Aerobic Oxidation of Alcohols Enabled by Nitrogen-Doped Copper Nanoparticle Catalysts

Fumiya Tobita, Tomohiro Yasukawa,* Yasuhiro Yamashita and Shū Kobayashi*

Electronic Supplementary Material

Contents

1. General

- JEOL JNM-ECA 500 or ECX 600 spectrometers were used for NMR measurement.
- Chloroform (δ = 7.24) was used as an internal standard for ^{1}H NMR and $CDCl_3$ (δ = 77.0) for ^{13}C NMR. DMSO (δ = 2.49) was used as an internal standard for ^{1}H NMR and DMSO (δ = 39.5) for ^{13}C NMR. Structures of known compounds were confirmed by comparison with commercially available compounds or data shown in literature.
- Preparative thin-layer chromatography was carried out using Wakogel B-5F.
- ICP analysis was performed on Shimadzu ICPS-7510 equipment.
- STEM/EDS images were obtained using a JEOL JEM-2100F instrument operated at 200 kV. All STEM specimens were prepared by placing a drop of the solution on carbon-coated copper grids and allowed to dry in air (without staining).
- GC analysis was performed on Shimadzu GC-2010 apparatus (Column = GL Science, TCWAX, 0.25 mm ID, 0.25 μm, 60.0 m; Gas pressure: 214.2 kPa; Total flow: 90.6 mL/min; Column flow: 1.86 mL/min; Velocity: 30.8 cm/sec; Purge flow: 3.0 mL/min; Sprit ratio: 46.0; Injector: 250 ˚C, FID: 250 ˚C; Column program: starting from 50.0 ˚C, 10 min hold, 10 ˚C/min to 220 ˚C, 5 min hold).
- XPS analysis was performed on JEOL JPS-9010MC with a Mg or an Al Kα X-ray source and the C 1s line at 294.2 eV was used as reference to correct the binding energies.
- Pyrolysis was conducted on ceramic tube furnace ARF-40K. The temperature was controlled by YKC-11 and gradually increased from room temperature to 500 ˚C over ca. 10 minutes.
- 4-Vinylpyridine (stabilized with HQ) was purchased from Sigma Aldrich Co. LLC. and was treated through alumina, activated before use.
- Alumina, Activated, for Column Chromatography, about 75 μm was purchased from Wako Pure Chemical Company.
- Chloroform-d and DMSO-d6 was purchased from Kanto Chemical Co. Inc..
- 2,2'-Azobis(4-methoxy-2,4-dimethylvaleronitrile) (V-70) was purchased from Wako Pure Chemical Company.
- $NaBH_4$ was purchased from Wako Pure Chemical Company and recrystallized from diglyme by heating according to the literature1 and stored in a glove box.
- Ketjen black EC300J was purchased from Lion Corporation.
- Deionized water from a MILLIPORE MilliQ machine (Gradient A 10) was used without further treatment.
- Oxidation reactions in batch were conducted with Carousel™.

- Amberlyst® A-26(OH), ion exchange resin (**A-26**) was purchased from Alfa Aesar.
- SBA-15 was prepared by following the literature.[1]
- 2,2,6,6-Tetramethylpiperidine 1-Oxyl (**TEMPO**) was purchased from Oakwood Products, Inc.
- 4-Acetamido-2,2,6,6-tetramethylpiperidine 1-Oxyl (**amide-TEMPO**) was prepared by following the literature.[2]
- Solvents were purchased in dried grade from Wako Pure Chemical Company and used without further purification.
- Flow reactions were conducted using following equipment,

  Pump: Smooth flow pump Q-5-6R-UP-S from Tacmina Corporation,
  Column heater: Aluminium heating block from Tokyo Rikakikai Co. Ltd.
  Column heater controller: TTM204 from Toho Electronics Inc.
  Mass flow controller: 8500MC from Kofloc Corp..

2. Preparation of NCI-Cu catalysts

2-1. Preparation of poly(4-vinylpyridine)[3]: To a solution of 4-vinylpyridine (6.43 g, 61.2 mmol) in chloroform (11 mL), V-70 (185 mg, 0.6 mmol) was added at room temperature, and the mixture was stirred until fully dissolved. The solution was degassed with sonication under Ar atmosphere and stirred for 48 h at room temperature. The mixture was added slowly to ethyl acetate (1000 mL) to generate precipitation, and the suspension was decanted. The polymer was dissolved in ethanol (5 mL), and reprecipitated for two times, followed by vacuum filtration. The polymer was dried in vacuo to afford poly(4-vinylpyridine) (4.46 g, 69% yield).

2-2. Preparation of NCI-Cu: To a stirring solution of poly(4-vinylpyridine) (150 mg) in ethanol (4 mL), a solution of $Cu(OAc)_2 \cdot H_2O$ (11.2 mg, 0.056 mmol) in ethanol (1 mL) was added dropwise at room temperature under air. To this solution was added ketjen black (250 mg), and the mixture was stirred for 1 h at room temperature under air. To this mixture, a solution of $NaBH_4$ (10.6 mg, 0.28 mmol) in ethanol (1 mL) was slowly added, and the mixture was continued to stir for 2 h at room temperature under air. To this mixture was added ethyl acetate (50 mL) at room temperature and stirred for 30 min. The catalyst was filtered and washed in water (50 mL). The catalyst was filtered and washed in ethyl acetate (50 mL). After filtration, the catalyst was grinded and dried *in vacuo*. The catalyst was treated by pyrolysis at 400℃ for 5 h under Ar atmosphere. After cooling to room temperature, the catalyst was washed in ethanol (30 mL) under

air. The catalyst was filtered, washed with ethanol, water, acetone and dried *in vacuo* to afford NCI-Cu-400-5 h (0.375) (276 mg). NCI-Cu-400-5 h (0.375) (10 mg) was heated in a mixture of sulfuric acid and nitric acid at 200℃, and the mixture was cooled to room temperature. The amount of Cu in the resulting solution was measured by ICP analysis to determine the loading of Cu (0.142 mmol/g).

2-2. Preparation of Copolymer for PI/CB Cu[4]: Styrene (2.1 g), 4-vinylbenzyl glycidyl ether (4.1 g), 2-(2-(2-(2-(4-vinylbenzyloxy)ethoxy)ethoxy)ethoxy)ethanol (6.0 g) and 2, 2'-azobis(4-methoxy)-2,4-dimethylvaleronitrile (V-70, 181.2 mg) were combined in chloroform (11.0 mL). The mixture was stirred for 48 h at room temperature. The resulting polymer solution was slowly poured into ether. Solvent was removed by decantation and remaining precipitated polymers were washed with ether several times. Polymers were dissolved in THF, repeated to precipitate for 2 times and dried *in vacuo* to afford the desired copolymer (6.86 g, 56 % yield). The molar ratio of the components was determined by ^{1}H NMR analysis (*x: y: z* = 29: 35: 36).

2-3. Preparation of PI/CB-Cu: The Copolymer (500.0 mg), ketjen black EC300J (500.0 mg) and $NaBH_4$ (105.9 mg, 2.8 mmol) were combined in diglyme (30 mL) at room temperature, to this solution was slowly added copper(II) acetate monohydrate (55.9 mg, 0.28 mmol) with 2 mL of ethanol. The mixture was stirred for 8 h at room temperature and diethyl ether (200 mL) was slowly added to the mixture at room temperature. After the catalysts, which were black powders, were filtered and crashed, they were washed with diethyl ether several times and dried at room temperature. Next, the catalysts were heated at 150 ˚C for 5 h without solvent. Then the prepared solid was washed with dichloromethane, water and THF and dried to afford black powder. This powder was heated at 170 ˚C for 5 h without solvent to afford PI/CB-Cu. PI/CB-Cu (10-20 mg) was heated in mixture of sulfuric acid and nitric acid at 200 ˚C, the mixture was cooled to room temperature and aqua regia was added. The amount of copper in the resulting solution was measured by ICP analysis to determine the loading of copper.

2-4. Preparation of SBA-15-Cu: To a suspension of SBA-15 (500 mg) in THF (10 mL), $NaBH_4$ (143.8 mg, 3.8 mmol) in diglyme (10 mL) was added at 0 °C. To this solution was slowly added copper(II) acetate monohydrate (69.0 mg, 0.35 mmol) in THF (10 mL). The mixture was stirred for 4 h at room temperature and MeOH (100 mL) was slowly added to the mixture at room temperature. After the catalysts, which were white powders, were filtered and grinded, they were washed with water, THF and dichloromethane and dried to afford SBA-15-Cu. SBA-15-Cu (10-20 mg) was heated in mixture of sulfuric acid and nitric acid at 200 ˚C, the mixture was cooled to room temperature and aqua regia was added. The amount of copper in the resulting solution was measured by ICP analysis to determine the loading of copper.

3. Aerobic oxidation of alcohols to aldehydes in batch

3-1. A typical procedure of aerobic oxidation of alcohols to aldehydes catalyzed by NCI-Cu: NCI-Cu-400-5 h (0.375) (Cu: 1 mol%) was added in a Carousel^{TM} tube and dried with heat gun *in vacuo*. 4-methyl benzyl alcohol (24.4 mg, 0.20 mmol), 2,2,6,6-tetramethylpiperidine 1-oxyl (1.6 mg, 0.01 mmol), 1-methylimidazole (1.6 μl, 0.02 mmol) and acetonitrile (1 mL) were added to the Carousel tube^{TM}. The mixture was stirred for 20 h under 1 bar of O_2 atmosphere at 60℃. If necessary, anisole (25~30 mg) as an internal standard was added to the mixture, and an aliquot of the reaction mixture (~0.02 mL) was filtered through a silica gel packed disposable Pasteur pipette and washed with ethyl acetate to inject to the GC analysis. Diethyl ether was added to the mixture and the solid catalyst was removed by filtration. After that, the solvents were removed *in vacuo* and the residue was purified by preparative TLC to afford methyl 4-methylbenzaldehyde.

3-2. A typical procedure of aerobic oxidation of alcohols to aldehydes catalyzed by NCI-Cu in batch (Other aromatic alcohols): NCI-Cu-400-5 h (0.375) (Cu: 1 mol%) was added in a Carousel^{TM} tube and dried with heat gun *in vacuo*. An alcohol (0.20 mmol), 2,2,6,6-tetramethylpiperidine 1-oxyl (1.6 mg, 0.01 mmol), 1-methylimidazole (0.80-1.6 μl, 0.01-0.02 mmol) and acetonitrile (1 mL) were added to the Carousel tube^{TM}. The mixture was stirred for 20 h under 1 bar of O_2 atmosphere at 60℃. If necessary, anisole (25~30 mg) as an internal standard was added to the mixture, and an aliquot of the reaction mixture (~0.02 mL) was filtered through a silica gel packed disposable Pasteur pipette and washed with ethyl acetate to inject to the GC analysis. Ethyl acetate was added to the mixture and the solid catalyst was removed by filtration. After that, the solvents

were removed *in vacuo* and the residue was purified by preparative TLC to afford a corresponding aldehyde.

3-3. A typical procedure of aerobic oxidation of alcohols to aldehydes catalyzed by NCI-Cu in batch (aliphatic alcohols): NCI-Cu-400-5 h (0.375) (Cu: 2 mol%) was added in a Carousel^{TM} tube and dried with heat gun *in vacuo*. An alcohol (0.20 mmol), 2,2,6,6-tetramethylpiperidine 1-oxyl (9.4 mg, 0.06 mmol), 1-methylimidazole (0.80 μl, 0.01 mmol) and acetonitrile (1 mL) were added to the Carousel tube^{TM}. The mixture was stirred for 20 h under 1 bar of O_2 atmosphere at 60℃. Anisole (25~30 mg) as an internal standard was added to the mixture, and an aliquot of the reaction mixture (~0.02 mL) was filtered through a silica gel packed disposable Pasteur pipette and washed with ethyl acetate to inject to the GC analysis to determine the yield. Ethyl acetate was added to the mixture and the solid catalyst was removed by filtration. After that, the solvents were removed *in vacuo* and the residue was purified by preparative TLC to afford a corresponding aldehyde.

3-4. Recovery and reuse experiments: NCI-Cu-400-5 h (0.375) (Cu: 1 mol%) was added in a Carousel^{TM} tube and dried with heat gun *in vacuo*. 4-methyl benzyl alcohol (48.8 mg, 0.40 mmol), 2,2,6,6-tetramethylpiperidine 1-oxyl (3.2 mg, 0.02 mmol), 1-methylimidazole (3.2 μl, 0.04 mmol) and acetonitrile (2 mL) were added to the Carousel tube^{TM}. The mixture was stirred for 20 h under 1 bar of O_2 atmosphere at 60℃. If necessary, anisole (25~30 mg) as an internal standard was added to the mixture, and an aliquot of the reaction mixture (~0.02 mL) was filtered through a silica gel packed disposable Pasteur pipette and washed with ethyl acetate to inject to the GC analysis. The catalyst was separated by centrifugation under Ar atmosphere. The supernatant was removed by syringe. The catalyst was washed with 3 mL of ethyl acetate for three times under Ar atmosphere and was subsequently dried under vacuum for the next run.

4. Aerobic oxidation of alcohols to aldehydes in flow

4-1. A typical procedure of aerobic oxidation of alcohols to aldehydes catalyzed by NCI-Cu in flow: A MeCN solution of benzyl alcohol (0.2 M), 2,2,6,6-tetramethylpiperidine 1-oxyl (5.0 mol%), 1-methylimidazole (5.0 mol%) was prepared in the volumetric flask. The heterogeneous NCI-Cu catalysts (0.6-0.7 g) were packed into the SUS column reactor (inner diameter = 10 mm, length = 50 mm L, column volume = 3.93 mL). Also, tiny amounts of cotton were packed into both sides of the column as a

filter. The column reactor was placed in the lab-made continuous-flow synthesis system. The column was set vertically and the flow reactions were performed with downward flow. The column reactor was washed with toluene (0.025 mL•min^{-1}) at 60 ºC for 30 min. After connecting O_2 gas line (2.0-12 mL•min^{-1}), the internal pressure of the column reactor was increased to 0.15 - 0.2 MPa. After the internal pressure have stabilized, MeCN solution of benzyl alcohol (0.025 mL•min^{-1}) and O_2 gas (2.0-12 mL•min^{-1}) were continuously flowed into the column reactor. The reaction solution containing the desired benzaldehyde was collected from the outlet and analyzed by gas chromatography (GC).

