Supplementary Material

Design, Synthesis and Biological Evaluation of Novel Podophyllotoxin Derivatives Bearing 4β-Disulfide/trisulfide Bond as Cytotoxic Agents†

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S1. General procedure for the synthesis of 2

Appropriate secondary amine (5 mmol) was added to a solution of anhydrous cesium carbonate (2.0g, 6mmol) in CH_3CN (20mL), 1-bromo-3-chloropropane (10 mmol) was added dropwise. The resulting mixture was stirred at room temperaturefor overnight. The mixture was filtered, and the filtrate wasevaporated. The residue was added brine solution andextracted with ethyl acetate (30 mL×3). Combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crudeproduct was purified by column chromatography on silica gelto give desired compound**2**.

S1.1Tert-butyl 4-(3-chloropropyl)piperazine-1-carboxylate2a

Reagents: tert-butyl piperazine-1-carboxylate (0.91 g, 5mmol) and 1-bromo-3-chloropropane (1.57 g, 10 mmol). The product was obtained as a colorlessoil, yield: 32%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58 (t, *J* = 6.5 Hz, 2H), 3.39 (s, 4H), 2.46 (t, *J* = 7.0 Hz, 2H), 2.35 (s, 4H), 1.92 (dt, *J* = 13.0, 6.5 Hz, 2H), 1.43 (s, 9H); ESI-MS: m/z $[M+H]^+$263.

S1.2 4-(3-Chloropropyl)morpholine 2b

Reagents: morpholine (435 mg, 5mmol) and 1-bromo-3-chloropropane (1.57 g, 10 mmol). The product was obtained as a colorlessoil, yield: 41%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73-3.63 (m, 4H), 3.57 (t, *J* = 6.5 Hz, 2H), 2.45 (t, *J* = 8.5 Hz, 2H), 2.49-2.33 (m, 4H), 1.95-1.87 (m, 2H).

S1.3 1-(3-Chloropropyl)-4-methylpiperazine2c

Reagents: *N*-methylpiperazine (500 mg, 5mmol) and 1-bromo-3-chloropropane (1.57 g, 10 mmol). The product was obtained as a colorlessoil, yield: 38 %; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.50 (dd, *J* = 8.8, 4.5 Hz, 2H), 2.42-2.30 (m, 10H), 2.19 (s, 3H), 1.91-1.81 (m, 2H).ESI-MS: m/z $[M+H]^+$177.

S1.4 1-(3-Chloropropyl)pyrrolidine 2d

Reagents: pyrrolidine (355 mg, 5mmol) and 1-bromo-3-chloropropane (1.57 g, 10 mmol). The product was obtained as a colorlessoil, yield: 40 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54 (t, *J* = 8.0 Hz, 2H), 2.51 (t, *J* = 8.5 Hz, 1H), 2.47-2.39 (m, 4H), 1.92 (dt, *J* = 13.5, 6.5 Hz, 3H), 1.79-1.63 (m, 4H).

S1.5 1-(3-Chloropropyl)piperidine 2e

Reagents: piperidine (425 mg, 5mmol) and 1-bromo-3-chloropropane (1.57 g, 10 mmol). The product was obtained as a colorlessoil, yield: 45%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 (t, *J* = 8.5 Hz, 2H), 2.34(t, *J* = 8.5 Hz, 2H), 2.32-2.22 (m, 4H), 1.84 (dt, *J* = 13.5, 6.5 Hz, 2H), 1.50-1.41 (m, 4H), 1.36-1.28 (m, 2H).

S1.6 1-(4-(3-Chloropropyl)piperazin-1-yl)ethan-1-one2f

Reagents: 1-(piperazin-1-yl)ethan-1-one (640 mg, 5mmol) and 1-bromo-3-chloropropane (1.57g , 10 mmol). The product was obtained as a colorlessoil, yield: 66%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.60 (t, *J* = 6.5 Hz, 4H,piperazine), 3.47-3.43 (m, 2H, -N-CH_2-), 2.50 (t, *J* = 7.0 Hz, 2H, -CH_2Cl), 2.48-2.36 (m, 4H, piperazine), 2.07 (s, 3H, -CH_3), 1.94 (p, *J* = 6.5 Hz, 2H, -CH_2-).ESI-MS: m/z $[M+H]^+$204

S1.7. 4-((Tert-butyldimethylsilyl)oxy)-1-(3-chloropropyl)piperidine2g

Reagents: 4-((tert-butyldimethylsilyl)oxy)piperidine (1.07 g, 5mmol) and 1-bromo-3-chloropropane (1.57 g, 10 mmol). The product was obtained as a light yellowoil, yield: 68%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71 (s, 1H, 3-H), 3.59 (t, *J* = 6.5 Hz, 2H,piperidine), 2.67 (s, 2H, 6-H), 2.49-2.42 (m, 2H, piperidine), 2.24 (d, *J* = 24.0 Hz, 2H, 8-H), 1.99-1.93 (m, 2H, piperidine), 1.76 (s, 2H, 7-H), 1.62-1.54 (m, 2H, piperidine), 0.88 (s, 9H), 0.04 (s, 6H); ESI-MS: m/z $[M+H]^+$292.

S1.82-(((Tert-butyldimethylsilyl)oxy)methyl)-1-(3-chloropropyl)piperidine 2h

Reagents: 2-(((tert-butyldimethylsilyl)oxy)methyl)piperidine (1.14 g, 5mmol) and 1-bromo-3-chloropropane (1.57 g, 10 mmol). The product was obtained as a light yellowoil, yield: 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (dd, *J* = 10.4, 5.0 Hz, 1H), 3.53 (t, *J* = 6.5 Hz, 1H), 3.46 (dd, *J* = 10.5, 5.5 Hz, 1H), 2.96-2.84 (m, 1H), 2.85-2.75 (m, 1H), 2.60-2.46 (m, 1H), 2.32 (d, *J* = 4.5 Hz, 1H), 2.19 (d, *J* = 2.5 Hz, 1H), 1.91 (dd, *J* = 14.0, 7.0 Hz, 2H), 1.81-1.39 (m, 5H), 1.35-1.18 (m, 2H), 0.86 (s, 9H), 0 (s, 6H); ESI-MS: m/z $[M+H]^+$306.

S1.9 3-Chloro-N,N-diethylpropan-1-amine 2i

Reagents: diethylamine (365 mg, 5mmol) and 1-bromo-3-chloropropane (1.57 g, 10 mmol). The product was obtained as a colorlessoil, yield: 32%; ^{1}H NMR (500 MHz, $CDCl_3$) 3.61 (t, *J* = 6.5 Hz, 2H), 2.73-2.65 (m, 6H), 2.09-1.98 (m, 2H), 1.12 (t, *J* = 7.0 Hz, 6H).

S1.103-Chloro-N,N-diisopropylpropan-1-amine 2j

Reagents: diisopropylamine (505 mg, 5mmol) and 1-bromo-3-chloropropane (1.57 g, 10 mmol). The product was obtained as a colorlessoil, yield: 31%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58 (dd, *J* = 13.2, 7.2 Hz, 2H), 3.10-3.02 (m, 2H), 2.68-2.59 (m, 2H), 1.90-1.84 (m, 2H), 1.05 (s, 6H), 1.04 (s, 6H).ESI-MS: m/z $[M+H]^+$178.

S2 General procedure for the synthesis of 4.

Appropriate secondary amine (5 mmol) was added to a solution of anhydrous cesium carbonate (2.0 g, 6 mmol) in CH_3CN (20 mL), 1-bromo-2-chloroethane (10 mmol) was added dropwise. The resulting mixture was stirred at room temperature for overnight. The mixture was filtered, and the filtrate wasevaporated. The residue was added brine solution andextracted with ethyl acetate (30 mL×3). Combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crudeproduct was purified by column chromatography on silica gelto give desired compound **4**.

S2.1Tert-butyl 4-(2-chloroethyl)piperazine-1-carboxylate4a

Reagents:tert-butyl piperazine-1-carboxylate (930 g, 5 mmol) and 1-bromo-2-chloroethane (1.42 g, 10 mmol). The product was obtained as a colorlessoil, yield: 31%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.58 (t, *J* = 7.0 Hz, 2H), 3.48-3.38 (m, 4H), 2.73 (t, *J* = 7.0 Hz, 2H), 2.53-2.41(m, 4H), 1.45 (s, 9H).ESI-MS: m/z $[M+H]^+$249.

S2.24-(2-Chloroethyl)morpholine 4b

Reagents:morpholine (435 g, 5 mmol) and 1-bromo-2-chloroethane (1.42 g, 10 mmol). The product was obtained as a colorlessoil, yield: 42%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.70-3.63 (m, 4H), 3.54 (td, *J* = 7.0, 1.0 Hz, 2H), 2.67 (td, *J* = 7.0, 1.0 Hz, 2H), 2.50-2.41 (m, 4H).

S2.33-((Tert-butyldimethylsilyl)oxy)-1-(2-chloroethyl)piperidine4c

Reagents: 3-((tert-butyldimethylsilyl)oxy)piperidine (1.07 g, 5 mmol) and 1-bromo-2-chloroethane (1.42 g, 10 mmol). The product was obtained as a light yellowoil, yield: 32%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73-3.64 (m, 1H), 3.56 (t, *J* = 7.0 Hz, 2H), 2.87 (ddd, *J* = 13.0, 7.5, 5.5 Hz, 1H), 2.77-2.69 (m, 3H), 2.01-1.91 (m, 2H), 1.89-1.82 (m, 1H), 1.71-1.63 (m, 1H), 1.57-1.45 (m, 1H), 1.23-1.13 (m, 1H), 0.86 (s, 9H), 0.04 (s, 6H) ; ESI-MS: m/z $[M+H]^+$278.

S3General procedure for the synthesis of 3 and 5

A mixture of **2** or **4** (1.8 mmol), KI（149 mg,0.9 mmol）and thiourea (206 mg，2.7 mmol) in 95% ethanol (10 mL) was heated to reflux for 24 hours. Then, sodium hydroxide (108mg,2.7 mmol) aqueous solution (2 mL) was added. The resulting mixture was refluxed for another 3 hours. After cooling, the mixture was evaporated *in vacuo*. The residue was dissolved in ethyl acetate, and then washed with brine, dried over anhydrous Na_2SO_4 and condensed*in vacuo* to give desired product**3** or**5**, which were used for next step reaction without purification.

S4General procedure for the synthesis of 7

2-Mercaptoacetic acid(552 mg, 6 mmol) was dissolved in DCM(20 mL), HOBt(810 mg, 6 mmol）and EDC(1.7 g, 9 mmol) were added at room temperature. The mixture was stirred for 1 hour to afford the active ester intermediate, then was added the appropriate amine(5 mmol). After the reaction was completed by TLC monitoring, the reaction was added water, and then extracted with CH_2Cl_2 (3×50 mL). The combined organic layer was washed with statured $NaHCO_3$, brine, dried over anhydrousNa_2SO_4, and evaporated *in vacuo.* The residue was purified by column chromatography using silica gel to give the desired products **7**.

S4.1 2-Mercapto-1-morpholinoethan-1-one7a

Reagents:morpholine(440 mg, 5 mmol). The product was obtained as a light redoil, yield: 32%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71-3.41 (m, 8H), 3.34-3.25 (m, 2H), 2.05 (t, *J* =8.0 Hz, 1H).ESI-MS: m/z $[M+H]^+$162.

S4.2Tert-butyl 4-(2-mercaptoacetyl)piperazine-1-carboxylate 7b

Reagents:tert-butyl piperazine-1-carboxylate (930 mg, 5 mmol). The product was obtained as a light redoil, yield: 58%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.64-3.54 (m, 2H,piperazine), 3.54-3.38 (m, 6H, piperazine), 3.34 (d, *J* = 6.5 Hz, 2H, -CH_2-), 2.09 (t, *J* = 7.5 Hz, 1H, -SH), 1.46 (s, 9H, Boc).

S4.3 1-(2-Mercaptoacetyl)piperidin-4-one7c

Reagents: piperidin-4-one (495 mg, 5 mmol). The product was obtained as a light redoil, yield: 59%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.68-3.54 (m, 4H), 3.38-3.32 (m, 2H), 2.27-1.96 (m, 4H), 2.09 (t, *J* = 9.0 Hz, 1H).ESI-MS: m/z $[M+H]^+$174.

S4.4 1-(3-((Tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-mercaptoethan-1-one 7d

Reagents:3-((tert-butyldimethylsilyl)oxy)piperidine (1.07 g, 5 mmol). The product was obtained as a colorlessoil, yield: 47%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80-3.42 (m, 3H), 3.38-3.22 (m, 2H), 3.18-3.10 (m, 1H), 2.15-2.07 (m, 1H), 1.93-1.71 (m, 2H), 1.59-1.36 (m, 2H), 0.84 (s, 9H), 0.09 (s, 6H) ; ESI-MS: m/z $[M+H]^+$290.

S4.51-(4-((Tert-butyldimethylsilyl)oxy)piperidin-1-yl)-2-mercaptoethan-1-one 7e

Reagents: 4-((tert-butyldimethylsilyl)oxy)piperidine (1.07 g, 5 mmol). The product was obtained as acolorlessoil, yield: 33%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.99-3.93 (m, 1H), 3.69-3.55 (m, 3H), 3.39-3.22 (m, 2H), 2.08-2.04 (m, 1H), 1.80-1.63 (m, 2H), 1.59-1.48 (m, 2H), 0.87 (d, *J* = 1.0 Hz, 9H), 0.04 (t, *J* = 2.0 Hz, 6H) ; ESI-MS: m/z $[M+H]^+$290.

S5General procedure for synthesis of 9 and 12

β-D-Galactosepentaacetate**8** or pentaacetyl-β-D-glucopyranose **11** (2 g, 5.13 mmol) dissolved in DCM (25 mL), thiolacetic acid (1.5 mL, 21.51 mmol) was added in ice bath with N_2 protection. Afterwards, $BF_3{\cdot}Et_2O$ (3.9 mL, 31.51 mmol) was added dropwise, the resulting mixture was allowed to stir at room temperature for 24 hours. The mixture was poured into ice water and extracted with DCM, the organic layer was washed with saturated $NaHCO_3$ aqueous solution and brine, successively. Combined organic layer was evaporated *in vacuo*, and the residue was purified by column chromatography on silica gel using PE/DCM/EtOAc (10/3/3, v/v/v) to give **9** as a light yellow oil, yield: 65%; ^{1}H NMR (500 MHz, $CDCl_3$) δ5.45 (d, *J* = 3.5 Hz, 1H), 5.36-5.22 (m, 2H), 5.10 (dd, *J* = 10.0, 3.5 Hz, 1H), 4.19-4.02 (m, 3H), 2.39 (s, 3H), 2.15 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.98 (s, 3H). The same procedure was employed using Pentaacetyl-β-D-glucopyranose **11** (2 g, 5.13 mmol) as starting material to afford compound **12** as a light yellow solid, yield: 68%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.29-5.22 (m, 2H), 5.14-5.07 (m, 2H), 4.25 (dd, *J* = 12.5, 4.5 Hz, 1H), 4.09 (dd, *J* = 12.5, 2.0 Hz, 1H), 3.83 (ddd, *J* = 10.0, 4.5, 2.0 Hz, 1H), 2.38 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H).

S6 General procedure for synthesis of 13a and 13c

Compound **9** (200 mg, 0.49 mmol) was dissolved in dry methanol (5 mL), and sodium methoxide (54 mg, 0.98 mmol) was added under N_2 protection with ice bath. The mixture was allowed to stir at room temperature for 2h and cation exchange resin was added to adjust the pH to 2. The reaction mixture was filtered to give crude product, which was purified by column chromatography on silica gel using DCM/Methanol(10/1, v/v) to give **13a**as a white solid, yield: 77%; ^{1}H NMR (500 MHz, MeOH-d_4) δ 4.36 (d, *J* = 9.0 Hz, 1H), 3.92-3.84 (m, 2H), 3.76-3.57 (m, 5H), 3.56-3.52 (m, 1H), 3.48-3.42 (m, 2H).ESI-MS: m/z $[M+NH_4]^+$382.

The same procedure was employed using compound **12** (200 mg, 0.49 mmol) as starting material to afford compound **13c**as a white solid, yield: 76%; ^{1}H NMR (500 MHz, MeOH-d_4) δ 4.40 (d, *J* = 9.5 Hz, 1H), 3.83 (dd, *J* = 12.0, 1.5 Hz, 1H), 3.63 (dd, *J* = 12.0, 5.5 Hz, 1H), 3.33-3.25 (m, 7H), 3.13-1.08 (m, 1H).ESI-MS: m/z $[M+NH_4]^+$197.

S7(2R,3S,4S,5R,6S)-2-(Acetoxymethyl)-6-bromotetrahydro-2H-pyran-3,4,5-triyl triacetate10

To a solution of β-D-Galactosepentaacetate**8**(1 g, 2.55 mmol) in DCM, hydrogen bromide (33 wt% solution in glacial acetic acid)(2.5 mL) was added dropwise. The mixture was stirred at room temperature until the reaction completed. Then, the reaction was extracted with DCM,the combined organic layer was washed with saturated $NaHCO_3$ aqueous solution, brine, and dried overanhydrous Na_2SO_4,successively. Then it was evaporated *in vacuo*, andthe residue was purified by column chromatography on silica gel using EtOAc-PE as eluent to give the corresponding product **10**as a light yellow oil, yield: 90%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68 (t, *J* = 4.0 Hz, 1H), 5.50 (t, *J* = 3.5 Hz, 1H), 5.38 (ddd, *J* = 10.5, 5.5, 3.5 Hz, 1H), 5.06-4.98 (m, 1H), 4.46 (dd, *J* = 11.0, 5.5 Hz, 1H), 4.23-4.03 (m, 2H), 2.13 (d, *J* = 5.0 Hz, 3H), 2.09 (d, *J* = 5.5 Hz, 3H), 2.04 (d, *J* = 5.5 Hz, 3H), 1.99 (d, *J* = 5.5 Hz, 3H).

S8(2R,3S,4S,5R,6S)-2-(Acetoxymethyl)-6-mercaptotetrahydro-2H-pyran-3,4,5-triyl triacetate 13b

To a solution of $Na_2S{\cdot}9H_2O$ (240 mg, 1 mmol) in DMF (5 mL), CS_2 (0.6 mL,10mmol) wasslowly added. Then, compound **13**(410 mg,10mmol) was added and stirred at room temperature for 15min. The mixture was diluted with water and extracted with EtOAc,the combined organic layer was washed withbrineand dried overanhydrous Na_2SO_4.Then it was evaporated *in vacuo*, andthe residue was purified by column chromatography on silica gel using EtOAc-PE as eluent to give the corresponding product**13b**as a colorless oil, yield: 52%, ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.42 (dd, *J* = 3.5, 1.0 Hz, 1H), 5.17 (t, *J* = 10.0 Hz, 1H), 5.01 (dd, *J* = 10.0, 3.5 Hz, 1H), 4.52 (t, *J* = 10.0 Hz, 1H), 4.12 (d, *J* = 6.5 Hz, 2H), 3.96-3.92 (m, 1H), 2.36 (d, *J* = 10.0 Hz, 1H), 2.15 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 1.97 (s, 3H); ESI-MS: m/z $[M+NH_4]^+$382.

