Supporting Information

Facile synthesis of mono- and polytopic β-cyclodextrin aromatic aldehydes by click chemistry

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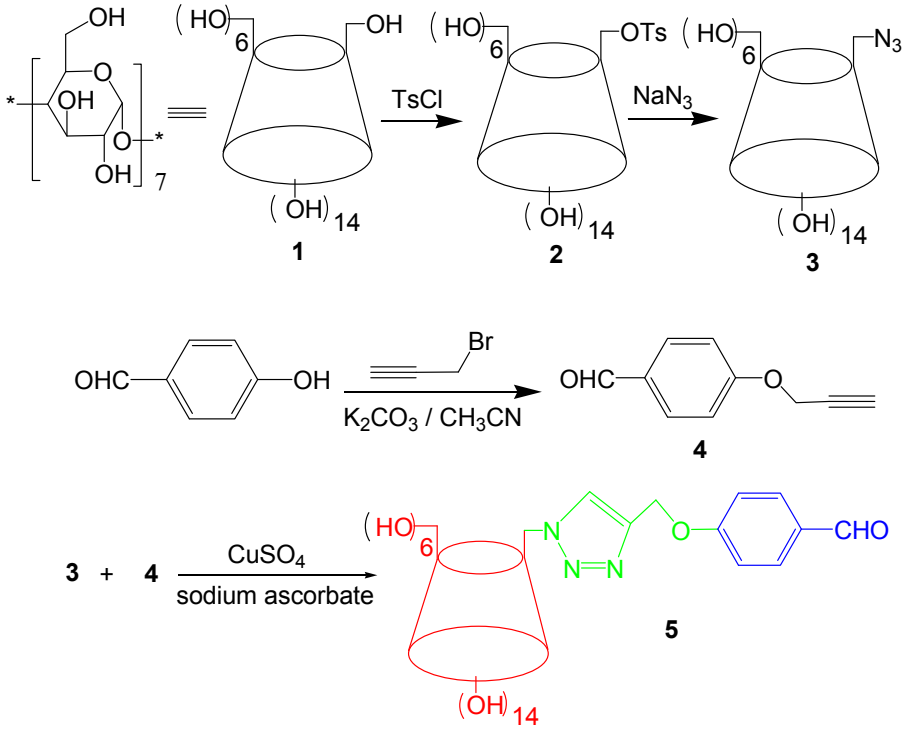
1. General