4-2. A typical procedure of aerobic oxidation of alcohols to aldehydes catalyzed by NCI-Cu in flow (Substrate scope): A MeCN solution of an alcohol (0.2 M), 2,2,6,6-tetramethylpiperidine 1-oxyl (5.0 mol%), 1-methylimidazole (5.0 mol%) was prepared in the volumetric flask. The heterogeneous NCI-Cu catalysts (0.6-0.7 g) were packed into the SUS column reactor (inner diameter = 10 mm, length = 50 mm L, column volume = 3.93 mL). Also, tiny amounts of cotton were packed into both sides of the column as a filter. The column reactor was placed in the lab-made continuous-flow synthesis system. The column was set vertically and the flow reactions were performed with downward flow. The column reactor was washed with toluene (0.025 mL•min^{-1}) at 60 ºC for 30 min. After connecting O_2 gas line (12 mL•min^{-1}), the internal pressure of the column reactor was increased to 0.15 - 0.2 MPa. After the internal pressure have stabilized, MeCN solution of benzyl alcohol (0.025 mL•min^{-1}) and O_2 gas (12 mL•min^{-1}) were continuously flowed into the column reactor. The reaction solution containing the desired aldehyde was collected 5 h and 10 h after the start of the reaction and analyzed by gas chromatography (GC).

4-3. An application to sequential- and continuous-flow systems: A toluene solution of benzyl alcohol (0.2 M), 2,2,6,6-tetramethylpiperidine 1-oxyl (5.0 mol%), 1-methylimidazole (5.0 mol%) was prepared in the volumetric flask. The heterogeneous NCI-Cu catalysts (0.6-0.7 g) were packed into the SUS column reactor (inner diameter = 10 mm, length = 50 mm L, column volume = 3.93 mL). Also, tiny amounts of cotton were packed into both sides of the column as a filter. The column reactor was placed in the lab-made continuous-flow synthesis system. The column was set vertically and the flow reactions were performed with downward flow. The column reactor was washed with toluene (0.075 mL•min^{-1}) at 60 ºC for 30 min. After connecting O_2 gas line (36 mL•min^{-1}), the internal pressure of the column reactor was increased to 0.15 - 0.2 MPa. After the internal pressure have stabilized, MeCN solution of benzyl alcohol (0.075 mL•min^{-1}) and O_2 gas (36 mL•min^{-1}) were continuously flowed into the column reactor.

The reaction solution containing the desired benzaldehyde was collected in a volumetric flask to remove O_2 gas. The crude solution and a toluene/iPrOH (4/1) solution of α-tetralone (1.2 equiv) were flowed into another volumetric flask and stirred, then the mixed solution was flowed into the second SUS column reactor (inner diameter = 10 mm, length = 150 mm L, column volume = 11.8 mL) packed with A-26 (11 g). The column was set vertically and the flow reactions were performed with upward flow. The desired unsaturated ketone **5** was obtained from the outlet and the crude solution was analyzed by gas chromatography (GC). A-26 catalysts were washed by toluene/iPrOH (4/1) solution in advance.

4-4. Further conversion of ketone 5 to dihydropyrimidinone 6 in batch: 1 mL of the crude solution (0.2 M) containing unsaturated ketone **5** after sequential- and continuous-flow reaction was added in a Carousel^{TM} tube and dried *in vacuo*. Then, thiourea (30.4 mg, 0.40 mmol) and A-26 (100 mg) and *i*PrOH (1 mL) were added to the Carousel tube^{TM}. The mixture was stirred for 24 h at 80℃. After 24 h, the precipitation was filtered and was washed with DCM to obtain pure dihydropyrimidinone **6** (78%, over 3 steps).

5. Kinetic study

5-1. Kinetic study in flow: A MeCN solution of benzyl alcohol (0.2 M), 2,2,6,6-tetramethylpiperidine 1-oxyl (5.0 mol%), 1-methylimidazole (5.0 mol%) was prepared in the volumetric flask. The heterogeneous NCI-Cu catalysts (0.6-0.7 g) were packed into the SUS column reactor (inner diameter = 10 mm, length = 50 mm L, column volume = 3.93 mL). Also, tiny amounts of cotton were packed into both sides of the column as a filter. The column reactor was placed in the lab-made continuous-flow synthesis system. The column was set vertically and the flow reactions were performed with downward flow. The column reactor was washed with toluene (0.25-0.45 mL•min^{-1}) at 60 ºC for 30 min. After connecting air or O_2 gas line (2.0-12 mL•min^{-1}), the internal pressure of the column reactor was increased to 0.15 - 0.2 MPa. After the internal pressure have stabilized, MeCN solution of benzyl alcohol (0.25-0.45 mL•min^{-1}) and air or O_2 gas (2.0-12 mL•min^{-1}) were continuously flowed into the column reactor. The reaction solution

containing the desired benzaldehyde was collected from the outlet and analyzed by gas chromatography (GC).

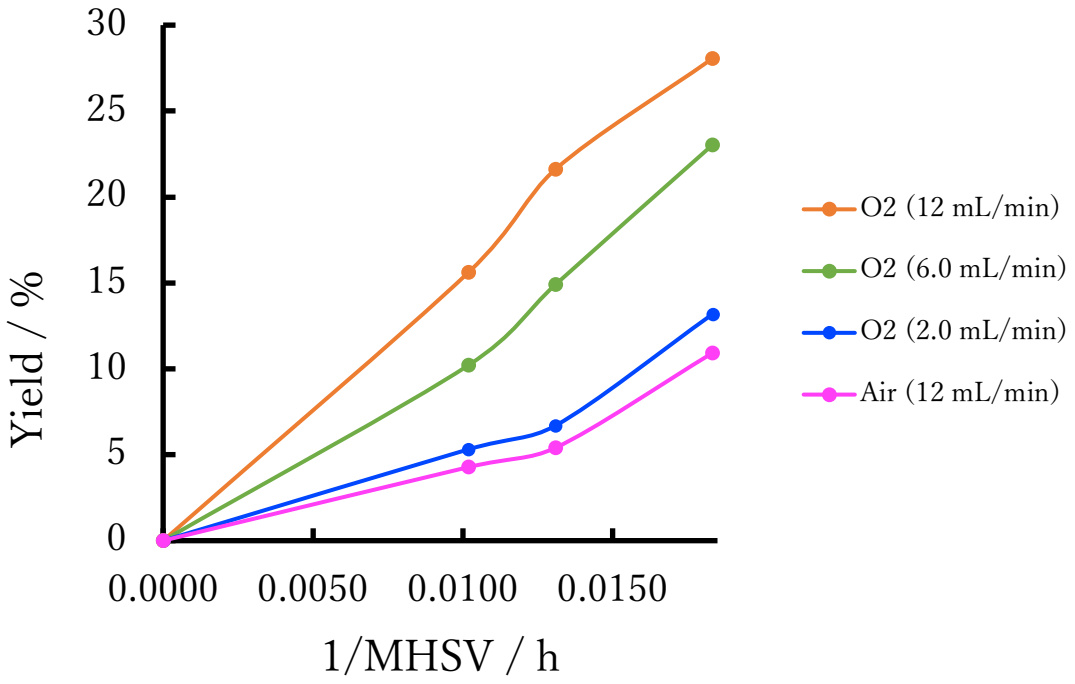


Figure S1. Kinetic study with a different flow rate of O2 or air in flow

5-2. Kinetic study with additives in batch: NCI-Cu-400-5 h (0.375) (Cu: 1 mol%) was added in a Carousel^{TM} tube and dried with heat gun *in vacuo*. 4-methyl benzyl alcohol (24.4 mg, 0.20 mmol), 2,2,6,6-tetramethylpiperidine 1-oxyl (1.6 mg, 0.01 mmol), 1-methylimidazole (1.6 μl, 0.02 mmol), additives (1-methylimidazole, H_2O or piperidine **7**) and acetonitrile (1 mL) were added to the Carousel tube^{TM}. The mixture was stirred for 20 h under 1 bar of O_2 atmosphere at 60 ℃. If necessary, anisole (25~30 mg) as an internal standard was added to the mixture, and an aliquot of the reaction mixture (~0.02 mL) was filtered through a silica gel packed disposable Pasteur pipette and washed with ethyl acetate to inject to the GC analysis.

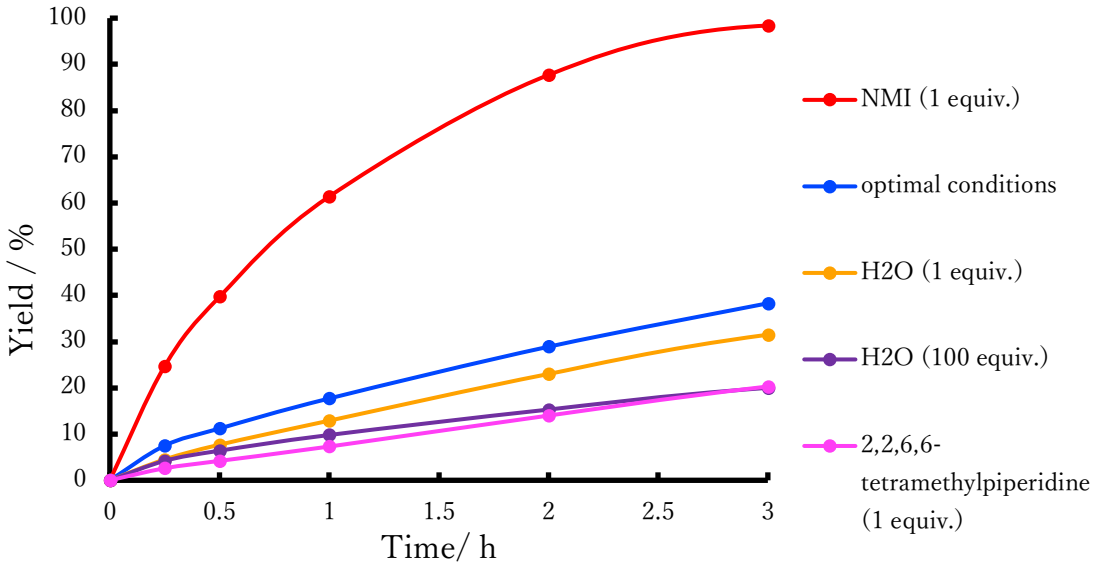
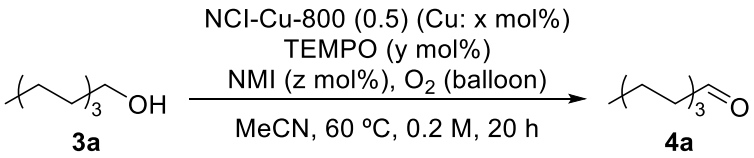


Figure S2. Kinetic study with additives in batch

6. Control experiments

Table S1. Control studies

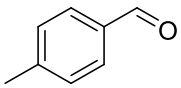


entry	x	y	z	yield (%)[a]
1	1	5	10	15
2	1	0	10	0
3	1	5	0	7
4	0	5	10	0

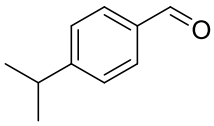
[a] Determined by GC analysis.

7. Compound characterization

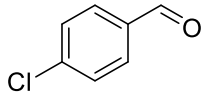
4-Methylbenzaldehyde (2a)[5]: Colorless liquid; determined by GC analysis. ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.41 (s, 3H), 7.30 (d, 2H, J = 7.6 Hz), 7.75 (d, 1H, J = 8.3 Hz), 9.95 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 21.8, 129.7, 129.8, 134.2, 145.5, 191.9.



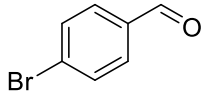
4-Isopropylbenzaldehyde (2b)[6]: Colorless liquid; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 1.28 (d, 6H, J = 6.8 Hz), 2.99 (septet, 1H, J = 6.8 Hz), 7.39 (d, 2H, J = 7.9 Hz), 7.81 (d, 2H, J = 7.9 Hz), 9.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 23.6, 34.4, 127.1, 129.9, 134.5, 156.2, 192.0.



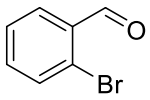
4-Chlorobenzaldehyde (2c)[5]: Colorless solid; ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 7.52 (d, 2H, J = 8.3 Hz), 7.83 (d, 2H, J = 8.3 Hz), 9.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 129.4, 130.9, 134.7, 140.9, 190.8.



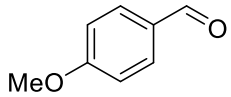
4-Bromobenzaldehyde (2d)[5]: Colorless solid; ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 7.68 (d, 1H, J = 8.3 Hz), 7.74 (d, 1H, J = 8.3 Hz), 9.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 129.7, 130.9, 132.4, 135.0, 191.0.



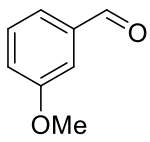
2-Bromobenzaldehyde (2e)[5]: Colorless solid; ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 7.42-7.47 (m, 2H), 7.65-7.66 (m, 1H), 7.92 (dt, 1H, J = 6.9, 1.4 Hz), 10.37 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 127.1, 127.9, 129.9, 133.5, 133.9, 135.3, 191.8.



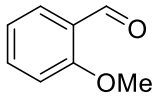
4-Methoxybenzaldehyde (2f)[5]: Colorless liquid; ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 3.85 (s, 3H), 6.97 (d, 2H, J = 8.9 Hz), 7.80 (d, 2H, J = 8.9 Hz), 9.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 55.5, 114.2, 129.9, 131.9, 164.6, 190.7.



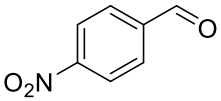
3-Methoxylbenzaldehyde (2g)[7]: Colorless liquid; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 3.86 (s, 3H), 7.18 (td, 1H, J = 4.5, 2.4 Hz), 7.39 (d, 1H, J = 2.3 Hz), 7.42-7.46 (m, 2H), 9.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 55.0, 111.6, 121.1, 123.1, 129.6, 137.3, 159.7, 191.7.



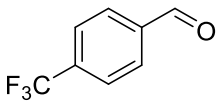
2-Methoxylbenzaldehyde (2h)[7]: Colorless liquid; ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 3.94 (s, 3H), 7.00 (d, 1H, J = 8.3 Hz), 7.03 (t, 1H, J = 7.2 Hz), 7.54-7.57 (m, 1H), 7.84 (dd, 1H, J = 7.5, 1.4 Hz), 10.48 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 55.6, 111.6, 120.6, 124.8, 128.5, 135.9, 161.8, 189.8.



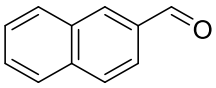
4-Nitrobenzaldehyde (2i)[5]: Pale yellow solid; ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 8.08 (d, 2H, J = 8.9 Hz), 8.39 (d, 2H, J = 8.3 Hz), 10.16 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 124.3, 130.4, 140.0, 151.1, 190.3.



