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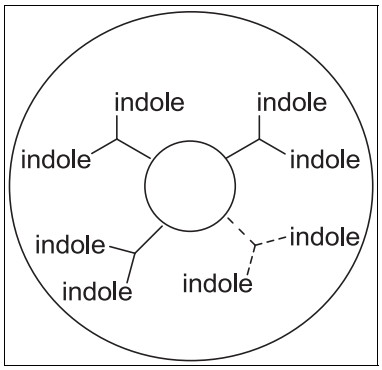

Syntheses of polyindolyl compounds from the Friedel–Crafts reaction of indoles and tri- or tetra-aldehydes catalyzed by silica sulfuric acid are described. These dendrimeric supramolecules were effectively prepared at room temperature in quantitative yield. These novel products have potential in the synthesis of dyes and pigments and also in various pharmaceutical applications.

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INTRODUCTION

Among the various heterocyclic compounds used in medical chemistry, the indole derivatives have a long tradition of biologically relevant compounds, and therefore, their synthesis and functionalization have been extensively investigated [1–4]. The indole unit forms the basis for the general structures of bisindolyl methanes (BIMs). BIM and its derivatives are also used as dietary supplements [5]. BIMs inhibit the growth activities of many cancer types such as lung [6], mammary [7], prostate [8], and colon cancer [9]. These compounds also exhibit antimicrobial and antifungal [10,11], antibiotic [12], and antibacterial activities [13]. Their oxidized forms are utilized as dyes [14] as well as colorimetric sensors [15]. Despite the extensive work on the chemistry of BIMs, there is no straight forward method for the synthesis of complex molecule by the reaction of indoles and molecules containing more than two aldehyde groups [16].

The chemistry of dendrimers, highly branched molecules grown outward from a multifunctional core, has been vigorously developed in the past decades [17].

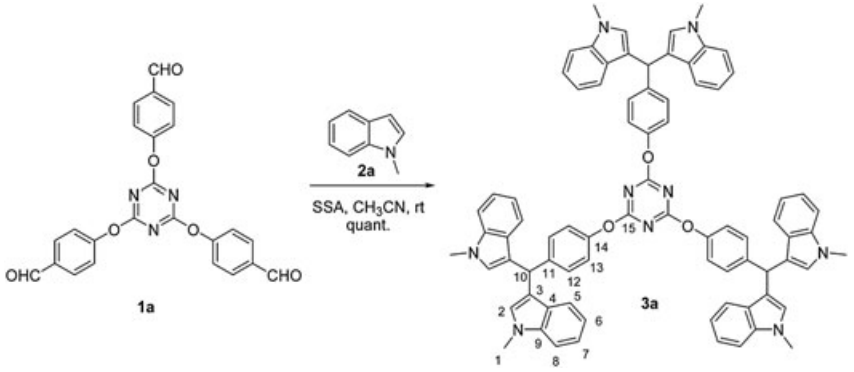
In our efforts aimed at the development of new syntheses of BIMs [18–21], combined with denderimer-like heterocyclic compounds [22], we were interested in the preparation of polyindolyl compounds. Here, we report the application of silica sulfuric acid (SSA; ref. 23) in the Friedel–Crafts (F–C) reaction of tri- or tetra-aldehydes and indoles.

RESULTS AND DISCUSSION

We first performed the F–C reaction between tripodal **1a** and 1-methylindole (**2a)** in the presence of SSA in acetonitrile (Scheme 1). The reaction was completed after 30 min at room temperature, and after purification with flash chromatography, the structure of **3a** was confirmed from the NMR (Figs. 1 and 2). Protons on C^1, C^{10}, and C^2 appeared at δ = 3.68, 5.85, and 6.86 ppm, respectively, as singlets with a ratio of 6:1:2 and other aromatic protons are recorded at 6.84–7.38 ppm with the expected ratio H-5/8 + H-6/7 and H-12 + H13. As marked in the structure, there are a maximum of 15 different carbons on **3a** that are matched with ^{13}C NMR by recording of 14 carbons (Scheme 1). Aliphatic carbons C^1 and C^{10} appeared in δ = 33.1 and 39.5 and deshielded aromatic C^{14} and C^{15} in 150.2 and 173.9 ppm, respectively. Other carbons were recorded from 110.5 to 137.8 ppm.

