Supplementary Information

Breaking New Ground in Direct Mechanocatalysis: Knoevenagel Condensation via Supported Organo-catalysts on Zirconia

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I. Materials and methods

a. Materials and chemicals

Sintered yttried-zirconia (3Y-TZP) milling balls (10 and 5 mm of diameter) from Retsch with a composition of 96-95 mol % of ZrO_2, 3 mol % of Y_2O_3, < 1 mol % of Al_2O_3, < 1 mol % of SiO_2 and < 1 mol % of HfO_2 and sintered yttried-zirconia (3Y-TZP) plates (20 x 20 x 1 mm) from Final Advanced Materials Sarl with the same composition as milling balls were cleaned and activated by Piranha solution (98 % H_2SO_4: 33 % H_2O_2, 3:1 (v/v)) for 90 min at room temperature. Afterward, the samples were rinsed with deionized water until the effluents reached a neutral pH. Then, the samples were placed in a beaker of ethanol (97 % purity) and cleaned in an ultrasonic bath for 10 min, followed by drying at 70 °C for 6 h. Poly(methyl vinyl ether-alt-maleic anhydride), average Mw ~216,000, average Mn ~80,000 (ANHY) and PAMAM dendrimer, ethylenediamine core, generation 4.0 solution (10 wt. % in methanol) from Sigma-Aldrich, 3-Aminopropylphosphonic acid hydrochloride salt (APPA, $C_3H_{11}ClNO_3P$, 97%) from Sikémia, acid orange 7 ($C_{16}H_{11}N_2NaO_4S$, 99 %) from Thermoscientific, sulfuric acid (H_2SO_4, NORMAPUR 98 %), hydrogen peroxide (H_2O_2, 33 %), hydrochloric acid (HCl, AnalaR NORMAPUR® Reag 37 %), sodium hydroxide (NaOH, pellets ACS), potassium tert-butoxide (tBuOK, ≥ 98%) sodium carbonate (Na_2CO_3, ≥ 97%) from VWR, tert-butyl 4-(2-bromoethyl)piperazine-1-carboxylate from BLD Pharm were used as purchased.

b. Chemical functionalization protocols

Functionalization with 3-aminopropylphosphonic acid hydrochloride salt (APPA), ZrO_2-APPA

Freshly activated zirconia samples were immediately introduced to a round-bottom flask with 15 mL solution of APPA in toluene, with a concentration of 2.8×10^{-2} mol.L^{-1}, at 95 °C. After 4 h, the samples were rinsed individually with distilled water (x 3), ethanol (x 3), and dried in an oven at 90 °C overnight.

Functionalization with Poly(methyl vinyl ether-alt-maleic anhydride) (ANHY), ZrO_2-ANHY

ZrO_2-APPA samples were immersed in an aqueous solution of Na_2CO_3 at pH =11 for 10 minutes at room temperature. The samples were then rinsed twice with distilled water and twice with ethanol. They were immediately introduced into a Schlenk flask. The flask was closed and purged with dinitrogen. 500 mg of Poly(methyl vinyl ether-alt-maleic anhydride) and 20 mL of anhydrous tetrahydrofuran were added to the flask under nitrogen. The reaction was carried out 4 h at 66 °C. After 4 h, the samples were rinsed individually with tetrahydrofuran (x 3), ethanol (x 3), and dried in an oven at 90 °C overnight to give ZrO_2-ANHY samples.

Functionalization with PAMAM dendrimer, ZrO_2-PAMAM

ZrO_2-ANHY samples were introduced into a Schlenk flask. The flask was closed and purged with dinitrogen. 2 mL of PAMAM dendrimer, ethylenediamine core, generation 4.0 solution (10 wt. % in methanol) and 30 mL of anhydrous dimethylsulfoxide were added to the flask under nitrogen. After 4 h at 80 °C, the samples were rinsed individually with dimethylsulfoxide (x 3), ethanol (x 3), and dried in an oven at 90 °C overnight to give ZrO2-PAMAM samples.

Covalent grafting of a piperazine analogue on amine functionalized surface, ZrO_2-APPA-N and ZrO_2-PAMAM-N

The piperazine grafting is carried out in three steps via the use of a Boc-protected alkylbromide derivative of piperazine on two types of amine-functionalized milling balls: ZrO_2-APPA and ZrO_2-PAMAM. Amine-functionalized samples were introduced in a round-bottom flask with 30 mL of acetonitrile, 73 mg of tert-butyl 4-(2-bromoethyl)piperazine-1-carboxylate (0,247 mmol) and 23 mg of potassium tert-butoxide. The solution was stirred overnight at 82 °C. Then, the samples were rinsed individually with acetonitrile (x 3), ethanol (x 3), and dried in an oven at 90 °C overnight. The samples are then immersed in an aqueous HCl solution (4 mol.L^{-1}) for 1 h at room temperature to remove the tert-butyloxycarbonyl (Boc) protecting group. After rinsing with deionized water, the samples are subsequently immersed in an aqueous Na_2CO_3 solution at pH 11 for 1 h at room temperature to deprotonate the formed ammonium groups.
XPS analyses indicate the absence of bromine on the ball surface after grafting (see Fig. S II-1 Supplementary Information). This demonstrates that covalent attachment of the piperazine occurred via substitution of the bromine atom by surface primary amines, and also suggests the absence of chemisorbed piperazine derivatives, which could otherwise leach into the reaction medium during mechanochemical tests and artificially contribute to the observed catalytic activity.

c. Mechanochemical reaction protocol

Starting with ZrO_2-APPA-N or ZrO_2-PAMAM-N functionalized milling balls, direct organo-mechanocatalytic tests for the Knoevenagel condensation were performed using both a vibratory and a planetary ball-mill. Following preliminary experiments, mild milling conditions were selected to minimize abrasion and preserve the ball surfaces. In the vibratory mill, reactions were thus carried out at 20 Hz in a 15 mL PTFE jar (softer than zirconia), whereas in the planetary mill, reactions were conducted at 250 rpm in a 20 mL zirconia jar (as PTFE jars deform under planetary milling). The milling load were 10.36 mg.mL^{-1} for the vibratory mill and 28.75 mg.mL^{-1} for the planetary mill. To assess the influence of ball size and number on reaction kinetics, various configurations were tested: in the vibratory mill, experiments were performed with one 1 cm ball, two 1 cm balls, or five 0.5 cm balls and in the planetary mill, forty balls of 0.5 cm diameter were used. As a control, initial reactions were performed with unfunctionalized zirconia balls under each conditions.

II. General information on characterizations

a. Polarization Modulation Infrared Reflection-Absorption Spectroscopy

PM-IRRAS spectra of functionalized and non-functionalized zirconia substrates were recorded on a ThermoNicolet Nexus 670 FTIR spectrometer at a resolution of 4 cm^{-1}, by coadding several blocks of 1500 scans (30 minutes acquisition time). Generally, ten blocks (5 hours acquisition time) were necessary to obtain PM-IRRAS spectra with good signal-to-noise ratios. Experiments were performed at an incidence angle of 75° using an external homemade goniometer reflection attachment[1,2]. The infrared parallel beam (modulated in intensity at frequency f_i lower than 5 KHz) was directed out of the spectrometer with an optional flipper mirror and made slightly convergent with a first BaF_2 lens (191 mm focal length). The IR beam passed through a BaF_2 wire grid polarizer (Specac) to select the s-polarized radiation and a ZnSe photoelastic modulator (PEM, Hinds Instruments, type III). The PEM modulated the polarization of the beam at a high fixed frequency, $2f_m$=100 KHz, between the parallel and perpendicular linear states. After reflection on the sample, the double modulated (in intensity and in polarization) infrared beam was focused with a second ZnSe lens (38.1 mm focal length) onto a photovoltaic MCT detector (Kolmar Technologies, Model KV104) cooled at 77 K. The polarization modulated signal $\mathrm{I_{AC}}$ was separated from the low frequency signal $\mathrm{I_{DC}}$ (f_i between 500 and 5000 Hz) with a 40 KHz high pass filter and then demodulated with a lock-in amplifier (Stanford Model SR 830). The two interferograms were high-pass and low-pas filtered (Stanford Model SR 650) and simultaneously sampled in the dual channel electronics of the spectrometer. In all experiments, the PEM was adjusted for a maximum efficiency at 2500 cm^{-1} to cover the mid-IR range in only one spectrum.

Using the experimental conditions described above, the PM-IRRAS signal is given by the relation[1,2]:

$$S_{PM-IRRAS} = \frac{2G\left|\left[R_s(d) - R_p(d)\right]J_2(\varphi_0)\right|}{\left[R_s(d) + R_p(d)\right] - \left[R_s(d) - R_p(d)\right]J_0(\varphi_0)}$$

where : $R_p(d)$ and $R_s(d)$ are the reflectances of the functionalized zirconia substrates, polarized parallel and perpendicular to the incidence plane, respectively, d is the film thickness, $J_0(\varphi_0)$ and $J_2(\varphi_0)$ are the zero- and second-order Bessel functions of the maximum dephasing φ_0 introduced by the PEM, and $G = 10 \cdot \frac{G_{AC}}{S \cdot G_{DC}} exp[-2V\bar{\upsilon}\tau]$ is a gain factor due to the different amplifications (G_{AC} and G_{DC}) on the two channels and to the demodulation adjustments (sensibility, S, and output time constant, τ of the lock-in amplifier). The absolute value in the equation comes simply from the usual computer algorithm of phase correction (Mertz) used on FTIR spectrometers that always stores and plots Fourier transforms of interferograms as positive single-beam spectra. The electronic parameters used during PM-IRRAS experiments were: $G_{AC} = G_{DC} = 1$, $S = 1$, V = 0.63 cm/s and τ = 1 ms.

Contrary to metallic substrates, the PM-IRRAS signal of zirconia substrates cannot be simplified and expressed in IRRAS unit from a calibration procedure[2,3]. In addition, due to the high value of the refractive index of zirconia (around 2 in the infrared spectral range), the difference between the polarized reflectances $R_p(d)$ and $R_s(d)$ at 75° is significantly higher than for metallic substrates, giving rise to a strong contribution of the zirconia substrate alone. Thus, to reveal the very small contribution of the thin grafted films, it was necessary to subtract the PM-IRRAS spectrum of the non-functionalized zirconia substrate from the PM-IRRAS spectrum of functionalized zirconia substrates.

b. X-ray Photoelectron Spectroscopy

XPS is a well-known surface analysis technique where 95% of the detected photoelectrons originate from a depth of about three times their mean free path, corresponding to approximately 10 nm. A Thermo Fisher Scientific K-Alpha X-ray photoelectron spectrometer was used for XPS surface analysis with a monochromatized Al-Kα source (hν = 1486.6 eV) and a 400 µm X-ray spot size. The full spectra (0-1350 eV) were obtained with a constant pass energy of 200 eV, while high-resolution spectra were recorded with a constant pass energy of 40 eV. Charge neutralization was applied during the analysis and was deemed to have been fully achieved by monitoring the C 1s signal for adventitious carbon. An additional analysis was performed with 200 µm X-ray spot size using ion sputtering following five sputtering times (0, 30, 90, 270, and 450 s), using an argon ion gun operated at 500 eV (high) or 1000 eV (low), with a raster size of 0.5 mm. High-resolution spectra (i.e., C 1s, O 1s, N 1s, Zr 3d) were quantified using the Avantage Software provided by ThermoFisher Scientific (Scofield Sensitivity Factors). A relative uncertainty of 5 to 10 % on the absolute value is considered for the atomic percentages of each element. In all cases, high-resolution spectra have been charge corrected versus the main component of the C 1s spectrum set to 284.8 eV.

