Electronic Supplementary Material (ESI) for ChemComm.

Octahydropyrimido[4,5-*g*]quinazoline-5,10-diones: Their multicomponent synthesis, self-assembly on graphite and electrochemistry

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Supporting information

Table of Contents

1. Experimental details

1.1. General information

NMR spectra

^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker Avance 400 (400 MHz working frequency) or Bruker Avance 300 (300 MHz working frequency). ^{19}F NMR spectra was recorded on a Bruker Avance 400 (377 MHz working frequency). Samples were dissolved in $CDCl_3$, and chemical shifts (d) were reported in parts per million (ppm) referenced to tetramethylsilane (^{1}H), or the internal (NMR) solvent signal (^{1}H and ^{13}C) as internal standards.[1]

High-resolution mass spectrometry

High-resolution mass spectra were acquired on a quadrupole orthogonal acceleration time-of-flight mass spectrometer (Synapt G2 HDMS, Waters, Milford, MA, USA). Samples were infused at 3 mL/ min and spectra were obtained in positive ionization mode with a resolution of 15,000 (FWHM: full width at half maximum) using leucine enkephalin as a lock mass.

Melting points

Melting points were determined using a Reichert Thermovar apparatus and are uncorrected.

Scanning Tunneling Microscopy

All compounds were dissolved in 1-phenyloctane (Sigma Aldrich) at the given concentrations. All samples were subsequently drop-casted on freshly cleaved HOPG (HOPG, grade ZYB, Advanced Ceramics Inc., Cleveland, OH, U.S.A.). Scanning Tunneling Microscopy (STM, Pico SPM, Agilent) measurements were performed in constant current mode at the liquid-solid interface at room temperature (20-25°C). Mechanically cut Pt/Ir wire (80/20, 0.25mm diameter) were used as STM tips. For analysis purposes, recording of a monolayer image was followed by imaging the graphite substrate under the same experimental conditions, except for increasing the current and lowering the bias. Analysis was performed after drift correction by using SPIP software (Image Metrology A/S). The unit cell parameters were determined by examining at least four images, and only the average values are reported. The imaging parameters are indicated in the caption of Figure 1 and Figure S1: tunneling current (I_{set}) and sample bias (V_{bias}). The molecular models were built using HyperchemTM 8.0.1 program.

Cyclic voltammetry (CV)

A three electrodes homemade Teflon electrochemical cell was used. As reference electrode a Ag/AgCl (KCl saturated) was employed. The counter electrode consists of a platinum wire and as working electrode a HOPG surface was used. The corresponding compound was dissolved in acetonitrile/$TBAPF_6$ 0.1M.

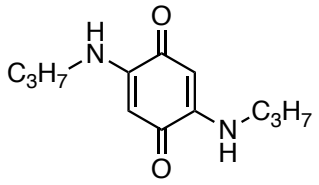
Materials (synthesis)

All reagents were obtained from Acros Organics (Geel, Belgium), Merck (Darm-stadt, Germany), Alfa Aesar (Kandel, Germany), Fluorochem (Hadfield, UK), and TCI Europe (Zwijndrecht, Belgium) and used as received. Reactions were run in screw-capped reaction tubes, with aluminium heating blocks and stirred magnetically. Conversion was monitored by TLC analysis using MilliporeSigmaTM Silica Gel 60 F254 Coated Aluminum-Backed TLC Sheets or Macherey-Nagel SILPre-coated ALUGRAM® Xtra SIL G/UV254 TLC sheets. Compounds were visualized under visible light, UV irradiation (254 nm) or with iodine coated silica. Column chromatography was performed with a CombiFlash EZ prep apparatus using BGB Scorpius Silica 60 Å Irregular - 50 mm cartridges or via standard column chromatography with silica 60, 70-230 mesh

(Acros, Geel, Belgium) as the stationary phase. Solvents were concentrated with a rotary evaporator at 50 ºC.

1.2. Synthesis of 2,5-bis(alkylamino)cyclohexa-2,5-diene-1,4-diones

2,5-Bis(propylamino)cyclohexa-2,5-diene-1,4-dione (1a)



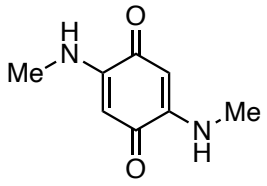
1a

Prepared via a modified literature procedure.[2]

To a heavily stirred suspension of 1,4-benzoquinone (10.8 g, 100 mmol) and $Co(OAc)_2.4H_2O$ (2.49 g, 10.0 mmol, 0.100 eq.) in dichloromethane (DCM, 1.5 L), in a 2L round bottom flask under oxygen atmosphere, n-propylamine (41.0 mL, 500 mmol, 5.00 eq.) was added dropwise. Following complete addition, the reaction mixture was stirred at room temperature for 48 hours. The mixture was coated on celite and purified by column chromatography using EtOAc/petroleum ether 20% - 100% as eluent, concentrated to dryness in vacuo and dried under vacuum at 40 ºC to afford the title compound **1a** (12.8 g, 57.7 mol, 58%) as a pink solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 6.62 (br. s, 2H), 5.31 (s, 2H), 3.16 – 3.10 (m, 4H), 1.74 – 1.64 (m, 4H), 0.99 (t, *J* = 7.4 Hz, 6H).

Spectral data were in agreement with the literature[3]

2,5-Bis(methylamino)cyclohexa-2,5-diene-1,4-dione (1b)



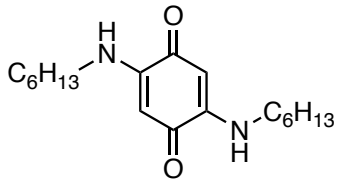
1b

To a heavily stirred solution of hydroquinone (1.100 g, 9.99 mmol) in methanol (20 mL), in a two-necked round bottom flask and under oxygen atmosphere, 40 % aqueous methylamine (0.87 mL, 10 mmol) was added dropwise. Following complete addition, the reaction mixture was stirred a room temperature for 1h 30 min, after which the mixture was concentrated in vacuo by half. The precipitate was filtered, washed with methanol and dried under vacuum at 40 ºC to afford the title compound **1b** as a red crystalline solid (346 mg, 2.98 mmol, 60 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 7.78 (br. s, 2H), 5.15 (s, 2H) 2.75 (d, *J* = 5.3 Hz, 6H).

Spectral data were in agreement with the literature[4]

2,5-Bis(hexylamino)cyclohexa-2,5-diene-1,4-dione (1c)



1c

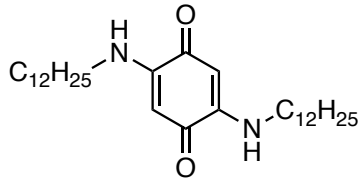
Prepared via a modified literature procedure.[2]

To a heavily stirred solution of p-benzoquinone (1.080 g, 10.0 mmol, 1.00 eq.) and $Co(OAc)_2.4H_2O$ (249 mg, 1.00 mmol) in dichloromethane (DCM, 100 mL), in a 500 mL round bottom flask and under oxygen atmosphere, a solution of n-hexylamine (4.1 ml, 5.0 mmol) in DCM (50 mL) was added dropwise. Following complete addition, the reaction mixture was stirred at room temperature for 48 hours. The mixture was coated on Celite and filtered over silica using EtOAc/DCM 80:20. After concentrating to dryness, the product was dissolved in ethanol and filtered while hot. The filtrate was concentrated to dryness and the obtained solid was recrystallized from ethanol. The obtained solid was filtered, washed with ice cold methanol and dried under vacuum at 40 ºC to afford the title compound **1c** as a pink solid (1.82g, 5.45 mmol, 55 %)

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 6.61 (br. s, 2H), 5.31 (s, 2H), 3.15 (q, *J* = 6.7 Hz, 4H), 1.65 (q, *J* = 7.3 Hz, 4H), 1.45 – 1.21 (m, 12H), 0.90 (t, *J* = 6.7 Hz, 6H)

Spectral data were in agreement with the literature.[5]

2,5-Bis(dodecylamino)cyclohexa-2,5-diene-1,4-dione (1d)



1d

Prepared via a modified literature procedure.[2]

To a heavily stirred solution of p-benzoquinone (1.080 g, 10.0 mmol) and $Co(OAc)_2.4H_2O$ (249 mg, 1.00 mmol) in dichloromethane (DCM, 100 mL), in a 500 mL round bottom flask and under oxygen atmosphere, a solution of n-hexylamine (4.1 ml, 5.0 mmol) in DCM (50 mL) was added dropwise. Following complete addition, the reaction mixture was stirred at room temperature for 48 hours. The mixture was coated on Celite and filtered over silica using EtOAc/DCM 80:20. After concentrating to dryness, the product was dissolved in ethanol and filtered while hot. The filtrate was concentrated to dryness and the obtained solid was recrystallized from ethanol. The obtained solid was filtered, washed with ice cold methanol and dried under vacuum (40 ºC) to afford the title compound **1d** as a pink solid (4.13g, 8.69 mmol, 87 %)

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 6.61 (br. s, 2H), 5.31 (s, 2H), 3.15 (q, *J* = 6.7 Hz, 4H), 1.71 – 1.61 (m, 4H), 1.36 – 1.20 (4H), 0.89 (t, *J* = 6.7 Hz, 6H)

Spectral data were in agreement with the literature.[6]

1.3. Optimization studies

From initial test reactions, two notable conclusions could be drawn. Firstly, at temperatures below 80ºC the reaction occurs very slowly. Secondly, paraformaldehyde is needed in twofold stoichiometric excess for obtaining smooth conversion. The use of lower stoichiometric quantities, or of formalin (37 % aqueous solution), resulted in significantly extended reaction times and concomitantly decreased yields. Therefore, during the entire optimization study, paraformaldehyde was used in 8 equivalents with respect to the starting material **1a**. In the first experiment (Entry 1), compound **1a** was reacted for 2h30 min in the presence of 2 equivalents of proline, 2 equivalents of aniline and 8 equivalents paraformaldehyde in 3 mL absolute ethanol, resulting in an NMR yield of 35 %. As a control experiment, the identical reaction in absence of proline was attempted (Entry 2), resulting in no conversion. Subsequently, different solvents were screened (Entries 3-7) and decreased yields were observed in all cases. Consequently, EtOH was selected as the optimal solvent. When attempting to lower the proline concentrations (Entry 8 – 11), TLC analysis indicated that a minimum reaction time of 5 hours was required for reaction completion. After a reaction time of 5 hours, 1 equivalent of proline proved superior compared to 0.5 and 0.2 equivalents, giving an NMR yield of 65 % (Entry 8) versus 38 % (Entry 9) and 28 % (Entry 10). Interestingly, from the reaction with 1 equivalent of proline compound **5a** precipitated out of this reaction mixture, presumably functioning as a thermodynamic driving force. When further extending the reaction time to 6 hours for these reaction conditions, a reduced yield of 54 % was obtained (Entry 11). Next, the solvent volume was reduced to further drive product precipitation (Entry 15 – 17). While both 1.5 mL and 1 mL gave similar NMR yields of 81 % (Entry 16) and 80 % (Entry 17), 1 mL of ethanol was selected as optimized condition for two reasons. Firstly, a reduced solvent volume is preferable from a viewpoint of sustainability. Secondly, this reduced solvent volume is anticipated to translate to better yields for substrates that might not precipitate as readily. Pleasingly, for this optimized reaction the compound **5a** could be isolated in 76 % yield by simple filtration.

Entry	Solvent (mL)	Proline eq.	Reaction time (h)	Yield (%)
1	EtOH (3)	2	2h 30	35
2	EtOH (3)	0	2h 30	0
3	DMSO (3)	2	2h 30	8
4	DMF (3)	2	2h 30	6
5	ACN (3)	2	2h 30	23
6	THF (3)	2	2h 30	8
7	DCE (3)	2	2h 30	8
8	EtOH (3)	1	5h	65
9	EtOH (3)	0.5	5h	38
10	EtOH (3)	0.2	5h	28
11	EtOH (3)	1	6h	54
12	EtOH (2)	1	5h	72
13	EtOH (1.5)	1	5h	81
14	**EtOH (1)**	**1**	**5h**	**80 (76)**

QNMR representative procedure:

Dialkylaminobenzoquinone **1a** (0.500 mmol, 1.00 eq.), aniline **2a** (1.00 mmol, 2.00 eq.), paraformaldehyde **3** (4.00 mmol, 8.00 eq.), L-proline **4** (58 mg, 0.50 mmol, 1.0 eq.) and absolute ethanol (1.0 mL) were added to a screw-capped 8 mL reaction tube equipped with a stir bar. The reaction mixture was stirred at 80°C for the specified time. After cooling down to room temperature, the reaction mixture was transferred to a 100 mL separatory funnel along with EtOAc (20 mL), and 10 mL water. Following a total of three extractions (20 mL EtOAc), the combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated to dryness in vacuo. The mixture was redissolved in $CHCl_3$ and a benzyl benzoate solution in $CHCl_3$ (internal standard, 0.5 mL of a solution with concentration of around 70 mg/g). After concentrating to dryness, 2 mL $CDCl_3$ was added in order to ensure complete dissolution of the reaction mixture. 0.1 mL of the reaction mixture solution was transferred to an NMR tube and 0.4 mL $CDCl_3$ was added.

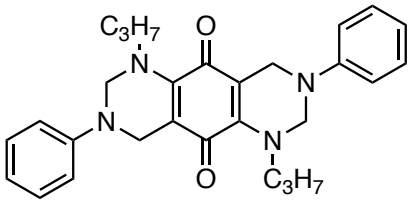
Note: The precise amount of added benzyl benzoate solution was determined by differential measurement of the 1 mL syringe that was used to draw up the stock solution. The benzyl benzoate stock solutions were stored in a sealed screw-capped vial, under refrigeration, and prepared freshly every 3 days. When removing the internal standard stock solution from the vial, the screwcap was replaced with a septum screwcap and a N_2-balloon was attached. Special care must be taken to prevent any evaporation of solvent from the stock solutions during these manipulations.

1.4. Synthesis of 1,2,3,4,6,7,8,9-octahydropyrimido[4,5-*g*]quinazoline-5,10-diones

2.4.1 General procedure

Dialkylaminobenzoquinone **1** (0.500 mmol, 1.00 eq.), aniline **2** (1.00 mmol, 2.00 eq.), paraformaldehyde **3** (4.00 mmol, 8.00 eq.), L-proline 4 (58 mg, 0.50 mmol, 1.0 eq.) and absolute ethanol (1.0 mL) were added to a screw-capped 8 mL reaction tube equipped with a stir bar. The reaction mixture was stirred at 80°C for 5-6 hours during which a grey-green precipitate formed. The reaction mixture was cooled in an ice bath, and water (0.5 mL) was added. The obtained precipitate was filtered, washed with ice cold MeOH/H_2O (2:1) and dried under vacuum at 40°C overnight to afford the title compounds **5** as grey-green solids.