In further experiments, the effect of substitution on the indole part was examined in the reaction. It was found that under the same conditions indole (**2b**), 2-methylindole (**2c**), and 5-bromoindole (**2d**) easily reacted with **1a** to give the corresponding products **3b–d** (Table 1, entries 2–4).

Scheme 1. Reaction of tripodal **1a** and 1-methylindole.



To explorate the scope of reaction, trialdehyde **1b** and tetra-aldehyde **1c** were synthesized from 4-hydroxybenzaldehyde and the corresponding bromobenzyl derivatives (Fig. 3).

Aldehyde **1b** reacted with indole to form hexa(3-indolyl) compound **3f** in quantitative yields (Table 1, entry 6). Also, the reaction of **1b** with other indoles containing electron deficient or electron withdrawing substituents such as 1-methylindole, 2-methylindole, and 5-bromoindole gave the corresponding polyindolyl compounds **3e** and **3g–h** in excellent yields (Table 1, entries 5, 7 and 8). Treatment of tetra-aldehyde **1c** with the respective indoles **2b–d** yielded a range of highly branched compounds **3i–k** containing octa indoles that will be in the "Experimental" section (Table 1, entries 9–11).

Although the reaction of steric hindered tripodal **1d** with indoles **2a–d** gave a complex mixture of unidentified products, surprisingly, it reacted with skatole (**2e**) in a clean process to give **3l** in high yield after 7.5 h (Scheme 2).

CONCLUSIONS

In summary, the chemistry described herein provides a facile and direct synthesis of diversely substituted indolyl compounds in quantitative yields. These compounds have potential in medicinal useful applications. From a synthetic point of view, the net transformation involves a one-step conversion of simple, readily available starting materials into an interesting class of heterocyclic derivatives. A solid and inexpensive catalyst has also been used.

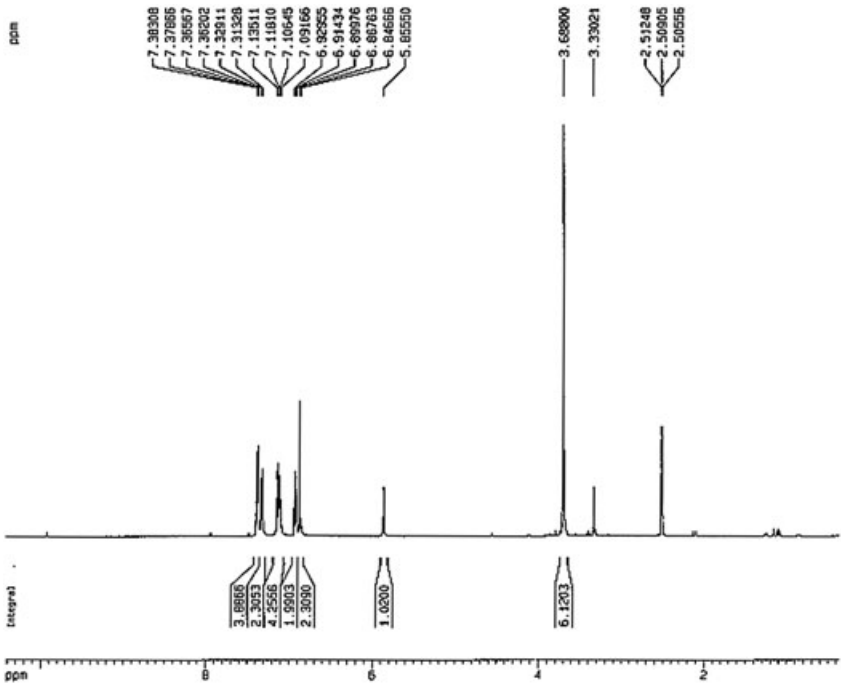


Figure 1. ^{1}H NMR **3a** in DMSO.