c. Colorimetric assay

A colorimetric method was used to quantify the amount of exposed primary amine groups on zirconia-activated surfaces after grafting. This method is based on the work of Uchida et al. with the use of acid Orange 7 as dye[4,5]. The grafted samples were immersed in 25 mL of dye solution (14 mg / mL) in an acidic solution (Milli-Q water adjusted to pH 3 with 1 M HCl) for 30 min at 40 °C. The samples were then intensively rinsed 3 times using the acidic solution (pH 3) to remove unbound dye. Once air-dried, the colored films were immersed in 2.7 mL of alkaline solution (Milli-Q water mixture adjusted to pH 12 with a 1 M NaOH solution). The pH of the solution containing the desorbed dye was adjusted to pH 3 by adding 0.3 mL of HCl 37%. The absorbance of the solution was then measured at 484 nm. A calibration curve in the range of 5 x 10^{-7} to 1 × 10^{-5} mol L-1 was established, allowing for the determination of a linear relationship between absorbance and concentration within the range of interest for this study. For the calculation of the number of NH_2 groups per nm^2, the surface area value is determined via the calculation of the geometrical surface area of a 1 cm diameter sphere.

d. ^1H and ^{13}C NMR

NMR Analyses were performed at the “Laboratoire de Mesures Physiques” (IBMM, Université de Montpellier). ^1H NMR spectra were recorded on a Bruker AVANCE 500 MHz and are reported in ppm using deuterated solvent (DMSO-d6 at 2.50 ppm) as internal standards. Data are reported as s = singlet, d = doublet, t = triplet; integration. ^{13}C NMR spectra were recorded on a Bruker AVANCE 126 MHz and are reported in ppm using deuterated solvent (DMSO-d6 at 39.5 ppm) as internal standards.

e. Liquid chromatography and mass spectroscopy

Mass spectra were obtained by LC-MS using as LC a Water Alliance 2695, coupled to a Waters ZQ spectrometer with an electrospray source, a single quadrupole analyzer and a Waters 2489 UV detector. HPLC conversion was measured on an Agilent technologies 1220 Infinity LC using a high resolution Chromolith® RP-18e50-4.6 mm column and a linear gradient of 0-100% CH_3CN/0.1% TFA in H_2O/0.1% TFA over 3 min, UV lamp detection on at 214 nm. Flow rate: 1 mL.min^{-1}. To monitor reactions in a ball-mill, a sample was taken from the milling jar, dissolved in 1 mL of CH_3CN or a mixture CH_3CN/H_2O, and submitted to HPLC analysis.

References

1. Buffeteau, T., Desbat, B. & Turlet, J. M. Polarization Modulation FT-IR Spectroscopy of Surfaces and Ultra-Thin Films: Experimental Procedure and Quantitative Analysis. *Appl. Spectrosc.* **45**, 380–389 (1991).
2. Ramin, M. A. *et al.* PM-IRRAS investigation of self-assembled monolayers grafted onto SiO2/Au substrates. *Langmuir ACS J. Surf. Colloids* **27**, 6076–6084 (2011).
3. Buffeteau, T., Desbat, B., Blaudez, D. & Turlet, J. M. Calibration Procedure to Derive IRRAS Spectra from PM-IRRAS Spectra. *Appl. Spectrosc.* **54**, 1646–1650 (2000).
4. Uchida, E., Uyama, Y. & Ikada, Y. Sorption of low-molecular-weight anions into thin polycation layers grafted onto a film. *Langmuir* **9**, 1121–1124 (1993).
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III. Supplementary figures

Figure S III-1: *Evolution of the N 1s signal as a function of sputtering time for ZrO_2-PAMAM sample.*

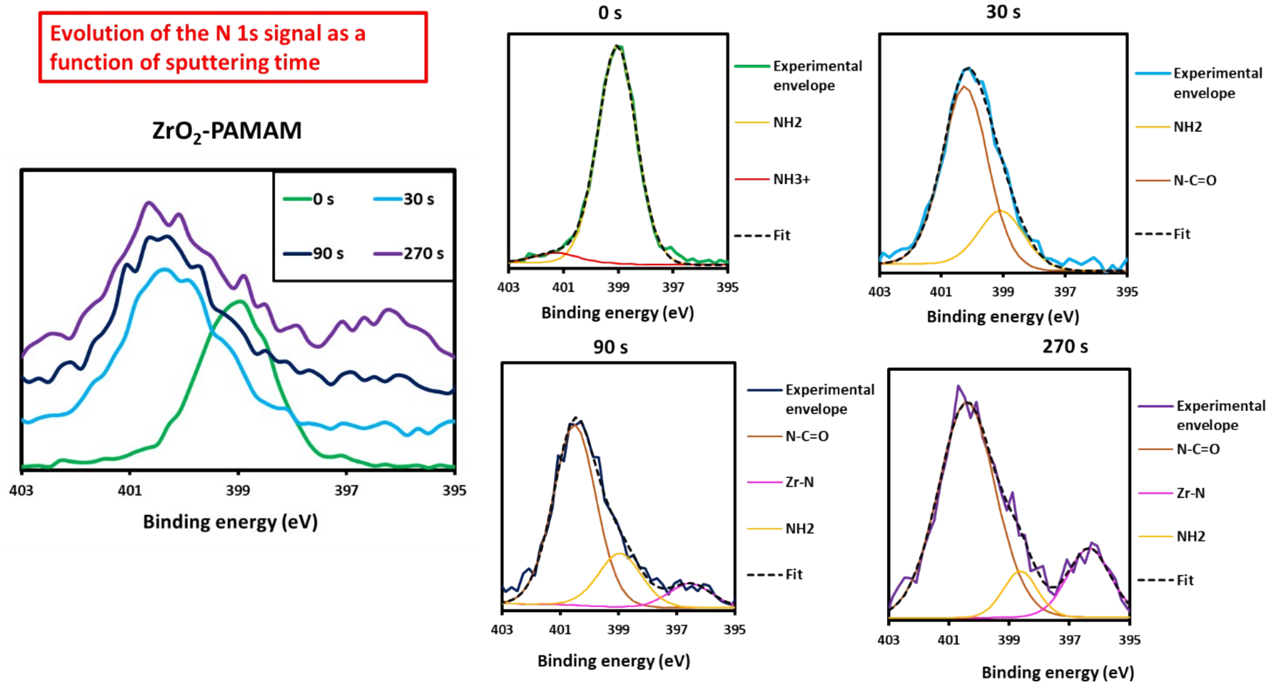


Figure S III-2: *Histogram of the number of amines functions per square nanometer measured from colorometric assay for ZrO_2-APPA and ZrO_2-PAMAM. For each sample, 5 repetitions were performed.*

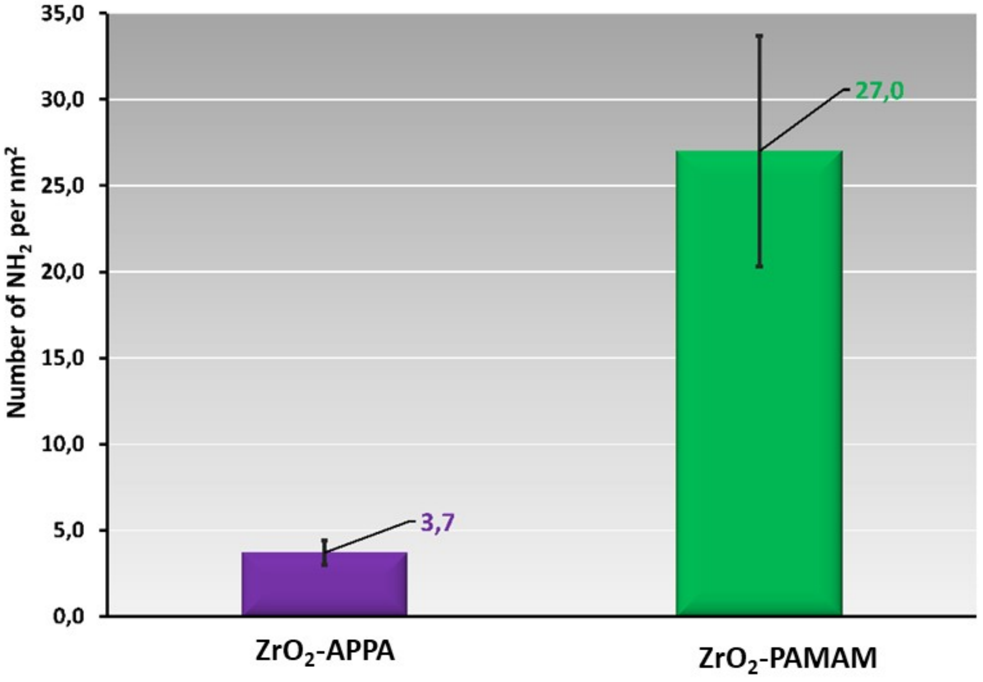


Figure S III-3: *Grafting of a piperazine analogue in three steps onto the surface of zirconia balls functionalized with amine groups to give ZrO2-APPA-N or ZrO2-PAMAM-N milling balls.*

