Supplementary Material (ESI) for Chemical Communications

First Syntheses of Two Quinoline Alkaloids from the Medicinal Herb *Ruta Chalepensis* via Cyclization of an *o*-Iodoaniline with an Acetylenic Sulfone

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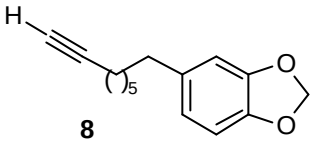
5-(7-Octynyl)-1,3-benzodioxole (8).

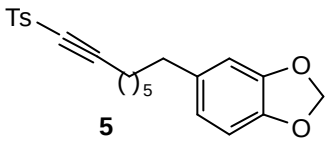


8

A solution of 4-bromo-1,2-(methylenedioxy)benzene (2.000 g, 9.949 mmol) in 20 mL of THF was cooled to –78 °C. A solution of *t*-butyllithium in pentane (1.7 M, 11.7 mL, 20 mmol) was added, and the resulting heterogeneous mixture was stirred for 15 min at -78 °C, then 10 min at –42 °C. The mixture was again cooled to –78 °C and 1-bromo-6-chlorohexane (1.48 mL, 9.95 mmol) was added, whereupon the mixture was warmed to room temperature for 1 h, then partitioned between saturated $(NH_4)_2SO_4$ (aq.) solution and dichloromethane. The aqueous layer was washed with dichloromethane and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was redissolved in 25 mL of acetone and NaI (7.5 g, 50 mmol) was added. The mixture was refluxed for 2 days, then partitioned between water and ether. The aqueous layer was washed with ether, and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was redissolved in 5 mL of THF and 1.7 mL of HMPA.

A solution of *n*-butyllithium in hexane (2.41 M, 8.26 mL, 19.9 mmol) was added to a solution of trimethylsilylacetylene (2.81 mL, 19.9 mmol) in 10 mL of THF at 0 °C. The solution was warmed to room temperature for 15 min, then transferred via cannula to the above alkyl iodide solution. The mixture was stirred for 2 days at room temperature, then partitioned between water and ether. The aqueous layer was washed with ether and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was redissolved in 20 mL of THF. A solution of tetrabutylammonium fluoride in THF (1.0 M, 20 mL, 20 mmol) was added and the solution was stirred for 30 min at room temperature, then partitioned between water and ether. The aqueous layer was washed with ether and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography over silica-gel (hexanes:ethyl acetate, 40:1) gave 1.38 g (60%) of **8** as a yellow oil, with properties in agreement with those reported in the literature.[1]

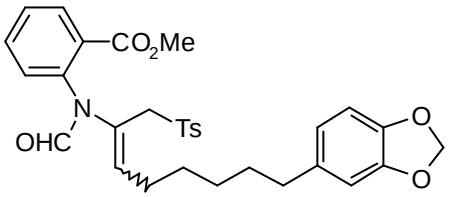
5-[8-(*p*-Toluene sulfonyl)-7-octynyl]-1,3-benzodioxole (5).



5

Acetylene **8** (2.26 g, 9.79 mmol) and *Se*-phenyl *p*-tolueneselenosulfonate[2] (3.05 g, 9.80 mmol) were dissolved in 20 mL of chloroform and irradiated for 2 h in a Rayonet reactor equipped with six 300 nm lamps. The solvent was evaporated, and the residue was redissolved in 100 mL of chloroform. *m*-Chloroperbenzoic acid (4.4 g, 77% purity, 20 mmol) was added in portions. The resulting mixture was stirred for 20 min, then was diluted to 250 mL with dichloromethane and washed with 500 mL of 5% NaOH (aq). The aqueous layer was extracted 3 times with 50 mL of dichloromethane and the combined organic layers were washed with 200 mL of 5% NaOH (aq). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in 300 mL of benzene. $MgSO_4$ (10 g) was added and the mixture was refluxed for 1 h, filtered to remove $MgSO_4$ and concentrated in vacuo. Flash chromatography over silica-gel (hexanes:ethyl acetate, 6:1 to 4:1) gave 2.70 g (72%) of **5** as a yellow oil, IR (film) 2198 cm^{-1}; ^1H NMR (200 MHz) δ 7.88 (d, J = 8.2 Hz, 2 H), 7.35 (d, J = 8.2 Hz, 2 H), 6.72 (d, J = 7.9 Hz, 1 H), 6.64 (d, J = 1.7 Hz, 1 H), 6.58 (dd, J = 7.9, 1.7 Hz, 1 H), 5.90 (s, 2 H), 2.49 (t, J = 7.4 Hz, 2 H), 2.44 (s, 3 H), 2.34 (t, J = 6.9 Hz, 2 H), 1.62-1.44 (m, 4 H), 1.43-1.18 (m, 4 H); ^{13}C NMR (50 MHz) δ 147.4, 145.3, 144.9, 139.1, 136.2, 129.7, 127.1, 120.8, 108.6, 107.9, 100.6, 97.1, 78.4, 35.3, 31.2, 28.4, 28.2, 26.8, 21.5, 18.7; MS (EI) *m/z* (%) 384 (M^+, 13), 147 (65), 135 (100). HRMS calcd. for $C_{22}H_{24}O_4S$: 384.1395. Found: 384.1384.

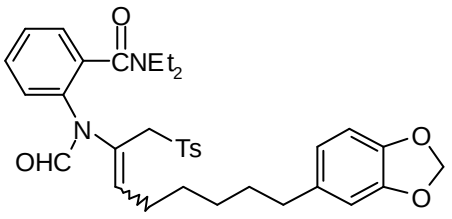
Preparation of 11 from amino ester 9 and acetylenic sulfone 5.



11

A mixture of methyl 2-(formylamino)benzoate (**9**)[3] (75.4 mg, 0.421 mmol), K_2CO_3 (58.6 mg, 0.424 mmol), and N,N-dimethylaminopyridine (52.8 mg, 0.432 mmol) was added in one portion to a stirred solution of sulfone **5** (162 mg, 0.421 mmol) in 0.5 mL of 10:1 DMF:H_2O. After 15 h at room temperature, the mixture was partitioned between ether and water. The aqueous layer was washed with ether and the combined organic fractions were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography over silica-gel (hexanes:ethyl acetate, 2:1 to 3:2) gave 61.0 mg (26%) of **11** as an off-white solid foam. NMR analysis showed the product to be a 2:1 mixture of geometrical isomers. The product was identical to that obtained from the carbonylation of **14** (vide infra).

Preparation of 12 from amino amide 10 and acetylenic sulfone 5.

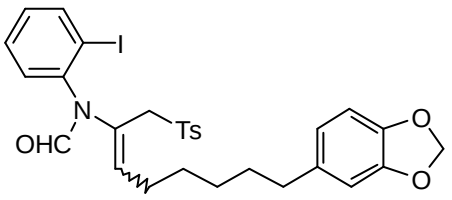


12

A mixture of N,N-diethyl-2-formylaminobenzamide (**10**)[4,5] (104.6 mg, 0.475 mmol), K_2CO_3 (58 mg, 0.42 mmol), and N,N-dimethylaminopyridine (52 mg, 0.43 mmol) was added in one portion to a stirred solution of sulfone **5** (161.5 mg, 0.420 mmol) in 0.5 mL of 10:1

DMF:H_2O. The mixture was stirred for 2 days at room temperature, then partitioned between ether and water. The aqueous layer was washed with ether and the combined organic fractions were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography over silica-gel (hexanes:ethyl acetate, 2:3) gave 168.7 mg (66%) of **12** as an off-white solid foam. NMR analysis showed the product to be a 4.5:1 mixture of geometrical isomers; IR (film) 1686, 1629 cm^{-1}; ^1H NMR (200 MHz, major isomer) δ 8.36 (s, 1 H), 7.76 (d, *J* = 8.2 Hz, 2 H), 7.45-7.22 (m, 6 H), 6.74 (d, *J* = 7.9 Hz, 1 H), 6.68 (d, *J* = 1.5 Hz, 1 H), 6.62 (dd, *J* = 7.9, 1.5 Hz, 1 H), 5.93 (s, 2 H), 5.70 (t, *J* = 7.5 Hz, 1 H), 4.15-2.90 (m, 6 H), 2.54 (t, *J* = 7.4 Hz, 2 H), 2.43 (s, 3 H), 2.16-1.90 (m, 2 H), 1.68-1.24 (m, 6 H), 1.19 (t, *J* = 7.2 Hz, 3 H), 1.01 (t, *J* = 7.1 Hz, 3 H); signals from the minor isomer were observed at δ 8.30 (s), 7.86 (d, *J* = 8.2 Hz), 5.82 (t, *J* = 7.5 Hz); ^{13}C NMR (50 MHz, both isomers) δ 167.8, 162.3, 147.3, 145.3, 144.8, 136.9, 136.6, 136.2, 136.0, 135.0, 132.3, 130.3, 129.7, 129.6, 129.6, 129.4, 128.8, 128.2, 128.0, 127.3, 120.9, 108.6, 107.9, 100.6, 54.8, 42.7, 38.7, 35.4, 31.3, 28.6, 28.1, 21.5, 13.8, 12.7; MS (EI) *m/z* (%) 449 (4.5, M^+ - Ts), 421 (50), 398 (20), 348 (42), 184 (100). HRMS calcd. for $C_{27}H_{33}N_2O_4$ (M^+ - Ts): 449.2440. Found: 449.2432.

Preparation of 14 from iodoaniline 13 and acetylenic sulfone 5.

