Supporting Information

Rods, Helices and Spherulites: Diverse self-assembled architectures from L-phenylalanine derivatives

Somnath D. Bhagat and Aasheesh Srivastava[#]

Department of Chemistry, Indian Institute of Science Education and Research Bhopal, Bhauri, Bhopal By-Pass Road, Bhopal – 462066, Madhya Pradesh, INDIA.

[#] Corresponding Author E-mail: asri@iiserb.ac.in

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Materials and methods:

1-Naphthylacetic acid (1-NAA) was purchased from Spectrochem Chemicals, 1,1-Carbonyl diimidazole (CDI) obtained from alfa aesar and Potassium hydroxide, hydrochloric acid, and triethylamine were obtained from Merck. Anhydrous Sodium sulphate was obtained from Rankem. All solvents used in the synthesis were purified, dried, and distilled, as a required. The Hydrazine monohydrate was purchased from Spectrochem and used as it is. 3-aminopropylimidazole, Ethylene diamine and ethanolamine were purchased from Alfa Aesar. ^{1}H NMR spectra were recorded by using Bruker Ultra shield (400 MHz, 500MHz) spectrometer. ^{13}C NMR spectra were recorded by using Bruker Ultra shield (100 MHz, 125 MHz) spectrometer. Mass spectra were recorded in LR-MS and HR-MS mode on Micro TOF-Q-II instrument manufactured by Bruker Daltonics; Scanning Electron microscopy (SEM) by Carl Zeiss and circular dichroism (CD) by JASCO J815 were used to analysis of chirality of synthesized compound. Powder X-ray diffraction patterns (PXRD) were recorded on a PANalytical EMPYREAN diffractometer using Cu Kα (λ = 1.5418 Å) incident X-rays. FTIR spectroscopy was performed on dry samples pelletized with KBr and recorded on an IRAffinity^{-1}, Shimadzu.

Synthetic Scheme:

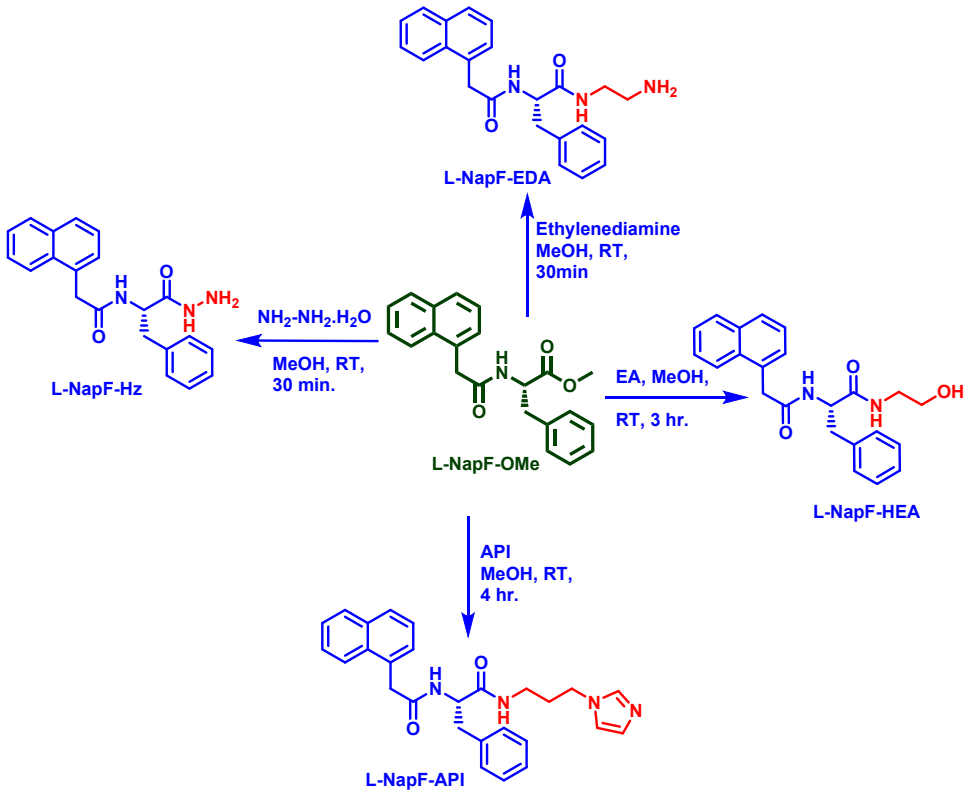


Figure S1. Outline of synthesis of different L-NapF derivatives prepared in this work.

Synthesis and characterizations:

(S)-N-(1-hydrazinyl-1-oxo-3-phenylpropan-2-yl)-2-(naphthalene-1-yl)acetamide (L-NapF-Hz): To the dry methanolic solution methyl (2-(naphthalen-1-yl)acetyl)-L-phenylalaninate, hydrazine monohydrate was added drop wise at 0 °C. The reaction mixture was further stirred for 30 min at RT. The complete consumption of starting material was not observed even after prolonged reaction time. Methanol was removed by rota vapour and the product purified by column chromatography (stationary phase was silica 100-200 mesh and eluent phase was MeOH/$CHCl_3$ 10% v/v) which resulted a white solid in 67% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm)= 9.07 (1H, N-H), 7.39-8.33 (7H, Nap-H), 7.38 (1H, NH), 7.19-7.14 (5H, Ar) 4.19-4.26 (1H, C-H), 4.17 (2H, NH_2), 3.87-3.96 (2H, Nap-CH_2), 1.16-1.18

(3H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ=171.99, 170.10, 133.77, 133.32, 132.48, 128.76, 128.16, 127.44, 126.35, 126.05, 125.94, 124.85, 47.33, 39.87, 19.14