3,8-Diphenyl-1,6-dipropyl-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-*g*]quinazoline-5,10-dione (5a)



5a

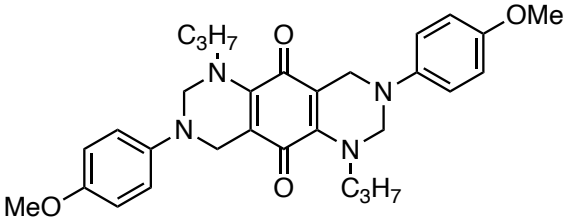
Prepared following the general procedure.

2,5-Bis(propylamino)cyclohexa-2,5-diene-1,4-dione **1a** (111 mg, 0.500 mmol, 1.00 eq.), aniline **2a** (93 μL, 1.0 mmol, 2.0 eq.), paraformaldehyde **3** (120 mg, 4.00 mmol, 8 eq.) and L-proline **4** (58 mg, 0.50 mmol, 1.0 eq.) in absolute ethanol (1.0 mL) were heated to 80°C for 5 hours, affording the title compound **5a** (176 mg, 0.385 mmol, 76%) as a green solid; mp 153-154°C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.31 – 7.24 (m, 4H), 7.01 – 6.95 (app. d, *J* = 8.0 Hz, 4H), 6.96 – 6.89 (app. t, *J* = 7.3 Hz, 2H), 4.60 (s, 4H), 4.20 (s, 4H), 3.74 - 3.66 (m, 4H), 1.69 - 1.57 (app. sext., *J* = 7.4 Hz 4H), 0.92 (t, *J* = 7.4 Hz, 6H);

^{13}C-NMR (101 MHz, $CDCl_3$): 178.3, 148.4, 146.8, 129.5, 121.2, 117.6, 108.0, 69.2, 54.0, 46.2, 22.8, 11.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{28}H_{32}N_4O_2$: 457.25978; found: 457.2602.

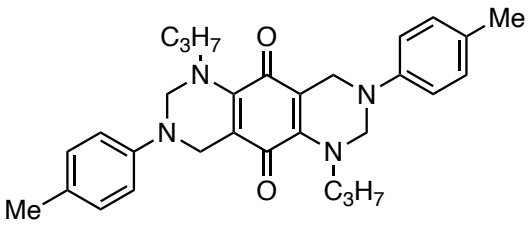
3,8-Bis(4-methoxyphenyl)-1,6-dipropyl-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-*g*]quinazoline-5,10-dione (5b)



5b

Prepared following the general procedure.
2,5-Bis(propylamino)cyclohexa-2,5-diene-1,4-dione **1a** (111 mg, 0.500 mmol, 1.00 eq.), *p*-anisidine **2b** (123 mg, 1.00 mmol, 2.00 eq.), paraformaldehyde **3** (120 mg, 4.00 mmol, 8.00 eq.) and L-proline **4** (58 mg, 0.50 mmol, 1.0 eq.) in absolute ethanol (1.0 mL) were heated to 80°C for 5 hours, affording the title compound **5b** (176 mg, 0.341 mmol, 68%) as a green solid; mp 136-137°C.
^{1}H NMR (300 MHz, $CDCl_3$): d (ppm) 6.96 (d, *J* = 8.9 Hz, 4H), 6.83 (d, *J* = 8.9 Hz, 4H), 4.52 (s, 4H), 4.14 (s, 4H), 3.77 (s, 3H), 3.72 – 3.61 (m, 4H), 1.68 – 1.51 (app sext., *J* = 7.4 Hz, 4), 0.90 (t, *J* = 7.3 Hz, 6H);
^{13}C NMR (300 MHz, $CDCl_3$): d (ppm) 178.2, 154.8, 146.9, 142.4, 120.0, 114.7 107.6, 70.6, 55.7, 53.9, 47.0, 22.8, 11.4;
HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{30}H_{36}N_4O_4$: 517.28091; found: 517.2808.

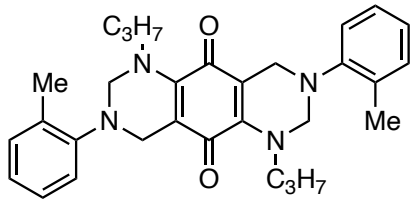
1,6-Dipropyl-3,8-bis(4-methylphenyl)-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-*g*]quinazoline-5,10-dione (5c)



5c

Prepared following the general procedure.
2,5-Bis(propylamino)cyclohexa-2,5-diene-1,4-dione **1a** (111 mg, 0.500 mmol, 1.00 eq.), *p*-toluidine **2c** (107 mg, 1.00 mmol, 2.00 eq.), paraformaldehyde **3** (120 mg, 4.00 mmol, 8.00 eq.) and L-proline **4** (58 mg, 0.50 mmol, 1.0 eq.) in absolute ethanol (1.0 mL) were heated to 80°C for 5 hours, affording the title compound **5c** (198 mg, 0.408 mmol, 82%) as a green solid; mp 175-176°C.
^{1}H-NMR (400 MHz, $CDCl_3$): 7.07 (d, *J* = 8.1 Hz, 4H), 6.88 (d, *J* = 8.6 Hz, 4H), 4.55 (s, 4H), 4.16 (s, 4H), 3.73 – 3.63 (m, 4H), 2.27 (s, 6H), 1.69 – 1.55 (app. sext, *J* = 7.5 Hz, 4H), 0.91 (t, *J* = 7.4 Hz, 6H);
^{13}C-NMR (101 MHz, $CDCl_3$): 178.2, 146.8, 146.1, 130.7, 130.0, 117.9, 107.8, 69.6, 53.9, 46.4, 22.8, 20.6, 11.4.
HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{30}H_{36}N_4O_2$: 485.29108; found: 485.2878.

1,6-Dipropyl-3,8-bis(2-methylphenyl)l-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-*g*]quinazoline-5,10-dione (5d)



5d

Prepared following the general procedure.

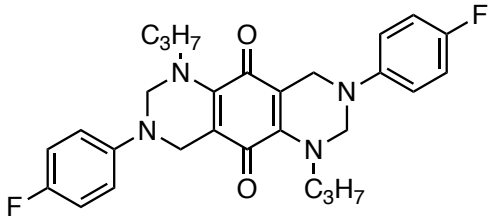
2,5-Bis(propylamino)cyclohexa-2,5-diene-1,4-dione **1a** (111 mg, 0.500 mmol, 1.00 eq.), *o*-toluidine **2d** (107 mg, 1.00 mmol, 2.00 eq.), paraformaldehyde **3** (120 mg, 4.00 mmol, 8.00 eq.) and L-proline **4** (58 mg, 0.50 mmol, 1.0 eq.) in absolute ethanol (1.0 mL) were heated to 80°C for 5 hours, affording the title compound **5d** (202 mg, 0.417 mmol, 83%) as a green solid; mp 116-117°C.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.18 (d, *J* = 7.0 Hz, 2H), 7.14 – 7.07 (m, 2H), 7.05 - 6.98 (m, 4H), 4.36 (s, 4H), 4.05 (s, 4H), 3.66 – 3.58 (m, 4H), 2.36 (s, 6H), 1.62 – 1.48 (app. sext, *J* = 7.5 Hz, 4H), 0.85 (t, *J* = 7.4 Hz, 6H);

^{13}C-NMR (75 MHz, $CDCl_3$): 178.2, 148.6, 147.0, 132.7, 131.3, 126.9, 124.2, 120.8, 108.0, 70.2, 53.6, 48.1, 22.7, 18.3, 11.4.

HRMS (ESI): *m/z* $[M-H]^-$ calcd. for $C_{30}H_{36}N_4O_2$: 483.27653; found: 483.2711.

3,8-Bis(4-fluorophenyl)-1,6-dipropyl-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-*g*]quinazoline-5,10-dione (5e)



5e

Prepared following the general procedure.

2,5-Bis(propylamino)cyclohexa-2,5-diene-1,4-dione **1a** (111 mg, 0.500 mmol, 1.00 eq.), 4-fluoroaniline **2e** (0.095 mL, 1.0 mmol, 2.0 eq.), paraformaldehyde **3** (120 mg, 4.00 mmol, 8.00 eq.) and L-proline **4** (58 mg, 0.50 mmol, 1.0 eq.) in absolute ethanol (1.0 mL) were heated to 80°C for 5 hours during, affording the title compound **5e** (188 mg, 0.382 mmol, 76%) as a green solid; mp 145-146°C.

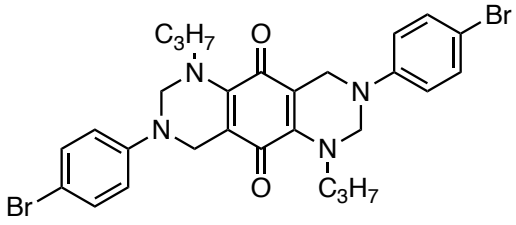
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.08 – 6.85 (d, *J* = 7.9, 8H), 4.54 (s, 4H), 4.15 (s, 4H), 3.77 – 3.58 (app. t, *J* = 7.6 Hz, 4H), 1.67 – 1.50 (app. sext, *J* = 7.4 Hz, 4H), 0.90 (t, *J* = 7.1 Hz, 6H);

^{13}C-NMR (101 MHz, $CDCl_3$): 178.1, 158.0 (J_{CF} = 240.6 Hz), 146.7, 144.9 (d, J_{CF} = 2.3 Hz), 119.7 (d, $J_{C,F}$ = 7.7 Hz), 116.0 (d, J_{CF} = 22.2 Hz), 107.5, 70.1, 53.8, 46.8, 22.8, 11.3;

^{19}F-NMR (400 MHz, $CDCl_3$): -122.4 (m, 1F)

HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{28}H_{30}F_2N_4O_2$: 493.24094; found: 493.2420.

3,8-Bis(4-bromophenyl)-1,6-dipropyl-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-*g*]quinazoline-5,10-dione (5f)

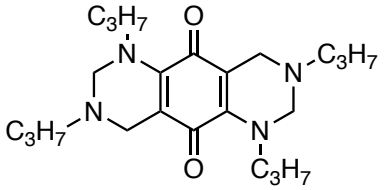


5f

Prepared following the general procedure.

2,5-Bis(propylamino)cyclohexa-2,5-diene-1,4-dione **1a** (111 mg, 0.500 mmol, 1.00 eq.), 4-bromoaniline **2f** (172 mg, 1.00 mmol, 2.00 eq.), paraformaldehyde **3** (120 mg, 4.00 mmol, 8.00 eq.) and L-proline **4** (58 mg, 0.50 mmol, 1.0 eq.) in absolute ethanol (1.0 mL) were heated to 80°C for 5 hours, affording the title compound **5f** (104 mg, 0.169 mmol, 34%) as a green solid; mp 143-144°C.
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.35 (d, *J* = 9.0 Hz, 4H), 6.83 (d, *J* = 9.0 Hz, 4H), 4.57 (s, 4H), 4.17 (s, 4H), 3.71 – 3.65 (m, 4H), 1.68 – 1.58 (app. sext, *J* = 7.6 Hz, 4H), 0.92 (t, *J* = 7.4 Hz, 6H);
^{13}C-NMR (101 MHz, $CDCl_3$): 178.1, 147.4, 146.6, 132.3, 119.2, 113.4, 107.7, 68.8, 53.9, 47.1, 22.8, 11.3;
HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{28}H_{30}Br_2N_4O_2$: 613.08091; found: 613.0730.

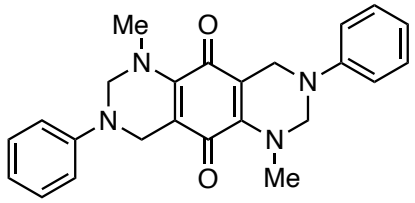
1,3,6,8-Tetrapropyl-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-*g*]quinazoline-5,10-dione (7)



7

2,5-Bis(propylamino)cyclohexa-2,5-diene-1,4-dione **1a** (1.11 g, 5.00 mmol), propylamine **6** (0.82 mL, 10 mmol, 2.0 eq.), paraformaldehyde **3** (1.2 g, 40 mmol, 8.0 eq.) and L-proline **4** (1.15 g, 10.0 mmol, 2.00 eq.) in absolute ethanol (30 mL) were heated to 80°C for 2 hours 30 min. After cooling to room temperature, the mixture was cooled down to room temperature the reaction mixture was transferred to a separatory and quenched with $NaHCO_3$. The aqueous phase was extracted with EtOAc, and the combined organic phases were dried over Na_2SO_4 and concentrated to dryness *in vacuo*. Flash chromatography on silica gel using EtOAc/petroleum ether 10% - 20% afforded the title compound **7** (206 mg, 0.530 mmol, 11%) as a green solid; mp 64-65°C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.01 (s, 4H), 3.68 – 3.55 (m, 8H), 2.52 – 2.40 (m, 4H), 1.71 – 1.60 (app. sext, *J* = 7.6 Hz, 4H), 1.60 – 1.49 (app. sext, *J* = 7.4 Hz, 4H), 0.92 (dt, *J* = 2.7, 7.4 Hz, 6H). ^{13}C-NMR (101 MHz, $CDCl_3$): 178.2, 146.0, 105.6, 71.4, 54.9, 53.4, 47.7, 22.5, 21.0, 11.7, 11.2.
HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{22}H_{36}N_4O_2$: 389.29108; found: 389.2903.

1,6-Dimethyl-3,8-bis(phenylamino)-1,2,3,6,7,8,9-octahydro-pyrimido[4,5-*g*]quinazoline-5,10-dione (8a)

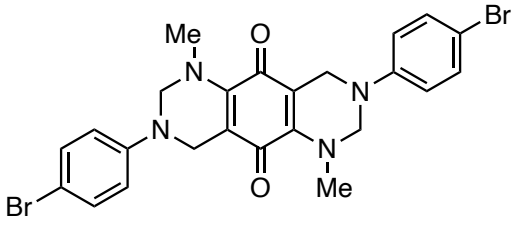


8a

2,5-Bis(methylamino)cyclohexa-2,5-diene-1,4-dione **1b** (83 mg, 0.50 mmol, 1.00 eq), aniline **2a** (93 μL, 1.0 mmol, 2.0 eq.), paraformaldehyde **3** (120 mg, 4.00 mmol, 8 eq.) and L-proline **4** (58 mg, 0.50 mmol, 1.0 eq.) in absolute ethanol (1 mL) were heated to 80°C for 5h, affording the title compound **8a** (131 mg, 0.327 mmol, 65%) as a grey-green solid. mp 178 – 180 ºC

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.31 – 7.22 (m, 4 H), 7.00 – 6.89 (m, 6H), 4.60 (s, 4H), 4.24 (s, 4H), 3.42 (s, 6H);
^{13}C NMR (101 MHz, $CDCl_3$): 178.2, 148.5, 146.8, 146.8, 129.5, 121.3, 117.8, 107.7, 70.4, 46.4, 39.9;
HRMS (ESI-Q-TOF): *m/z* $[M+H]^+$ calcd. for $C_{24}H_{24}N_4O_2$: 401.19719; found: 401.1964.

