Electronic Supplementary Information

Remarkable Isomer-Selective Gelation of Aromatic Solvents by a Polymorph of a Urea-linked Bile acid-Amino acid Conjugate

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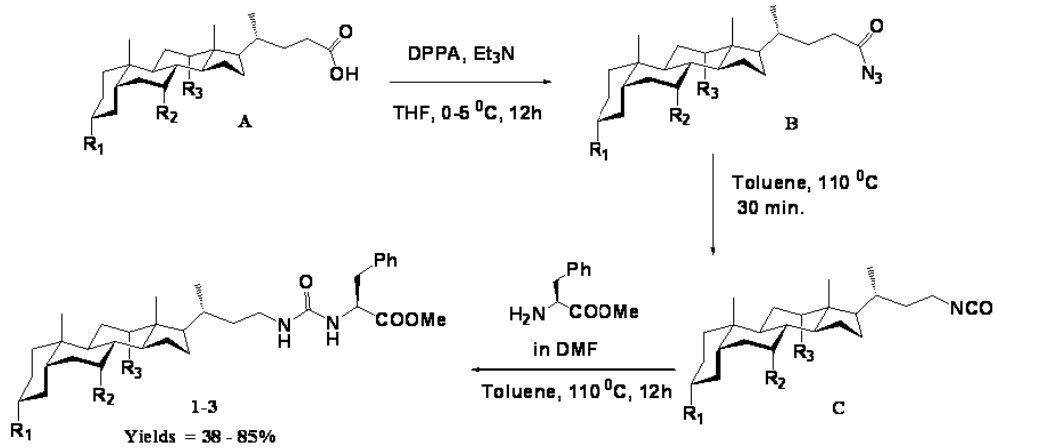
General methods

All reactions were carried out in oven dried glass wares. Reagents were purchased from Aldrich/Fluka. Solvents used were dried as per standard procedures. Column chromatography was done using silica gel (100-200 mesh). Different percentages of methanol in chloroform were used as eluents. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz and 100 MHz respectively. IR spectra were recorded on Perkin Elmer spectrum BX system. HRMS and elemental analysis were done on Micromass Q-TOF and ThermoFinnigan Flash EA 1112 series respectively. Scanning electron microscopy was done on SERION machine after gold coating. AFM images were recorded on JPK Nanowizard II in tapping mode. Samples were prepared by drop-casting 5- 10 μL of gel on freshly cleaved mica sheet followed by air drying and vaccum drying. TEM images were recorded on a JEM 2100F machine. Thin layer of gel was made on carbon coated copper grids and uranyl acetate staining was used for the samples. Powder XRD analysis was done on a Bruker D8 Discover machine using CuK_{α} as radiation and CuKα as a filter (λ = 1.54 Å). DLS pattern was recorded on a Malvern instrument.

Synthetic route towards urea linked bile acid-amino acid derivatives

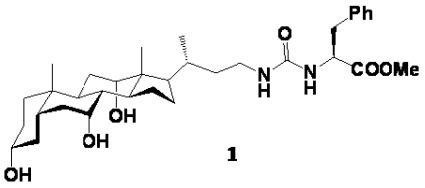


Scheme 1

General procedure for the preparation of urea derivatives

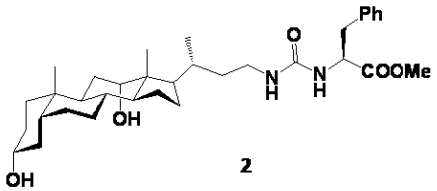
Azide (**B**) and isocyanate (**C**) of bile acids were prepared using reported procedures.[1] The (L or D)-phenylalanine methyl ester (1 equiv. with respect to azide) solution in DMF was then added to the isocyanate in toluene at room temperature. This mixture was heated at 110°C for 12h to yield the corresponding urea derivative. Compounds **2** and **3** got precipitated out from the reaction mixture owing to their poor solubility. In these cases precipitate was filtered, washed with chloroform and dried in vacuo to yield the product as white crystalline solid. In the case of **1,** upon completion of the reaction work-up and column chromatography (silica gel, 100-200 mesh) using methanol-chloroform solvent mixtures was done to get the product as an off-white amorphous material.