2-aminoethyl (2-(naphthalen-1-yl) acetyl)-L-phenylalaninate (L-NapF-EDA): To the dry methanolic solution methyl (2-(naphthalen-1-yl) acetyl)-L-phenylalaninate, ethylene diamine was added drop wise at 0 °C. The reaction mixture was further stirred for 2 h at RT. The complete consumption of starting material was not observed even after overnight stirring of reaction. Methanol was removed by rota vapour and the product purified by column chromatography (stationary phase was silica 100-200 mesh and eluent phase was MeOH/$CHCl_3$ 10% v/v) which resulted a white solid in 94 % yield. ^1H NMR (400 MHz, $CDCl_3$) δ(ppm) = 9.07 (1H, N-H), 7.39-8.33 (7H, Nap-H), 7.38 (1H, NH), 7.19-7.14 (5H, Ar), 4.90-4.96 (1H, C-H), 3.87-3.96 (2H, Nap-CH_2), 3.35-3.40 (2H, CH_2-NH), 2.75-2.8(2H, CH_2-NH_2), 3.15-3.20 (2H, CH_2-Ar), 7.19-7.14 (5H, Ar), 1.15 (2H, NH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) =171.54, 170.03, 138.49, 138.27, 133.72, 133.13, 132.40, 129.65, 128.72, 128.48, 128.15, 127.33, 126.68, 126.33, 125.99, 125.82, 124.71, 56.50, 54.64, 42.60, 41.54.

1H-imidazol-1-yl)propyl (2-(naphthalen-1-yl)acetyl)-L-phenylalaninate (L-NapF-API): To the dry methanolic solution methyl (2-(naphthalen-1-yl)acetyl)-L-phenylalaninate, 3-aminopropylimidazole was added drop wise at 0 °C. The reaction mixture was further stirred for 8 h at RT. The complete consumption of starting material was not observed even after prolonged reaction time. Methanol was removed under reduced pressure by rota vapour and the product purified by column chromatography (stationary phase was silica 100-200 mesh and eluent phase was MeOH/$CHCl_3$ 10% v/v) which resulted a white solid in 60 % yield. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.07 (1H, N-H), 7.39-8.33 (7H, Nap-H), 7.38 (1H, NH), 7.19-7.14 (5H, Ar), 4.90-4.96 (1H, C-H), 3.87-3.96 (2H, Nap-CH_2), 3.35-3.40 (2H, CH_2-NH), 2.75-2.8 (2H, CH_2-NH_2), 3.15-3.20 (2H, CH_2-Ar), 7.19-7.14 (5H, Ar), 1.15 (2H, NH_2),

6.7-7.8 (S, 1H, CH-Imi). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 171.75, 170.45, 133.72, 133.67, 133.31, 133.24, 132.40, 132.34, 129.76, 128.73, 128.53, 128.16, 127.41, 126.74, 126.32, 125.99, 125.87, 124.72, 119.81, 54.83, 43.81, 38.36, 36.06, 31.02, 29.47.

2-hydroxyethyl (2-(naphthalen-1-yl) acetyl)-L-phenylalaninate (L-NapF-HEA): To the dry methanolic solution methyl-(2-(naphthalen-1-yl) acetyl)-L-phenylalaninate, ethanolamine was added drop wise at 0 °C. The reaction mixture was further stirred for 3 h at RT. The complete consumption of starting material was not observed even after prolonged reaction time. Methanol was removed by vacuum and the product purified by column chromatography (stationary phase was silica 100-200 mesh and eluent phase was MeOH/$CHCl_3$ 10% v/v) which resulted a white solid in 92 % yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 9.07 (1H, N-H), 7.39-8.33 (7H, Nap-H), 7.38 (1H, NH), 7.19-7.14 (5H, Ar), 4.90-4.96 (1H, C-H), 3.87-3.96 (2H, Nap-CH_2), 3.35-3.40 (2H, CH_2-NH), 2.75-2.8 (2H, CH_2-NH_2), 3.15-3.20 (2H, CH_2-Ar), 7.19-7.14 (5H, Ar), 1.15 (2H, NH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 171.67, 170.23, 138.35, 133.70, 133.10, 132.39, 129.68, 128.71, 129.64, 128.15, 127.39, 126.66, 126.36, 126.02, 125.87, 124.70, 60.17, 54.46, 41.94, 38.49, 31.25.

Gelation and evaluating Minimum Gel Concentrations: 10 mg gelator (L-NapF-Hz or L-NapF-EDA) was weighed in a vial and 1 ml water was added to it. This mixture was heated in a water bath maintained at 100 °C until the solid dissolved in water (approx. 8-10 min). The resulting solution was allowed to cool to room temperature. Hydrogel was considered to have formed with no flow of solvent was observed upon inversion of the vial. In such case, incremental addition of 200 μl of water was added and the process repeated until flow of solvent was observed.

Rheology: Rheological measurements were carried out on a Rheoplus MCR302 (Anton paar) rheometer with parallel plate geometry and obtained data were processed with start rheometer software. For the oscillatory shear measurements, parallel top plate with a 25 mm diameter and 1.0 mm gap distance were used. Gels (prepared at 2x MGC) for rheological experiments were transferred on the bottom plate of the rheometer. The shear modulus (storage modulus, G', and loss modulus, G'') were plotted against % strain from 0.1 % to 100 %. Frequency sweep experiment was performed from 0.1 to 100 rad/s at constant strain of 1 %.

Field Emission Scanning Electron Microscopy (FE-SEM): For FESEM, the samples were scooped from the surface of the vial using a spatula and spread on SEM stubs having double sided carbon tape on them. The stubs were dried inside a vacuum desiccator for 48 h and subsequently gold coated for 120 s. Images were recorded on Carl Zeiss (Ultra plus) FE-SEM at an accelerating voltage of 5 kV and 10 kV.

