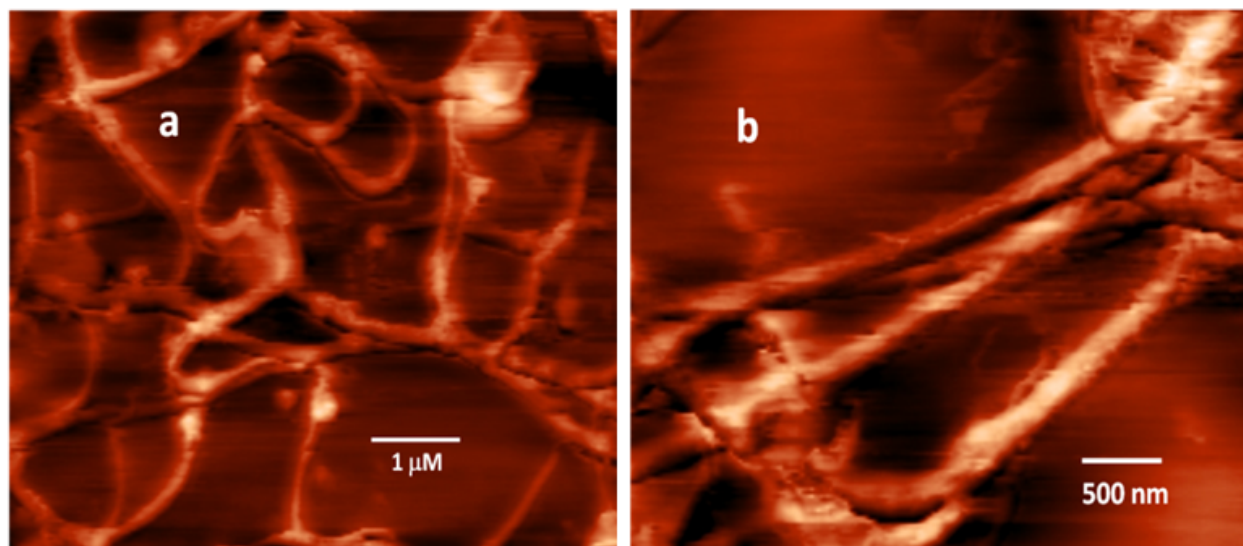


Supporting information

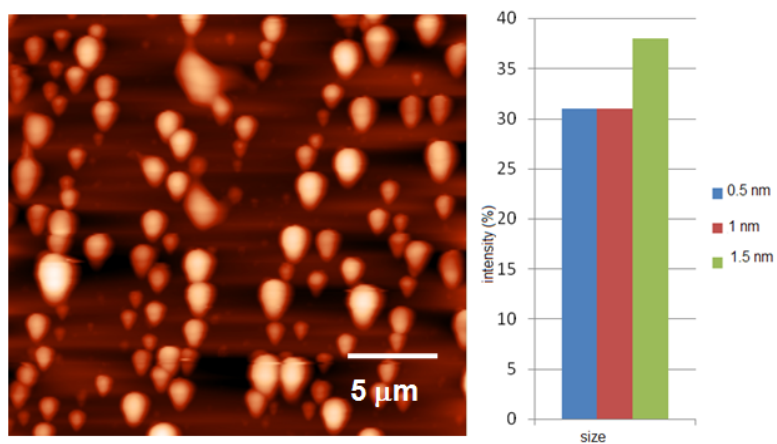
Proportional release of nicotinamide from peptidomimetic microspheres by hydrogen peroxide†

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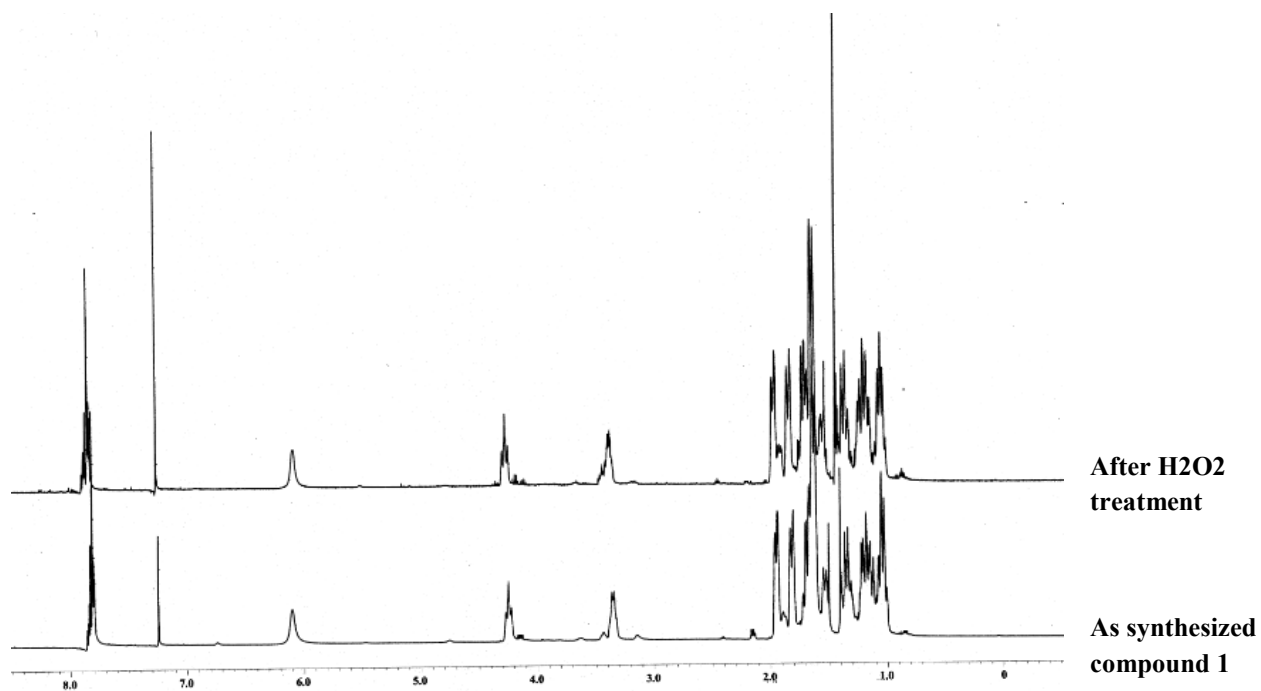
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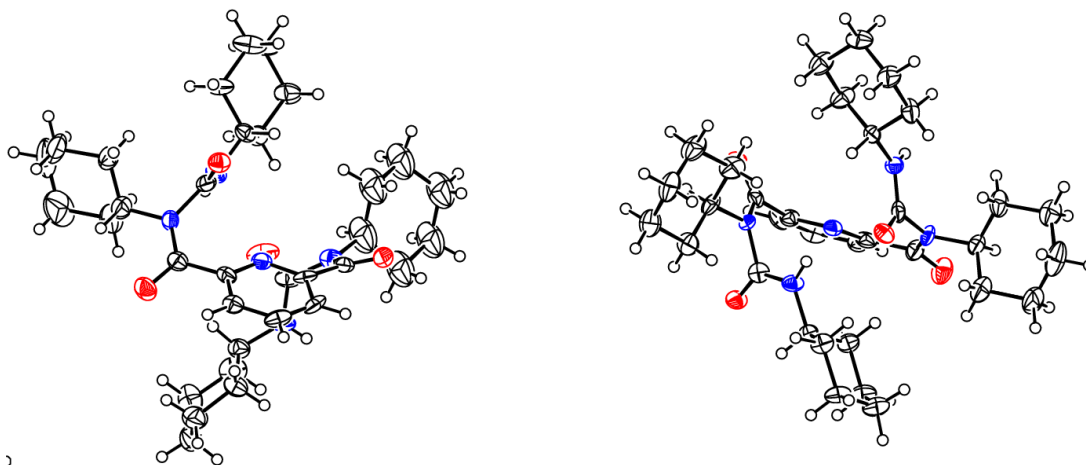
ESI Fig. 1a: AFM images showing tape like morphology of compound 2.



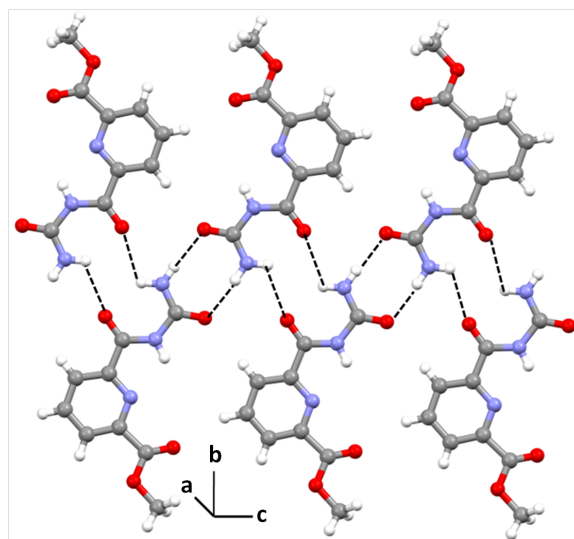
ESI Fig. 1b: Size distribution diagram from AFM image of compound 1.



