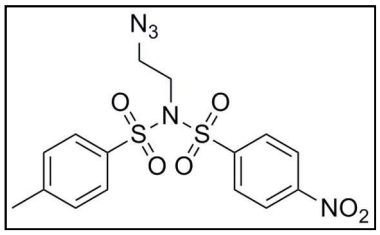
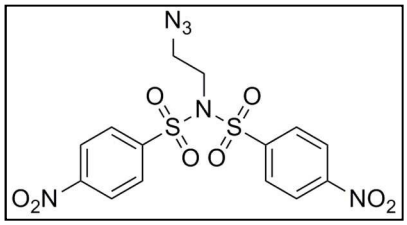
C<u>H₃</u>); ^{13}C NMR (75 MHz, $CDCl_3$) 145.2, 136.3, 129.7, 128.3, 50.3, 46.9, 21.6; **Chemical Formula:** $C_{16}H_{18}N_4O_4S_2$, **Elemental Analysis:** Calculated; C, 48.72; H, 4.60; N, 14.20; S, 16.26 Found; C, 48.76; H, 4.65; N, 14.22; S, 16.20.



Dendron 5b: Azide derivative **4a** (2.0 g, 8.32 mmol) was allowed to react with TEA (4.21 mL, 33.29 mmol) and p-Nitro sulfonylchloride (7.38 g, 33.29 mmol) in dry DCM (20 mL) according to step 3. Lemon color crystalline product was isolated; Yield 3.5 g (98%); m.p. 110-117 °C; IR (ν_{max}/cm^{-1}) 2924, 2110, 1528, 1345; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.47 (d, 2 H, J = 8.6 HZ, **Ar-<u>H</u>**), 8.40 (d, 2 H, J = 8.6 HZ, **Ar-<u>H</u>**), 7.95 (d, 2 H, J = 8.4 Hz, **Ar-<u>H</u>**), 7.39 (d, 2 H, J = 8.6 HZ, **Ar-<u>H</u>**), 3.85 (t, 2 H, J = 6 Hz, **-C<u>H₂</u>**), 3.56 (t, 2 H, J = 6 Hz, **-C<u>H₂</u>**), 2.48 (s, 3 H, **-C<u>H₃</u>**); ^{13}C NMR (75 MHz, $CDCl_3$) 150.6, 146.0, 135.4, 129.9, 128.5, 124.2, 50.4, 47.4, 21.7; **Chemical Formula**: $C_{15}H_{15}N_5O_6S_2$**, Elemental Analysis:** Calculated; C, 42.35; H, 3.55; N, 16.46; S, 15.07 Found; C, 42.37; H, 3.51; N, 16.50; S, 15.00.



Dendron 5c: Azide derivative (2.0 g 7.37 mmol) was allowed to react with TEA (3.7 mL, 29.49 mmol) and p-Nitrosulfonylchloride (6.6 g, 29.49 mmol) in dry DCM according to step 3. Yellow solid; Yield 2.5 g, (79%); m.p. 83-85 °C; IR (ν_{max}/cm^{-1}) 2929, 2117, 1530, 1353; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.45 (d, 4 H, J = 8.9 Hz, **Ar-<u>H</u>**), 8.33 (d, 4 H, J = 8.6 Hz, **Ar-<u>H</u>**), 3.94 (t, 2 H, J = 6 Hz, **-C<u>H₂</u>**), 3.62 (t, 2 H, J = 6 Hz, **-C<u>H₂</u>**); ^{13}C NMR (75 MHz, $CDCl_3$) 150.9, 144.1, 130.01, 124.4, 50.59, 48.15; **Chemical Formula:** $C_{14}H_{12}N_6O_8S_2$, **Elemental Analysis:** Calculated; C, 36.84; H, 2.65; N, 18.41; S, 14.05 Found ; C, 36.80; H, 2.60; N, 18.45; S, 14.10.

