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Supporting Information

Hybrid Sequences that Express both Aromatic Amide and α-Peptidic Folding Features

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S1 Crystallization and X-ray diffraction measurements

S1.1 Crystallization and X-ray diffraction measurements of **2**

A stock solution of **2** was prepared by dissolving the lyophilized powder in a12.5mM solution of ammonium acetate (pH 9.0)to reach a concentration of 2.5mM. Crystallization trials were performed using standard aqueous sitting-drop vapor diffusion method in Crystal Quick Plus 96-well polystyrene microplates, at 293 K. Screening of crystallization conditions was carried out using commercial sparse-matrix screens JB Screen Basic and Nuc-Pro from Jena Bioscience. Nucleation within 24 hours was observed in drops composed of 1.0µL of **2** and 1.0µL of the crystallization reagent Nuc-Pro2 C7, i.e. 30% w/v polyethylene glycol 4000, 50mM TRIS buffer (pH 8.5), 150mM ammonium chloride, 10mM calcium chloride. The drops were equilibrated against 50µL of the crystallization reagent in reservoir. X-ray quality crystallogenesis was optimized by using the hanging drop vapor diffusion method in EasyXtal 15-well plates at 293 K. The initial drop contained 0.5µL of **2** and 1.5µL of the crystallization reagent. The drop was equilibrated against 500µL of the crystallization reagent in reservoir. X-ray quality crystals appeared in 5 days.

A single crystal was fished using MiTeGen microloops and plunged directly into liquid nitrogen such that the mother liquor served as cryoprotectant. The low temperature X-ray diffraction data were collected at the ID30b beamline[1] in European Synchrotron Radiation facility, Grenoble with a Dectris Pilatus 6M detector. Diffraction data were measured at T = 100 K and λ = 0.8000 Å. The crystal was exposed for 0.02 s and 0.05° oscillation per frame. Diffraction data was processed using the program *XDS*.[2]The crystal belonged to the space group $P2_12_12_1$ with unit cell parameters: a = 20.125 (4) Å, b = 27.206 (5) Å and c = 50.260 (1) Å; V = 27518 (10) and 2 molecules per asymmetric unit (Z = 8).

S1.2 Crystallization and X-ray diffraction measurements of **3**

X-ray quality crystals of compound **3** was obtained by slow diffusion of CH_3CN into a dichloromethane solution of **3** in standard NMR tubes. A single crystal was quickly soaked in Paratone-N oil from Hampton Research and measured at the IECB X-ray facility (UMS3033) using a 3kW microfocus Rigaku FRX rotating anode (Cu Kα wavelength) and a hybrid Dectris Pilatus 200K detector. The diffraction data were processed with the program *CrystalClear*.[3]The crystal also belonged to the space group $P2_12_12_1$ with unit cell parameters: a = 25.701 (4) Å, b = 34.146 (6) Å and c = 35.576 (6) Å; V = 31220 (9) and 2 molecules per asymmetric unit (Z = 8).

S1.3 Structure determination and refinement of **2** and **3**

The structures of **2** and **3** were solved with the program *SHELXD*[4] and refinedby full-matrix least-squares method on F^2 with *SHELXL-2014*[5] within *Olex2*.[6] After each refinement step, visual inspection of the model and the electron-density maps were carried out using *Olex2* and *Coot*.[7]AFIX, DFIX and FLAT instructions were used to improve the geometry of molecules. Restraints on anisotropic displacement parameters were implemented with DELU, SIMU, RIGU and ISOR instructions. After several attempts to model the disordered side chains, *SQUEEZE* procedure was used to flatten the electron density map.[8] Very disordered solvent molecules were removed. Hydrogen atoms were placed at idealized positions except for those at disordered/missing side chains.

Table S1: Crystallographic data and refinement statistics for **2** and **3**.

Foldamers	**2**	**3**
Formula	$C_{129.3}H_{95.5}Ca_{0.4}N_{19}O_{33.1}$	$C_{251}H_{265}Cl_2N_{38}O_{51}$
M	2459.62	4700.89
Crystal system	Orthorhombic	Orthorhombic
Z, Z’	8, 2	8, 2
Space group	$P2_12_12_1$	$P2_12_12_1$
a/Å	20.125 (4)	25.701 (4)
b/Å	27.206 (5)	34.146 (6)
c/Å	50.260 (1)	35.576 (6)
V/Å^3	27518 (10)	31220 (9)
T/K	100	130
ρ/gcm^{-3}	1.187	1.000
Color and shape	Pale yellow, prism	Clear yellowish, prism
Size (mm)	0.15 x 0.05 x 0.03	0.1 x 0.1 x 0.1mm
λ/Å	0.8000	1.5417
μ/mm^{-1}	0.130	0.734
Collected reflections	74766	63844
unique data [*Fo>2σFo*)]	37585	25221
R_{int} %	0.0367	0.0736
Parameters/restraints	2407/1311	3121/883
R_1, wR_2 *(I > 2σ(I))*	0.1525, 0.4040	0.0635, 0.1386
R_1, wR_2 *(all data)*	0.1596, 0.4195	0.1209, 0.1714
Largest diff. Peak/hole e/Å^3	0.65/-0.57	0.26/-0.20
Goodness of fit	1.960	1.006
Total potential solvent accessible void volume from SQUEEZE Å^3	6091.0	10248.4
Electron count/cell	3673	2906
CCDC number	2002649	2002410