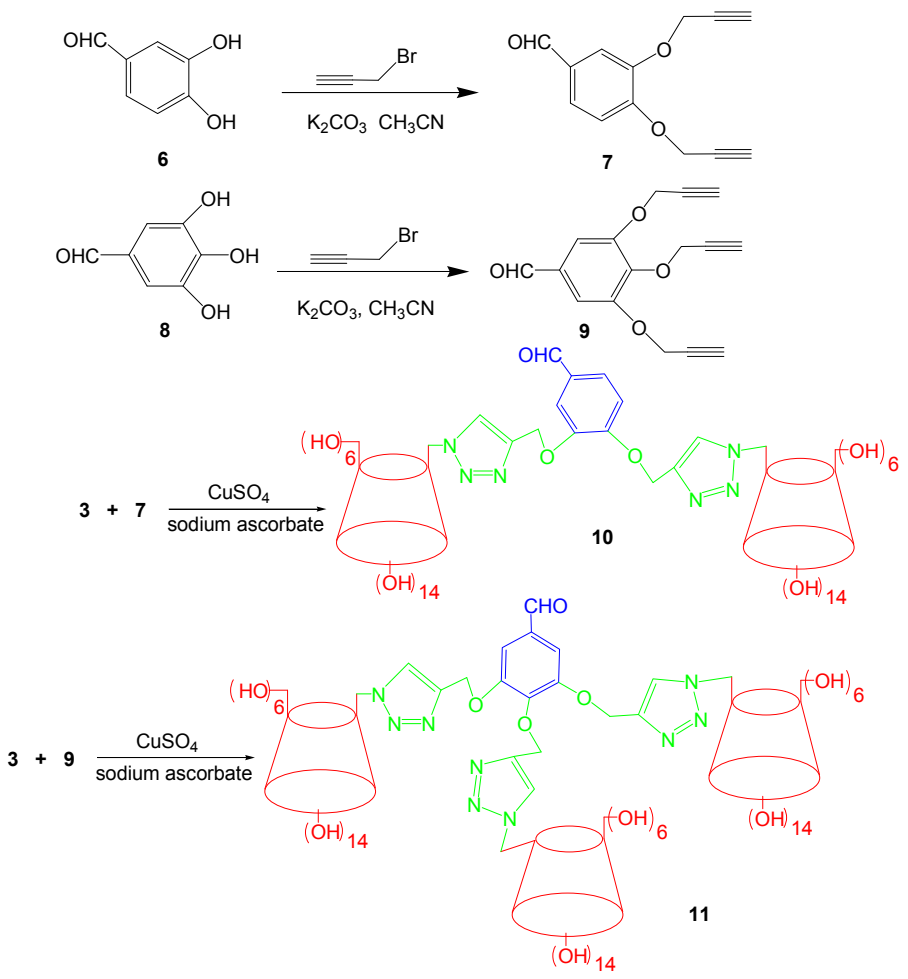
All chemicals were purchased from commercial suppliers and used without further purification. The other organic solvents and inorganic reagents were purified according to standard anhydrous methods before use. Distilled water was used in all experiments.TLC analysis was performed using pre-coated glass plates. IR spectra were recorded on a Perkin-Elmer PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. ^1H NMR spectra was recorded in DMSO on a Bruker-ARX 600 instrument at 30°C. Chemical shifts are reported in ppm, using tetramethylsilane (TMS) as internal standard. ESI-MS spectra were obtained from DECAX-30000 LCQ Deca XP mass spectrometer. Elemental analyses were performed at Vario EL III Elemental Analyzer.

4-(prop-2-ynyloxy)benzaldehyde **4**, 3,4-bis(prop-2-ynyloxy)benzaldehyde **7** and 3,4,5-tris(prop-2-ynyloxy)benzaldehyde **9** were conveniently prepared by reacting 4-hydroxybenzaldehyde, 3,4-dihydroxybenzaldehyde **6** or 3,4,5-trihydroxybenzaldehyde **8** with 3-bromoprop-1-yne under K2CO3/MeCN system in yields of 87%, 86% and 80%, respectively (*Eur. J. Org. Chem*. 2008, 5723-5730).

2. The synthetic procedure of 6a、6b and 6c



Scheme 1 Synthetic route of compound **5**



Scheme 2 Synthetic route of compounds **10** and **11**

2.1 Synthesis of compound 2

According to the published method [*Journal of Chromatography A*, **2009**, 1216(2),257-63], β-CD (6.0 g, 5.3mmol) and NaOH (3.6 g, 0.09mol) were stirred in a water solution (120 mL) at 0-5℃. Then p-tolylsulfonyl chloride (TsCl, 1.2 g, 6.3mmol) was added into the solution at 0-5℃. After 5h at 0-5℃, the precipitate was removed by filtration. 10% HCl was added into the filtrate, and the pH was adjusted to pH=7. The mixture was kept in the refrigerator overnight to afford a white solid product. The white solid was recrystallized in hot water to afford 2.3 g of product (yield 38.3%). The characteristic data were in accordance with literature [*Journal of Chromatography A*, **2009**, 1216(2),257-63].

2.2 Synthesis of compound 3

According to the published method [*Journal of Controlled Release*, **2007**, 122(1): 54–62], the compound **2** (3g, 2.2mmol) and sodium azide (0.94g, 14.5mmol) dissolve into the DMF(20mL) and H_2O (3mL). The mixture was stirred at 80℃for 5h and then cooled to room temperature. The resulting solution was precipitated by acetone (80mL) to produce the raw azide product as a white powder. The crude product was recrystallized with little hot water and acetone to give white

compound **3** in yield of 65%. The characteristic data were in accordance with literature [*Journal of Controlled Release*, **2007**, 122(1): 54–62].