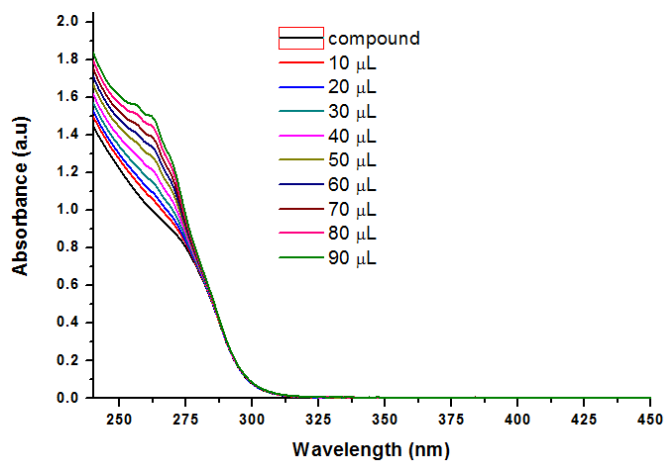
ESI Fig. 2: Stack plot of NMR spectra of the reported compound after 50 mmol H₂O₂ treatment for 48 hours with as synthesized compound.



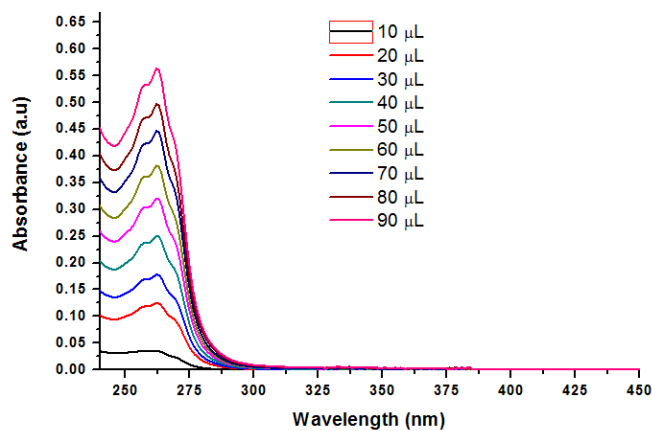
ESI Fig. 3: ORTEP diagram of the reported compound 1. Ellipsoids are drawn at the 50% probability level.



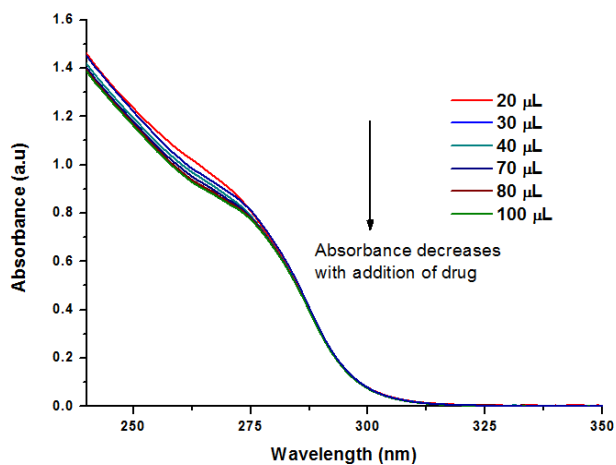
ESI Fig. 4 Ball and stick model of supramolecular sheet obtained from compound **2**. Intramolecular hydrogen bonds are shown as dotted lines.



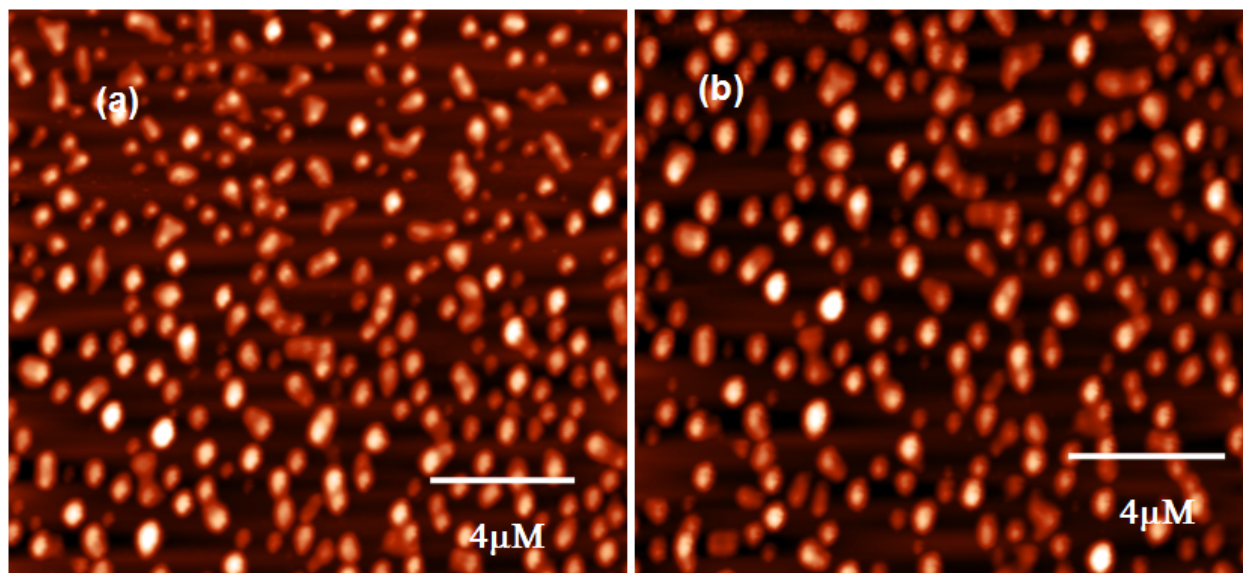
(a)



(b)



ESI Fig. 5: (a) UV titration spectra of the reported peptidomimetic compound **1** with gradual addition of drug solution. (b) The control experimental spectra (c) The spectra of free drug have been subtracted from the spectra of drug with compound **1**.



ESI Fig. 6: AFM images showing sphere like morphology of compound **1** at (a) pH 6 and (b) pH 1 in absence of H₂O₂.

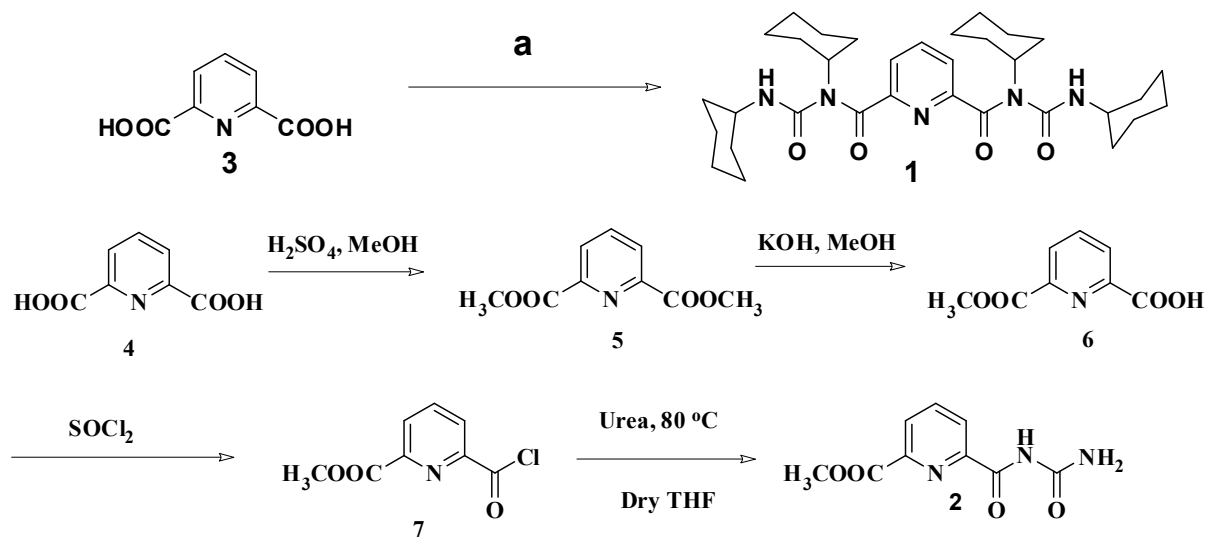


Fig. S1: Schematic presentation of synthesis of compounds **1** and **2**. Reactions and conditions: (a) *N,N'*-dicyclohexylurea, DCC, Chloroform.

