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Redox-controlled hybridization of helical foldamers

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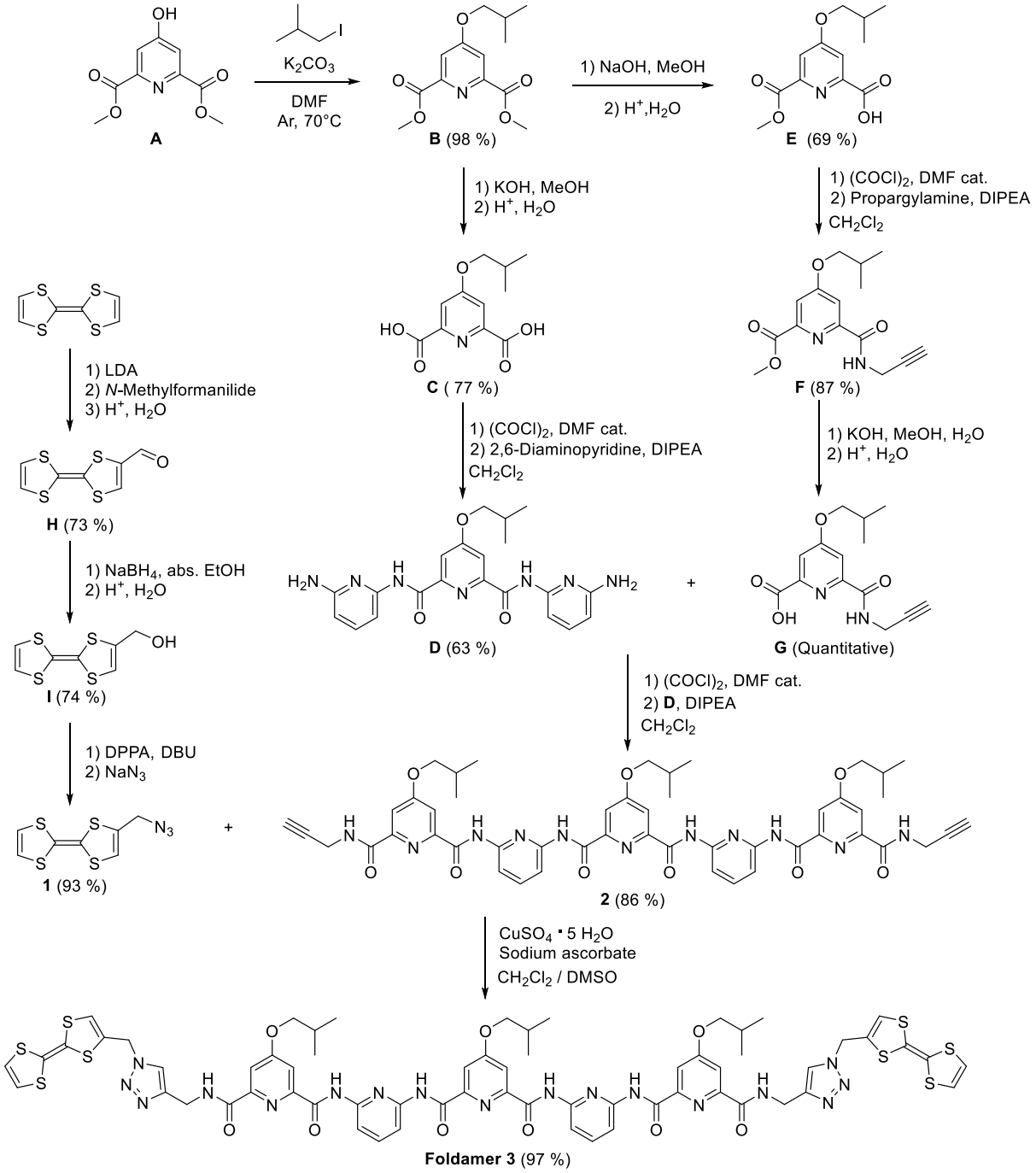
Supporting information



Scheme S1. Synthetic route followed to prepare foldamer **3**.

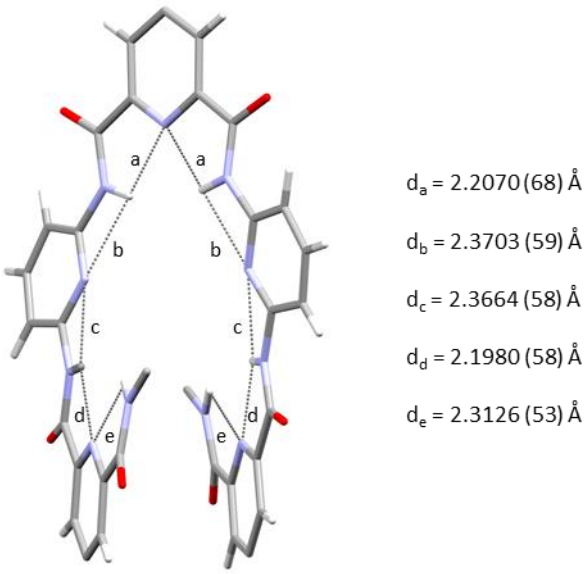


Figure S1. Partial X-ray crystal structure of foldamer **3** and intramolecular hydrogen bonds. Crystals grown by slow diffusion of methanol into a dichloromethane solution of **3**.

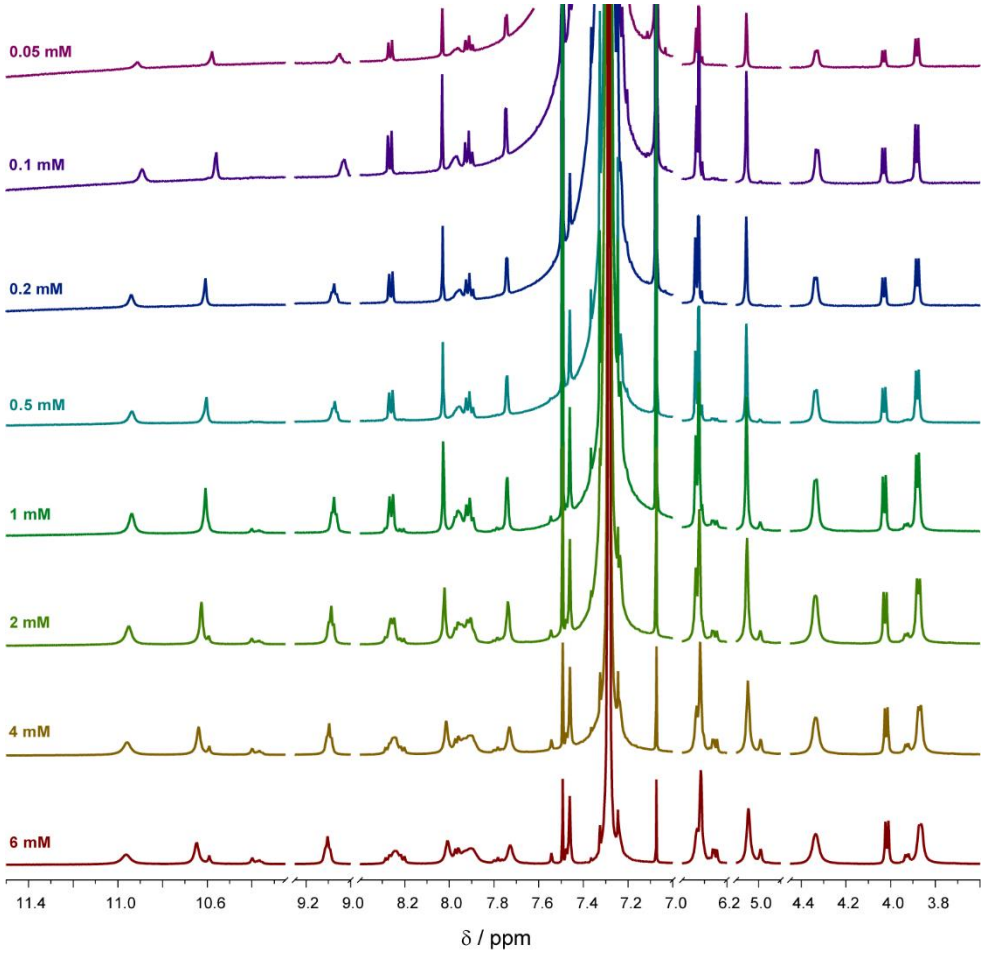


Figure S2. Variable-concentration ^{1}H NMR experiments ($CDCl_3$, 273 K, 500 MHz).

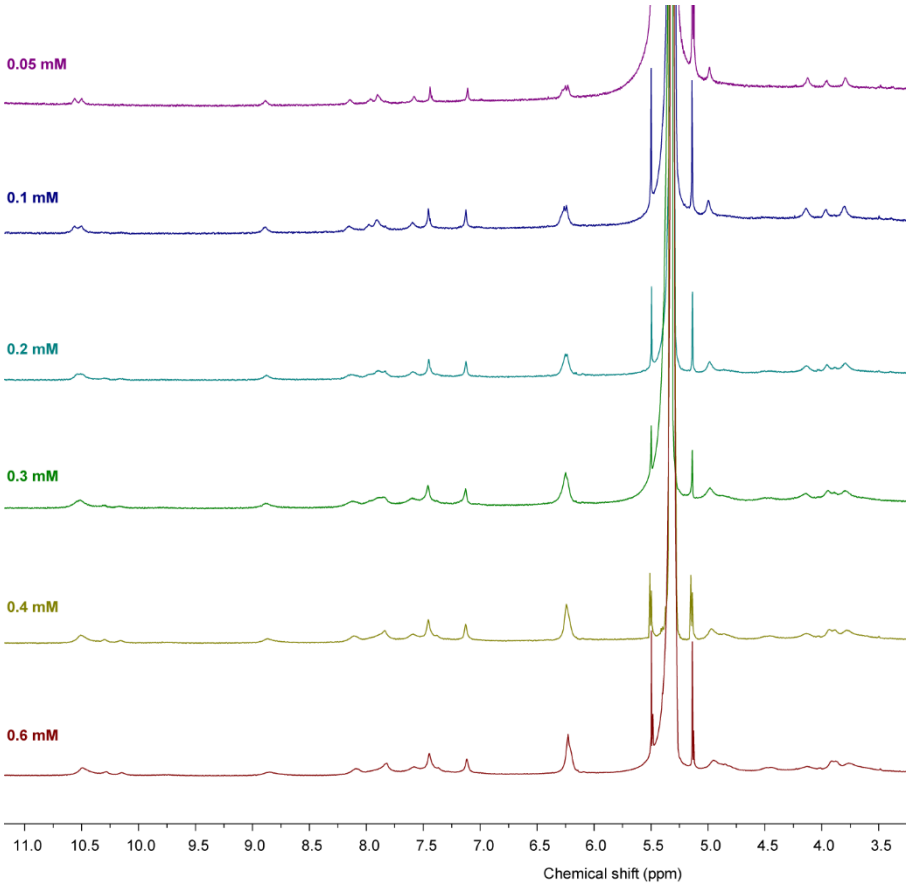


Figure S3. Variable-concentration ^{1}H NMR experiments (solvent: CD_2Cl_2/CD_3CN (1/1) (*v/v*), 273 K, 500 MHz).