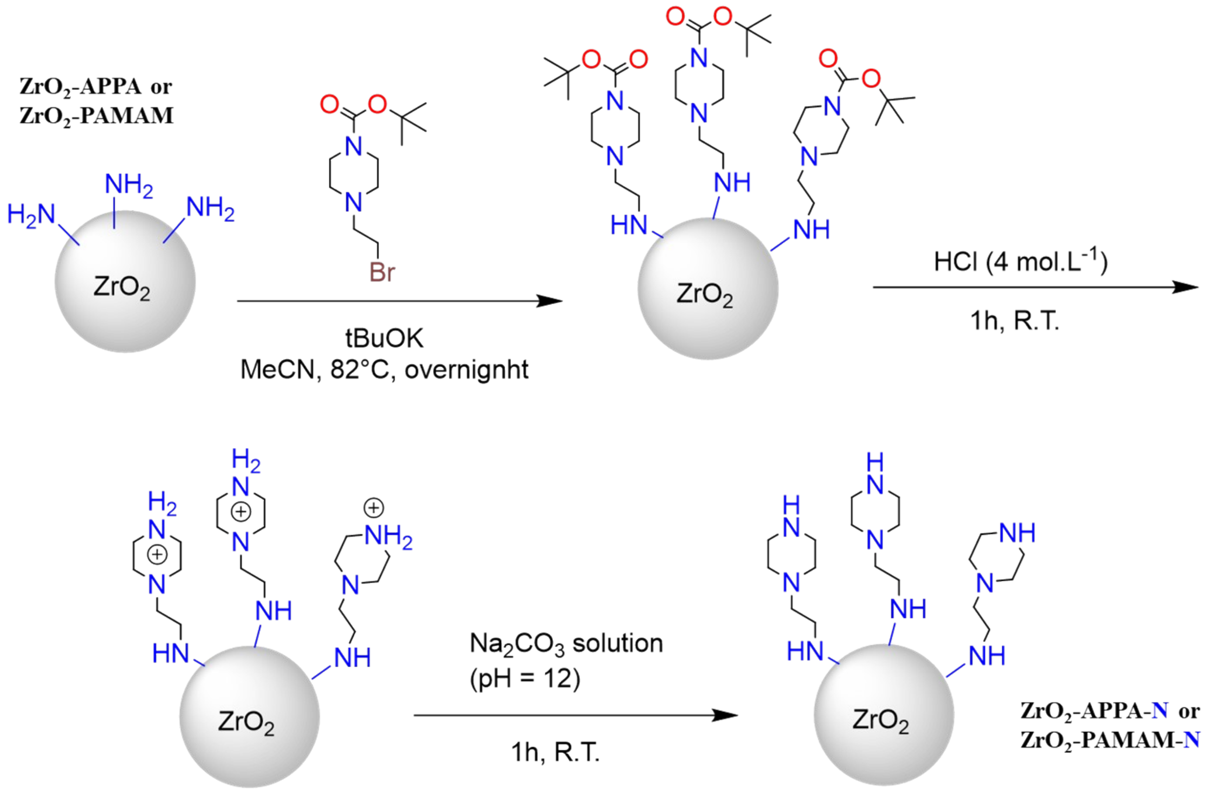
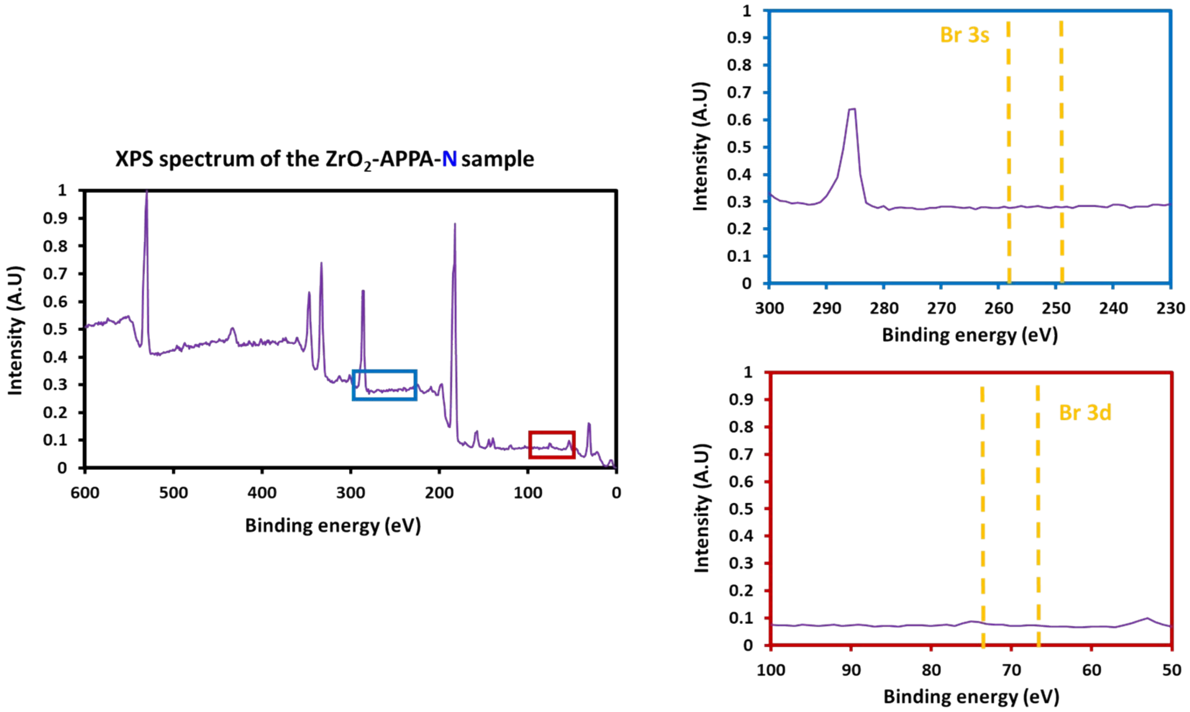
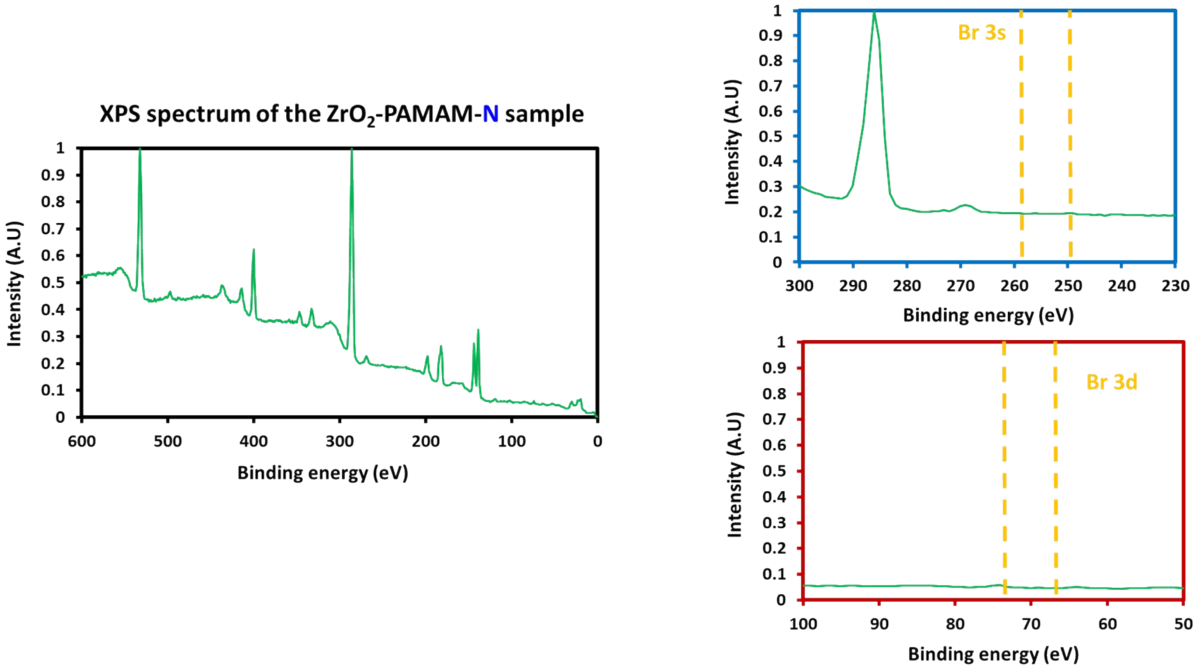


Figure S III-4: *XPS spectra, survey and high resolution in the Br 3s and Br 3d ranges for the ZrO_2-APPA-N sample, highlighting the lack of peaks in the Br 3s and Br 3d orbital regions.*



<u>Figure S III-5:</u> *XPS spectra, survey and high resolution in the Br 3s and Br 3d ranges for the sample ZrO_2-PAMAM-N, highlighting the lack of peaks in the Br 3s and Br 3d orbital regions.*



IV. Procedures for direct organo-catalysed reactions

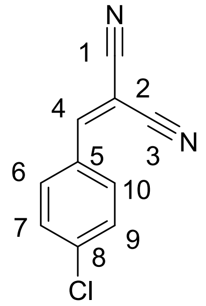
<u>Synthesis of 2-(4-chlorobenzylidene)malononitrile (1867-38-5)</u>

A 20 mL zirconium oxide milling jar was charged with 4-chlorobenzaldehyde (2.42 mmol) and malononitrile (2.42 mmol). Forty 0.5 cm ZrO_2-PAMAM-N milling balls were then introduced into the jar. The reactor was placed in a P7 planetary ball mill. After 3 hours at 250 Hz, milling was stopped, and the crude reaction mixture was recovered using acetone and concentrated under reduced pressure to yield 2-(4-chlorobenzylidene)malononitrile as a white solid (452 mg, 2.40 mmol, 99%). ML = 28.75 mg mL^{-1}.

^{1}H NMR (DMSO-d_6, 500 MHz): 8.56 (s, 1H, H4), 7.95 (d, 8.5 Hz, 2H,H6 and H10 or H7 and H9), 7.73 (d, 8.5 Hz, 2H, H7 and H9 or H6 and H10).

^{13}C (DMSO-d_6, 126 MHz): 160.16 (C4), 139.02 (C5 or C8), 132.20 (C6 and C10 or C7 and C9), 130.14 (C5 or C8), 129.79 (C6 and C10 or C7 and C9), 114.13 (C1 or C3), 113.09 (C1 or C3), 82.31 (C2).

HRMS: (ESI) m/z calculated for $C_{10}H_6ClN_2^+$: 189.0214 $[M+H]^+$; found : 189.0214.



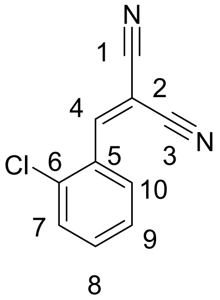
Synthesis of 2-(2-chlorobenzylidene)malononitrile (2698-41-1)

A 20 mL zirconium oxide milling jar was charged with 2-chlorobenzaldehyde (2.42 mmol) and malononitrile (2.42 mmol). Forty 0.5 cm ZrO_2-PAMAM-N milling balls were then introduced into the jar. The reactor was placed in a P7 planetary ball mill. After 3 hours at 250 Hz, milling was stopped, and the crude reaction mixture was recovered using acetone and concentrated under reduced pressure to yield 2-(2-chlorobenzylidene)malononitrile as a white solid (447 mg, 2.37 mmol, 98%). ML = 28.75 mg/mL.

^{1}H NMR (DMSO-d$_6$, 500 MHz): 8.68 (s, 1H, H4), 8.03 (dd, 1.5 and 7.5 Hz, 1H, H7 or H10), 7.71 (dd, 1.5 and 7.5 Hz, 1H, H7 or H10), 7.67 (td, 1.5 and 7.5 Hz, 1H, H8 or H9), 7.59 (td, 1.5 and 7.5 Hz, 1H, H8 or H9).

^{13}C (DMSO-d$_6$, 126 MHz): 158.07 (C4), 134.92 (C7/C8/C9 or C10), 134.29 (C5 or C6), 130.42 (C7/C8/C9 or C10), 129.91 (C7/C8/C9 or C10), 129.67 (C5 or C6), 128.05 (C7/C8/C9 or C10), 113.50 (C1 or C3), 112.44 (C1 or C3), 86.70 (C2).

HRMS: (ESI) m/z calculated for $C_{10}H_6ClN_2^+$: 189.0214 $[M+H]^+$; found : 189.0214.



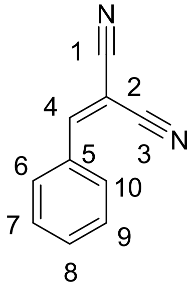
Synthesis of 2-benzylidenemalononitrile (2700-22-3)

A 20 mL zirconia milling jar was charged with benzaldehyde (2.90 mmol) and malononitrile (2.90 mmol). Forty 0.5 cm ZrO_2-PAMAM-N milling balls were then introduced into the jar. The reactor was placed in a P7 planetary ball mill. After 4 hours at 250 Hz, milling was stopped, and the crude reaction mixture was recovered using acetone and concentrated under reduced pressure to yield 2-benzylidenemalononitrile as a brown solid (430 mg, 2.79 mmol, 96%). ML = 28.75 mg/mL.

^{1}H NMR (DMSO-d$_6$, 500 MHz): 8.56 (s, 1H, H4), 7.95 (dd, 1.5 and 7.5 Hz, 1H, H6 and H10), 7.70 (tt, 1.5 and 7.5 Hz, 1H, H8), 7.62 (t, 7.5 Hz, 2H, H7 and H9).

^{13}C (DMSO-d$_6$, 126 MHz): 161.60 (C4), 134.44 (C8), 131.33(C5), 130.55 (C6 and C10 or C7 and C9), 129.58 (C6 and C10 or C7 and C9), 114.26 (C1 or C3), 113.27 (C1 or C3), 81.64 (C2).

HRMS: (ESI) m/z calculated for $C_{10}H_7N_2^+$: 155.0604 [M+H]$^+$; found : 155.0606.



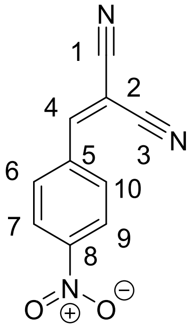
Synthesis of 2-(4-nitrobenzylidene)malononitrile (2700-23-4)

A 20 mL zirconium oxide milling jar was charged with 4-nitrobenzaldehyde (2.30 mmol) and malononitrile (2.30 mmol). Forty 0.5 cm ZrO_2-PAMAM-N milling balls were then introduced into the jar. The reactor was placed in a P7 planetary ball mill. After 3 hours at 250 Hz, milling was stopped, and the crude reaction mixture was recovered using acetone and concentrated under reduced pressure to yield 2-(4-nitrobenzylidene)malononitrile as a yellow solid (445 mg, 2.23 mmol, 97%). ML = 28.75 mg/mL.

^{1}H NMR (DMSO-d$_6$, 500 MHz): 8.73 (s, 1H, H4), 8.44 (d, 8.5 Hz, 2H, H7 and H9), 8.14 (d, 8.5 Hz, 2H, H6 and H10).

^{13}C (DMSO-d$_6$, 126 MHz): 159.34 (C4), 149.73 (C8), 136.73 (C5), 131.50 (C6 and C10), 124.47 (C7 and C9), 113.71 (C1 or C3), 112.60 (C1 or C3), 86.02 (C2).

HRMS: (ESI) m/z calculated for $C_{10}H_4O_2N_3^-$: 198.0309 [M-H]$^-$; found : 198.0310.



