SUPPORTING INFORMATION

Catalytic Asymmetric Synthesis of Quaternary Barbituric Acids

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1. Materials and Generals Techniques

General experimental: All non-aqueous reactions were performed using oven-dried glassware and were magnetically stirred unless otherwise stated. Yields refer to chromatographically purified and spectroscopically pure compounds, unless otherwise stated.

Solvents and reagents: All reagents bought from commercial sources were used as sold. Organic solvents were evaporated under reduced pressure using a Büchi rotary evaporator. Anhydrous dichloromethane was dried over CaH_2, diethyl ether and tetrahydrofuran were dried by filtration through activated alumina (powder ≈ 150 mesh, pore size 58 Å, basic, Sigma Aldrich) columns. Anhydrous MeOH and ^{i}PrOH was dried over CaO and the rest of the solvents are commercially available with analytical reagent grade. $(DHQ)_2Pyr$ was purchased from Sigma Aldrich, quinine was purchased from Alfa Aesar.

Chromatography: Reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F254 plates and visualized by fluorescence quenching under UV light. In addition, TLC plates were stained with a dipping solution of potassium permanganate (1 g) in 100 mL of water (limited lifetime), followed by heating. Chromatographic purification was performed on ROCC 60 silica gel 40-63 μm, or non acid silica gel. Non acid silica gel was prepared by mixing silica gel with a saturated aqueous solution of sodium bicarbonate (300 mL of solution for 100 g of silica gel) during 24 hours and subsequent evaporation of water in an oven at 80 °C for 72 hours.

Melting points: Melting points were obtained on a Stuart SHP3 melting point apparatus and microscope and are uncorrected.

Mass spectra: MS spectra were recorded on an ESI-ion trap Mass spectrometer (Agilent 1100 series LC/MSD, SL model)

Infrared spectra: Infrared spectra were recorded on a Bruker Alpha FT-IR spectrometer as a thin film. Only selected maximum absorbances are reported.

NMR spectra: NMR spectra were recorded using a Bruker Avance 300 MHz or 500 MHz spectrometer, chemical shifts (δ) are quoted in parts per million referenced to the residual

solvent peak. In case of diastereomeric mixture, data of the major diastereomer are provided unless otherwise stated. The multiplicity of each signal is designated using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; brs, broad singlet. Coupling constants (*J*) are reported in Hertz (Hz).

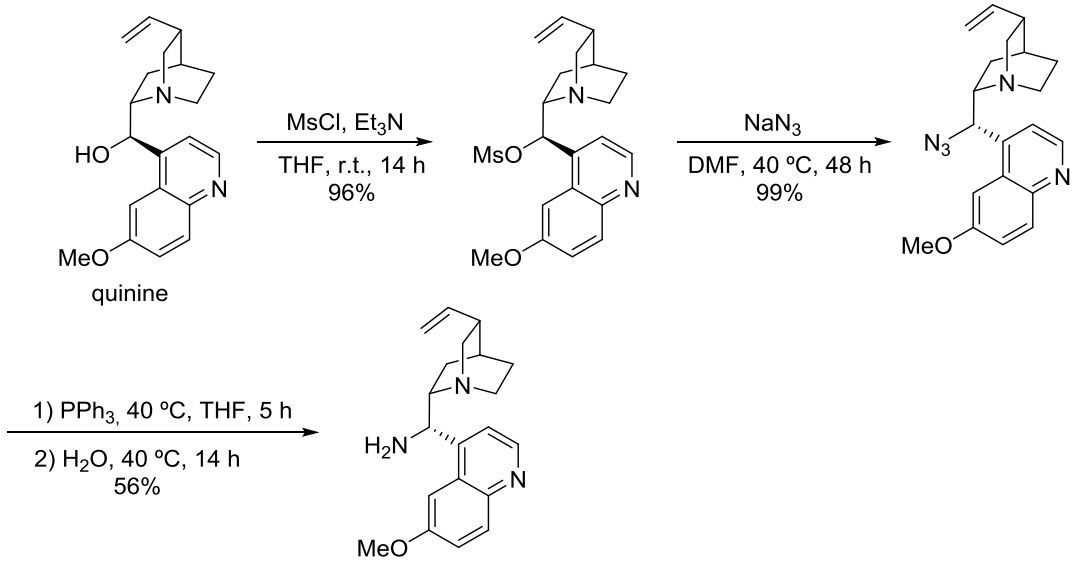
Determination of enantiomeric excesses: Enantiomeric excesses were determined using analytical high performance liquid chromatography (HPLC) performed on a Waters 600 (Photodiode Array Detector Waters 2996) (column and solvent conditions are given with the compound).

Optical rotations: Optical rotations were recorded using a Jasco P-2000 polarimeter; specific rotation ([α]*D*) are reported in 10-1 deg·cm2·g-1; concentrations (*c*) are quoted in g/100 mL; *D* refers to the D-line of sodium (589 nm); temperatures (*T*) are given in degree Celsius (°C).

2. Experimental procedures, analytical and spectroscopic data

2.1. Preparation of catalysts C1–C9

2.1.1. Preparation of 9-amino-(9-deoxy)epiquinine[1]



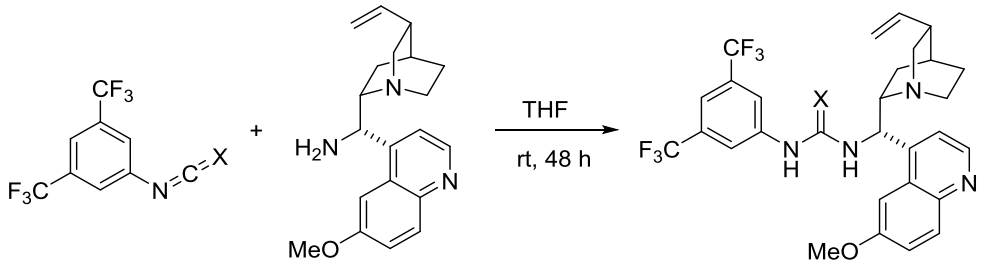
Step 1: A mixture of quinine (1 equiv., 16.2 g, 50 mmol) and triethylamine (3.6 equiv., 25.1 mL, 180 mmol) in dry THF (250 mL) was cooled to 0 °C and then methanesulfonyl chloride (1.8 equiv., 7.0 mL, 90 mmol) was added dropwise. The mixture was stirred overnight at room temperature. The reaction was quenched with water (40 mL) and then THF was removed under vacuum. The residue was dissolved in dichloromethane (40 mL) and washed with water (30 mL) and saturated sodium bicarbonate (30 mL). The organic layer was dried over $MgSO_4$, filtered and concentred under vacuum to afford the crude product in 96 % yield, which was used in the next step without further purification.

Step 2: The crude product (1 equiv., 19.3 g, 48 mmol) was dissolved in DMF (150 mL). The solution was cooled to 0 °C and NaN_3 (2 equiv., 6.2 g, 96 mmol) was added portionwise. The mixture was stirred at 40 ^{o}C for 48 h and after this time the reaction was quenched with water (80 mL) and then ethyl acetate (150 mL) was added. The organic layer was separated and washed with saturated NaCl (5 x 60 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to obtain the crude product in quantitative yield, which was used in the next step without further purification.

Step 3: The crude product was dissolved in THF (250 mL) and PPh_3 (1 equiv., 12.6 g, 48 mmol) was added. The reaction mixture was heated to 40 °C and stirred until the gas evolution

ceased (~5 h). Then H_2O (8 mL) was added and the mixture was stirred overnight at 40 °C. The solvent was removed under vacuum and the residue was dissolved in dichloromethane (150 mL). HCl 6M (250 mL) was added and the aqueous phase was separated and washed with dichloromethane (2 x 100 mL). Then the aqueous layer was cooled to 0 °C and basified until pH > 10 with NaOH 40%. The aqueous phase was then extracted with dichloromethane (3 x 150 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford 9-amino-(9-deoxy)*epi*quinine as a yellow viscous oil. Yield: 8.7 g, 26.9 mmol, 56 %. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ 8.75 (d, *J* = 4.6 Hz, 1H), 7.36–8.05 (m, 4H), 5.79 (m, 1H), 4.97 (m, 2H), 4.57 (d, *J* = 10.4 Hz, 1H), 3.97 (s, 3H), 3.02–3.34 (m, 3H), 2.77 (m, 2H), 2.27 (m, 1H), 2.08 (s, 2H), 1.26–1.63 (m, 4H), 0.80 (m, 1H).

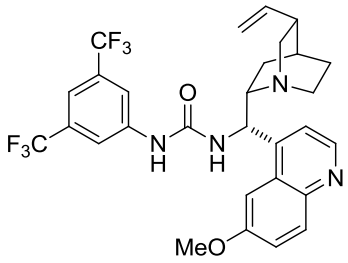
2.1.2. Preparation of catalysts C1[2] and C2[2b,3]



C1 X = O
C2 X = S

To a solution of 9-amino-(9-deoxy)*epi*quinine (1 equiv., 1.6 g, 5 mmol) in dry THF (7.5 mL) at 0 °C, a solution of bis(trifluomethyl)phenyl isothiocyanate (1.1 equiv., 1.5 g, 5.5 mmol) or bis(trifluomethyl)phenyl isocyanate (1.1 equiv., 0.6 mL, 5.5 mmol) in dry THF (2.5 mL) was added dropwise. The reaction mixture was stirred overnight at room temperature and then concentrated under reduced pressure. The residue was purified by flash column chromatography on non acid silica gel (eluent with hexane/ethyl acetate, 80:20 → ethyl acetate).

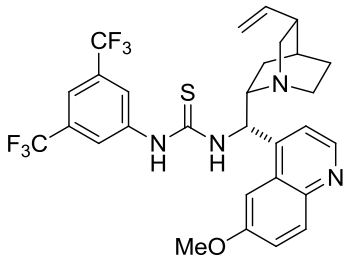
1-(3,5-Bis(trifluoromethyl)phenyl)-3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)urea C1



White solid, yield: 2.4 g, 4.1 mmol, 82 %. m. p. 132 – 134 °C. All data were consistent with those previously reported.[2] ^{1}H NMR (300 MHz, CD_3OD) δ 8.58 (d, *J* = 4.5 Hz, 1H), 7.84–7.90 (m, 3H), 7.66 (d, *J* = 2.5 Hz, 1H), 7.51 (d, *J* = 4.5 Hz, 1H), 7.36 (d, *J* = 1.5 Hz, 1H), 7.34 (d, *J* = 2.5 Hz, 1H), 5.83–5.89 (m, 1H), 5.65 (bs, 1H),

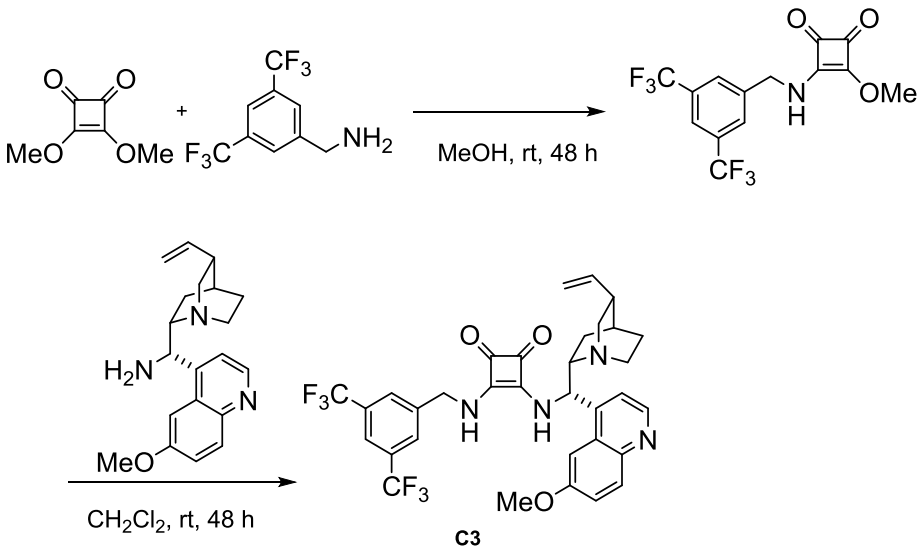
5.18 (d, *J* = 17.5 Hz, 1H), 5.09 (d, *J* = 10.5 Hz, 1H), 3.91 (s, 3H), 3.47–3.52 (m, 1H), 3.35–3.41 (m, 1H), 3.03–3.15 (m, 4H), 2.41–2.43 (m, 1H), 1.40–1.73 (m, 3H), 1.17–1.25 (m, 3H).

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)thiourea C2



White solid, yield: 2.6 g, 4.4 mmol, 88 %. m. p. 123 – 125 °C. All data were consistent with those previously reported.[2b,3] ^{1}H NMR (300 MHz, CD_3OD) δ 8.68 (d, *J* = 4.7 Hz, 1H), 8.11 (brs, 2H), 8.07 (d, *J* = 2.6 Hz, 1H), 7.95 (d, *J* = 9.3 Hz, 1H), 7.59 (br s, 1H), 7.55 (d, *J* = 4.7 Hz, 1H), 7.44 (dd, *J* = 9.3, 2.6 Hz, 1H), 6.32 (d, *J* = 11.0 Hz, 1H), 5.84 (ddd, *J* = 17.2, 10.5, 6.2 Hz, 1H), 5.02 (dt, *J* = 10.5, 1.5 Hz, 1H,), 4.98 (dt, *J* = 17.2, 1.5 Hz, 1H), 4.03 (s, 3H), 3.56–3.53 (m, 1H), 3.39–3.37 (m, 1H), 3.29 (dd, *J* = 13.6, 9.9 Hz, 1H), 2.82 (ddd, *J* = 15.6, 13.8, 4.9 Hz, 1H), 2.79 (ddd, *J* = 13.6, 4.7, 2.3 Hz, 1H), 2.38–2.35 (m, 1H), 1.71–1.68 (m, 2H), 1.64–1.61 (m, 1H), 1.45 (ddd, *J* = 13.3, 10.4, 2.7 Hz, 1H), 0.89 (dd, *J* = 13.3, 10.4 Hz, 1H).

2.1.3. Preparation of catalyst C3[4]



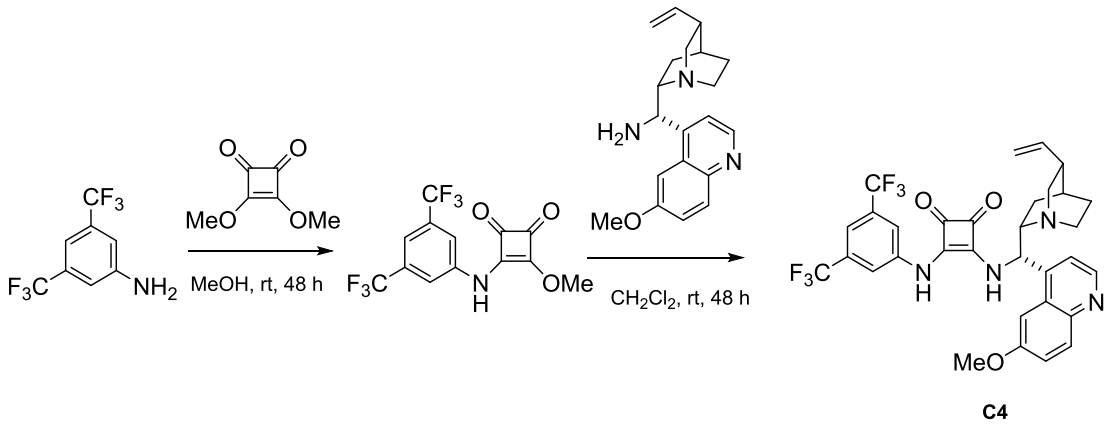
Step 1: synthesis of squaric ester monoamide intermediate

To a solution of dimethyl squarate (142 mg, 1.00 mmol) in CH_2Cl_2 (4 mL) was added a solution of 3,5-bis(trifluoromethyl)benzylamine (255 mg, 1.05 mmol) in CH_2Cl_2 (1 mL) and the mixture was stirred at room temperature for 48 h. The reaction mixture was filtered, and the filtrate was washed with (aq) 1 M HCl (10 mL), dried with Na_2SO_4, filtered again, and concentrated to afford 3-((3,5-bis(trifluoromethyl)benzyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (309 mg, 87%) as a white solid. All spectroscopic data were identical to those reported in the literature.[4] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.77 (s, 2H), 4.78 (bs, 1H), 4.41 (s, 3H).

Step 2: coupling to final squaramide **C3**

To a solution of previously obtained material (309 mg, 0.87 mmol) in MeOH (10 mL) at room temperature was added a solution of 9-amino-(9-deoxy)*epi*quinine (236 mg, 0.73 mmol) in MeOH (3 mL). After stirring the mixture for 24 h, the solvent was evaporated under reduced pressure and the residue was purified by non acid column chromatography (50:50 Hex:EtOAc) to afford the desired squaramide **C3** as a white solid (227 mg, 0.35 mmol, 50 % yield). All spectroscopic data were identical to those reported in the literature.[4] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.91-7.94 (m, 1H), 7.77 (s, 1H), 7.51-7.34 (m, 5H), 5.74-5.68 (m, 1H), 5.00-4.91 (m, 2H), 4.52 (bs, 2H), 3.88 (s, 3H), 3.24-3.19 (m, 3H), 2.77-2.68 (m, 1H), 2.31 (bs, 1H), 1.69-1.43 (m, 5H), 0.88 (bs, 1H).

2.1.4. Preparation of catalyst C4[5]



C4

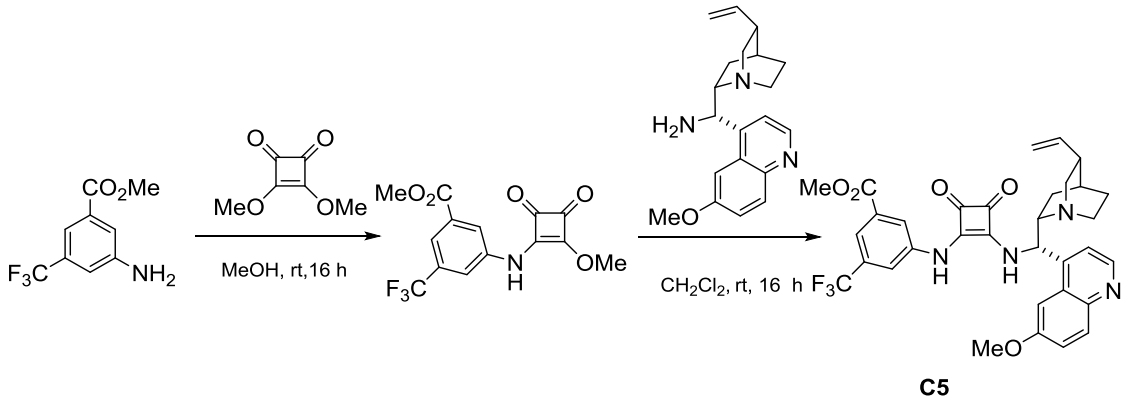
Step 1: Preparation of squaric ester monoamide intermediate

To a solution of dimethyl squarate (1.42 g, 10.0 mmol) in MeOH (20 mL) was added 3,5-bis(trifluoromethyl)aniline (1.56 mL, 10.0 mmol). The reaction mixture was stirred at room temperature for 48 h. The formed precipitate was filtered and dried in vacuo to give the desired product (2.25 g, 6.6 mmol, 66 %). m.p. 179 – 181 °C. All spectroscopic data where consistent with those reported in literature.[5] ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.18 (s, 1H), 8.04 (s, 2H), 7.78 (s, 1H), 4.41 (s, 3H).

Step 2: coupling to final squaramide **C4**

To a solution of the above obtained material (339 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) 9-amino-(9-deoxy)epiquinine (323 mg, 1.0 mmol), was added. The reaction mixture was stirred at room temperature for 48 h. Then the solvent was evaporated, and the product submitted to purification by silica gel column chromatography (eluent dichloromethane/methanol, 98:2). White solid (441 mg, 0.70 mmol, 70% yield); m.p. 224 – 225 °C. All spectroscopic data were identical to those reported in the literature.[5] ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.88 (br s, 1H), 8.80 (d, *J* = 4.5 Hz, 1H), 8.36 (br s, 1H), 8.04 – 7.86 (m, 3H), 7.76 (d, *J* = 10.0 Hz, 1H), 7.67 (d, *J* = 4.5 Hz, 1H), 7.58 (s, 1H), 7.47 (d, *J* = 6.8 Hz, 1H), 6.19 – 5.73 (m, 2H), 5.13 – 4.92 (m, 2H), 3.95 (s, 3H), 3.52-3.42 (m, 1H), 3.30- 3.25 (m, 1H) 2.77 – 2.58 (m, 2H), 2.35 – 2.20 (m, 1H), 1.60 – 1.47 (m, 4H), 0.66 (m, 1H).

2.1.5. Preparation of catalyst C5



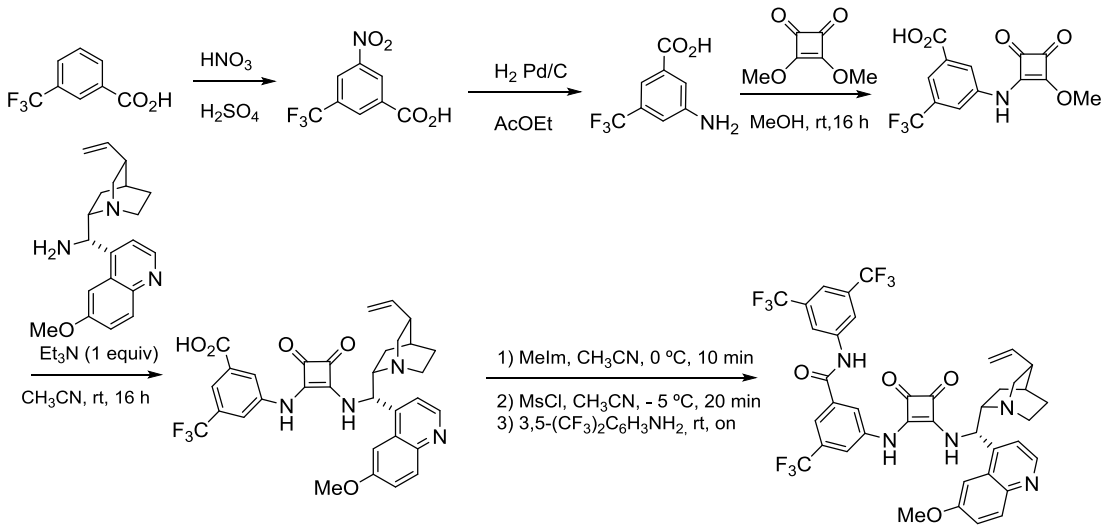
Step 1: preparation of ester monoamide intermediate

To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (147 mg, 1 mmol, 1 equiv) in MeOH (5 mL) the methyl 3-amino-5-(trifluoromethyl)benzoate (1 mmol, 227 mg, 1 equiv) was added at room temperature. The mixture was stirred at room temperature for 15 h. The white precipitate was filtered and washed with MeOH. The solid residue was dried in vacuum to give the title product as a white solid (403 mg, 0.65 mmol, 65 % yield); m.p. 219 – 221 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, *J* = 15.0 Hz, 2H), 7.83 (d, *J* = 2.4 Hz, 1H), 4.58 (s, 3H), 4.02 (s, 3H). UPLC-DAD-QTOF: $C_{14}H_{10}F_3NO_5$ $[M+H]^+$ calcd.: 330.0511, found: 330.0411.

Step 2: coupling to final squaramide **C5**

To a solution of the above obtained material (150 mg, 0.5 mmol) in CH_2Cl_2 (2.5mL) 9-amino-(9-deoxy)epiquinine (180 mg, 0.5 mmol) was added and the reaction mixture was stirred at room temperature for 16 h. The solvent was evaporated, and the residue was submitted to purification by silica gel column chromatography (eluent dichloromethane/methanol, 98:2). White solid (441 mg, 0.34 mmol, 67 % yield); m.p. 184 – 187 °C. $[\alpha]_D^{24}$= –42.8° (*c*= 0.5, 90 % ee, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (d, *J* = 4.4 Hz, 1H), 7.98 (d, *J* = 9.1 Hz, 1H), 7.88 (s, 1H), 7.74 (d, *J* = 23.1 Hz, 2H), 7.62 (s, 2H), 7.38 – 7.32 (m, 1H), 6.28 (s, 1H), 5.93 – 5.72 (m, 1H), 5.12 – 4.87 (m, 2H), 3.94 (s, 3H), 3.70 (s, 3H), 3.47 (dd, *J* = 11.4, 5.7 Hz, 1H), 3.20 (q, *J* = 9.4 Hz, 1H), 3.00 – 2.62 (m, 2H), 2.40 – 2.23 (m, 1H), 1.75 – 1.52 (m, 4H), 0.82 (d, *J* = 11.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.3, 181.8, 170.2, 165.5, 163.6, 159.3, 148.2, 145.3, 143.5, 141.35, 139.9, 132.5, 132.4, 132.3, 132.1, 128.5, 123.1, 122.1, 121.9, 121.1, 119.9, 115.7, 102.0, 60.9, 56.5, 56.4, 54.5, 53.1, 41.1, 39.9, 28.1, 28.0, 26.5. UPLC-DAD-QTOF: $C_{33}H_{31}F_3N_4O_5$ $[M+H]^+$ calcd.: 620.2247, found: 620.2330.

2.1.6. Preparation of catalyst C6[6]



Step 1: preparation of 3-nitro-5-(trifluoromethyl)benzoic acid

To a solution of 3- trifluoromethylbenzoic acid (10 mmol, 2 g) in concentrated sulphuric acid (10 mL) was added nitric acid (2 mL) at 0 °C over 15 min. The mixture was stirred at 35 °C for 3 h, and slowly poured onto ice. The precipitate was filtered and dissolved in ethyl acetate (50 mL). The ethyl acetate solution was washed with water (100 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure to give 3- nitro-5-(trifluoromethyl) benzoic acid (2,16 g, 92 % yield) as a white powder. All spectroscopic data were identical to those reported in the literature.[6a] ^{1}H-NMR (300 MHZ, $CDCl_3$) δ 8.69 (1H, s), 8.74 (1H, s), 9.1 (1H, s).

Step 2: preparation of 3-amino-5-(trifluoromethyl)benzoic acid

To a solution of the nitrocompound (1.56 g, 6.68 mmol) in EtOAc (15 mL) under inert atmosphere, Pd/C (Pd 10% in activated carbon, 10 % in weight) was added and the reaction mixture was stirred under H_2 atmosphere (1 atm) at room temperature for 20 h. The solution was filtered over celite and the filtrate was concentrated under reduced pressure to 3-amino-5-(trifluoromethyl)benzoic acid (1.08 g, 79 %) as a white solid. All spectroscopic data were identical to those reported in the literature.[6a] ^{1}H-NMR (300 MHZ, $CDCl_3$): δ 7.10 (1H, s), 7.53 (1H, s), 7.72 (1H, s).

Step 3: preparation of 3-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzoic acid

To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (710 mg, 5 mmol, 1 equiv) in MeOH (5 mL) at room temperature the 3-amino-5-(trifluoromethyl)benzoic acid (5 mmol, 685 mg, 1 equiv) was added. The mixture was stirred at the same temperature for 15 h. The white precipitate was filteredand washed with MeOH. The obtained yellow solid was dried in vacuo (1.5 g, 4.8 mmol, 96 %). All spectroscopic data were identical to those reported in the literature.[6a] ^{1}H NMR (300 MHz, Acetone-d6) δ 9.88 (s, 1H), 8.38 (s, 1H), 8.16 (s, 1H), 8.00 (s, 1H), 4.50 (s, 3H).

Step 4: preparation of 3-((2-(((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzoic acid

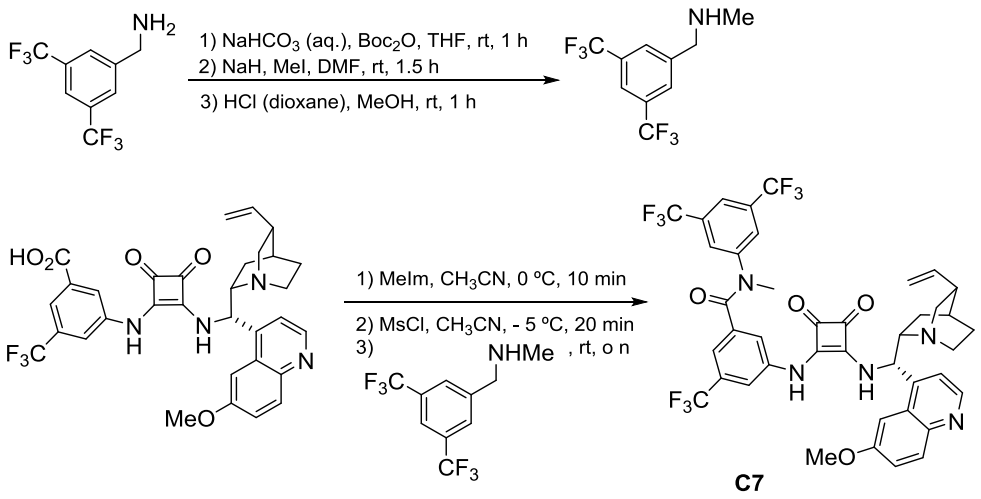
To a suspension of the above obtained material (630 mg) in CH_3CN (2 mL) at room temperature, Et_3N (2 mmol, 1 equiv) and (*R,R*)-9-deoxy-9-epiaminoquinine (2 mmol, 1 equiv) was added . The reaction mixture was stirred vigorously at room temperature for 16 h. The reaction mixture was directly submitted to purification by purified by flash column chromatography (CH_2Cl_2/ MeOH, 99:1).The obtained yellow solid was dried in vacuo (570 mg, 0.94 mmol, 47 %). All spectroscopic data were identical to those reported in the literature.[6a] ^{1}H NMR (300 MHz, Acetonitrile-*d*3) δ 11.51 (bs, 1H), 10.17 (bs, 1H), 8.85 (d, *J* = 4.5 Hz, 1H), 8.38 (s, 1H), 8.07 – 7.56 (m, 5H), 7.32 (dd, *J* = 9.2, 2.5 Hz, 1H), 6.40 (bs, 1H), 5.86 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.32 – 4.97 (m, 2H), 4.50 (s, 1H), 4.05 – 3.53 (m, 5H), 3.51 – 3.11 (m, 2H), 2.84 (d, *J* = 9.0 Hz, 1H), 2.25 – 1.97 (m, 4H), 1.78 (t, *J* = 12.4 Hz, 1H), 1.22 (d, *J* = 13.9 Hz, 1H).

Step 5: preparation of N-(3,5-bis(trifluoromethyl)phenyl)-3-((2-(((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzamide

1-Methylimidazole (0.2 mL, 2.5 mmol, 2.5 equiv) was added to a slurry of the above obtained material (570 mg, 1 mmol, 1 equiv) in CH_3CN (2.5 mL) at 0 °C, and the mixture was stirred for 10 min then a solution of MsCl (0.17 mL, 1.5 mmol, 1.5 equiv) in CH_3CN (0.1 mL) was added. After the mixture was stirred at 0°C for 20 min, 3,5-bis(trifluoromethyl)aniline (0.15 mL, 1 mmol, 1 equiv) was added and the mixture was stirred at room temperature over night. H_2O (10 mL) was added to the mixture causing a precipitate, which upon addition of EtOAc (10 mL) redissolved. The layers were separated and the organic layer was washed with brine (3 x 50 mL) and dried with anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the crude was crushed with diethyl ether to afford the compound **C6** as a yellow solid. Yield: 556 m g, 6.8 mmol, 68 %. All spectroscopic data were identical to those reported in the literature.[6] $[\alpha]_D^{25} = -52.7°$ (C = 0.5, MeOH); m.p. 195.6 - 197.2 °C. ^{1}H NMR

(300 MHz, DMSO-d_6) 10.94 (s, 1H), 10.16 (s, 1H), 8.80 (d, *J* = 4.5 Hz, 1H), 8.47 (d, *J* = 1.8 Hz, 2H), 8.27 (s, 1H), 8.17 (s, 1H), 7.97 (t, *J* = 4.5 Hz, 3H), 7.84 (s, 1H), 7.76 (s, 1H), 7.67 (d, *J* = 4.6 Hz, 1H), 7.45 (dd, *J* = 9.2, 2.4 Hz, 1H), 6.22 – 5.82 (m, 2H), 5.30 – 4.81 (m, 2H), 3.96 (s, 3H), 3.56 – 3.06 (m, 4H), 2.85 – 2.55 (m, 2H), 2.28 (q, J = 8.0, 7.2 Hz, 1H), 1.84 – 1.34 (m, 4H), 0.68 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ184.6, 180.1, 168.5, 164.4, 163.0, 157.9, 147.8, 144.3, 143.1, 142.1, 140.7, 140.3, 136.0, 131.5, 130.9, 130.5, 127.5, 125.1, 121.2, 120.0, 118.0, 117.5, 116.8, 114.3, 101.5, 58.9, 55.7, 27.3, 26.0. UPLC-DAD-QTOF: $C_{40}H_{33}N_5O_4F_9$ $[M+H]^+$ calcd.: 818.2389, found: 818.2398.

2.1.7. Preparation of catalyst C7[6a]



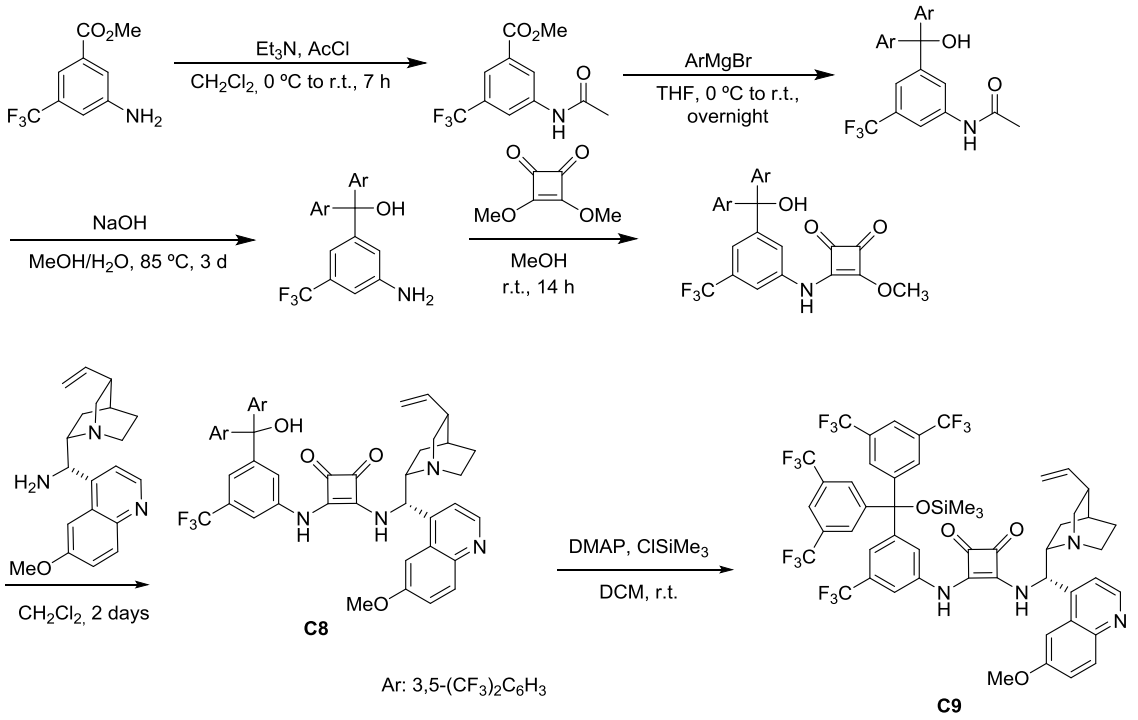
Step 1:

To a stirred solution of 3,5-bistrifluoromethylbenzylmine (1.22 g, 5 mmol, 1 equiv.) in THF (15 mL) Boc_2O (1.30 g, 6 mmol, 1.2 equiv.) was added and an aqueous saturated solution of $NaHCO_3$ (15 mL) were successively added. The resulting mixture was stirred at room temperature for 1 h, quenched with water (15 mL) and extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was eliminated under reduced pressure. The product obtained was dissolved in DMF (15 mL) and cooled to 0 °C. NaH (60 % in oil) previously washed with hexane (383 mg, 10 mmol, 2 equiv.) was slowly added to the solution and the resulting mixture was allowed to stir at room temperature for 20 min.Then iodomethane (0.75 mL, 12 mmol, 2.4 equiv.) was added and the mixture was allowed to stir for a further 1.5 h. The reaction was stopped by adding water (15 mL) and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (5 x 15 mL), dried over $MgSO_4$, filtered, and the solvent was eliminated under reduced pressure. The crude obtained was then dissolved in MeOH (7.5 mL) and a 4 M HCl solution was added and the resulting solution was stirred at room temperature for 3 h. The reaction was slowly quenched with a saturated aqueous solution of $NaHCO_3$ (3 x 15 mL). The mixture was extracted with EtOAc (3 x 15 mL) and the combined organic layers were washed with brine (3 x 15 mL), dried over $MgSO_4$, filtrate, and the solvent was eliminated under reduced pressure. The product obtained was used without further purification. All spectroscopic data were identical to those reported in the literature.[6a] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 2H), 7.77 (s, 1H), 3.89 (s, 2H), 2.48 (s, 3H), 1.47 (s, 1H).

Step 2:

1-Methylimidazole (0.2 mL, 2.5 mmol, 2.5 equiv) was added to a slurry of previously prepared 3-((2-(((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzoic acid (606 g, 1 mmol, 1 equiv) in CH_3CN (2.5 mL) at 0 °C, and the mixture was stirred for 10 min. MsCl (0.17 mL, 1.5 mmol, 1.5 equiv) in CH_3CN (0.1 mL) was added at the same temperature, and the mixture was stirred for 20 min. 3,5-bis(trifluoromethyl)methyl aniline (0.15 mL, 1 mmol, 1 equiv) was then added and the mixture was stirred at room temperature over night. H_2O (10 mL) was added to the mixture, causing a precipitate, which upon addition of EtOAc (10 mL) redissolved. The organic layer was washed with brine (3 x 50 mL), dried with anhydrous $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure and the crude was crushed with diethyl ether to afford the title compound **C7** as a white solid. Yield: 0.64 mmol, 532 mg, 64%. All spectroscopic data were identical to those reported in the literature.[6a] $[\alpha]_D^{25} = -115.9°$ (C = 1.0, CH_2Cl_2).^{1}H NMR (300 MHz, CDCl3) δ 8.56 (d, *J*= 4.1 Hz, 1H), 7.94 (d, *J*= 9.2 Hz, 1H), 7.80 (s, 1H), 7.75 (d, *J*= 16.0 Hz, 2H), 7.54–7.28 (m, 4H), 6.98 (s, 2H), 6.89–6.73 (m, 1H), 6.22 (s, 1H), 5.87–5.69 (m, 1H), 5.04–4.87 (m, 2H), 4.85–4.54 (m, 2H), 3.95 (s, 3H), 3.63–3.34 (m, 2H), 3.17 (t, *J*= 11.4 Hz, 1H), 2.87 (s, 3H), 2.81–2.63 (m, 2H), 2.35–2.19 (m, 1H), 1.75–1.42 (m, 4H), 0.78–0.64 (m, 1H). 13C NMR (75 MHz, CDCl3) δ 183.7, 181.3, 171.5, 168.7, 163.3, 158.7, 147.2, 144.5, 143.4, 141.0, 139.3, 138.5, 136.0, 132.2, 131.8, 131.3, 129.4, 127.9, 127.0, 124.8, 122.6, 121.7, 121.2, 120.4, 118.7, 117.4, 114.7, 101.1, 77.2, 59.7, 55.9, 50.4, 40.7, 39.3, 37.4, 27.4, 26.1. UPLC-DAD-QTOF: C41H38N5O4F6 $[M+H]^+$ calcd.: 778.2823, found: 778.2818.

2.1.8. Preparation of catalysts C8 and C9[7]



Step 1: preparation of Methyl 3-acetamido-5-(trifluoromethyl)benzoate[8]

To a solution of the obtained methyl 3-amino-5-(trifluoromethyl)benzoate (2.192 g, 10 mmol) and Et_3N (1.40 mL, 10 mmol) in CH_2Cl_2 (50 mL) acetyl chloride (0.757 mL, 10.5 mmol) was added dropwise at 0 °C. After 7 h at room temperature, the reaction mixture was washed with water and brine, dried over $MgSO_4$ and concentrated to provide the title compound as white solid (2.534 g, 9.7 mmol, 97%) which was used in the next step without further purification. ^{1}H-RMN (300 MHz, $CDCl_3$) δ 8.20 (d, *J* = 5.4 Hz, 2H), 8.03 (s, 1H), 7.44 (s, 1H), 3.95 (s, 3H), 2.23 (s, 3H).

Step 2: preparation of N-(3-(Hydroxy-bis(3,5-bis(trifluoromethyl)phenyl)methyl)-5-(trifluoromethyl)phenyl)acetamide[8]

A solution of the crude material of the previous reaction (5.0 mmol, 1.31 g) in THF (10 mL) was added dropwise at 0 °C to a solution of 3,5-bis(trifluoromethyl)-phenyl magnesium bromide (0.5M in THF, 15 mmol). The mixture was stirred at reflux overnight. The reaction was quenched with NH_4Cl saturated solution, the solvent was evaporated under reduced pressure and diluted wit water (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers was dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 7/3) to give the title compound as a brown solid (2.70 g, 4.1 mmol, 82%). M.p.=

190-198 °C. ^{1}H NMR (300 MHz, MeOD) δ 8.08 – 8.04 (m, 1H), 8.01 – 7.96 (m, 2H), 7.91 – 7.85 (m, 4H), 7.63 (t, *J* = 1.8 Hz, 1H), 7.40 – 7.35 (m, 1H), 2.09 (s, 3H). ^{13}C NMR (75 MHz, MeOD) δ 172.1, 150.0, 148.2, 141.2, 133.2, 129.2, 126.4, 123.4, 123.0, 120.2, 120.2, 117.0, 117.0, 81.3, 23.9. UPLC-DAD-QTOF: $C_{26}H_{15}NO_2F_{15}$ $[M+H]^+$ calcd.: 658.0863, found: 658.0859.

Step 3: preparation of (3-Amino-5-(trifluoromethyl)phenyl)-bis(3,5-bis(trifluoromethyl)phenyl) methanol[8]

To a solution of the acetamide obtained above (1.31 g, 2.0 mmol) was added in MeOH (15 mL) and water (2 mL) NaOH (1.60 g, 40 mmol, 20 equiv.) and the mixture was heated at 85 °C for 3 d. The reaction mixture was neutralized with HCl 1M until pH 7, extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with CH_2Cl_2/MeOH 98:2) to give the title compound as a brown solid (1.14 g, 1.9 mmol, 93%).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 – 7.85 (m, 2H), 7.85 – 7.78 (m, 4H), 6.92 (t, *J* = 1.8 Hz, 1H), 6.78 (td, *J* = 1.6, 0.8 Hz, 1H), 6.53 (t, *J* = 1.9 Hz, 1H), 3.98 (s, 2H), 2.96 (s, 1H).

Step 4: preparation of 3-((3-(Hydroxyl-bis(3,5-bis(trifluoromethyl)phenyl)methyl)-5-(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione[7]

To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (142 mg, 1.0 mmol, 1 equiv.) in MeOH (4 mL) was added the free aniline obtained above (615 mg, 1.0 mmol, 1 equiv.) and the mixture was stirred at room temperature for 14 h. The solvent was evaporated under reduced pressure and the crude material was purified by flash column chromatography on silica gel (eluting with Hexane/ ethyl acetate 7/3) to give the title compound as a yellow solid (616 mg, 0.85 mmol, 85%).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 2H), 7.80 (s, 4H), 7.55 (s, 2H), 7.22 (s, 1H), 4.42 (s, 3H), 4.02 (s, 1H).

Step 5: preparation of 3-((3-(Hydroxy-bis(3,5-bis(trifluoromethyl)phenyl)methyl)-5-(trifluoromethyl)phenyl)amino)-4-(((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione **C8**[7]

To a suspension of the hemisquaramide obtained above (363 mg, 0.5 mmol, 1 equiv.) in CH_2Cl_2 (2 mL) was added (*R,R*)-9-deoxy-9-epiaminoquinine (162 mg, 0.5 mmol, 1 equiv.) and the reaction mixture was stirred at room temperature for 2 days. The solvent was evaporated in the rotary evaporator and the oil residue was submitted to purification by silica column

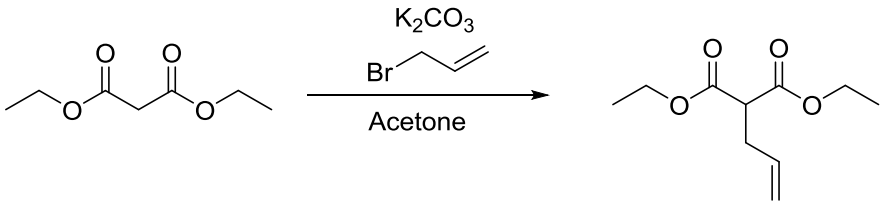
chromatography (CH_2Cl_2/MeOH, 98/2) to give the pure **C8** catalyst as a yellow solid (346 mg, 0.34 mmol, 68%). M.p.= 175-183 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.14 – 9.71 (m, 1H), 8.78 (d, *J* = 4.5 Hz, 1H), 8.13 – 8.03 (m, 2H), 8.03 – 7.89 (m, 5H), 7.79 (s, 1H), 7.74 – 7.65 (m, 2H), 7.62 (d, *J* = 4.6 Hz, 1H), 7.50 – 7.38 (m, 2H), 7.33 (s, 1H), 6.03 – 5.88 (m, 1H), 5.11 – 4.88 (m, 2H), 3.90 (s, 3H), 3.23 – 3.10 (m, 2H), 2.75 – 2.54 (m, 2H), 2.36 – 2.19 (m, 1H), 1.65 – 1.39 (m, 4H), 0.63 (d, *J* = 14.3 Hz, 1H). ^{13}C NMR (75 MHz, DMSO) δ 184.4, 179.6, 168.3, 163.0, 157.9, 148.3, 147.7, 147.4, 144.3, 142.9, 142.1, 139.7, 131.5, 130.3 (q), 128.6, 128.2, 127.4, 125.5, 124.9, 121.9, 121.3, 120.8, 117.7, 117.6, 114.4, 114.1, 101.4, 79.5, 64.9, 58.8, 55.6, 38.5, 38.2, 27.3, 26.0, 15.1. UPLC-DAD-QTOF: $C_{48}H_{36}N_4O_4F_{15}$ $[M+H]^+$ calcd.: 1017.2497, found: 1017.2518.

Step 6: preparation of 3-((3-(Bis(3,5-bis(trifluoromethyl)phenyl)((trimethylsilyl)oxy)methyl)-5-(trifluoromethyl) phenyl)amino)-4-(((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl) amino)cyclobut-3-ene-1,2-dione **C9**

To a suspension of catalyst **C8** (102 mg, 0.1 mmol, 1 equiv.) and DMAP (20 mg, 0.15 mmol, 1.5 equiv.) in CH_2Cl_2 (0.2 mL) was added dropwise chlorotrimethylsilane (20 µL, 0.15 mmol, 1.5 equiv.) and the reaction mixture was stirred for 14 h at r.t. Then, CH_2Cl_2 (2 mL) was added and the organic layer was washed twice with water and HCl 1M, dried over $MgSO_4$ and the solvent was evaporated. The product was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 98:2) to give pure catalyst **C9** as a yellow solid (93.6 mg, 0.086 mmol, 86%). All spectroscopic data were identical to those reported in the literature.[7] M.p.= 160-165 °C. ^{1}H NMR (300 MHz, MeOD) δ 8.74 (d, *J* = 4.6 Hz, 1H), 8.07 (t, *J* = 1.8 Hz, 1H), 8.00 (s, 6H), 7.98 – 7.92 (m, 2H), 7.76 (d, *J* = 2.6 Hz, 1H), 7.71 – 7.63 (m, 2H), 7.41 (dd, *J* = 9.3, 2.5 Hz, 1H), 7.32 (s, 1H), 6.34 (d, *J* = 11.4 Hz, 1H), 5.96 (ddd, *J* = 17.4, 10.4, 7.2 Hz, 1H), 5.27 – 5.06 (m, 2H), 4.04 (d, *J* = 10.3 Hz, 1H), 3.97 (s, 3H), 3.82 – 3.67 (m, 1H), 3.52 (dd, *J* = 13.4, 10.2 Hz, 1H), 3.25 – 2.98 (m, 2H), 2.71 – 2.57 (m, 1H), 1.37 – 1.11 (m, 2H), 1.02 – 0.87 (m, 1H), -0.12 (s, 9H). ^{13}C NMR (75 MHz, MeOD) δ 185.8, 181.3, 169.5, 166.0, 160.7, 149.1, 148.4, 145.5, 143.8, 141.6, 140.7, 133.3, 132.8, 131.8, 129.4, 129.1, 126.3, 124.6, 123.3, 122.7, 122.3, 120.4, 119.6, 119.1, 116.4, 115.9, 115.9, 101.7, 84.6, 61.2, 56.7, 56.1, 42.2, 39.4, 28.4, 26.8, 26.3, 1.4. UPLC-DAD-QTOF: $C_{42}H_{22}NO_3F_{24}$ $[M+H]^+$ calcd.: 1044.1216, found: 1044.1239.

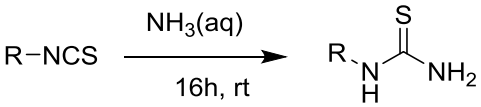
2.2. Synthesis of barbituric acid derivatives 1 and 4.

2.2.1. Synthesis of diethyl 2-allylmalonate[9]



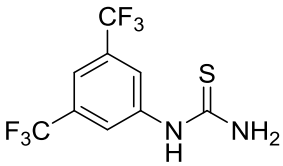
Diethyl malonate (5.9 mL, 37.5 mmol) and allyl bromide (2.16 mL, 25 mmol) were added to a solution of potassium carbonate (17.27 g, 75 mmol) in acetone (124 mL) and the mixture was stirred for 24h at 23 °C. The reaction mixture was quenched by addition of saturated aqueous ammonium chloride solution (200 mL) and extracted with methylene chloride (3 x 100 mL). The combined organic layers were dried over sodium sulphate and the solvent was removed under reduced pressure. The oily residue was purified by flash-chromatography through silica gel (Hexane/ethyl acetate 99:1). The product containing fractions were evaporated and the oily residue was distillated under reduced pressure (2 mbar, 45 °C, rotary evaporator/heat gun) to remove the excess of diethyl malonate. Diethyl 2-allylmalonate was obtained as a colorless oil (6.8 g, 24.0 mmol, 90%). All the analytical data are consistent with the previously published data.[9] ^{1}H NMR (300MHz, $CDCl_3$) 5.78 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.15-5.03 (m, 2H), 4.19 (dd, *J* = 7.2, 1.0 Hz, 4H), 3.45-3.34 (m, 1H), 2.71-2.56 (m, 3H), 1.27 (d, *J* = 7.2Hz, 6 H).

2.2.2. Synthesis of monosustituted thioureas



To a solution of 30% aqueous ammonium (6 mL) was added the corresponding isocyanate (6 mmol) at room temperature. The mixture was stirred at room temperature for 16 h. The product precipitated as a white solid which was filtrated and washed with MeOH and the solid residue was dried in vacuo.

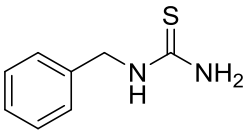
1-(3,5-Bis(trifluoromethyl)phenyl)thiourea



Prepared according to the general procedure starting from bis(3,5-trifluoro-methyl)phenylisothiocyanate. M.p: 180-185 °C. Yield: 98%

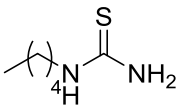
(1.69 g). ^{1}H NMR (300 MHz, acetone) δ 9.67 (s, 1H), 8.41 (s, 2H), 7.77 (s, 1H), 7.38 (bs, 2H).^{13}C NMR (75 MHz, acetone) δ 184.3, 143.2, 132.2, 126.6, 124.0, 123.9, 122.9, 118.3, 118.3. UPLC-DAD-QTOF: calcd for $C_9H_7N_2SF_6$ (M, H^+), 289.0243; found ,289.0234.

1-Benzylthiourea



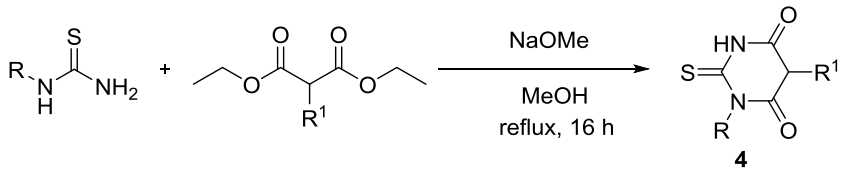
Prepared according to the general procedure starting from benzylisothiocyanato. M.p: 217 - 220 °C. Yield: 100% (1.00 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 5H), 5.67 (bs, 1H), 4.72 (s, 2H). UPLC-DAD-QTOF: calcd for $C_8H_{11}N_2S$ (M, H^+), 167.0641; found, 167.0643.

1-Pentylthiourea



Prepared according to the general procedure starting from pentylisothiocyanato**.** M.p: 234-236 °C. Yield: 100% (790 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.16 (t, 2H), 1.61 (m, 2H), 1.35 (m, 4H), 0.95 (t, 3H).MS (ESI, *m*/*z*): calcd for $C_6H_{11}N_2S$ (M, H^+), 129.0612; found, 129.17413.

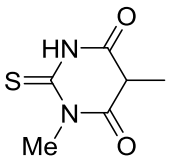
2.2.3. Coupling of thioureas with malonic esters[10] (synthesis of 4)



4

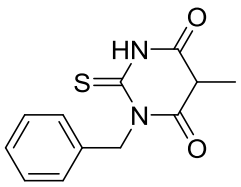
In a 250 mL round-bottom flask fitted with a reflux condenser protected with a calcium chloride tube, sodium metal were placed 1.150 g (50 mmol) and 20 mL of anhydrous MeOH. The mixture was stirred until all the sodium disappeared. Then a solution of the respective N-alkyl or N-aryl thiourea (50 mmol) in 20 mL of anhydrous MeOH,(warming was required in order to set thioureas completly dissolved) was added, followed by a dropwise addition of the corresponding malonate (50 mmol). The mixture was refluxed for 16 h. A white solid formed rapidly. After the reaction was completed, 100 mL of hot (50 °C) water was added and then enough hydrochloric acid (2 M) to make the solution acidic. The precipitate was washed with MeOH and dried at vacuum (735 mmHg) in a bath at 80 °C.

1, 5-Dimethyl-2-thioxodihydropyrimidine-4,6 (1*H,5H)*-dione (4Aa)



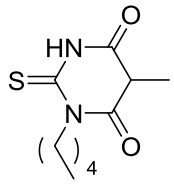
Prepared according to the general procedure starting from 1-methylthiourea and diethyl 2-methylmalonate**.** The title compound was obtained as a white solid. M.p: 211-212 °C. Yield: 64% (5.5 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.78 (s, 1H), 3.91 (s, 3H), 2.92 (p, *J* = 1.8 Hz, 1H), 2.18 (s, 3H).^{13}C NMR (75 MHz, DMSO) δ 173.4, 162.7, 155.9, 89.6, 33.2, 8.3. UPLC-DAD-QTOF: calcd for $C_6H_9N_2O_2S$ (M, H^+), 173.0385; found, 173.0387.

1-Benzyl-5-methyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*) (4Ab)



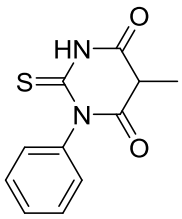
Prepared according to the general procedure starting from 1-benzylthiourea and diethyl 2-methylmalonate**.** The title compound was obtained as a white solid. M.p: 148 - 151 °C Yield: 85% (10.5 g). ^{1}H NMR (300 MHz, MeOD) δ 7.29 (m, 5H), 5.65 (s, 2H), 1.88 (s, 3H). ^{13}C NMR (75 MHz, MeOD) δ 175.9, 165.4, 158.1, 138.1, 129.1, 129.1, 128.7, 128.7, 128.0, 91.4, 50.3, 8.01. UPLC-DAD-QTOF: calcd for $C_{12}H_{13}N_2O_2S$: 249.0698; found, 249.0702.

5-Metil-1-pentil-2-tioxodihidropirimidin-4,6(1*H,*5*H*)-diona (4Ac)



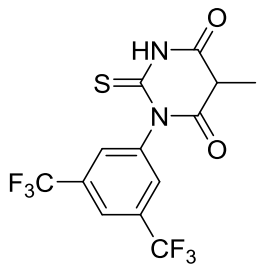
Prepared according to the general procedure from the 1-pentylthiourea and diethyl 2-methylmalonate**.** The title compound was obtained as a white solid. M.p: 176 - 177 °C Yield: 83% (9.5 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.29 (s, 1H), 4.59 (m, 2H), 3.52 (q, 1H), 1.66 (m, 2H), 1.62 (d, 3H), 1.34 (m, 4H), 0.90 (t, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 167.8, 166.1, 47.2, 44.9, 28.9, 26.8, 22.4, 14.1, 13.6. UPLC-DAD-QTOF: calcd for $C_{10}H_{17}N_2O_2S$: 229.1011; found, 229.1012.

5-Methyl-1-phenyl-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (4Ad)



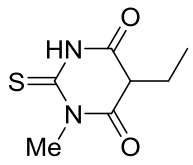
Prepared according to the general procedure starting from 1-phenylthiourea and diethyl 2-methylmalonate. The title compound was obtained as a white solid. M.p: 173-175 °C. Yield: 73% (8.5 g). ^{1}H NMR (300 MHz, DMSO) δ 12.37 (s, 1H), 7.47 – 7.33 (m, 4H), 7.13 (d, *J* = 8.0 Hz, 2H), 3.17 (s, 3H), 1.77 (s, 3H). ^{13}C NMR (75 MHz, DMSO) δ 174.21, 162.91, 156.66, 139.77, 128.88, 128.76, 127.78, 89.97, 48.59, 8.14.UPLC (DAD-QTOF $[M+H]^+$) MS (ESI, *m*/*z*): calcd for C10H10N2O2S: 234.0463; found, 234.0476.

1-(3,5-Bis(trifluoromethyl)phenyl)-5-methyl-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (4Ae)



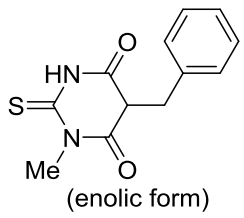
Prepared according to the general procedure starting from 1-(3,5-bis(trifluoromethyl)phenyl)thiourea and diethyl 2-methylmalonate**.** The title compound was obtained as a white solid. M.p: 165 - 170 °C Yield: 71% (13.1 g). ^{1}H NMR (300 MHz, DMSO) δ ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.66 (s, 1H), 8.13 (s, 1H), 8.04 (d, *J* = 1.6 Hz, 2H), 1.79 (s, 3H). ^{13}C NMR (75 MHz, DMSO) δ ^{13}C NMR (75 MHz, DMSO) δ 174.2, 162.8, 157.3, 141.9, 131.0, 130.9, 130.6, 124.9, 121.8, 121.3, 90.0, 8.2 .UPLC-DAD-QTOF : calcd for $C_{13}H_9N_2O_2SF_6$: 371.0289; found, 371.0284.

5-Ethyl-1-methyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione (4Ba)



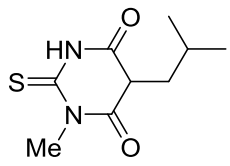
Prepared according to the general procedure starting from 1-methylthiourea and diethyl 2-ethylmalonate**.** The title compound was obtained as a white solid. M.p: 164 - 165 °C. Yield: >99% (10.3 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (s, 1H), 3.64 (s, 3H), 3.51 (t, *J* = 5.3 Hz, 1H), 2.22 (qd, *J* = 7.4, 5.4 Hz, 2H), 0.99 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, DMSO) δ 173.6, 162.4, 155.6, 96.1, 33.3, 15.8, 13.2. UPLC-DAD-QTO: calcd for $C_7H_{11}N_2O_2S$ (M, H^+), 187.0541; found, 187.0539.

5-Benzyl-1-methyl-2-thoxodihydropyrimidine-4,6(1*H*,5*H*)-dione (4Ca)



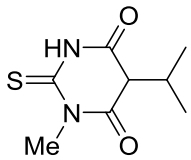
Prepared according to the general procedure starting from 1-methylthiourea and diethyl 2-benzylmalonate**.** The title compound was obtained as a white solid. M.p: 163 - 164 °C. Yield: 73% (4.3 g). ^{1}H NMR (300 MHz, DMSO) δ 12.17 (s, 1H), 7.34 – 7.00 (m, 5H), 3.64 (s, 2H), 3.49 (s, 3H) ^{13}C NMR (75 MHz, DMSO) δ 173.71, 162.32, 156.74, 140.5 127.99, 127.92, 125.58, 93.35, 33.17, 27.88. UPLC-DAD-QTOF: calcd for $C_{12}H_{13}N_2O_2S$ (M, H^+),249.0698; found, 249.0694.

5-Isobutyl-1-methyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione (4Da)



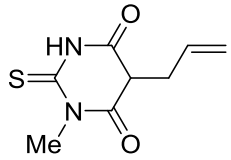
Prepared according to the general procedure starting from 1-methylthiourea and diethyl 2-isobutylmalonate**.** The title compound was obtained as a white solid. M.p: 107 - 111 °C. Yield: 97% (5.2 g).^{1}H NMR (400 MHz, DMSO) δ 12.24 (s, 1H), 3.50 (s, 3H), 2.20 (d, *J* = 7.3 Hz, 2H), 1.84 – 1.71 (m, 1H), 0.83 (d, *J* = 6.6 Hz, 6H).^{13}C NMR (75 MHz, DMSO) δ 12.34, 7.37, 7.36, 7.34, 7.29, 7.29, 7.29, 7.28, 3.56.UPLC-DAD-QTOF: calcd for $C_9H_{15}N_2O_2S$ (M, H^+),215.0854; found, 215.0857.

5-Isopropyl-1-methyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione (4Ea)



Prepared according to the general procedure starting from 1-methylthiourea and diethyl 2-isopropylmalonate**.** The title compound was obtained as a white solid. M.p: 94 - 95 °C. Yield: 90% (2.3 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.43 (s, 1H), 3.65 (s, 3H), 3.42 (d, *J* = 4.1 Hz, 1H), 2.65 (qt, *J* = 7.0, 3.5 Hz, 1H), 1.14 (dd, *J* = 7.0, 3.0 Hz, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 179.09, 167.64, 165.67, 55.76, 34.68, 33.53, 19.60, 19.47.UPLC-DAD-QTOF: calcd for $C_8H_{13}O_2S$ (M, H^+), 201.0698; found, 201.0700.

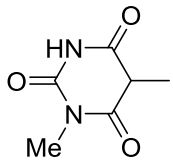
5-Allyl-1-methyl-2-thioxodihydropyrimidine-4,6 (1*H*,5*H*)-dione (4Fa)



Prepared according to the general procedure starting from 1-methylthiourea and diethyl 2-allylmalonate**.** The title compound was obtained as a white solid. M.p: 171 - 173 °C. Yield: 71% (3.3 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.15 (s, 1H), 5.70 (ddt, *J* = 17.2, 10.1, 7.2 Hz, 1H), 5.23 – 5.11 (m, 2H), 3.62 (s, 4H), 2.95 – 2.89 (m, 2H).^{13}C NMR (75 MHz, DMSO) δ 173.7, 162.1, 156.1, 135.4, 114.5, 92.0, 33.2, 26.1. UPLC-DAD-QTOF: calcd for $C_8H_{11}N_2O_2S$ (M, H^+), 199.0542; found, 199.0542.

2.2.4. Synthesis of barbituric acid 1

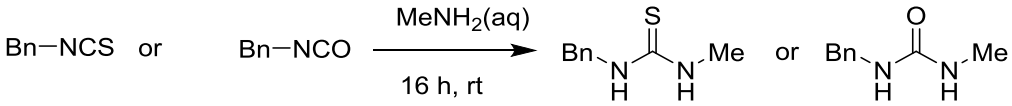
1,5-Dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (1)



The same procedure employed for the synthesis of thiobarbiturates (section 2.2.3) was used except that N-methyl urea (450 mg, 5 mmol) was used instead of the thioureas and using 1-methylthiourea and diethyl 2-methylmalonate**.** The title compound was obtained as a white solid. M.p: 213 - 216 °C. Yield: 63% (350 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1H), 3.48 (q, *J* = 7.5 Hz, 1H), 3.29 (s, 3H), 1.63 (d, *J* = 7.5 Hz, 3H).^{13}C NMR (75 MHz, DMSO) δ 171.2, 170.3, 152.3, 44.7, 28.2, 13.1. UPLC-DAD-QTOF: calcd for $C_6H_9N_2O_3$ (M, H^+), 157.0613; found, 157.0614.

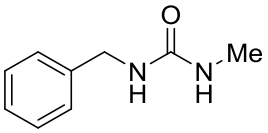
2.3-Synthesis of N,N`-disubstituted (thio)barbituric acid derivatives 2 and 3

2.3.1. Synthesis of N-benzyl-N-methyl urea and thiourea



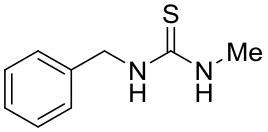
To a solution of aqueous methyl amine (6 mL) was added the corresponding N-benzyl isocyanate or thioisocyanate (6 mmol) at room temperature, and the mixture was stirred for 15 h. The white precipitate was filtrated and washed with MeOH. The solid was dried in vacuo and the products used in the next step without further purification.

1-Benzyl-3-methylurea



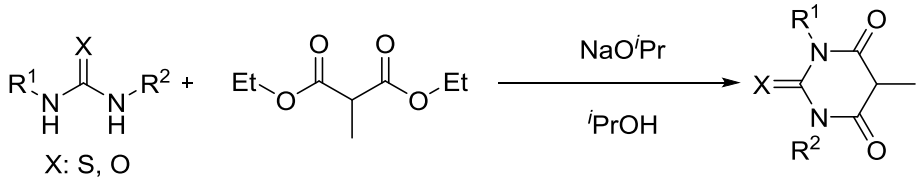
White solid. M.p: 72 - 74 °C. Yield: 97% (0.95 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.26 (m, 5H), 5.38 (brs, 1H), 5.02 (bs, 1H), 4.32 (s, 2H), 2.70 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 139.4, 128.5, 127.7, 127.1, 44.3, 27.0. MS (ESI, *m/z*): calcd for $C_9H_{13}N_2O$ (M, H^+), 165.1030; found, 165.1028.

1-Benzyl-3-methylthiourea



Yellow solid. M.p: 67 - 68 °C. Yield: 100% (1.08 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.32 (m, 5 H), 7.30 (brs, 1 H), 4.82 (d, J = 5.0 Hz, 2H), 2.59 (s, 3 H). MS (ESI, *m/z*): calcd for $C_9H_{13}N_2S$ (M, H^+), 181.0800; found, 181.0799.

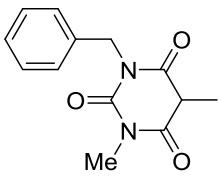
2.3.2. Condensation of N,N´disustituted (thio)ureas with diethyl methylmalonate.[10]



In a 250 mL round-bottom flask fitted with a reflux condenser and protected with a calcium chloride tube, sodium metal was placed 1.150 g (50 mmol) and then 20 mL of anhydrous ^{i}PrOH. The mixture was stirred until all the solid sodium disappeared. Then a solution of N-benzyl-N´-methyl (thio)urea (50 mmol) in 20 mL of anhydrous ^{i}PrOH, (warming was required in

order the (thio)urea to get completely dissolved) was added followed by a dropwise addition of diethyl methylmalonate (50 mmol). The mixture was refluxed for 16 h, and a white solid formed rapidly. After the reaction was completed, 100 mL of hot (50 °C) water was added and then enough hydrochloric acid (2 M) to make the solution acidic. The precipitate was washed with MeOH and dried at vacuum (735 mmHg) in a bath at 80 °C.

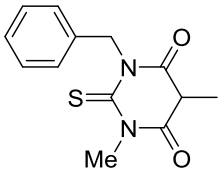
1-benzyl-3,5-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (2)



(enolic form)

White solid. M.p: 97 - 98 °C. Yield: 65% (8.0 g). ^{1}H NMR (300 MHz, acetone) δ 7.59 – 7.19 (m, 5H), 5.03 (d, *J* = 3.8 Hz, 2H), 3.22 (s, 3H), 1.55 (s, 3H).^{13}C NMR (75 MHz, acetone) δ 170.5, 170.3, 153.2, 138.5, 129.5, 128.5, 45.9, 13.6. UPLC-DAD-QTOF: calcd for $C_{13}H_{15}N_2O_3$ (M, H^+), 247.1083; found, 247.1082.

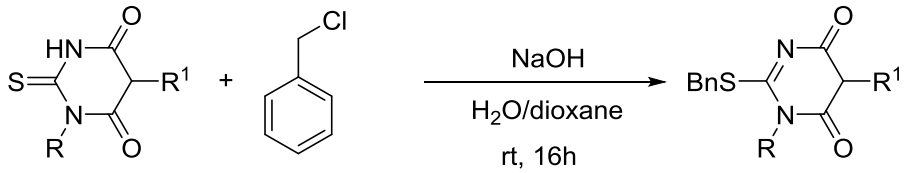
1-Benzyl-3,5-dimethyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione (3)



(enolic form)

White solid. M.p: 109 - 110 °C. Yield: 72%. ^{1}H NMR (300 MHz, acetone) δ 7.41 – 7.20 (m, 4H), 5.62 (s, 2H), 3.62 (s, 3H), 1.58 (s, 3H).^{13}C NMR (75 MHz, acetone) δ: 205.7, 138.1, 129.4, 128.8, 128.2, 51.8, 36.3, 12.6. UPLC-DAD-QTOF : calcd for $C_{13}H_{15}N_2O_2S$ (M, H^+),263.0851; found, 263.0854.

2.4. Synthesis of 2-pyrimidine-4,6(1*H*,5*H*)-diones 5.[11]

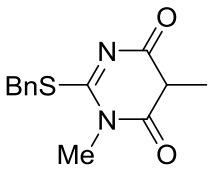


4 **5**

To a suspension of the corresponding thiobarbituric acid derivative **4** (10 mmol, 1 equiv.) in a mixture of water (10 mL) and dioxane (26 mL) a solution of sodium hydroxide (813 mg, 20mmol, 2 equiv.) in 15 mL of water was added dropwise. The mixture was stirred until the mixture became completly homogeneous. Then, a solution of benzyl chloride (3.45 mL, 30 mmol, 3 equiv.) in dioxane 5 mL was added. The mixture was stirred at room temperature for 16 h. After the reaction was completed, enough hydrochloric acid (4 M) to make the solution

acidic was added and the precipitate was washed with MeOH and dried at vacuum (735 mmHg) in a bath at 80 °C.

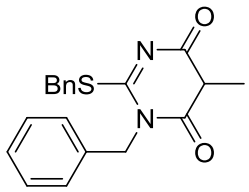
2-(Benzylthio)-6-hydroxy-3,5-dimethylpyrimidin-4(3*H*)-one 5Aa



(enolic form)

Prepared according to the general procedure starting from 1,5-dimethyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione **4Aa**. The title compound was obtained as a white solid. M.p: 175 - 176 °C. Yield: 91% (1.8 g).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H), 4.36 (s, 2H), 3.46 (s, 3H), 1.97 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 162.9, 157.6, 136.8, 129.3, 128.5, 127.4, 92.5, 34.8, 33.2, 29.9, 8.4. UPLC-DAD-QTOF: calcd for $C_{13}H_{15}N_2O_2S$ (M, H^+), 263.854; found, 263.858.

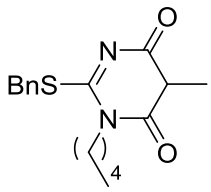
3-Benzyl-2-(benzylthio)-6-hydroxy-5-methylpyrimidin-4(3*H*)-one 5Ab



(enolic form)

Prepared according to the general procedure starting from 1-benzyl-5-methyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione **4Ab.** The title compound was obtained as a white solid. M.p: 186-188 °C. Yield: 48% (1.6 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.21 (m, 8H), 5.26 (s, 2H), 4.33 (s, 2H), 3.73 (s, 1H), 2.02 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 162.4, 159.5, 136.0, 135.9, 129.8, 129.4, 129.21, 128.5, 128.4, 67.8, 48.3, 37.3, 8.9. UPLC-DAD-QTOF: calcd for $C_{19}H_{19}N_2O_2S$ (M, H^+), 339.1167; found, 339.1175.

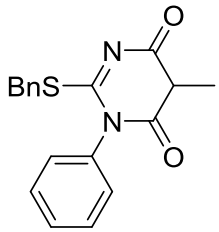
2-(Benzylthio)-3-pentyl-6-hydroxy-5-methylpyrimidin-4(3H)-one 5Ac



(enolic form)

Prepared according to the general procedure starting from 5-methyl-1-pentyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione **4Ac.** The title compound was obtained as a white solid. M.p: 174 - 176 °C. Yield: 51% (1.8 g). ^{1}H NMR (300 MHz, $CDCl_3$) 7.42-7.28 (m, 5H), 5.93 (s, 1H), 4.34 (s, 2H), 3.95 (m, 2H), 1.96 (s, 3H), 1.68 (m, 2H), 1.32 (m, 4H), 0.88 (t, 3H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 162.1, 158.1, 135.6, 129.3, 129.3, 128.9, 128.9, 128.0, 95.3, 45.2, 36.4, 29.1, 27.5, 22.4, 14.1, 8.3. UPLC-DAD-QTOF: calcd for $C_{17}H_{23}N_2O_2S$ (M, H^+),319.1480; found, 319.1482.

2-(Benzylthio)-5-methyl-1-phenylpyrimidine-4,6(1*H*,5*H*)-dione 5Ad

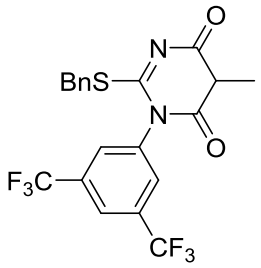


(enolic form)

Prepared according to the general procedure starting from 5-methyl-1-phenyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione **4Ad.** The title compound was obtained as a white solid. M.p: 189-192 °C. Yield: 57% (1.8 g). ^{1}H NMR

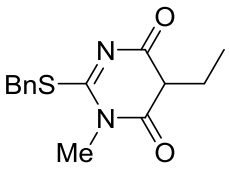
(300 MHz, DMSO) δ 7.49 (dd, *J* = 5.3, 1.8 Hz, 3H), 7.41 (dd, *J* = 7.9, 1.7 Hz, 2H), 7.33 – 7.21 (m, 5H), 4.33 (s, 2H), 1.80 (s, 3H).[13]C NMR (75 MHz, DMSO) δ 163.5, 163.4, 158.18, 136.7, 136.2, 129.5, 129.3, 129.2, 129.0, 128.4, 127.3, 93.1, 35.3, 8.2. MS (ESI, *m*/*z*): calcd for $C_{18}H_{16}N_2O_2S$ (M, H^+), 324.0932; found, 324.0740.

2-(Benzylthio)-1-(3,5-bis(trifluoromethyl)phenyl)-5-methylpyrimidine-4,6(1H,5H)-dione 5Ae



Prepared according to the general procedure starting from 1-(3,5-bis(trifluoromethyl)phenyl)-5-methyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione **4Ae.** The title compound was obtained as a yellow solid. M.p: 192 - 194 °C. Yield: 46% (2.1 g). [1]H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.72 (s, 2H), 7.30 (m, 3H), 6.05 (s, 1H), 4.28 (s, 2H), 1.98 (s, 3H).[13]C NMR (75 MHz, DMSO) δ 164.7, 163.4, 158.5, 137.4, 135.0, 134.1, 133.6, 133.2, 132.7, 129.9, 129.2, 129.2, 128.9, 128.9, 128.1, 124.5, 124.2, 95.7,37.0, 8.0. UPLC-DAD-QTOF: calcd for $C_{20}H_{15}N_2O_2SF_6$ (M, H^+), 461.0758; found, 461.0759.

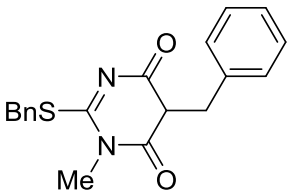
2-(Benzylthio)-5-ethyl-6-hydroxy-3-methylpyrimidin-4(3*H*)-one 5Ba



(enolic form)

Prepared according to the general procedure starting from 5-ethyl-1-methyl-2-thioxodihydropyrimidine-4,6(1H,5H)-dione **4Ba.** The title compound was obtained as a white solid. M.p: 186 – 188 °C. Yield: 58% (1.6 g). [1]H NMR (300 MHz, $CDCl_3$) δ 11.00 (s,1H), 7.54-7.50 (m, 2H), 7.37-7.28 (m, 3H), 4.49 (s, 2H), 3.33 (s, 3H), 2.33 (q, *J* = 9, 6 Hz, 2H), 0.99 (t, *J* = 6Hz, 3H).[13]C NMR (75 MHz, DMSO) δ 162.8, 162.7, 157.8, 136.8, 129.2, 128.4, 127.4, 98.7, 34.8, 29.8, 16.1, 12.6. UPLC-DAD-QTOF : calcd for $C_{14}H_{17}N_2O_2S$ (M, H^+), 277.1011; found, 277.1015.

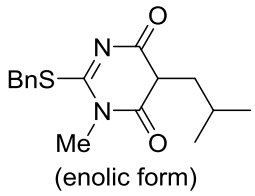
5-Benzyl-2-(benzylthio)-6-hydroxy-3-methylpyrimidin-4(3*H*)-one 5Ca



(enolic form)

Prepared according to the general procedure starting from 5-benzyl-1-methyl-2-thioxodihydropyrimidine-4,6-(1*H*,5*H*)-dione **4Ca.** The title compound was obtained as a white solid. M.p: 209 - 211 °C. Yield: 68% (1.9 g).[1]H NMR (300 MHz, DMSO) δ 7.44 – 7.10 (m, 10H), 4.35 (s, 2H), 3.80 (s, 2H), 3.44 (s, 3H).[13]C NMR (75 MHz, DMSO) δ 163.1, 158.7, 141.0, 136.7, 129.3, 128.5, 128.2, 128.0, 127.5, 125.5, 96.8, 34.9, 30.0, 28.6. UPLC-DAD-QTOF: calcd for $C_{19}H_{19}N_2O_2S$ (M, H^+), 339.1167; found, 339.1166.

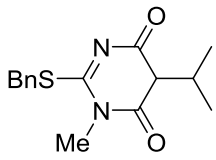
2-(Benzylthio)-6-hydroxy-5-isobutyl-3-methylpyrimidin-4(3*H*)-one 5Da



(enolic form)

Prepared according to the general procedure starting from 5-isobutyl-1-methyl-2-thioxodihydropyrimidine-4,6(1H,5H)-dione **4Da.** The title compound was obtained as a white solid. M.p: 176 - 177 °C. Yield: 52% (1.5 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 5H), 4.37 (s, 2H), 3.45 (s, 3H), 2.34 (d, *J* = 7.3 Hz, 2H), 2.06 – 1.89 (m, 1H), 0.93 (d, *J* = 6.6 Hz, 6H).^{13}C NMR (75 MHz, DMSO) δ 163.3, 163.2, 157.9, 136.7, 129.3, 128.4, 127.4, 96.4, 34.9, 31.9, 29.8, 27.0, 22.4, 22.4. UPLC-DAD-QTOF: calcd for $C_{16}H_{21}N_2O_2S$ (M, H^+), 305.1324; found, 305.1325.

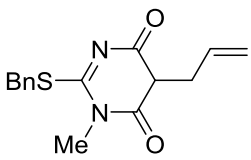
2-(Benzylthio)-6-hydroxy-5-isopropyl-3-methylpyrimidin-4(3*H*)-one 5Ea



(enolic form)

Prepared according to the general procedure starting from 5-isopropyl-1-methyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione **4Ea.** The title compound was obtained as a white solid. M.p: 196 - 197 °C. Yield: 78% (2.3 g). ^{1}H NMR (300 MHz, DMSO) δ 7.41 – 7.27 (m, 5H), 4.35 (s, 2H), 3.41 (s, 3H), 3.25 (p, *J* = 7.1 Hz, 1H), 1.25 (d, *J* = 7.1 Hz, 6H).^{13}C NMR (75 MHz, DMSO) δ 179.09, 167.64, 165.67, 55.76, 34.68, 33.53, 19.60, 19.47. UPLC-DAD-QTOF: calcd for $C_{15}H_{19}N_2O_2S$ (M, H^+), 291.1167; found, 291.1171.

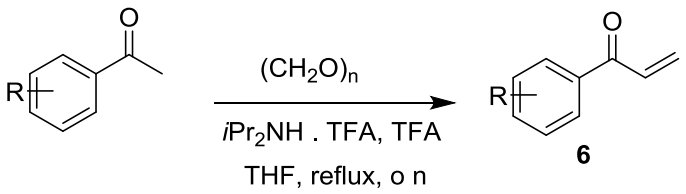
5-Allyl-2-(benzylthio)-6-hydroxy-3-methylpyrimidin-4(3*H*)-one 5Fa



(enolic form)

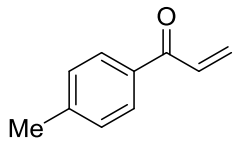
Prepared according to the general procedure starting from 5-allyl-1-methyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione **4Fa**. The title compound was obtained as a white solid. M.p: 143 - 144 °C. Yield: 57% (1.6 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 5H), 5.96 (ddt, *J* = 17.1, 10.0, 6.4 Hz, 1H), 5.20 – 5.02 (m, 2H), 4.36 (s, 2H), 3.47 (s, 3H), 3.29 – 3.26 (m, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 162.6, 159.1, 135.3, 135.1, 129.5, 129.1, 128.7, 128.1, 127.8, 115.1, 97.0, 36.3, 30.6, 27.4. UPLC-DAD-QTOF: calcd for $C_{15}H_{17}N_2O_2S$ (M, H^+), 289.1011; found, 289.1014.

2.5-Synthesis of vinyl aryl ketones 6.[12]



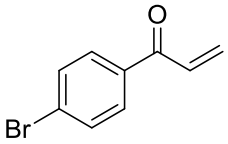
To a solution of the corresponding acetophenone (10.0 mmol) and paraformaldehyde (20.0 mmol, 606 mg) in dry THF (10.0 mL) was added diisopropylammonium trifluoroacetate (10.0 mmol, 2.05 g) and trifluoroacetic acid (1 mmol, 0.08 mL). The reaction mixture was stirred at reflux for 2 h, then cooled down to room temperature and a second addition of paraformaldehyde (20.0 mmol, 606 mg) was performed. Next, the reaction mixture was stirred at reflux overnight. Then the mixture was cooled down and the solvent was removed under reduced pressure. The residue was dissolved in Et_2O and washed with 1N HCl (3 x 10 mL), 1N NaOH (3 x 10 mL), and brine (3 x 10 mL). The resulting solution was dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by silica gel column chromatography (eluent hexane/ethyl acetate, 99:1).

1-(p-Tolyl)prop-2-en-1-one) (6a)



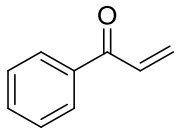
Prepared according to the general procedure starting from 1-(*p*-tolyl)ethan-1-one**.** The title compound was obtained as a yellow oil. Yield: 54% (723.9 mg) ^{1}H NMR (300 MHz, $CDCl_3$ δ 7.93 – 7.77 (m, 2H), 7.31 – 7.05 (m, 3H), 6.42 (ddd, *J* = 17.1, 2.9, 1.5 Hz, 1H), 5.87 (d, *J* = 10.5 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 190.3, 143.8, 134.7, 132.3, 129.5, 129.3, 128.8, 21.6. UPLC-DAD-QTOF: calcd for $C_{10}H_{10}O$ (M, H^+), 146.0810; found, 147.0811.

1-(4-Bromophenyl)prop-2-en-1-one (6b)



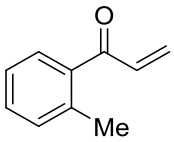
Prepared according to the general procedure starting from 1-(4-bromophenyl)ethan-1-one**.** The title compound was obtained as a yellow oil. Yield: 51% (1.07 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 8.6 Hz, 2H), 7.10 (dd, *J* = 17.1, 10.5 Hz, 1H), 6.43 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.93 (dd, *J* = 10.6, 1.6 Hz, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ = 189.9, 135.8, 131.7, 131.6, 130.5, 130.0, 128.0, 125.8, 98.2. UPLC-DAD-QTOF: calcd for C_9H_7BrO (M, H^+), 209.9680; found, 209.9781.

1-Phenylprop-2-en-1-one (6c)



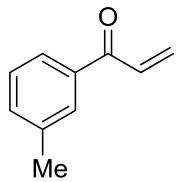
Prepared according to the general procedure starting from acetophenone**.** The title compound was obtained as a yellow oil. Yield: 58% (765.9 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 – 7.84 (m, 2H), 7.61 – 7.37 (m, 3H), 7.21 – 7.04 (m, 1H), 6.42 (dt, *J* = 17.1, 1.8 Hz, 1H), 5.93 – 5.83 (m, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ = 191.0, 137.4, 133.2, 132.5, 130.2, 128.8, 128.8, 128.4. UPLC-DAD-QTOF: calcd for C_9H_8O (M, H^+), 132.0575; found, 132.0508.

1-(*o*-Tolyl)prop-2-en-1-one (6d)



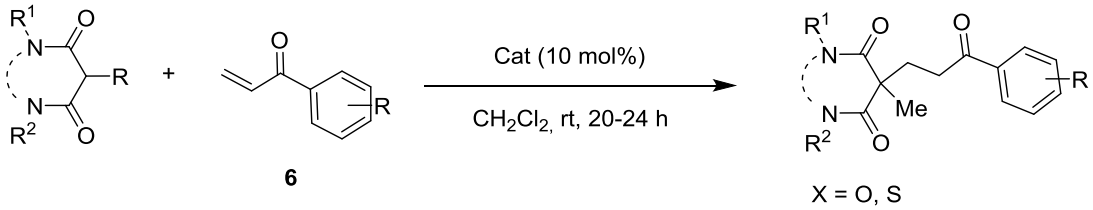
Prepared according to the general procedure starting from 1-(*o*-tolyl)ethan-1-one**.** The title compound was obtained as a yellow oil. Yield: 57% (838.3 mg) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.42 (m, 1H), 7.42 – 7.28 (m, 1H), 7.29 – 7.17 (m, 2H), 6.87 – 6.71 (m, 1H), 6.21 – 6.08 (m, 1H), 6.03 – 5.91 (m, 1H), 2.42 (d, *J* = 1.6 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ = 196.6, 138.1, 137.5, 136.7, 131.6, 131.3, 130.9, 128.6, 125.6, 20.5. UPLC-DAD-QTOF: calcd for $C_{10}H_{10}O$ (M, H^+), 146.0810; found, 147.0807.

1-(*m*-Tolyl)prop-2-en-1-one(6e)



Prepared according to the general procedure starting from 1-(*m*-tolyl)ethan-1-one**.** The title compound was obtained as a yellow oil. Yield: 56% (818.04 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 – 7.67 (m, 2H), 7.36 (dd, *J* = 4.4, 2.6 Hz, 2H), 7.15 (ddd, *J* = 17.1, 10.5, 1.3 Hz, 1H), 6.43 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.94 – 5.83 (m, 1H), 2.40 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ = 191.0, 138.4, 137.3, 133.7, 132.5, 129.8, 129.2, 128.4, 125.8, 21.3. UPLC-DAD-QTOF: calcd for $C_{10}H_{10}O$ (M, H^+), 146.0810; found, 147.0804.