2.3 Synthesis of mono-CD aromatic aldehyde derivatives 5

Compound **4** (0.16g, 1mmol) with compound **3** (1.16g, 1mmol) was carried out in DMF (35mL) in the presence of Cu^{I} generated by the reduction of copper sulfate (0.28g,1.1mmol) with sodium ascorbate (0.48g, 2.4mmol). The mixture was stirred at room temperature for 15 h. TLC detection indicated the disappearance of materials of compounds **3** and **4**. After reaction, most of the solvent was evaporated under reduced pressure and 20 mL of distilled water was added with vigorous stirring at room temperature. The mixture was stored in the refrigerator overnight and then the precipitate was collected by filtration. The precipitate was further purified by recrystallization in DMF/acetone for three times. Compound **5** was obtained as grey white solid in yield of 80%. Compound **5**: IR/cm^{-1}: 3387, 2927, 1679, 1599, 1509, 1157, 1031, 756; ^{1}H NMR (400 MHz, DMSO-d_6) δppm: 2.78~4.10 (m, 40H, CH and CH_2), 4.25~4.68 (8H, OH and NCH_2), 4.69~5.10 (m, 7H, CH), 5.23 (s, 2H, CH_2O), 5.53~5.99 (m, 14H, OH), 7.24 (d, *J*=8.0Hz, 2H, ArH), 7.88 (d, *J*=8.0Hz, 2H, ArH), 8.22 (s, 3H, NCH); 9.87 (s, 1H, CHO). ^{13}C NMR (100 MHz, DMSO-d_6) δppm: 191.9, 163.5, 142.4, 132.3, 130.3, 126.2, 115.6, 102.6, 101.7, 83.9, 82.5, 82.1, 81.4, 73.7, 73.6, 73.4, 73.1, 72.9, 72.6, 72.2, 70.5, 61.8, 60.4, 60.0, 59.5, 50.5. MS *m*/*z*(%): 1342.3(MNa^{+}, 100). Anal. Calcd. For $C_{52}H_{77}N_3O_{36}$: C47.31, H5.88, N3.18; found C47.38, H5.82, N3.22%.