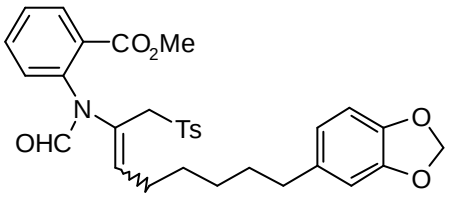


14

A mixture of N-(2-iodophenyl)formamide (**13**)[5] (628.9 mg, 2.546 mmol), K_2CO_3 (351 mg, 2.54 mmol), and N,N-dimethylaminopyridine (310 mg, 2.54 mmol) was added in one portion to a stirred solution of sulfone **5** (978.3mg, 2.544 mmol) in 3 mL of 10:1 DMF:H_2O. The mixture was stirred for 2 days at room temperature, then partitioned between ether and

water. The aqueous layer was washed with ether, and the combined organic fractions were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography over silica-gel (hexanes:ethyl acetate:dichloromethane, 4:1:5) gave 1.233 g (77%) of **14** as a yellow solid foam. NMR analysis showed the product to be a 2:1 mixture of geometrical isomers; IR (film) 1689 cm^{-1}; ^1H NMR (200 MHz) δ 8.40 (s, major isomer) and 8.18 (s, minor isomer, total 1 H), 7.95-7.75 (m, 3 H), 7.55-7.32 (m, 4 H), 7.17-7.04 (m, 1 H), 6.75-6.55 (m, 3 H), 6.01 (t, *J* = 7.6 Hz, major isomer) and 5.69 (t, *J* = 7.5 Hz, minor isomer, total 1 H), 5.93 (s, 2 H), 4.22 (br s, minor isomer) and 3.68 (br s, major isomer, total 2 H), 2.52 (t, *J* = 7.4 Hz, 2 H), 2.46 (s, 3 H), 1.95-1.15 (m, 8 H); ^{13}C NMR (50 MHz, both isomers) δ 162.3, 161.8, 147.4, 145.4, 145.2, 144.8, 142.5, 140.7, 140.1, 138.5, 137.9, 136.9, 136.2, 136.1, 131.4, 131.1, 130.2, 130.1, 130.0, 129.7, 129.3, 128.5, 128.2, 125.3, 124.8, 120.9, 108.7, 108.0, 100.6, 99.7, 97.8, 54.4, 54.1, 35.3, 31.2, 28.7, 28.6, 28.5, 28.0, 27.3, 21.5; MS (EI) *m/z* (%) 631 (M^+, 0.9), 476 (18), 448 (20), 270 (18), 229 (61), 156 (61), 147 (100); HRMS calcd. for $C_{22}H_{23}INO_3$ (M^+ - Ts): 476.0723. Found 476.0732.

Preparation of 11 from the carbonylation of iodoaniline 14.

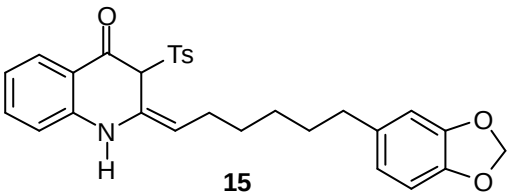


11

Iodoaniline **14** (1.135 g, 1.797 mmol) was dissolved in 30 mL of MeOH and 2.5 mL of dichloromethane. Triethylamine (250 μL, 1.79 mmol) and $Pd(OAc)_2$ (40 mg, 0.18 mmol) were added. The mixture was sealed inside a Parr high-pressure reaction vessel, flushed three times with CO, then pressurized to 27 atm (400 psi) with CO, and heated and stirred at 70 °C for 2 days. The apparatus was cooled to room temperature, vented, and the mixture was filtered to remove Pd, and concentrated in vacuo. Flash chromatography over silica-gel (hexanes:ethyl

acetate, 4:1 to 3:2) gave 156.7 mg (14%) of recovered **4** and 831.3 mg (82%; 95% based on recovered starting material) of **11** as an off-white solid foam. NMR analysis showed the product to be a 2:1 mixture of geometrical isomers; IR (film) 1727, 1687 cm^{-1}; ^1H NMR (200 MHz) δ 8.36 (s, major isomer) and 8.12 (s, minor isomer, total 1 H), 7.94-7.24 (m, 8 H), 6.75-6.56 (m, 3 H), 5.92 (s, major isomer) and 5.91 (s, minor isomer, total 2 H), 5.86 (t, *J* = 7.5 Hz, major isomer) and 5.61 (t, *J* = 7.5 Hz, minor isomer, total 1 H), 4.27 (s, minor isomer) and 3.72 (s, major isomer, total 2 H), 3.82 (s, both isomers, 3 H), 2.56-2.43 (s at δ 2.44 superimposed on m, total 5 H), 2.01-1.77 (m, 2 H), 1.70-1.13 (m, 6 H); ^{13}C NMR (50 MHz, both isomers) δ 166.1, 166.0, 161.8, 161.7, 147.4, 147.3, 145.4, 145.3, 145.1, 144.7, 140.1, 137.1, 136.8, 136.4, 136.2, 136.0, 135.6, 133.5, 132.6, 131.1, 131.0, 130.2, 129.9, 129.7, 129.5, 129.5, 129.1, 128.3, 128.1, 126.5, 126.4, 120.8, 108.6, 107.9, 100.6, 55.1, 54.5, 52.4, 52.2, 35.4, 31.2, 28.7, 28.5, 28.1, 27.5, 21.5; MS (EI) *m/z* (%) 504 (1.5), 408 (21), 380 (94), 357 (29), 348 (36), 184 (72), 147 (100); HRMS calcd. for $C_{24}H_{26}NO_5$ (M^+ - Ts): 408.1811. Found: 408.1792.

Preparation of quinolin-4-one 15.

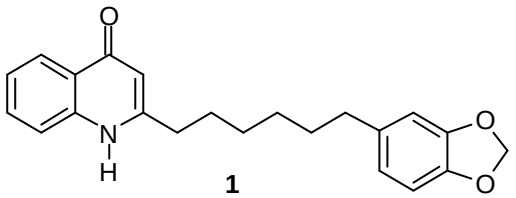


15

Ester **11** (1.0428 g, 1.8500 mmol) was dissolved in 15 mL of THF. The solution was cooled to −78 °C, and LiHMDS (13.9 mL, 0.267 M, 3.71 mmol) was added. The resulting red solution was stirred for 70 min at −78 °C and the reaction was then quenched with saturated $(NH_4)_2SO_4$ (aq.). The mixture was partitioned between ether and dilute $(NH_4)_2SO_4$ (aq.). The aqueous layer was washed with ether and the combined organic fractions were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography over silica-gel (hexanes:ethyl acetate, 2:1) gave 927.7 mg (99%) of a single geometrical isomer of **15** as a solid white foam; IR (film) 1684 cm^{-1}; ^1H NMR (200 MHz) δ 8.66 (br s, 1 H), 8.21 (br s, 1 H), 8.00 (d, *J* = 7.7 Hz, 1 H),

7.78-7.58 (m, 3 H), 7.40-7.20 (m, 3 H), 6.72 (d, *J* = 7.7 Hz, 1 H), 6.65 (s, 1 H), 6.60 (d, *J* = 7.7 Hz, 1 H), 5.96 (t, *J* = 7.7 Hz, 1 H), 5.93 (s, 2 H), 4.95 (s, 1 H), 2.51 (t, *J* = 7.5 Hz, 2 H), 2.43 (s, 3 H), 2.22-1.91 (m, 2 H), 1.69-1.20 (m, 6 H); a 10% nOe was observed between the proton of C-3 (δ 4.95 ppm) and those of C-2' (δ 2.2 ppm), indicating the *E* geometry; ^{13}C NMR (50 MHz) δ 182.8, 161.2, 147.4, 145.8, 145.4, 136.3, 136.1, 134.6, 129.8, 129.2, 128.0, 125.0, 122.0, 120.9, 108.7, 108.0, 100.7, 71.7, 35.4, 31.3, 28.6, 28.5, 26.7, 21.6; MS (EI) *m/z* (%) 348 (7.1), 276 (38), 248 (100); HRMS calcd. for $C_{29}H_{29}NO_5S$: 503.1767. Found: 503.1756. Anal. calcd. for $C_{29}H_{29}NO_5S$: C, 69.16; H, 5.80; N, 2.78. Found: C, 68.86; H, 6.16; N, 2.84.

Preparation of *Ruta Chalepensis* alkaloid 1.[6]

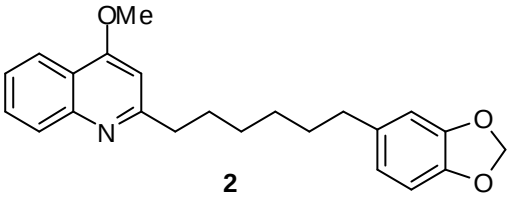


1

Mercuric chloride (123 mg, 0.453 mmol) was dissolved in 3 mL of 2:1 MeOH:THF. Thin strips of aluminum metal (50 mg, 1.9 mg-atom) were added, and the mixture was stirred for 5 min, whereupon keto sulfone **15** (57.5 mg, 0.114 mmol) was added in one portion. The mixture was stirred for 20 min at room temperature, then partitioned between dichloromethane and brine. The aqueous layer was washed with dichloromethane and the combined organic fractions were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography over silica-gel (chloroform:methanol, 40:1) gave 25.6 mg (64%) of **1** as a white solid, mp 156-157 °C (from dichloromethane), (lit.[6] mp 163 °C); IR (film) 1635, 1594, 1548, 1501 cm^{-1}; ^{1}H NMR (200 MHz) δ 12.35 (br s, 1 H), 8.36 (dd, *J* = 8.1, 1.3 Hz, 1 H), 7.73 (d, *J* = 8.0 Hz, 1 H), 7.58 (ddd, *J* = 8.0, 7.0, 1.3 Hz, 1 H), 7.31 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1 H); 6.67 (d, *J* = 7.9 Hz, 1 H), 6.59 (d, *J* = 1.5 Hz, 1 H), 6.52 (dd, *J* = 7.9, 1.5 Hz, 1 H), 6.27 (s, 1 H), 5.87 (s, 2 H), 2.71 (t, *J* = 7.7 Hz, 2 H), 2.41 (t, *J* = 7.5 Hz, 2 H), 1.80-1.63 (m, 2 H), 1.54-1.38 (m, 2 H),

1.38-1.15 (m, 4 H); ^{13}C NMR (100 MHz) δ 178.8, 155.5, 147.4, 145.4, 140.7, 136.3, 131.7, 125.1, 124.9, 123.5, 120.9, 118.7, 108.7, 108.0, 108.0, 100.6, 35.5, 34.3, 31.4, 29.1, 29.0, 28.8; MS (EI) *m/z* (%) 349 (M^+, 0.8), 184 (19), 172 (100). HRMS calcd. for $C_{22}H_{23}NO_3$: 349.1678. Found 349.1699. Anal. calcd. for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.46; H, 6.13; N, 3.98.