2.6-Catalytic reactions of barbituric acid derivatives with vinyl aryl ketones 6.

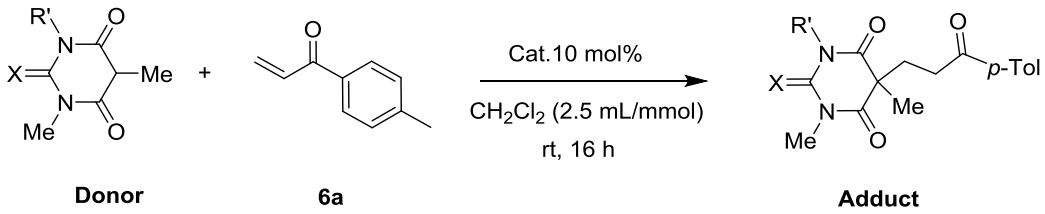


2.6.1 General procedure

To a mixture of the corresponding donor barbituric acid or equivalent (0.2 mmol, 1 equiv.) and vinyl aryl ketone (0.6 mmol, 3 equiv.) in CH_2Cl_2 (0.5 mL), was added the catalyst (10 mol%) and

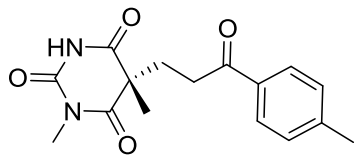
the resulting mixture was stirred at room temperature for 20–24 h. Then the mixture was quenched with HCl 0.1 M and the organic layer was washed with water (0.7 mL), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluent hexane/ethyl acetate 3:1).

2.6.2 Screening of donor barbituric substrates (Scheme 1)



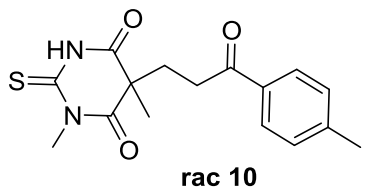
R	X	Donor/adduct	Catalyst	Yield (%)	*ee* (%)
H	O	**1/7**	**C1**	71	19
			C4	63	0
			C6	64	0
H	S	**4Aa/10**	**C1**	74	0
			C4	67	0
			C6	69	0
$PhCH_2$	O	**2/8**	**C1**	74	0
			C4	70	0
			C6	74	0
$PhCH_2$	S	**3/9**	**C1**	72	0
			C4	75	0
			C6	79	0

(R)-1,5-Dimethyl-5-(3-oxo-3-(p-tolyl)propyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (7)



Prepared according to the general procedure starting from 1,5-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione **1** and 1-(p-tolyl)prop-2-en-1-one **6a.** The title compound was obtained as a white oil. Yield: 71% (41 mg). $[\alpha]_D^{23}$= –54.32° (*c*= 0.29, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (s, 1H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 3.28 (d, *J* = 1.0 Hz, 3H), 2.93 (dt, *J* = 10.0, 7.5 Hz, 2H), 2.40 (d, *J* = 11.1 Hz, 5H), 1.58 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 172.5, 171.8, 150.0, 144.1, 133.8, 129.3, 128.1, 50.7, 33.4, 32.4, 28.1, 24.3, 21.6. UPLC-DAD-QTOF: calcd for $C_{16}H_{18}N_2O_4$ (M, H^+), 303.1345; found, 303.1353.

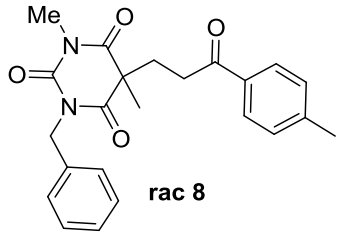
Rac-1,5-Dimethyl-5-(3-oxo-3-(p-tolyl)propyl)-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione (10)



rac 10

Prepared according to the general procedure starting from 1-(p-tolyl)prop-2-en-1-one and 1-(p-tolyl)prop-2-en-1-one **4Aa** and 1-(p-tolyl)prop-2-en-1-one **6a.** The title compound was obtained as a white oil. Yield: 74% (45 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 (s, 1H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.32 – 7.24 (m, 2H), 3.67 (s, 3H), 2.99 (dt, *J* = 9.2, 7.4 Hz, 2H), 2.51 – 2.42 (m, 5H), 1.64 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 178.6, 171.3, 169.2, 144.7, 134.3, 129.7, 129.7, 128.6, 51.9, 34.6, 33.7, 32.8, 24.4, 22.1. UPLC-DAD-QTOF: calcd for $C_{16}H_{18}N_2O_3S$ (M, H^+), 319.1116; found, 319.1116.

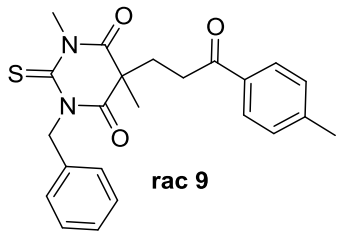
Rac-1-Benzyl-3,5-dimethyl-5-(3-oxo-3-(p-tolyl)propyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (8)



rac 8

Prepared according to the general procedure starting from 1-benzyl-3,5-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione **(2)** and 1-(*p*-tolyl)prop-2-en-1-one **(6a).** The title compound was obtained as a white oil. Yield: 74% (58.8 mg).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 – 7.48 (m, 2H), 7.52 – 7.22 (m, 7H), 5.11 (s, 2H), 3.35 (s, 3H), 2.97 – 2.67 (m, 2H), 2.43 (s, 5H), 1.61 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 171.8, 171.7, 150.9, 138.4, 136.4, 134.0, 128.8, 128.7, 128.6, 128.4, 127.9, 125.2, 50.7, 45.2, 33.5, 33.2, 28.8, 24.4, 21.3 . UPLC-DAD-QTOF: calcd for $C_{23}H_{25}N_2O_4$ (M, H^+), 393.1814; found, 393.1818.

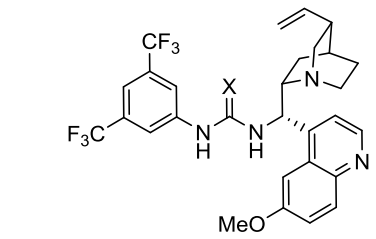
Rac-1-benzyl-3,5-dimethyl-5-(3-oxo-3-(p-tolyl)propyl)-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione(9)

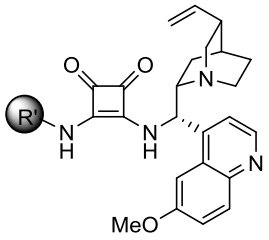


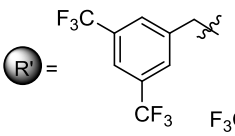
rac 9

Prepared according to the general procedure starting from 1-benzyl-3,5-dimethyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione **(3)** and 1-(*p*-tolyl)prop-2-en-1-one **(6a).** The title compound was obtained as a white oil. Yield: 72% (64.4 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.58 (m, 2H), 7.48 – 7.16 (m, 7H), 5.81 – 5.56 (m, 2H), 3.73 (s, 3H), 3.02 – 2.71 (m, 2H), 2.49 – 2.39 (m, 5H), 1.63 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.3, 180.2, 170.3, 170.3, 138.4, 136.4, 136.1, 134.0, 128.4, 128.4, 128.2, 127.6, 125.2, 51.6, 50.8, 36.0, 33.3, 32.8, 23.5, 21.3. UPLC-DAD-QTOF: calcd for $C_{23}H_{25}N_2O_3S$ (M, H^+), 409.1592; found, 405.1586.

2.6.3 Catalyst screening for the reaction of 5Aa with 6a[a]



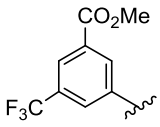


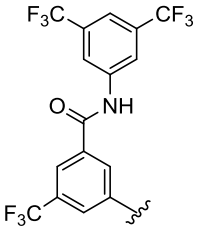


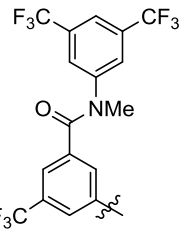
C1 X: O 67%,66% *ee*
C2 X: S 71%, 36% *ee*

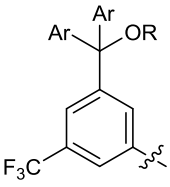
C3
--,--

C4
69%, 32% *ee*









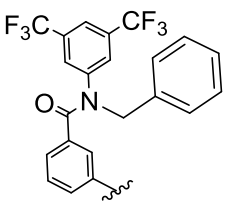
Ar = 3,5-$CF_3C_6H_3$

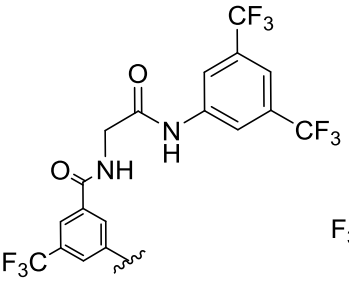
C5
67%, 73% *ee*

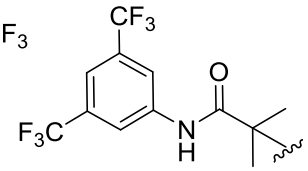
C6
59%, 54% *ee*

C7
66%, 75% *ee*

C8 R= H, 72%, 80% *ee* (96% *ee*)[c]
C9 R= $SiMe_3$, 62%, 78% *ee*





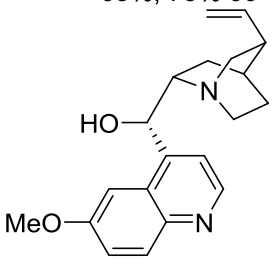


C10
68%, 73% *ee*

C11
62%, 63% *ee*

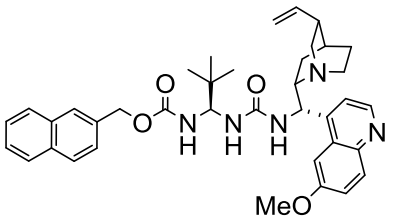
C12
62%, 63% *ee*

C13
60%, 65% *ee*



$(DHQD)_2PyR$

C15
--,--

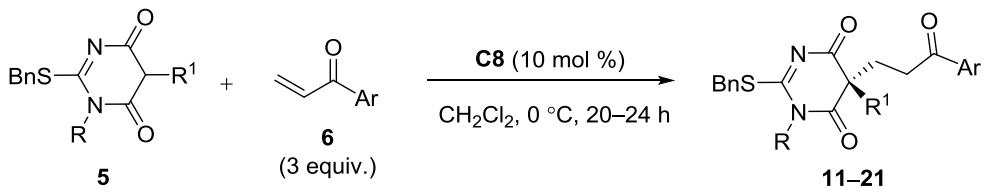


C14
36%, 15% *ee*

C16
63%, 40% *ee*

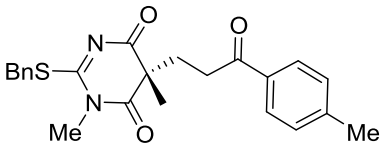
[a] Reactions carried out at room temperature using 0.2 mmol of **5Aa**, 0.6 mmol of enone **6a** and 10 mol% catalyst in 0.5 mL of CH_2Cl_2. Reaction time 16 h except for catalyst **C3** (48 h). [b] ee determined by chiral HPLC [c] Reaction carried out at 0 °C.

2.6.4 Data for the reaction of templates 5 with enones 6



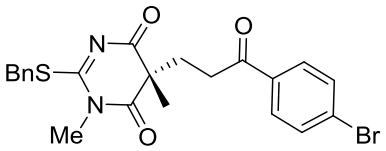
The same general procedure described in section 2.6.1 (p 30) was employed but the reaction temperature was 0 °C instead of rt.

(R)-2-(Benzylthio)-1,5-dimethyl-5-(3-oxo-3-(p-tolyl)propyl)pyrimidine-4,6(1*H*,5*H*)-dione (11)



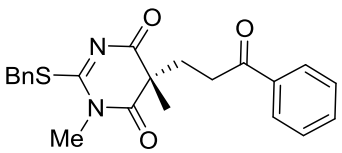
Prepared according to the general procedure starting from 2-(benzylthio)-1,5-dimethylpyrimidine-4,6(1*H*,5*H*)-dione **5Aa** and 1-(p-tolyl)prop-2-en-1-one **6a.** The title compound was obtained as a white oil. Yield: 72% (55 mg). $[\alpha]_D^{23}$= –67.7° (*c*= 0.23, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.2 Hz, 2H), 7.44 – 7.20 (m, 7H), 4.47 (d, *J* = 2.0 Hz, 2H), 3.35 (s, 3H), 3.11 – 2.98 (m, 1H), 2.92 – 2.80 (m, 1H), 2.47 – 2.28 (m, 5H), 1.54 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5, 179.5, 174.0, 173.3, 144.4, 134.9, 134.4, 129.8, 129.6, 129.3, 129.2, 128.9, 128.5, 128.4, 53.5, 37.8, 34.0, 32.9, 30.4, 22.6, 22.0 UPLC-DAD-QTOF: calcd for $C_{23}H_{24}N_2O_3S$ (M, H^+), 409.1586; found, 409.1589.

(*R*)-2-(Benzylthio)-5-(3-(4-bromophenyl)-3-oxopropyl)-1,5-dimethylpyrimidine-4,6(1*H*,5*H*)-dione (12)



Prepared according to the general procedure starting from 2-(benzylthio)-1,5-dimethylpyrimidine-4,6(1*H*,5*H*)-dione **5Aa** and 1-(4-bromophenyl)prop-2-en-1-one **6b.** The title compound was obtained as a white oil. Yield: 63% (59 mg). $[\alpha]_D^{23}$= –63.2° (*c*= 0.34, 95 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.6 Hz, 2H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.47 – 7.27 (m, 5H), 4.50 (s, 2H), 3.38 (s, 3H), 3.13 – 2.98 (m, 1H), 2.93 – 2.79 (m, 1H), 2.38 (td, *J* = 6.3, 3.0 Hz, 2H), 1.57 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6, 179.0, 173.5, 172.9, 135.2, 134.5, 131.9, 129.6, 129.4, 128.8, 128.4, 128.1, 53.1, 37.4, 33.8, 31.8, 30.0, 22.9. UPLC-DAD-QTOF: calcd for $C22H21BrN_2O_3S$ (M, H^+), 473.0535; found, 473.0529.

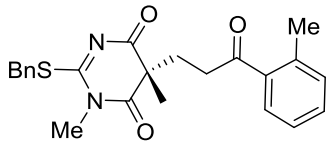
(*R*)-2-(Benzylthio)-1,5-dimethyl-5-(3-oxo-3-phenylpropyl)pyrimidine-4,6(1*H*,5*H*)-dione (13)



Prepared according to the general procedure starting from 2-(benzylthio)-1,5-dimethylpyrimidine-4,6(1*H*,5*H*)-dione **5Aa** and 1-

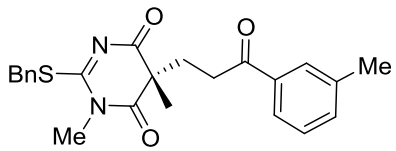
phenylprop-2-en-1-one **6c.** The title compound was obtained as a white oil. Yield: 61% (48 mg). $[\alpha]_D^{23}$= –64.3° (*c*= 0.27, 92 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.69 – 7.25 (m, 8H), 4.50 (s, 2H), 3.38 (d, *J* = 2.9 Hz, 3H), 3.10 (ddd, *J* = 17.1, 9.1, 6.4 Hz, 1H), 2.93 (td, *J* = 9.1, 6.8 Hz, 1H), 2.47 – 2.32 (m, 2H), 1.57 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5, 179.1, 173.6, 172.9, 136.5, 134.5, 133.2, 129.4, 128.8, 128.6, 128.1, 128.0, 53.1, 37.4, 33.7, 32.2, 30.0, 22.3. UPLC-DAD-QTOF: calcd for $C_{22}H_{22}N_2O_3S$ (M, H^+), 395.1429; found, 395.1433.

(*R*)-2-(Benzylthio)-1,5-dimethyl-5-(3-oxo-3-(*o*-tolyl)propyl)pyrimidine-4,6(1*H*,5*H*) (14)



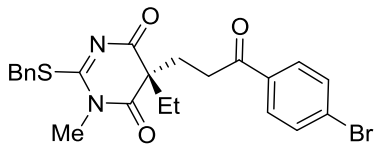
Prepared according to the general procedure starting from 2-(benzylthio)-1,5-dimethylpyrimidine-4,6(1*H*,5*H*)-dione (**5Aa**) and 1-(*o*-tolyl)prop-2-en-1-one (**6d**)**.** The title compound was obtained as a white oil. Yield: 72% (58 mg). $[\alpha]_D^{23}$= –70.3° (*c*= 0.28, 85 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 6.9 Hz, 1H), 7.51 – 7.18 (m, 8H), 4.51 (s, 2H), 3.38 (s, 3H), 2.99 (dd, *J* = 9.2, 5.9 Hz, 1H), 2.91 – 2.78 (m, 1H), 2.50 (s, 3H), 2.36 (dt, *J* = 9.0, 5.9 Hz, 2H), 1.56 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 174.2, 168.8, 168.0, 133.3, 132.5, 129.6, 127.1, 126.5, 124.5, 124.0, 123.7, 23.2, 120.8, 48.2, 32.5, 31.5, 27.4, 25.1, 17.6, 16.4. UPLC-DAD-QTOF: calcd for $C_{23}H_{24}N_2O_3S$ (M, H^+),409.1586; found, 409.1587.

(*R*)-2-(Benzylthio)-1,5-dimethyl-5-(3-oxo-3-(m-tolyl)propyl)pyrimidine-4,6(1*H*,5*H*)-dione (15)



Prepared according to the general procedure starting from 2-(benzylthio)-1,5-dimethylpyrimidine-4,6(1*H*,5*H*)-dione **(5Aa)** and 1-(*m*-tolyl)prop-2-en-1-one **(6e).** The title compound was obtained as a white oil. Yield: 62% (50 mg). $[\alpha]_D^{23}$= –69.2° (*c*= 0.24, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 9.0 Hz, 2H), 7.54 – 7.17 (m, 7H), 4.50 (d, *J* = 3.0 Hz, 2H), 3.38 (s, 3H), 3.09 (ddd, *J* = 17.0, 9.0, 6.2 Hz, 1H), 3.02 – 2.80 (m, 1H), 2.44 (s, 3H), 2.43 – 2.24 (m, 2H), 1.57 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 198.7, 179.1, 173.6, 172.8, 138.3, 136.6, 134.5, 133.9, 129.4, 128.8, 128.5, 128.4, 128.0, 125.2, 53.1, 37.4, 33.7, 32.3, 30.0, 22.2, 21.3. UPLC-DAD-QTOF: calcd for $C_{23}H_{25}N_2O_3S$ (M, H^+), 409.1586; found, 409.1587.

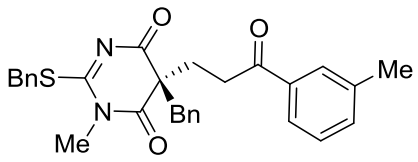
(*R*)-2-(Benzylthio)-5-(3-(4-bromophenyl)-3-oxopropyl)-5-ethyl-1-methylpyrimidine-4,6(1*H*,5*H*)-dione (16)



Prepared according to the general procedure starting from 2-(benzylthio)-5-ethyl-1-methylpyrimidine-4,6(1*H*,5*H*)-dione **(5Ba)** and 1-(4-bromophenyl)prop-2-en-1-one **(6b).** The title compound was obtained as a white oil. Yield: 71% (69 mg).

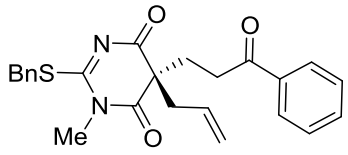
$[\alpha]_D^{23}$= – 64.2° (*c*= 0.42, 97 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.6 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.49 – 7.21 (m, 5H), 4.51 (t, *J* = 5.8 Hz, 2H), 3.39 (s, 3H), 3.11 – 2.95 (m, 1H), 2.95 – 2.72 (m, 1H), 2.41 (t, *J* = 7.6 Hz, 2H), 2.02 (dd, *J* = 7.5, 1.6 Hz, 2H), 0.89 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7, 178.3, 173.4, 173.1, 135.2, 134.4, 131.8, 129.6, 129.4, 128.8, 128.2, 128.1, 127.7, 127.5, 121.3, 110.4, 58.4, 37.4, 34.0, 33.0, 9.26. UPLC-DAD-QTOF: calcd for $C_{23}H_{23}BrN_2O_3S$ (M, H^+), 487.0691; found, 487.0698.

(*S*)-5-Benzyl-2-(benzylthio)-1-methyl-5-(3-oxo-3-(m-tolyl)propyl)pyrimidine-4,6(1*H*,5*H*)-dione (17)



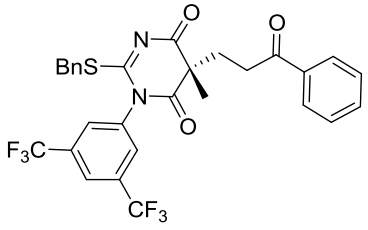
Prepared according to the general procedure starting from 5-benzyl-2-(benzylthio)-1-methylpyrimidine-4,6(1*H*,5*H*)-dione **(5Ca)** and 1-(*m*-tolyl)prop-2-en-1-one **(6e).** The title compound was obtained as a white oil. Yield: 75% (80 mg). $[\alpha]_D^{22}$= –71.2° (*c*= 0.22, 94 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 – 7.70 (m, 2H), 7.44 – 7.16 (m, 10H), 7.14 – 7.04 (m, 2H), 4.27 (d, *J* = 3.4 Hz, 2H), 3.29 – 3.03 (m, 6H), 2.88 – 2.77 (m, 1H), 2.64 (ddd, *J* = 9.6, 5.6, 2.9 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 177.7, 173.6, 172.6, 138.3, 136.5, 134.5, 134.3, 133.8, 129.4, 129.4, 128.7, 128.5, 128.4, 128.1, 128.0, 127.5, 125.3, 59.9, 48.2, 37.3, 34.4, 31.3, 29.6, 21.3. UPLC-DAD-QTOF: calcd for $C_{29}H_{28}N_2O_3S$ (M, H^+), 485.1899; found, 485.1901.

(*S*)-5-Allyl-2-(benzylthio)-1-methyl-5-(3-oxo-3-phenylpropyl)pyrimidine-4,6(1*H*,5*H*)-dione (18)



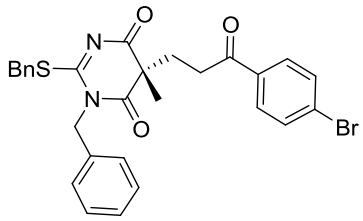
Prepared according to the general procedure starting from 5-allyl-2-(benzylthio)-1-methylpyrimidine-4,6(1*H*,5*H*)-dione **(5Fa)** and 1-phenylprop-2-en-1-one **(6c).** The title compound was obtained as a white oil. Yield: 65% (54 mg). $[\alpha]_D^{23}$= – 62.8° (*c*= 0.25, 92 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 – 7.89 (m, 2H), 7.64 – 7.53 (m, 1H), 7.52 – 7.29 (m, 7H), 5.64 (dddd, *J* = 17.0, 10.1, 7.9, 6.8 Hz, 1H), 5.20 – 5.04 (m, 2H), 4.58 – 4.41 (m, 2H), 3.37 (s, 3H), 3.15 – 3.02 (m, 1H), 2.91 – 2.78 (m, 1H), 2.78 – 2.63 (m, 2H), 2.50 – 2.42 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.6, 177.8, 173.6, 172.7, 136.5, 134.6, 133.1, 131.1, 129.4, 128.8, 128.7, 128.5, 128.0, 120.2, 58.0, 43.6, 37.4, 34.0, 31.1, 29.8. UPLC-DAD-QTOF: calcd for $C_{24}H_{24}N_2O_3S$ (M, H^+), 421.1586; found, 421.1593.

(*R*)-2-(Benzylthio)-1-(3,5-bis(trifluoromethyl)phenyl)-5-methyl-5-(3-oxo-3-phenylpropyl)pyrimidine-4,6(1*H*,5*H*)-dione (19)



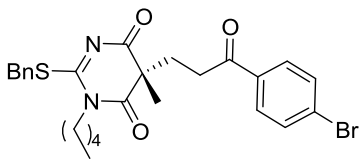
Prepared according to the general procedure starting from 2-(benzylthio)-1-(3,5-bis(trifluoromethyl)phenyl)-5-methylpyrimidine-4,6(1*H*,5*H*)-dione **(5Ae)** and 1-phenylprop-2-en-1-one **(6c).** The title compound was obtained as a white oil. Yield: 65% (77 mg). $[\alpha]_D^{23}$= –63.02° (*c*= 1.4, 90 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 8.07 – 7.92 (m, 3H), 7.71 (s, 1H), 7.68 – 7.57 (m, 1H), 7.50 (dd, *J* = 8.3, 6.9 Hz, 2H), 7.38 – 7.24 (m, 4H), 4.44 (t, *J* = 6.9 Hz, 2H), 3.32 (dt, *J* = 17.4, 6.2 Hz, 1H), 3.17 – 3.00 (m, 1H), 2.62 (dt, *J* = 13.8, 6.4 Hz, 1H), 2.53 – 2.40 (m, 1H), 1.68 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.5, 178.6, 173.1, 171.4, 136.3, 136.2, 133.9, 133.5, 130.8, 130.1, 130.0, 129.4, 128.8, 128.7, 128.1, 128.0, 124.3, 124.3, 124.2, 53.2, 38.2, 33.1, 32.2, 22.5. UPLC-DAD-QTOF: calcd for $C_{29}H_{22}F_6N_2O_3S$ (M, H^+), 593.1334; found, 593.1337.

(*R*)-1-Benzyl-2-(benzylthio)-5-(3-(4-bromophenyl)-3-oxopropyl)-5-methylpyrimidine-4,6(1*H*,5*H*)-dione (20)



Prepared according to the general procedure starting from 1-benzyl-2-(benzylthio)-5-methylpyrimidine-4,6(1*H*,5*H*)-dione **(5Ab)** and 1-(4-bromophenyl)prop-2-en-1-one **(6b)**. The title compound was obtained as a white oil. Yield: 67% (74 mg). $[\alpha]_D^{22}$= –70.02° (*c*=0.22, 90 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.6 Hz, 2H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.47 – 7.20 (m, 8H), 5.23 – 4.99 (m, 2H), 4.49 (s, 2H), 3.07 – 2.74 (m, 2H), 2.50 – 2.30 (m, 2H), 1.59 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 178.8, 173.7, 172.4, 134.88, 131.9, 129.4, 128.8, 128.3, 128.1, 128.1, 127.5, 53.3, 47.1, 37.8, 33.7, 31.7, 22.9. UPLC-DAD-QTOF: calcd for $C_{28}H_{25}BrN_2O_3S$ (M, H^+), 549.0848; found, 549.0855.

(*R*)-2-(Benzylthio)-5-(3-(4-bromophenyl)-3-oxopropyl)-5-methyl-1-pentylpyrimidine-4,6(1*H*,5*H*)-dione(21)

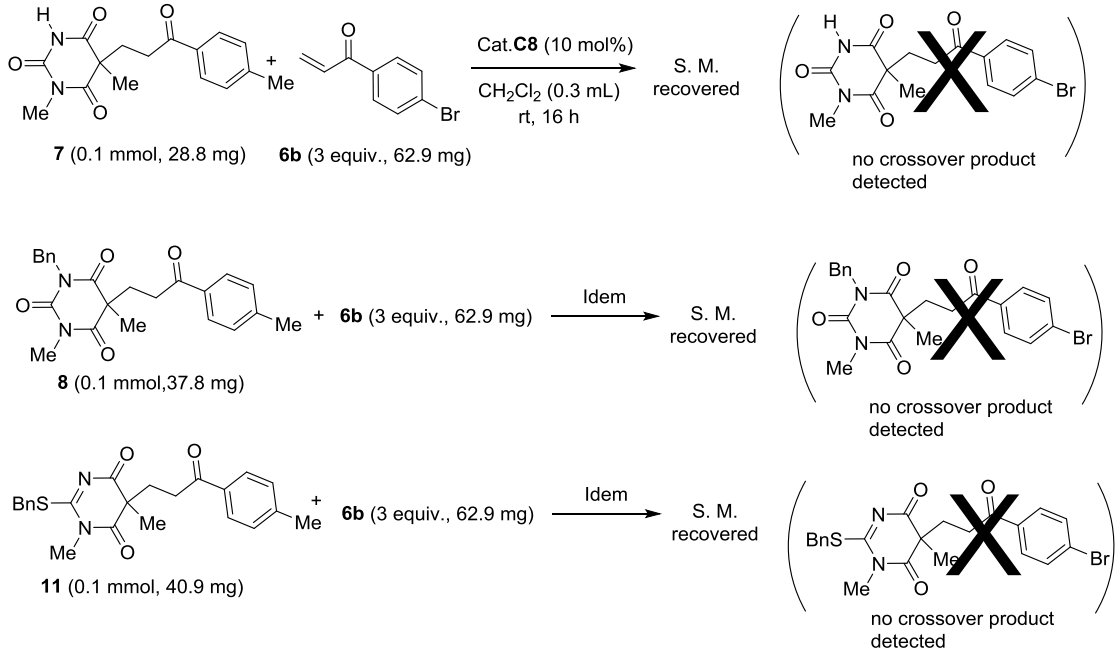


Prepared according to the general procedure starting from 2-(benzylthio)-5-methyl-1-pentylpyrimidine-4,6(1*H*,5*H*)-dione **(5Ac)** and 1-(4-bromophenyl)prop-2-en-1-one **(6b).** The title compound was obtained as a white oil. Yield: 73% (78 mg). $[\alpha]_D^{22}$= –73.13° (*c*= 0.23, 92 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.6 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.45 – 7.26 (m, 4H), 4.48 (s, 2H), 3.93 – 3.75 (m, 2H), 3.11 – 2.94 (m, 1H), 2.94 – 2.75 (m,

1H), 2.44 – 2.28 (m, 2H), 1.75 – 1.59 (m, 3H), 1.60 – 1.51 (m, 3H), 1.33 (dd, *J* = 6.9, 3.5 Hz, 5H), 0.97 – 0.84 (m, 3H).^{13}C NMR (300 MHz, $CDCl_3$) δ 198.7, 180.2, 174.5, 173.6, 136.4, 135.6, 133.0, 130.7, 130.6, 130.0, 129.5, 129.2, 54.2, 45.4, 38.6, 34.9, 32.7, 29.9, 29.1, 24.0, 23.3, 15.0. UPLC-DAD-QTOF: calcd for $C_{26}H_{30}N_2O_3SBr$ (M, H^+), 529.1161; found, 529.1165.

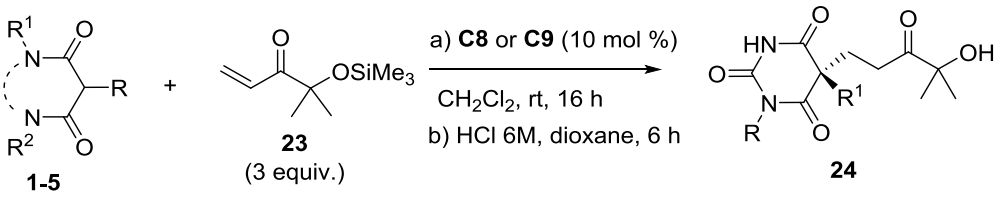
2.6.5 Crossover control experiments

The following control experiments were carried out to discard the possibility of retroaddition reaction taking place under the working conditions. In all the three cases tested starting adducts (**7**, **8**, and **11**) and the enone **6b** were recovered in essentially quantitative amount with no formation of crossover product observed at all.



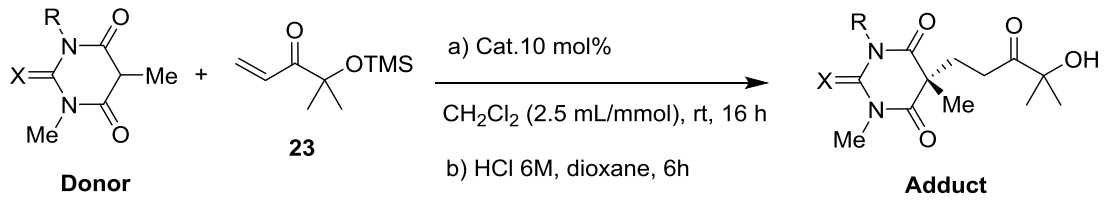
2.7-Catalytic reactions with vinyl ketone 23

2.7.1 General procedure



To a suspension of the corresponding donor barbituric acid derivative **1**-**5** (0.2 mmol, 1 equiv.) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one **23** (0.6 mmol, 3 equiv.) in CH_2Cl_2 (0.5 mL), was added catalyst **C8** or **C9** (10 mol %) and the reaction was stirred at rt for 16 h. Then the mixture was quenched with HCl 0.1 M and the organic layer was washed with water (0.7 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The crude material was dissolved in dioxane/HCl 6M (0.5 ml/0.5 mL), and the resulting mixture was stirred for 6 h (until consumption of the silyl ether compound). The mixture was quenched with an aqueous solution of $NaHCO_3$, diluted with water and extracted with EtOAc (3 x 3 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvents were evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel.

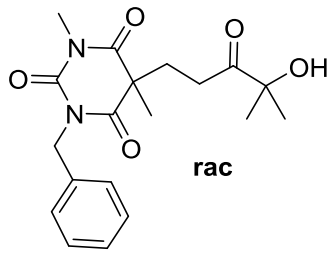
2.7.2 Screening of donor barbituric substrates



R	X	Donor/adduct	Cat	Yield (%)	ee(%)
			C1	62	0
H	O	**1/24Aa**	**C4**	61	0
			C6	61	0
			C1	67	0
H	S	**4Aa/**	**C4**	64	0
			C6	69	0

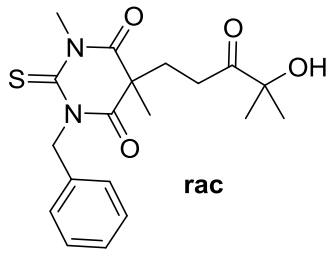
R	X	Donor/adduct	Cat	Yield (%)	ee(%)
			C1	72	0
$PhCH_2$	O	**2/**	**C4**	60	0
			C6	68	0
			C1	63	0
$PhCH_2$	S	**3/**	**C4**	73	0
			C6	74	0

1-Benzyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-3,5-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (40)



Prepared according to the general procedure starting from 1-benzyl-3,5-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione **(2).** The crude material was purified by flash column chromatography on silica gel (eluent with hexane/ethyl acetate, 4:1) to give the title compound as a white oil. Yield: 68 % (48.9 mg).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.24 (m, 5H), 5.20 – 4.98 (m, 2H), 3.34 (s, 3H), 2.54 – 2.41 (m, 2H), 2.32 (d, *J* = 6.9 Hz, 2H), 1.56 (s, 3H), 1.29 (d, *J* = 1.7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.4, 172.1, 172.0, 151.3, 136.7, 129.3, 129.0, 128.4, 51.0, 45.7, 32.7, 31.0, 30.1, 29.3, 28.7, 26.8, 25.2. UPLC-DAD-QTOF: calcd for $C_{19}H_{24}N_2O_5$ (M, H^+), 360.1685; found, 360.1682.

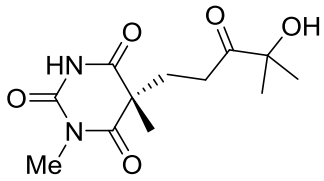
1-benzyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-3,5-dimethyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione (41)



Prepared according to the general procedure starting from 1-benzyl-3,5-dimethyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione **(3).** The title compound was obtained as a white oil. The crude material was purified by flash column chromatography on silica gel (eluent with hexane/ethyl acetate, 4:1) to give the title compound as a white oil. Yield: 74% (52.7 mg).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.22 (m, 5H), 5.79 – 5.54 (m, 2H), 3.71 (s, 3H), 2.64 – 2.40 (m, 2H), 2.40 – 2.25 (m, 2H), 1.58 (s, 3H), 1.32 (d, *J* = 3.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 213.0, 180.1, 170.1, 136.0, 128.4, 128.2, 127.7, 51.4, 50.8, 36.0, 31.7, 30.5, 26.4, 24.1. UPLC-DAD-QTOF: calcd for $C_{19}H_{24}N_2O_4S$ (M, H^+), 376.1457; found, 376.1456.

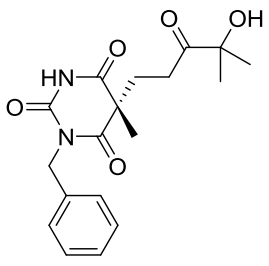
2.7.3 Data for the reaction of templates 5 with enone 23

(*R*)-5-(4-Hydroxy-4-methyl-3-oxopentyl)-1,5-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*) (24Aa)



Prepared according to the general procedure starting from 2-(benzylthio)-1,5-dimethylpyrimidine-4,6(1*H*,5*H*)-dione **(5Aa).** The crude material was purified by flash column chromatography on silica gel (elutent with hexane/ ethyl acetate, 1:1) to give the title compound as colourless oil. Yield: 82% (43 mg). $[\alpha]_D^{23}$= +0.76° (*c*= 0.97, 90 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.26 (s, 3H), 2.56 (q, *J* = 7.5, 7.1 Hz, 2H), 2.28 (t, *J* = 7.3 Hz, 2H), 1.54 (s, 3H), 1.51 (s, 3H), 1.31 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 214.5, 173.5, 172.7, 151.0, 51.6, 32.6, 31.8, 29.2, 27.5, 25.9. UPLC-DAD-QTOF: calcd for $C_{12}H_{19}N_2O_5$ (M, H^+), 271.1294; found, 271.1301.

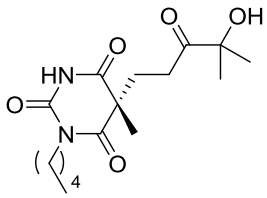
(*R*)-1-Benzyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-5-methylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (24Ab)



Prepared according to the general procedure starting from 1-benzyl-2-(benzylthio)-5-methylpyrimidine-4,6(1*H*,5*H*)-dione **(5Ab).** The crude material was purified by flash column chromatography on silica gel (eluent with hexane/ethyl acetate, 1:1) to give the title compound as a colorless oil. Yield: 61% (47.2 mg). $[\alpha]_D^{23}$= – 3.8° (*c*= 0.73, 87% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.94 (s, 1H), 7.47 – 7.38 (m, 2H), 7.38 – 7.26 (m, 3H), 5.14 – 4.93 (m, 2H), 2.56 – 2.38 (m, 2H), 2.29 (d, *J* = 7.0 Hz, 2H), 1.55 (s, 3H), 1.26 (s, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 214.2, 173.2, 172.8,

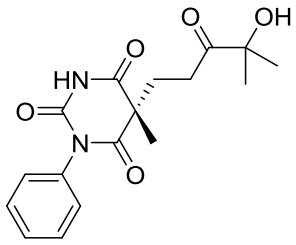
150.9, 137.1, 129.9, 129.8, 129.7, 129.2, 51.6, 45.7, 32.9, 31.7, 27.4, 27.3, 25.7. UPLC-DAD-QTOF: calcd for $C_{18}H_{22}N_2O_5Na$ (M, Na^+), 369.1426; found, 369.1433.

(*R*)-1-Pentyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-5-methylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (24Ac)



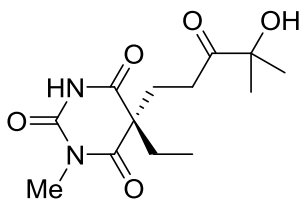
Prepared according to the general procedure starting from 2-(benzylthio)-5-methyl-1-pentylpyrimidine-4,6(1*H*,5*H*)-dione **(5Ac).** The crude material was purified by flash column chromatography on silica gel (eluent with hexane/ethyl acetate, 1:1) to give the title compound as a colorless oil. Yield: 63% (42 mg). $[\alpha]_D^{23}$= –0.21° (*c*= 0.45, 87% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.92 (s, 1H),3.84 (m, 2H), 2.57 (m, 2H), 2.30 (m, 2H), 1.59 (m, 2H), 1.55 (m, 2H), 1.34 (s, 6H), 1.32 (m, 4H), 0.90 (t, 3H, *J*= 6.9 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ 213.3, 172.5, 172.3, 150.1, 64.4, 50.6, 41.6, 31.5, 30.9, 28.9, 27.6, 26.4, 25.3, 24.9, 22.3, 14.0. UPLC-DAD-QTOF: calcd for $C_{16}H_{26}N_2O_5Na$ (M, Na^+), 349.1739; found, 349.1739.

***(R)*-5-(4-hydroxy-4-methyl-3-oxopentyl)-5-methyl-1-phenylpyrimidine-2,4,6(*1H,3H,5H)*-trione (24Ad)**



Prepared according to the general procedure starting from 2-(benzylthio)-5-methyl-1-phenylpyrimidine-4,6(1*H*,5*H*)-dione **(5Ad).** The crude material was purified by flash column chromatography on silica gel (eluent with hexane/ethyl acetate, 1:1) to give the title compound as a colorless oil. Yield: 62% (42 mg). $[\alpha]_D^{23}$= – 0.21° (*c*= 0.45, 90% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.22 (brs, 1H), 7.38 (m, 2H), 7.28 (m, 3H), 5.00 (m, 2H), 3.45 (s, 1H), 2.43 (m, 2H), 2.29 (m, 2H), 1.50 (s, 3H), 1.22 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ UPLC-DAD-QTOF: calcd for $C_{18}H_{22}N_2O_5Na$, 369.1426; found, 369.1433.

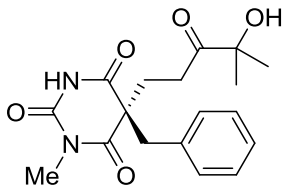
(*R*)-5-Ethyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (24Ba)



Prepared according to the general procedure starting from 2-(benzylthio)-5-ethyl-1-methylpyrimidine-4,6(1*H*,5*H*)-dione **(5Ba).** The crude material was purified by flash column chromatography on silica gel (eluent with hexane/ ethyl acetate, 2:1) to give the title compound as a yellow oil. Yield: 71% (40 mg). $[\alpha]_D^{23}$= –2.8° (*c*= 1, 94 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (s, 1H), 3.29 (s, 3H), 2.63 – 2.51 (m, 2H), 2.28 (t, *J* = 7.2 Hz, 2H), 2.01 (q, *J* = 7.4 Hz, 2H), 1.32 (d, *J* = 1.0 Hz, 6H), 0.86 (t, *J* = 7.4 Hz, 3H).^{13}C NMR (300

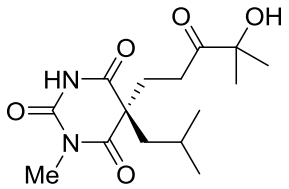
MHz, $CDCl_3$) δ 213.7, 172.4, 171.5, 150.2, 77.0, 56.3, 33.8, 31.5, 31.3, 28.3, 26.9, 9.7. UPLC-DAD-QTOF: calcd for $C_{13}H_{21}N_2O_5$ (M, H^+), 285.1450; found, 285.1451.

(*S*)-5-Benzyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methylpyrimidine-2,4,6(1*H*,3*H*,5*H*) (24Ca)



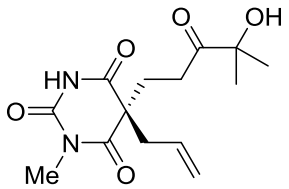
Prepared according to the general procedure starting from 5-benzyl-2-(benzylthio)-1-methylpyrimidine-4,6(1*H*,5*H*)-dione **(5Ca).** The crude material was diluted with 0.2 mL of water and 0.3 mL of acetone and 96 mg of oxone (1.5 equiv.) in 0.1 mL of water was added and the reaction mixture was stirred 24 h at room temperature.The crude material was purified by flash column chromatography on silica gel (eluent with hexane/ ethyl acetate, 2:1) to give the title compound as a white solid. M.p: 227 - 230 °C. Yield: 70% (48 mg). $[\alpha]_D^{22}$= –1.72° (*c*= 0.84, 92% *ee,* CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.33 – 7.25 (m, 3H), 7.08 – 7.03 (m, 2H), 3.27 (s, 2H), 3.09 (s, 3H), 2.70 – 2.43 (m, 4H), 1.38 (s, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 213.4, 171.8, 170.8, 149.2, 134.2, 129.5, 129.2, 129.1, 128.6, 57.9, 47.4, 31.8, 31.7, 31.5, 28.0, 26.9. UPLC-DAD-QTOF: calcd for $C_{18}H_{23}N_2O_5$ (M, H^+), 347.1607; found, 347.1606.

(*S*)-5-(4-Hydroxy-4-methyl-3-oxopentyl)-5-isobutyl-1-methylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (24Da)



Prepared according to the general procedure starting from 2-(benzylthio)-5-isobutyl-1-methylpyrimidine-4,6(1*H*,5*H*)-dione **(5Da).** The crude material was purified by flash column chromatography on silica gel (eluent with hexane/ ethyl acetate, 3:1) to give the title compound as a yellow oil. Yield: 68% (42 mg). $[\alpha]_D^{22}$= –1.25° (*c*= 0.27, 93 % *ee,* CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 3.34 – 3.23 (m, 3H), 2.66 – 2.41 (m, 2H), 2.23 (t, *J* = 7.3 Hz, 2H), 1.95 (d, *J* = 6.6 Hz, 2H), 1.31 (s, 6H), 0.80 (dd, *J* = 12.2, 6.6 Hz, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 213.3, 172.5, 171.6, 150.1, 54.6, 47.7, 34.2, 30.9, 30.1, 28.4, 27.0, 25.8, 23.8, 23.5, 1.4. UPLC-DAD-QTOF: calcd for $C_{15}H_{25}N_2O_5$ (M, H^+), 313.1763; found, 313.1769.

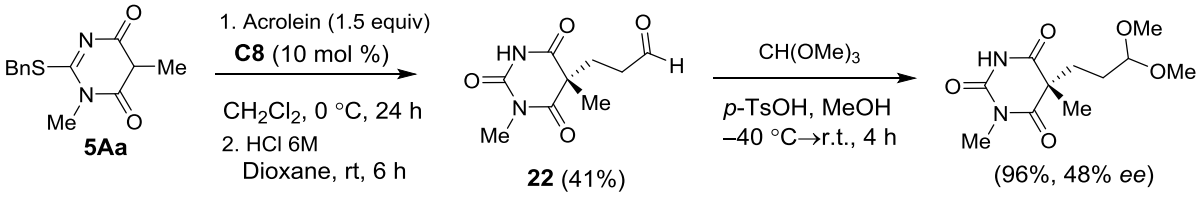
(*S*)-5-Allyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione(24Fa)



Prepared according to the general procedure starting from 5-allyl-2-(benzylthio)-1-methylpyrimidine-4,6(1*H*,5*H*)-dione **(5Fa).** The crude material was purified by flash column chromatography on silica gel (eluent with hexane/ethyl acetate, 2:1) to give the title compound as a colourless oil. Yield: 72% (42 mg). $[\alpha]_D^{23}$= –4.84° (*c*= 0.75, 92 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz,

$CDCl_3$) δ 8.65 (s, 1H), 5.63 – 5.46 (m, 1H), 5.16 – 5.06 (m, 2H), 3.23 (s, 3H), 2.66 – 2.49 (m, 4H), 2.34 – 2.26 (m, 2H), 1.30 (s, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 213.6, 171.9, 170.99, 150.1, 130.4, 121.7, 56.0, 44.5, 31.3, 31.2, 28.2, 26.8. UPLC-DAD-QTOF: calcd for $C_{14}H_{21}N_2O_5$ (M, H^+), 297.1450; found, 297.1455.

2.7.4 Reaction of 5Aa with acrolein



To a mixture of **5Aa** (0.2 mmol, 1equiv.) and acrolein (0.02 mL, 0.3 mmol, 1.5 equiv.) in CH_2Cl_2 (0.5 mL), catalyst **C8** (10.1 mg, 10 mol%) was added and the he resulting mixture was stirred at 0 °C for 24 h. Then the reaction mixture was concentrated in the rotary evaporator, the residue was dissolved in dioxane/HCl 6M (0.5ml/0.5mL), and the resulting mixture was stirred at room temperature for 6 h. Then, it was quenched with an aqueous solution of $NaHCO_3$ (1 mL), diluted with water (1 mL) and the mixture extracted with EtOAc (3 × 3 mL). The organic layer was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate, 1/1) to give aldehyde **22** as a colorless oil. Yield: 41% (17.3 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.66 (s, 1H), 8.92 (s, 1H), 3.27 (s, 3H), 2.48- 2.33 (m, 2H), 2.31-2.28 (m, 2H), 1.56 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ = 200.0, 172.3, 171.5, 149.8, 50.5, 39.1, 30.0, 28.1, 24.5. MS (ESI, *m*/*z*): calcd for $C_9H_{12}N_2O_4Na$ (M, +Na), 235.0695; found, 235.0683.

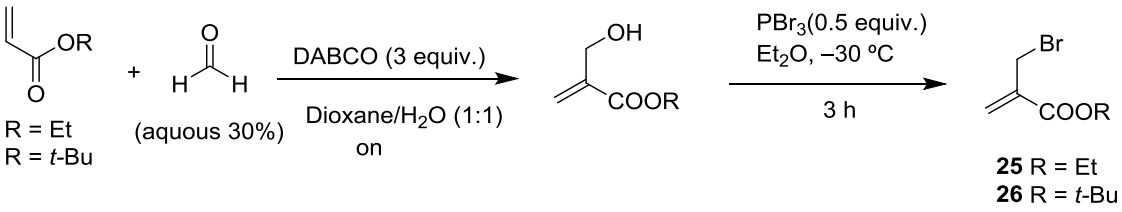
The enantiomeric purity of this material was determined by chiral HPLC analysis after derivatisation into the corresponding dimethyl acetal, as follow:

Derivatization of **22** onto the corresponding dimethyl acetal: To a solution of aldehyde **22** (0.15 mmol, 31.6 mg, 1 equiv.) in MeOH (0.6 mL) at -40 °C trimethyl orthoformiate (0.03 mL, 1 equiv., 0.15 mmol) and *p*-toluensulfonic acid (5 mg, 20 mol %) were added. The resulting mixture was allowed to reach the room temperature and stirred for 4 h at that temperature. Water (3 mL) was added to the reaction flask and the resulting mixture was extracted with EtOAc (3 × 3 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under pressure. Thus obtained product was essentially pure (yellow oil) and submitted to HPLC

analysis (see Section 4, page 136). Yield: 38.7 mg, 0.15 mmol, >99%. ^{1}H NMR (300 MHz, $CDCl_3$). $[\alpha]_D^{22}$= = –3.6° (*c*= 0.1, 92 % ee, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.28 (s, 3H), 3.22 (d, *J* = 1.8 Hz, 6H), 2.09 (t, *J* = 7.8 Hz, 2H), 1.62 – 1.44 (m, 6H). ^{13}C NMR (300 MHz, $CDCl_3$) δ = 173.1, 172.1, 150.3, 103.8, 53.0, 52.9, 51.4, 33.1, 28.6, 28.4, 26.4. MS (ESI, *m*/*z*): calcd for $C_{11}H_{18}N_2O_5Na$ (M, Na^+), 281.1113; found, 281.1118.

2.8. Catalytic reactions with allyl bromides 25 and 26

2.8.1 Synthesis of 2-(bromomethyl)acrylates 25 and 26



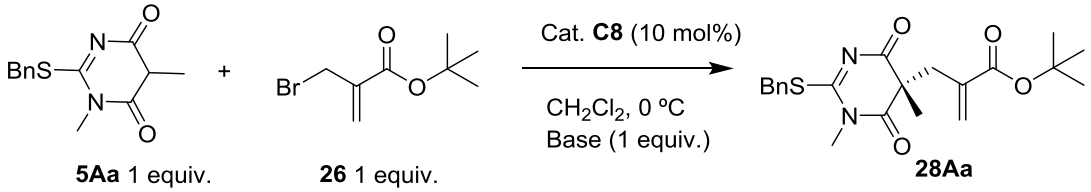
Step 1:[13] A solution of formaldehyde (30% aqueous, 1.0 equiv., 30 mmol, 2.5 mL) and tert-butyl or ethyl acrylate (3.0 equiv. 90 mmol) in 200 mL of a mixture of 1,4-dioxane water (1:1, v/v) was stirred at room temperature over night. Then DABCO (3 equiv., 90 mmol, 10 g) was added and the mixture was stirred until the starting acrylate disappeared (monitored by TLC). The reaction mixture was then partitioned with ether (100 ml) and water (80 ml). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give *tert*-butyl 2-(hydroxymethyl)acrylateas (2.13 g, 68%) and the ethyl 2-(hydroxymethyl)acrylate (2.7 g, 58%), respectively, as a yellow oil.

and the ethyl 2-(hydroxymethyl)acrylate r

Step 2:[14] The material obtained in the previous step (1 equiv., 5 mmol), was dissolved in ether (5 mL) and cooled down in an ice/salt bath to –30 °C. A solution of PBr_3 (0.5 equiv., 2.5 mmol, 1.24 mL) in ether (7 mL) and added dropwise over a period of 5 min to the chilled reaction mixture, and the mixture was allowed to stir at 0 °C for 3 h. The reaction flask was cooled to –10 °C, and H_2O (5 mL) was added slowly with stirring. The mixture was then diluted with hexane (15 mL) and washed with H_2O (20 mL). The organic layer was separated, dried, filtered, and the solvent evaporated to afford an oil product wich was purified by flash column chromatography (eluent hexane/ethyl acetate, 10:1). Physical and spectroscopic data of thus obtained products **25** and **26** were identical to those reported in the literature. Compound **25**, yield: 599 mg (62%); ^{1}H NMR (300 MHz, $CDCl_3$), δ 6.27 (d, *J* = 1.0, 0.8 Hz, 1H), 5.85 (q, *J* = 1.1 Hz,

1H), 4.35 (d, *J* = 1.1 Hz, 2H), 4.27 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H). Compound **26**, yield: 545 mg (63%); ^{1}H NMR (300 MHz, $CDCl_3$), δ 6.25 (d, *J* = 1.0 Hz, 1H), 5.88 (q, *J* = 0.9 Hz, 1H), 4.17 (d, *J* = 0.9 Hz, 2H), 1.55 (s, 9H).

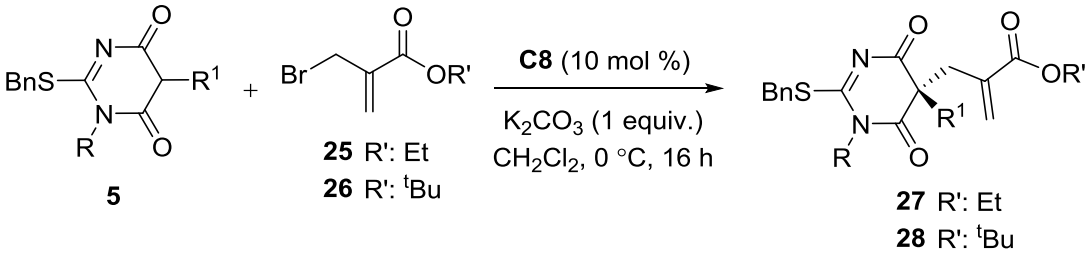
2.8.2 Screening of bases for the reaction of 5Aa with 26 using catalyst C8



Base	Conversion (%, overnight)	Yield (%)	*ee* (%)
K_2CO_3	100	63	99
K_2CO_3[(a)]	80	62	0
K_2CO_3[(b)]	<5	--	--
K_3PO_4	100	61	97
Cs_2CO_3	100	65	77
Et_3N	100	71	10
DMAP	100	68	24
Without base	0	--	--

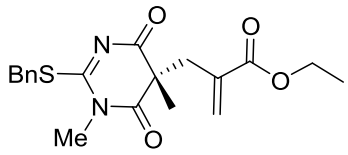
[(a)] Reaction carried out without cat **C8** at rt for 72 h.
[(b)] Reaction carried out without cat **C8** at 0 °C for 72 h.

2.8.3 General procedure and data of adducts



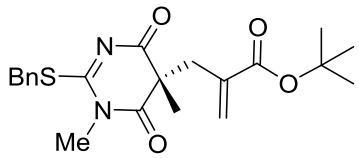
To a mixture of the corresponding template **5** (0.2 mmol, 1.0 equiv.) and allylic bromide **25** or **26** (0.20 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL), was added catalyst **C8** (10 mol%) and K_2CO_3 (0.2 mmol, 1.0 equiv.) and the reaction was stirred at 0 °C for 16 h. Then the mixture was quenched with HCl 1 M and extracted with CH_2Cl_2 (3 x 2 mL). The organic layer was washed with water (3 x 2 mL), dried over $MgSO_4$, filtered, and solvent was evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluent hexane/ethyl acetate, 4:1).

(*R*)-2-((2-(Benzylthio)-1,5-dimethyl-4,6-dioxo-1,4,5,6-tetrahydropyrimidin-5-yl)methyl)acrylate (27Aa)



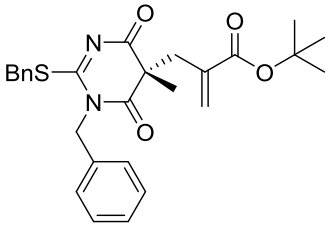
Prepared according to the general procedure starting from 2-(benzylthio)-1,5-dimethylpyrimidine-4,6(1*H*,5*H*)-dione (**5Aa**) and ethyl 2-(bromomethyl)acrylate (**25**). The title compound was obtained as a yellow oil. Yield: 62% (45.6 mg).). $[\alpha]_D^{23}$= +81.25° (*c*= 0.24, 48 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41- 7.34 (m, 5H), 6.25 (s, 1H), 5.55 (s, 1H), 4.47 (d, *J* = 1.5 Hz, 2H), 4.17 (dd, J = 7, 1Hz, 2 H), 3.31 (s, 3H), 3.01 (dd, *J* = 13, 1 Hz, 1 H), 2.79 (dd, J = 13,1 Hz, 1H), 1.52 (s, 3H), 1.30 (t, J = 7 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 178.8, 173.3, 173.2, 166.6, 135.3, 134.8, 129.7, 129.3, 129.1, 128.2, 125.6, 61.3, 53.8, 44.6, 41.6, 37.6, 30.2, 21.2, 14.3. MS (ESI, *m*/*z*): calcd for $C_{19}H_{22}N_2O_4S$ (M, H^+), 375.1300; found, 375.1400.

***tert*-Butyl (*R*)-2-((2-(benzylthio)-1,5-dimethyl-4,6-dioxo-1,4,5,6-tetrahydropyrimidin-5-yl)methyl)acrylate (28Aa)**



Prepared according to the general procedure starting from 2-(benzylthio)-1,5-dimethylpyrimidine-4,6(1*H*,5*H*)-dione **(5Aa)** and *tert*-butyl 2-(bromomethyl)acrylate **(26).** The title compound was obtained as a yellow oil. Yield: 63% (50.7 mg). $[\alpha]_D^{22}$= +45.47° (*c*= 0.17, 99 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.25 (m, 5H), 6.17 (d, *J* = 1.3 Hz, 1H), 5.50 (d, *J* = 1.2 Hz, 1H), 4.48 (s, 2H), 3.31 (s, 3H), 2.98 (dd, *J* = 13.5, 0.9 Hz, 1H), 2.71 (dd, *J* = 13.6, 0.9 Hz, 1H), 1.52 (s, 3H), 1.48 (s, 9H).^{13}C NMR (75 MHz, $CDCl_3$) δ 179.5, 173.7, 166.3, 136.9, 135.3, 130.2, 129.5, 129.3, 129.1, 128.7, 81.9, 67.8, 54.3, 42.4, 38.0, 30.7, 30.4, 28.6, 28.6, 21.3. MS (ESI, *m*/*z*): calcd for $C_{21}H_{26}N_2O_4S$ (M, H^+), 403.1613; found, 143.1614.

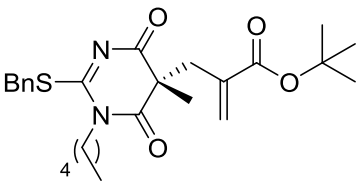
***tert*-Butyl (*R*)-2-((1-benzyl-2-(benzylthio)-5-methyl-4,6-dioxo-1,4,5,6-tetrahydropyrimidin-5-yl)methyl)acrylate (28Ab)**



Prepared according to the general procedure starting from 1-benzyl-2-(benzylthio)-5-methylpyrimidine-4,6(1*H*,5*H*)-dione **(5Ab)** and *tert*-butyl 2-(bromomethyl)acrylate **(26).** The title compound was obtained as a yellow oil. Yield: 68% (65.1 mg). $[\alpha]_D^{22}$= +36.45° (*c*= 0.27, 90 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.19 (m, 12H), 6.13 (d, *J* = 1.1 Hz, 1H), 5.40 (q, *J* = 1.0 Hz, 1H), 5.18 (d, *J* = 16.1 Hz, 1H), 4.90 (d, *J* = 16.1 Hz, 1H), 4.53 – 4.38 (m, 2H), 3.01 (dd, *J* = 13.9, 1.0 Hz, 1H), 2.82 (dd, *J* = 13.9, 1.0 Hz, 1H), 1.54 (s, 3H), 1.50 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.51, 174.47, 173.51, 166.77, 137.43, 136.14, 135.64, 130.54,

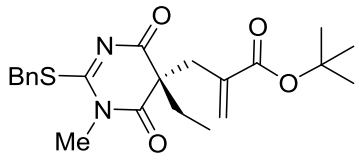
129.86, 129.74, 129.15, 129.04, 128.76, 82.26, 54.82, 48.27, 41.78, 38.71, 29.03, 28.96, 22.66.MS (ESI, *m*/*z*): calcd for $C_{27}H_{30}N_2O_4S$ (M, H^+), 479.1926; found, 479.18263.

tert-Butyl (R)-2-((2-(benzylthio)-1-pentyl-5-methyl-4,6-dioxo-1,4,5,6-tetrahydropyrimidin-5-yl)methyl)acrylate(28Ac)



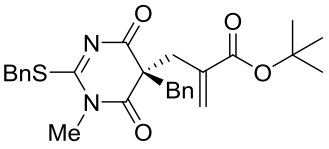
Prepared according to the general procedure starting from 1-benzyl-2-(pentylthio)-5-methylpyrimidine-4,6(1*H*,5*H*)-dione **(5Ac)** and *tert*-butyl 2-(bromomethyl)acrylate **(26).** The title compound was obtained as colorless oil. Yield: 73% (68.6 mg). $[\alpha]_D^{22}$= +77.65° (*c*= 0.25, 98 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.22 (m, 5H), 6.15 (d, *J* = 1.2 Hz, 1H), 5.43 (d, *J* = 1.1 Hz, 1H), 4.47 (s, 2H), 3.91 – 3.63 (m, 2H), 2.97 (dd, *J* = 13.9, 1.0 Hz, 1H), 2.77 (dd, *J* = 13.9, 1.0 Hz, 1H), 1.67 – 1.61 (m, 3H), 1.50 (d, *J* = 5.5 Hz, 12H), 1.32 (ddd, *J* = 9.3, 7.7, 5.5 Hz, 3H), 0.90 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.42, 173.73, 173.10, 166.25, 137.16, 135.32, 130.18, 129.50, 128.66, 128.58, 81.80, 54.13, 45.14, 41.59, 38.01, 29.50, 28.61, 28.52, 22.80, 22.27, 14.56 . MS (ESI, *m*/*z*): calcd for $C_{25}H_{34}N_2O_4S$ (M, H^+), 459.2239; found, 459.2240.

tert-Butyl (*R*)-2-((2-(benzylthio)-5-ethyl-1-methyl-4,6-dioxo-1,4,5,6-tetrahydropyrimidin-5-yl)methyl)acrylatetert-butyl (28Ba)



Prepared according to the general procedure from 2-(benzylthio)-5-ethyl-1-methylpyrimidine-4,6(1*H*,5*H*)-dione **(5Ba)** and *tert*-butyl 2-(bromomethyl)acrylate **(26).** The title compound was obtained as a yellow oil. Yield: 67% (54.1 mg). $[\alpha]_D^{22}$= –55.63° (*c*= 0.19, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.24 (m, 5H), 6.12 (d, *J* = 1.3 Hz, 1H), 5.49 (d, *J* = 1.2 Hz, 1H), 4.47 (s, 2H), 3.33 (s, 3H), 3.04 – 2.77 (m, 2H), 2.09 (q, *J* = 7.4 Hz, 2H), 1.47 (s, 10H), 0.83 (t, *J* = 7.3 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 174.2, 173.4, 166.4, 137.3, 135.3, 130.1, 129.5, 128.9, 128.7, 81.8, 59.9, 42.1, 38.0, 31.6, 30.5, 28.6, 10.3.MS (ESI, *m*/*z*): calcd for $C_{22}H_{28}N_2O_4S$ (M, H^+), 417.1770; found, 417.1774.

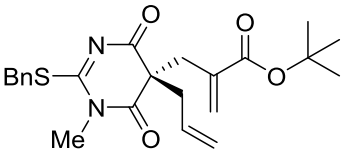
tert-Butyl (*R*)-2-((5-benzyl-2-(benzylthio)-1-methyl-4,6-dioxo-1,4,5,6-tetrahydropyrimidin-5-yl)methyl)acrylate (28Ca)



Prepared according to the general procedure starting from 5-benzyl-2-(benzylthio)-1-methylpyrimidine-4,6(1*H*,5*H*)-dione **(5Ca)** and *tert*-butyl 2-(bromomethyl)acrylate **(26).** The title compound was obtained

as a yellow oil. Yield: 63% (60.2 mg). $[\alpha]_D^{22}$= +70.30° (*c*= 0.20, 86 % ee, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.01 (m, 10H), 6.11 (d, *J* = 1.0 Hz, 1H), 5.43 (d, *J* = 1.1 Hz, 1H), 4.28 (d, *J* = 1.9 Hz, 2H), 3.44 – 3.20 (m, 2H), 3.13 (d, *J* = 9.5 Hz, 5H), 1.48 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 174.6, 173.4, 166.9, 138.2, 136.3, 135.7, 130.9, 130.5, 129.9, 129.2, 129.0, 128.3, 128.3, 82.19, 61.1, 46.9, 41.4, 38.3, 30.7, 29.0.MS (ESI, *m*/*z*): calcd for $C_{27}H_{30}N_2O_4S$ (M, H^+), 479.1926; found, 479.19263.

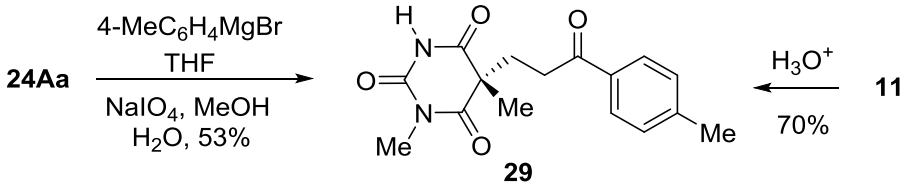
***tert*-Butyl (*R*)-2-((5-allyl-2-(benzylthio)-1-methyl-4,6-dioxo-1,4,5,6-tetrahydropyrimidin-5-yl)methyl)acrylate (28Fa)**



Prepared according to the general procedure starting from 5-allyl-2-(benzylthio)-1-methylpyrimidine-4,6(1*H*,5*H*)-dione **(5Fa)** and *tert*-butyl 2-(bromomethyl)acrylate **(26).** The title compound was obtained as a yellow oil. Yield: 65% (54.8 mg).). $[\alpha]_D^{22}$= +69.68° (*c*= 0.25, 92 % ee, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.27 (m, 4H), 6.14 (s, 1H), 5.72 – 5.54 (m, 1H), 5.49 (d, *J* = 1.2 Hz, 1H), 5.19 – 5.00 (m, 2H), 4.46 (s, 2H), 3.31 (s, 3H), 3.02 – 2.83 (m, 2H), 2.81 – 2.66 (m, 2H), 1.47 (s, 9H).^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 174.3, 172.9, 166.3, 137.2, 135.3, 132.5, 130.5, 130.1, 129.5, 128.9, 128.8, 128.7, 120.6, 81.8, 59.1, 42.3, 41.6, 38.0, 30.47, 28.6. MS (ESI, *m*/*z*): calcd for $C_{23}H_{18}N_2O_4S$ (M, H^+), 429.1770; found, 429.1870.

2.9. Elaborations of Adducts

2.9.1. Conversion of 24Aa into ketone 29 (chemical correlation to 11)

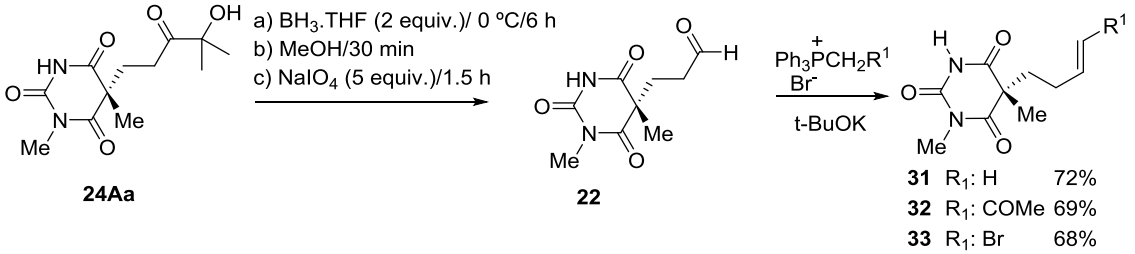


p-Tolylmagnesium bromide (5M in THF, 5 equiv., 1 mmol) was added to a solution of **24Aa** (1 equiv., 0.2 mmol, 54 mg) in dry THF (1 mL) at 0 °C and the resulting solution was stirred at the same temperature until the reaction was finished (monitored by TLC). Then a saturated aqueous solution of NH_4Cl (2 mL) was added at 0 °C and the resulting mixture was extracted with CH_2Cl_2 (3 × 3 mL). The solvents were evaporated under reduced pressure and the residue thus obtained was dissolved in MeOH (1 mL). A suspension of $NaIO_4$ (5 equiv., 1 mmol, 214 mg) in water (0.4 mL) was added to the solution at room temperature and the resulting mixture was stirred at the same temperature for 1 h. Then solvents were evaporated under reduced pressure, water (2

mL) was added to the residue and the resulting mixture was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 3:1) to give ketone **29** as a white oil. Yield: 32 mg (53%). $[\alpha]_D^{24}$= –58.70° (*c*= 0.27, CH_2Cl_2, 90 % *ee*). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.89 (s, 1H), 7.77 (d, *J* = 9 Hz, 2H), 7.22 (d, *J* = 9 Hz, 2H), 3.28 (s, 3H), 2.97-2.80 (m, 2H), 2.44-2.38 (m, 5H), 1.58 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ = 198.0, 172.5, 171.8, 150.0, 144.2, 133.8, 129.26, 128.1, 50.7, 33.4, 32.4, 28.1, 24.3, 21.6. MS (ESI, *m*/*z*): calcd for $C_{16}H_{18}N_2O_4$ (M, H^+), 303.1345; found, 303.1353.

On the other hand, adduct **11** (1 equiv., 60.6 mg, 0.2 mmol) was dissolved in dioxane/6M HCl (0.5 ml/0.5 mL), and the resulting mixture was stirred at r.t. for 6 h. Then the mixture was quenched with an aqueous solution of $NaHCO_3$ (2 mL), diluted with water (2 mL) and extracted with EtOAc (3 × 4 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvents were evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 3:1) to give ketone **29** as a white oil. Yied 45 mg (70%). $[\alpha]_D^{23}$= –54.32° (*c*= 0.29, CH_2Cl_2).

2.9.2. Conversion of 24Aa into alkenes 31-33



Step 1: BH_3•THF complex (1M in THF, 0.4 mL, 0.4mmol, 2 equiv.) was added to a solution of adduct **24Aa** (54 mg, 0.2 mmol, 1 equiv.) in dry THF (0.8 mL) at 0 °C and the resulting solution was stirred at the same temperature until the starting material disappeared (6 h). MeOH (0.4 mL) was added and the resulting mixture was stirred at room temperature for 30 min. The solvents were evaporated under reduced pressure and the residue thus obtained was dissolved in MeOH (0.4 mL) and a suspension of sodium periodate (107 mg, 1 mmol, 5 equiv.) in water (0.5 mL) was added to the solution at room temperature. The reaction mixture was stirred at the same temperature for 1.5 h and solvents were evaporated under reduced pressure. Water 3 mL was added to the crude product and the resulting mixture was extracted with EtOAc (3 X 3 mL). The combined organic phases were dried over $MgSO_4$, filtered, and the solvent was

evaporated under reduced pressure, affording the aldehyde **22** as essentially pure compound. Yellow oil. Yield: 88% (41.3 mg). $[\alpha]_D^{23}$= +0.84° (*c*= 0.34, 94 % *ee*, CH_2Cl_2). For *ee* determination and spectroscopic data, see Section 2.7.4 (page S44)

Step 2:

(Method A)[15] Synthesis of (*R*)-5-(but-3-en-1-yl)-1,5-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione 31

Methyltriphenylphosphonium bromide (2 equiv., 0.4 mmol, 142.8 mg) was dissolved in THF (0.5 mL). Then *t*-BuOK (3 equiv. 0.6 mmol, 67.2 mg) was added and the yellow suspension was stirred at 0 °C for 45 min. To this suspension a solution of the aldehyde (**22**) (1 equiv., 0.2 mmol, 42 mg) in THF (0.3 mL) was added dropwise and the resulting mixture was stirred at room temperature for 6 h. After reaction completation the solvents were evaporated under reduced pressure. The crude was purified by flash column chromatography on silica gel (eluent hexane/ethyl acetate 4:1) to give the title compound as a white oil. Yield: 72% (26 mg). $[\alpha]_D^{23}$= +1.34 °(*c*= 0.88, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1H), 5.77 – 5.62 (m, 1H), 5.05 – 4.92 (m, 2H), 3.30 (s, 3H), 2.16 (dd, *J* = 8.2, 1.2 Hz, 2H), 2.08 – 1.97 (m, 2H), 1.58 (s, 4H).^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 171.5, 149.5, 136.4, 116.1, 51.1, 37.9, 29.9, 29.7, 25.1. UPLC-DAD-QTOF: calcd for $C_{10}H_{13}N_2O_3$ (M, H^+), 209.0926; found, 209.0949.

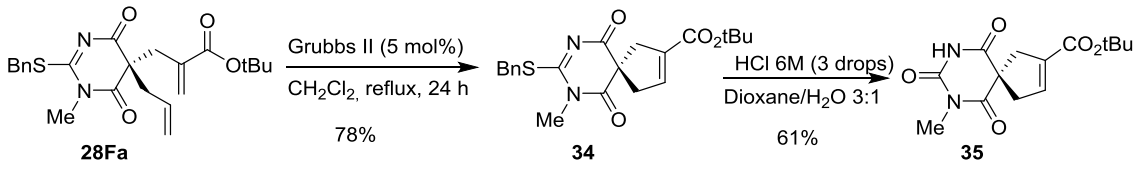
(Method B) Synthesis of (*R,E*)-1,5-dimethyl-5-(5-oxohex-3-en-1-yl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione 32

1-(Triphenylphosphoranylidene)-2-propanone (2 equiv., 0.4 mmol, 127.3 mg) was dissolved in THF (0.5 mL). Then *t*-BuOK (3 equiv. 0.6 mmol, 33.6 mg) was added and the yellow suspension was stirred at 0 °C for 45 min. To this suspension a solution of aldehyde **22** (1 equiv., 0.2mmol, 42 mg) in THF (0.3 mL) was added dropwise and the resulting mixture was stirred at room temperature for 6 h. After reaction completion the solvents were evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluent with hexane/ethyl acetate 4:1) to give the title compound as a single diastereomer as a white oil. Yield: 69% (55.7 mg). $[\alpha]_D^{23}$= +0.87°(*c*= 0.47, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1H), 6.68 (d, *J* = 16.0 Hz, 1H), 6.05 (d, *J* = 16.2 Hz, 1H), 3.31 (s, 3H), 2.28 – 2.12 (m, 7H), 1.60 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 198.7, 173.0, 172.0, 150.2, 145.7, 132.6, 51.9, 36.9, 29.0, 28.8, 27.8, 26.2. UPLC-DAD-QTOF: calcd for $C_{12}H_{17}N_2O_4$ (M, H^+), 253.1188; found, 253.1197.

(Method C)[15] **Synthesis of (*R,E*)-5-(4-bromobut-3-en-1-yl)-1,5-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione 33**

To a solution of bromomethyl triphenylphosphonium bromide (1.1 equiv., 0.22 mmol, 95.8 mg.) in anhydrous THF (1 ml), at –78 °C, *t*-BuOK (1.1 equiv., 0.22 mmol, 26.6 mg) was added. After stirring the mixture for 1 h at –78 °C, a solution of aldehyde **22** (1 equiv., 0.2 mmol, 42 mg) in anhydrous THF (0.2 mL) was added dropwise and the reaction mixture was stirred for a further 1 h at –78 °C. The reaction was then warmed to room temperature over 1 h. The solvents were evaporated under reduced pressure, the residue was purified by flash column chromatography on silica gel (eluent hexane/ethyl acetate 2:1) to give the title compound as a mixture of diastereomers (dr 17:3) as a white oil. Yield: 68% (34.4 mg). $[\alpha]_D^{23}$= +1.34° (*c*= 0.52, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 6.19 (d, *J* = 6.9 Hz, 1H), 6.07 – 5.93 (m, 1H), 3.32 (s, 3H), 2.24 – 2.19 (m, 4H), 1.59 (s, 4H).^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 172.2, 150.2, 133.3, 110.1, 51.7, 37.2, 28.8, 26.8, 26.2. UPLC-DAD-QTOF: calcd for $C_9H_{13}N_2O_2$ (M, H^+), 287.0031; found, 207.0034.

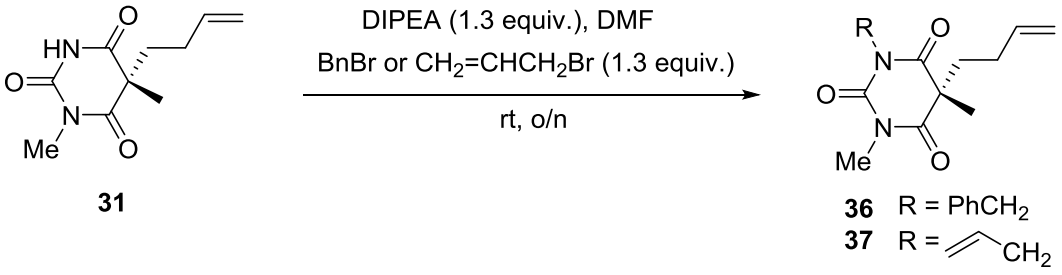
2.9.3. Conversion of adduct 28Fa into spiranic compounds 34 and 35



Step 1: To a solution of **28Fa** (1 equiv., 0.2 mmol, 85.7 mg) in CH_2Cl_2 (8 mL) was added 2nd Generation Grubbs Catalyst (6.4 mg, 5 mol %) and the reaction was stirred a reflux for 24 h. The resulting mixture was directly submitted to a flash column chromatography on silica gel (eluent hexane/ethyl acetate 8:1) to give compound **34** as a red oil. Yield: 78% (63.1 mg). $[\alpha]_D^{22}$= +5.07° (*c*= 0.16, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.31 (m, 4H), 6.61 (d, *J* = 2.4 Hz, 1H), 4.50 (s, 2H), 3.38 (s, 3H), 3.34 – 3.02 (m, 4H), 1.49 (s, 9H).^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 173.7, 173.5, 163.7, 139.6, 135.2, 134.2, 130.1, 129.6, 128.8, 81.5, 58.2, 43.9, 41.7, 38.1, 30.9, 28.8, 28.6. UPLC-DAD-QTOF: calcd for $C_{21}H_{24}N_2O_4S$ (M^+), 400.1457; found, 400.1455.

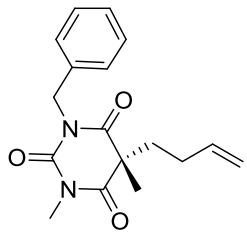
Step 2: To a solution of spiranic compound **34** (1 equiv., 0.1 mmol, 40.1 mg) in a mixture of dioxane/H_2O (3:1, 0.4 mL) was added HCl 6M (3 drops). The reaction was stirred at room temperature for 1 h. Then the mixture was directly submitted to a column chromatography on silica gel (eluent hexane/ethyl acetate, 2:1) to give the title compound as a red oil. Yield: 61% (17.9 mg). $[\alpha]_D^{22}$= + 3.05° (*c*= 0.07, CH_2Cl_2).^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 – 6.57 (m, 1H), 3.33 (s, 3H), 3.21 (s, 4H), 1.50 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 170.9, 162.7, 149.5, 138.2, 134.3, 81.1, 54.5, 44.9, 43.3, 28.5, 28.1.UPLC-DAD-QTOF: calcd for $C_{14}H_{18}N_2O_5$ (M^+), 294.1216; found, 294.1214.

2.9.4. N-Alkylation of adduct 31



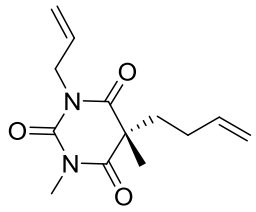
To a solution of adduct **31** (1 equiv., 0.2 mmol, 54 mg) in DMF (0.4 mL) was added DIPEA (1.3 equiv., 0.26 mmol, 44 µL) and after stirring for 5 minutes at room temperature benzyl or allyl bromide was added (1.3 equiv., 0.26 mmol).The resulting solution was stirred at the same temperature until disappearance of starting material as monitored by ^{1}H NMR. Water (1 mL) was added and the resulting mixture was extracted with EtOAc (3 X 1 mL). The combined organic layers were washed with brine (10 X 3 mL), dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluent hexane/ethyl acetate, 6:1)

(*R*)-1-Benzyl-5-(but-3-en-1-yl)-3,5-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (36)



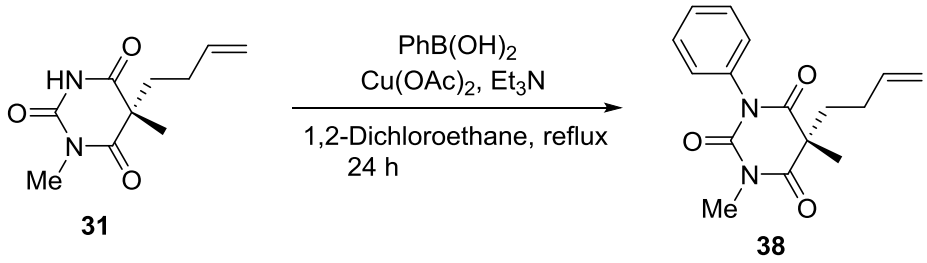
Prepared according to the general procedure using benzyl bromide**.** Colorless oil. Yield: 71 % (42.6 mg). $[\alpha]_D^{23}$= +1.23° (*c*= 0.23, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.23 (m, 5H), 5.70 – 5.45 (m, 1H), 5.08 (d, *J* = 1.4 Hz, 2H), 4.84 – 4.67 (m, 2H), 3.30 (s, 3H), 2.18 – 2.09 (m, 2H), 1.94 – 1.81 (m, 2H), 1.54 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 172.7, 151.6, 137.2, 129.8, 129.2, 128.7, 116.5, 51.8, 45.8, 39.4, 30.5, 29.3, 26.0. UPLC-DAD-QTOF: calcd for $C_{17}H_{20}N_2O_3$ (M, H^+), 301.1474; found, 301.1476.

(*R*)-1-Allyl-5-(but-3-en-1-yl)-3,5-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (37)



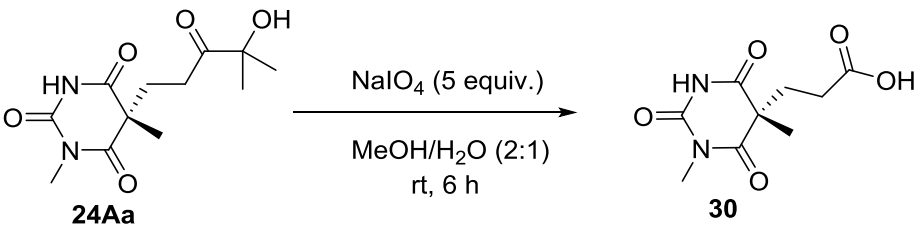
Prepared according to the general procedure using allyl bromide. Colorless oil. Yield: 63 % (31.5 mg). $[\alpha]_D^{23}$= +0.87° (*c*= 0.27, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (dd, *J* = 17.1, 10.2 Hz, 1H), 5.75 – 5.58 (m, 1H), 5.39 – 5.19 (m, 2H), 5.04 – 4.83 (m, 2H), 4.50 (dd, *J* = 6.1, 1.3 Hz, 2H), 3.31 (d, *J* = 0.7 Hz, 3H), 2.16 (dd, *J* = 9.2, 6.5 Hz, 2H), 2.05 – 1.88 (m, 2H), 1.55 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 172.33, 151.3, 137.3, 132.0, 119.6, 116.6, 51.8, 44.7, 39.2, 30.6, 29.3, 26.2.UPLC-DAD-QTOF: calcd for $C_{13}H_{18}N_2O_3$ (M, H^+),251.1317; found, 251.1319.

2.9.5. Arylation of adduct 31[17]



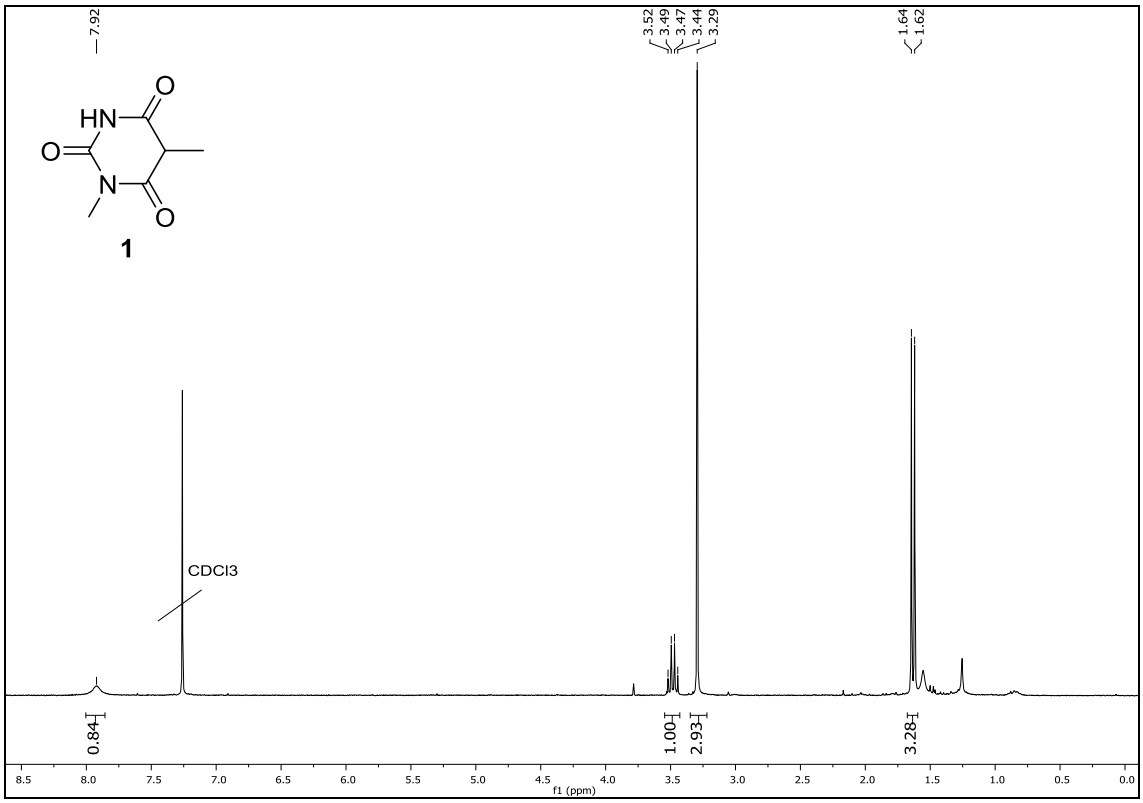
A slurry of adduct **31** (1 equiv., 0.2 mmol, 42 mg), phenylboronic acid (3 equiv., 0.6 mmol, 73.0 mg), anhydrous $Cu(OAc)_2$ (2 equiv, 0.4 mmol, 72.6 mg), and triethylamine (3 equiv. 0.6 mmol, 80 µL) in ethylene chloride (0.2 mL) was stirred a reflux for 24 h. Then the mixture was directly submitted to a flash column chromatography on silica gel (eluent hexane/ethyl acetate, 8:1) to give the title compound as a yellow oil. Yield: 68 % (38.9 mg). $[\alpha]_D^{22}$= +0.34° (*c*= 0.12, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 – 7.43 (m, 3H), 7.21 – 7.17 (m, 2H), 5.86 – 5.65 (m, 1H), 5.12 – 4.97 (m, 2H), 3.37 (s, 3H), 2.30 – 2.21 (m, 2H), 2.17 – 2.07 (m, 2H), 1.66 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 171.9, 150.8, 136.7, 134.5, 129.4, 129.1, 128.2, 116.1, 51.5, 38.5, 30.1, 28.7, 25.6.UPLC-DAD-QTOF: calcd for $C_{16}H_{18}N_2O_3$ (M, H^+), 286.1317; found, 286.1315.