S1.4 CheckCIF validation

IUCr's checkcif algorithm detected a number of A- and B-level alerts which are listed below and have been divided into two groups. They are inherent to the data and refinement procedure of large foldamer crystal structures and do not reflect errors. Crystals of **2** and **3** were observed to have large volume fractions of disordered solvent molecules, weak diffraction intensity, and incompleteness of the data, moderate to low resolution. They illustrate the limited practicality of the checkciftool for medium sized molecule crystallography.

Checkcif validation of **2**

Group 1 (alerts illustrate weak quality of the data and refinement statistics if compare to that expected for small molecule structures from highly diffracting crystals):

THETM01_ALERT_3_B The value of sine(theta_max)/wavelength is less than 0.575

Calculated sin(theta_max) = 0.5618

PLAT029_ALERT_3_B_diffrn_measured fraction_theta_full value Low 0.953 Why?

PLAT084_ALERT_3_BHigh wR2 Value (i.e. > 0.25) ……. 0.42 Report

PLAT241 ALERT_2_B High 'MainMol' Ueq as Compared to Neighbors

PLAT242 ALERT_2_B Low 'MainMol' Ueq as Compared to Neighbors

Group 2 alerts are connected with decision made during refinement and explained below:

PLAT410 ALERT_2_ Short intra H… H contact

This alert is due to the disorder in the *N*-terminal diethylene-glycol-derived chain

PLAT413 ALERT_2_ Short interXH3… XHn contact

This alert is due to the disorder in the *N*-terminal diethylene-glycol-derived chain

PLAT430 ALERT_2_ Short interD… A contact

This alert is due to the disorder in side chains

Checkcif validation of **3**

Group 1

THETM01_ALERT_3_B The value of sine(theta_max)/wavelength is less than 0.550

Calculated sin(theta_max) = 0.4673

PLAT089 ALERT_3_B Poor Data / Parameter Ratio (Zmax < 18) …… 4.52 Note

PLAT220 ALERT_2_B NonSolvent Resd 1 C ueq (max)/Ueq (min) Range 8.9 Ratio

PLAT242 ALERT_2_B Low ’MainMol’ Ueq as Compared to Neighbors
PLAT369 ALERT_2_B Long C(sp2)-C(sp2) Bond
PLAT375 ALERT_2_B Strange C-O-H geometry (C-O > 1.45 Ang)…. O054 Check

Group 2

PLAT213 ALERT_2_ Atom … has ADP max/min Ratio …. Oblate/Prolate

This alert is due to disorder in side chain atoms

PLAT412 ALERT_2_ Short intraXH3… XHn contact Check
This alert is due to the disorder in side chain atoms
PLAT416 ALERT_2_ Short intraD-H… H-D contact Check
This alert is due to the disorder in side chain atoms
PLAT417 ALERT_2_ Short interD-H… H-D contact Check
This alert is due to the disorder in side chain atoms
PLAT420 ALERT_2_ D-H Without acceptor O114 –H114 Check
This alert is due to the disorder in side chain atoms
PLAT430 ALERT_2_ Short interD… A contact Check
This alert is due to the disorder in side chains

