Electronic Supporting Information

Self-assembly pattern directed sustained release from porous microspheres of discotic tripeptides†

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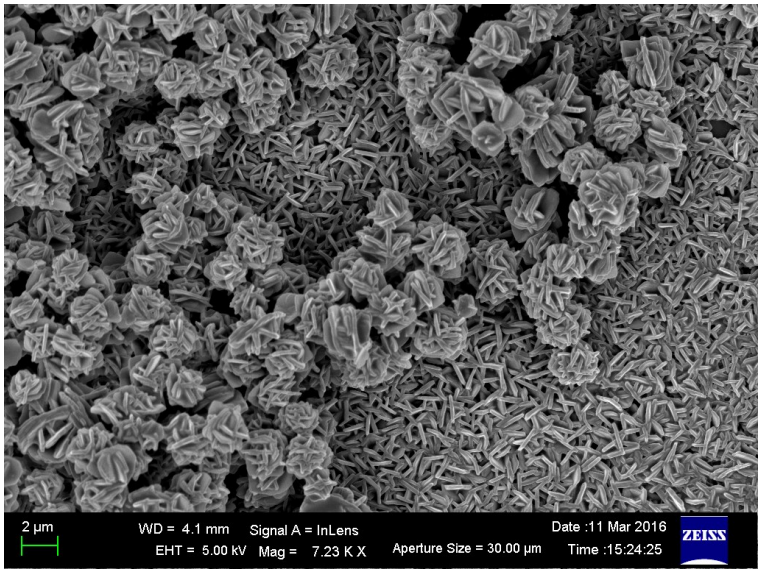
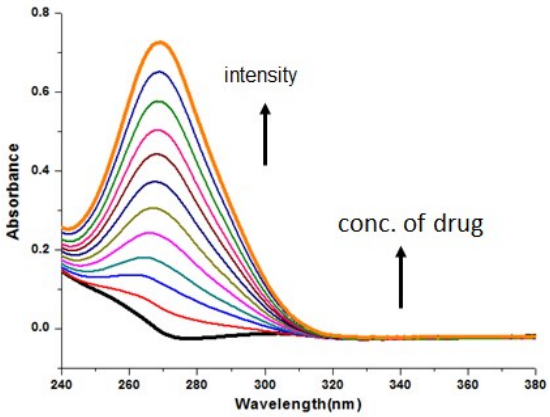
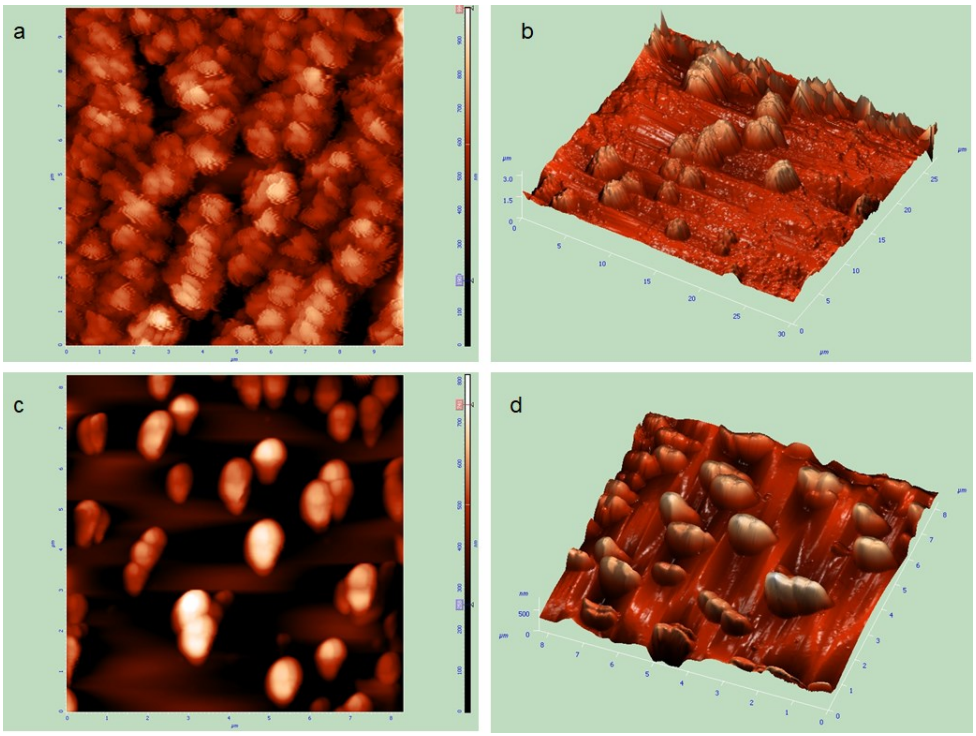