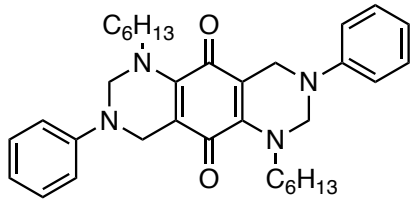
1,6-dimethyl-3,8-bis(4-bromophenylamino)-1,2,3,6,7,8,9-octahydro-pyrimido[4,5-*g*]quinazolin-5,10-dione (8b)



8b

2,5-Bis(methylamino)cyclohexa-2,5-diene-1,4-dione **1b** (83 mg, 0.50 mmol, 1.00 eq.), 4-bromoaniline **2f** (172 mg, 1.00 mmol, 2.00 eq.), paraformaldehyde **3** (120 mg, 4.00 mmol, 8.00 eq.) and L-proline **4** (58 mg, 0.50 mmol, 1.0 eq.) in absolute ethanol (1.0 mL) were heated to 80°C for 5 hours, affording the title compound **8b** (139 mg, 0.249 mmol, 50 %) as a light green-brown solid. mp = 209 – 211ºC.
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.39 – 7.33 (app. d, *J* = 8.9 Hz, 4H), 6.86 – 6.80 (app. *d*, *J* = 8.9 Hz, 4H), 4.58 (s, 4H), 4.21 (s, 4H), 3.42 (s, 6H);
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 178.1, 147.6, 146.6, 132.4, 119.4, 113.7, 107.5, 70.2, 46.44, 39.9.

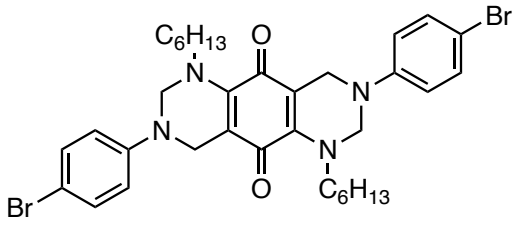
1,6-dihexyl-3,8-bis(phenylamino)-1,2,3,6,7,8,9-octahydro-pyrimido[4,5-*g*]quinazolin-5,10-dione (9a)



9a

Prepared following the general procure.
2,5-Bis(hexylamino)cyclohexa-2,5-diene-1,4-dione (153 mg, 0.50 mmol, 1 eq.), aniline **2a** (93 μL, 1.0 mmol, 2.0 eq.), paraformaldehyde **3** (120 mg, 4.00 mmol, 8 eq.) and L-proline **4** (58 mg, 0.50 mmol, 1.0 eq.) in absolute ethanol (1 mL) were heated to 80°C for 6 hours, affording the title compound **9a** (168 mg, 0.311 mmol, 62 %) as a grey solid. mp 163 – 165 ºC
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.30 -7.22 (m, 4H), 7.00 – 6.95 (app. d, *J* = 7.9 Hz, 4H), 6.94 – 6.88 (app. t, *J* = 7.3 Hz), 4.58 (s, 4H), 4.19 (s, 4H), 3.77 – 3.68 (m, 4H), 1.63 - 1.53 (m, 4H), 1.28 (s, 12 H), 0.88 (t, *J* = 6.6 Hz, 6H);
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 178.2, 148.4, 146.8, 129.4, 121.2, 117.7, 108.0, 69.2, 59.4, 46.1, 31.7, 29.6, 26.7, 22.7, 14.1;
HRMS (ESI-Q-TOF): *m/z* $[M+H]^+$ calcd. for $C_{34}H_{44}N_4O_2$: 540.34640; found 540.3759.

1,6-Dihexyl-3,8-bis(4-bromophenylamino)-1,2,3,6,7,8,9-octahydro-pyrimido[4,5-*g*]quinazoline-5,10-dione (9b)



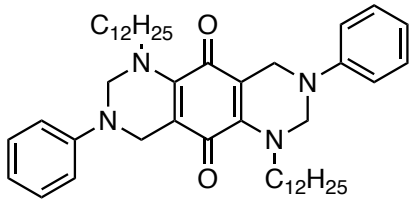
9b

2,5-Bis(hexylamino)cyclohexa-2,5-diene-1,4-dione (153 mg, 0.50 mmol, 1 eq.), 4-bromoaniline **2f** (172 mg, 1.00 mmol, 2.00 eq.), paraformaldehyde **3** (120 mg, 4.00 mmol, 8.00 eq.) and L-proline **4** (58 mg, 0.50 mmol, 1.0 eq.) were weighed in a screw-capped 8 mL reaction tube equipped with a stir bar. Absolute ethanol (1.0 mL) was added, and the reaction mixture was stirred at 80°C for 6 hours, during which a grey-green precipitate formed. After cooling down to room temperature, the reaction mixture was transferred to a 100 mL separatory funnel along with EtOAc (20 mL), and 10 mL water. Following a total of three extractions (3x20 mL EtOAc), the combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated to dryness in vacuo. Flash chromatography using DCM/PE afforded the title compound **8b** (101 mg, 0.145 mmol, 29 %) as a grey-green solid. mp 133 – 135 ºC

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35 (d, *J* = 8.8 Hz, 4H), 6.83 (d, *J* = 8.8 Hz, 4H), 4.55 (s, 4H), 4.16 (s, 4H), 3.80 – 3.60 (m, 4H), 1.65 – 1.51 (m, 4H), 1.29 (s, 12H), 0.89 (t, *J* = 6.1 Hz, 6H);

^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 178.0, 147.5, 146.6, 132.2, 119.3, 113.5, 107.6, 68.9, 52.4, 46.1, 32.0, 29.78, 29.76, 29.74, 29.73, 29.67, 29.6, 29.5, 27.1, 22.8, 14.3;

1,6-di(Dodecylamino)-3,8-di(phenylamino)-1,2,3,6,7,8,9-octahydro-pyrimido[4,5-*g*]quinazoline-5,10-dione (10a)



10a

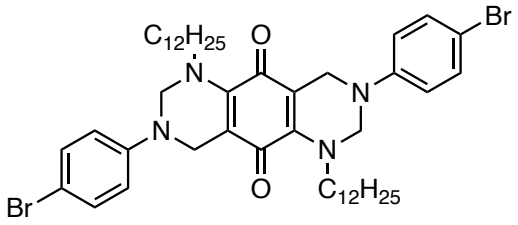
Prepared following the general procure.

2,5-Bis(dodecylamino)cyclohexa-2,5-diene-1,4-dione (237 mg, 0.50 mmol, 1.00 eq.), aniline **2a** (93 μL, 1.0 mmol, 2.0 eq.), paraformaldehyde **3** (120 mg, 4.00 mmol, 8 eq.) and L-proline **4** (58 mg, 0.50 mmol, 1.0 eq.) in absolute ethanol (1 mL) were heated to 80°C for 6 hours, affording the title compound **10a** (266 mg, 0.375 mmol, 75 %) as a grey solid. Tm = 110 – 119 ºC

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.34 – 7.22 (app. t, *J* =7.5 Hz, 4H), 7.03 - 6.88 (m, 6H), 4.61 (s, 4H), 4.22 (s, 4H), 3.82 – 3.69 (app.t, *J* = 7.3 Hz, 4H), 1.69 – 1.53 (m, 4H), 1.29 (s, 36H), 0.91 (t, *J* = 6.6 Hz, 6H)

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.2, 148.4, 146.8, 129.4, 121.1, 117.6, 108.1, 69.2, 52.4, 46.1, 32.0, 29.77, 29.74, 29.71, 29.66, 29.57, 29.43, 29.33, 27.1, 22.8, 14.2;

1,6-Di(dodecyl)-3,8-di(4-bromophenyl)-1,2,3,6,7,8,9-octahydro-pyrimido[4,5-*g*]quinazoline-5,10-dione (10b)



10b

Prepared following the general procure.

2,5-Bis(dodecylamino)cyclohexa-2,5-diene-1,4-dione (237 mg, 0.50 mmol, 1.00 eq.), 4-bromoaniline **2f** (172 mg, 1.00 mmol, 2.00 eq.), paraformaldehyde **3** (120 mg, 4.00 mmol, 8.00 eq.) and L-proline **4** (58 mg, 0.50 mmol, 1.0 eq.) in absolute ethanol (1.0 mL) were heated to 80°C for 6 hours. After cooling down to room temperature, the reaction mixture was transferred to a 100 mL separatory funnel along with DCM (20 mL), and 10 mL water. Following a total of three extractions (20 mL DCM), the combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated to dryness in vacuo. Flash chromatography using 0 – 100 % DCM/PE afforded the title compound **10b** as (159 mg, 0.183 mmol, 37 %) as a grey-green solid. Tm = 88 – 95 ºC.

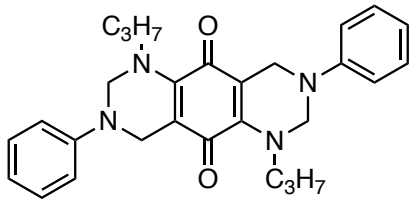
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.35 (d, *J* = 8.7 Hz, 4H), 6.84 (d, *J* = 8.8 Hz, 4H), 4.56 (s, 4H), 4.16 (s, 4H), 3.72 (t, *J* = 7.5 Hz, 4H), 1.65 – 1.51 (m, 4H), 1.26 (s, 36H), 0.88 (t, *J* = 6.2 Hz, 6H);

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 178.0, 147.5, 146.6, 132.3, 119.3, 113.5, 107.6, 68.9, 52.3, 46.1, 32.0, 29.79, 29.74, 29.73, 29.67, 29.58, 29.48, 27.1, 22.8, 14.3;

HRMS (ESI-Q-TOF): *m/z* $[M+H]^+$ calcd. for $C_{46}H_{66}Br_2N_4O_2$: 865.36260; found: 865.3455

2.4.2 Procedure for Gram-Scale synthesis

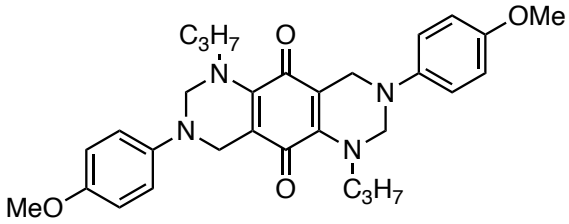
1,6-Di(propylamino)-3,8-di(phenylamino)-1,2,3,6,7,8,9-octahydro-pyrimido[4,5-*g*]quinazolin-5,10-dione (5a)



5a

2,5-Bis(propylamino)cyclohexa-2,5-diene-1,4-dione **1a** (1.112 g, 5.00 mmol, 1.00 eq.), aniline **2a** (0.90 mL, 10 mmol, 2.0 eq.) paraformaldehyde **3** (1.200 g, 4.00 mmol, 8.00 eq.), proline **4** (575 mg, 5.00 mmol, 1.00 eq.) and absolute ethanol (10 ml) were added to a screw-capped 20 mL reaction tube, equipped with a stir bar. The reaction mixture was stirred at 80°C for 6 hours, during which a grey-green precipitate formed. Next, the reaction mixture was cooled in an ice bath, and water (5 mL) was added. The obtained precipitate was filtered, washed with ice cold MeOH/H_2O (2:1) and dried under vacuum at 40°C overnight to afford the title compound **5a** (1. 341 g, 2.94 mmol, 59 %) as a grey-green solid.

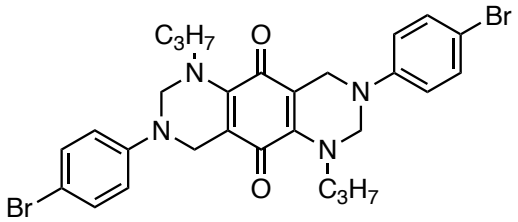
1,6-Di(propylamino)-3,8-di(4-methoxyphenylamino)-1,2,3,6,7,8,9-octahydro-pyrimido[4,5-*g*]quinazolin-5,10-dione (5b)



5b

2,5-Bis(propylamino)cyclohexa-2,5-diene-1,4-dione **1a** (1.112 g, 5.00 mmol, 1.00 eq.), p-anisidine **2b** (1.232 g, 10.0 mmol, 2.0 eq.), paraformaldehyde **3** (1.20 g, 4.00 mmol, 8.00 eq.), proline **4** (575 mg, 5.00 mmol, 1.00 eq.) and absolute ethanol (10 mL) were added to a 20 mL screw-capped reaction tube, equipped with a stir bar. The reaction mixture was stirred at 80°C for 6 hours, during which a grey-green precipitate formed. Next, the reaction mixture was cooled in an ice bath, and water (5 mL) was added. The obtained precipitate was filtered, washed with ice cold MeOH/H2O (2:1) and dried under vacuum at 40°C overnight to afford the title compound **5b** (1.79 g, 3.45 mmol, 69 %) as a grey-green solid.

1,6-Di(propylamino)-3,8-di(4-bromophenylamino)-1,2,3,6,7,8,9-octahydro-pyrimido[4,5-*g*]quinazolin-5,10-dione (5f)



5f

2,5-Bis(propylamino)cyclohexa-2,5-diene-1,4-dione **1a** (1.112 g, 5.00 mmol, 1.00 eq.), 4-bromoaniline **2f** (1.720 g, 10.0 mmol, 2.0 eq.), paraformaldehyde **3** (1.200 g, 4.00 mmol, 8.00 eq.), proline **4** (575 mg, 5.00 mmol, 1.00 eq.) and absolute ethanol (10 ml) were added to a screw-capped 20 mL reaction tubes, equipped with a stir bar. The reaction mixture was stirred at 80°C for 6 hours, during which a grey-green precipitate formed. Next, the reaction mixture was cooled in an ice bath, and water (5 mL) was added. The obtained precipitate was filtered, washed with ice cold MeOH/H2O (2:1) and dried under vacuum at 40°C overnight to afford the title compound afford **5f** (1.329 g, 2.16 mmol, 43 %) as a grey-green solid.

1.5. Crystal structure determination of 9a

Compound **9a** crystallizes in space group P-1 with a half molecule as asymmetric unit and the second half is generated by inversion (Fig. S1). The tetrahydropyrimidine ring has an envelope conformation with atom N3 acting as flap [puckering parameters: Q = 0.456(2) Å, θ = 126.2(3)°, ϕ = 301.9(4)°]. Phenyl ring C13-C18 makes a dihedral angle of 85.11(5)° with the central benzoquinone ring.

The crystal packing is characterized by C-H…π interactions (Fig. S2) between C2-H2A and phenyl ring C12-C18 [H2A…*Cg*1^{i} = 2.90 Å; *Cg*1 is the centroid of ring C12-C18; symmetry code: (i) 1 + *x*, *y*, *z*] and between C7-H7A and the benzoquinone ring [H7A…Cg2^{ii} = 2.85 Å; *Cg*2 is the centroid of the benzoquinone ring, symmetry code: (ii) 2 – *x*, 1 – *y*, 1 – *z*]. Furthermore, the crystal packing shows planes of molecules (Fig. S3) by very weak O20…H14^{iii} interactions [O20…H14^{iii} = 2.62 Å; symmetry code: (iii) –*x*, –*y*, 1 – *z*] and alignment of hexyl chains.