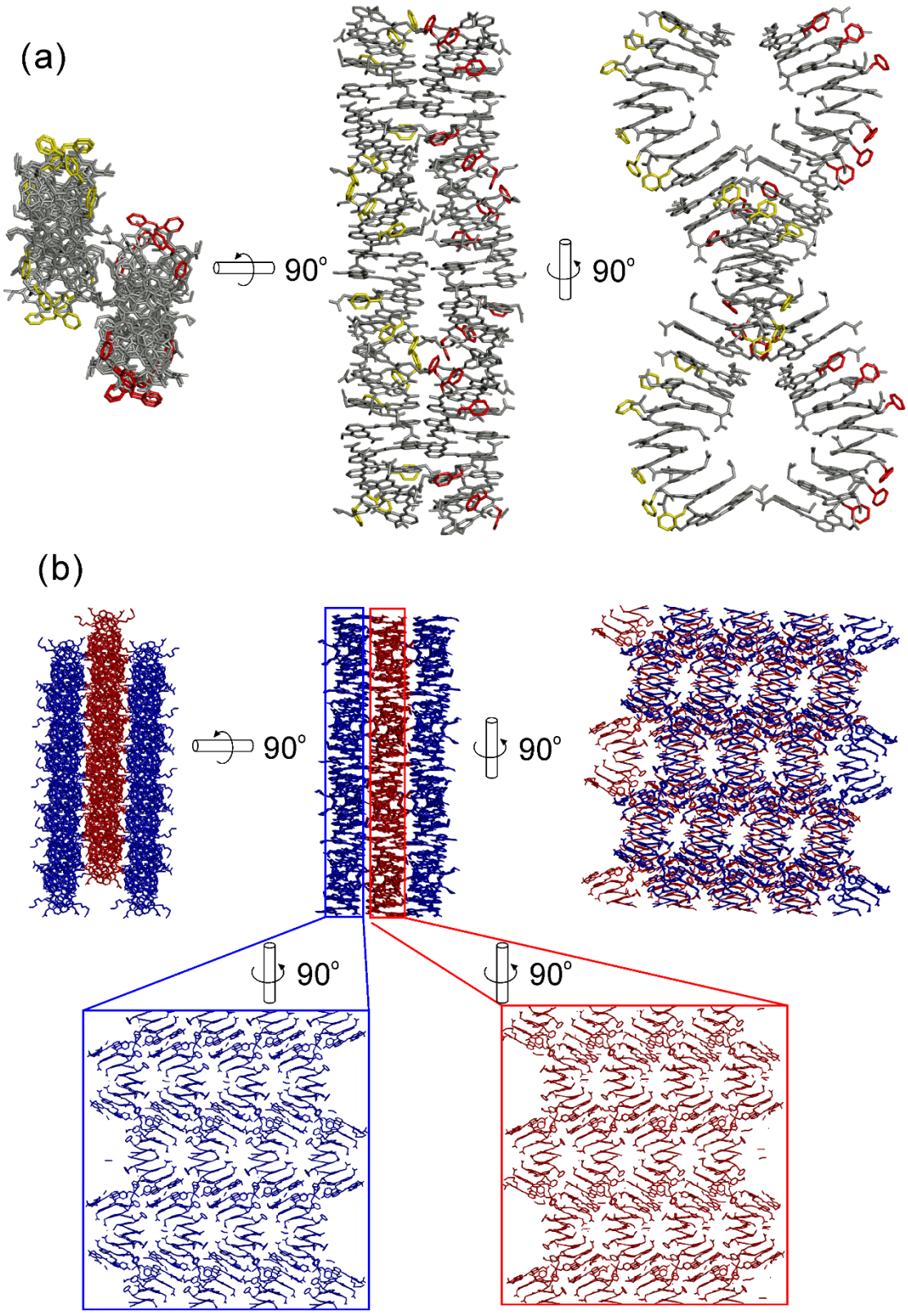


Figure S1. Crystal packing of **2**.(a) Phenylalanine side chains are highlighted in golden or red in different strands. (b) Undulating helices pack in three planes.

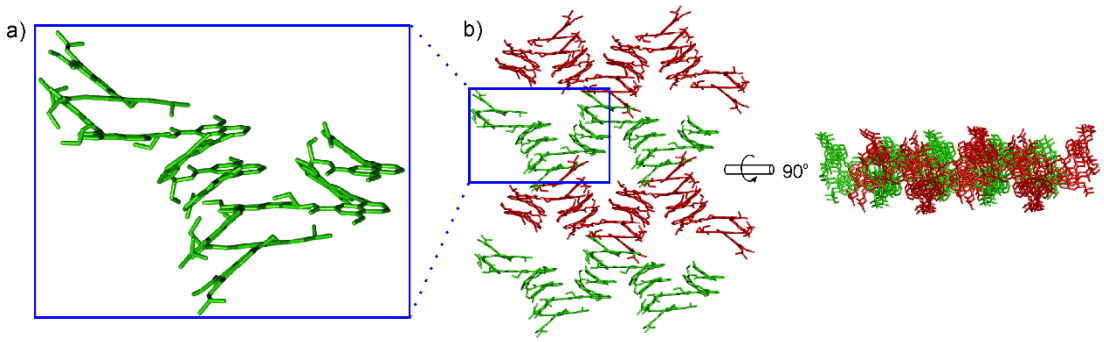


Figure S2. a) Shows that two molecules have contacts at their *N*-terminal cross section (from one molecule) and a quinoline adjacent to the turn (from the other molecule). b) Crystal packing of **3**.

Table S2. Complete table ofϕ and ψ dihedral angles of α-amino acid residues of foldamers**2** and **3**.

Foldamer **2**	Phe3[a]	Phe6[a]	Phe9[a]
ϕ_1	61.1	72.6	69.1
ϕ_2	67.5	71.9	61.8
ϕ (average)	64.3	72.3	65.5
ψ_1	29.8	16.3	22.3
ψ_2	18.1	18.1	25.4
ψ (average)	24.0	17.2	23.9
Foldamer3	Ser3[a]	Ser6[a]	Ser9[a]
ϕ_1	-142.1	-167.2	-149.4
ϕ_2	-136.0	-155.5	-143.1
ϕ (average)	-139.1	-161.4	-146.3
ψ_1	25.4	-171.6	7.4
ψ_2	10.8	-169.7	2.0
ψ (average)	18.1	-170.7	4.7

[a]The numbering of α-amino acid residues is done from N- to C-terminus. There are two sets of dihedral angle value and the averaged ϕ and ψ values are used in this paper.