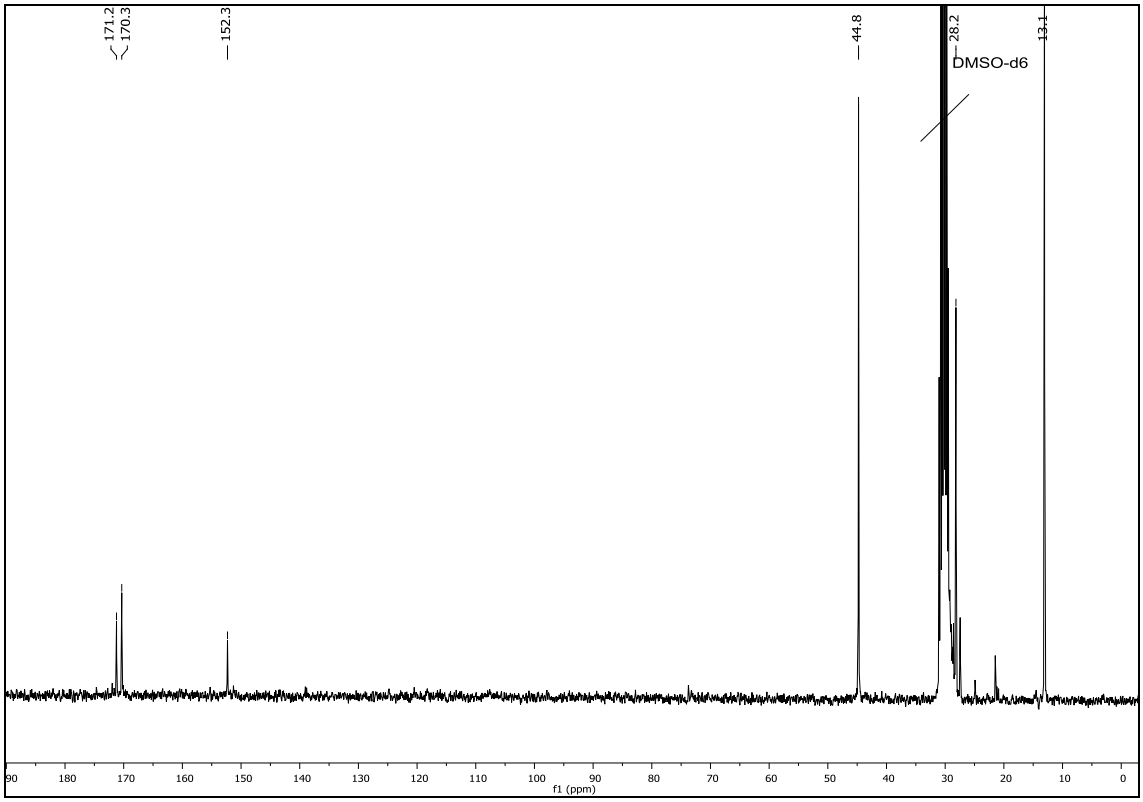
2.9.6. Synthesis of carboxylic acid 30

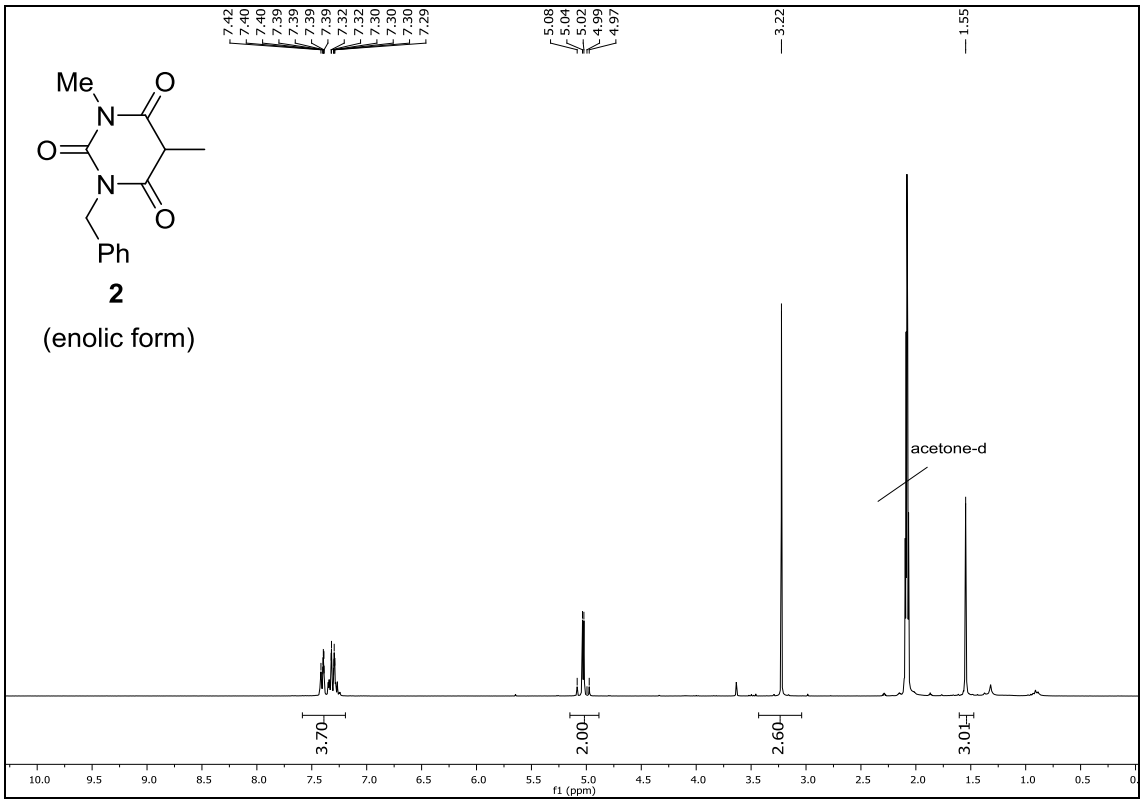


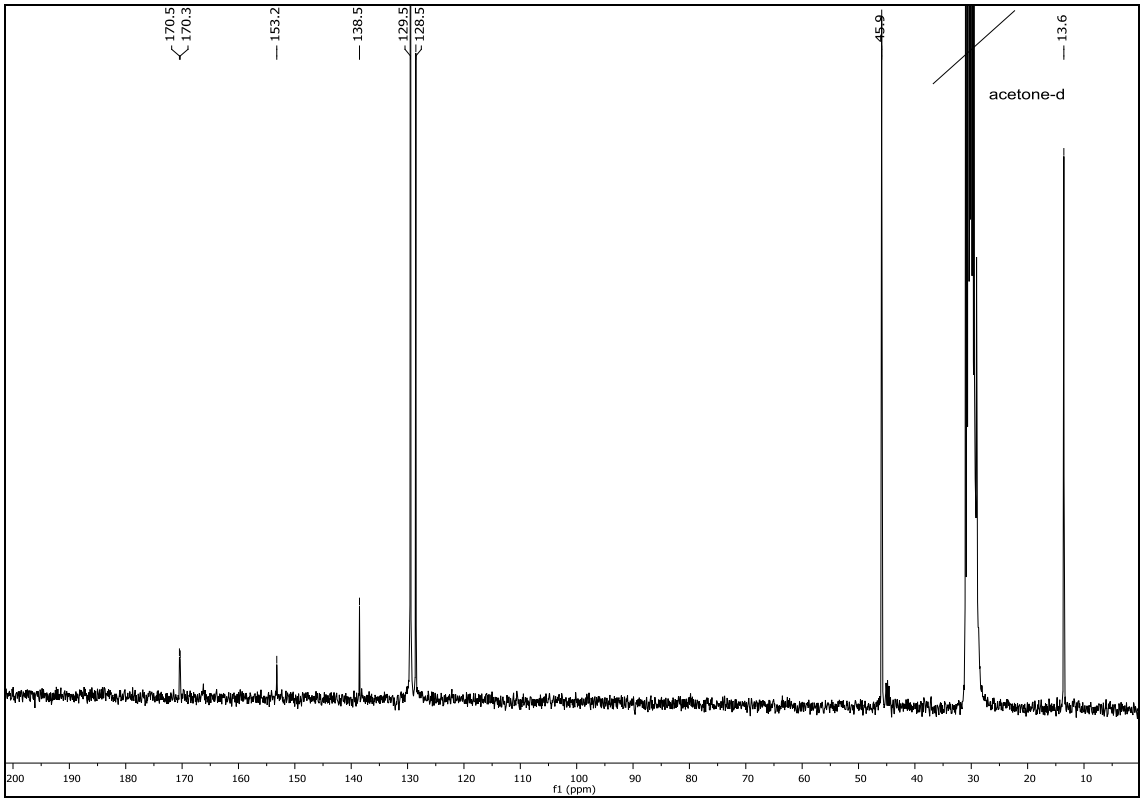
Adduct **24Aa** (0.2 mmol, 54 mg, 1 equiv.) was dissolved in 2 mL of methanol, and to this solution a suspension of sodium periodate (200 mg, 1.0 mmol, 5 equiv.) in water (1.0 mL) was added. The reaction mixture was stirred at room temperature for 6 h, until disappearance of starting material as monitored by TLC. Then the solvent was evaporated under reduced pressure. The residue was partitioned between water (3 mL) and EtOAc (6 mL) and the aqueous phase was extracted with EtOAc (2 X 6 mL) three times). The combined organic phases were dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure, to afford essentially pure (*R*)-3-(1,5-dimethyl-2,4,6-trioxohexahydropyrimidin-5-yl)propanoic acid **30**. Yellow oil. Yield: 97% (43.3 mg). $[\alpha]_D^{22}$= +2.1° (*c*= 0.18, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.52 (s, 1H), 3.30 (s, 3H), 2.49 – 2.24 (m, 4H), 1.56 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 173.0, 172.6, 150.6, 50.8, 32.8, 30.2, 28.5, 25.8. UPLC-DAD-QTOF: calcd for $C_9H_{13}N_2O_2$ (M, H^+), 229.0824; found, 229.0822.

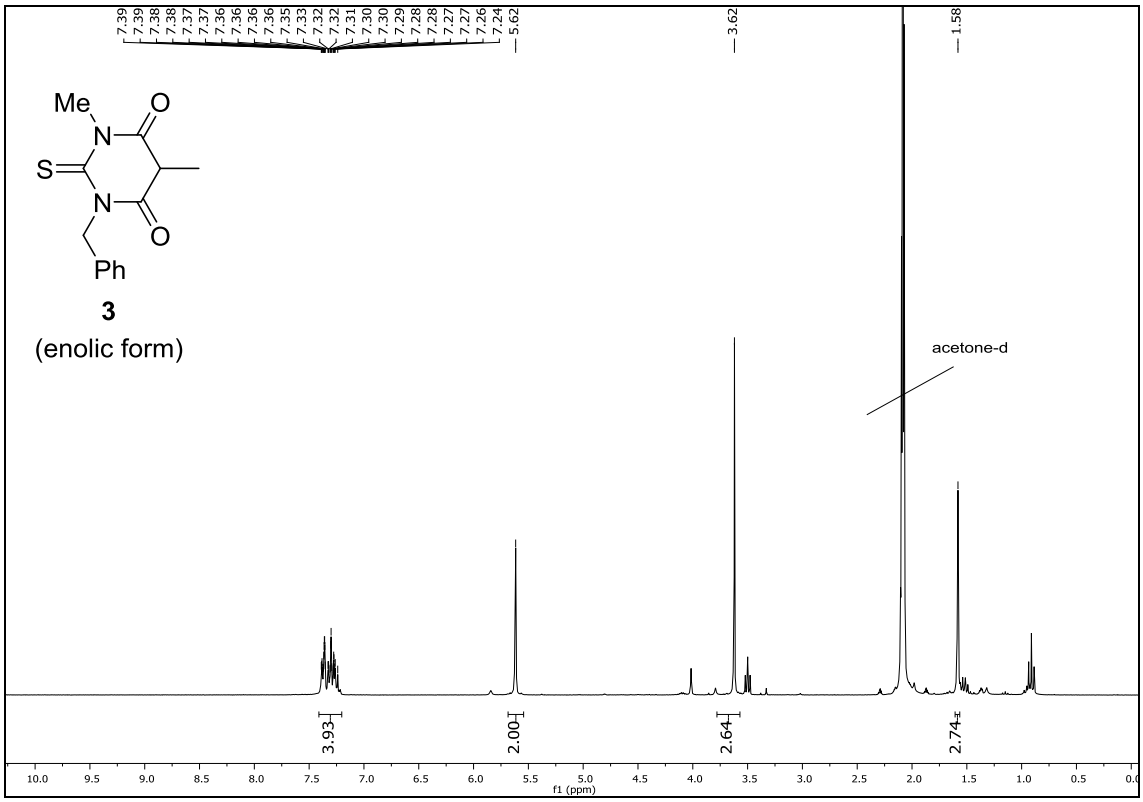
3.0. ^{1}H and ^{13}C NMR Spectra

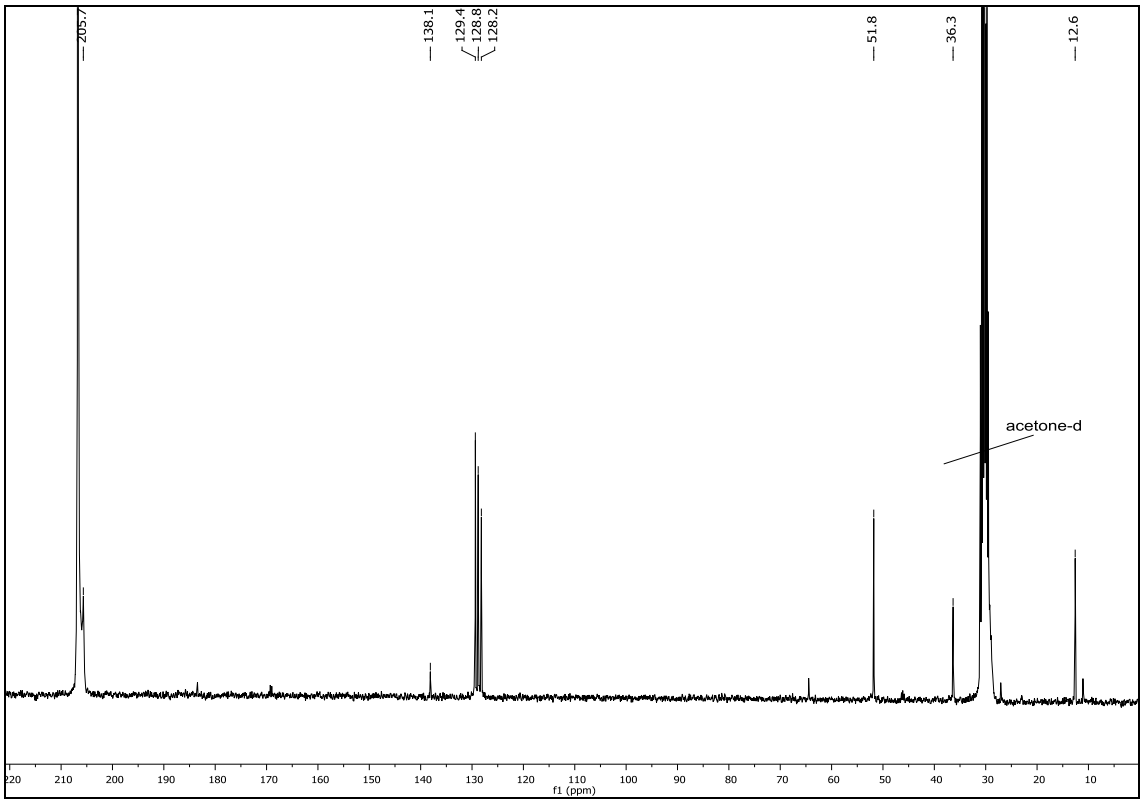


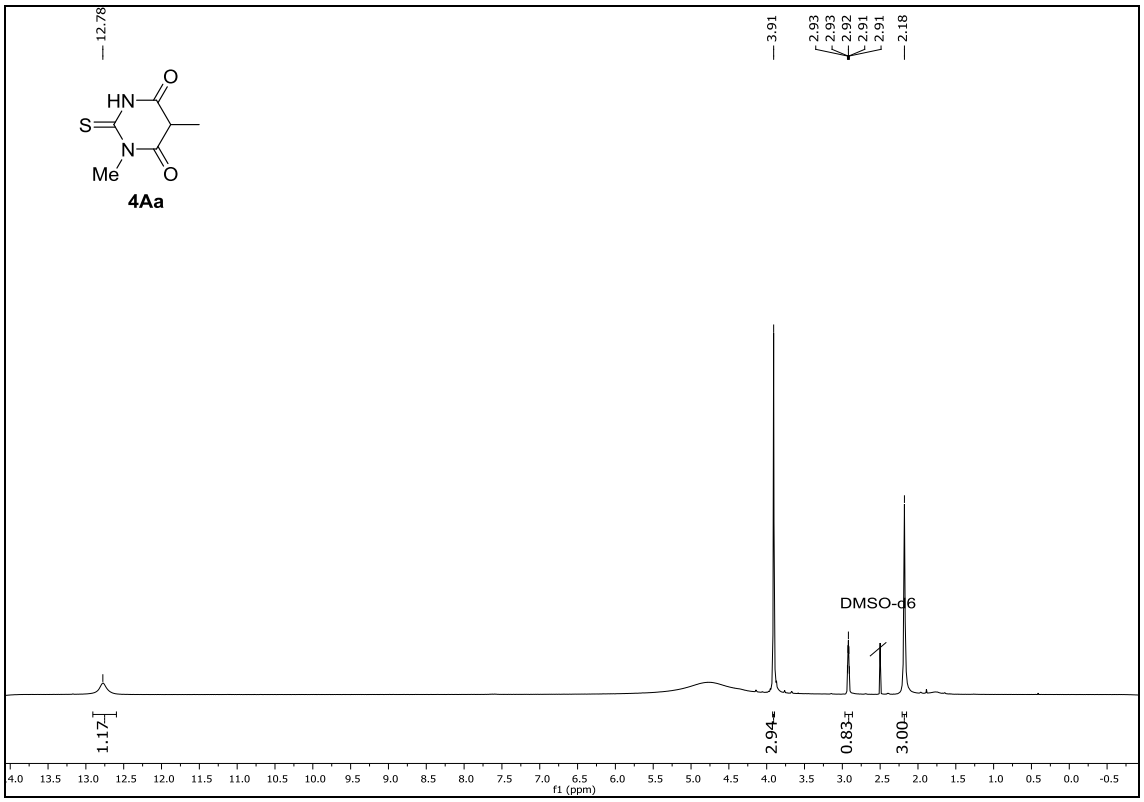


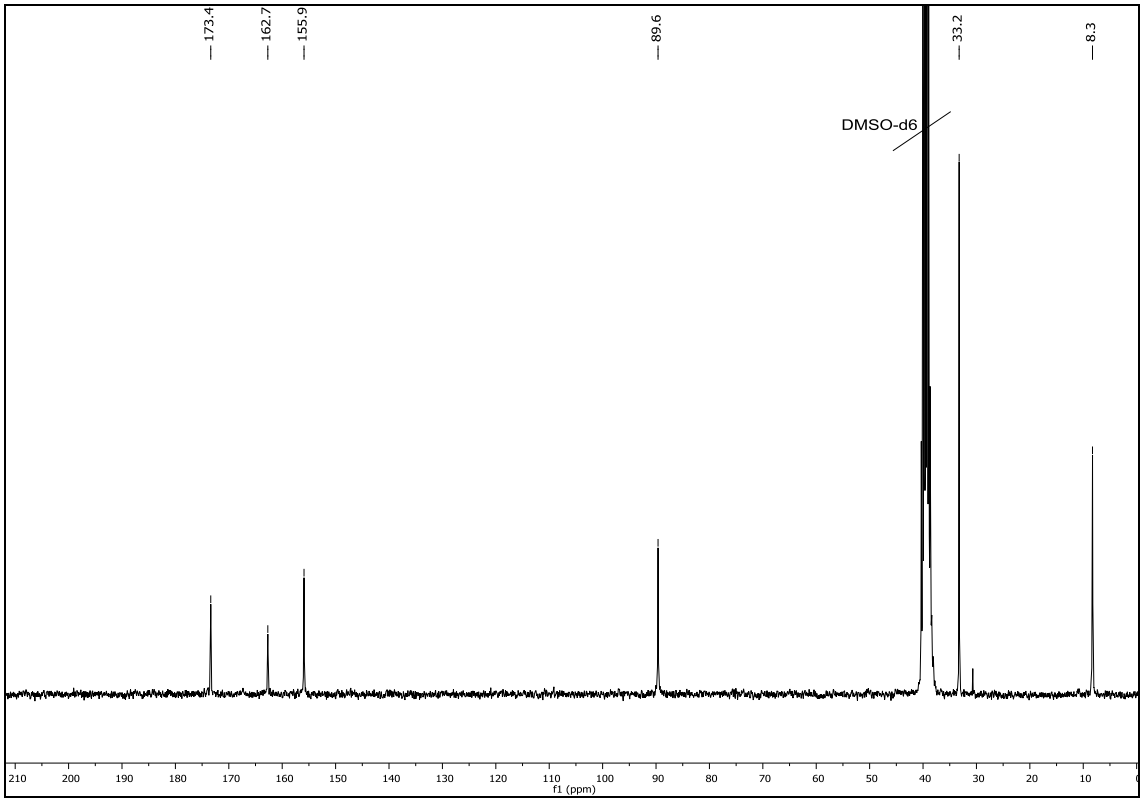

Me
O
N
O
N
O
Ph
2
(enolic form)
7.42
7.40
7.40
7.39
7.39
7.39
7.39
7.32
7.32
7.30
7.30
7.30
7.29
5.08
5.04
5.02
4.99
4.97
3.22
1.55
acetone-d
3.70
2.00
2.60
3.01
f1 (ppm)

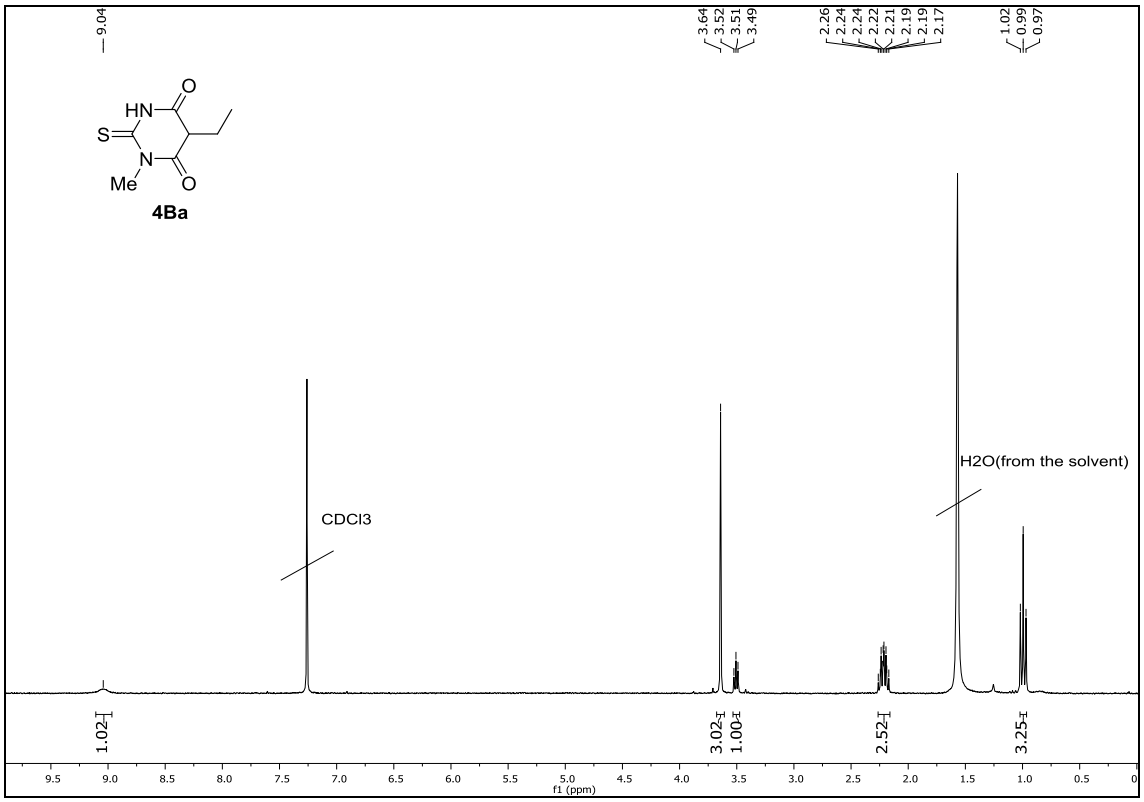

170.5
170.3
153.2
138.5
129.5
128.5
45.9
13.6
acetone-d
f1 (ppm)

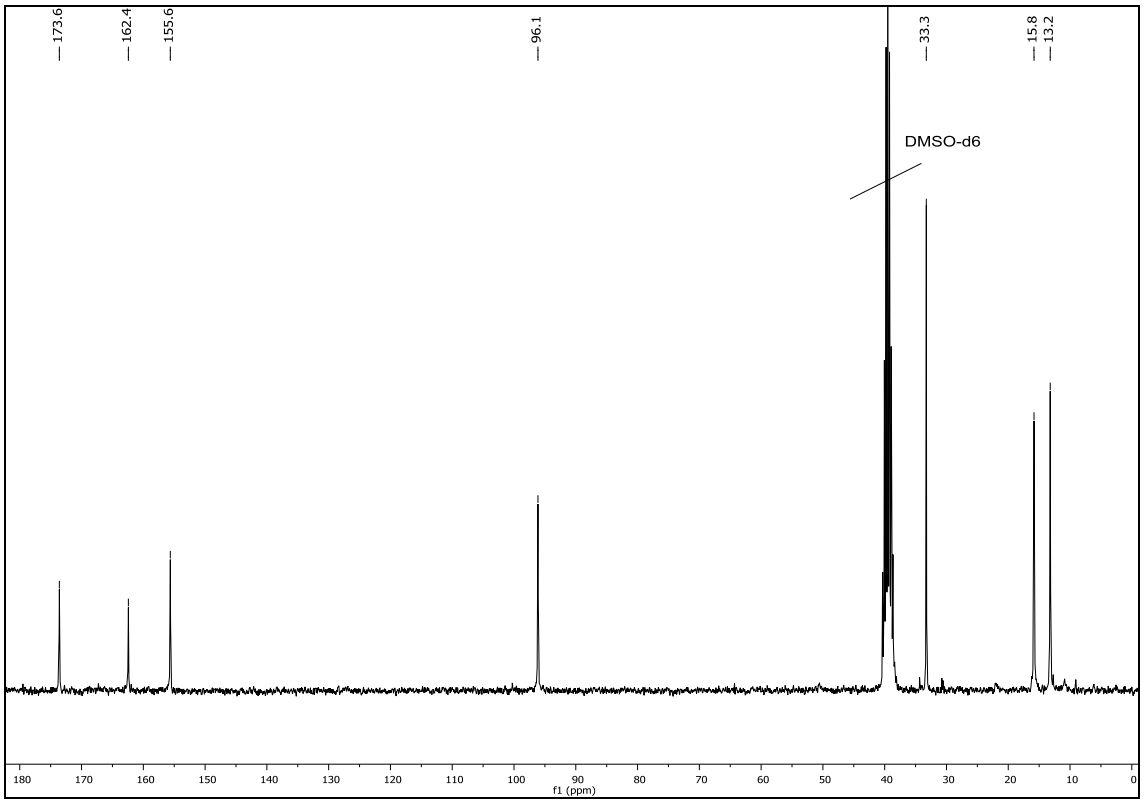

Me
O
N
S
N
O
Ph
3
(enolic form)
acetone-d
3.93
2.00
2.64
2.74
f1 (ppm)

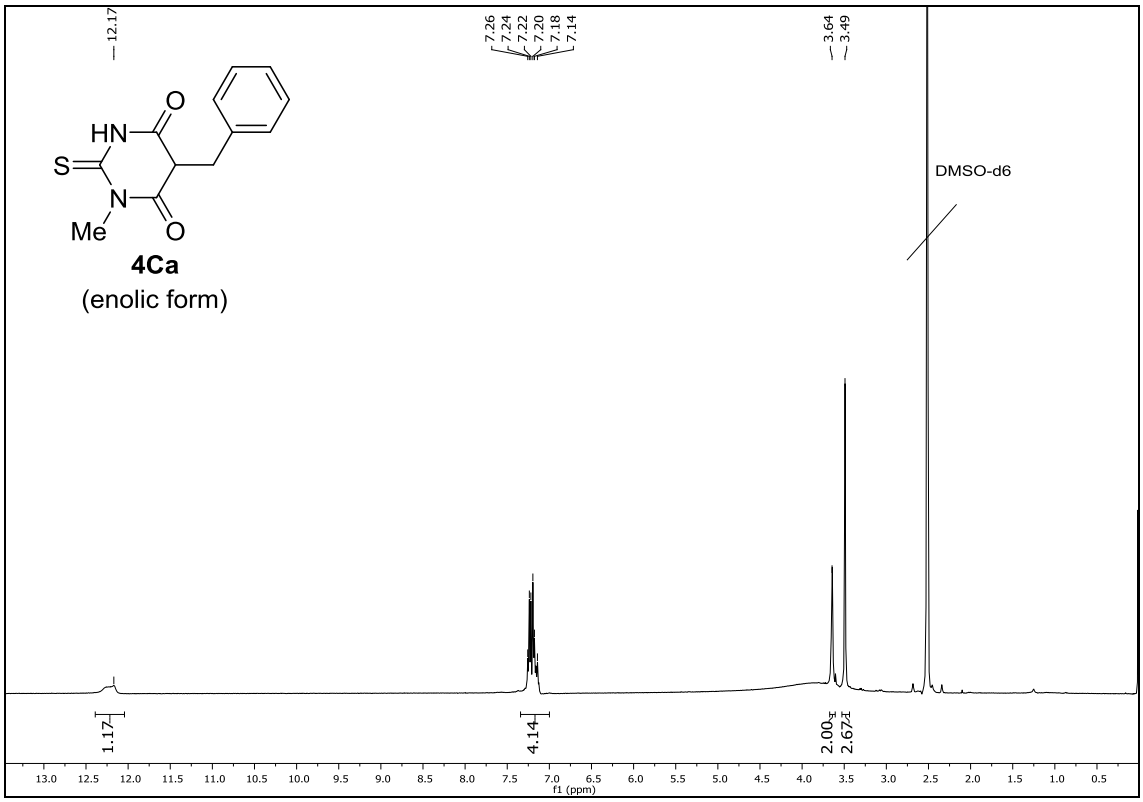

138.1
129.4
128.8
128.2
51.8
36.3
12.6
acetone-d
f1 (ppm)

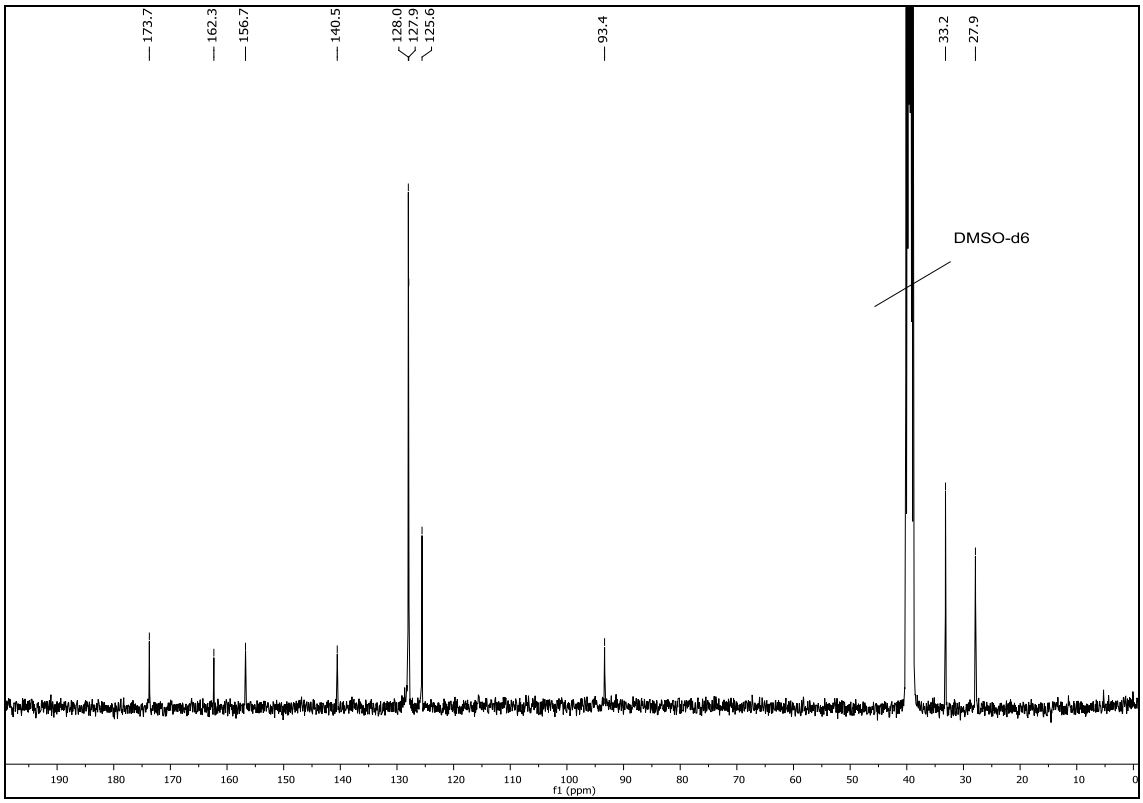

12.78
3.91
2.93
2.93
2.92
2.91
2.91
2.18
HN
O
S
N
Me
O
4Aa
DMSO-d6
1.17
2.94
0.83
3.00
f1 (ppm)

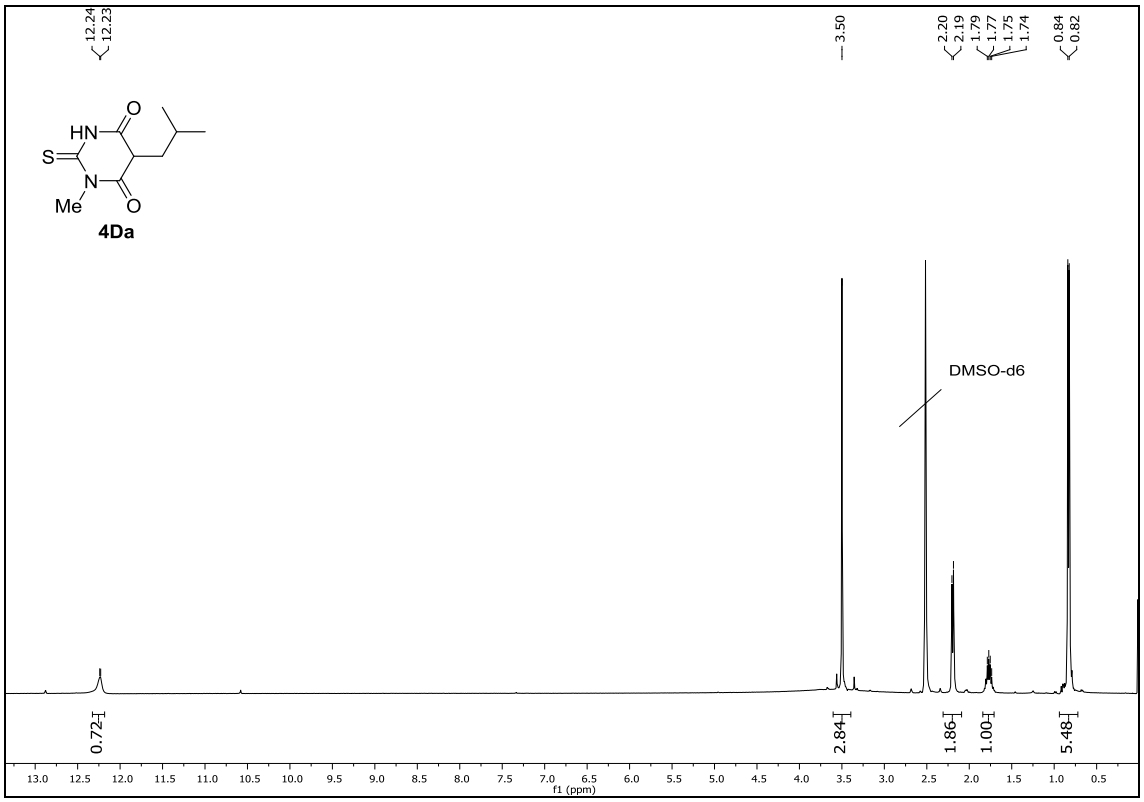

173.4
162.7
155.9
89.6
33.2
8.3
DMSO-d6
f1 (ppm)

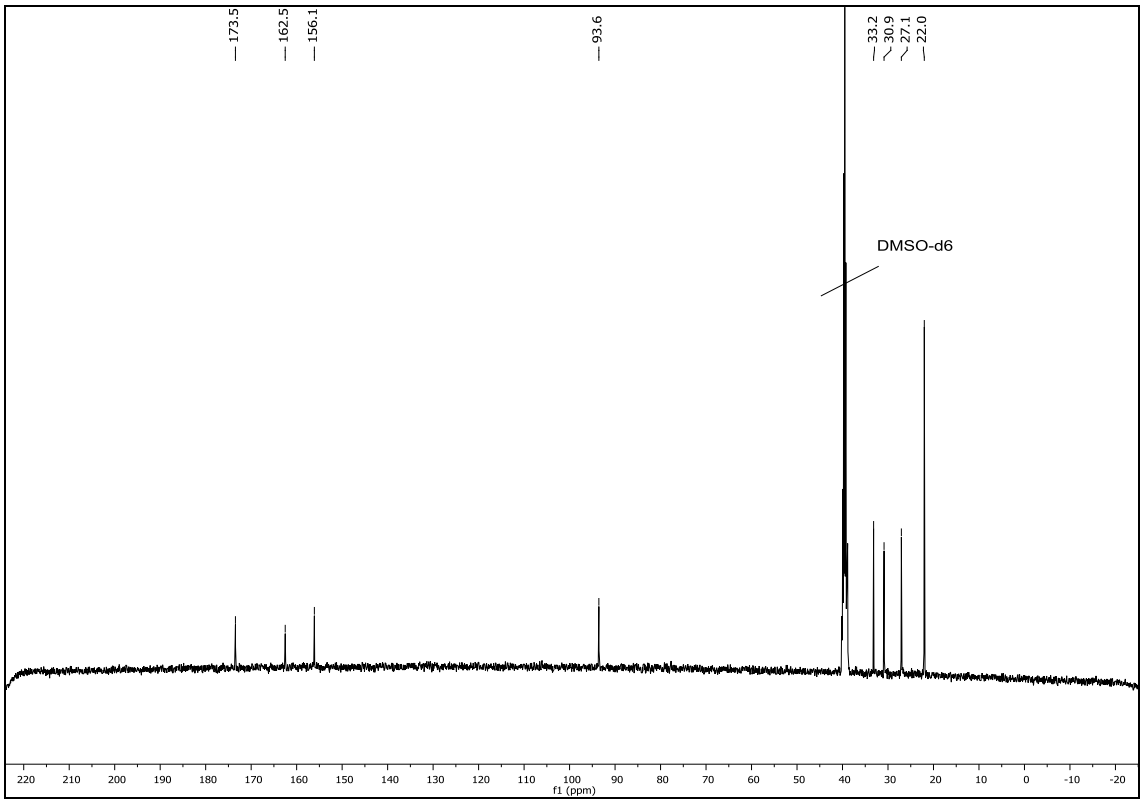

9.04
3.64
3.52
3.51
3.49
2.26
2.24
2.24
2.22
2.21
2.19
2.19
2.17
1.02
0.99
0.97
HN
O
S
N
Me
O
4Ba
CDCl3
H2O(from the solvent)
1.02
3.02
1.00
2.52
3.25
f1 (ppm)

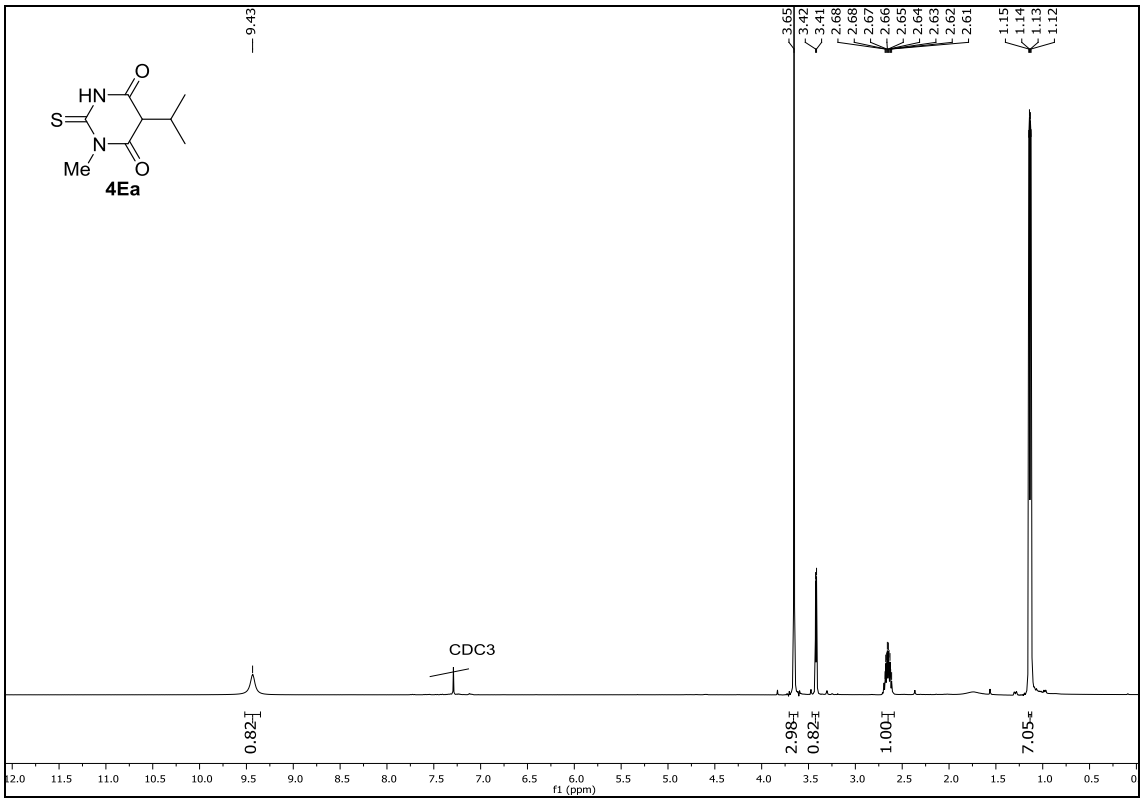

173.6
162.4
155.6
96.1
33.3
15.8
13.2
DMSO-d6
f1 (ppm)

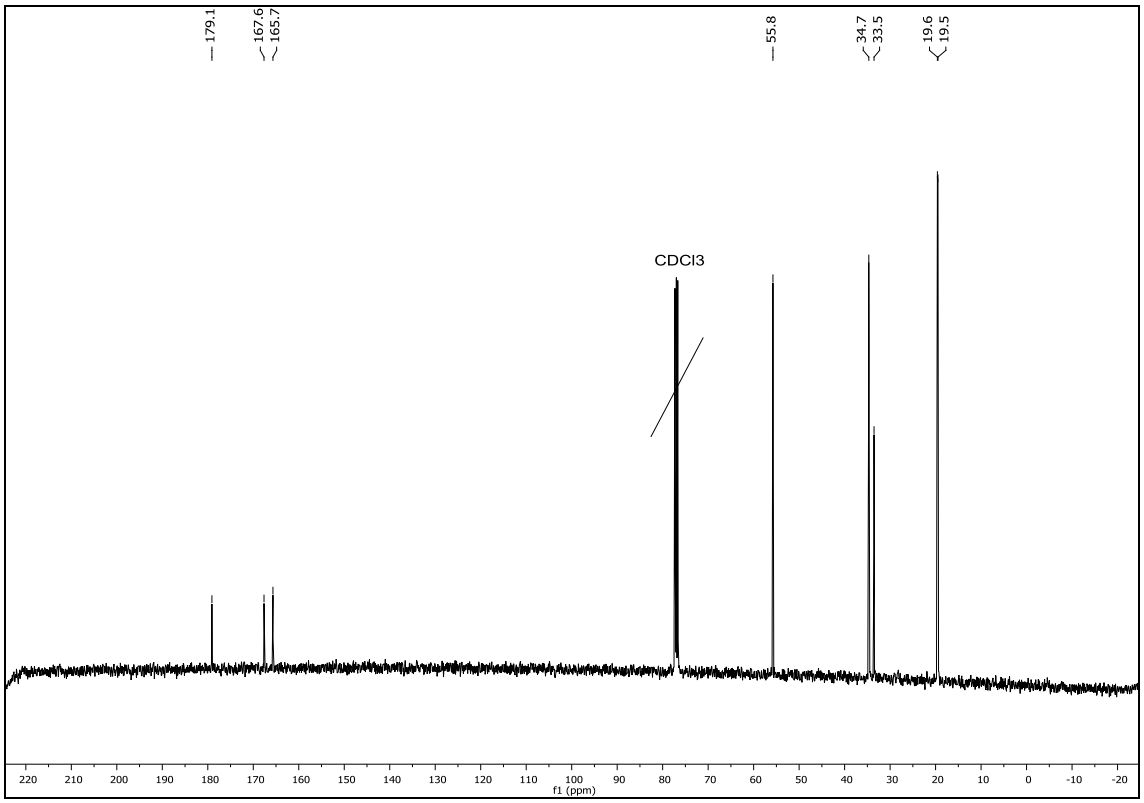

12.17
7.26
7.24
7.22
7.20
7.18
7.14
3.64
3.49
DMSO-d6
HN
O
S
N
Me
O
4Ca
(enolic form)
1.17
4.14
2.00
2.67
f1 (ppm)

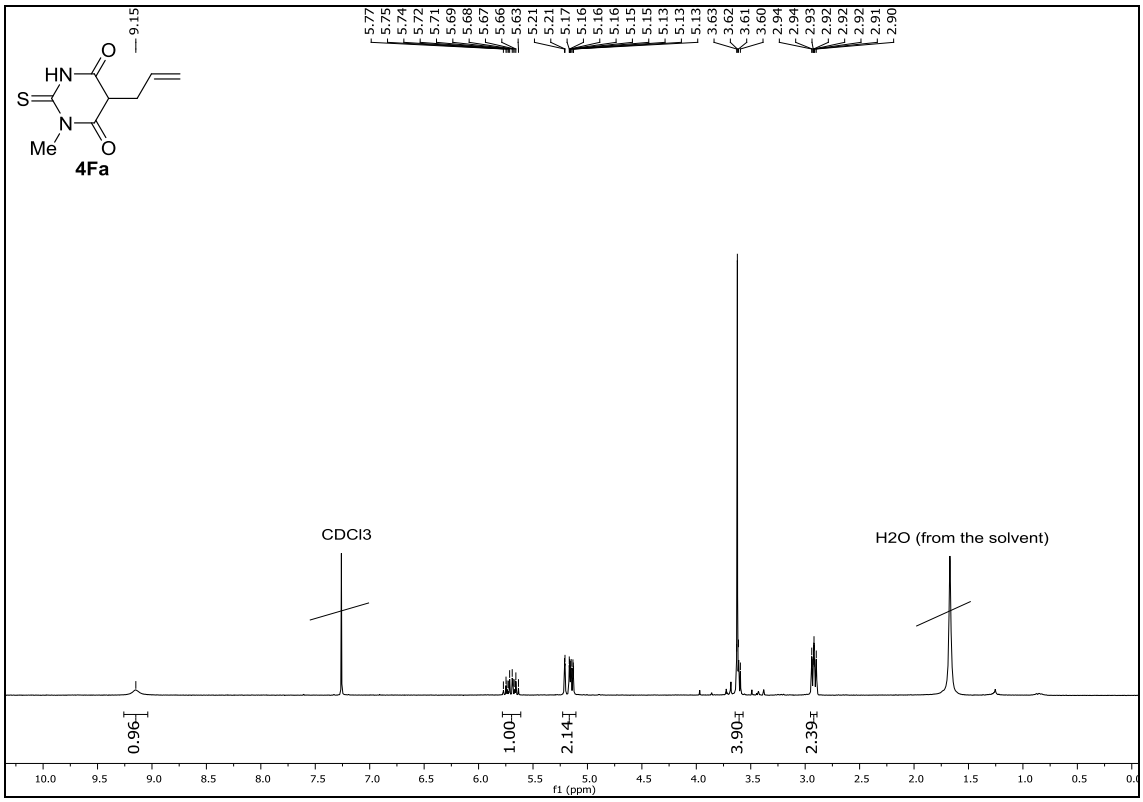

173.7
162.3
156.7
140.5
128.0
127.9
125.6
93.4
33.2
27.9
DMSO-d6
f1 (ppm)

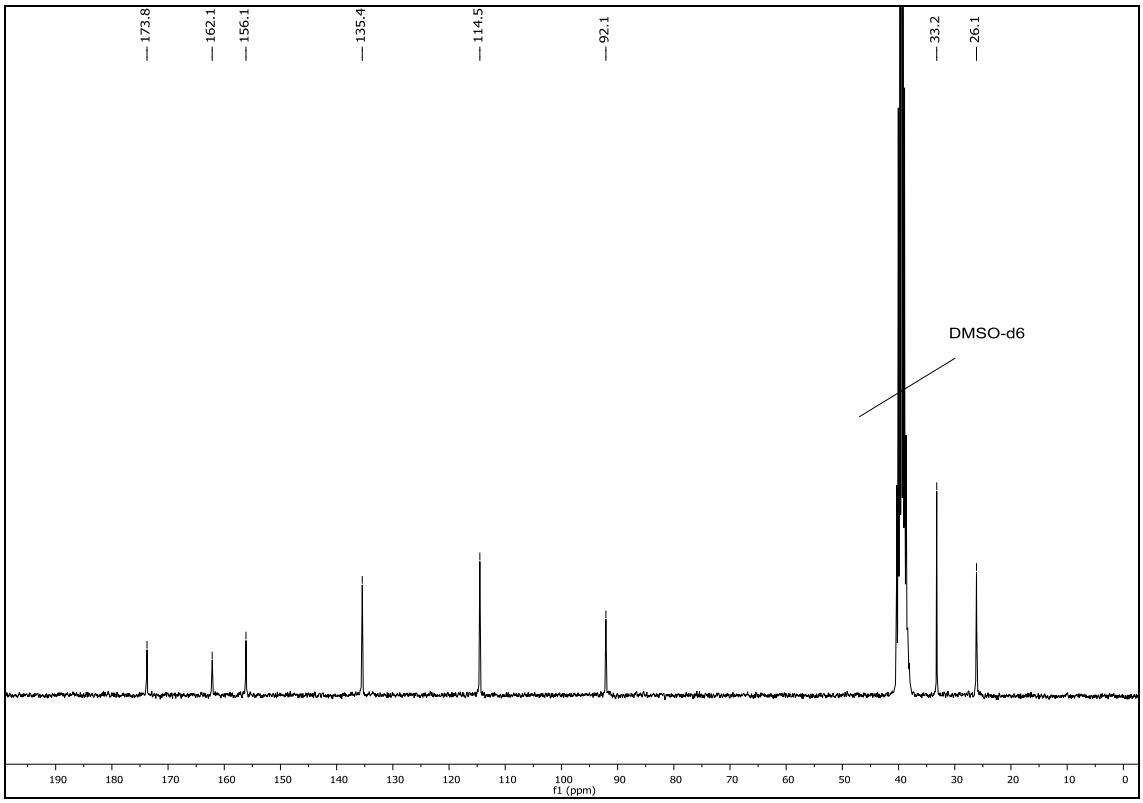

12.24
12.23
3.50
2.20
2.19
1.79
1.77
1.75
1.74
0.84
0.82
HN
O
S
N
Me
O
4Da
DMSO-d6
0.72
2.84
1.86
1.00
5.48
f1 (ppm)

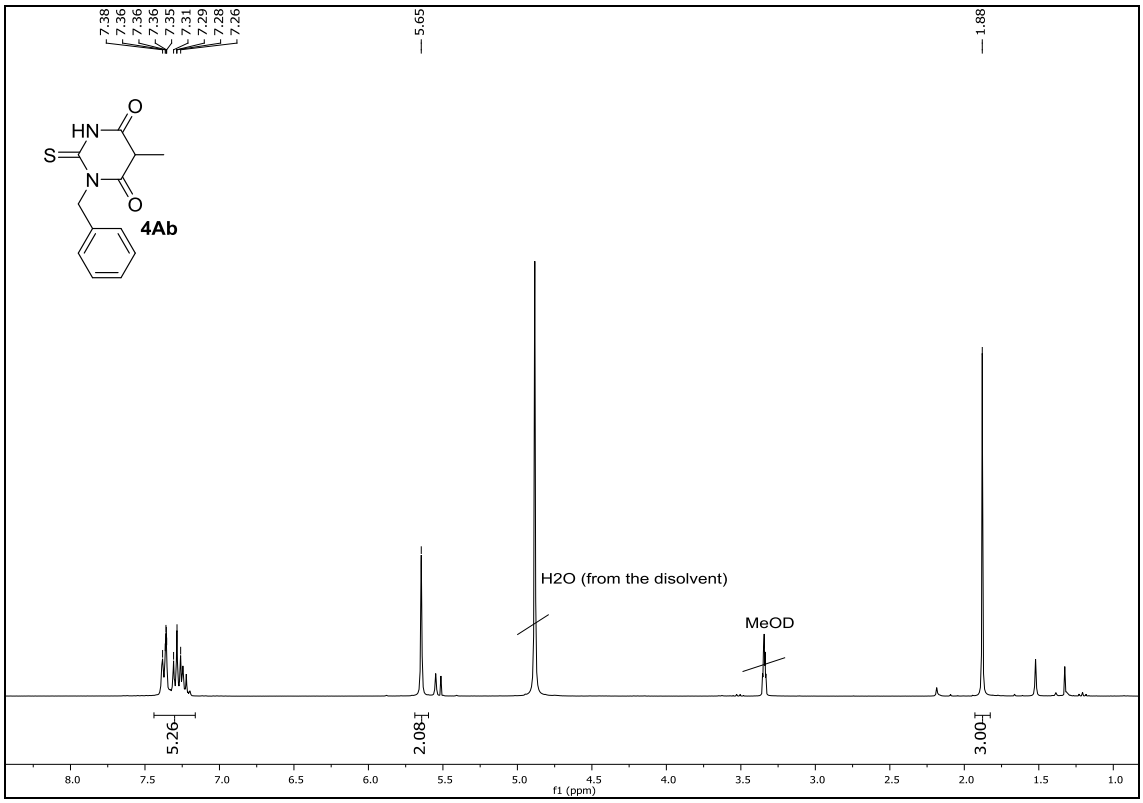

173.5
162.5
156.1
93.6
33.2
30.9
27.1
22.0
DMSO-d6
f1 (ppm)

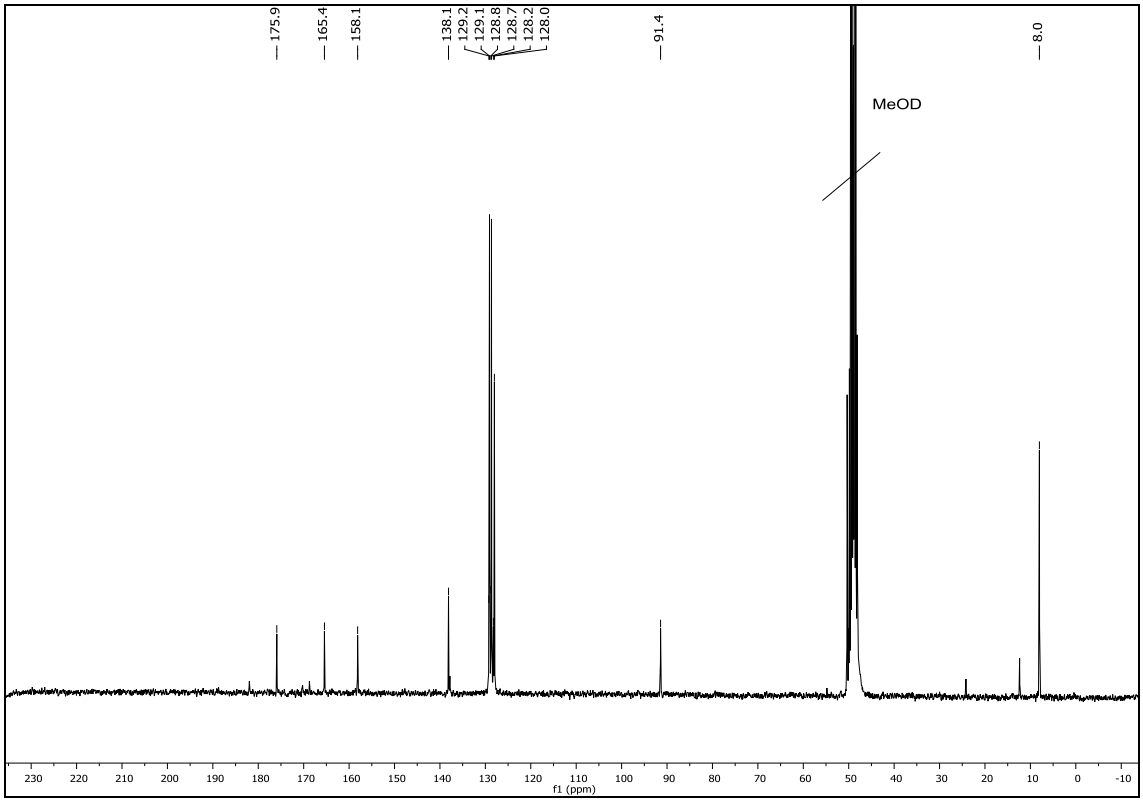

9.43
3.65
3.42
3.41
2.68
2.67
2.66
2.65
2.64
2.63
2.62
2.61
1.15
1.14
1.13
1.12
HN
O
S
N
Me
O
4Ea
CDC3
0.82
2.98
0.82
1.00
7.05
f1 (ppm)

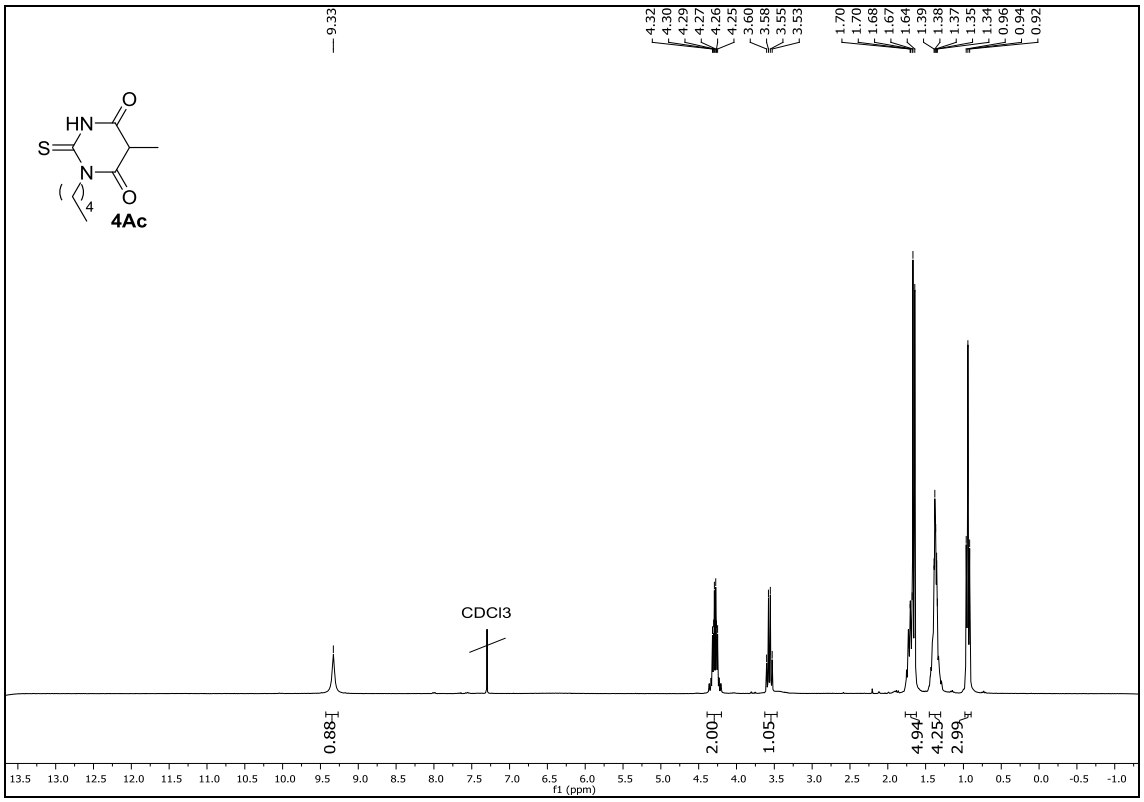

179.1
167.6
165.7
55.8
34.7
33.5
19.6
19.5
CDCl3
f1 (ppm)

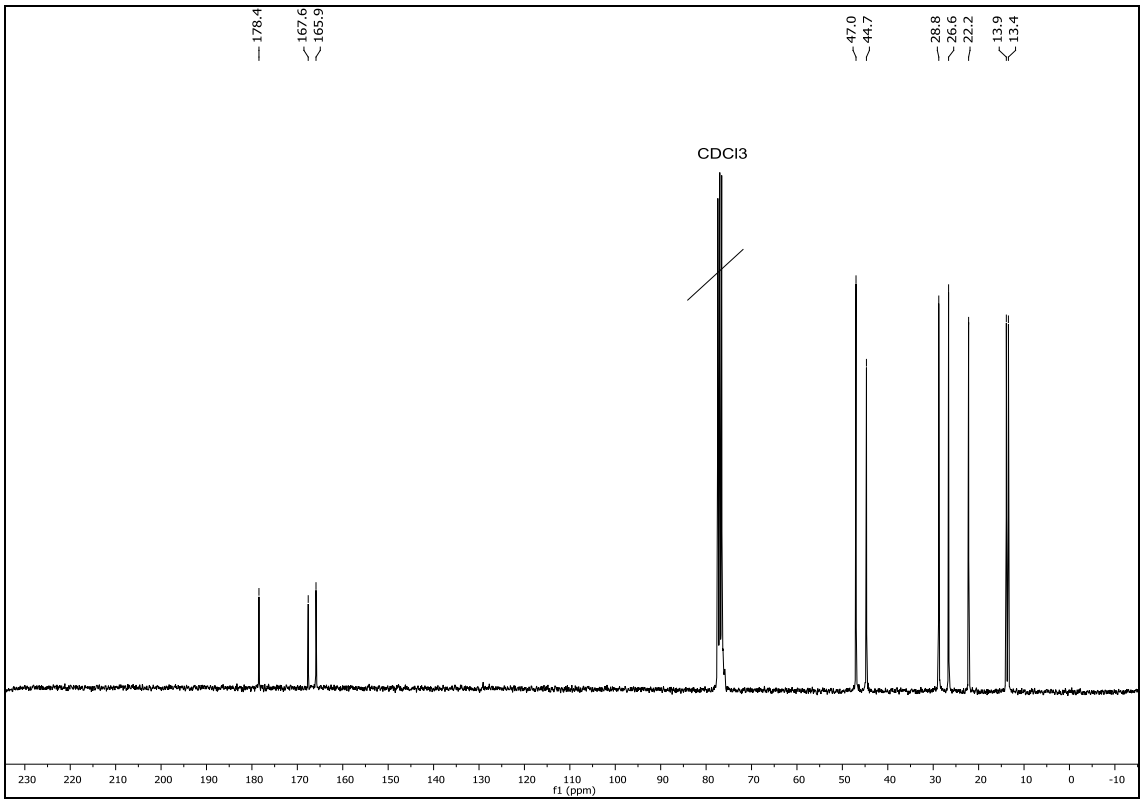

9.15
5.77
5.75
5.74
5.72
5.71
5.69
5.68
5.67
5.66
5.63
5.21
5.21
5.17
5.16
5.16
5.15
5.15
5.13
5.13
3.63
3.62
3.61
3.60
2.94
2.94
2.93
2.92
2.92
2.92
2.91
2.90
HN
O
S
N
Me
O
4Fa
CDCl3
H2O (from the solvent)
0.96
1.00
2.14
3.90
2.39
f1 (ppm)

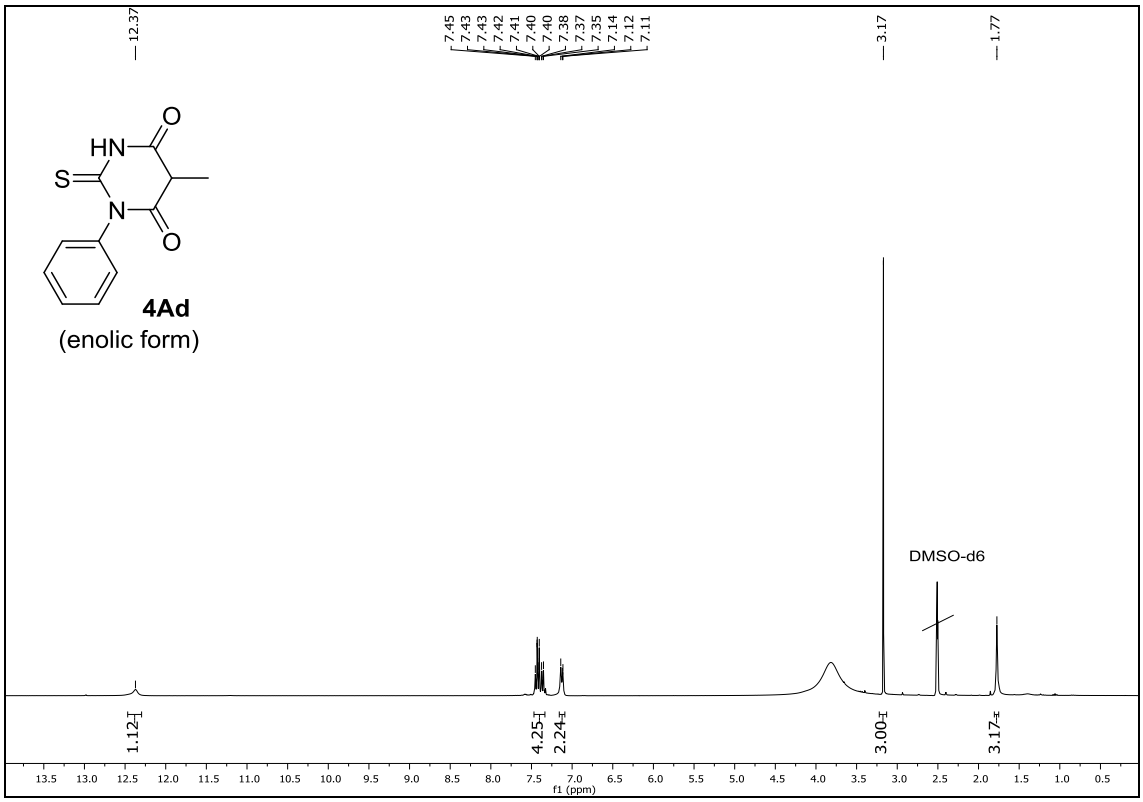

173.8
162.1
156.1
135.4
114.5
92.1
33.2
26.1
DMSO-d6
f1 (ppm)

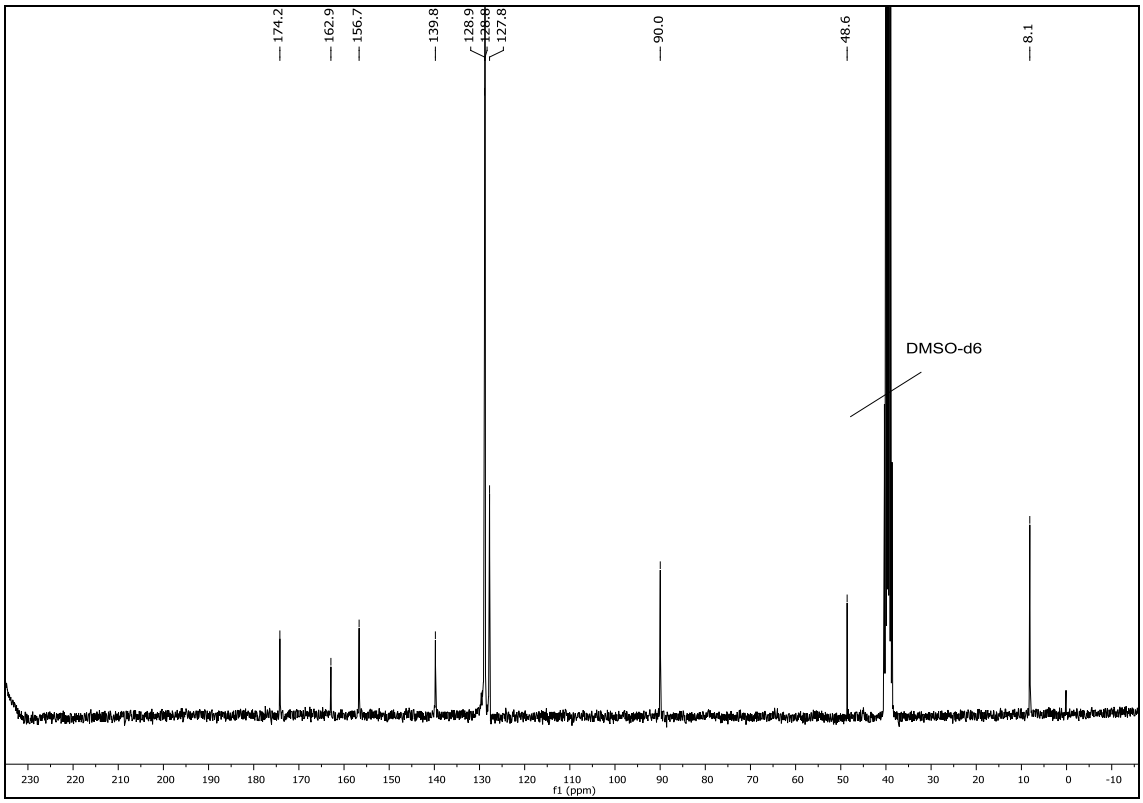

7.38
7.36
7.36
7.36
7.35
7.31
7.29
7.28
7.26
5.65
1.88
HN
O
S
N
O
O
4Ab
H2O (from the disolvent)
MeOD
5.26
2.08
3.00
f1 (ppm)

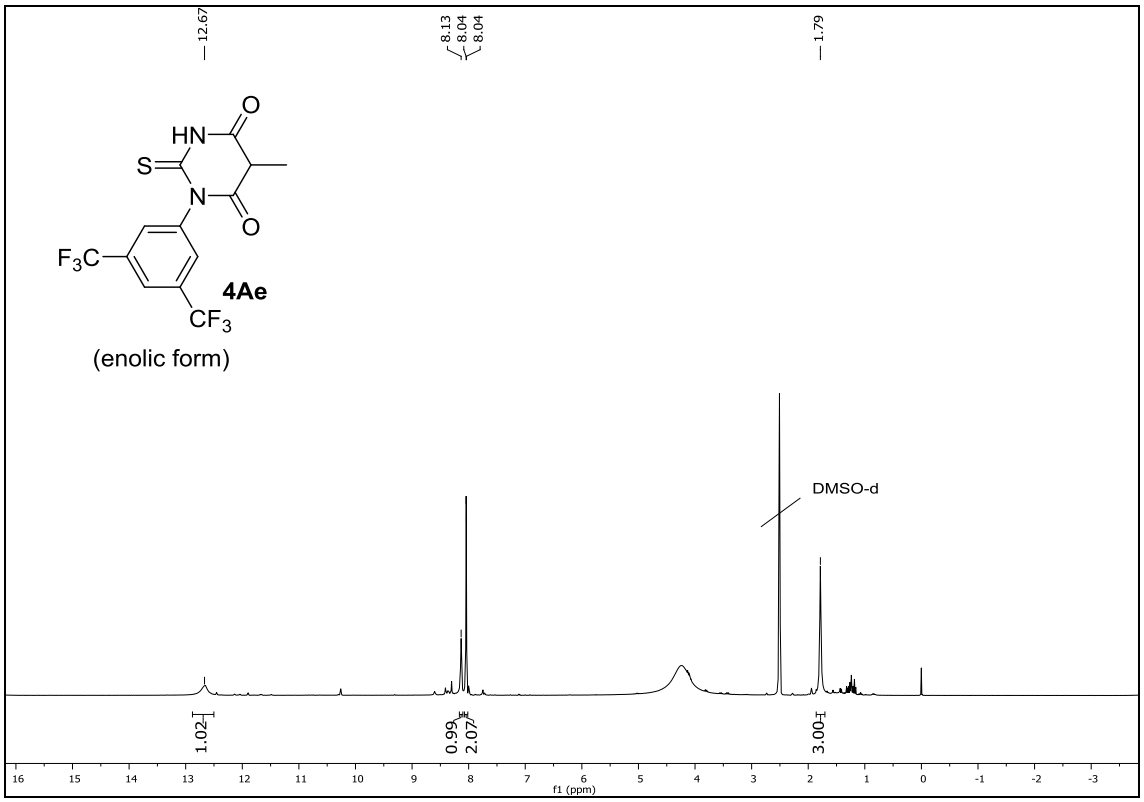

175.9
165.4
158.1
138.1
129.2
129.1
128.8
128.7
128.2
128.0
91.4
8.0
MeOD
f1 (ppm)

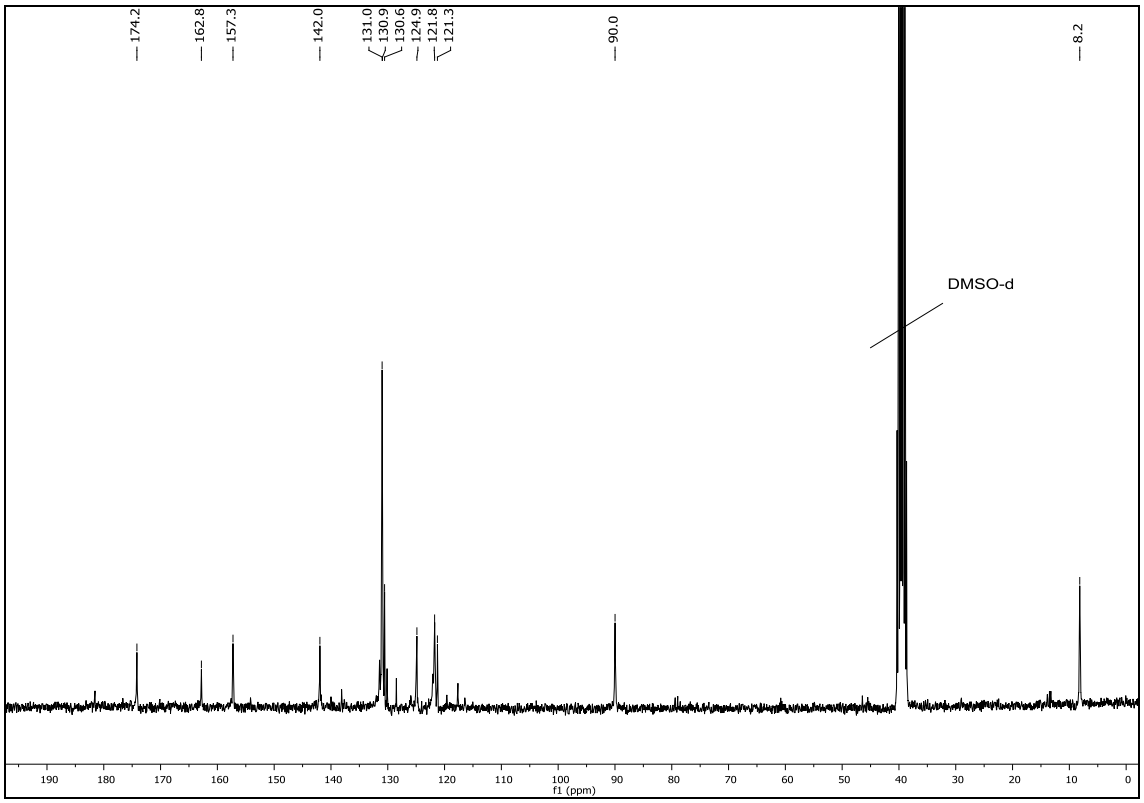

9.33
4.32
4.30
4.29
4.27
4.26
4.25
3.60
3.58
3.55
3.53
1.70
1.70
1.68
1.67
1.64
1.39
1.38
1.37
1.35
1.34
0.96
0.94
0.92
HN
O
S
N
O
4
4Ac
CDCl3
0.88
2.00
1.05
4.94
4.25
2.99
f1 (ppm)

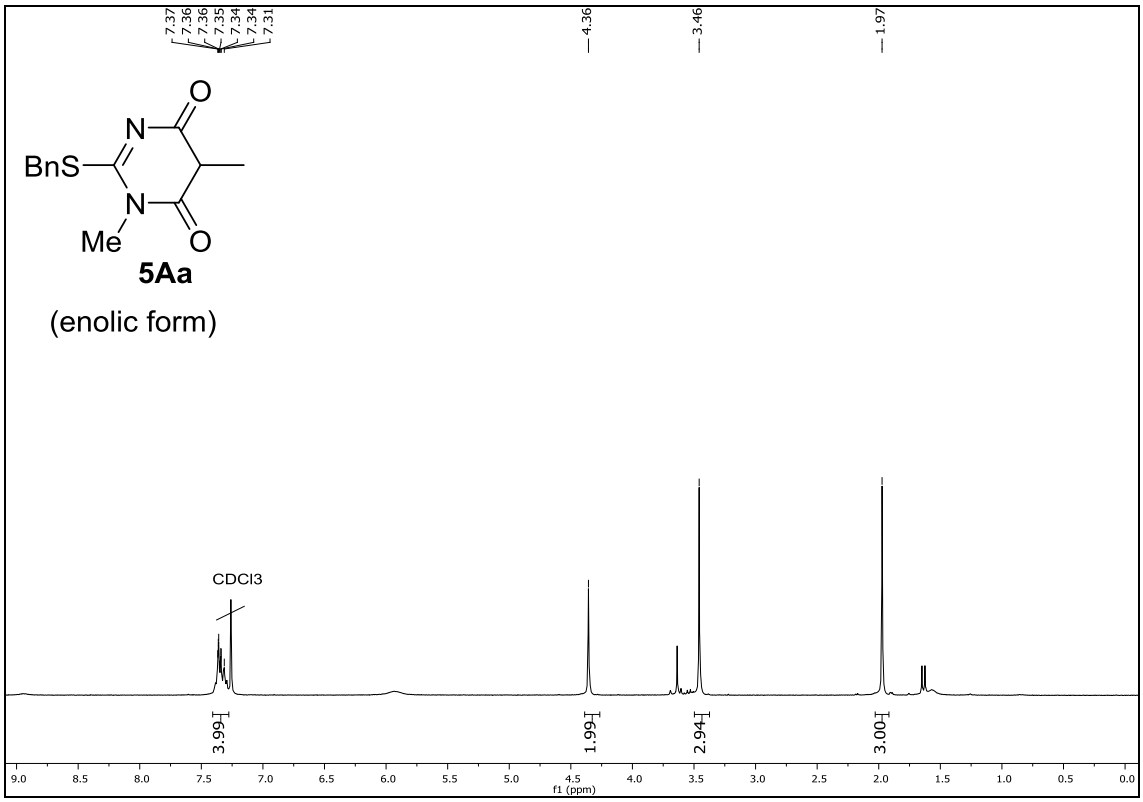

178.4
167.6
165.9
47.0
44.7
28.8
26.6
22.2
13.9
13.4
CDCl3
f1 (ppm)

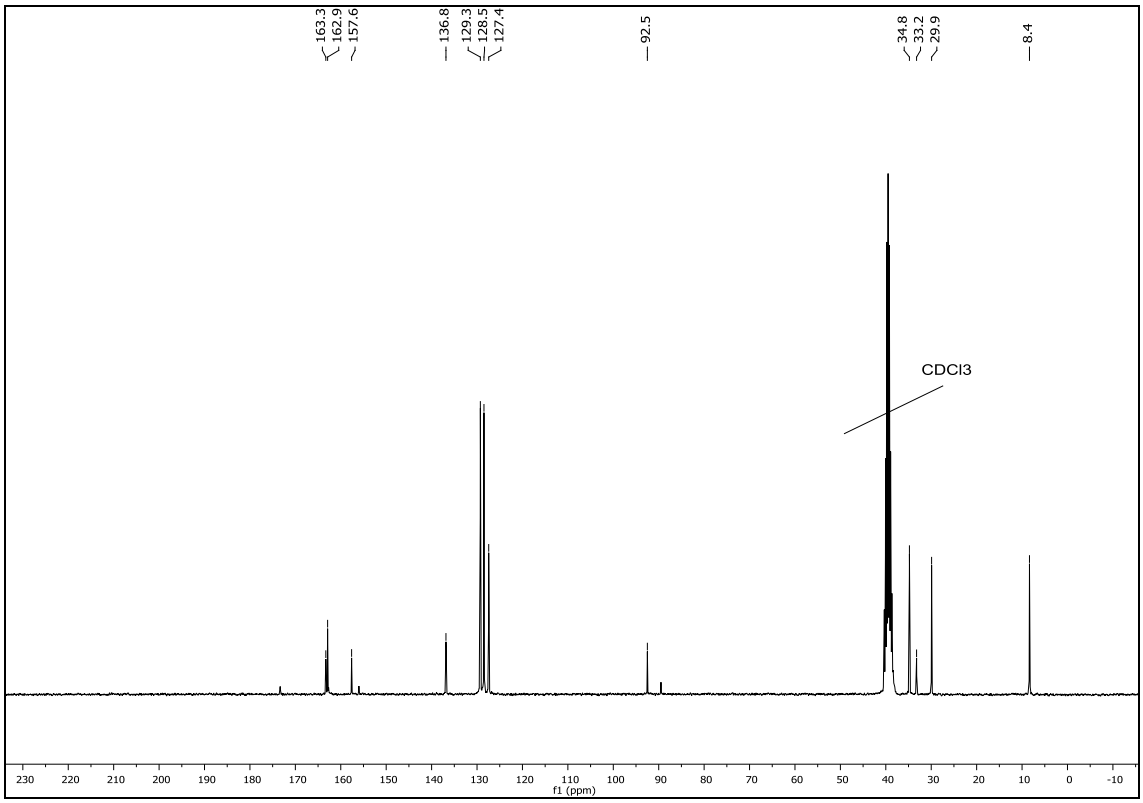

12.37
7.45
7.43
7.43
7.42
7.41
7.40
7.40
7.38
7.37
7.35
7.14
7.12
7.11
3.17
1.77
HN
S
N
O
O
O
4Ad
(enolic form)
DMSO-d6
1.12
4.25
2.24
3.00
3.17
f1 (ppm)

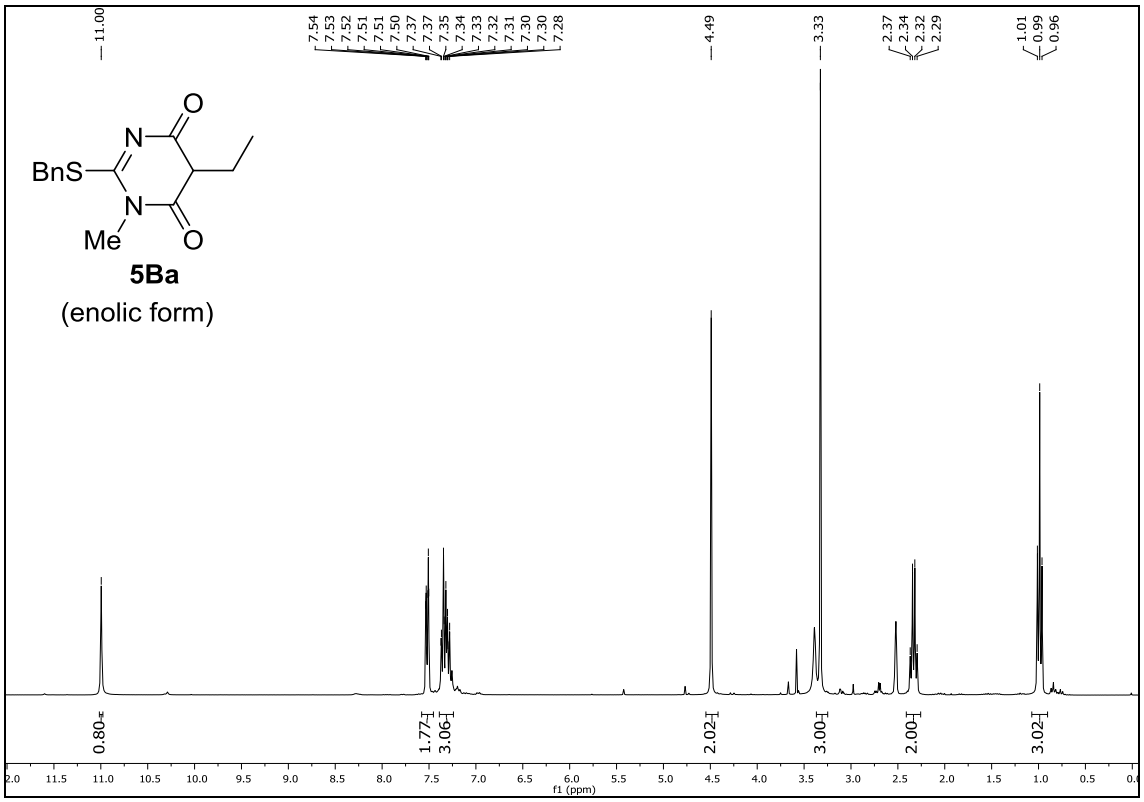

174.2
162.9
156.7
139.8
128.9
128.6
127.8
90.0
48.6
8.1
DMSO-d6
f1 (ppm)

