Electronic Supplementary Material (ESI) for ChemComm.

Supplementary Information

A small molecule peptidomimetic of spider silk and web

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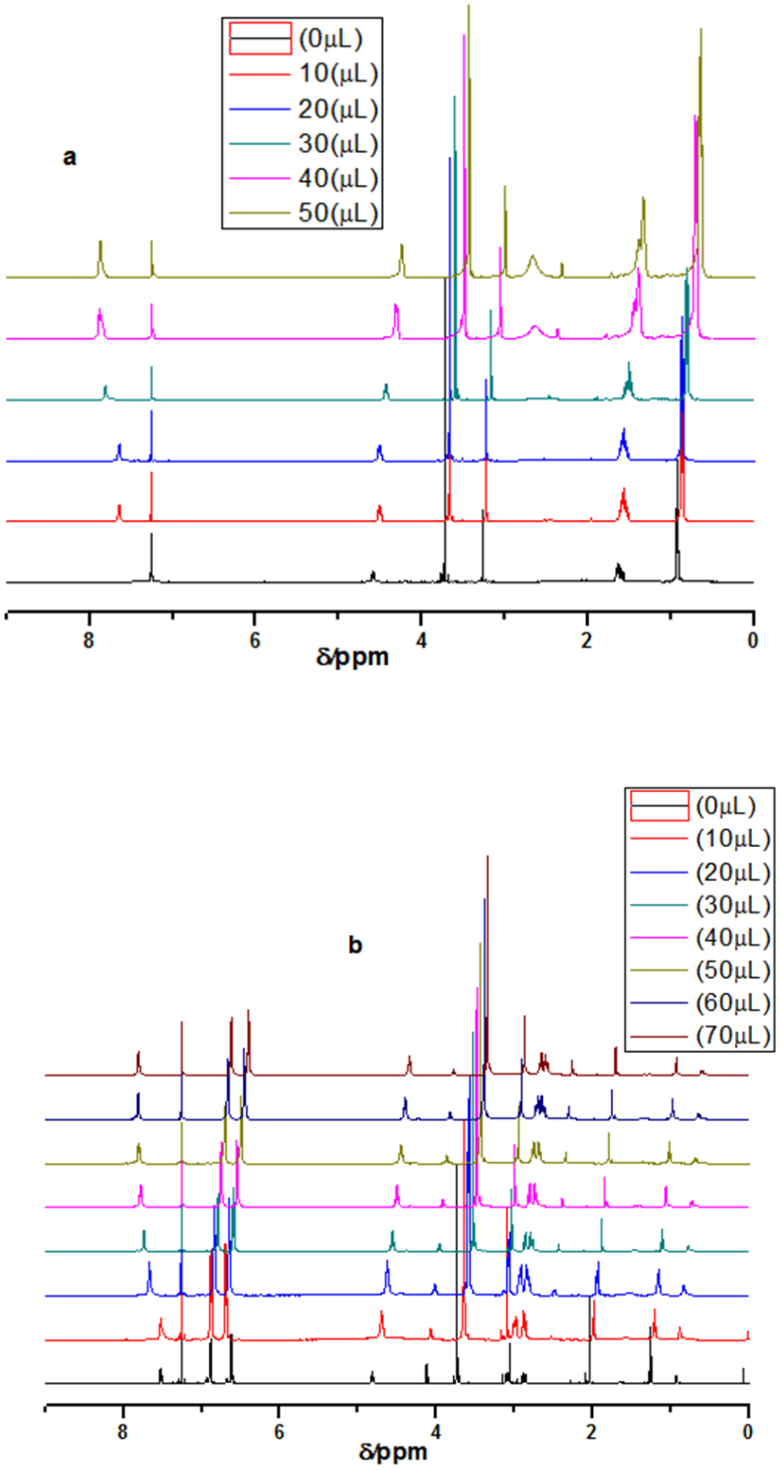

ESI Fig. 1: The solvent dependence of NH chemical shifts of (a) compound **1** and (b) compound **3** at varying concentrations of $(CD_3)_2SO$ in $CDCl_3$ solutions.