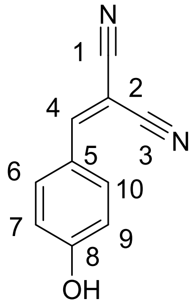
Synthesis of 2-(4-hydroxybenzylidene)malononitrile (3785-90-8)

A 20 mL zirconium oxide milling jar was charged with 4-hydroxybenzaldehyde (2.66 mmol) and malononitrile (2.66 mmol). Forty 0.5 cm ZrO_2-PAMAM-N milling balls were then introduced into the jar. The reactor was placed in a P7 planetary ball mill. After 3 hours at 250 Hz, milling was stopped, and the crude reaction mixture was recovered using acetone and concentrated under reduced pressure to yield 2-(4-hydroxybenzylidene)malononitrile as a yellow solid (434 mg, 2.55 mmol, 96%). ML = 28.75 mg/mL.

^{1}H NMR (DMSO-d$_6$, 500 MHz): 11.09 (s, 1H, -OH), 8.32 (s, 1H, H4), 7.89 (d, 8.5 Hz, 2H, H6 and H10), 6.98 (d, 8.5 Hz, 2H, H7 and H9).

^{13}C (DMSO-d$_6$, 126 MHz): 163.93 (C8), 160.57 (C4), 133.94 (C6 and C10), 122.84 (C5), 116.67 (C7 and C9), 115.15 (C1 or C3), 114.24 (C1 or C3), 75.13 (C2).

HRMS: (ESI) m/z calculated for $C_{10}H_7ON_2^+$: 171.0553 $[M+H]^+$; found : 171.0552.



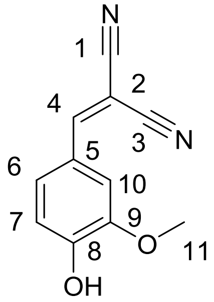
Synthesis of 2-(4-hydroxy-3-methoxybenzylidene)malononitrile (36938-01-9)

A 20 mL zirconium oxide milling jar was charged with 4-hydroxy-3-methoxybenzaldehyde (2.29 mmol) and malononitrile (2.29 mmol). Forty 0.5 cm ZrO_2-PAMAM-N milling balls were then introduced into the jar. The reactor was placed in a P7 planetary ball mill. After 4 hours at 250 rpm, milling was stopped, and the crude reaction mixture was recovered using acetone and concentrated under reduced pressure to yield 2-(4-hydroxy-3-methoxybenzylidene)malononitrile as an orange solid (436 mg, 2.18 mmol, 95%). ML = 28.75 mg/mL.

^{1}H NMR (DMSO-d$_6$, 500 MHz): 10.85 (s, 1H, -OH), 8.29 (s, 1H, H4), 7.64 (d, 2.0 Hz, 1H, H10), 7.50 (dd, 2.0 and 8.5 Hz, 1H, H6), 6.98 (d, 8.5 Hz, 1H, H7), 3.81 (s, 3H, H11).

^{13}C (DMSO-d$_6$, 126 MHz): 160.69 (C4), 153.87 (C8 or C9), 147.91 (C8 or C9), 127.72 (C6), 123.12 (C5), 116.18 (C7), 115.16 (C1 or C3), 114.41 (C1 or C3), 113.11 (C10) 75.03 (C2), 55.57 (C11).

HRMS: (ESI) m/z calculated for $C_{11}H_9O_2N_2^+$: 201.0658 $[M+H]^+$; found : 201.0659.



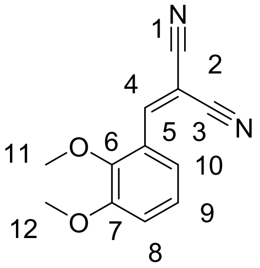
Synthesis of 2-(2,3-dimethoxybenzylidene)malononitrile (36937-95-8)

A 20 mL zirconium oxide milling jar was charged with 2,3-dimethoxybenzaldehyde (2.15 mmol) and malononitrile (2.15 mmol). Forty 0.5 cm ZrO_2-PAMAM-N milling balls were then introduced into the jar. The reactor was placed in a P7 planetary ball mill. After 5 hours at 250 Hz, milling was stopped, and the crude reaction mixture was recovered using acetone and concentrated under reduced pressure to yield 2-(2,3-dimethoxybenzylidene)malononitrile as an orange solid (443 mg, 2.07 mmol, 96%). ML = 28.75 mg/mL.

^{1}H NMR (DMSO-d$_6$, 500 MHz): 8.52 (s, 1H, H4), 7.60 (dd, 1.5 and 8.0 Hz, 1H, H8 or H10), 7.40 (dd, 1.5 and 8.0 Hz, 1H, H8 or H10), 7.28 (t, 8.0 Hz, 1H, H9), 3.87 (s, 3H, H11 or H12), 3.85 (s, 3H, H11 or H12).

^{13}C (DMSO-d$_6$, 126 MHz): 156.43 (C4), 152.59 (C6 or C7), 148.85 (C6 or C7), 125.01 (C5), 124.72 (C8), 119.30 (C9 or C10), 118.83 (C9 or C10), 114.29 (C1 or C3), 113.15 (C1 or C3), 82.94 (C2), 61.68 (C11 or C12), 56.13 (C11).

HRMS: (ESI) m/z calculated for $C_{12}H_{11}O_2N_2^+$: 215.0815 [M+H]$^+$; found : 215.0813.



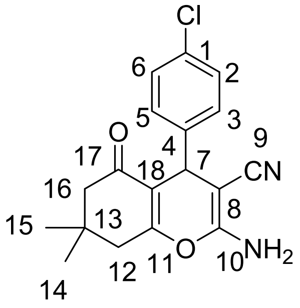
Synthesis of 2-amino-3-cyano-7,7-dimethyl-4-(4-chlorophenyl)-5-oxo-5,6,7,8-tetra-4H-chromene

A 20 mL zirconium oxide milling jar was charged with 4-chlorobenzaldehyde (1.44 mmol), malononitrile (1.44 mmol) and 5,5-dimethyl-1,3-cyclohexanedione (1.44 mmol) . Forty 0.5 cm ZrO_2-PAMAM-N milling balls were then introduced into the jar. The reactor was placed in a P7 planetary ball mill. After 6 hours at 250 Hz, milling was stopped, and the crude reaction mixture was recovered to yield 2-amino-3-cyano-7,7-dimethyl-4-(4-chlorophenyl)-5-oxo-5,6,7,8-tetra-4H-chromene as a white solid (449 mg, 1.37 mmol, 95%). ML = 28.75 mg/mL.

^{1}H NMR (DMSO-d$_6$, 500 MHz): 7.35 (d, 8.5 Hz, 2H, H2 and H6 or H3 and H5), 7.17 (d, 8.5 Hz, 2H, H2 and H6 or H3 and H5), 7.09 (s, 2H, NH_2), 4.19 (s, 1H, H7), 2.24 (d, 15 Hz, 1H, H12 or H16), 2.10 (d, 15Hz, 1H, H12 or H16), 2.08 (s, 1H, H12 or H16), 1.99 (s, 1H, H12 or H16), 1.03 (s, 3H, H14 or H15), 0.94 (s, 3H, H14 or H15).

^{13}C (DMSO-d$_6$, 126 MHz): 195.76 (C17), 162.68 (C11), 158.52 (C10), 143.82 (C4 or C1), 132.21 (C4 or C1), 129.17 (C2 and C6 or C3 and C5), 128.35 (C2 and C6 or C3 and C5), 119.64 (C9), 112.34 (C18), 57.66 (C8), 49.96 (C12 or C16), 39.58 (C12 or C16), 35.13 (C7), 31.87 (C13), 28.36 (C14 or C15), 26.89 (C14 or C15).

HRMS: (ESI) m/z calculated for $C_{18}H_{17}ClO_2N_2^+$: 329.1051 [M+H]$^+$; found : 329.1052.



V. Green metrics

The E-Factor focuses on the total amount of waste produced relative to the desired product, offering a global view of process cleanliness. A low E-Factor indicates a more environmentally friendly process.

$$E = \frac{total\ mass\ of\ waste\ (unreacted\ reagents, by\text{-}products, and\ solvents)}{mass\ of\ isolated\ product}$$

RME measures how efficiently the reactant masses are incorporated into the final product, directly reflecting the intrinsic efficiency of the chemical transformation itself. A high RME reflects an efficient reaction with minimal material loss and is particularly useful for comparing synthetic routes or optimizing a procedure.

$$RME\ (\%) = \frac{mass\ of\ isolated\ product}{total\ mass\ of\ reagents\ used} \times 100$$

Solvent Intensity (SI) focuses specifically on the environmental impact of solvents. It accounts for the mass of solvents required per mass unit of product, highlighting the frequently dominant contribution of solvents to the environmental footprint of processes. A high SI value indicates a solvent-intensive process.

$$SI = \frac{total\ mass\ of\ solvents\ used}{mass\ of\ isolated\ product}$$

VI. NMR Spectra

Figure S V-1: *^{1}H NMR (DMSO-d_6, 500 MHz) of 2-(4-chlorobenzylidene)malononitrile*

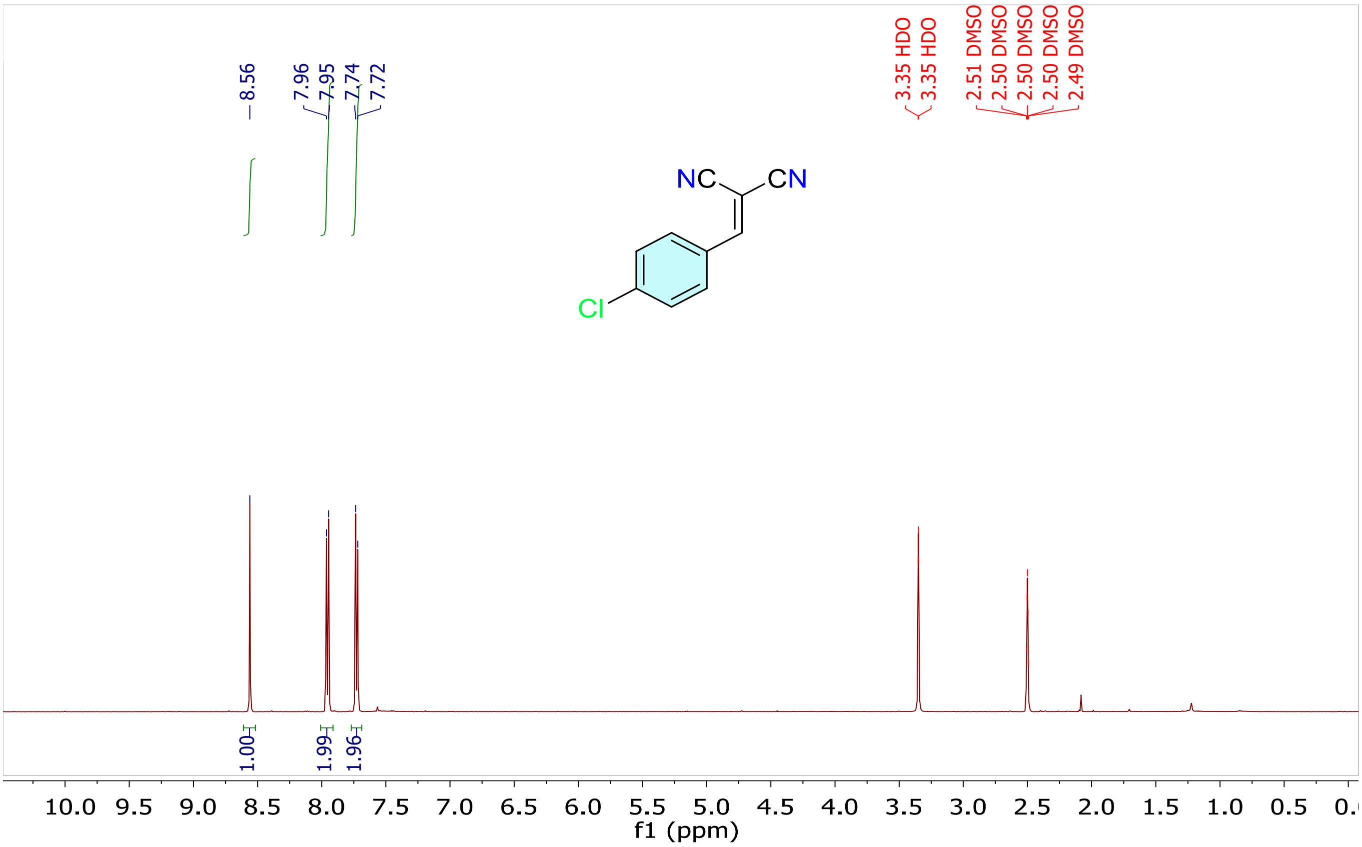


Figure S V-2: *^{13}C NMR (DMSO-d_6, 126 MHz) of 2-(4-chlorobenzylidene)malononitrile*