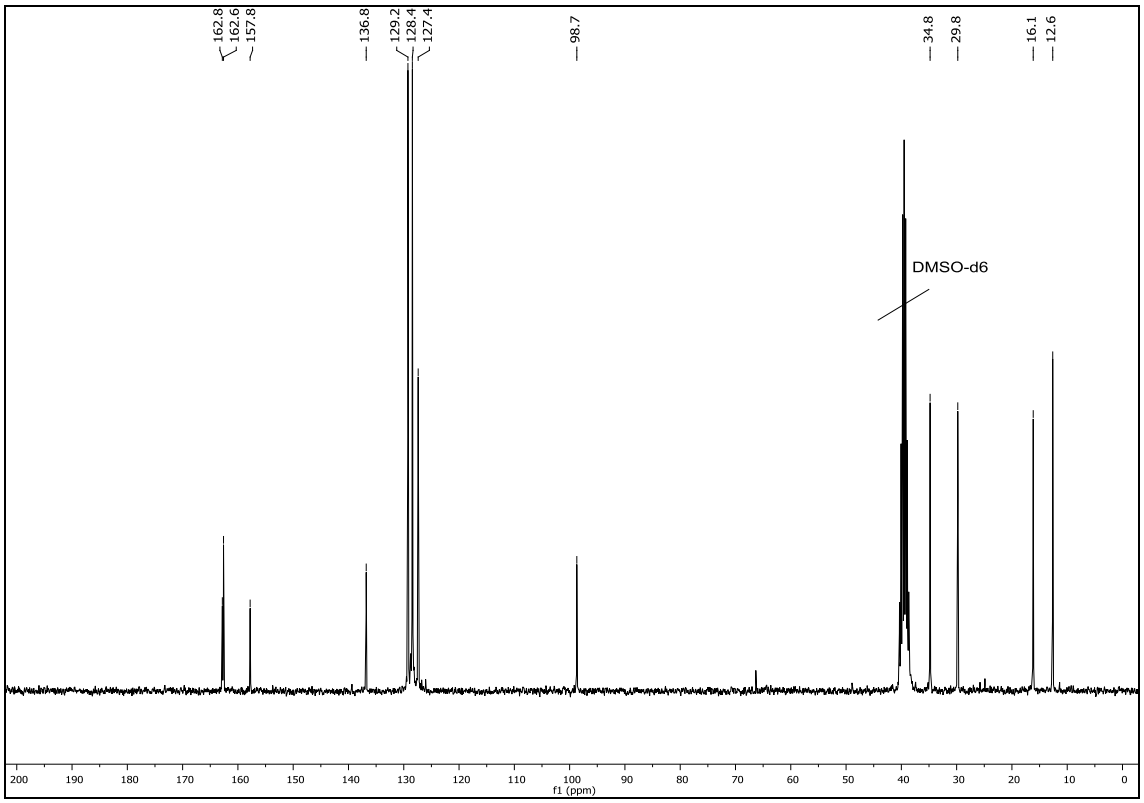

12.67
8.13
8.04
8.04
1.79
HN
O
S
N
O
F3C
CF3
4Ae
(enolic form)
DMSO-d
1.02
0.99
2.07
3.00
f1 (ppm)

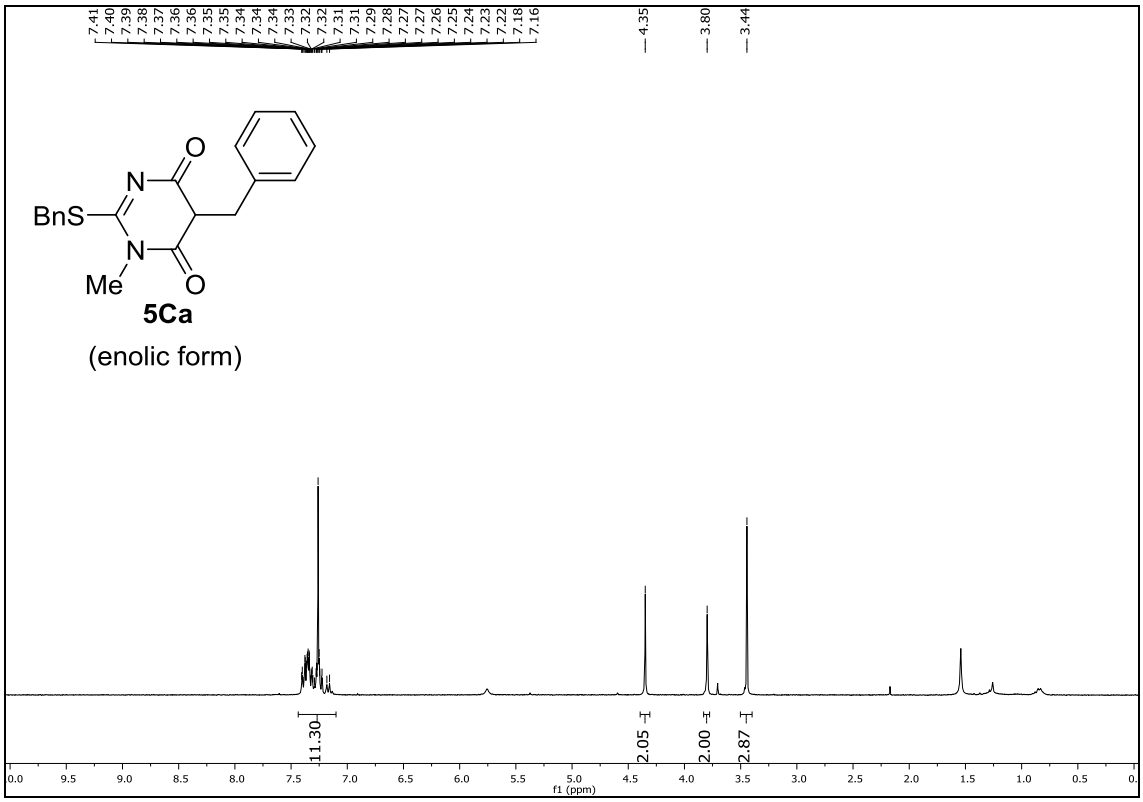

174.2
162.8
157.3
142.0
131.0
130.9
130.6
124.9
121.8
121.3
90.0
8.2
DMSO-d
f1 (ppm)

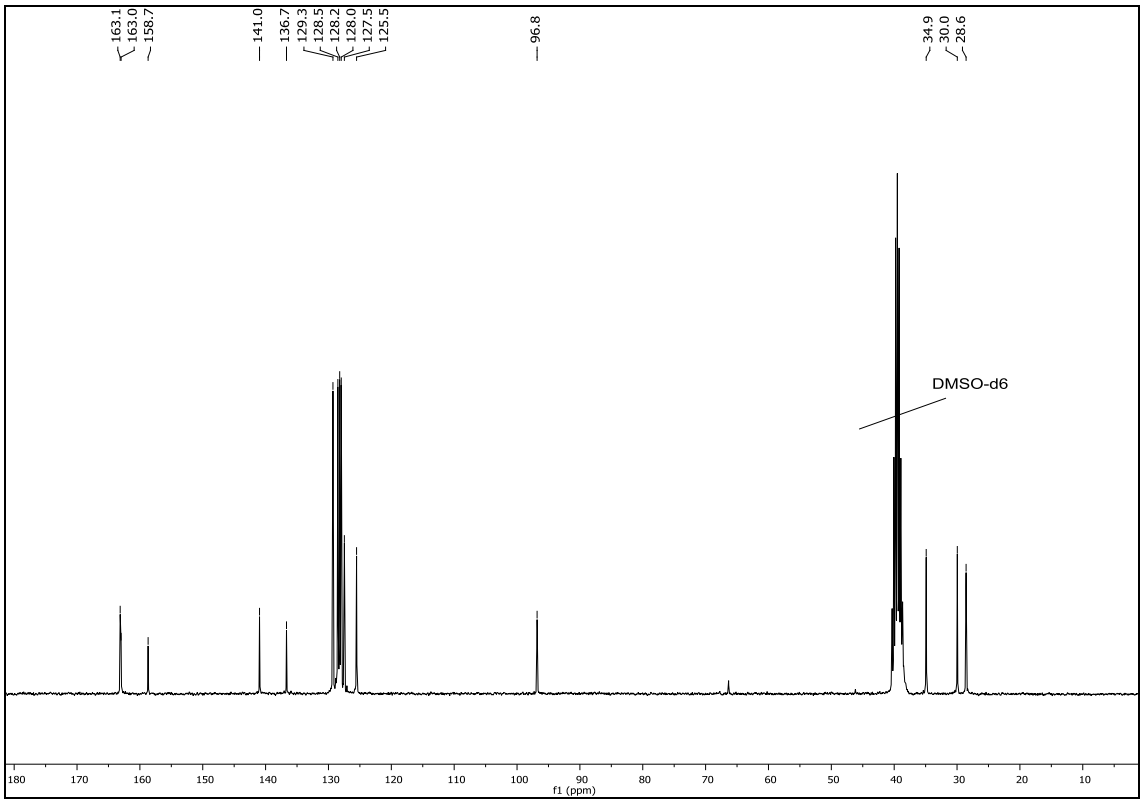

7.37
7.36
7.36
7.35
7.34
7.34
7.31
4.36
3.46
1.97
O
N
BnS
N
Me
O
5Aa
(enolic form)
CDCl3
3.99
1.99
2.94
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

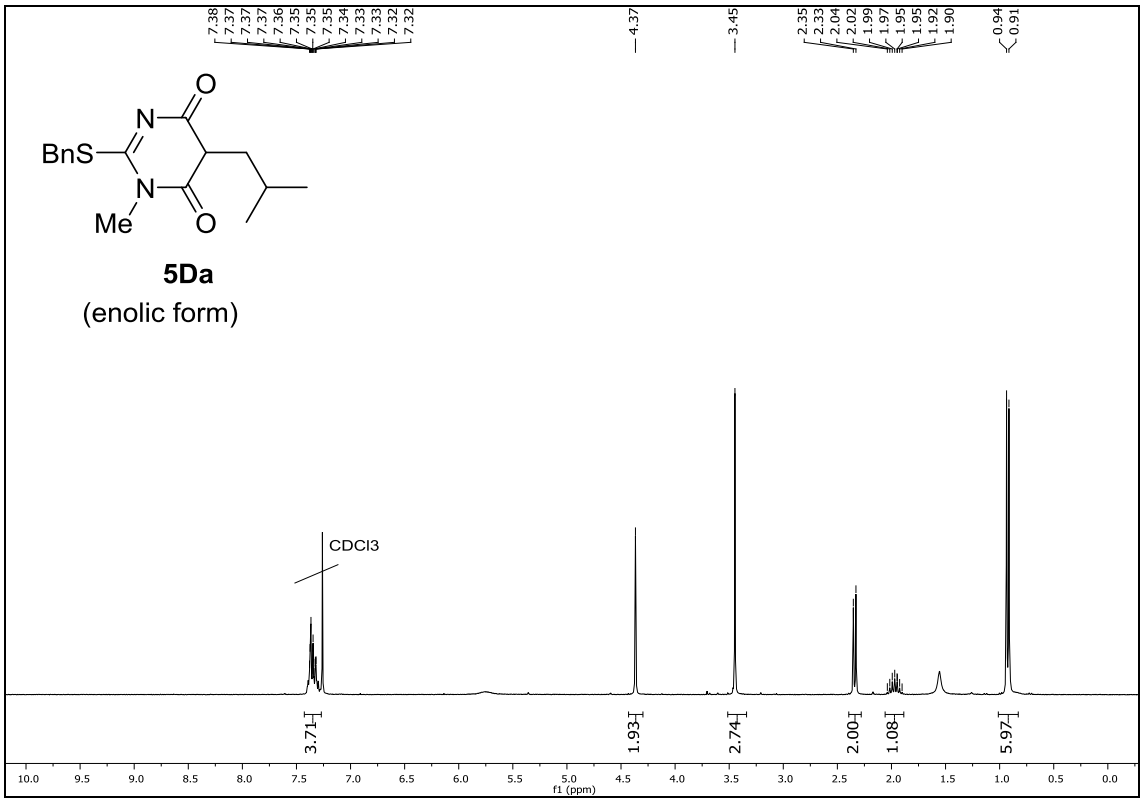

163.3
162.9
157.6
136.8
129.3
128.5
127.4
92.5
34.8
33.2
29.9
8.4
CDCl3
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

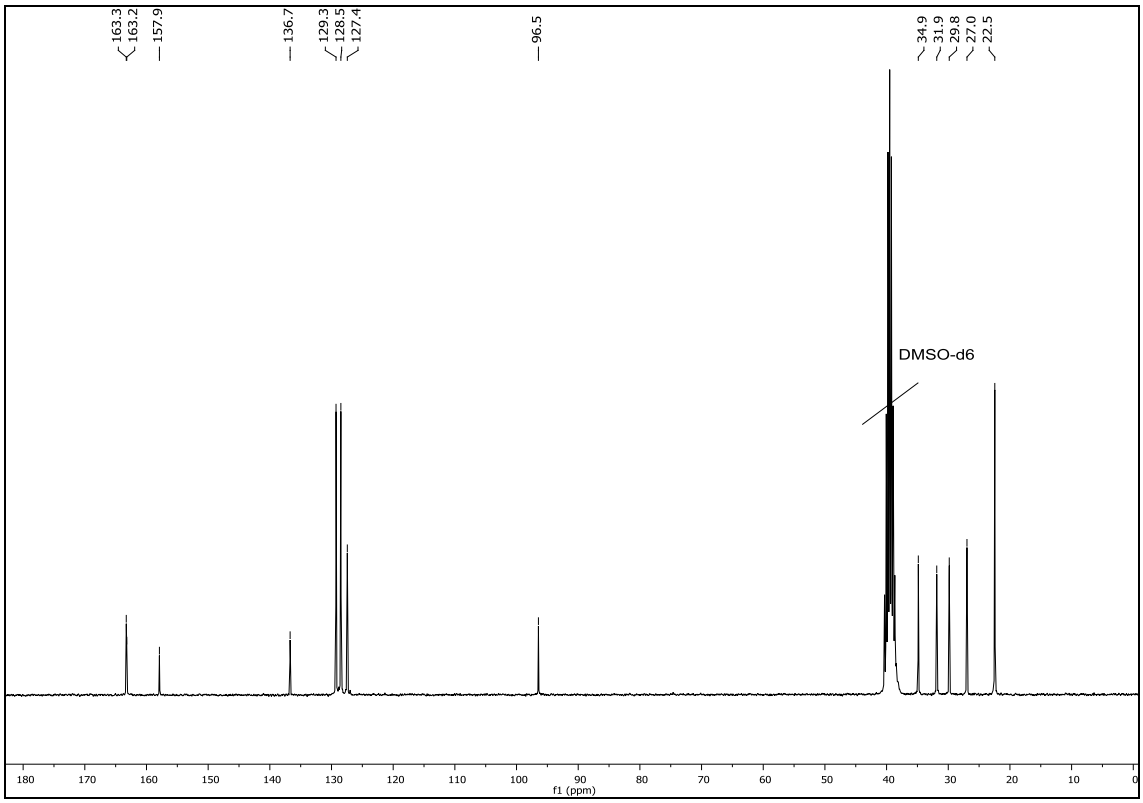

11.00
7.54
7.53
7.52
7.51
7.51
7.50
7.37
7.37
7.35
7.34
7.33
7.32
7.31
7.30
7.30
7.28
4.49
3.33
2.37
2.34
2.32
2.29
1.01
0.99
0.96
O
N
BnS
N
Me
O
5Ba
(enolic form)
0.80
1.77
3.06
2.02
3.00
2.00
3.02
f1 (ppm)

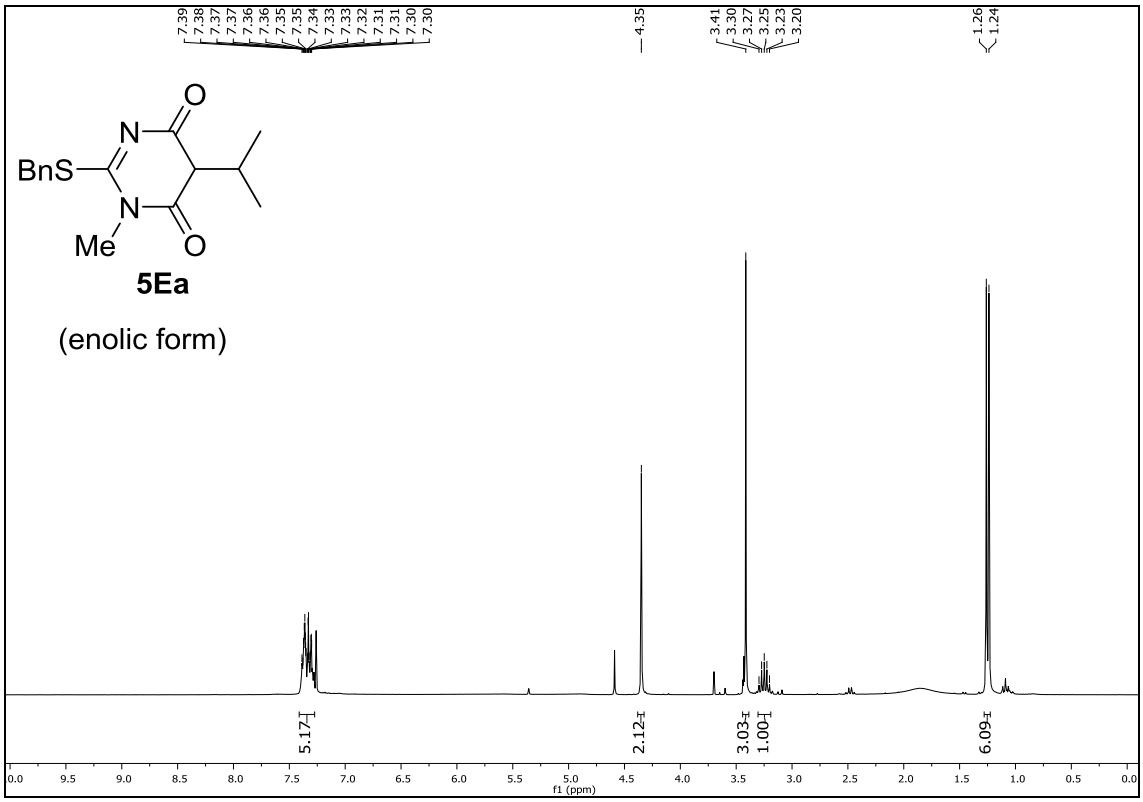

162.8
162.6
157.8
136.8
129.2
128.4
127.4
98.7
34.8
29.8
16.1
12.6
DMSO-d6
f1 (ppm)

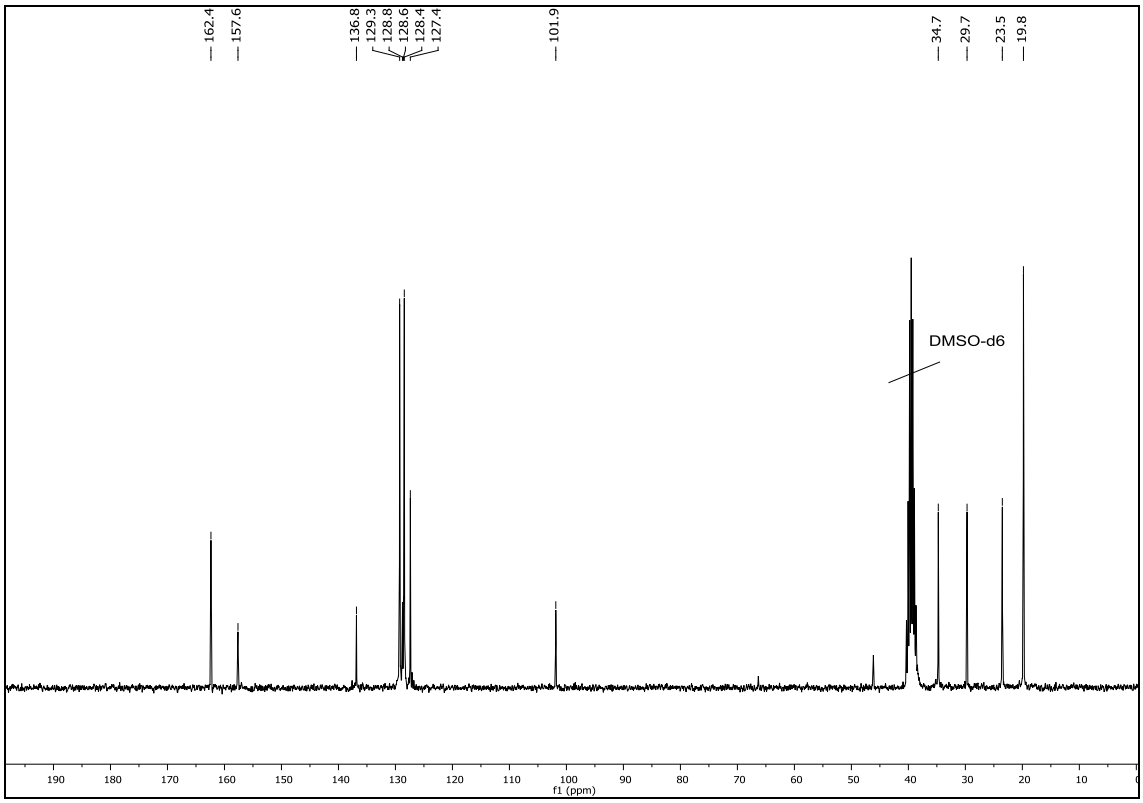

7.41
7.40
7.39
7.38
7.37
7.36
7.36
7.35
7.35
7.34
7.34
7.34
7.33
7.32
7.32
7.31
7.31
7.29
7.28
7.27
7.27
7.26
7.25
7.24
7.23
7.22
7.18
7.16
4.35
3.80
3.44
O
N
BnS
N
Me
O
O
5Ca
(enolic form)
11.30
2.05
2.00
2.87
f1 (ppm)

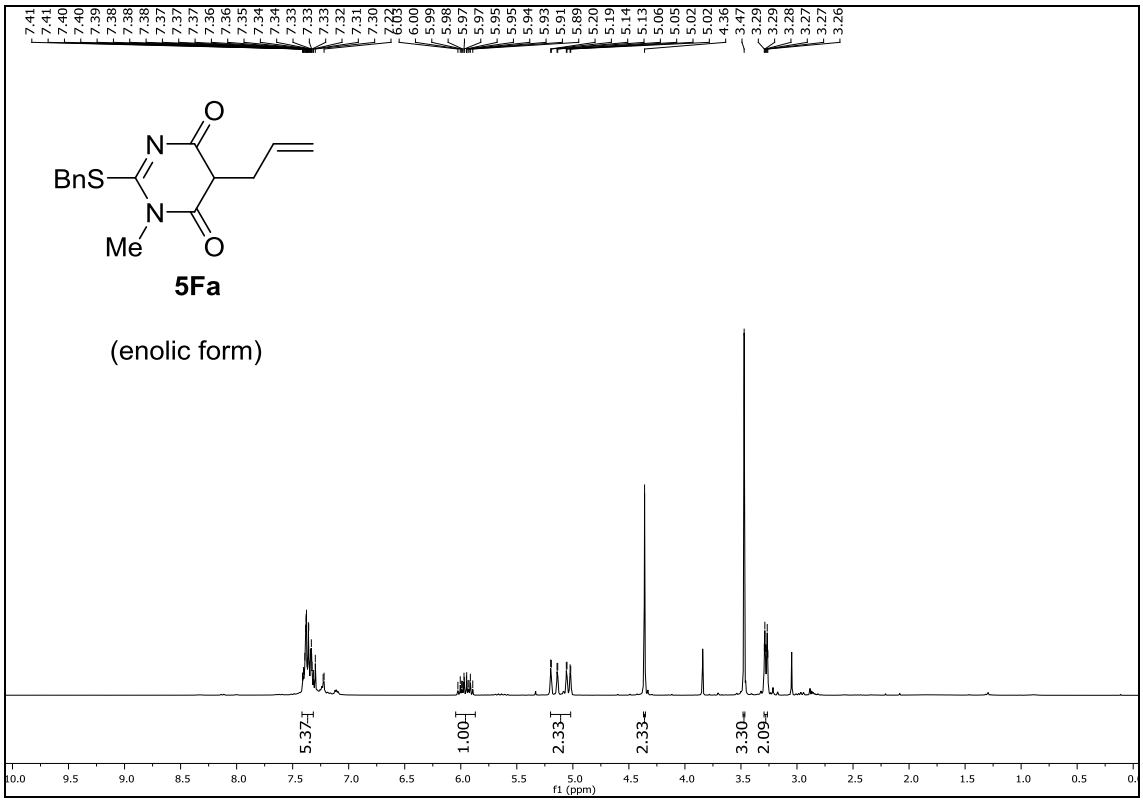

163.1
163.0
158.7
141.0
136.7
129.3
128.5
128.2
128.0
127.5
125.5
96.8
34.9
30.0
28.6
DMSO-d6
f1 (ppm)

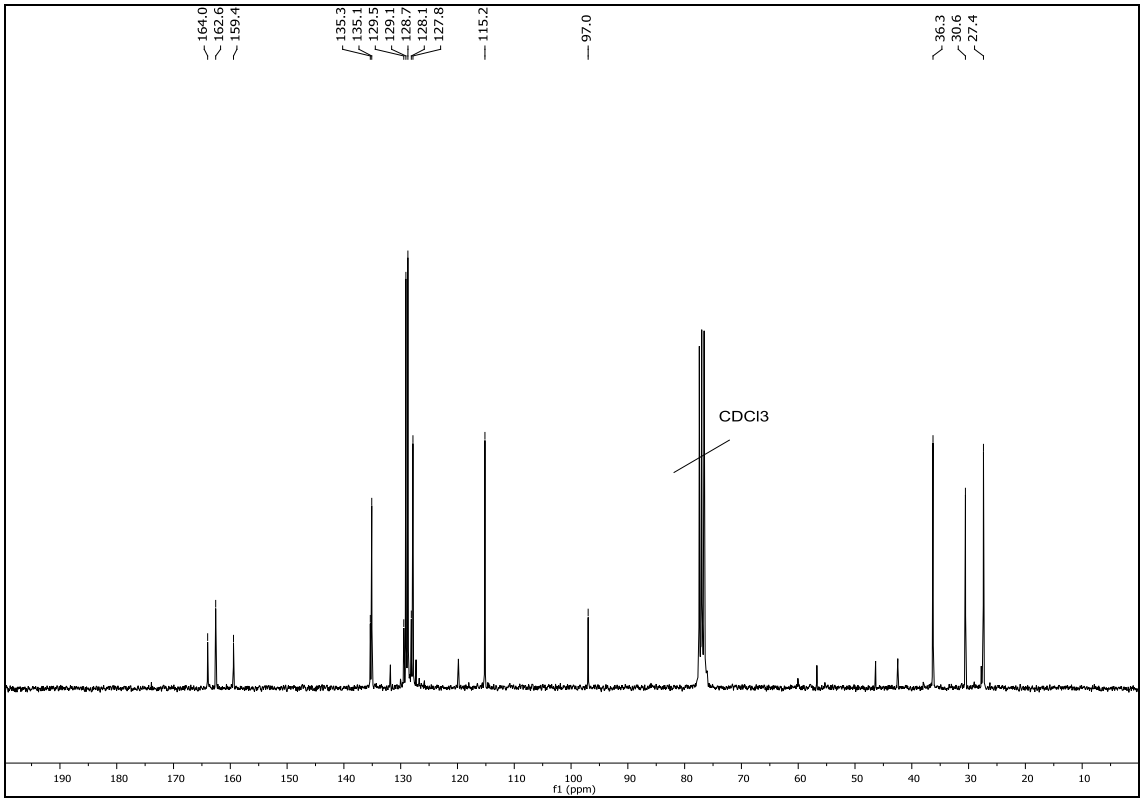

7.38
7.37
7.37
7.37
7.36
7.35
7.35
7.35
7.34
7.33
7.33
7.32
7.32
4.37
3.45
2.35
2.33
2.04
2.02
1.99
1.97
1.95
1.95
1.92
1.90
0.94
0.91
O
N
BnS
N
Me
O
5Da
(enolic form)
CDCl3
3.71
1.93
2.74
2.00
1.08
5.97
f1 (ppm)

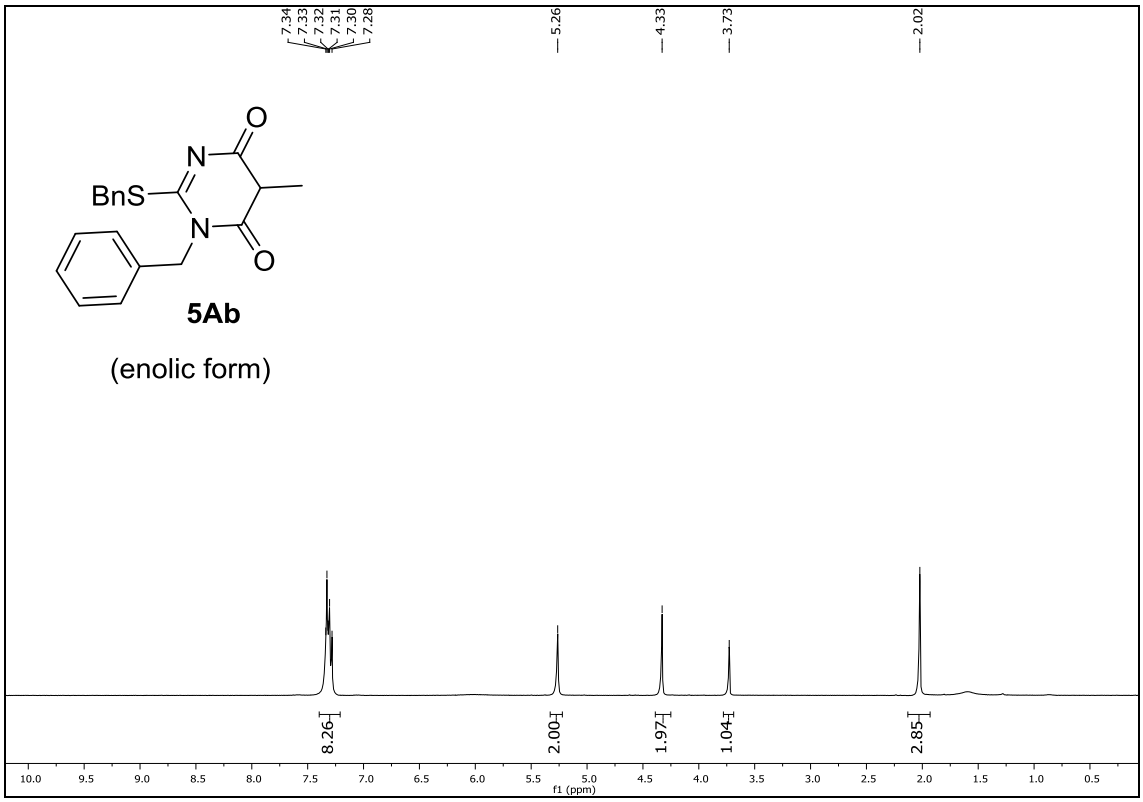

163.3
163.2
157.9
136.7
129.3
128.5
127.4
96.5
34.9
31.9
29.8
27.0
22.5
DMSO-d6
f1 (ppm)


7.39
7.38
7.37
7.37
7.36
7.36
7.35
7.35
7.34
7.33
7.33
7.32
7.31
7.31
7.30
7.30
4.35
3.41
3.30
3.27
3.25
3.23
3.20
1.26
1.24
BnS
N
N
Me
O
O
O
5Ea
(enolic form)
5.17
2.12
3.03
1.00
6.09
f1 (ppm)


162.4
157.6
136.8
129.3
128.8
128.6
128.4
127.4
101.9
34.7
29.7
23.5
19.8
DMSO-d6
f1 (ppm)

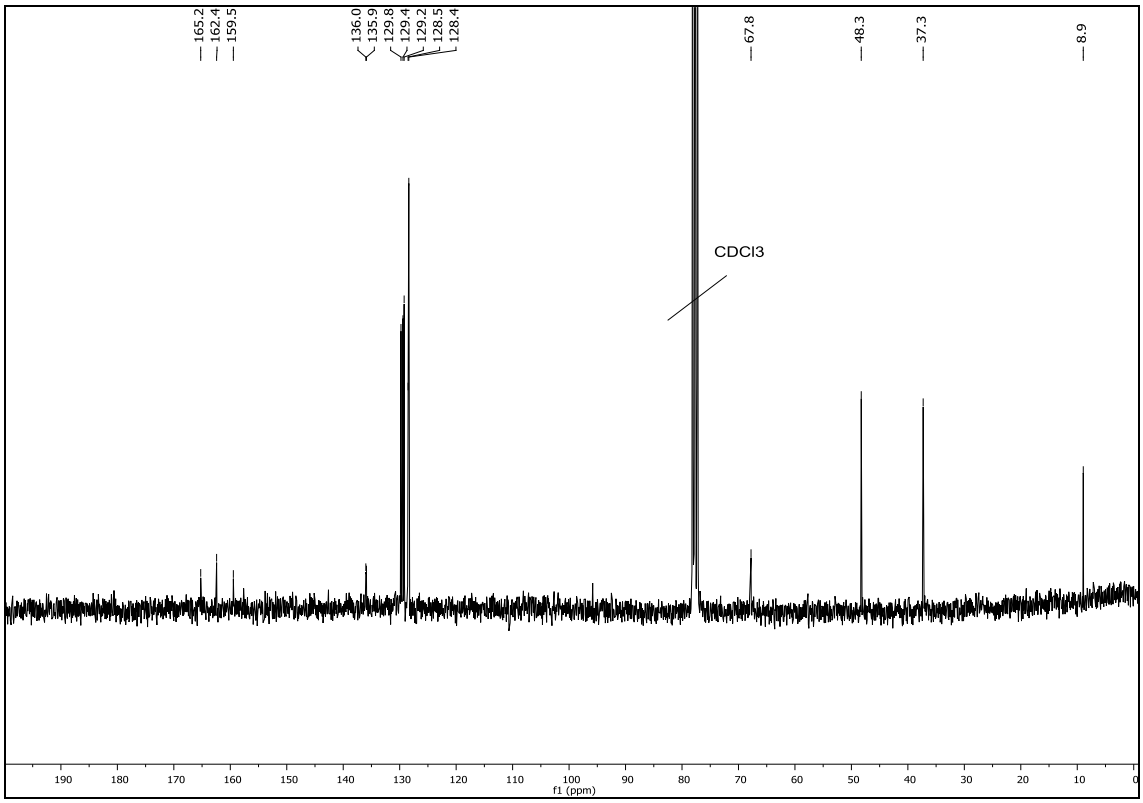

7.41 7.41 7.40 7.40 7.39 7.38 7.38 7.37 7.37 7.37 7.36 7.35 7.34 7.34 7.33 7.33 7.33 7.32 7.31 7.30 7.22 6.03 6.00 5.99 5.98 5.97 5.97 5.95 5.95 5.94 5.93 5.91 5.89 5.20 5.19 5.14 5.13 5.06 5.05 5.02 5.02 4.36 3.47 3.29 3.29 3.28 3.27 3.27 3.26
O
N
BnS
N
Me
O
5Fa
(enolic form)
5.37
1.00
2.33
2.33
3.30
2.09
f1 (ppm)

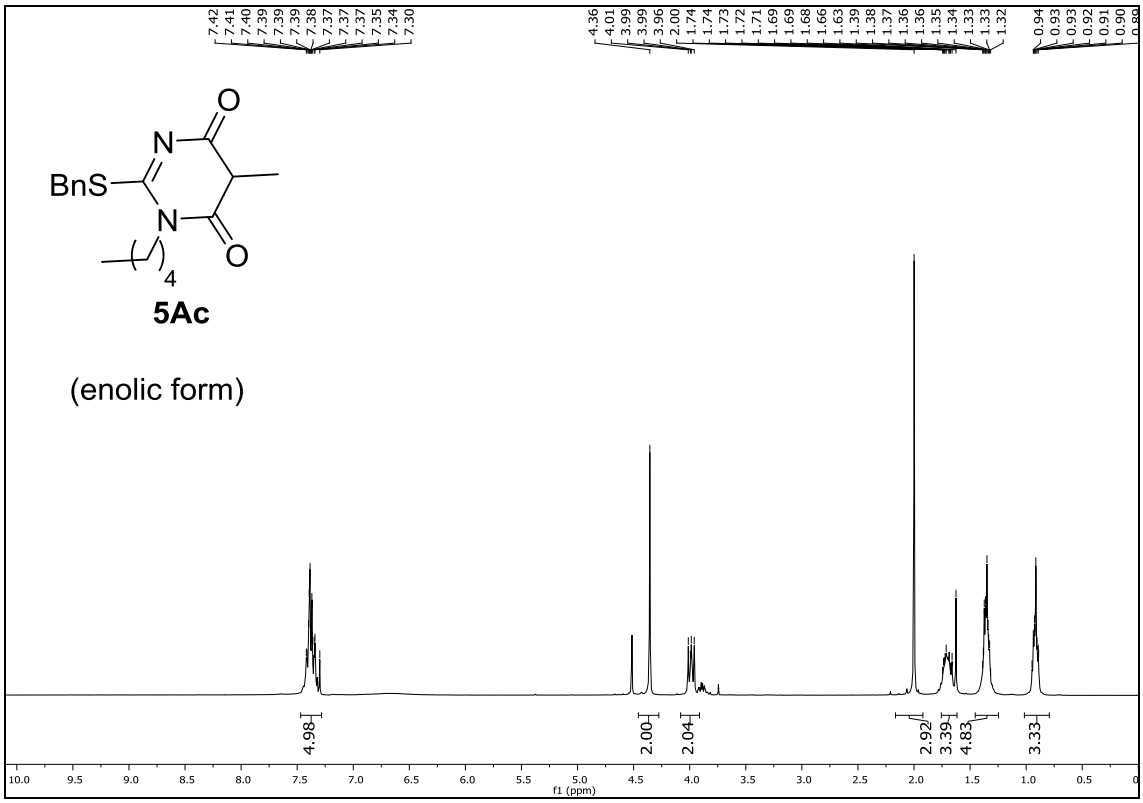

164.0 162.6 159.4 135.3 135.1 129.5 129.1 128.7 128.1 127.8 115.2 97.0 36.3 30.6 27.4
CDCl3
f1 (ppm)

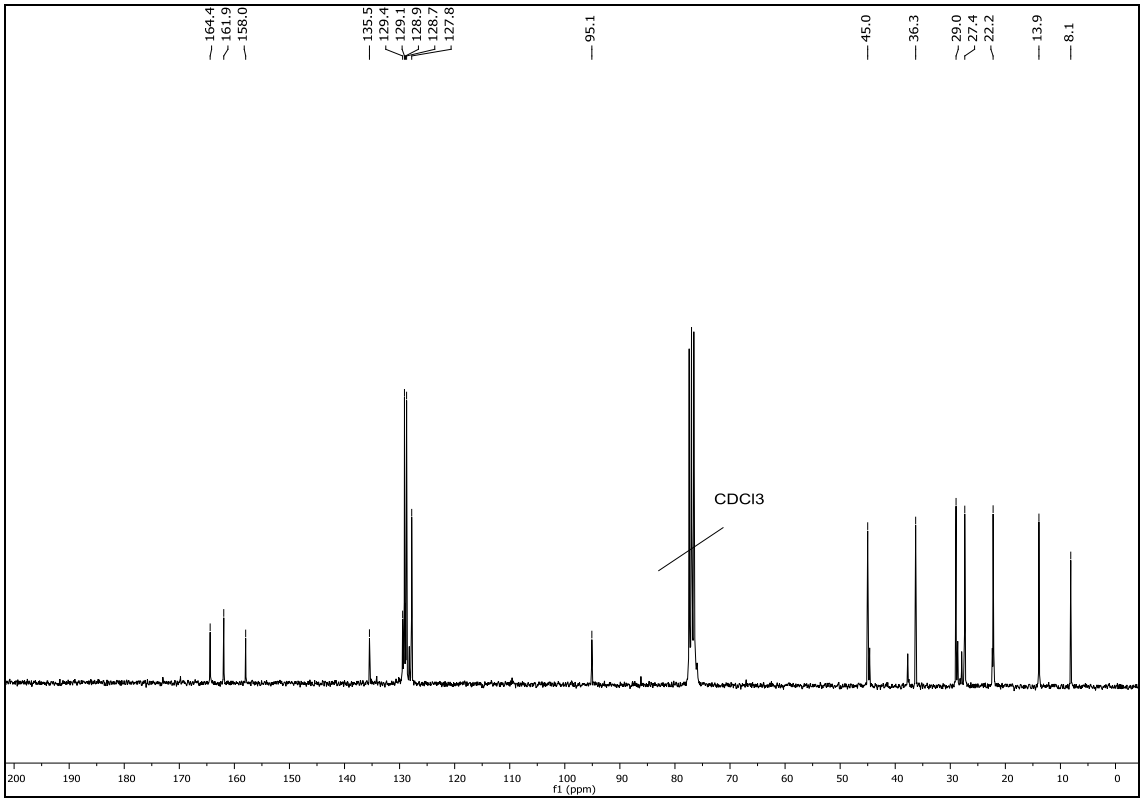


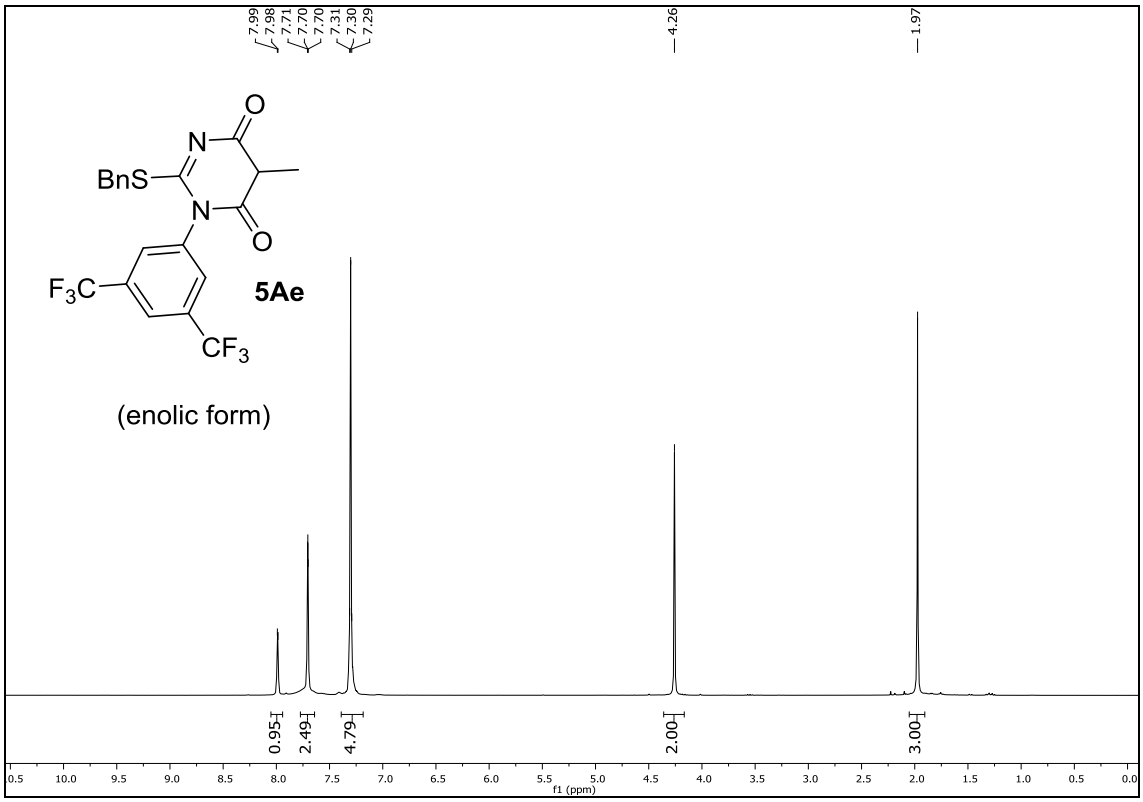
5Ab

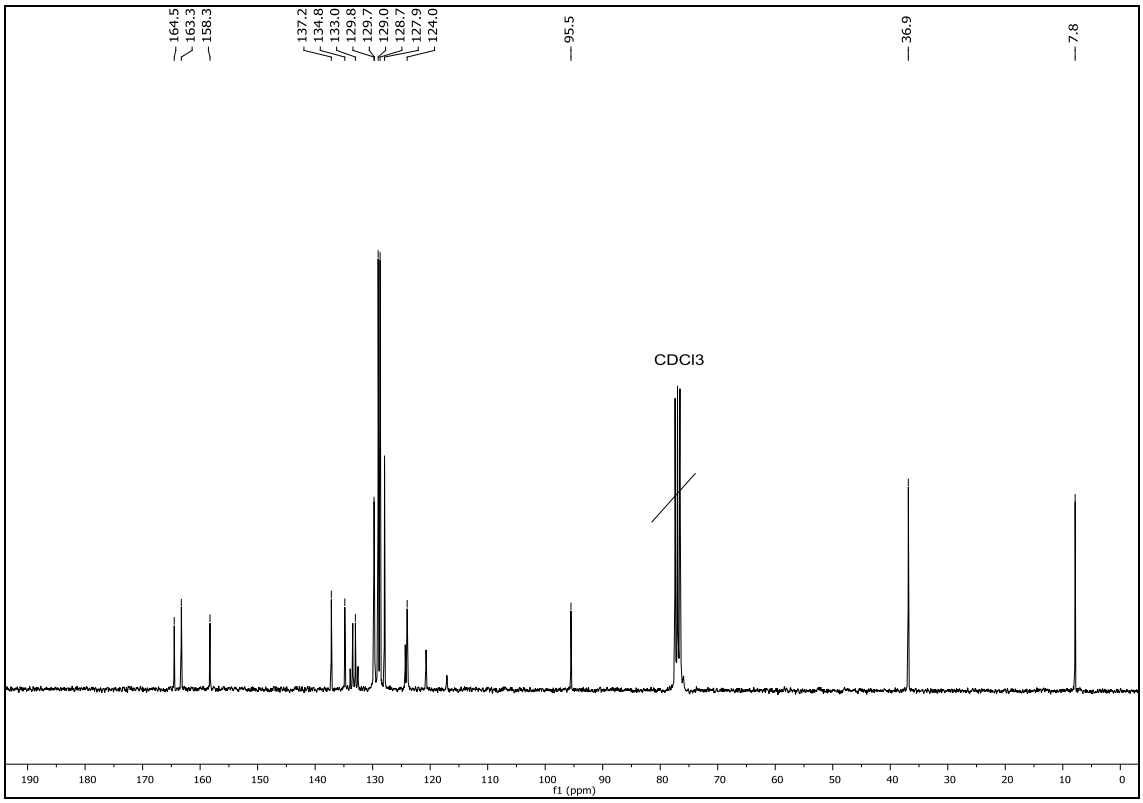
(enolic form)

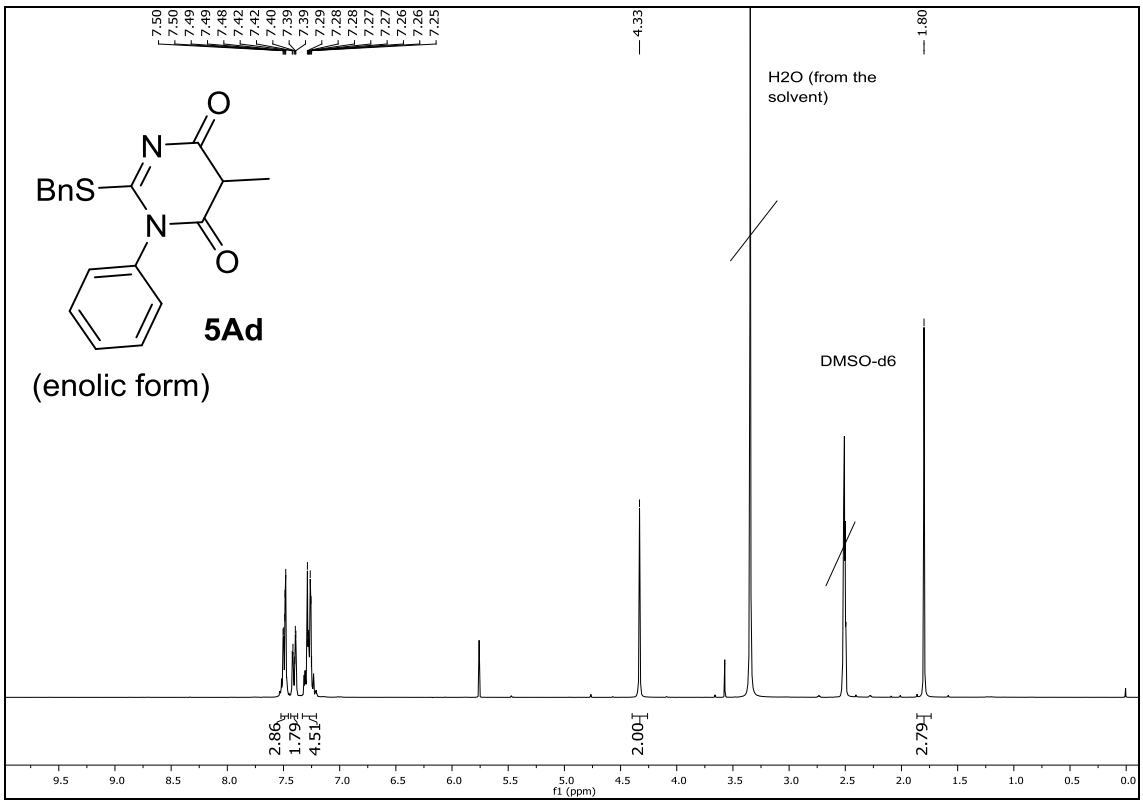


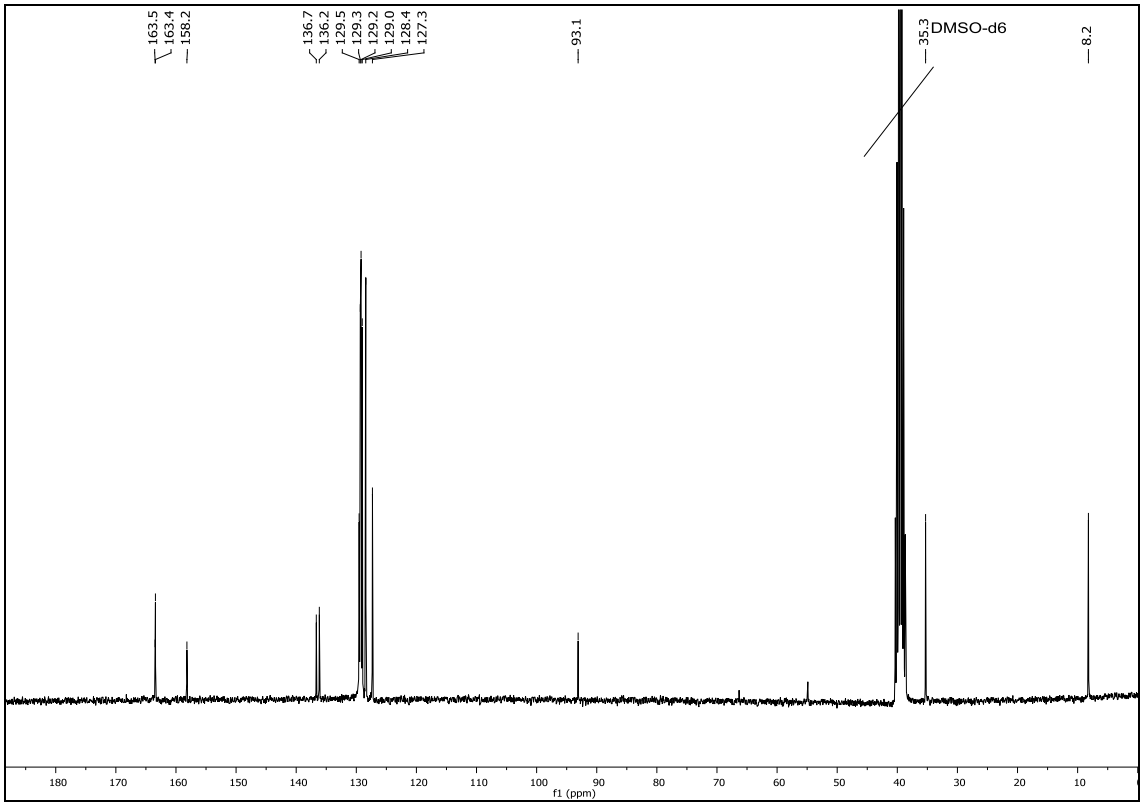

BnS
N
N
O
O
4
5Ac
(enolic form)
4.98
2.00
2.04
2.92
3.39
4.83
3.33
f1 (ppm)

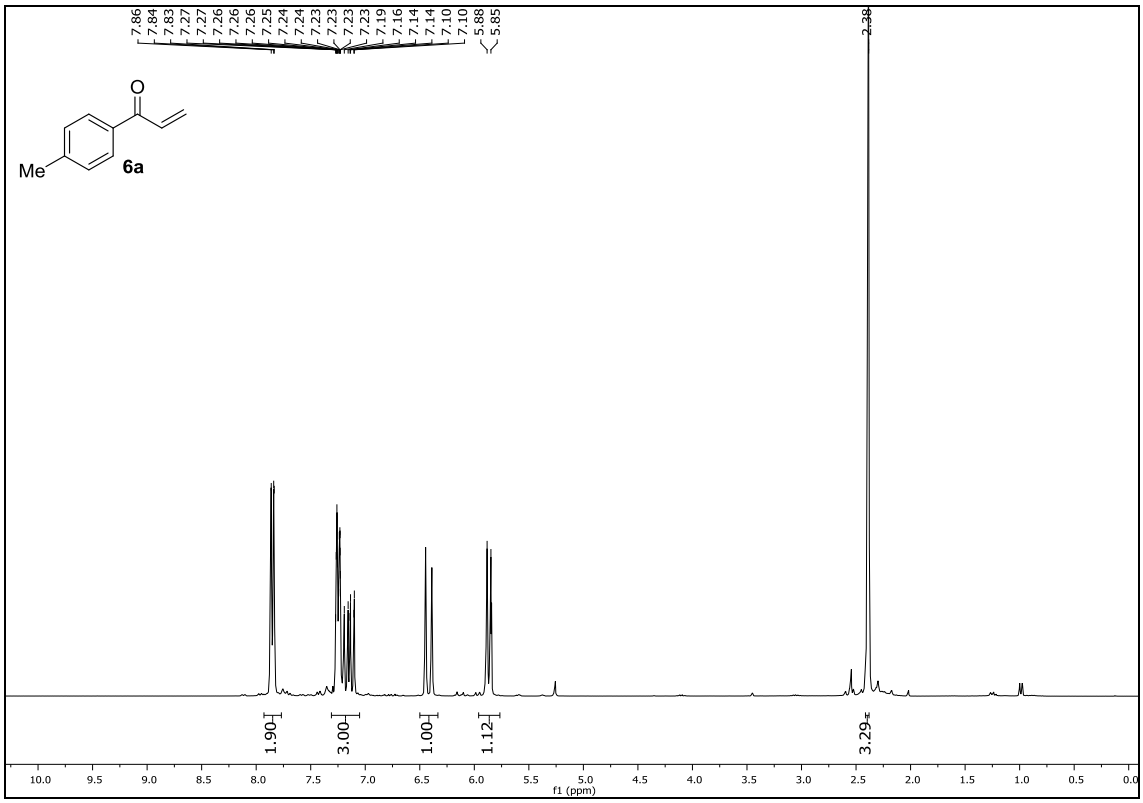

164.4
161.9
158.0
135.5
129.4
129.1
128.9
128.7
127.8
95.1
45.0
36.3
29.0
27.4
22.2
13.9
8.1
CDCl3
f1 (ppm)

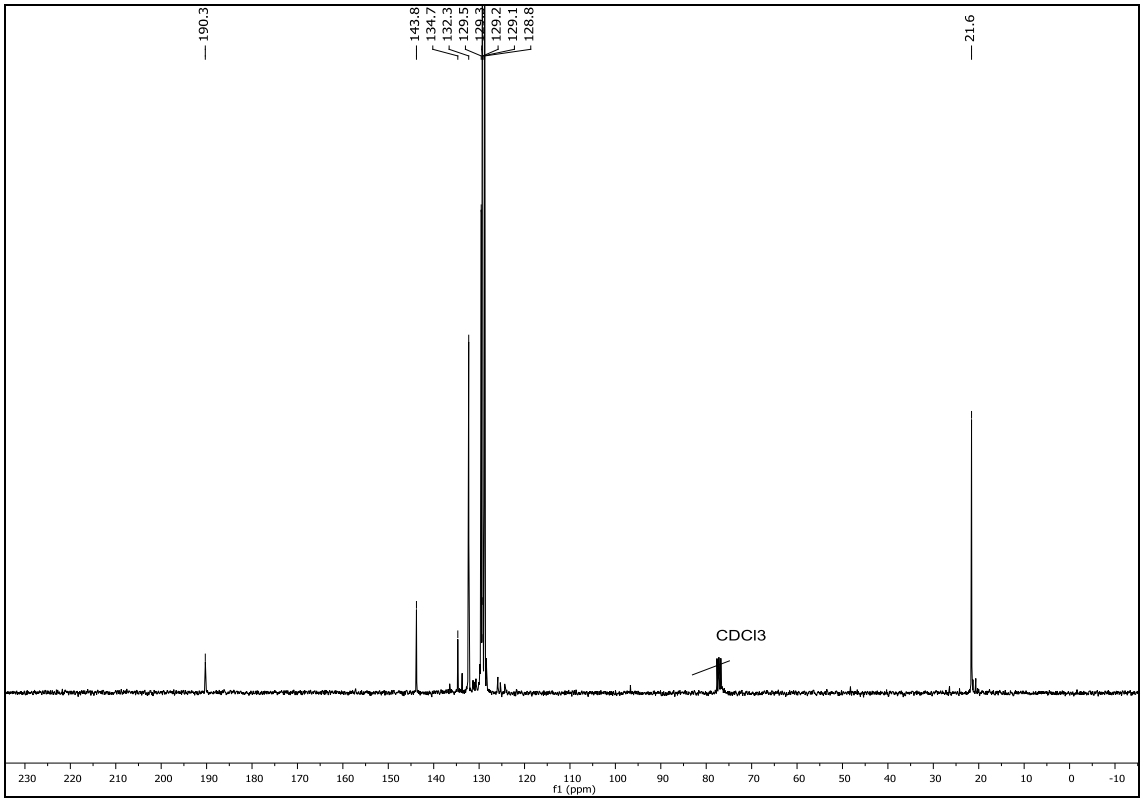

7.99
7.98
7.71
7.70
7.70
7.31
7.30
7.29
4.26
1.97
BnS
N
N
O
O
O
F3C
CF3
5Ae
(enolic form)
0.95
2.49
4.79
2.00
3.00
f1 (ppm)

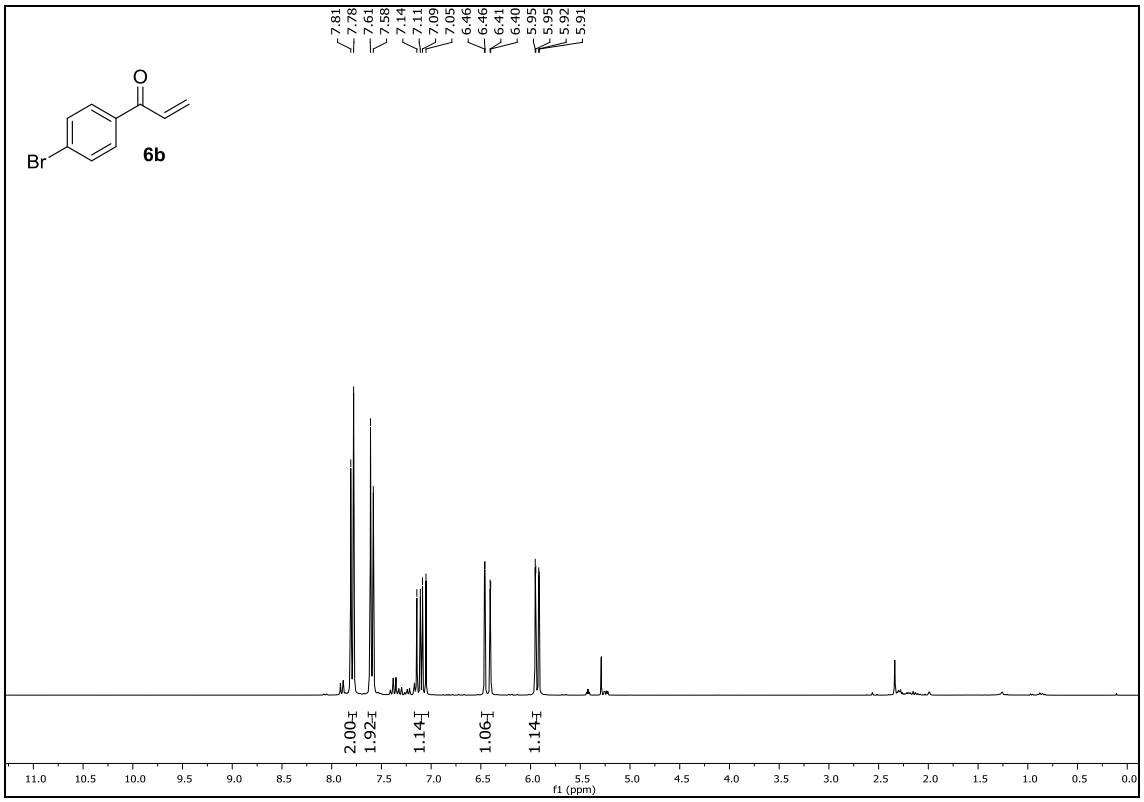

164.5
163.3
158.3
137.2
134.8
133.0
129.8
129.7
129.0
128.7
127.9
124.0
95.5
36.9
7.8
CDCl3
f1 (ppm)

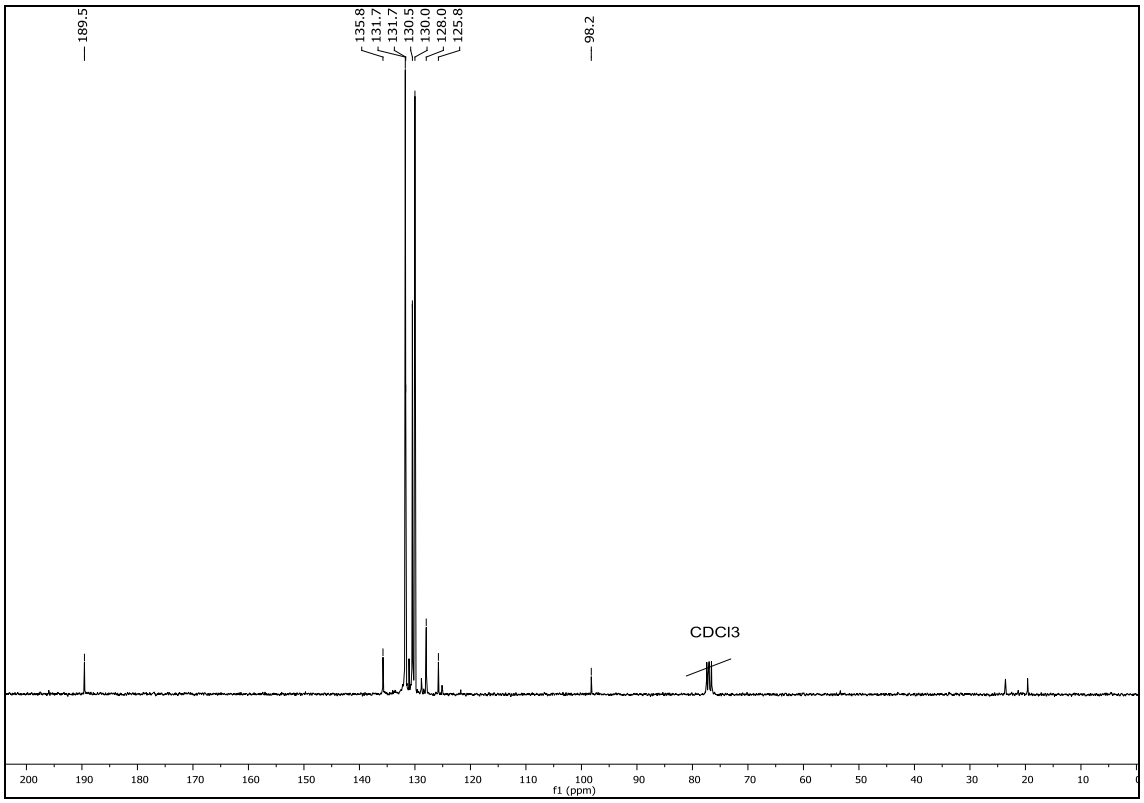

7.50
7.50
7.49
7.49
7.48
7.42
7.42
7.40
7.39
7.39
7.29
7.28
7.28
7.27
7.27
7.26
7.26
7.25
4.33
1.80
H2O (from the solvent)
DMSO-d6
BnS
N
N
O
O
5Ad
(enolic form)
2.86
1.79
4.51
2.00
2.79
f1 (ppm)

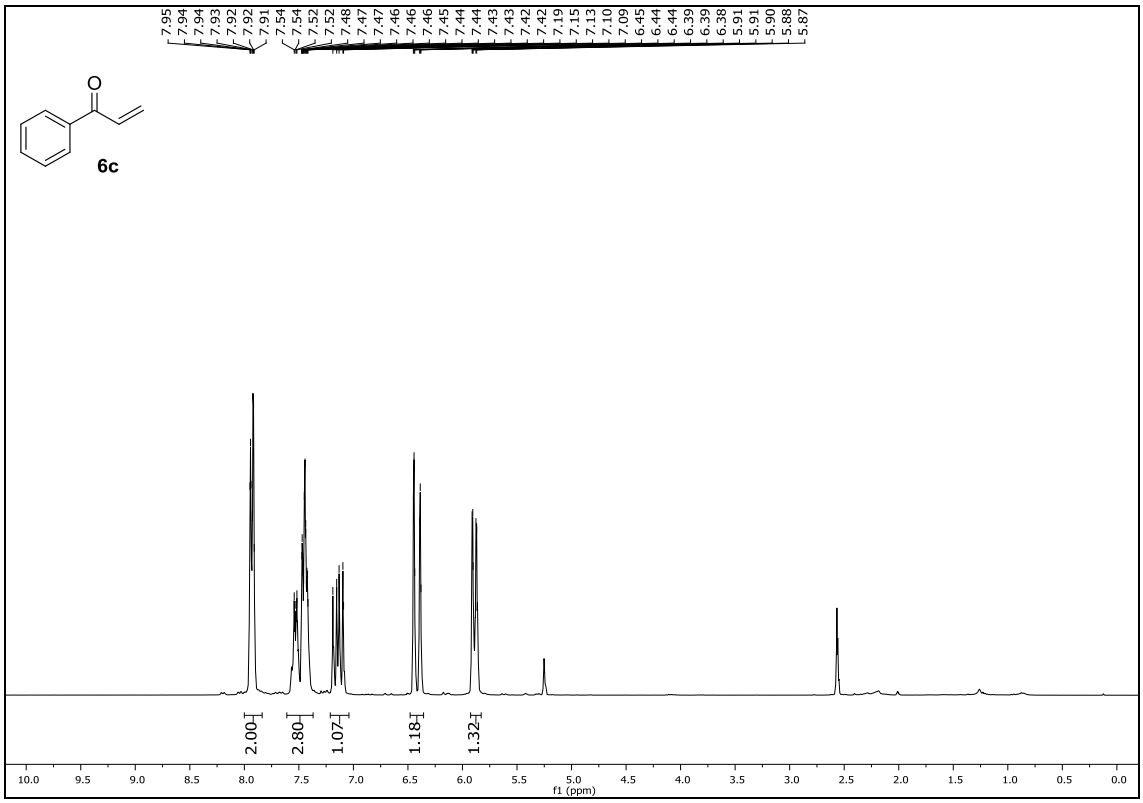

163.5
163.4
158.2
136.7
136.2
129.5
129.3
129.2
129.0
128.4
127.3
93.1
35.3
DMSO-d6
8.2
f1 (ppm)

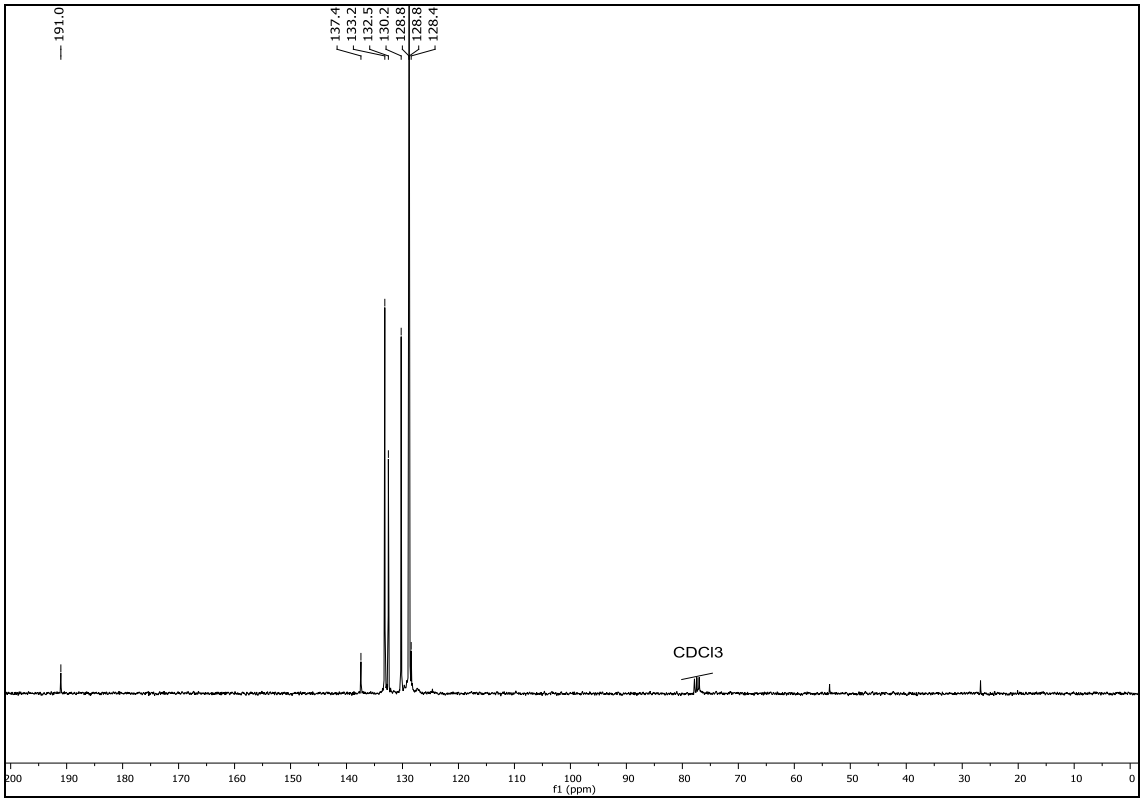

7.86
7.84
7.83
7.27
7.27
7.26
7.26
7.26
7.25
7.24
7.24
7.23
7.23
7.23
7.23
7.19
7.16
7.14
7.14
7.10
7.10
5.88
5.85
2.38
O
Me
6a
1.90
3.00
1.00
1.12
3.29
f1 (ppm)

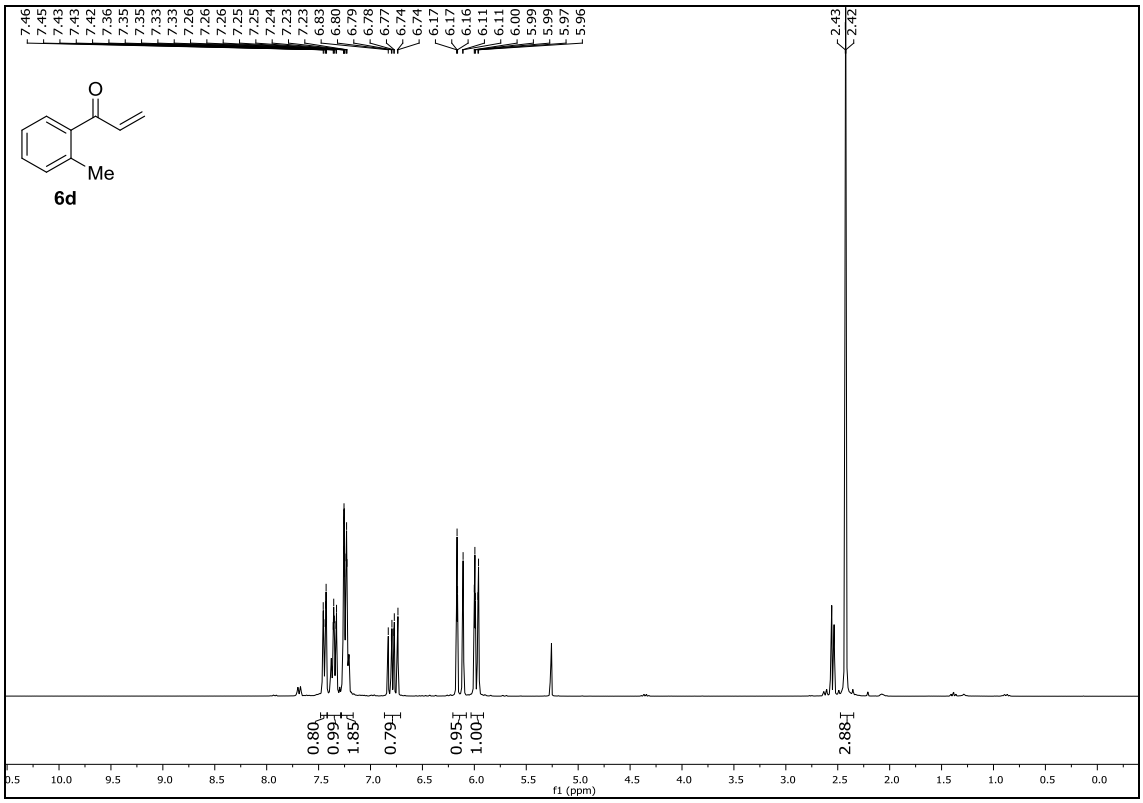

190.3
143.8
134.7
132.3
129.5
129.2
129.2
129.1
128.8
21.6
CDCl3
f1 (ppm)

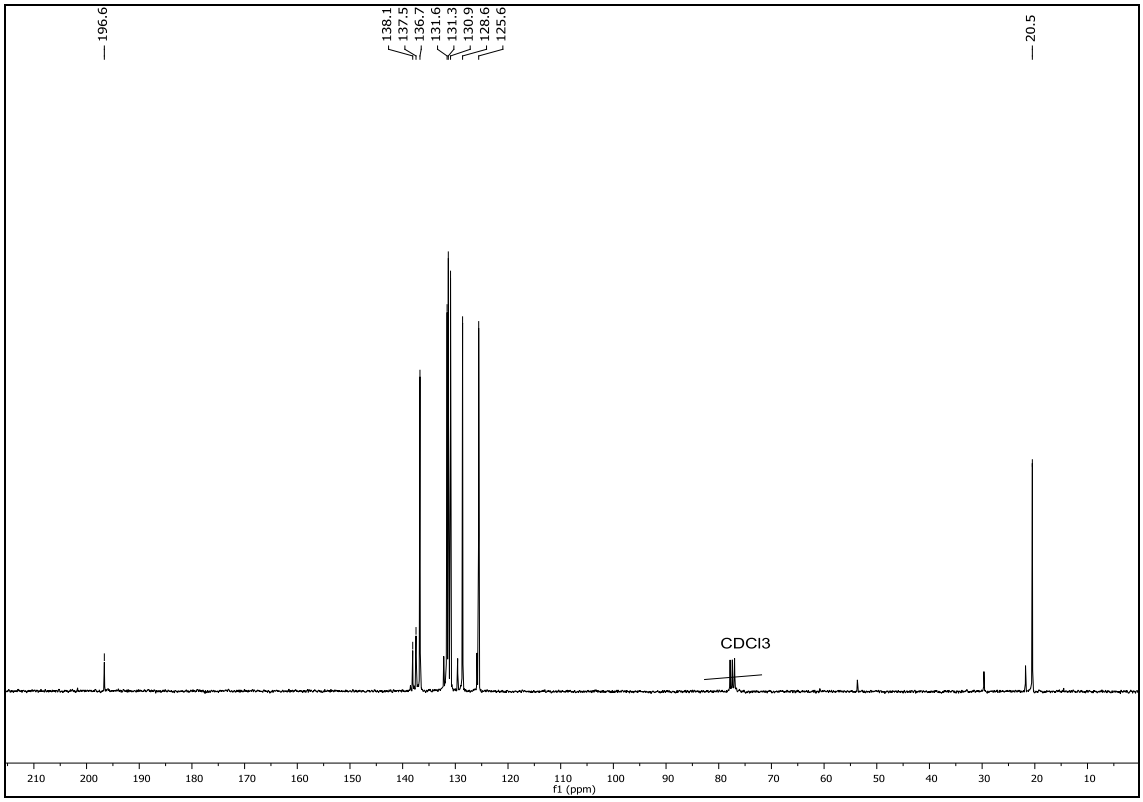

7.81
7.78
7.61
7.58
7.14
7.11
7.09
7.05
6.46
6.41
6.40
5.95
5.92
5.91
O
Br
6b
2.00
1.92
1.14
1.06
1.14
f1 (ppm)

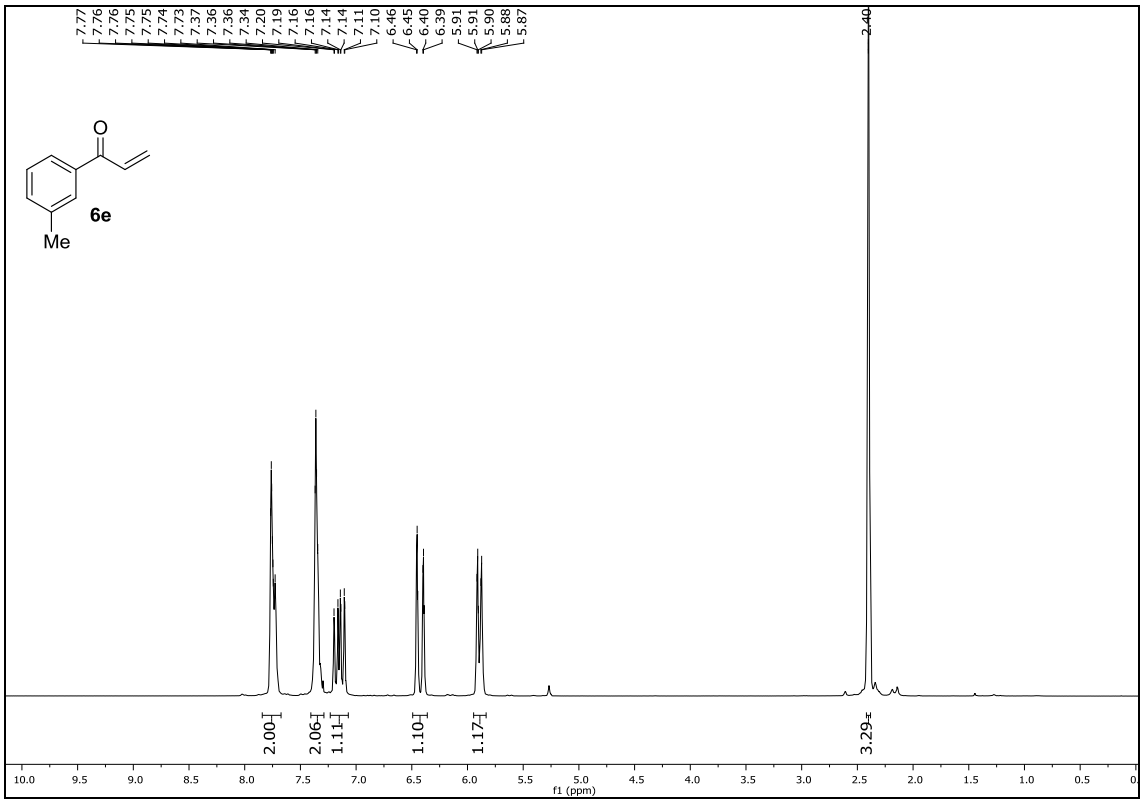

189.5
135.8
131.7
131.7
130.5
130.0
128.0
125.8
98.2
CDCl3
f1 (ppm)

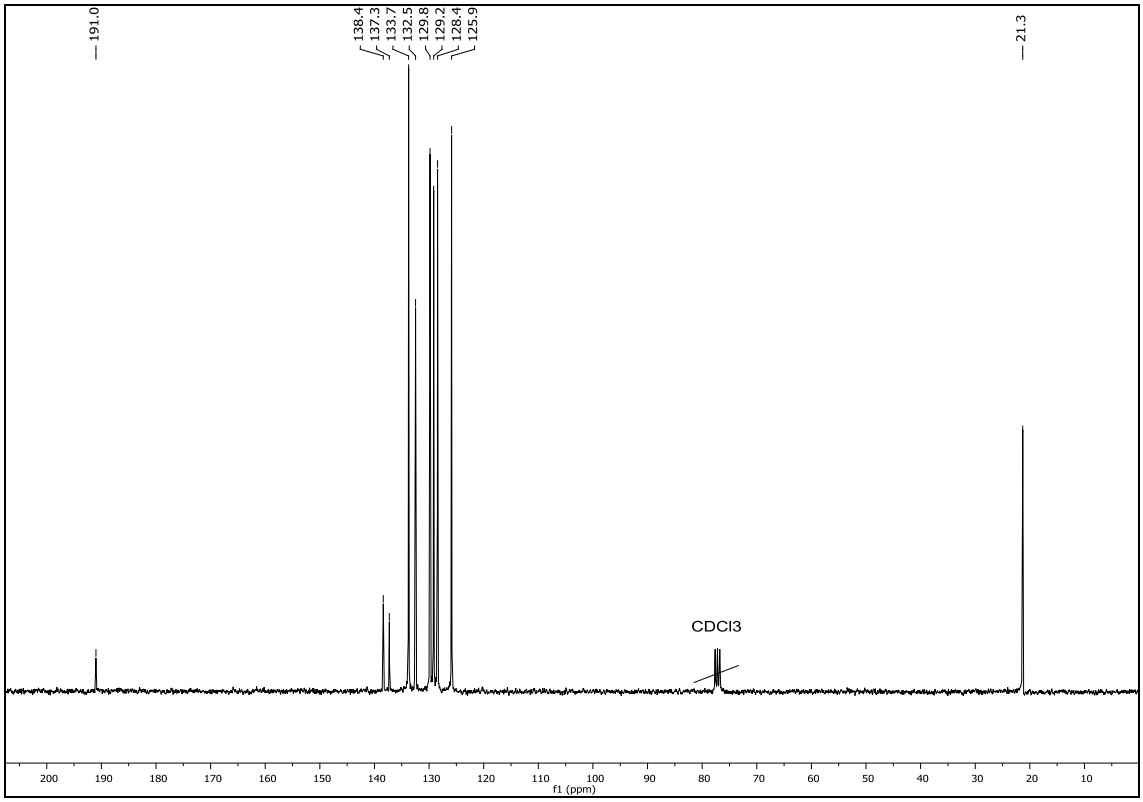

7.95
7.94
7.94
7.93
7.92
7.92
7.91
7.54
7.54
7.52
7.52
7.48
7.47
7.47
7.46
7.46
7.46
7.45
7.44
7.44
7.43
7.43
7.42
7.42
7.19
7.15
7.13
7.10
7.09
6.45
6.44
6.44
6.39
6.39
6.38
5.91
5.91
5.90
5.88
5.87
O
6c
2.00
2.80
1.07
1.18
1.32
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

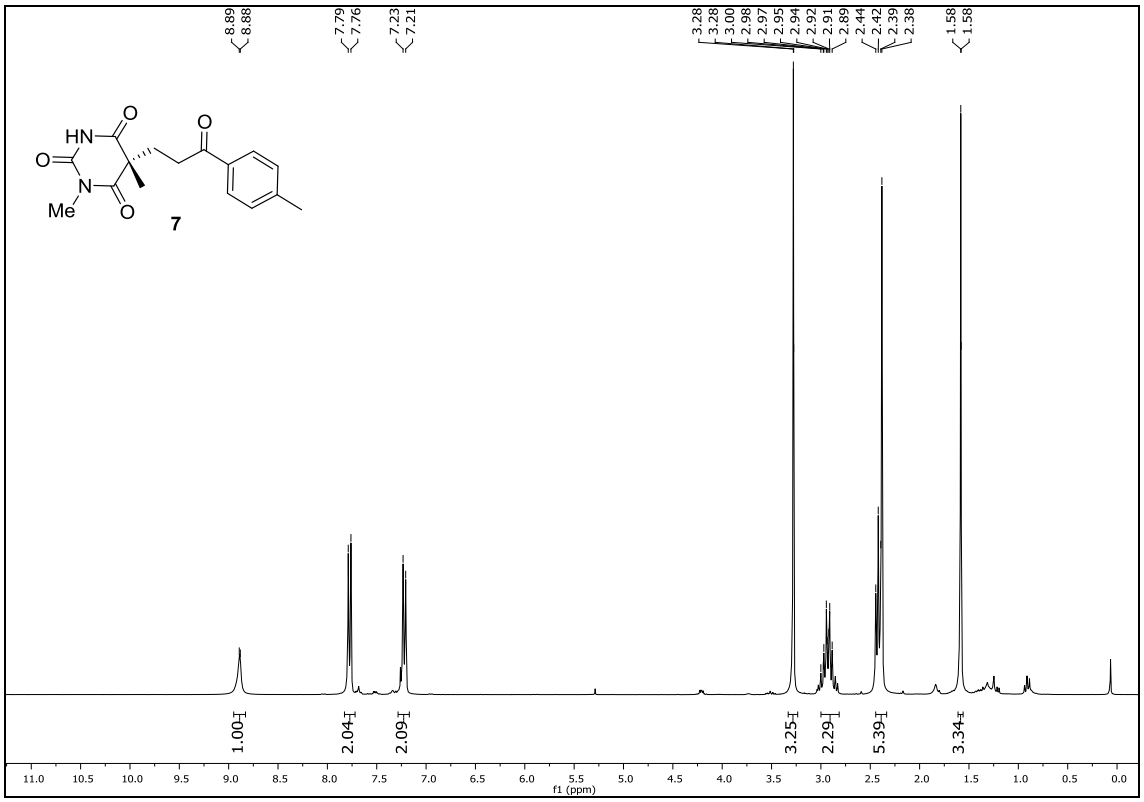

191.0
137.4
133.2
132.5
130.2
128.8
128.8
128.4
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