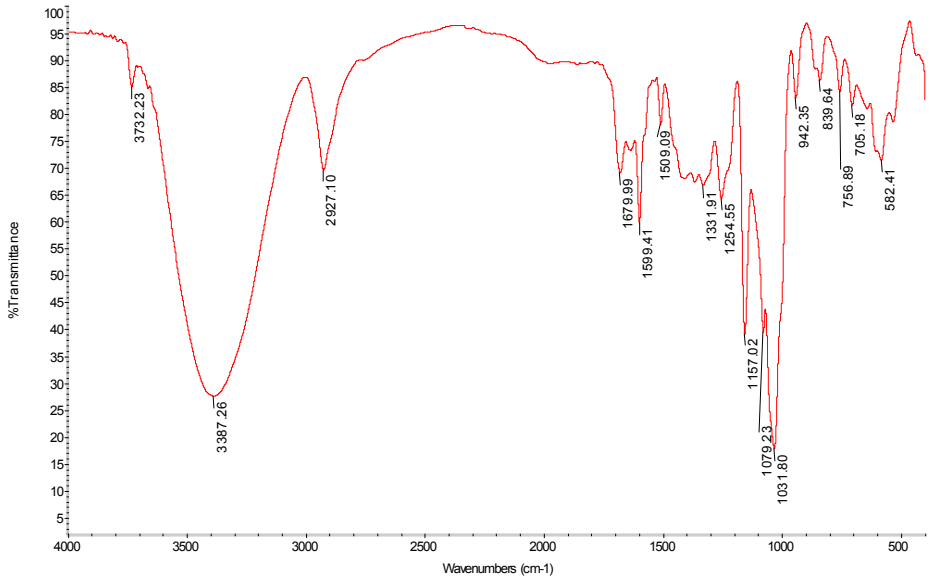


Figure 1 The IR spectrum of compound **5**

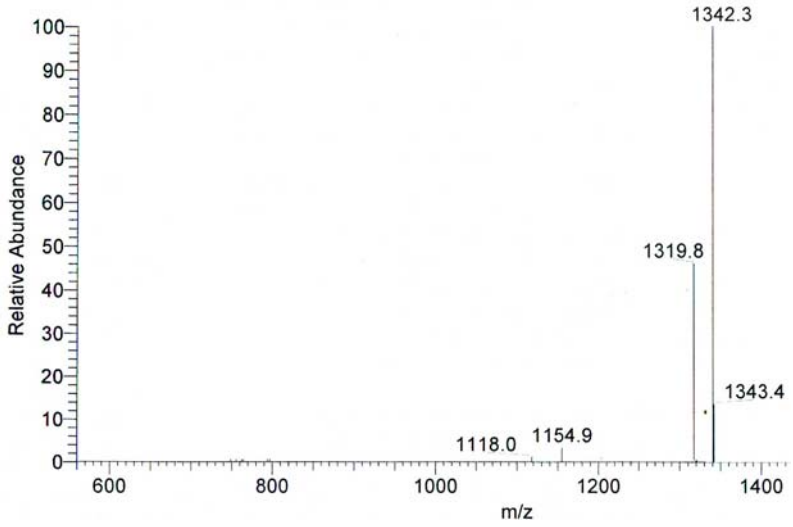


Figure 2 ESI-MS spectra of mono CD aromatic aldehyde derivative **5**

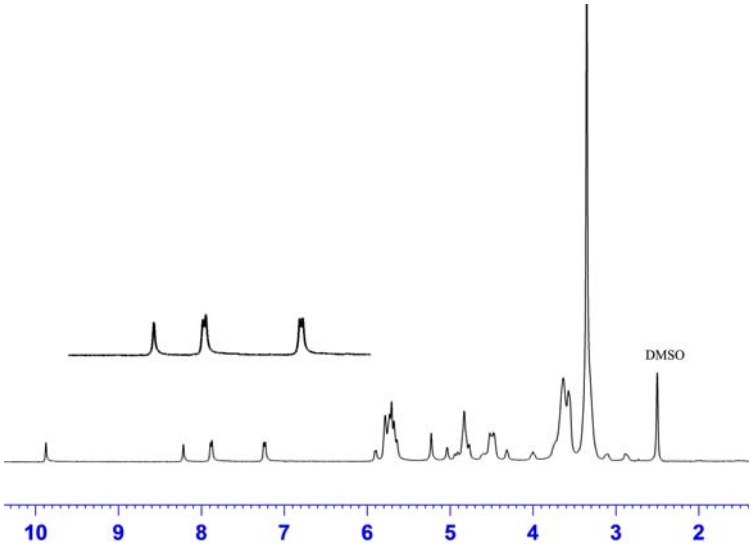


Figure 3 ^{1}H NMR spectrum of mono CD aromatic aldehyde derivative **5**

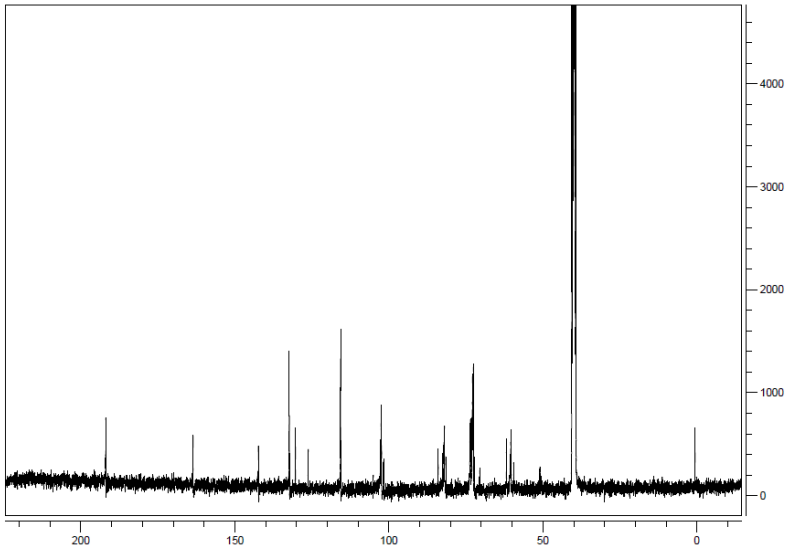


Figure 4 ^{13}C NMR spectrum of mono CD aromatic aldehyde derivative **5**

2.4 Synthesis of dimeric-CD aromatic aldehyde derivatives 10

Compound **7** (0.107g, 0.5mmol) with compound **3** (1.16g, 1mmol) was carried out in DMF(35mL) in the presence of Cu^{I} generated by the reduction of copper sulfate (0.28g,1.1mmol) with sodium ascorbate (0.48g, 2.4mmol). The mixture was stirred at 90°C for 48 h. TLC detection indicated the disappearance of materials of compounds **3** and **7**. After reaction, most of the solvent was evaporated under reduced pressure