S2 CD spectra

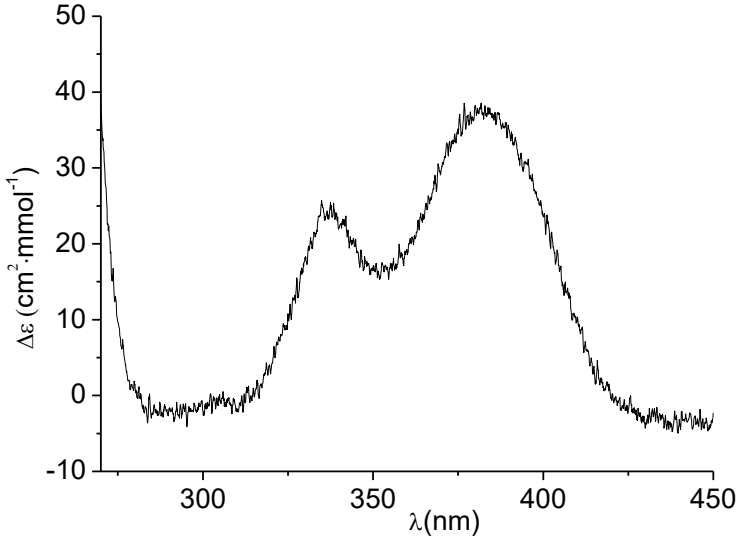


Figure S3. CD spectrum of **2** in H_2O (containing 12.5 mM solution of ammonium acetate, pH = 8.5) at 25 ºC. Concentration of **2**: 50 μM.

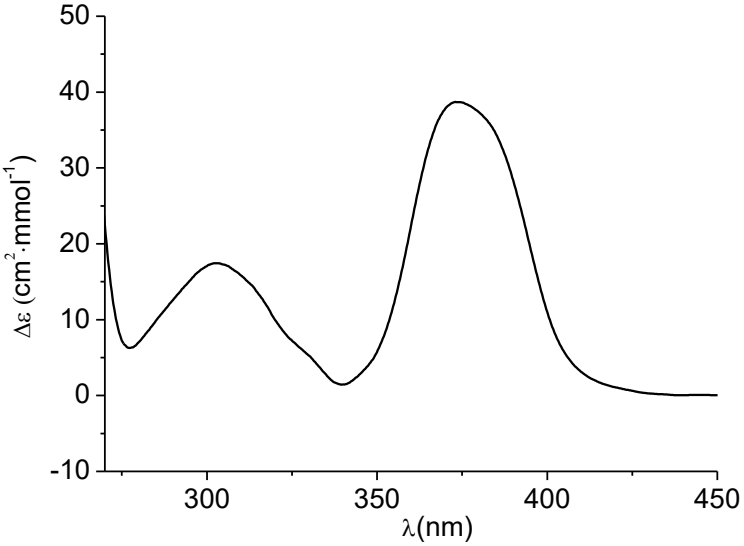
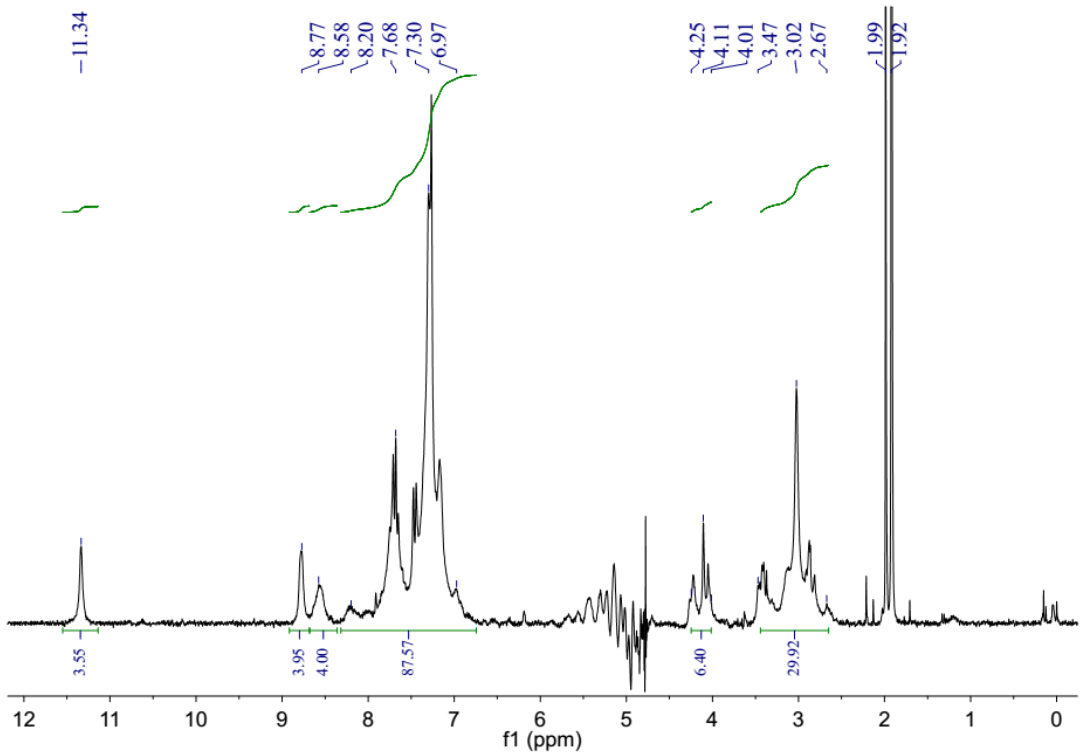