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Synthesis of dendrimers:

The alkyne terminated core molecules (1.0 eq.) and azide functionalized dendrons (1.1 eq. per alkyne group) followed by $Cu(PPh_3)_3Br$ (0.1 mol% per alkyne group) as copper(I) catalyst and Me_6TREN (0.1 mol% per alkyne group) were dissolved in dry DCM and stirred at room temperature for 8-10 h. After confirming the completion of reaction by TLC, chloroform was added to the reaction mixture and washed with saturated solution of NH_4Cl in water (10 mL) followed by brine (10mL). The separated organic layer was dried over Na_2SO_4 and solvent was evaporated under reduced pressure to obtain the crude product. The desired products were obtained after purification by flash column chromatography.

Dendrimer D1: Compound **1a** (0.2 g, 0.83 mmol) was reacted with **5a** (1.08 g, 2.75 mmol), $Cu(PPh_3)_3Br$ (2.12 mg, 2.50 µmol), and Me_6TREN (700 µL, 2.62 µmol) in Dry DCM (10 mL) according to the above procedure. Pure compound **D1** was isolated by column chromatography with hexane/ethyl acetate (3/7). White solid; Yield 1.15 g (98%); IR (ν_{max}/cm^{-1}) 3126, 3039, 2914, 2843, 1180; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.76 (s, 3 H, Triazol-**H**) 7.68 (d, 12 H, J = 7.8 Hz, **Ar-H**), 7.12 (d, 12 H, J = 7.8 Hz, **Ar-H)** 6.35 (s, 3 H, **Ar-H**), 5.63 (t, 6 H, J = 7.8 Hz, -C**H**$_2$), 4.78 (s, 6 H, -C**H**$_2$), 4.21 (t, 6 H, J = 7.2 Hz, -C**H**$_2$), 2.48 (s, 18 H, -C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 158.7, 145.3, 144.1, 135.8, 129.8, 128.2, 122.1, 98.1, 58.1, 49.2, 47.5, 29.2, 27.7, 21.1; **SEC** shows polydispersity 1.01; m/z **MALDI-TOF MS** Calculated; for $C_{61}H_{57}N_{15}O_{21}S_6$ 1422.31, Found; 1423.67 **$[M + H]^+$.**

Dendrimer D2: Compound **1a** (0.2 g, 0.83 mmol) was reacted with **5b** (1.17 g, 2.75 mmol), $Cu(PPh_3)_3Br$ (2.12 mg, 2.50 µmol), and Me_6TREN (700 µL, 2.62 µmol) in Dry DCM (10 mL) according to the above procedure. Pure compound **D2** was isolated by column chromatography

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with hexane/ethyl acetate (1/3). Off white solid; Yield 1.2 g (95%); IR (ν_{max}/cm^{-1}) 3130, 3041, 2924, 2853, 1172; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.34 (d, 6 H, J = 8.1 Hz, **Ar-H**), 8.06 (d, 2 H, J = 8.4, **Ar-H**), 7.80 (d, 6 H, J = 7.7 Hz, **Ar-H**), 7.79 (s, 3 H, Triazole-**H**), 7.36 (d, 6 H, J = 7.8 Hz, **Ar-H**), 6.35 (s, 3 H, **Ar-H**), 5.64 (t, 6 H, J = 6.2 Hz, -C**H$_2$**), 5.08 (s, 6 H, -C**H$_2$**), 4.31 (t, 6 H, J = 6 Hz, -C**H$_2$**), 2.48 (s, 9 H, -C**H$_3$**); ^{13}C NMR (75 MHz, $CDCl_3$) 158.1, 150.7, 148.6, 146.1, 144.1, 139.2, 129.9, 126.9, 124.6, 106.2, 86.9, 66.8, 31.9, 29.6, 21.7; **SEC** shows polydispersity 1.01; m/z **MALDI-TOF MS** Calculated; for $C_{61}H_{57}N_{15}O_{21}S_6$ 1515.22, Found; 1516.68 **[M + H]$^+$.**