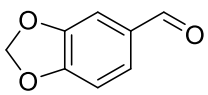
4-(Trifluoromethyl)benzaldehyde (2j)[5]: Colorless liquid; ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 7.81 (d, 2H, J = 8.3 Hz), 8.01 (d, 2H, J = 7.6 Hz), 10.10 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 123.4 (q, J = 271.5 Hz), 126.1 (q, J = 4.3 Hz), 129.9, 135.6 (q, J = 33.0 Hz), 138.6, 191.0.



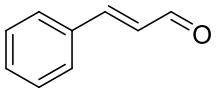
2-Naphthaldehyde (2k)[5]: Pale orange solid; ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 7.58 (dd, 1H, J = 8.3, 6.9 Hz), 7.64 (t, 1H, J = 7.2 Hz), 7.89 (d, 1H, J = 8.3 Hz), 7.91-7.96 (m, 2H), 7.99 (d, 1H, J = 7.6 Hz), 8.32 (s, 1H), 10.15 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 122.7, 127.0, 128.0, 129.0, 129.1, 129.5, 132.6, 134.0, 134.5, 136.4, 192.2.



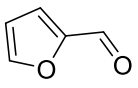
Piperonal (2l)[5]: Colorless solid; ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 6.07 (s, 2H), 6.93 (d, 1H, J = 8.3 Hz), 7.33 (d, 1H, J = 1.4 Hz), 7.41 (dd, 1H, J = 7.9, 1.7 Hz), 9.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 102.0, 106.8, 108.3, 128.6, 131.8, 148.6, 153.0, 190.2.



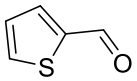
***trans*-Cinnamaldehyde (2m)[5]:** Colorless liquid; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 6.73 (dd, 1H, J = 15.9, 7.4 Hz), 7.41-7.46 (m, 3H), 7.48 (d, 1H, J = 15.9 Hz), 7.56-7.58 (m, 2H), 9.71 (d, 1H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 128.4, 128.6, 129.1, 131.2, 134.0, 152.7, 193.7.



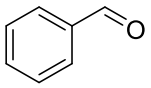
Furfural (2n)[8]: Colorless liquid; ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 6.59 (dd, 1H, J = 3.4, 1.4 Hz), 7.24 (d, 1H, J = 3.4 Hz), 7.68 (s, 1H), 9.65 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 112.4, 121.1, 147.9, 152.7, 177.6.



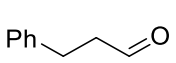
Thiophene-2-carboxaldehyde (2o)[5]: Colorless liquid; ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 7.22 (t, 1H, J = 4.5 Hz), 7.77 (d, 1H, J = 4.8 Hz), 7.79 (d, 1H, J = 4.1 Hz), 9.95 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 127.8, 134.6, 135.8, 143.5, 182.4.



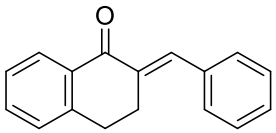
Benzaldehyde (2p)[5]: Colorless liquid; ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 7.53 (t, 2H, J = 7.6 Hz), 7.61-7.64 (m. 1H), 7.88 (d, 2H, J = 6.9 Hz), 10.02 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 128.9, 129.7, 134.4, 136.4, 192.3.



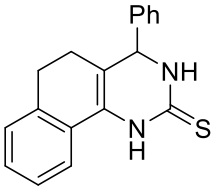
3-Phenylpropionaldehyde (4b)[8]: Colorless liquid; ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.77 (t, 2H, J = 7.6 Hz), 2.95 (t, 2H, J = 7.6 Hz), 7.18-7.21 (m, 3H), 7.28 (t, 2H, J = 7.6 Hz), 9.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 28.1, 45.2, 126.3, 128.2, 128.6, 140.3, 201.5.



(*E*)-2-Benzylidene-3,4-dihydronaphthalen-1(2H)-one (5)[9]: Colorless solid; ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.94 (t, 2H, J = 6.5 Hz), 3.12 (td, 2H, J = 6.5, 2.1 Hz), 7.24 (d, 1H, J = 6.9 Hz), 7.33-7.36 (m, 2H), 7.39-7.44 (m, 4H), 7.48 (td, 1H, J = 7.6, 1.4 Hz), 7.86 (s, 1H), 8.12 (dd, 1H, J = 8.3, 1.4 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 27.2, 28.9, 127.0, 128.17, 128.22, 128.4, 128.5, 129.9, 133.3, 133.5, 135.5, 135.8, 136.6, 143.2, 187.9.



4-Phenyl-3,4,5,6-tetrahydrobenzo[h]quinazoline-2(1H)-thione (6)[10]: White solid; ^{1}H-NMR (DMSO-d_6, 600 MHz) δ = 1.80-1.86 (m, 1H), 2.15-2.20 (m, 1H), 2.54-2.60 (m, 1H), 2.68-2.74 (m, 1H), 4.94 (s, 1H), 7.15 (d, 1H, J = 6.9 Hz), 7.18-7.22 (m, 2H), 7.29-7.31 (m, 3H), 7.37 (t, 2H, J = 7.6 Hz), 7.67 (d, 1H, J = 6.8 Hz), 9.06 (s, 1H), 9.73 (s, 1H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ = 23.6, 27.3, 58.5, 111.2, 122.7, 126.3, 126.6, 127.0, 127.6, 127.7, 127.8, 127.9, 128.7, 135.4, 142.9, 174.3.



8. STEM analysis

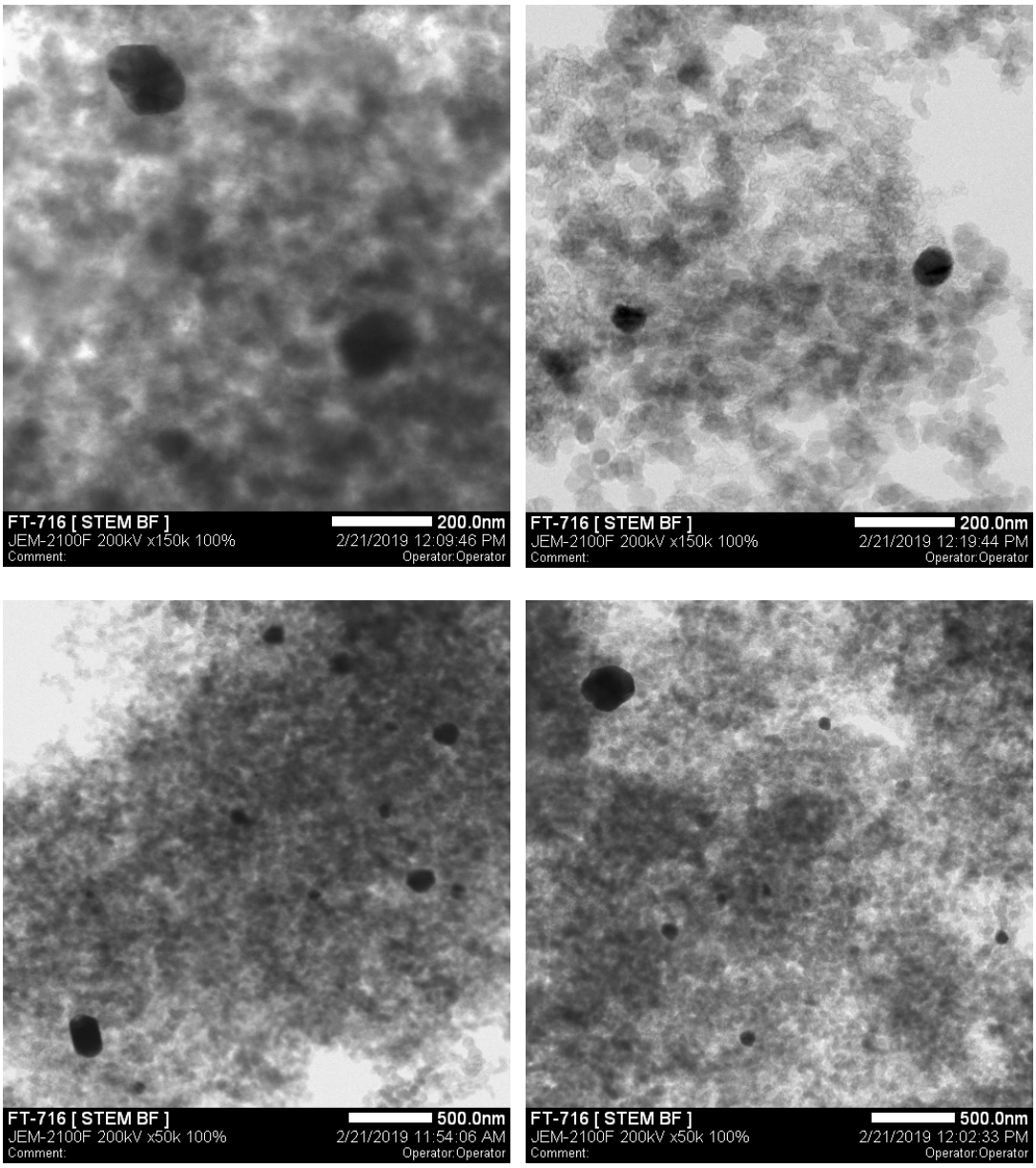


Figure S3 STEM analysis of NCI-Cu-500 (0.500)

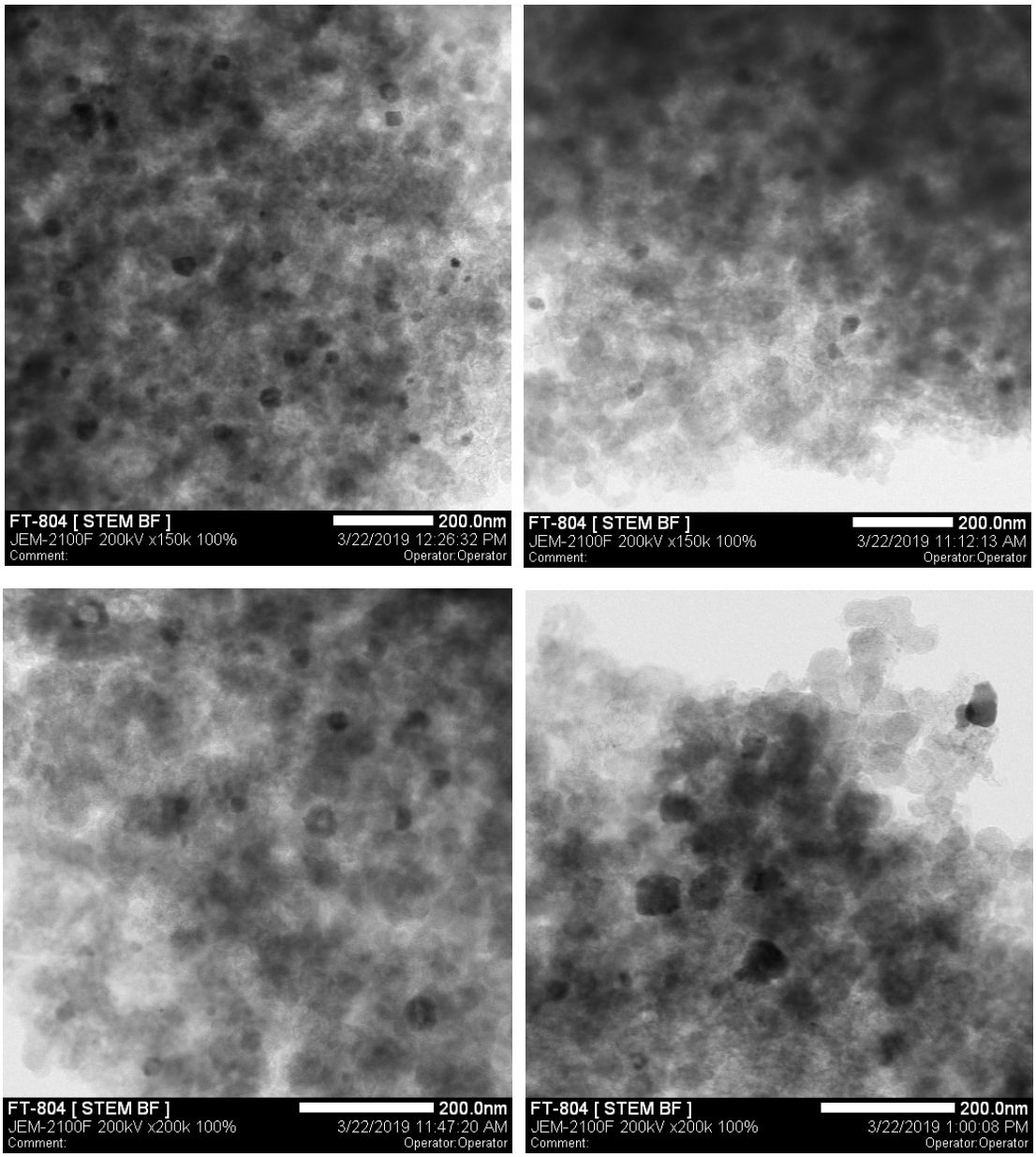
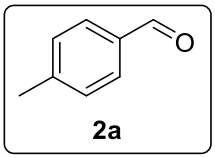
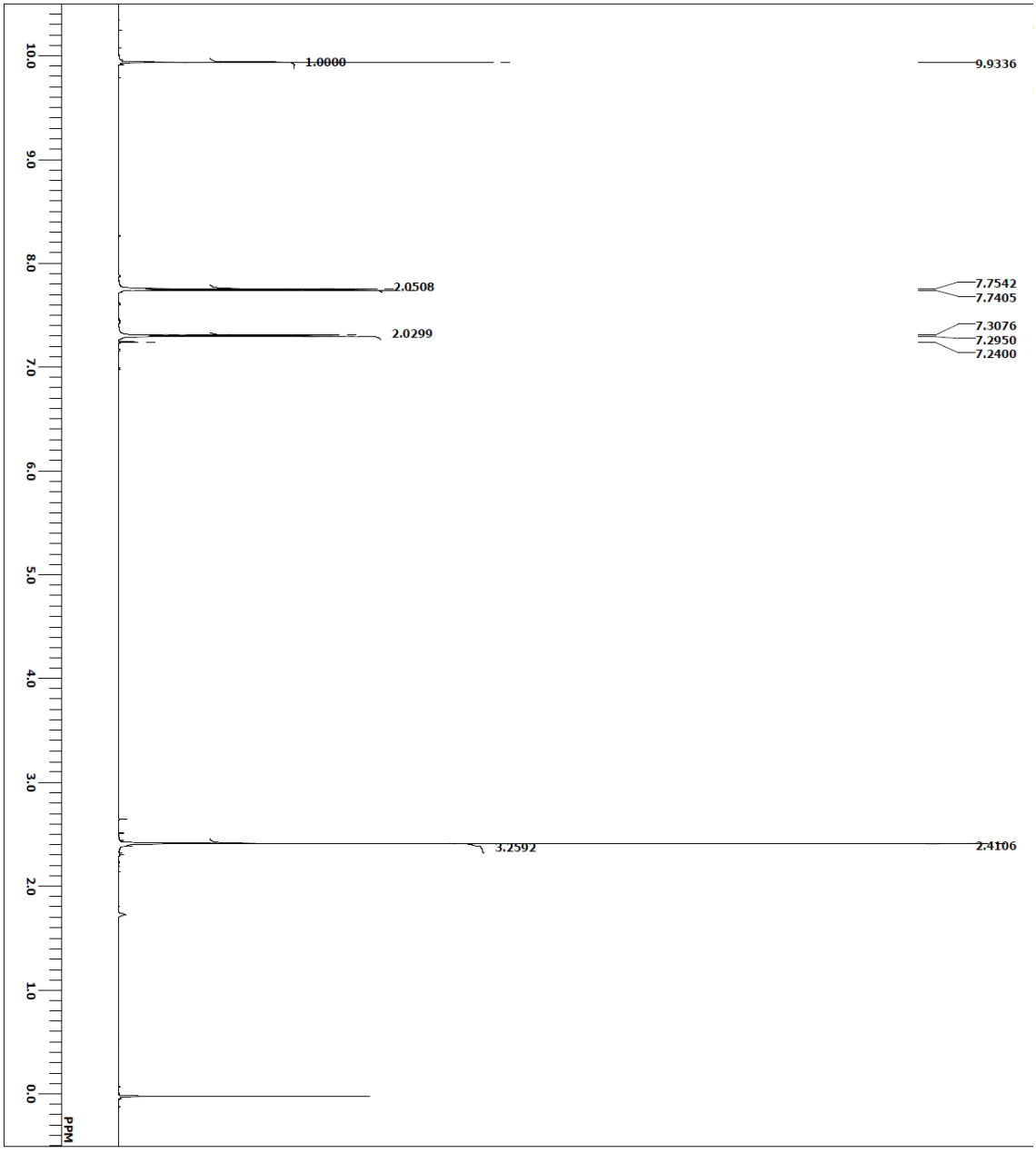