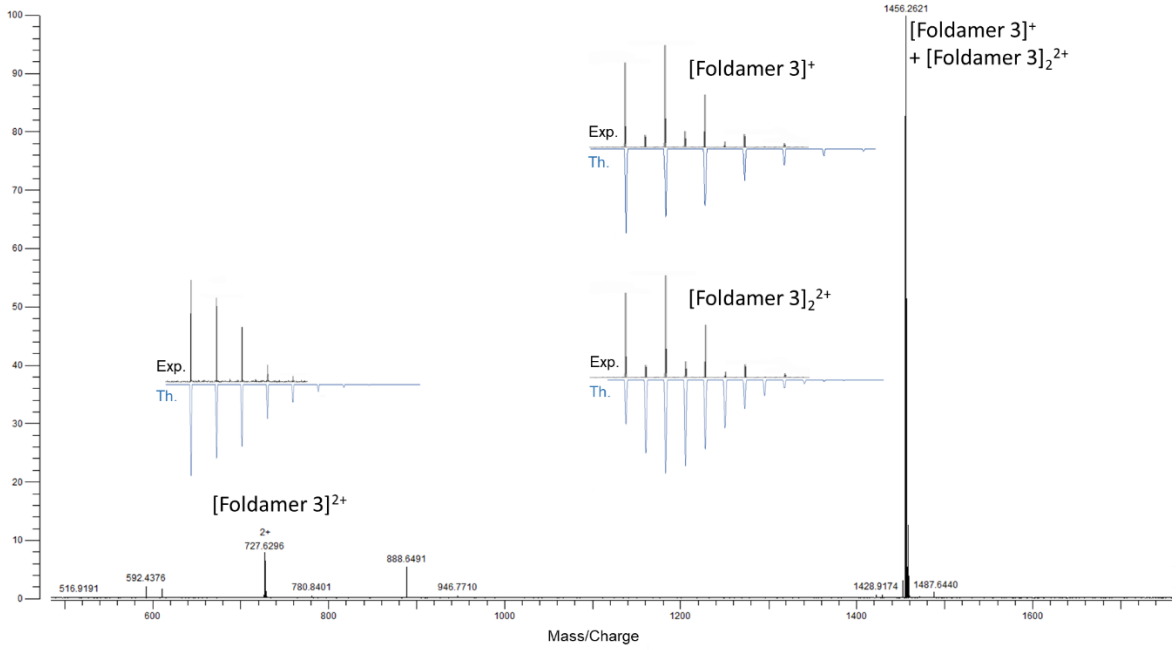


Figure S4. Mass spectrum of foldamer **3** measured by Fourier-Transform Ionic Cyclotronic Resonance spectrometry (injection solvent: CH_2Cl_2/CH_3CN 1/1 (*v/v*), [**3**] = 1 mmol.L^{-1}).

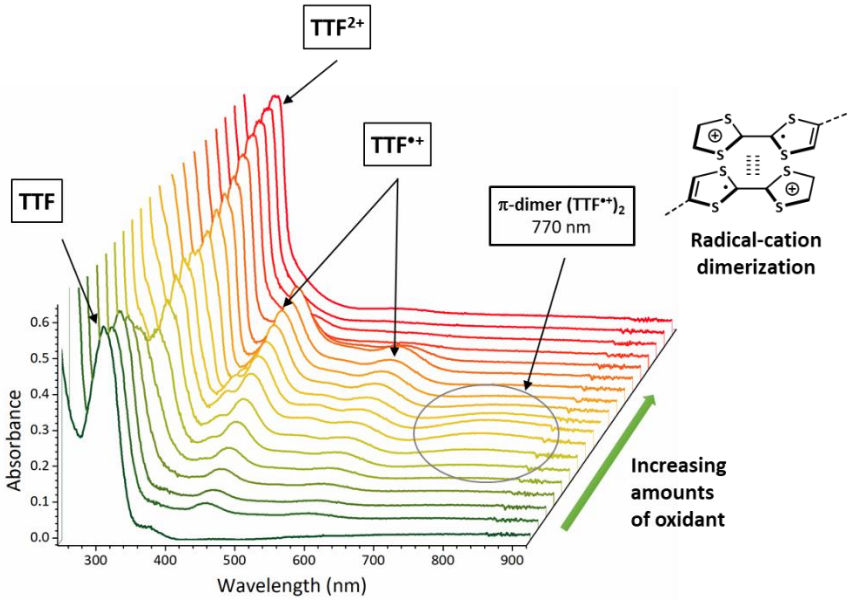


Figure S5. Evolution of the UV-visible absorption spectrum of foldamer **3** (10^{-5} M, V = 3 mL, CH_2Cl_2, CH_3CN (1/1)) upon injections of a $ThBF_4$ solution (60 mM, CH_3CN), l = 1 cm, 298 K).

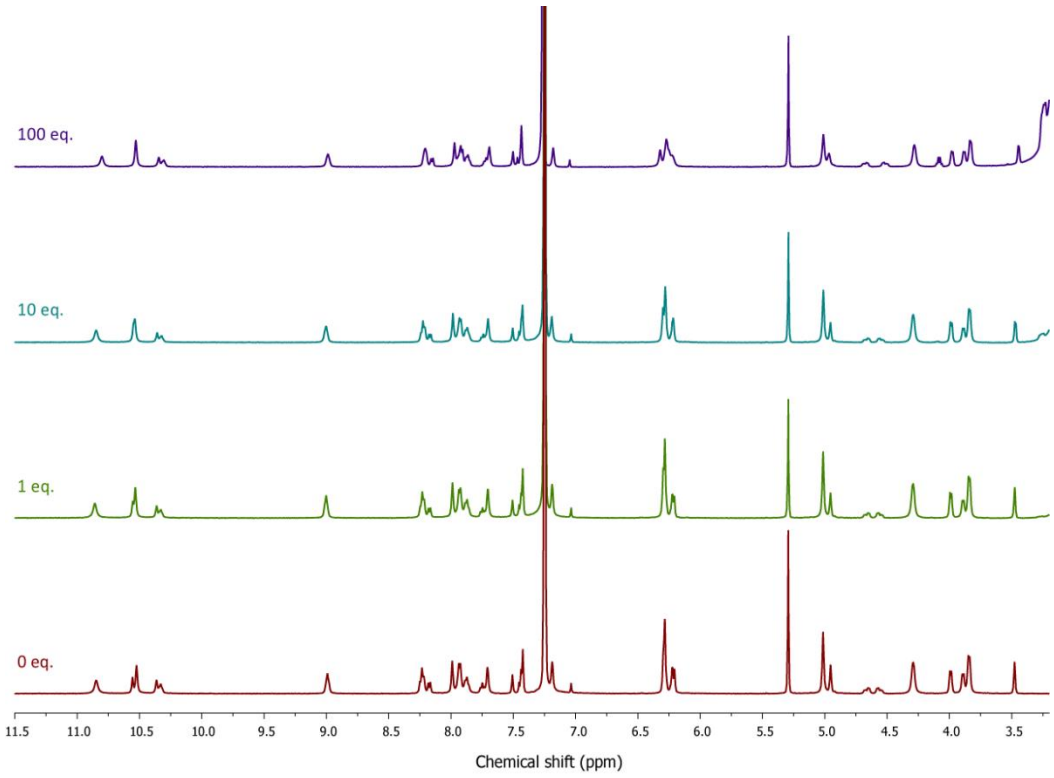


Figure S6. ^1H NMR spectrum of foldamer **3** in the presence of tetrabutylammonium hexafluorophosphate ($CDCl_3$, [**3**] = 2.4 mM, 293 K, 300 MHz).

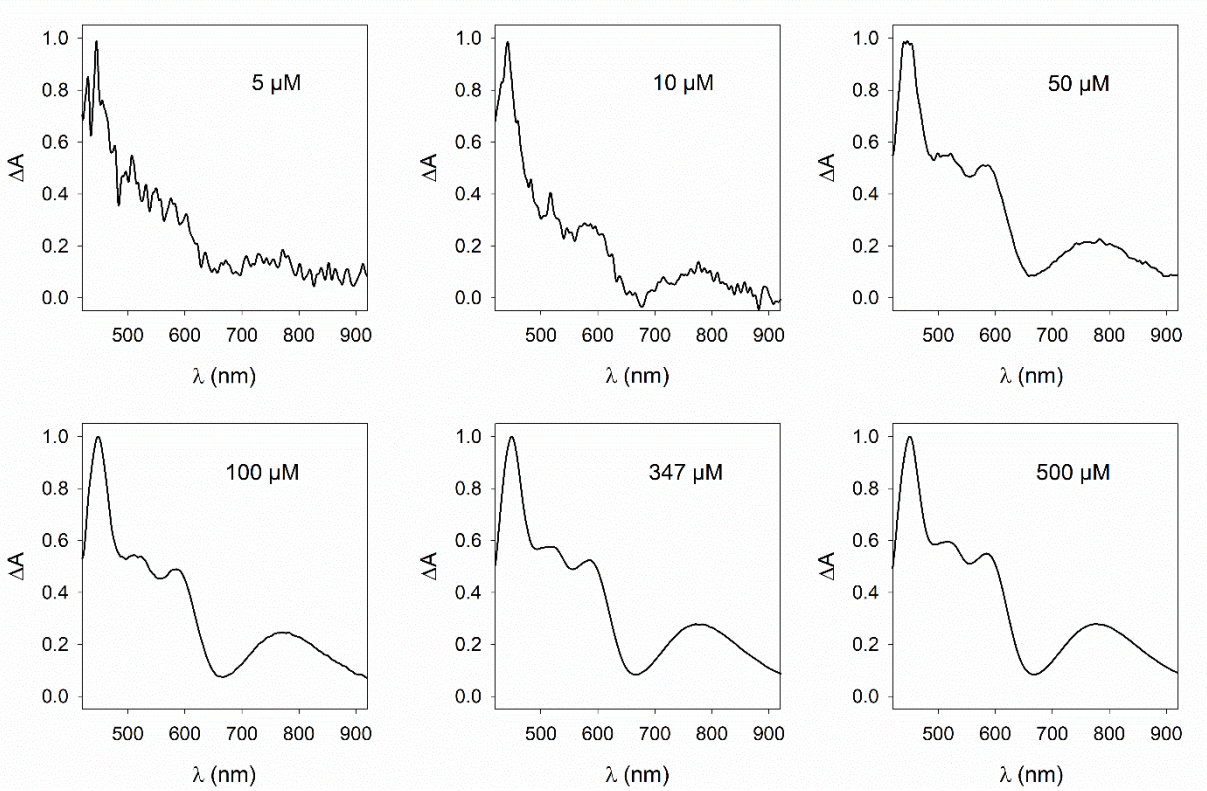


Figure S7. Variation of the UV-visible absorption spectrum of **3** measured through variable-concentration spectroelectrochemical measurements (CH_2Cl_2/CH_3CN 1/1 (*v/v*), Bu_4NPF_6 (0.1 M), E = 0.3 V *vs* $Ag/AgNO_3$, Pt working electrode).