S92,2'-Thiobis(isoindoline-1,3-dione)20

To a solution of phthalimide (1.47 g, 10 mmol) was dissolved in anhydrous DMF (8 mL), sulfurmonochloride (1.3 g, 10 mmol) was added in severalportions at room temperature. The resulting yellow mixture wasstirred for 20 h. The precipitation was collectted by filtration, and then further purified by column chromatography on silica gel using DCM as eluent to give the corresponding product, yield 80%; mp: 315.8-318.6^{o}C; ESI-MS: m/z$[M+H]^+$325.

S10 General procedure for synthesis of 21a-f

To a solution of compound **20** (253 mg, 0.78 mmol) in DCM (10 mL), mercaptan (0.78 mmol) and triethylamine (5 drops) was added dropwise. After stirring for 0.5 h, the mixture was diluted with DCM, and washed with water, brine. The organic layer was dried over anhydrous $NaSO_4$ and condensed*in vacuo*. The residue was purified by column chromatography on silica gel using PE-DCM as eluent to give the desired product.

S10.1 2-(Ethyldisulfanyl)isoindoline-1,3-dione21a

Reagent:ethanethiol (48.4 mg, 0.78 mmol). The product was obtained as a white solid, yield: 83%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96-7.91 (m, 2H), 7.82-7.77 (m, 2H), 3.04 (q, *J* = 7.5 Hz, 1H), 1.43 (t, *J* = 7.5 Hz, 2H); ESI-MS: m/z[M+Na]$^+$261.

S10.2 2-((2-Hydroxyethyl)disulfanyl)isoindoline-1,3-dione21b

Reagent:mercaptoethanol (60.8 mg, 0.78 mmol). The product was obtained as a light yellow oil, yield: 33%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (m, 2H), 7.82-7.79 (m, 2H), 4.06 (t, *J* = 6.0 Hz, 2H), 3.23 (t, *J* = 6.0 Hz, 2H); ESI-MS: m/z [M+H]$^+$256.

S10.3 2-((2,3-Dihydroxypropyl)disulfanyl)isoindoline-1,3-dione21c

Reagent: 3-mercaptopropane-1,2-diol (84.2 mg, 0.78 mmol). The product was obtained as alight yellow oil, yield: 17%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.81 (dd, *J* = 5.5, 3.0 Hz, 2H), 3.87-3.79 (m, 1H), 3.72 (dd, *J* = 11.5, 5.5 Hz, 1H), 3.65-3.60 (m, 1H), 3.24 (dd, *J* = 14.0, 5.0 Hz, 1H), 3.15-3.06 (m, 1H); ESI-MS: m/z [M+H]$^+$286.

S10.42-((3-Morpholinopropyl)disulfanyl)isoindoline-1,3-dione 21d

Reagent:**3b** (48.4 mg, 0.78 mmol). The product was obtained as a light yellow oil, yield: 22%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92-7.84 (m, 2H), 7.79-7.73 (m, 2H), 3.73 (t, *J* = 4.5 Hz, 4H), 2.61-2.50 (m, 2H), 2.50-2.41 (m, 4H), 2.06-1.95 (m, 2H), 1.79 (dt, *J* = 14.5, 7.5 Hz, 2H).ESI-MS: m/z [M+H]$^+$339.

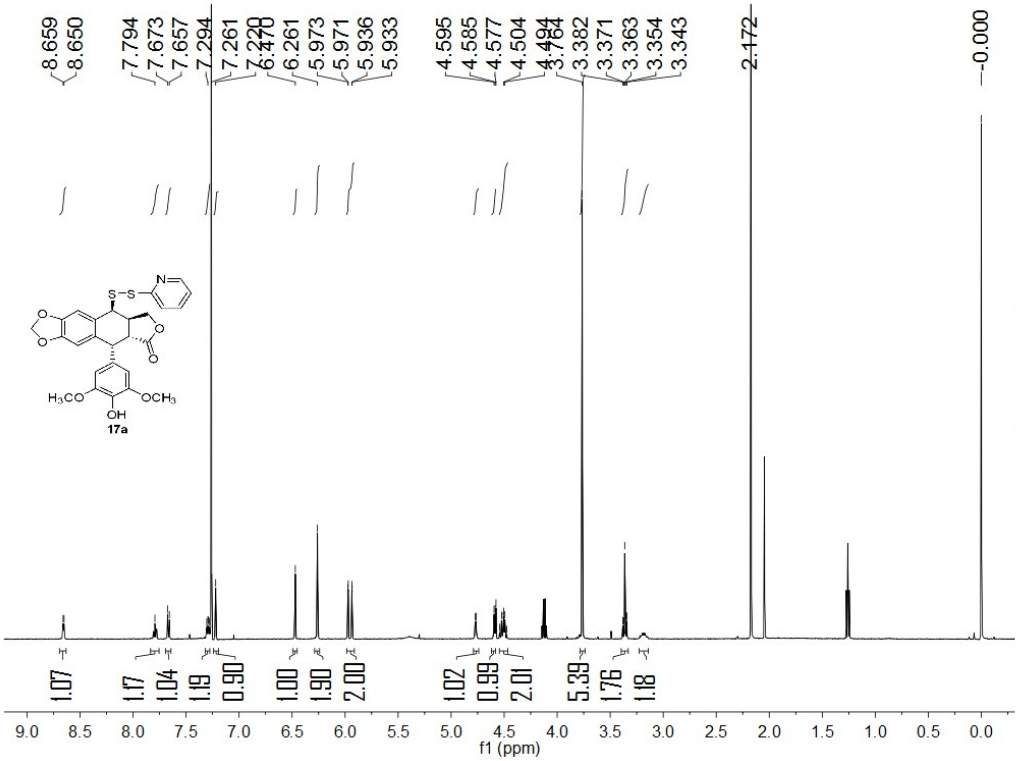
S10.5 2-(((2R,3S,4R,5R,6S)-3,4,5-Trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)disulfanyl)isoindoline-1,3-dione21e

Reagent:**13c** (152.9 mg, 0.78 mmol). The product was obtained as a white solid, yield: 42%; ^{1}H NMR (400 MHz, MeOD) δ 7.94 (dd, *J* = 5.6, 3.1 Hz, 2H), 7.87 (dd, *J* = 5.6, 3.1 Hz, 2H), 4.68 (d, *J* = 9.6 Hz, 1H), 3.77-3.70 (m, 4H), 3.53 (dd, *J* = 12.0, 5.5 Hz, 1H), 3.45-3.36 (m, 3H), 3.36-3.31 (m, 2H).ESI-MS: m/z [M+H]$^+$374.

S10.6 Tert-butyl 4-(2-((1,3-dioxoisoindolin-2-yl)disulfanyl)acetyl)piperazine-1-carboxylate21f

Reagent:**7b** (202.9 mg, 0.78 mmol). The product was obtained as a white solid, yield: 51%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.74 (dd, *J* = 5.5, 3.0 Hz, 2H), 4.13 (s, 2H), 3.53 (dd, *J* = 11.5, 5.5 Hz, 4H), 3.49-3.43 (m, 2H), 3.37 (d, *J* = 5.0 Hz, 2H), 1.41 (s, 9H). ESI-MS: m/z [M+H]$^+$438.