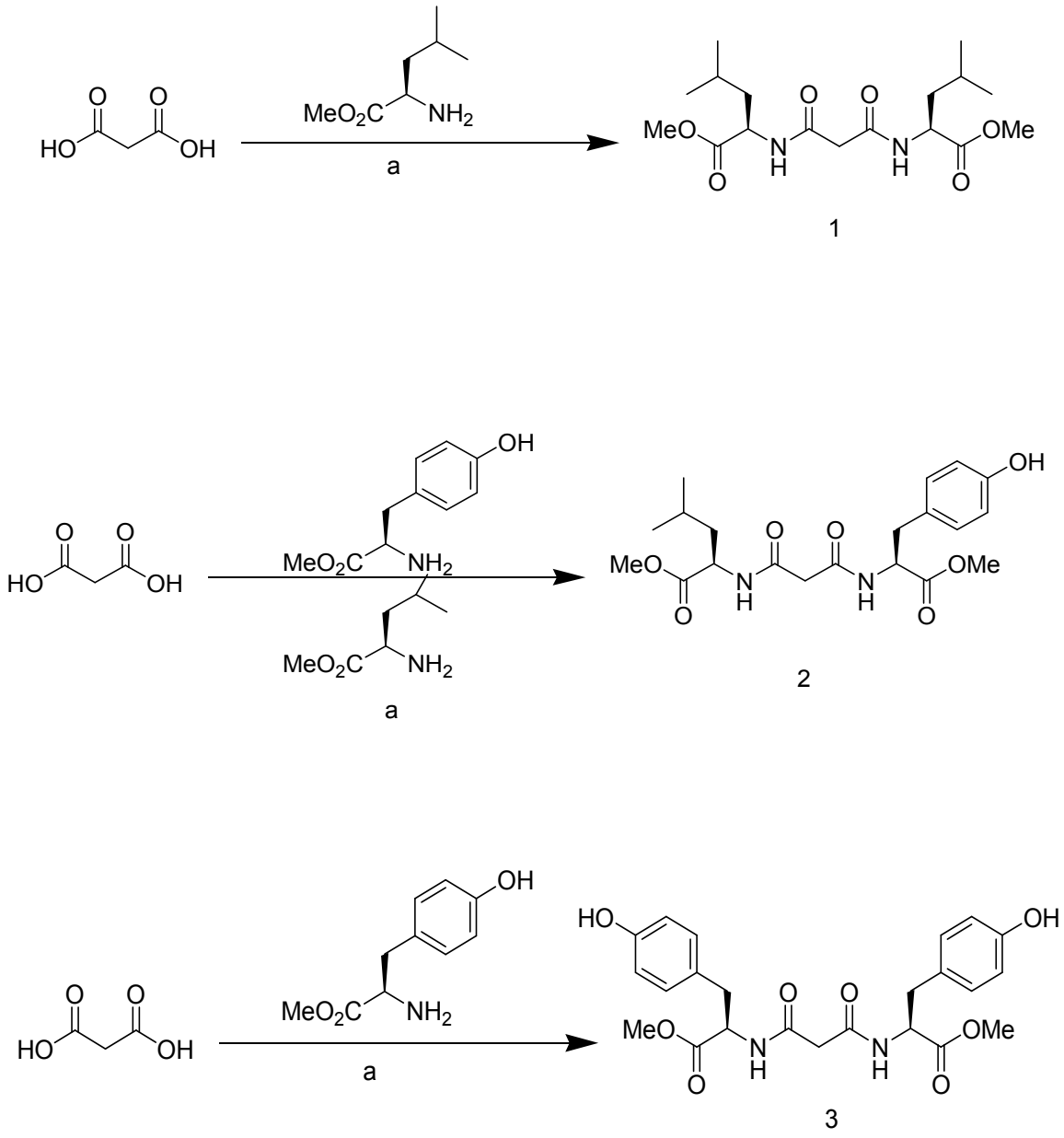

Fig. S1: Scheme 1: Reactions and conditions: (a) Dry DCM, DCC, HOBt, 0^0C, 48h.

Experimental

General methods and materials:

Malonic acid was purchased from Merck Chemicals and Leucine, Tyrosine, HOBt (1 hydroxybenzotriazole) and DCC (dicyclohexylcarbodiimide) were purchased from SRL.

Synthesis:

The compounds **1**, **2** and **3** were synthesized by conventional solution phase methodology using a racemisation free fragment condensation strategy. The coupling reaction was done by using DCC (dicyclohexylcarbodiimide) and HOBt (1-hydroxybenzotriazole) **.** The final compounds were fully characterized by 400 and 500 MHz ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy, IR spectroscopy and mass spectroscopy.

(a) Synthesis of Compound 1: 1.04 g (10 mmol) of malonic acid was dissolved in 30 mL dry DCM in an ice-water bath. The methyl ester of leucine was isolated from 3.620g (20 mmol) of the corresponding methyl ester hydrochloride by neutralization with saturated sodium carbonate solution and subsequent extraction with ethyl acetate, and the ethyl acetate extract was concentrated to 10 mL. The concentrated solution was then added to the reaction mixture, followed by immediate addition of 4.12 g (20 mmol) DCC and 2.70g (20 mmol) of HOBt. The reaction mixture was allowed to come at room temperature and stirred for 48 hrs. After that, DCM was evaporated and the residue was dissolved in ethyl acetate (60 mL) and dicyclohexyl urea (DCU) was filtered off. The organic layer was washed with 2 (M) HCl (3 × 50 mL), brine (2 × 50 mL), dilute sodium carbonate (2 × 20 mL), and brine (2 × 50 mL), and dried over anhydrous sodium sulfate. Then, the solution was evaporated under vacuum to yield the compound as a white solid. The product was purified by silica gel (100-200 mesh) using hexane-ethyl acetate (3:1) as eluent.