Peptide synthesis:

(a) Synthesis of DCU-Pyr-DCU 1: 0.334 gm (2 mmol) pyridine dicarboxylic acid was dissolved in DCM and cooled in an ice bath. 0.897 gm (4 mmol) *N,N'*-dicyclohexylurea (DCU) was added to the reaction mixture followed by 0.825 gm (4 mmol) dicyclohexylcarbodiimide (DCC). The reaction mixture was allowed to come to room temperature and stirred for 48 h. DCM was evaporated, and the residue was taken in ethyl acetate (60 mL); dicyclohexylurea (DCU) was filtered off. The organic layer was washed with 2 N HCl (3 × 50 mL), brine, 1 M sodium carbonate (3 × 50 mL), and brine (2 × 50 mL), dried over anhydrous sodium sulfate, and evaporated under vacuum to yield compound **1** as a white solid. Purification was done on a silica gel column (100-200 mesh) using ethyl acetate: hexane (3:1) as the eluent.

Yield: 0.927 gm (80%)

¹H NMR (500 MHz, DMSO-*d*₆, δppm): 7.81-7.86 [3H, m, pyridine aromatic protons], 6.12 [2H, s, DCU NH], 4.24-4.29 [2H, m, CαH cyh], 3.34-3.38 [1H, m, CαH cyh], 1.95-1.98 [4H, d, cyh], 1.82-1.85 [4H, d, cyh], 1.73-1.63 [12H, m, cyh], 1.54-1.56 [3H, m, cyh], 1.32-1.42 [6H, m, cyh], 1.03-1.22 [15H, m, cyh].
¹³C NMR (125 MHz, DMSO-*d*₆, δppm): 154.1, 150.82, 138.16, 124.93, 55.28, 50.70, 31.98, 30.89, 25.97, 25.34, 25.23, 24.84. FTIR (in cm⁻¹): 3306, 2928, 2852, 1680, 1649, 1527.

Anal. Calcd for C₃₃H₄₉N₅O₄ (579.37): C, 68.36; H, 8.52; N, 12.08.

Found: C, 68.35; H, 8.51; N, 12.09.

TOF MS *m/z* 602.03 [M + Na]⁺; *M*calcd: 579.37.

(b) Synthesis of Dimethyl pyridine-2,6-dicarboxylate 5: A solution of dipicolinic acid (1.67 g, 10 mmol) and concentrated sulphuric acid (3.3 mL) in methanol (30 mL) was heated at 70°C for two days. After cooling to room temperature the suspension was neutralized with a saturated aqueous sodium hydrogencarbonate solution. The methanol was removed under reduced pressure, and the aqueous suspension was dissolved in chloroform (30 mL). The organic layer was separated, washed with water (3×10 mL) and brine (15 mL), and dried over Na₂SO₄. The solvent was removed in vacuum to provide dimethyl pyridine-2,6-dicarboxylate (1.5 g, 78%) as a white solid. This crude product was used in the following step without further purification.

(c) Synthesis of 6-(Methoxycarbonyl)pyridine-2-carboxylic acid 6: A solution of dimethyl pyridine-2,6-dicarboxylate (0.95 g, 4.86 mmol) in methanol (30 mL) was cooled to 0°C. KOH pellets (0.27 g, 4.86 mmol) were added, and the reaction mixture was stirred at 0°C for 2 h and then at room temperature for

24 h. The solvent was removed under reduced pressure, and the residue was suspended in ethyl acetate (150 mL). The white potassium salt was collected by filtration and was then dissolved in water (100 mL). The solution was acidified to pH 3 with concentrated hydrochloric acid and extracted with chloroform (4x40 mL). The collected organic layers were dried over Na₂SO₄, and the chloroform was removed in vacuum to provide the desired product (0.62 g, 70%) as a white solid:

¹H NMR (400 MHz, CDCl₃, δ ppm): 4.04 (s, 3 H, CH₃), 8.10–8.14 (m, 1H, aromatic proton), 8.35–8.37 (d, 1H, J=8Hz, aromatic proton), 8.41–8.43 (d, 1H, J=8Hz, aromatic proton). ¹³C NMR (100 MHz, CDCl₃, δ ppm): 52.6, 127.6, 127.8, 139.0, 147.6, 148.8, 164.8, 165.6.

(d) Synthesis of compound 2: 3.03 mmol (0.55 g) half ester was refluxed with SOCl₂ in N₂ atmosphere for 40 min. Then SOCl₂ was evaporated to dryness with toluene. The resulting mass was dissolved in dry THF and 3.2 mmol (192 mg) of urea was added to it. The mixture was refluxed at 70–80 °C for overnight. The solvent was evaporated and the resulting mass was dissolved in methanol. The solution was subjected to column chromatography for purification with silica gel (100–200 mesh size) and ethyl acetate: hexane (1:1) as eluent.

¹H NMR (500 MHz, CDCl₃, δ ppm): 10.02 (s, 1H, urea NH), 8.40–8.42 (d, 1H, J=8Hz, aromatic proton), 8.33–8.35 (d, 1H, J=8Hz, aromatic proton), 8.27 (s, 1H, urea NH), 8.11–8.07 (m, 1H, aromatic proton), 5.442 (s, 1H, urea NH), 4.02 (s, 3H, CH₃). ¹³C NMR (125 MHz, CDCl₃, δ ppm): 53.05, 126.03, 128.66, 139.04, 147.25, 147.78, 153.26, 163.94, 164.53. FTIR (in cm⁻¹): 3415, 2925, 2854, 1740, 1720, 1600.

TOF MS *m/z* 246.3122 [M + Na]⁺; *M*_{calcd}: 223.0593.

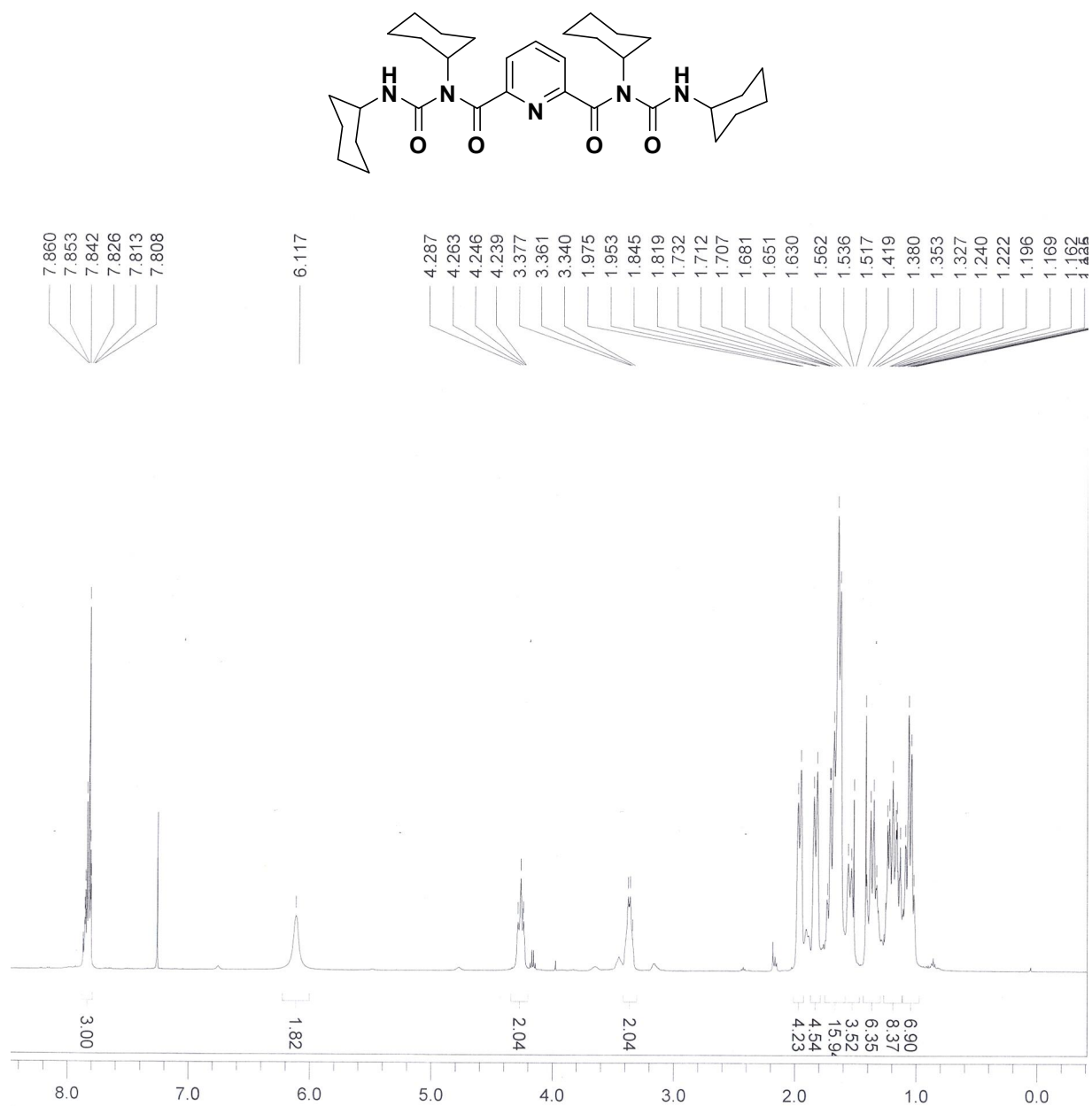


Fig. S2: ^1H NMR (500 MHz, CDCl_3 , δ ppm) spectrum of compound 1.