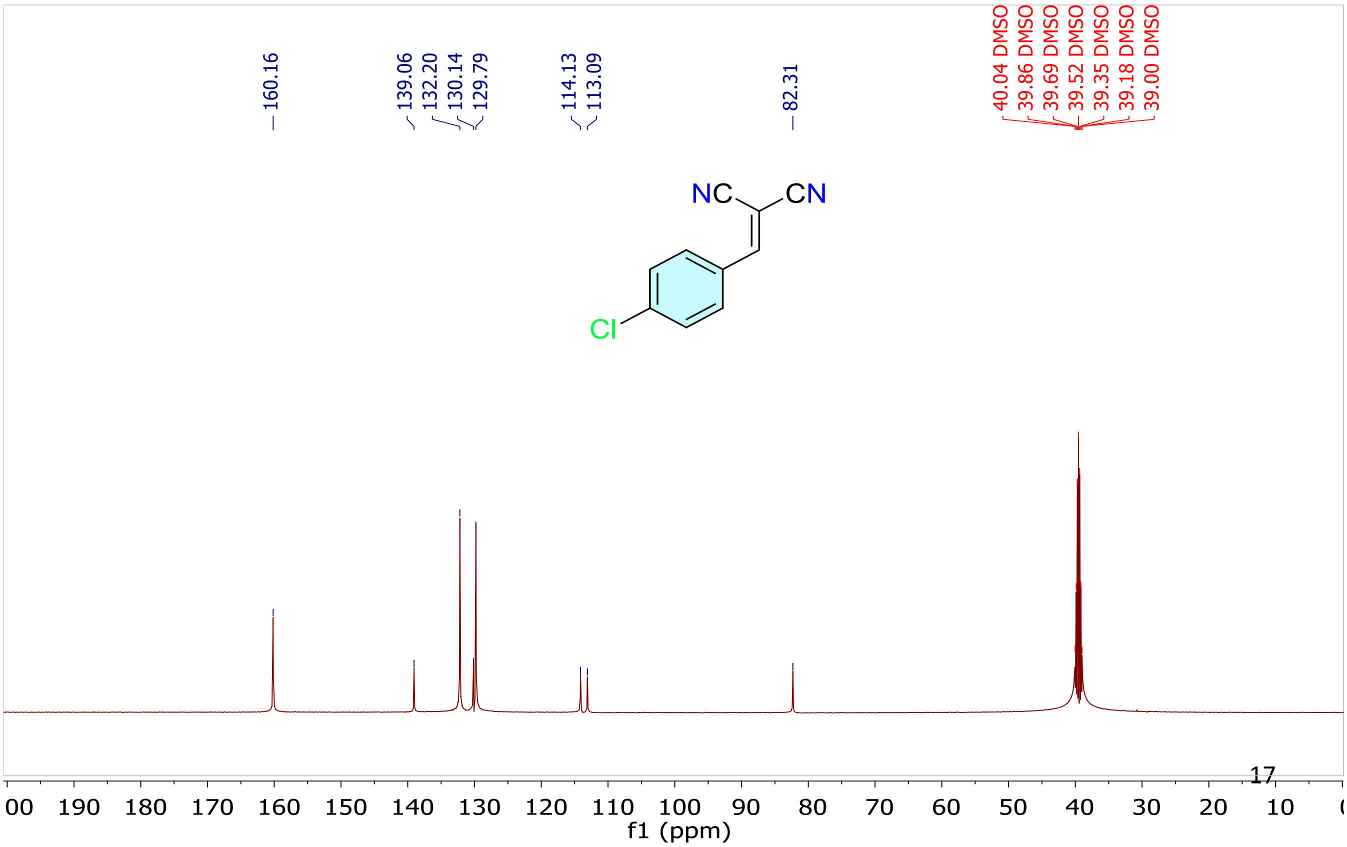


Figure S V-3: ^{1}H NMR (DMSO-d_6, 500 MHz) of 2-(2-chlorobenzylidene)malononitrile

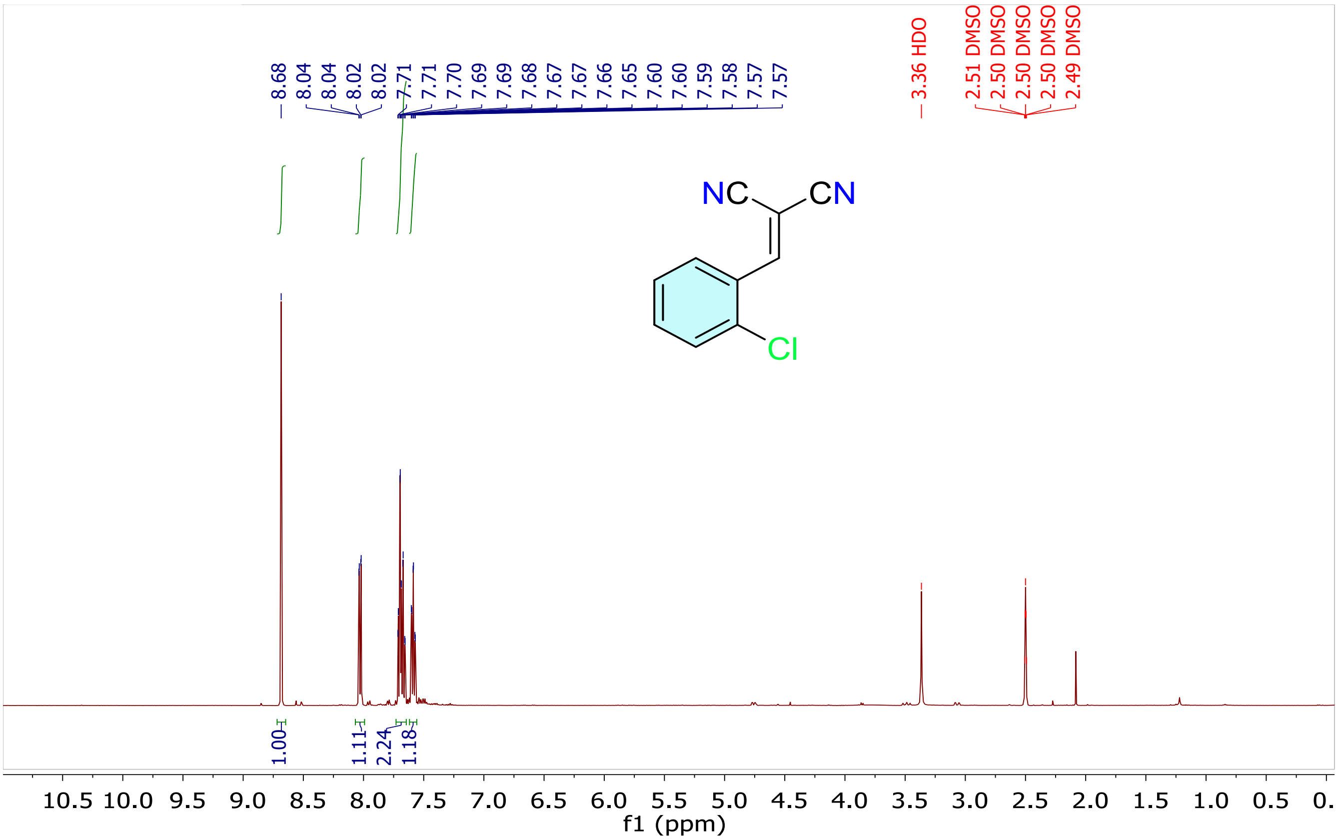


Figure S V-4: *^{13}C NMR (DMSO-d_6, 126 MHz) of 2-(2-chlorobenzylidene)malononitrile*