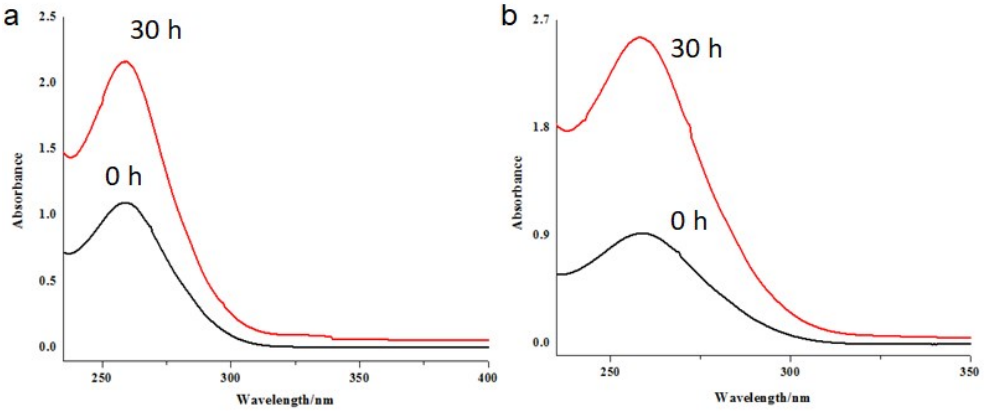
ESI Figure S1. FE-SEM image of discotic tripeptide **1** showing existence of both nano rods and bird nest like microspheres formed by self-assembly of the nano rods.



ESI Figure S2. UV-vis absorption spectra of discotic tripeptide **1** with increasing concentration of drug sulfamethoxazole in methanol.



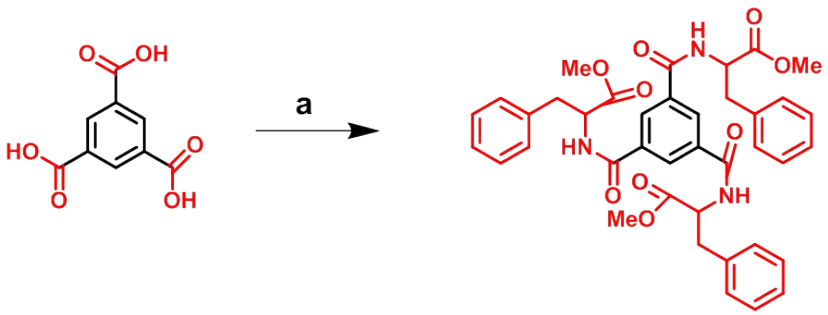
ESI Fig. S3. (a) The AFM image of discotic tripeptide **1**, (b) The 3D image of the microspheres morphology of discotic tripeptide **1**, (c) The AFM image of discotic tripeptide **2**, (d) The 3D image of the microspheres morphology of discotic tripeptide **2**.



ESI Fig. S4. Drug release profile from microspheres of (a) discotic tripeptide **1** and (b) discotic tripeptide **2** in tris buffer at pH 7.4.