Circular Dichroism: All circular dichroism (CD) measurements were carried out on a J815 CD spectro-polarimeter (JASCO Inc., Japan) equipped with a 450 W Xe lamp and water cooled Peltier temperature control unit. For investigating thermal disassembly process of aggregates formed by L-NapF-Hz and L-Nap-EDA in water, sample concentrations were adjusted to 1.0 mg/ml in water, which corresponded to an absorbance value at 295 nm (A_{295}) = 0.1. Data were averaged over at least three accumulations; blank subtracted and smoothened (Figure S3).

Doxorubicin encapsulation studies: Doxorubicin encapsulation was studied by adding desired amount of commercial doxorubicin hydrochloride to the hot solution of gelator in water, and allowing the resultant solution to cool naturally to room temperature. It was left undisturbed for about 30 min before testing the gel formation. The molecular interaction between the drug and the gelator was investigated using MALDI-MS (Figure S3).

Powder X-ray diffraction (PXRD): Diffraction patterns for as prepared L-NapF derivatives were obtained. The as prepared L-NapF-Hz and L-NapF-EDA which having gelation ability showed broad peaks, representing amorphous characteristics. However, L-NapF-API and L-NapF-HEA showed sharp distinct peaks and was therefore inferred to be crystalline in nature. As prepared L-NapF derivatives (~20 mg) were vacuum-dried for 2 h and placed on sample holder. Diffraction data were collected in a 2θ range of 5-60° (degree) (Figure S4).

FTIR Spectroscopy: The as-prepared and lyophilized xerogel samples of different L-NapF derivatives were dried in a vacuum desiccator for 24 h. FTIR spectra were recorded as KBr pellets on a Perkin Elmer Spectrum BX FTIR spectrometer. (Figure S5)

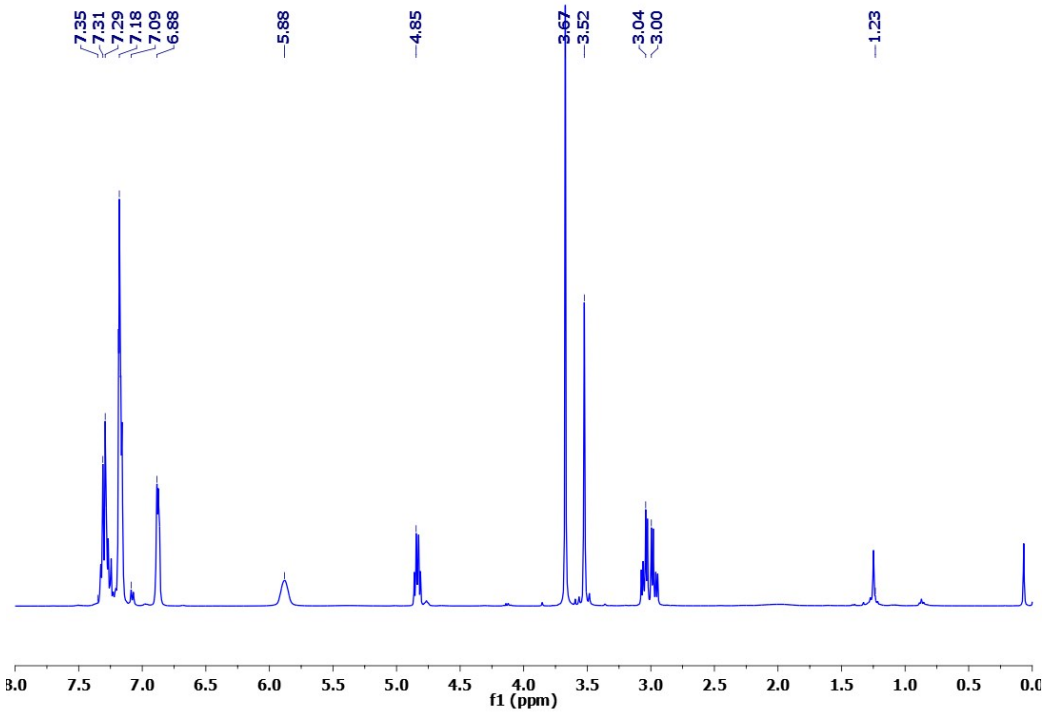


Figure S2 (a): ^{1}H NMR of synthesized L-NapF-Hz (400 MHz, $CDCl_3$).