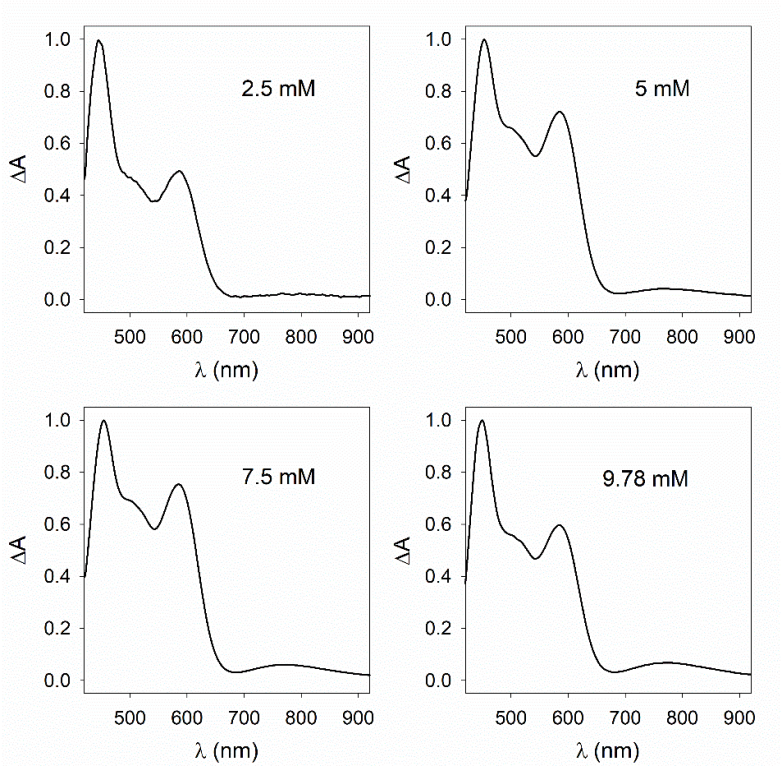


Figure S8. Variation of the UV-visible absorption spectrum of **4** measured through variable-concentration spectroelectrochemical measurements (CH_2Cl_2/CH_3CN (1/1 (*v/v*), Bu_4NPF_6 (0.1 M), E = 0.3 V *vs* $Ag/AgNO_3$, Pt working electrode).

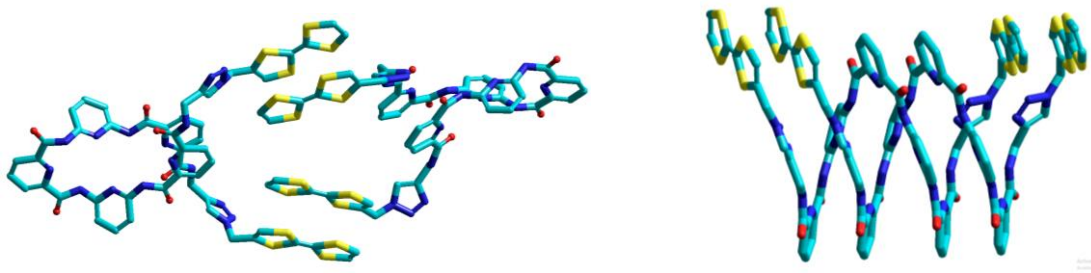


Figure S9. Molecular models showing possible supramolecular arrangements of $\mathbf{3}^{2(+\bullet)}$ upon dimerization. *Left*. Macrocyclic dimer. *Right*. Double helical arrangement.

Generalities.

The mass spectra were recorded on a Jeol JMS 700 (high resolution mass spectra (HRMS) or a Bruker Biflex III spectrometer (MALDI-TOF). X-Ray single-crystal diffraction data were collected at 120 K on an Agilent SuperNova diffractometer equipped with an Atlas CCD detector and micro-focus Cu-Kα radiation (λ = 1.54184 Å). The structure was solved by direct methods, expanded and refined on F2 by full matrix least-squares techniques using SHELX programs (G.M. Sheldrick, 2016). All non-H atoms were refined anisotropically and the hydrogen atoms were included in the calculation without refinement. Multiscan empirical absorption was corrected using CrysAlisPro program (CrysAlisPro, Agilent Technologies, V1.171.38.41r, 2015). The structure refinement showed disordered electron density which could not be reliably modelled and the program PLATON/SQUEEZE were used to remove the scattering contribution corresponding to methanol molecules. The unit cell contains many voids of 1196 $Å^3$ containing 348 electrons which can be attributed to approximately 20 methanol molecules. The assumed solvent composition (5 methanol molecules per foldamer) was used in the calculation of the empirical formula, formula weight, density, linear absorption coefficient and F(000). The cyclic voltammetry experiments were carried out on a potentiostat-galvanostat EG&G PAR model 273. Tetrabutylammonium hexafluorophosphate (0.1 M) was used as supporting electrolyte. The cell was equipped with three electrodes: a platinum working electrode (Ø = 2 mm), a platinum wire as auxiliary electrode and a silver/silver nitrate reference electrode.

Crystallographic data

3 + 5 CH_3OH: $C_{68}H_{81}N_{17}O_{14}S_8$, M = 1616.97, orange needle, 0.253 x 0.079 x 0.056 mm^3, monoclinic, space group C2/c, a = 16.915(8) Å, b = 29.802(5) Å, c = 15.018(2) Å, β = 90.90(1)°, V = 7570(2) Å3, Z = 4, ρcalc = 1.419 g/cm^3, μ(CuKα) = 2.807 mm^{-1}, F(000) = 3392, θmin = 2.966°, θmax = 73.695°, 16017 reflections collected, 7172 unique (Rint = 0.0828), parameters / restraints = 446 / 15, R1 = 0.1199 and wR2 = 0.3202 using 2420 reflections with I>2σ(I), R1 = 0.2038 and wR2 = 0.3892 using all data, GOF = 0.937, -0.355 < Δρ < 0.378 e.$Å^{-3}$. CCDC-1891841 contains the supplementary crystallographic data for this paper.

Calculation of dimerization constants through variable-concentration NMR experiments

Considering the dimerization equilibrium (1), where two simple helices (M) form a double helix (D), the corresponding dimerization constant K_{dim} is expressed according to equation (2) by assimilating activities and concentrations.

$$M + M \rightleftharpoons D \quad ; \quad K_{dim} \qquad (1)$$

$$K_{dim} = \frac{[D]}{[M]^2} \qquad (2)$$

$$[D] = K_{dim}[M]^2 \qquad (3)$$

The concentration of the double helix (D) can then be written according to equation (3). Taking into account the mass balance law, one can express the total concentration in foldamer (C_t) according to the concentration of the species present in solution (M) and (D) (Equation (4)).

$$C_t = [M] + 2[D] \qquad (4)$$

By introducing equality (3) in equation (4), equation (5) is obtained:

$$2K_{dim}[M]^2 + [M] - C_t = 0 \qquad (5)$$

The resolution of this equation gives a single scientifically sound solution (6).

$$[M] = \frac{-1 + \sqrt{1 + 8K_{dim}C_t}}{4K_{dim}} \qquad (6)$$

Equation (6) is used to perform a nonlinear fit from a series of experiments, by calculating the concentration of single helices [M] with respect to the total concentration of the foldamer in each experiment. These concentrations are calculated from the integration of the appearing or disappearing NMR signals corresponding to each species.

Spectroelectrochemical measurements

The spectroelectrochemical setup under consideration was previously described. See:
O. Alévêque, E. Levillain and L. Sanguinet, *Electrochemistry Communications*, 2015, **51**, 108–112.

Calculation of dimerization constants through variable-concentration spectroelectrochemistry
The dimerization constant of the oxidized foldamer $3^{2(\bullet+)}$ was determined according to Equation *(7)*:

The following reasoning allowed its determination:

$$A = \varepsilon_M.l.[M] + \varepsilon_D.l.[D] \qquad (7)$$

Where ε_M and ε_D define the molar extinction coefficients of the monomer and the dimer respectively, and l the optical path of the spectroelectrochemical setup.

Through Equations 4 and 5, it is possible to express [M] and [D] as a function of the dimerization constant K_{dim} and the total concentration C_t.

$$[M] = \frac{-1 + \sqrt{1 + 8K_{dim}C_t}}{4K_{dim}} \qquad [D] = \frac{1 + 4K_{dim}C_t - \sqrt{1 + 8K_{dim}C_t}}{8K_{dim}}$$

Combining these expressions within Equation *(7)* affords Equation *(8)*:

$$A = \varepsilon_M.l.\left(\frac{-1+\sqrt{1+8K_{dim}C_t}}{4K_{dim}}\right) + \varepsilon_D.l.\left(\frac{1+4K_{dim}C_t-\sqrt{1+8K_{dim}C_t}}{8K_{dim}}\right) \qquad (8)$$

Which is simplified when considering a wavelength were monomer M does not absorb light and dimer D does, such as λ = 770 nm, the maximum absorption wavelength typical for radical cation dimers:

$$A_{770} = \varepsilon_D . l . \left(\frac{1+4K_{dim}C_t - \sqrt{1+8K_{dim}C_t}}{8K_{dim}} \right) \qquad (9)$$

By analogy, the variation of absorbance measured after application of a given potential is given by:

$$\Delta A_{770} = \Delta\varepsilon_D . l . \left(\frac{1+4K_{dim}C_t - \sqrt{1+8K_{dim}C_t}}{8K_{dim}} \right) \qquad (10)$$

When all the foldamer is in the dimer form, the variation of absorption reaches a maximum:

$$\Delta_{max} A_{770} = \Delta\varepsilon_D . l . \frac{C_t}{2}$$

As a consequence, one can write:

$$\frac{\Delta A_{770}}{\Delta_{max} A_{770}} = \frac{\Delta\varepsilon_D . l . \left(\frac{1 + 4K_{dim}C_t - \sqrt{1 + 8K_{dim}C_t}}{8K_{dim}} \right)}{\Delta\varepsilon_D . l . \frac{C_t}{2}}$$

And obtain the expression of ΔA_{770} as a function of C_t, K_{dim}, and $\Delta_{max}A$:

$$\Delta A_{770} = \Delta_{max} A_{770} \left(\frac{1 + 4K_{dim}C_t - \sqrt{1 + 8K_{dim}C_t}}{4K_{dim}C_t} \right)$$

Eventually, this equation can be fitted to experimental data to determine K_{dim} and $\Delta_{max}A_{770}$.