Experimental

Synthesis of discotic tripeptide 1

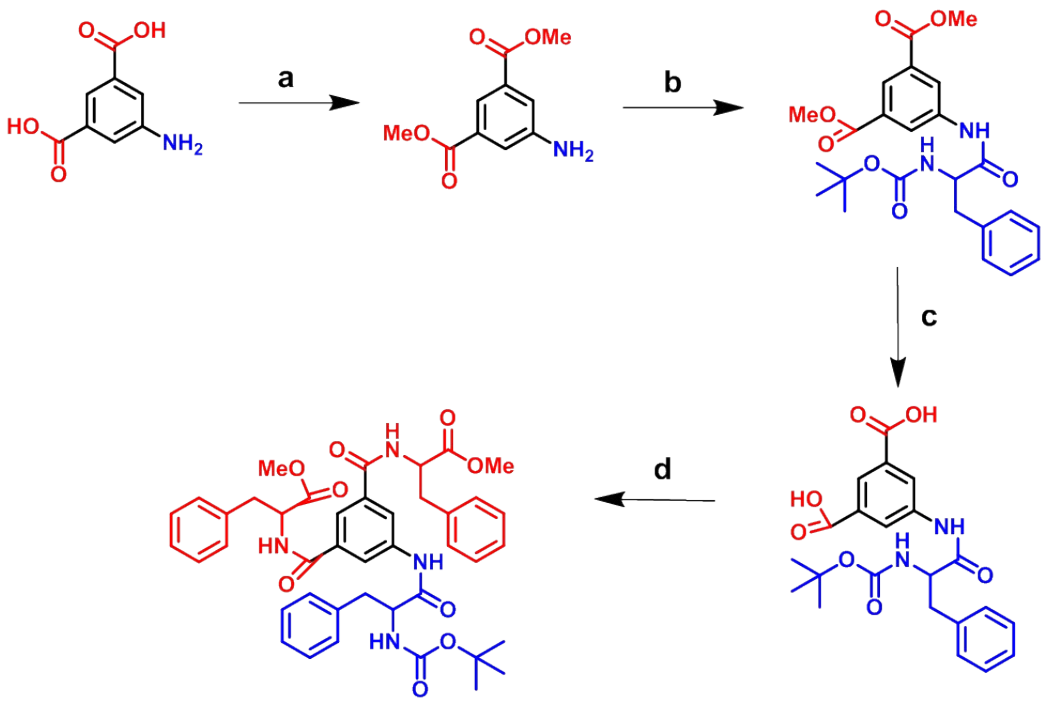


Scheme 1: Synthesis of discotic tripeptide **1**. Reagent and condition: (a) H-Phe-OMe, DCC, HOBt, DMF, 0°C.

500 mg (2.37 mmol) of benzene-1,3,5-tricarboxylic acid was dissolved in a mixture of 10 mL of N,N-dimethylformamide (DMF) and cooled in an ice-water bath. H-Phe-OMe was isolated from 2.5 g (11.6 mmol) of the corresponding methyl ester hydrochloride by neutralization with saturated sodium carbonate, subsequent extraction with ethyl acetate, and concentration (10 mL), and this was added to the reaction mixture, followed immediately by 1.85g (9 mmol) of dicyclohexylcarbodiimide (DCC) and 1.21g (9 mmol) of HOBt. The reaction mixture was allowed to come to room temperature and stirred for 24 h. DMF was evaporated, and the residue was taken in ethyl acetate (60 mL); dicyclohexylurea (DCU) was filtered off. The organic layer was washed with 2 M HCl (3 X 50 mL), brine, 1 M sodium carbonate (3 X 50 mL), and brine (2 X 50 mL), dried over anhydrous sodium sulphate, and evaporated under vacuum to yield 1.2 g (1.73 mmol, 72%) of compound **1**.

^{1}H NMR ($CDCl_3$, 400 MHz, δ_{ppm}): 8.16-8.15 (d, J = 2.3Hz, 3H, NH), 7.26-7.17 (m, 18H, ring H), 5.04-5.02 *(*m, 3H, CαH Phe), 3.73 (*s*, 9H, OCH3), 3.24-3.17 (m, 6H, CβH Phe). ^{13}C NMR ($CDCl_3$, 100 MHz, δ_{ppm}): 172.45, 165.42, 136.09, 134.66, 129.32, 128.85, 127.34, 54.28, 52.72, 37.96. ESI-MS (MeOH): m/z (Calc): $C_{39}H_{39}N_3O_9$ $[M+H]^+$ 694.27; found: 694.2756.

Synthesis of discotic tripeptide 2



Scheme 2: Synthesis of discotic tripeptide **2**. Reagent and condition: (a) $SOCl_2$, MeOH (b) Boc-Phe-OH, DCC, HOBt, DMF, 0°C (c) NaOH, MeOH (d) H-Phe-OMe, DCC, HOBt, DMF, 0°C.