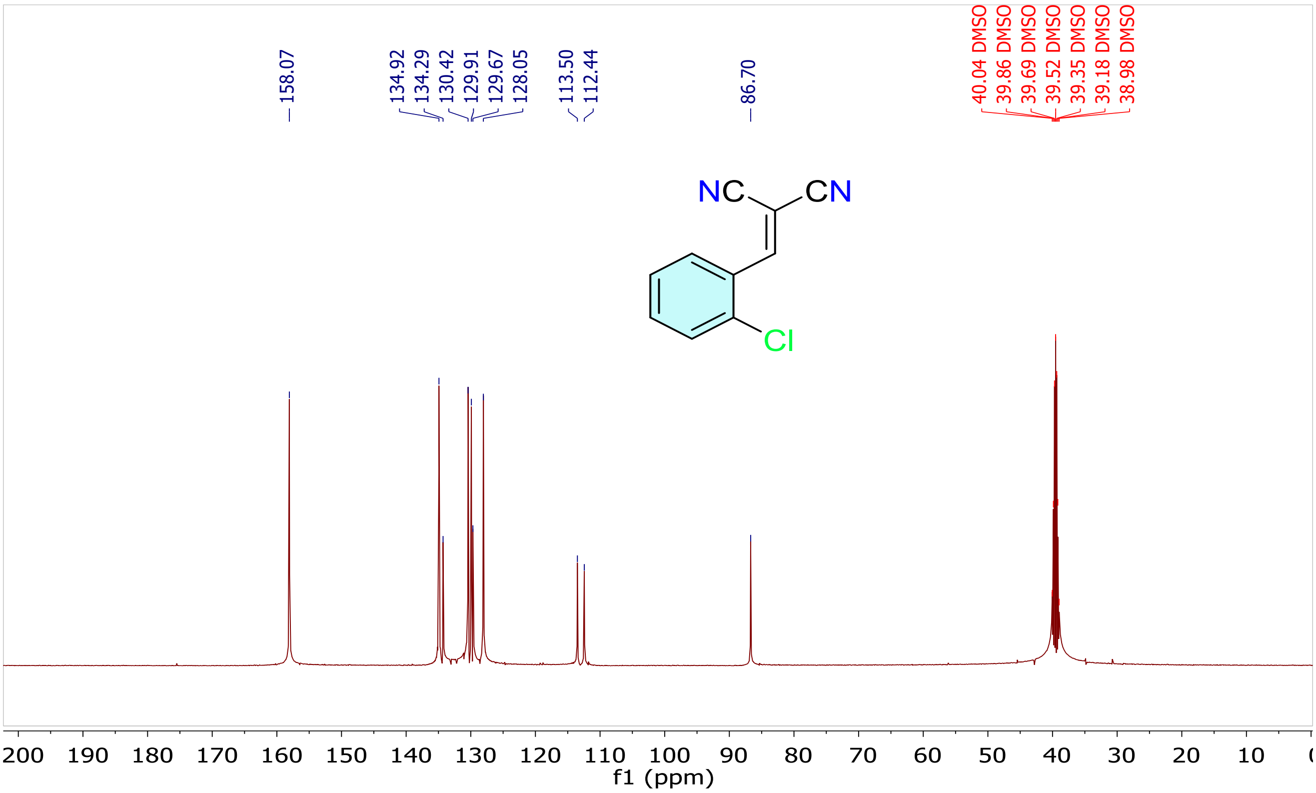


Figure S V-5: *^{1}H NMR (DMSO-d_6, 500 MHz) of 2-benzylidenemalononitrile*

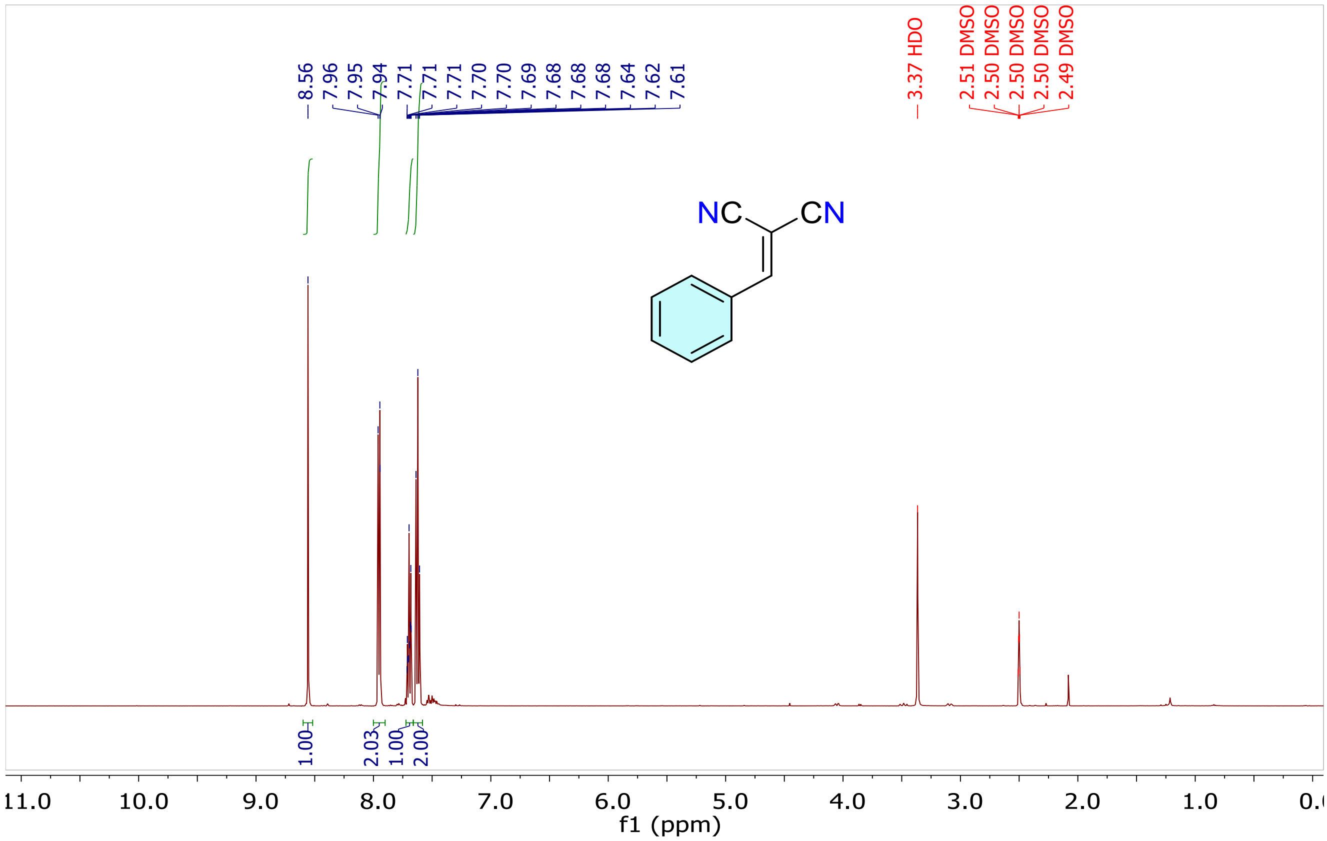


Figure S V-6: *^{13}C NMR (DMSO-d_6, 126 MHz) of 2-benzylidenemalononitrile*

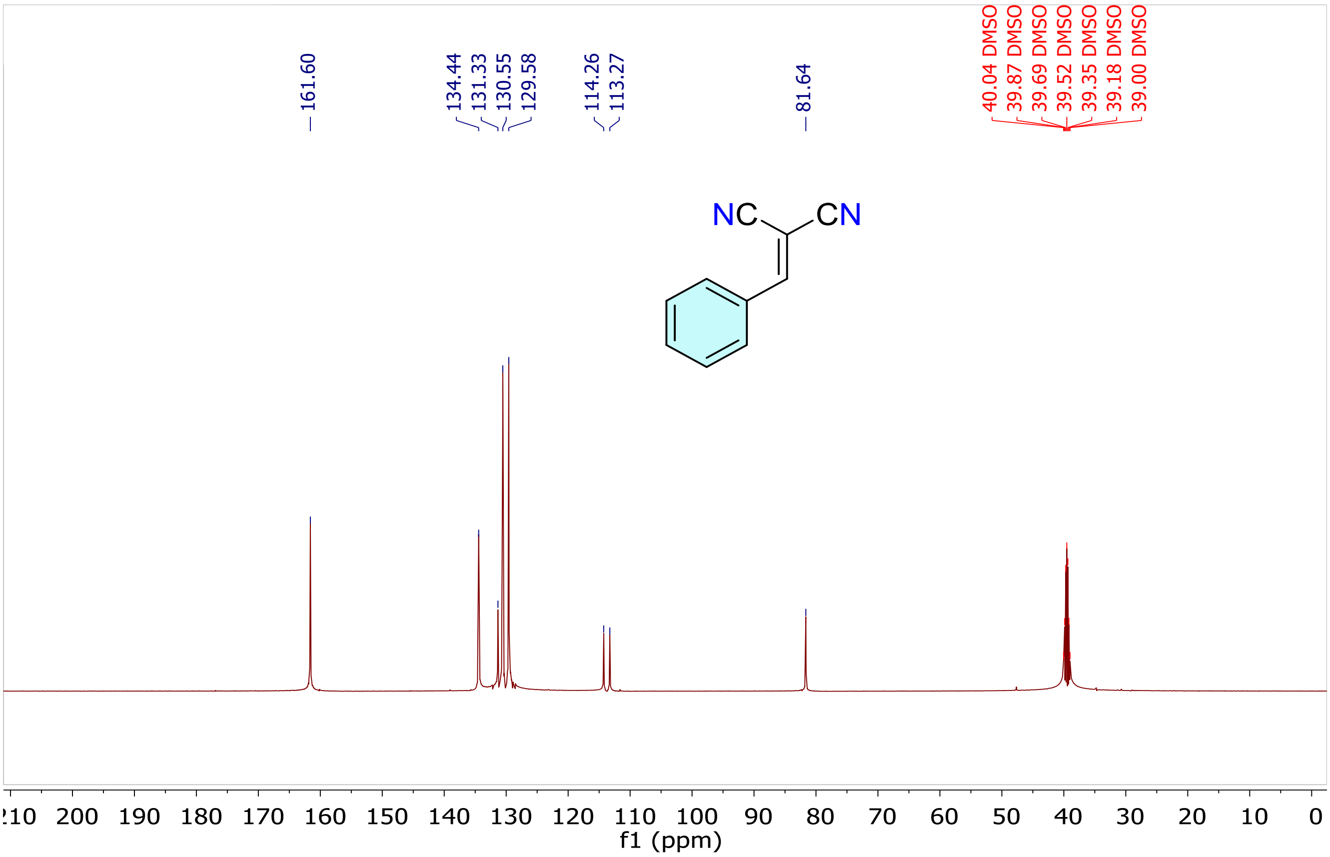


Figure S V-7: *^{1}H NMR (DMSO-d_6, 500 MHz) of 2-(4-nitrobenzylidene)malononitrile*

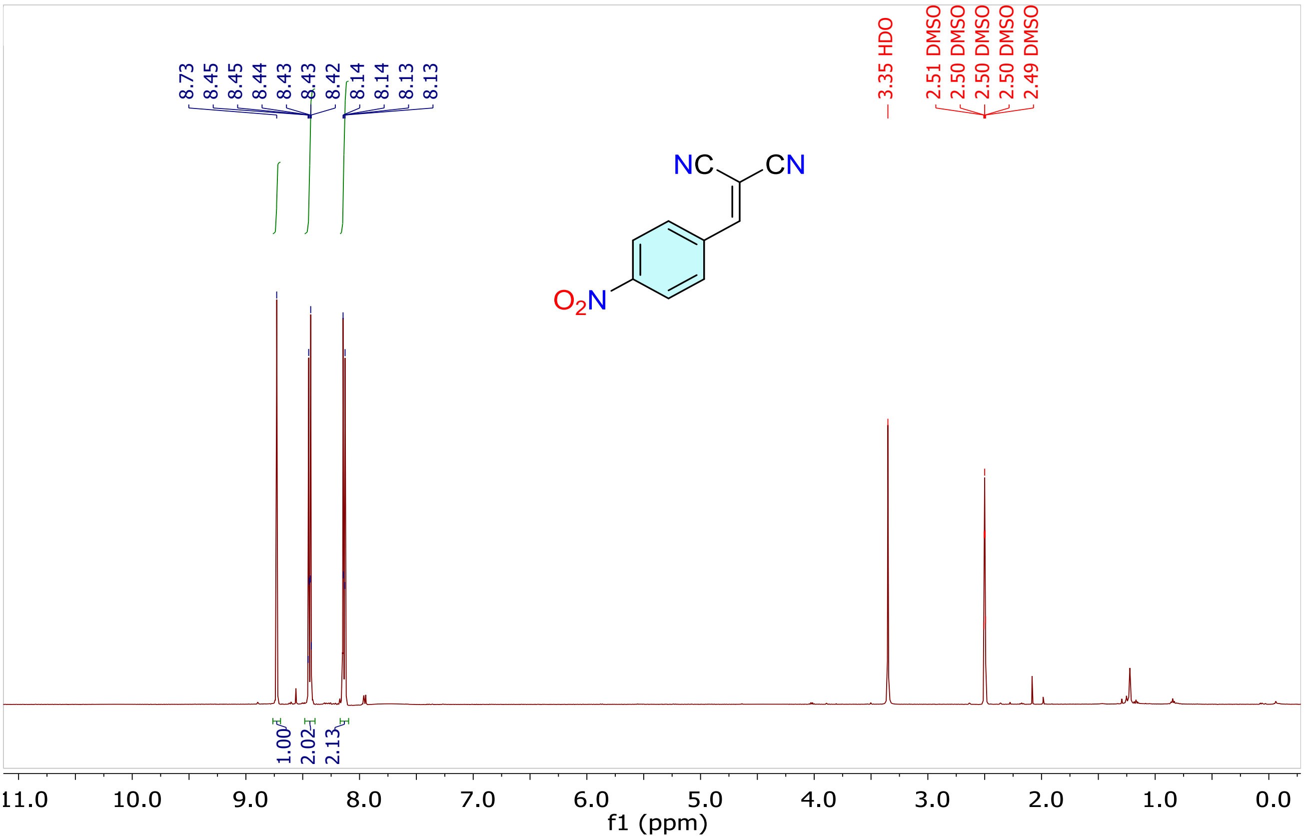


Figure S V-8: *^{13}C NMR (DMSO-d_6, 126 MHz) of 2-(4-nitrobenzylidene)malononitrile*

Figure S V-9: *^{1}H NMR (DMSO-d_6, 500 MHz) of 2-(4-hydroxybenzylidene)malononitrile*