Synthetic details and characterizations

2,6-Diaminopyridine was purchased from a commercial source. Dimethyl 4-hydroxypyridine-2,6-dicarboxylate,[1] formyltetrathiafulvalene **H**,[2] hydroxymethyltetrathiafulvalene **I**[2] were prepared by following previously reported procedures and showed identical spectroscopic properties to those reported therein.

1) M. Di Antonio, K. I. E. McLuckie, S. J. Balasubramanian, *J. Am. Chem. Soc.* 2014, **136**, 5860.
2) J. Lyskawa, D. Canevet, M. Allain and M. Sallé, *Tetrahedron Lett.*, 2010, **51**, 5868.

All solvents and reagents were dried according to standard procedures (Sodium/benzophenone for tetrahydrofuran and diethyl ether, CaH_2 for dichloromethane, acetonitrile, triethylamine and *N,N*-diisopropylethylamine, P_2O_5 for chloroform).

Thin-layer chromatography (TLC) was performed on aluminium plates coated with MerckSilica gel 60 F254. Developed plates were air-dried and scrutinized under a UV lamp. Silica gel SIGMA Aldrich Chemistry (SiO_2, pore size 60 Å, 40-63 µm technical grades) was used for preparative silica gel chromatography.

Coupling constants (J) are denoted in Hz and chemical shifts (δ) in parts per million (ppm). Multiplicities are described as follows: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. The mass spectra were recorded on a Jeol JMS 700 (high resolution mass spectra (HRMS) or a Bruker Biflex III spectrometer (MALDI-TOF).

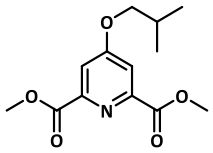
General procedure for acid chloride activation.

Under argon conditions, the dry carboxylic acid derivatives were dissolved with dry dichloromethane. Oxalyl chloride and a drop of dry dimethylformamide were added and the mixture is stirred for one hour under inert armosphere. Dichloromethane and oxalyl chloride were evaporated under vacuum using liquid nitrogen trap and the resulting solid was dried for two hours under vacuum. The corresponding acid chloride was dissolved in dry dichloromethane and reacted with the desired amines.

General procedure for CuAAC reactions.

Alkyne derivatives and **TTF-CH_2-N_3** were dissolved in a mixture of DMSO:DCM 1/1 (*v/v*) (2 mL) and the solution was argon flushed for 5 minutes. Then, copper sulfate pentahydrate and sodium ascorbate (0.1 equivalent) were added to the mixture, which was stirred for 16 hours at room temperature. The solution was diluted with dichloromethane (20 mL), washed three times with water and dried over magnesium sulfate. The solvent was evaporated *in vacuo* and the desired compound was purified as indicated below.

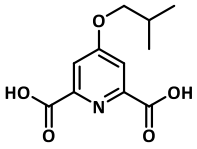
*Dimethyl 4-isobutoxypyridine-2,6-dicarboxylate (**B**)*



Chemical Formula: $C_{13}H_{17}NO_5$
Molecular Weight: 267.28

Diester **B** was synthesized according to the literature (Huc and coll., *Chem. Asian. J.*, 2010, **5**, 1364–1375).

*4-isoButoxypyridine-2,6-dicarboxylic acid (**C**)* – Adapted from Huc and coll., *Chem. Asian. J.*, 2010, **5**, 1364–1375.



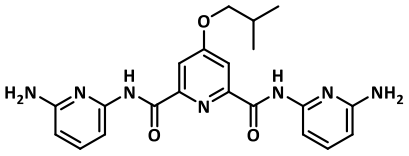
Chemical Formula: $C_{11}H_{13}NO_5$
Molecular Weight: 239.23

Potassium hydroxide (1.57 g, 28.0 mmol) was dissolved in methanol (15 mL) and added to a solution of diester **B** (1.87 g, 7.0 mmol) in methanol (20 mL). The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the white residue was dissolved in water (50 mL). The aqueous phase was washed with diethyl ether (3 × 50 mL) and acidified with 1 M hydrochloric acid. The resulting precipitate was filtered, washed with water and dried under vacuum to afford **C** as a white powder (1.29 g, 77 %).

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.68 (s, 2H), 3.98 (d, *J* = 6.5 Hz, 2H), 2.05 (m, 1H), 0.98 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (75 MHz, DMSO-d_6): δ 166.9, 165.3, 149.7, 74.5, 27.4, 18.7.

*N^2,N^6-bis(6-aminopyridin-2-yl)-4-isobutoxypyridine-2,6-dicarboxamide (**D**)*



Chemical Formula: $C_{21}H_{23}N_7O_3$
Molecular Weight: 421.46

4-*iso*Butoxypyridine-2,6-dicarbonyl dichloride was obtained from **C** (977 mg, 4.08 mmol) and oxalyl chloride (2.12 g, 16.34 mmol) using the general procedure for acid chloride activation (see above).

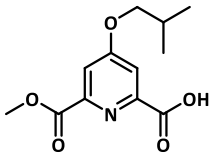
2,6-Diaminopyridine (2.23 g, 20.46 mmol) and DIPEA (2.07 g, 20.46 mmol) were mixed in dry dichloromethane (100 mL) under argon atmosphere. 4-*iso*Butoxypyridine-2,6-dicarbonyl dichloride (1.13 g, 4.08 mmol) was dissolved in dry dichloromethane (20 mL) and was added dropwise via a pressure-equalizing dropping funnel over a period of 30 minutes. The mixture was stirred for 16 hours. The solvent was removed under reduced pressure and the crude was subjected to a silica gel chromatography (eluent EtOAc:Pentane 1:1, solid deposit in tetrahydrofuran) to afford **D** as a light yellow solid (1.08 g, 63 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.02 (s, 2H), 7.95 (s, 2H), 7.76 (d, *J* = 7.9 Hz, 2H), 7.53 (t, *J* = 7.9 Hz, 2H), 6.30 (d, *J* = 8.0 Hz, 2H), 4.73 (br, 4H), 3.95 (d, *J* = 6.5 Hz, 2H), 2.17 (m, 1H), 1.06 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (MHz, $CDCl_3$): δ 168.5, 161.6, 157.7, 150.7, 149.4, 140.5, 112.0, 105.1, 103.8, 75.5, 28.2, 19.2.

HRMS (EI) calcd. for $C_{21}H_{23}N_7O_3$ $[M]^+$, 421.1862; found, 421.1851.

*4-isoButoxy-6-(methoxycarbonyl)picolinic acid (**E**)* – Adapted from Huc and coll., *Chem. Asian. J.*, 2010, **5**, 1364–1375.



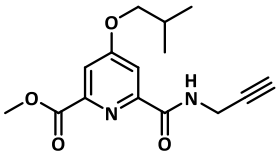
Chemical Formula: $C_{12}H_{15}NO_5$
Molecular Weight: 253.25

Sodium hydroxide (342 mg, 8.53 mmol) was dissolved in methanol (25 mL) and was added slowly to a solution of diester **B** (2.28 g, 8.53 mmol) in methanol (25 mL). The mixture was stirred at room temperature overnight. Then, methanol was evaporated under reduced pressure and water was added (50 mL). The aqueous phase was washed with dichloromethane (3 x 50 mL) to recover the starting material acidified with 1 M hydrochloric acid. The resulting solution was extracted with dichloromethane (3 x 50 mL). Organic layers were combined, dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford **E** as a white solid (1.49 g, 69 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 – 7.79 (m, 2H), 4.01 (s, 3H), 3.92 (d, *J* = 6.5 Hz, 2H), 2.24 – 2.09 (m, 1H), 1.06 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (76 MHz, $CDCl_3$): δ 168.2, 164.4, 164.0, 148.2, 148.0, 116.0, 112.3, 75.6, 53.2, 28.0, 19.0.

*Methyl 4-isobutoxy-6-(prop-2-yn-1-ylcarbamoyl)picolinate (**F**)*



Chemical Formula: $C_{15}H_{18}N_2O_4$
Molecular Weight: 290.32

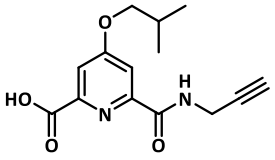
Methyl 6-(chlorocarbonyl)-4-*iso*butoxypicolinate was obtained from **E** (200 mg, 0.8 mmol) and oxalyl chloride (205 mg, 1.6 mmol) using the general procedure for acid chloride activation (see above). The resulting yellow oil was dissolved in dry dichloromethane (4 mL) and cooled down to 0°C. A solution of propargylamine (66 mg, 1.2 mmol) and diisopropylethylamine (305 mg, 2.4 mmol) in dry dichloromethane (5 mL) was added dropwise. The mixture was stirred for 16 hours at room temperature under argon atmosphere. The product was purified by silica gel chromatography (eluent pentane:ethyl acetate 2:1) to afford **F** as a yellow oil (200 mg, 87 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.43 (t, *J* = 5.8 Hz, 1H), 7.79 (d, *J* = 2.5 Hz, 1H), 7.65 (d, *J* = 2.5 Hz, 1H), 4.21 (dd, *J* = 5.8, 2.5 Hz, 2H), 3.91 (s, 3H), 3.82 (d, *J* = 6.5 Hz, 2H), 2.26 (t, *J* = 2.5 Hz, 1H), 2.14 – 2.00 (m, 1H), 0.97 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.6, 165.1, 163.4, 151.6, 148.2, 114.9, 111.1, 79.4, 75.3, 71.6, 53.0, 29.2, 28.1, 19.1.

HRMS (EI^+) calcd. for $C_{15}H_{18}N_2O_4$ $[M]^+$, 290.1267; found, 290.1264.