and 20 mL of distilled water was added with vigorous stirring at room temperature. The mixture was stored in the refrigerator overnight and then the precipitate was collected by filtration. The precipitate was further purified by recrystallization in DMF/acetone for three times. Compound **10** was obtained as grey white solid in yield of 78%. Compound **10**: IR/cm^{-1}: 3387, 2926, 1661, 1594, 1504, 1154, 1082, 756; ^{1}H NMR (400 MHz, DMSO-d_6) δppm: 2.68~3.98 (m, 114H), 4.18~4.67 (m, 6H), 4.68~4.99 (m, 6H), 5.48~6.05 (m, 16H), 7.24~8.28 (m, 5H, ArH and NCH), 9.88 (s, 1H, CHO). ^{13}C NMR (100 MHz, DMSO-d_6) δppm: 195.4, 165.2, 143.1, 134.1, 131.1, 128.4, 127.1, 118.3, 102.4, 100.4, 84.2, 81.9, 81.8, 81.1, 73.6, 73.5, 73.3, 73.1, 72.8, 72.5, 72.3, 70.2, 61.7, 60.6, 60.3, 51.1. MS *m*/*z*(%): 2556.4 (MNa^{+}, 100). Anal. Calcd. For $C_{97}H_{148}N_6O_{71}$: C45.97, H5.89, N3.32; found C46.02, H5.82, N3.26%.