Yield: 2.20gm (6.13 mmol, 61%).

^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 7.50-7.49 [d, 2H, NH, *J*=5], 4.57-4.53 [m, 2H, Leu$^{\alpha}$ H], 3.70 [s, 6H, -OMe], 3.28 [s, 2H, mal methelene H], 1.63-1.56 [m, 6H, Leu$^{\beta}$ H, Leu$^{\gamma}$ H], 0.91-0.98 [m, 12H, Leu$^{\delta}$ H]. ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm: 173.03, 167.17, 77.25, 77.00, 76.74, 52.25, 50.95, 42.95, 40.79, 24.70, 22.75, 21.60.

TOF MS m/z: 359.35 $[M + H]^+$; 381.31 $[M + Na]^+$; Mcalcd: 358.21.

(b) Synthesis of Compound 2: 520 mg (5 mmol) of malonic acid was dissolved in 20 mL dry DCM in an ice-water bath. The methyl esters of leucine and tyrosine were isolated from 0.905 g (5 mmol) and 1.15g (5 mmol) of the corresponding methyl ester hydrochloride respectively by neutralization with saturated sodium carbonate solution and subsequent extraction with ethyl acetate. The ethyl acetate extracts were concentrated to 10 mL for both the cases. These two solutions were then added to the reaction mixture, followed by immediate addition of 2.06 g (10 mmol) DCC and 1.35 g (10mmol) of HOBt. The reaction mixture was allowed to come at room temperature and stirred for 48 hrs. After that, DCM was evaporated, and the residue was dissolved in ethyl acetate (60 mL). Then, dicyclohexyl urea (DCU) was filtered off and the organic layer was washed with 2 M HCl (3 × 50 mL), brine (2 × 50 mL), dilute sodium carbonate (2 × 20 mL), and brine (2 × 50 mL) and dried over anhydrous sodium sulfate. The solution was evaporated under vacuum and the product was purified by silica gel (100-200 mesh) using hexane-ethyl acetate (3:1) as eluent.

Yield: 0.70gm (1.7 mmol, 34%).

^{1}H NMR (400 MHz, DMSO-d_6, δppm): 9.24 [s, 1H, OH], 8.39-8.34 [m, 2H, NH], 6.97-6.95 [d, J=8, 2H, ArH], 6.66-6.63 [d, J=8, 2H, ArH], 4.43-4.83 [m, 1H, Tyr$^{\alpha}$ H], 4.31-4.25 [m, 1H, Leu$^{\beta}$ H], 3.61 [s, 3H, OMe] 3.58 [s, 3H, OMe], 3.21-3.11 [m, 2H, mal methelene H], 2.89-2.76 [m, 2H, Tyr$^{\beta}$ H], 1.62-1.46 [m, 3H, Leu$^{\beta}$ H, Leu$^{\gamma}$ H] 0.89-0.82 [m, 6H, Leu$^{\delta}$ H]. ^{13}C NMR (100 MHz, DMSO-d_6, δppm): 172.7, 171.7, 166.6, 166.4, 156.0, 129.9, 126.7, 115.05, 53.90, 51.8, 51.7, 50.2, 42.3, 36.1, 24.1, 22.6, 21.3.

TOF MS m/z: 409.28 $[M + H]^{+}$; 431.22 $[M + Na]^{+}$; 447.18 $[M+K]^{+}$; Mcalcd: 408.19.

(c) Synthesis o**f Compound 3:** 1.04g (10 mmol) of malonic acid was dissolved in 30 mL dry DCM in an ice-water bath. The methyl ester of tyrosine was isolated from 4.630 g (20 mmol) of the corresponding methyl ester hydrochloride by neutralization with saturated solution of sodium carbonate and subsequent extraction with ethyl acetate, and ethyl acetate extract was concentrated to 10 mL. The concentrated solution was then added to the reaction mixture, followed by the immediate addition of 4.12 g (20 mmol) DCC and 2.70g (20 mmol) of HOBt. The reaction mixture was allowed to come at room temperature and stirred for 48 hrs. DCM was evaporated and the residue was dissolved in ethyl acetate (60 mL) and dicyclohexyl urea (DCU) was filtered off. The organic layer was washed with 2(M) HCl (3 × 50 mL), brine (3 × 50 mL), dilute sodium carbonate (2 × 20 mL), and brine (2 × 50 mL), dried over anhydrous sodium sulfate and evaporated under vacuum and the product was purified by silica gel (100-200 mesh) using hexane-ethyl acetate (2:1) as eluent.