*4-isoButoxy-6-(prop-2-yn-1-ylcarbamoyl)picolinic acid (**G**)*



Chemical Formula: $C_{14}H_{16}N_2O_4$
Molecular Weight: 276.29

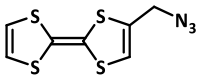
Potassium hydroxide (377 mg, 6.7 mmol) was dissolved in methanol (5 mL) and was added to a solution of ester **F** (390 mg, 1.3 mmol) in methanol (20 mL). The reaction was followed by thin layer chromatography (eluent pentane:ethyl acetate 2:1). After three hours, the solvent was removed under reduced pressure and the solid was dissolved in water (50 mL). Hydrochloric acid (1 mol.L^{-1}) was added until complete precipitation. The resulting solid was isolated by filtration, washed with water and dried under vacuum to afford **G** as a white powder with a quantitative yield.

^{1}H NMR (300 MHz, Acetone-d_6): δ 9.21 (br, 1H), 7.85 (d, *J* = 2.5 Hz, 1H), 7.78 (d, *J* = 2.5 Hz, 1H), 4.28 – 4.22 (m, 2H), 4.08 (d, *J* = 6.5 Hz, 2H), 2.71 (t, *J* = 2.5 Hz, 1H), 2.23 – 2.11 (m, 1H), 1.07 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (75 MHz, Acetone-d_3): δ 169.1, 164.7, 163.3, 152.0, 152.0, 148.7, 113.3, 112.8, 81.0, 81.0, 75.9, 72.2, 19.1.

HRMS (EI$^+$) calcd. for $C_{14}H_{16}N_2O_4$ $[M]^+$, 276.1110; found, 276.1107.

*4-(Azidomethyl)tetrathiafulvalene (TTF-CH_2-N_3) (**1**)*



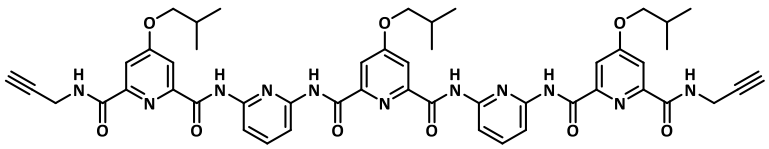
Chemical Formula: $C_7H_5N_3S_4$
Molecular Weight: 259.38

4-(Hydroxymethyl)tetrathiafulvalene **I** (208 mg, 0.9 mmol) was dissolved in dry DMF (20 mL), then diphenyl phosphoryl azide (DPPA) (1.26 g, 4.4 mmol) was added. The mixture was cooled in an ice bath and 1,8-diazabicyclo[5.4.0]undec-7-ene **(**DBU) (152 mg, 1.0 mmol) was added. After stirring for 4 hours under argon atmosphere at room temperature, sodium azide (292 mg, 4.4 mmol) was added and the mixture was stirred overnight. DMF was partially evaporated and dichloromethane (50 mL) was added. The organic layer was washed with water (3 x 100 mL), dried over magnesium sulfate and the solvent was partially evaporated under reduced pressure. The desired product was purified by silica gel chromatography (DCM:EP:Et_3N 39:60:1, solid deposit in DCM:Et_3N) to afford **1** as a yellow oil that solidifies upon standing at rt (215 mg, 93 %).

^{1}H NMR (300 MHz, Acetonitrile-d_3): δ 6.49 (t, *J* = 1.1 Hz, 1H), 6.47 (s, 2H), 4.15 (br, 2H).

HRMS (EI) calcd. for $C_7H_5N_3S_4$ $[M]^+$, 258.9366; found, 258.9361.

*Foldamer **2***



Chemical Formula: $C_{49}H_{51}N_{11}O_9$
Molecular Weight: 938.02

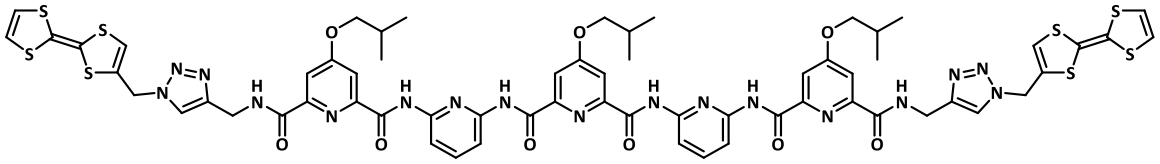
4-*iso*Butoxy-6-(prop-2-yn-1-ylcarbamoyl)picolinoyl chloride was obtained from **G** (22 mg, 0.7 mmol) and oxalyl chloride (375 mg, 2.9 mmol) using the general procedure for acid chloride activation (see above). The resulting yellow oil was dissolved in dry dichloromethane (3 mL) and cooled down to 0°C. A solution of diamine **D** (100 mg, 0.2 mmol) and DIPEA (122 mg, 0.94 mmol) in dry dichloromethane (1 mL) was added dropwise. The mixture was stirred for 16 hours at room temperature under argon atmosphere. The dichloromethane was evaporated under reduced pressure and the crude was subjected to a silica gel chromatography (eluent: CH_2Cl_2/EtOAc from 100/0 to 95/5). The desired compound was subsequently recrystallized (DCM/EtOAc), affording foldamer **2** as a white solid (193 mg, 86 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.58 (s, 2H), 10.41 (s, 2H), 10.01 (t, *J* = 5.7 Hz, 2H), 8.22 (d, *J* = 8.2 Hz, 4H), 8.03 – 7.93 (m, 4H), 7.80 – 7.69 (m, 4H), 4.34 – 4.21 (m, 2H), 4.11 – 3.99 (m, 2H), 3.93 (d, *J* = 6.5 Hz, 6H), 3.23 (t, *J* = 8.0 Hz, 1H), 2.76 – 2.65 (m, 1H), 2.26 – 2.07 (m, 3H), 1.05 (d, *J* = 6.7 Hz, 12H), 0.49 (br, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 168.0, 165.7, 163.6, 162.8, 153.2, 151.5, 150.7, 150.3, 148.4, 140.8, 112.5, 112.4, 112.1, 111.9, 110.5, 79.8, 75.4, 74.9, 70.5, 31.1, 29.1, 28.1, 27.3, 19.1, 18.6, 18.5.

HRMS (FAB$^+$) calcd. for $C_{49}H_{51}N_{11}O_9$ $[M+H]^+$, 938.3871; found, 938.3951.

*Foldamer **3***



Chemical Formula: $C_{63}H_{61}N_{17}O_9S_8$
Molecular Weight: 1456.77

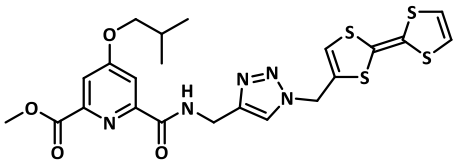
Foldamer **2** (122 mg, 0.1 mmol) and **TTF-CH_2-N_3 1** (168 mg, 0.6 mmol) were mixed following the general procedure for the *click* reaction (see above). The desired compound was purified by silica gel chromatography (eluent: DCM/Et_3N 99/1 to recover excess TTF-CH_2-N_3, then DCM/MeOH/Et_3N 96/3/1) and recrystallized (CH_2Cl_2/CH_3OH) to afford foldamer **3** as an orange solid (185 mg, 97 %).

^{1}H NMR (300 MHz, DMSO-d_6): δ 11.23 (s, 2H), 11.15 (s, 2H), 9.95 (t, *J* = 6.3 Hz, 2H), 8.15 – 8.01 (m, 6H), 7.89 (s, 2H), 7.85 (s, 2H), 7.71 (d, *J* = 2.5 Hz, 2H), 7.37 (d, *J* = 2.5 Hz, 2H), 6.80 (s, 2H), 6.68 – 6.58 (m, 4H), 5.31 (s, 4H), 4.23 (d, *J* = 6.1 Hz, 4H), 4.10 (d, *J* = 6.5 Hz, 2H), 4.00 (d, *J* = 6.4 Hz, 4H), 2.21 – 2.03 (m, 3H), 1.04 (t, *J* = 6.5 Hz, 18H).

^{13}C NMR (75 MHz, DMSO-d_6): δ 167.9, 166.8, 162.8, 162.2, 161.7, 150.4, 150.3, 150.2, 150.0, 149.6, 145.4, 141.0, 130.1, 123.0, 120.6, 120.0, 119.9, 111.8, 111.7, 111.3, 110.6, 107.3, 74.9, 74.4, 55.0, 48.6, 47.9, 34.3, 27.5, 18.9, 18.8.

HRMS (FAB$^+$) calcd. for $C_{63}H_{61}N_{17}O_9S_8$ $[M]^+$, 1455.2604; found, 1455.2604.

*Reference **4***



Chemical Formula: $C_{22}H_{23}N_5O_4S_4$
Molecular Weight: 549.70

Alkyne F (80 mg, 0.23 mmol) and **TTF-CH_2-N_3 1** (107 mg, 0.41 mmol) were mixed following the general procedure for the *click* reaction (see above). The crude was purified by silica gel chromatography (eluent: DCM/Et_3N 99/1 to recover excess TTF-CH_2-N_3, then DCM/MeOH/Et_3N 96/3/1) to afford **4** as an orange solid (70 mg, 46 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.63 (t, *J* = 6.3 Hz, 1H), 7.84 (d, *J* = 2.5 Hz, 1H), 7.71 (d, *J* = 2.5 Hz, 1H), 7.66 (s, 1H), 6.32 (s, 1H), 6.30 (s, 2H), 5.20 (s, 2H), 4.77 (d, *J* = 6.3 Hz, 2H), 3.98 (s, 3H), 3.89 (d, *J* = 6.5 Hz, 2H), 2.22 – 2.05 (m, 1H), 1.04 (d, *J* = 6.7 Hz, 6H).

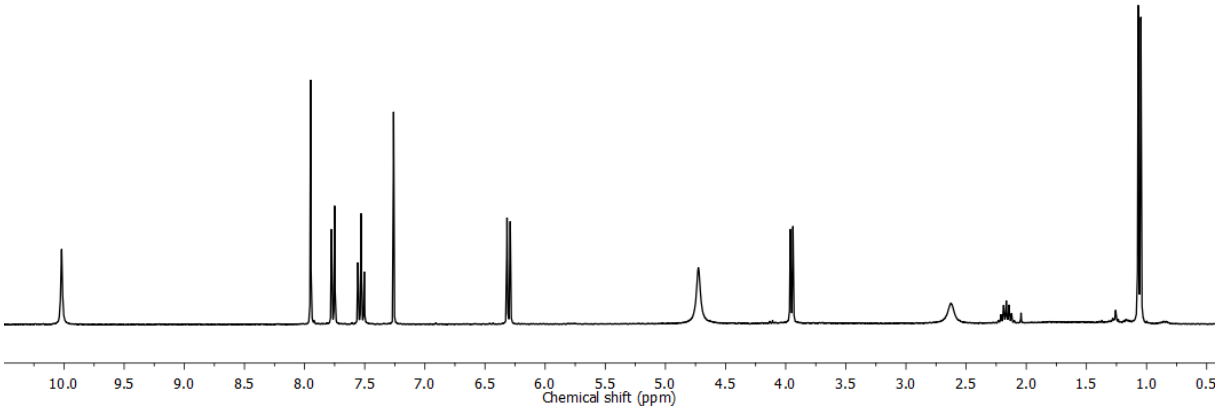
^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 165.2, 164.0, 151.7, 148.4, 145.6, 129.3, 122.4, 120.0, 119.3, 114.8, 111.1, 75.3, 53.0, 53.0, 35.2, 28.1, 19.1.