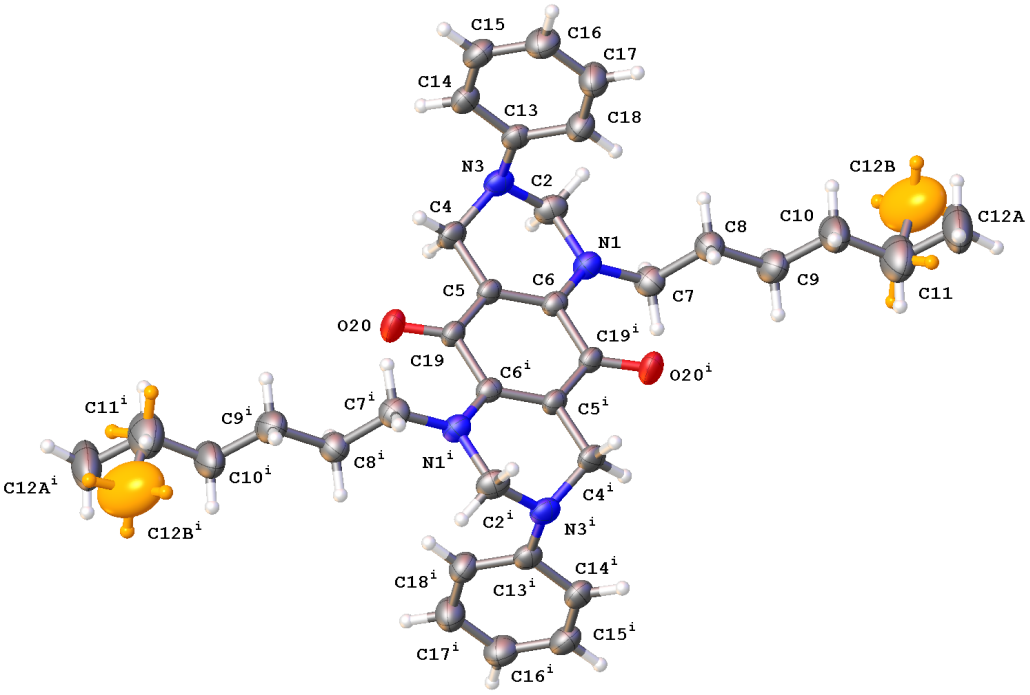


Figure S1. *Crystal structure of **9a** with atom labeling scheme and thermal ellipsoids drawn at the 30% probability level. The disordered part with population parameter 0.202(11) is shown in orange. Symmetry code: (i) 1 – x, 1 – y, 1 – z.*

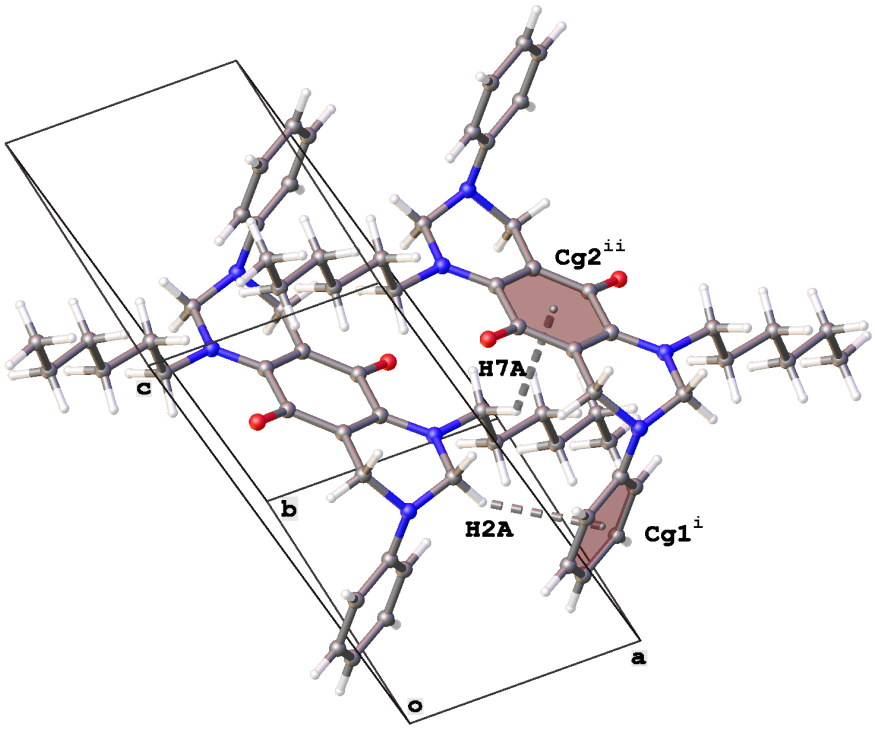


Figure S2. Partial crystal packing of **9a** showing the C-H…π interactions. Only the major disordered part is shown. Symmetry codes: (i) 1 + x, y, z; (ii) 2 – x, 1 – y, 1 – z.

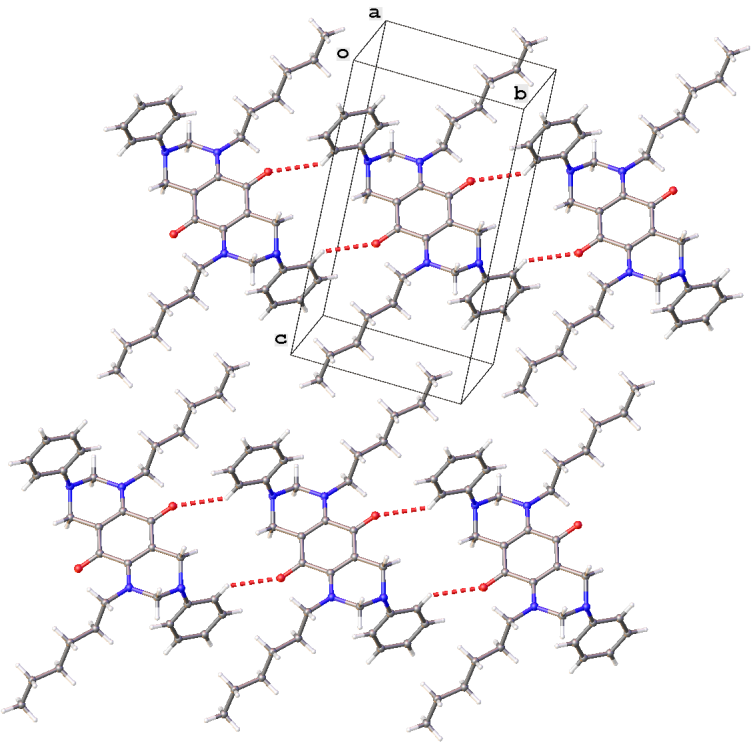


Figure S3. *Partial crystal packing of **9a** showing the C-H…π interactions. Only the major disordered part is shown. Symmetry code: (i) 1 + x, y, z.*

Experimental

Single crystals of **9a** were grown by slow evaporation of deuterated chloroform ($CDCl_3$) from an NMR tube. A suitable crystal was selected and X-ray diffraction data were collected on an Agilent SuperNova diffractometer, equipped with an Eos CCD detector, using Mo Kα radiation (λ = 0.71073 Å). The crystal was kept at 293(2) K during data collection. Using Olex2,[7] the structure was solved with the SHELXT[8] structure solution program using Intrinsic Phasing and refined with the SHELXL[9] refinement package using full-matrix least-squares minimisation on F^2. The final methyl group C12 of the hexyl chain was found to be disordered over two positions with population parameters of 0.798(11) and 0.202(11). CCDC 2163478 contains the supplementary crystallographic data for **9a** and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; or deposit@ccdc.cam.ac.uk). Crystal data and structure refinement details are given in Table S1.

Table S1. Crystal data and structure refinement for 9a.

Empirical formula	$C_{34}H_{44}N_4O_2$
Formula weight	540.73
Temperature/K	294(2)
Crystal system	triclinic
Space group	P-1

a/Å	5.8021(2)
b/Å	9.3374(5)
c/Å	14.8870(7)
α/°	94.653(4)
β/°	93.966(4)
γ/°	105.856(4)
Volume/Å^3	769.77(6)
Z	1
ρ_{calc}g/cm^3	1.166
μ/mm^{-1}	0.073
F(000)	292.0
Crystal size/mm^3	0.3 × 0.15 × 0.1
Radiation	Mo Kα (λ = 0.71073 Å)
2Θ range for data collection/°	5.078 to 52.736
Index ranges	-7 ≤ h ≤ 7, -11 ≤ k ≤ 11, -18 ≤ l ≤ 18
Reflections collected	15763
Independent reflections	3143 [R_{int} = 0.0325, R_{sigma} = 0.0338]
Data/restraints/parameters	3143/22/191
Goodness-of-fit on F^2	1.073
Final R indexes [I>=2σ (I)]	R_1 = 0.0642, wR_2 = 0.1721
Final R indexes [all data]	R_1 = 0.1022, wR_2 = 0.1977
Largest diff. peak/hole / e Å^{-3}	0.18/-0.17

1.6. Cyclic voltammetry

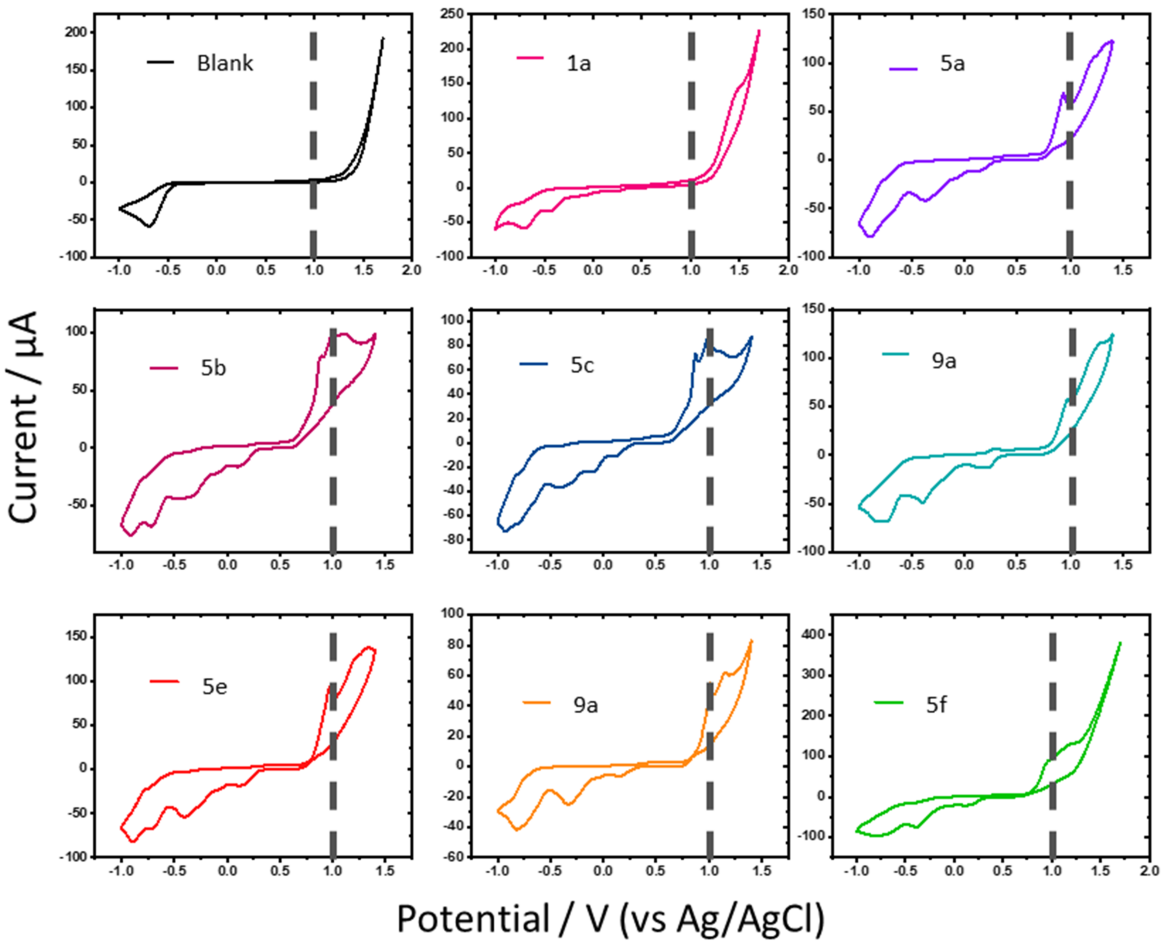
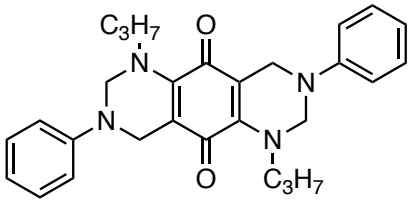


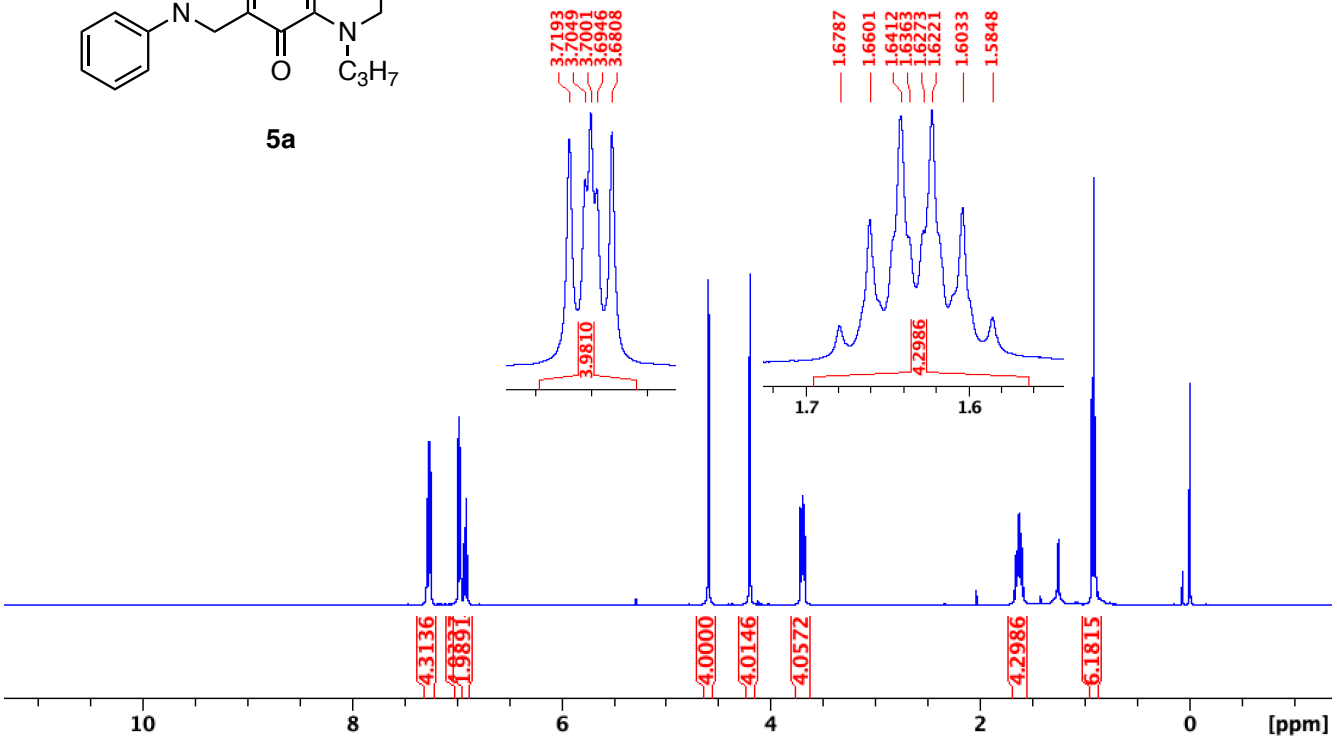
Figure S4. Cyclic voltammogram for 1 mM of the quinone compound in ACN/TBAPF6 0.1M. (v=0.1 Vs-1). A vertical line is included in the voltammograms at 1 V to better observe the differences for the oxidation peaks in the different compounds.