Dendrimer D3: Compound **1a** (0.2 g, 0.83 mmol) was reacted with **5c** (1.25 g, 2.75 mmol), $Cu(PPh_3)_3Br$ (2.12 mg, 2.50 μmol), and Me_6TREN (700 μL, 2.62 μmol) in Dry DCM (10 mL) according to the above procedure. Pure compound **D3** was isolated by silica gel column chromatography with hexane/ethyl acetate (1/4). Yellow solid; Yield 0.82 g (65%); IR (ν_{max}/cm^{-1}) 3426., 2924, 2853; 1596, 1480; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.40 (d, 12 H, J = 8.1 Hz, **Ar-H**) 8.24 (d, 12 H, J = 8.1 Hz, **Ar-H**), 8.06 (s, 3 H, Triazole-**H**), 6.62 (s, 3 H, **Ar-H**), 5.80 (t, 6 H, J = 6.6 Hz, -C**H$_2$**), 5.10 (s, 6 H, -C**H$_2$**), 4.91 (t, 6 H, J = 6.1, -C**H$_2$**); ^{13}C NMR ($CDCl_3$, 75 MHz) 159.6, 150.7, 146.3, 144.4, 134.9, 130.1, 129.6, 128.4, 124.4, 123.5, 98.6, 59.6, 49.0, 47.8, 29.6;. **SEC** shows polydispersity 1.02; m/z **MALDI-TOF MS** Calculated for $C_{58}H_{50}N_{18}O_{26}S_6$ 1608.52, Found 1609.52 **[M + H]$^+$.**

Dendrimer D4: Compound **2a** (0.2 g, 0.68 mmol) was reacted with 5c (0.90 g, 2.26 mmol), $Cu(PPh_3)_3Br$ (1.92 mg, 2.06 μmol), and Me_6TREN (550 μL, 2.06 μmol) in Dry DCM (10 mL) according to the above procedure. Pure compound **D4** was isolated by column chromatography with hexane/ethyl acetate (1/7). Off-white solid; Yield 1.01g (98%); IR (ν_{max}/cm^{-1}) 2924, 2853, 1596, 1480; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.76 (d, 12 H, J = 7.8 Hz, **Ar-H**) 7.54 (s, 3 H,

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Triazole-**H**), 7.31 (s, 12 H, J = 7.5 Hz, **Ar-H**), 4.52 (t, 6 H, J = 6.2 Hz, C**H**$_2$), 4.35 (t, 6 H, J = 6.8 Hz, C**H**$_2$), 4.08 (s, 6 H, **CH**$_2$), 2.49 (s, 18 H, -C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 178.7, 145.5, 135.8, 129.8, 128.2, 122.1, 49.2, 47.5, 29.2, 21.6; **SEC** shows polydispersity 1.03; m/z **MALDI-TOF MS** Calculated for $C_{60}H_{63}N_{15}O_{12}S_9$ 1473.23, Found 1474.75 **[M + H]$^+$.**

Dendrimer D5: Compound **2a** (0.2 g, 0.686 mmol) was reacted with **5b** (0.96 g, 2.26 mmol), $Cu(PPh_3)_3Br$ (1.92 mg, 2.06 μmol), and Me_6TREN (550 μL, 2.06 μmol) in Dry DCM (10 mL) according to the above procedure. Pure compound **D5** was isolated by column chromatography with hexane/ethyl acetate (1/4). Light yellow solid; Yield 1.00 g (92%); IR (ν_{max}/cm^{-1}) 3099, 2927, 2850, 1533, 1480, 1380, 1166; ^{1}H NMR(300 MHz, $CDCl_3$) δ_H 8.35 (d, 6 H, J = 8.1 Hz, **Ar-H**) 8.08 (d, 6 H, J =8.4 Hz, **Ar-H**), 7.83 (d, 6 H, J = 7.7 Hz, **Ar-H**), 7.53 (s, 3 H, Triazole-**H**), 7.35 (d, 6 H, **Ar-H**) 4.52 (t, 6 H, J = 7.2 Hz, **CH**$_2$), 4.36 (t, 6 H, J = 7.2 Hz, **CH**$_2$) 4.15 (s, 6 H, **CH**$_2$), 2.47 (s, 9 H, **CH**$_3$); ^{13}C NMR (75 MHz, CDCl3,) 178.6, 150.7, 146.3, 144.4, 144.1, 134.9, 130.1, 129.6, 128.4, 124.4, 123.5, 49.0, 47.8, 29.6, 24.9, 21.7; **SEC** shows polydispersity 1.03; m/z **MALDI-TOF MS** calculated for $C_{57}H_{54}N_{18}O_{18}S_9$ 1566.13, Found 1568.74 **[M + H]$^+$.**