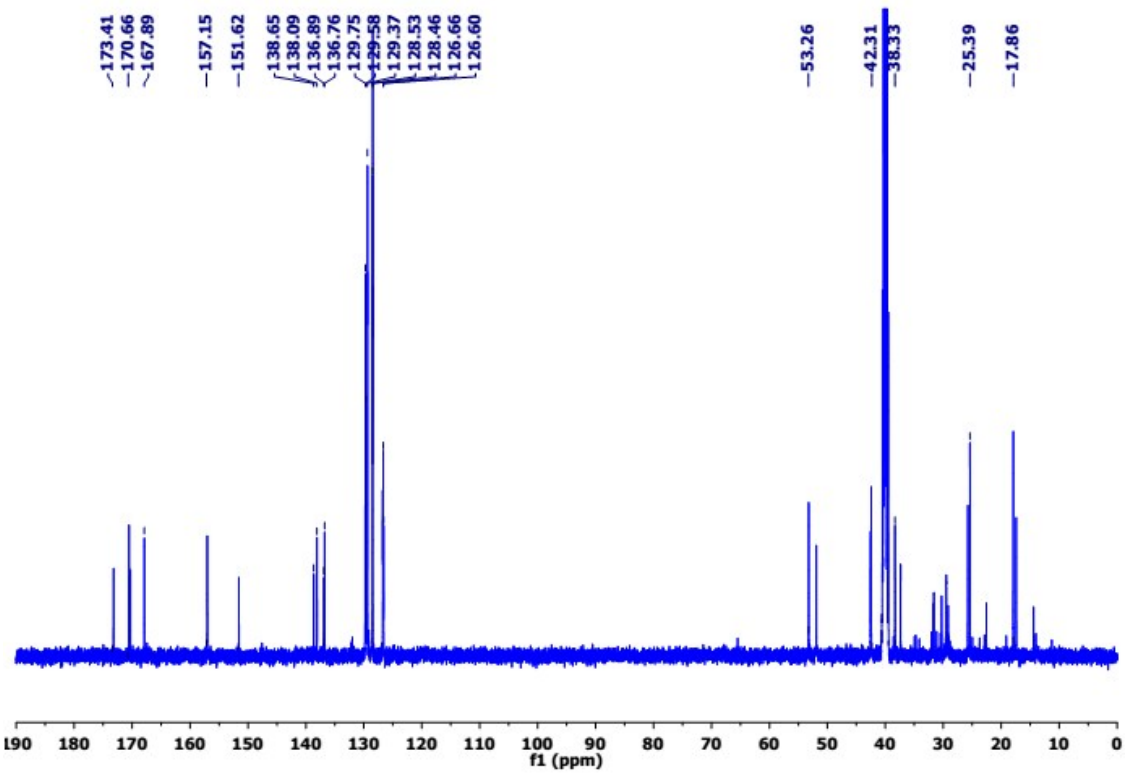


Figure S2 (b): ^{13}C NMR of synthesized L-NapF-Hz (100 MHz, DMSO-d6).

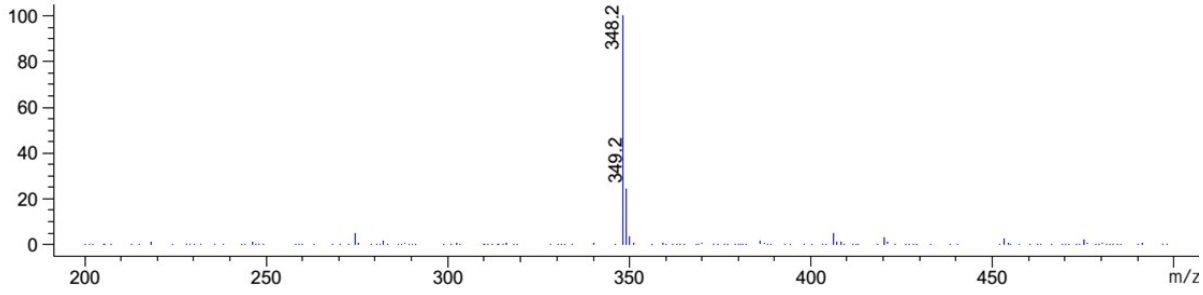


Figure S2 (c): LR-MS data of synthesized L-NapF-Hz.

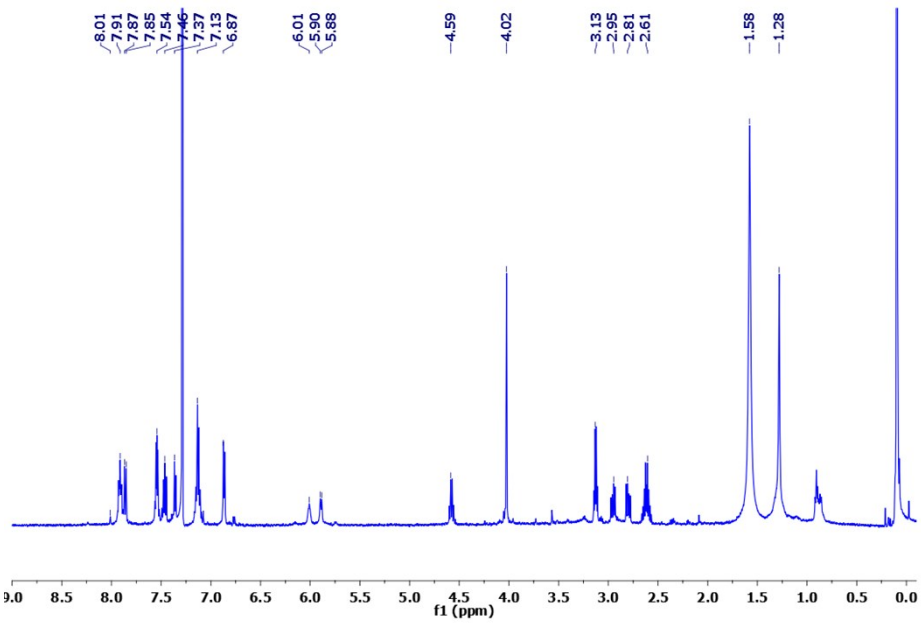


Figure S2(d): ^{1}H NMR of synthesized L-NapF-EDA (500 MHz, $CDCl_3$).