Spectrum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0.99
2.01
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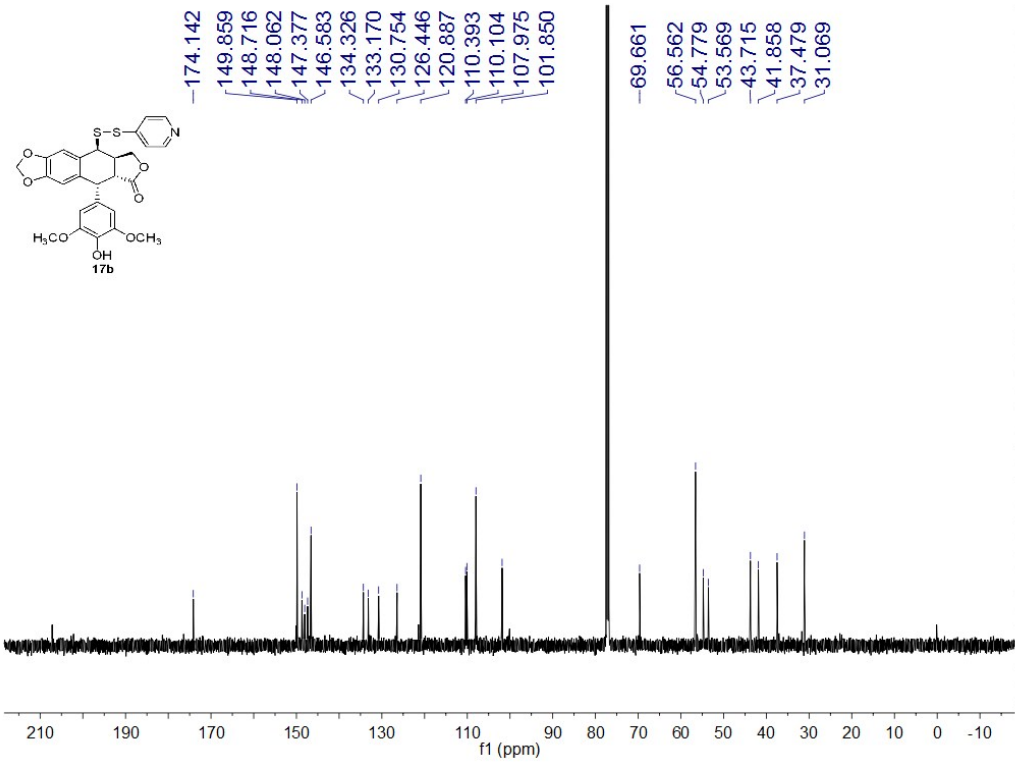
1.18
f1 (ppm)
17a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133.170
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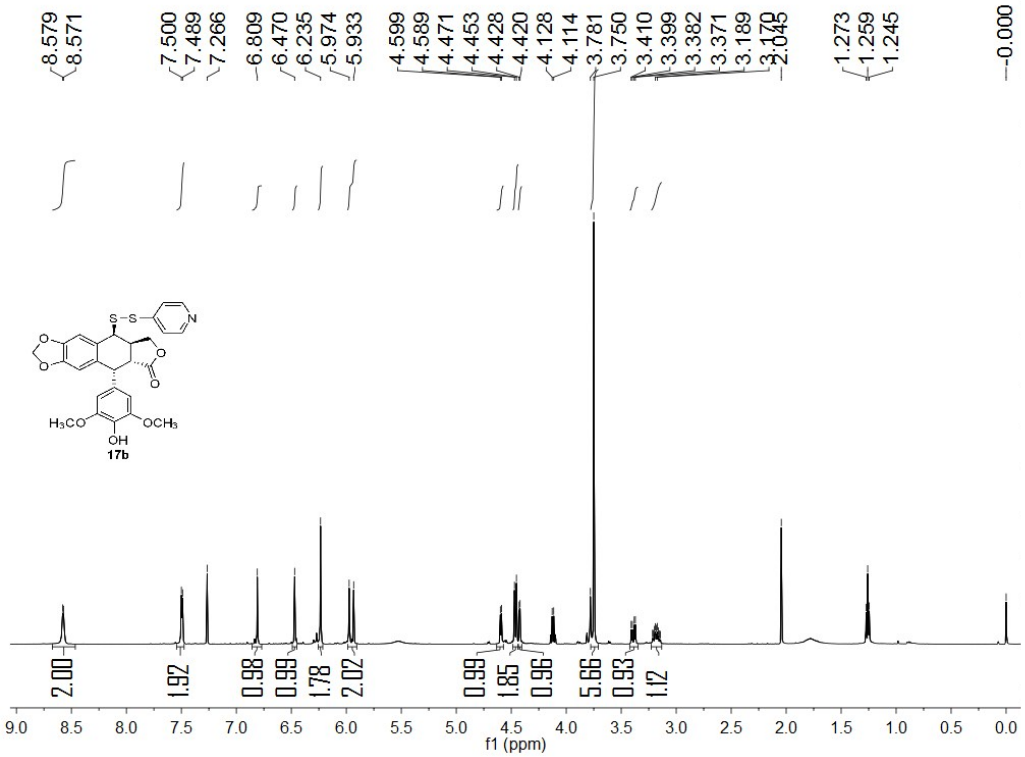
126.446
120.887
110.393
110.104
107.975
101.850
69.661
56.562
54.779
53.569
43.715
41.858
37.479
31.069
f1 (ppm)
17b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6.470
6.235
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5.933
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4.589
4.471
4.453
4.428
4.420
4.128
4.114
3.781
3.750
3.410
3.399
3.382
3.371
3.189
3.170
2.045
1.273
1.259
1.245
0.000
S
S
N
O
O
O
O
H3CO
OCH3
OH
17b
2.00
1.92
0.98
0.99
1.78
2.02
0.99
1.85
0.96
5.66
0.93
1.12
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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3.5
3.0
2.5
2.0
1.5
1.0
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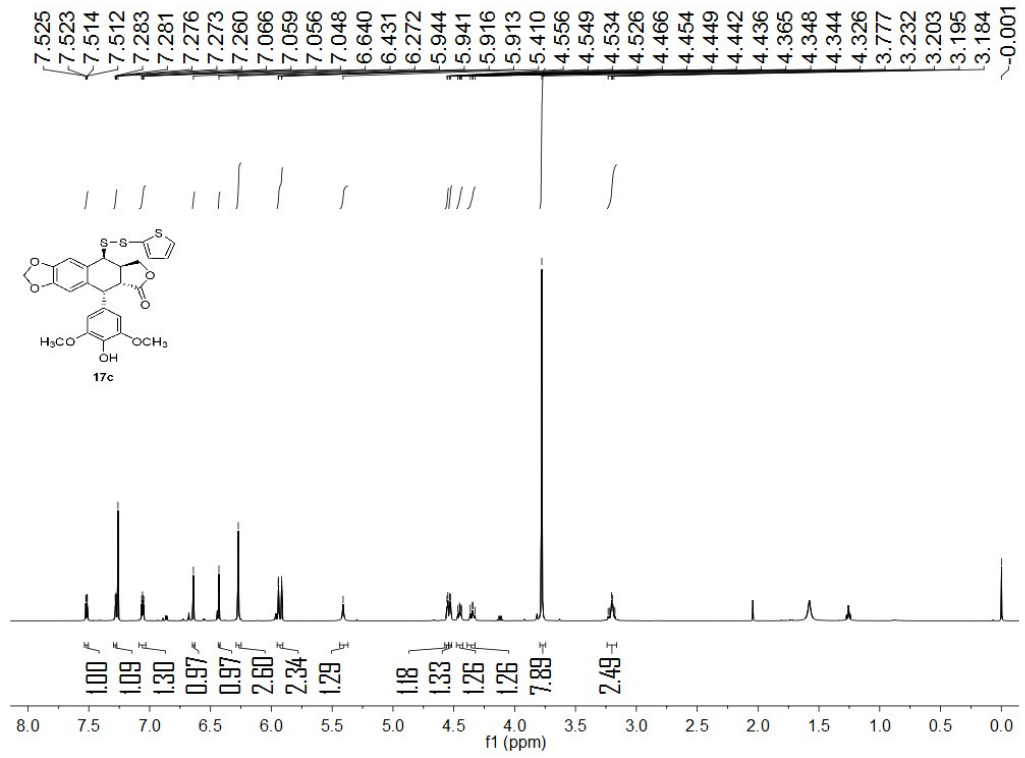
0.0
f1 (ppm)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7.276
7.273
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7.059
7.056
7.048
6.640
6.431
6.272
5.944
5.941
5.916
5.913
5.410
4.556
4.549
4.534
4.526
4.466
4.454
4.449
4.442
4.436
4.365
4.348
4.344
4.326
3.777
3.232
3.203
3.195
3.184
0.001
S
S
S
O
O
O
O
H3CO
OCH3
OH
17c
1.00
1.09
1.30
0.97
0.97
2.60
2.34
1.29
1.18
1.33
1.26
1.26
7.89
2.49
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
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1.0
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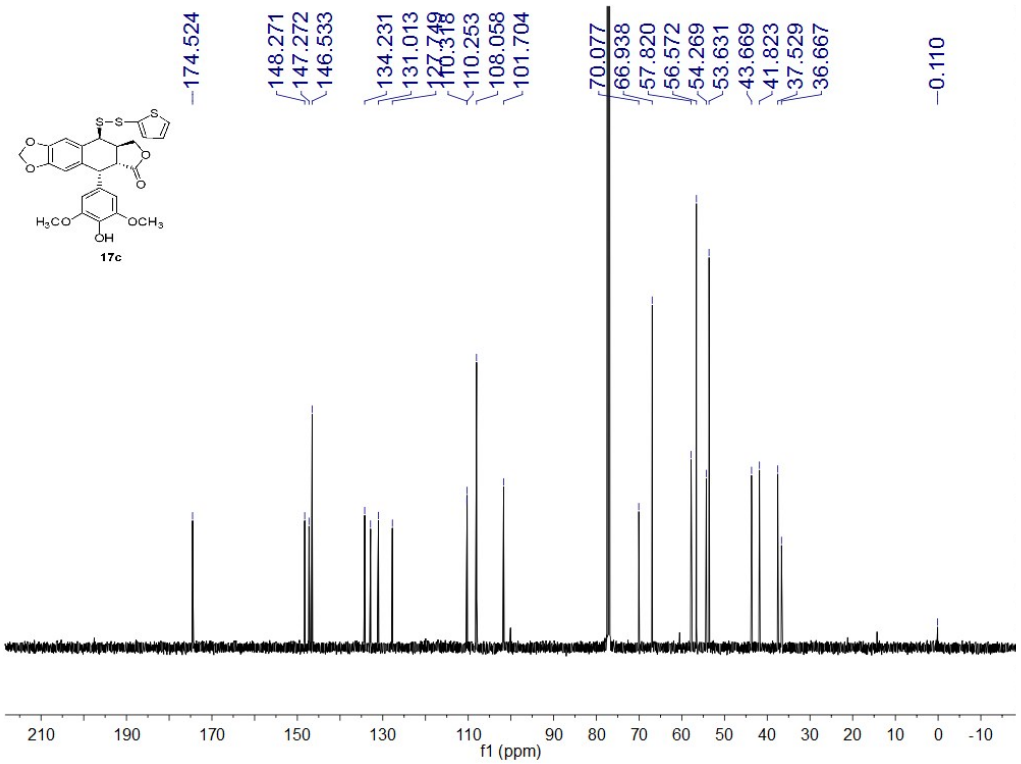
0.0
f1 (ppm)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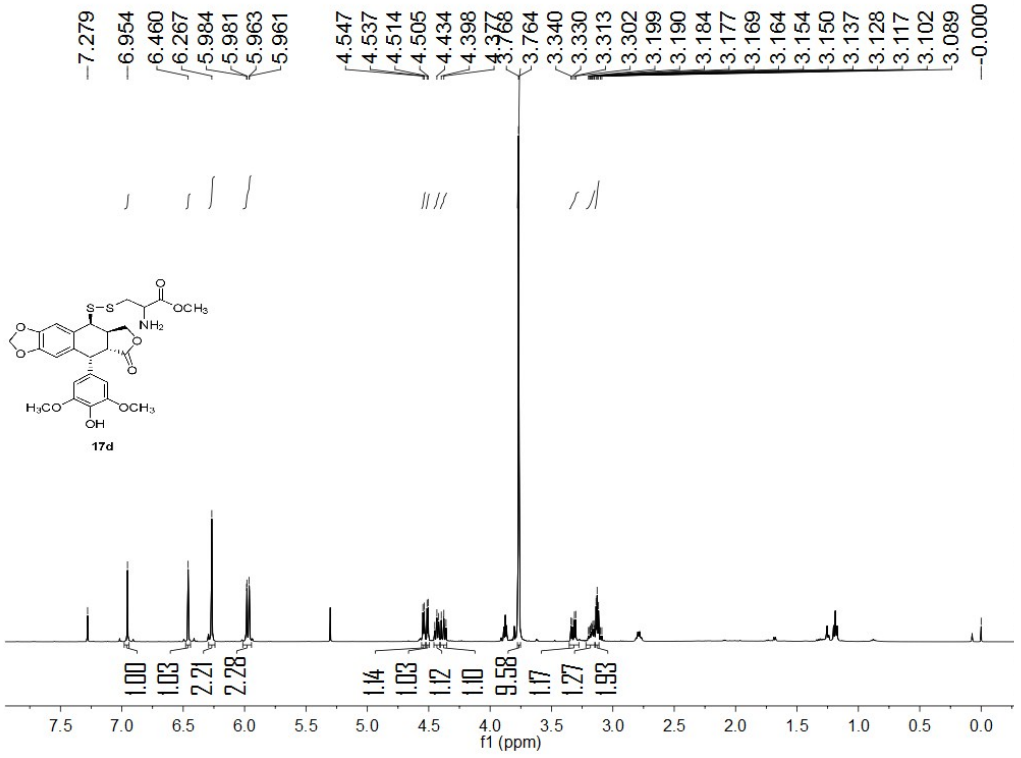
70.077
66.938
57.820
56.572
54.269
53.631
43.669
41.823
37.529
36.667
0.110
17c
f1 (ppm)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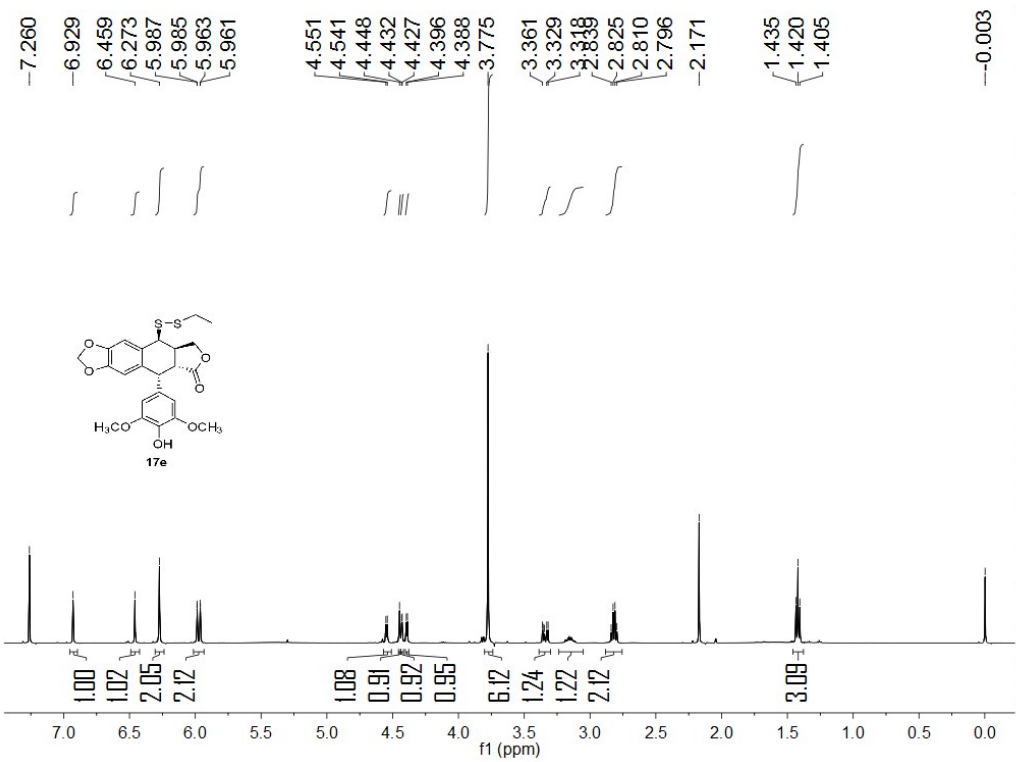
5.963
5.961
4.547
4.537
4.514
4.505
4.434
4.398
4.377
3.768
3.764
3.340
3.330
3.313
3.302
3.199
3.190
3.184
3.177
3.169
3.164
3.154
3.150
3.137
3.128
3.117
3.102
3.089
0.000
1.00
1.03
2.21
2.28
1.14
1.03
1.12
1.10
9.58
1.17
1.27
1.93
17d
f1 (ppm)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5.961
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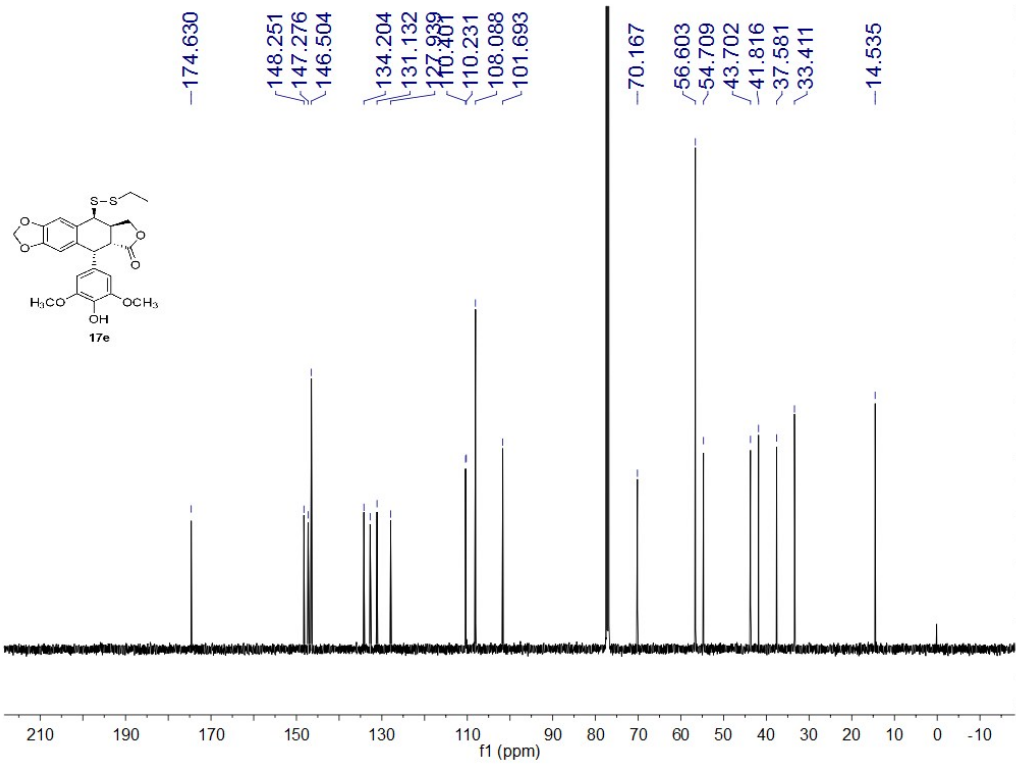
4.541
4.448
4.432
4.427
4.396
4.388
3.775
3.361
3.329
2.839
2.825
2.810
2.796
2.171
1.435
1.420
1.405
0.003
1.00
1.02
2.05
2.12
1.08
0.91
0.92
0.95
6.12
1.24
1.22
2.12
3.09
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
H3CO
OCH3
OH
17e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147.276
146.504
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131.132
127.939
110.401
110.231
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101.693
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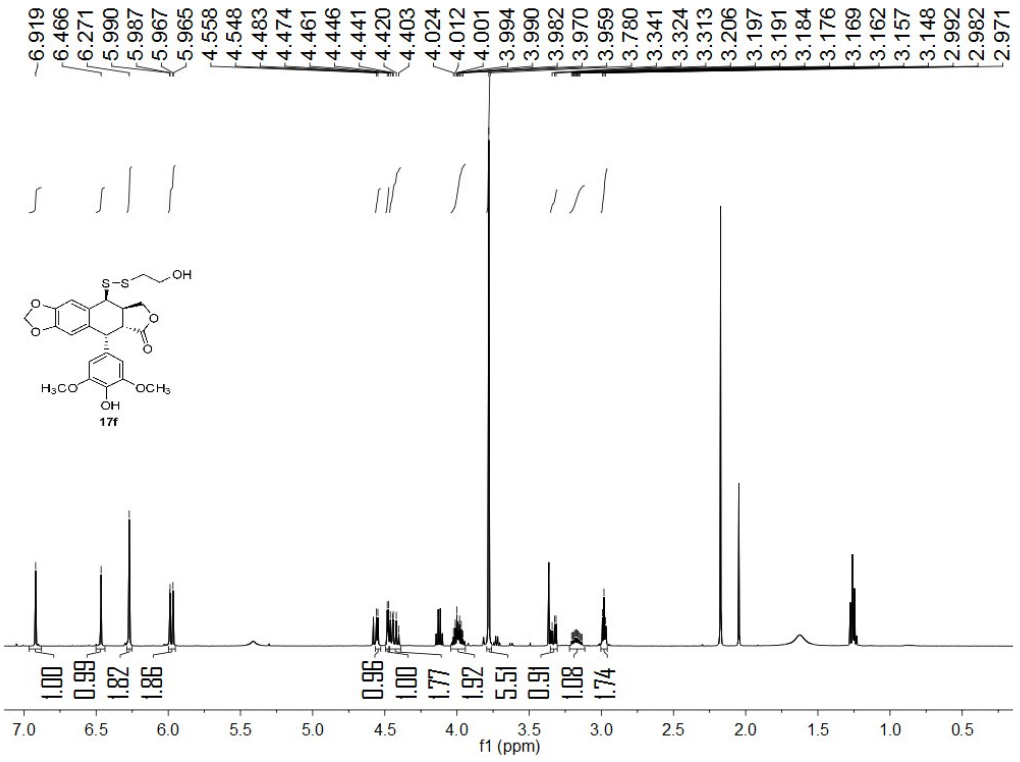
56.603
54.709
43.702
41.816
37.581
33.411
14.535
17e
f1 (ppm)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5.965
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4.548
4.483
4.474
4.461
4.446
4.441
4.420
4.403
4.024
4.012
4.001
3.994
3.990
3.982
3.970
3.959
3.780
3.341
3.324
3.313
3.206
3.197
3.191
3.184
3.176
3.169
3.162
3.157
3.148
2.992
2.982
2.971
17f
1.00
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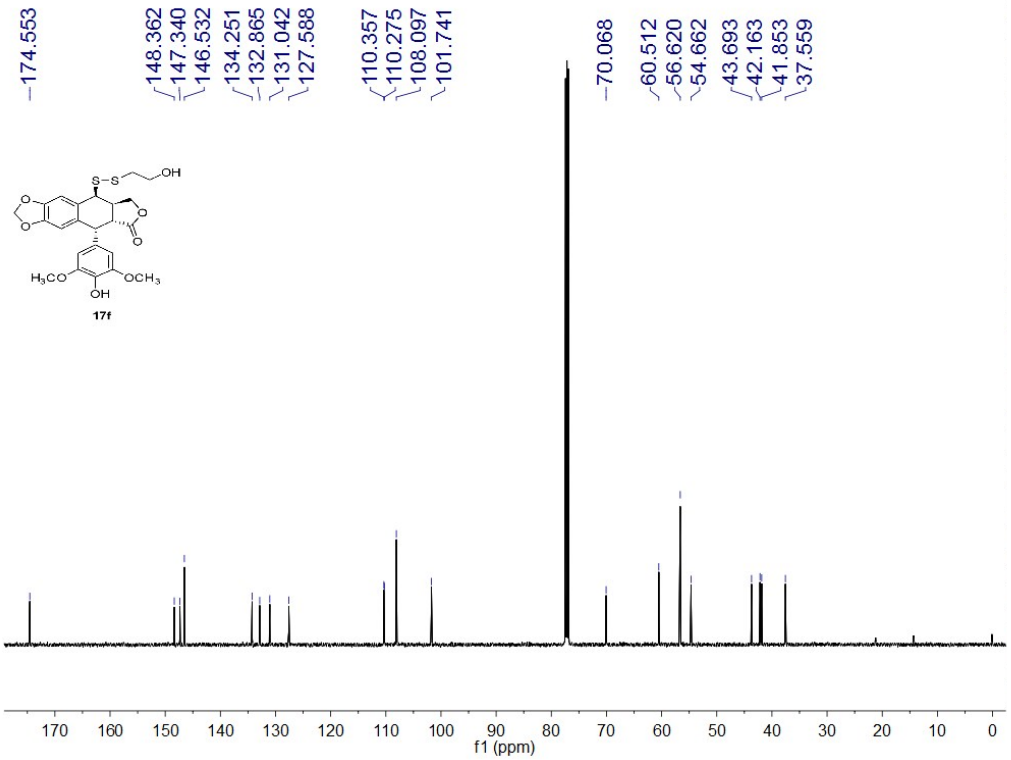
1.82
1.86
0.96
1.00
1.77
1.92
5.51
0.91
1.08
1.74
f1 (ppm)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127.588
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110.275
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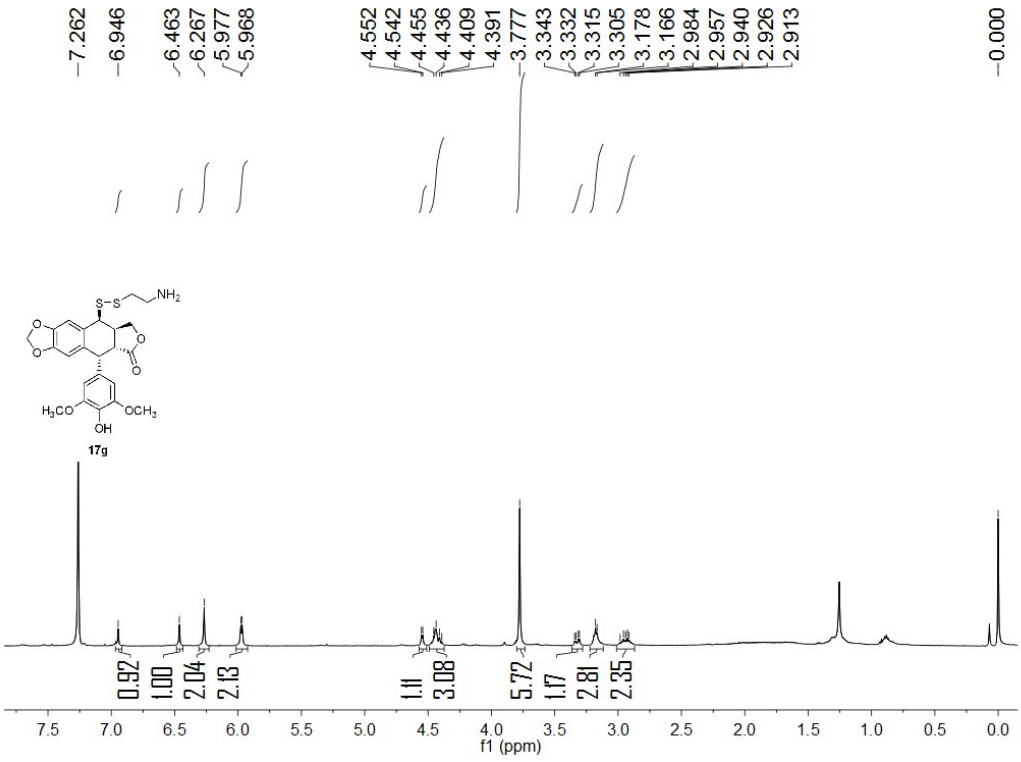
101.741
70.068
60.512
56.620
54.662
43.693
42.163
41.853
37.559
17f
f1 (ppm)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6.463
6.267
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5.968
4.552
4.542
4.455
4.436
4.409
4.391
3.777
3.343
3.332
3.315
3.305
3.178
3.166
2.984
2.957
2.940
2.926
2.913
0.000
17g
0.92
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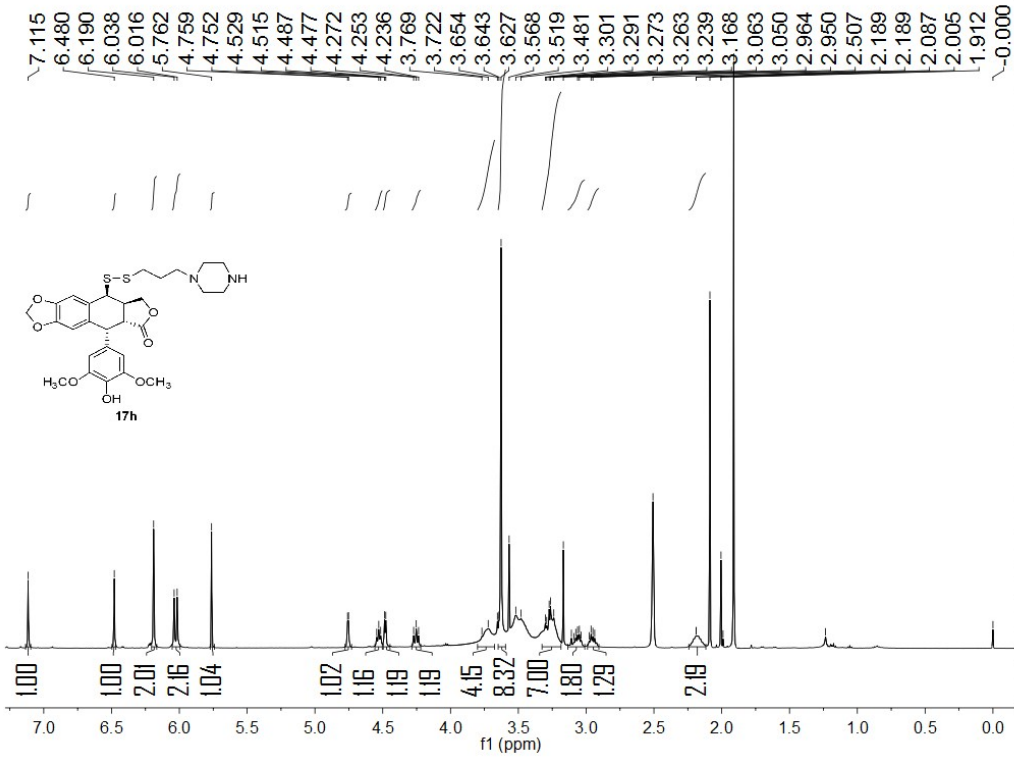
2.04
2.13
1.11
3.08
5.72
1.17
2.81
2.35
f1 (ppm)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4.752
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4.477
4.272
4.253
4.236
3.769
3.722
3.654
3.643
3.627
3.568
3.519
3.481
3.301
3.291
3.273
3.263
3.239
3.168
3.063
3.050
2.964
2.950
2.507
2.189
2.189
2.087
2.005
1.912
-0.000
17h
1.00
1.00
2.01
2.16
1.04
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1.19
1.19
4.15
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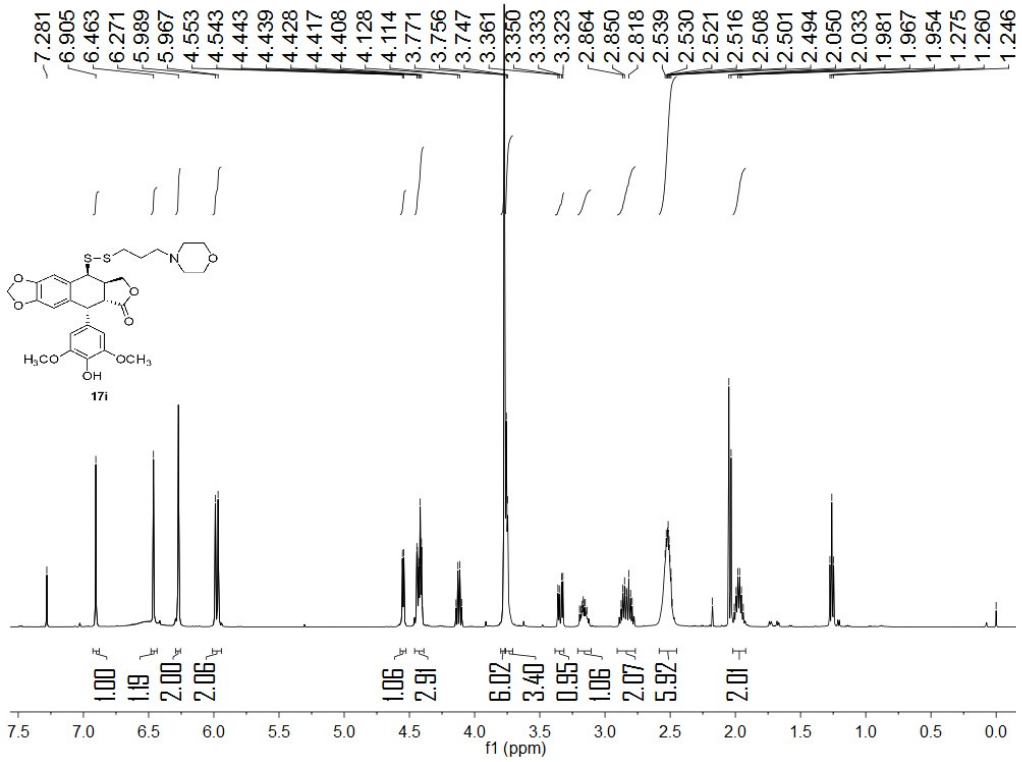
1.29
2.19
f1 (ppm)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4.408
4.128
4.114
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3.756
3.747
3.361
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3.333
3.323
2.864
2.850
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2.539
2.530
2.521
2.516
2.508
2.501
2.494
2.050
2.033
1.981
1.967
1.954
1.275
1.260
1.246
17i
1.00
1.19
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1.06
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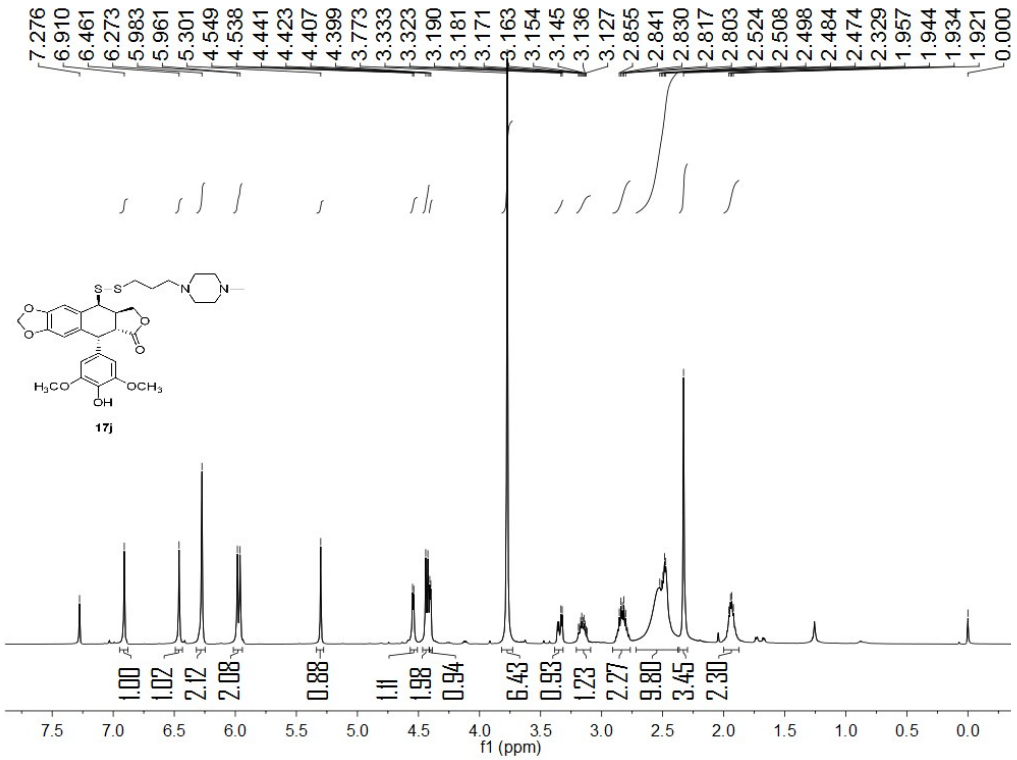
2.07
5.92
2.01
f1 (ppm)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4.538
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4.423
4.407
4.399
3.773
3.333
3.323
3.190
3.181
3.171
3.163
3.154
3.145
3.136
3.127
2.855
2.841
2.830
2.817
2.803
2.524
2.508
2.498
2.484
2.474
2.329
1.957
1.944
1.934
1.921
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1.00
1.02
2.12
2.08
0.88
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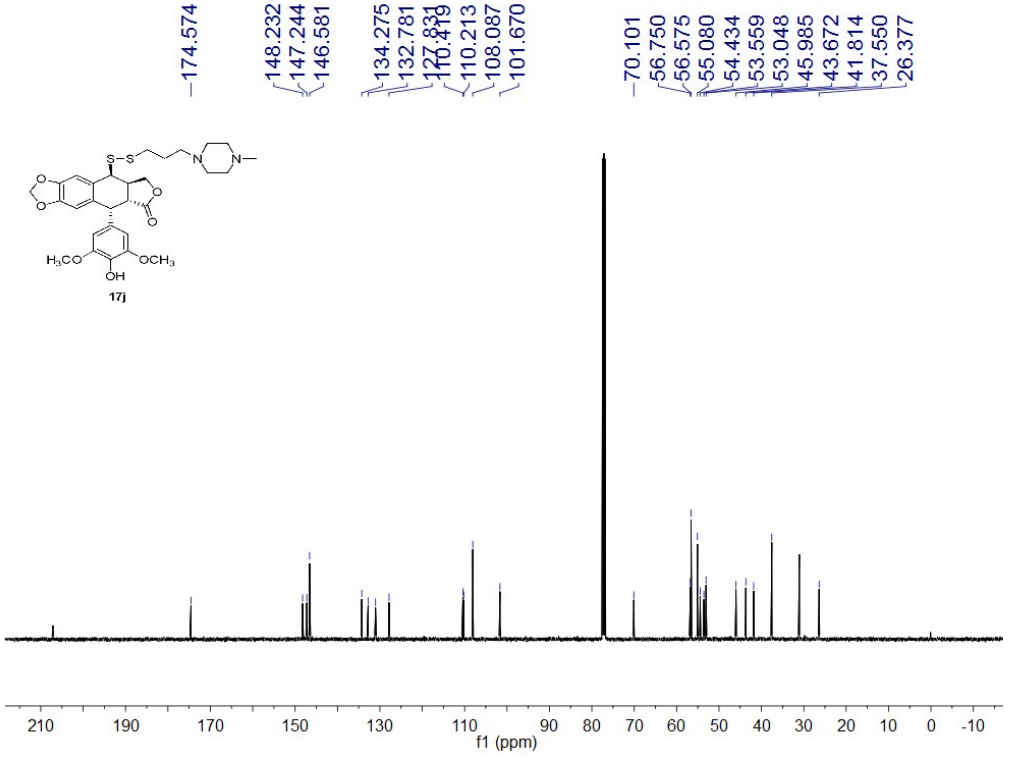
1.23
2.27
9.80
3.45
2.30
f1 (ppm)