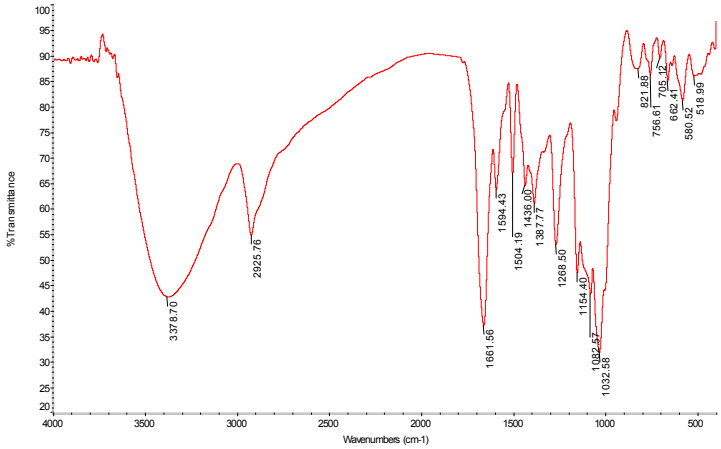


Figure 5 The IR spectrum of compound **10**

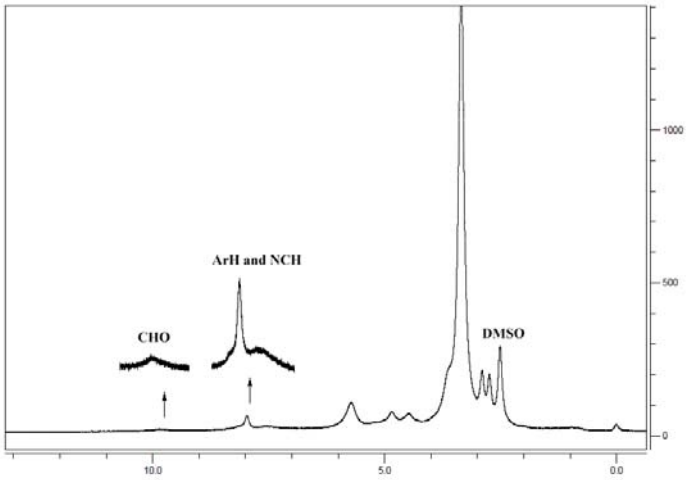


Figure 6 The ^{1}H NMR spectrum of Compound **10**

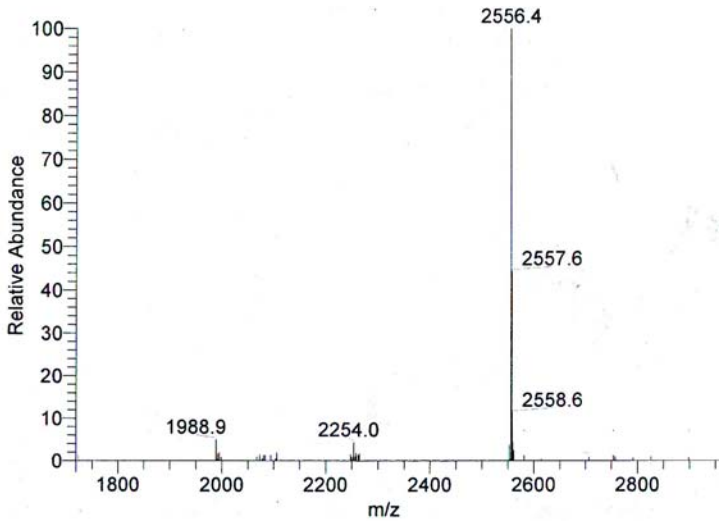


Figure 7 ESI-MS spectra of dimeric CD aromatic aldehyde derivative **10**

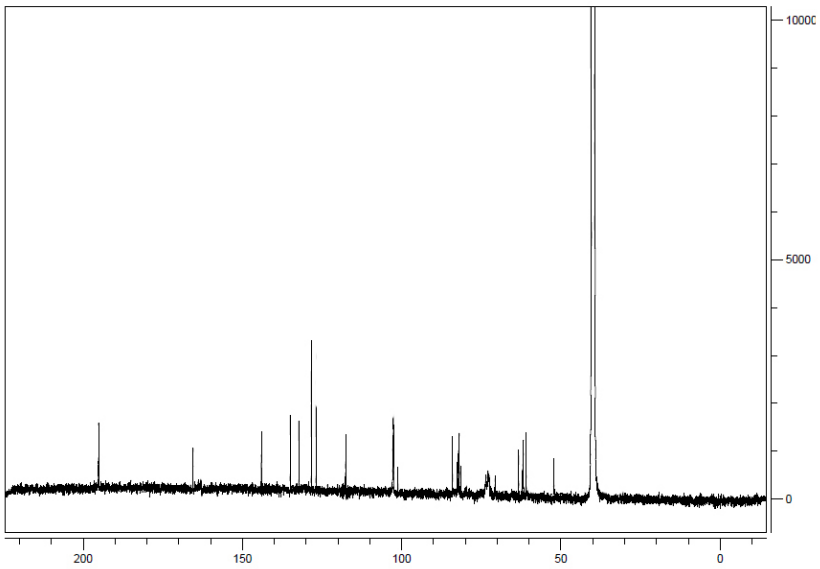


Figure 8 ^{13}C NMR spectrum of dimeric CD aromatic aldehyde derivative **10**

2.5 Synthesis of trimeric-CD aromatic aldehyde derivatives 11

Compound **9** (0.090g, 0.34mmol) with compound **3** (1.16g,1mmol) was carried out in DMF(35mL) in the presence of Cu^{I} generated by the reduction of copper sulfate (0.28g,1.1mmol) with sodium ascorbate (0.48g, 2.4mmol). The mixture was stirred at 90^{o}C for 60 h. TLC detection indicated the disappearance of materials of compounds **3** and **9**. After reaction, most of the solvent was evaporated under reduced pressure and 20 mL of distilled water was added with vigorous stirring at room temperature. The mixture was stored in the refrigerator overnight and then the precipitate was collected by filtration. The precipitate was further purified by recrystallization in DMF/acetone for three times. Compound **11** was obtained as grey white solid in yield of 75%. Compound **11**: IR/cm^{-1}: 3393, 2925, 1664, 1589,