HRMS (FAB^+) calcd. for $C_{22}H_{23}N_5O_4S_4$ $[M]^+$, 549.0633; found, 549.0623.

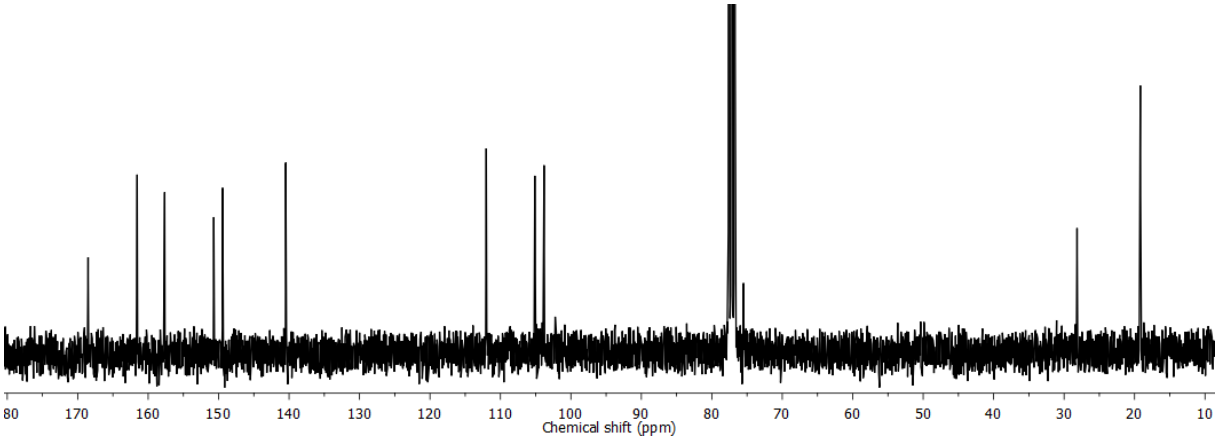
Collection of spectra

*N^2,N^6-bis(6-aminopyridin-2-yl)-4-isobutoxypyridine-2,6-dicarboxamide (**D**)*

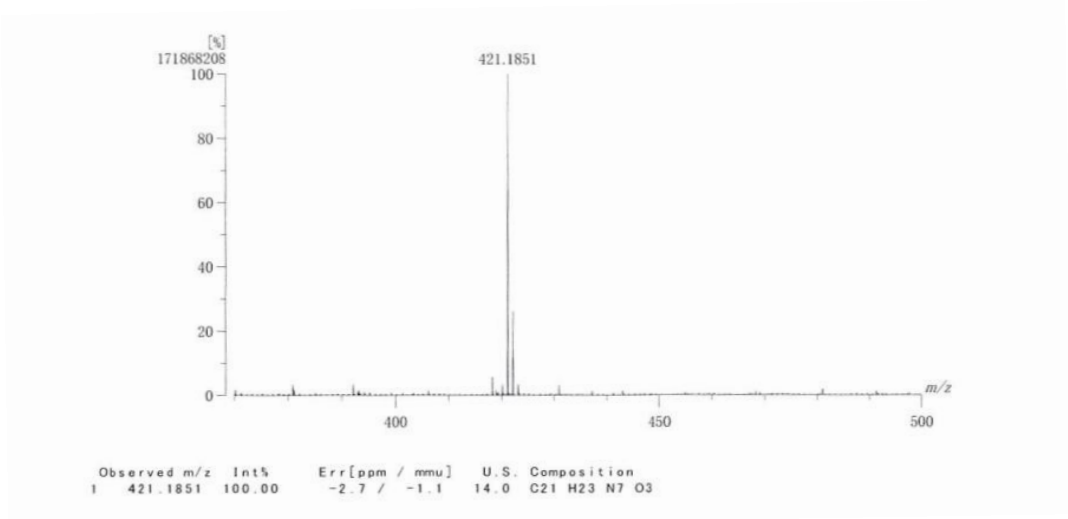
^{1}H NMR ($CDCl_3$)



^{13}C NMR ($CDCl_3$)

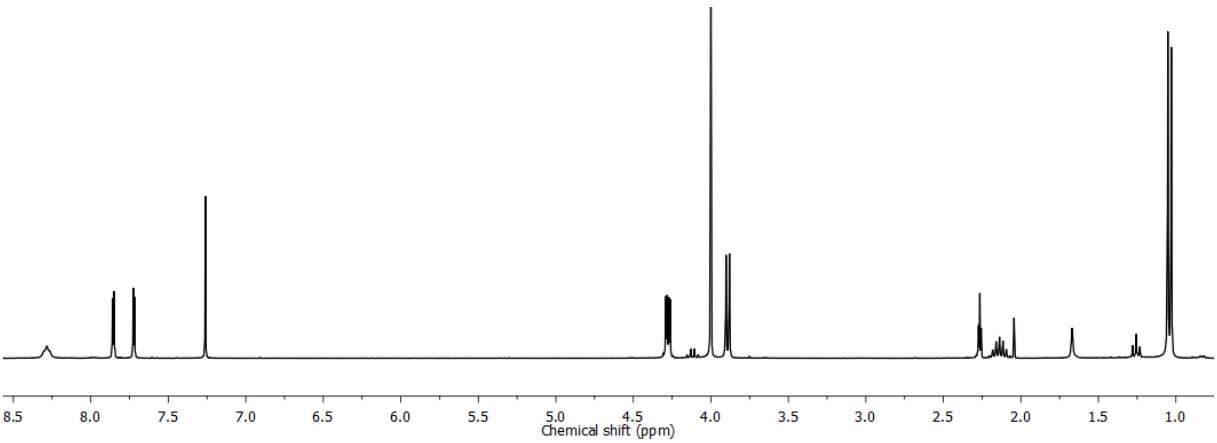


HRMS

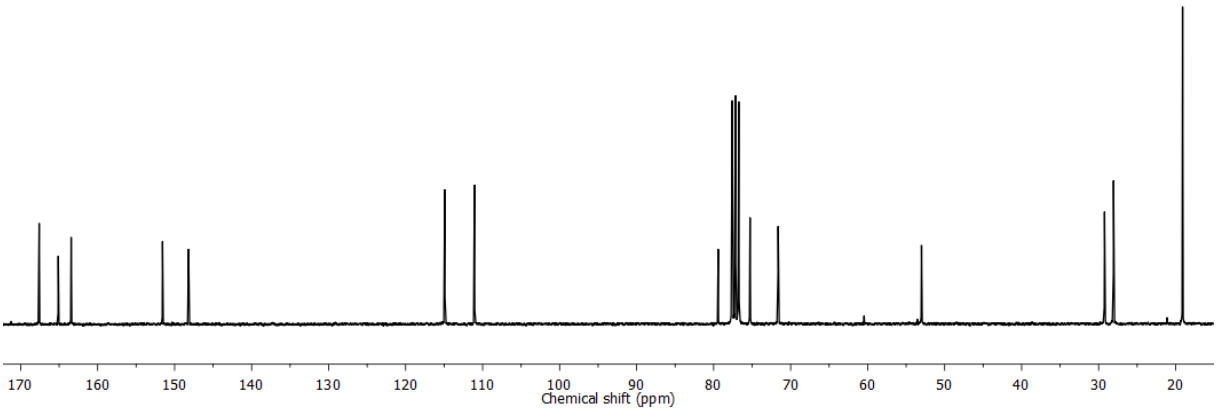


*Methyl 4-isobutoxy-6-(prop-2-yn-1-ylcarbamoyl)picolinate (**F**)*

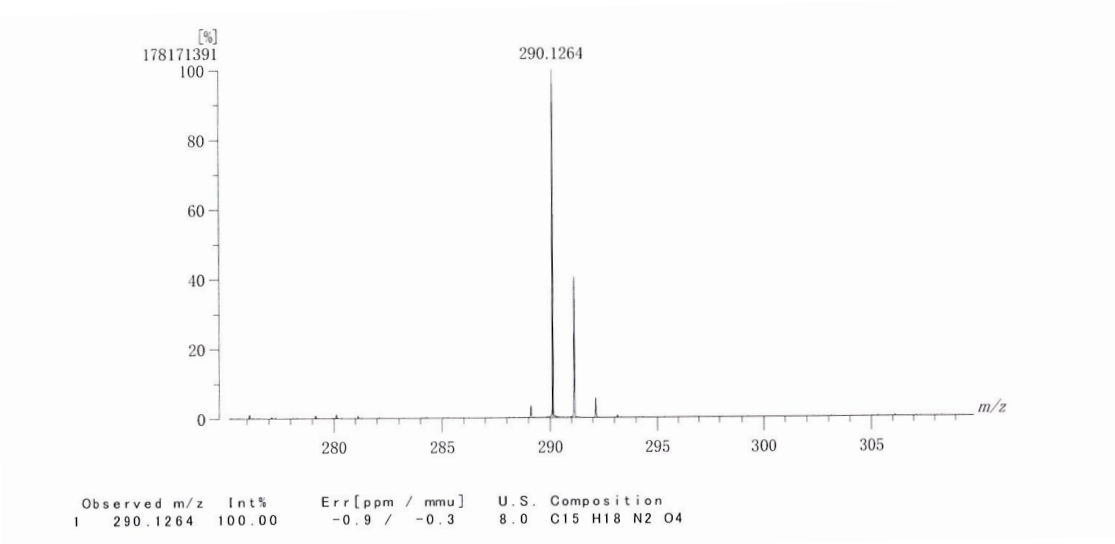
^{1}H NMR ($CDCl_3$)



^{13}C NMR ($CDCl_3$)