The methyl ester of 5-aminoisophthalic acid was isolated from the corresponding methyl ester hydrochloride by neutralization, subsequent extraction with ethyl acetate and evaporation. 2.51 g (9.43 mmol) of Boc-Phe-OH was dissolved in 25 ml dry DMF in an ice-water bath. 1.97 g (9.43 mmol) of 5-aminoisophthalic methyl ester was then added to the reaction mixture, followed immediately by 1.946 g (9.43 mmol) dicyclohexylcarbodiimide (DCC) and 1.274 g (9.43 mmol) of HOBt. The reaction mixture was allowed to come to room temperature and stirred for 48 h. DMF was evaporated and the residue was dissolved in ethyl acetate (60 mL) and the dicyclohexylurea (DCU) was filtered off. The organic layer was washed with 2 M HCl (3

x 50 mL), brine (2 x 50 mL), 1 M sodium carbonate (3 x 50 mL) and brine (2 x 50 mL) and dried over anhydrous sodium sulphate; and evaporated in a vacuum. The product was purified by silica gel (100–200 mesh) using n-hexane–ethyl acetate (3: 1) as eluent. Yield: 3.18 g (6.99 mmol, 75.16%).

The obtained compound was dissolved in 50 mL of methanol/water mixture (9:1), cooled and 680 mg of NaOH was added and stirred for 6 h. Then methanol was evaporated under reduced pressure, about 20 mL water was added and washed with diethylether. The water portion was acidified with dilute HCL solution, the compound was extracted with ethyl acetate. The organic layer was then dried over anhydrous Na_2SO_4 and dried under reduced pressure. Yield: 2.59 g (6.05 mmol, 86.5%).

Next the compound was dissolved in 25 ml dry DMF in an ice-water bath. H-Phe-OMe was isolated from 3.332 g (15.5 mmol) of the corresponding methyl ester hydrochloride by neutralization, subsequent extraction with ethyl acetate and the ethyl acetate extract was concentrated to 10 ml. It was then added to the reaction mixture, followed immediately by 2.78 g (13.5 mmol) dicyclohexylcarbodiimide (DCC) and 1.82 g (13.5 mmol) of HOBt. The reaction mixture was allowed to come to room temperature and stirred for 48 h. DMF was evaporated and the residue was dissolved in ethyl acetate (60 mL) and the dicyclohexylurea (DCU) was filtered off. The organic layer was washed with 2 M HCl (3 x 50 mL), brine (2 x 50 mL), 1 M sodium carbonate (3 x 50 mL)and brine (2 x 50 mL) and dried over anhydrous sodium sulfate; and evaporated in a vacuum to yield BTC 2 as a white solid. The product was purified by silica gel (100–200 mesh) using n-hexane–ethyl acetate (3: 1) as eluent. Yield: 3.15 g (4.2 mmol, 69.42%).

^{1}H NMR ($CDCl_3$, 400 MHz, δ_{ppm}): 8.71 (b, 1H, NH), 7.62 (s, 3H, NH), 7.25-7.16 (m, 18H, ring H), 4.96-4.94 *(*m, 3H, CαH Phe), 3.68 (*s*, 6H, OCH_3), 3.22-3.20 (m, 6H, CβH Phe), 1.35 (s, 9H, Boc). ^{13}C NMR ($CDCl_3$, 100 MHz, δ_{ppm}):172.94, 172.66, 166.44, 156.95, 136.44, 135.40, 135.15, 129.50, 128.93, 127.37, 121.57, 81.17, 54.57, 52.83, 52.70, 38.19, 38.09, 28.56. ESI-MS (MeOH): m/z (Calc): $C_{42}H_{46}N_4O_9$ $[M+Na]^+$ 773.33; found: 773.3165.