17j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110.213
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56.750
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53.048
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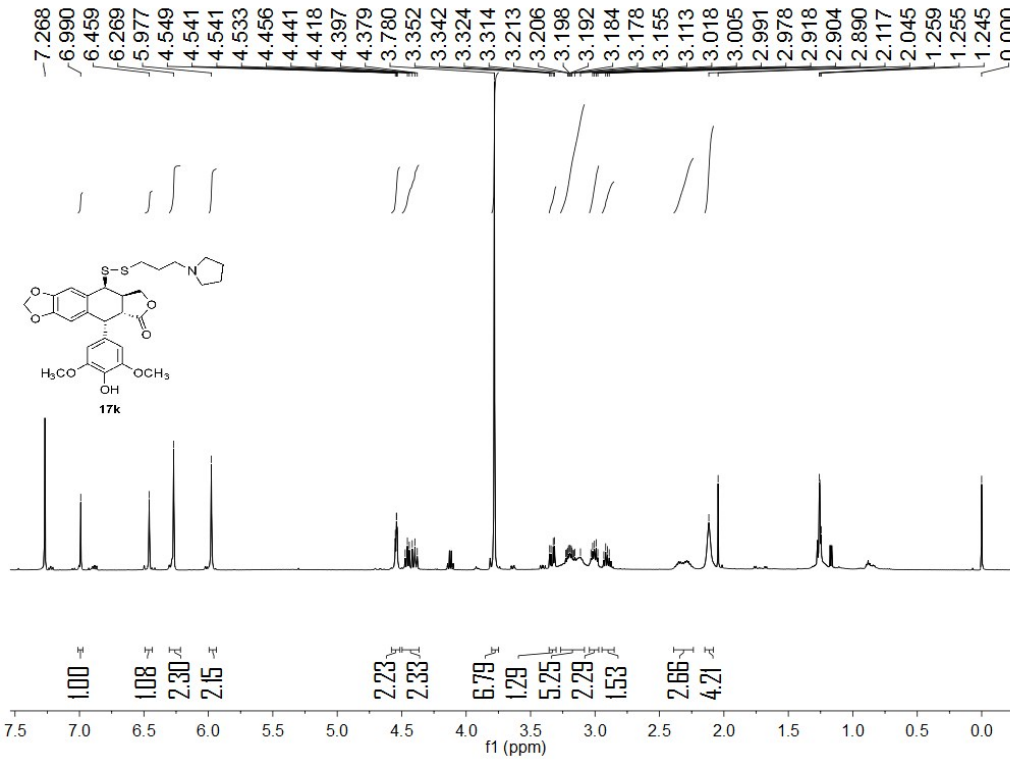
26.377
f1 (ppm)