Preparation and characterization of urea derivatives



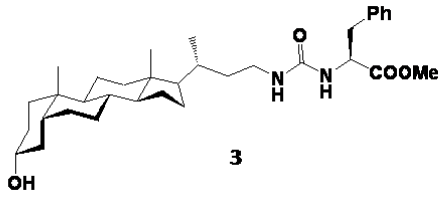
1

Cholic acid azide (770mg, 1.78 mmol) was heated at 110°C in toluene (6 mL) for 30 minutes to afford the corresponding isocyanate to which the methyl ester of (L)-phenylalanine (385 mg, 1.78 mmol) in DMF (3 mL) was added and stirred at 110°C for 12h. After completion of the reaction toluene was removed under reduced pressure and the resultant crude mixture was dissolved in chloroform (100 mL). The chloroform solution was then washed with dist. water (30 mL X 3). Chloroform layer was then dried over Na_2SO_4 and rotary evaporated to yield the crude mixture as a brownish sticky mass. The crude material was purified by column chromatography (silica gel, 100-200 mesh) using methanol-chloroform (3 : 97) solvent mixtures to get the product **1-A** as an off-white amorphous material (620 mg, 60%). IR (KBr): ν_{max} (cm^{-1}) 3388, 2929, 2866, 1743, 1649, 1562, 1497, 1454, 1438, 1376, 1256, 1214, 1176, 1112, 1077, 1042, 980, 950, 913, 856, 813, 794, 754, 700, 668, 611. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.11 (m, 5H, Ar), 5.23 (d, 1H, *J* = 8 Hz, NH), 5.04 (s, 1H, NH), 4.77-.4.72 (m, 1H, CH-Bn), 3.94 (s, 1H), 3.81 (s, 1H), 3.69 (s, 3H, COOMe), 3.40-2.97 (m,8H), 2.20-1.12 (m, steroid skeletal protons), 1.00 (d, 3H, *J* = 6.4 Hz), 0.87 (s, 3H, Me), 0.66 (s, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 157.7, 136.6, 129.4, 128.5, 127.0, 73.2, 72.0, 68.6, 54. 1, 52.3, 46.7, 46.5, 41.7, 41.6, 39.7, 39.5, 38.7, 37.8, 36.1, 35.5, 34.9, 34.8, 34.3, 30.6, 28.1, 27.9, 26.4, 23.4, 22.5. HRMS: m/z calcd for $C_{34}H_{52}N_2O_6$ (M + Na) = 607.3723 Observed = 607.3726.