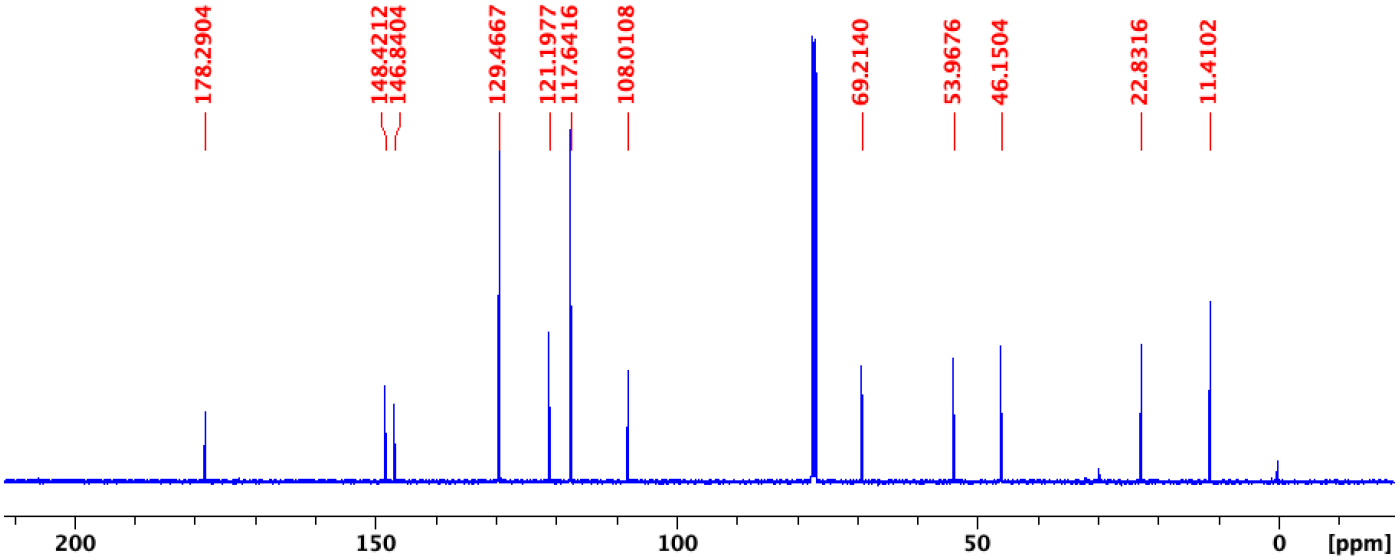
2. NMR spectra

3,8-Diphenyl-1,6-dipropyl-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-*g*]quinazoline-5,10-dione (5a)

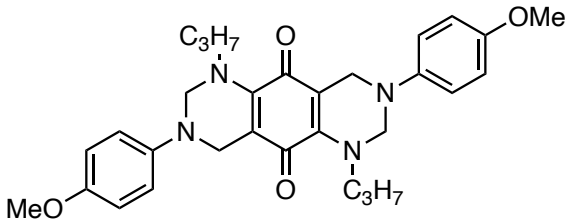


5a

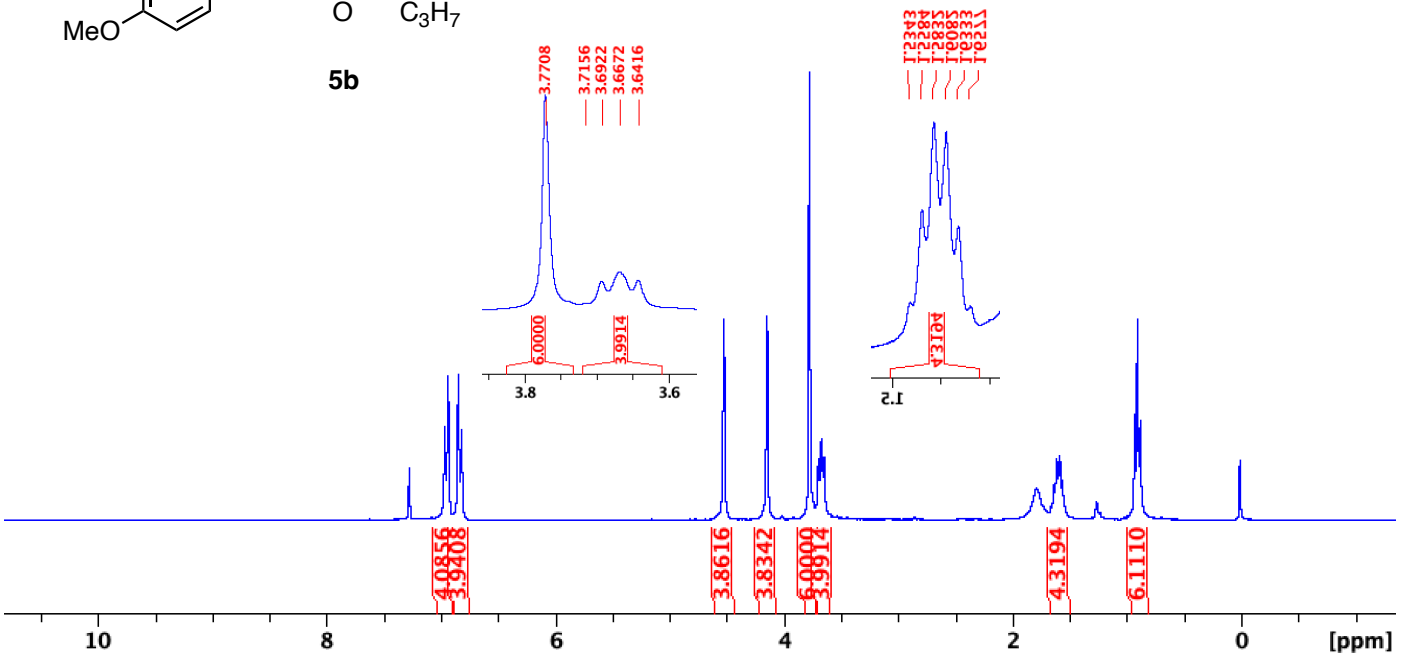


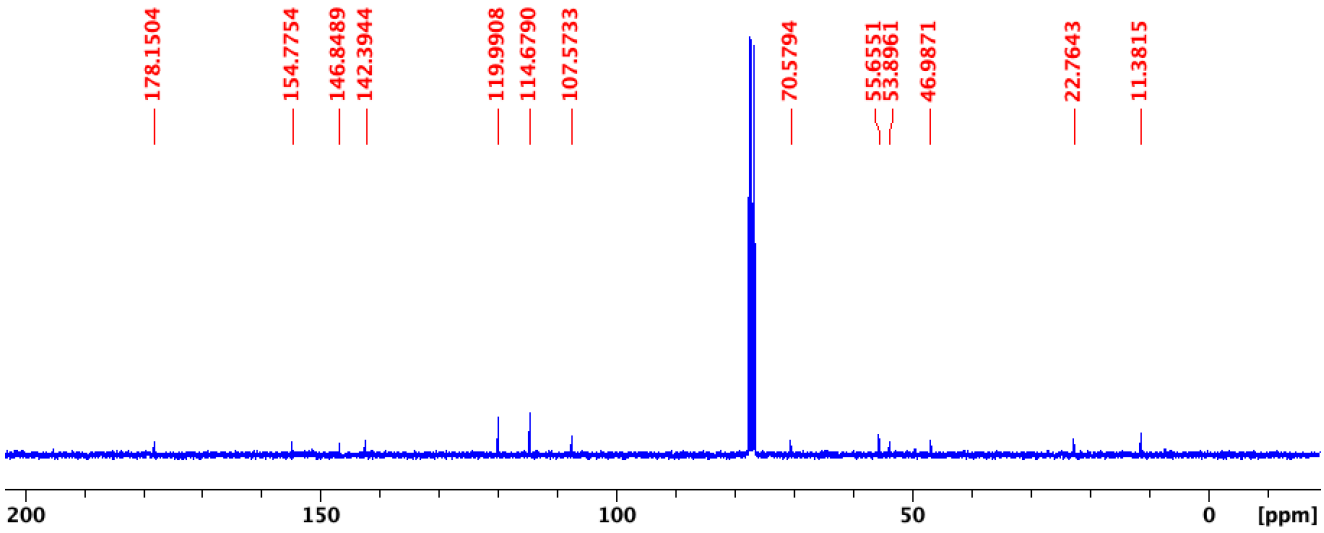


3,8-Bis(4-methoxyphenyl)-1,6-dipropyl-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-*g*] quinazoline-5,10-dione (5b)

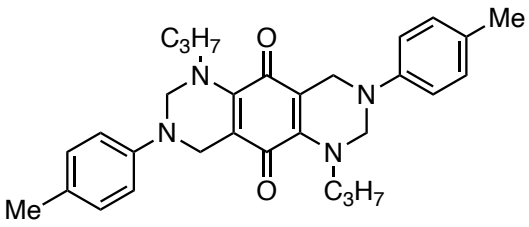


5b

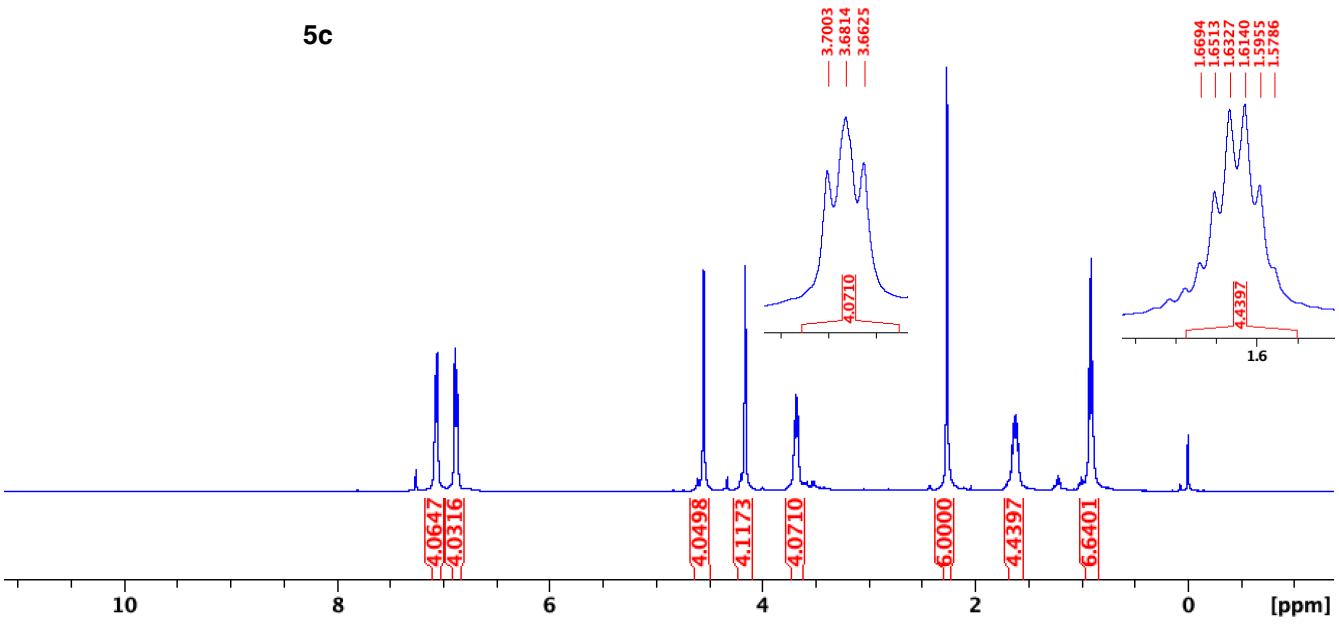


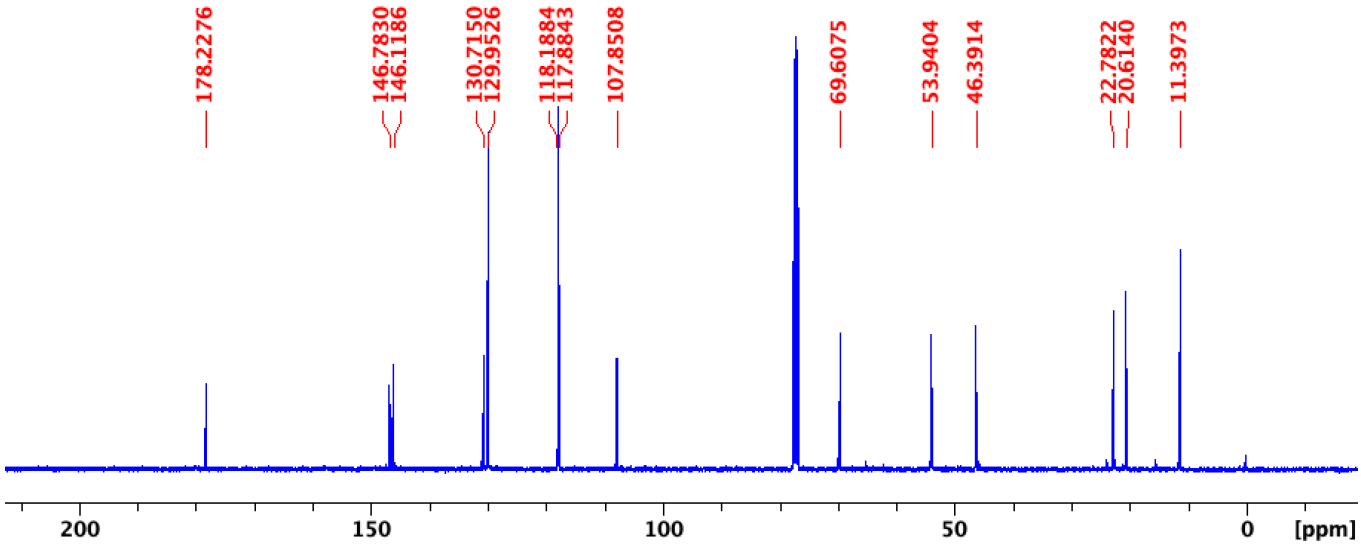


1,6-Dipropyl-3,8-bis(4-methylphenyl)-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-*g*]quinazoline-5,10-dione (5c)