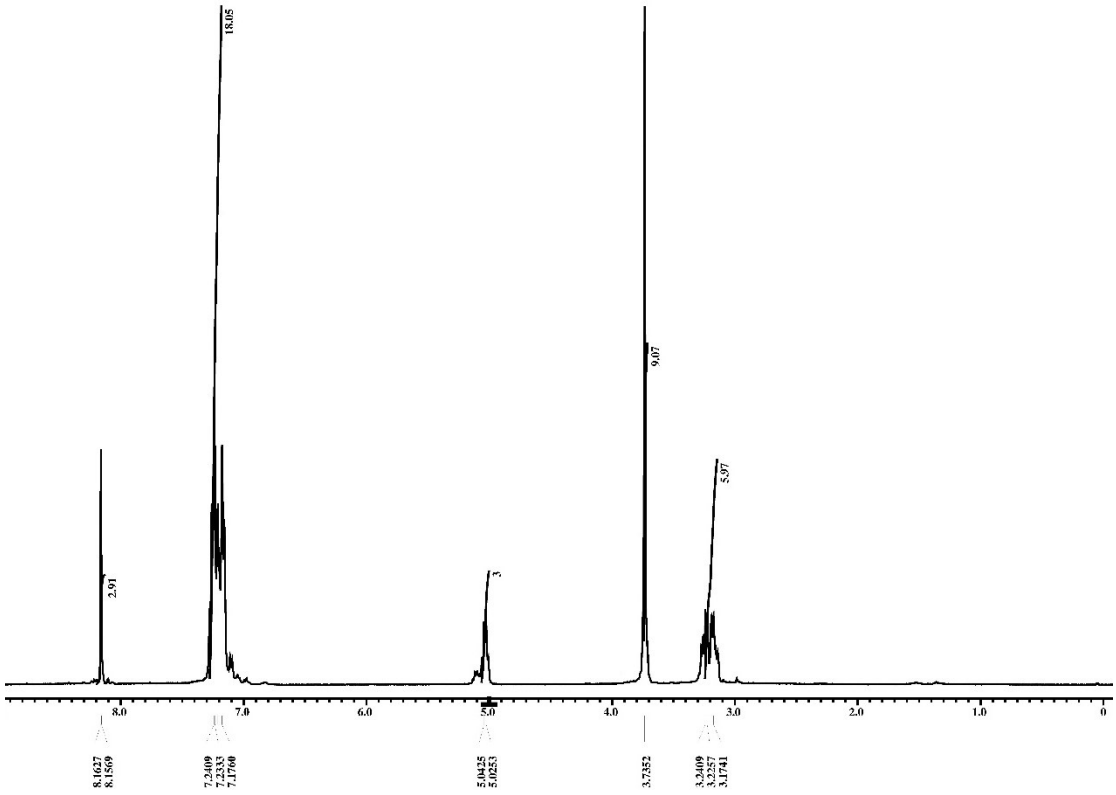


Fig. S5. ^{1}H NMR ($CDCl_3$, 400 MHz, δ_{ppm}) of discotic tripeptide **1.**

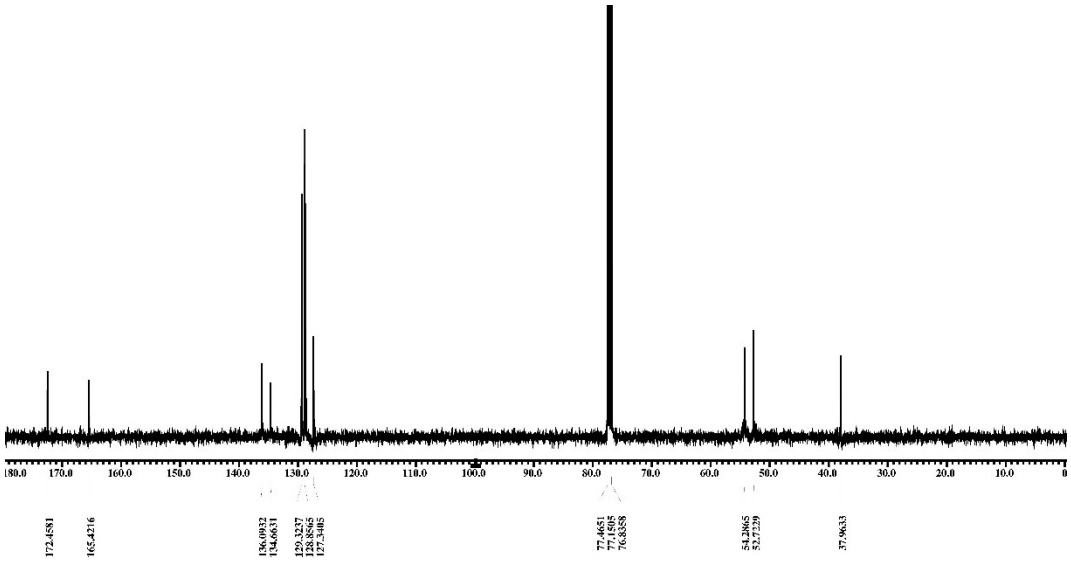


Fig. S6. ^{13}C NMR ($CDCl_3$, 100 MHz, δ_{ppm}) of discotic tripeptide **1.**