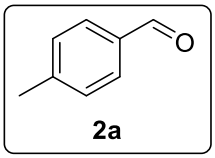
Figure S4 STEM analysis of Cu/C-500

9. NMR charts

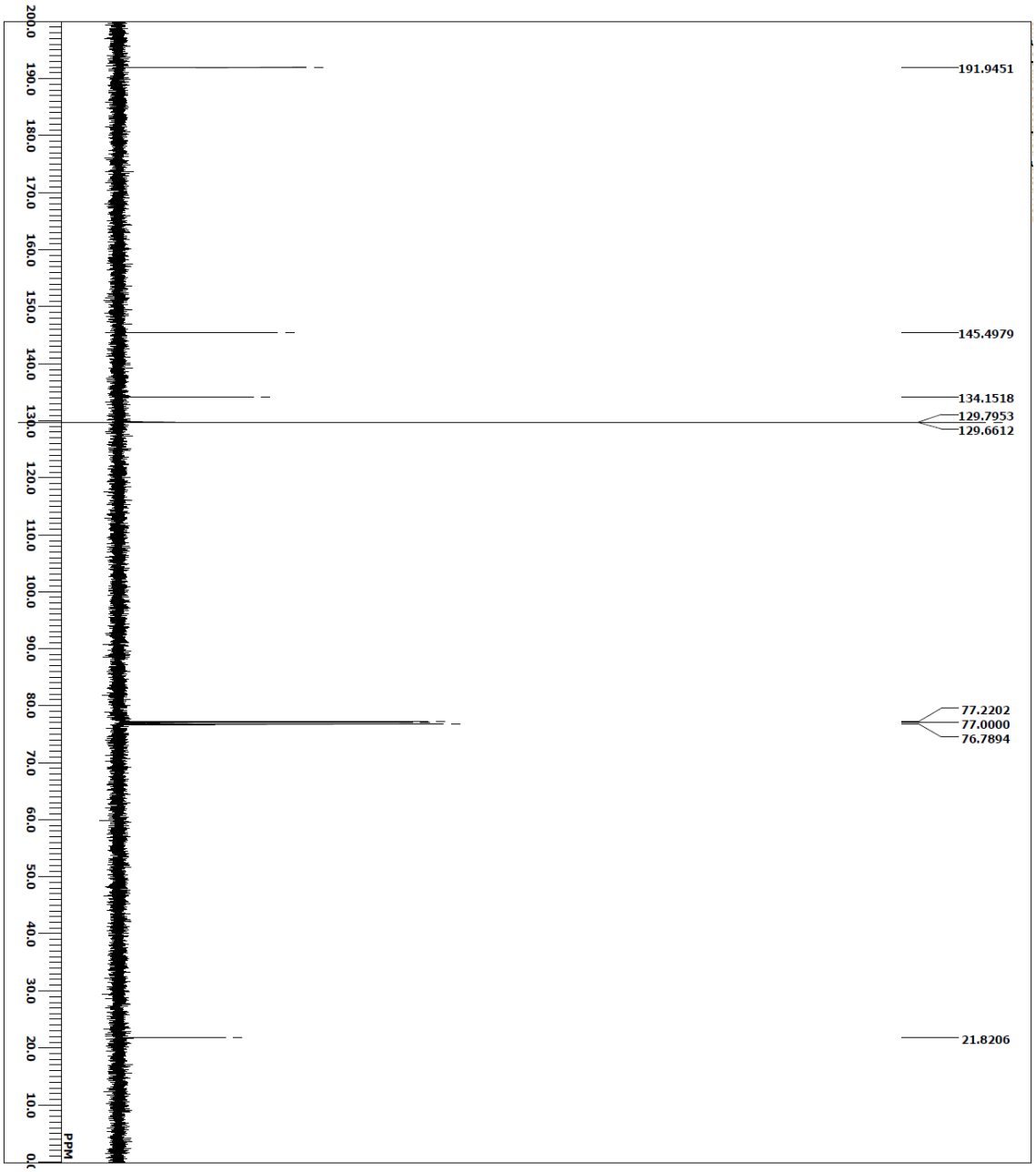


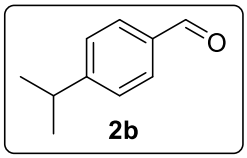
2a

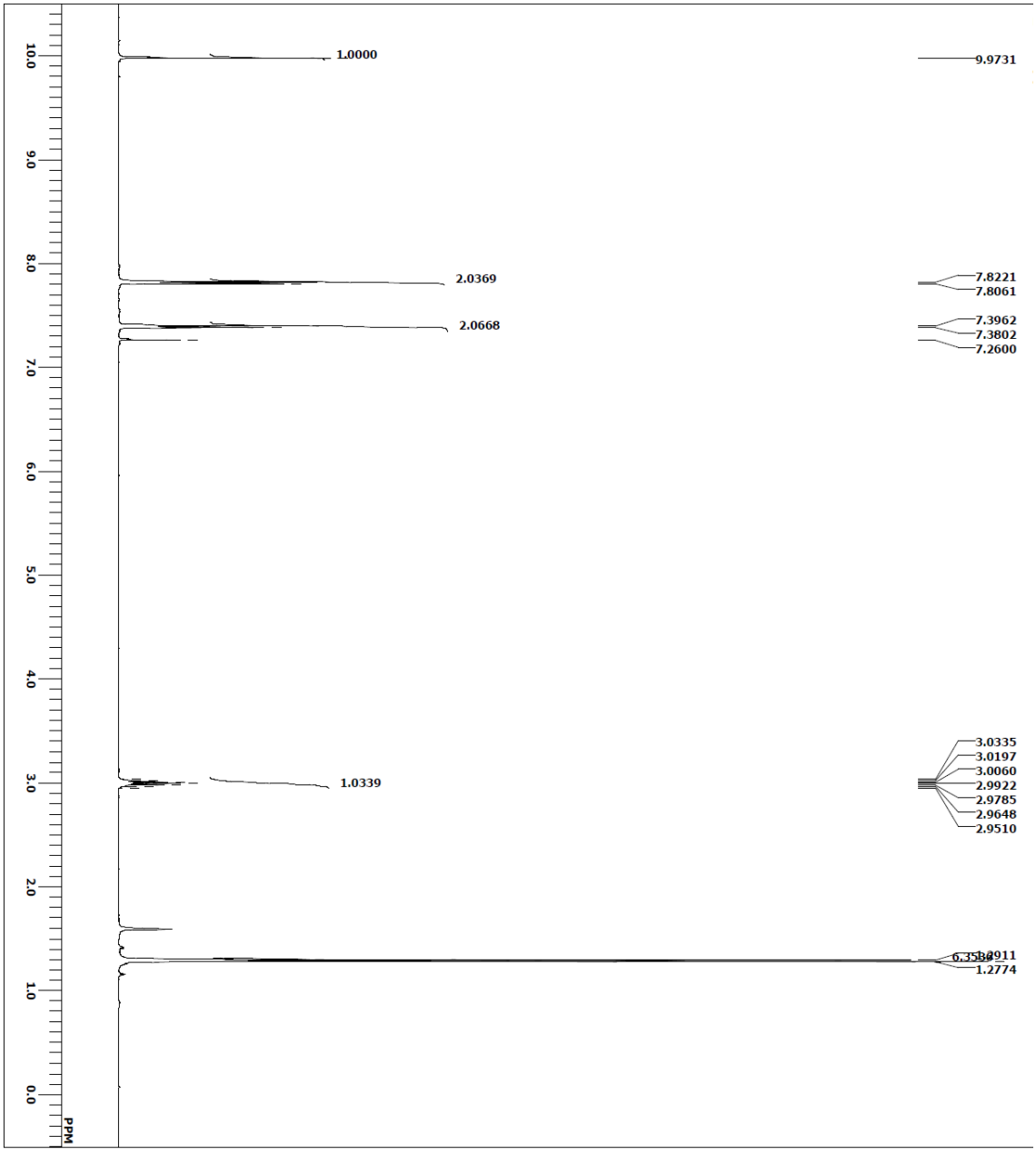


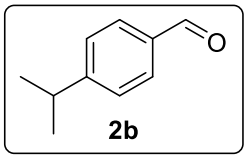

O

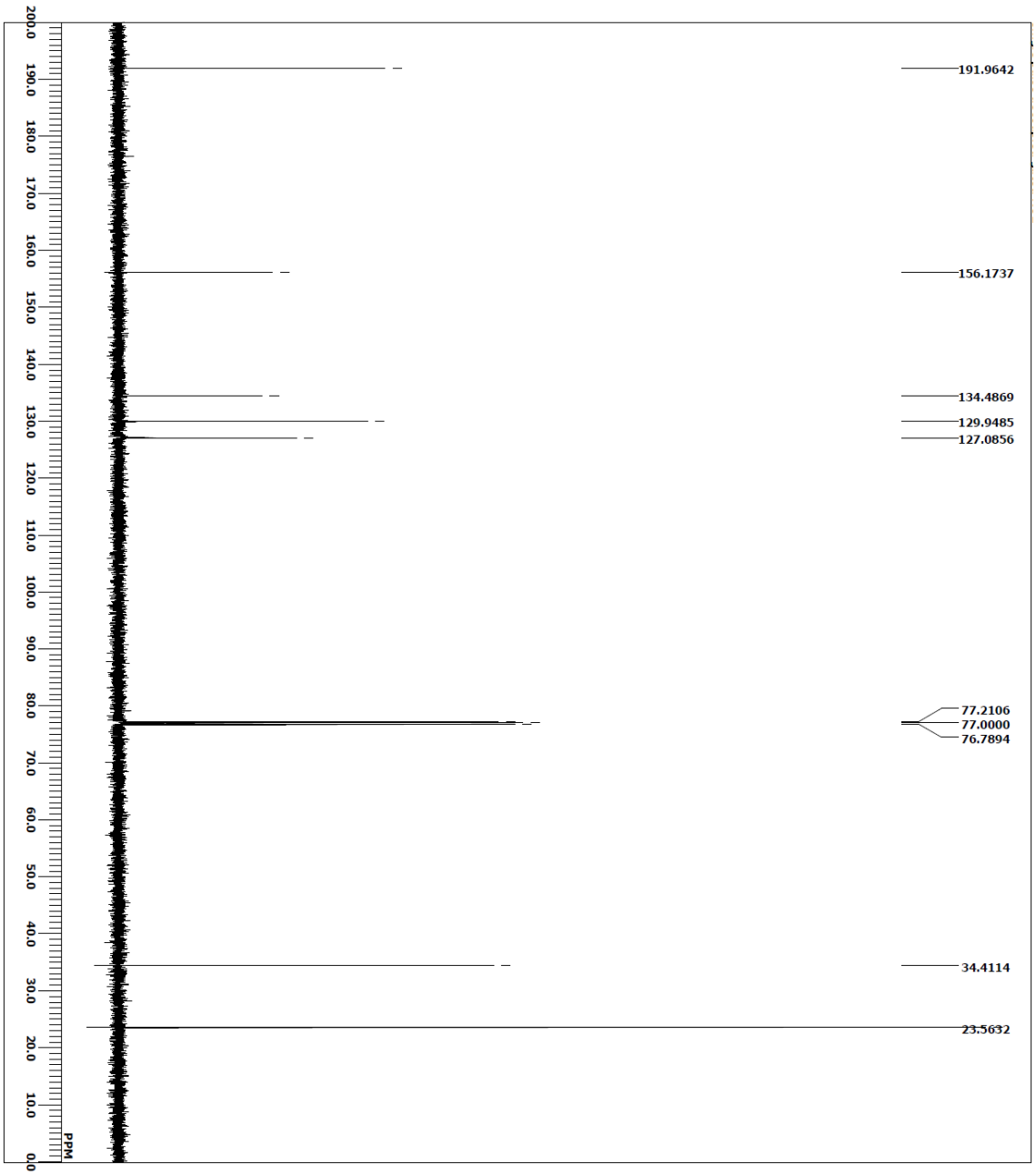
2a

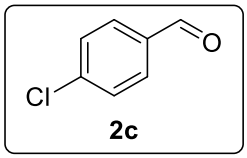

191.9451
145.4979
134.1518
129.7953
129.6612
77.2202
77.0000
76.7894
21.8206
PPM


O
2b

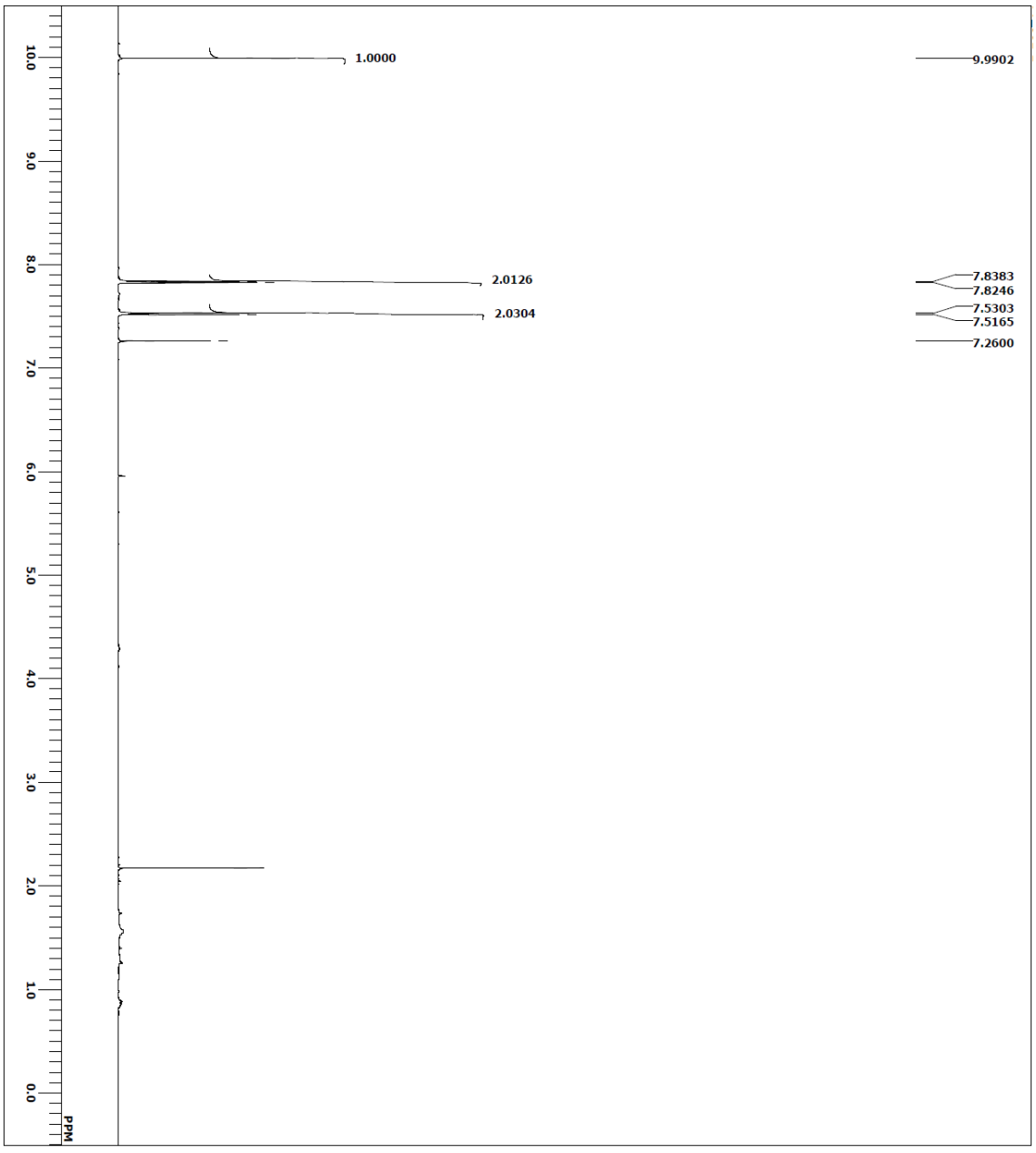