Preparation of *Ruta Chalepensis* alkaloid 2. [6]



2

Sodium bicarbonate (15.5 mg, 0.185 mmol) and dimethyl sulfate (17.4 μL, 0.184 mmol) were added to a solution of **1** (32.2 mg, 0.0922 mmol) in 5 mL of THF. The mixture was stirred at room temperature for 1 h, then refluxed for 17 h. It was then partitioned between brine and ether. The aqueous layer was washed with ether and the combined organic fractions were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography over silica-gel (hexanes:ethyl acetate, 4:1 to 2:1) gave 13.9 mg of **2** as a yellow oil. Elution of the column with dichloromethane:methanol, 10:1, followed by rechromatography of the product with chloroform:methanol, 40:1, gave another 11.2 mg of **2** (total yield, 75%) as a yellow oil; IR 1595, 1503, 1485, 1246 cm^{-1}; ^{1}H NMR (200 MHz) δ 8.14 (dd, *J* = 8.2, 1.5 Hz, 1 H), 7.98 (d, *J* = 8.4 Hz, 1 H), 7.66 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1 H), 7.44 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1 H), 6.72 (d, *J* = 7.7 Hz, 1 H), 6.67 (d, *J* = 1.5 Hz, 1 H), 6.63 (s, 1 H), 6.61 (dd, *J* = 7.7, 1.5 Hz, 1 H), 5.92 (s, 2 H), 4.04 (s, 3 H), 2.92 (t, *J* = 7.9 Hz, 2 H), 2.53 (t, *J* = 7.4 Hz, 2 H), 1.90-1.25 (m, 8 H); ^{13}C NMR (50 MHz) δ 164.1, 162.3, 148.7, 147.4, 145.3, 136.6, 129.6, 128.2, 124.7, 121.5, 121.0, 120.0, 108.8, 108.0, 100.6, 99.7, 55.5, 39.9, 35.6, 31.6, 30.0, 29.4, 29.0; MS (EI) *m/z* (%) 363 (M^+, 2), 306 (2), 228 (6), 186 (100). HRMS calcd. for $C_{23}H_{25}NO_3$: 363.1834. Found: 363.1861.