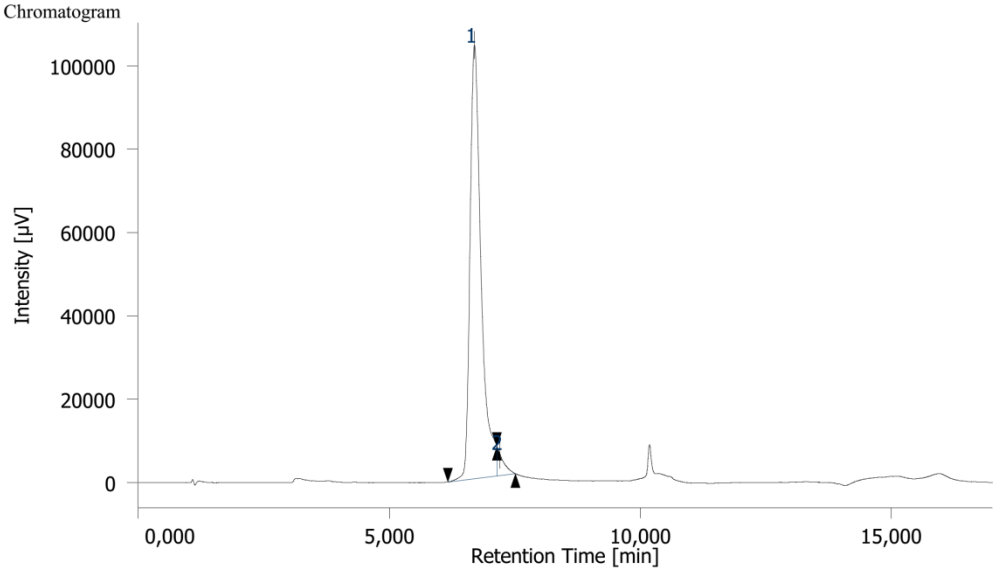
Figure S4. CD spectrum of **3** in $CHCl_3$ at 25 ºC. Concentration of **3**: 50 μM.

S3 [1]HNMR spectra, RP-HPLC chromatograms and high-resolution ESI-TOF mass spectra

Compound 2: ^{1}H NMR (300 MHz, 9:1D_2O/H_2O vol/vol)