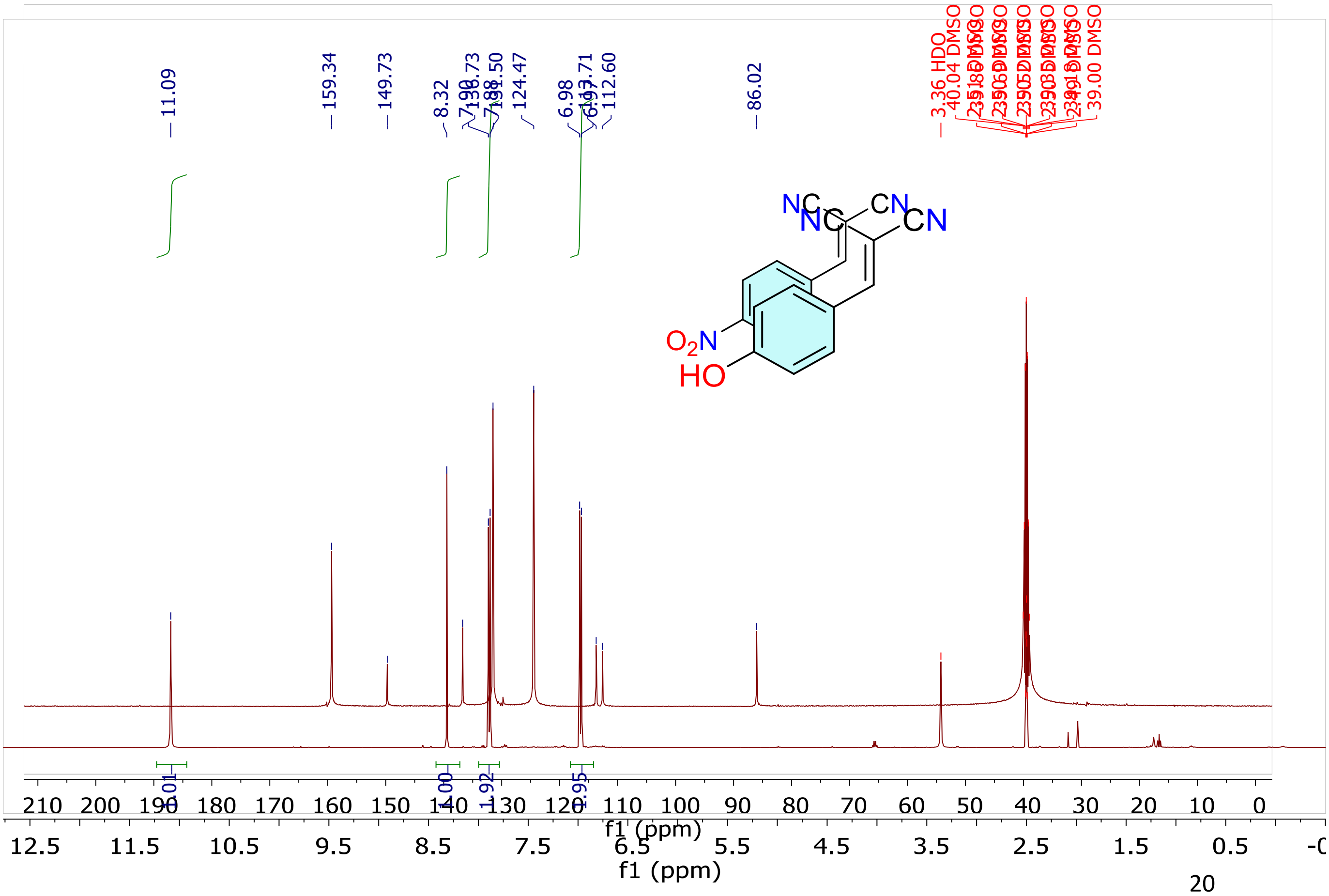
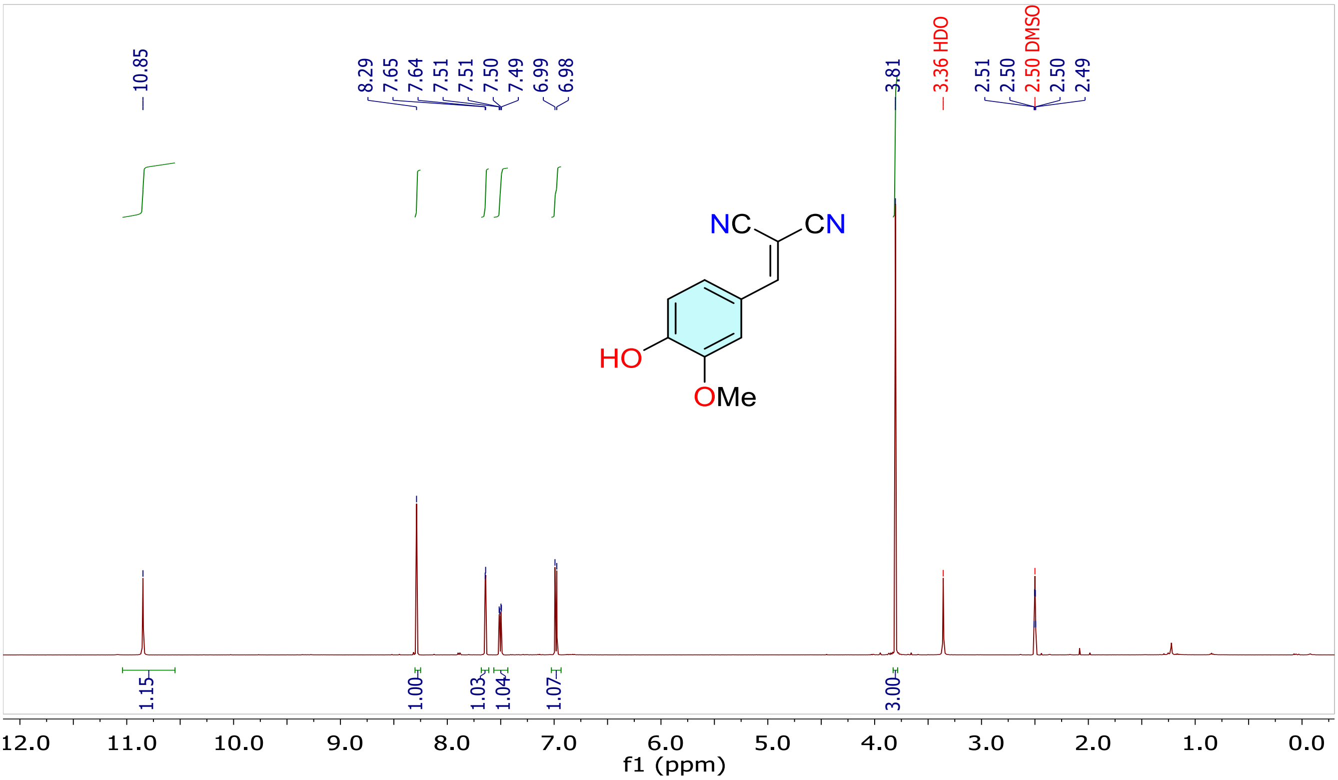


Figure S V-10: *^{13}C NMR (DMSO-d_6, 126 MHz) of 2-(4-hydroxybenzylidene)malononitrile*

Figure S V-11: *^{1}H NMR (DMSO-d_6, 500 MHz) of 2-(4-hydroxy-3 methoxybenzylidene)malononitrile*



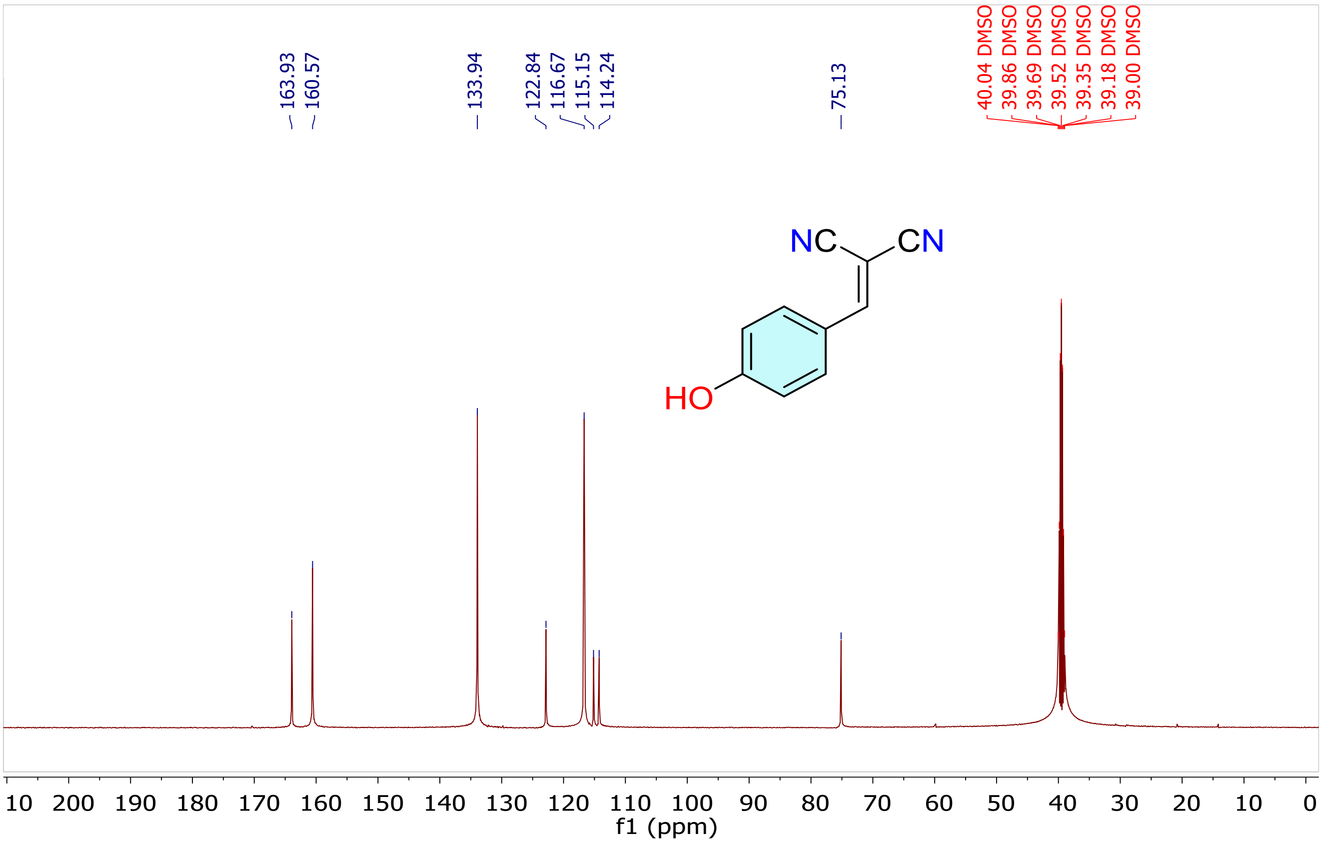


Figure S V-12: *^{13}C NMR (DMSO-d_6, 126 MHz) of 2-(4-hydroxy-3-methoxybenzylidene)malononitrile*

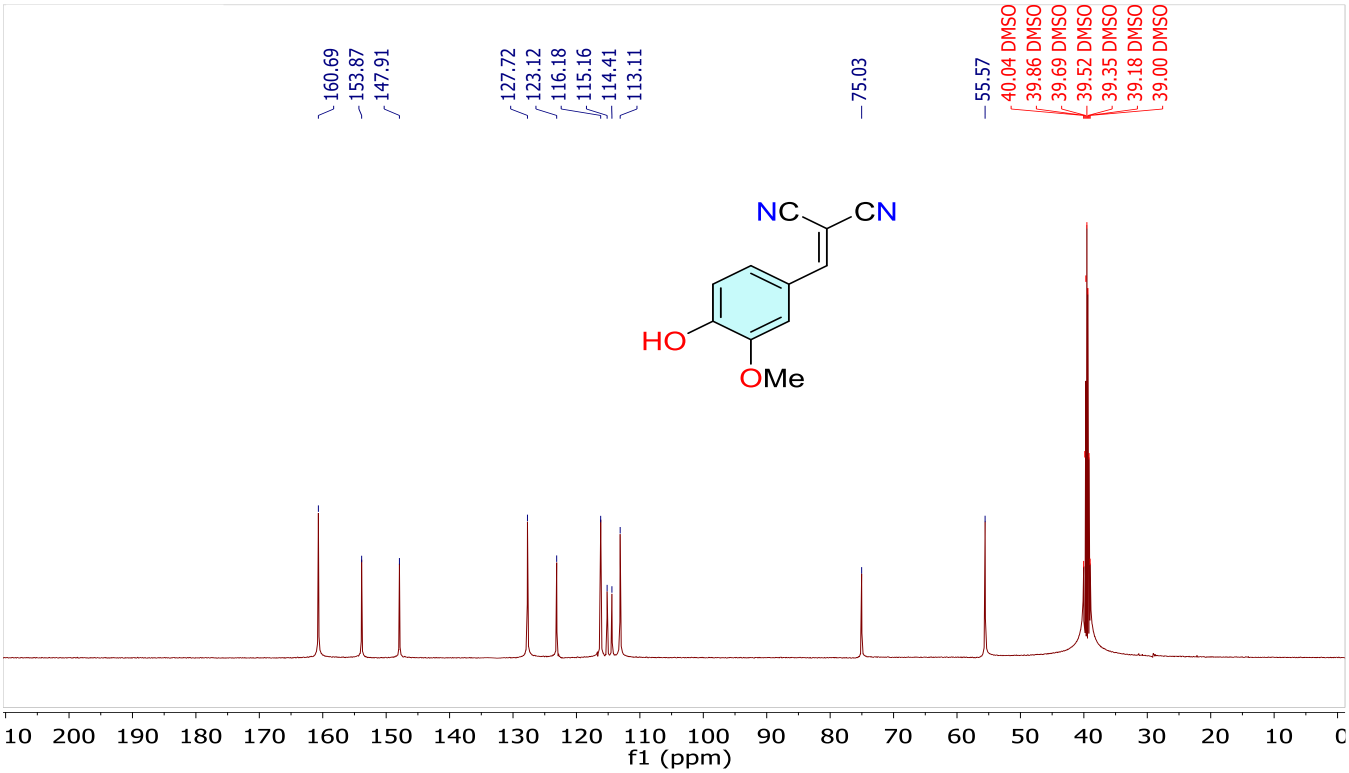


Figure S V-13: *^{1}H NMR (DMSO-d_6, 500 MHz) of 2-(2,3-dimethoxybenzylidene)malononitrile*