References for ESI

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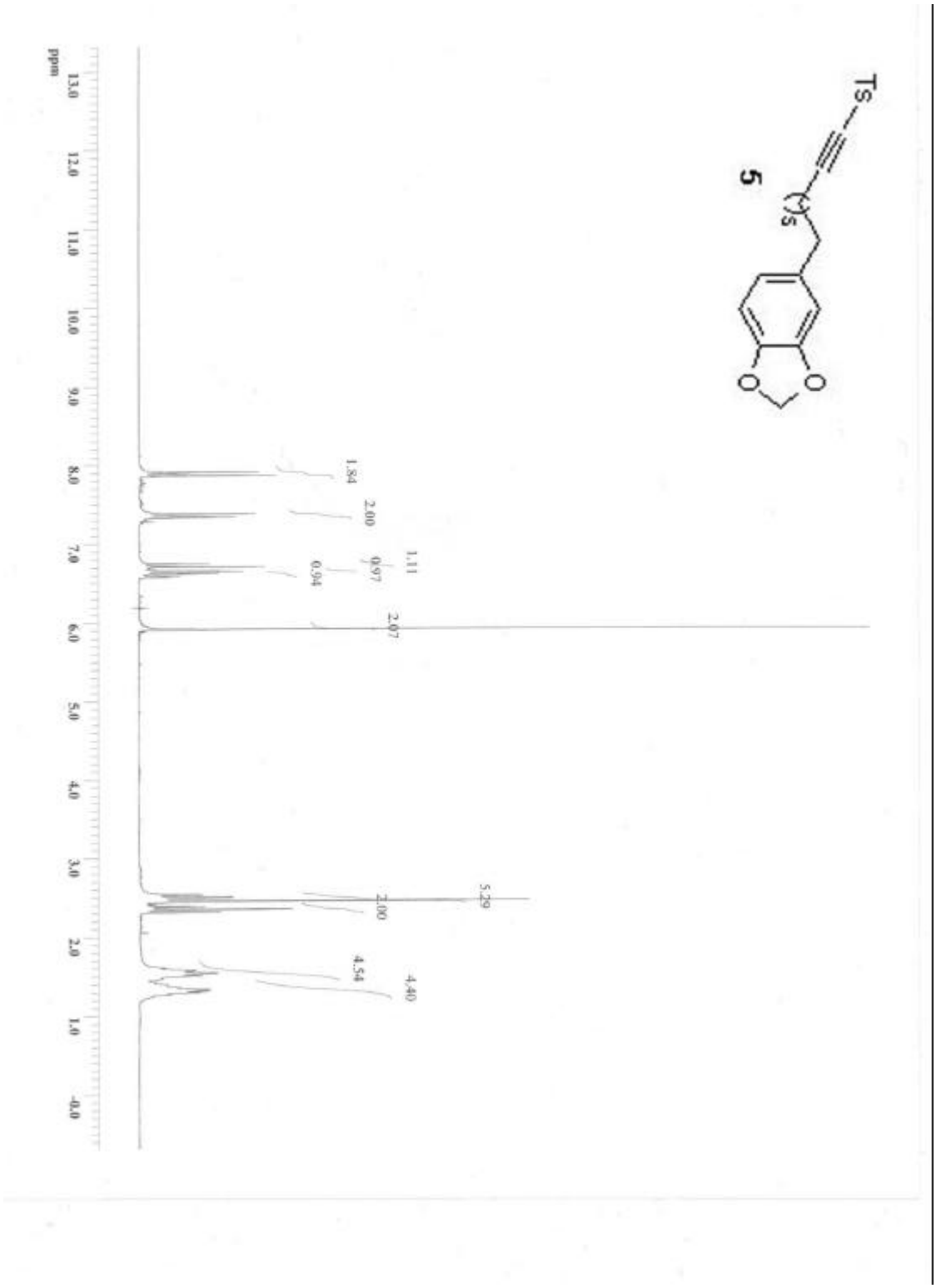
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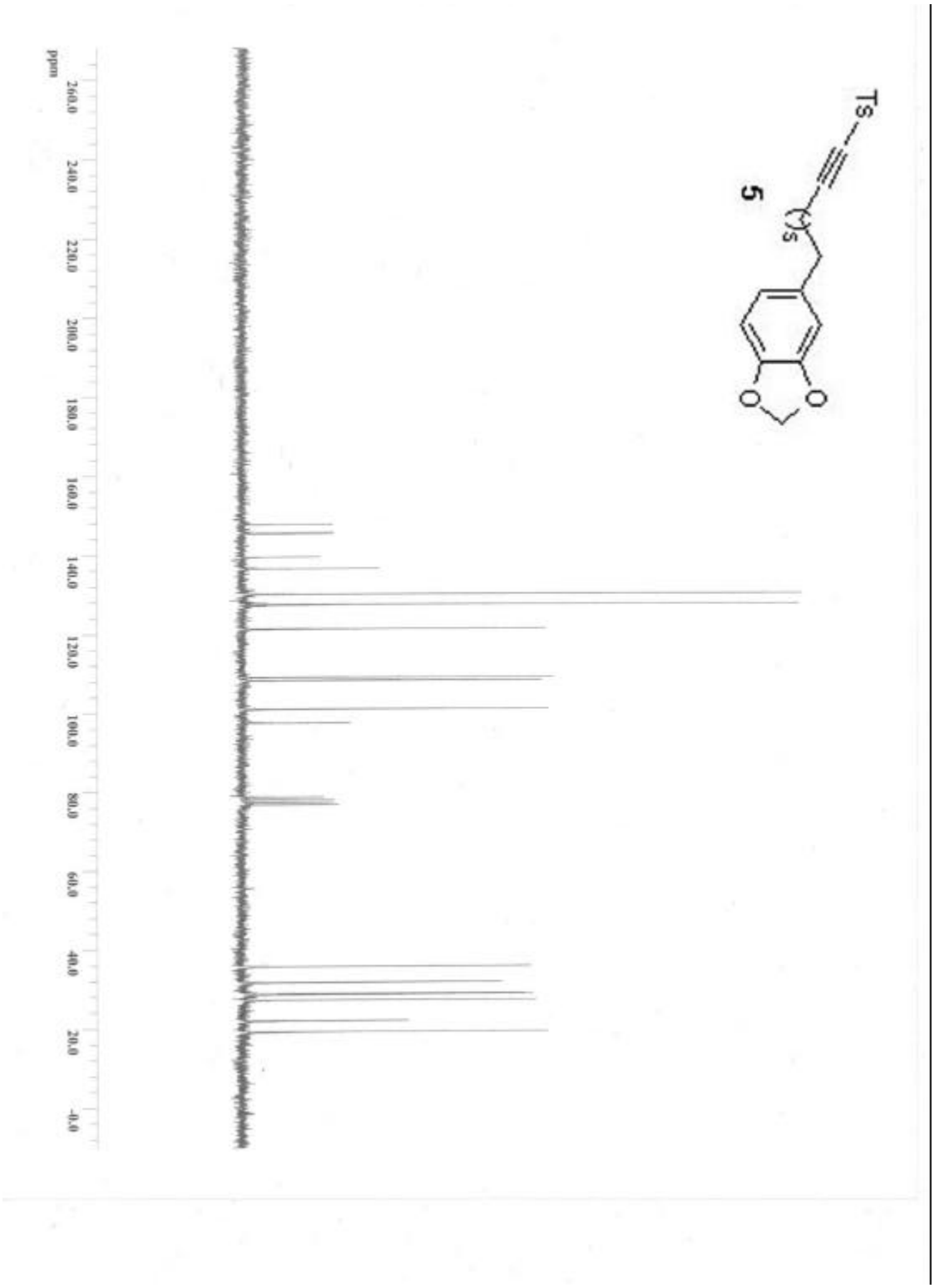
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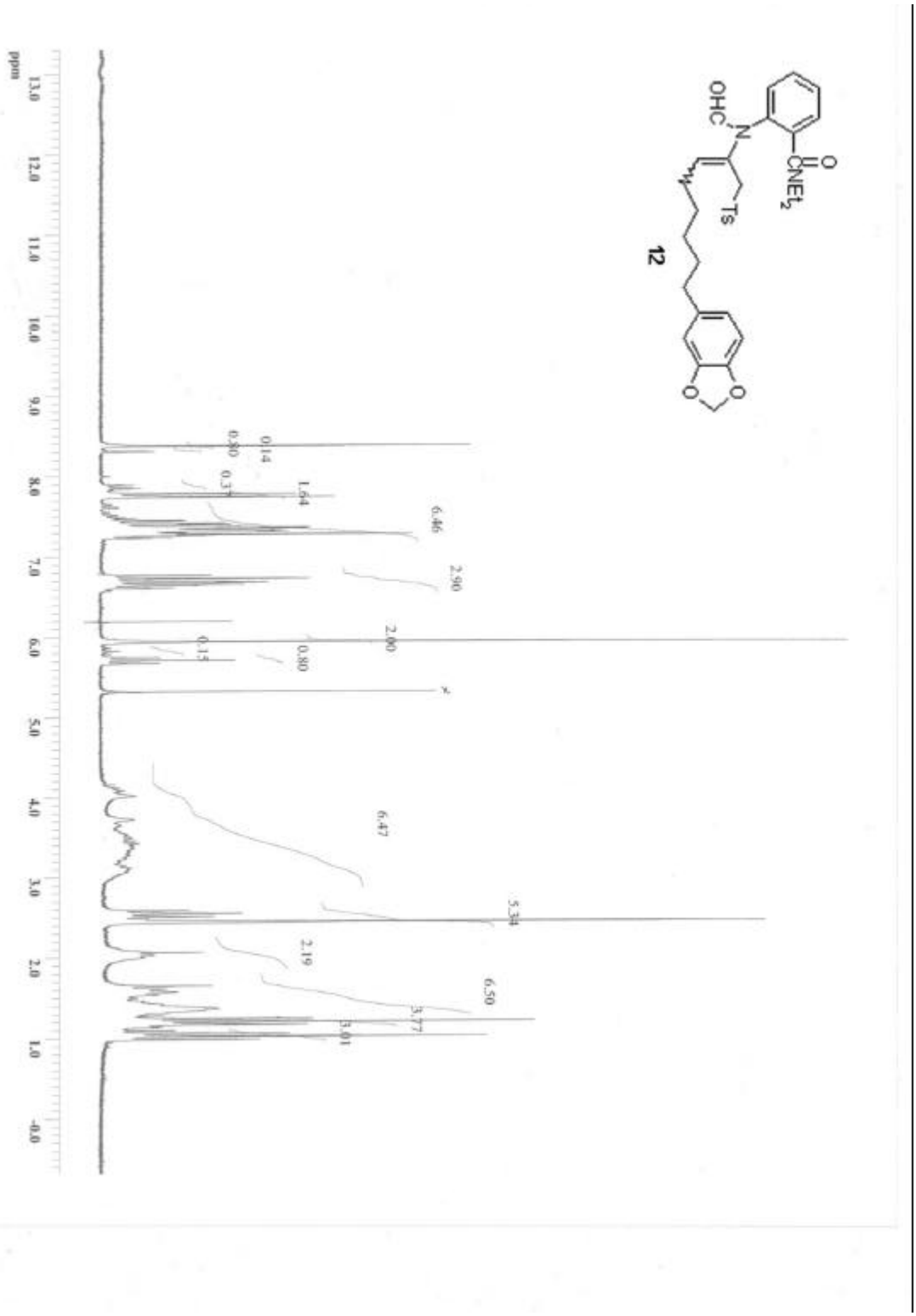
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0.37