Yield: 2.58gm (5.63 mmol, 56.3%).

^{1}H NMR (400 MHz, DMSO-d_6, δppm) (Fig. 6): 9.22 [b, 2H, OH], 8.36 [s, 1H, NH], 8.35 [s, 1H, NH], 6.96-6.94 [d, 4H, *J*=8, ArH], 6.65-6.63 [d, 4H, *J*=8, ArH], 4.03-3.98 [m, 2H, Tyr$^{\alpha}$ H], 3.57 [s, 6H, -OMe], 3.1 [s ,2H, mal methelene H], 2.87-2.75 [m, 4CH, Tyr^{b} H]. ^{13}C NMR (100 MHz, DMSO-d_6, δppm): 172.30, 167.04, 156.57, 130.54, 127.20, 115.57, 60.01, 54.01, 52.0, 42.2, 38.0, 36.2.

TOF MS m/z: 459.43 $[M + H]^+$; 481.37 [M + Na]+; Mcalcd: 458.17.

NMR experiments

All NMR studies were carried out Brüker AVANCE 500 MHz and JEOL 400 MHz spectrometer at 298 K. Compound concentrations were in the range 1–10 mmol in $CDCl_3$ and DMSO-d_6.

FTIR spectroscopy

All reported solid-state FTIR spectra were obtained with a Perkin Elmer Spectrum RX1 spectrophotometer with the KBr disk technique.

Field emission scanning electron microscopy

The morphology of the compound was investigated using field emission scanning electron microscopy (FE-SEM). The images were taken in an FE-SEM apparatus (ZEISS).

Mass spectrometry

Mass spectrum was recorded on a Q-Tof Micro YA263 high-resolution (Waters Corporation) mass spectrometer by positive-mode electro-spray ionization.

Rheology

The viscoelastic properties of peptidomimetic compounds were measured with a commercial rheometer (AR-G2, TA Instruments, New Castle, USA).

Fiber preparation

The fibers have prepared using a spatula or a glass rod deep inside highly viscous compound **2** and pull it out. Moreover, an injection syringe can provide soft fiber with uniform diameter like a spigot of a spider. The highly viscous compound **2** upon contact with air at 20°C facilitate the phase transition and solidification to form soft fiber.