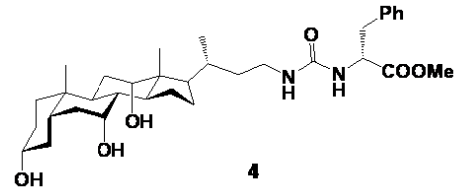
2

Deoxycholic acid azide (500g, 1.2 mmol) was heated at 110°C in toluene (5 mL) for 30 minutes to afford the corresponding isocyanate to which the methyl ester of (L)-phenylalanine (260 mg, 1.2 mmol) in DMF (2 mL) was added and stirred at 110°C. After 10 minutes tubidity was developed in the reaction mixture and white precipitate was observed with time. Stirring was continued for 12h and the precipitate was filtered and washed with chloroform (30 mL) and dried in vacuo to afford the product **2** (358 mg, 52%). M. P.:- 248-250°C. IR (KBr): ν_{max} (cm^{-1}) 3373, 3030, 2937, 2871, 1811, 1773, 1745, 1663, 11566, 1508, 1466, 1450, 1429, 1377, 1367, 1335, 1260, 1220, 1193, 1174, 1113, 1095, 1064, 1043, 1013, 945, 855, 766, 735, 700, 618. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.28-7.14 (m, 5H, Ar), 6.11 (d, 1H, *J* = 8 Hz, NH), 5.98-5.95 (m, 1H, NH), 4.46 (d, 1H, *J* = 4.4 Hz, OH), 4.41-4.36 (m, 1H, CH-Bn), 4.20 (d, 1H, *J* = 3.6 Hz, OH), 3.79 (s, 1H, C_{12}-H), 3.59 (s, 3H, COOMe), 3.03-3.01 (m, 1H, C_3-H), 2.97-2.84 (m, 2H, CH_2-Ph), 1.85-0.98 (Steroid skeletal protons), 0.91 (d, 3H, *J* = 6.4 Hz, Me), 0.84 (s, 3H, Me), 0.59 (s, 3H, Me). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.5, 157.7, 129.6, 126.9, 90.4, 54.4, 52.1, 47.9, 46.4, 36.1, 34.2, 33.3, 29.0, 23.5, 17.6, 12.9. HRMS: m/z calcd for $C_{34}H_{52}N_2O_5$ (M + Na) = 591.3876 0bserved = 591.3935. Elemental analysis calc. for $C_{34}H_{52}N_2O_5$: C, 71.80; H, 9.21; N, 4.93. Found: C, 71.58; H, 8.98; N, 5.05.



3

Lithocholic acid azide (300g, 0.75 mmol) was heated at 110°C in toluene (5 mL) for 30 minutes to afford the corresponding isocyanate to which the methyl ester of (L)-phenylalanine (162 mg, 0.75 mmol) in DMF (1.5 mL) was added and stirred at 110°C. Within 5 minutes tubidity was developed in the reaction mixture and thick white precipitate was observed with time. Stirring was continued for 12h and the precipitate was filtered and washed with chloroform (30 mL) and dried in vacuo to afford the product **3** (345 mg, 85%). M. P.:- 254-256°C. IR (KBr): ν_{max} (cm^{-1}) 3371, 3031, 2975, 2935, 2867, 1745, 1662, 1567, 1512, 1451, 1429, 1366, 1286, 1258, 1193, 1174, 1095, 1039, 965, 946, 766, 700, 618. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.27-7.14 (m, 5H, Ar), 6.10 (d, 1H, *J* = 8.4 Hz, NH), 5.98 (brs, 1H, NH), 4.45-4.38 (m, 2H, C3-H & CH-Bn), 3.58 (s, 3H, COOMe), 3.02-2.84 (m, 4H, CH_2-Ph &NH-CH_2), 0.87 (s, 3H, CH_3), 0.61 (s, 3H, CH_3). HRMS: m/z calcd for $C_{34}H_{52}N_2O_4H$ (M + H) = 553.4005 Observed 553.4000 (M + H). Elemental analysis calc. for $C_{34}H_{52}N_2O_4$: C, 73.87; H, 9.48; N, 5.07. Found: C, 73.74; H, 9.54; N, 5.38.



4

Cholic acid azide (600 mg, 1.38 mmol) was heated at 110°C in toluene (6 mL) for 30 minutes to afford the corresponding isocyanate to which the methyl ester of (D)-phenylalanine (300 mg, 1.38 mmol) in DMF (3 mL) was added and stirred at 110°C for 12h. After completion of the reaction toluene was removed under reduced pressure and the resultant crude mixture was dissolved in chloroform (100 mL). The chloroform solution was then washed with dist. water (30 mL X 3). Chloroform layer was then dried over Na_2SO_4 and rotary evaporated to yield the crude mixture as a brownish sticky mass. The crude material was purified by column chromatography (silica gel, 100-200 mesh) using methanol-chloroform (3 : 97) solvent mixtures to get the product **4** as an off-white amorphous material (300 mg, 38%). M. P.: Decomposes above 230°C. IR (KBr): ν_{max} (cm^{-1}) 3387, 2935, 2867, 1742, 1654, 1647, 1638, 1560, 1497, 1457, 1438, 1376, 1255, 1211, 1177, 1112, 1078, 1042, 980, 950, 913, 857, 754, 700, 669, 611. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.11 (m, 5H, Ar), 5.11 (d, 1H, *J* = 8 Hz, NH), 4.88-4.87 (m, 1H, NH), 4.78-4.75 (m, 1H, CH-Bn), 3.95 (s, 1H), 3.84 (s, 1H), 3.69 (s, 3H, COOMe), 3.41-3.38 (m, 1H), 3.21-3.19 (m, 1H), 3.10-2.99 (m, 2H, CH_2-Ph), 2.20-1.10 (m, steroid skeletal protons), 1.00 (d, 3H, *J* = 6.4 Hz, Me), 0.88 (s, 3H, Me), 0.67 (s, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 157.6, 136.5, 129.3, 128.4, 126.9, 73.1, 71.8, 68.5, 53.9, 52.2, 46.5, 46.4, 41.5, 39.6, 39.4, 38.5, 35.9, 35.4, 34.7, 34.6, 34.2, 30.4, 27.9, 27.8, 26.2, 23.2, 22.4. HRMS: m/z calcd for $C_{34}H_{52}N_2O_6$ (M + Na) = 607.3723 Observed = 607.3729.