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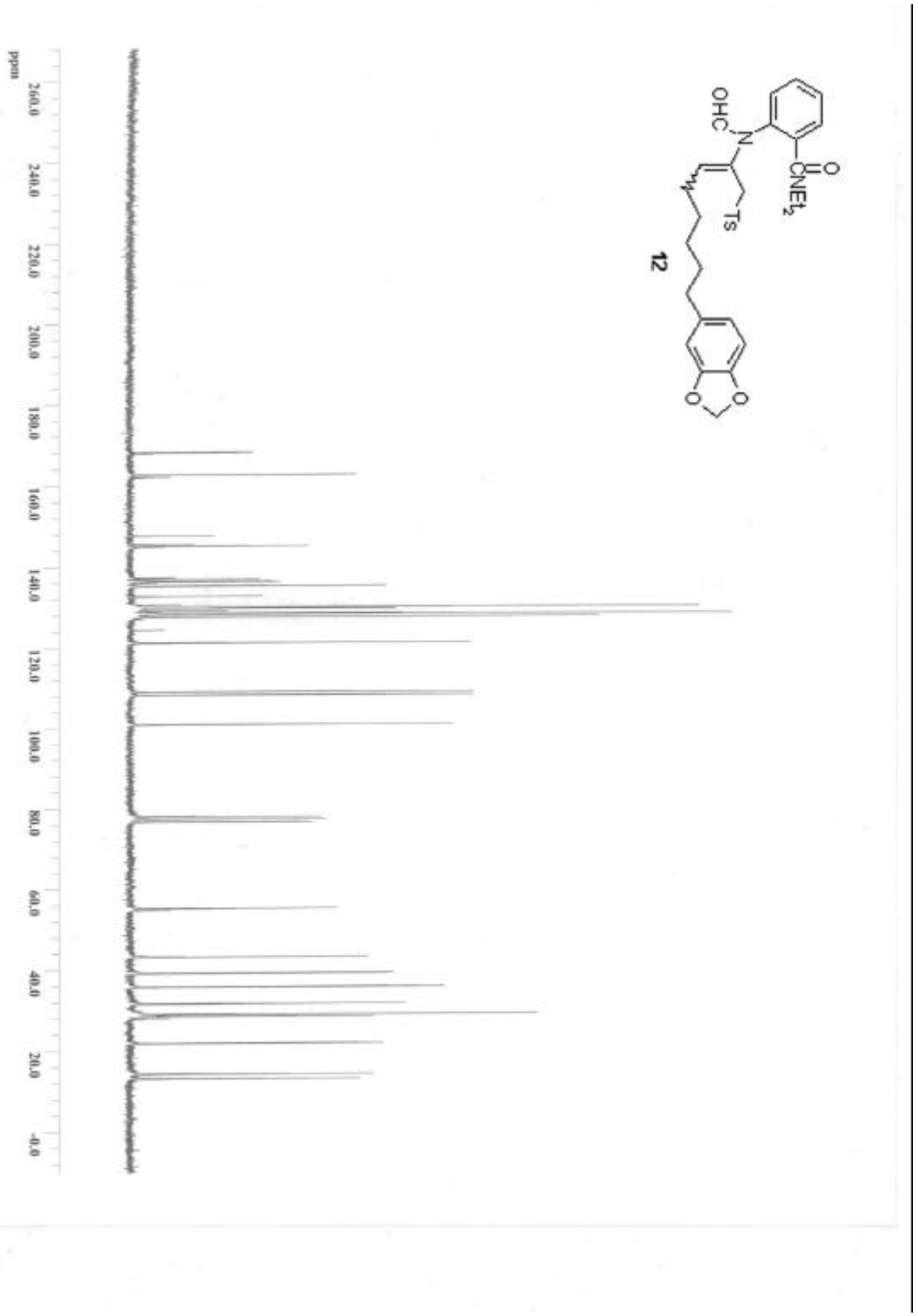
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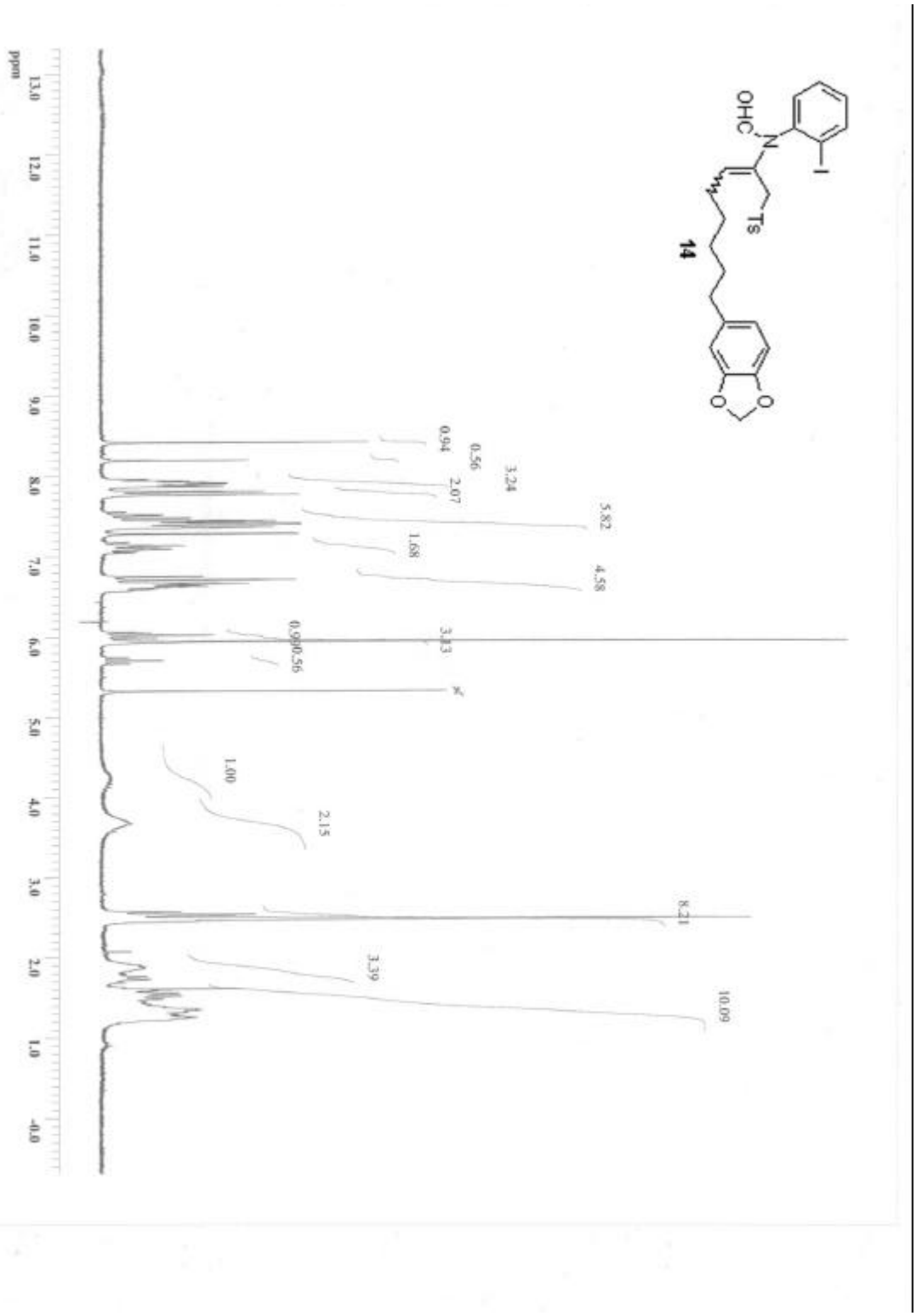
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O
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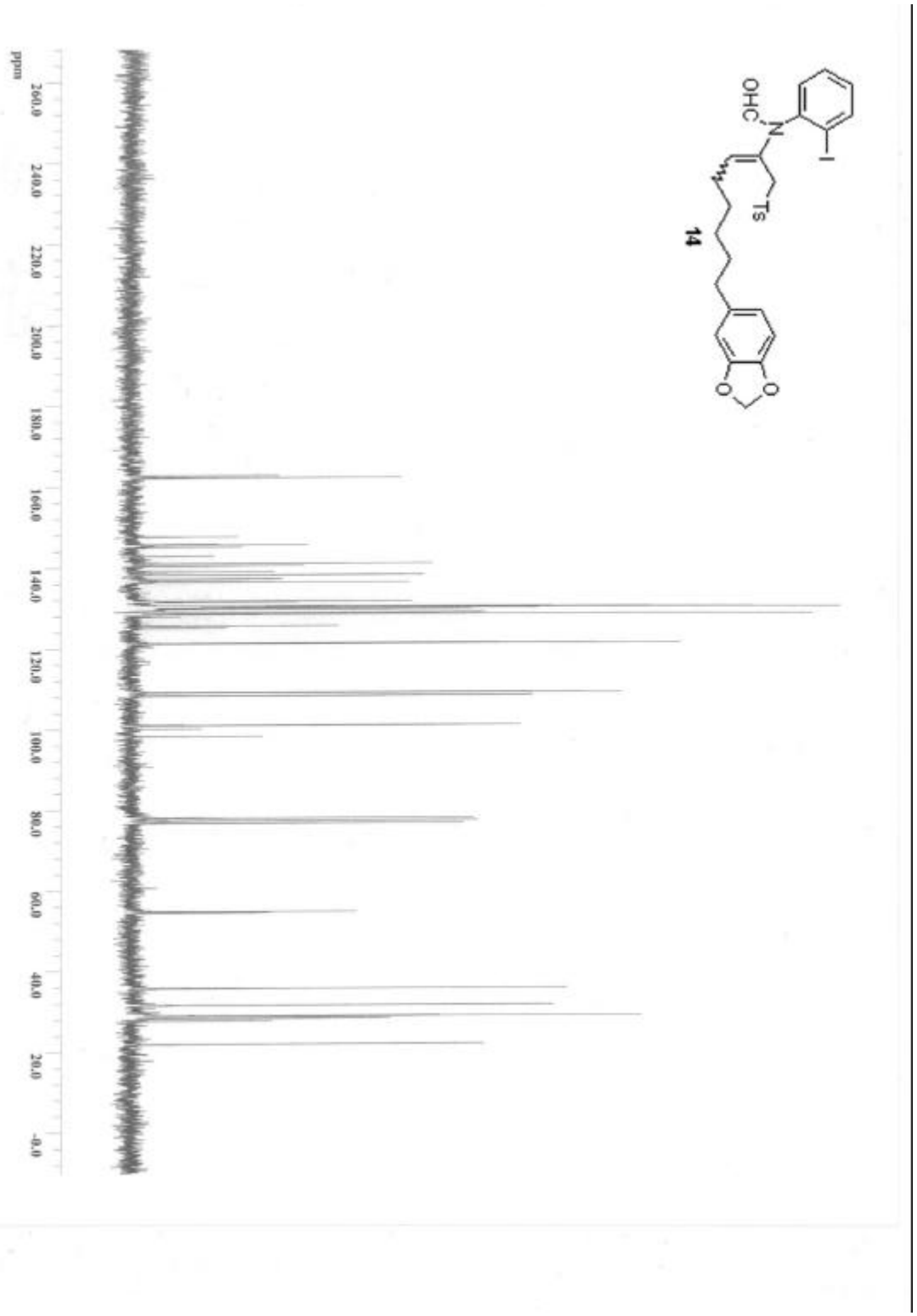