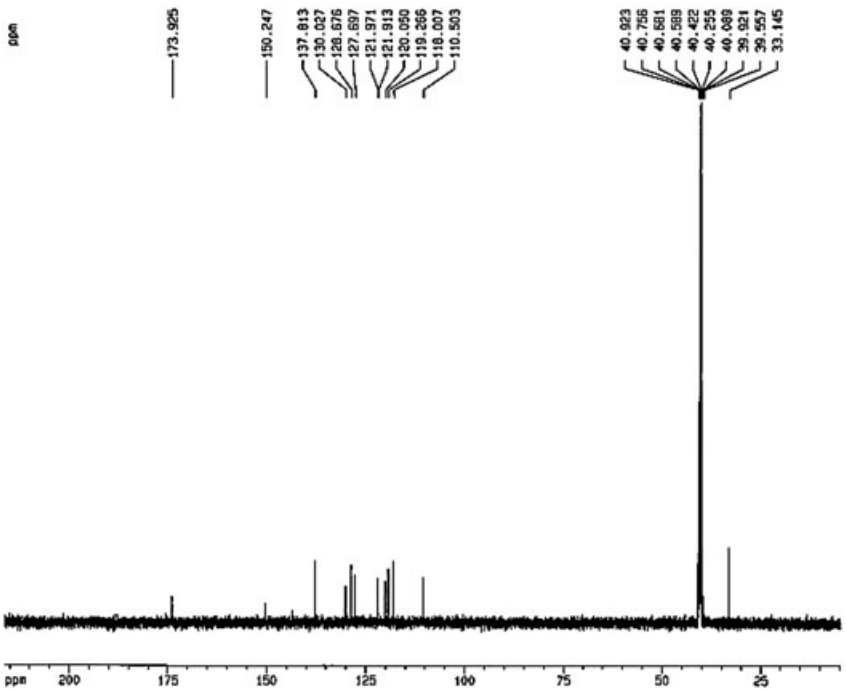


Figure 2. ^{13}C NMR **3a** in DMSO.

EXPERIMENTAL

General. Chemicals were purchased from Fluka (St. Louis, MO), Merck (Darmstadt, Germany), and Aldrich (St. Louis, MO) chemical companies. IR spectra were run on a Shimadzu Infra Red Spectroscopy IR-435. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 500 MHz Spectrometer in DMSO-d_6 as solvent. Elemental analyses for C, H, and N were performed using a Heraus CHN rapid analyzer. All the products have colorless powdered form and before melting point in ranging 200–230°C were decomposed.

General procedures for the preparation of polyindolyl compounds. To a stirring solution of tri- or tetra-aldehyde (0.1 mmol) and indole (2.3 equiv. to each aldehyde) in CH_3CN (5 mL), SSA [0.1 equiv. to each aldehyde (1 g SSA containing 4.3 mmol H^+)] was added at room temperature. After appropriate time (Table 1), solvent was evaporated under reduced pressure. The product was purified by flash column chromatography using *n*-hexane–ethyl acetate as eluent.

Table 1

Preparation of polyindolyl compounds.

Entry	Aldehyde 1	Indole 2	Polyindole 3	Time (h)
1	**1a**	**2a**	**3a**	0.5
2	**1a**	**2b**	**3b**	2
3	**1a**	**2c**	**3c**	0.6
4	**1a**	**2d**	**3d**	2
5	**1b**	**2a**	**3e**	5
6	**1b**	**2b**	**3f**	5
7	**1b**	**2c**	**3g**	5.5
8	**1b**	**2d**	**3h**	3.5
9	**1c**	**2b**	**3i**	2.6
10	**1c**	**2c**	**3j**	1.2
11	**1c**	**2d**	**3k**	3

Spectral data. 3a: FT-IR (KBr) = v (cm^{-1}): 3450 (N—H). ^{1}H NMR (DMSO-d_6, 500 Hz); δ 3.68 (s, 18H), 5.85 (s, 3H), 6.86 (s, 6H), 6.91 (t, *J* = 7.44 Hz, 6H), 7.11 (m, 12H), 7.32 (d, *J* = 7.91 Hz, 6H), 7.37 (dd, *J* = 8.70, 2.21 Hz, 12H). ^{13}C NMR (DMSO-d_6, 125 Hz); δ 33.1, 39.5, 110.5, 118.0, 119.2, 120.0, 121.91, 121.97, 127.6, 128.6, 130.0, 137.8, 150.2, 173.9. Anal. Calcd. for $C_{78}H_{63}N_9O_3$: C, 79.77; H, 5.41; N, 10.73. Found: C, 79.27; H, 5.22; N, 10.82.