17j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4.541
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4.397
4.379
3.780
3.352
3.342
3.324
3.314
3.213
3.206
3.198
3.192
3.184
3.178
3.155
3.113
3.018
3.005
2.991
2.978
2.918
2.904
2.890
2.117
2.045
1.259
1.255
1.245
0.000
17k
1.00
1.08
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2.33
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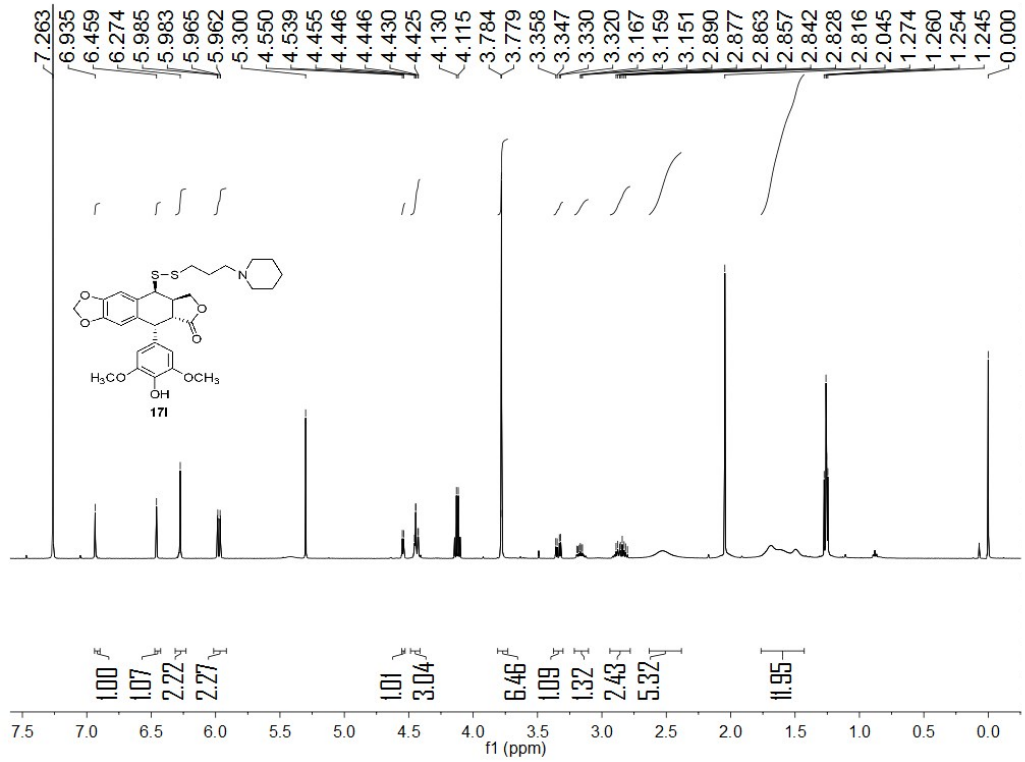
1.29
5.25
2.29
1.53
2.66
4.21
f1 (ppm)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4.446
4.446
4.430
4.425
4.130
4.115
3.784
3.779
3.358
3.347
3.330
3.320
3.167
3.159
3.151
2.890
2.877
2.863
2.857
2.842
2.828
2.816
2.045
1.274
1.260
1.254
1.245
0.000
17l
1.00
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6.46
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2.43
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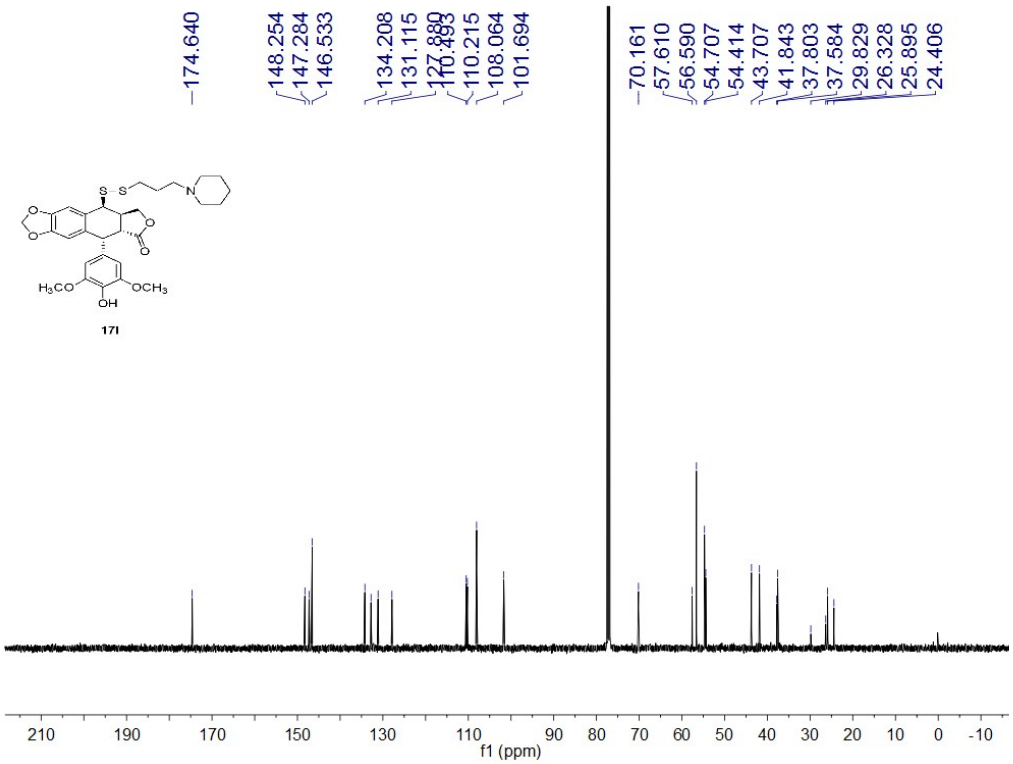
11.95
f1 (ppm)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70.161
57.610
56.590
54.707
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37.803
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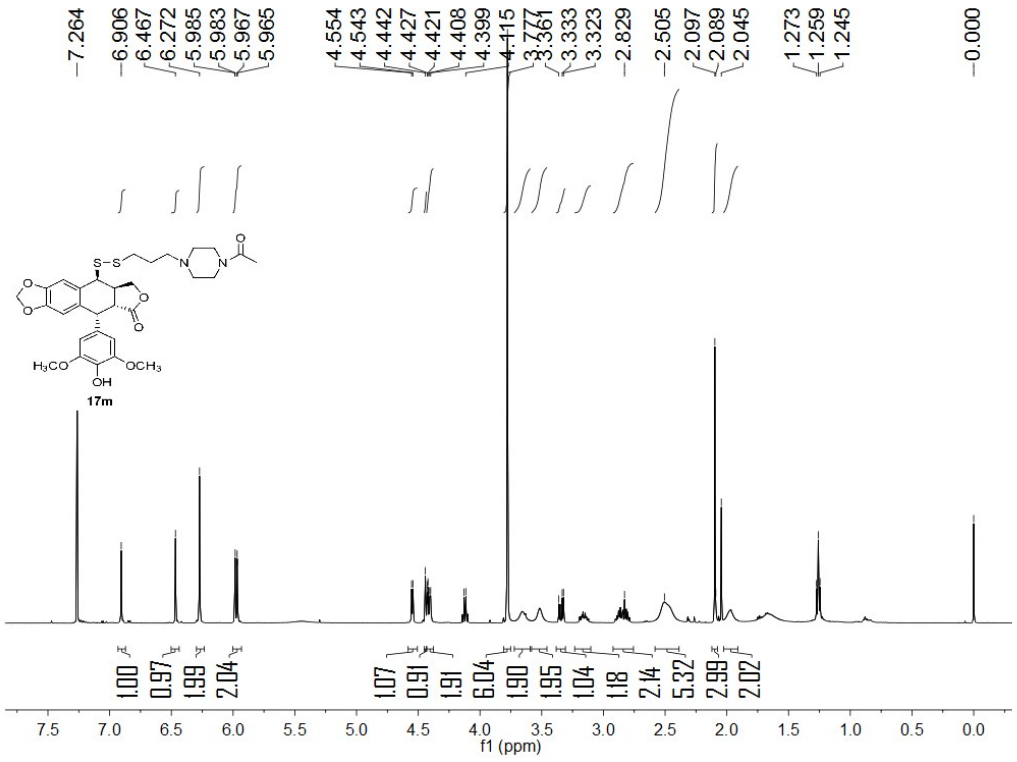
25.895
24.406
17l
f1 (ppm)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4.421
4.408
4.399
4.415
3.777
3.361
3.333
3.323
2.829
2.505
2.097
2.089
2.045
1.273
1.259
1.245
0.000
17m
1.00
0.97
1.99
2.04
1.07
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1.90
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1.04
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5.32
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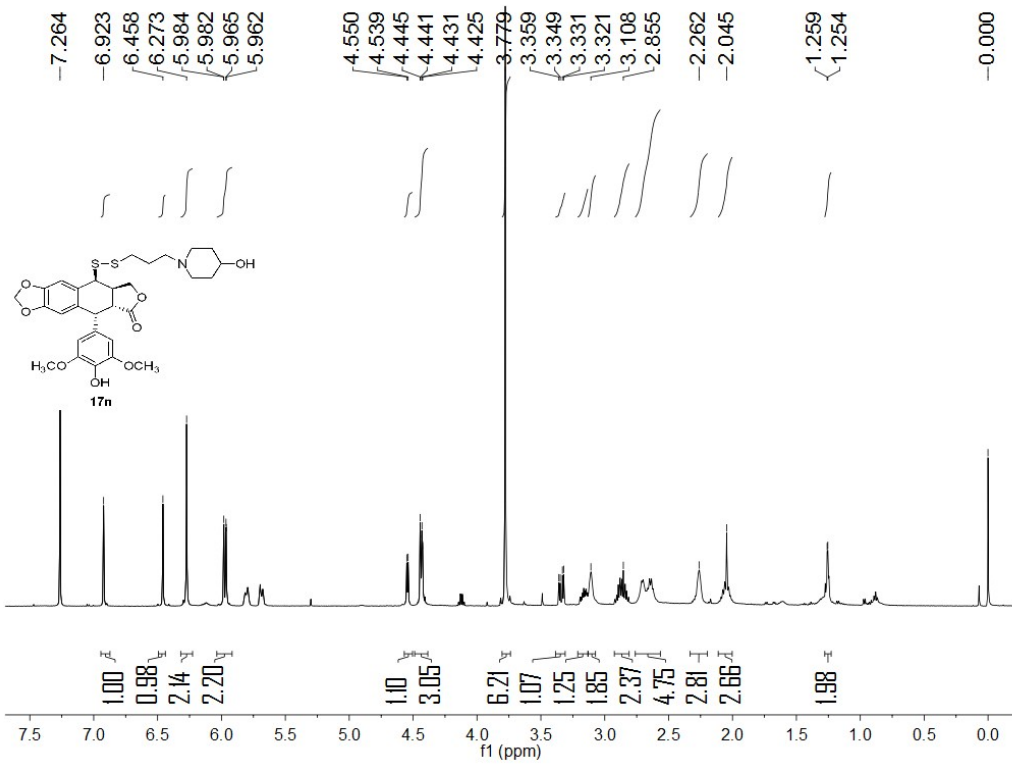
f1 (ppm)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4.431
4.425
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3.349
3.331
3.321
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1.259
1.254
0.000
17n
1.00
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2.14
2.20
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1.25
1.85
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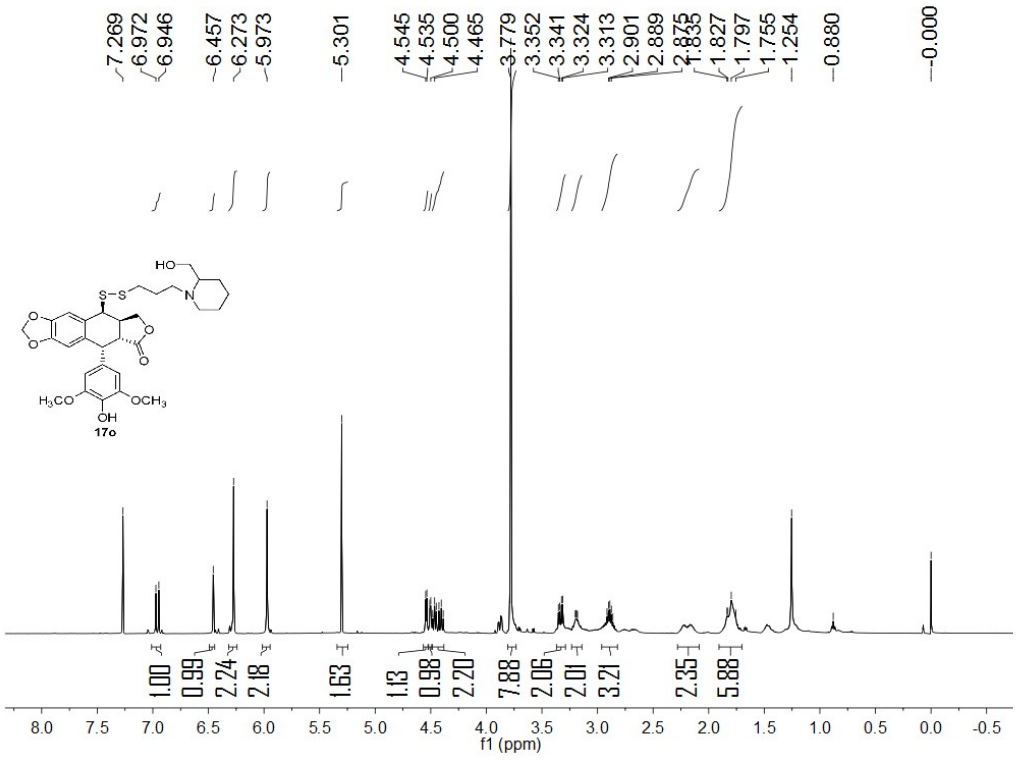
f1 (ppm)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3.324
3.313
2.901
2.889
1.827
1.797
1.755
1.254
0.880
0.000
17o
1.00
0.99
2.24
2.18
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0.98
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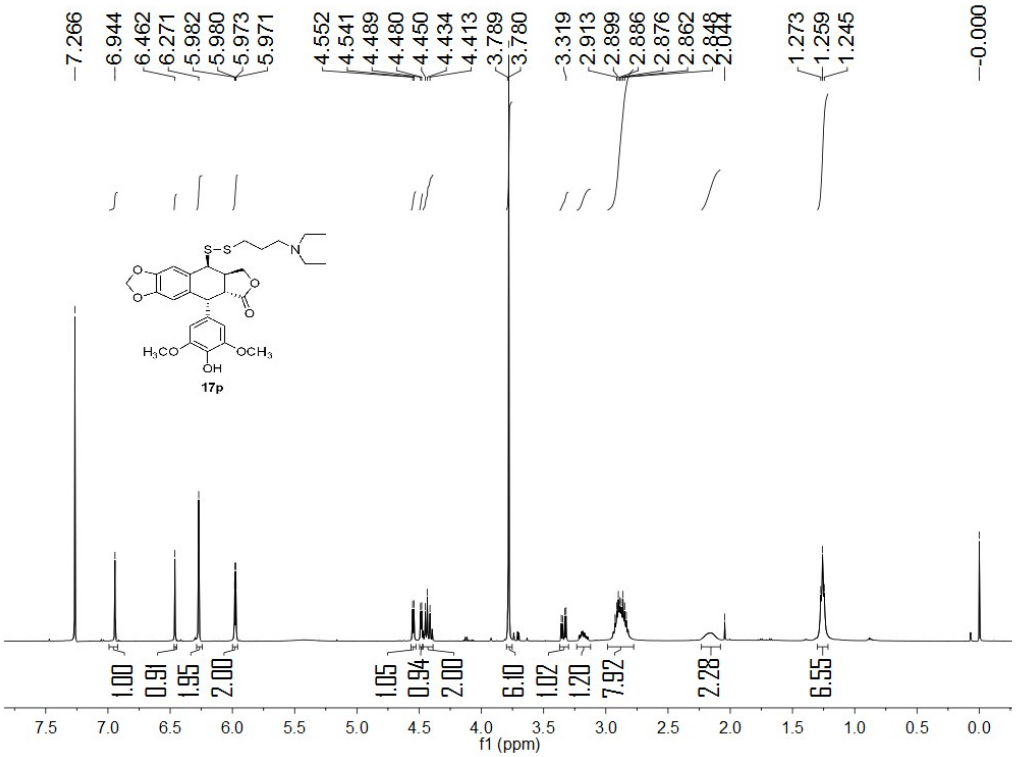
7.88
2.06
2.01
3.21
2.35
5.88
f1 (ppm)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4.434
4.413
3.789
3.780
3.319
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2.886
2.876
2.862
2.848
2.044
1.273
1.259
1.245
0.000
1.00
0.91
1.95
2.00
1.05
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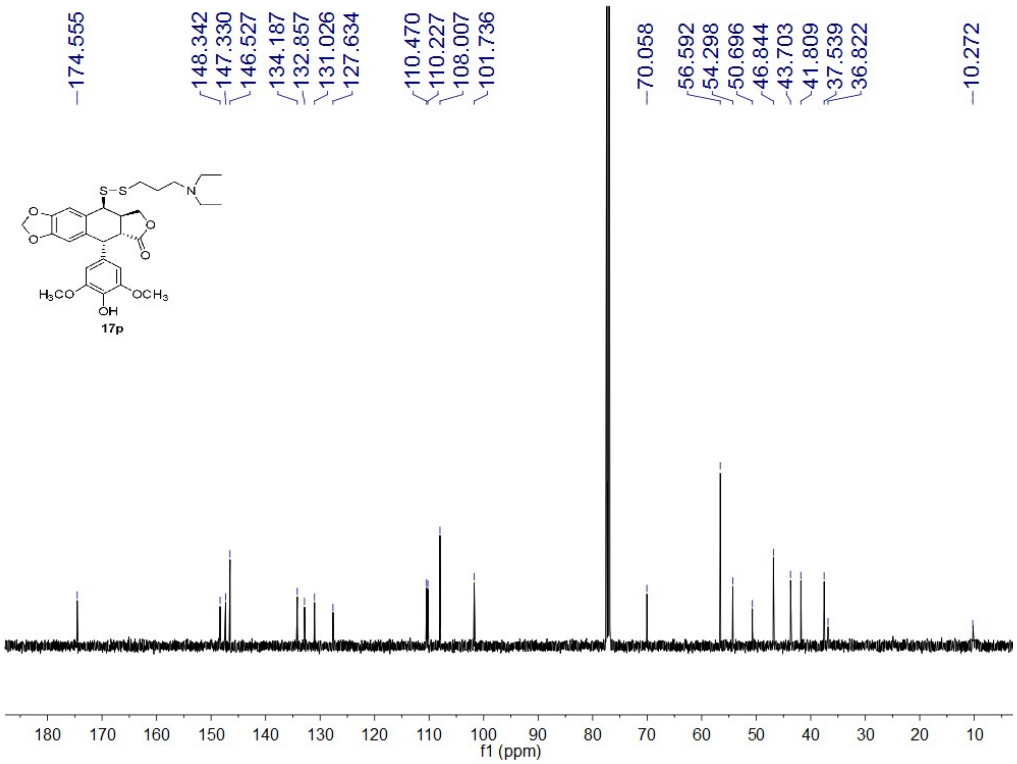
2.00
6.10
1.02
1.20
7.92
2.28
6.55
f1 (ppm)
17p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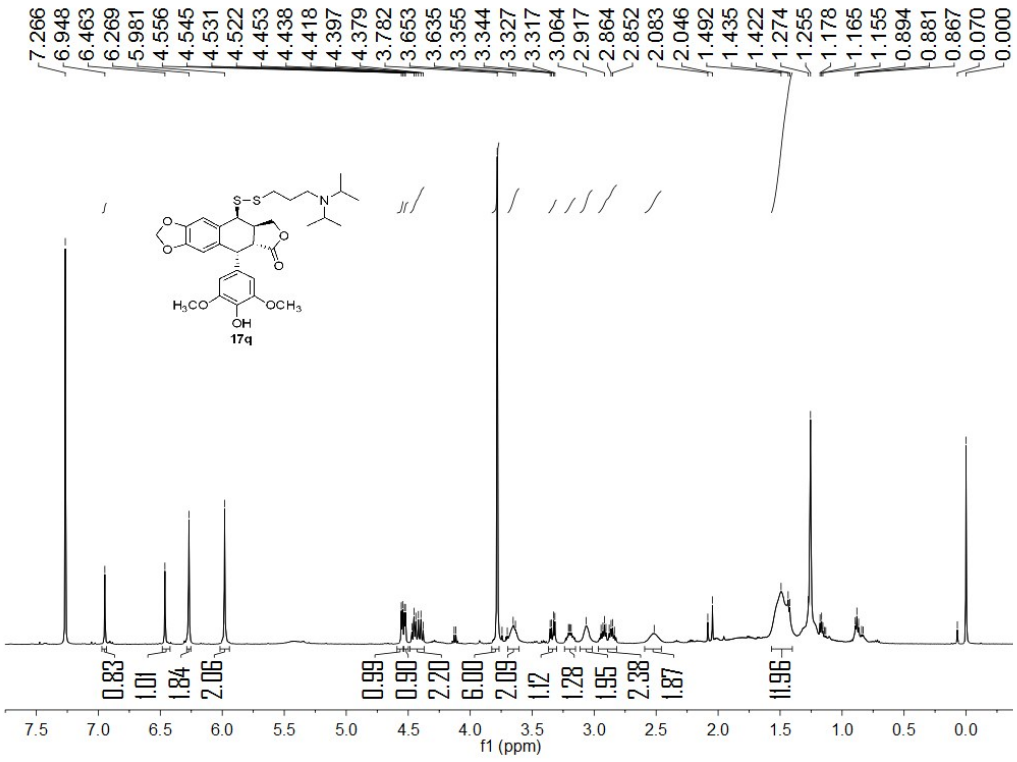
50.696
46.844
43.703
41.809
37.539
36.822
10.272
17p
f1 (ppm)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4.397
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3.782
3.653
3.635
3.355
3.344
3.327
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3.064
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1.255
1.178
1.165
1.155
0.894
0.881
0.867
0.070
0.000
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1.01
1.84
2.06
0.99
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1.87
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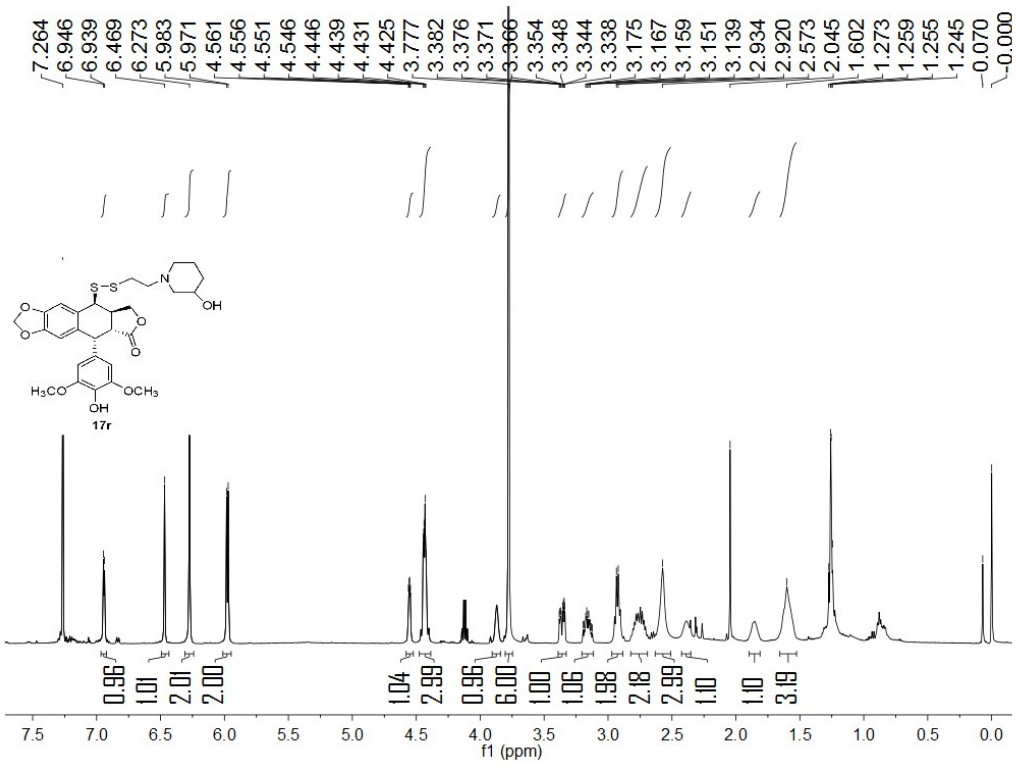
17q
f1 (ppm)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4.439
4.431
4.425
3.777
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3.366
3.354
3.348
3.344
3.338
3.175
3.167
3.159
3.151
3.139
2.934
2.920
2.573
2.045
1.602
1.273
1.259
1.255
1.245
-0.070
-0.000
17r
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1.01
2.01
2.00
1.04
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1.10
1.10
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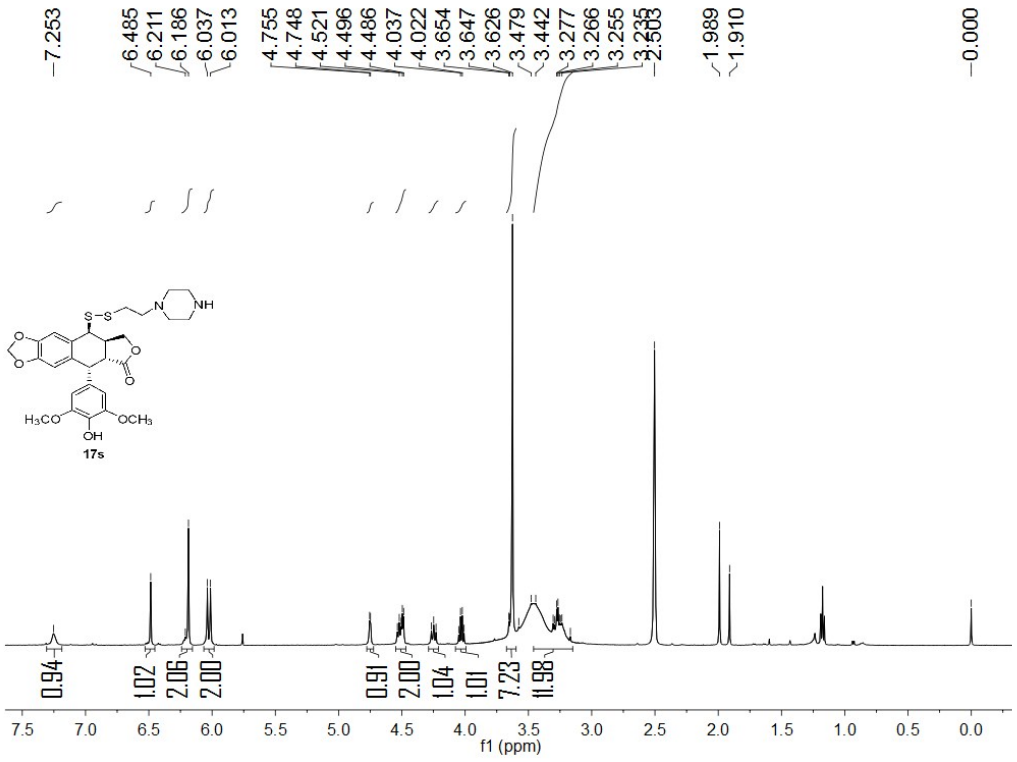