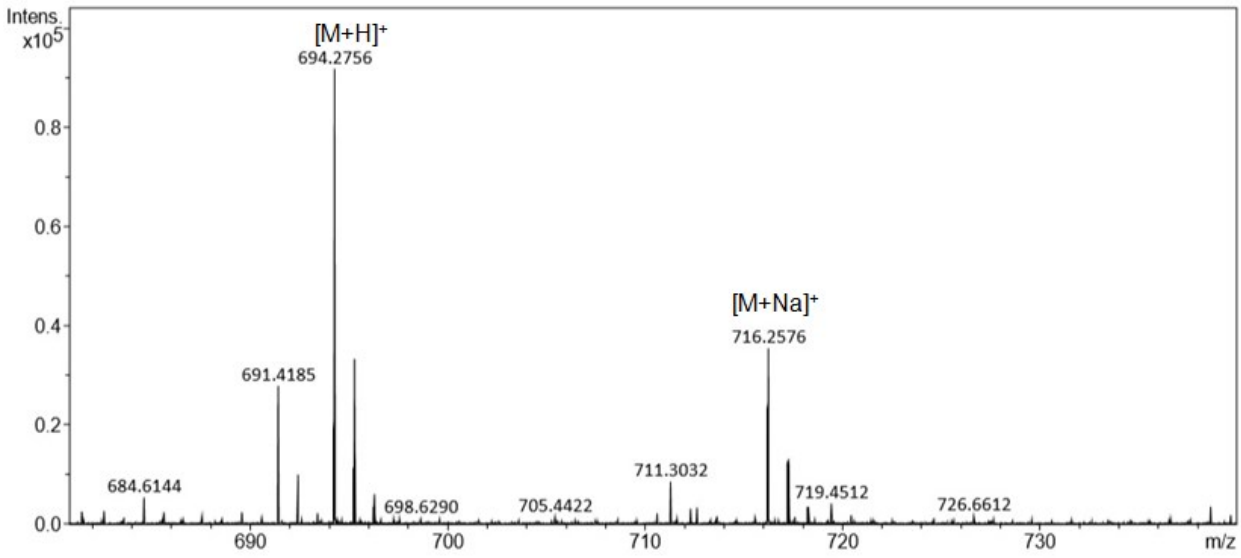


Fig. S7. MS spectra of discotic tripeptide **1.**

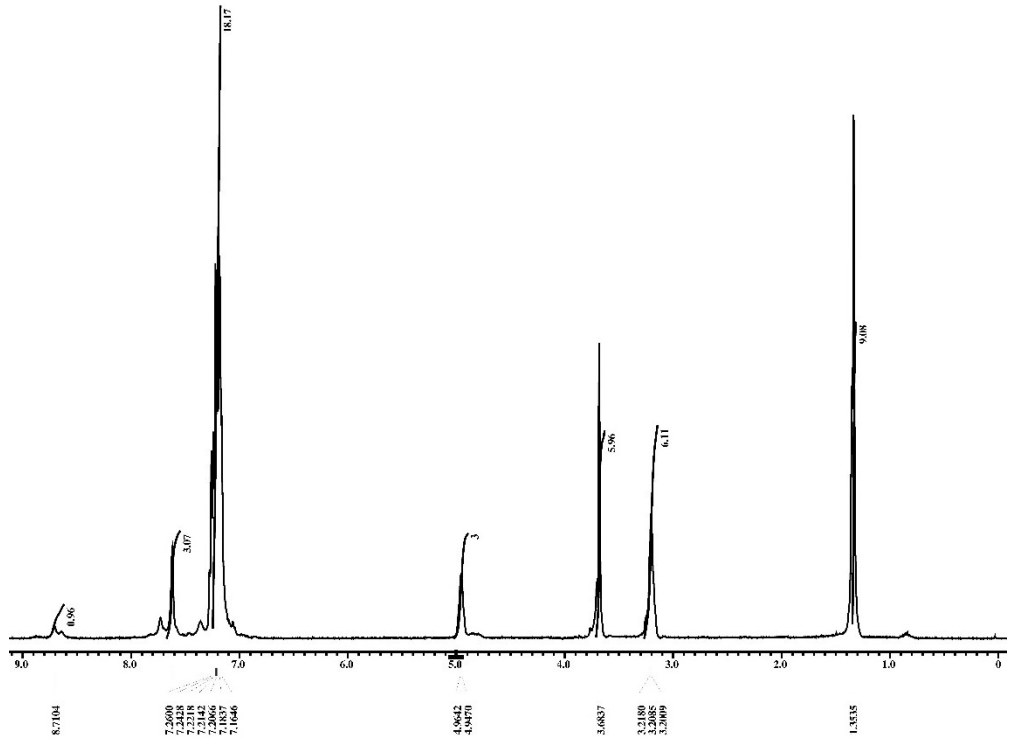


Fig. S8. ^{1}H NMR ($CDCl_3$, 400 MHz, δ_{ppm}) of discotic tripeptide **2.**