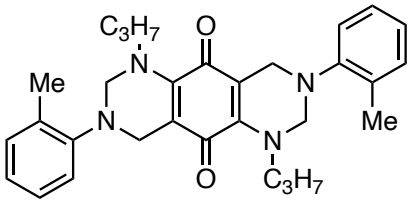


5c

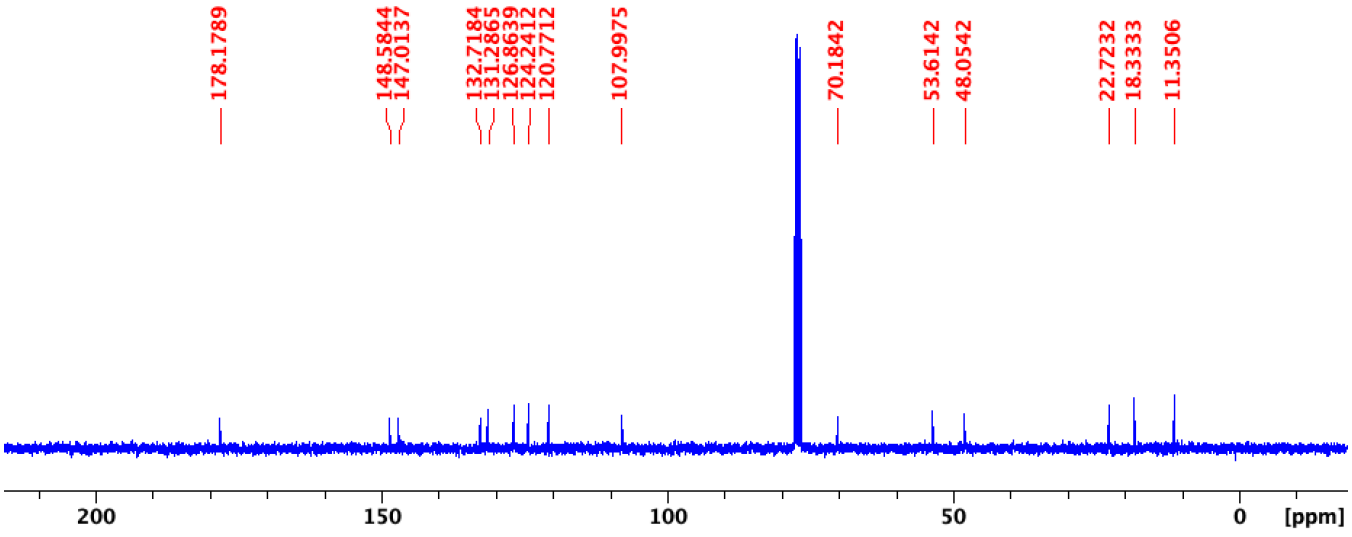




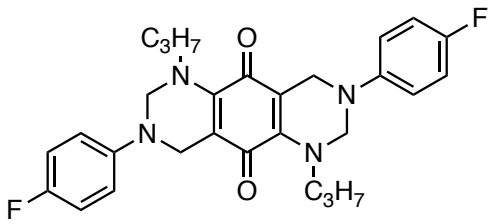
1,6-Dipropyl-3,8-bis(2-methylphenyl)l-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-*g*]quinazoline-5,10-dione (5d)



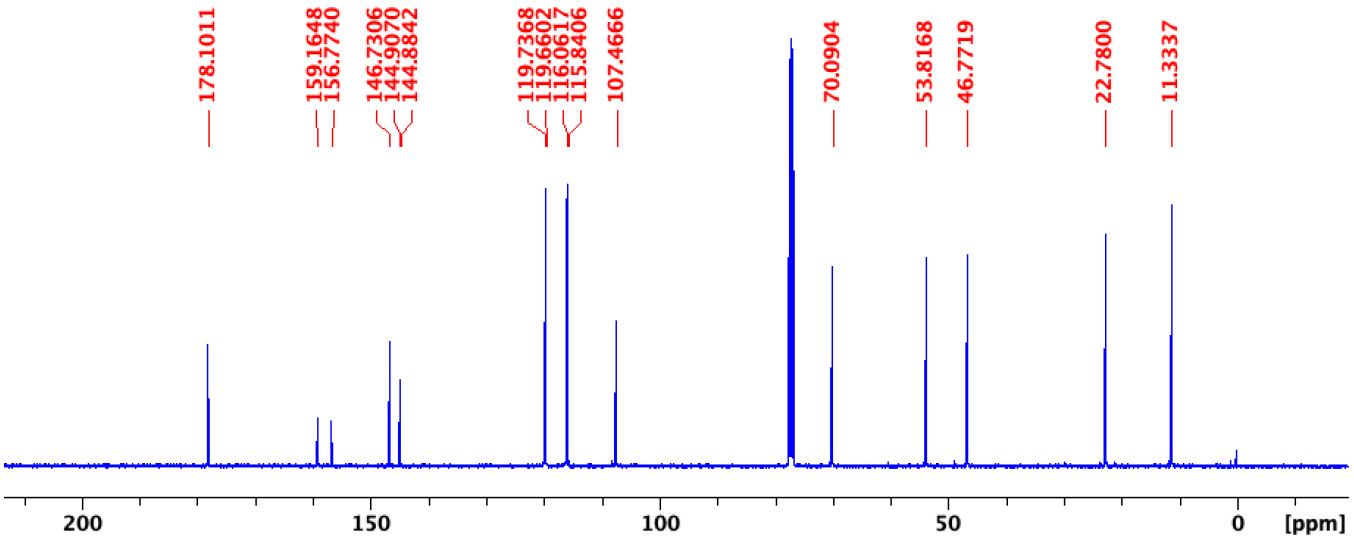
5d

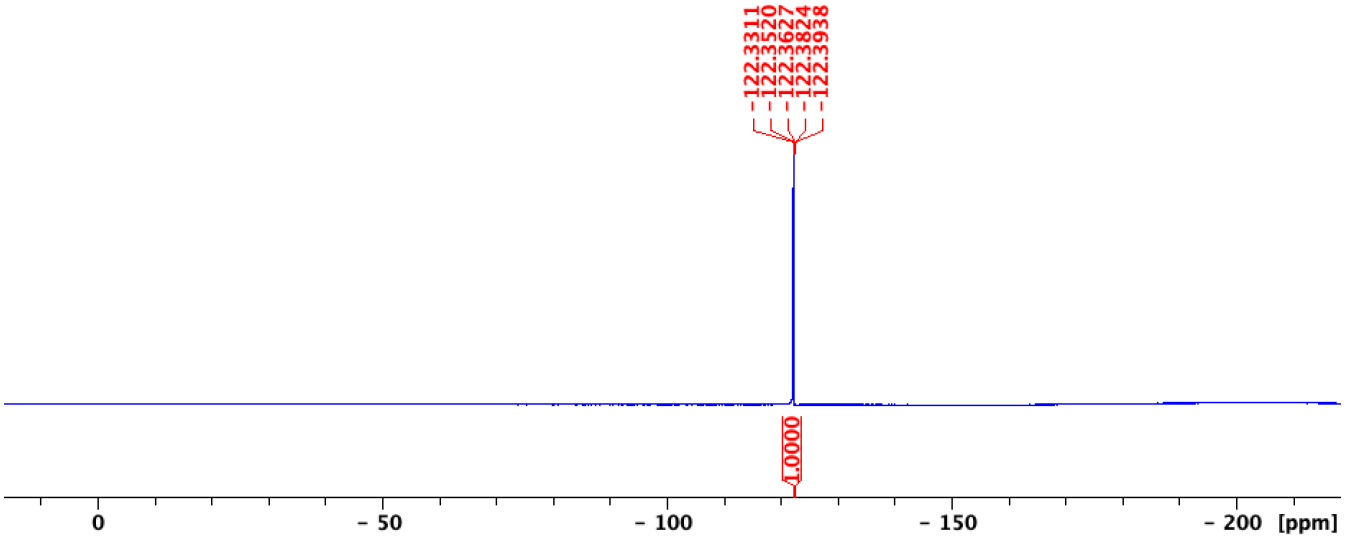


3,8-Bis(4-fluorophenyl)-1,6-dipropyl-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-*g*]quinazoline-5,10-dione (5e)

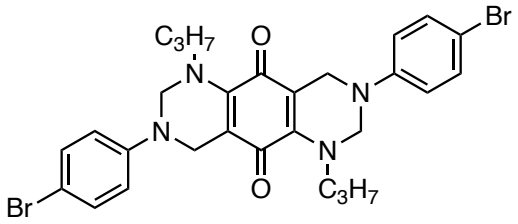


5e

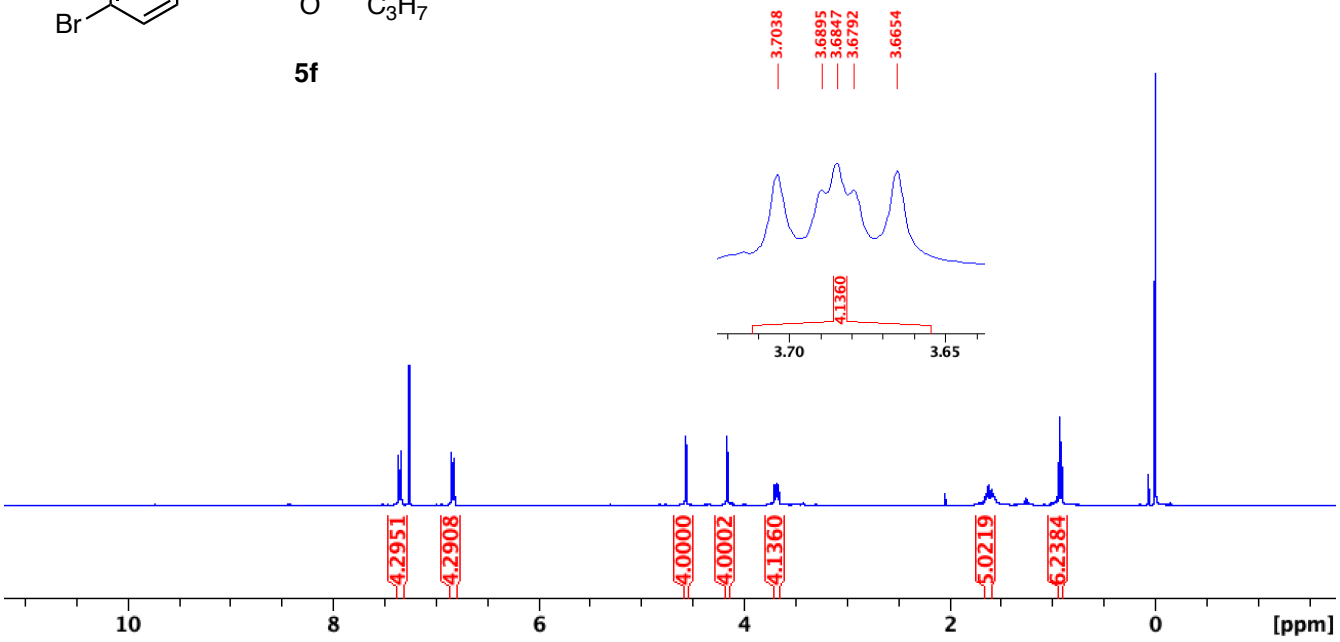


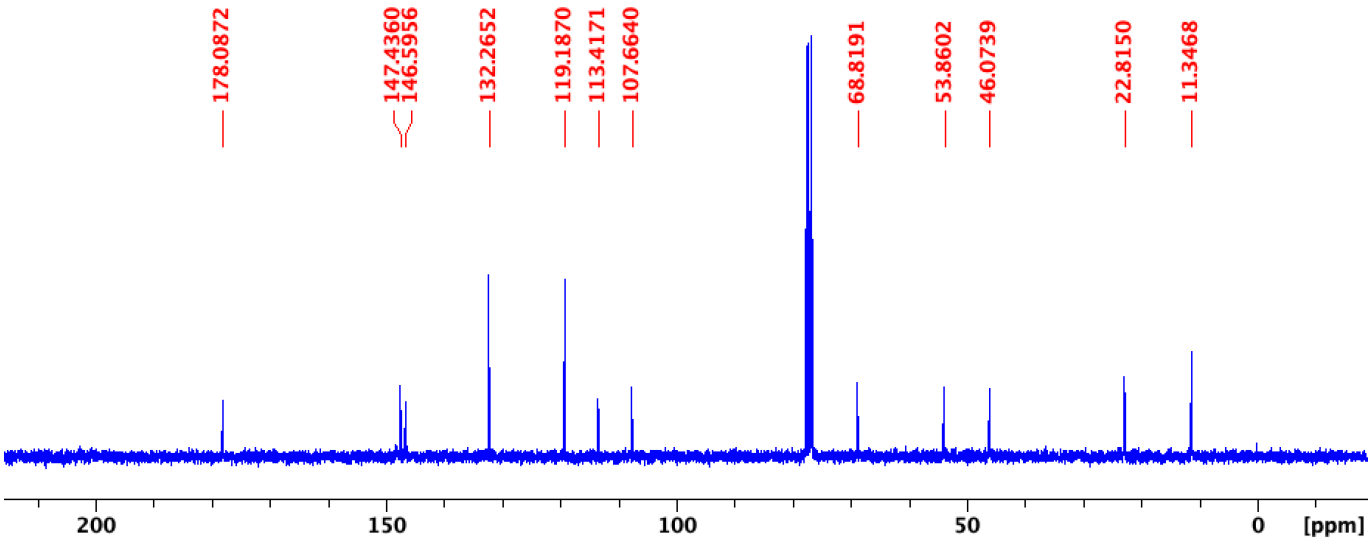

-122.3311
-122.3520
-122.3627
-122.3824
-122.3938
1.0000
0
-50
-100
-150
-200
[ppm]

3,8-Bis(4-bromophenyl)-1,6-dipropyl-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-*g*]quinazoline-5,10-dione (5f)

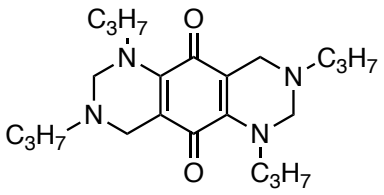


5f





1,3,6,8-Tetrapropyl-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-*g*]quinazoline-5,10-dione (7)