f1 (ppm)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4.022
3.654
3.647
3.626
3.479
3.442
3.277
3.266
3.255
2.503
1.989
1.910
-0.000
17s
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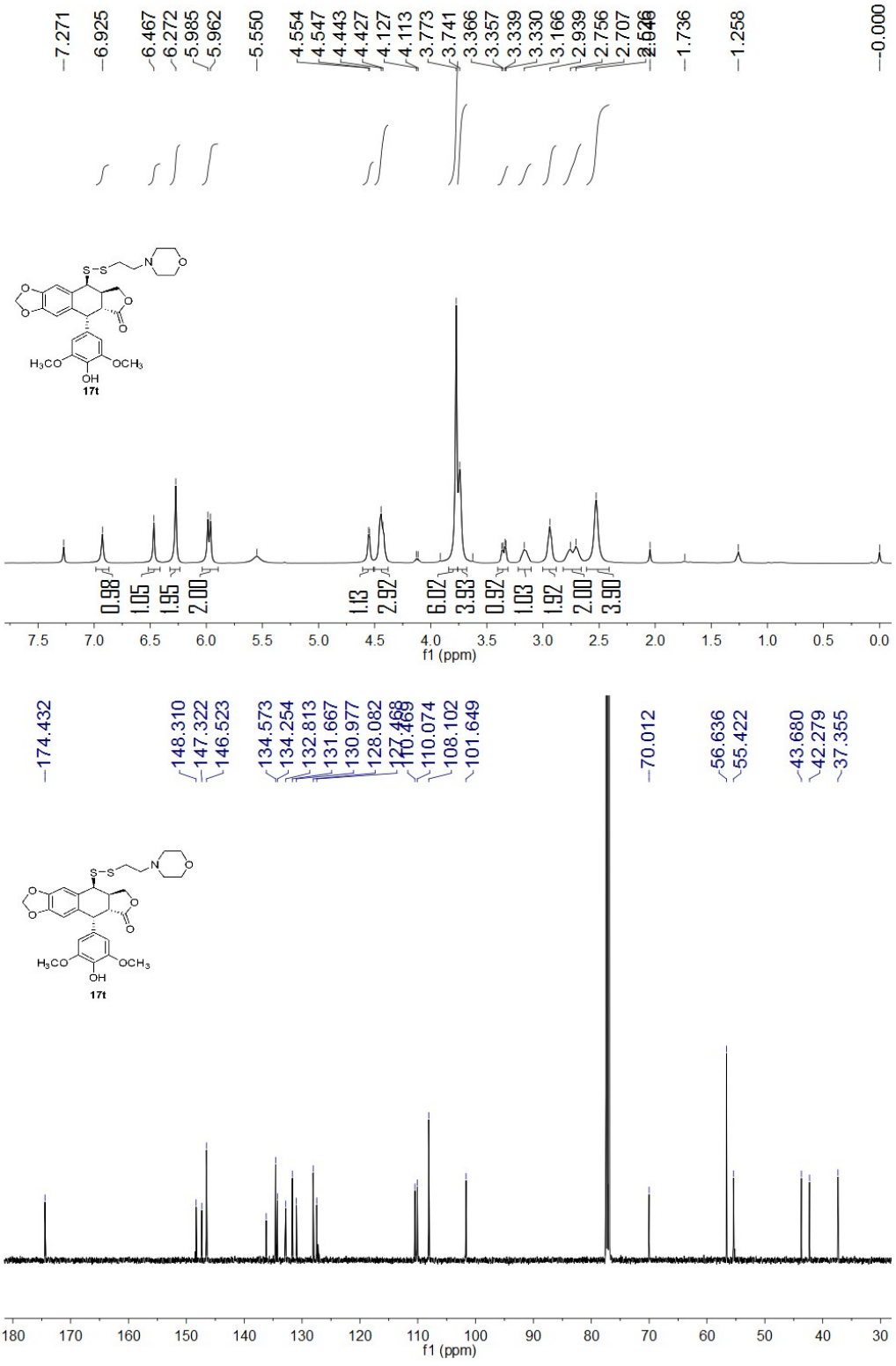
2.00
0.91
2.00
1.04
1.01
7.23
11.98
f1 (ppm)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4.113
3.773
3.741
3.366
3.357
3.339
3.330
3.166
2.939
2.756
2.707
1.736
1.258
0.000
17t
0.98
1.05
1.95
2.00
1.13
2.92
6.02
3.93
0.92
1.03
1.92
2.00
3.90
f1 (ppm)
174.432
148.310
147.322
146.523
134.573
134.254
132.813
131.667
130.977
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43.680
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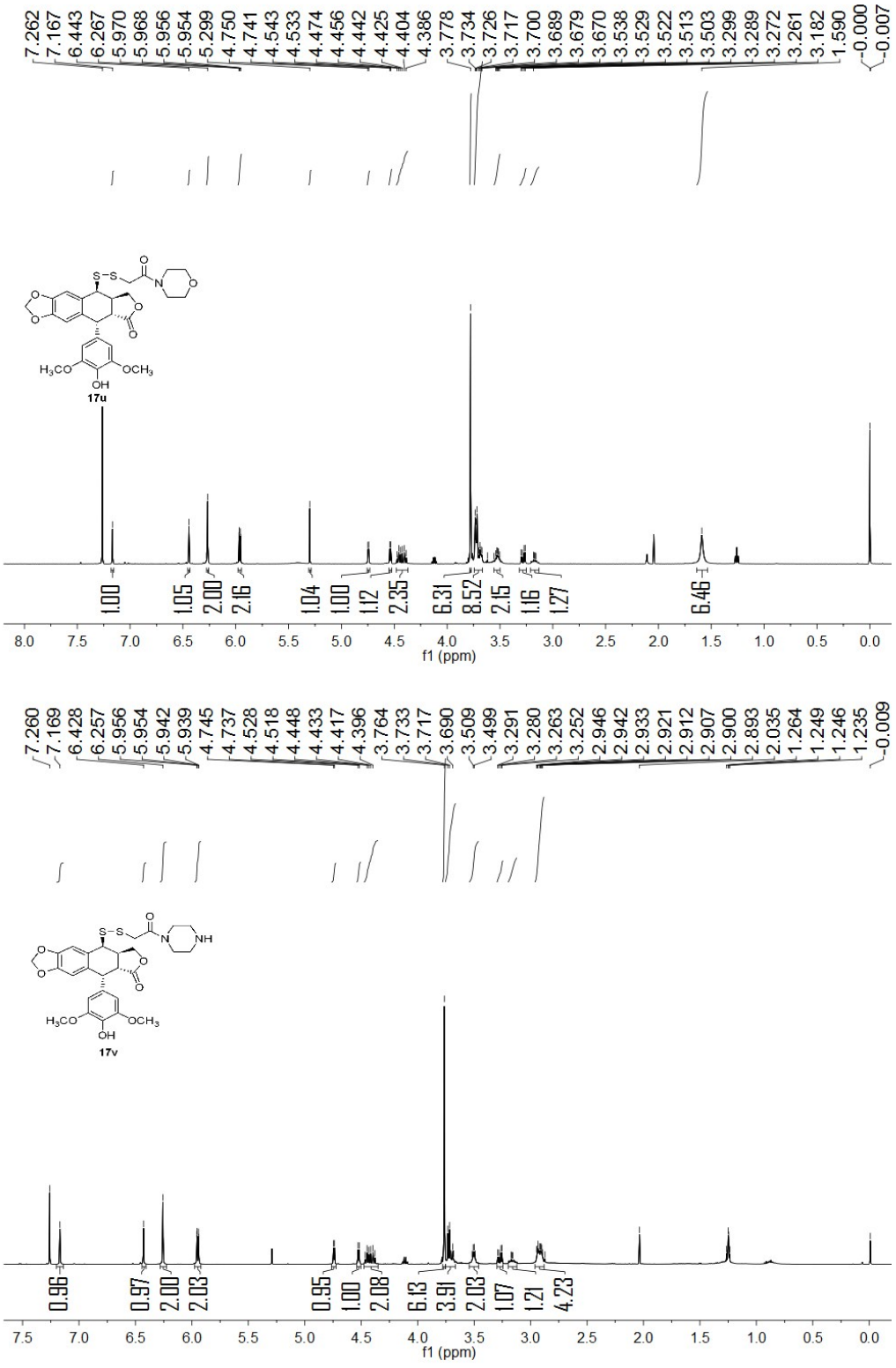
17t
f1 (ppm)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4.533
4.474
4.456
4.442
4.425
4.404
4.386
3.778
3.734
3.726
3.717
3.700
3.689
3.679
3.670
3.538
3.529
3.522
3.513
3.503
3.299
3.289
3.272
3.261
3.182
1.590
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17u
1.00
1.05
2.00
2.16
1.04
1.00
1.12
2.35
6.31
8.52
2.15
1.16
1.27
6.46
f1 (ppm)
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6.428
6.257
5.956
5.954
5.942
5.939
4.745
4.737
4.528
4.518
4.448
4.433
4.417
4.396
3.764
3.733
3.717
3.690
3.509
3.499
3.291
3.280
3.263
3.252
2.946
2.942
2.933
2.921
2.912
2.907
2.900
2.893
2.035
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1.249
1.246
1.235
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17v
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0.97
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6.13
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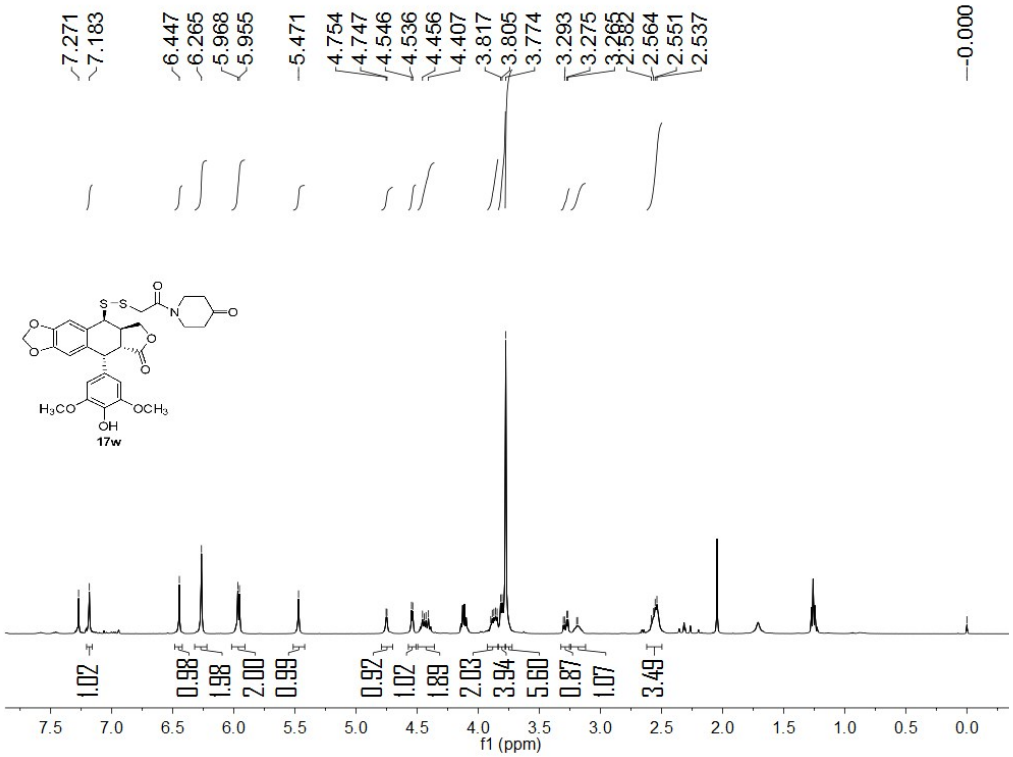
2.03
1.07
1.21
4.23
f1 (ppm)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5.471
4.754
4.747
4.546
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4.407
3.817
3.805
3.774
3.293
3.275
2.564
2.551
2.537
0.000
17w
1.02
0.98
1.98
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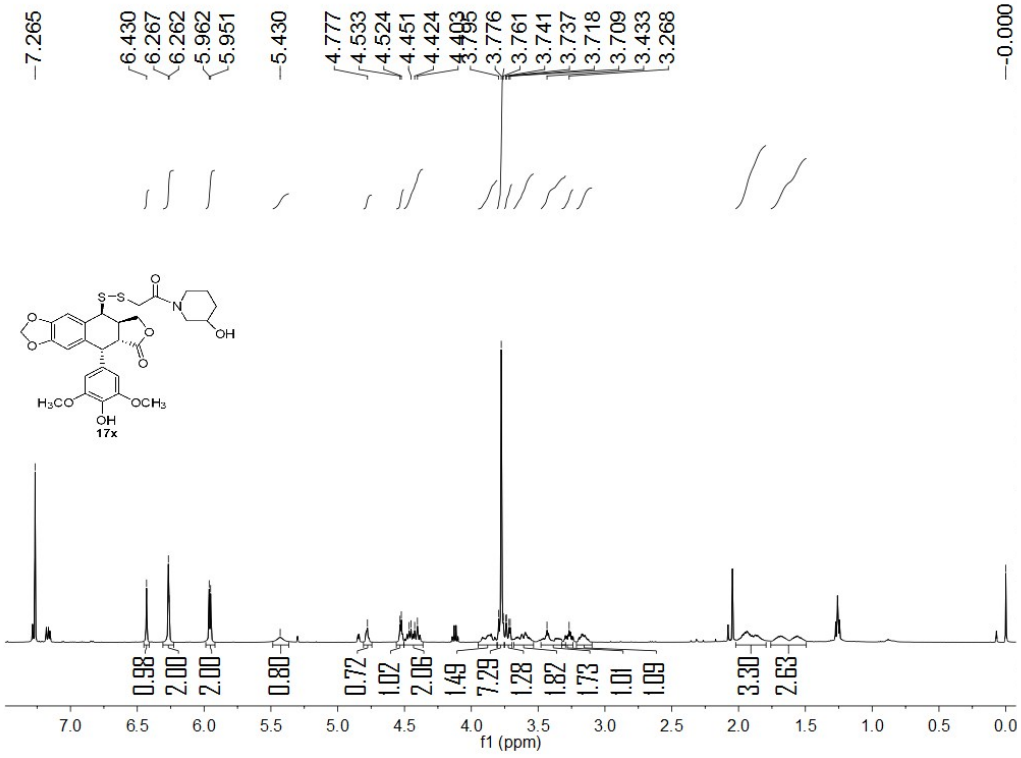
1.02
1.89
2.03
3.94
5.60
0.87
1.07
3.49
f1 (ppm)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6.267
6.262
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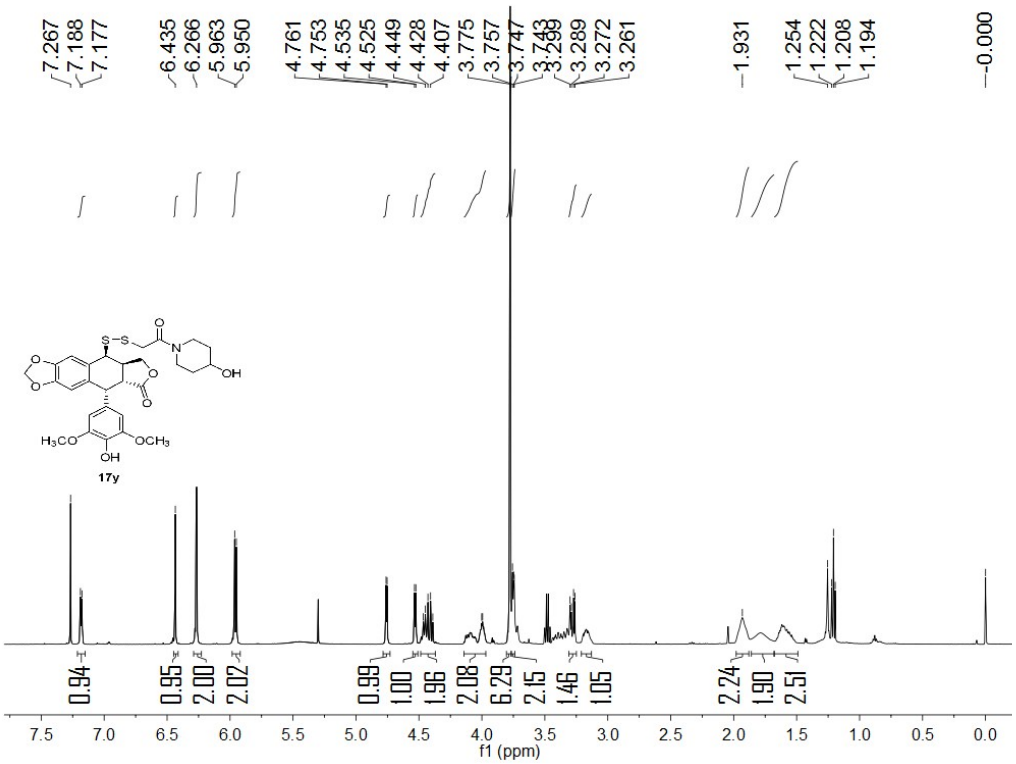
5.951
5.430
4.777
4.533
4.524
4.451
4.424
3.776
3.761
3.741
3.737
3.718
3.709
3.433
3.268
0.000
17x
0.98
2.00
2.00
0.80
0.72
1.02
2.06
1.49
7.29
1.28
1.82
1.73
1.01
1.09
3.30
2.63
f1 (ppm)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5.963
5.950
4.761
4.753
4.535
4.525
4.449
4.428
4.407
3.775
3.757
3.747
3.743
3.299
3.289
3.272
3.261
1.931
1.254
1.222
1.208
1.194
0.000
17y
0.94
0.95
2.00
2.02
0.99
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2.08
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2.15
1.46
1.05
2.24
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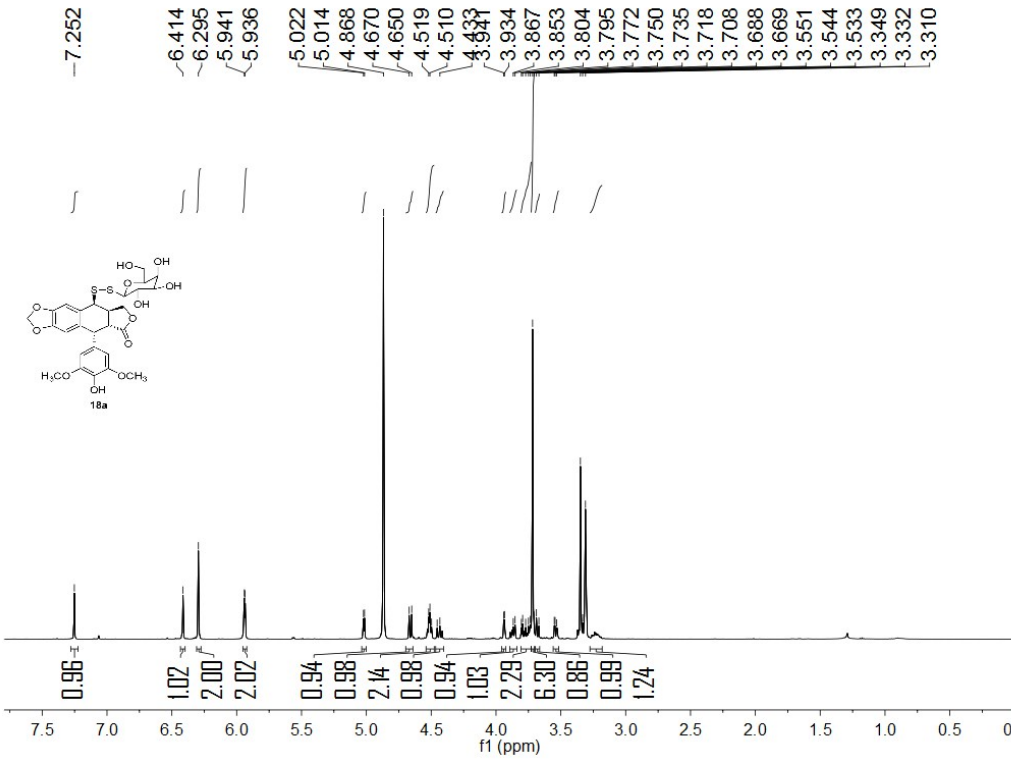
2.51
f1 (ppm)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4.670
4.650
4.519
4.510
4.433
3.941
3.934
3.867
3.853
3.804
3.795
3.772
3.750
3.735
3.718
3.708
3.688
3.669
3.551
3.544
3.533
3.349
3.332
3.310
18a
0.96
1.02
2.00
2.02
0.94
0.98
2.14
0.98
0.94
1.03
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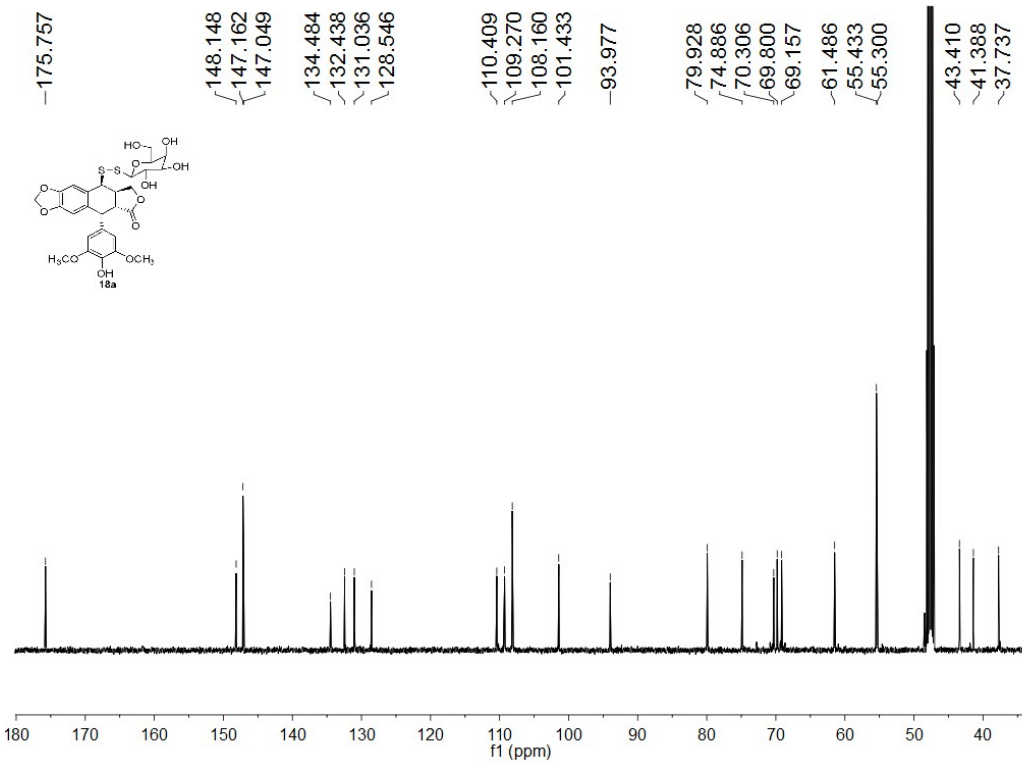
6.30
0.86
0.99
1.24
f1 (ppm)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108.160
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79.928
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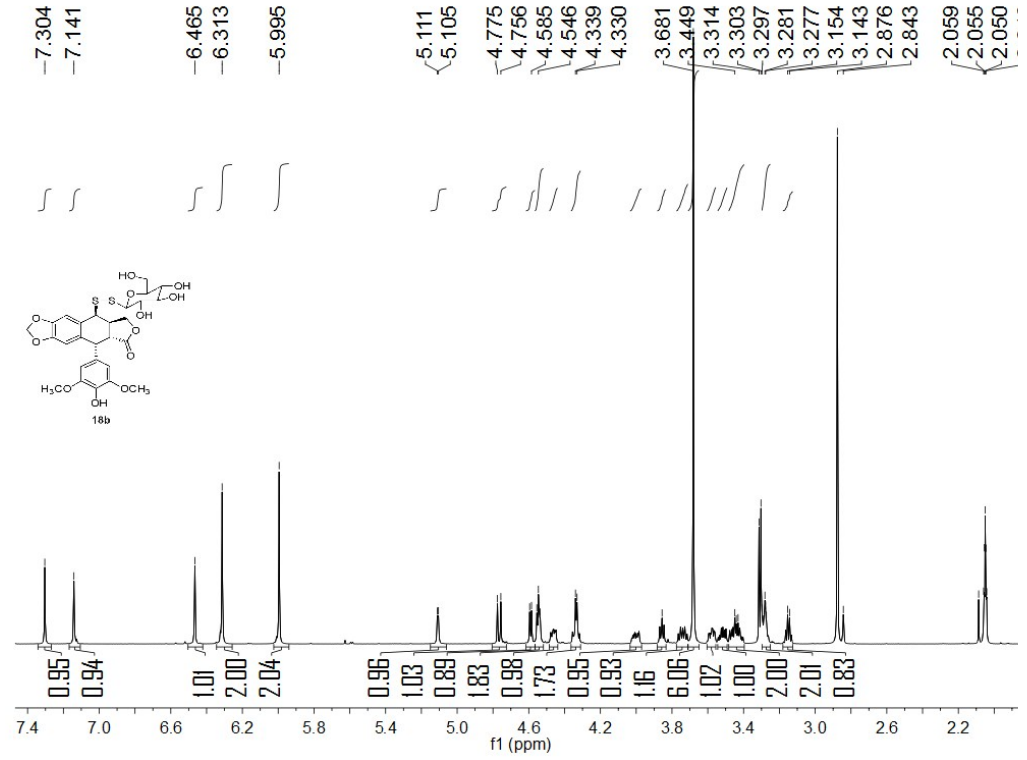
69.157
61.486
55.433
55.300
43.410
41.388
37.737
18a
f1 (ppm)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4.546
4.339
4.330
3.681
3.449
3.314
3.303
3.297
3.281
3.277
3.154
3.143
2.876
2.843
2.059
2.055
2.050
0.95
0.94
1.01
2.00
2.04
0.96
1.03
0.89
1.83
0.98
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0.95
0.93
1.16
6.06
1.02
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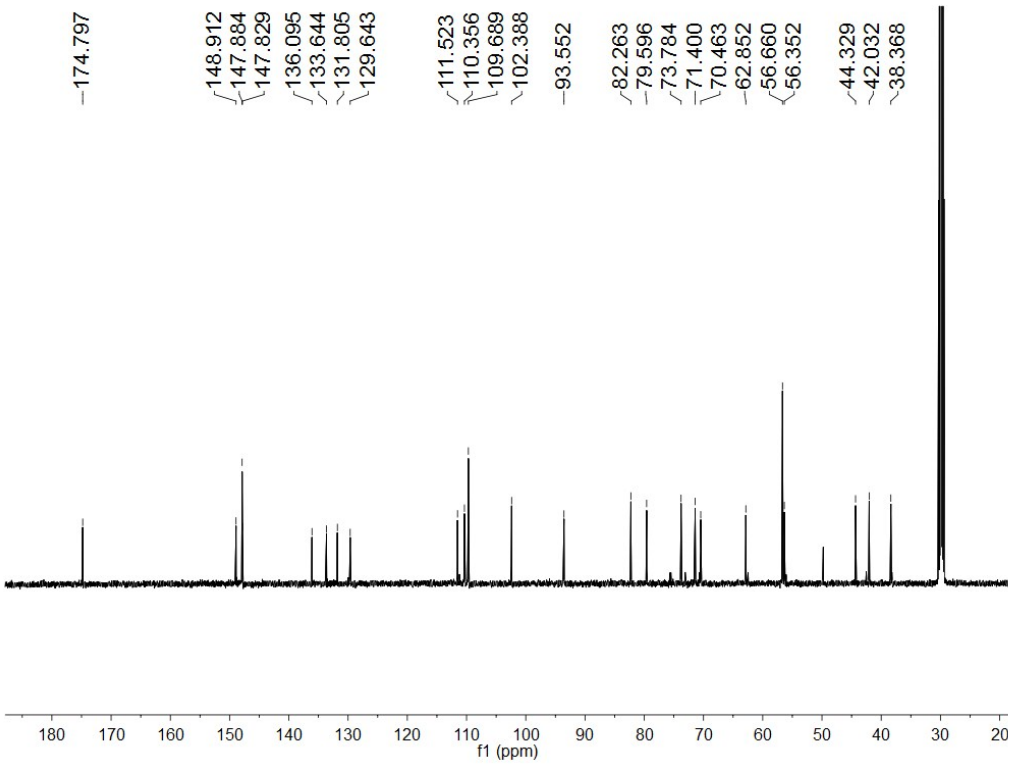
2.00
2.01
0.83
18b
f1 (ppm)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109.689