1.0000
2.0369
2.0668
1.0339
9.9731
7.8221
7.8061
7.3962
7.3802
7.2600
3.0335
3.0197
3.0060
2.9922
2.9785
2.9648
2.9510
1.2774
PPM

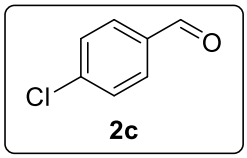

O
2b


191.9642
156.1737
134.4869
129.9485
127.0856
77.2106
77.0000
76.7894
34.4114
23.5632
PPM

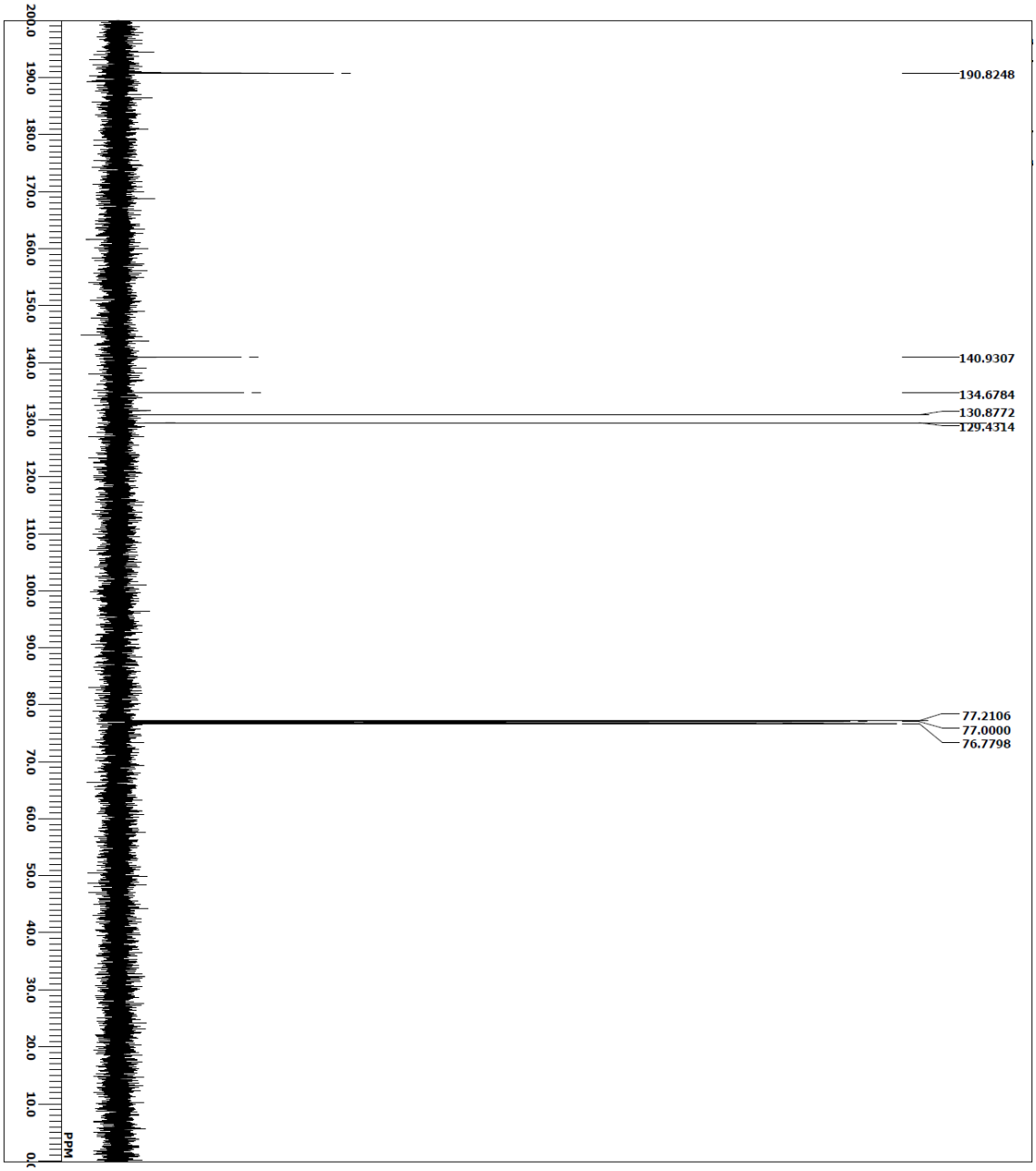

O
Cl

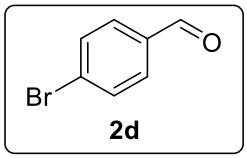
2c


1.0000
2.0126
2.0304
9.9902
7.8383
7.8246
7.5303
7.5165
7.2600
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