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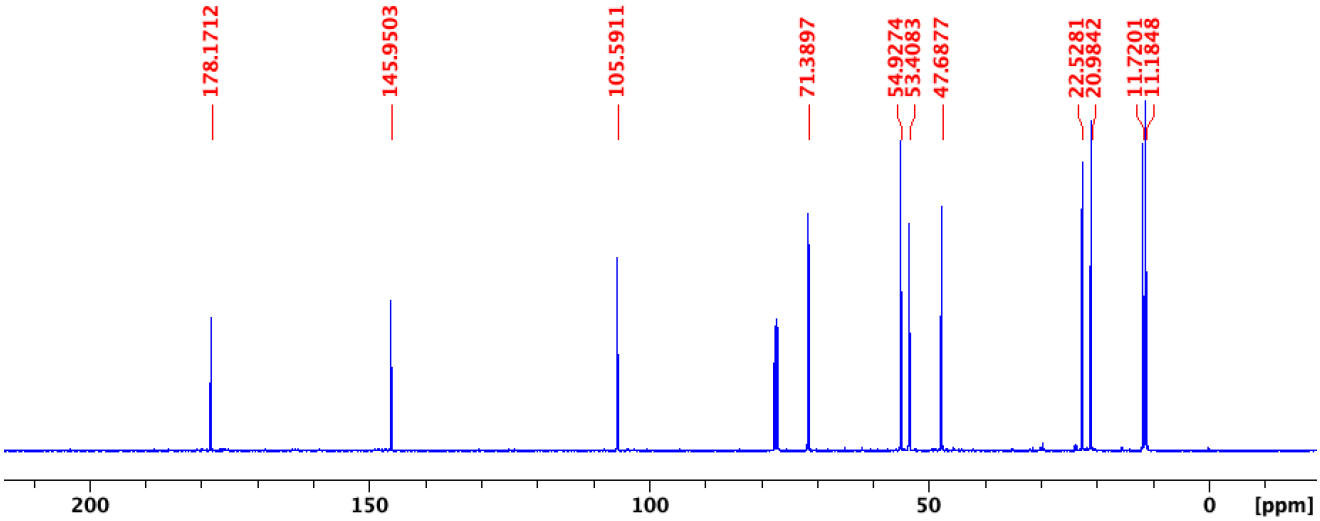
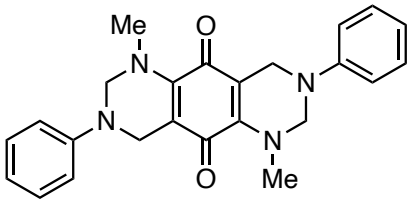
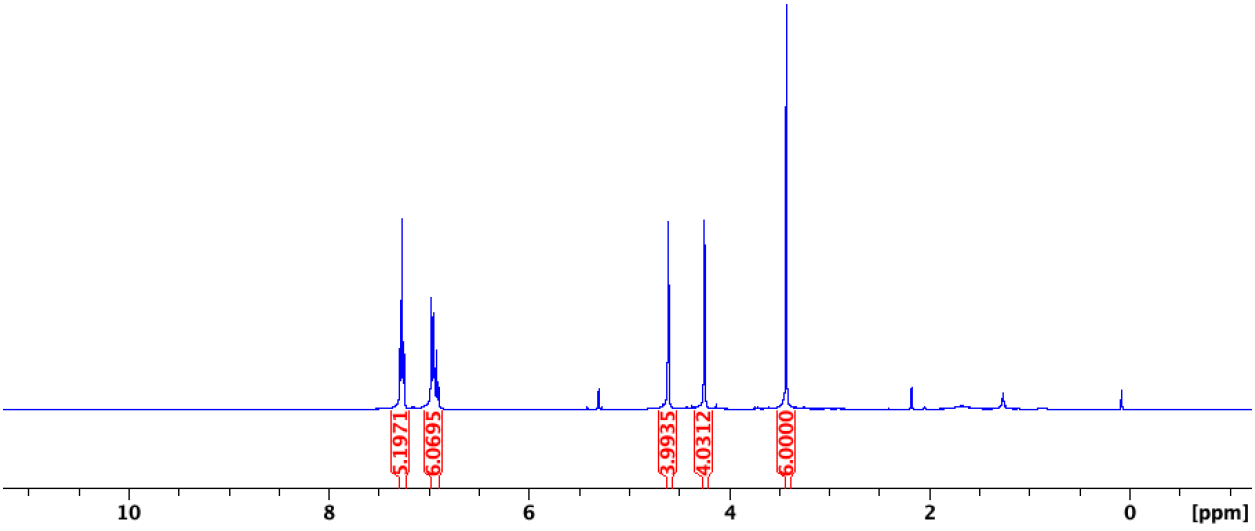
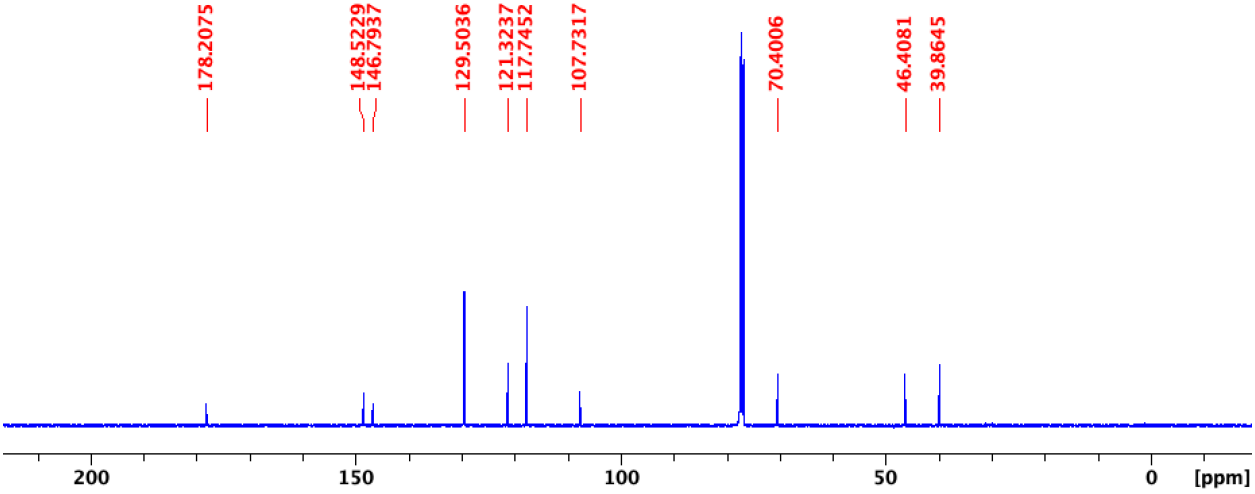


1,6-Dimethyl-3,8-bis(phenylamino)-1,2,3,6,7,8,9-octahydro-pyrimido[4,5-*g*]quinazolin-5,10-dione (6a)

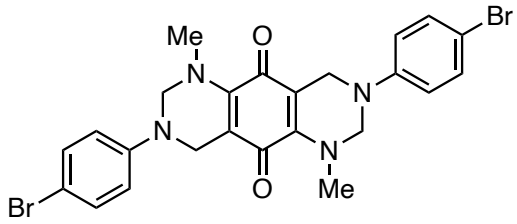


6a

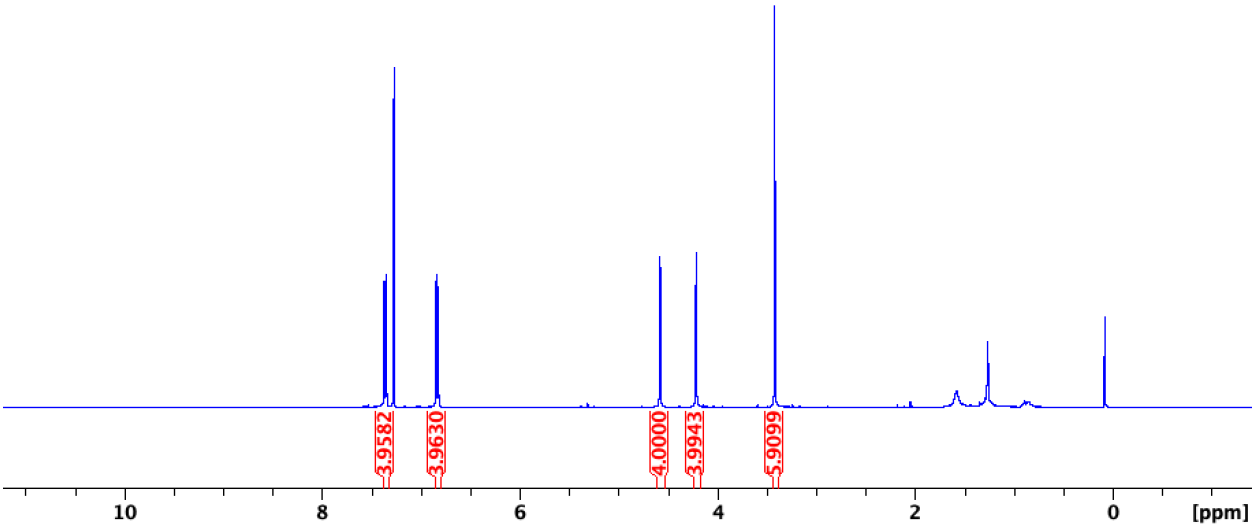


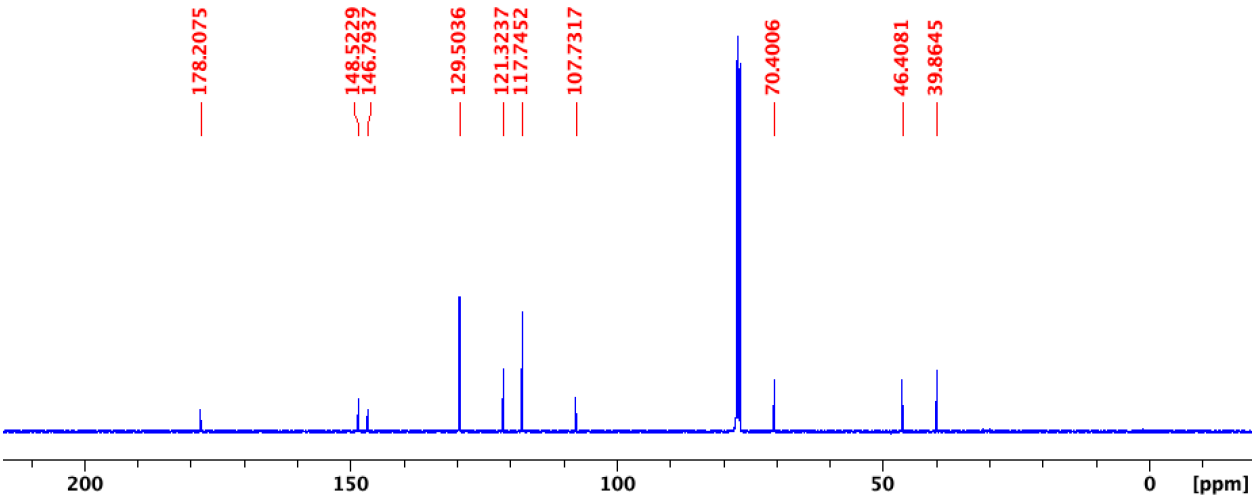


1,6-Dimethyl-3,8-bis(4-bromophenylamino)-1,2,3,6,7,8,9-octahydro-pyrimido[4,5-*g*]quinazolin-5,10-dione (6b)

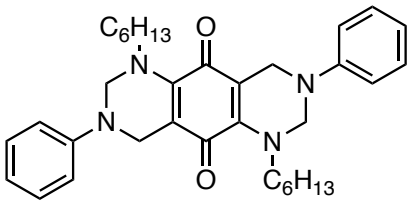


6b

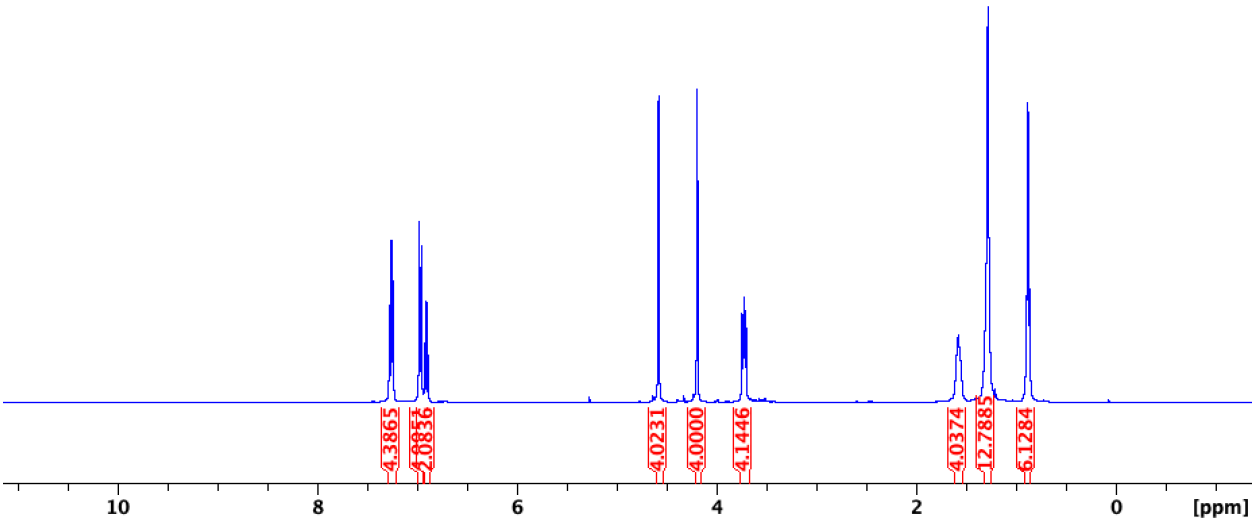


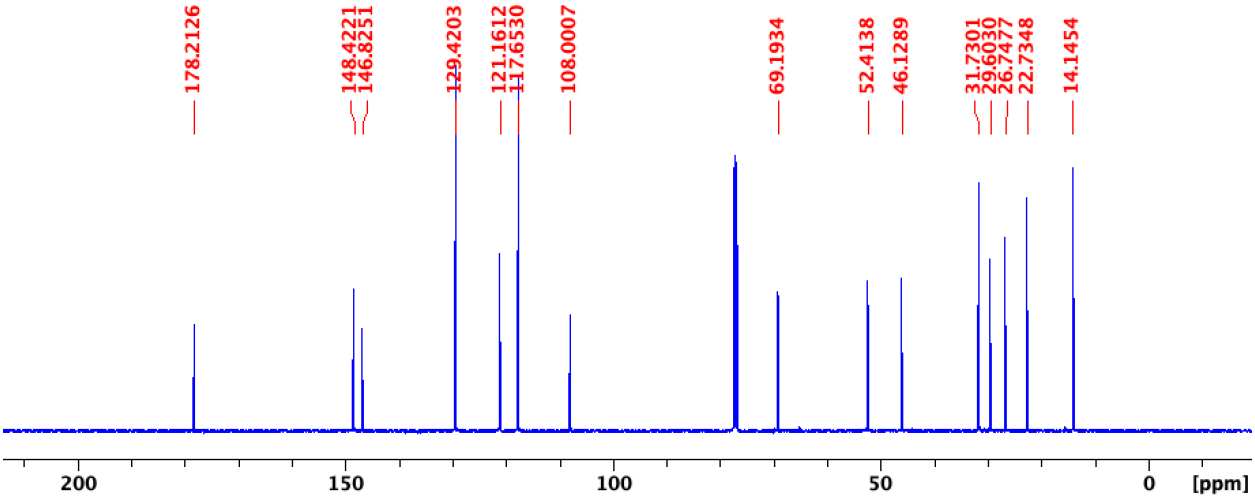


1,6-Dihexyl-3,8-bis(phenylamino)-1,2,3,6,7,8,9-octahydro-pyrimido[4,5-*g*]quinazolin-5,10-dione