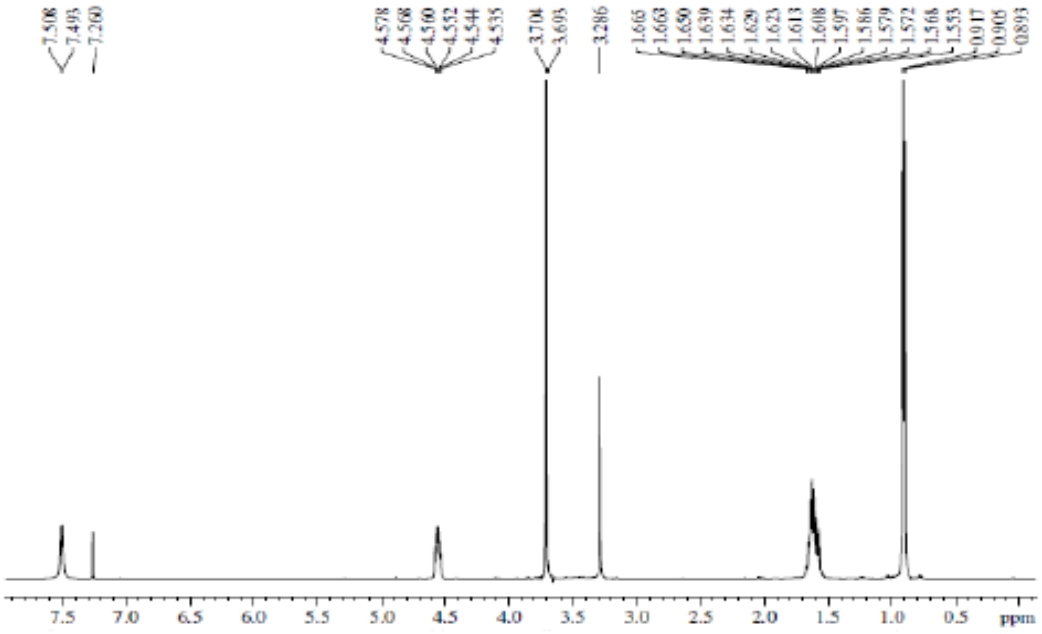

Fig. S2: ^{1}H NMR (500 MHz, $CDCl_3$, δppm) spectra of compound **1.**

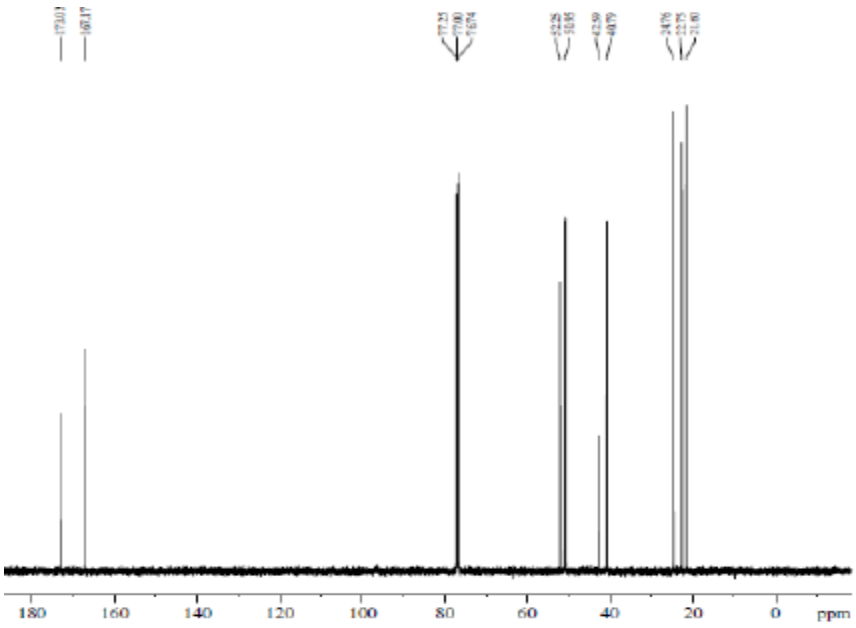

Fig. S3: ^{13}C NMR (125 MHz, $CDCl_3$, δppm) spectra of compound **1.**