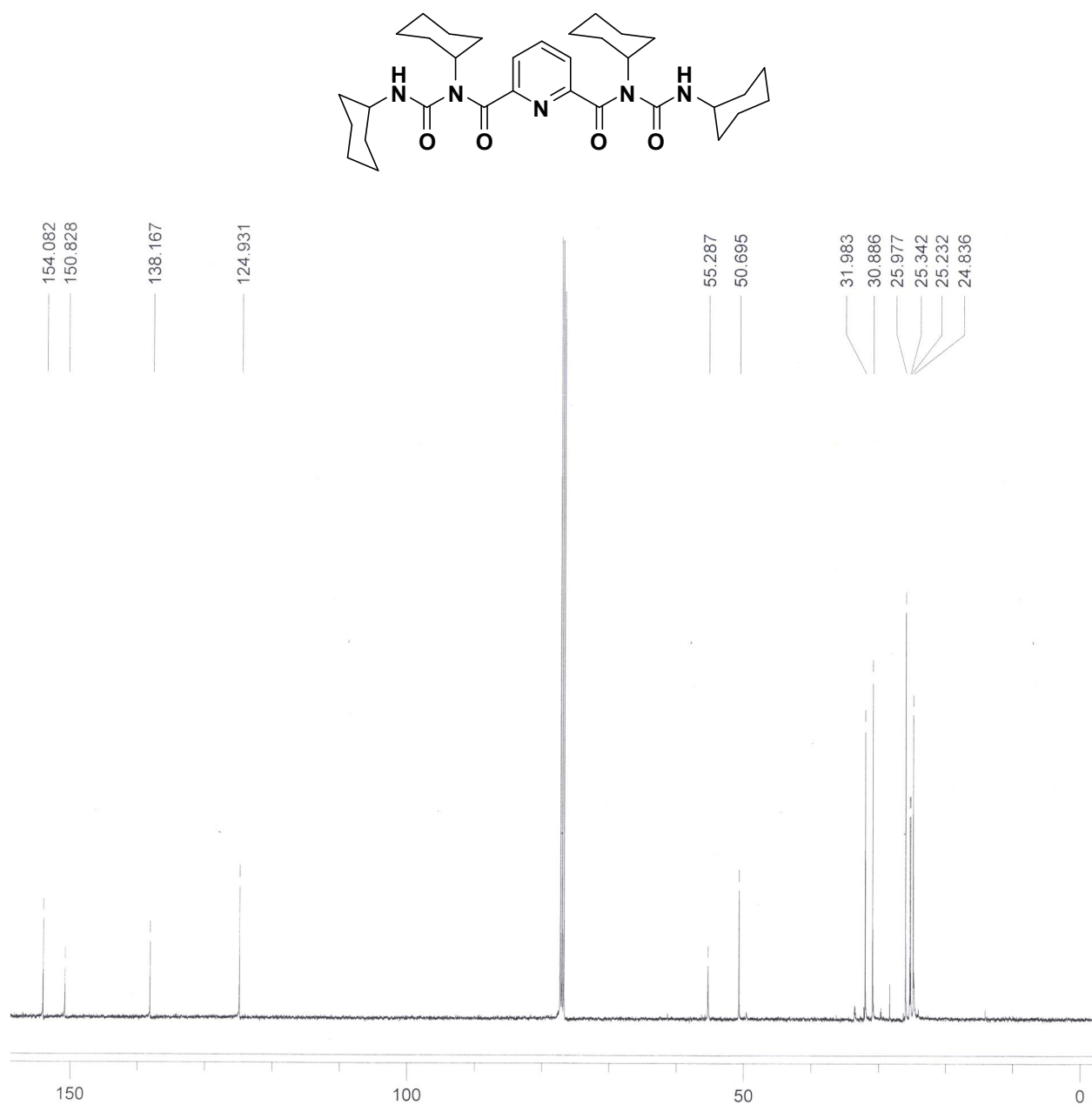


Fig. S3: ^{13}C NMR (125 MHz, CDCl_3 , δppm) spectrum of compound **1**.

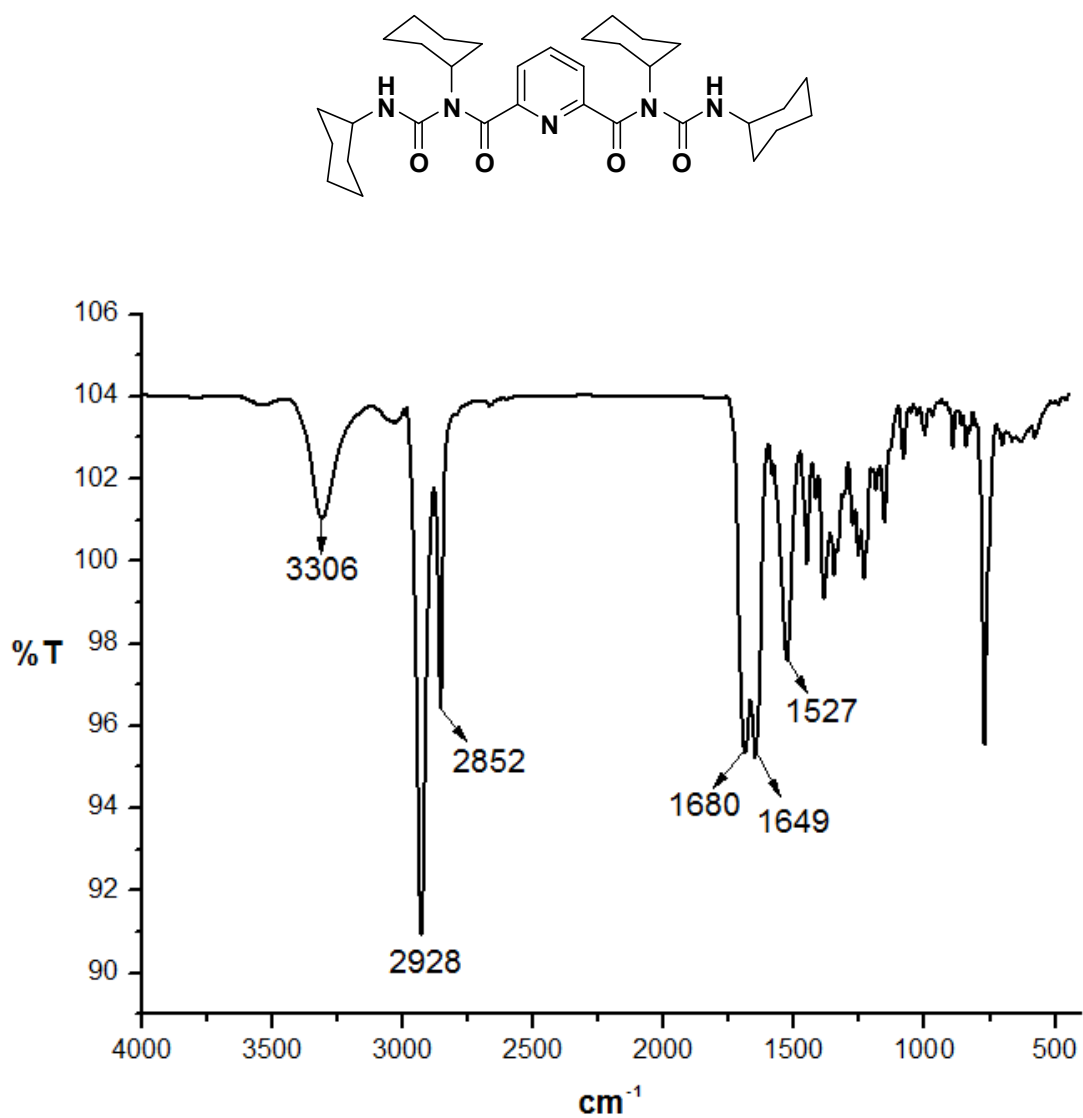


Fig. S4: FTIR spectrum of compound 1.