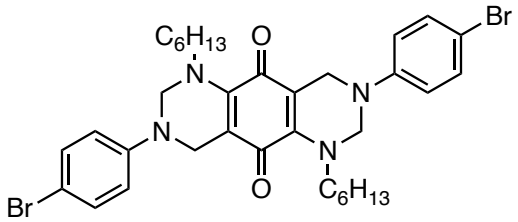


7a





1,6-dihexyl-3,8-bis(4-bromophenylamino)-1,2,3,6,7,8,9-octahydro-pyrimido[4,5-*g*]quinazolin-5,10-dione (7b)



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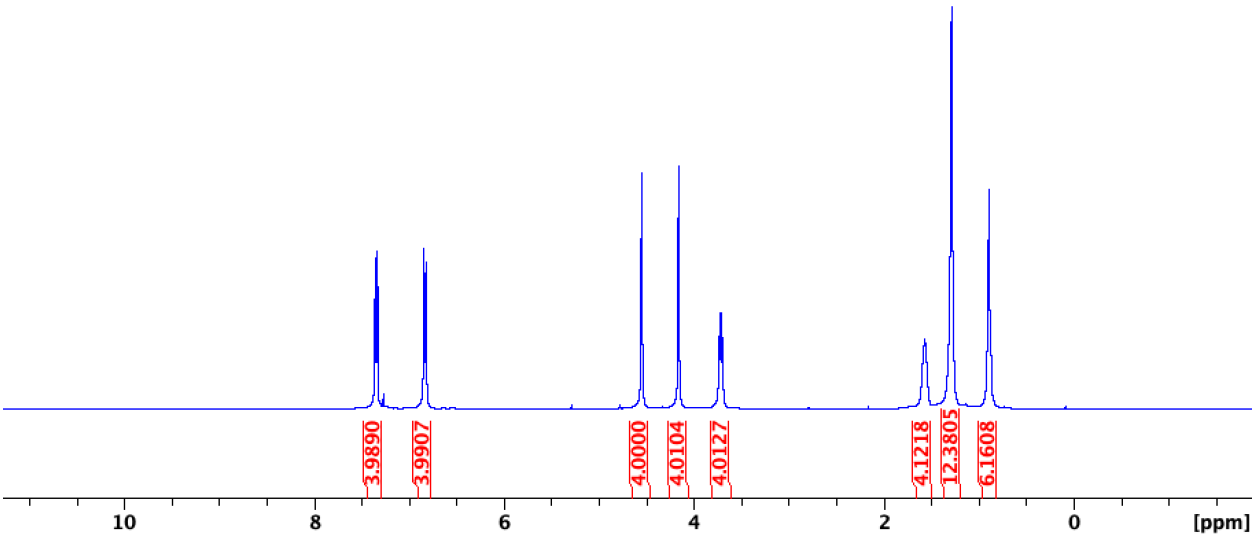
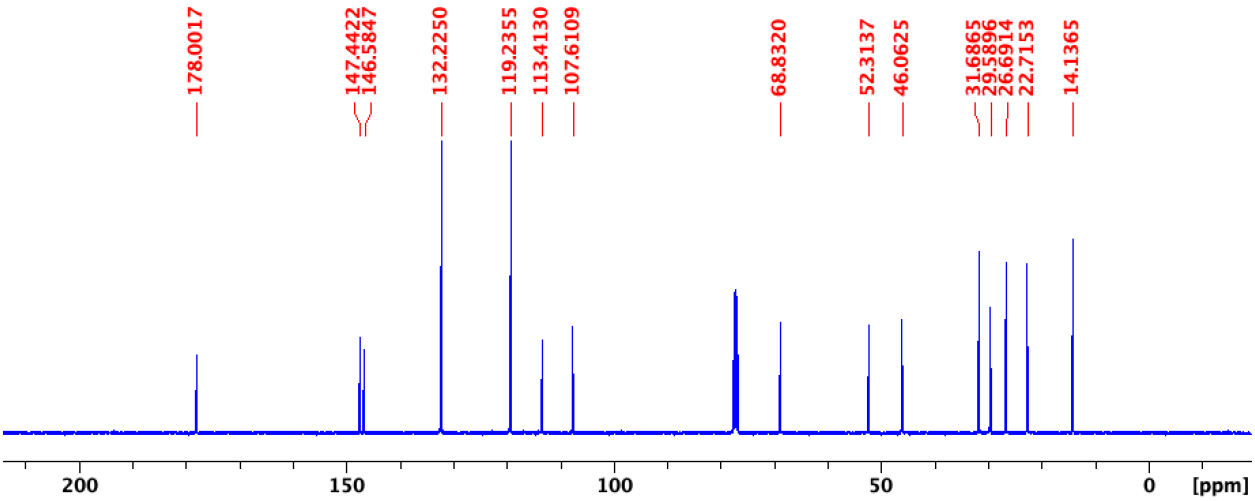
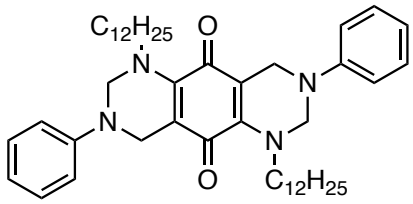
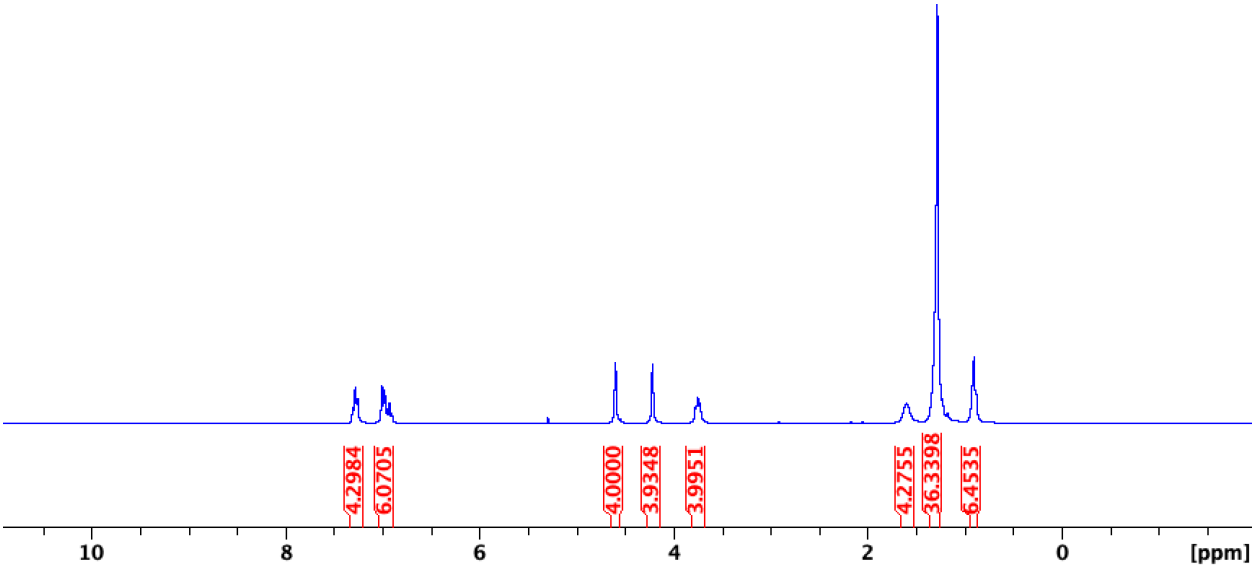


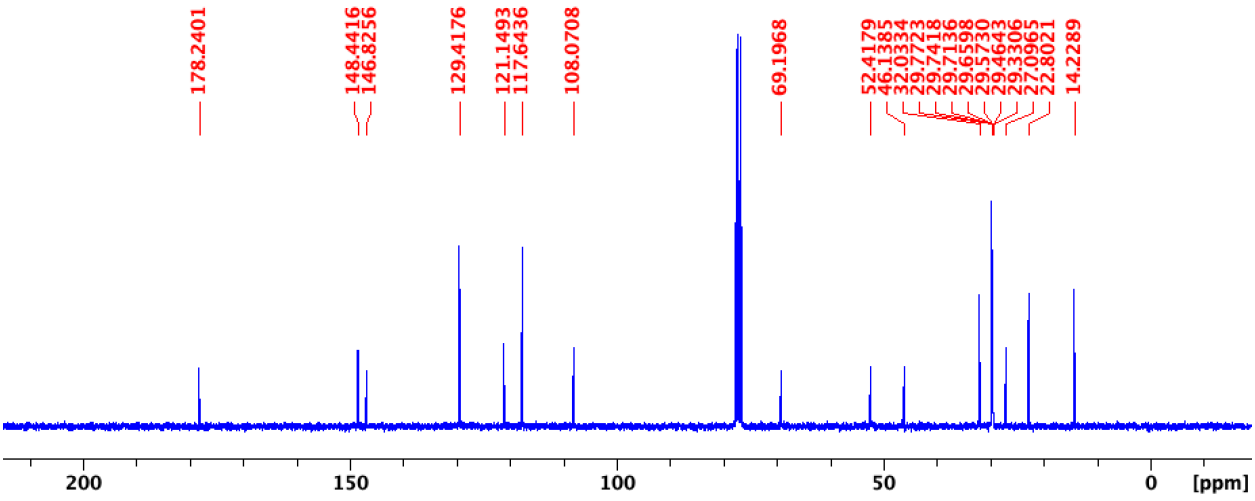


1,6-di(dodecylamino)-3,8-di(phenylamino)-1,2,3,6,7,8,9-octahydro-pyrimido[4,5-*g*]quinazolin-5,10-dione (8a)

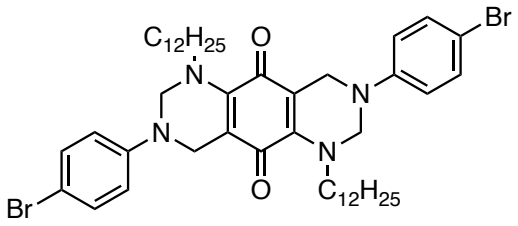


8a





1,6-di(dodecyl)-3,8-di(4-bromophenyl)-1,2,3,6,7,8,9-octahydro-pyrimido[4,5-*g*]quinazolin-5,10-dione



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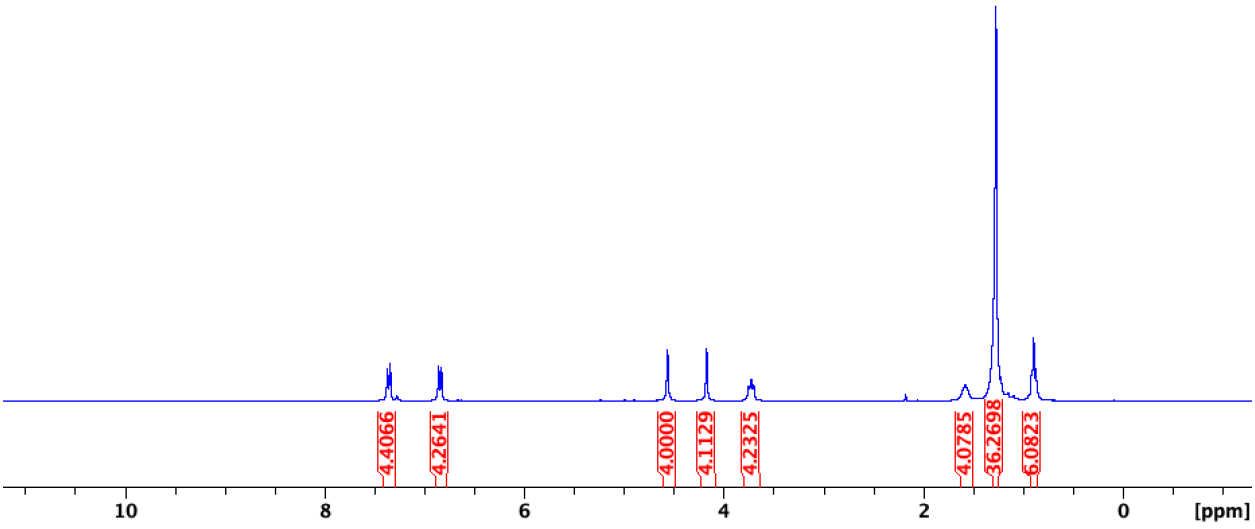

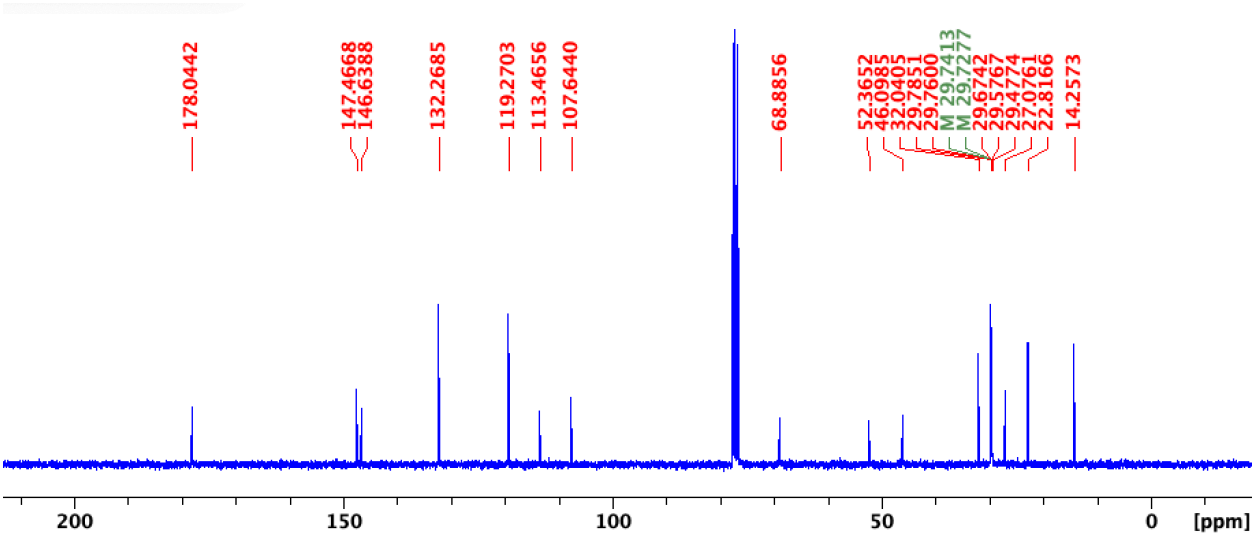

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