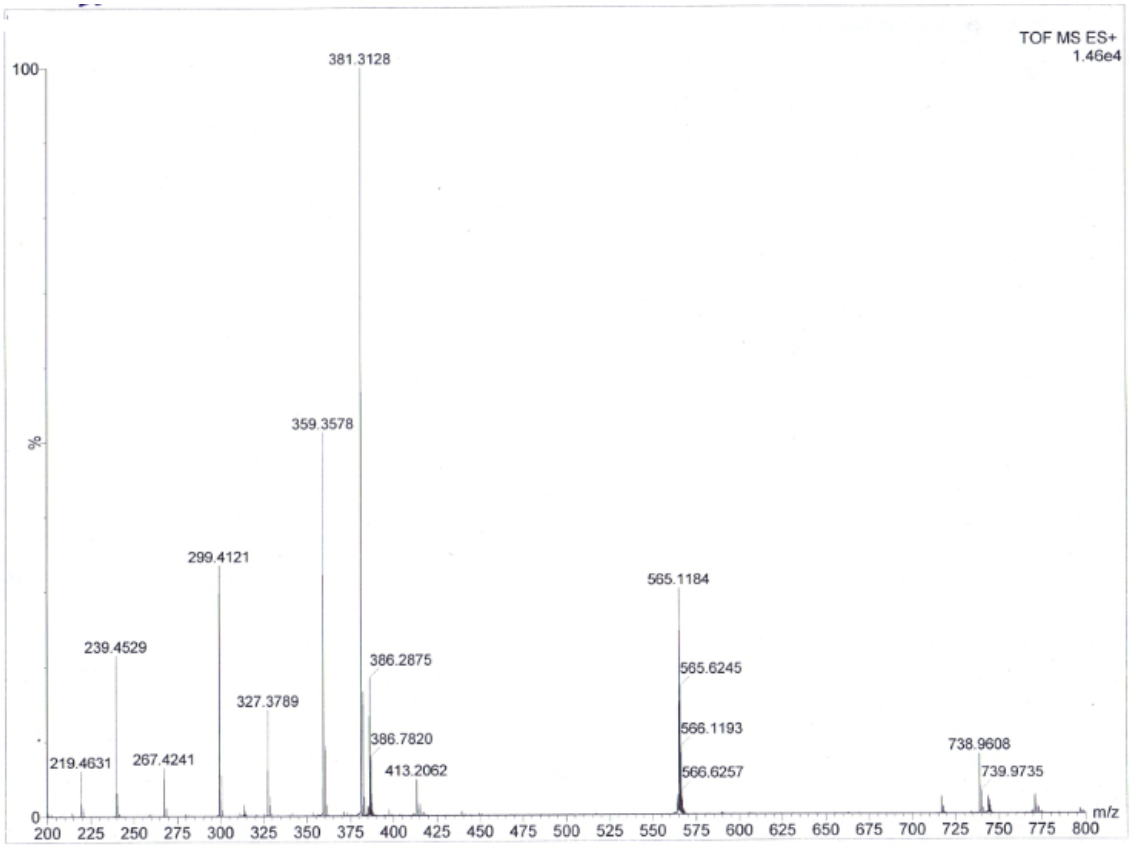

Fig. S4: Mass spectra of compound **1**

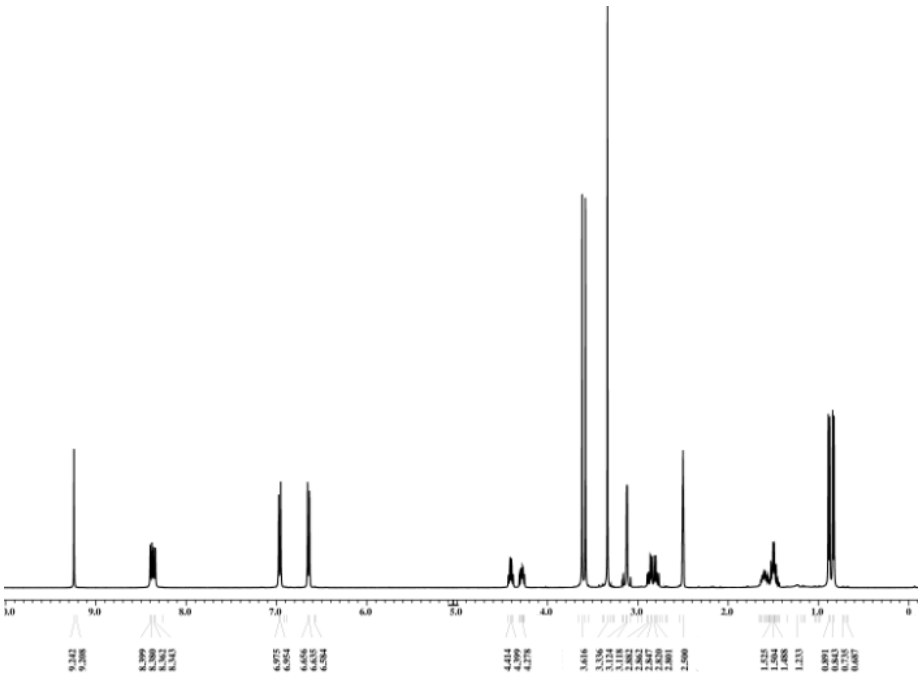

Fig. S5: ^{1}H NMR (400 MHz, DMSO-d_6, δppm) spectra of compound **2.**

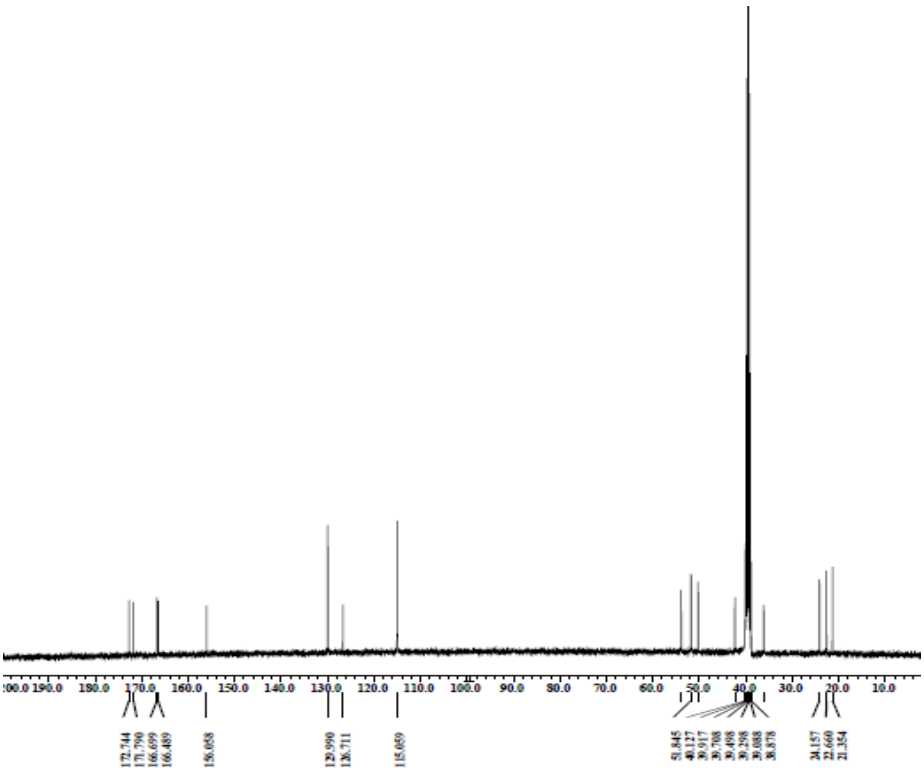