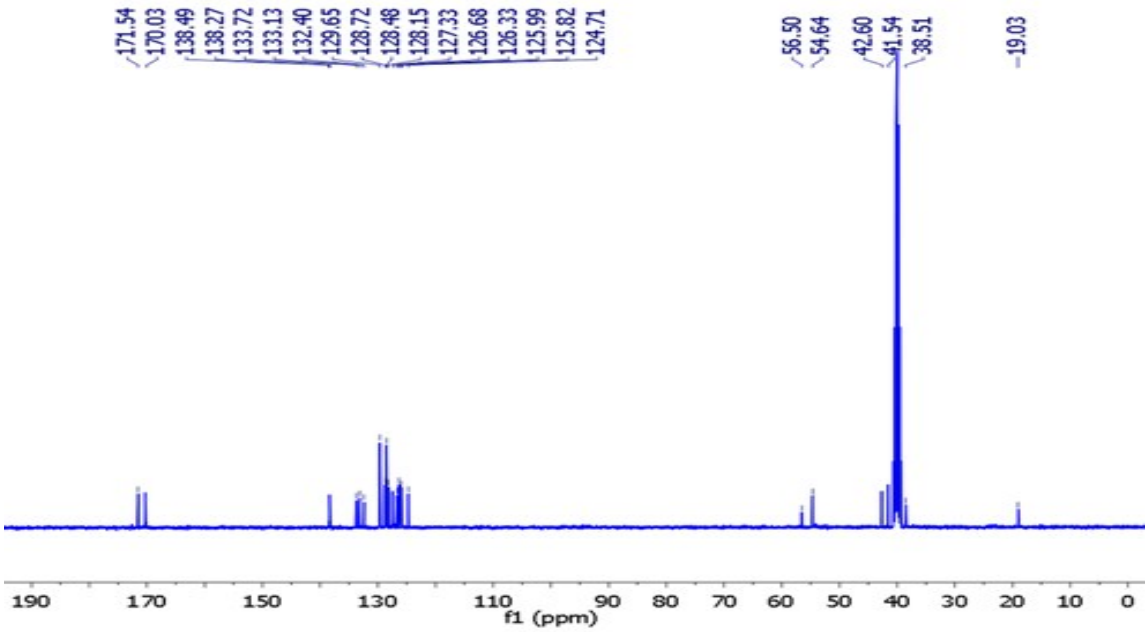


Figure S2(e): ^{13}C NMR of synthesized L-NapF-EDA (125 MHz, $CDCl_3$).

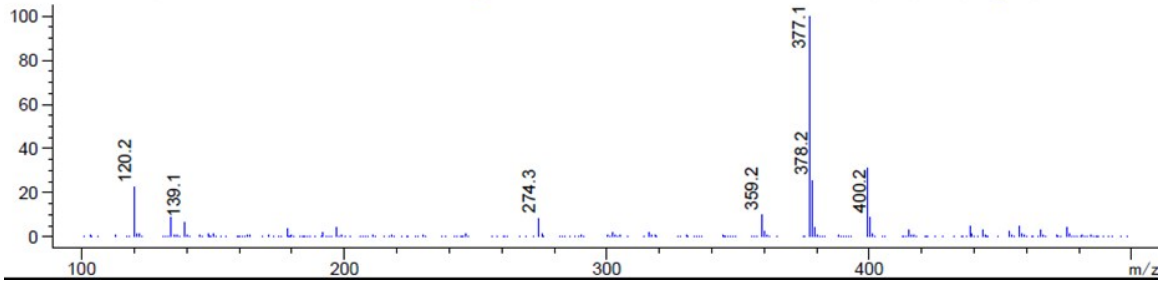


Figure S2(f): LR-MS data of synthesized L-NapF-EDA.

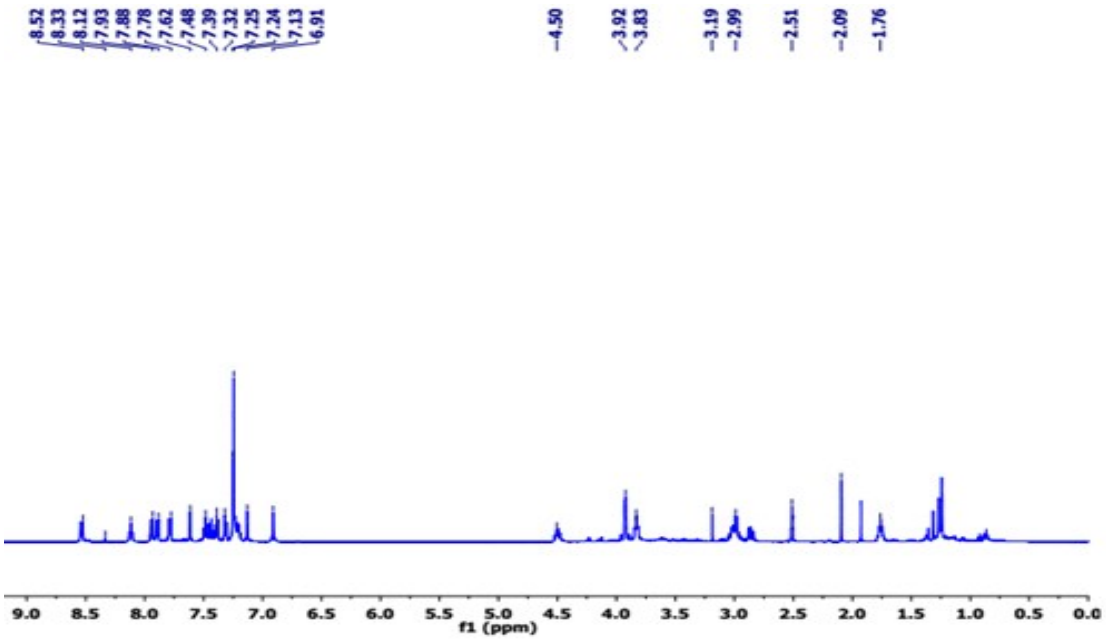


Figure S2(g): ^{1}H NMR of synthesized L-NapF-API (500 MHz, DMSO-d_6).