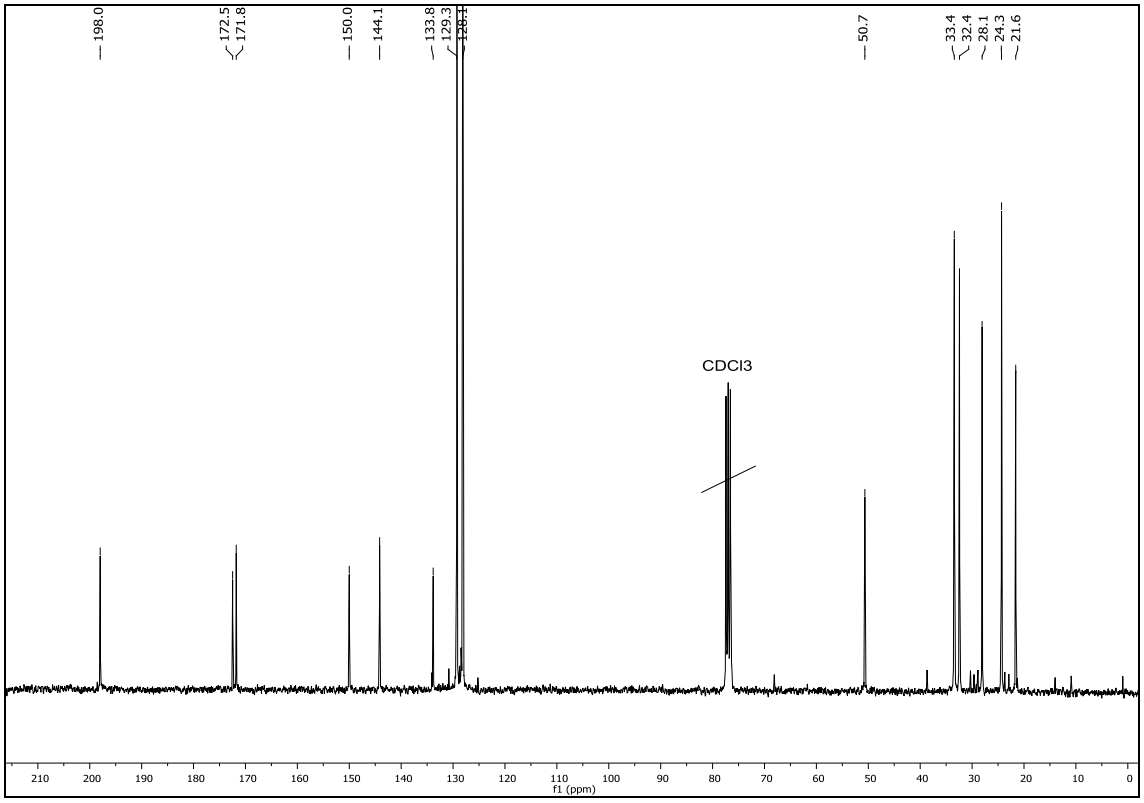

7.46
7.45
7.43
7.43
7.42
7.36
7.35
7.35
7.33
7.33
7.26
7.26
7.26
7.25
7.25
7.24
7.23
7.23
6.83
6.80
6.80
6.79
6.78
6.77
6.74
6.74
6.17
6.16
6.11
6.11
6.00
5.99
5.99
5.97
5.96
2.43
2.42
O
Me
6d
0.80
0.99
1.85
0.79
0.95
1.00
2.88
f1 (ppm)

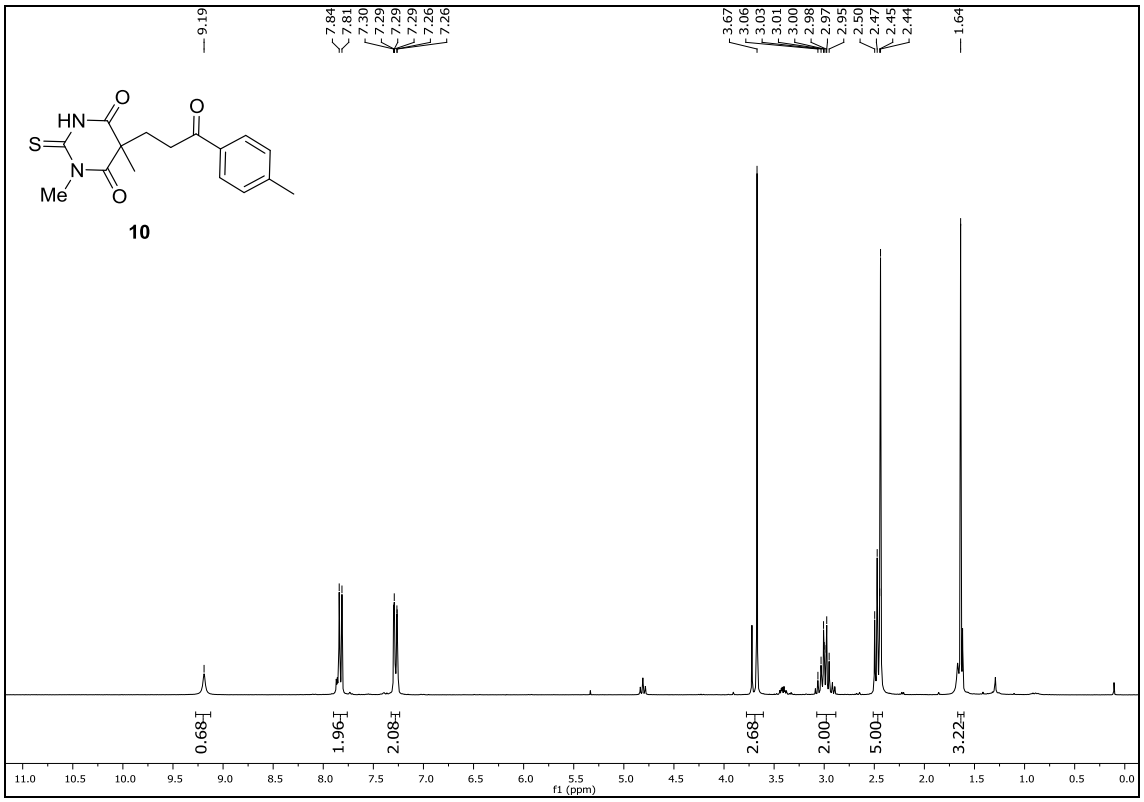

196.6
138.1
137.5
136.7
131.6
131.3
130.9
128.6
125.6
20.5
CDCl3
f1 (ppm)

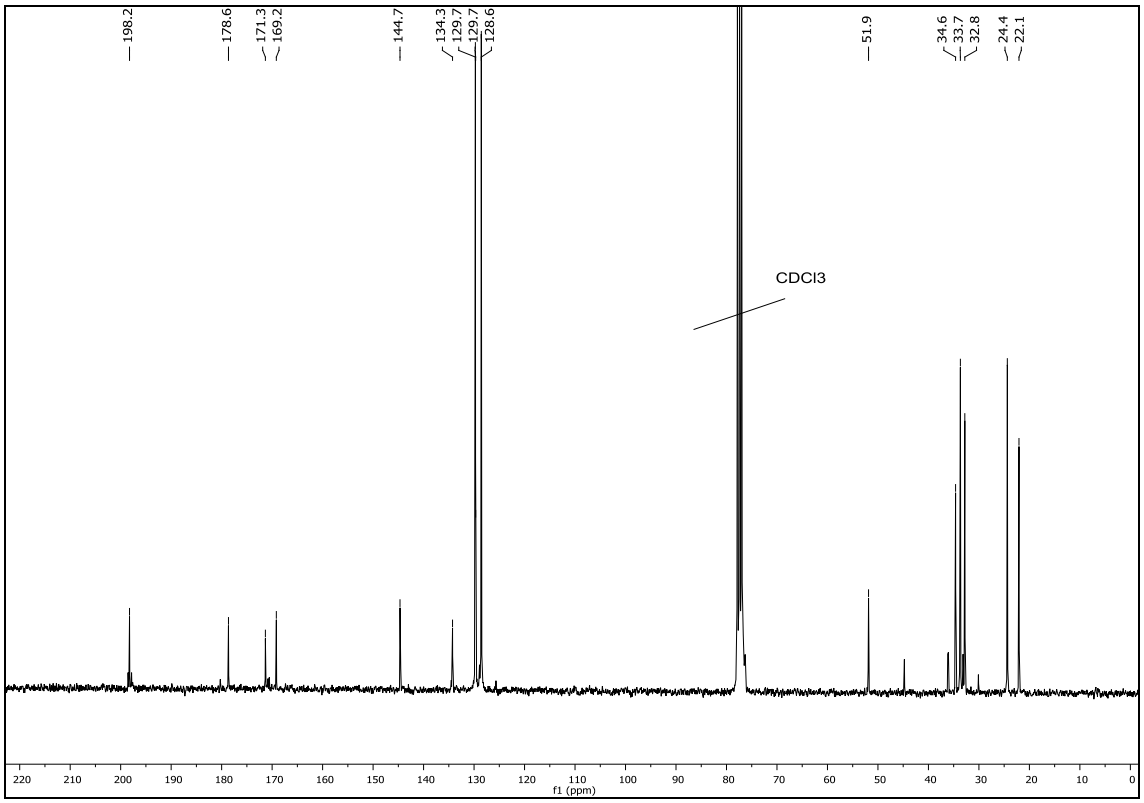

7.77
7.76
7.76
7.75
7.75
7.74
7.73
7.37
7.36
7.36
7.34
7.20
7.19
7.16
7.16
7.14
7.14
7.11
7.10
6.46
6.45
6.40
6.39
5.91
5.91
5.90
5.88
5.87
2.40
O
6e
Me
2.00
2.06
1.11
1.10
1.17
3.29
f1 (ppm)

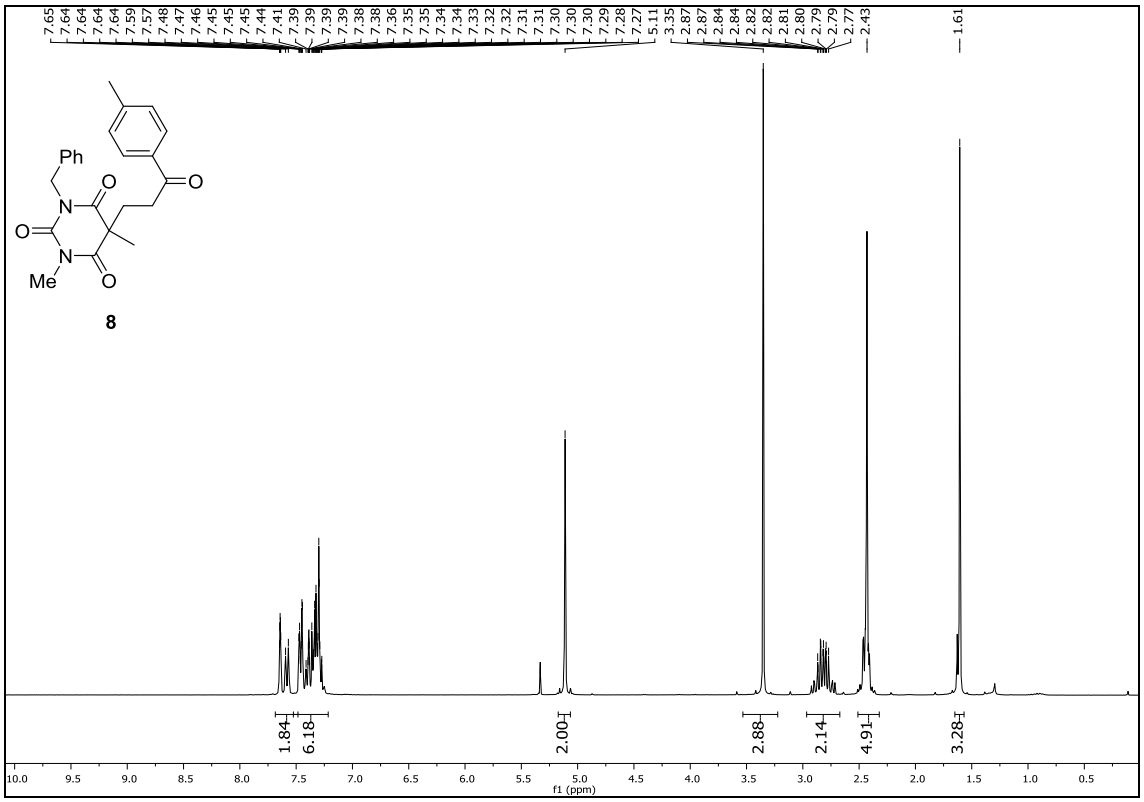

191.0
138.4
137.3
133.7
132.5
129.8
129.2
128.4
125.9
21.3
CDCl3
f1 (ppm)

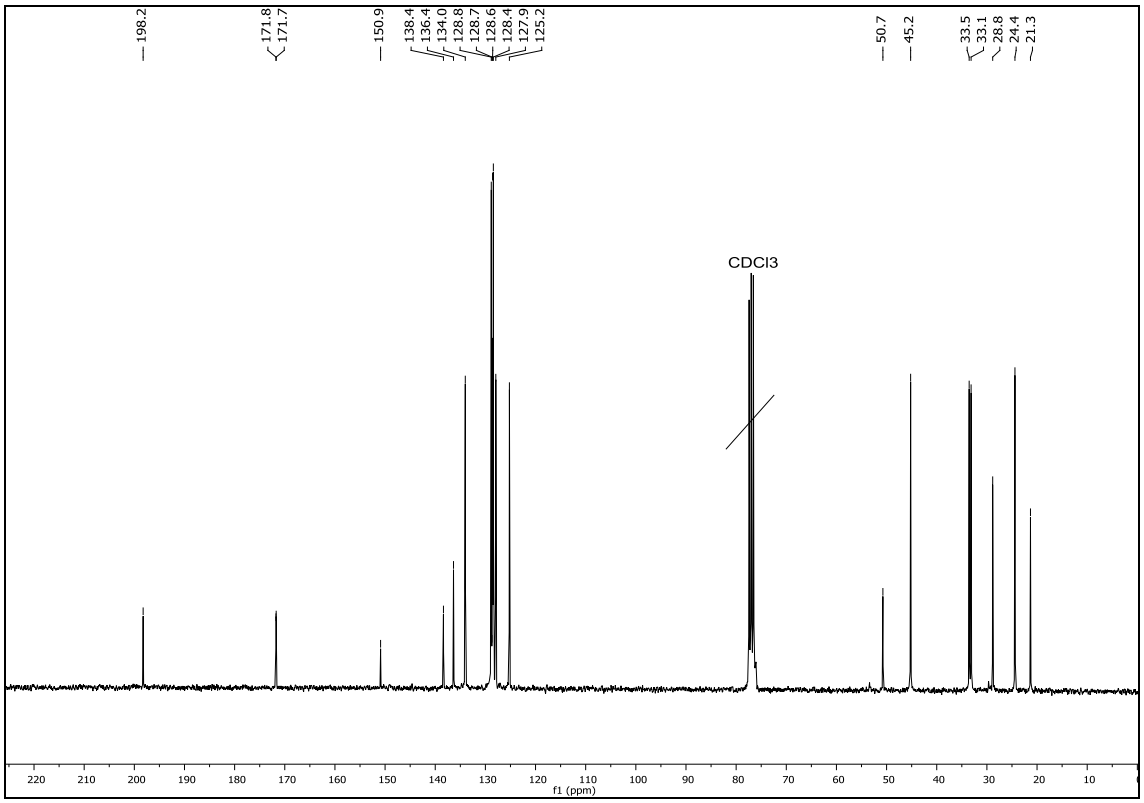

8.89
8.88
7.79
7.76
7.23
7.21
3.28
3.28
3.00
2.98
2.97
2.95
2.94
2.92
2.91
2.89
2.44
2.42
2.39
2.38
1.58
1.58
HN
O
O
N
Me
O
O
7
1.00
2.04
2.09
3.25
2.29
5.39
3.34
f1 (ppm)

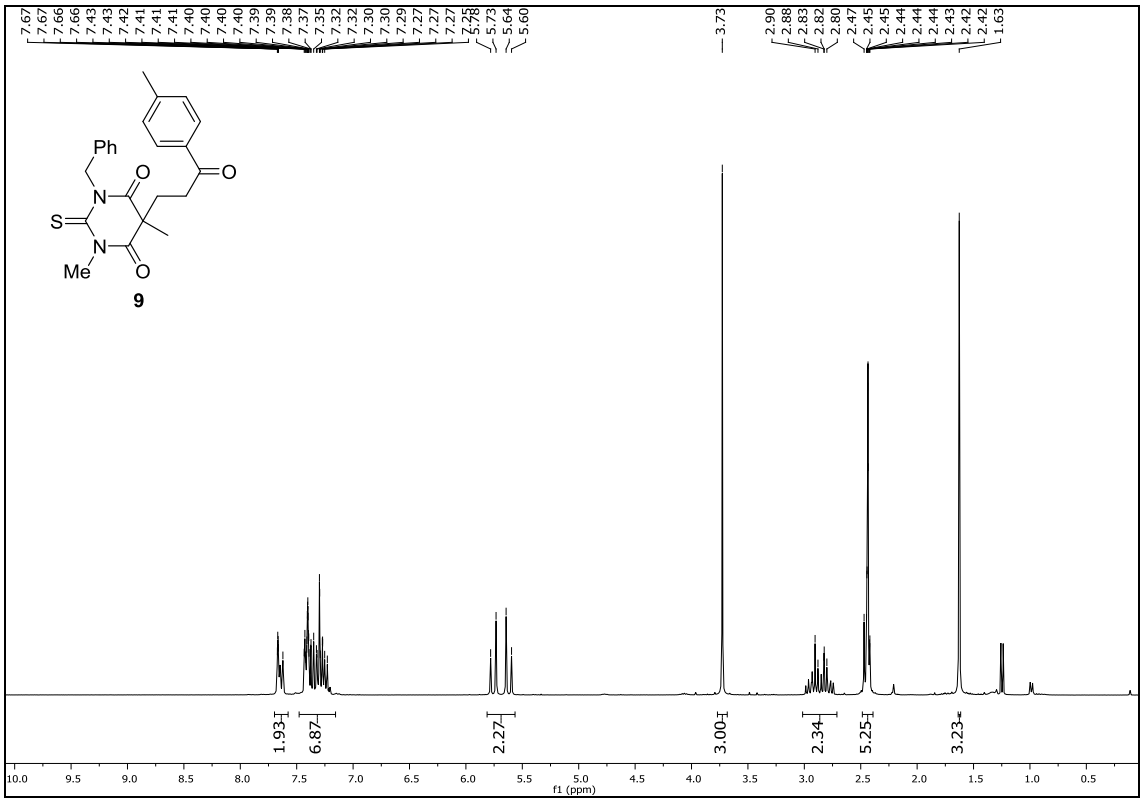

198.0
172.5
171.8
150.0
144.1
133.8
129.3
128.1
50.7
33.4
32.4
28.1
24.3
21.6
CDCl3
f1 (ppm)

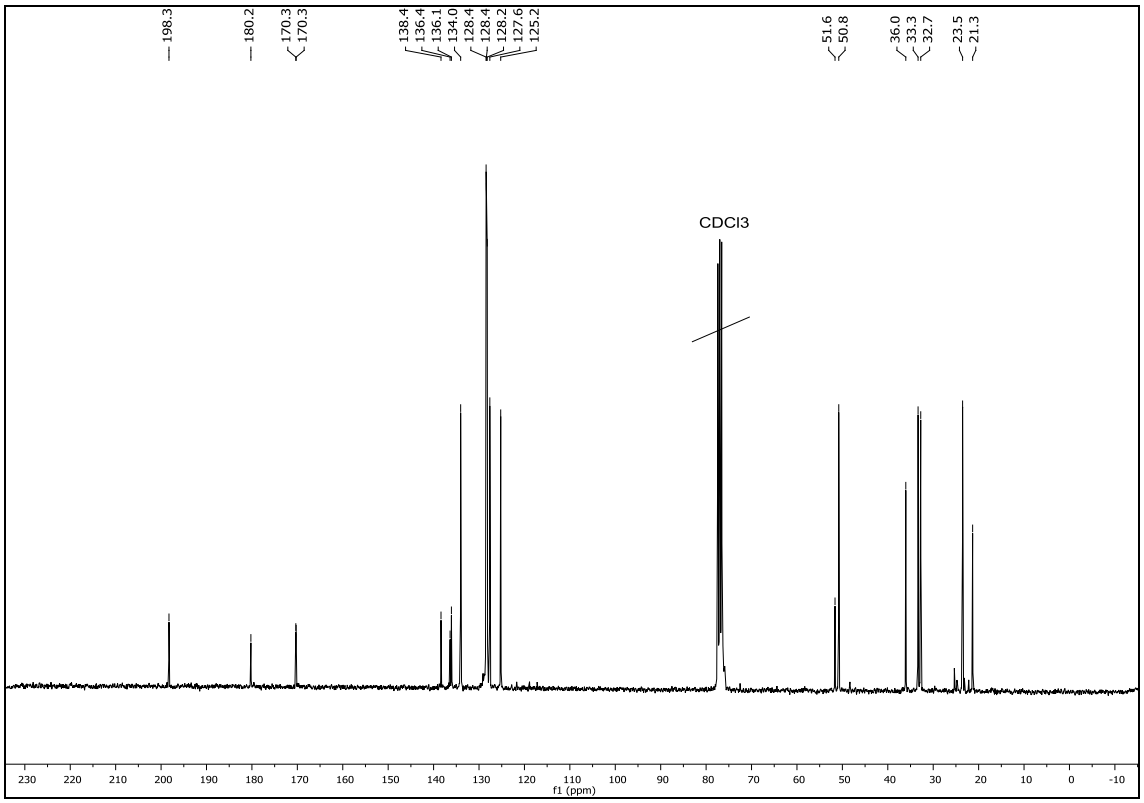

9.19
7.84
7.81
7.30
7.29
7.29
7.29
7.26
7.26
3.67
3.06
3.03
3.01
3.00
2.98
2.97
2.95
2.50
2.47
2.45
2.44
1.64
HN
O
S
N
Me
O
O
10
0.68
1.96
2.08
2.68
2.00
5.00
3.22
f1 (ppm)

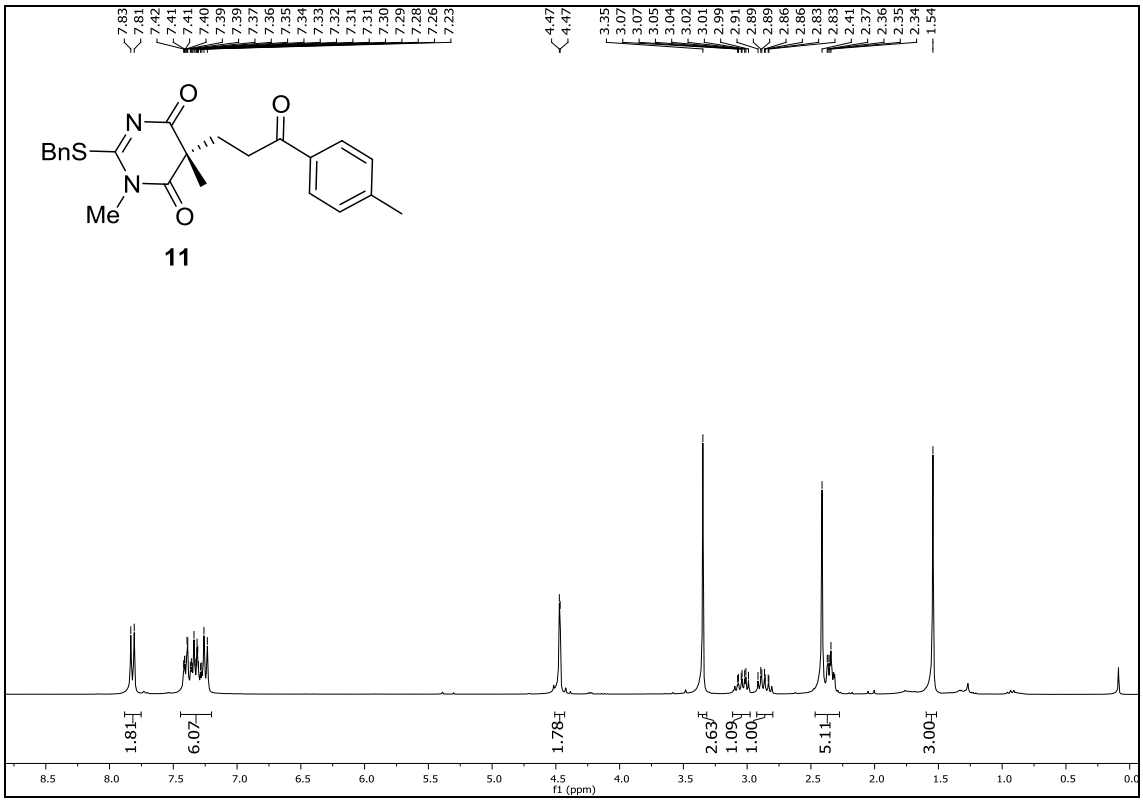

198.2
178.6
171.3
169.2
144.7
134.3
129.7
129.7
128.6
51.9
34.6
33.7
32.8
24.4
22.1
CDCl3
f1 (ppm)

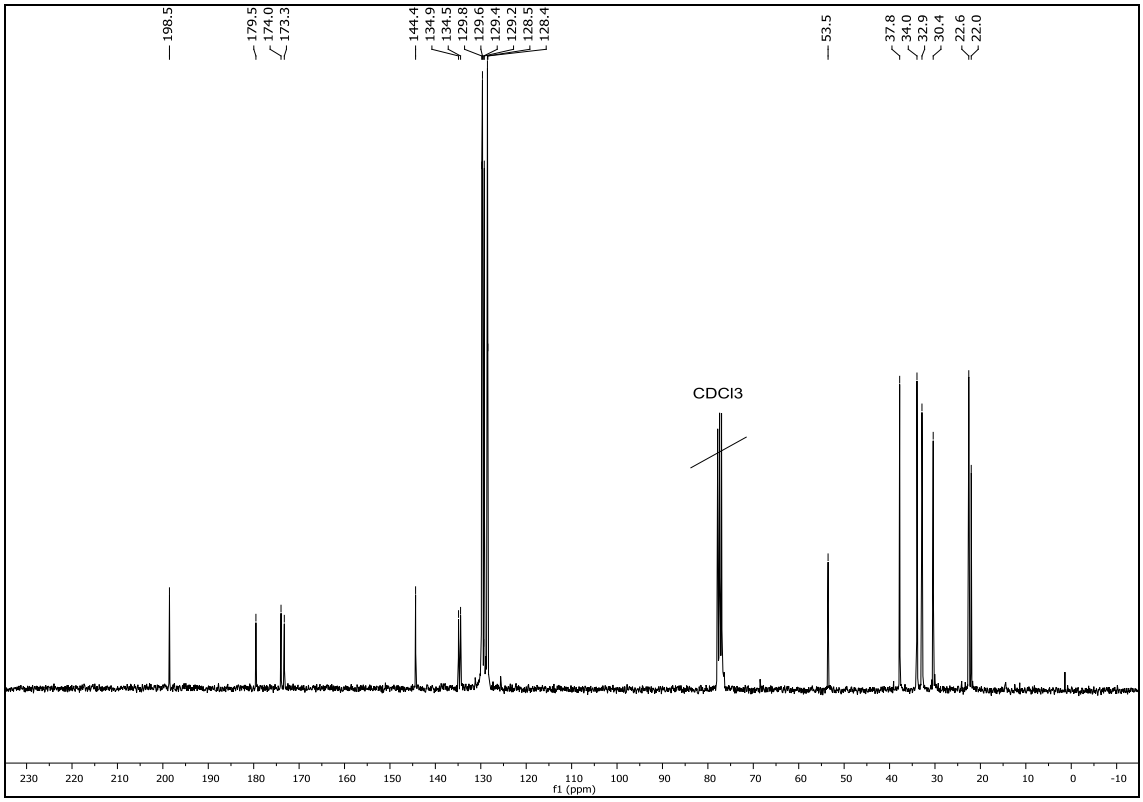

Ph
O
O
N
O
N
Me
O
8
1.84
6.18
2.00
2.88
2.14
4.91
3.28
f1 (ppm)

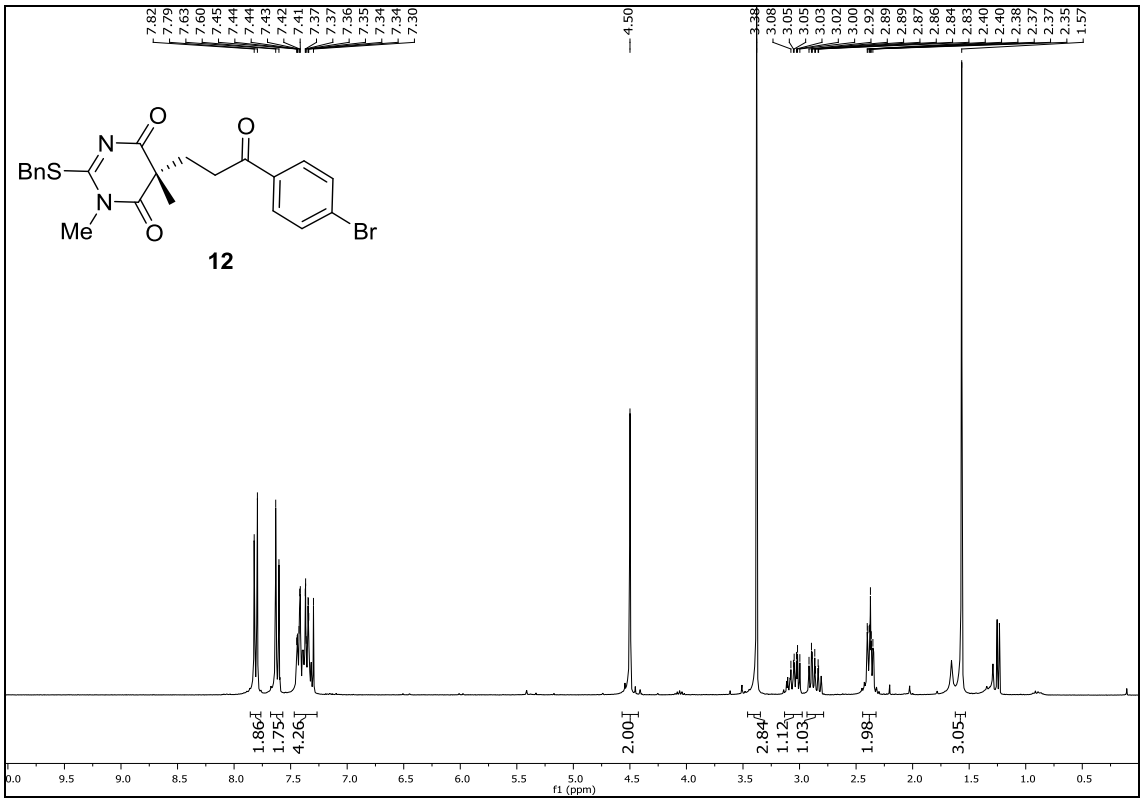

198.2
171.8
171.7
150.9
138.4
136.4
134.0
128.8
128.7
128.6
128.4
127.9
125.2
50.7
45.2
33.5
33.1
28.8
24.4
21.3
CDCl3
f1 (ppm)

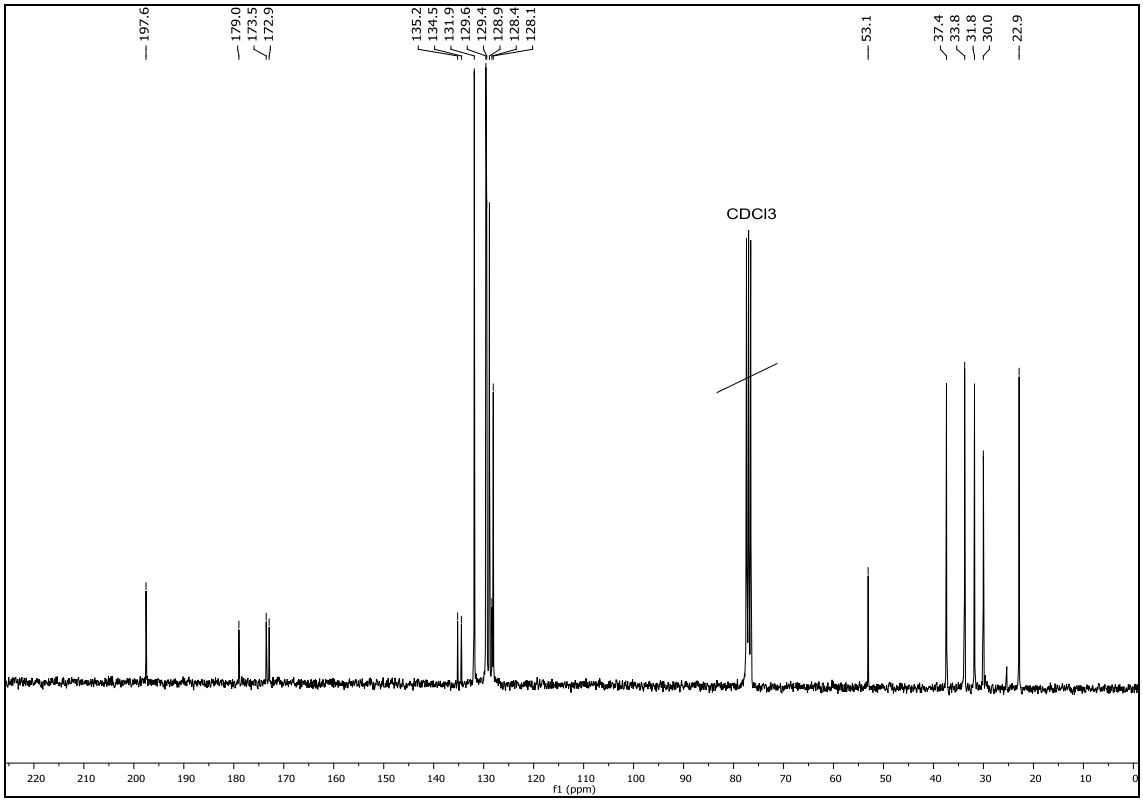

Ph
O
O
N
S
N
Me
O
9
1.93
6.87
2.27
3.00
2.34
5.25
3.23
f1 (ppm)

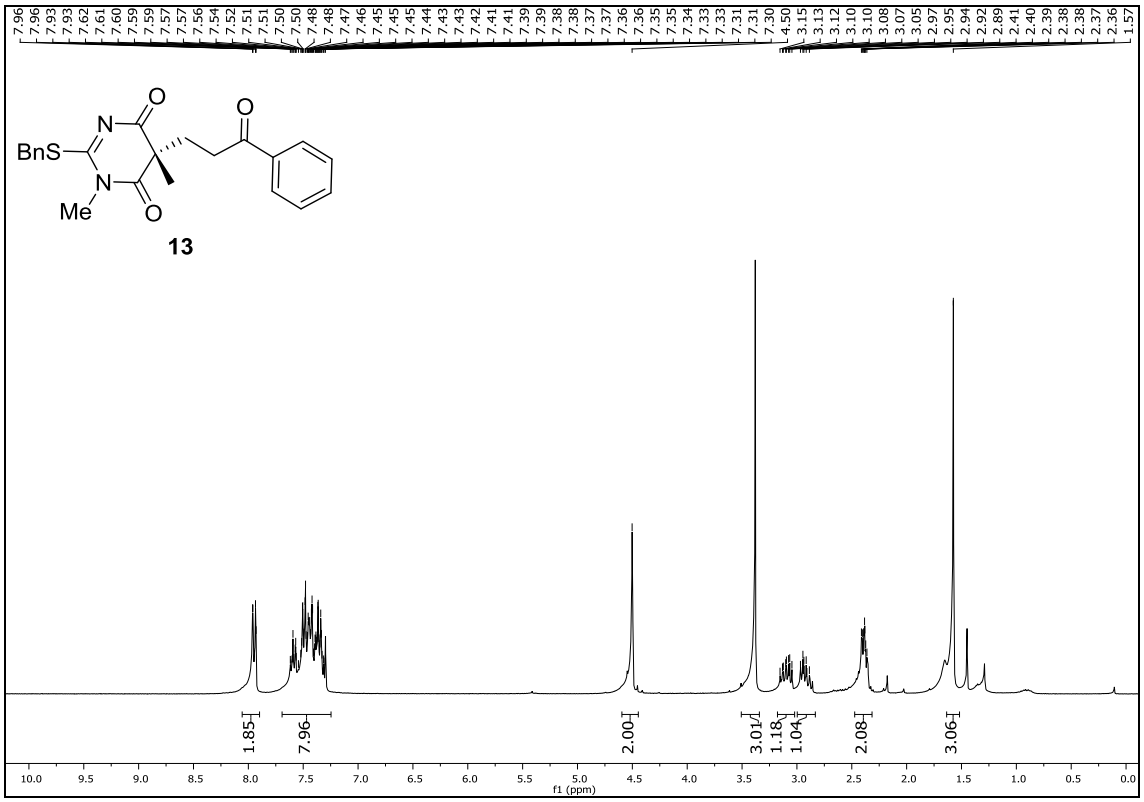

198.3
180.2
170.3
170.3
138.4
136.4
136.1
134.0
128.4
128.4
128.2
127.6
125.2
51.6
50.8
36.0
33.3
32.7
23.5
21.3
CDCl3
f1 (ppm)

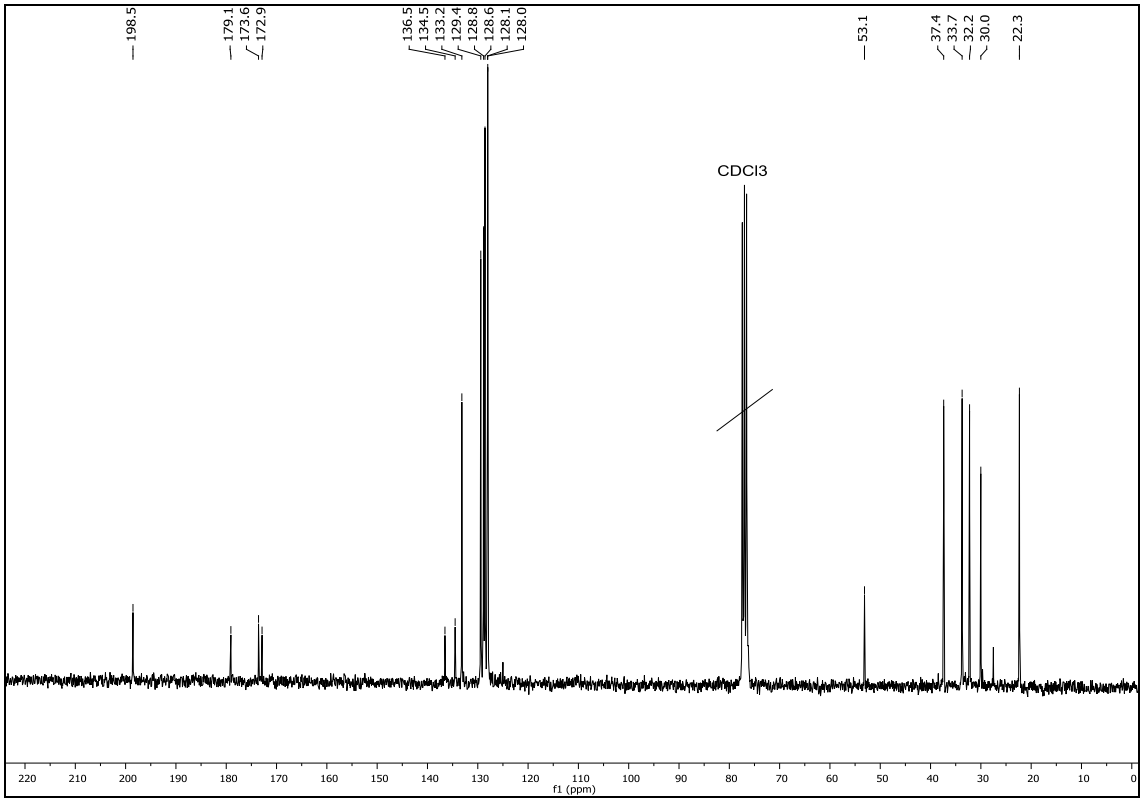

7.83 7.81 7.42 7.41 7.41 7.40 7.39 7.39 7.37 7.36 7.35 7.34 7.33 7.32 7.31 7.31 7.30 7.29 7.28 7.26 7.23
4.47 4.47
3.35 3.07 3.07 3.05 3.04 3.02 3.01 2.99 2.91 2.89 2.89 2.86 2.86 2.83 2.83 2.41 2.37 2.36 2.35 2.34 1.54
BnS
N
N
Me
O
O
O
O
11
1.81 6.07 1.78 2.63 1.09 1.00 5.11 3.00
f1 (ppm)

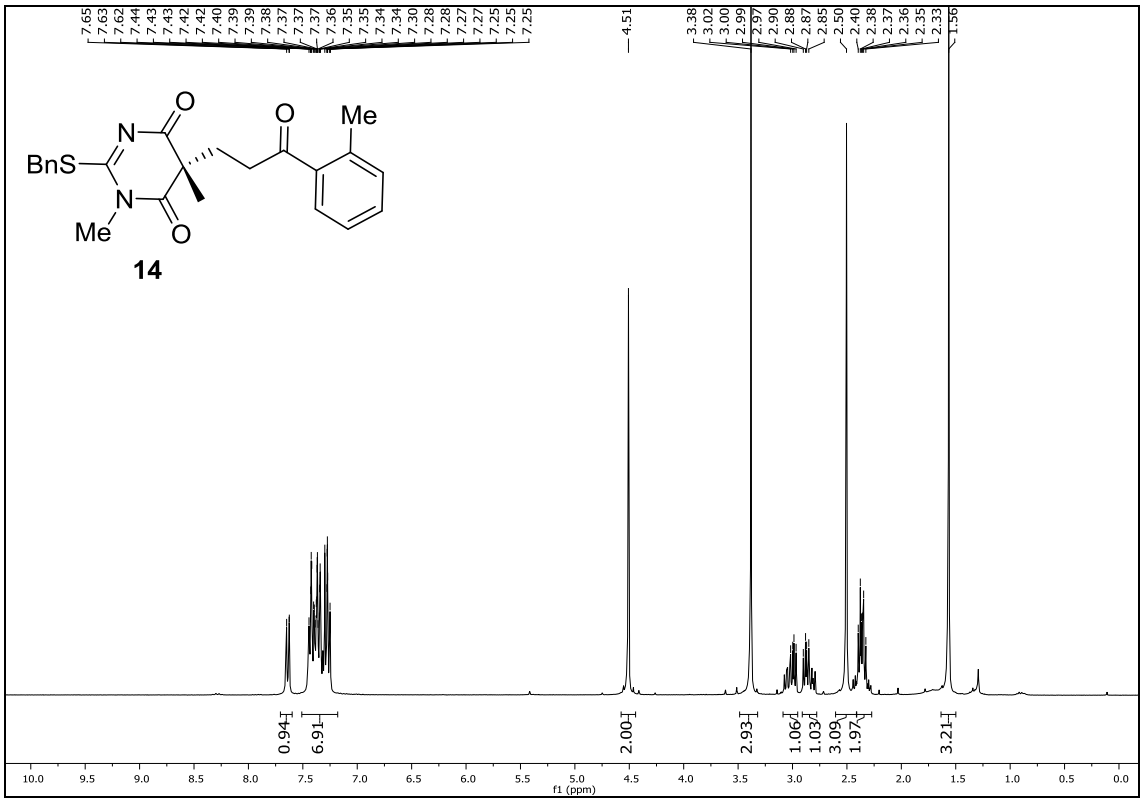

198.5
179.5 174.0 173.3
144.4 134.9 134.5 129.8 129.6 129.4 129.2 128.5 128.4
53.5
37.8 34.0 32.9 30.4 22.6 22.0
CDCl3
f1 (ppm)

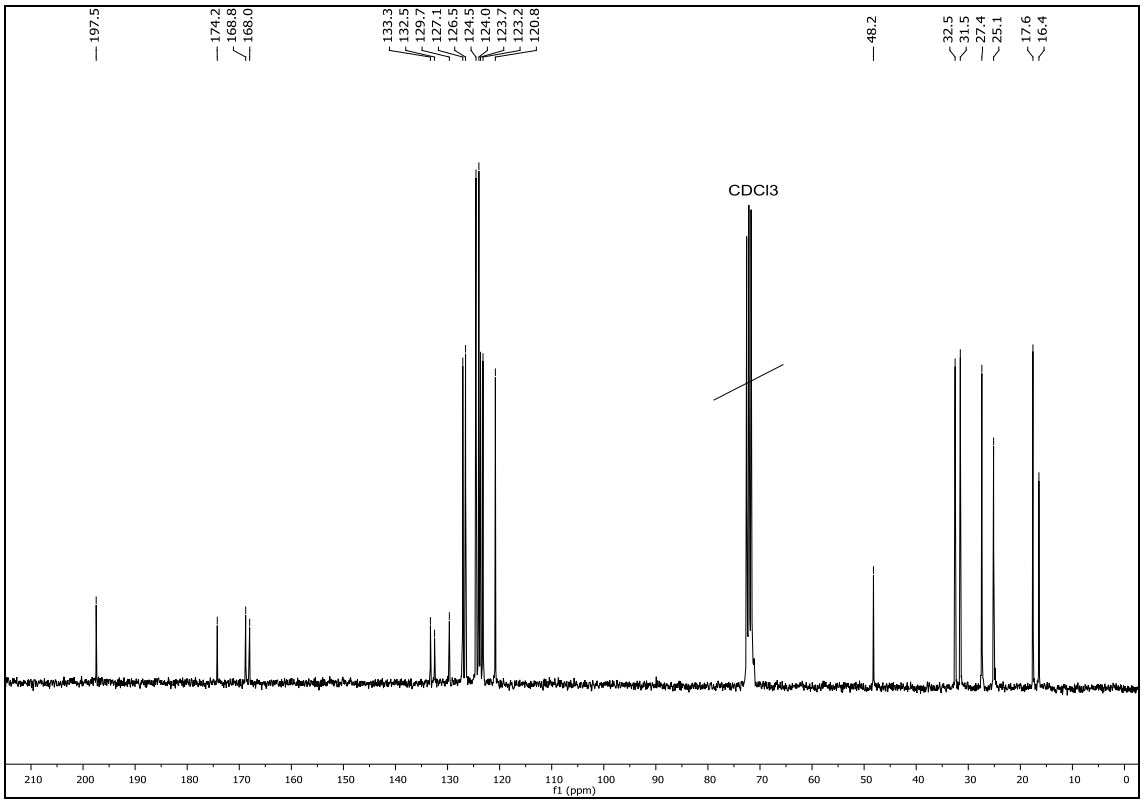

7.82
7.79
7.63
7.60
7.45
7.44
7.44
7.43
7.42
7.41
7.37
7.37
7.36
7.35
7.34
7.34
7.30
4.50
3.38
3.08
3.05
3.05
3.03
3.02
3.00
2.92
2.89
2.89
2.87
2.86
2.84
2.83
2.40
2.40
2.38
2.37
2.37
2.35
1.57
BnS
N
N
Me
O
O
O
O
Br
12
1.86
1.75
4.26
2.00
2.84
1.12
1.03
1.98
3.05
f1 (ppm)

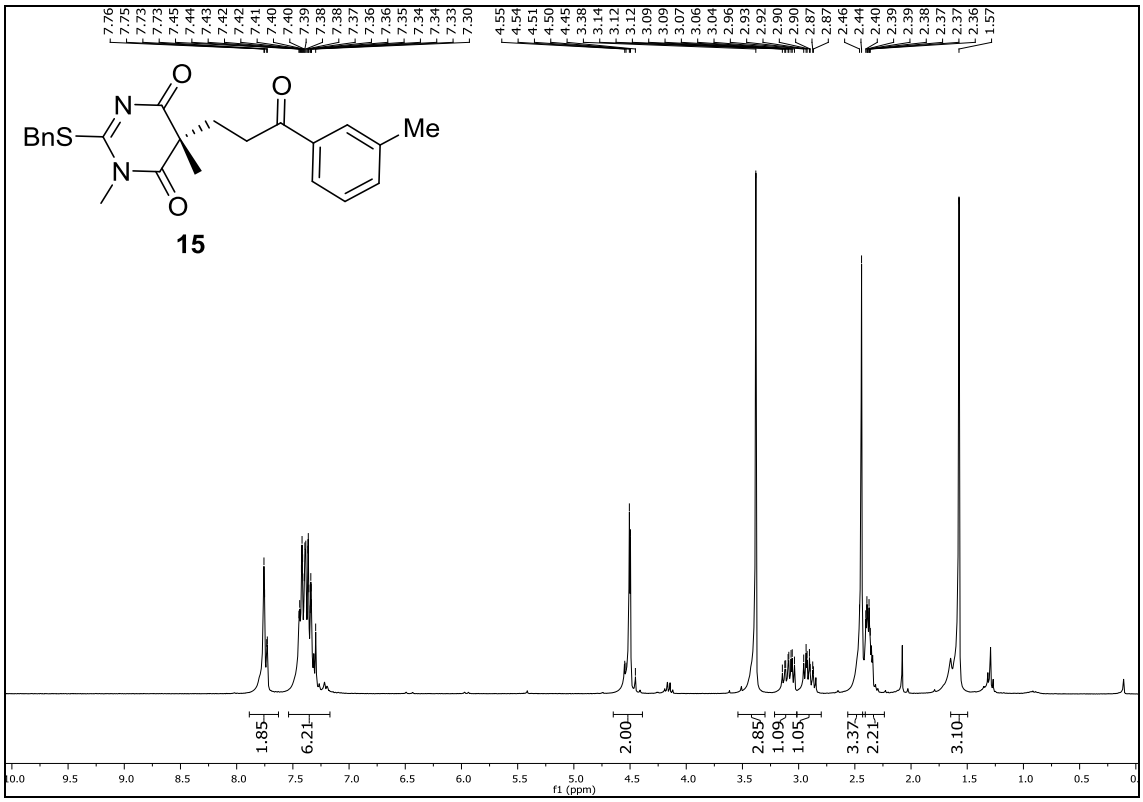

197.6
179.0
173.5
172.9
135.2
134.5
131.9
129.6
129.4
128.9
128.4
128.1
53.1
37.4
33.8
31.8
30.0
22.9
CDCl3
f1 (ppm)

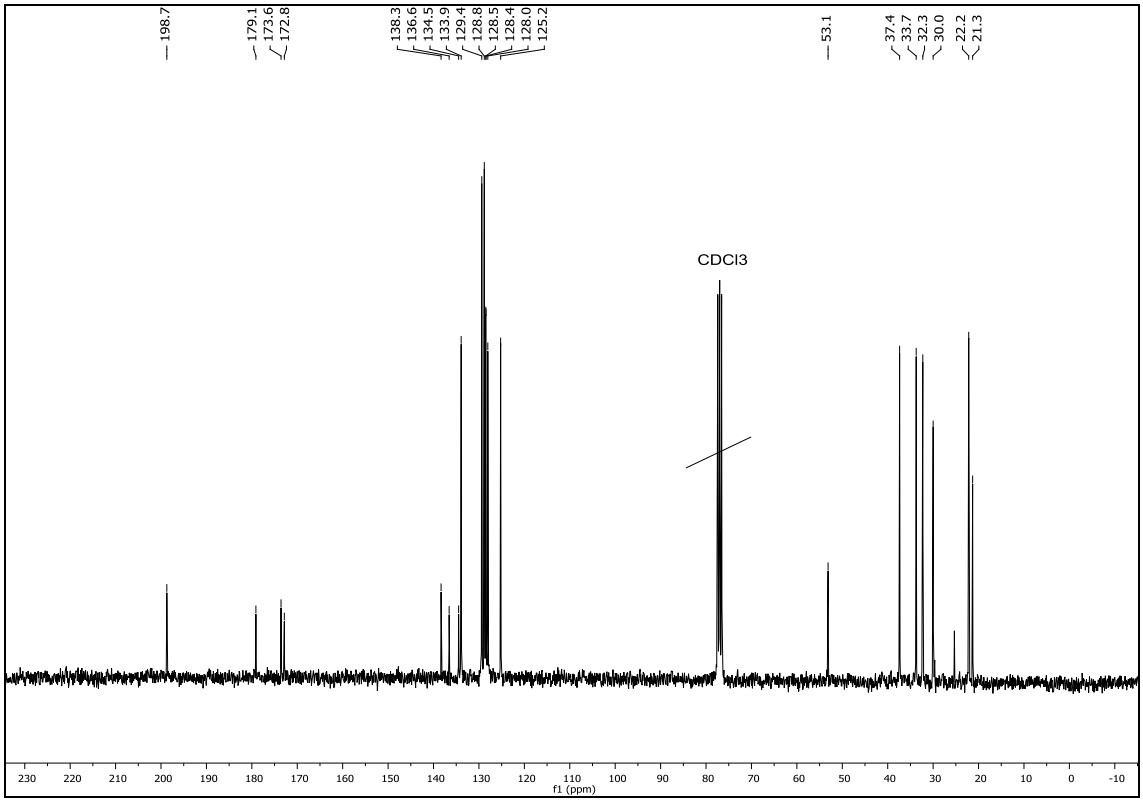

BnS
N
N
Me
O
O
O
13
1.85
7.96
2.00
3.01
1.18
1.04
2.08
3.06
f1 (ppm)

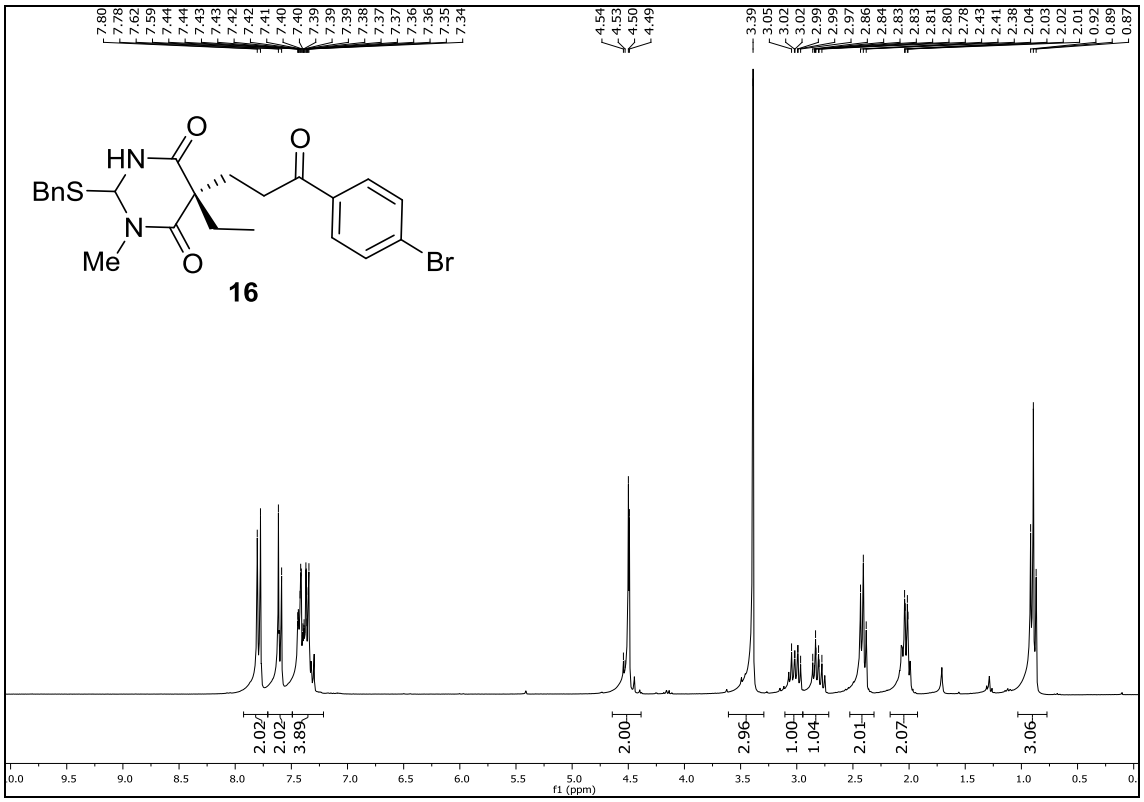

198.5
179.1
173.6
172.9
136.5
134.5
133.2
129.4
128.8
128.6
128.1
128.0
53.1
37.4
33.7
32.2
30.0
22.3
CDCl3
f1 (ppm)

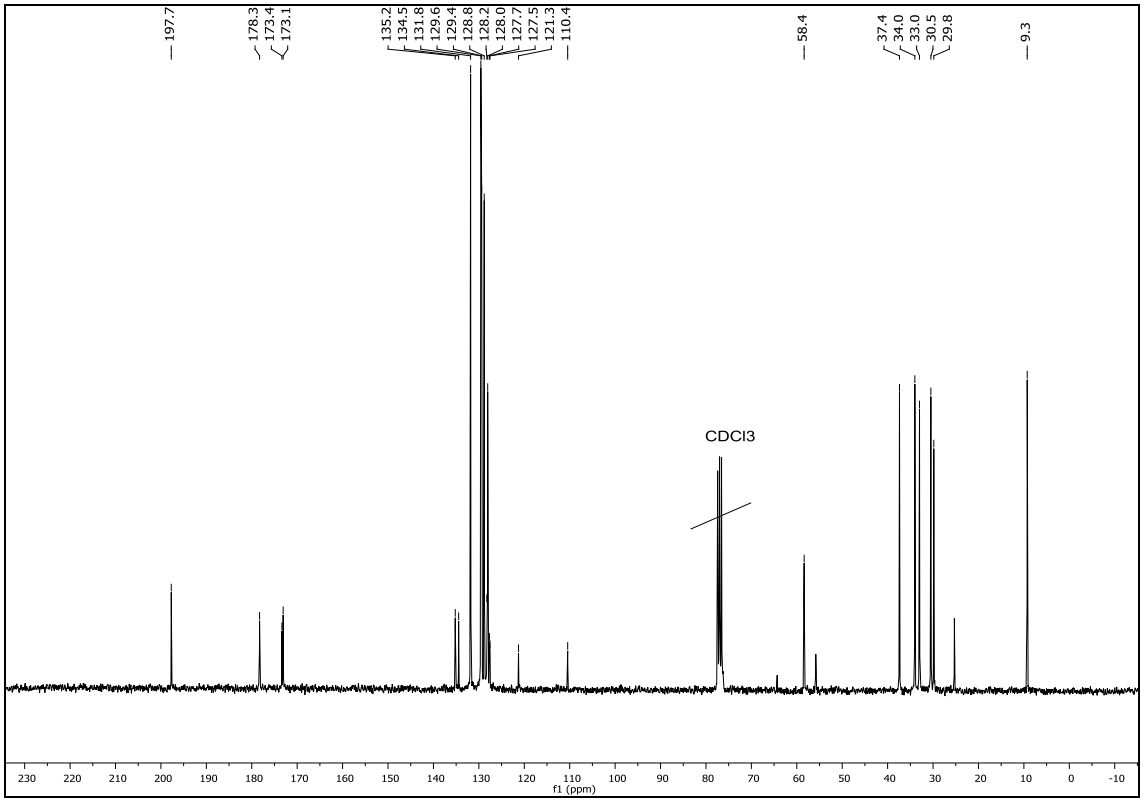

BnS
N
N
Me
O
O
O
Me
14
f1 (ppm)

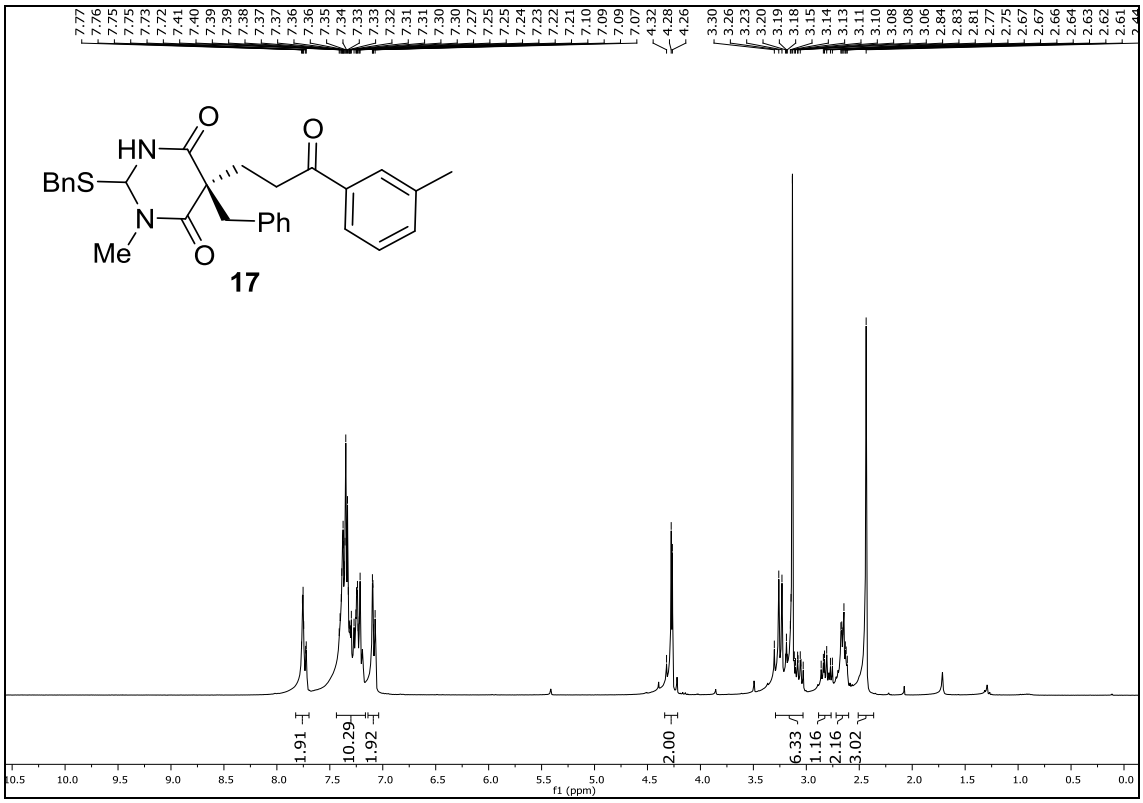

CDCl3
f1 (ppm)

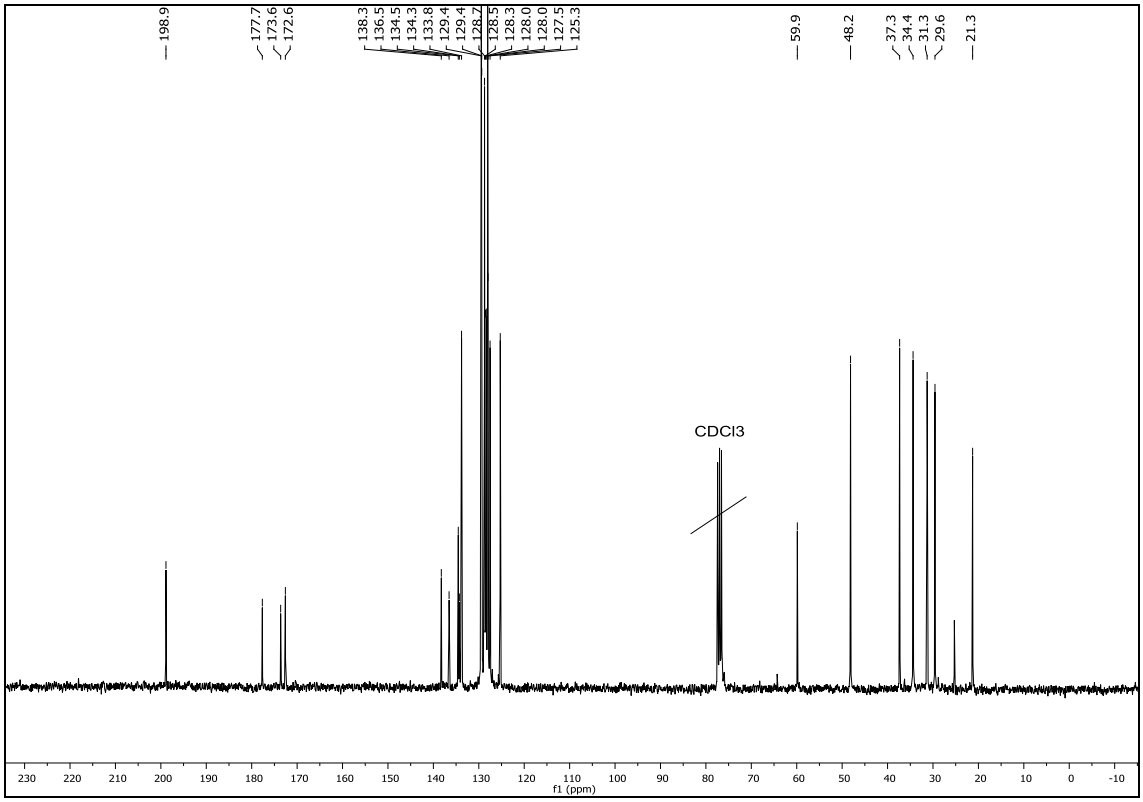

7.76 7.75 7.73 7.73 7.45 7.44 7.43 7.42 7.42 7.41 7.40 7.40 7.39 7.38 7.38 7.37 7.36 7.36 7.35 7.34 7.34 7.33 7.30
4.55 4.54 4.51 4.50 4.45 3.38 3.14 3.12 3.12 3.09 3.09 3.07 3.06 3.04 2.96 2.93 2.92 2.90 2.90 2.87 2.87 2.46 2.44 2.40 2.39 2.39 2.38 2.37 2.37 2.36 1.57
BnS
N
N
O
O
O
Me
15
1.85
6.21
2.00
2.85
1.09
1.05
3.37
2.21
3.10
f1 (ppm)

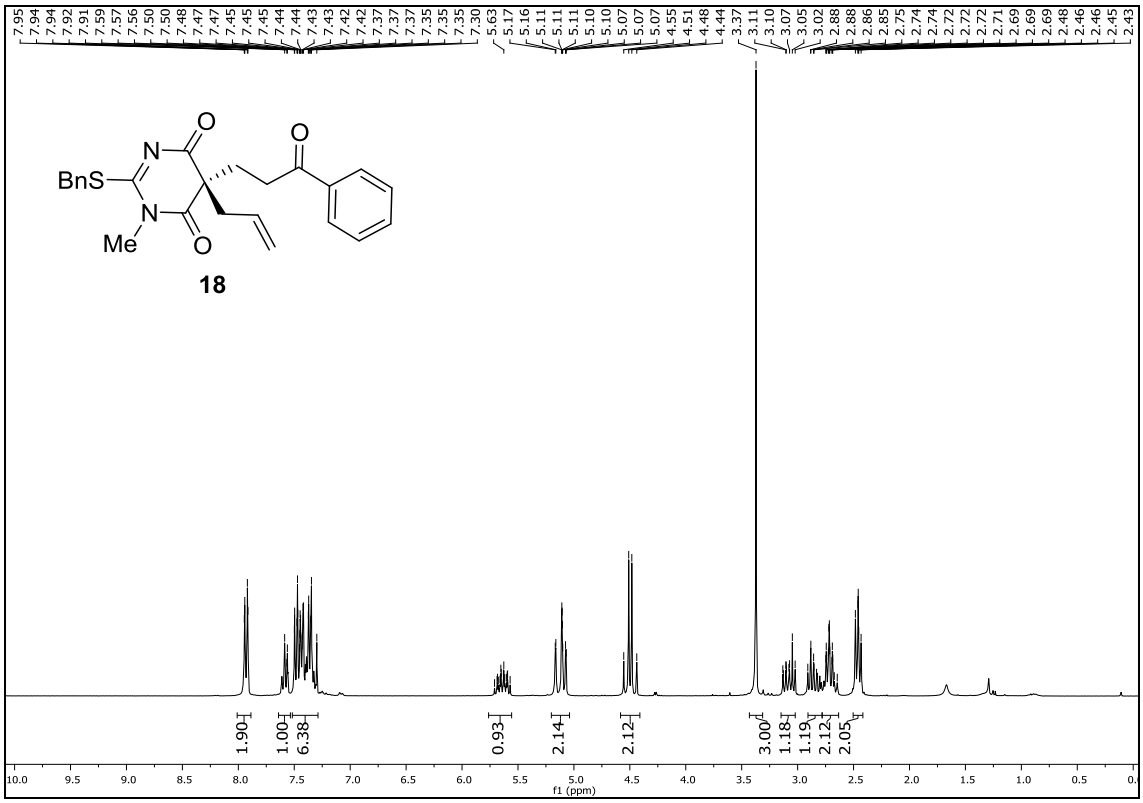

198.7
179.1
173.6
172.8
138.3
136.6
134.5
133.9
129.4
128.8
128.5
128.4
128.0
125.2
53.1
37.4
33.7
32.3
30.0
22.2
21.3
CDCl3
f1 (ppm)

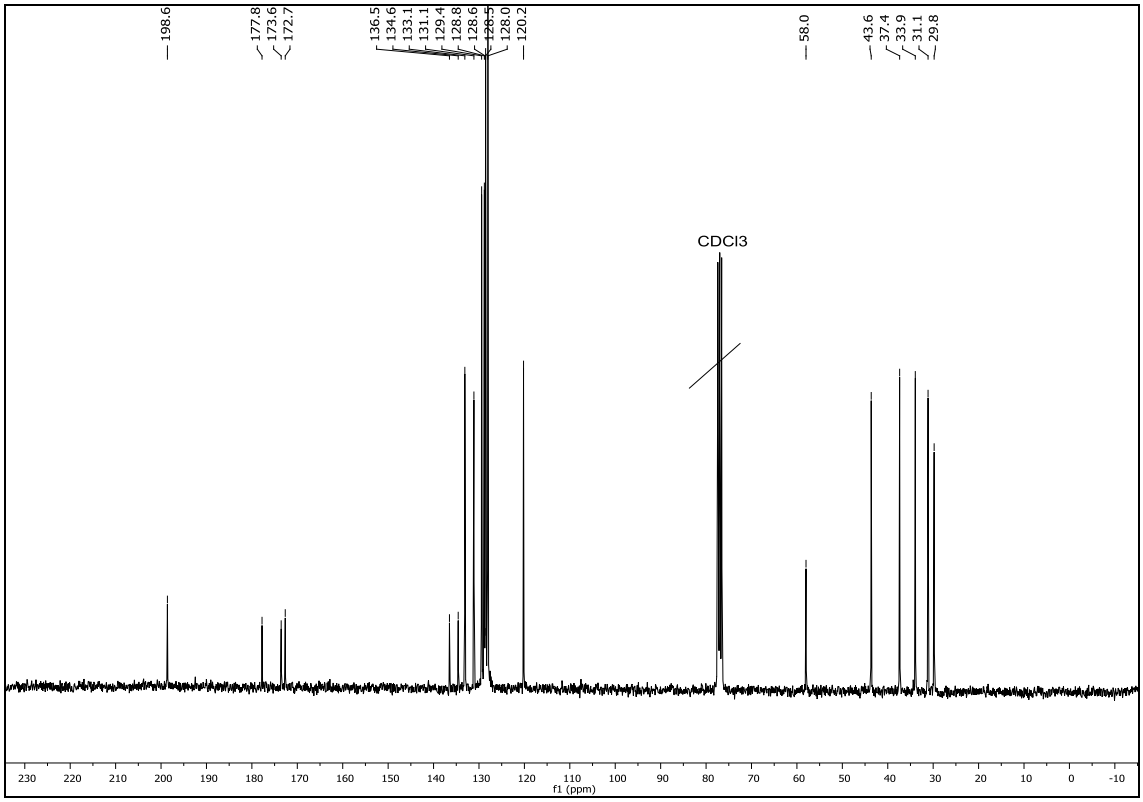

7.80 7.78 7.62 7.59 7.44 7.44 7.43 7.43 7.42 7.42 7.41 7.40 7.40 7.39 7.39 7.39 7.38 7.37 7.36 7.36 7.35 7.34
4.54 4.53 4.50 4.49
3.39 3.05 3.02 3.02 2.99 2.99 2.97 2.86 2.84 2.83 2.83 2.81 2.80 2.78 2.43 2.41 2.38 2.04 2.03 2.02 2.01 0.92 0.89 0.87
HN
BnS
N
Me
O
O
O
O
Br
16
2.02 2.02 3.89 2.00 2.96 1.00 1.04 2.01 2.07 3.06
f1 (ppm)

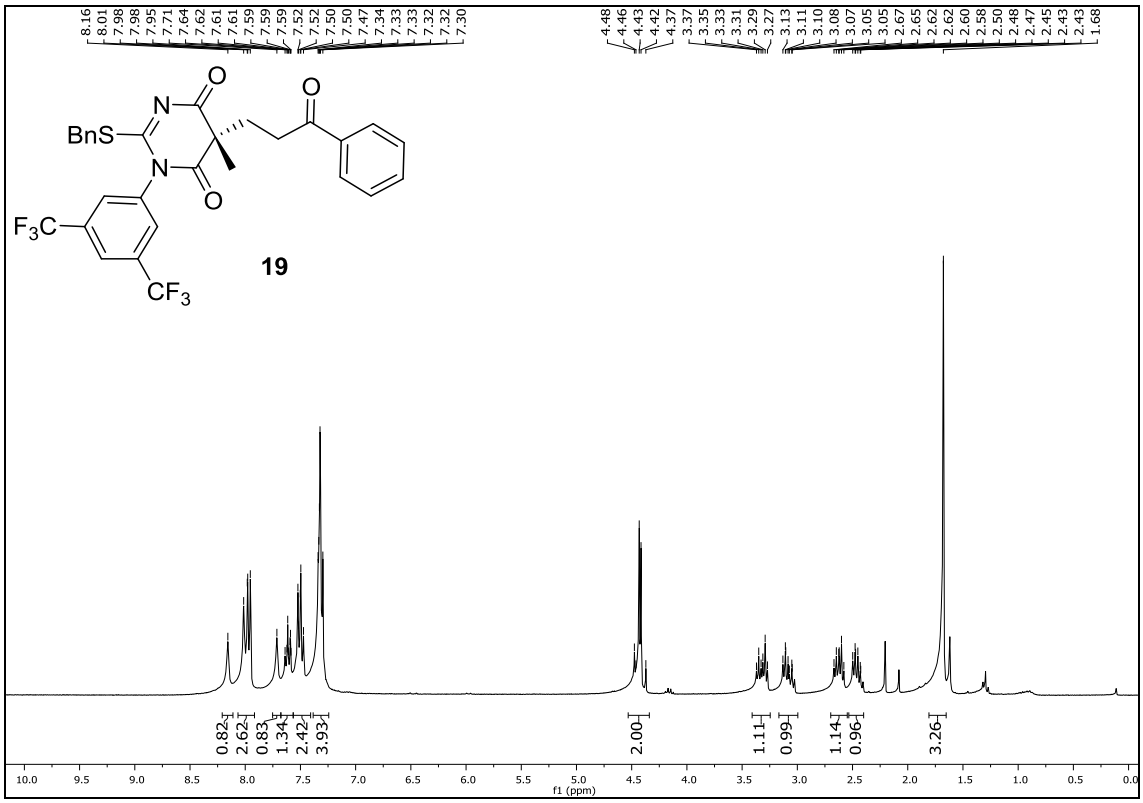

197.7
178.3 173.4 173.1
135.2 134.5 131.8 129.6 129.4 128.8 128.2 128.0 127.7 127.5 121.3 110.4
58.4
37.4 34.0 33.0 30.5 29.8
9.3
CDCl3
f1 (ppm)


HN
BnS
N
Me
O
O
O
Ph
17
1.91
10.29
1.92
2.00
6.33
1.16
2.16
3.02
f1 (ppm)


198.9
177.7
173.6
172.6
138.3
136.5
134.5
134.3
133.8
129.4
129.4
128.7
128.5
128.3
128.0
128.0
127.5
125.3
59.9
48.2
37.3
34.4
31.3
29.6
21.3
CDCl3
f1 (ppm)


BnS
N
N
Me
O
O
O
18
f1 (ppm)


CDCl3
f1 (ppm)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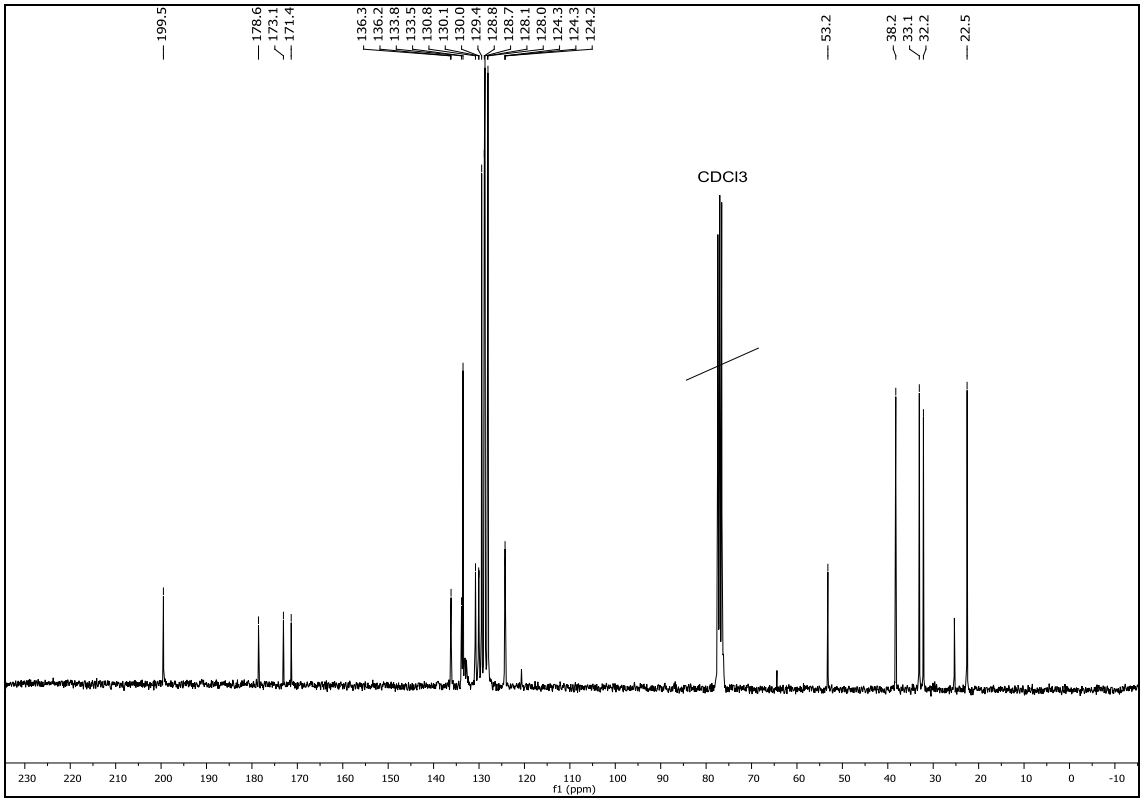
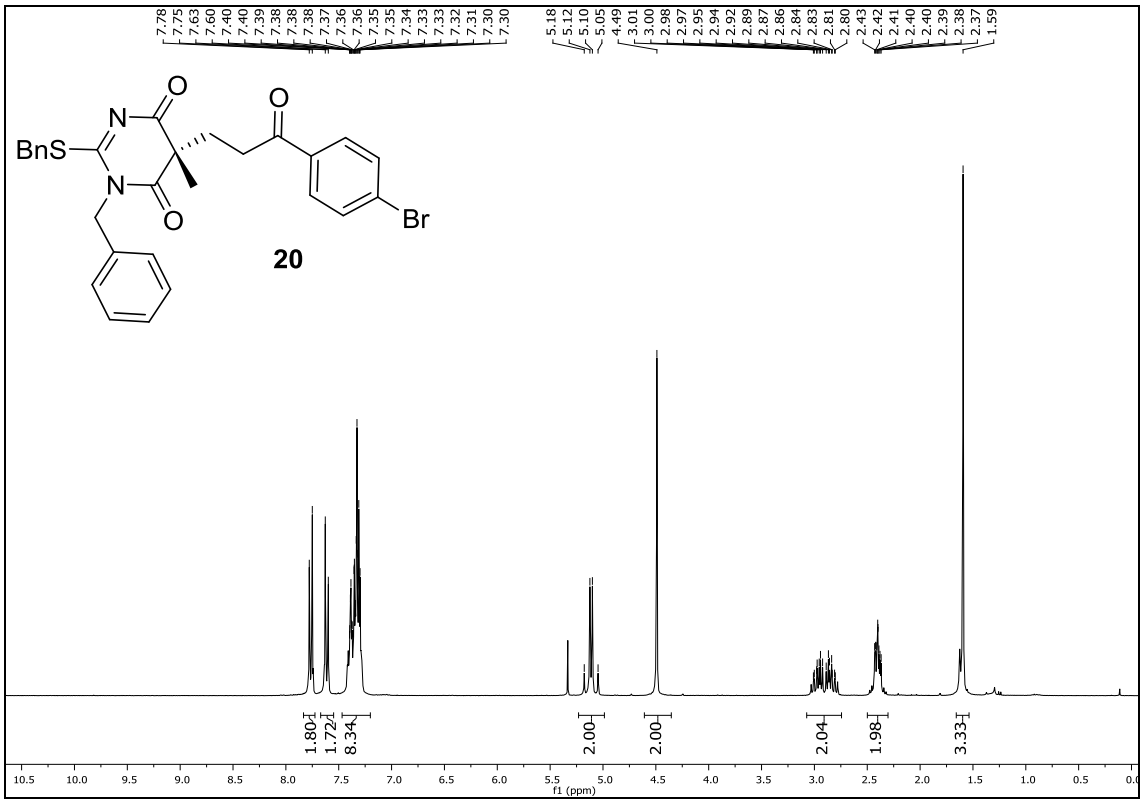
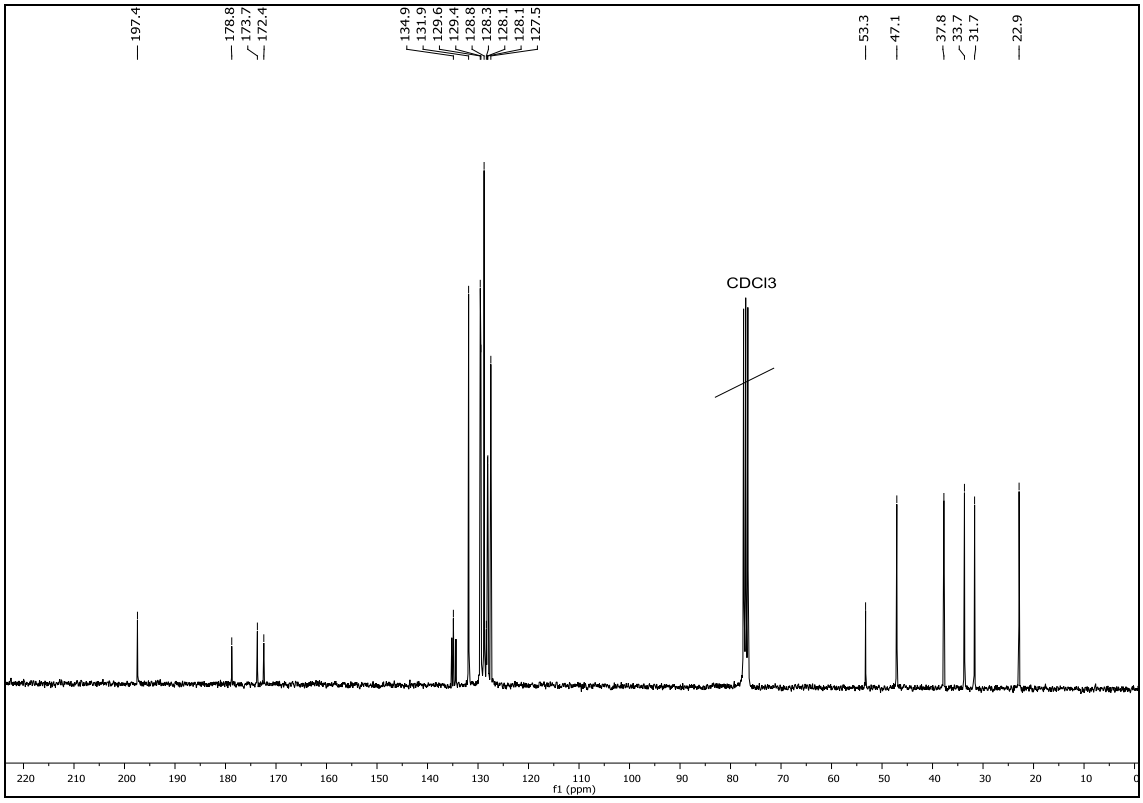
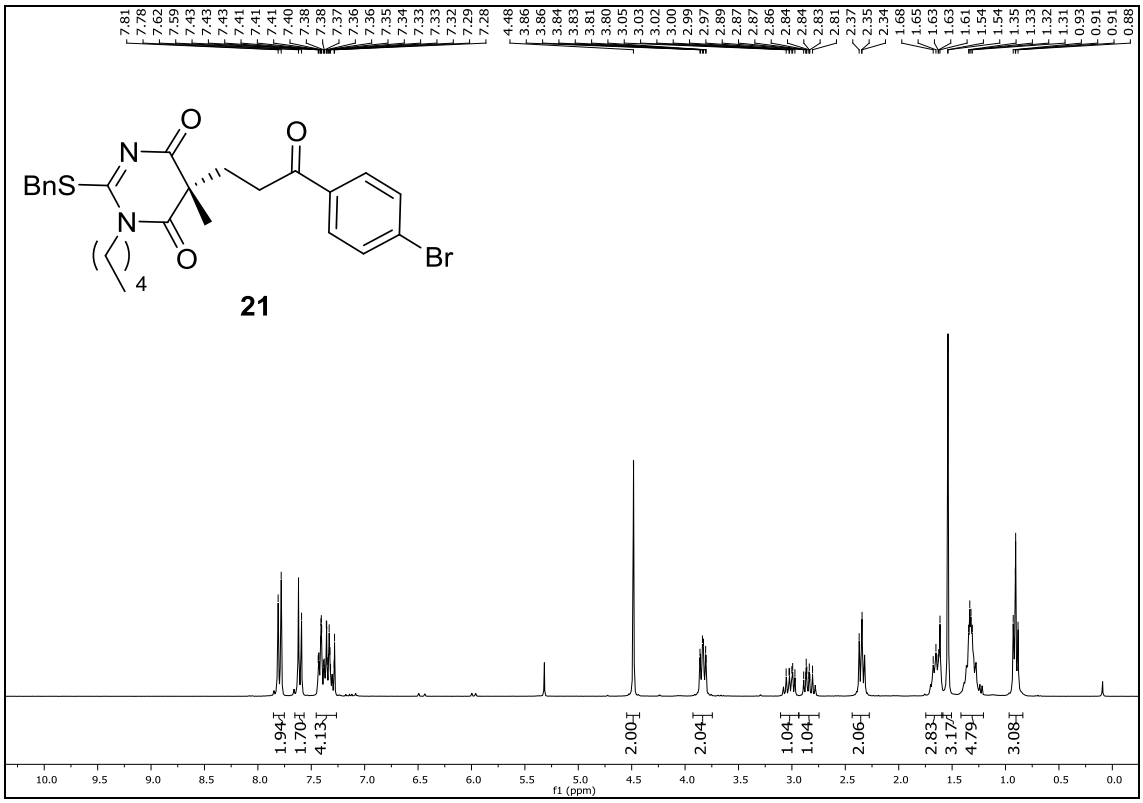
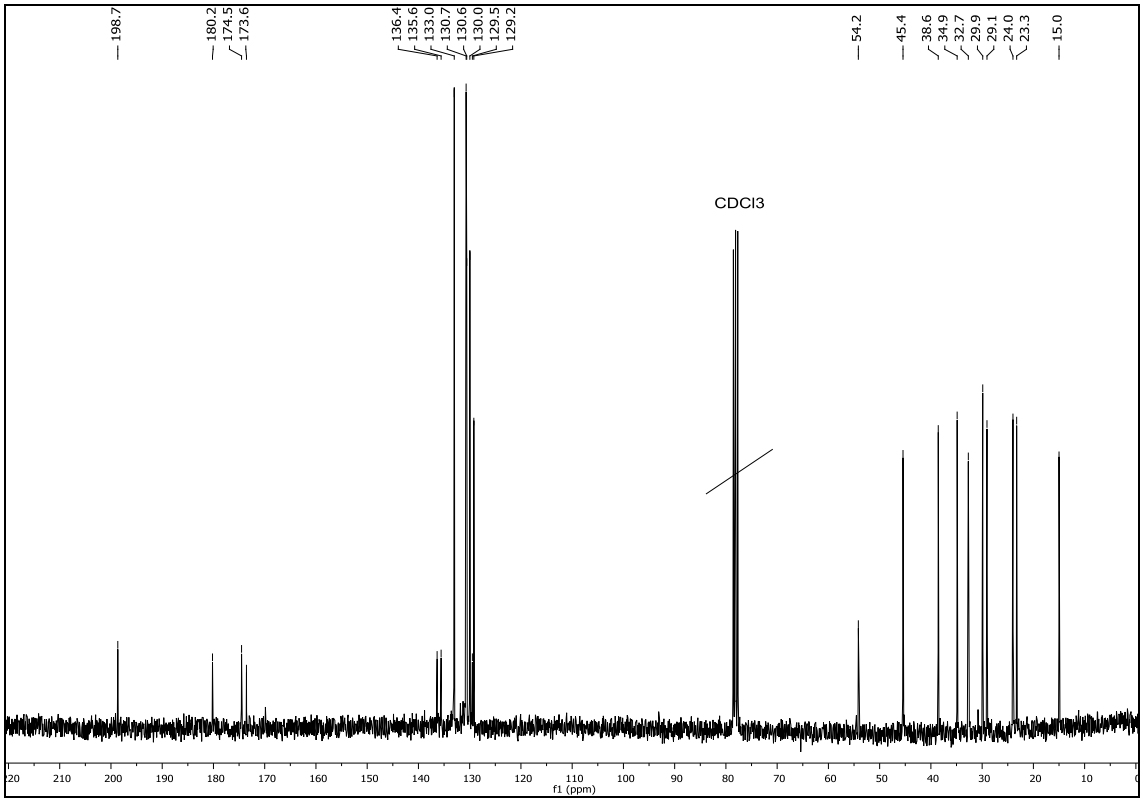
8.01
7.98
7.98
7.95
7.71
7.64
7.62
7.61
7.61
7.59
7.59
7.59
7.52
7.52
7.50
7.50
7.47
7.34
7.33
7.33
7.32
7.32
7.30
4.48
4.46
4.43
4.42
4.37
3.37
3.35
3.33
3.31
3.29
3.27
3.13
3.11
3.10
3.08
3.07
3.05
3.05
2.67
2.65
2.62
2.62
2.60
2.58
2.50
2.48
2.47
2.45
2.43
2.43
1.68
O
N
O
BnS
N
O
F3C
CF3
19
0.82
2.62
0.83
1.34
2.42
3.93
2.00
1.11
0.99
1.14
0.96
3.26
f1 (ppm)