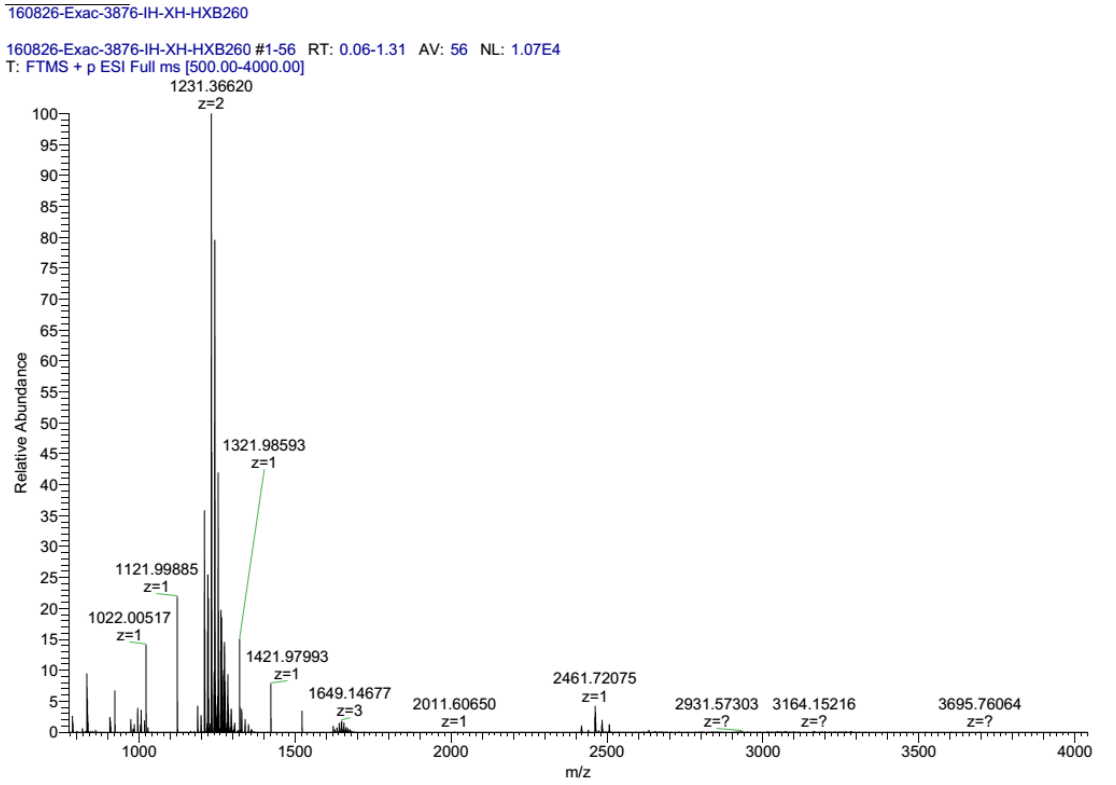
Compound 2: RP-HPLC

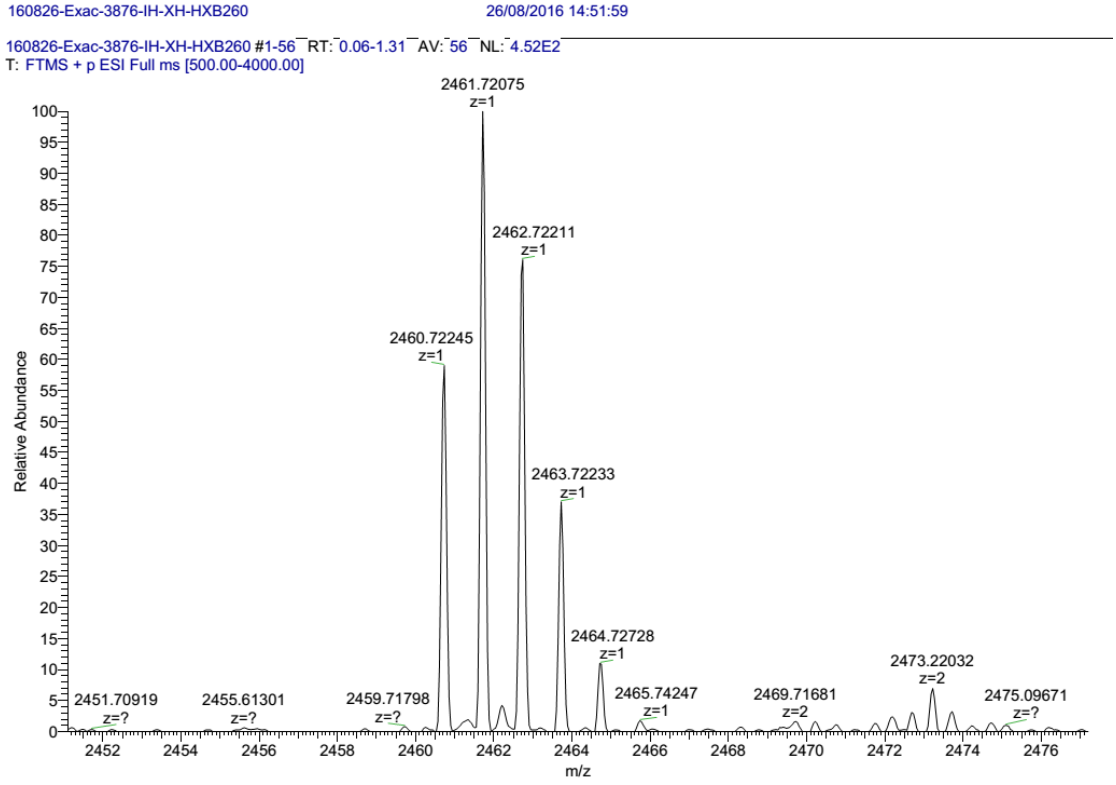


Peak Information

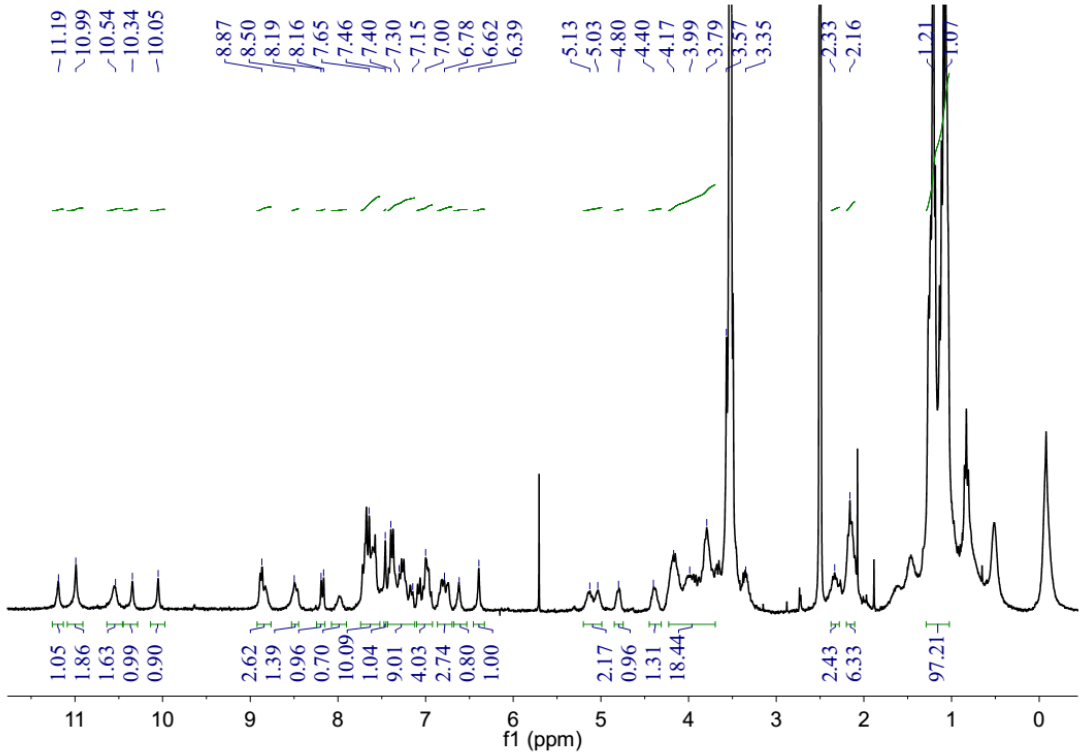
#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	3	6,692	1597480	104026	96,580	95,346	N/A	5096	N/A	N/A	
2	Unknown	3	7,200	56574	5077	3,420	4,654	N/A	N/A	N/A	N/A	