3b: FT-IR (KBr): v (cm^{-1}): 3421 (N—H). ^{1}H NMR (DMSO-d_6, 300 MHz); δ 5.84 (s, 3H), 6.83–6.89 (m, 12H), 7.020 (t, *J* = 7.4 Hz, 6H), 7.110 (d, *J* = 8.4 Hz, 6H), 7.278 (d, *J* = 7.8 Hz, 6H), 7.34 (m, 12H), 10.83 (s, 6H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz); δ 30.06, 111.93, 118.36, 118.70, 119.53, 121.39, 121.46, 124.00, 127.02, 129.66, 137.03, 143.23, 149.80, 173.58. Anal. Calcd. for $C_{72}H_{51}N_9O_3$: C, 79.32; H, 4.72; N, 11.56. Found: C, 78.93; H, 4.44; N, 11.22.

3c: ^{1}H NMR (DMSO-d_6, 500 MHz); δ 2.09 (s, 18H), 5.95 (s, 3H), 6.70 (t, *J* = 7.48 Hz, 6H), 6.85 (d, *J* = 7.96 Hz, 6H), 6.90 (t, *J* = 7.51 Hz, 6H), 7.10 (d, *J* = 8.56 Hz, 6H), 7.20 (dd, *J* = 8.30, 3.36 Hz, 12H), 10.76 (s, 6H). ^{13}C NMR (DMSO-d_6, 125 MHz);

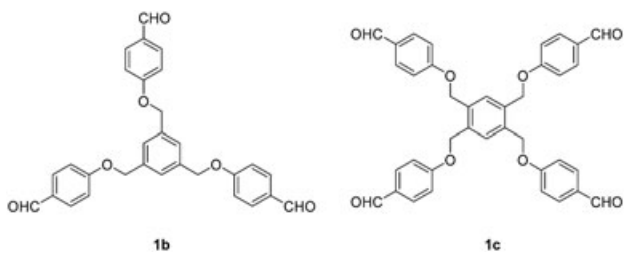
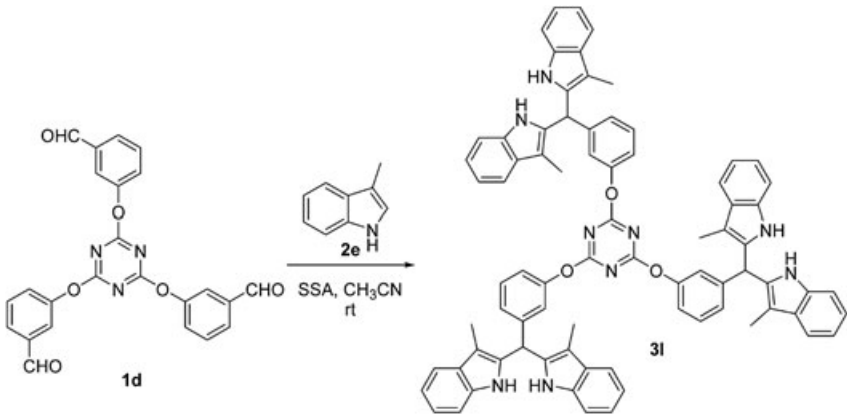


Figure 3. Structure of trialdehyde **1b** and tetra-aldehyde **1c**.

Scheme 2. Reaction of tripodal **1d** and skatole.



δ 12.8, 38.9, 111.2, 112.9, 118.8, 119.3, 120.4, 121.7, 129.0, 130.4, 132.9, 135.9, 142.8, 150.3, 174.0. Anal. Calcd. for $C_{78}H_{63}N_9O_3$: C, 79.77; H, 5.41; N, 10.73. Found: C, 79.31; H, 5.13; N, 10.44.