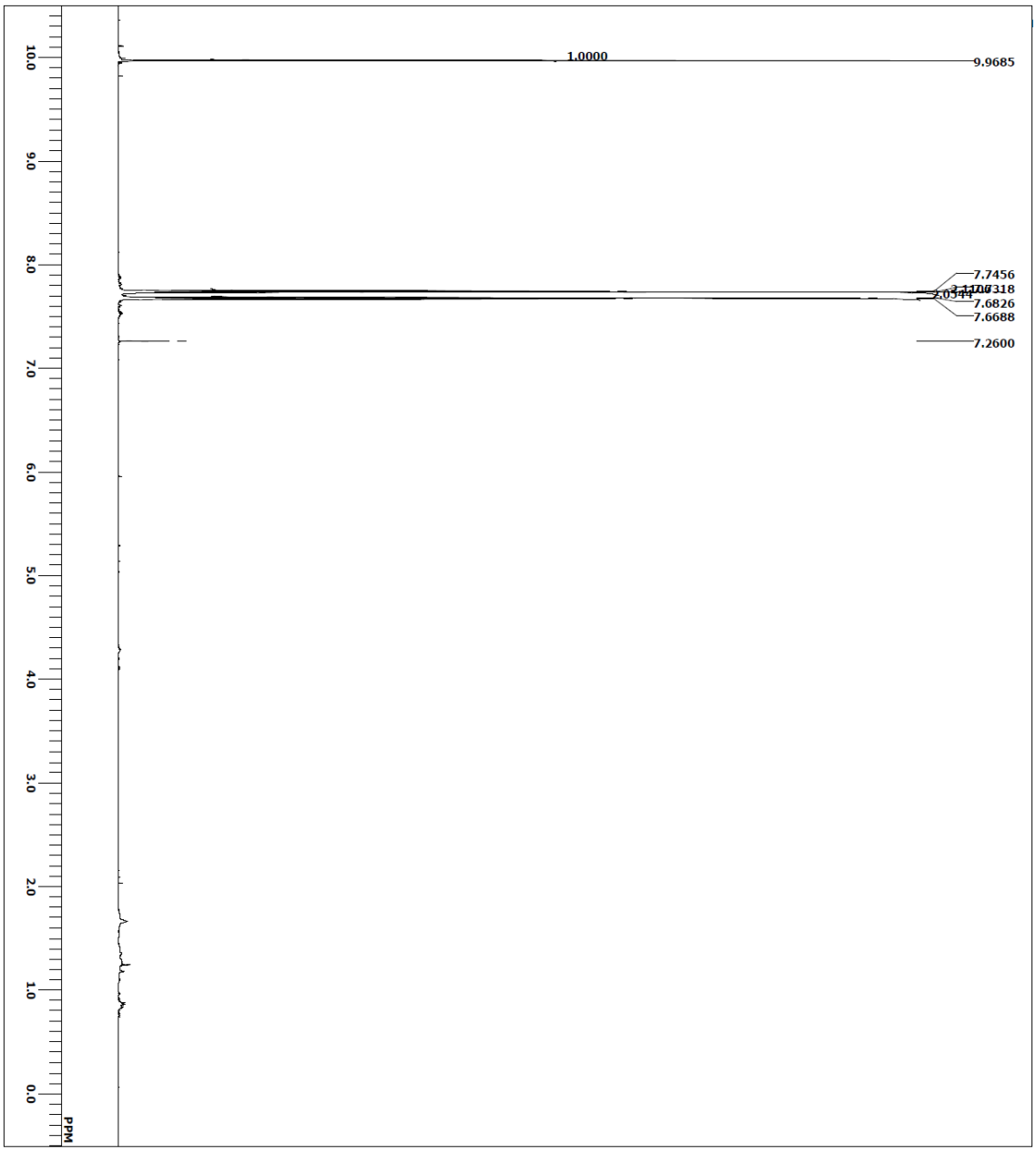

O
Cl

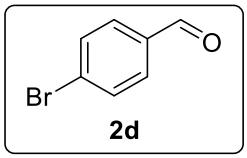
2c


190.8248
140.9307
134.6784
130.8772
129.4314
77.2106
77.0000
76.7798
PPM

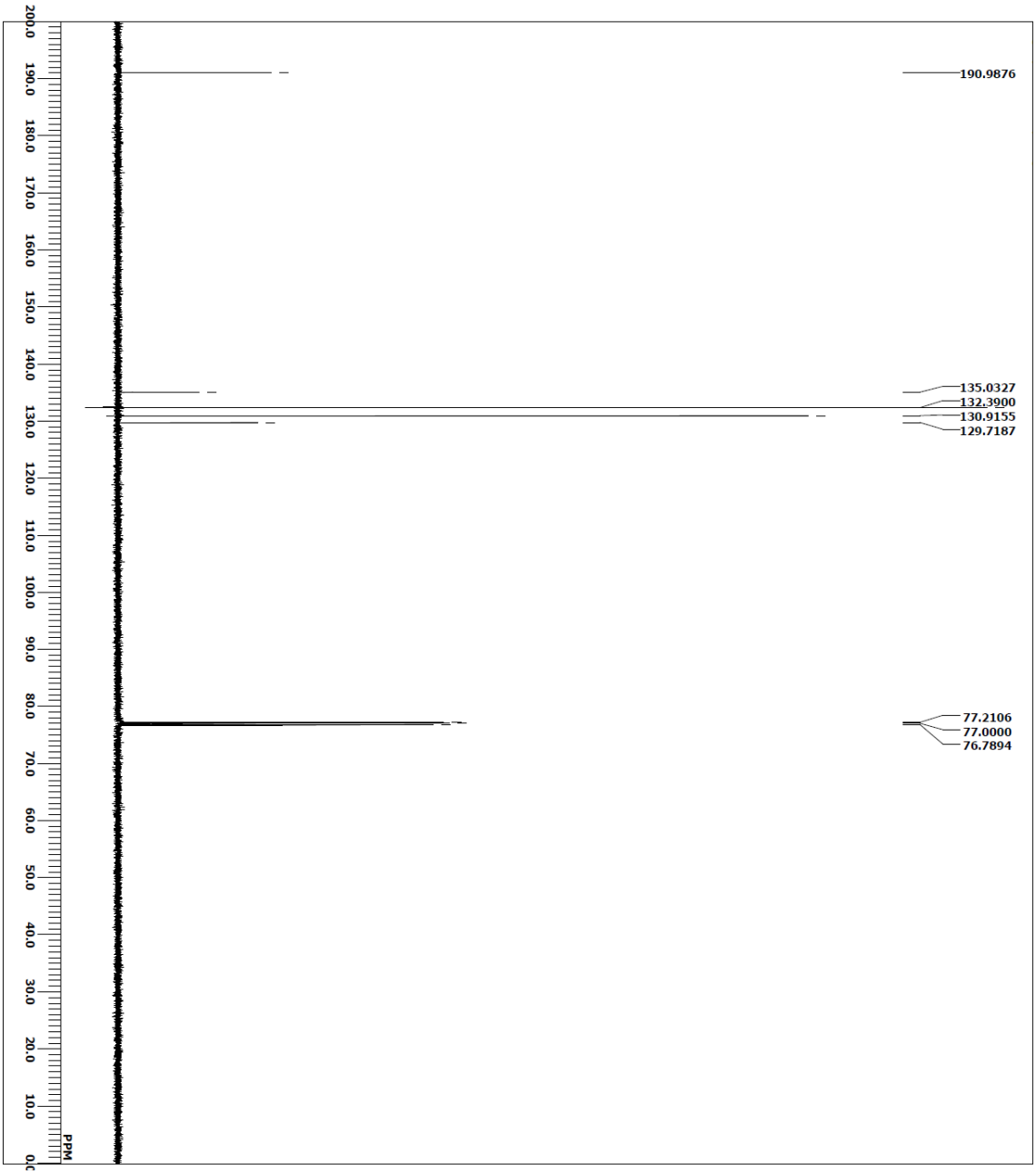

O
Br

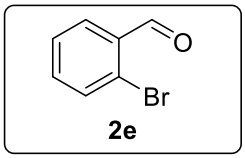
2d


1.0000
9.9685
7.7456
7.7318
7.6826
7.6688
7.2600
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

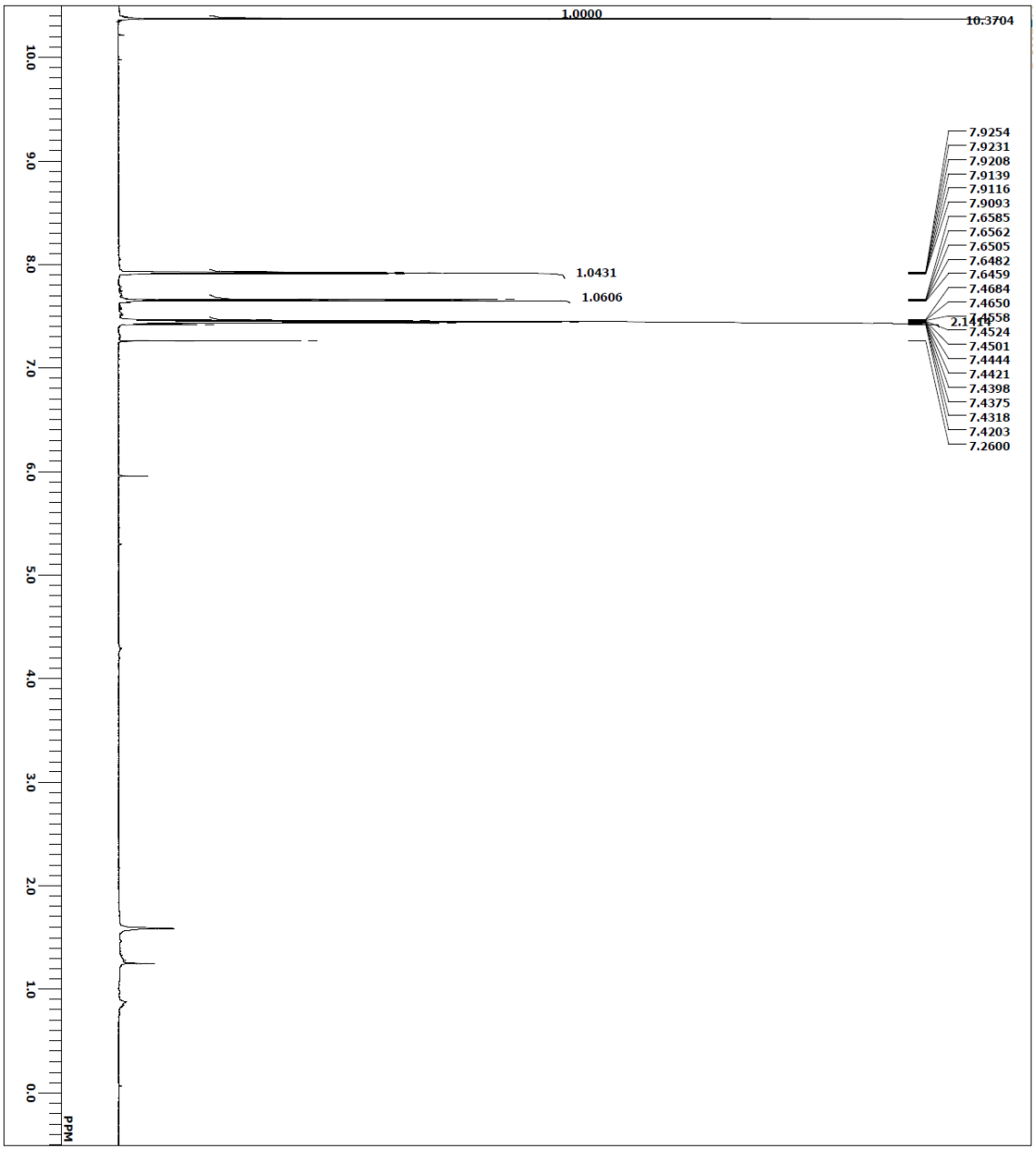

O
Br

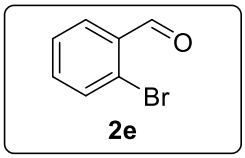
2d


190.9876
135.0327
132.3900
130.9155
129.7187
77.2106
77.0000
76.7894
PPM

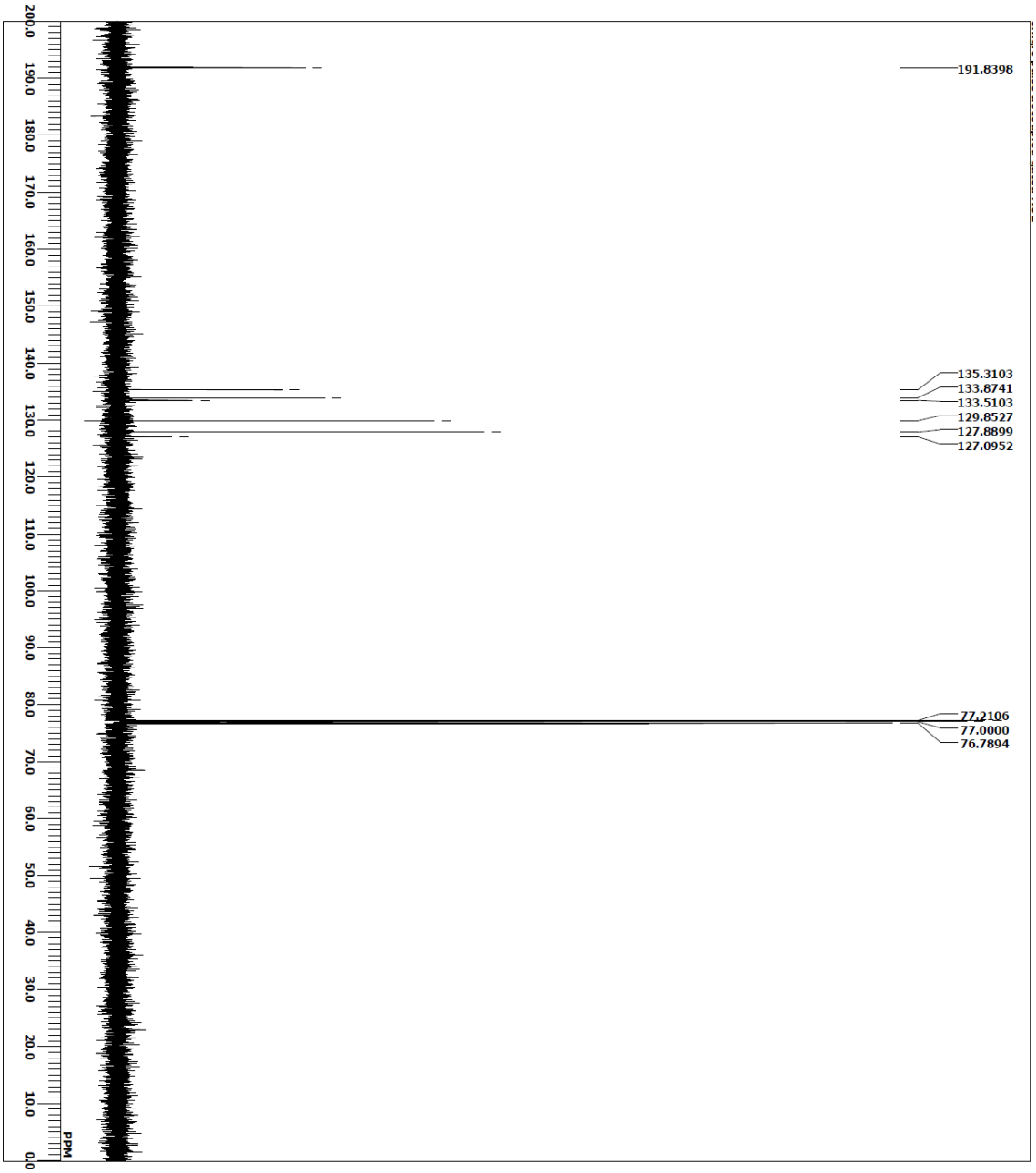

O
Br

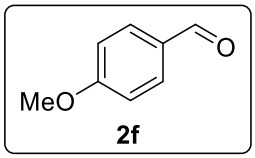
2e


1.0000
10.3704
7.9254
7.9231
7.9208
7.9139
7.9116
7.9093
7.6585
7.6562
7.6505
7.6482
7.6459
7.4684
7.4650
7.4558
2.1419
7.4524
7.4501
7.4444
7.4421
7.4398
7.4375
7.4318
7.4203
7.2600
1.0431
1.0606
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