1286, 1153, 1032, 758; ^{1}H NMR (400 MHz, DMSO-d_6) δppm: 2.80~3.99 (m, 171H), 4.37~4.68 (m, 9H), 4.69~4.92(m, 9H), 5.39~5.98 (m, 24H), 7.89 (m, 5H, NCH and ArH), 9.89 (s, 1H, CHO). ^{13}C NMR (100 MHz, DMSO-d_6) δppm: 188.2, 161.1, 143.5, 131.8, 130.0, 127.5, 126.3, 117.2, 103.2, 101.8, 101.4, 100.8, 83.3, 82.4, 81.0, 72.8, 72.6, 72.3, 71.9, 71.7, 71.4, 71.1, 70.6, 61.4, 60.7, 60.2, 50.4. MS *m*/*z*(%): 3774.3 (MNa^+, 100). Anal. Calcd. For $C_{142}H_{219}N_9O_{106}$: C45.50, H5.89, N3.32; found C45.56, H5.83, N3.25%.

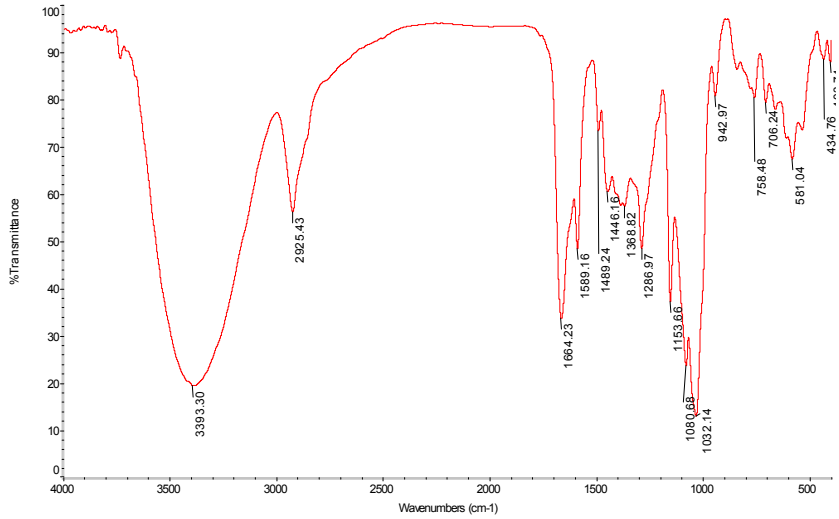


Figure 9 The IR spectrum of compound **11**

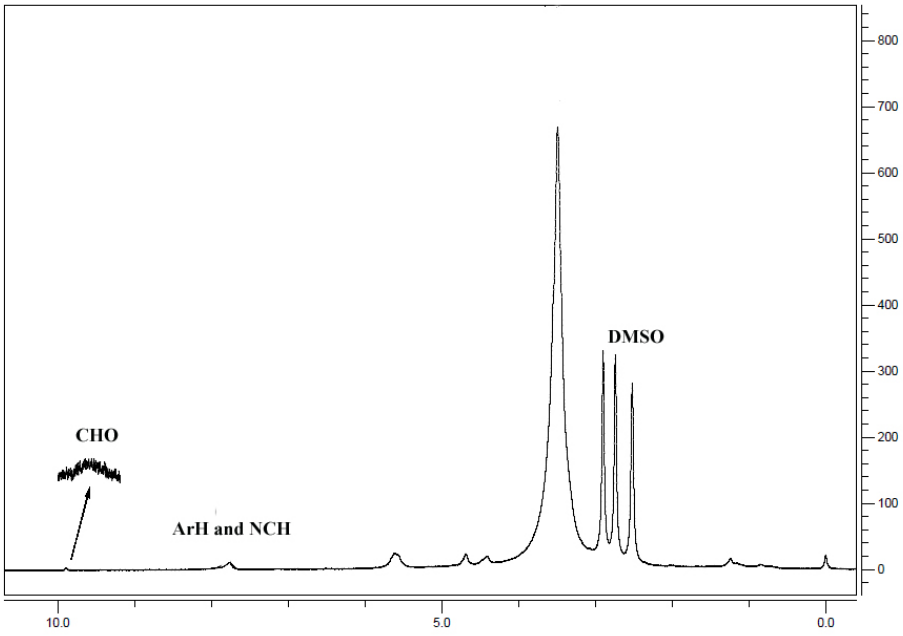


Figure 10 The ^{1}H NMR spectrum of compound **11**

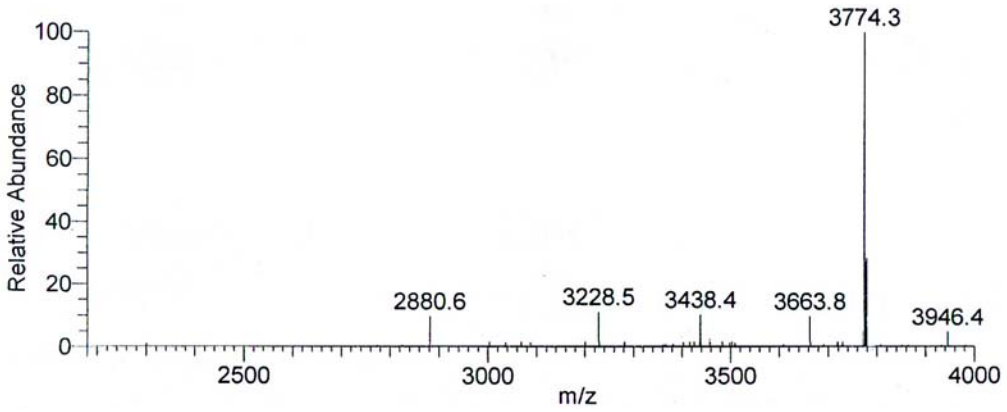


Figure 11 ESI-MS spectra of trimeric CD aromatic aldehyde derivative **11**

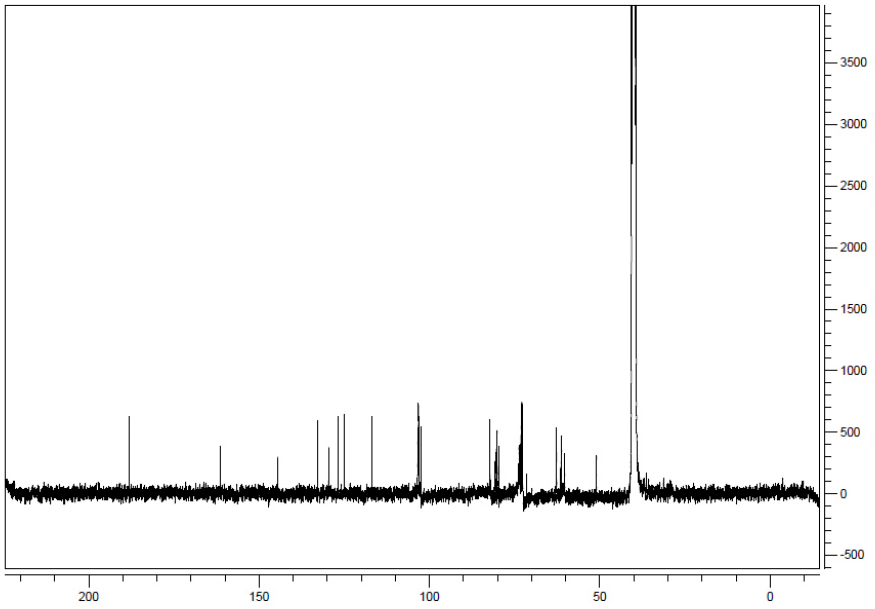


Figure 12 ^{13}C NMR spectrum of trimeric CD aromatic aldehyde derivative **11**