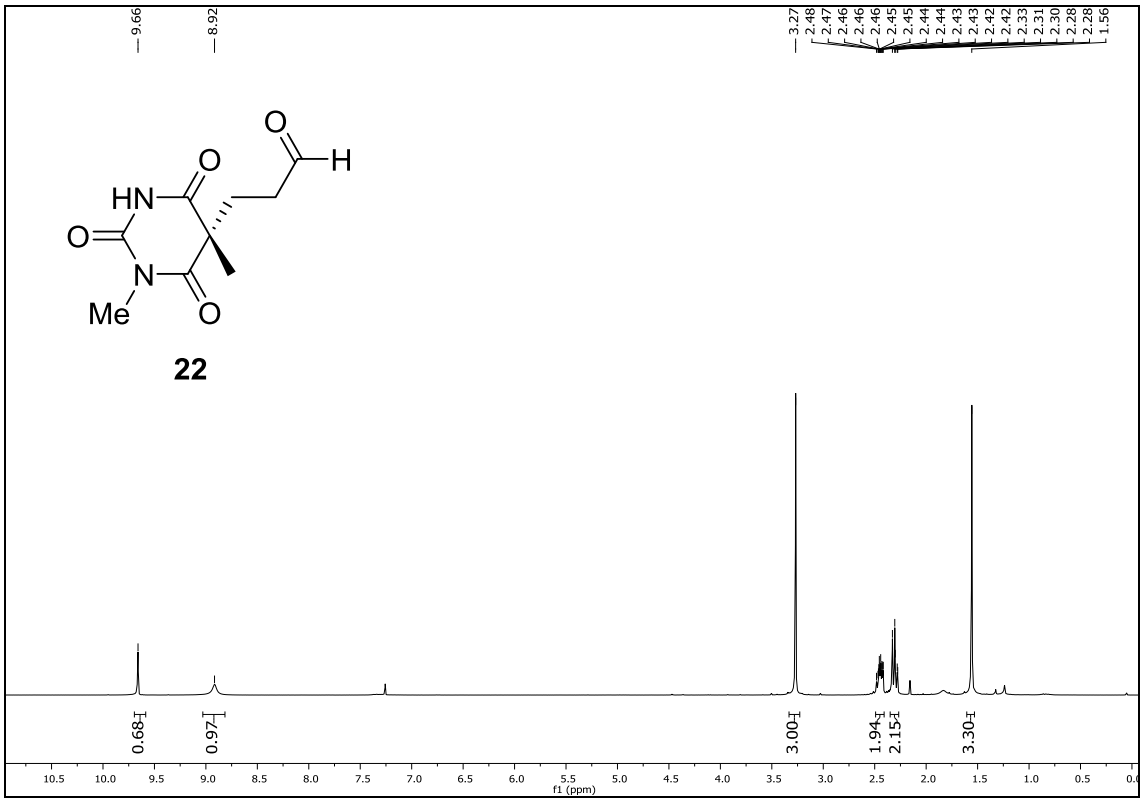

199.5
178.6
173.1
171.4
136.3
136.2
133.8
133.5
130.8
130.1
130.0
129.4
128.8
128.7
128.1
128.0
124.3
124.3
124.2
53.2
38.2
33.1
32.2
22.5
CDCl3
f1 (ppm)


BnS
N
N
O
O
O
Br
20
f1 (ppm)

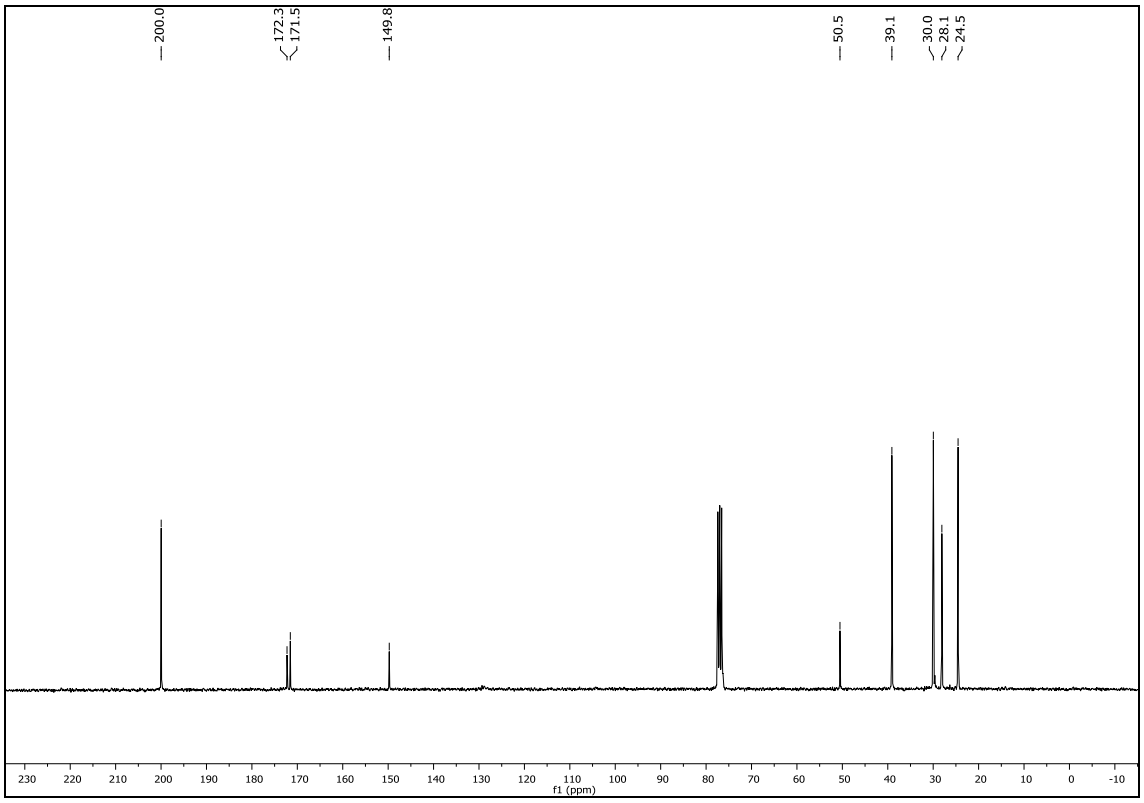

CDCl3
f1 (ppm)

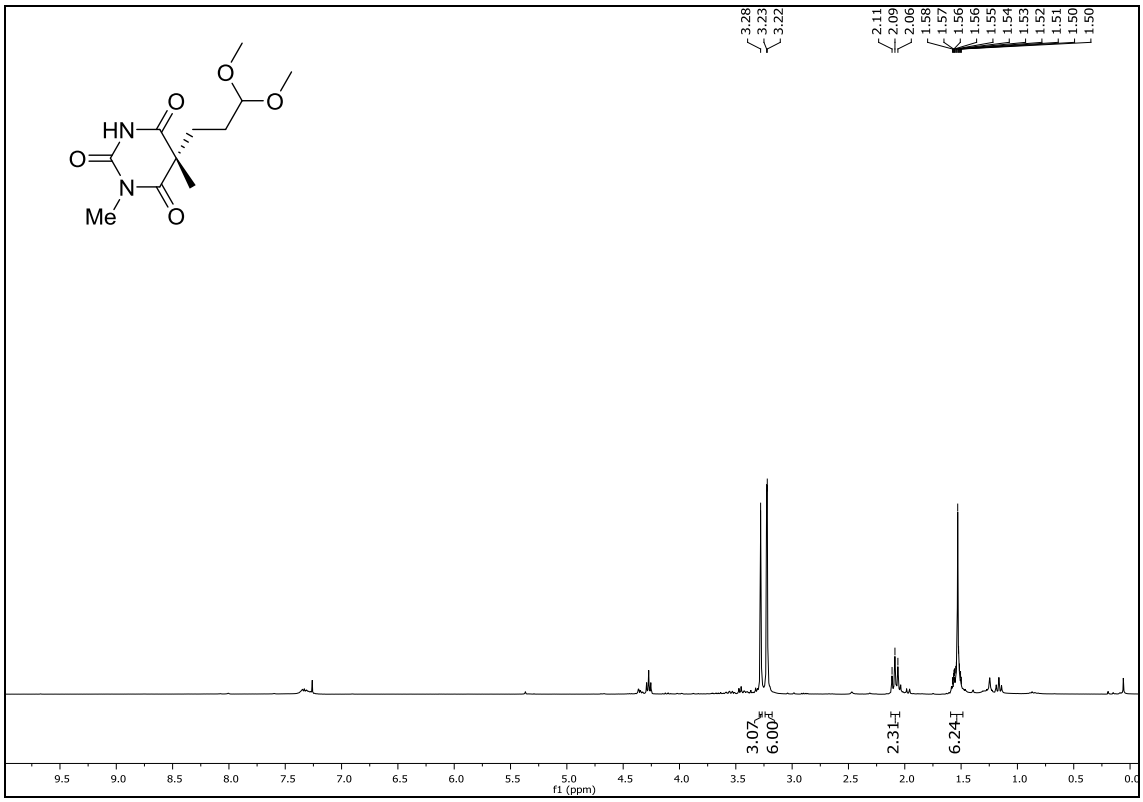

BnS
N
N
O
O
O
Br
4
21
f1 (ppm)

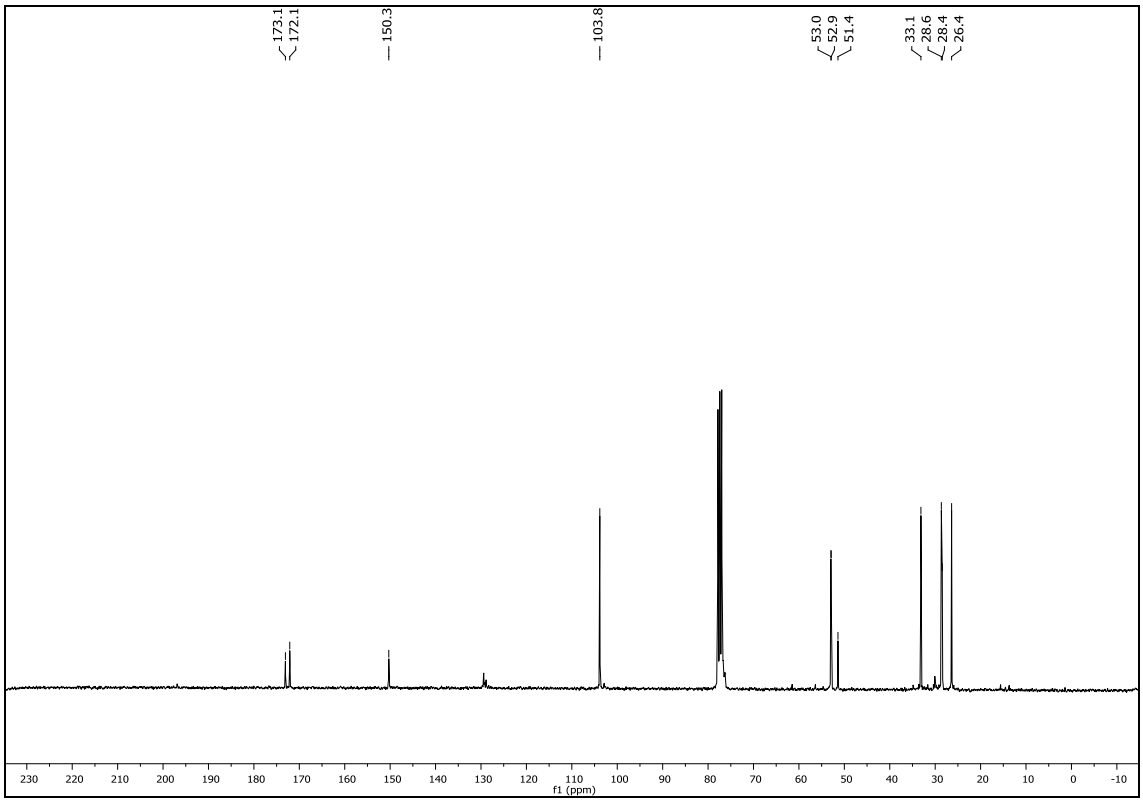

CDCl3
f1 (ppm)

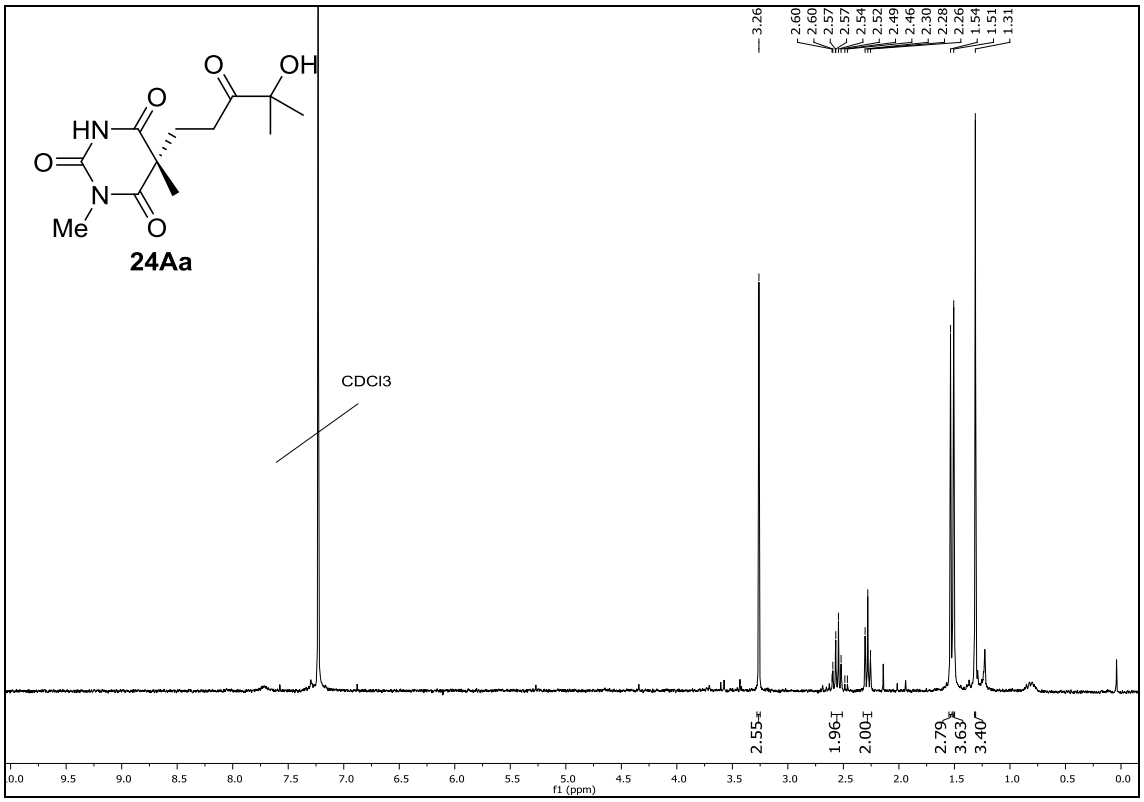

9.66
8.92
3.27
2.48
2.47
2.46
2.46
2.46
2.45
2.45
2.44
2.44
2.43
2.43
2.42
2.42
2.33
2.31
2.30
2.28
2.28
1.56
O
H
O
HN
O
N
Me
O
0.68
0.97
3.00
1.94
2.15
3.30
f1 (ppm)

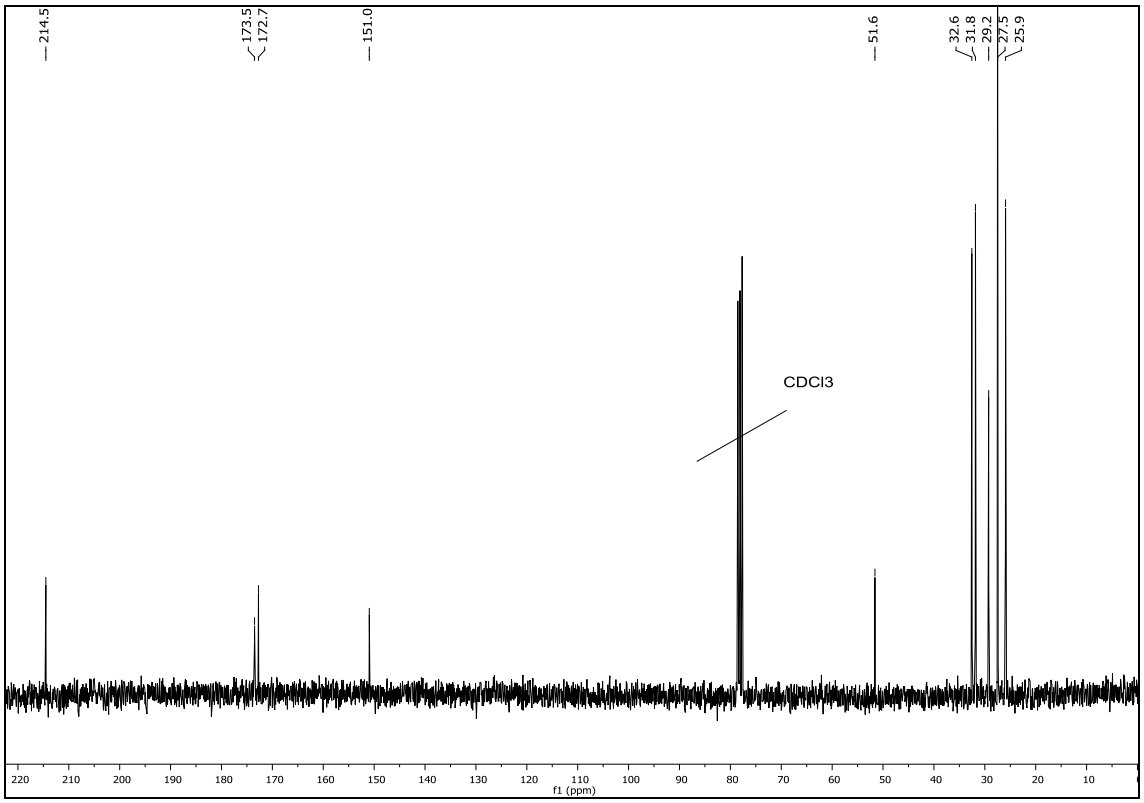
22

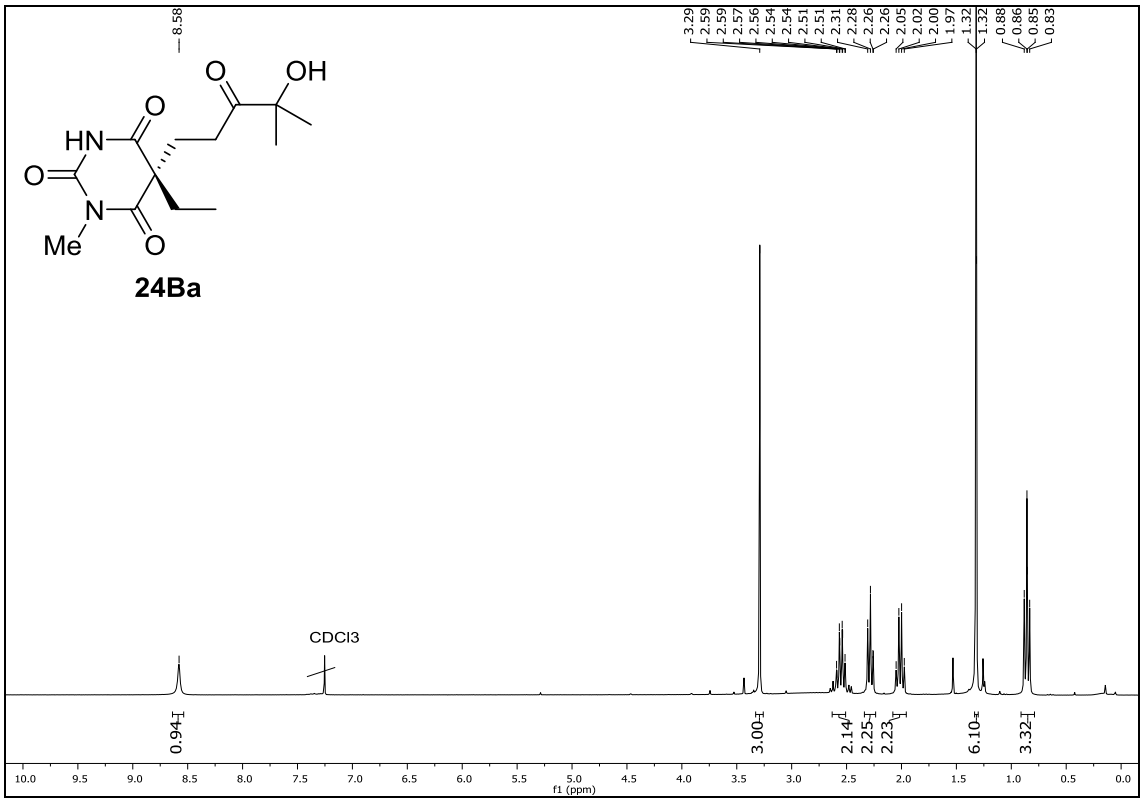

200.0
172.3
171.5
149.8
50.5
39.1
30.0
28.1
24.5
f1 (ppm)


3.28
3.23
3.22
2.11
2.09
2.06
1.58
1.57
1.56
1.56
1.55
1.54
1.53
1.52
1.51
1.50
1.50
HN
O
O
N
Me
O
O
O
3.07
6.00
2.31
6.24
f1 (ppm)


173.1
172.1
150.3
103.8
53.0
52.9
51.4
33.1
28.6
28.4
26.4
f1 (ppm)


24Aa
CDCl3
f1 (ppm)


CDCl3
f1 (ppm)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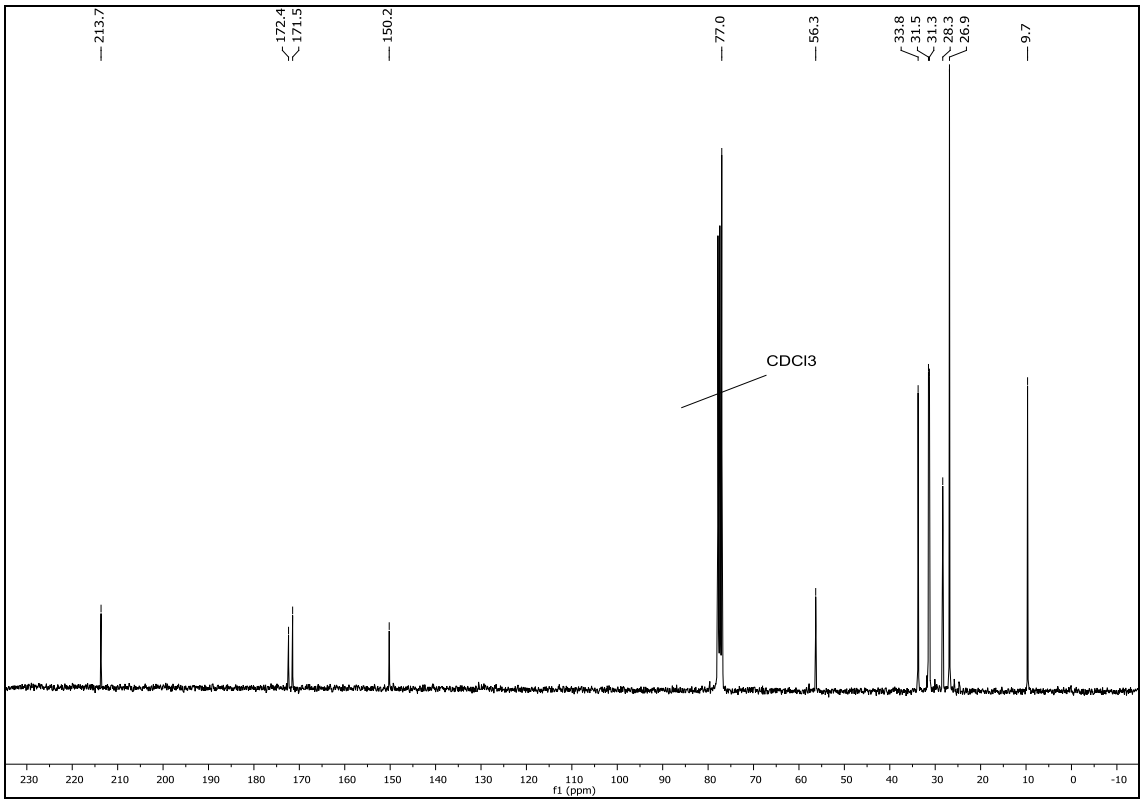
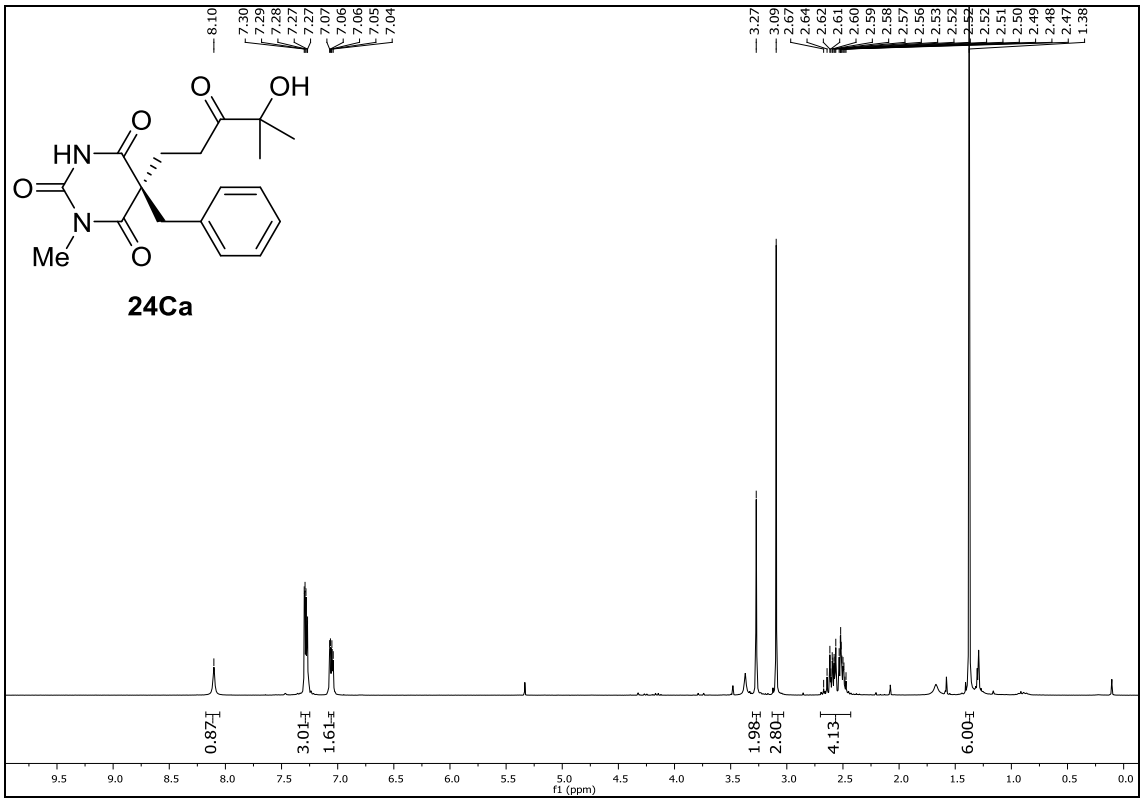
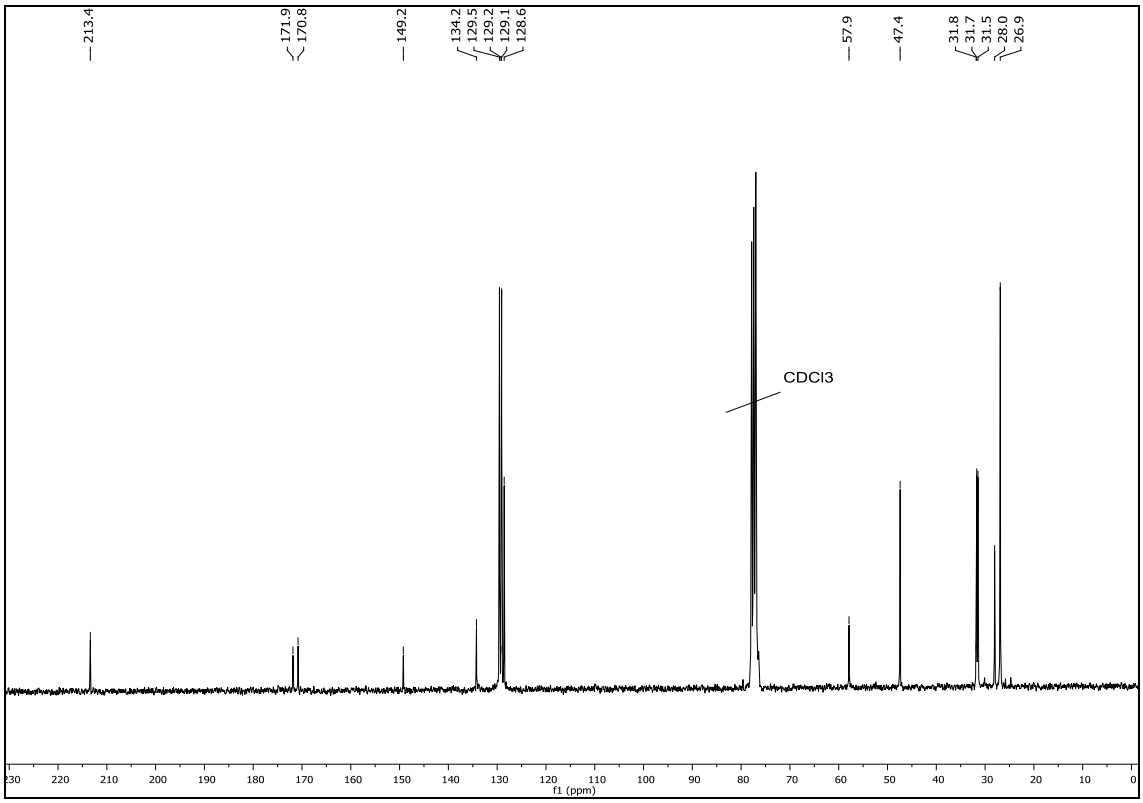
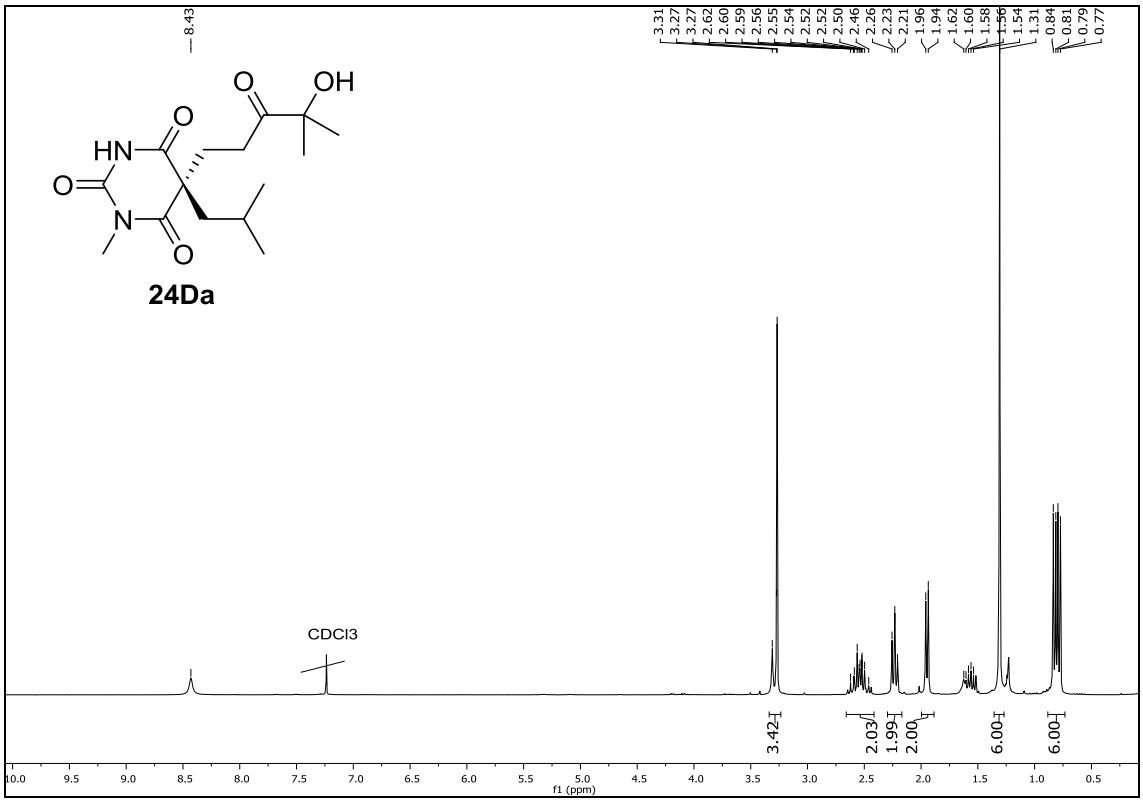
3.29
2.59
2.59
2.57
2.56
2.54
2.54
2.51
2.51
2.31
2.28
2.26
2.26
2.05
2.02
2.00
1.97
1.32
1.32
0.88
0.86
0.85
0.83
O
OH
HN
O
N
Me
O
O
24Ba
CDCl3
0.94
3.00
2.14
2.25
2.23
6.10
3.32
f1 (ppm)


213.7
172.4
171.5
150.2
77.0
56.3
33.8
31.5
31.3
28.3
26.9
9.7
CDCl3
f1 (ppm)


8.10
7.30
7.29
7.28
7.27
7.27
7.07
7.06
7.06
7.05
7.04
3.27
3.09
2.67
2.64
2.62
2.61
2.60
2.59
2.58
2.57
2.56
2.53
2.52
2.52
2.52
2.51
2.50
2.49
2.48
2.47
1.38
O
OH
HN
O
N
Me
O
O
24Ca
0.87
3.01
1.61
1.98
2.80
4.13
6.00
f1 (ppm)


213.4
171.9
170.8
149.2
134.2
129.5
129.2
129.1
128.6
57.9
47.4
31.8
31.7
31.5
28.0
26.9
CDCl3
f1 (ppm)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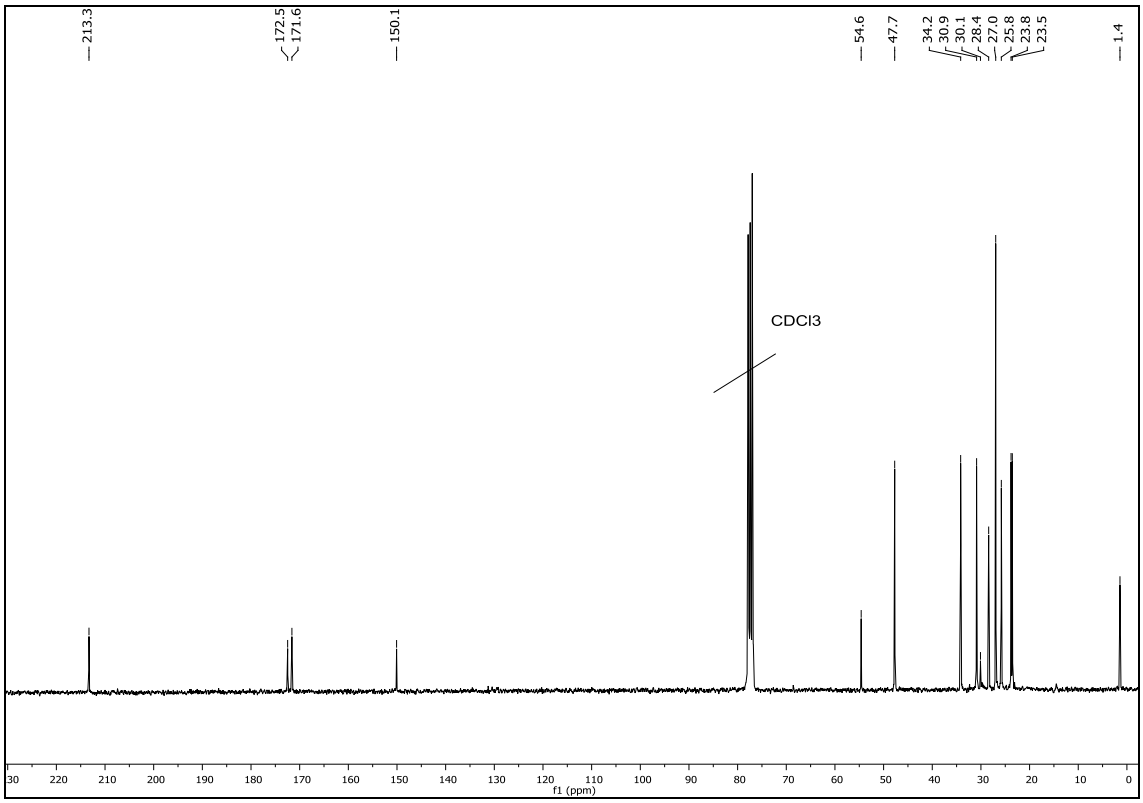
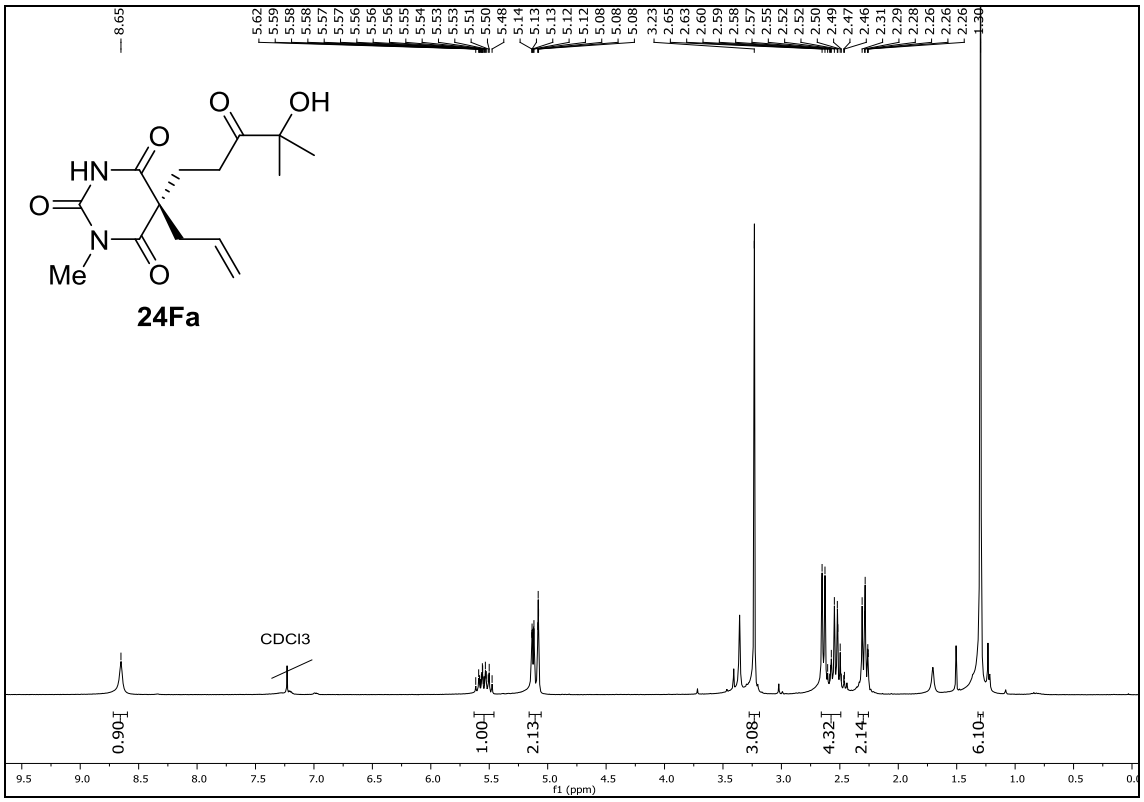
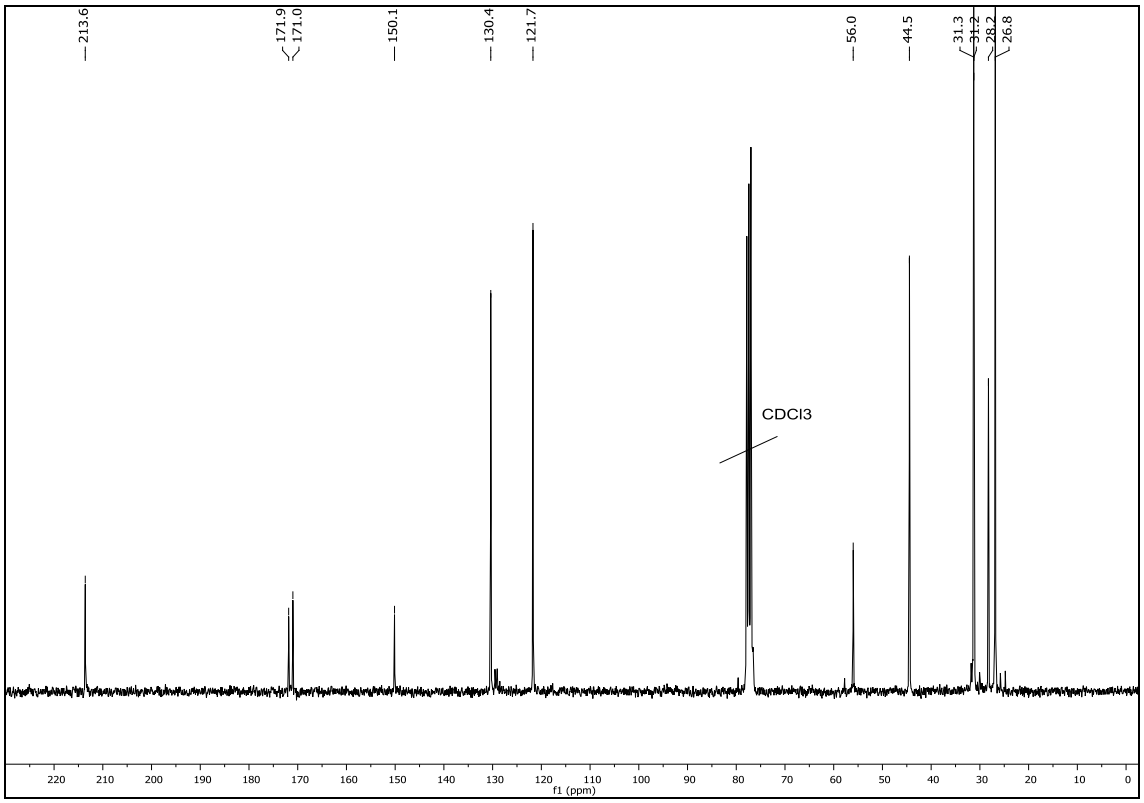
3.27
3.27
2.62
2.60
2.59
2.56
2.55
2.54
2.52
2.52
2.50
2.46
2.26
2.23
2.21
1.96
1.94
1.62
1.60
1.58
1.56
1.54
1.31
0.84
0.81
0.79
0.77
O
OH
O
HN
O
N
O
24Da
CDCl3
3.42
2.03
1.99
2.00
6.00
6.00
f1 (ppm)


213.3
172.5
171.6
150.1
54.6
47.7
34.2
30.9
30.1
28.4
27.0
25.8
23.8
23.5
1.4
CDCl3
f1 (ppm)


8.65
5.62 5.59 5.58 5.58 5.57 5.57 5.56 5.56 5.56 5.55 5.54 5.53 5.53 5.51 5.50 5.48 5.14 5.13 5.13 5.12 5.12 5.08 5.08 5.08 3.23 2.65 2.63 2.60 2.59 2.58 2.57 2.55 2.52 2.52 2.50 2.49 2.47 2.46 2.31 2.29 2.28 2.26 2.26 2.26 1.30
O
OH
HN
O
N
Me
O
O
24Fa
CDCl3
0.90
1.00
2.13
3.08
4.32
2.14
6.10
f1 (ppm)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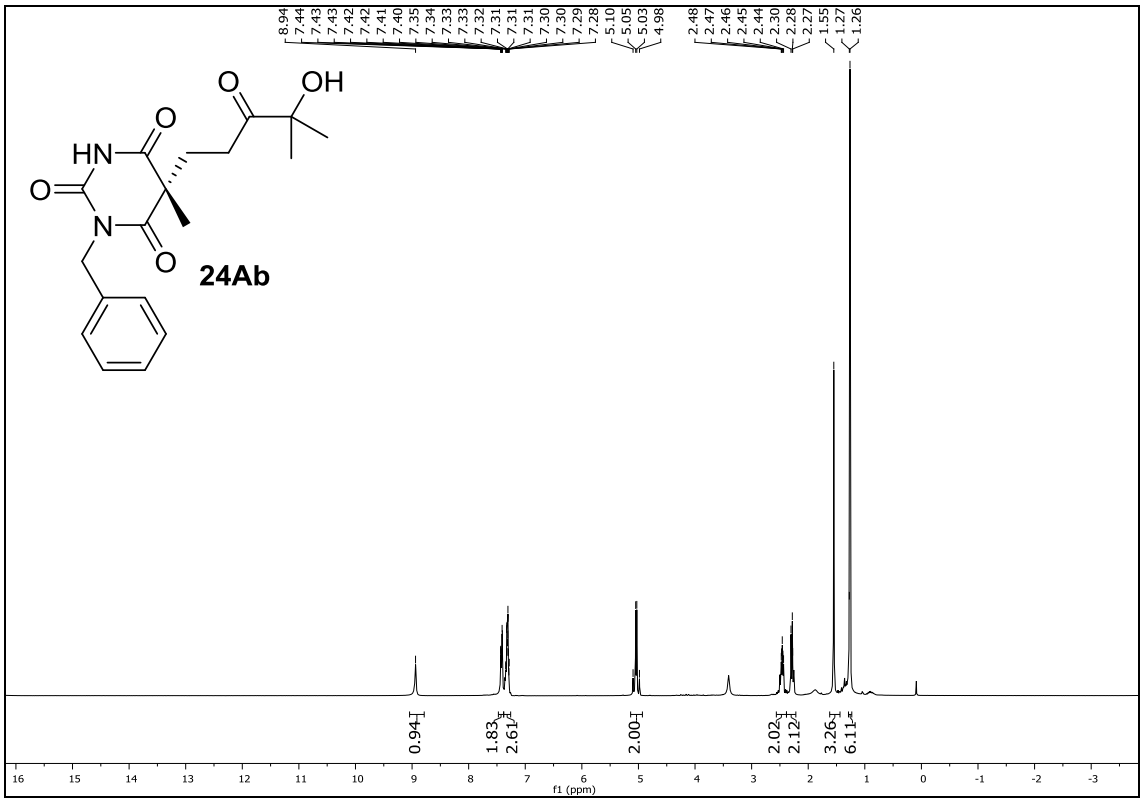
171.9
171.0
150.1
130.4
121.7
56.0
44.5
31.3
31.2
28.2
26.8
CDCl3
f1 (ppm)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7.43
7.42
7.42
7.41
7.40
7.35
7.34
7.33
7.33
7.32
7.31
7.31
7.31
7.30
7.30
7.29
7.28
5.10
5.05
5.03
4.98
2.48
2.47
2.46
2.45
2.44
2.30
2.28
2.27
1.55
1.27
1.26
O
OH
HN
O
O
N
O
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0.94
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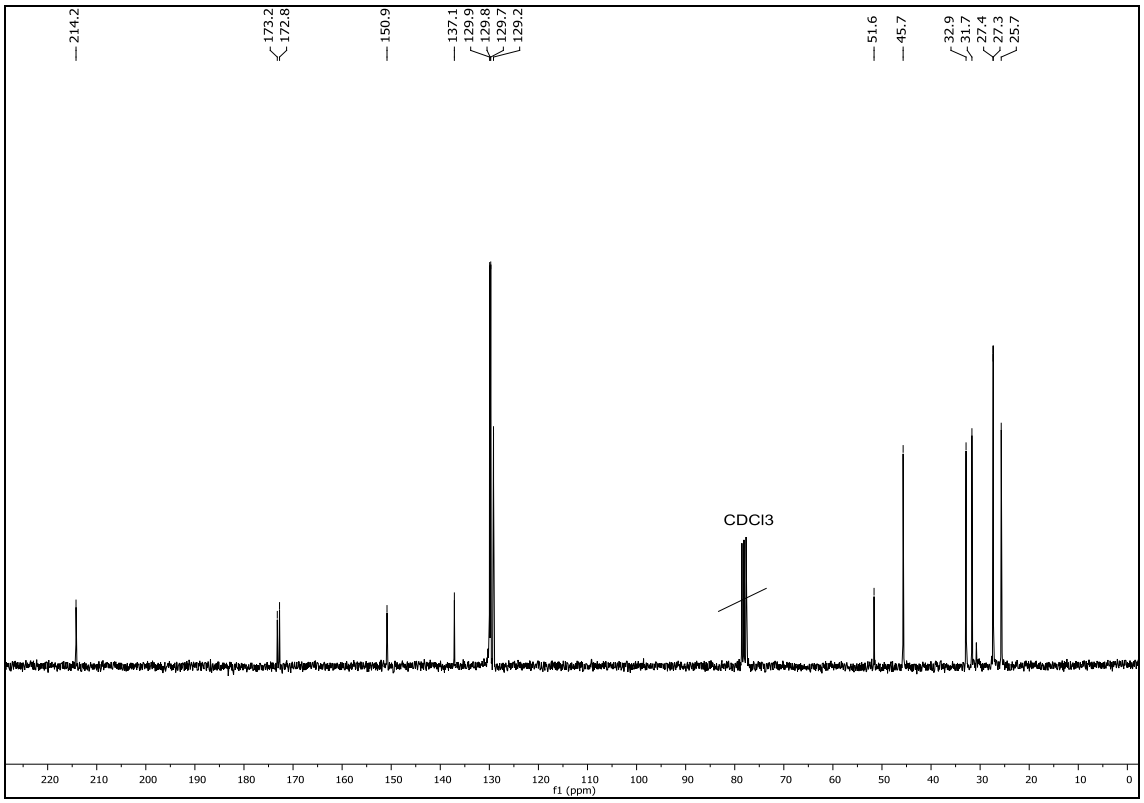
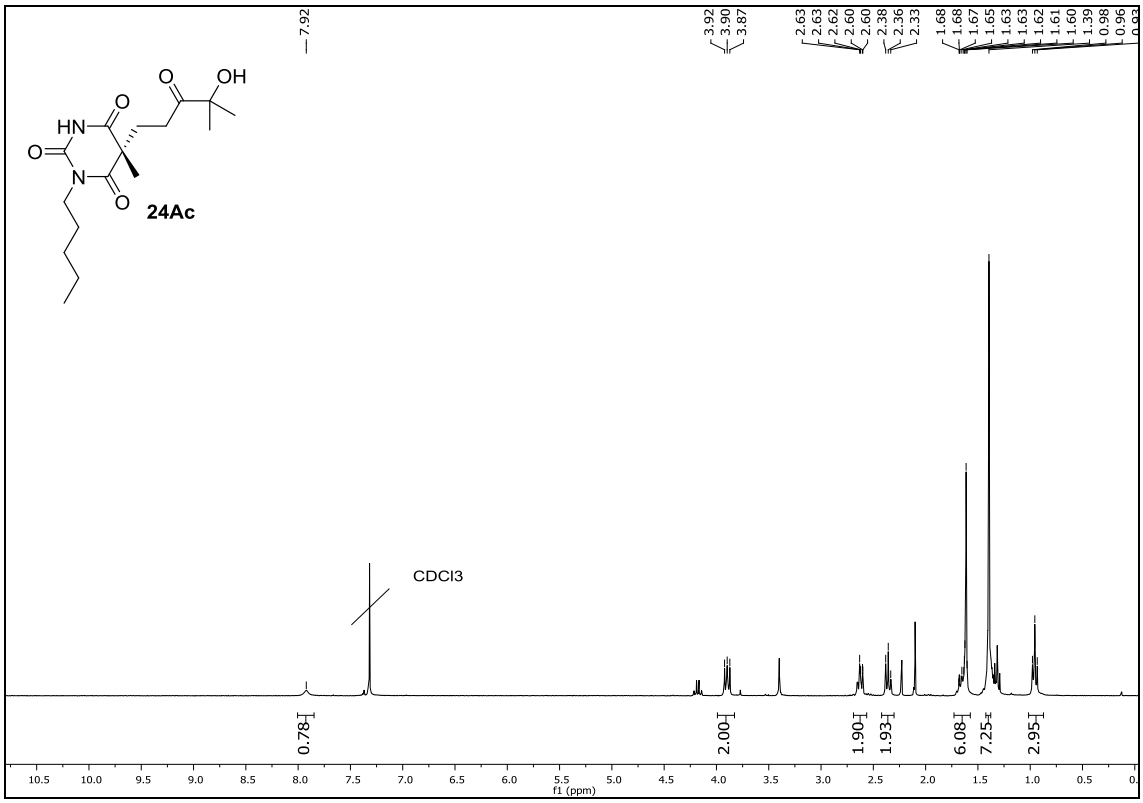
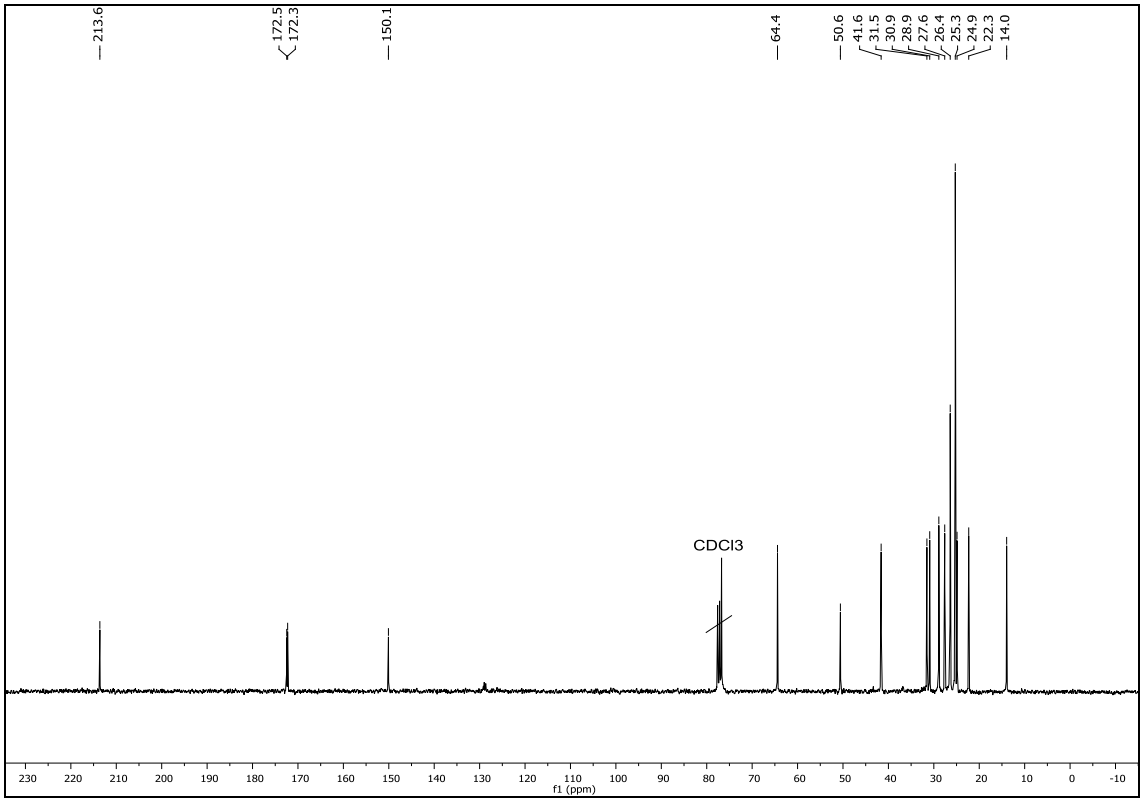
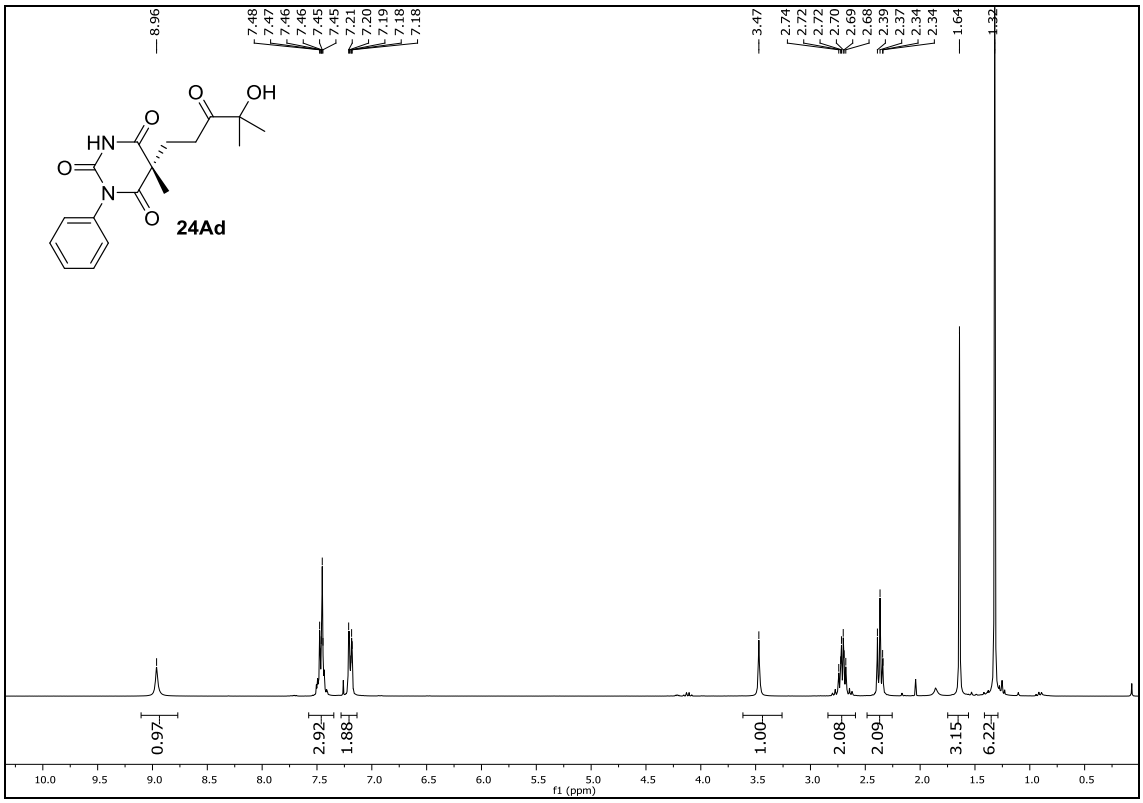
2.61
2.00
2.02
2.12
3.26
6.11
f1 (ppm)


214.2
173.2
172.8
150.9
137.1
129.9
129.8
129.7
129.2
51.6
45.7
32.9
31.7
27.4
27.3
25.7
CDCl3
f1 (ppm)


7.92
3.92
3.90
3.87
2.63
2.63
2.62
2.60
2.60
2.38
2.36
2.33
1.68
1.68
1.67
1.65
1.63
1.63
1.62
1.61
1.60
1.39
0.98
0.96
O
OH
HN
O
O
N
O
24Ac
CDCl3
0.78
2.00
1.90
1.93
6.08
7.25
2.95
f1 (ppm)


213.6
172.5
172.3
150.1
64.4
50.6
41.6
31.5
30.9
28.9
27.6
26.4
25.3
24.9
22.3
14.0
CDCl3
f1 (ppm)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7.48
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7.45
7.45
7.21
7.20
7.19
7.18
7.18
3.47
2.74
2.72
2.72
2.70
2.69
2.68
2.39
2.37
2.34
2.34
1.64
1.32
O
OH
HN
O
N
O
O
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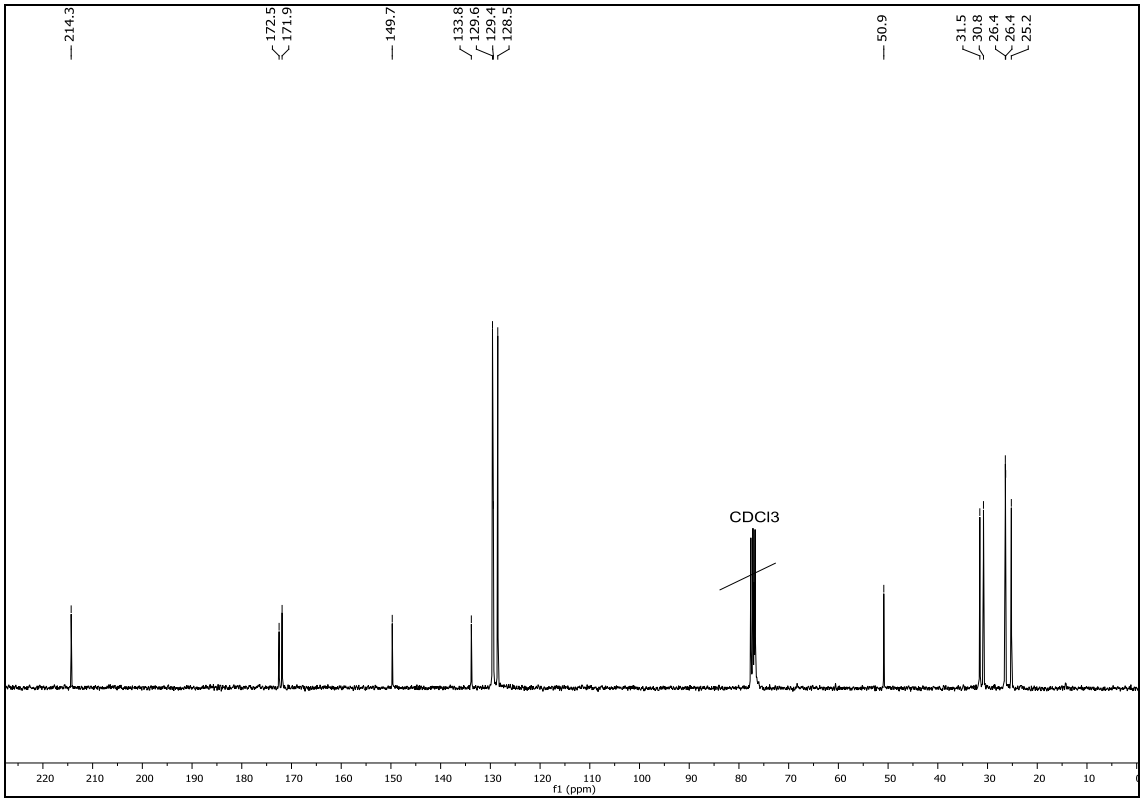
1.88
1.00
2.08
2.09
3.15
6.22
f1 (ppm)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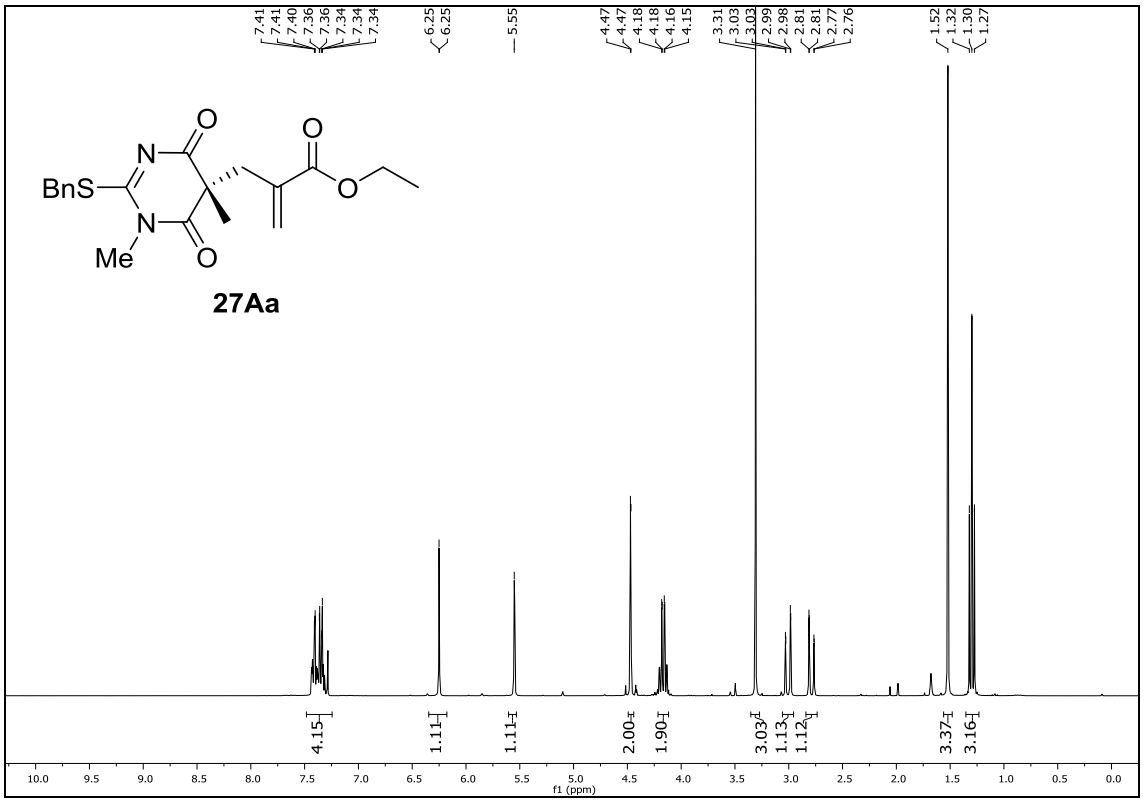
172.5
171.9
149.7
133.8
129.6
129.4
128.5
50.9
31.5
30.8
26.4
26.4
25.2
CDCl3
f1 (ppm)


7.41
7.41
7.40
7.36
7.36
7.34
7.34
7.34
6.25
6.25
5.55
4.47
4.47
4.18
4.16
4.15
3.31
3.03
3.03
2.99
2.98
2.81
2.77
2.76
1.52
1.32
1.30
1.27
BnS
N
N
Me
O
O
O
O
27Aa
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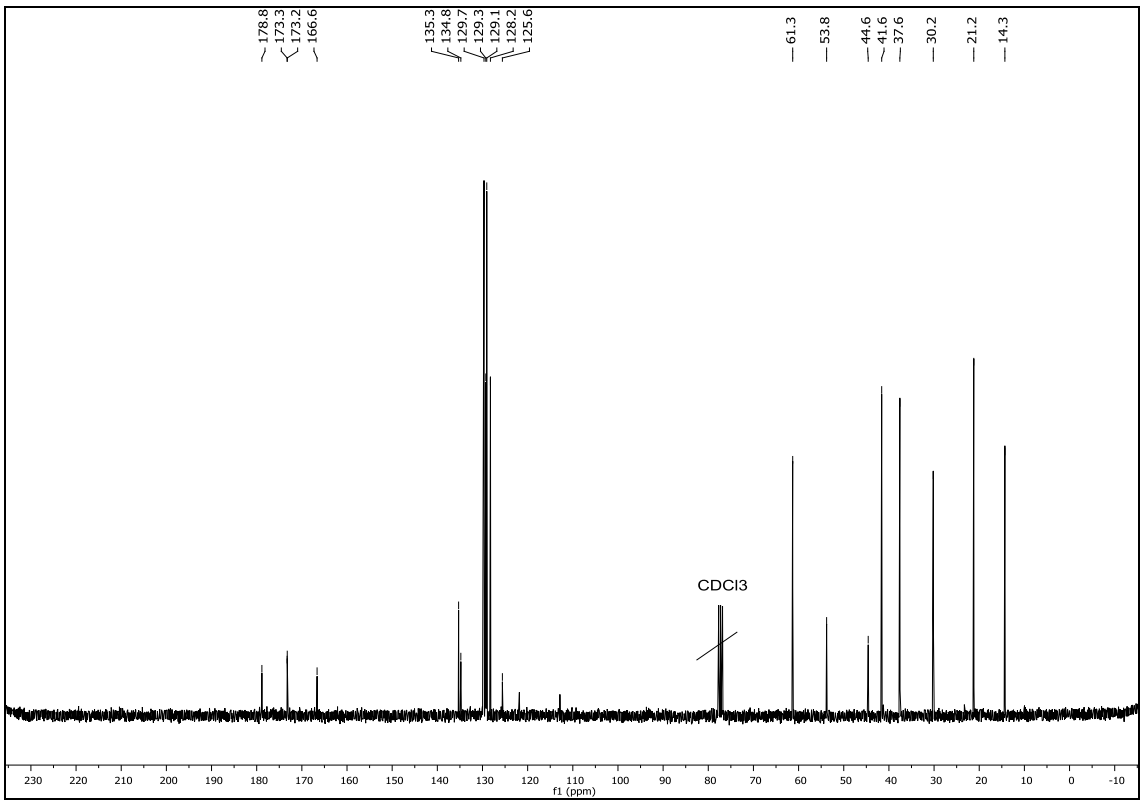
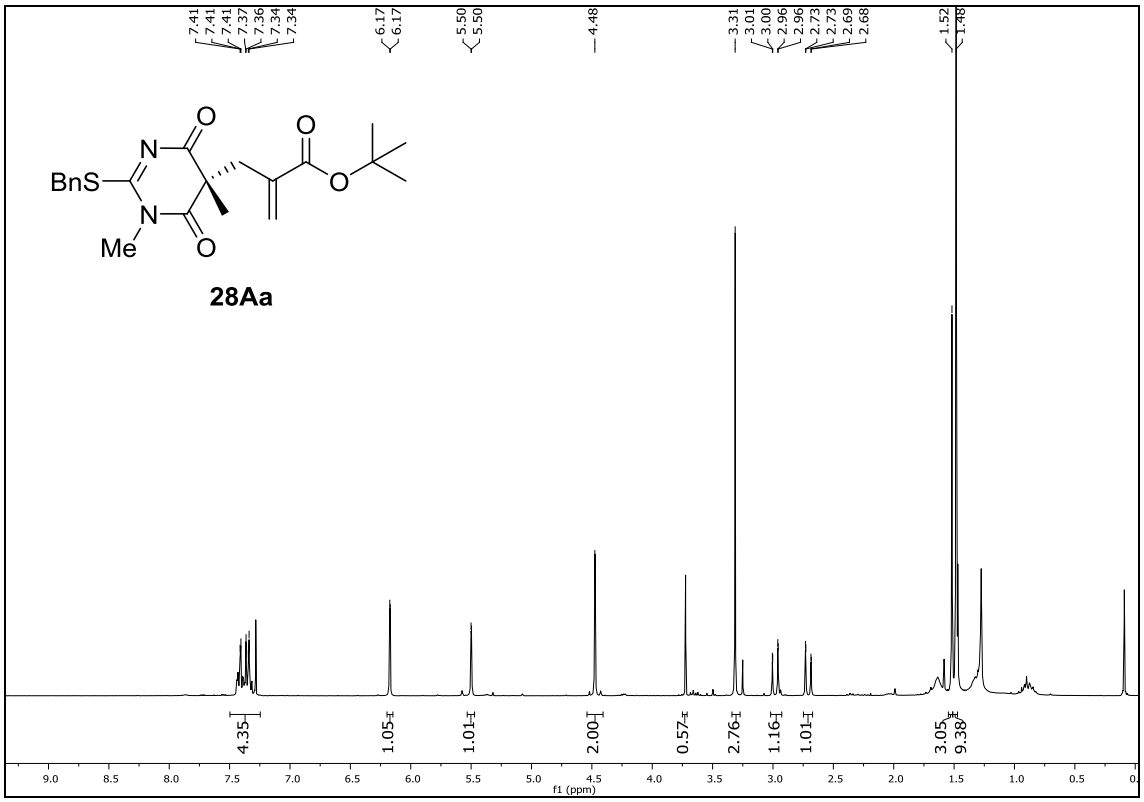
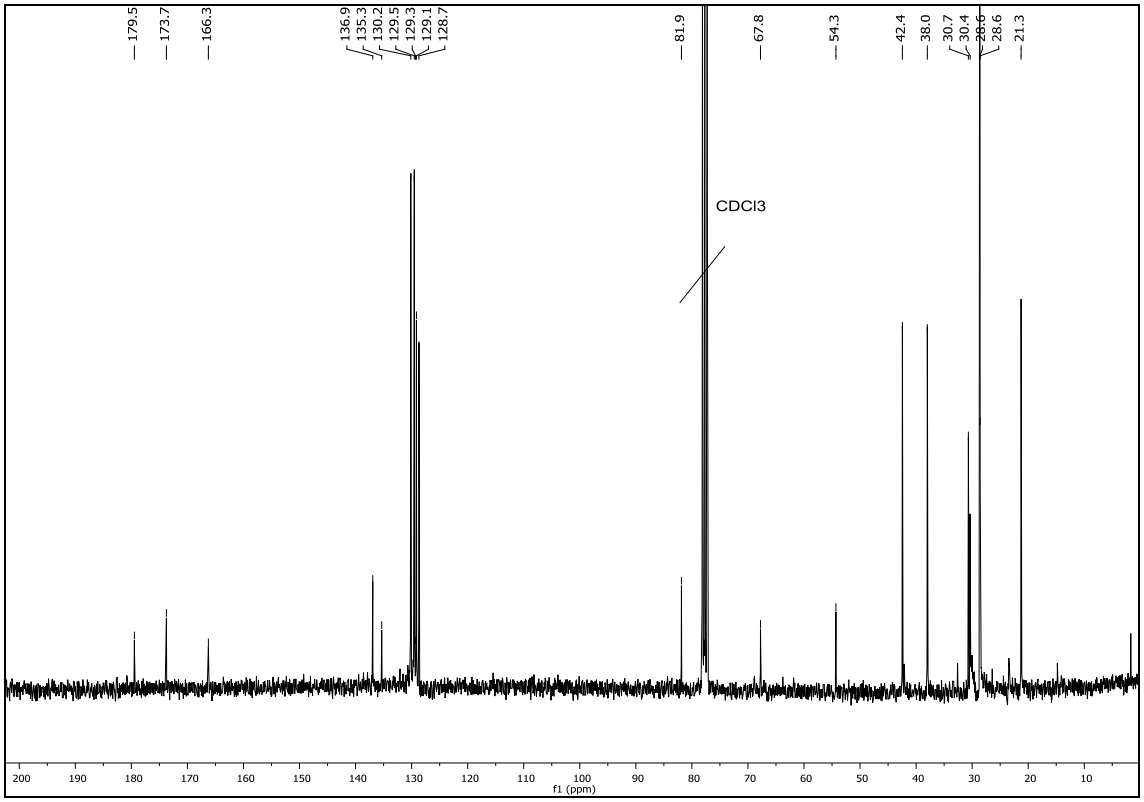
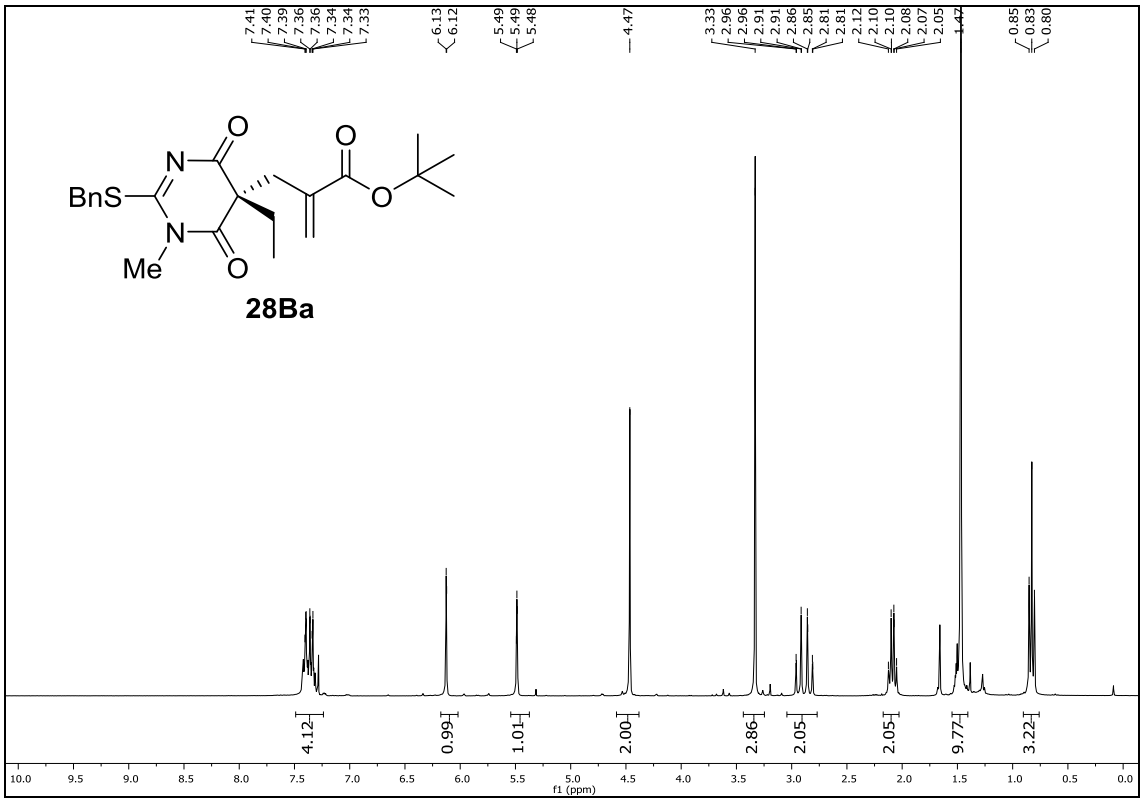
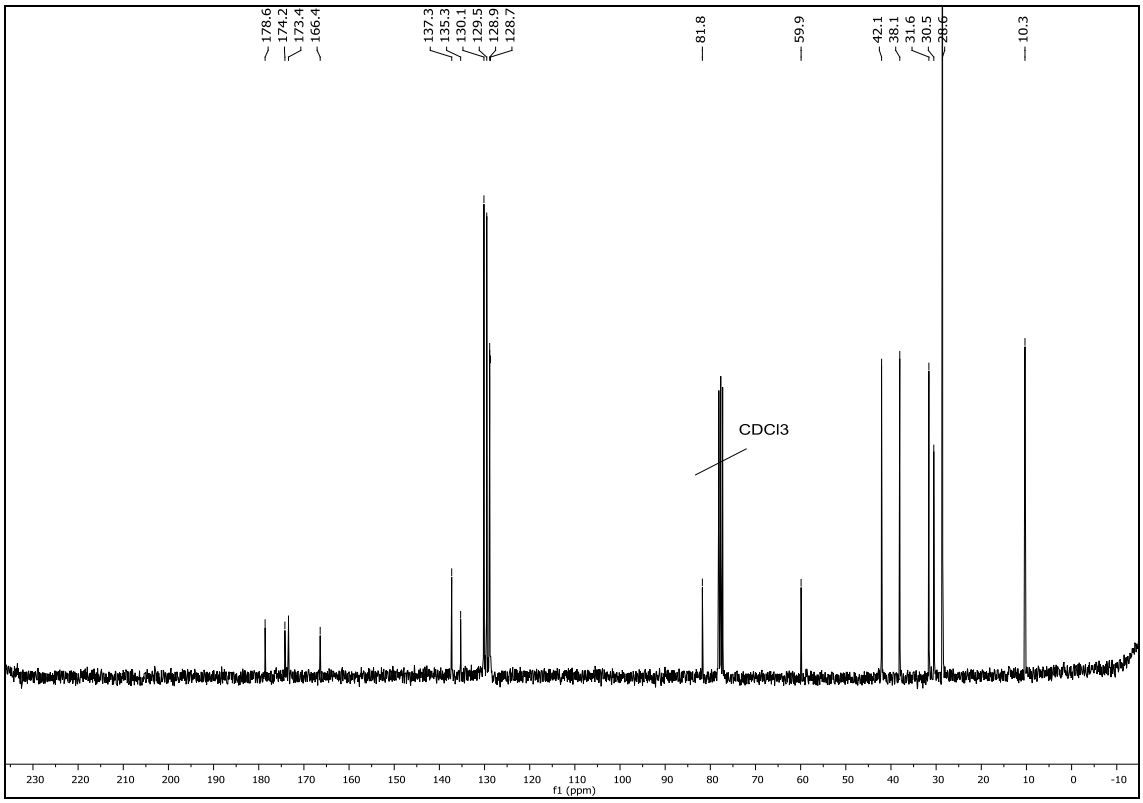
1.11
2.00
1.90
3.03
1.13
1.12
3.37
3.16
f1 (ppm)

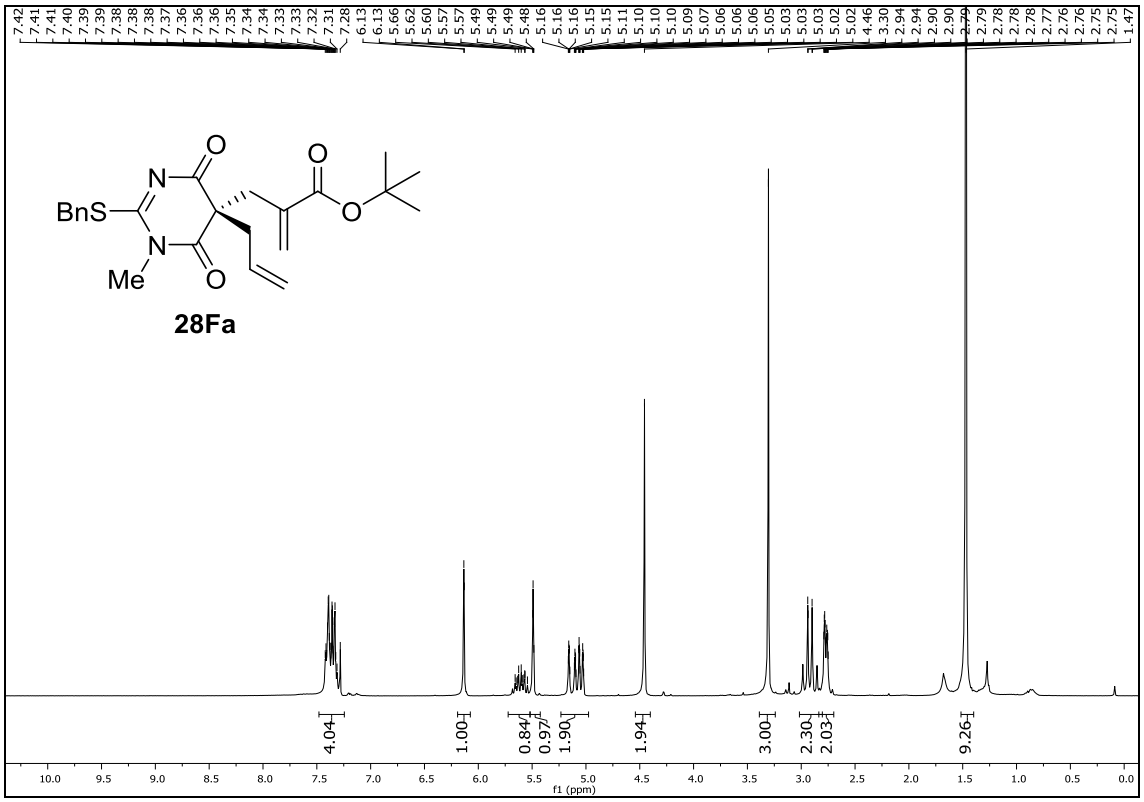

178.8
173.3
173.2
166.6
135.3
134.8
129.7
129.3
129.1
128.2
125.6
61.3
53.8
44.6
41.6
37.6
30.2
21.2
14.3
CDCl3
f1 (ppm)