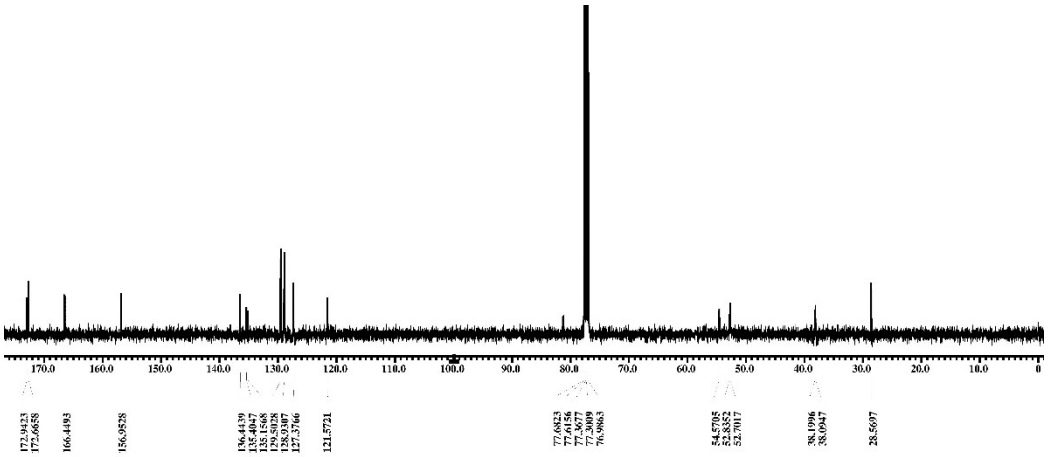


Fig. S9. ^{13}C NMR ($CDCl_3$, 100 MHz, $\delta_{ppm)}$ of discotic tripeptide **2.**

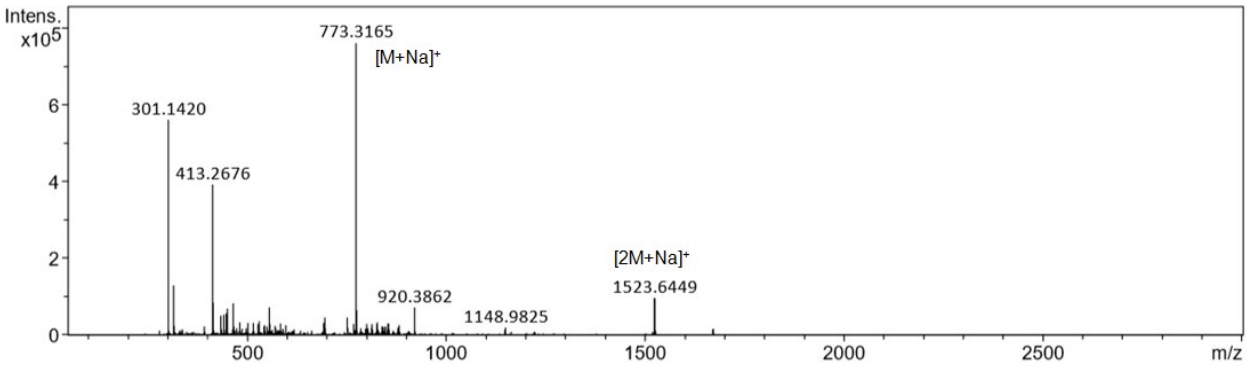


Fig. S10. MS spectra of discotic tripeptide **2.**