Compound 2: high-resolution ESI-TOF mass spectra

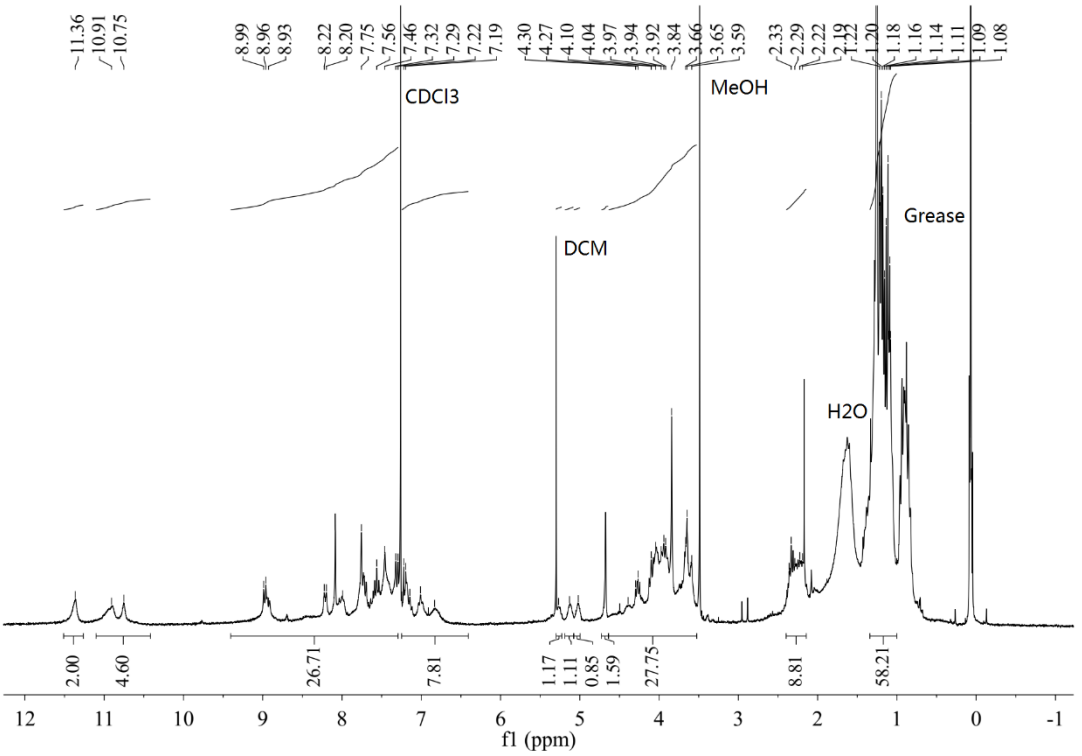




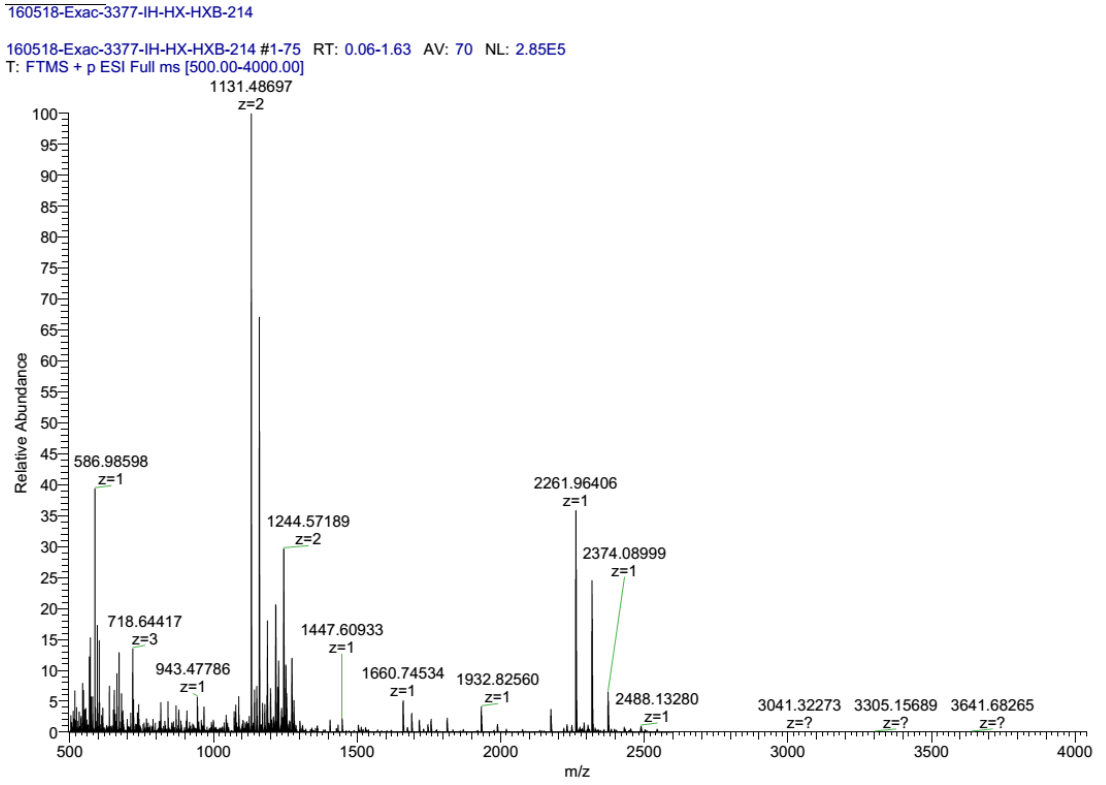
Compound 3: ^{1}H NMR (300 MHz, DMSO-d_6)

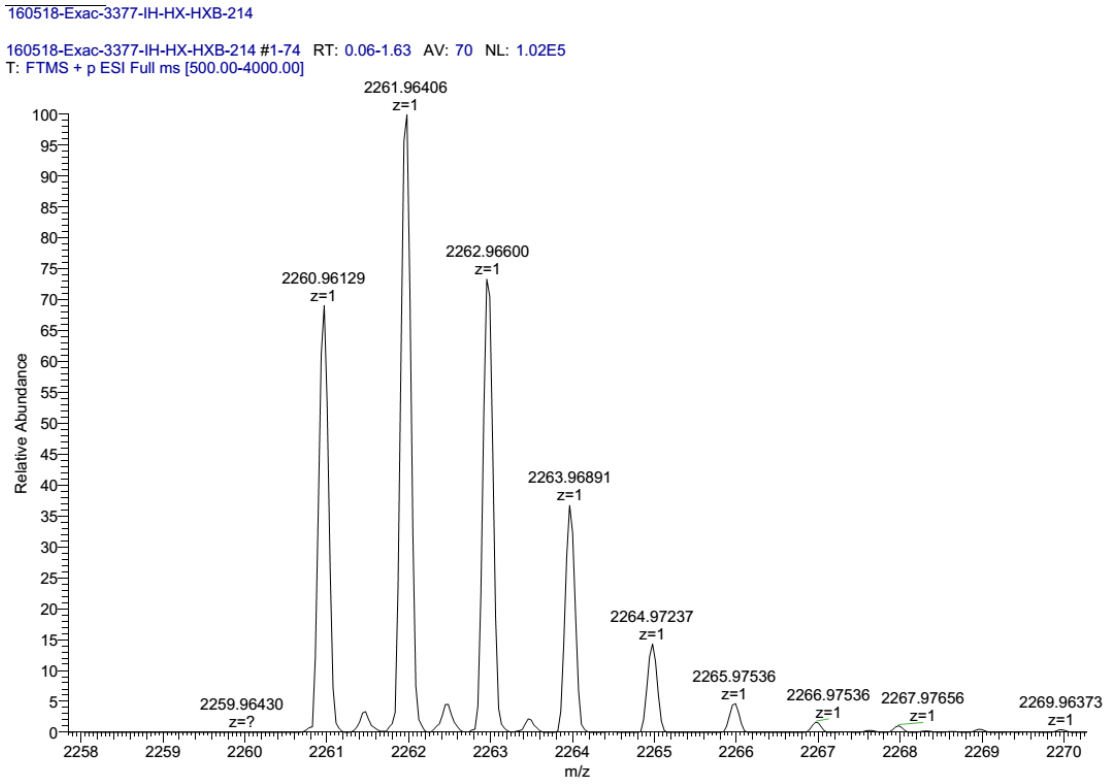


^{1}H NMR (300 MHz, $CDCl_3$)



Compound 3: high-resolution ESI-TOF mass spectra





S4 References:

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