Dendrimer D6: Compound **2a** (0.2 g, 0.68 mmol) was reacted with **5c** (1.0 g, 2.26 mmol), $Cu(PPh_3)_3Br$ (1.92 mg, 2.06 μmol), and Me_6TREN (550 μL, 2.06 μmol) in Dry DCM (10 mL) according to the above procedure. Pure compound **D6** was isolated by column chromatography hexane/ethyl acetate (1/8). Yellow solid; Yield 0.70 g (62%); IR (ν_{max}/cm^{-1}) 3109, 2914, 2823, 1530, 1482, 1382, 1156; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.41 (d, 6 H, J = 8.4 Hz, **Ar-H**) 8.20 (d, 6 H, J = 8.4 Hz, **Ar-H**), 8.06 (s, 3 H, Triazole-**H**), 5.09 (t, 6 H, J = 6 Hz, C**H**$_2$), 4.48 (s, 6 H, **CH**$_2$), 4.37 (t, 6 H, J =6.2 Hz, **CH**$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) 177.7, 155.4, 132.7, 131.1, 129.9, 126.9, 124.5, 54.6, 52.5, 42.7, 33.1; **SEC** shows polydispersity 1.03; m/z **MALDI-TOF MS** calculated for $C_{54}H_{45}N_{21}O_{24}S_9$ 1660.04, Found 1660.97 **[M + H]$^+$.**

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Dendrimer D7: Compound **3a** (0.2 g, 0.84 mmol) was reacted with **5a** (1.10 g, 2.75 mmol), $Cu(PPh_3)_3Br$ (2.35 mg, 2.53 µmol), and Me_6TREN (700 µL, 2.62 µmol) Dry DCM (10 mL) according to the above procedure. Pure compound **D7** was isolated by column chromatography with hexane/ethyl acetate (1/9). Off-white solid; Yield 1.0 g (83%); IR (ν_{max}/cm^{-1}) 3475, 3068, 2924, 2855, 1452, 1161;^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7. 85 (d, 12 H, J = 8.4 Hz, **Ar-H**), 7.73 (s, 3 H, Triazole-**H)** 7.54 (s, 3 H, **-NH**), 7.32 (d, 12 H, J = 7.5 Hz, **Ar-H**), 4.53 (s, 6 H, J = 6.2 Hz, **CH_2**), 4.37 (s, 6 H, **CH_2**), 4.06 (t, 6 H, J = 6 Hz, **CH_2**), 2.49 (s, 18 H, **CH_3**); ^{13}C NMR (75 MHz, $CDCl_3$) 165.5, 148.3, 137.1, 129.1, 128.3, 124.8, 47.1, 31.9, 29.3, 21.6; **SEC** shows polydispersity 1.01; m/z **MALDI-TOF MS** calculated for $C_{60}H_{66}N_{18}O_{12}S_6$ 1423.67, Found 1423.98 **$[M + H]^+$.**