DSC profile of **4**

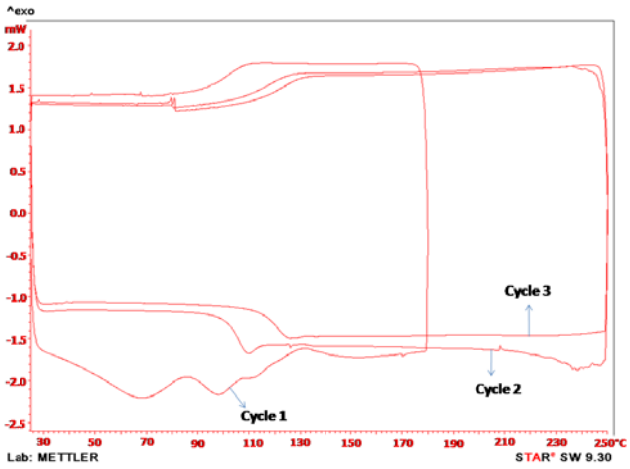


Figure 1: DSC profile of **4**

AFM images of the gels of **4**

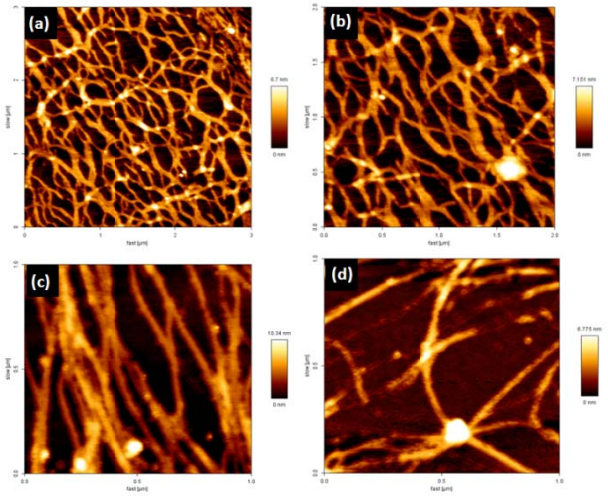
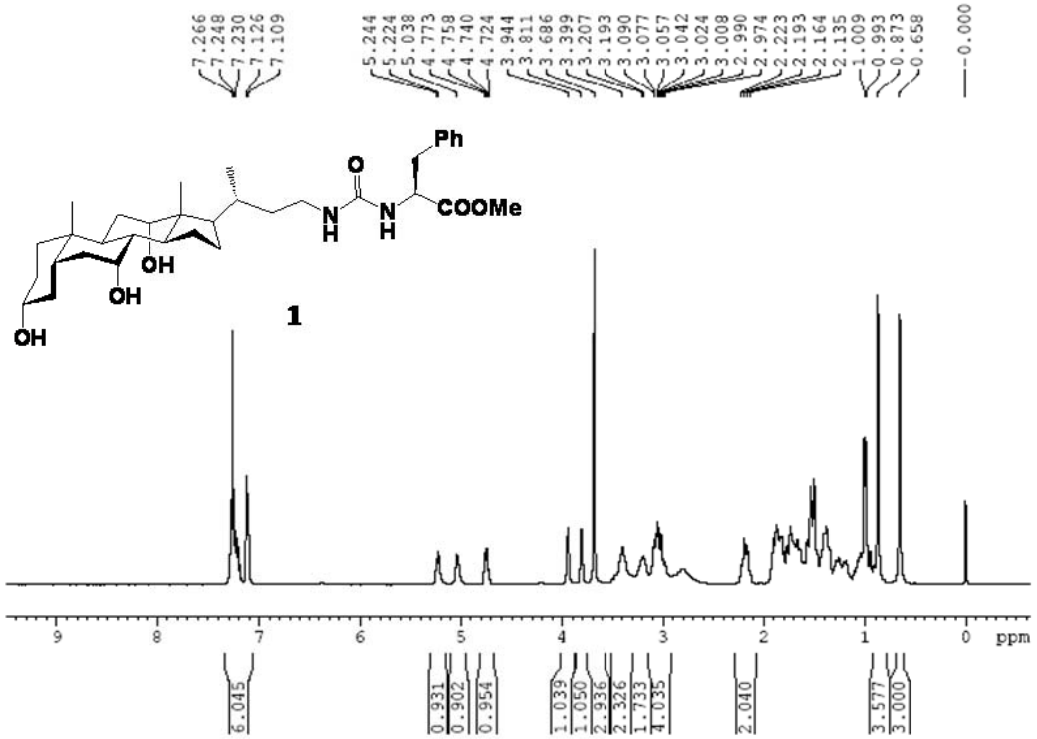