3d: FT-IR (KBr) = ν (cm^{-1}): 3425 (N—H). ^{1}H NMR (DMSO-d_6, 500 MHz); δ 5.88 (s, 3H), 6.90 (s, 6H), 7.10 (s, 12H), 7.30 (s, 12H), 7.47 (s, 6H), 11.10 (s, 6H). ^{13}C NMR (DMSO-d_6, 125 Hz); δ 39.0, 111.8, 114.4, 118.3, 122.0, 122.1, 124.3, 126.1, 129.1, 130.0, 136.1, 150.4, 174.0. Anal. Calcd. for $C_{72}H_{45}Br_6N_9O_3$: C, 55.31; H, 2.90; N, 8.06. Found: C, 55.14; H, 2.45; N, 8.15.

3e: ^{1}H NMR (DMSO-d_6, 500 MHz); δ 3.66 (s, 18H), 5.04 (s, 6H), 5.78 (s, 3H), 6.78 (s, 6H), 6.89 (m, 12H) , 7.09 (t, J = 7.56 Hz, 2H), 7.25 (d, J = 8.04 Hz, 2H), 7.29 (d, J = 7.88 Hz, 2H), 7.35 (d, J = 8.20 Hz, 2H), 7.44 (s, 3H). ^{13}C NMR (DMSO-d_6, 125 Hz); δ 33.0, 39.4, 69.8, 110.4, 115.1, 118.5, 119.1, 120.1, 121.1, 121.2, 121.8, 127.1, 127.7, 128.6, 130.0, 137.9, 137.8, 138.5, 157.3. Anal. Calcd. for $C_{84}H_{72}N_6O_3$: C, 83.14; H, 5.98; N, 6.93. Found: C, 83.01; H, 5.81; N, 6.77.

3f: FT-IR (KBr) = ν (cm^{-1}): 3406 (N—H). ^{1}H NMR (DMSO-d_6, 500 MHz); δ 5.06 (s, 6H), 5.77 (s, 3H), 6.80 (s, 6H), 6.91 (d, J = 8.60 Hz, 6H), 6.85 (t, J = 7.37 Hz, 6H), 7.02 (t, J = 7.40 Hz, 6H), 7.26 (m, 12H), 7.34 (d, J = 8.05 Hz, 6H), 7.46 (s, 3H), 10.78 (s, 6H). Anal. Calcd. for $C_{78}H_{60}N_6O_3$: C, 82.95; H, 5.35; N, 7.44. Found: C, 83.01; H, 5.23; N, 7.35.

3g: FT-IR (KBr) = ν (cm^{-1}): 3419 (N—H). ^{1}H NMR (DMSO-d_6, 500 MHz); δ 2.08 (s, 18H), 5.08 (s, 8H), 5.88 (s, 3H), 6.68 (t, J = 7.37 Hz, 6H), 6.85–6.97 (m, 18H), 7.11 (d, J = 8.35 Hz, 6H), 7.22 (d, J = 7.99 Hz, 6H), 7.51 (s, 3H), 10.72 (s, 6H). ^{13}C NMR (DMSO-d_6, 125 Hz); δ 12.8, 38.6, 69.8, 111.1, 113.3, 115.0, 118.7, 119.4, 120.8, 127.1, 129.1, 130.4, 132.8, 135.9, 137.3, 138.5, 157.3. Anal. Calcd. for $C_{84}H_{72}N_6O_3$: C, 83.14; H, 5.98; N, 6.93. Found: C, 83.11; H, 5.92; N, 6.82.

3h: FT-IR (KBr) = ν (cm^{-1}): 3415 (N—H). ^{1}H NMR (DMSO-d_6, 500 MHz); δ 5.08 (s, 6H), 5.81 (s, 3H), 6.87 (s, 6H), 6.95 (d, J = 8.67 Hz, 6H), 7.16 (dd, J = 5.15, 1.73 Hz, 6H), 7.24 (d, J = 8.62 Hz, 6H), 7.44 (d, J = 1.38 Hz, 6H), 7.49 (s, 2H), 11.05 (s, 6H). ^{13}C NMR (DMSO-d_6, 125 Hz); δ 38.9, 69.9, 111.7, 114.4, 115.2, 118.8, 122.1, 124.2, 126.0, 127.2, 129.2, 130.0, 136.1, 137.4, 138.5, 157.5. Anal. Calcd. for $C_{78}H_{54}Br_6N_6O_3$: C, 58.45; H, 3.40; N, 5.24. Found: C, 58.39; H, 3.42; N, 5.18.