Dendrimer D8: Compound **3a** (0.2 g, 0.84 mmol) was reacted with **5b** (1.10 g, 2.75 mmol), $Cu(PPh_3)_3Br$ (2.15 mg, 2.53 µmol), and Me_6TREN (700 µL, 2.62 µmol) Dry DCM (10 mL) according to the above procedure. Pure compound D8 was isolated by silica gel column chromatography with $MeOH/CHCl_3$ (1/20). Light yellow solid; Yield 1.10 g (87%); IR (ν_{max}/cm^{-1}) 3475, 3065, 2918, 2856, 1524, 1452, 1350, 1161; ^{1}H NMR(300 MHz, $CDCl_3$) δ_H 8.44 (d, 6 H, J = 8.1 Hz, **Ar-H**), 8.36 (d, 6 H, J = 8.4 Hz, **Ar-H**), 7.83 (d, 6 H, J = 7.8 Hz, **Ar-H**) 7.63 (s, 3 H, Triazole-**H)**, 7.48 (d, 6 H, J = 7.8 Hz , **Ar-H**), 7.36 (s, 3 H, **-NH**), 4.52 (t, 6 H, J = 6.8 Hz, **-CH_2**), 4.36 (s, 6H, **-CH_2**), 4.15 (t, 6 H, J = 6.3 Hz, **-CH_2**), 2.47 (s, 9 H, **-CH_3**);^{13}C NMR (75 MHz, $CDCl_3$) 165.5, 151.7, 149.3, 146.4, 134.9, 130.1, 129.6, 128.4, 124.4, 123.5, 51.7, 50.0, 21.7; **SEC** shows polydispersity 1.03; m/z **MALDI-TOF MS** calculated for $C_{57}H_{58}N_{21}O_{18}S_6$ 1515.76, Found 1516.58 **$[M + H]^+$.**

Dendrimer D9: Compound **3b** (0.2 g, 0.39 mmol) was reacted with **5a** (0.50 g, 1.28 mmol) $Cu(PPh_3)_3Br$ (1.08 mg, 1.16 µmol), and Me_6TREN (310 µL, 1.16 µmol) in Dry DCM (10 mL)

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according to the above procedure. Pure compound **D9** was isolated by column chromatography with hexane/ethyl acetate (3/17). Light brown solid; Yield 0.62 g (95%); IR (ν_{max}/cm^{-1}) 3426, 2924, 2853, 1596, 1480; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.34 (s, 3 H, Triazole-**H**), 8.13 (d, 12 H, J = 10 Hz, Ar**H**), 7.87 (s, 6 H, J = 6.6 Hz, A**rH**), 7.39 (s, 3 H, N**H**), 7.37 (d, 18 H, J = 6.6 Hz, Ar**H**), 5.24 (t, 6 H, J = 6.2 Hz, **CH_2**), 4.65 (s, 6 H, **CH_2**), 4.22 (t, 6 H, J = 6 Hz, **CH_2**), 2.46 (s, 18 H, **CH_3**); ^{13}C NMR (75 MHz, $CDCl_3$) 164.1, 150.1, 148.3, 146.3, 144.3, 142.5, 135.0, 130.1, 129.7, 128.5, 124.5, 114.4, 70.4, 46.6, 36.6, 21.7; **SEC** shows polydispersity 1.03; m/z **MALDI-TOF MS** calculated $C_{78}H_{79}N_{18}O_{15}S_6$ 1699.96, Found 1700.04 **$[M + H]^+$.**

Dendrimer D10: Compound **3b** (0.2 g, 0.39 mmol) was reacted with **5b** (0.55 g, 1.28 mmol), $Cu(PPh_3)_3Br$ (1.08 mg, 1.16 μmol), and Me_6TREN (310 μL, 1.16 μmol) in Dry DCM (10 mL) according to the above procedure. Pure compound **D10** was isolated by column chromatography with hexane/ethyl acetate (1/9); Light brown solid; Yield 1.2 g (96%); IR (ν_{max}/cm^{-1}) 3416, 2914, 2843, 1586, 1560, 1440; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.32 (d, 9 H, J = 8.7 Hz, Ar**H**), 8.13 (d, 6 H, J = 8.6 Hz, Ar**H**), 7.87 (d,12 H, J = 8.2 Hz, Ar**H**), 7.87 (s, 3 H, Triazole-**H**), 7.36 (d, 6 H, J = 7.8 Hz, Ar**H**), 7.39 (s, 3 H, -N**H**), 7.29 (d, 6 H, J = 7.8 Hz, Ar**H**), 5.22 (t, 6 H, J = 6.2 Hz, -**CH_2**), 4.67 (s, 6 H, -**CH_2**), 4.24 (t, 6 H, J = 6 Hz, -**CH_2**), 2.46 (s, 18 H, -**CH_3**); ^{13}C NMR (75 MHz, $CDCl_3$) 164.1, 150.5, 145.2, 142.1, 137.4, 136.1, 129.6, 128.2, 127.8, 126.1, 124.6, 115.2, 48.2, 38.6, 21.7; **SEC** shows polydispersity 1.03; m/z **MALDI-TOF MS** Calculated $C_{75}H_{70}N_{21}O_{21}S_6$, 1791.33 Found 1792.87 **$[M + H]^+$.**