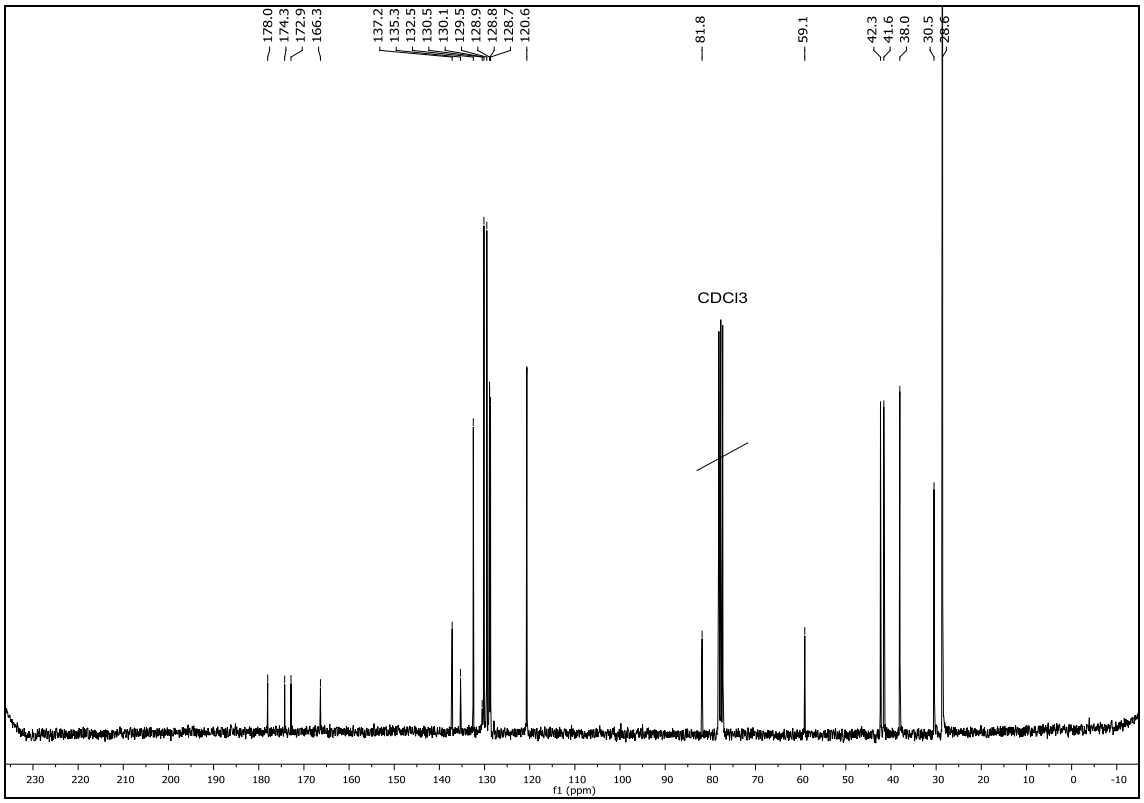

7.41
7.41
7.41
7.37
7.36
7.34
7.34
6.17
6.17
5.50
5.50
4.48
3.31
3.01
3.00
2.96
2.96
2.73
2.73
2.69
2.68
1.52
1.48
BnS
N
N
Me
O
O
O
O
28Aa
4.35
1.05
1.01
2.00
0.57
2.76
1.16
1.01
3.05
9.38
f1 (ppm)


179.5
173.7
166.3
136.9
135.3
130.2
129.5
129.3
129.1
128.7
81.9
67.8
54.3
42.4
38.0
30.7
30.4
28.6
28.6
21.3
CDCl3
f1 (ppm)


7.41
7.40
7.39
7.36
7.36
7.34
7.34
7.33
6.13
6.12
5.49
5.49
5.48
4.47
3.33
2.96
2.96
2.91
2.91
2.86
2.85
2.81
2.81
2.12
2.10
2.10
2.08
2.07
2.05
1.42
0.85
0.83
0.80
BnS
N
N
Me
O
O
O
O
28Ba
4.12
0.99
1.01
2.00
2.86
2.05
2.05
9.77
3.22
f1 (ppm)


178.6
174.2
173.4
166.4
137.3
135.3
130.1
129.5
128.9
128.7
81.8
59.9
42.1
38.1
31.6
30.5
28.6
10.3
CDCl3
f1 (ppm)


BnS
N
N
Me
O
O
O
O
28Fa
4.04
1.00
0.84
0.97
1.90
1.94
3.00
2.30
2.03
9.26
f1 (ppm)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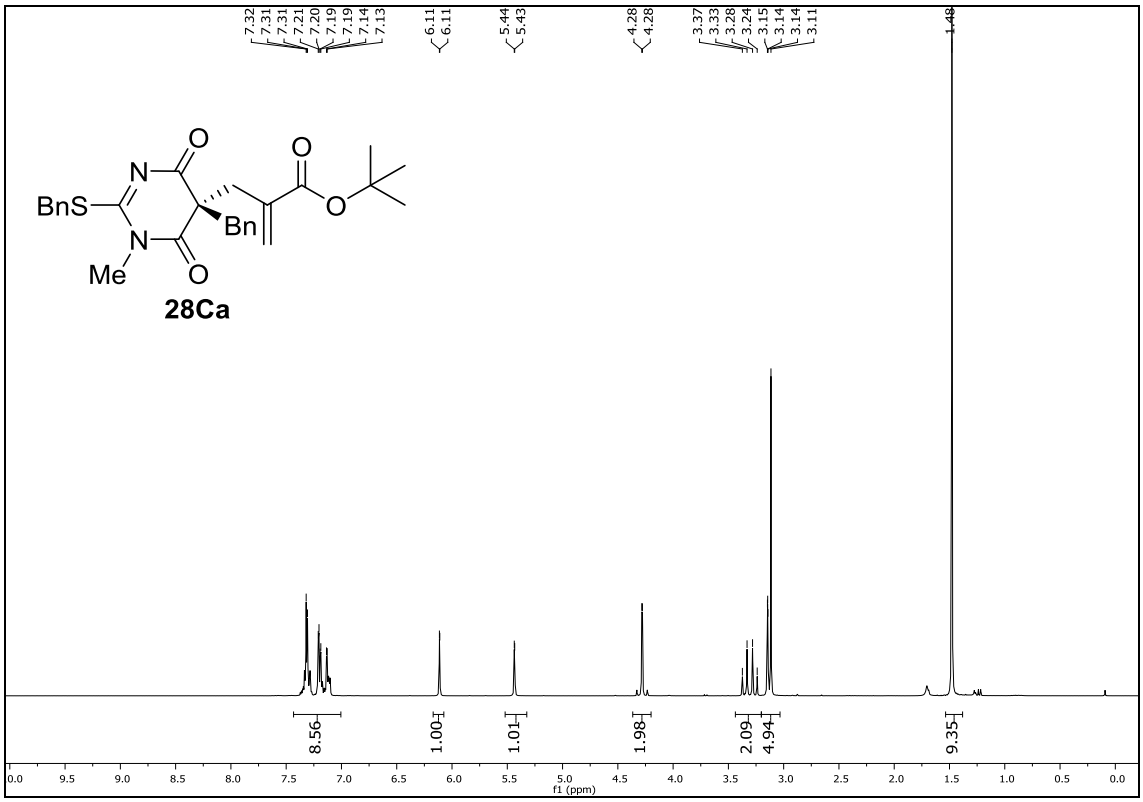
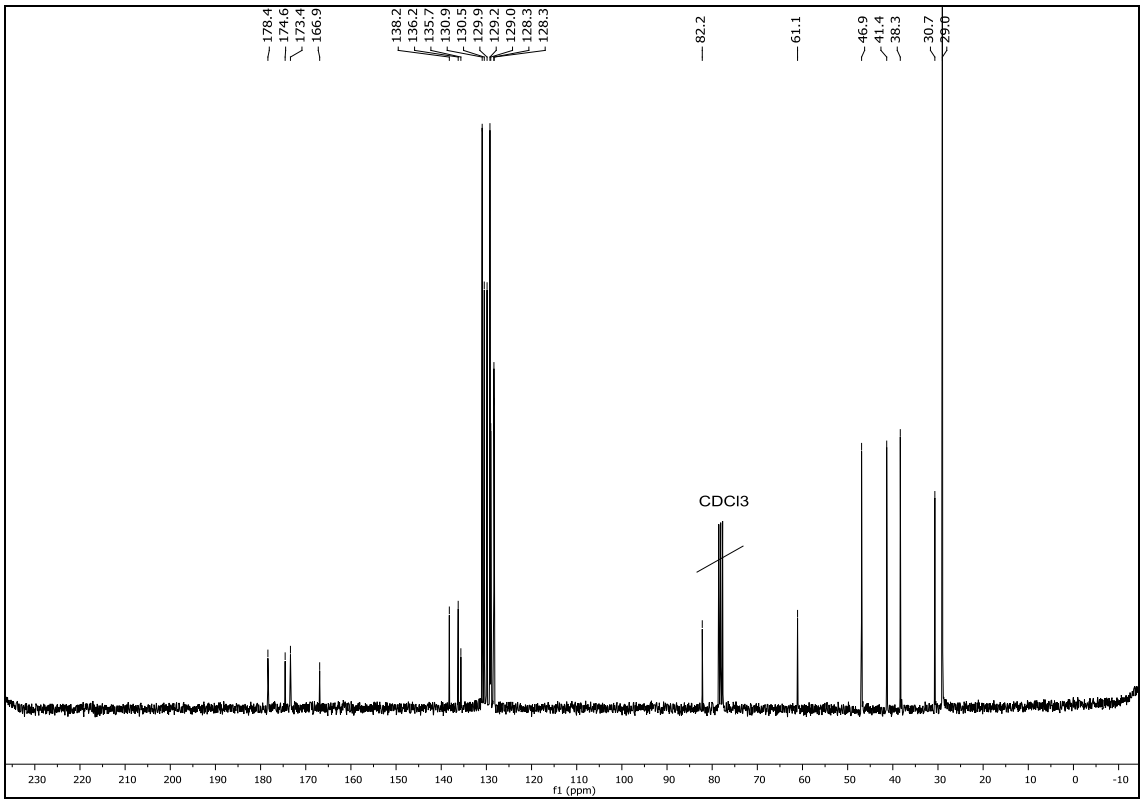
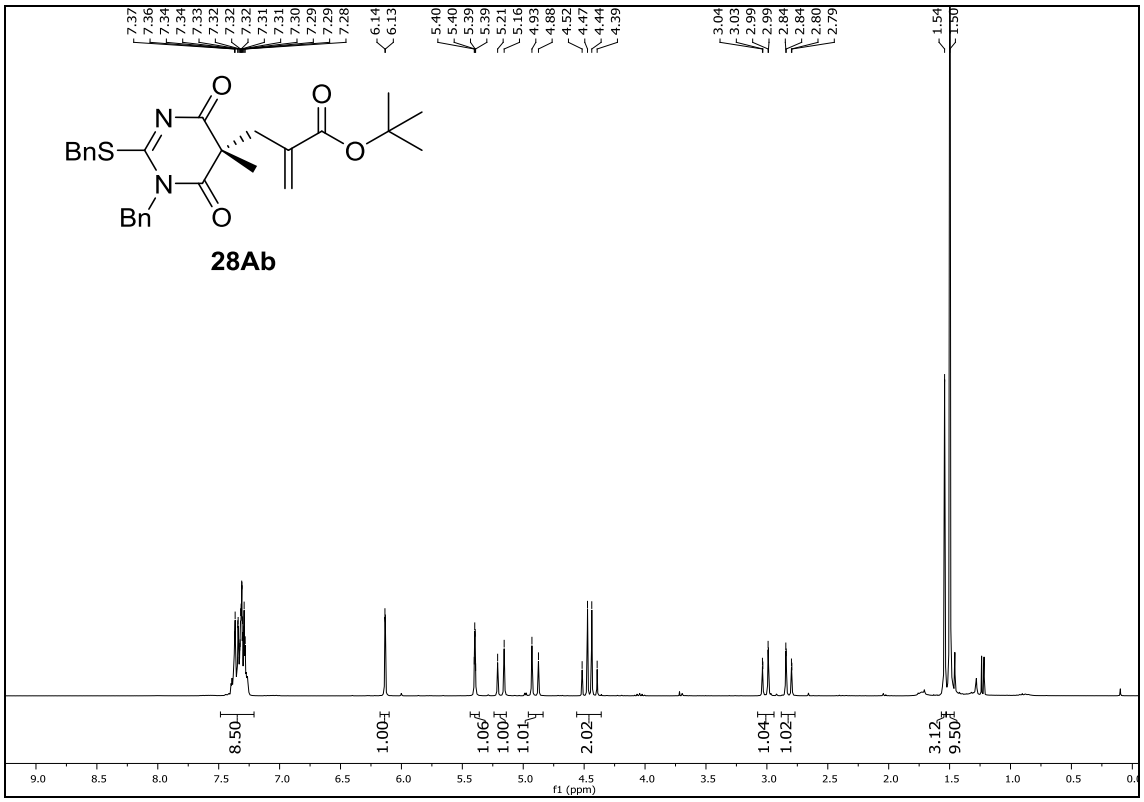
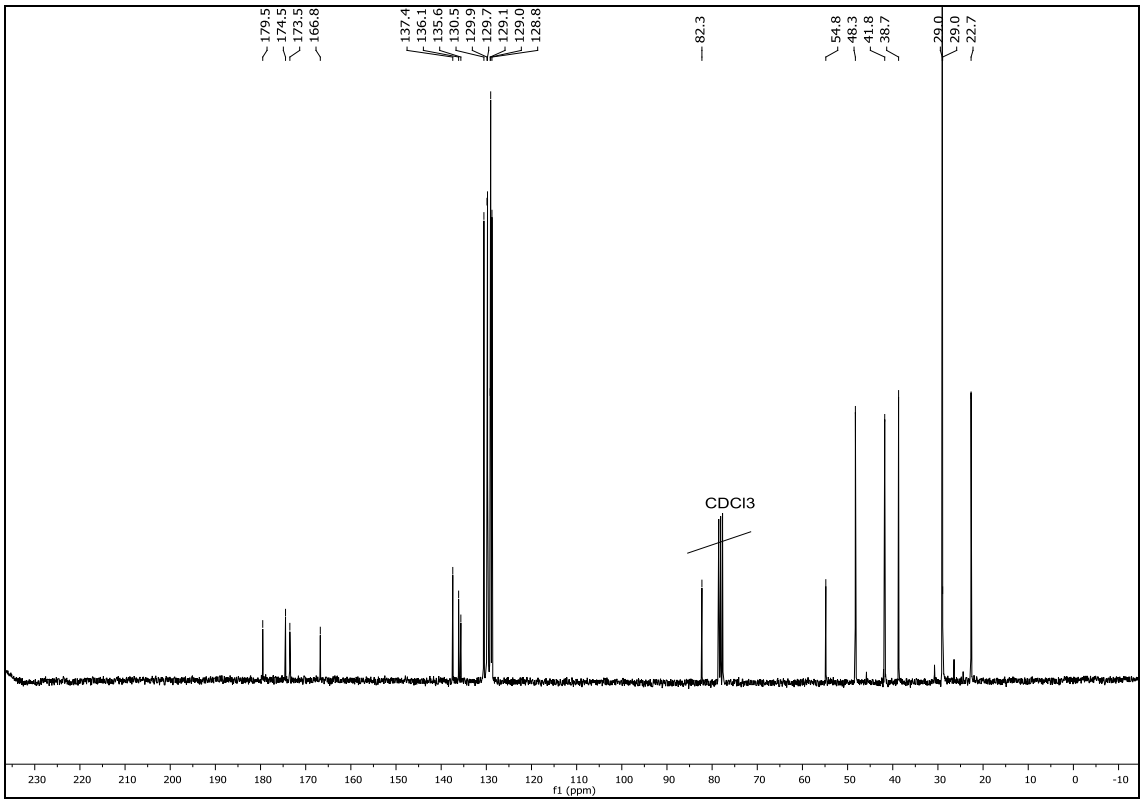
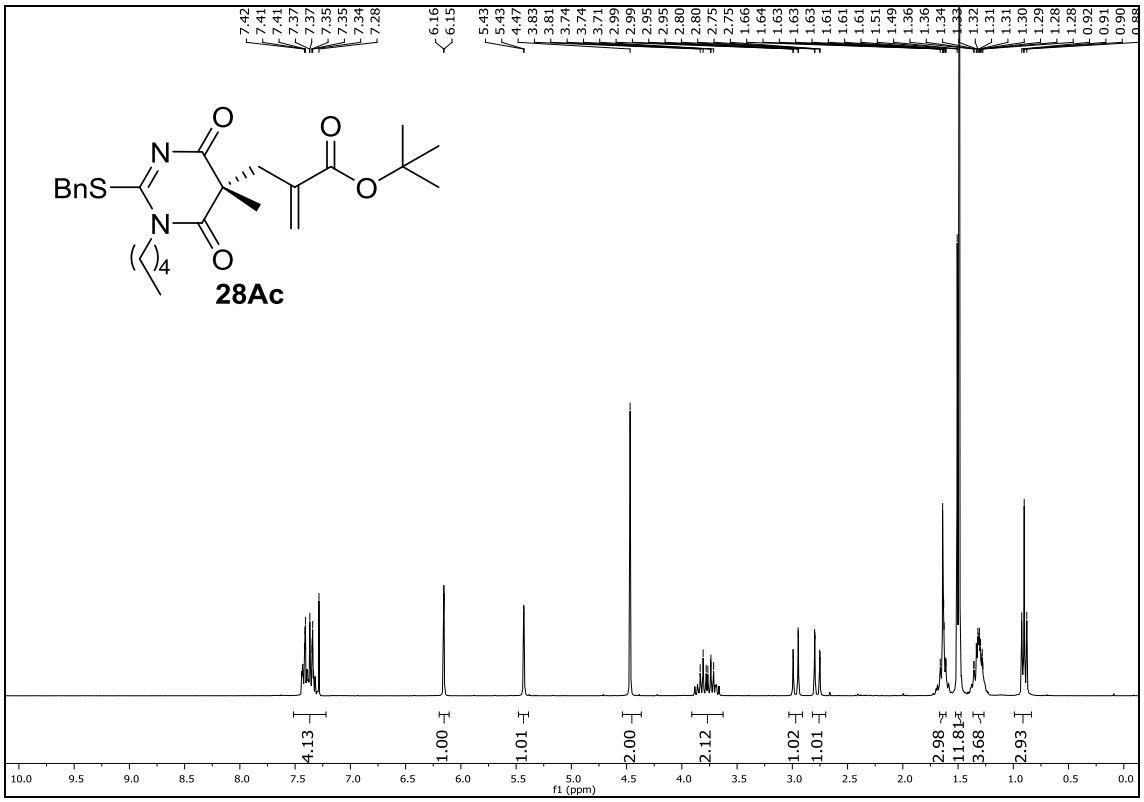
174.3
172.9
166.3
137.2
135.3
132.5
130.5
130.1
129.5
128.9
128.8
128.7
120.6
81.8
59.1
42.3
41.6
38.0
30.5
28.6
CDCl3
f1 (ppm)

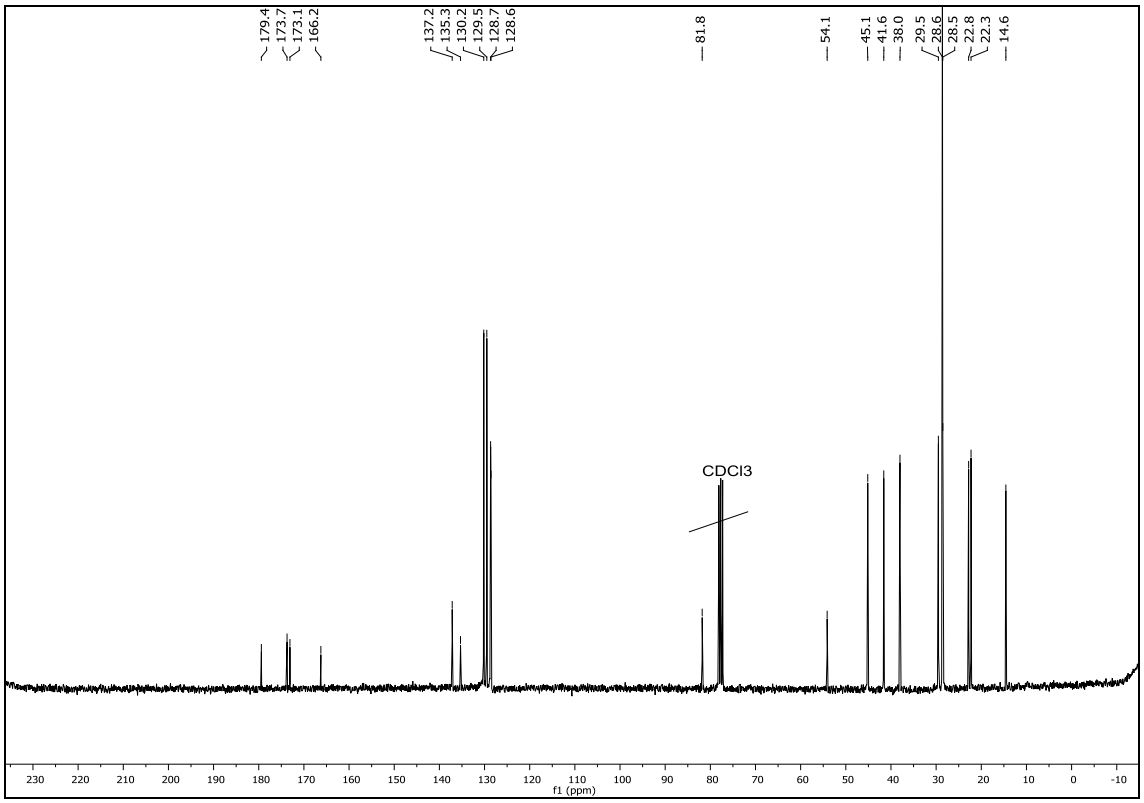

7.32
7.31
7.31
7.21
7.20
7.19
7.19
7.14
7.13
6.11
6.11
5.44
5.43
4.28
4.28
3.37
3.33
3.28
3.24
3.15
3.14
3.14
3.11
1.48
BnS
N
N
Me
O
O
O
O
O
Bn
28Ca
8.56
1.00
1.01
1.98
2.09
4.94
9.35
f1 (ppm)

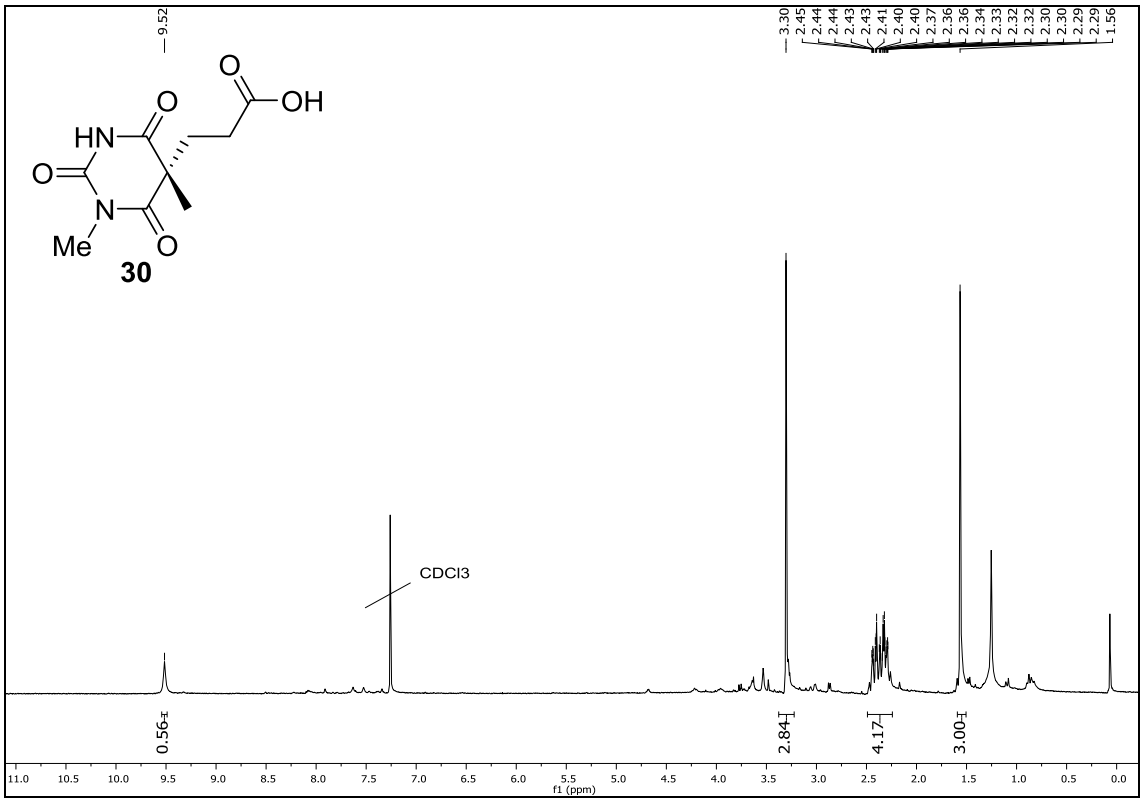

178.4
174.6
173.4
166.9
138.2
136.2
135.7
130.9
130.5
129.9
129.2
129.0
128.3
128.3
82.2
61.1
46.9
41.4
38.3
30.7
29.0
CDCl3
f1 (ppm)

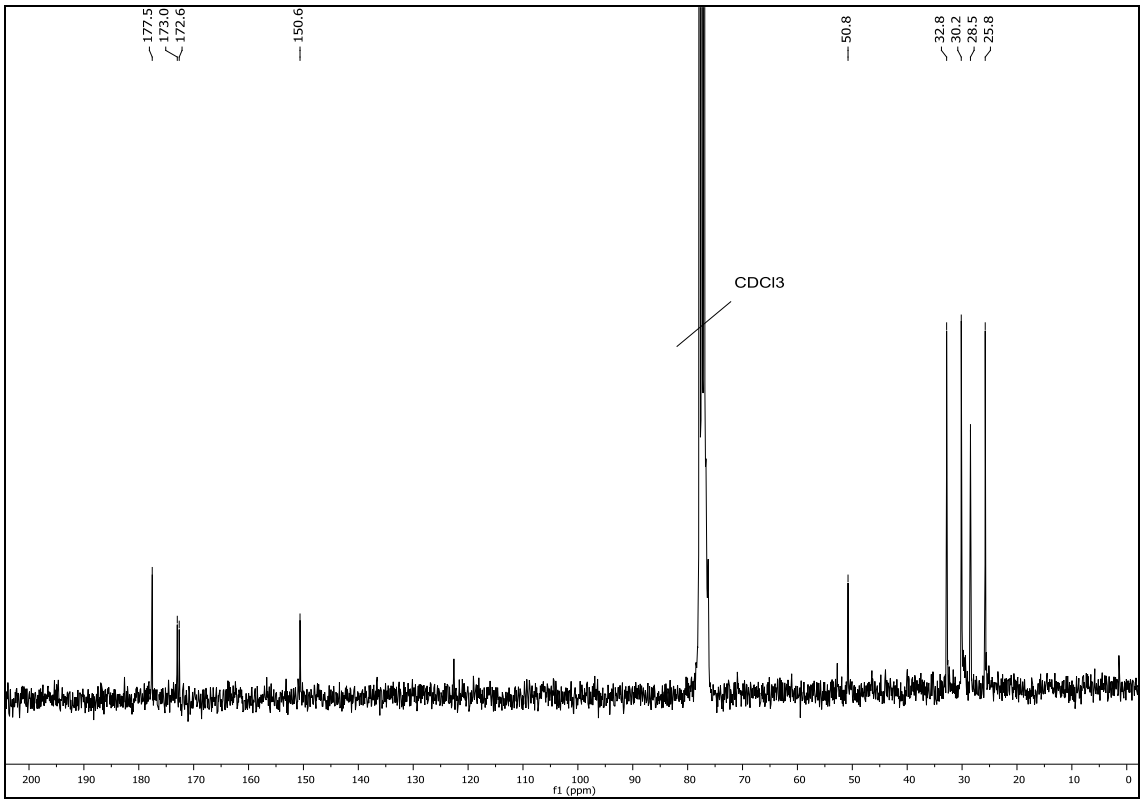

7.37
7.36
7.34
7.34
7.33
7.32
7.32
7.32
7.31
7.31
7.30
7.29
7.29
7.28
6.14
6.13
5.40
5.40
5.39
5.39
5.21
5.16
4.93
4.88
4.52
4.47
4.44
4.39
3.04
3.03
2.99
2.99
2.84
2.84
2.80
2.79
1.54
1.50
BnS
N
N
Bn
O
O
O
O
O
28Ab
8.50
1.00
1.06
1.00
1.01
2.02
1.04
1.02
3.12
9.50
f1 (ppm)

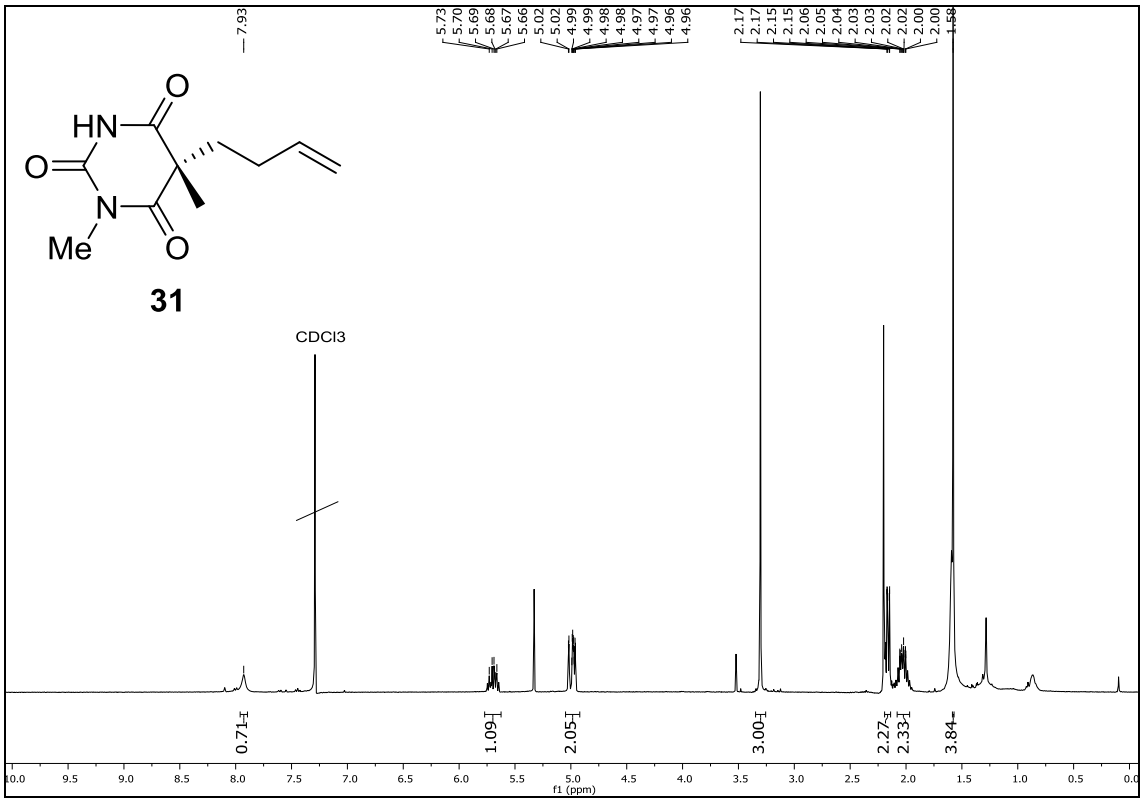

179.5
174.5
173.5
166.8
137.4
136.1
135.6
130.5
129.9
129.7
129.1
129.0
128.8
82.3
54.8
48.3
41.8
38.7
29.0
29.0
22.7
CDCl3
f1 (ppm)

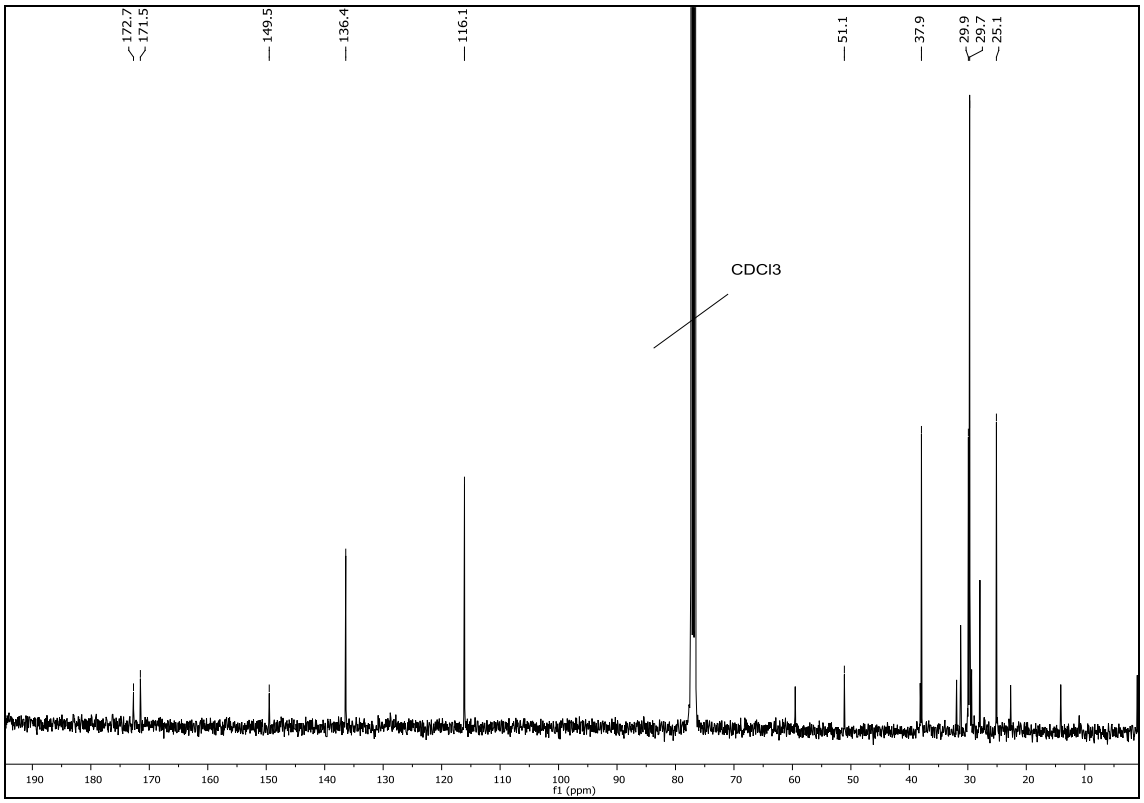

BnS
N
N
O
O
O
O
4
28Ac
7.42 7.41 7.41 7.37 7.37 7.35 7.35 7.34 7.28
6.16 6.15
5.43 5.43 4.47 3.83 3.81 3.74 3.74 3.71 2.99 2.99 2.95 2.95 2.80 2.80 2.75 2.75 1.66 1.64 1.63 1.63 1.63 1.61 1.61 1.61 1.51 1.49 1.36 1.36 1.34 1.33 1.32 1.31 1.31 1.30 1.29 1.28 1.28 0.92 0.91 0.90 0.88
4.13 1.00 1.01 2.00 2.12 1.02 1.01 2.98 11.81 3.68 2.93
f1 (ppm)

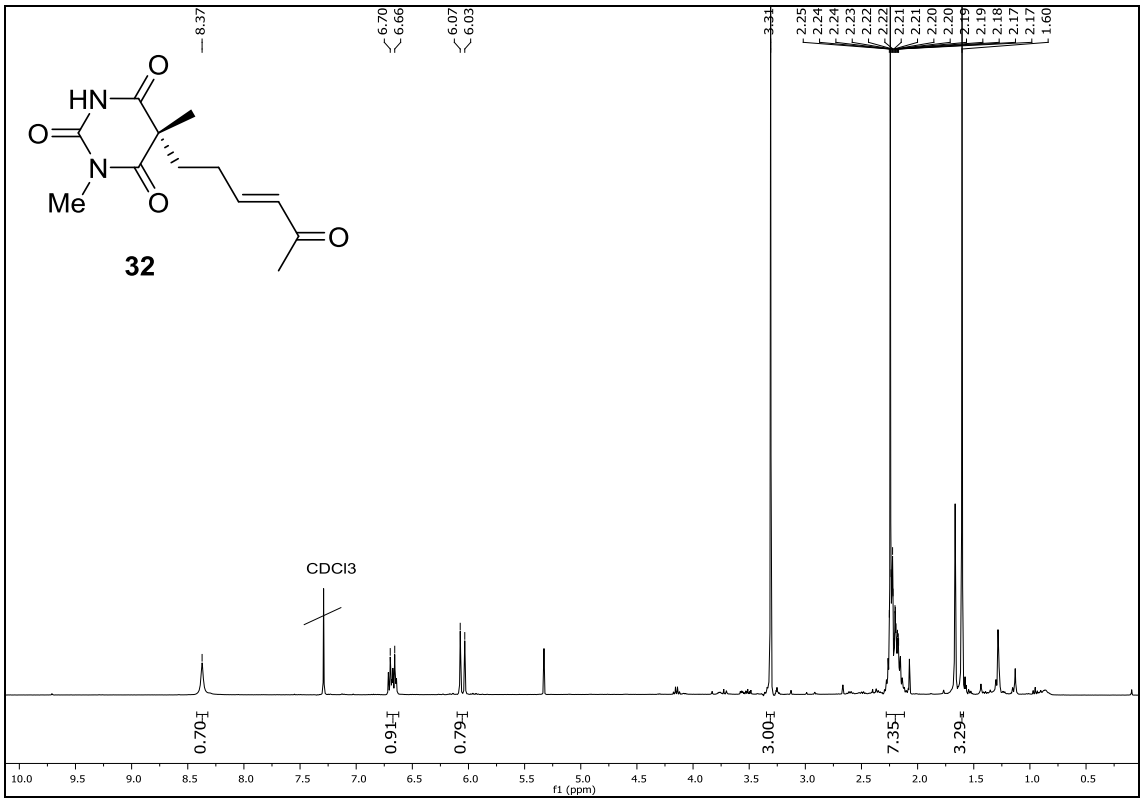

179.4 173.7 173.1 166.2
137.2 135.3 130.2 129.5 128.7 128.6
81.8
54.1
45.1 41.6 38.0 29.5 28.6 28.5 22.8 22.3 14.6
CDCl3
f1 (ppm)

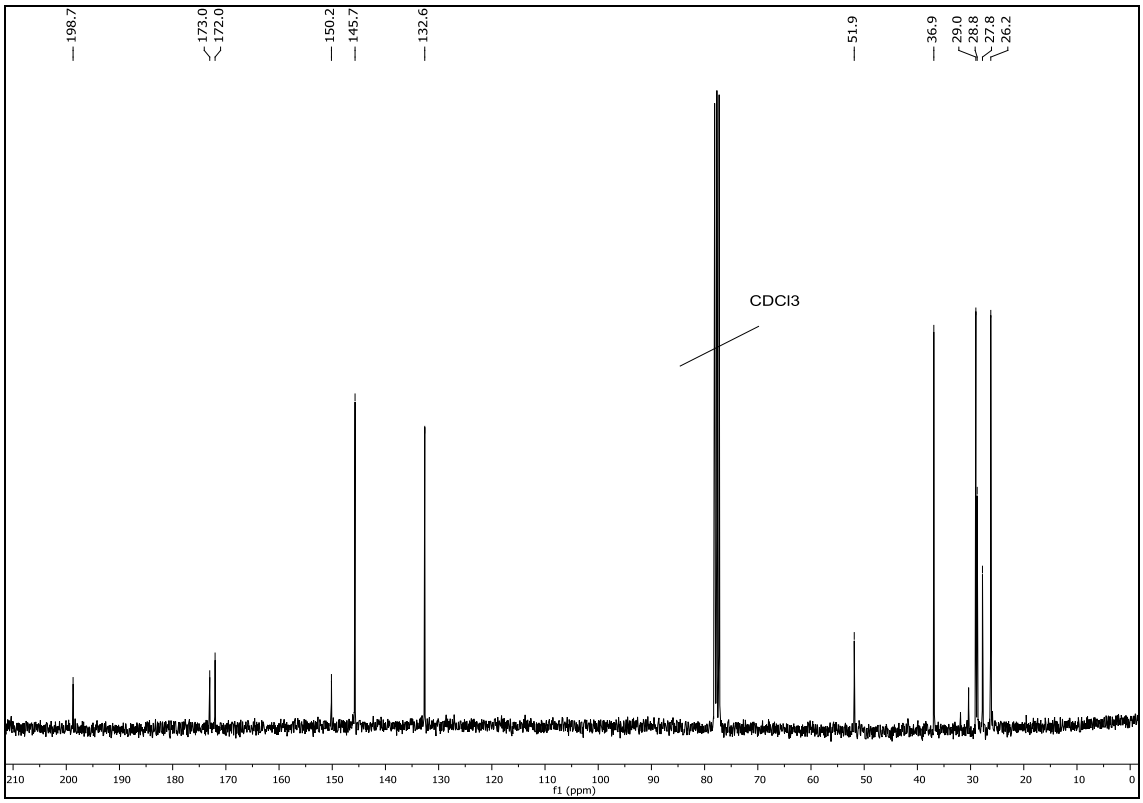

9.52
3.30
2.45
2.44
2.44
2.43
2.43
2.41
2.40
2.40
2.37
2.36
2.36
2.34
2.33
2.32
2.32
2.30
2.30
2.29
2.29
1.56
O
OH
HN
O
O
N
Me
O
30
CDCl3
0.56
2.84
4.17
3.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

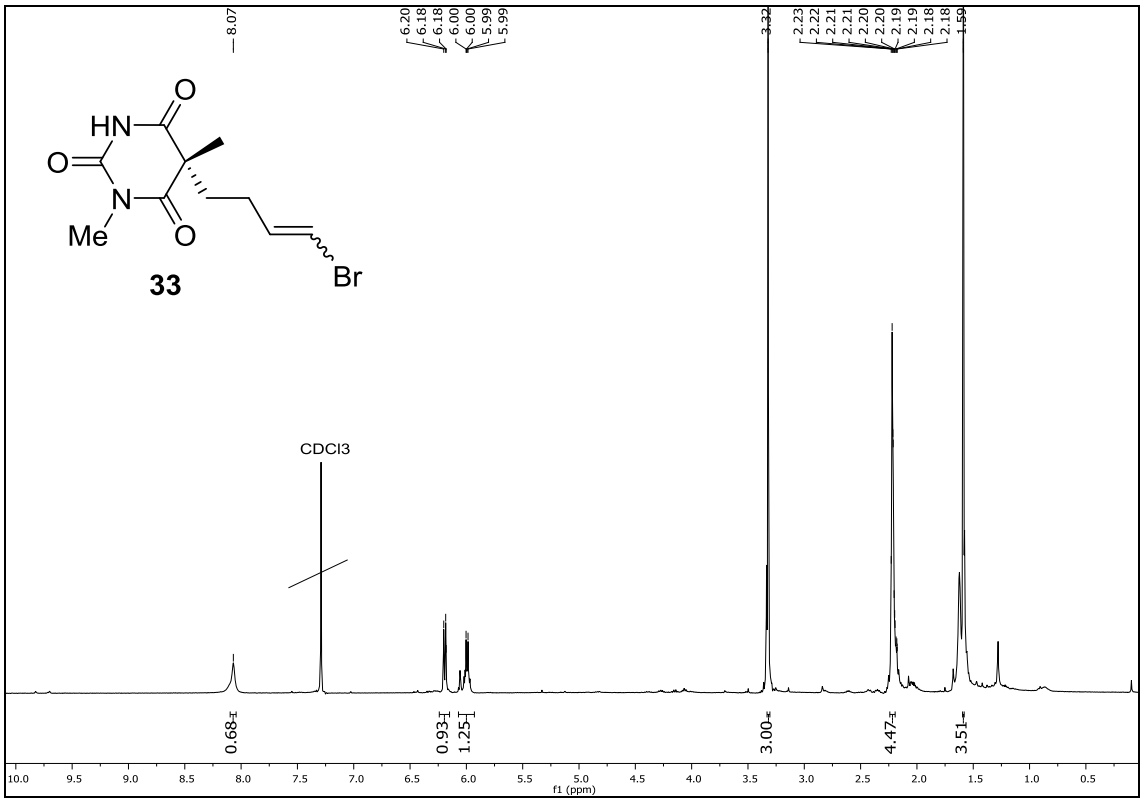

177.5
173.0
172.6
150.6
50.8
32.8
30.2
28.5
25.8
CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

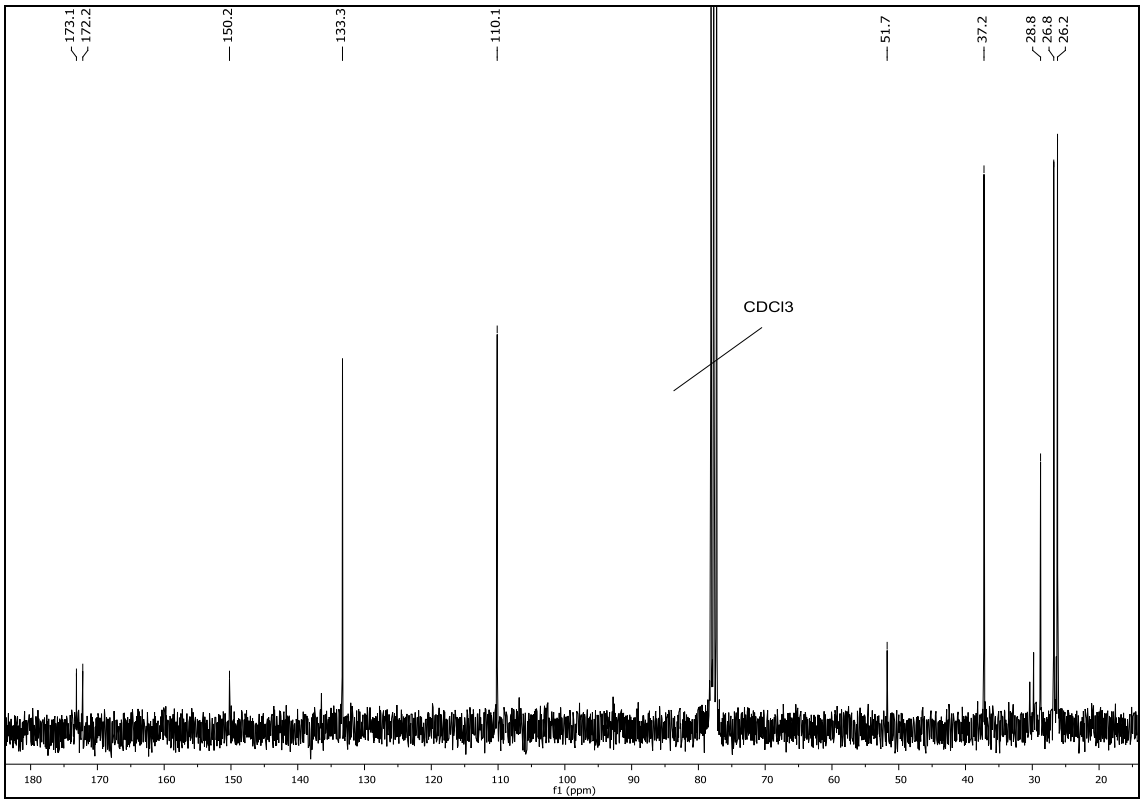

7.93
5.73
5.70
5.69
5.68
5.67
5.66
5.02
5.02
4.99
4.99
4.98
4.98
4.97
4.97
4.96
4.96
2.17
2.17
2.15
2.15
2.06
2.05
2.04
2.03
2.03
2.02
2.02
2.00
2.00
1.58
HN
O
O
N
Me
O
O
31
CDCl3
0.71
1.09
2.05
3.00
2.27
2.33
3.84
f1 (ppm)

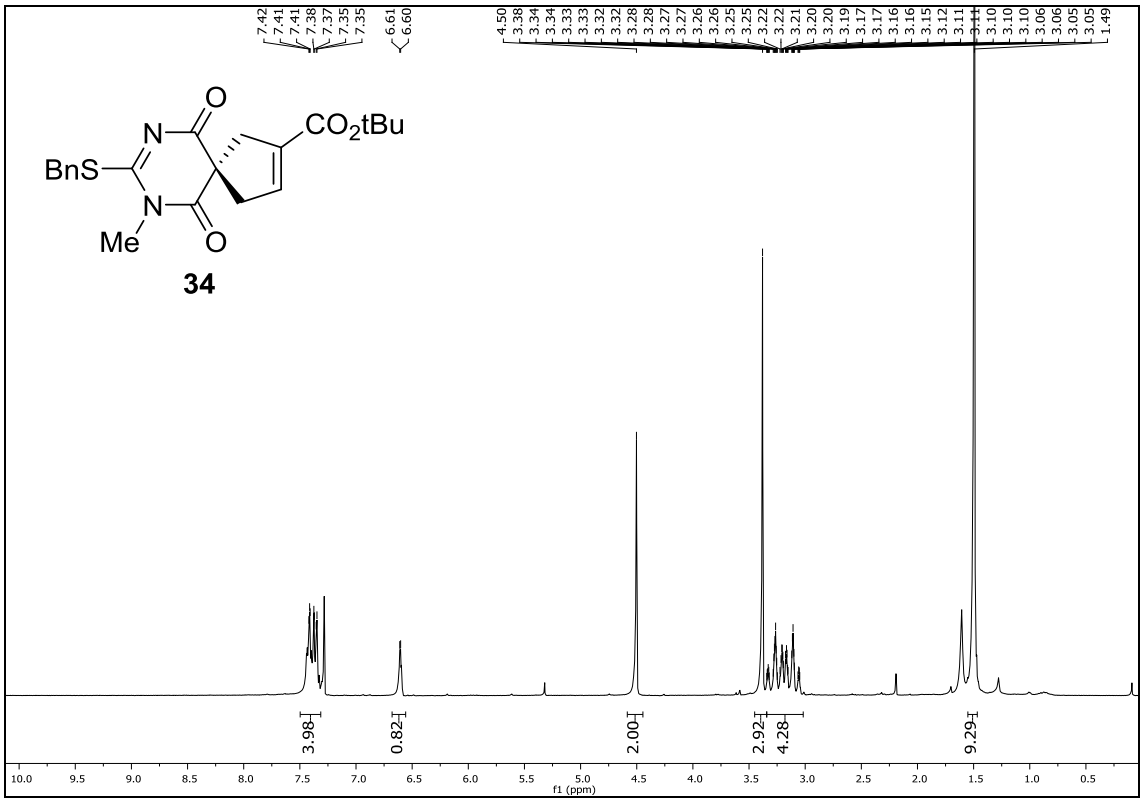

172.7
171.5
149.5
136.4
116.1
51.1
37.9
29.9
29.7
25.1
CDCl3
f1 (ppm)

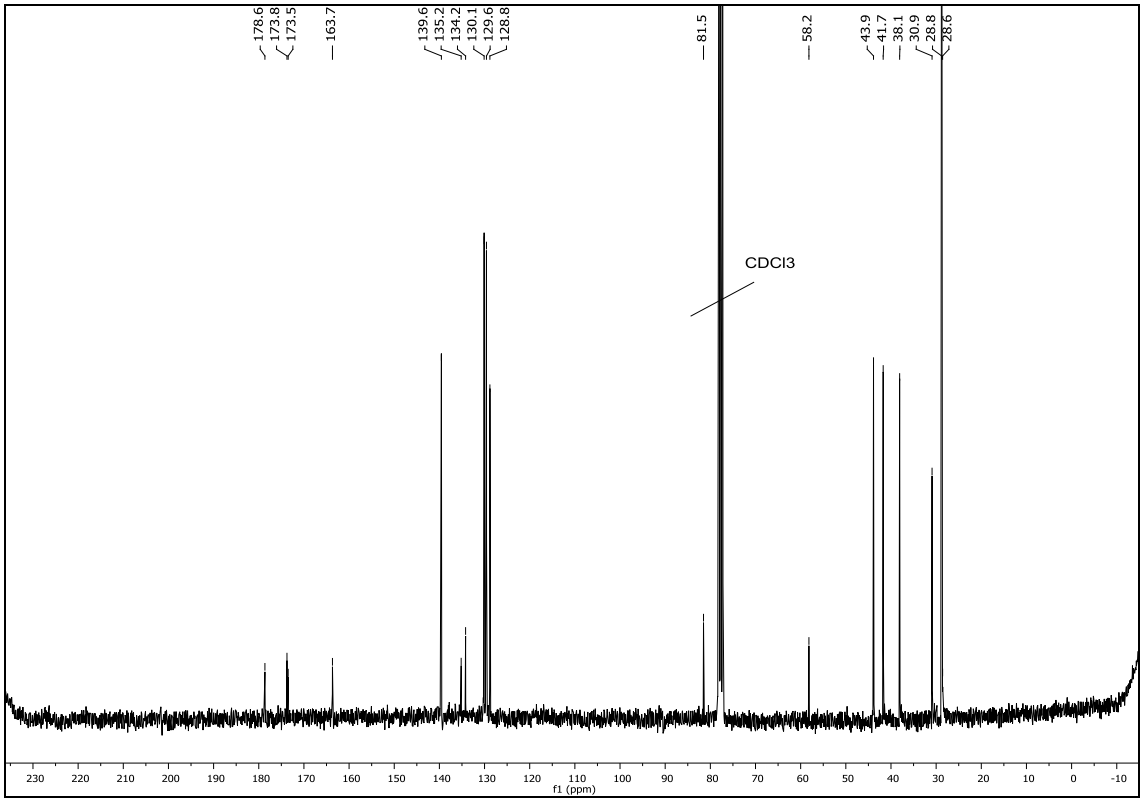

8.37
6.70
6.66
6.07
6.03
3.31
2.25
2.24
2.24
2.23
2.22
2.22
2.21
2.21
2.20
2.20
2.19
2.19
2.18
2.17
2.17
1.60
HN
O
O
N
Me
O
O
32
CDCl3
0.70
0.91
0.79
3.00
7.35
3.29
f1 (ppm)

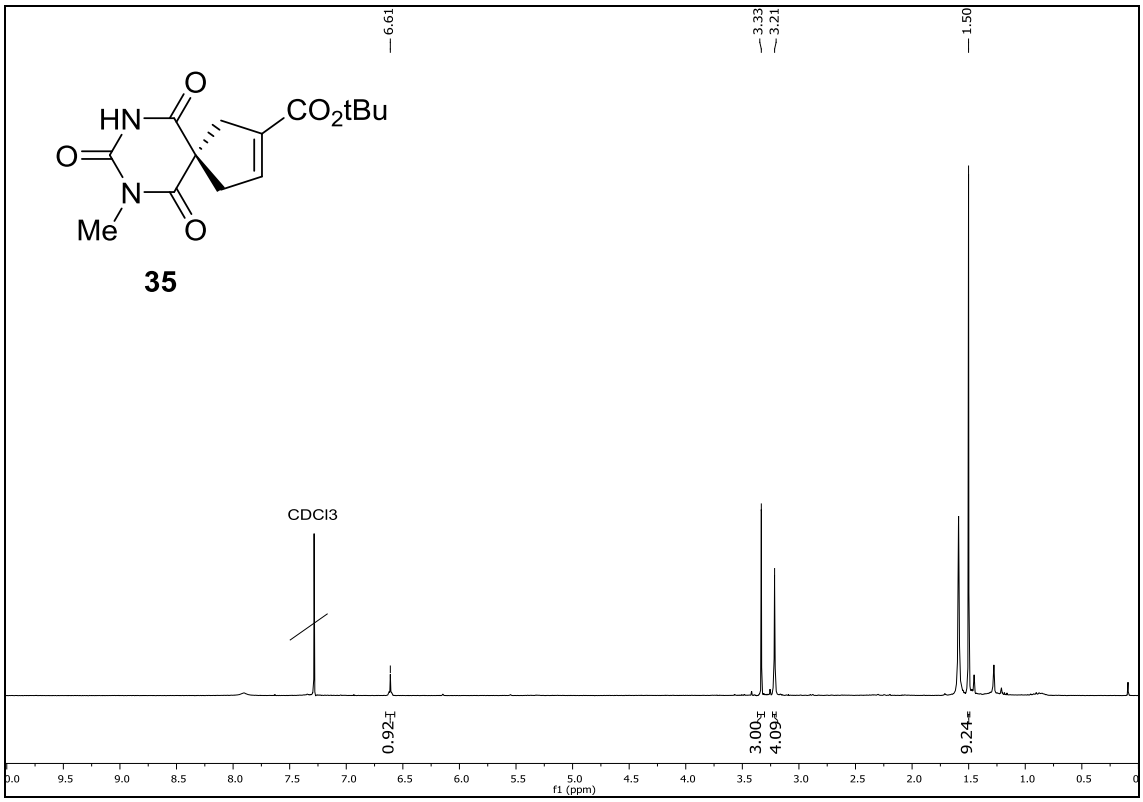

198.7
173.0
172.0
150.2
145.7
132.6
51.9
36.9
29.0
28.8
27.8
26.2
CDCl3
f1 (ppm)


8.07
6.20
6.18
6.18
6.00
6.00
5.99
5.99
3.32
2.23
2.22
2.21
2.21
2.20
2.20
2.19
2.19
2.18
2.18
1.59
HN
O
O
N
Me
O
O
Br
33
CDCl3
0.68
0.93
1.25
3.00
4.47
3.51
f1 (ppm)

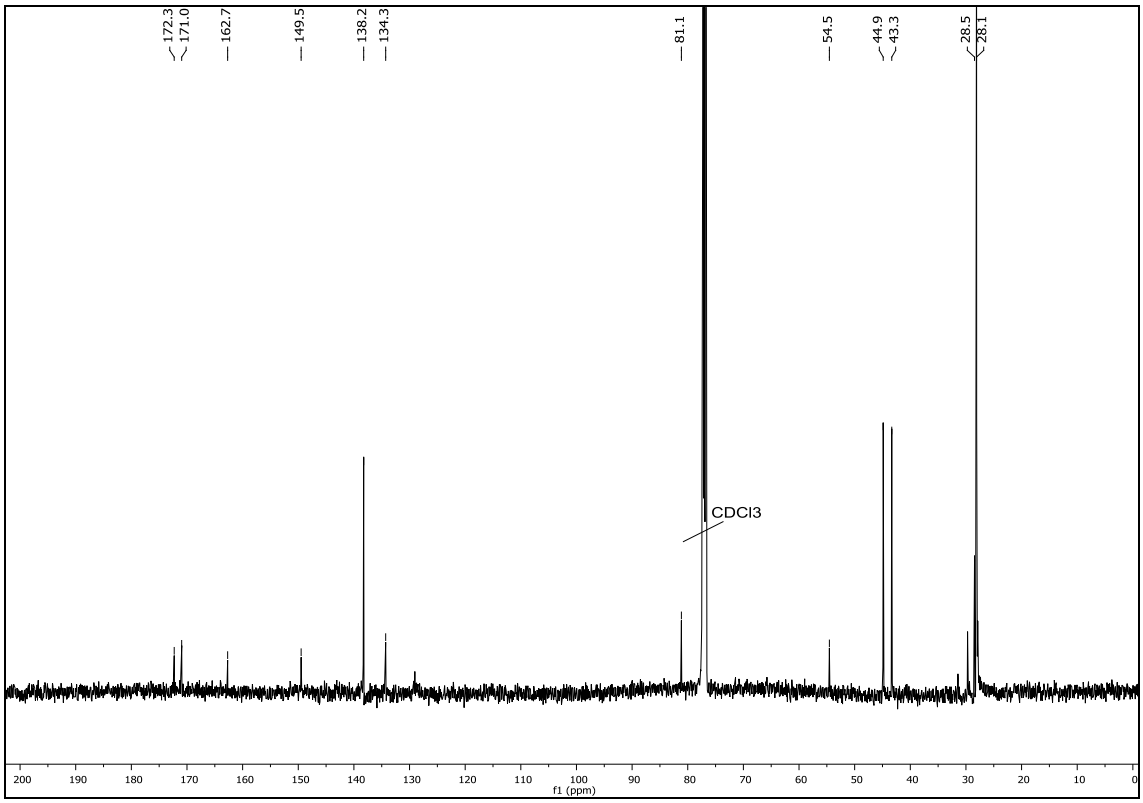

173.1
172.2
150.2
133.3
110.1
51.7
37.2
28.8
26.8
26.2
CDCl3
f1 (ppm)

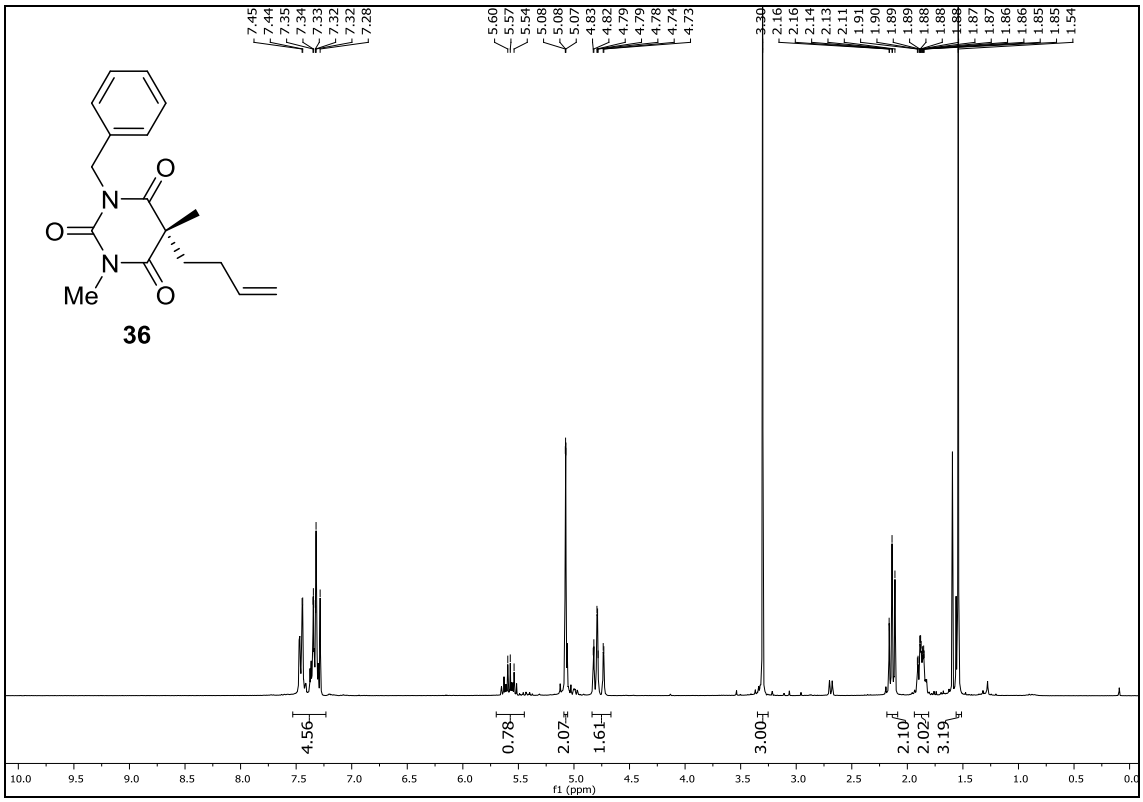

7.42 7.41 7.41 7.38 7.37 7.35 7.35 6.61 6.60
4.50 3.38 3.34 3.34 3.33 3.33 3.32 3.32 3.28 3.28 3.27 3.27 3.26 3.26 3.25 3.25 3.22 3.22 3.21 3.20 3.20 3.19 3.17 3.17 3.16 3.16 3.15 3.12 3.11 3.11 3.10 3.10 3.06 3.06 3.05 3.05 1.49
O
N
CO2tBu
BnS
N
Me
O
34
3.98
0.82
2.00
2.92
4.28
9.29
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

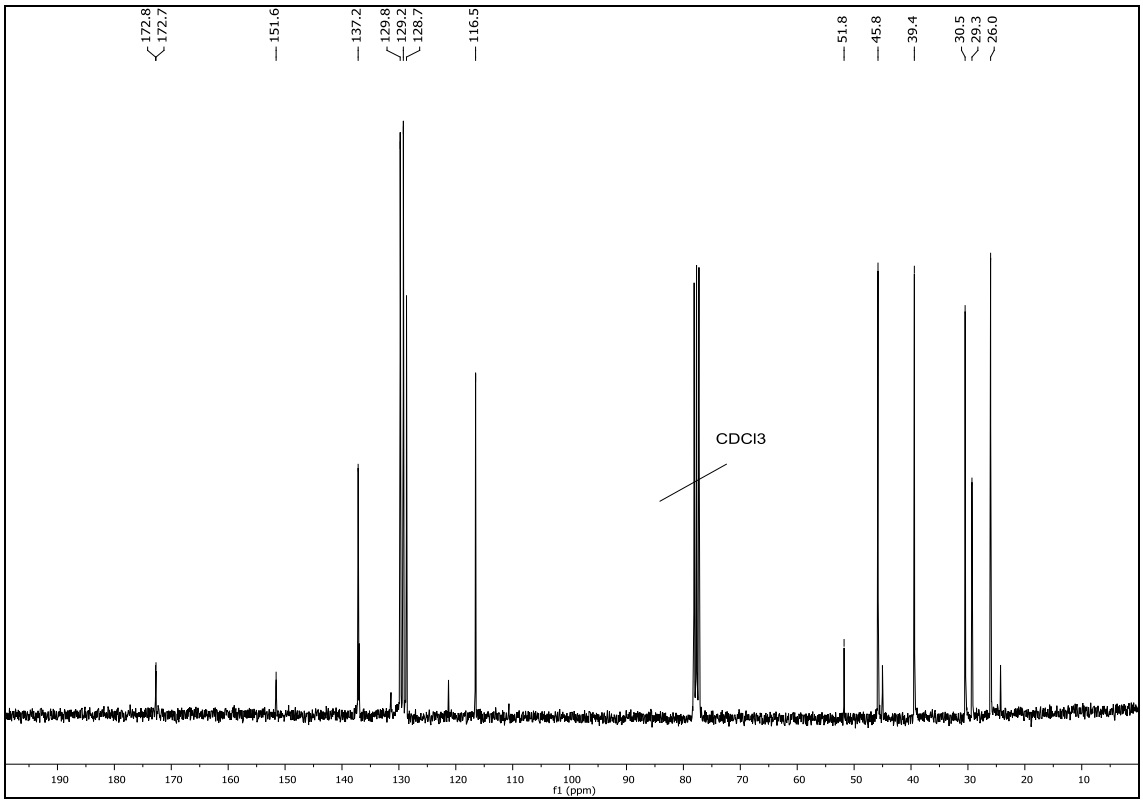

178.6 173.8 173.5 163.7 139.6 135.2 134.2 130.1 129.6 128.8 81.5 58.2 43.9 41.7 38.1 30.9 28.8 28.6
CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

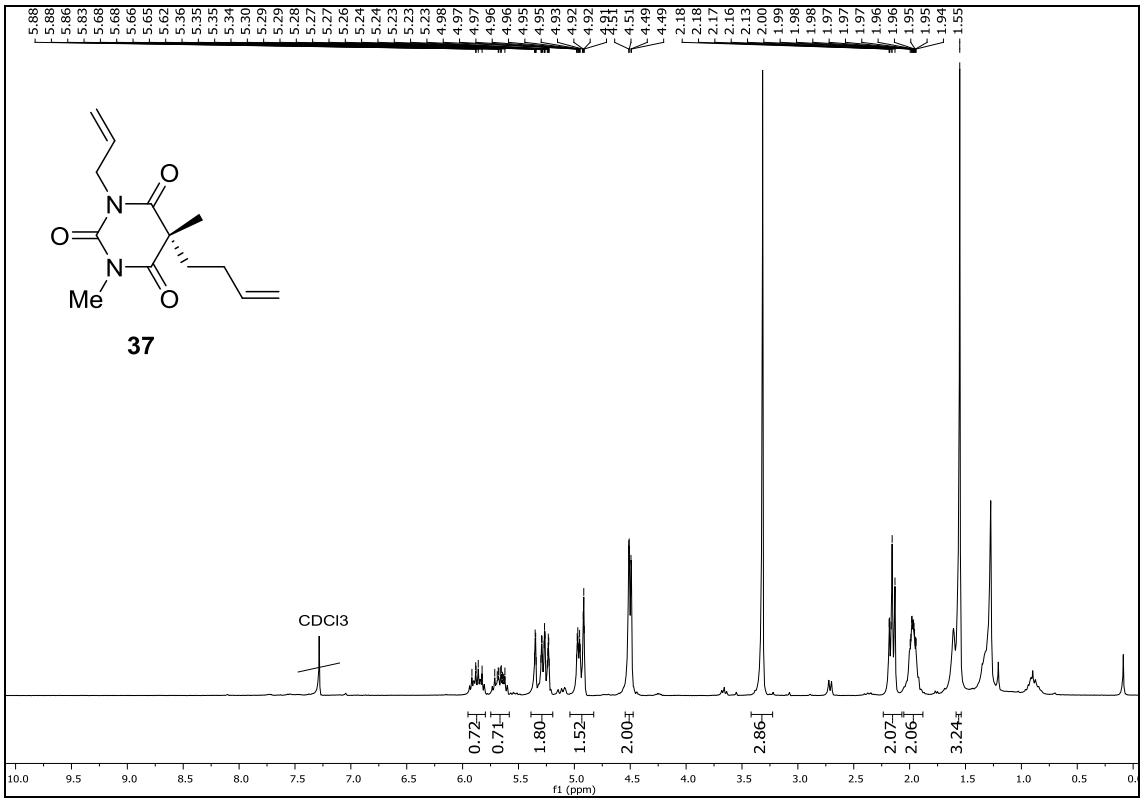

6.61
3.33
3.21
1.50
HN
O
O
N
Me
O
O
CO2tBu
CDCl3
0.92
3.00
4.09
9.24
f1 (ppm)

35


172.3
171.0
162.7
149.5
138.2
134.3
81.1
54.5
44.9
43.3
28.5
28.1
CDCl3
f1 (ppm)


7.45
7.44
7.35
7.34
7.33
7.32
7.32
7.28
5.60
5.57
5.54
5.08
5.08
5.07
4.83
4.82
4.79
4.79
4.78
4.74
4.73
3.30
2.16
2.16
2.14
2.13
2.11
1.91
1.90
1.89
1.89
1.88
1.88
1.88
1.87
1.87
1.86
1.86
1.85
1.85
1.54
O
N
O
N
Me
O
O
36
4.56
0.78
2.07
1.61
3.00
2.10
2.02
3.19
f1 (ppm)


172.8
172.7
151.6
137.2
129.8
129.2
128.7
116.5
51.8
45.8
39.4
30.5
29.3
26.0
CDCl3
f1 (ppm)


5.88
5.88
5.86
5.83
5.68
5.68
5.66
5.65
5.62
5.36
5.35
5.35
5.34
5.30
5.29
5.29
5.28
5.27
5.27
5.26
5.24
5.24
5.23
5.23
5.23
4.98
4.97
4.97
4.96
4.96
4.95
4.95
4.93
4.92
4.92
4.51
4.51
4.49
4.49
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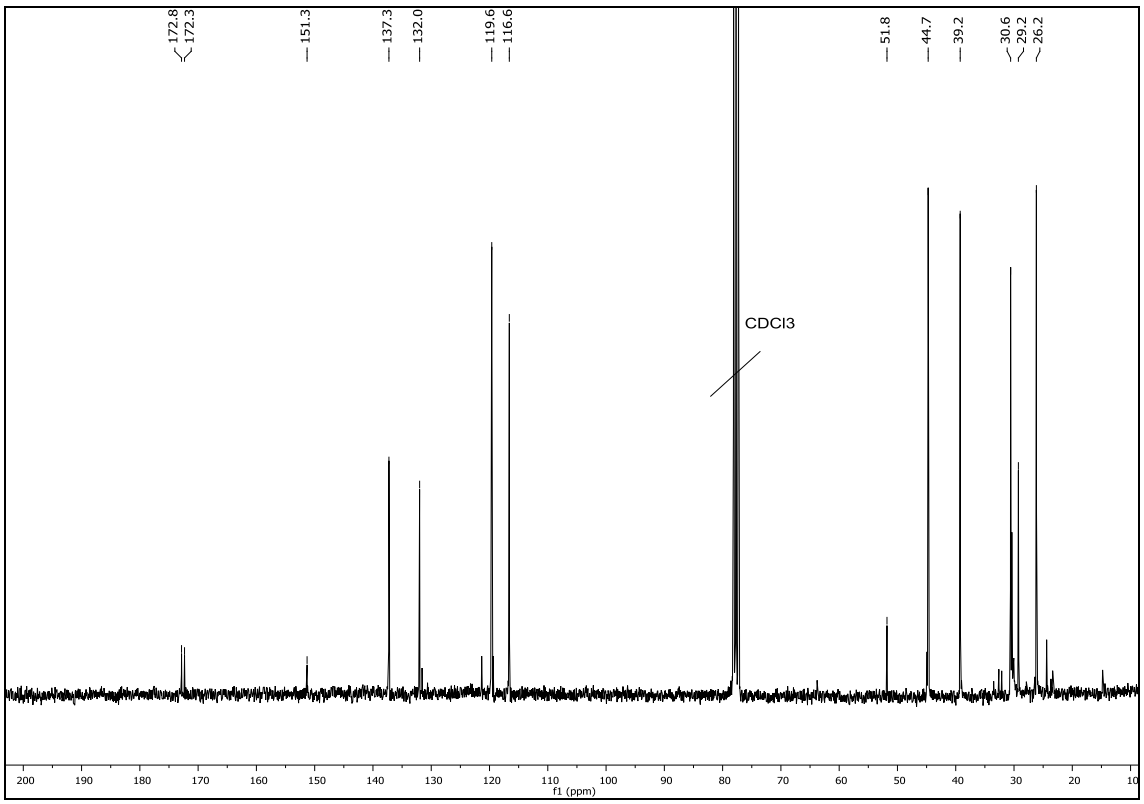
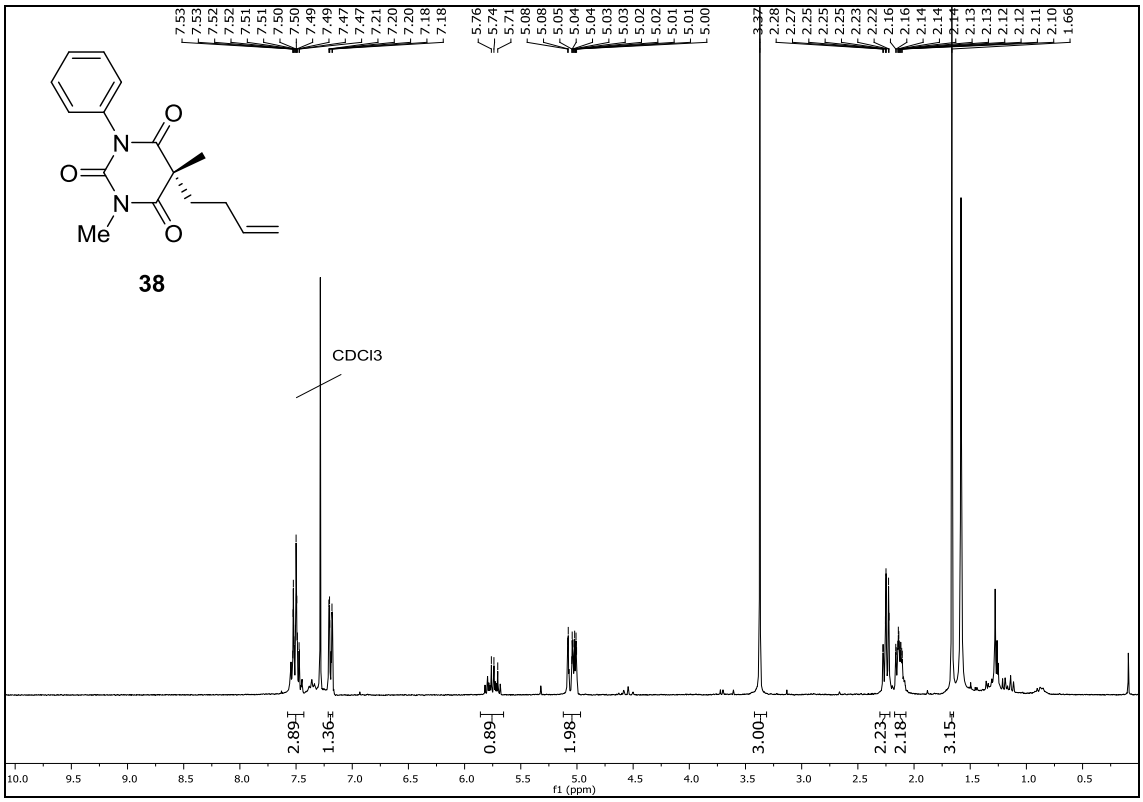
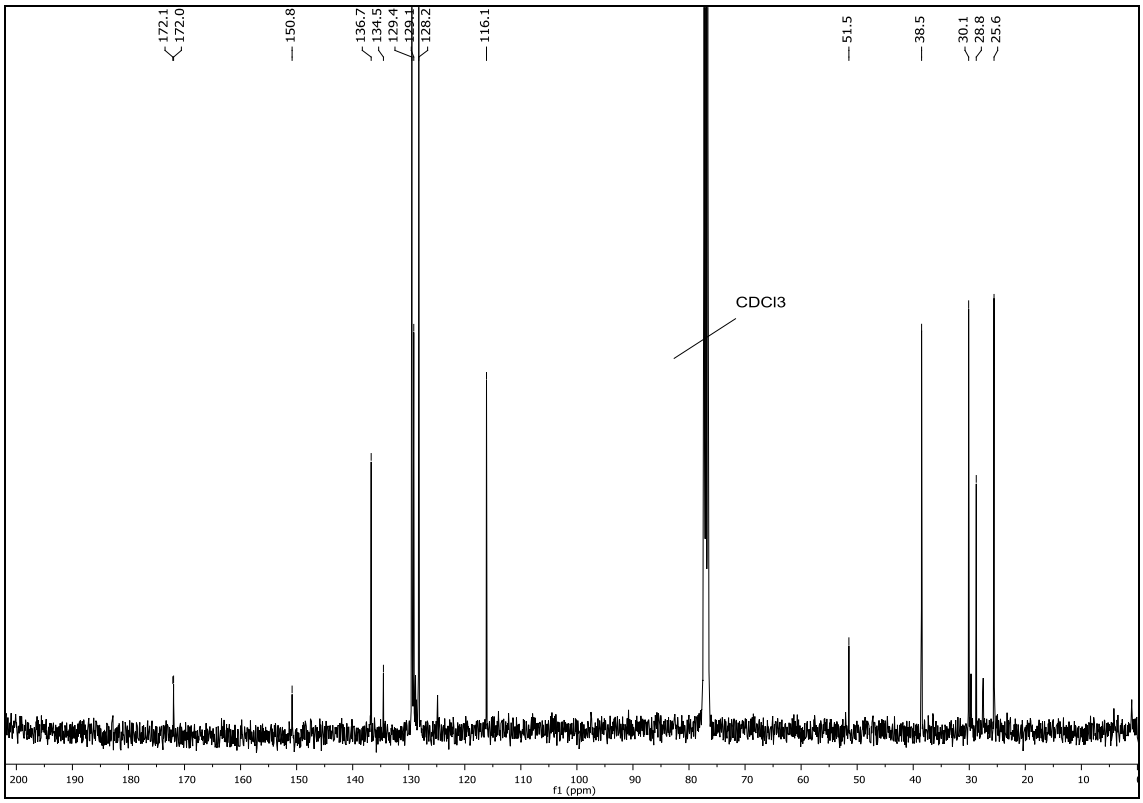
2.18
2.17
2.16
2.13
2.00
1.99
1.98
1.98
1.97
1.97
1.96
1.96
1.95
1.94
1.55
O
N
O
N
Me
O
37
CDCl3
0.72
0.71
1.80
1.52
2.00
2.86
2.07
2.06
3.24
f1 (ppm)

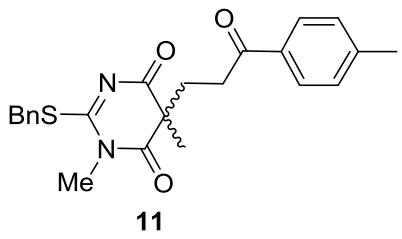

172.8
172.3
151.3
137.3
132.0
119.6
116.6
51.8
44.7
39.2
30.6
29.2
26.2
CDCl3
f1 (ppm)


38
CDCl3
f1 (ppm)


CDCl3
f1 (ppm)

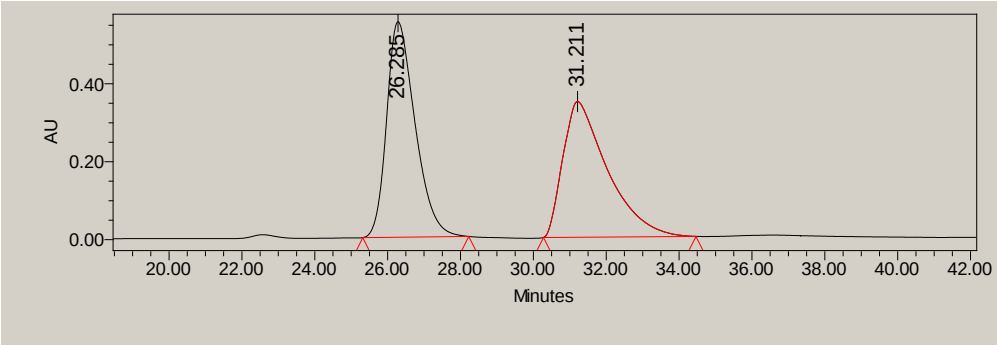
4. HPLC chromatograms of representative compounds:

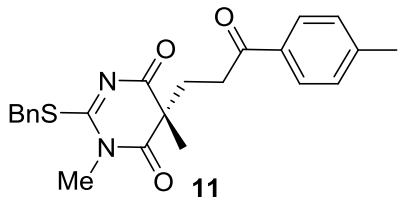
Chiralpack IA 0.5 mL/min, hexano:isopropanol 80:20, λ= 210 nm



11

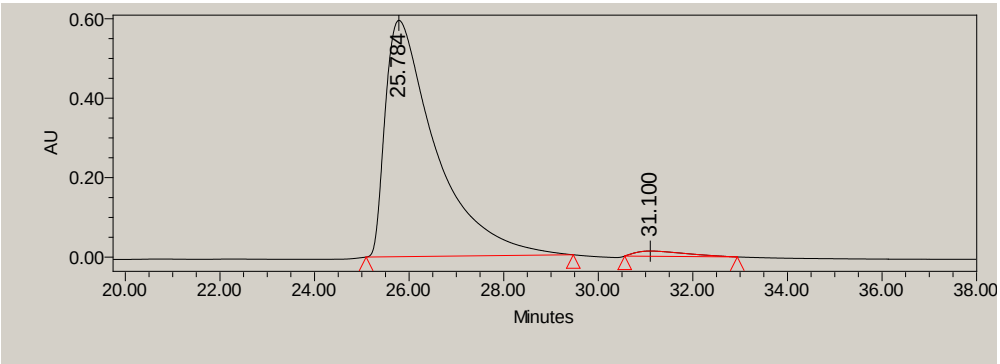
	Retention Time	% Area
1	26.285	50.43
2	31.211	49.57



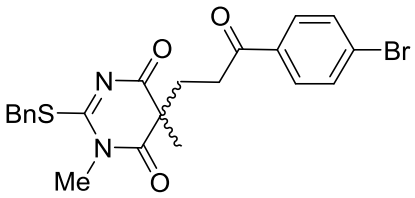


11

	Retention Time	% Area
1	25.784	97.81
2	31.100	2.19

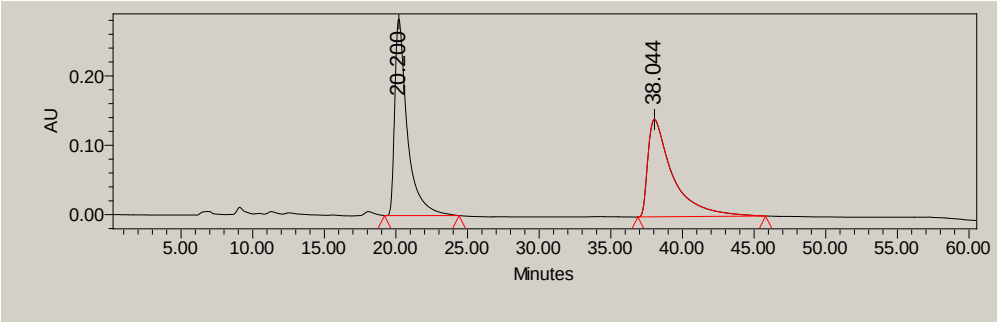


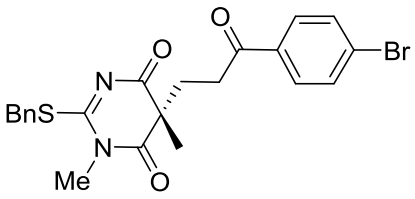
Chiralpack IA 0.5 mL/min, hexano:isopropanol 50:50, λ = 210 nm



12

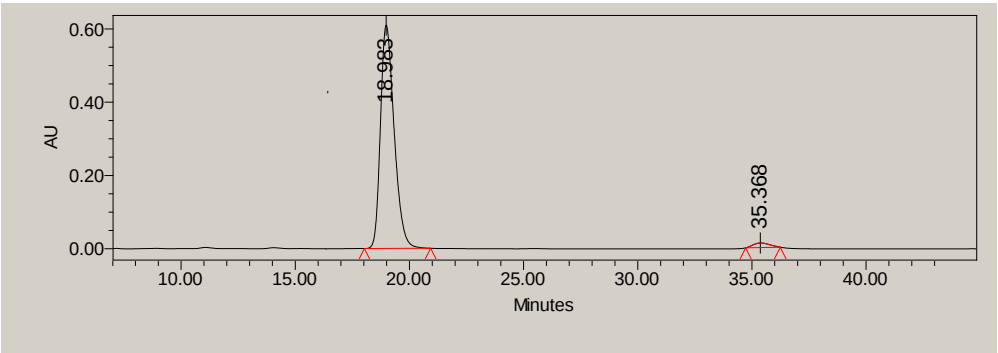
	Retention Time	% Area
1	20.200	50.54
2	38.044	49.46



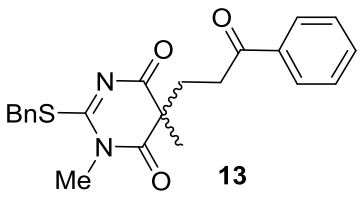


12

	Retention Time	% Area
1	18.983	97.58
2	35.368	2.42

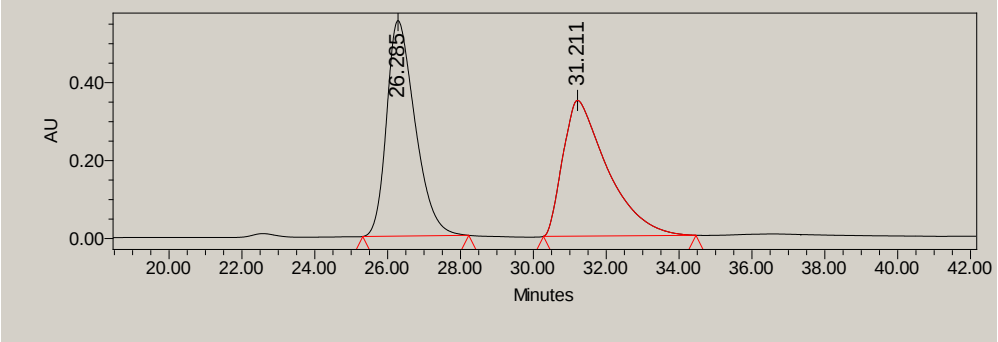


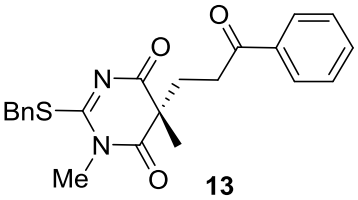
Chiralpack IA 0.5 mL/min, hexano:isopropanol 80:20, λ = 210 nm