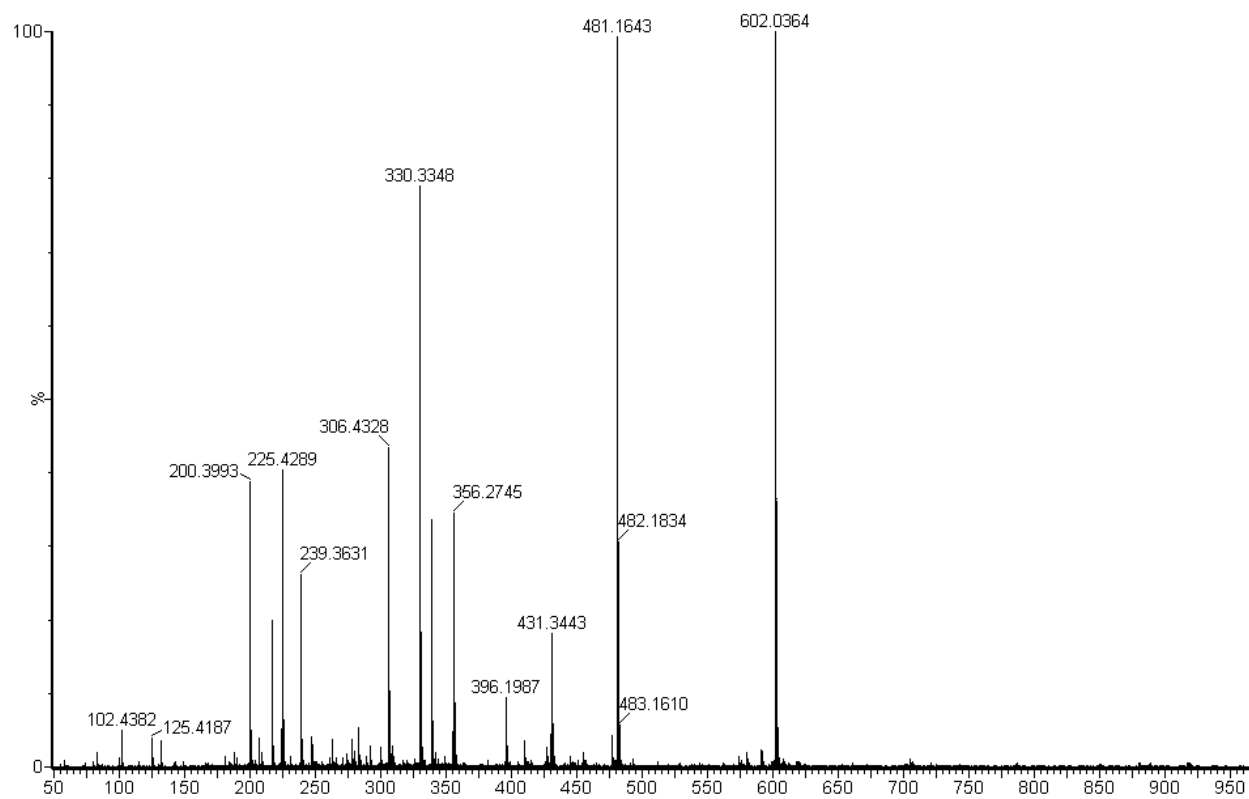
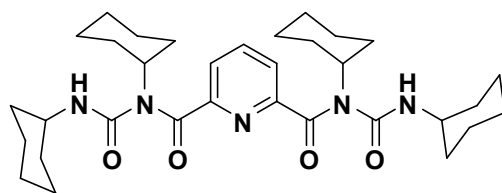


Fig. S5: Mass spectrum of compound 1.

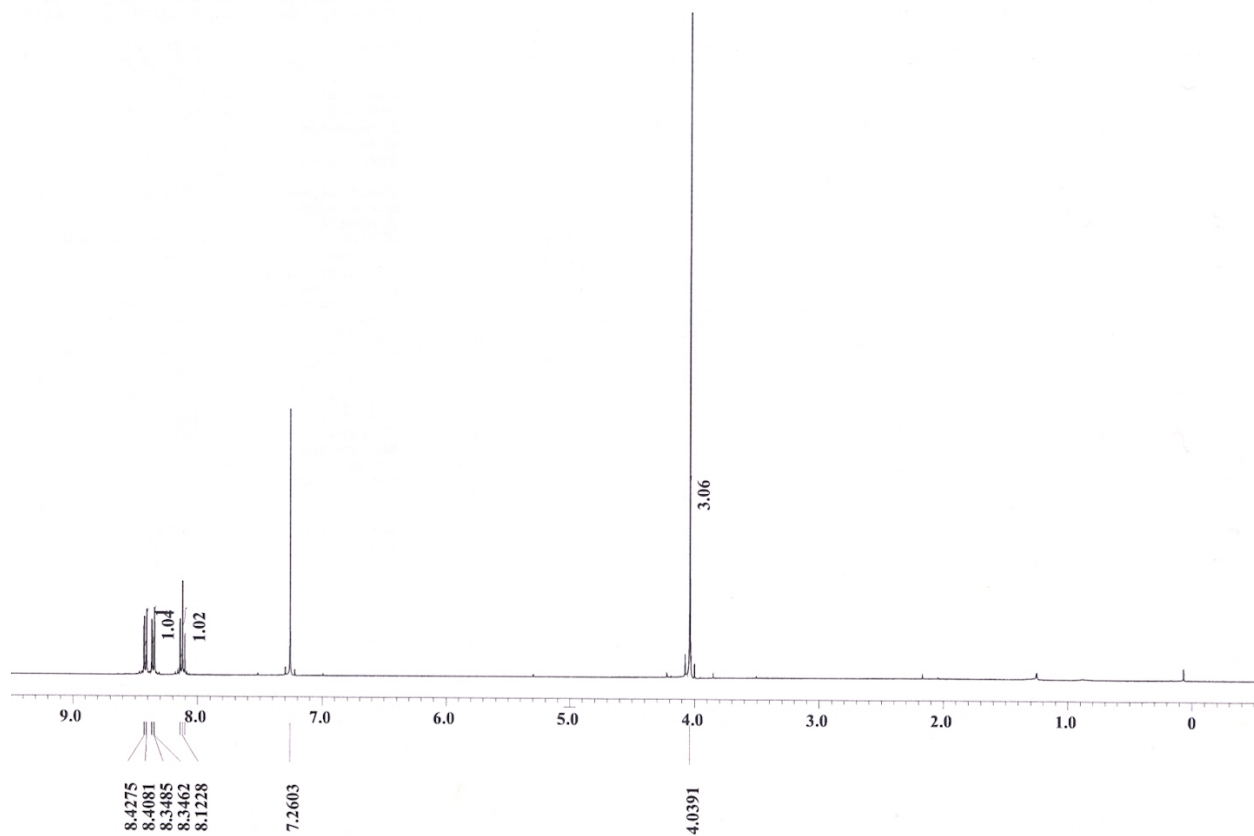
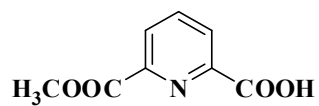


Fig. S6. ^1H NMR (400 MHz, CDCl_3) spectrum of 6-(Methoxycarbonyl)pyridine-2-carboxylic acid **6**.

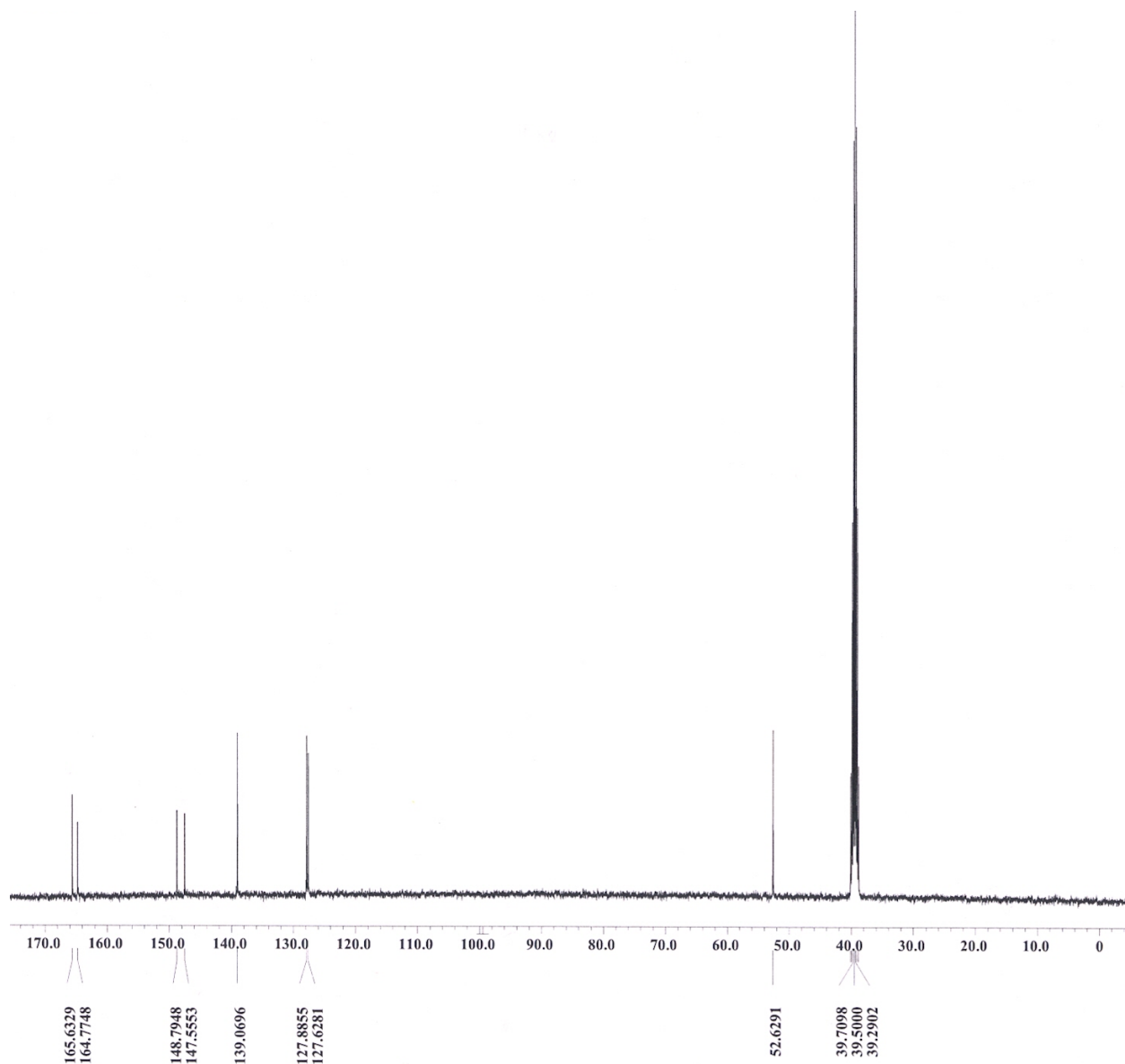
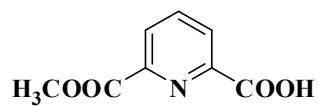