Dendrimer D11: Compound **3c** (0.2 g, 0.30 mmol) was reacted with **5a** (0.77g, 1.94 mmol), $Cu(PPh_3)_3Br$ (1.64 mg, 1.77 μmol), and Me_6TREN (480 μL, 1.80 μmol) in Dry DCM (10 mL) according to the above procedure. Pure compound **D11** was isolated by column chromatography with hexane/ethyl acetate (1/9). Off white solid; Yield 0.88g, (98%); IR (ν_{max}/cm^{-1}) 3421, 2923,

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2843, 1590, 1478; ^{1}H NMR(500 MHz, $CDCl_3$) δ_H 8.13 (d, 24 H, J = 8.1 Hz, Ar**H**), 8.13 (d, 24 H, 7.5 Hz, Ar**H**) 7.65 (s, 6 H- Triazole-**H**), 7.40 (d, 24 H, J = 7.2 Hz, Ar**H**), 7.39 (s, 6 H, -N**H**), 7.32 (s, 3 H, Ar**H**), 7.18 (d, 3 H, J = 7.5 Hz, Ar**H**) 4.67 (t, 12 H, J = 6.Hz, -C**H**$_2$), 4.42 (s, 12 H, -C**H**$_2$), 4.13 (t, 12 H, J = 6.2 Hz, -C**H**$_2$), 2.46 (s, 36 H, -C**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) 164.6, 150.0, 145.1, 142.1, 137.4, 136.1, 129.6, 128.2, 127.8, 126.1, 124.6, 119.9, 114.1, 106.0, 76.5, 43.3, 29.7 21.0; **SEC** shows polydispersity 1.03; m/z **MALDI-TOF MS** Calculated $C_{135}H_{138}N_{30}O_{30}S_{12}$, 3044.20 Found 3045.50 **[M + H]$^+$.**

Dendrimer D12: Compound **3c** (0.2 g, 0.30 mmol) was reacted with **5b** (0.83 g, 1.94 mmol), $Cu(PPh_3)_3Br$ (1.64 mg, 1.77 μmol), and Me_6TREN (480 μL, 1.80 μmol) in Dry DCM (10 mL) according to the above procedure. Pure compound **D12** was isolated by column chromatography with MeOH/$CHCl_3$ (1/20). Light yellow solid; Yield 0.90 g (94%); IR (ν_{max}/cm^{-1}) 3426, 2924, 2853, 1596, 1480; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.20 (d, 12 H, J = 8.7 Hz, Ar**H**), 8.13 (d, 12 H, J = 7.4 Hz, Ar**H**), 8.05 (d, 12 H, J = 7.8 Hz, Ar**H**), 8.02 (d, 3 H, J = 7.5 Hz, Ar**H**), 7.64 (s, 6 H, Ar**H**) 7.80 (s, 3 H, Triazole-**H**), 7.39 (d, 12 H, J = 7 Hz, Ar**H**), 7.38 (s, 6 H, -N**H**), 7.27 (s, 3 H, Ar**H**), 7.16 (d, 3 H, J = 7.5 Hz, Ar**H**), 5.36 (t, 12 H, J = 6. Hz, **C**H$_2$), 4.48 (s, 12 H, -C**H**$_2$), 4.27 (t, 12 H, J = 6.2 Hz, -C**H**$_2$), 2.48 (s, 18 H, -C**H**$_3$) ^{13}C NMR (125 MHz, $CDCl_3$) 164.8, 152.3,143.8, 140.1, 137.1, 129.2, 128.2, 125.9, 120.5, 119.2, 110.2, 108.7, 108.6, 49.7, 42.3, 40.2, 25.8; **SEC** shows polydispersity 1.02; m/z **MALDI-TOF MS** calculated for $C_{129}H_{120}N_{36}O_{42}S_{12}$, 3231.33 Found 3232.34 **[M + H]$^+$.**

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SUPPORTING INFORMATION

Electronic Supplementary Information (ESI) for copies of ^{1}H and ^{13}C NMR of synthesized compounds, MALDI-TOF of dendrimers, UV-spectrum of dendrons and GPC data of dendrimers.