13

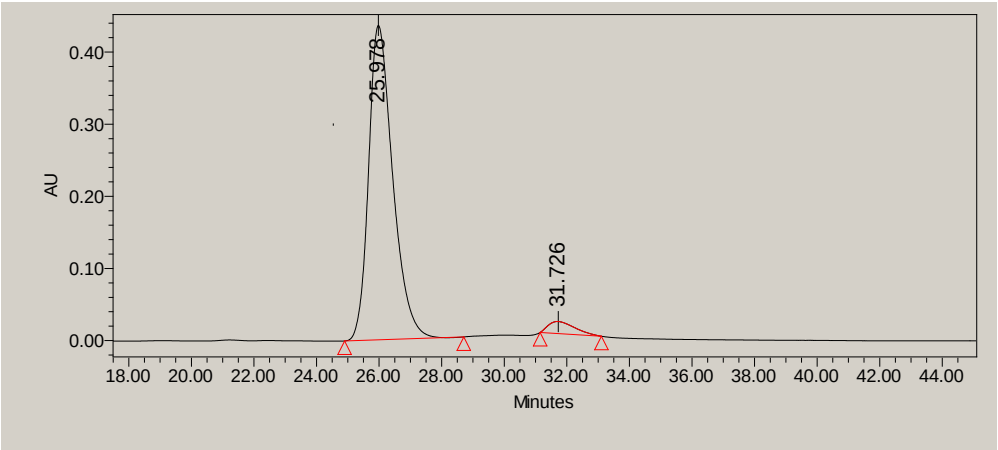
	Retention Time	% Area
1	26.285	50.43
2	31.211	49.57



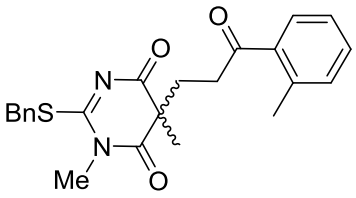


13

	Retention Time	% Area
1	25.978	95.92
2	31.726	4.08

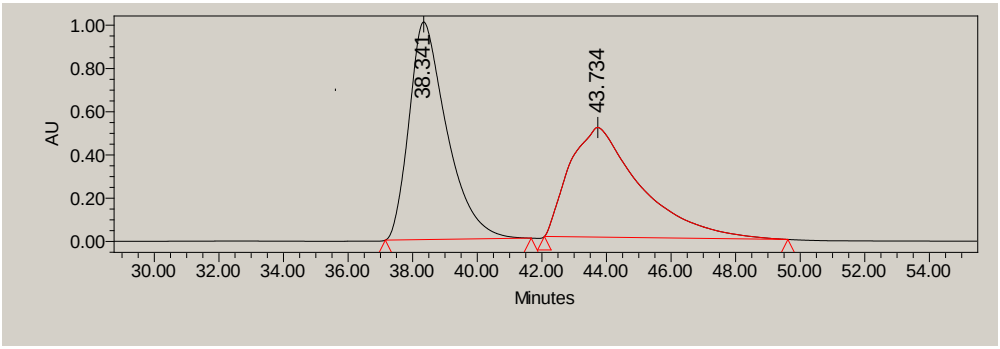


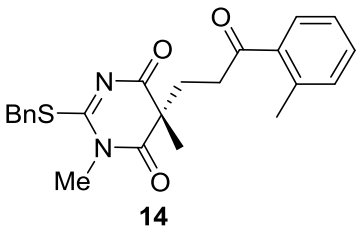
Chiralpack IA 0.5 mL/min, hexano:isopropanol 90:10, λ = 210 nm



14

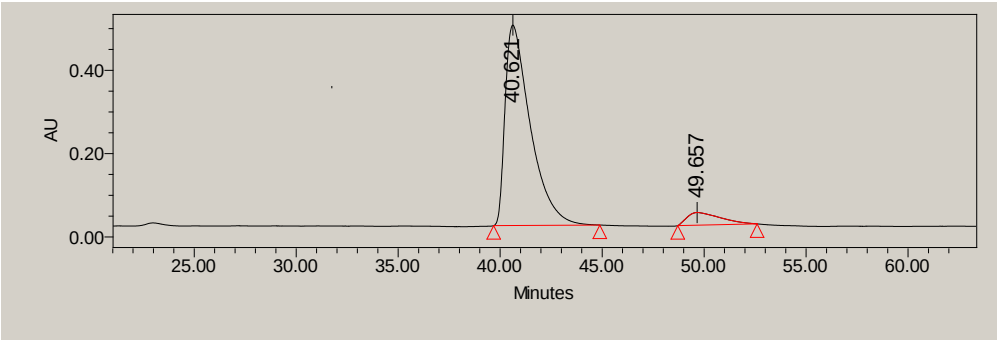
	Retention Time	% Area
1	38.341	51.22
2	43.734	48.78



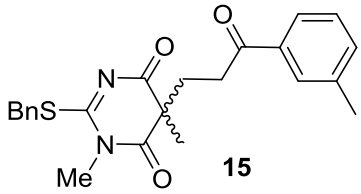


14

	Retention Time	% Area
1	40.621	92.32
2	49.657	7.68

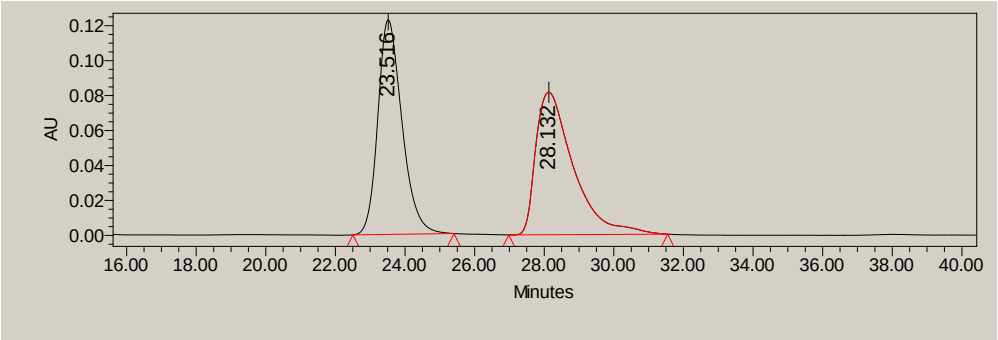


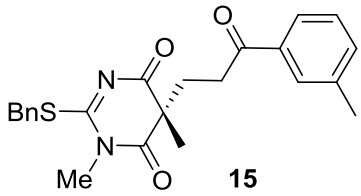
Chiralpack IA 0.5 mL/min, hexano:isopropanol 80:20, λ = 210 nm



15

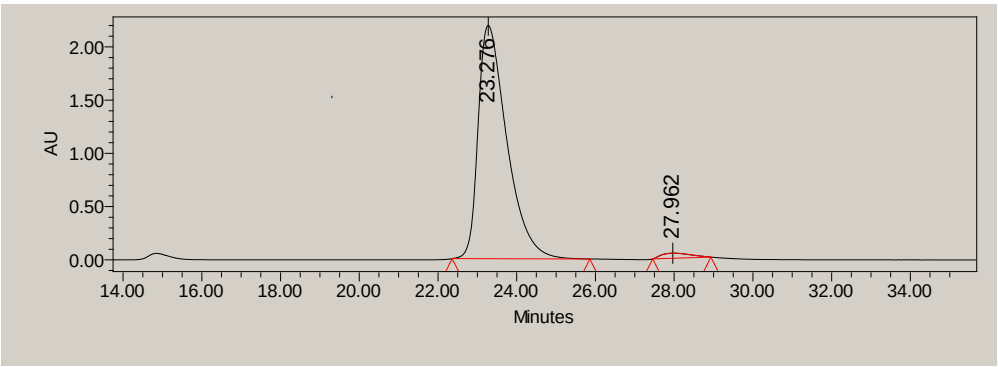
	Retention Time	% Area
1	23.516	49.20
2	28.132	50.80



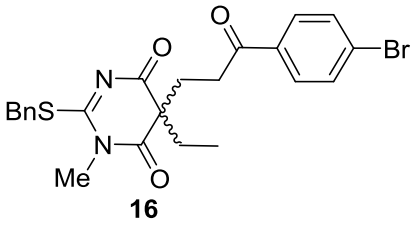


15

	Retention Time	% Area
1	23.276	97.83
2	27.962	2.17

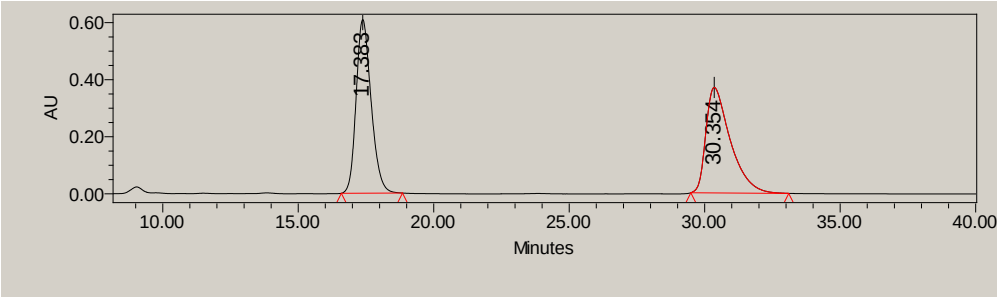


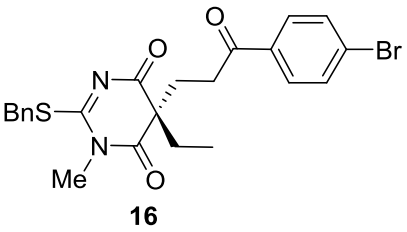
Chiralpack IA 0.5 mL/min, hexano:isopropanol 50:50, λ = 210 nm



16

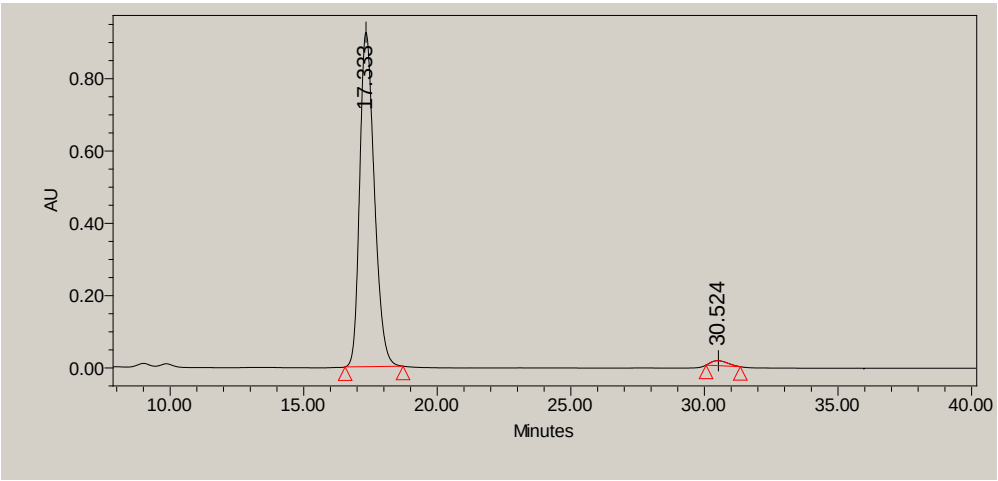
	Retention Time	% Area
1	17.383	50.34
2	30.354	49.66



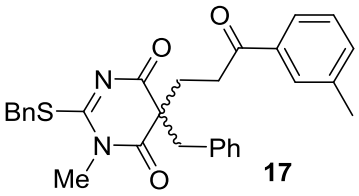


16

	Retention Time	% Area
1	17.333	98.35
2	30.524	1.65

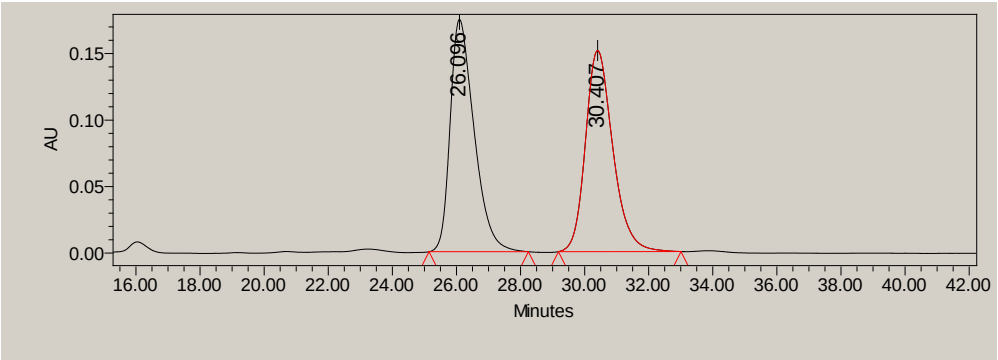


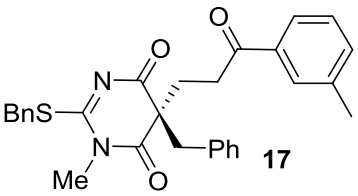
Chiralpack IA 0.5 mL/min, hexano:isopropanol 80:20, λ = 210 nm



17

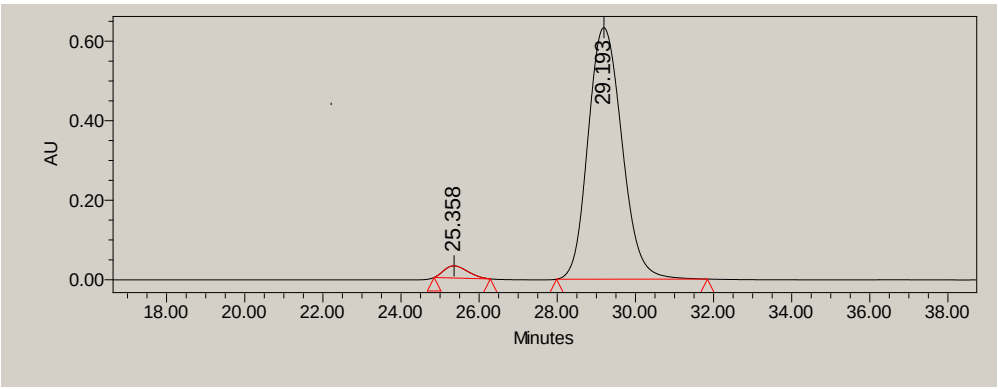
	Retention Time	% Area
1	26.096	50.26
2	30.407	49.74



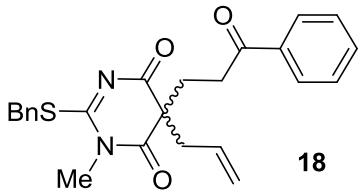


17

	Retention Time	% Area
1	25.358	3.26
2	29.193	96.74

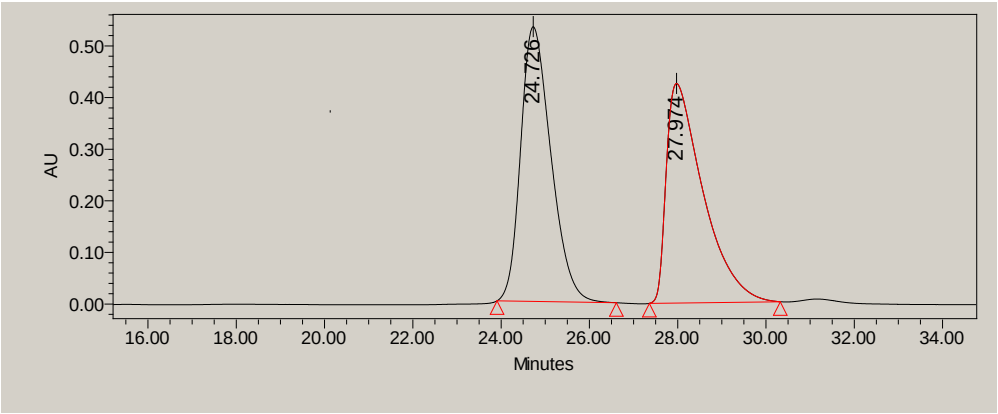


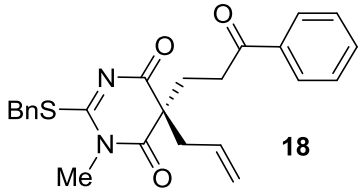
Chiralpack IA 0.5 mL/min, hexano:isopropanol 80:20, λ = 210 nm



18

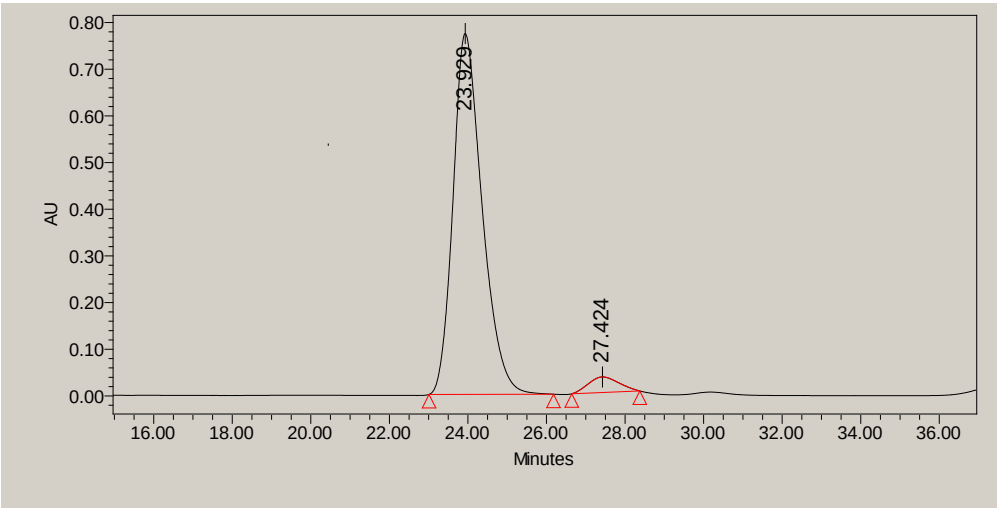
	Retention Time	% Area
1	24.726	50.79
2	27.974	49.21



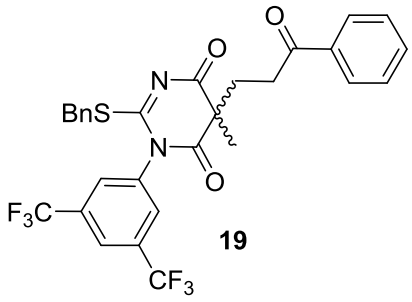


18

	Retention Time	% Area
1	23.929	95.67
2	27.424	4.33

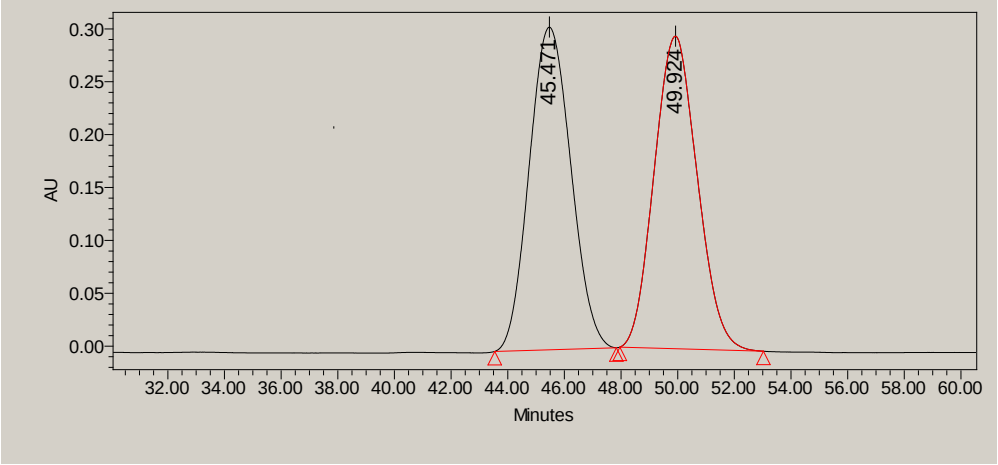


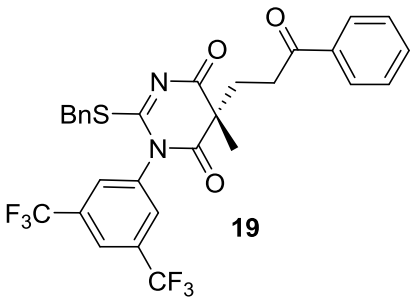
Chiralpack IC 0.5 mL/min, hexano:isopropanol 95:5, λ = 210 nm



19

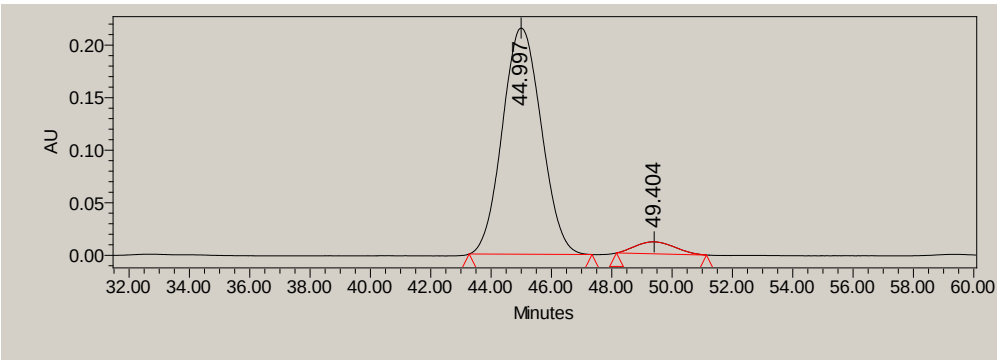
	Retention Time	% Area
1	45.471	49.98
2	49.924	50.02



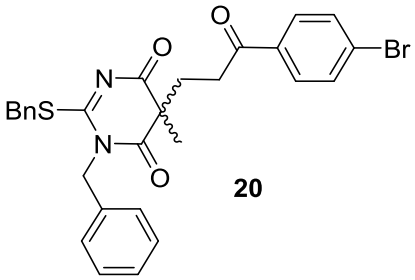


19

	Retention Time	% Area
1	44.997	94.93
2	49.404	5.07

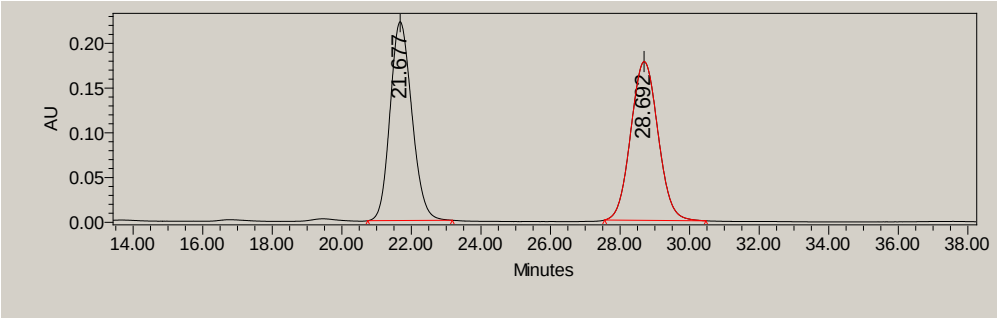


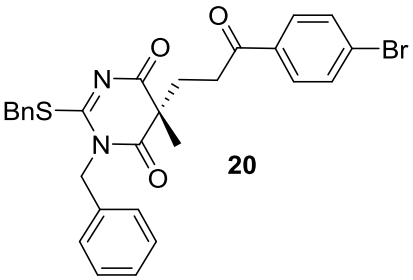
Chiralpack IA 0.5 mL/min, hexano:isopropanol 50:50, λ = 210 nm



20

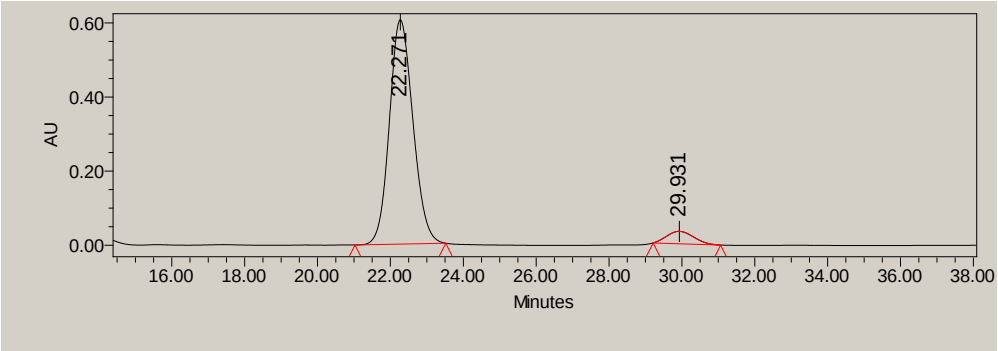
	Retention Time	% Area
1	21.677	50.01
2	28.692	49.99



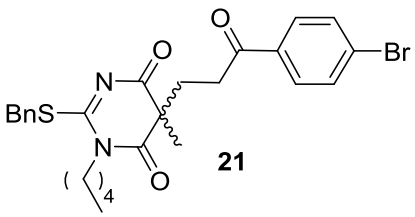


20

	Retention Time	% Area
1	22.271	94.96
2	29.912	5.04

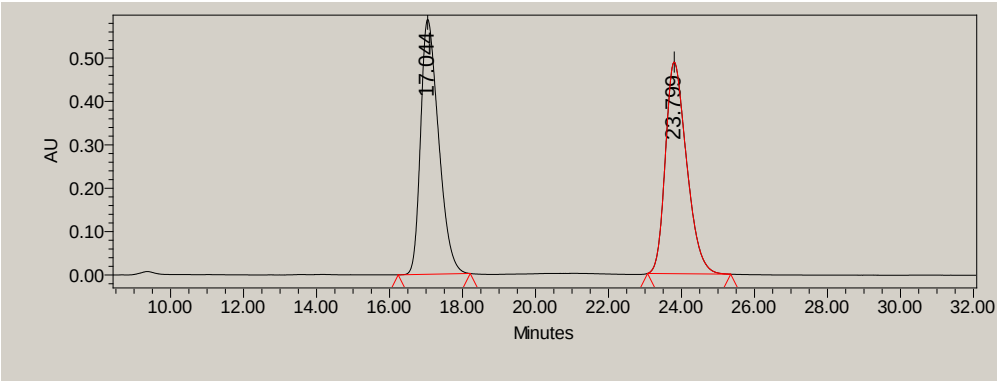


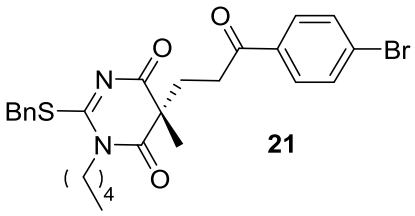
Chiralpack IB 0.5 mL/min, hexano:isopropanol 80:20, λ = 210 nm



21

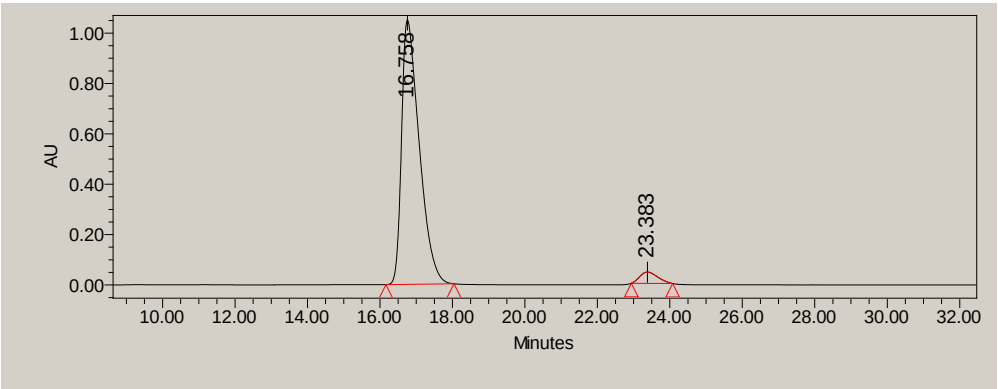
	Retention Time	% Area
1	17.044	50.50
2	23.799	49.50





21

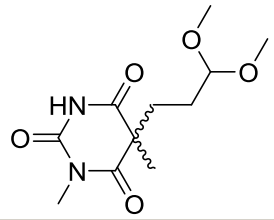
	Retention Time	% Area
1	16.758	95.83
2	23.383	4.17



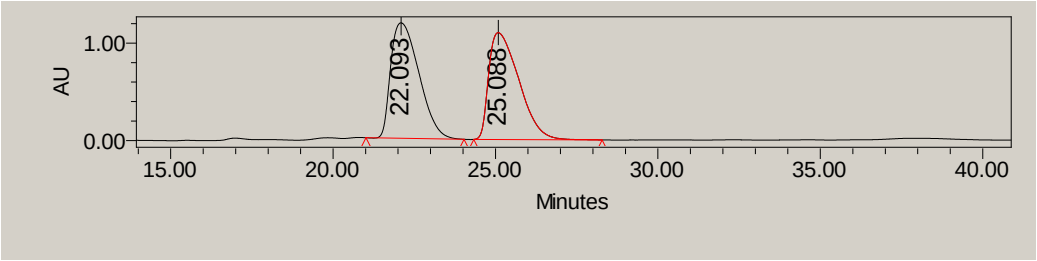
HPLC analyses of aldehyde **22** were carried out after derivatization of **22** onto the corresponding dimethyl acetal.

Chiralpack IB 0.5 mL/min, hexano:isopropanol 80:20, λ= 210 nm

(from rac-**22**)

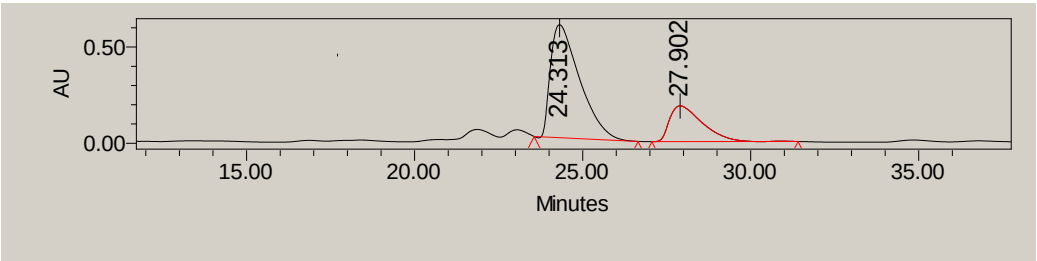


	Retention Time	% Area
1	22.093	50.38
2	25.088	49.62



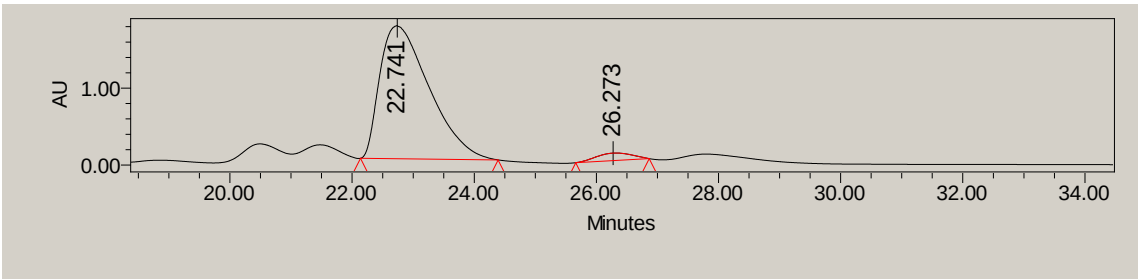
a) Obtained from the conjugate addition to acrolein and derivatization (Section 2.7.4, p S44)

	Retention Time	% Area
1	24.313	73.77
2	27.902	26.23

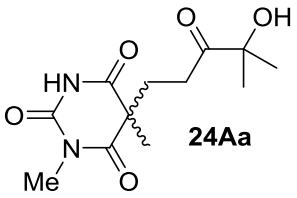


b) Obtained from the oxidative scission of adduct **24Aa** and derivatization (Section 2.9.2, p S50)

	Retention Time	% Area
1	22.741	96.07
2	26.273	3.93

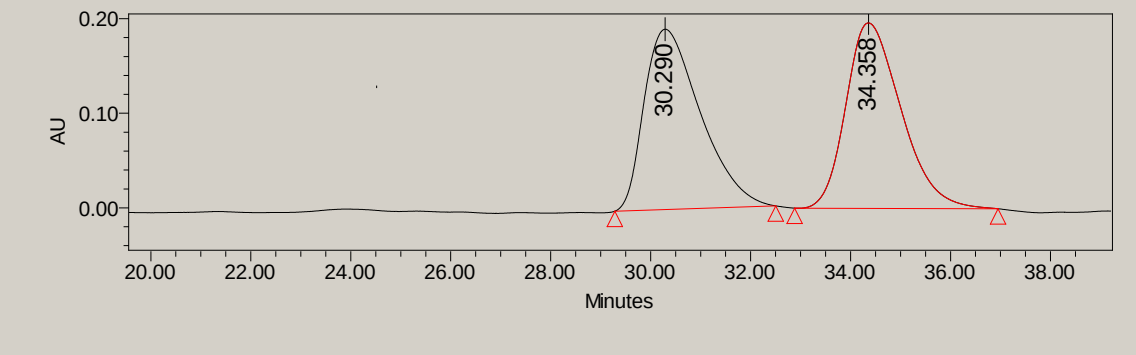


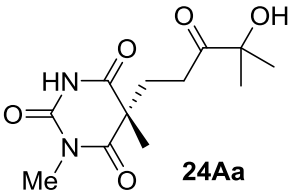
Chiralpack IA 0.5 mL/min, hexano:isopropanol 80:20, λ = 210 nm



24Aa

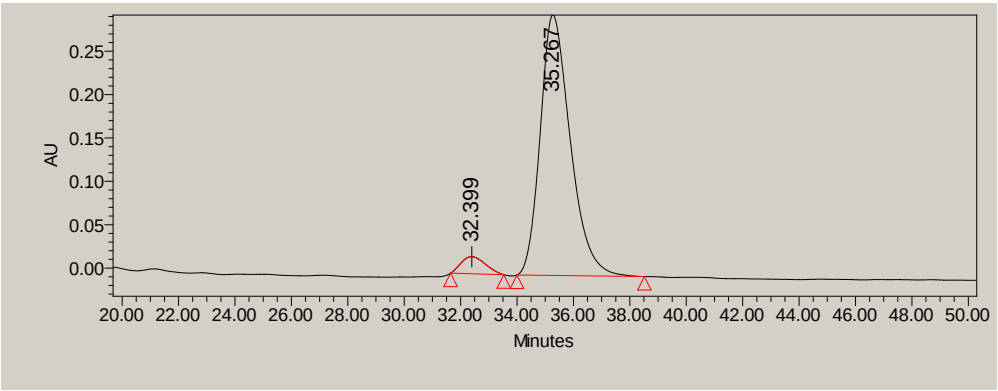
	Retention Time	% Area
1	30.290	49.78
2	34.358	50.22



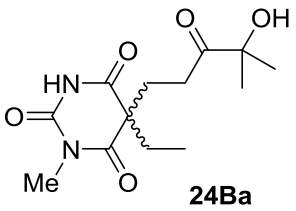


24Aa

	Retention Time	% Area
1	32.399	5.05
2	35.267	94.95

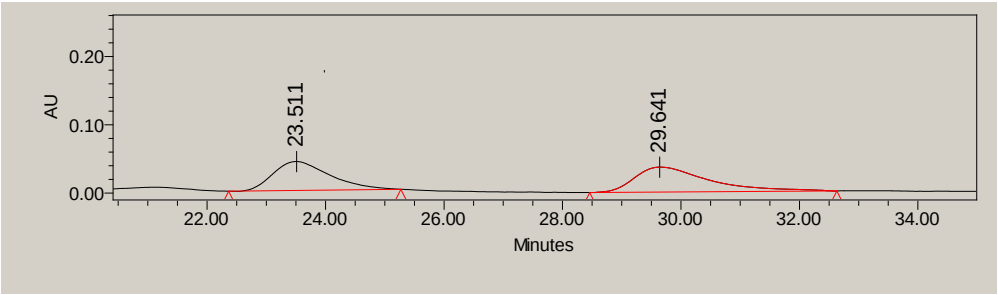


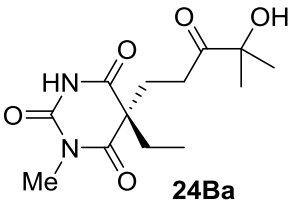
Chiralpack IA 0.5 mL/min, hexano:isopropanol 80:20, λ = 210 nm



24Ba

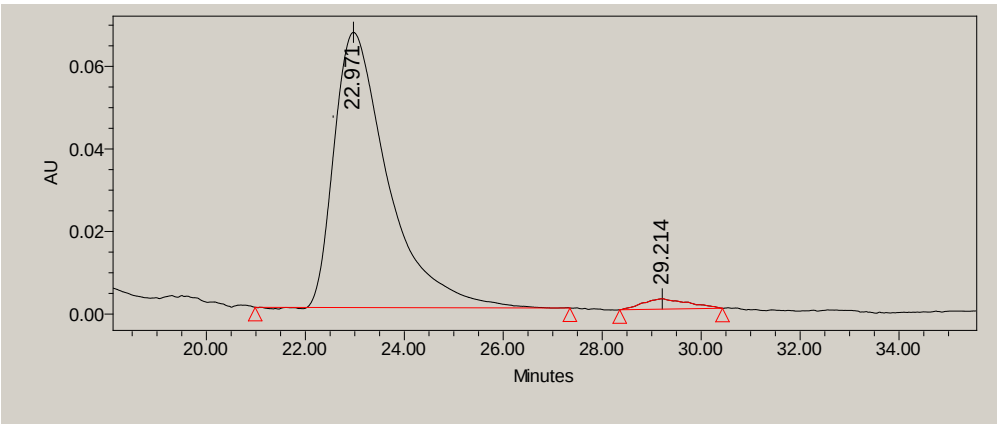
	Retention Time	% Area
1	23.511	46.97
2	29.641	53.03



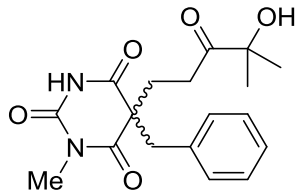


24Ba

	Retention Time	% Area
1	22.971	96.92
2	29.214	3.08

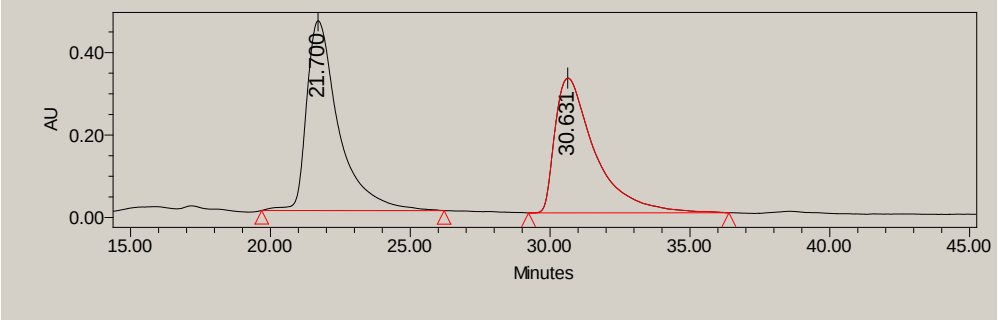


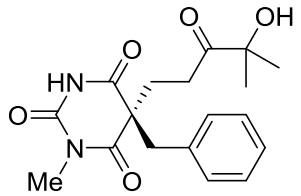
Chiralpack IA 0.5 mL/min, hexano:isopropanol 80:20, λ = 210 nm



24Ca

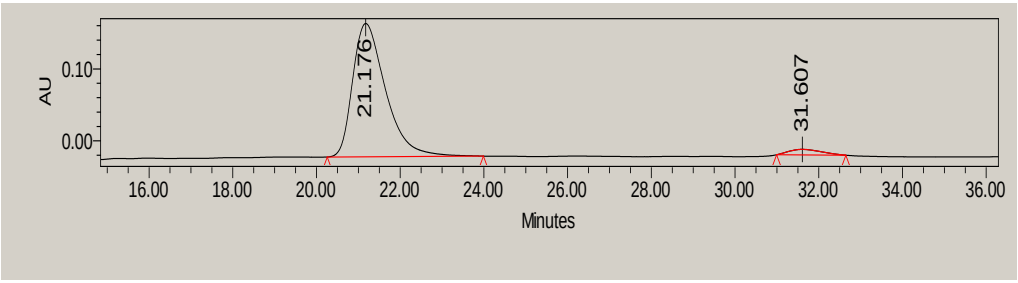
	Retention Time	% Area
1	21.700	53.82
2	30.631	46.18



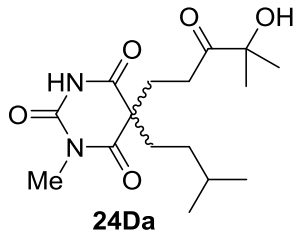


24Ca

	Retention Time	% Area
1	21.176	96.02
2	31.607	3.98

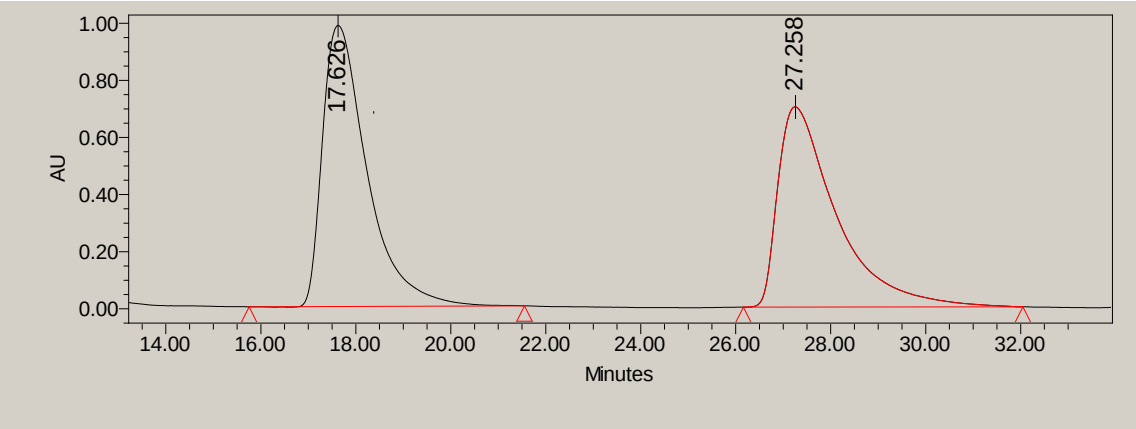


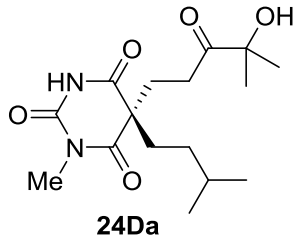
Chiralpack IA 0.5 mL/min, hexano:isopropanol 80:20, λ = 210 nm



24Da

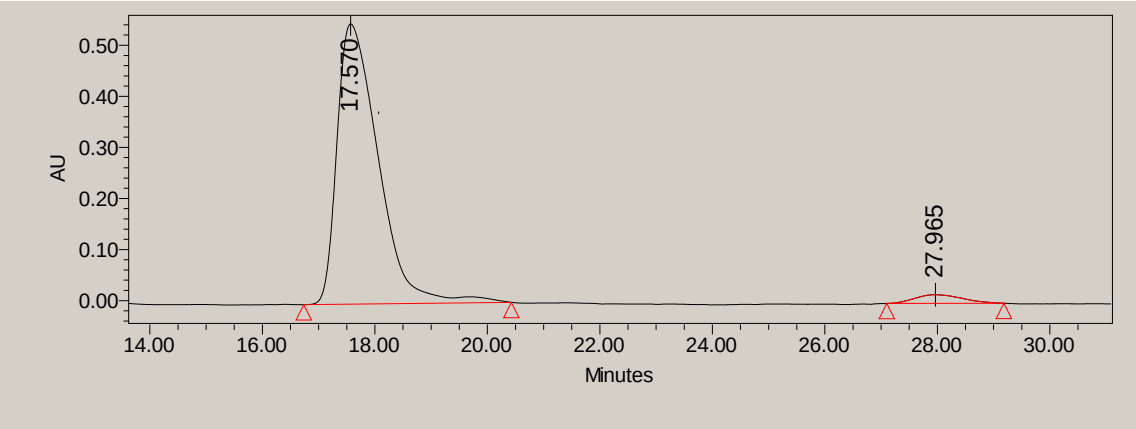
	Retention Time	% Area
1	17.626	51.71
2	27.258	48.29



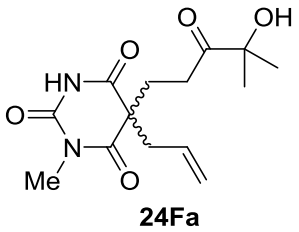


24Da

	Retention Time	% Area
1	17.570	96.59
2	27.965	3.41

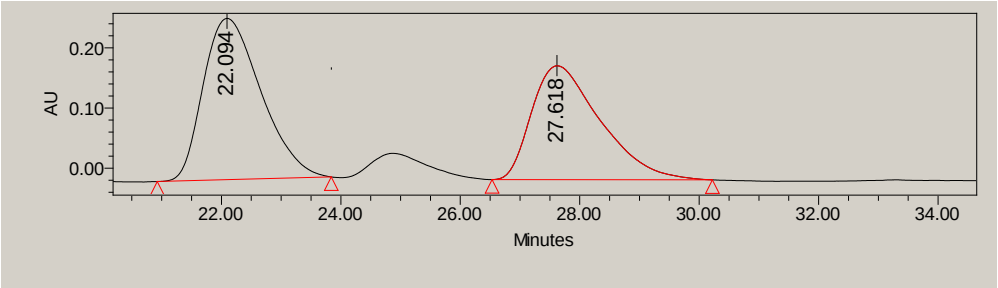


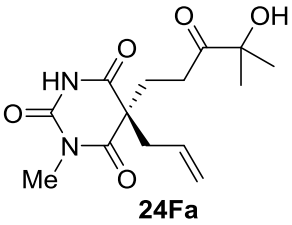
Chiralpack ADH 0.5 mL/min, hexano:isopropanol 80:20, λ = 210 nm



24Fa

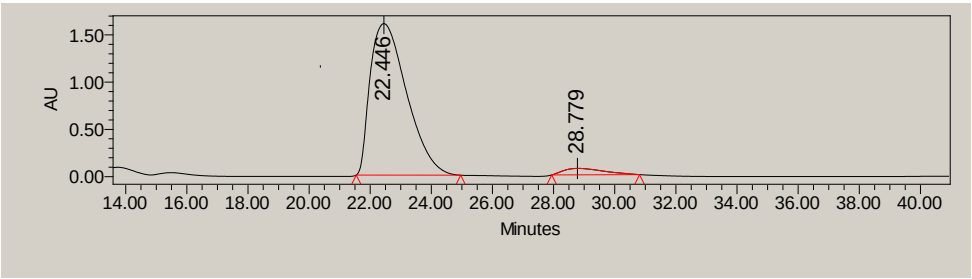
	Retention Time	% Area
1	22.094	54.40
2	27.618	45.60



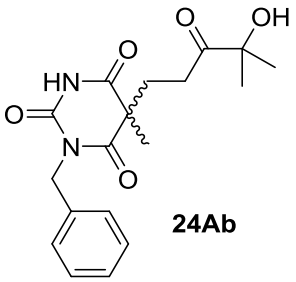


24Fa

	Retention Time	% Area
1	22.446	95.51
2	28.779	4.49

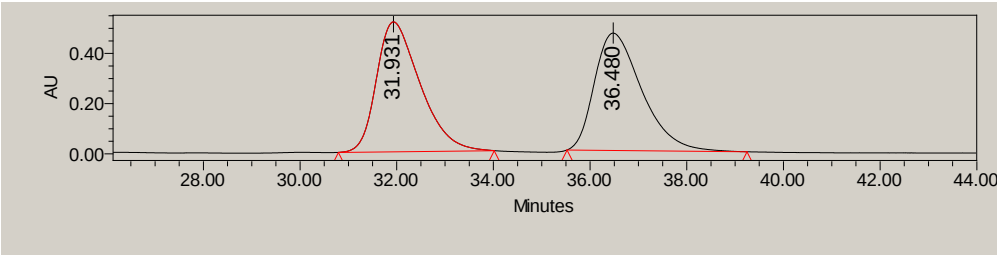


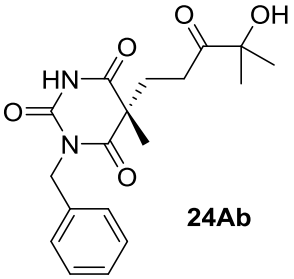
Chiralpack IA 0.5 mL/min, hexano:isopropanol 80:20, λ = 210 nm



24Ab

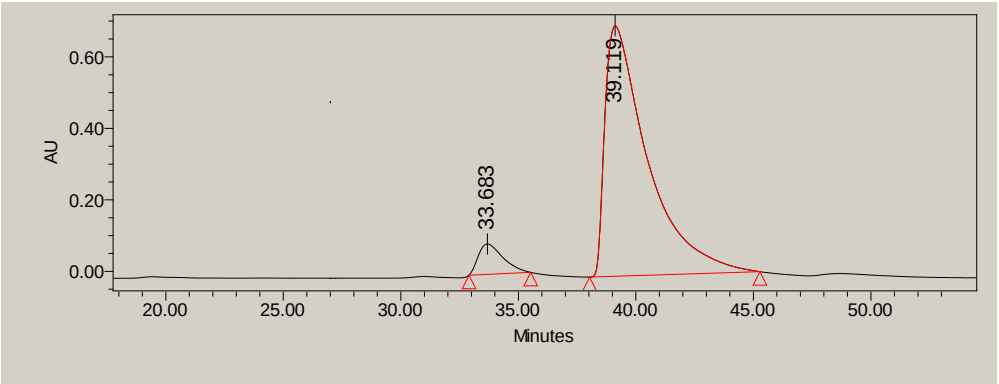
	Retention Time	% Area
1	31.931	50.41
2	36.480	49.59



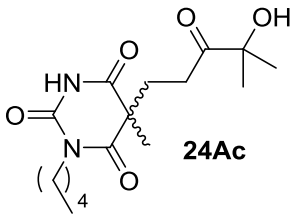


24Ab

	Retention Time	% Area
1	33.683	6.57
2	39.119	93.43

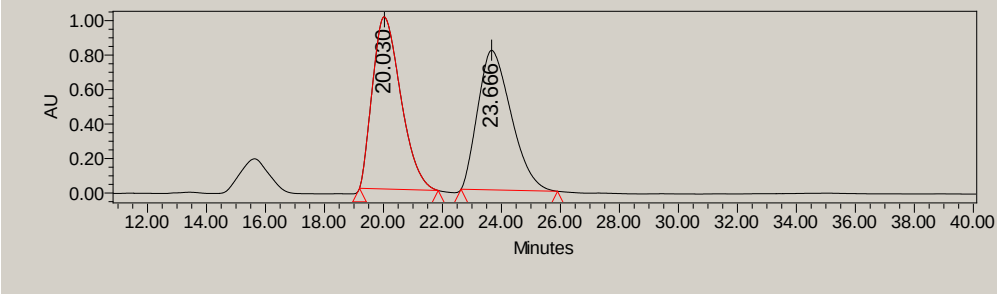


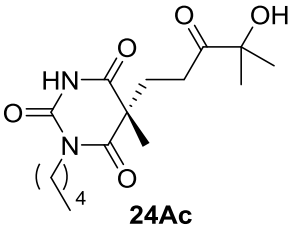
Chiralpack IB 0.5 mL/min, hexano:isopropanol 90:10, λ = 210 nm



24Ac

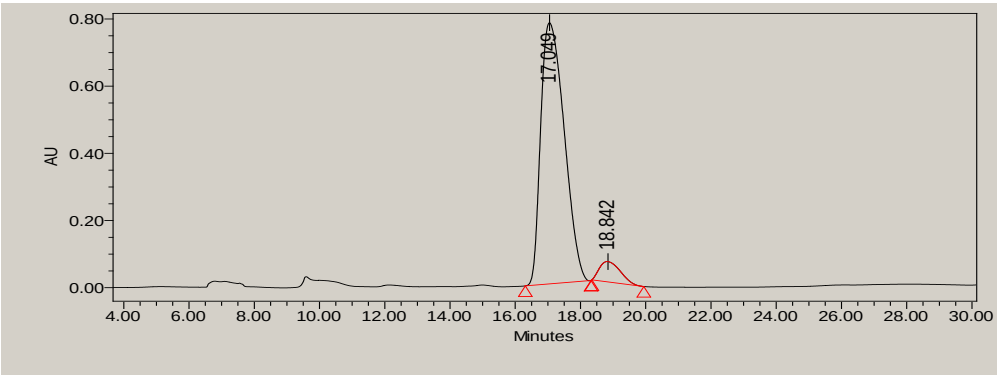
	Retention Time	% Area
1	20.030	51.17
2	23.666	48.83



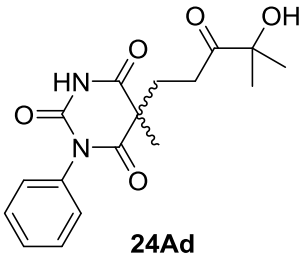


24Ac

	Retention Time	% Area
1	17.049	93.48
2	18.842	6.52

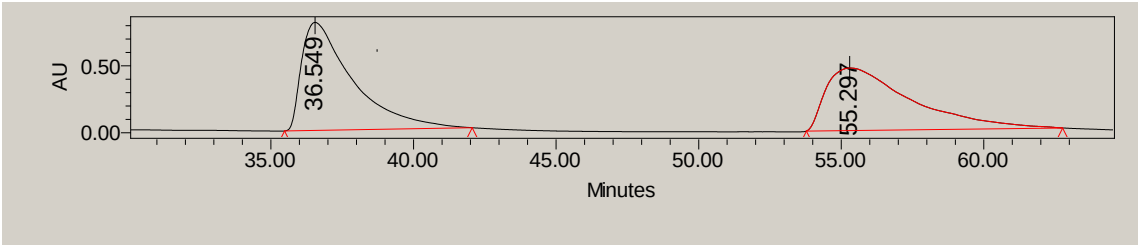


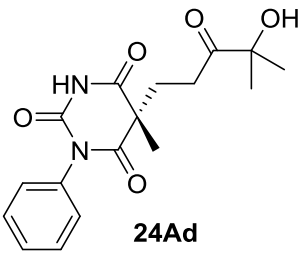
Chiralpak IA, 80:20 Hexano:*i*-PrOH, 0.5 mL/min, λ=210 nm



24Ad

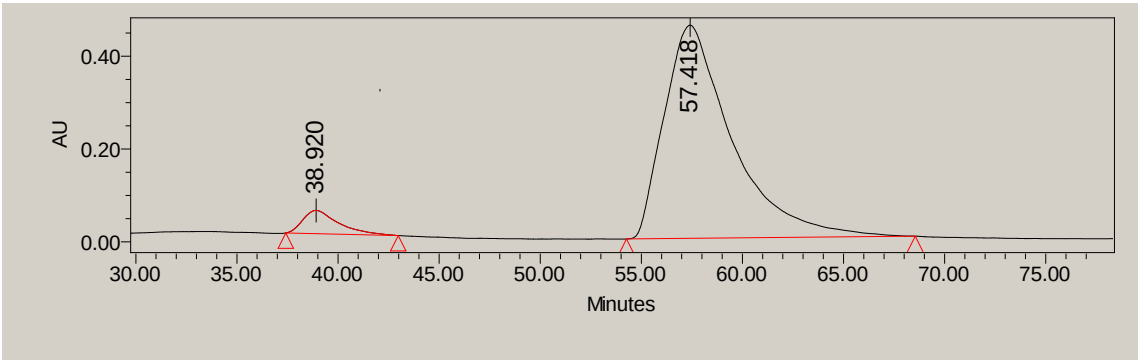
	Retention Time	% Area
1	36.549	50.83
2	55.297	49.17



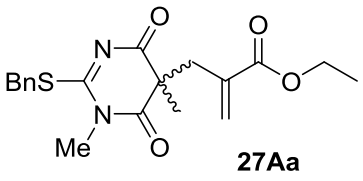


24Ad

	Retention Time	% Area
1	38.920	5.42
2	57.418	94.58

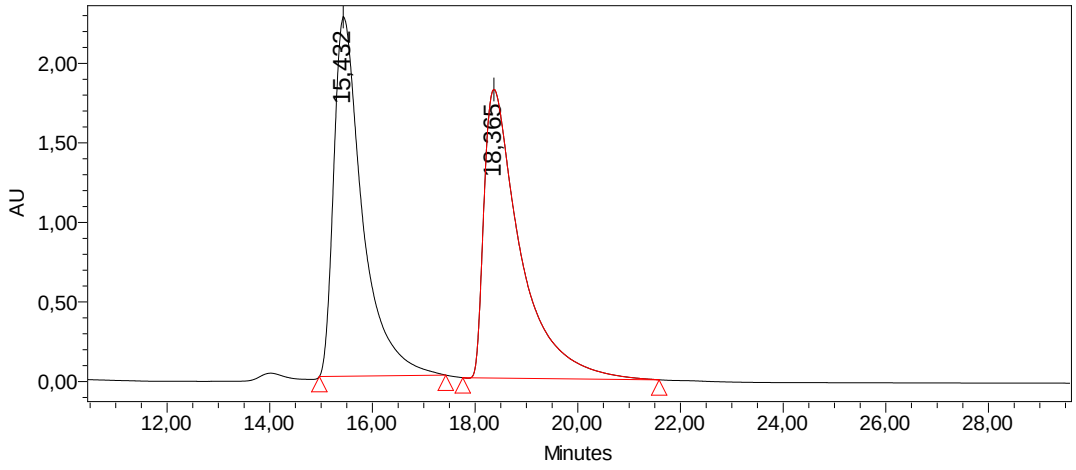


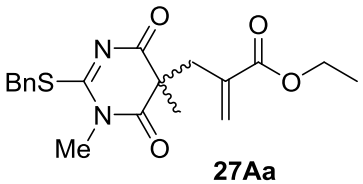
Chiralpak IA, 80:20 Hexano:*i*-PrOH, 0.5 mL/min, λ=210 nm



27Aa

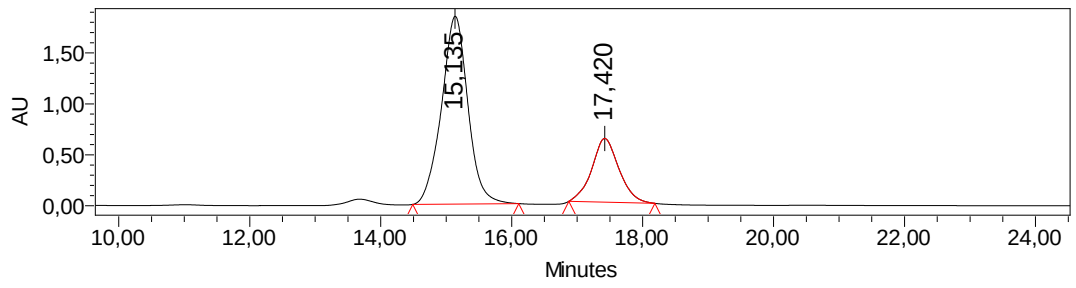
	Migration Time	% Area
1	15,432	49,46
2	18,365	50,54



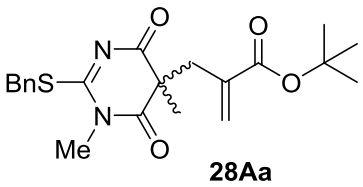


27Aa

	Migration Time	% Area
1	15,135	74,15
2	17,420	25,85

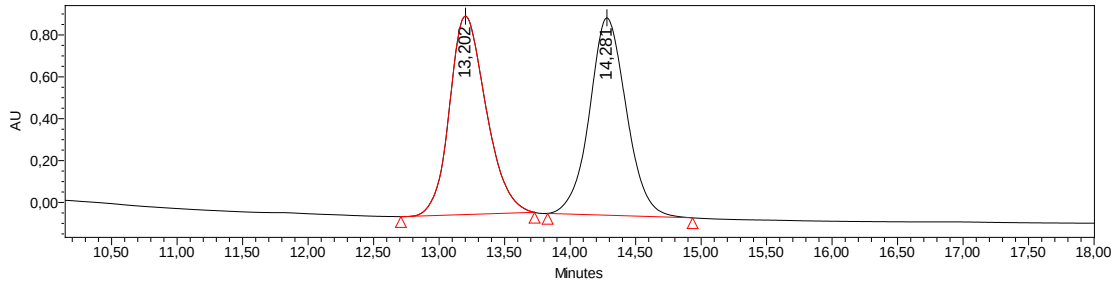


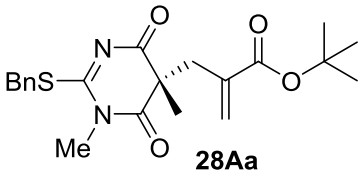
Chiralpak IA, 80:20 Hexano:*i*-PrOH, 0.5 mL/min, λ=210 nm



28Aa

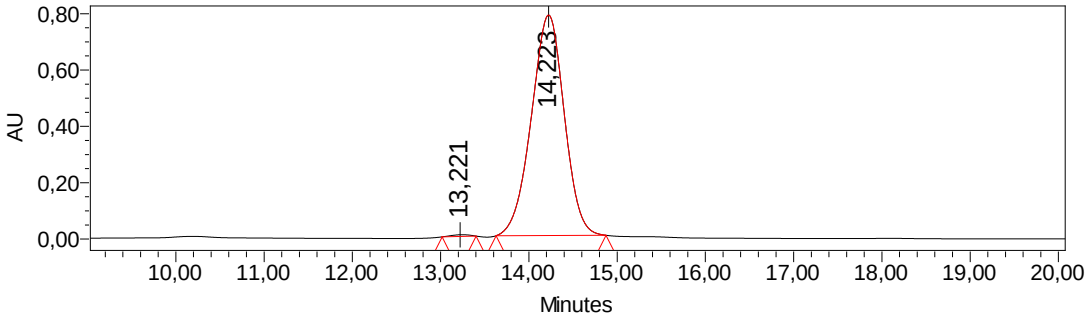
	Migration Time	% Area
1	13,202	49,93
2	14,281	50,07



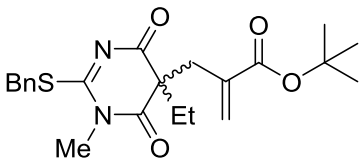


28Aa

	Migration Time	% Area
1	13,221	0,42
2	14,223	99,58

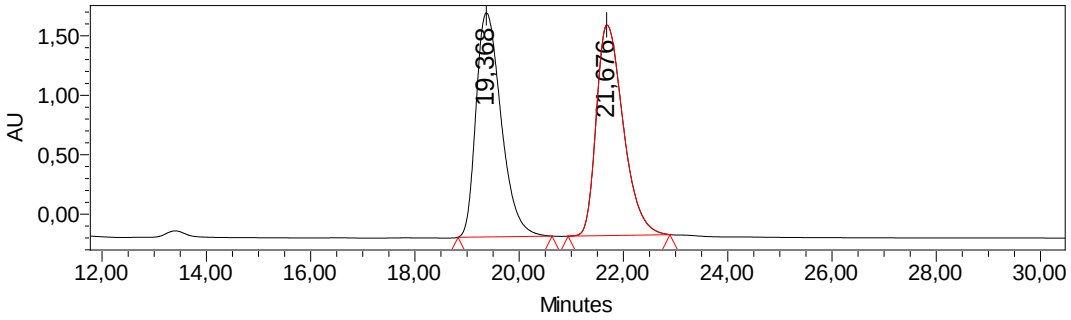


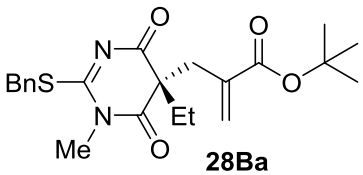
Chiralpak IC, 80:20 Hexano:*i*-PrOH, 0.5 mL/min, λ=210 nm



28Ba

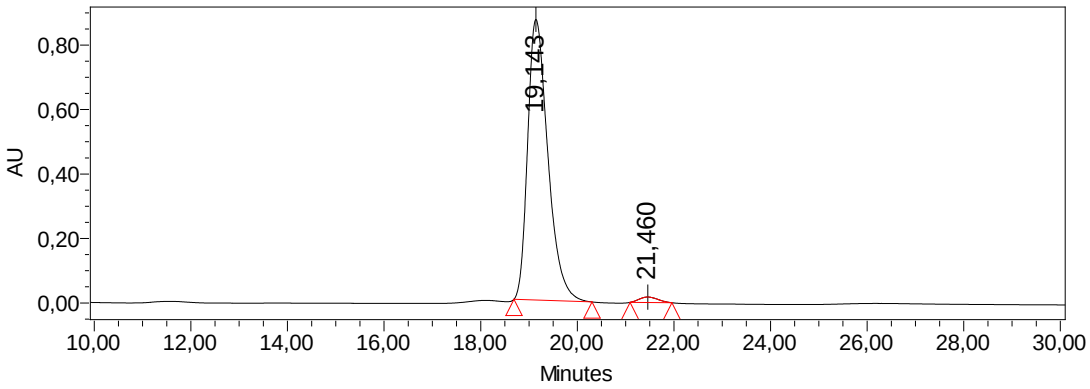
	Migration Time	% Area
1	19,368	49,89
2	21,676	50,11



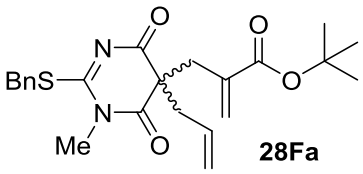


28Ba

	Migration Time	% Area
1	19,143	98,23
2	21,460	1,77

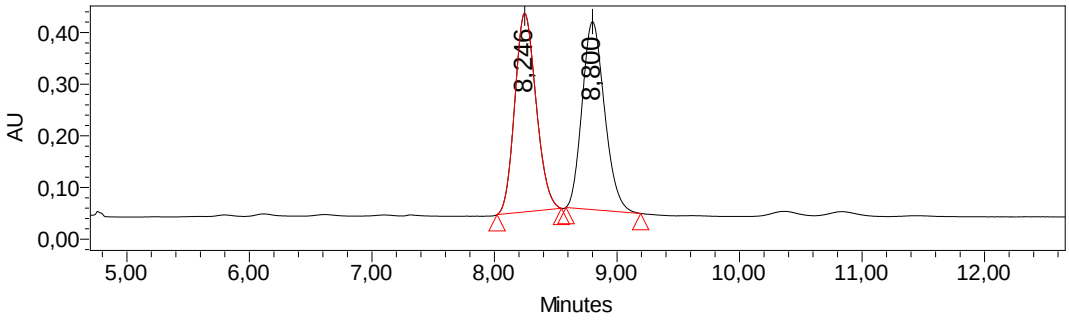


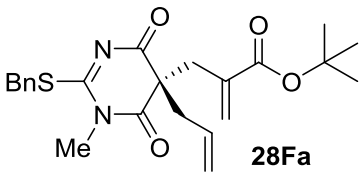
Chiralpak IC, 90:10 Hexano:EtOH, 1.0 mL/min, λ=210 nm



28Fa

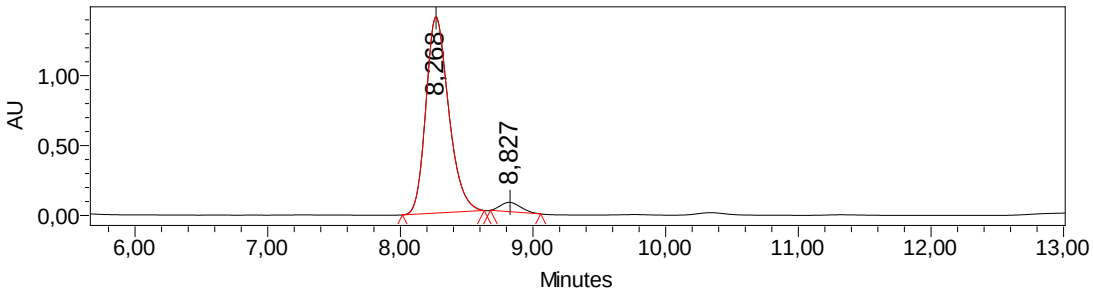
	Migration Time	% Area
1	8,246	50,13
2	8,800	49,87



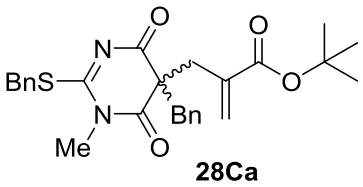


28Fa

	Migration Time	% Area
1	8,268	95,91
2	8,827	4,09

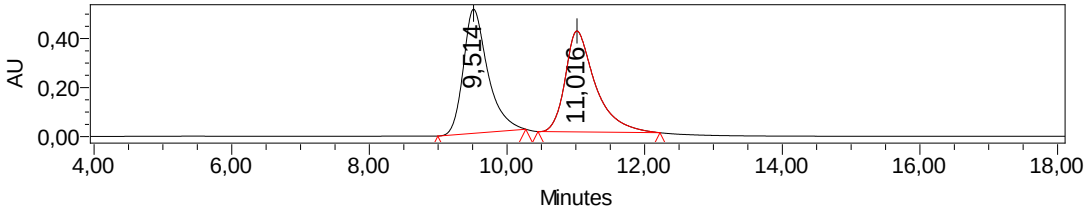


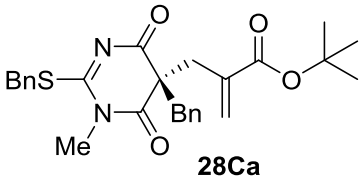
Chiralpak IA, 90:10 Hexano:*i*-PrOH, 1.0 mL/min, λ=210 nm



28Ca

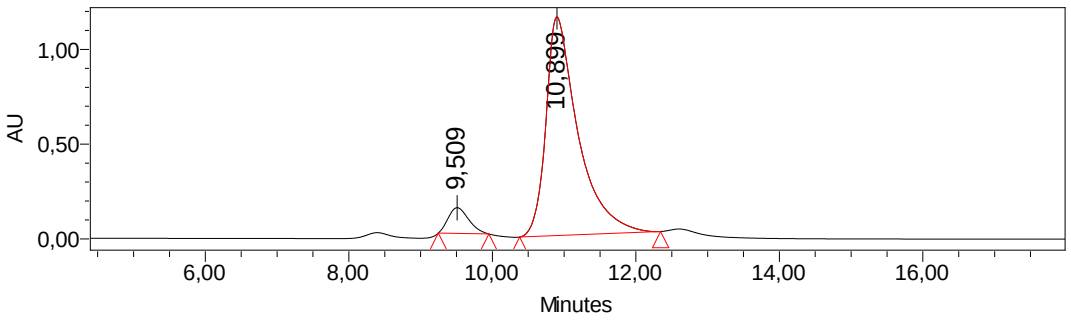
	Migration Time	% Area
1	9,514	49,81
2	11,016	50,19



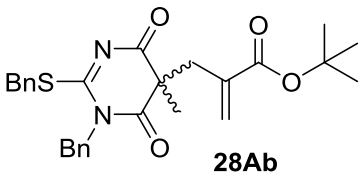


28Ca

	Migration Time	% Area
1	9,509	7,02
2	10,899	92,98

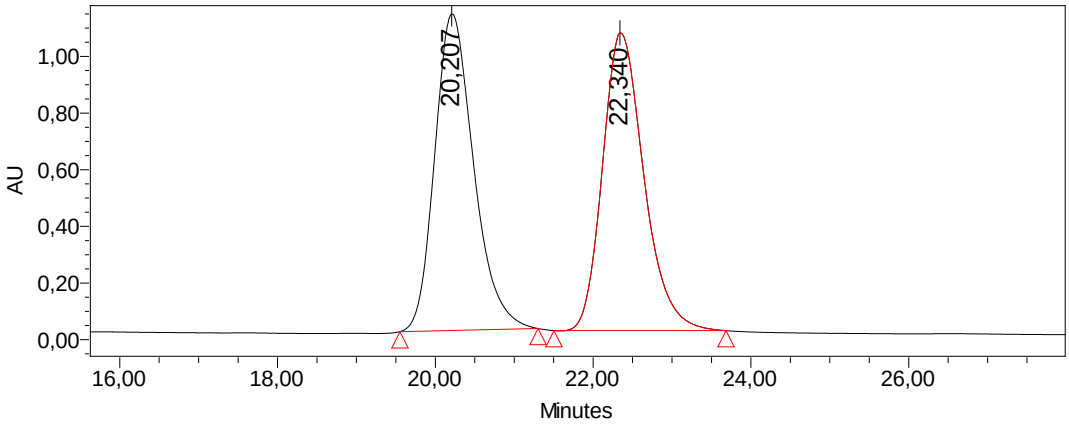


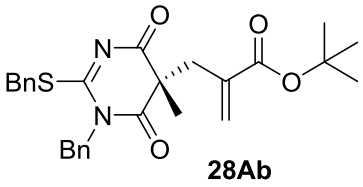
Chiralpak IC, 80:20 Hexano:*i*-PrOH, 0.5 mL/min, λ=210 nm



28Ab

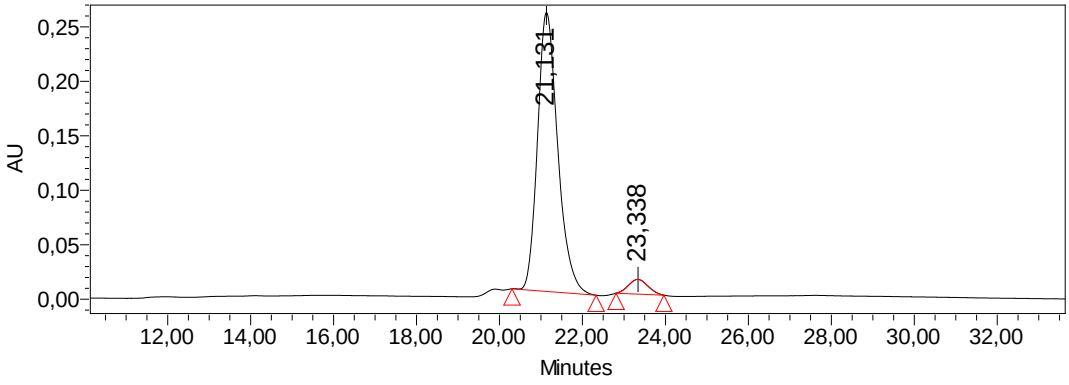
	Migration Time	% Area
1	20,207	50,03
2	22,340	49,97



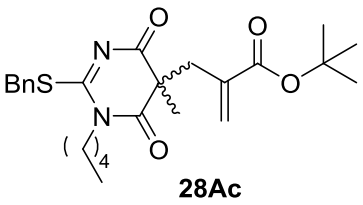


28Ab

	Migration Time	% Area
1	21,131	95,13
2	23,338	4,87

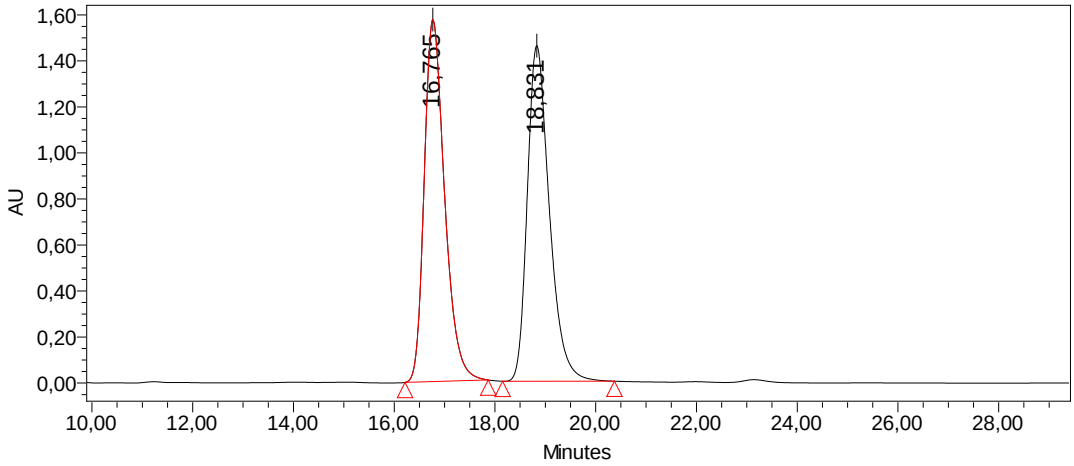


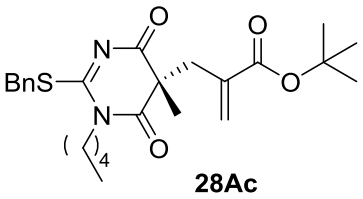
Chiralpak IC, 80:20 Hexano:*i*-PrOH, 0.5 mL/min, λ=210 nm



28Ac

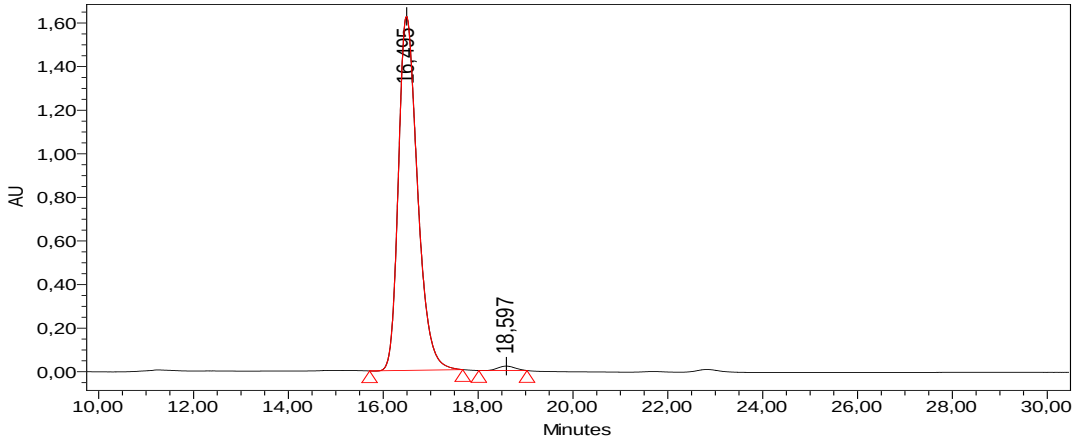
	Migration Time	% Area
1	16,765	49,94
2	18,831	50,06



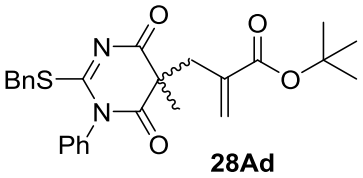


28Ac

	Migration Time	% Area
1	16,495	98,89
2	18,597	1,11

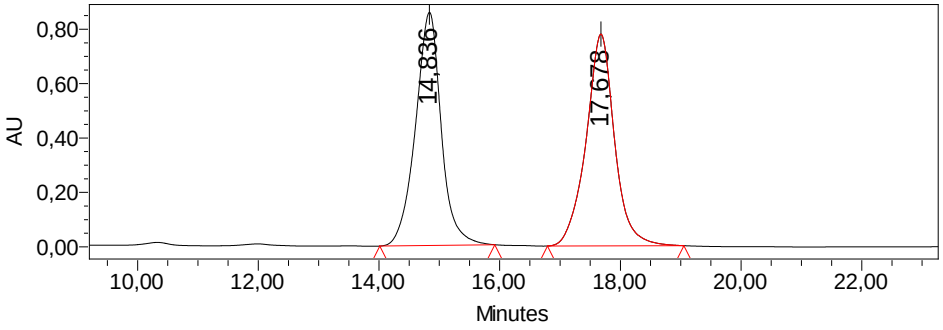


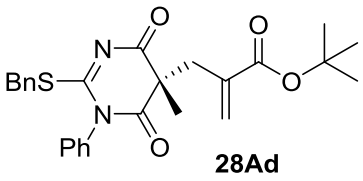
Chiralpak IA, 80:20 Hexano:*i*-PrOH, 0.5 mL/min, λ=210 nm



28Ad

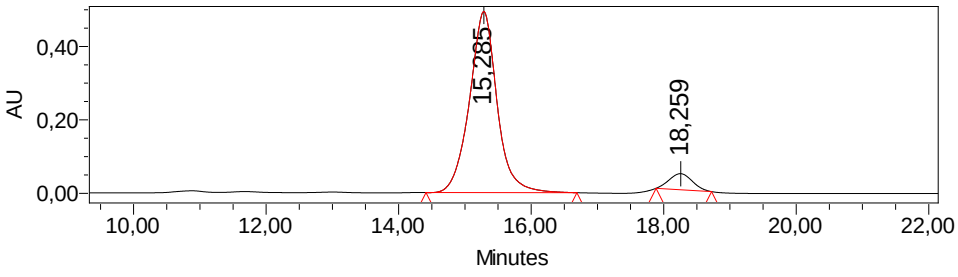
	Migration Time	% Area
1	14,836	49,84
2	17,678	50,16



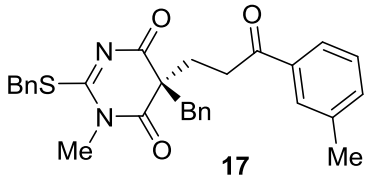


28Ad

	Migration Time	% Area
1	15,285	93,08
2	18,259	6,92

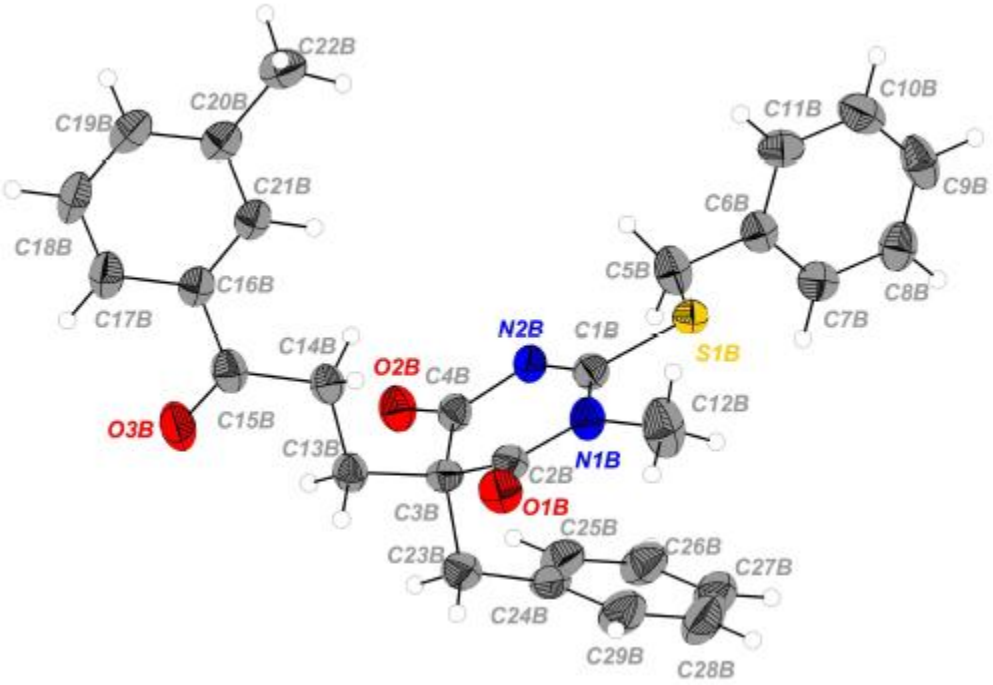


5. X-Ray analysis: ORTEP diagrams of compounds 17 and 24Ad

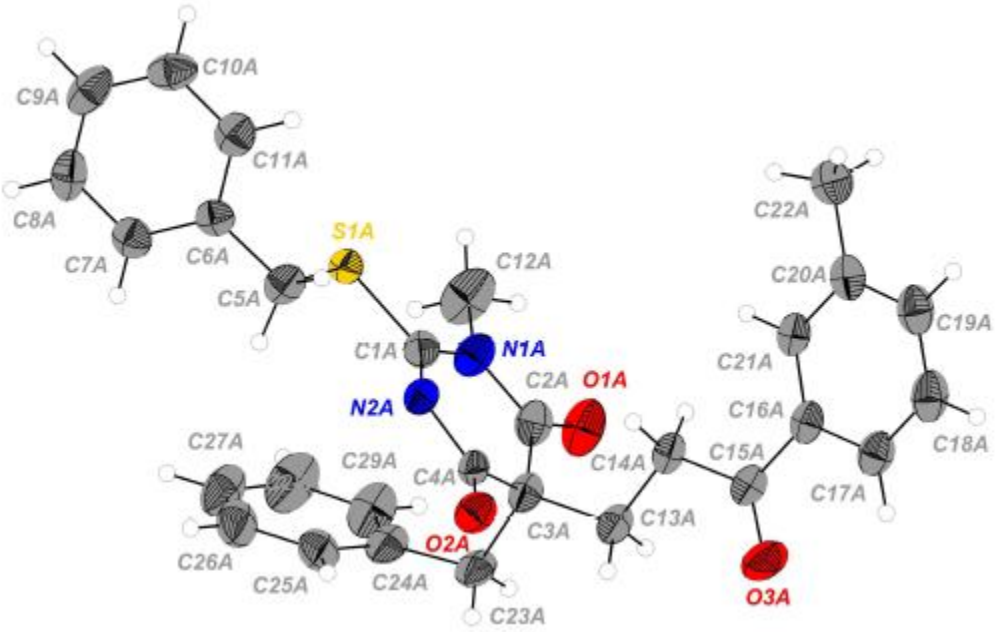


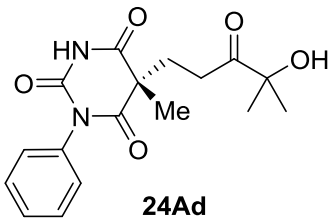
17

Molecule A

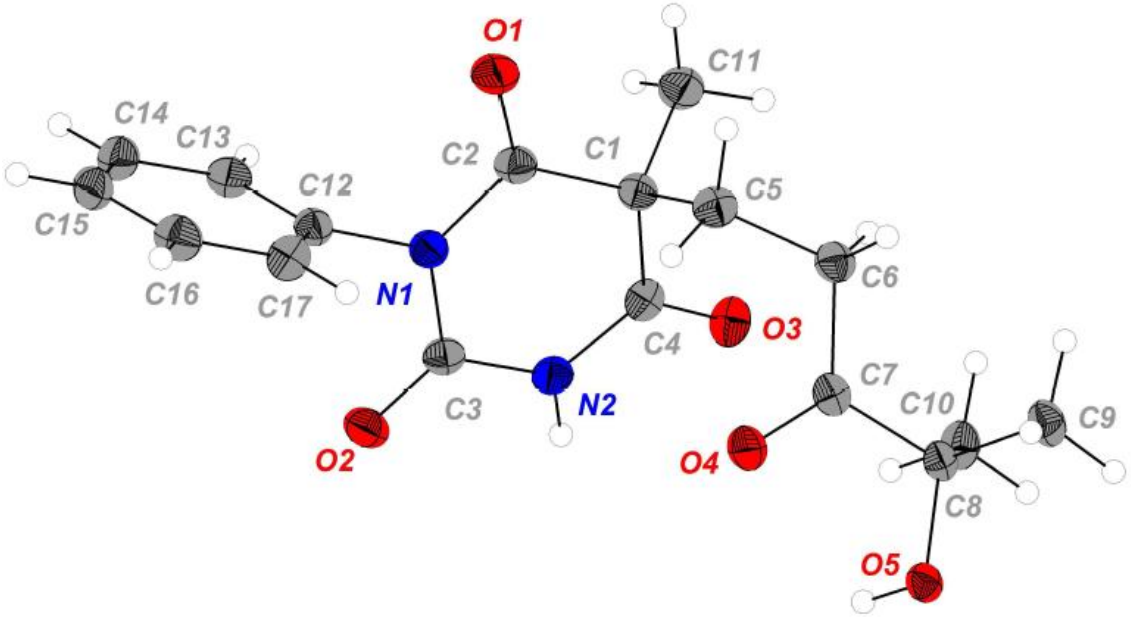


Molecule B




O
HN
O
N
Me
O
O
OH
O

24Ad


O1
C11
C14
C13
C2
C1
C12
C5
C15
C6
C16
C17
N1
C4
O3
C7
C3
N2
C10
C9
O2
O4
C8
O5

6. References

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