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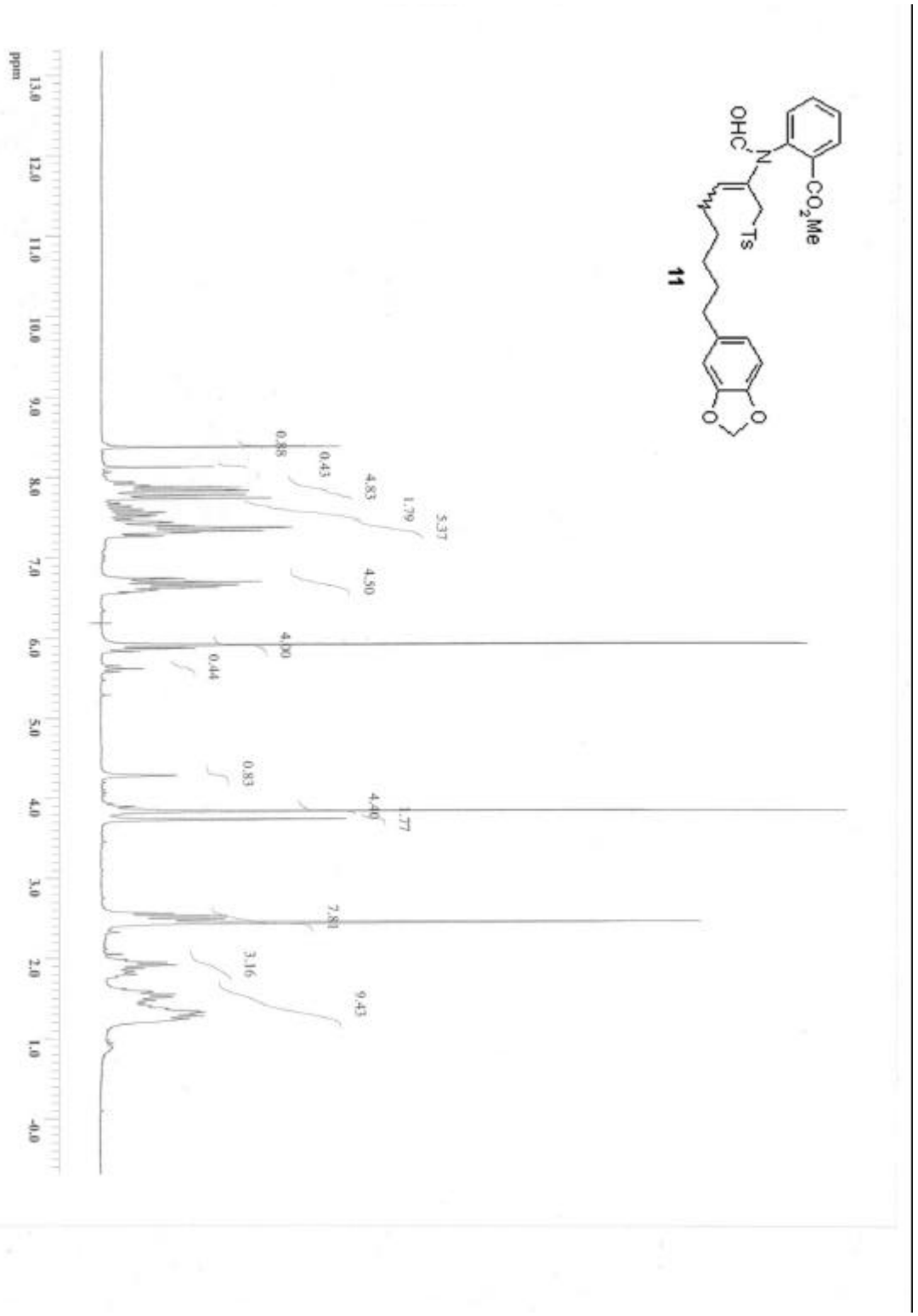
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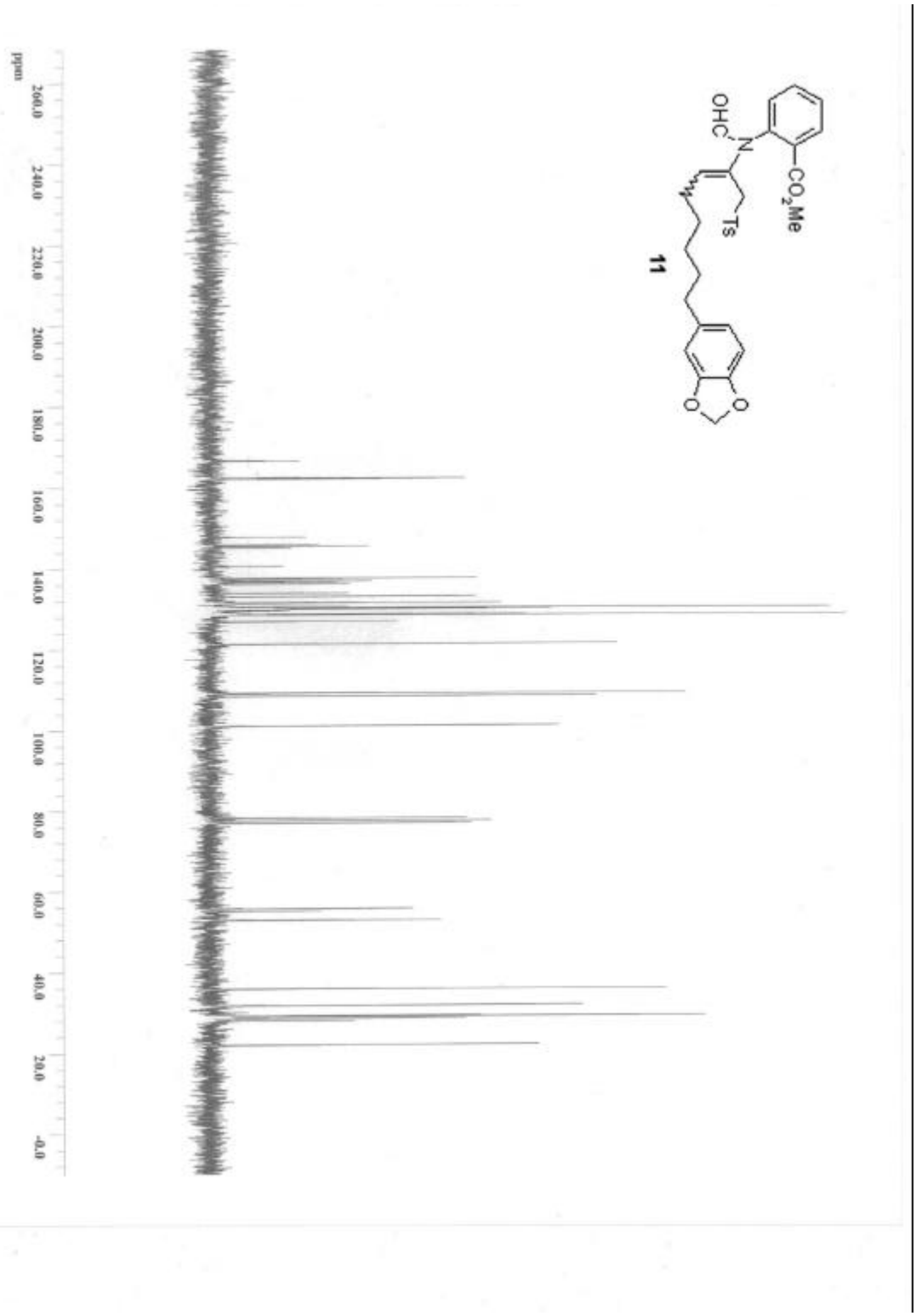
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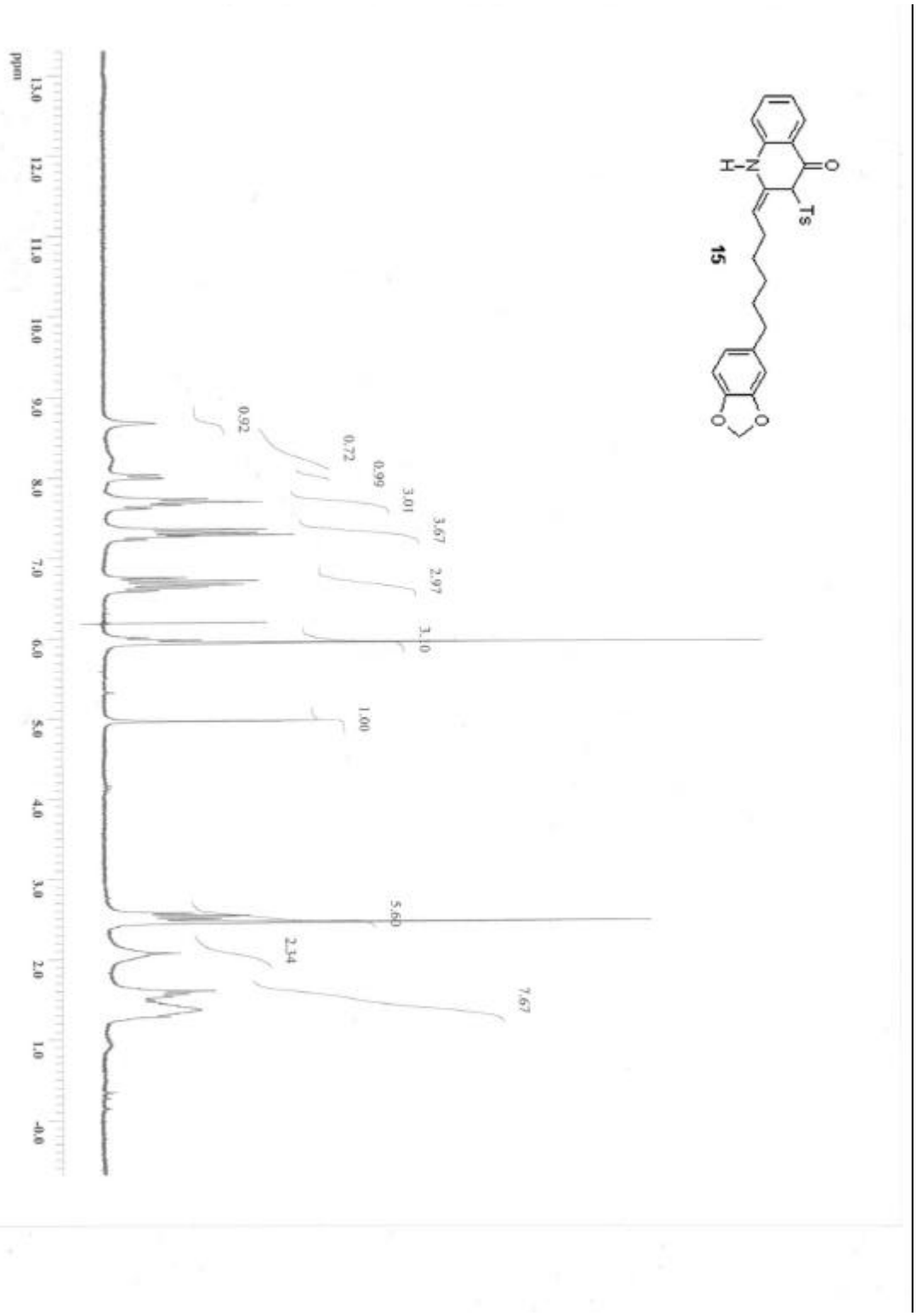