REFERENCES

(1) M. Elsabahy, G. S. Heo, S. M. Lim, G. Sun and K. L. Wooley, *Chem. Rev,* 2015, **115**, 10967-11011.

(2) K. R. Raghupathi, J. Guo, O. Munkhbat, P. Rangadurai and S. Thayumanavan, *Acc. Chem. Res,* 2014, **47**, 2200-2211.

(3) C. G. Palivan, R. Goers, A. Najer, X. Zhang, A. Car and W. Meier, *Chem. Soc. Rev.* 2016*,* **55(2)***,* 377-411.

(4) J. Yang, Q. Zhang, H. Chang and Y. Cheng, *Chem. Rev,* 2015*,* **115***,* 5274-5300.

(5) S. H. Medina and M. E. El-Sayed, *Chem. Rev,* 2009*,* **109 (7)***,* 3141-3157.

(6) Q. M. Kainz and O. Reiser, *Acc. Chem. Res,* 2014, **47(2)**, 667-677.

(7) A. M. Caminade and J. P. Majoral, *Acc. Chem. Res,* 2004*,* **37(6)***,* 341-348.

(8) D. K. Smith, *Chem. Commun,* 2006, **1**, 34-44.

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DOI: 10.1039/C6RA09929G

Published on 03 June 2016. Downloaded by UNIVERSITY OF NEBRASKA on 10/06/2016 00:01:46.

(9) D. G. Mullen, A. Desai, M. A. van Dongen, M. Barash, J. R. Baker Jr, and M. M. Banaszak Holl, *Macromolecules,* 2012*,* **45(12)***,* 5316-5320.

(10) T.-K. Ho, Tactics of Organic Synthesis*, Wiley: New York,* 1994.

(11) N. Feuerbacher and F. Vögtle, "Iterative synthesis in organic chemistry." Dendrimers. Springer Berlin Heidelberg, 1998. 1-18.

(12) M. V. Walter and M. Malkoch, *Chem. Soc. Rev,* 2012, **41(13)**, 4593-4609.

(13) D. Astruc, L. Liang, A. Rapakousiou and J. Ruiz, *Acc. Chem. Res,* 2011, **45(4)**, 630-640.

(14) F. H. Jardine, L. Rule, and A. G. Vohra, *J. Chem. Soc, A*, 1970, **2**, 238-240.

(15) S. Díez-González, *Catal. Sci. Technol,* 2011, **1(2)**, 166-178.

(16) F. Vögtle, H. Fakhrnabavi, and O. Lukin, *Org. Lett,* 2004, **6(7)**, 1075-1078.

(17) O. Lukin, V. Gramlich, R. Kandre, I. Zhun, T. Felder, C. A. Schalley and G. Dolgonos, *J. Am. Chem. Soc,* 2006, **128(27)**, 8964-8974.

(18) O. Lukin, D. Schubert, C. Müller, M. Corda and R. Kandre, *J. Org. Chem,* 2008, **73(9)**, 3562-3565.

(19) M. Sowinska and Z. Urbanczyk-Lipkowska, *New J. Chem,* 2014, **38(6)**, 2168-2203.

(20) N. Candelon, D. Lastécouères, A. K. Diallo, J. R. Aranzaes, D. Astruc, and J. M. Vincent, *Chem. Commun,* 2008, 6, 741-743.

RSC Advances Accepted Manuscript

View Article Online
DOI: 10.1039/C6RA09929G

Published on 03 June 2016. Downloaded by UNIVERSITY OF NEBRASKA on 10/06/2016 00:01:46.

(21) B. Trastoy, M. E. Pérez-Ojeda, R. Sastre, and J. L. Chiara, *Chem. Eur. J,* 2010, **16(12)**, 3833-3841.