Fig. S6: ^{13}C NMR (100 MHz, DMSO-d_6, δppm) spectra of compound **2.**

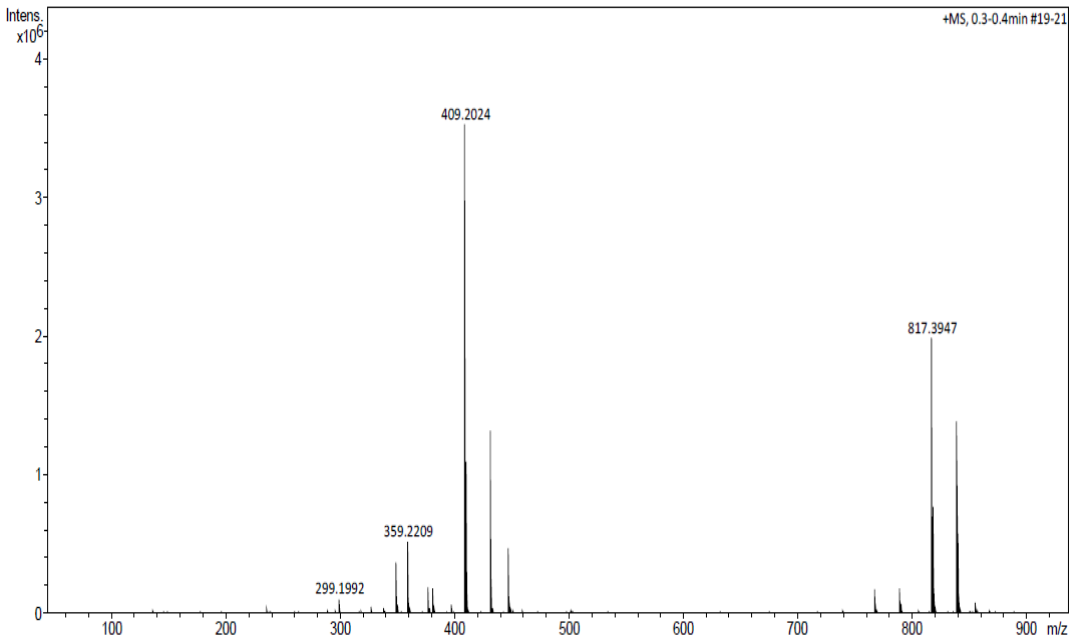

Fig. S7: Mass spectra of compound **2**

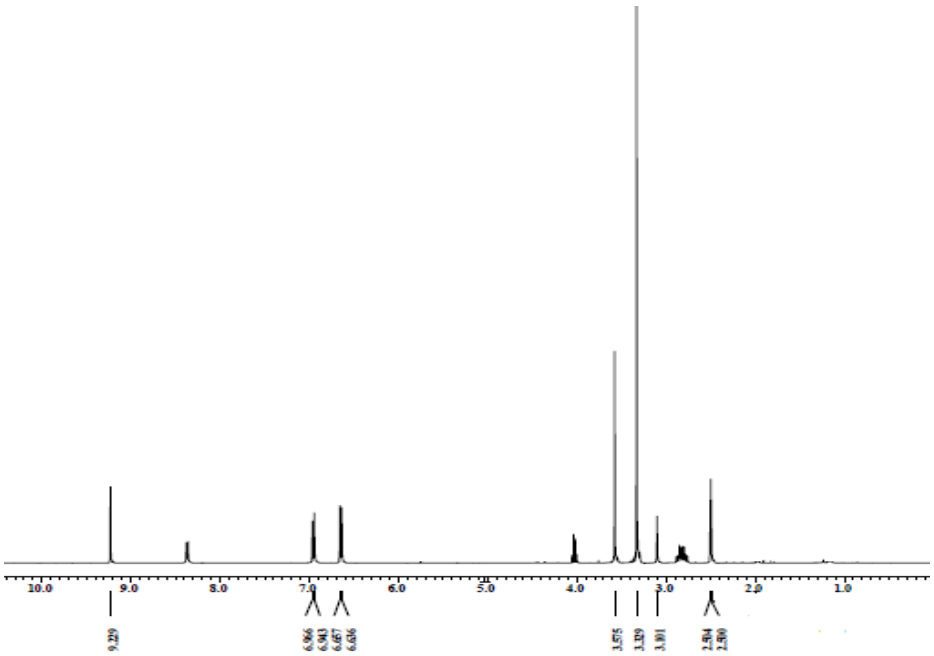

Fig. S8: ^{1}H NMR (400 MHz, DMSO-d_6, δppm) spectra of compound **3.