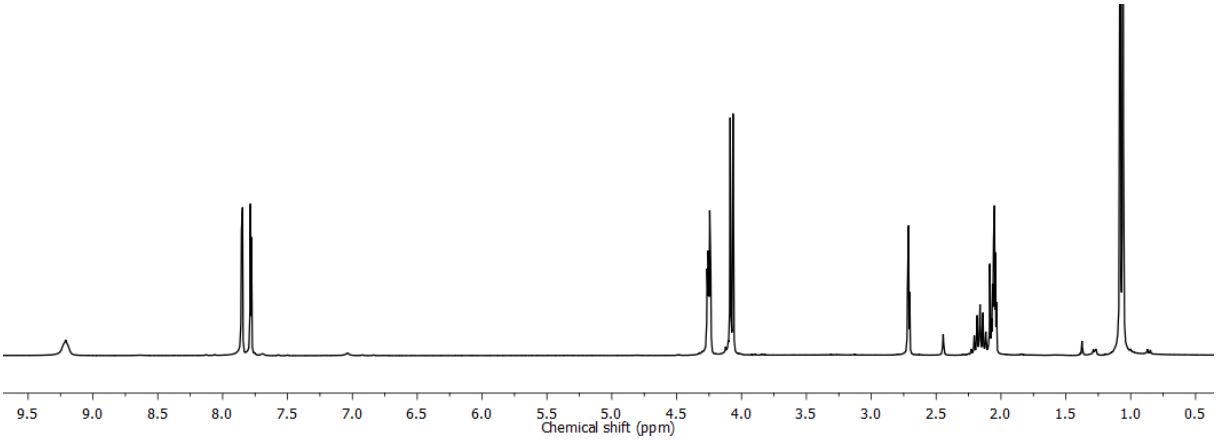


HRMS

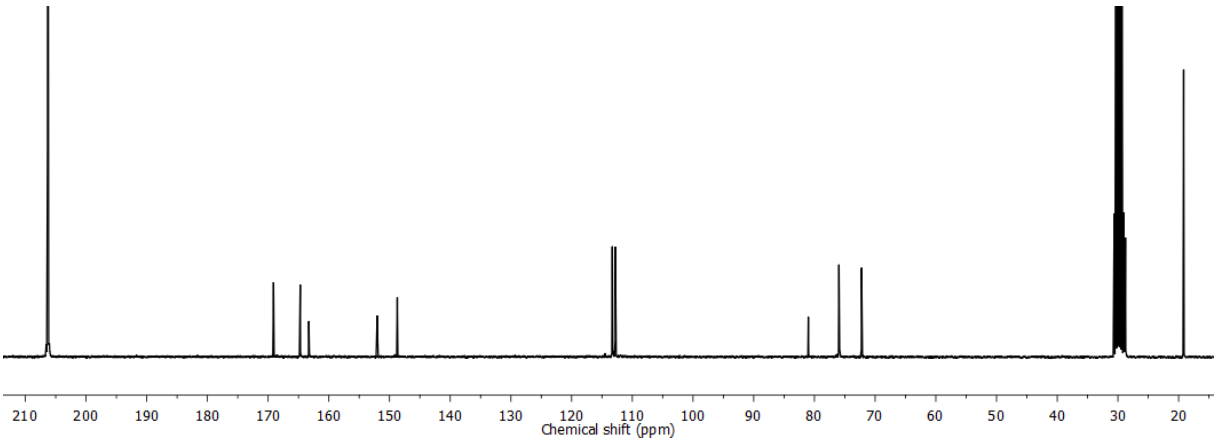


*4-isoButoxy-6-(prop-2-yn-1-ylcarbamoyl)picolinic acid (**G**)*

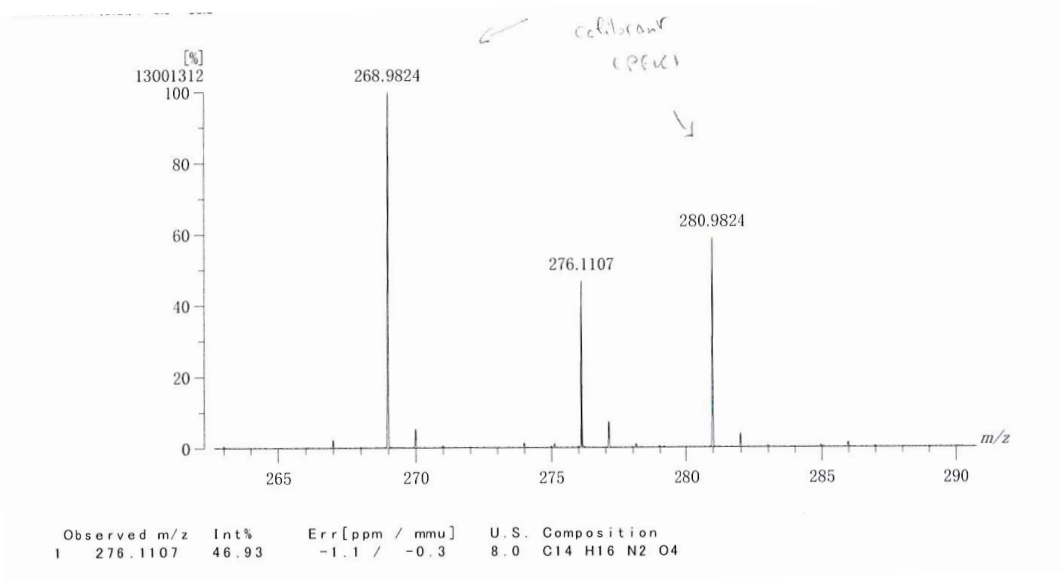
^{1}H NMR ($(CD_3)_2CO$)



^{13}C NMR ($(CD_3)CO$)

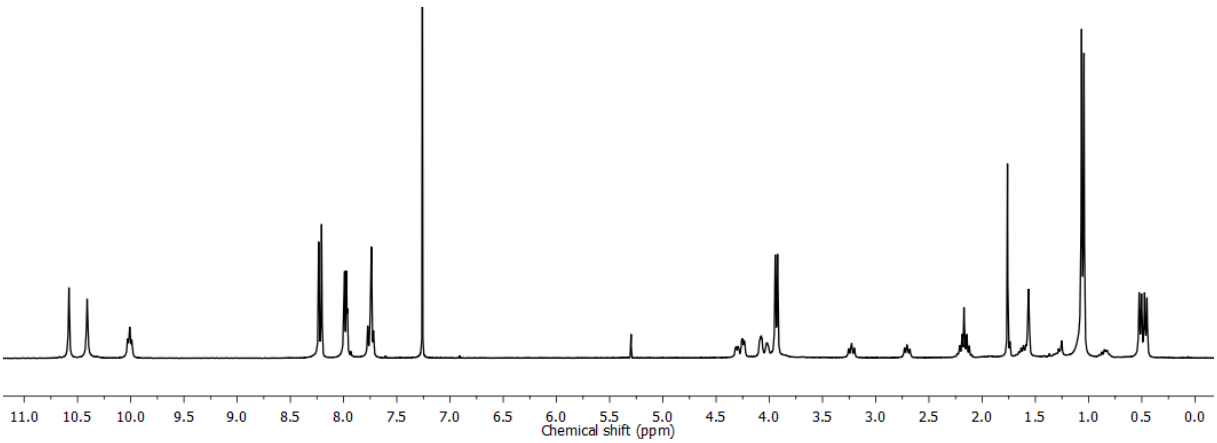


HRMS

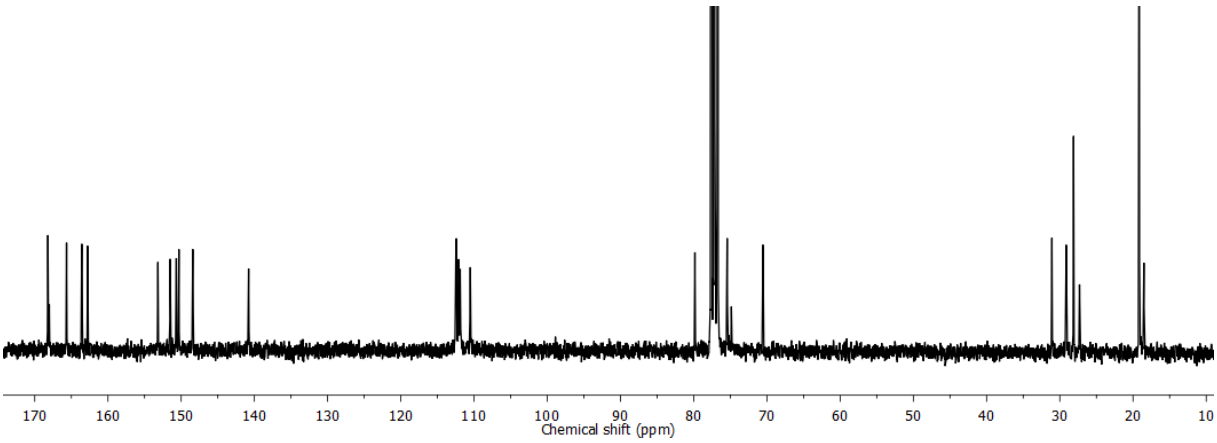


*Foldamer **2***

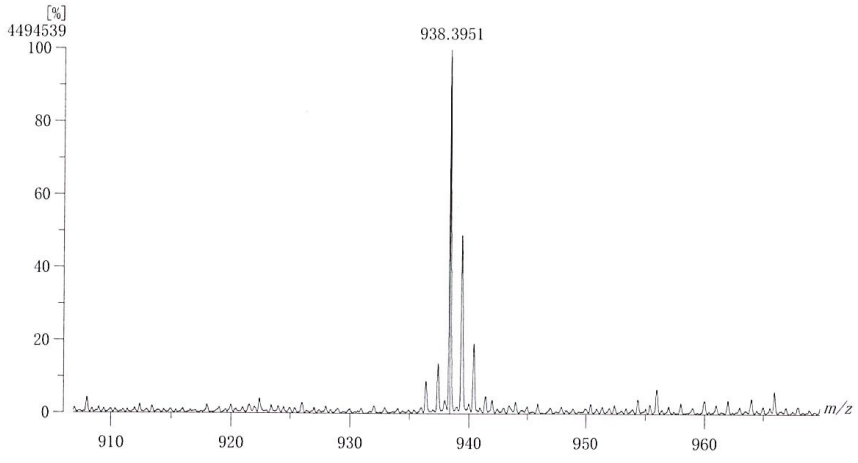
^{1}H NMR ($CDCl_3$)



^{13}C NMR ($CDCl_3$)