Fig. S7. ^{13}C NMR (100 MHz, CDCl_3) spectrum of 6-(Methoxycarbonyl)pyridine-2-carboxylic acid **6**.

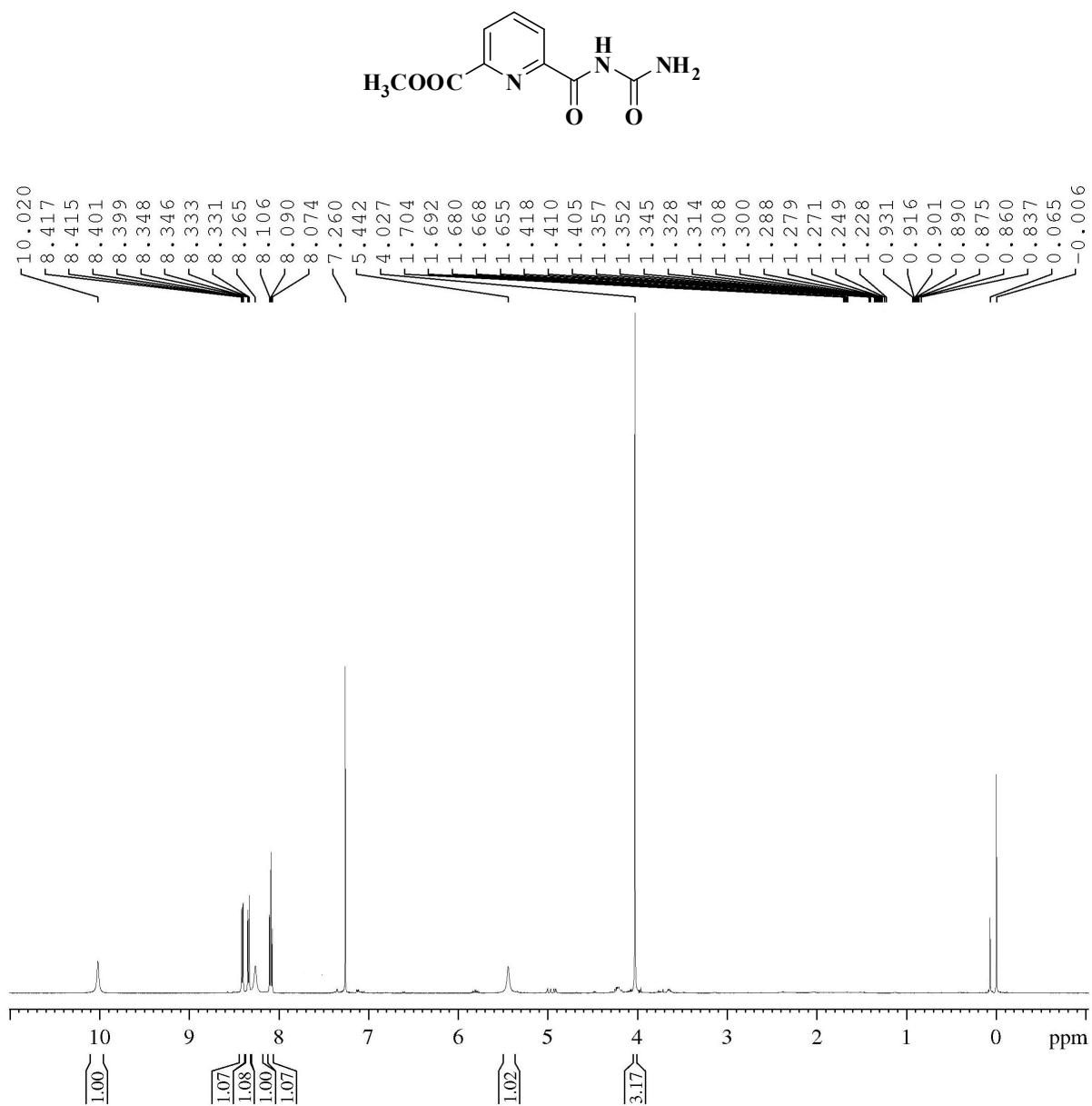


Fig. S8. ¹H NMR (500 MHz, CDCl₃) spectrum of the reported compound **2**.

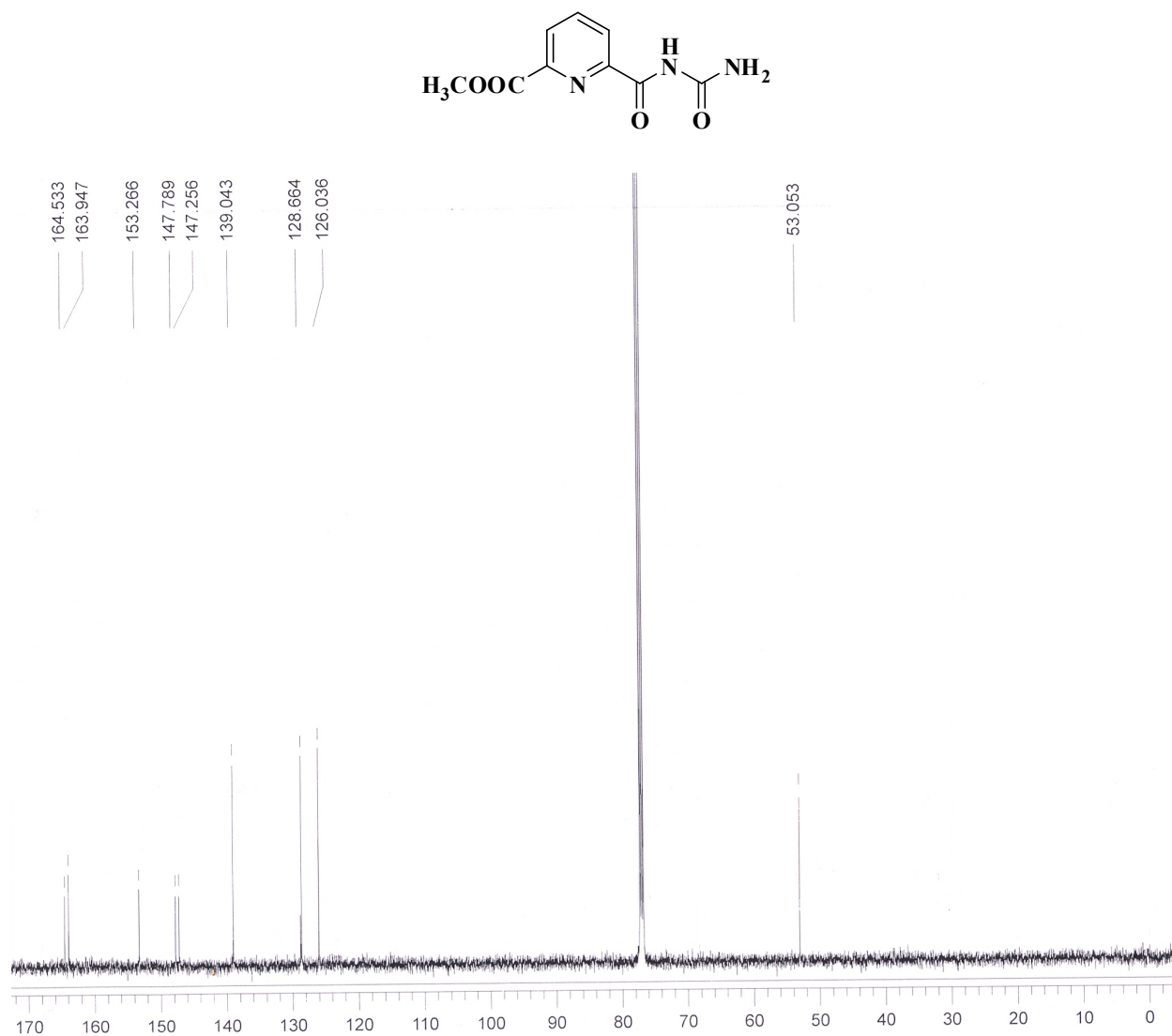


Fig. S9. ^{13}C NMR (125 MHz, CDCl_3) spectrum of the reported compound 2.