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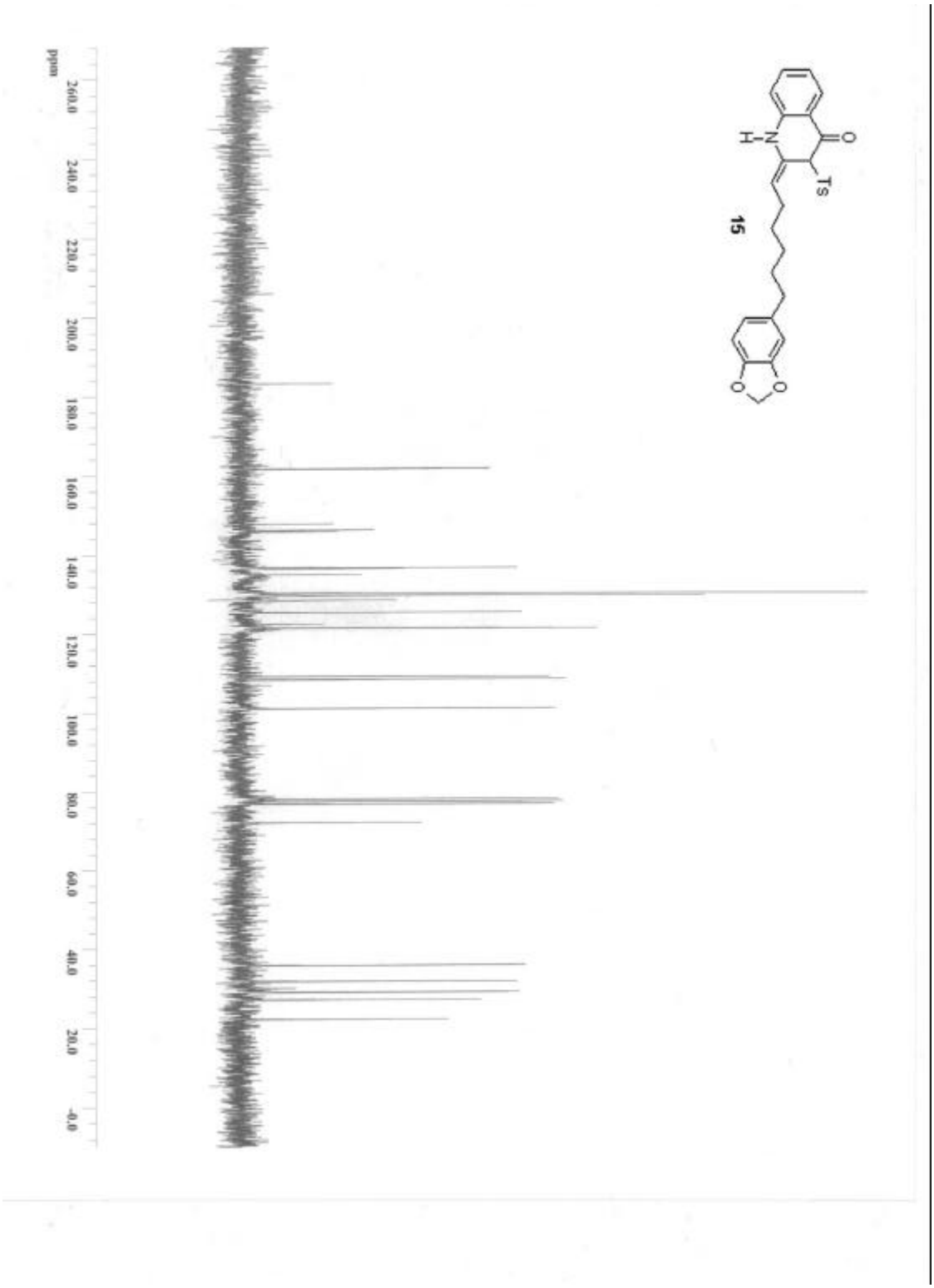
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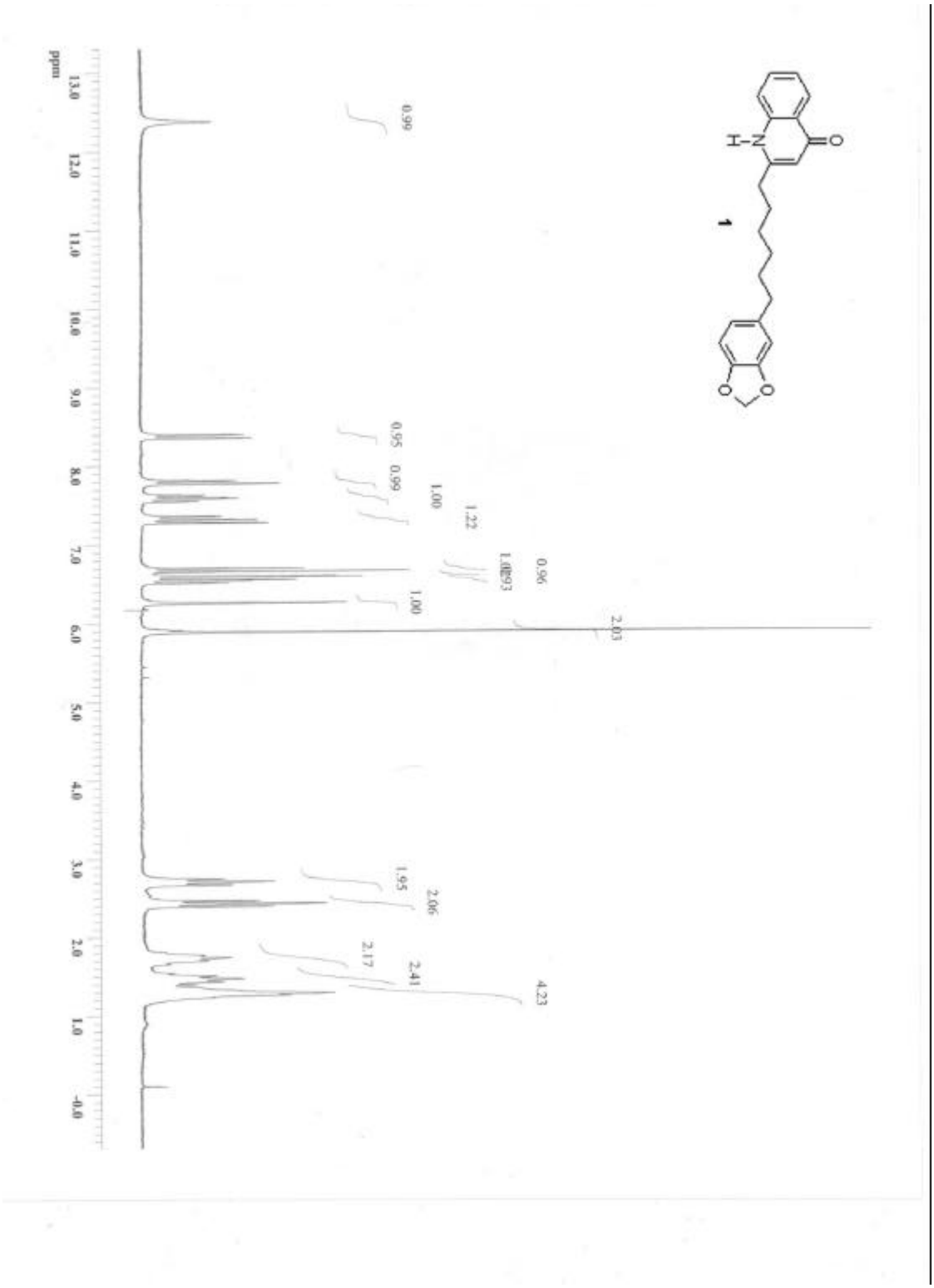
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2.41
4.23
ppm
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12.0
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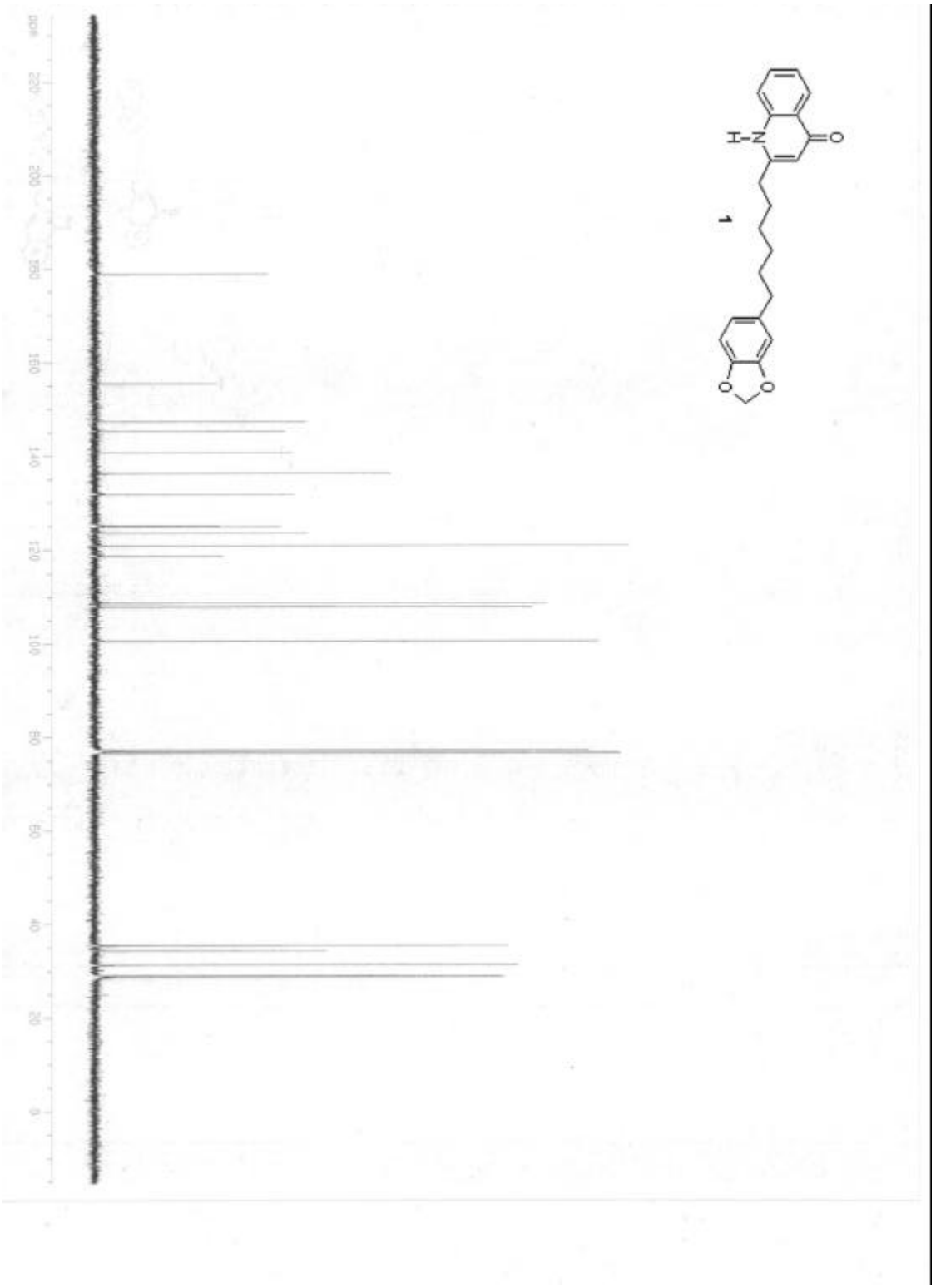