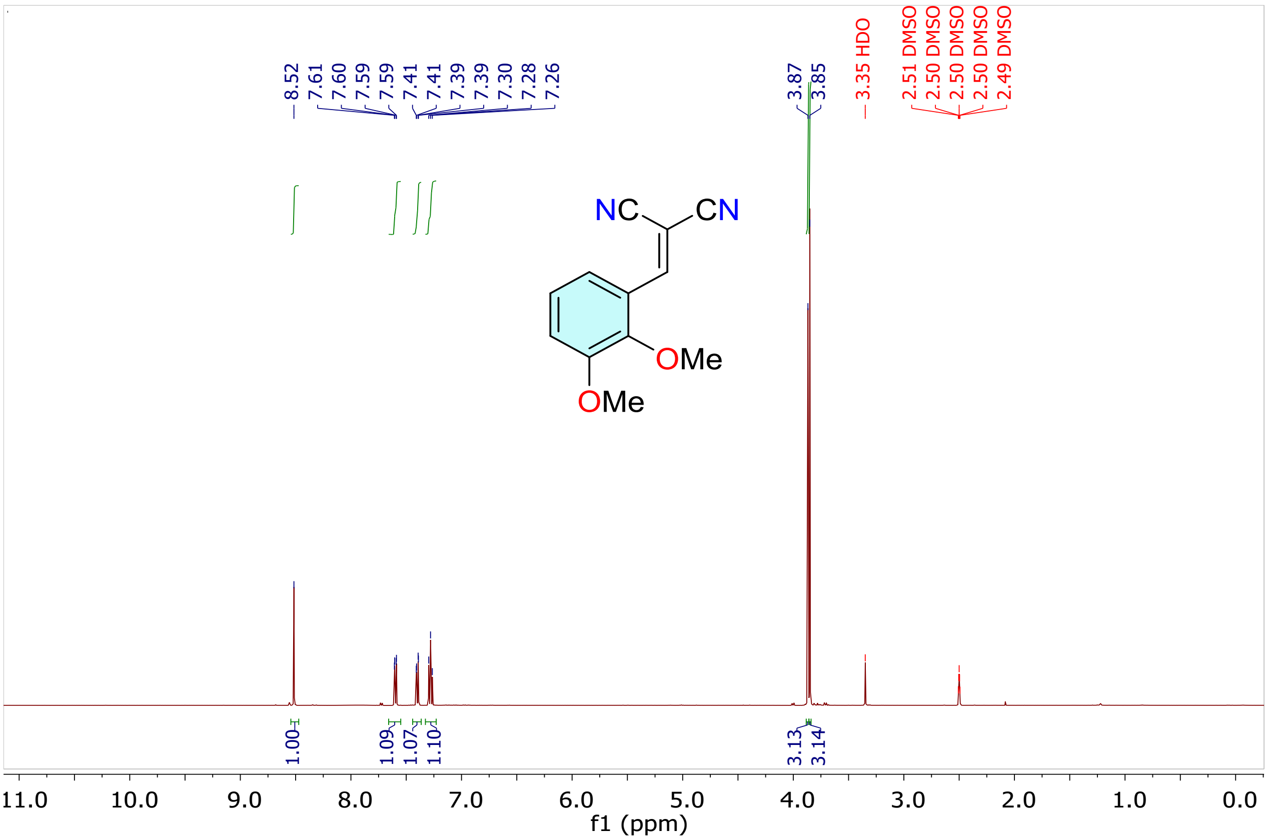


Figure S V-14: *^{13}C NMR (DMSO-d_6, 126 MHz) of 2-(2,3-dimethoxybenzylidene)malononitrile*

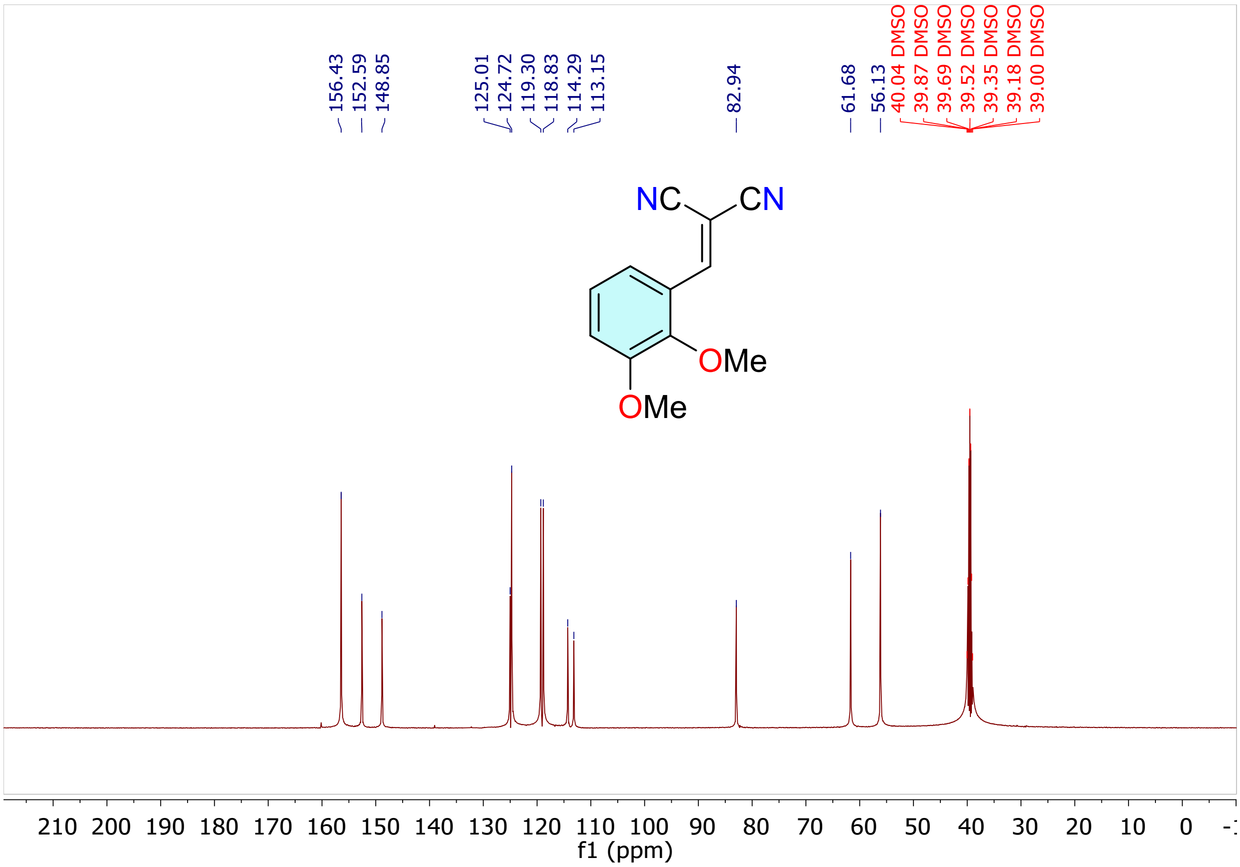


Figure S V-15: ^{1}H NMR (DMSO-d_6, 500 MHz) of 2-amino-3-cyano-7,7-dimethyl-4-(4-chlorophenyl)-5-oxo-5,6,7,8-tetra-4H-chromene*

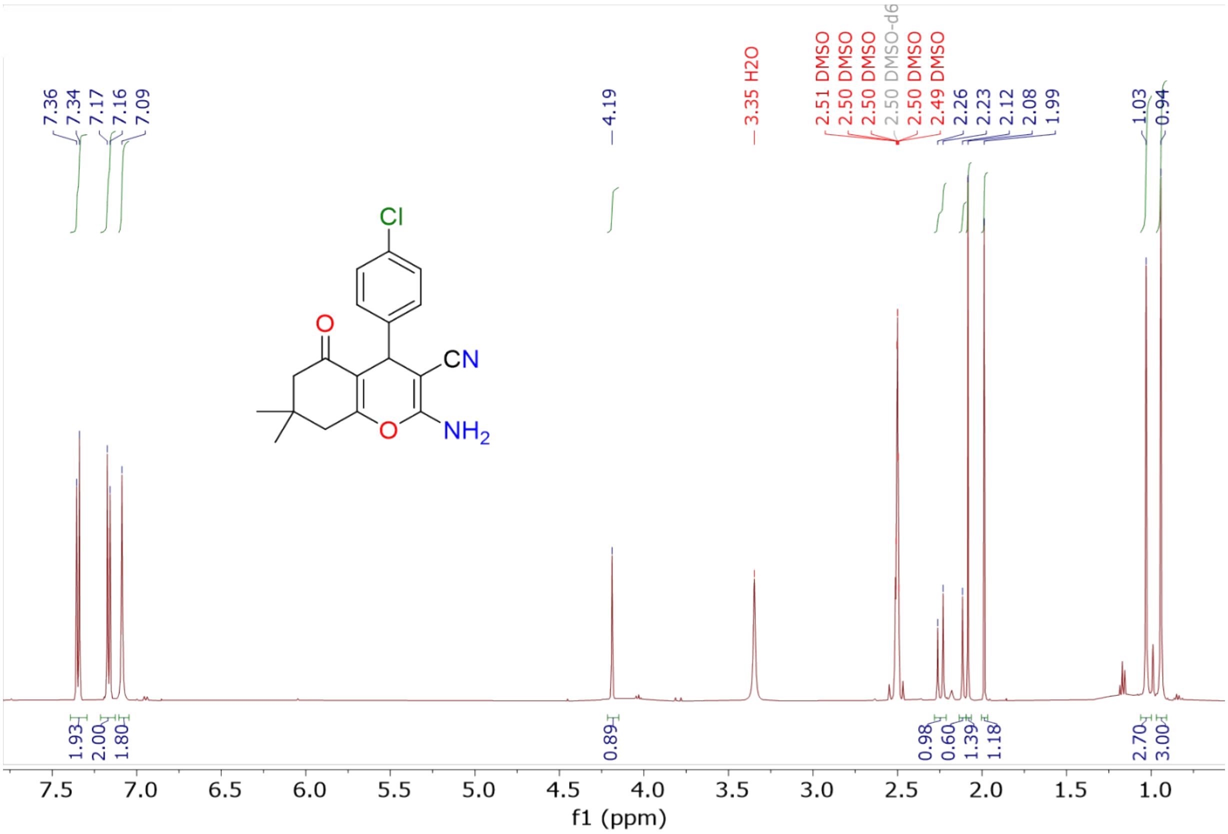


Figure S V-16: ^{13}C NMR (DMSO-d_6, 126 MHz) of 2-amino-3-cyano-7,7-dimethyl-4-(4-chlorophenyl)-5-oxo-5,6,7,8-tetra-4H-chromene*