Figure 2: AFM images of the (a, b) 1,2-DCB and (c,d) 1,2-DMB gels of **4**

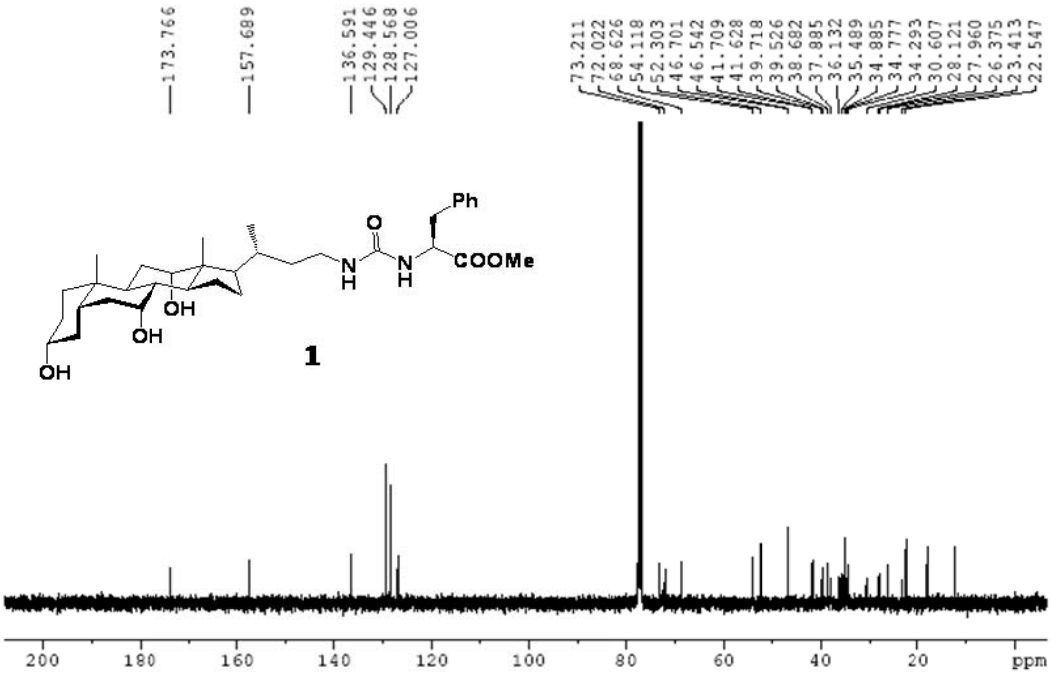
Preparation of DLS samples

DLS samples were prepared by injecting 20 μL of stock solution of **1** (10 mM in MeOH) into a rapidly stirring (Heidolph magnetic stirrer, rpm = 1200) 2 mL of solvent (1,2-DMB or water). Stirring was continued for 5 minutes followed by stabilization at room temperature for 15 minutes, sonication for 10 seconds and filtration through 0.2 μm nylon membrane. The filtered solutions were immediately used for DLS analysis.