3i:FT-IR (KBr) = ν (cm^{-1}): 3412 (N—H). ^{1}H NMR (DMSO-d_6, 500 MHz); δ 5.15 (s, 8H), 5.77 (s, 4H), 6.81–6.84 (m, 16H), 6.89–7.02 (m, 16H), 7.23–7.36 (m, 24H), 10.77 (s, 8H). ^{13}C NMR (DMSO-d_6, 125 Hz); δ 31.5, 67.6, 112.1, 112.2, 115.2, 118.3, 119.2, 120.0, 121.0, 121.6, 124.3, 127.4, 130.0, 135.7, 137.4, 138.2, 157.2. Anal. Calcd. for $C_{102}H_{78}N_8O_4$: C, 82.79; H, 5.31; N, 7.57. Found: C, 82.68; H, 5.33; N, 7.44.

3j: FT-IR (KBr) = ν (cm^{-1}): 3401 (N—H). ^{1}H NMR (DMSO-d_6, 500 MHz); δ 2.07 (s, 24H), 5.19 (s, 8H), 5.86 (s, 4H), 6.66 (t, J = 7.49 Hz, 8H), 6.85 (t, J = 8.03 Hz, 12H), 6.90 (t, J = 8.81 Hz, 12H), 7.09 (d, J = 8.44 Hz, 8H), 7.23 (d, J = 7.98 Hz, 8H), 7.70 (s, 2H), 10.69 (s, 8H). ^{13}C NMR (DMSO-d_6, 125 Hz); δ 12.79, 38.6, 67.7, 111.1, 111.3, 113.3, 115.1, 118.7, 119.4, 119.7, 120.3, 129.1, 130.4, 132.7, 135.8, 135.9, 137.4, 157.2. Anal. Calcd. for $C_{110}H_{94}N_8O_4$: C, 82.99; H, 5.95; N, 7.04. Found: C, 82.65; H, 5.72; N, 7.14.

3k: FT-IR (KBr) = ν (cm^{-1}): 3445 (N—H). ^{1}H NMR (DMSO-d_6, 500 MHz); δ 5.17 (s, 8H), 5.77 (s, 4H), 6.85 (s, 8H), 6.92 (d, J = 8.42 Hz, 8H), 7.14 (d, J = 8.47 Hz, 8H), 7.19 (d, J = 8.35 Hz, 8H), 7.32 (d, J = 8.51 Hz, 8H), 7.41 (s, 8H), 7.68 (s, 2H), 11.02 (s, 8H). ^{13}C NMR (DMSO-d_6, 125 Hz); δ 38.9, 65.7, 111.7, 114.4, 115.3, 118.8, 122.0, 124.2, 126.0, 129.2, 130.0, 136.1, 157.4. Anal. Calcd. for $C_{102}H_{70}Br_8N_8O_4$: C, 58.04; H, 3.34; N, 5.31. Found: C, 58.10; H, 3.25; N, 5.27.

3l: FT-IR (KBr) = ν (cm^{-1}): 3433 (N—H). ^{1}H NMR (DMSO-d_6, 500 MHz); δ 2.19 (s, 18H), 6.08 (s, 3H), 6.90 (s, 3H), 6.98 (m, 6H), 7.03 (m, 6H), 7.10 (m, 6H), 7.28 (m, 6H), 7.34 (m, 3H), 7.42 (m, 6H), 10.49 (s, 6H). ^{13}C NMR (DMSO-d_6, 125 Hz); δ 10.4, 31.5, 108.0, 111.8, 112.0, 118.8, 118.9, 119.0, 119.2, 120.8, 121.6, 121.7, 123.5, 126.7, 128.7, 129.2, 130.3, 134.5, 136.4, 137.1, 144.0, 152.3, 173.7. Anal. Calcd. for $C_{78}H_{63}N_9O_3$: C, 79.77; H, 5.41; N, 10.73. Found: C, 79.21; H, 5.25; N, 10.55.

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