(22) P. L. Golas, N. V. Tsarevsky, B. S. Sumerlin and K. Matyjaszewski, *Macromolecules*, 2006, **39(19)**, 6451-6457.

(23) W. H. Binder and R. Sachsenhofer, *Macromol. Rapid Commun.*, 2008, **29(12-13)**, 952–981

(24) T. Felder, C. A. Schalley, H. Fakhrnabavi and O. Lukin, *Chem. Eur. J,* 2005, **11(19)**, 5625-5636.

(25) M. Smadhi, S. D. Bentzmann, A. Imberty, M. Gingras, R. Abderrahim and P. G. Goekjian, *Beilstein J. Org. Chem,* 2014, **10(1)**, 1981-1990.

(26) V. Udumula, J. H. Tyler, D. A. Davis, H. Wang, M. R. Linford, P. S. Minson and D. J. Michaelis, *ACS Catal.,* 2015*,* **5(6)**, 3457-3462.

(27) J. Morales-Sanfrutos, M. Ortega-Munõz, J. Lopez-Jaramillo, F. Hernandez-Mateo, and F. Santoyo-Gonzalez*, J. Org. Chem.,* 2008, **73(19)**, 7772-7774.

(28) N. D. Elshan, T. Jayasundera, B. L. Anglin, C. S. Weber, R. M. Lynch and E. A. Mash, *Org. Biomol. Chem*, 2015, **13(6)**, 1778-1791.

(29) K.K. Bansal, D. Kakde, U. Gupta and N.K. Jain, *J. Nanosci. Nanotechnol.*, 2010, **10**, 8395–8404.

(30) Y. Sha and Y. Dong, *Synth. Commun.,* 2003*,* **33(15)**, 2599-2604.

RSC Advances Accepted Manuscript

View Article Online
DOI: 10.1039/C6RA09929G

(31) R. Srinivasan, L. P. Tan, H. Wu, P. Y. Yang, K. A. Kalesh and S. Q. Yao, *Org. Biomol. Chem*, 2009, **7(9)**, 1821-1828.

(32) M. S. Kumar and G. Panda, *RSC Adv.*, 2013, **3(40)**, 18332-18338.

(33) M. C. Holden, S. Sohel and M. F. Greaney, *Angew. Chem., Int. Ed.*, 2016, **55(7)**, 2450-2453.

(34) M. Iwata and H. Kuzuhara, *Bull. Chem. Soc. Jpn.*, 1986, **59(4)**, 1031-1036.

(35) A. D. Martino, C. Galli, P. Gargano and L. Mandolini, *J. Chem. Soc., Perkin Trans. 2*, 1985, 1345-1349.

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An Efficient and Controlled Synthesis of Persulfonylated G1 Dendrimers Via Click Reaction

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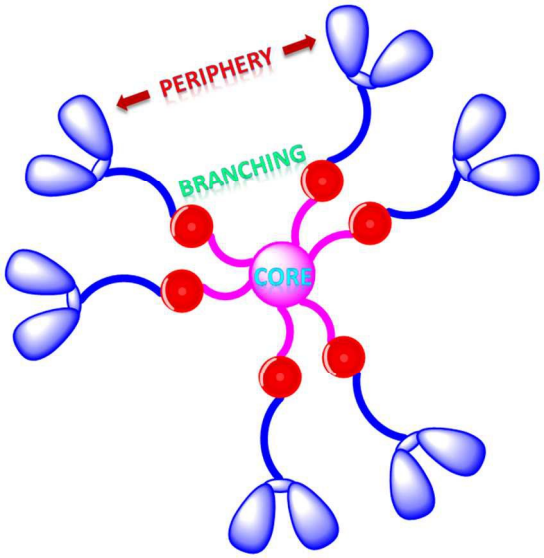
ABSTRACT: A controlled synthesis of clickable dendrimers at room temperature using aromatic/heteroaromatic cores and persulfonylated dendrons has been performed. Click reactions went smoothly with $Cu(PPh_3)_3Br$ complex in the presence of tridentate chelating ligands and produced copper free G1 dendrimers in excellent yield.



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