102.388
93.552
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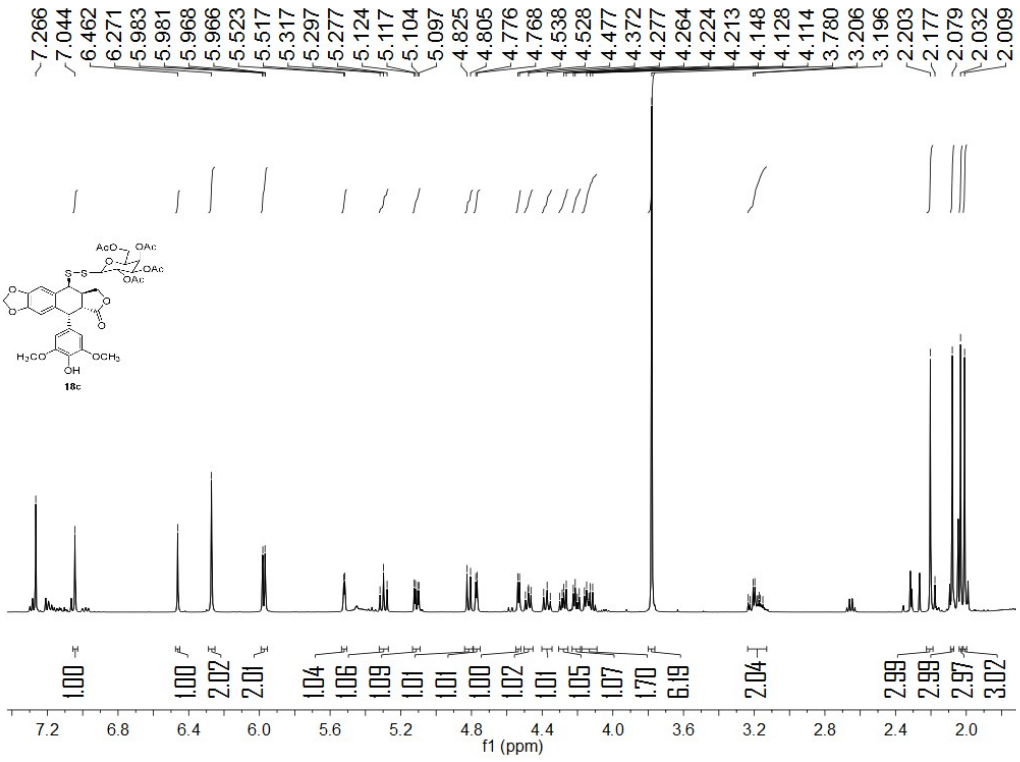
38.368
f1 (ppm)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5.523
5.517
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5.297
5.277
5.124
5.117
5.104
5.097
4.825
4.805
4.776
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4.538
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4.477
4.372
4.277
4.264
4.224
4.213
4.148
4.128
4.114
3.780
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3.196
2.203
2.177
2.079
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1.00
1.00
2.02
2.01
1.04
1.06
1.09
1.01
1.01
1.00
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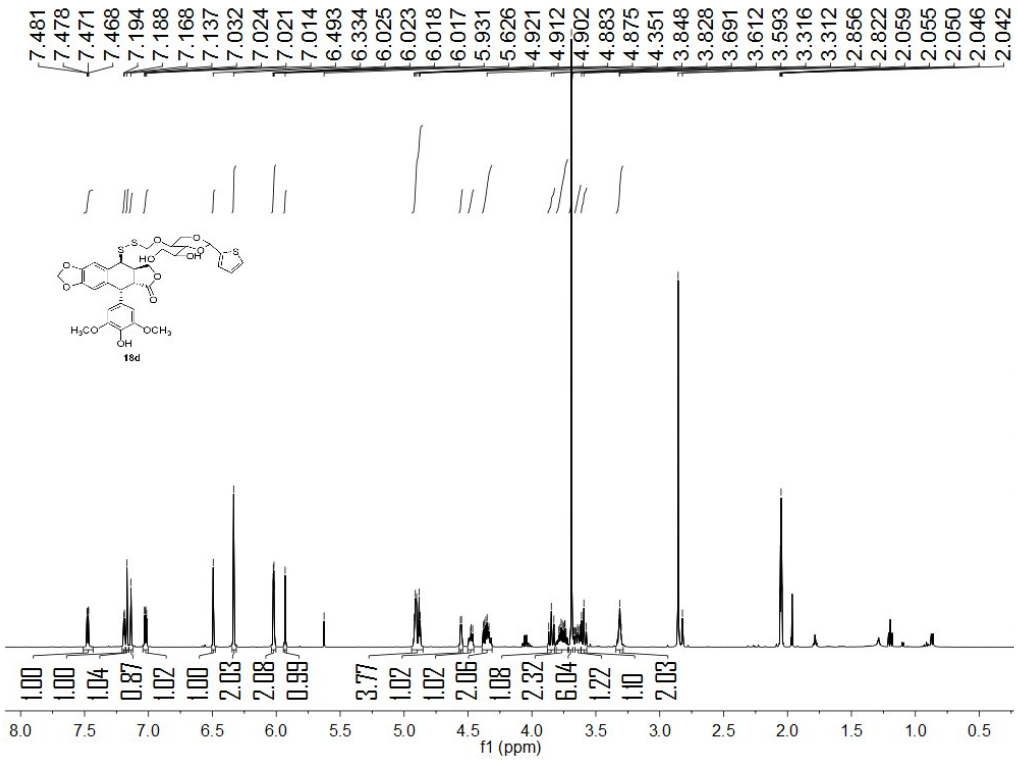
2.98
2.97
3.02
f1 (ppm)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6.334
6.025
6.023
6.018
6.017
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4.921
4.912
4.902
4.883
4.875
4.351
3.848
3.828
3.691
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3.316
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2.055
2.050
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2.042
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1.00
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1.02
1.00
2.03
2.08
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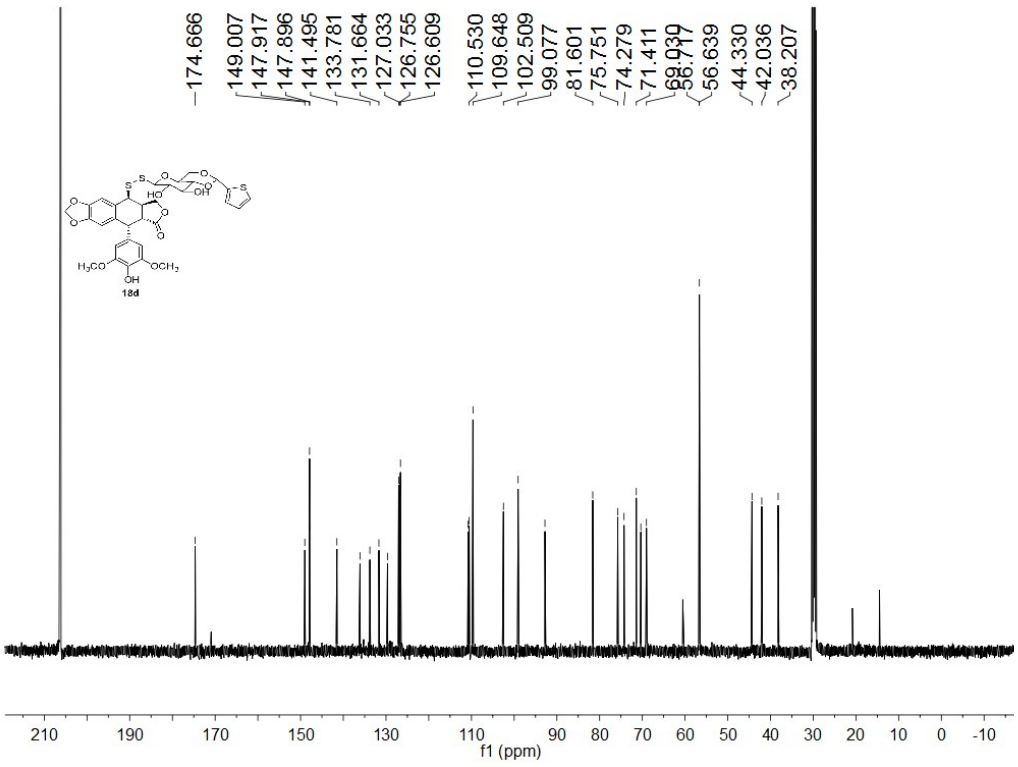
f1 (ppm)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102.509
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81.601
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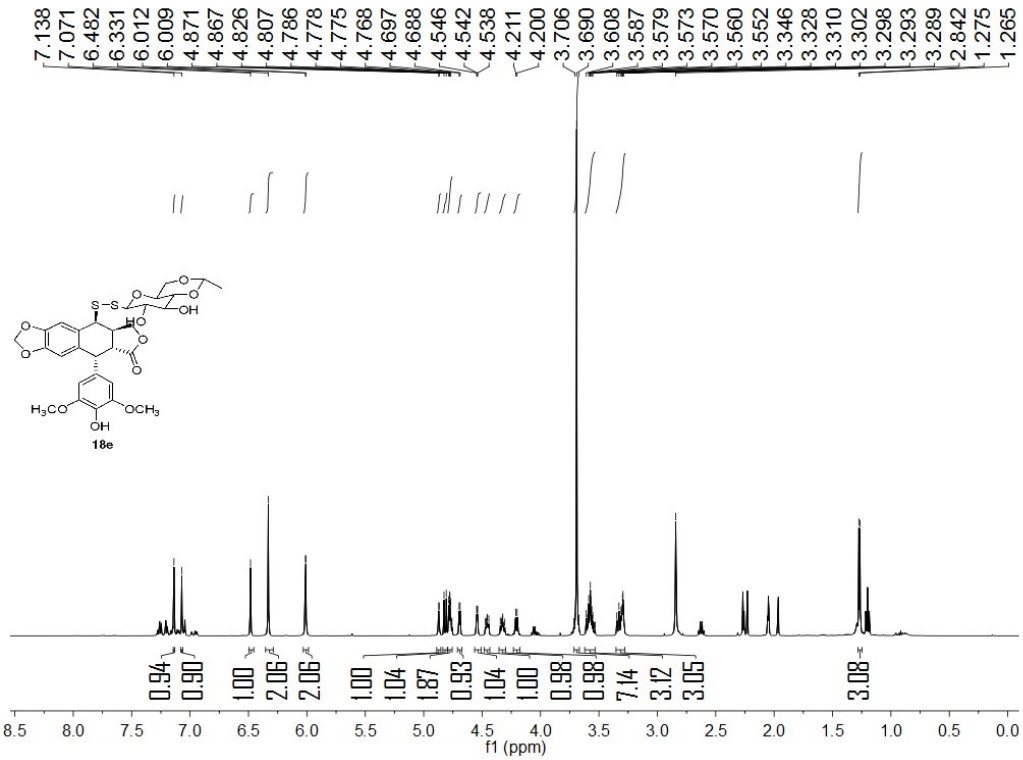
74.279
71.411
69.030
56.717
56.639
44.330
42.036
38.207
f1 (ppm)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4.778
4.775
4.768
4.697
4.688
4.546
4.542
4.538
4.211
4.200
3.706
3.690
3.608
3.587
3.579
3.573
3.570
3.560
3.552
3.346
3.328
3.310
3.302
3.298
3.293
3.289
2.842
1.275
1.265
18e
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0.90
1.00
2.06
2.06
1.00
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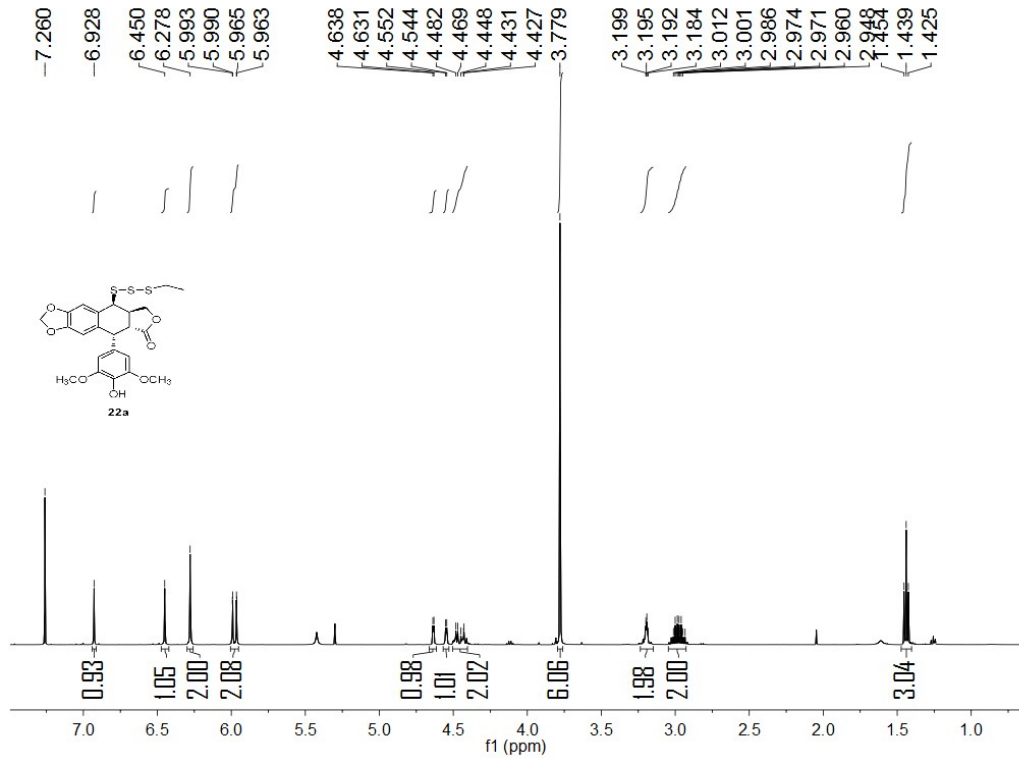
1.04
1.00
0.98
0.98
7.14
3.12
3.05
3.08
f1 (ppm)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4.482
4.469
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4.431
4.427
3.779
3.199
3.195
3.192
3.184
3.012
3.001
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2.974
2.971
2.960
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1.439
1.425
22a
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1.98
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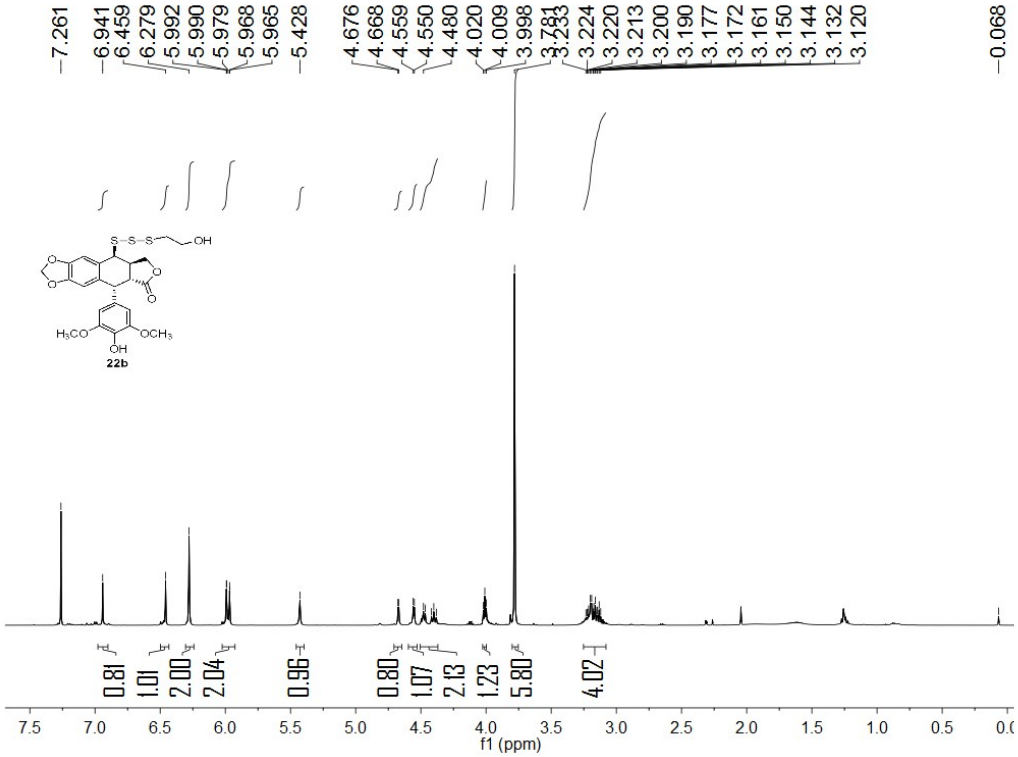
3.04
f1 (ppm)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4.668
4.559
4.550
4.480
4.020
4.009
3.998
3.781
3.233
3.224
3.220
3.213
3.200
3.190
3.177
3.172
3.161
3.150
3.144
3.132
3.120
0.068
22b
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0.80
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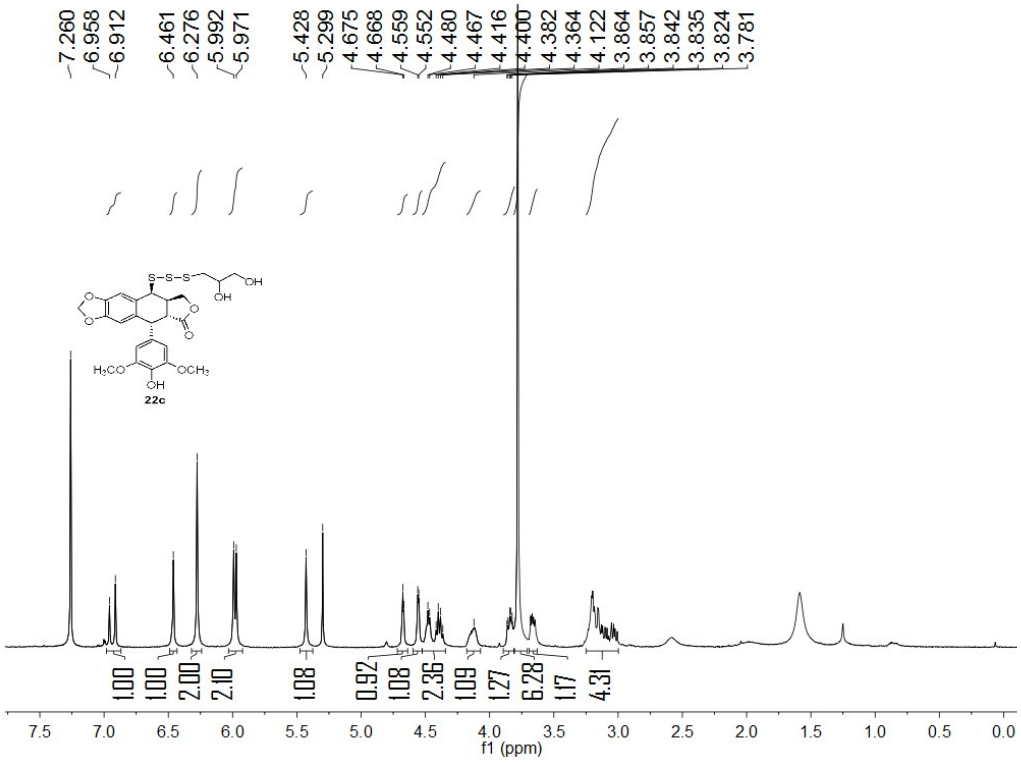
f1 (ppm)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4.416
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3.864
3.857
3.842
3.835
3.824
3.781
22c
1.00
1.00
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1.27
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1.17
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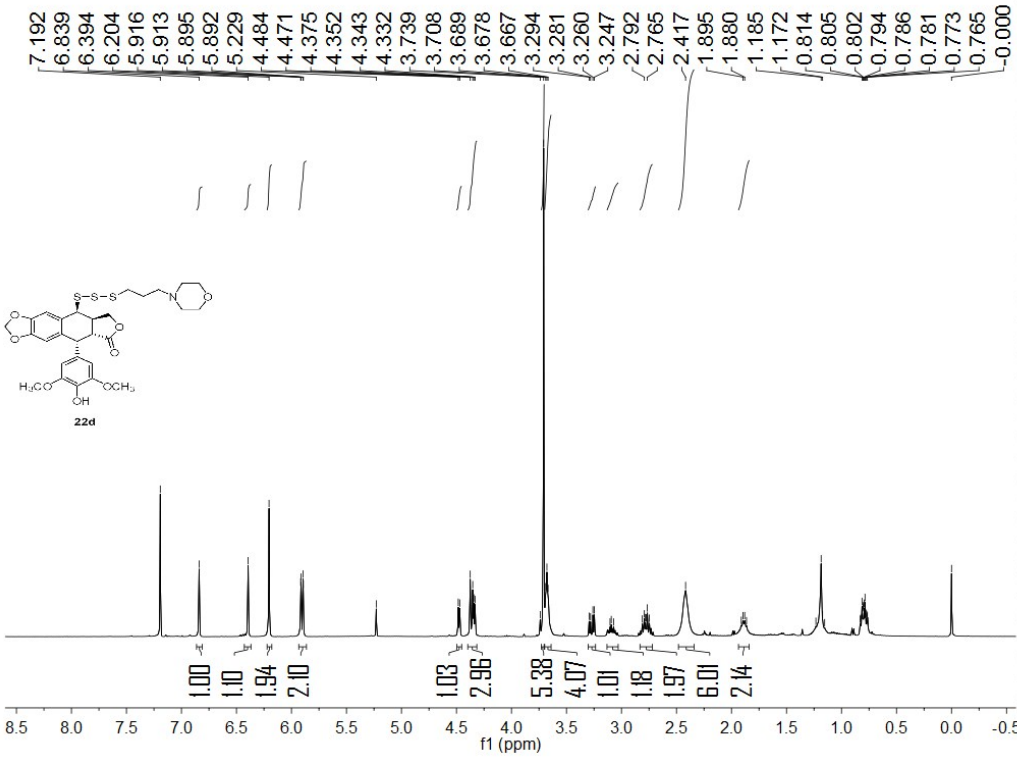
f1 (ppm)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4.352
4.343
4.332
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3.678
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3.294
3.281
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1.880
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1.172
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0.794
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0.781
0.773
0.765
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1.10
1.94
2.10
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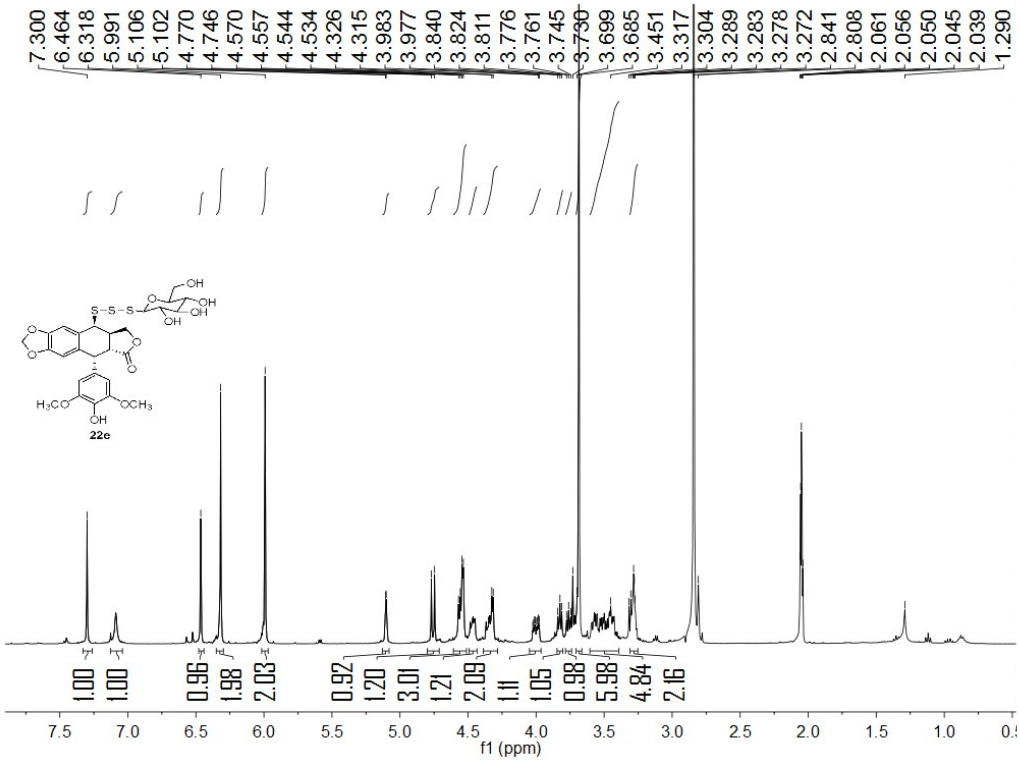
2.14
f1 (ppm)