**

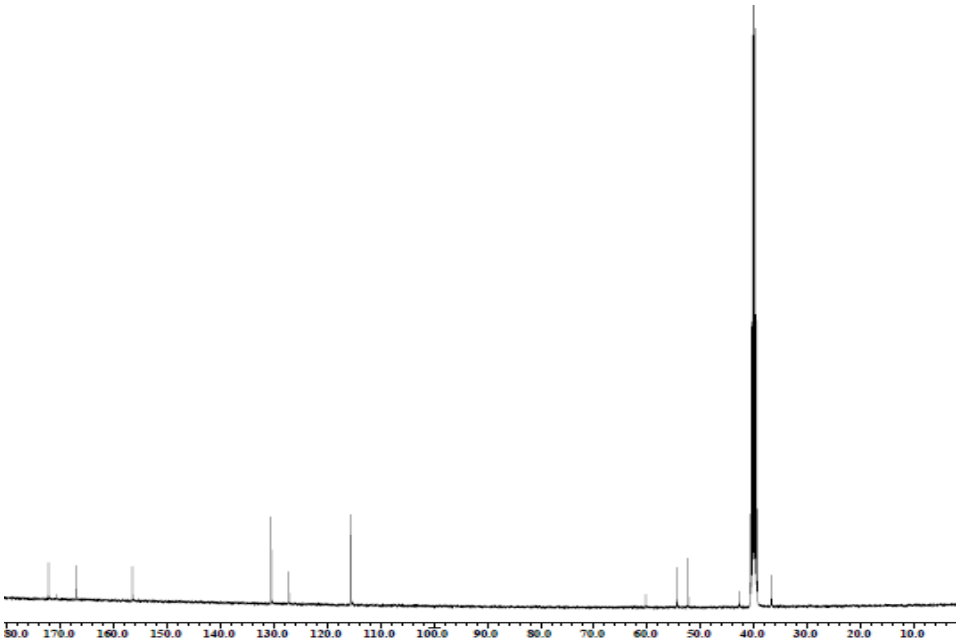

Fig. S9: ^{13}C NMR (100 MHz, DMSO-d_6, δppm) spectra of compound **3**

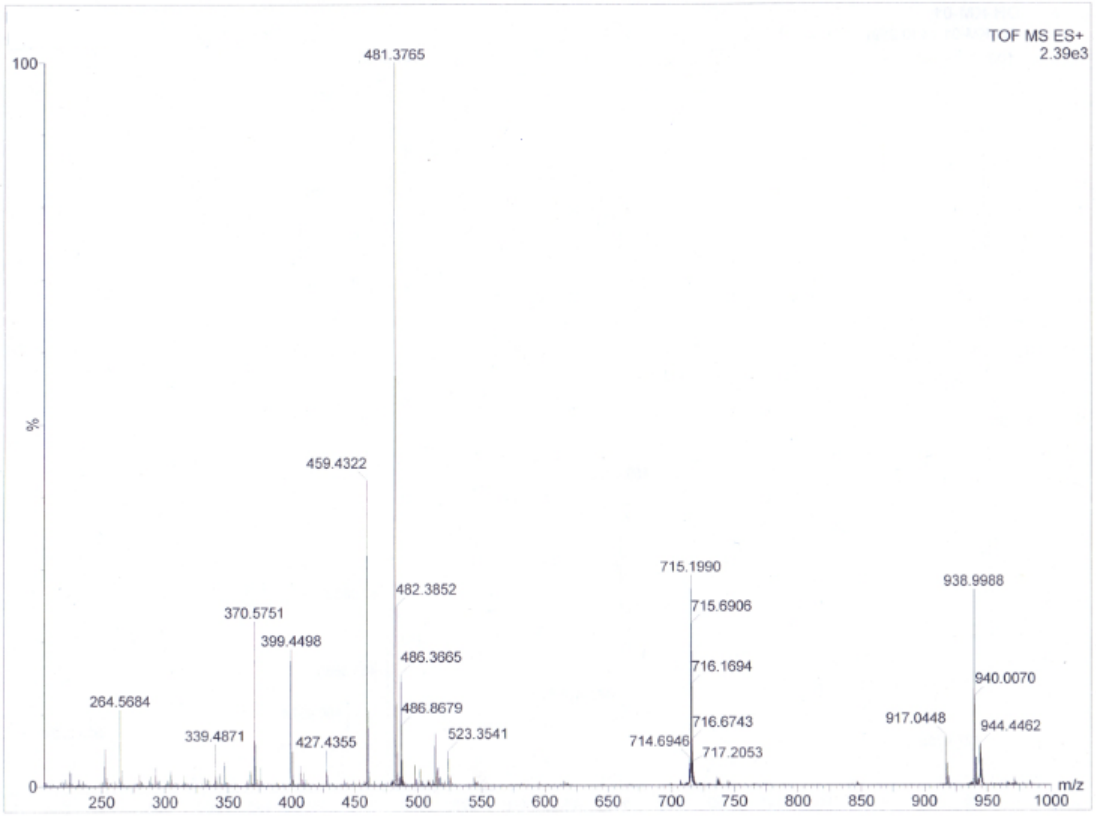

Fig. S10: Mass spectra of compound **3.**