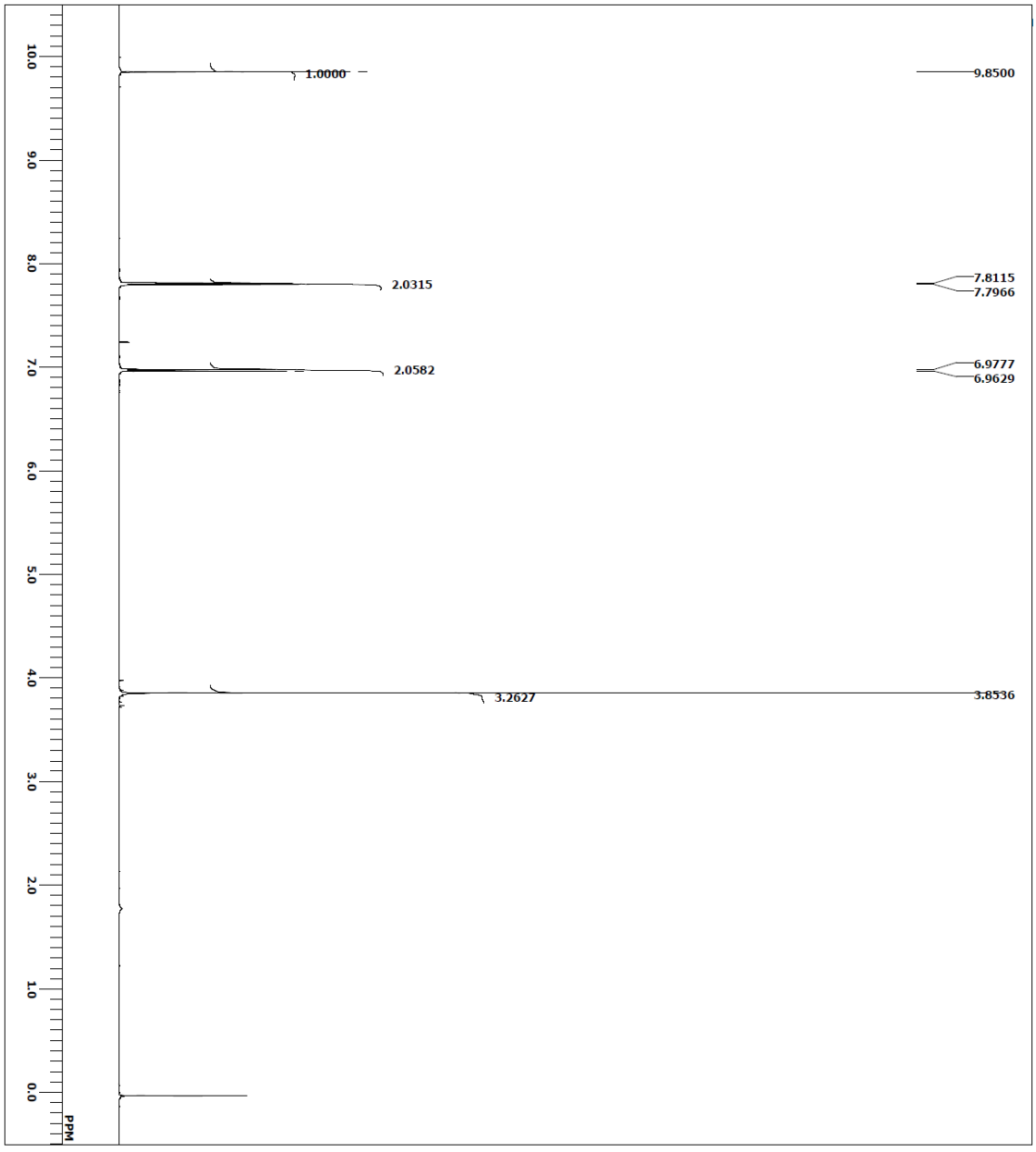

O
Br

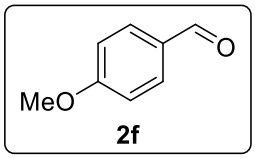
2e


191.8398
135.3103
133.8741
133.5103
129.8527
127.8899
127.0952
77.2106
77.0000
76.7894
PPM

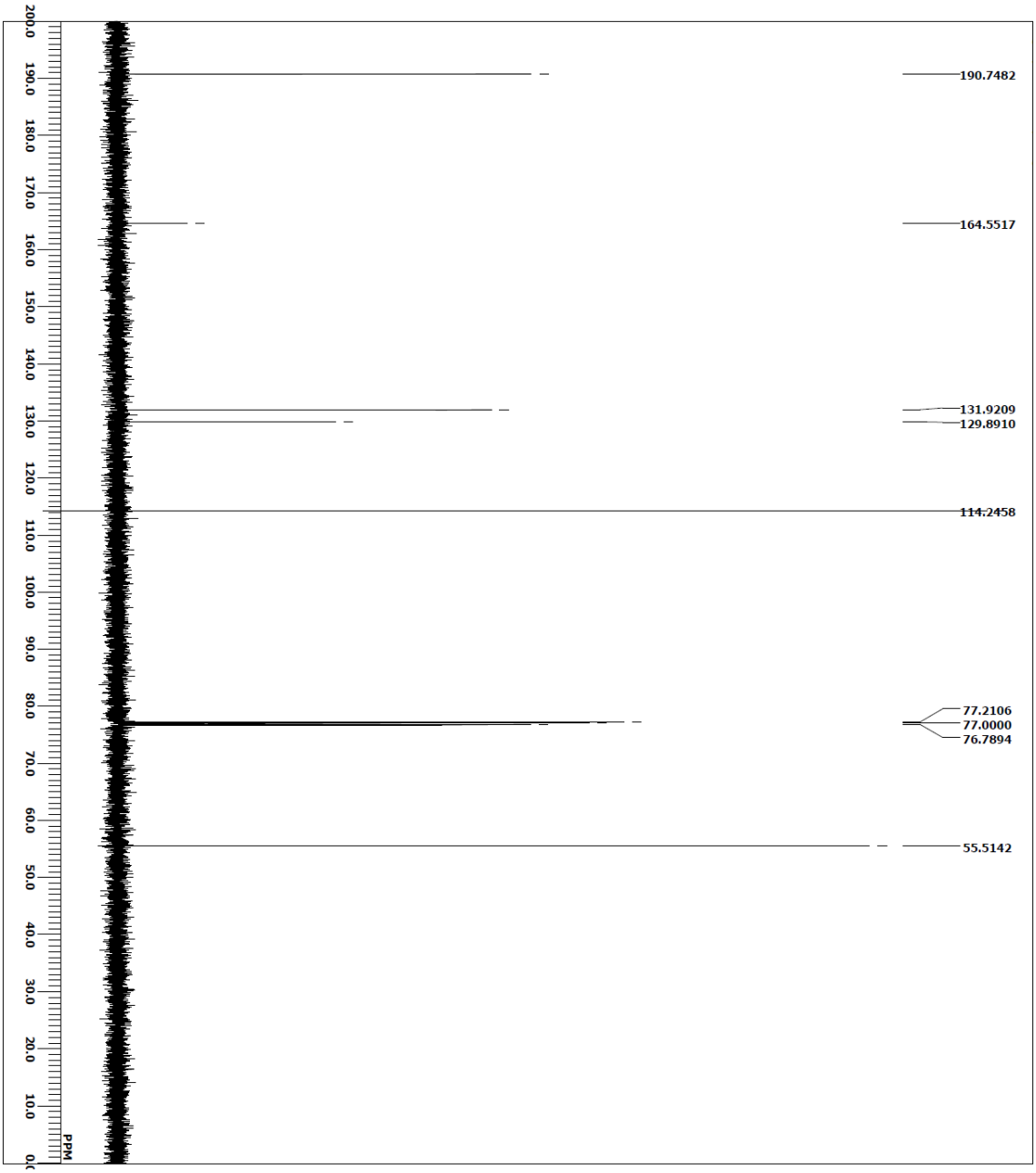

MeO
O

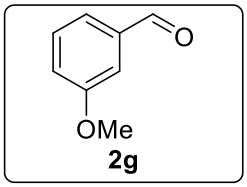
2f


1.0000
2.0315
2.0582
3.2627
9.8500
7.8115
7.7966
6.9777
6.9629
3.8536
PPM

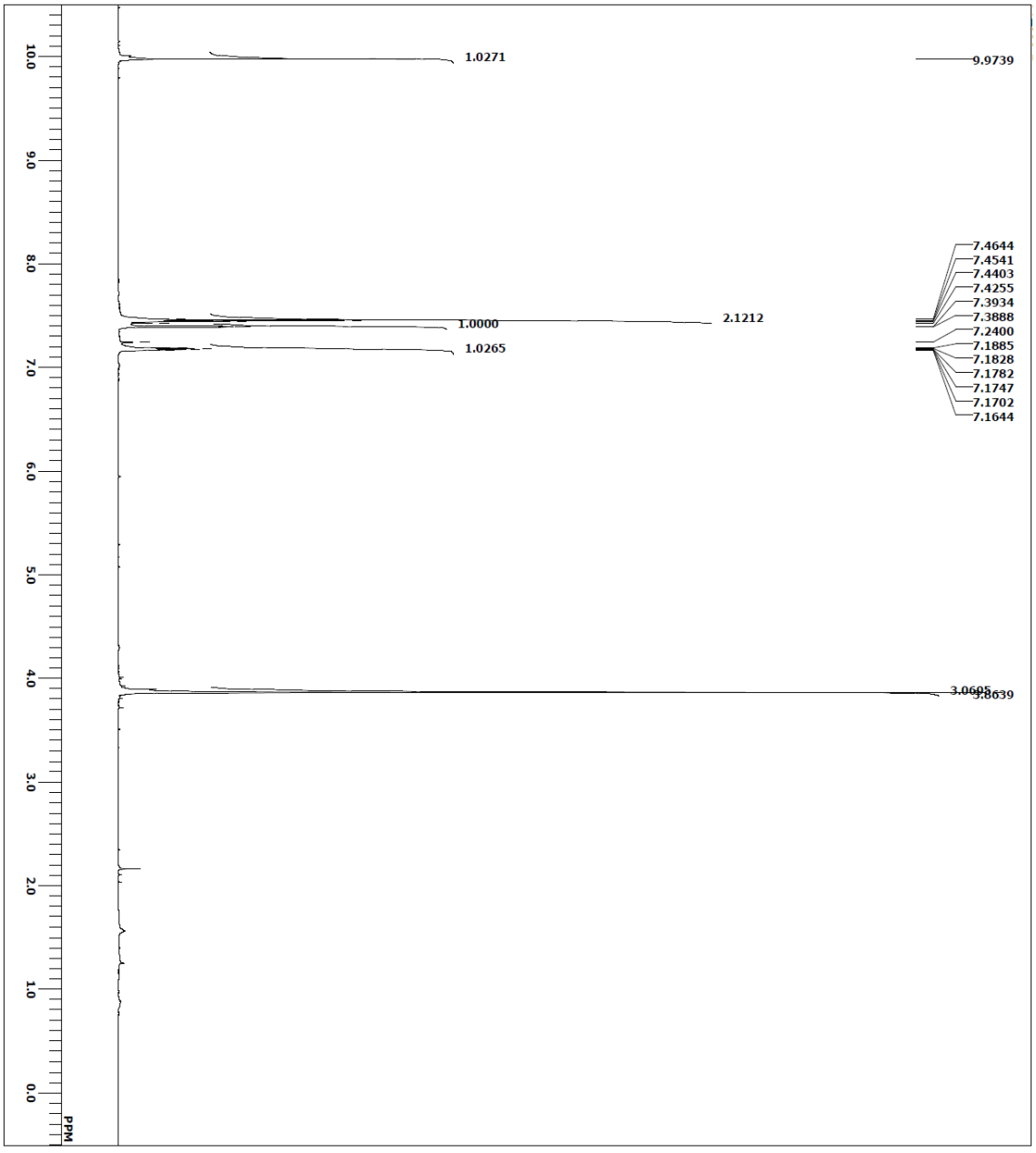

MeO
O

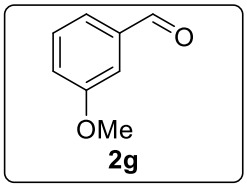
2f


190.7482
164.5517
131.9209
129.8910
114.2458
77.2106
77.0000
76.7894
55.5142
PPM

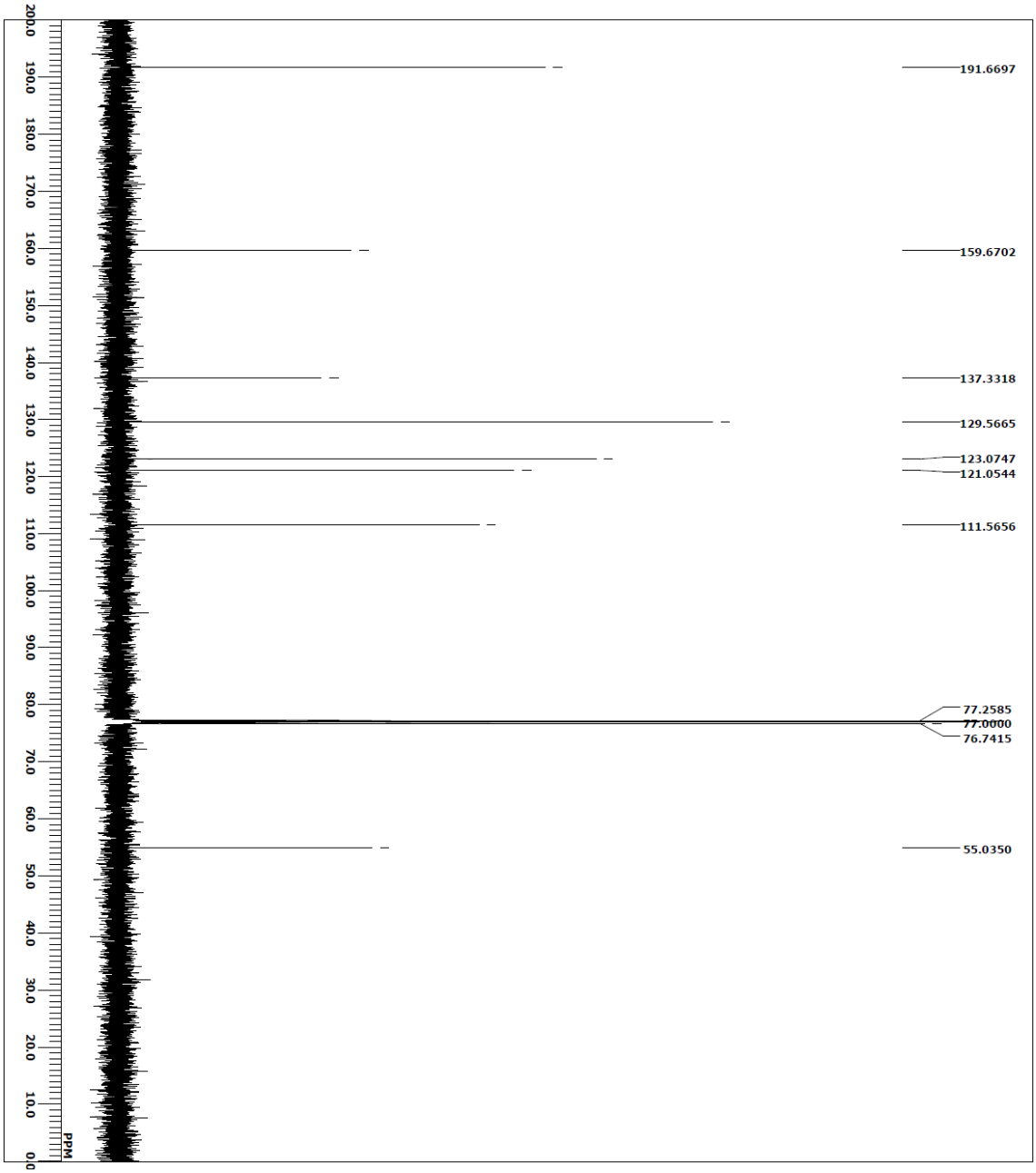

O
OMe

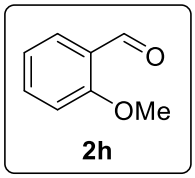
2g


1.0271
9.9739
7.4644
7.4541
7.4403
7.4255
7.3934
7.3888
7.2400
7.1885
7.1828
7.1782
7.1747
7.1702
7.1644
2.1212
1.0000
1.0265
3.0605
3.0639
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