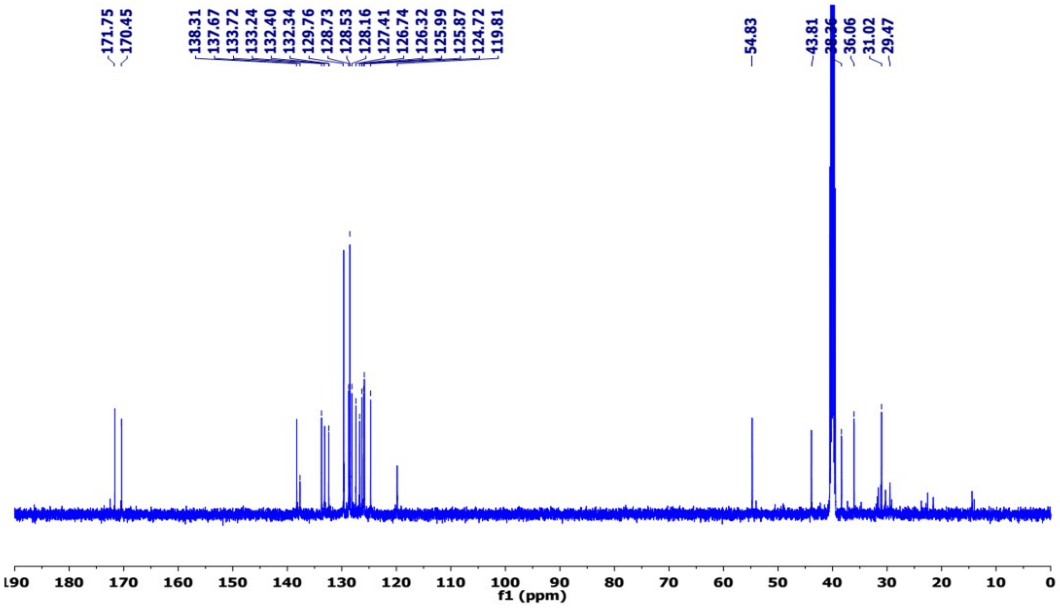
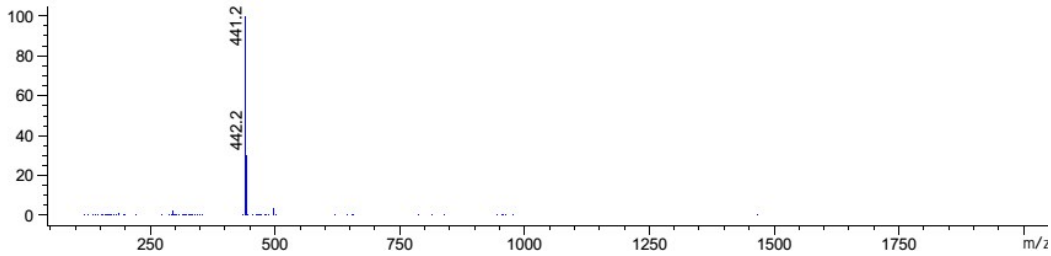


Figure S2 (h):^{13}C NMR of synthesized L-NapF-API (125 MHz, DMSO-d_6).



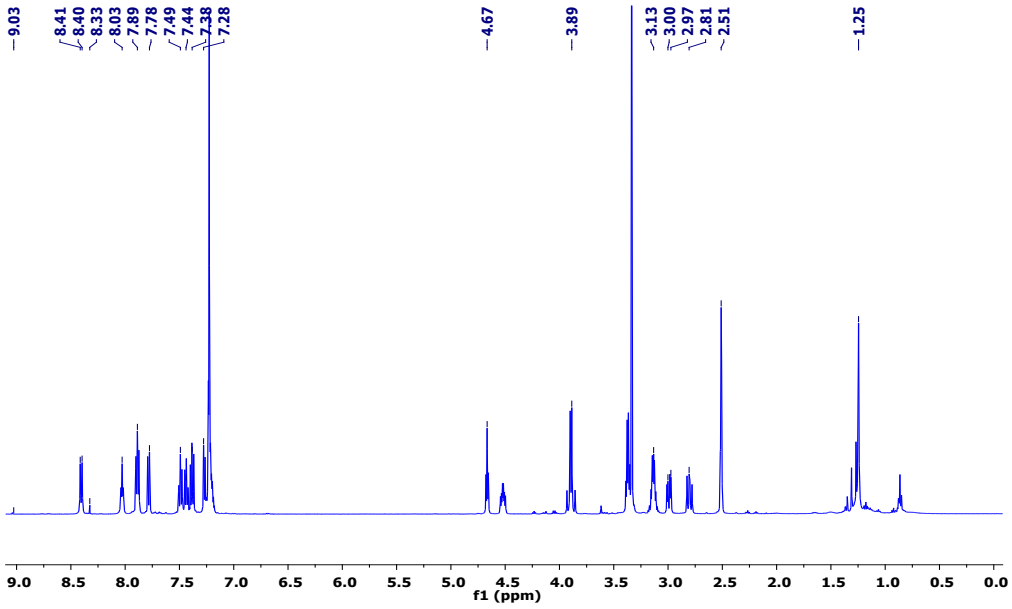


Figure S2(i): LR-MS data of synthesized L-NapF-API.

Figure S2(j): ^{1}H NMR of synthesized L-NapF-HEA (500 MHz, DMSO-d_6).