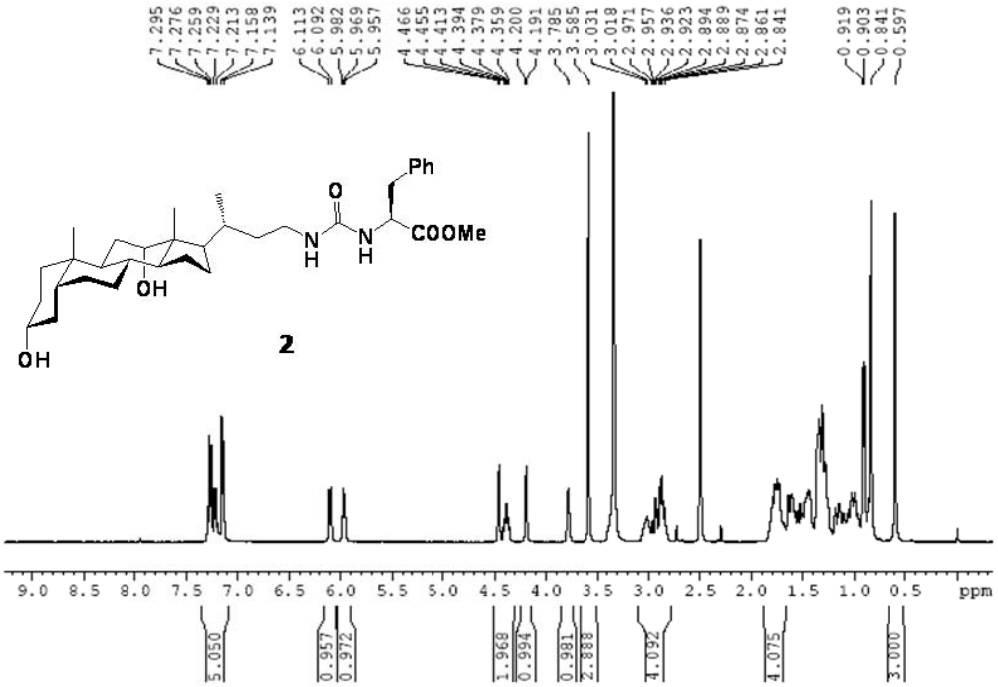
^{1}H NMR spectrum of **1**



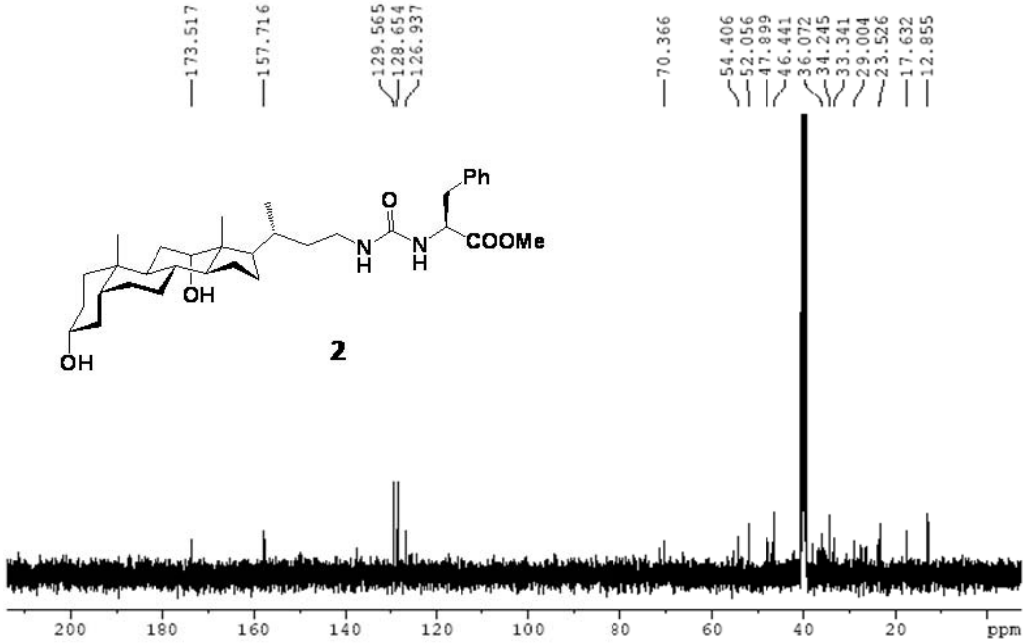
^{13}C NMR spectrum of **1**