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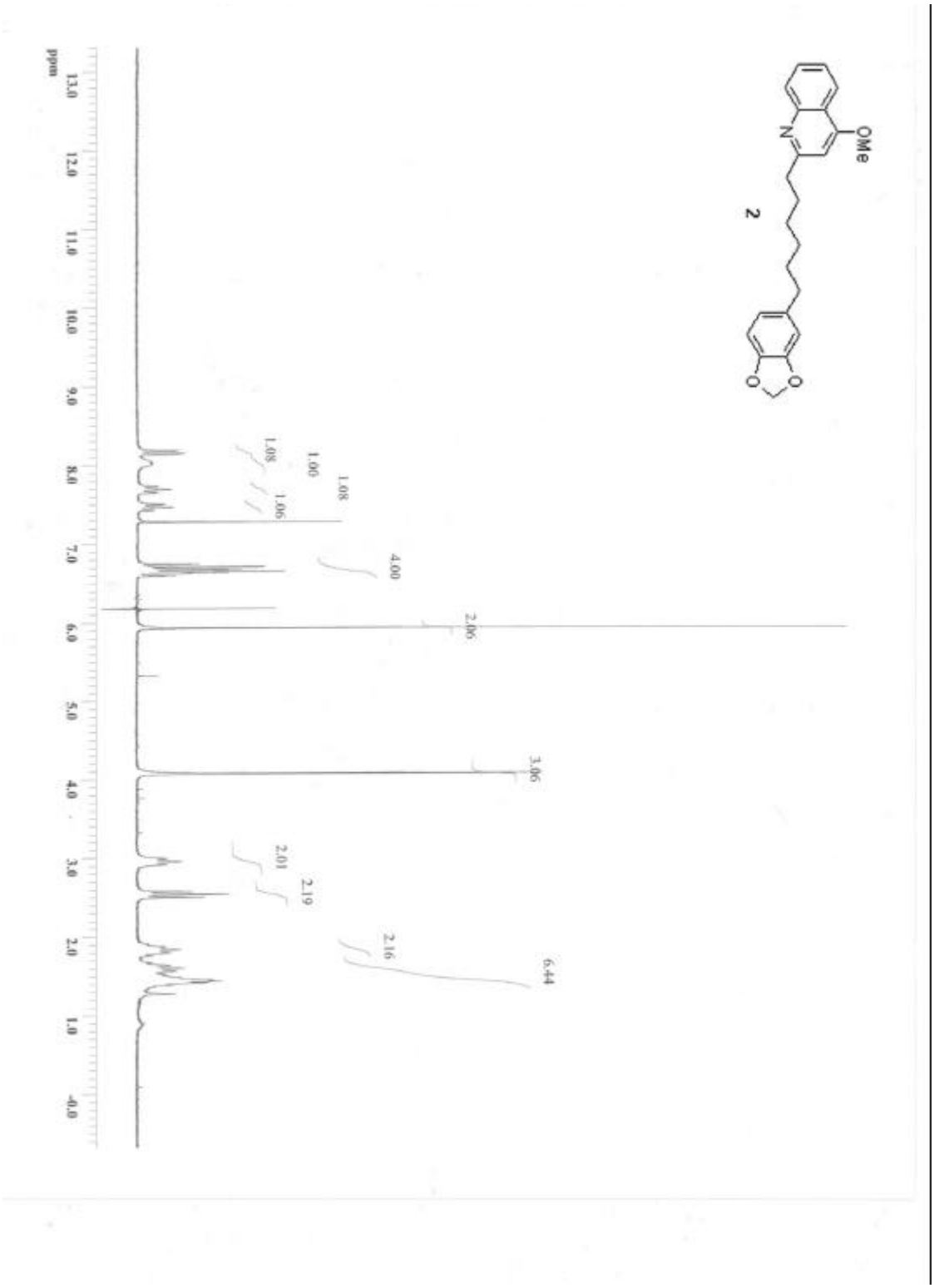
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O
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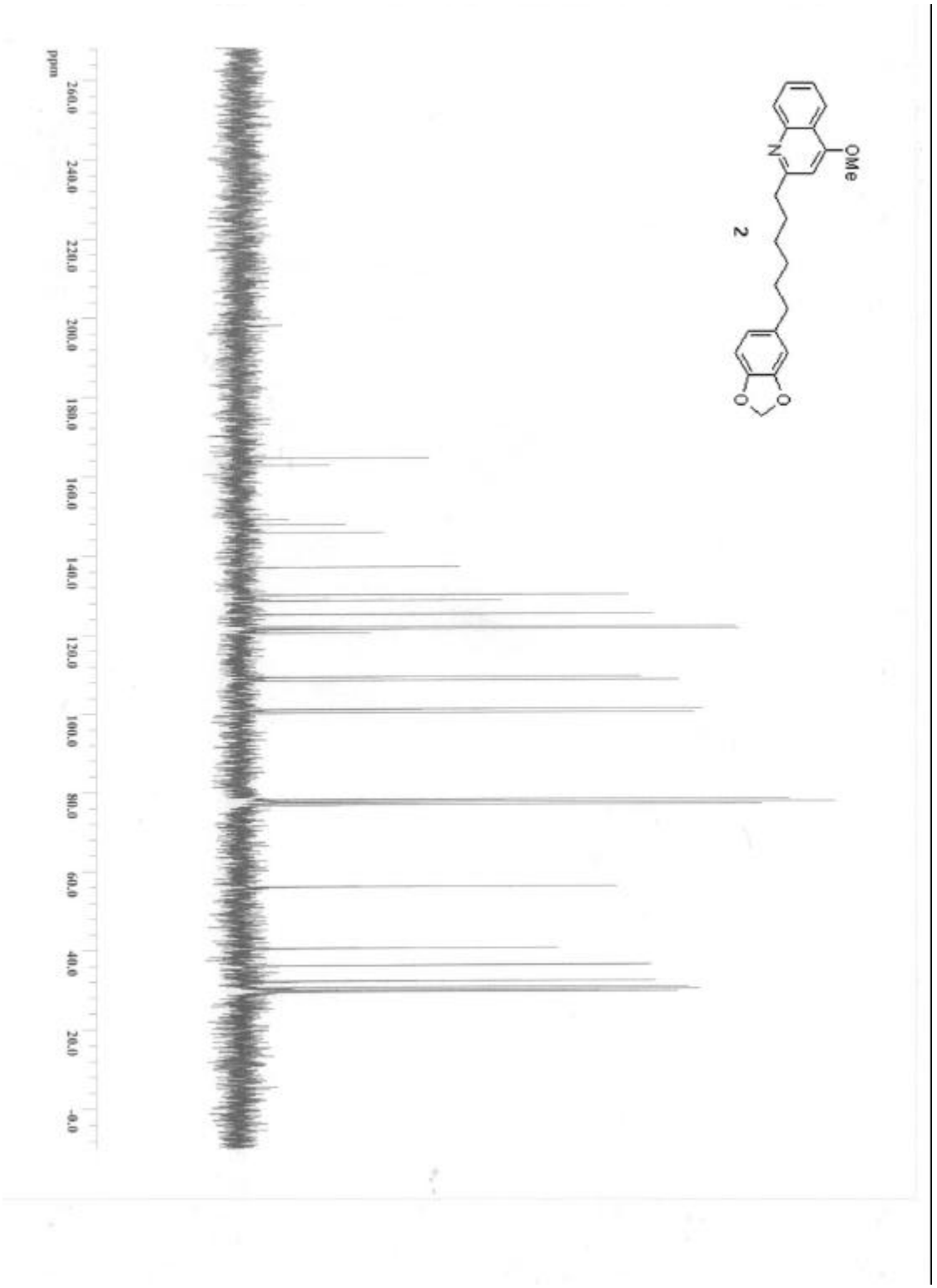
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-0.0
OMe
N
O
O
2