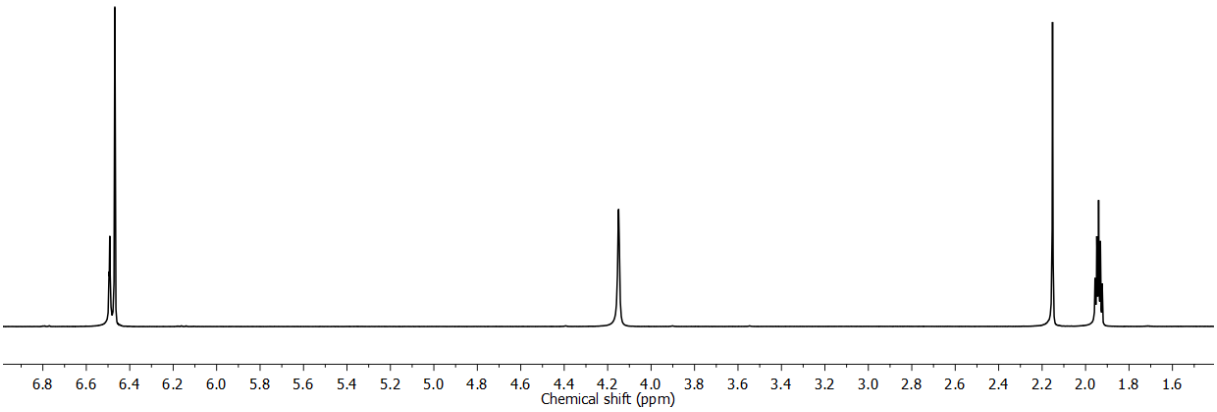
HRMS



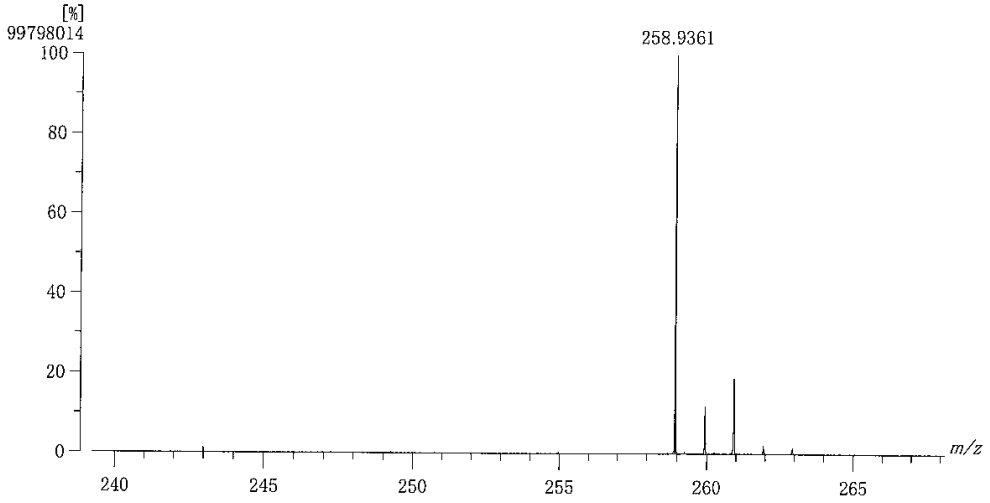
	Observed m/z	Int%	Err[ppm / mmu]	U.S.	Composition
1	938.3951	100.00	+0.2 / +0.2	29.5	C49 H52 N11 O9

*Azidomethyltetrathiafulvalene **1***

^{1}H NMR (CD_3CN)



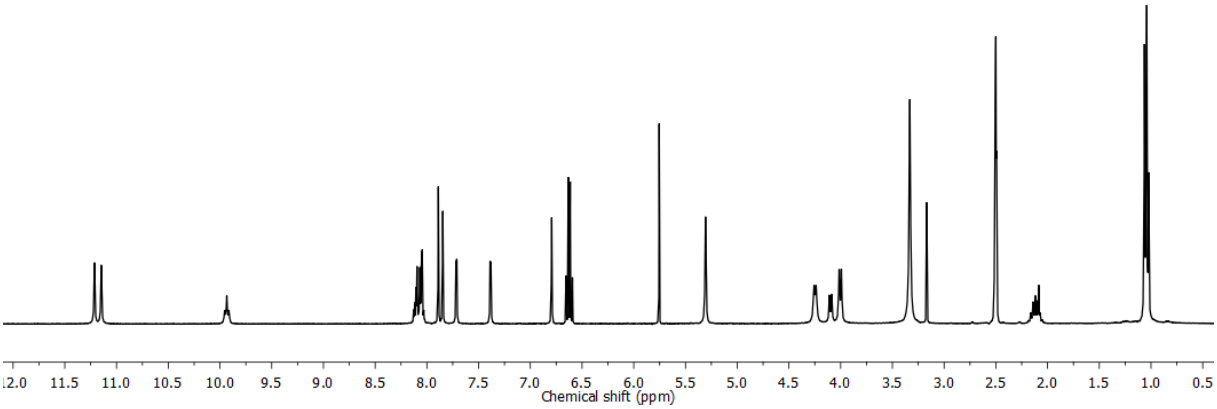
[Mass Spectrum]
Data : LF220azoture-EI001 Date : 01-Oct-2018 14:27
RT : 4.31 min Scan# : (207,239)
Elements : C 24/0, H 49/0, N 3/0, S 4/0
Mass Tolerance : 1000ppm, 1mmu if m/z > 1
Unsaturation (U.S.) : -0.5 - 20.0



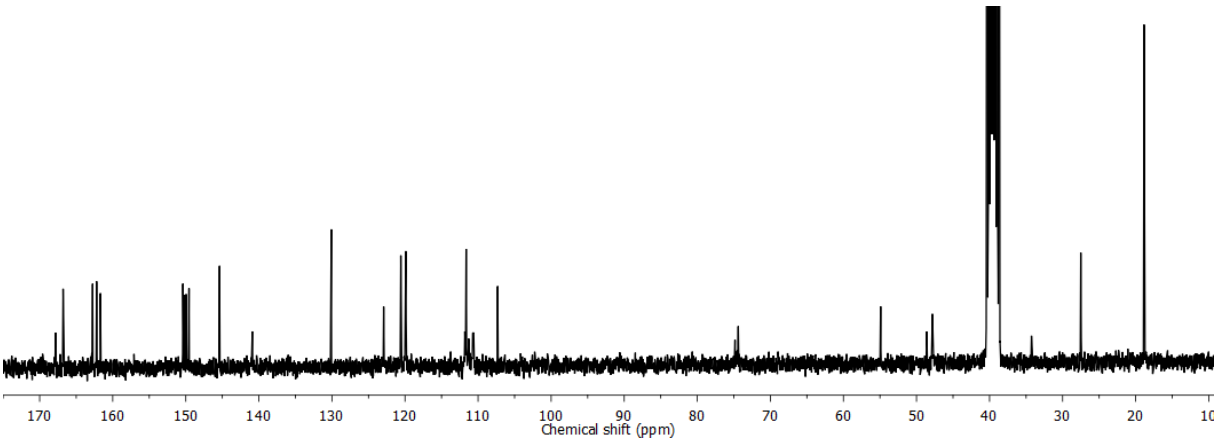
	Observed m/z	Int%	Err[ppm / mmu]	U.S.	Composition
1	258.9361	100.00	-2.1 / -0.5	11.0	C7 H5 N3 S4

*Foldamer **3***

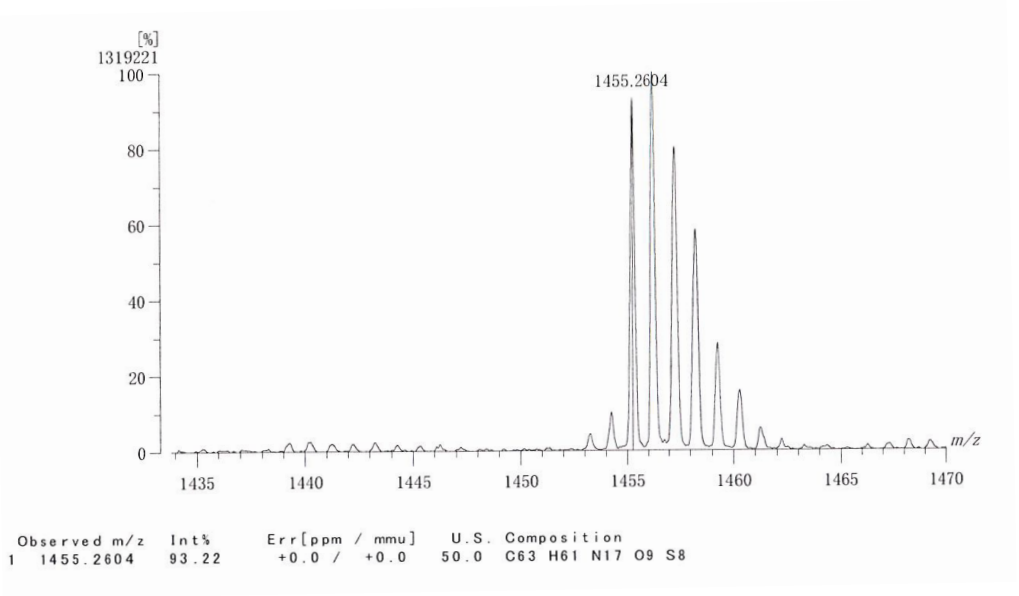
^{1}H NMR ($CDCl_3$)



^{13}C NMR ($CDCl_3$)

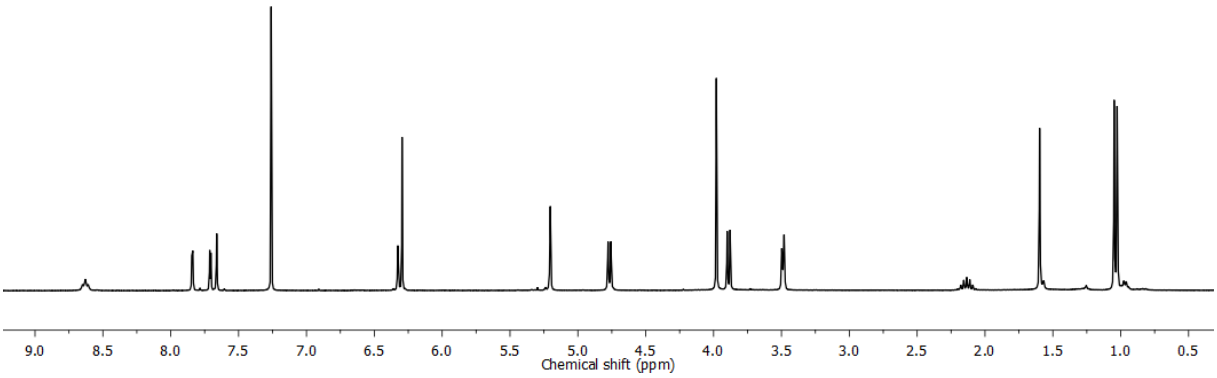


HRMS



*Reference **4***

^{1}H NMR ($CDCl_3$)



^{13}C NMR ($CDCl_3$)