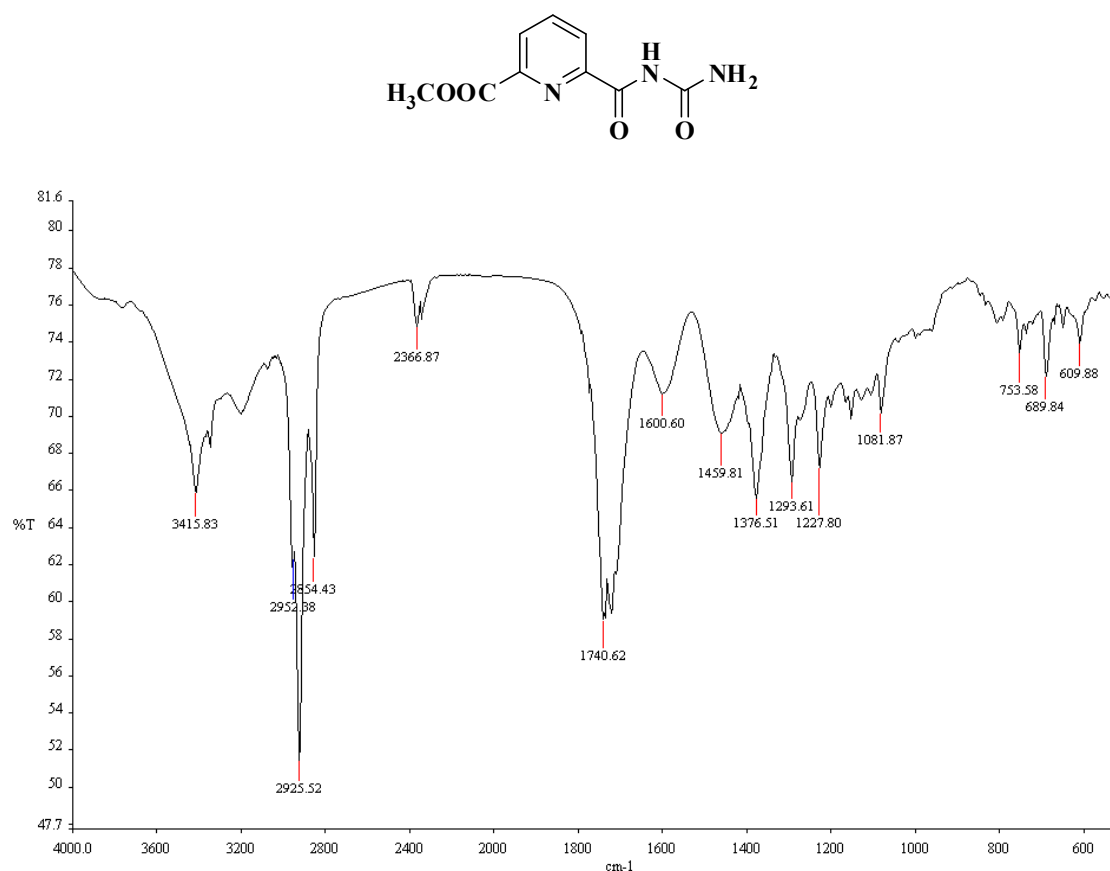


Fig. S10: FTIR spectrum of compound 2.

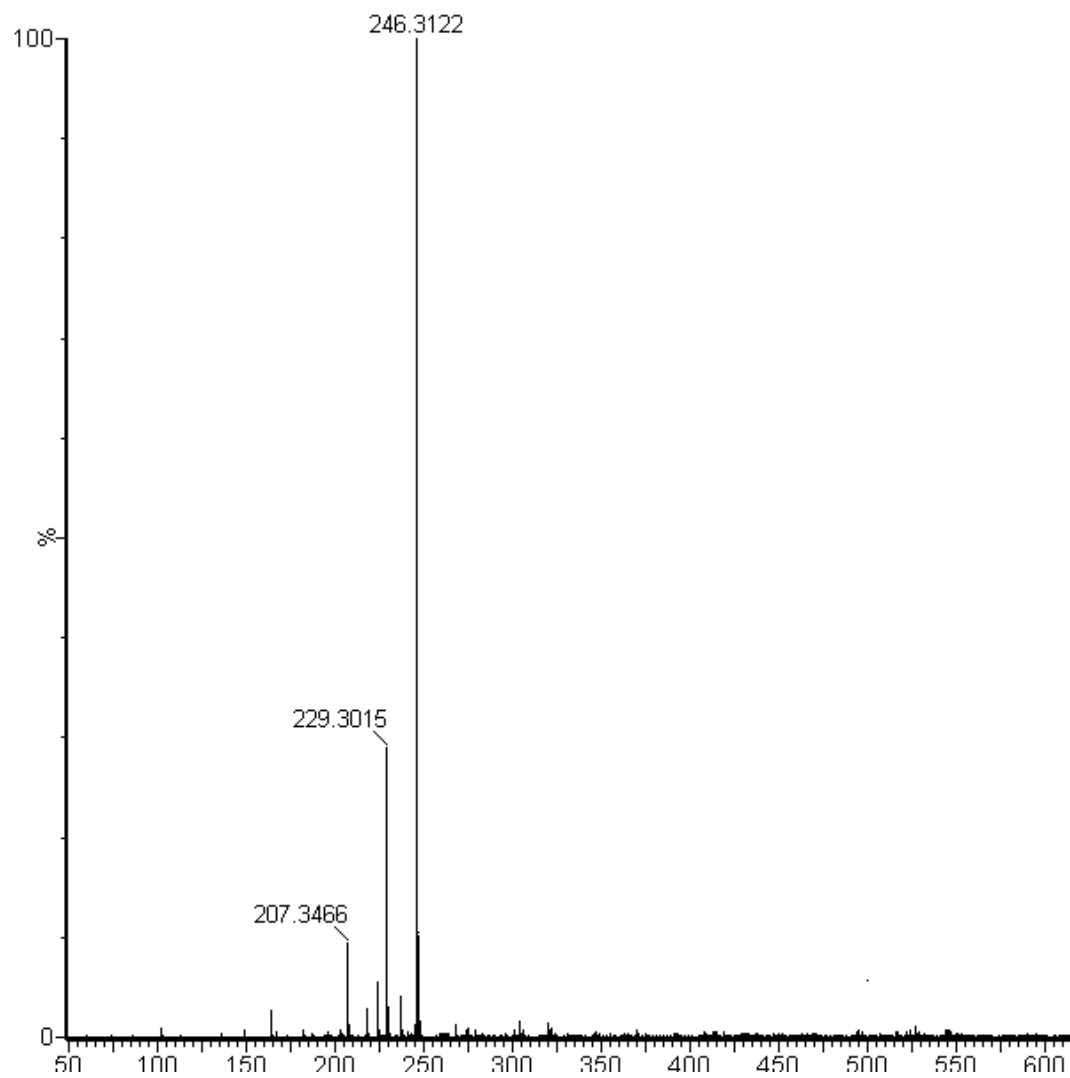
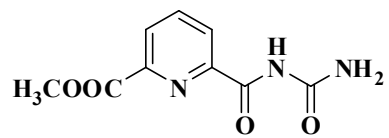


Fig. S11. Mass spectrum of the reported compound 2.