22d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4.315
3.983
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3.824
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2.045
2.039
1.290
1.00
1.00
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2.03
0.92
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1.05
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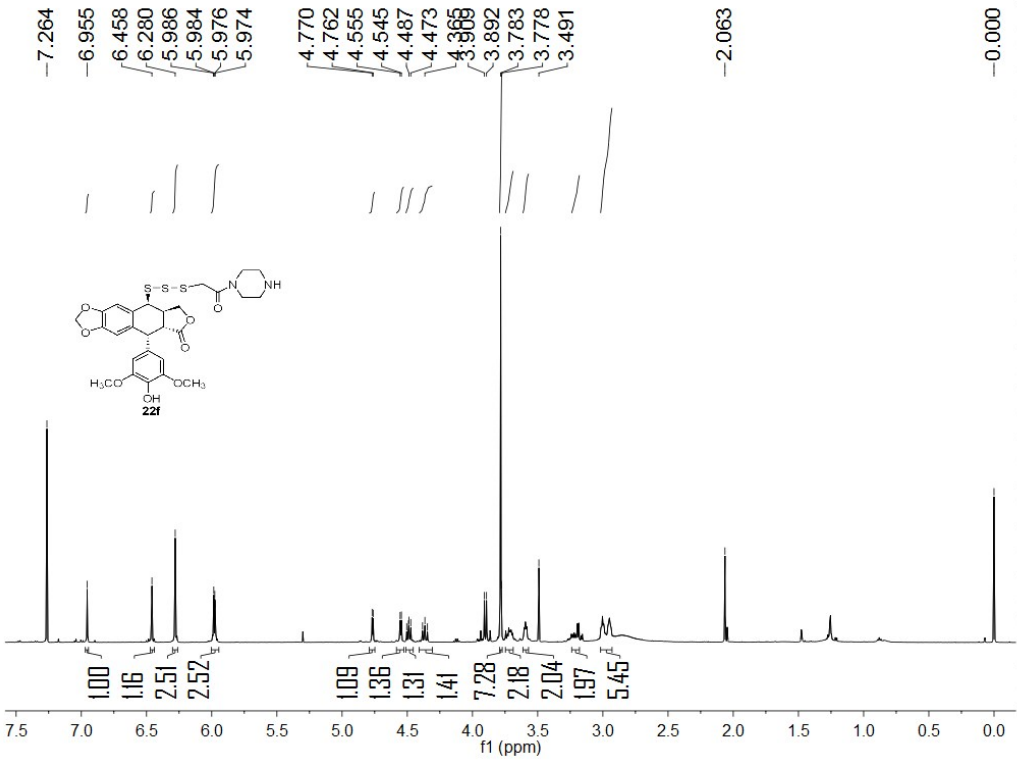
2.16
f1 (ppm)

22e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4.770
4.762
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4.545
4.487
4.473
3.892
3.783
3.778
3.491
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0.000
22f
1.00
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2.51
2.52
1.09
1.36
1.31
1.41
7.28
2.18
2.04
1.97
5.45
f1 (ppm)