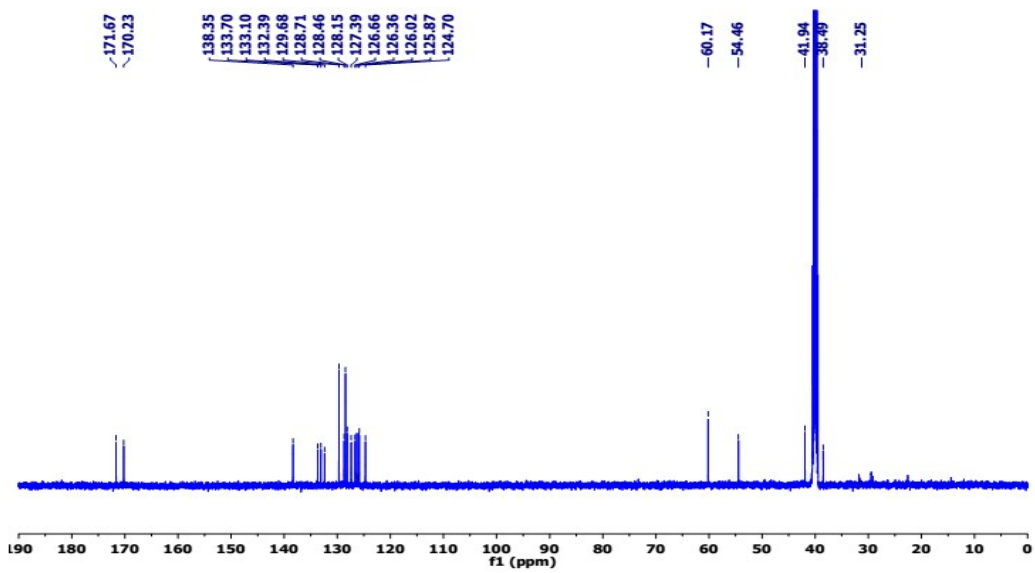


Figure S2(k): ^{13}C NMR of synthesized L-NapF-HEA (125 MHz, DMSO-d_6).

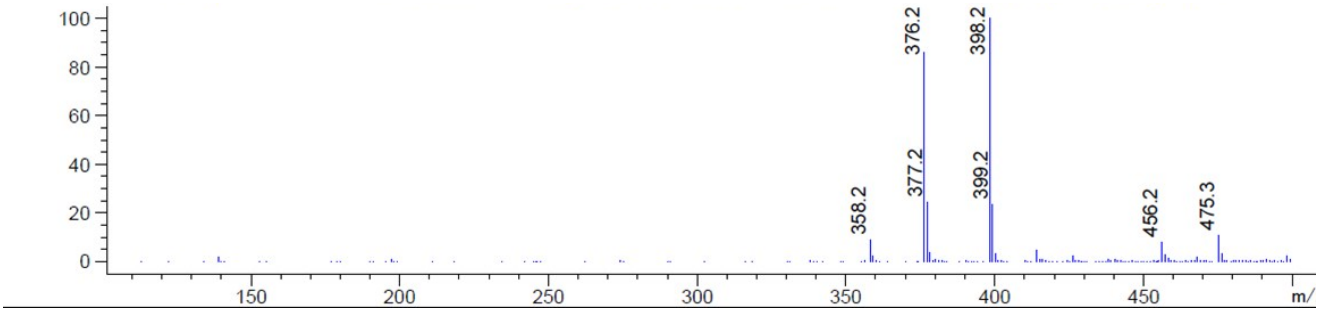


Figure S2(l): LR-MS data of synthesized L-NapF-HEA.

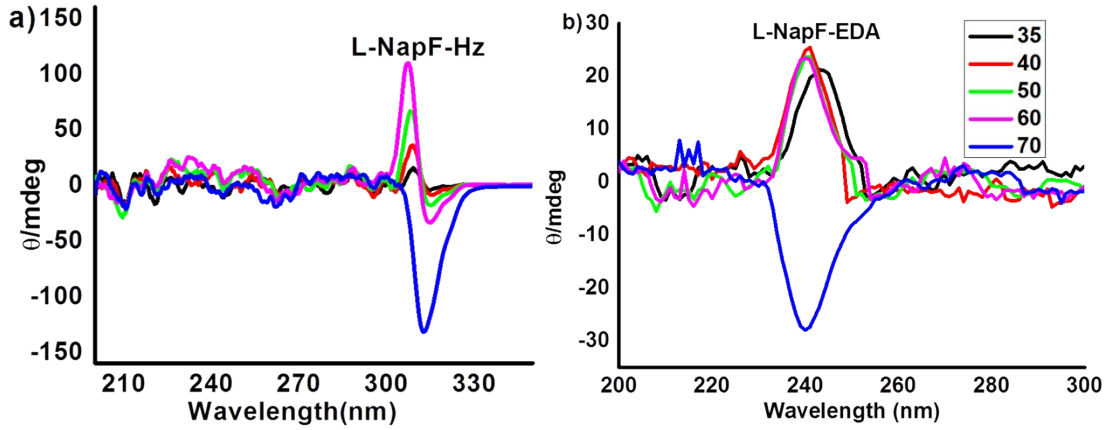


Figure S3: Temperature dependent CD spectra of L-NapF-Hz and L-NapF-EDA (4 mg/mL, 6 mg/mL respectively) in water.