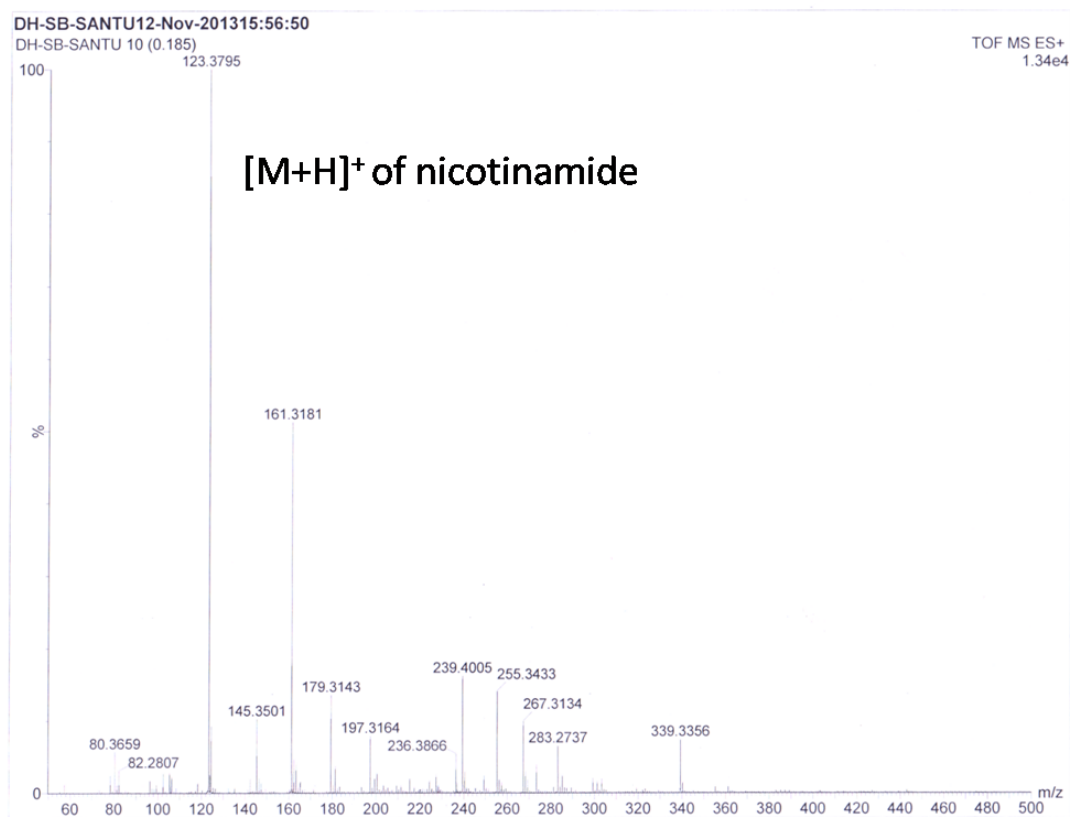


Fig. S12. Mass spectrum of the released material after 3h that confirms nicotinamide release.

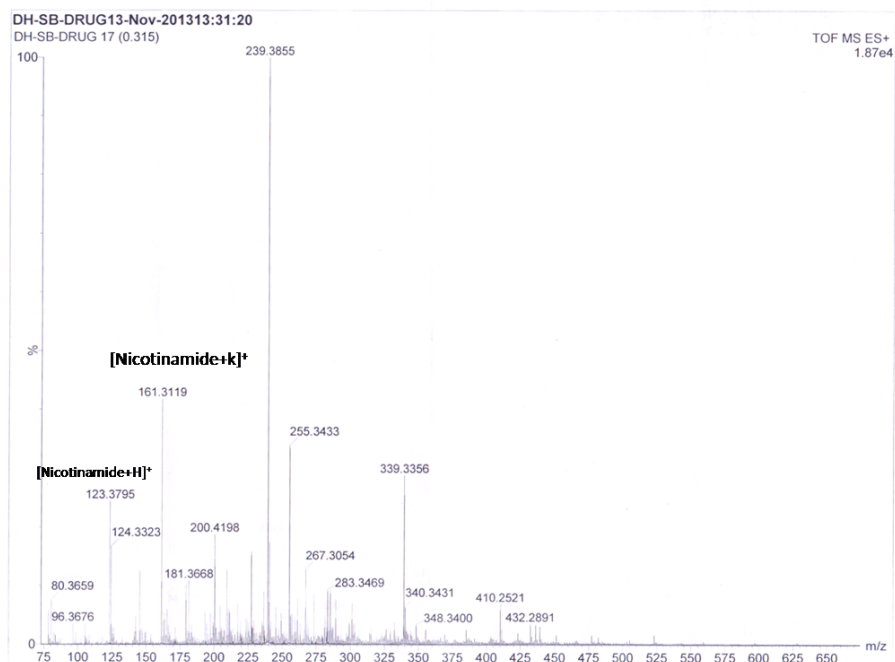


Fig. S13 Mass spectrum of the released material after 24h that confirms nicotinamide release.

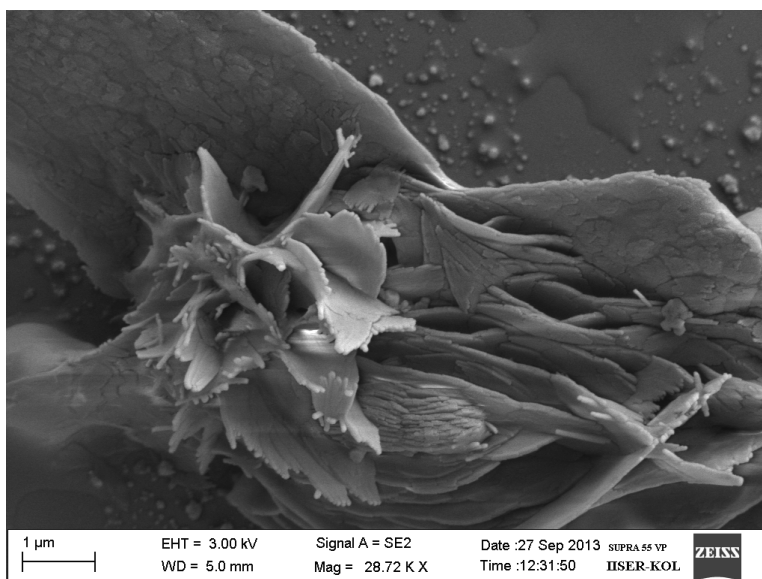
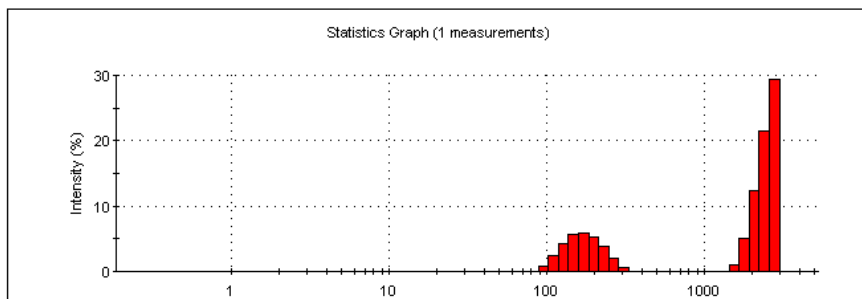


Fig. S14 FE-SEM image of the disrupted drug loaded microspheres when treated with 10 mM H_2O_2 for 22 hours. High concentration of H_2O_2 may have changed the assembly pattern of the reported compound.

Z-Average (nm): 1931.97 **Derived Count Rate (kcps):** 423473.670750...
Standard Deviation: 0 **Standard Deviation:** 0
%Std Deviation: 0 **%Std Deviation:** 0
Variance: 0 **Variance:** 0

Size r.nm	Mean Intensity %	Std Dev Intensity %	Size r.nm	Mean Intensity %	Std Dev Intensity %	Size r.nm	Mean Intensity %	Std Dev Intensity %	Size r.nm	Mean Intensity %	Std Dev Intensity %
0.2000	0.0		2.807	0.0		39.41	0.0		553.2	0.0	
0.2316	0.0		3.251	0.0		45.64	0.0		640.7	0.0	
0.2682	0.0		3.765	0.0		52.85	0.0		741.9	0.0	
0.3106	0.0		4.360	0.0		61.21	0.0		859.2	0.0	
0.3597	0.0		5.050	0.0		70.89	0.0		995.1	0.0	
0.4166	0.0		5.848	0.0		82.09	0.0		1152	0.0	
0.4825	0.0		6.772	0.0		95.07	0.8		1335	0.0	
0.5587	0.0		7.843	0.0		110.1	2.4		1545	0.9	
0.6470	0.0		9.083	0.0		127.5	4.2		1790	5.1	
0.7493	0.0		10.52	0.0		147.7	5.6		2073	12.4	
0.8678	0.0		12.18	0.0		171.0	6.0		2400	21.4	
1.005	0.0		14.11	0.0		198.0	5.3		2780	29.4	
1.164	0.0		16.34	0.0		229.3	3.8		3219	0.0	
1.348	0.0		18.92	0.0		265.6	2.0		3728	0.0	
1.561	0.0		21.91	0.0		307.6	0.6		4317	0.0	
1.808	0.0		25.37	0.0		356.2	0.0		5000	0.0	
2.093	0.0		29.39	0.0		412.5	0.0				
2.424	0.0		34.03	0.0		477.7	0.0				



File Name: DIDCU.dts **Dispersant Name:** Methanol
Record Number: 10 **Dispersant RI:** 1.326
Material RI: 1.59 **Viscosity (cP):** 0.5476
Material Absorption: 0.01 **Measurement Date and Time:** Friday, November 02, 2012 4:36:50...

Temperature (°C): 25.0 **Duration Used (s):** 100
Count Rate (kcps): 254.3 **Measurement Position (mm):** 4.65
Cell Description: Glass cuvette with round aperture **Attenuator:** 10

Z-Average (r.nm): 966.0 **Peak 1:** 2446 69.2 339.7
Pdl: 1.000 **Peak 2:** 174.7 30.8 48.06
Intercept: 0.133 **Peak 3:** 0.000 0.0 0.000

Result quality : Refer to quality report