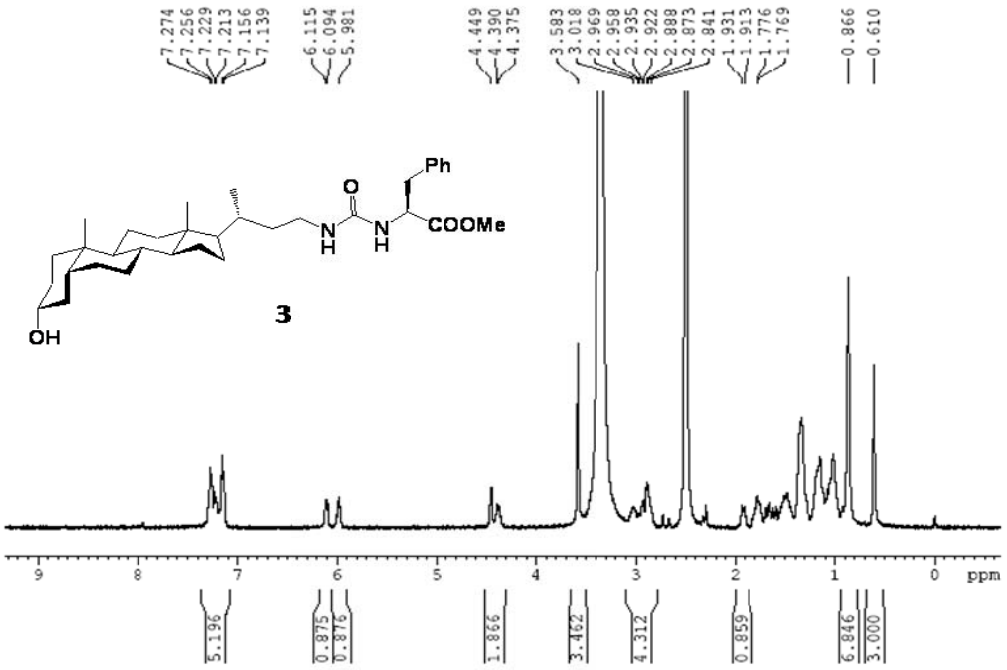
[1]H NMR spectrum of **2**



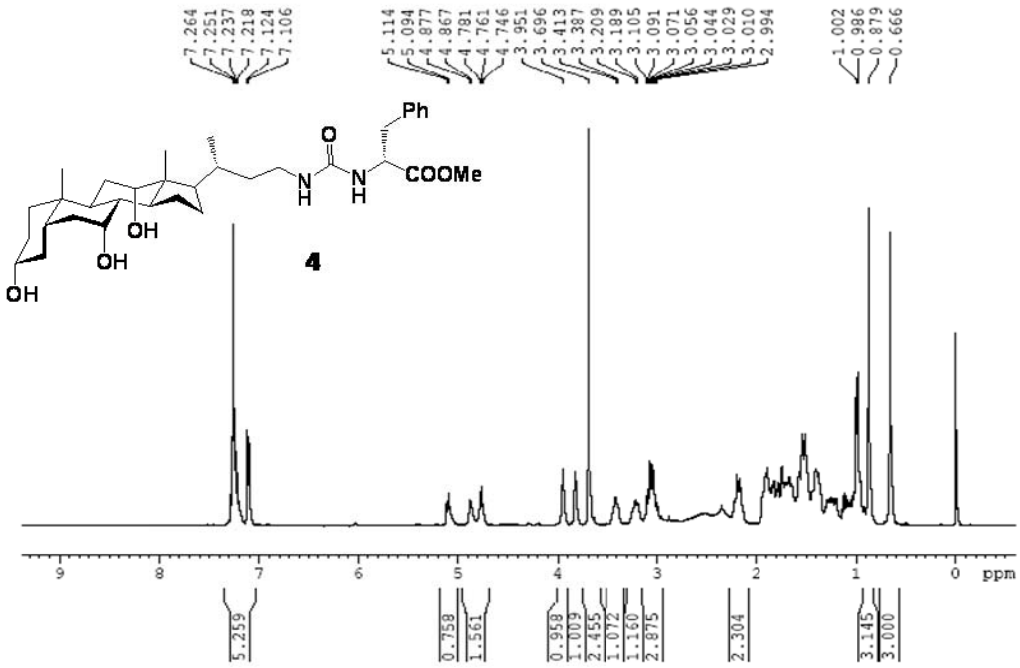
[13]C NMR spectrum of **2**



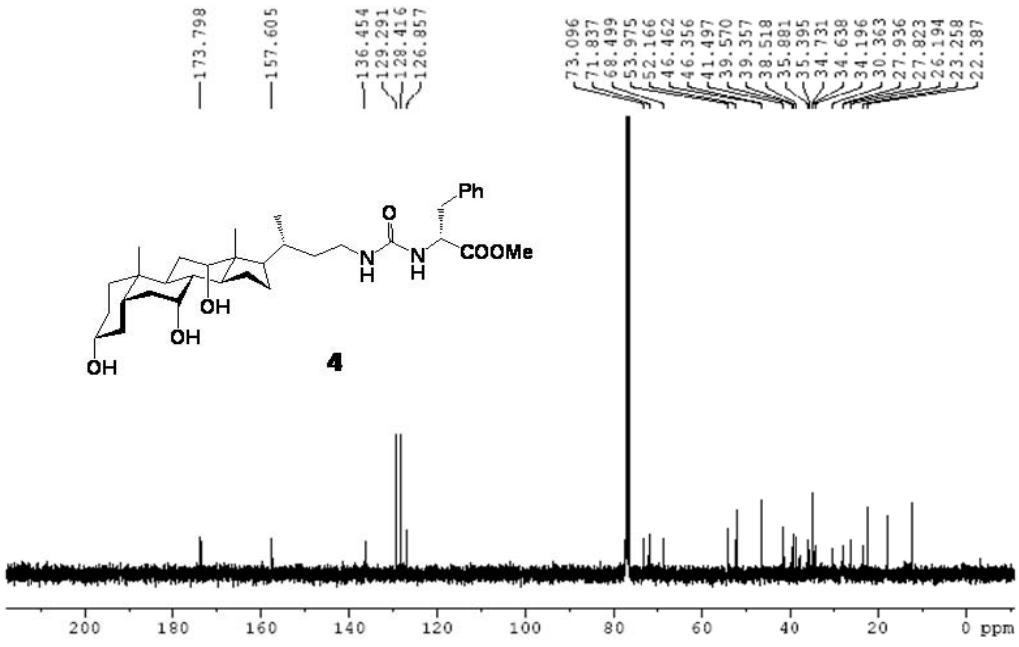
^{1}H NMR spectrum of **3**



^{1}H NMR spectrum of **4**



^{13}C NMR spectrum of **4**



Reference

1. J. Luo, Y. Chen, X. X. Zhu, *Synlett* 2007, **14**, 2201.