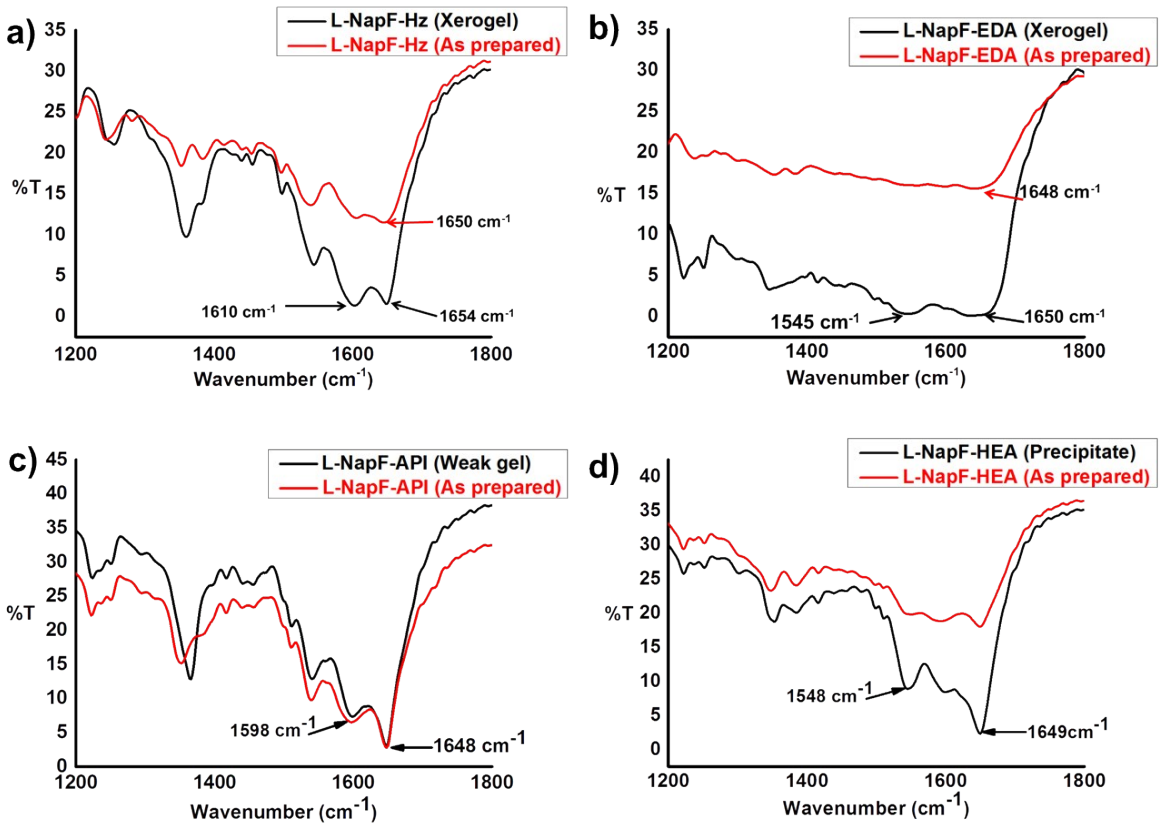


Figure S4: FTIR spectra of L-NapF derivatives. As prepared (red) and as lyophilized aqueous suspensions/gels (black). (a) L-NapF-Hz, (b) L-NapF-EDA, (c) L-NapF-API, (d) L-NapF-HEA.

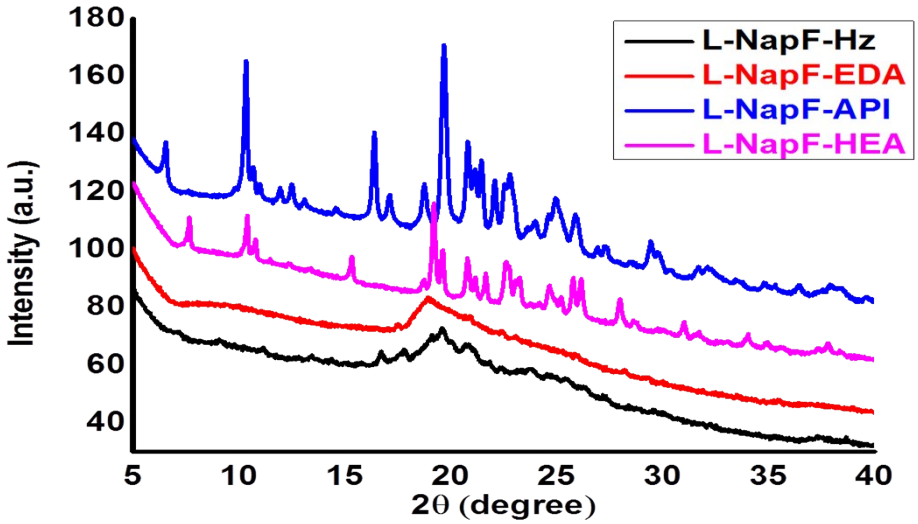


Figure S5: Powder XRD data for L-NapF derivatives.

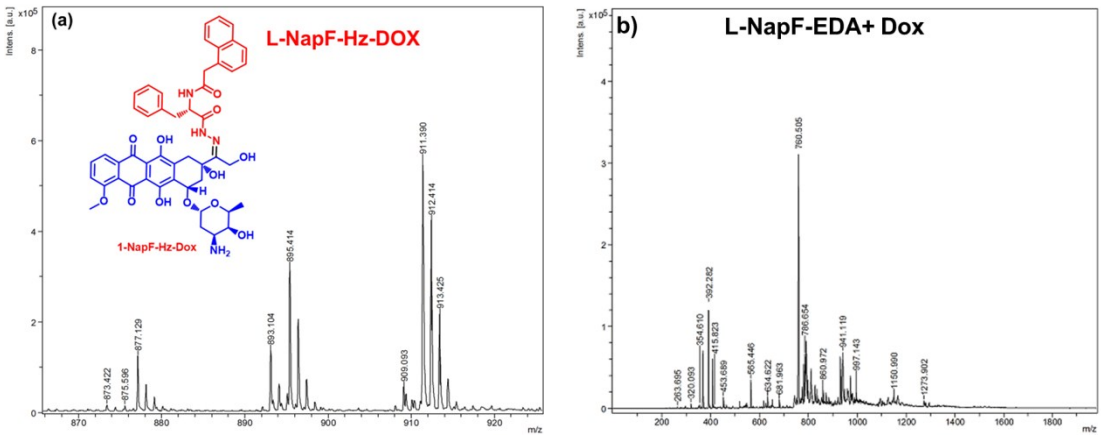


Figure S6: MALDI MS of gels subsequent to entrapment of Doxorubicin hydrochloride. (a) For L-NapF-Hz; and (b) For L-NapF-EDA. Stable gels were obtained only for Doxorubicin entrapped in L-NapF-EDA.