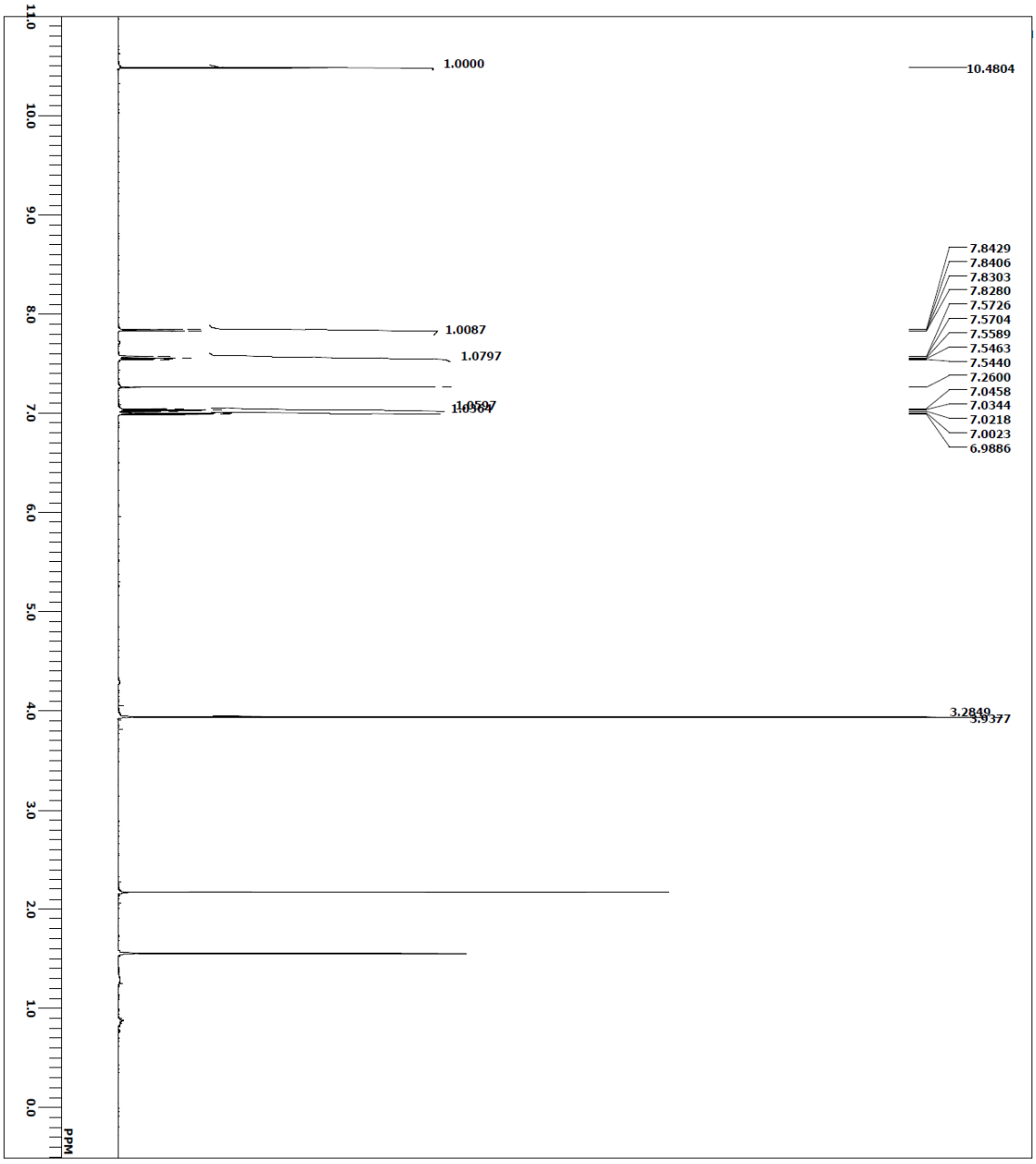

O
OMe

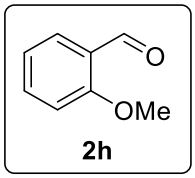
2g


191.6697
159.6702
137.3318
129.5665
123.0747
121.0544
111.5656
77.2585
77.0000
76.7415
55.0350
PPM

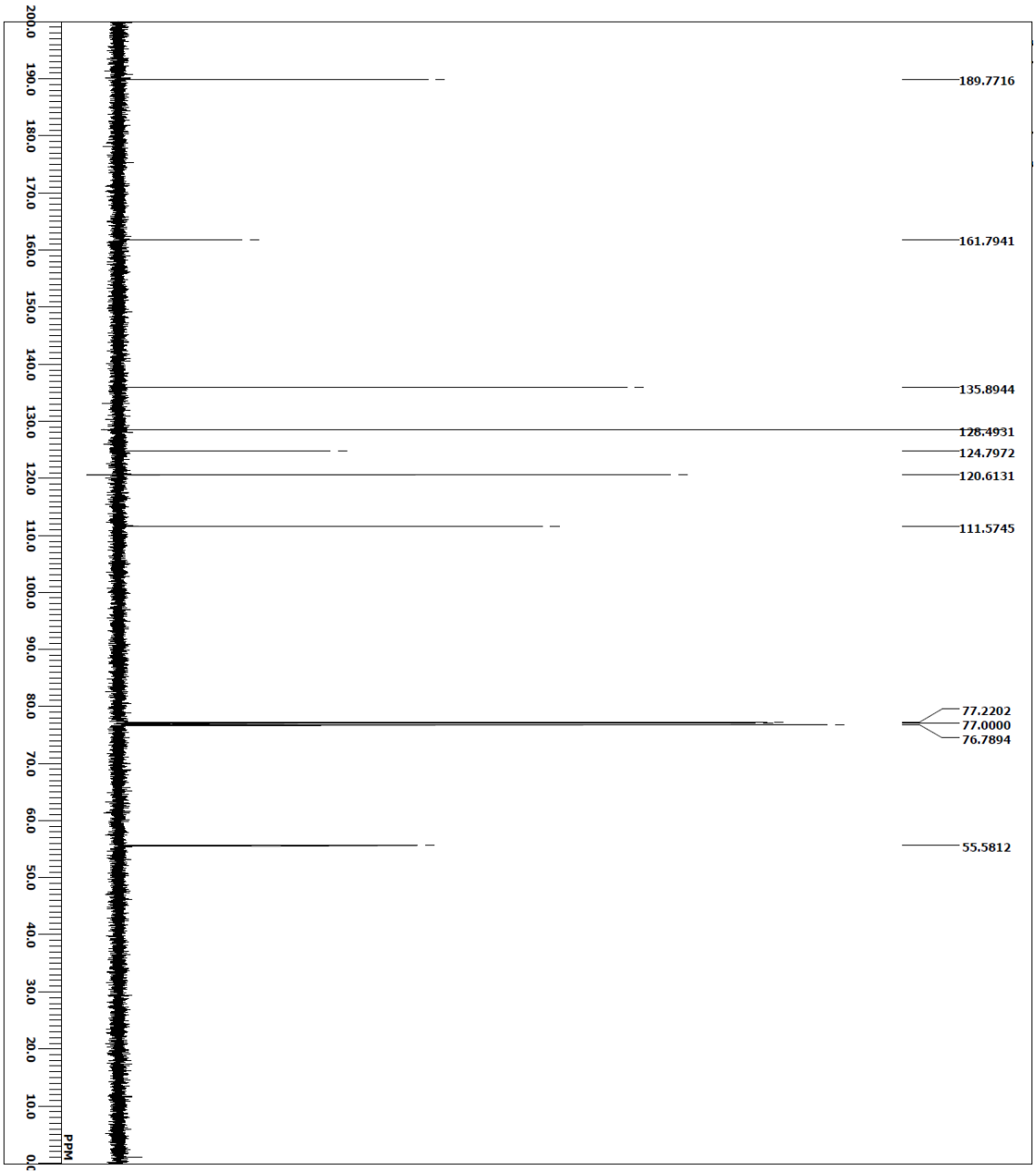

O
OMe

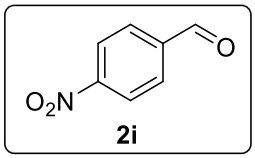
2h


1.0000
10.4804
1.0087
1.0797
7.8429
7.8406
7.8303
7.8280
7.5726
7.5704
7.5589
7.5463
7.5440
7.2600
7.0458
7.0344
7.0218
7.0023
6.9886
3.2849
PPM

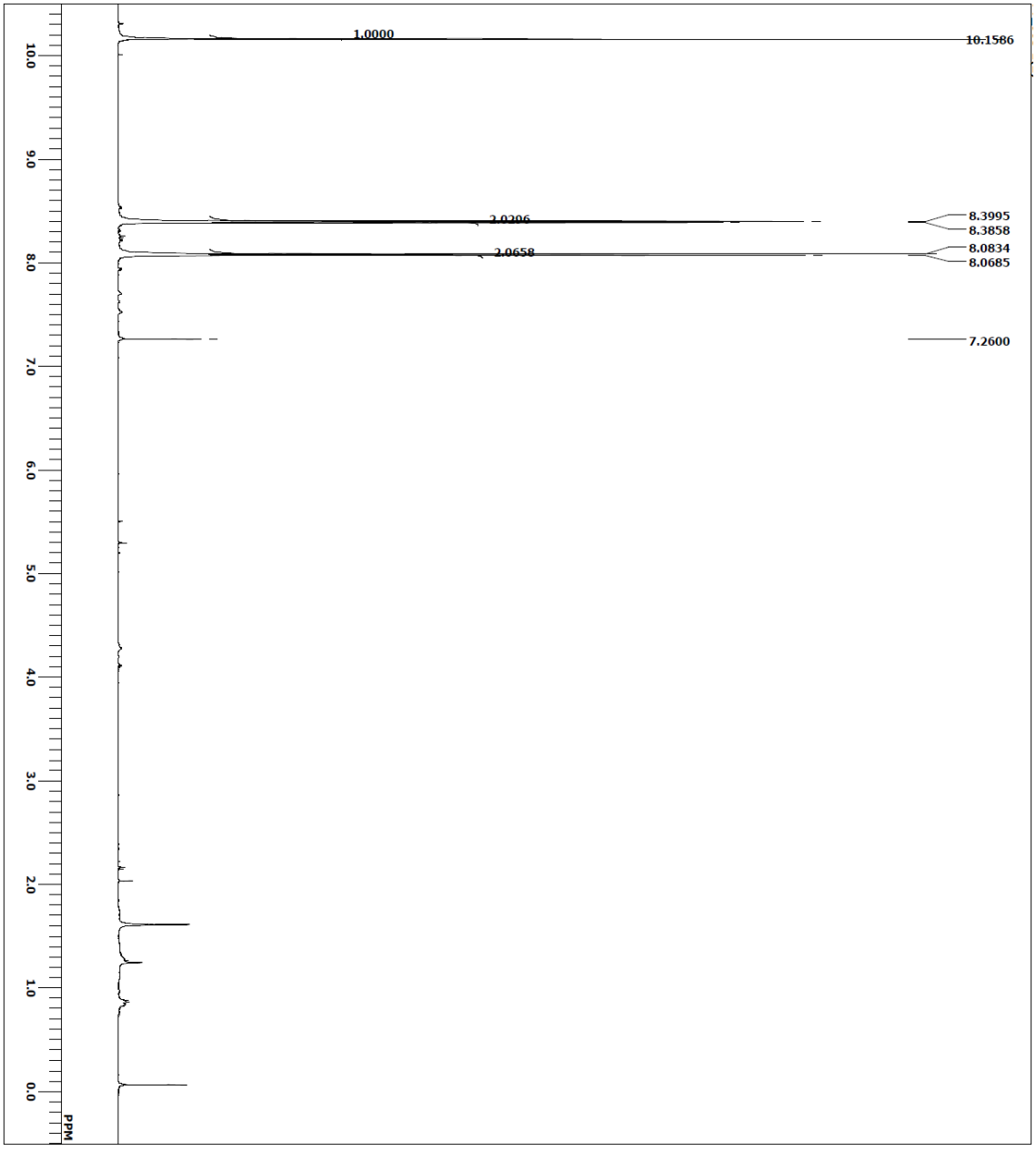

O
OMe

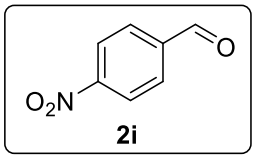
2h

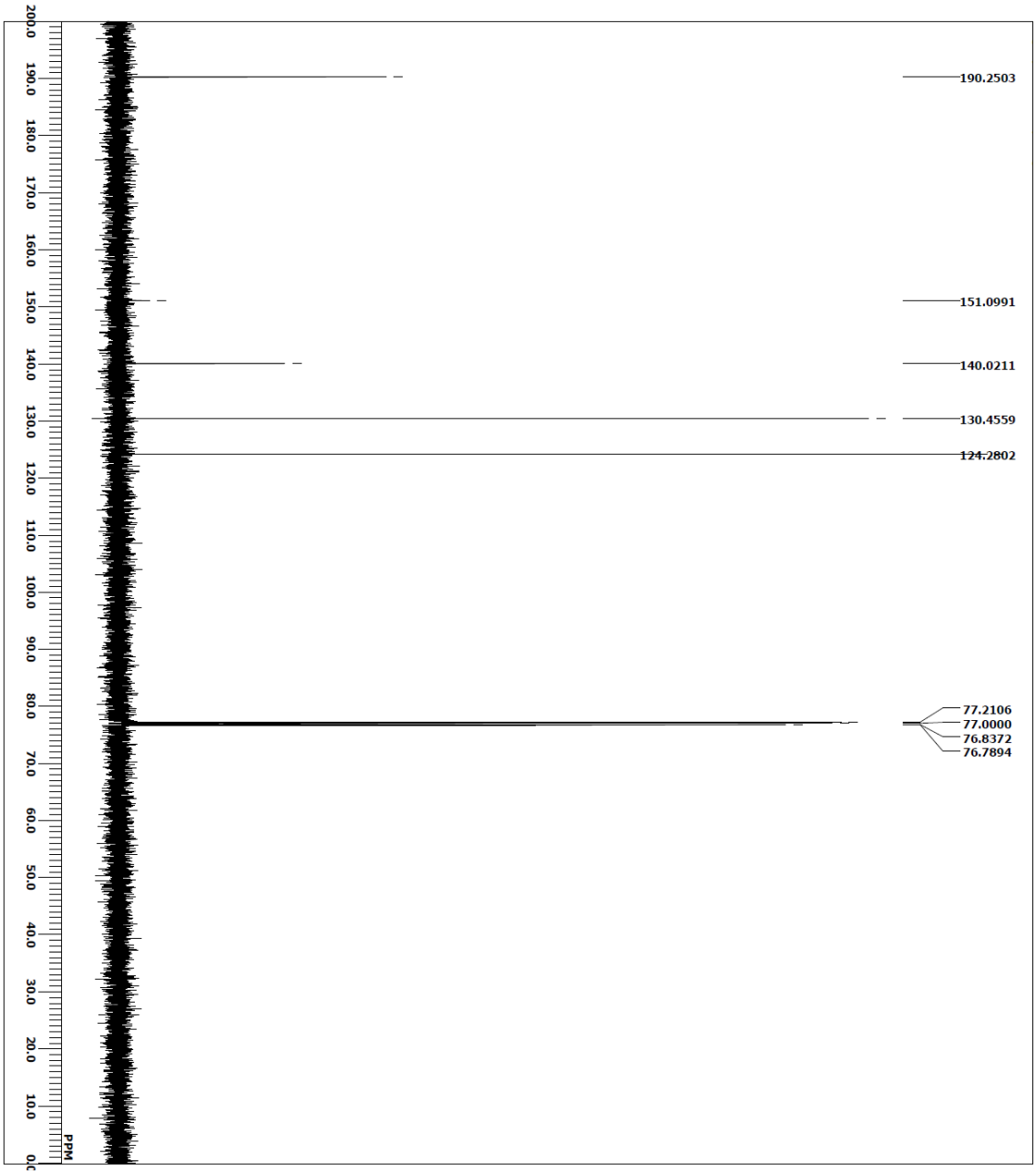

189.7716
161.7941
135.8944
128.4931
124.7972
120.6131
111.5745
77.2202
77.0000
76.7894
55.5812
PPM

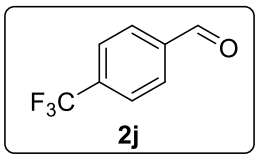

O
O2N

2i

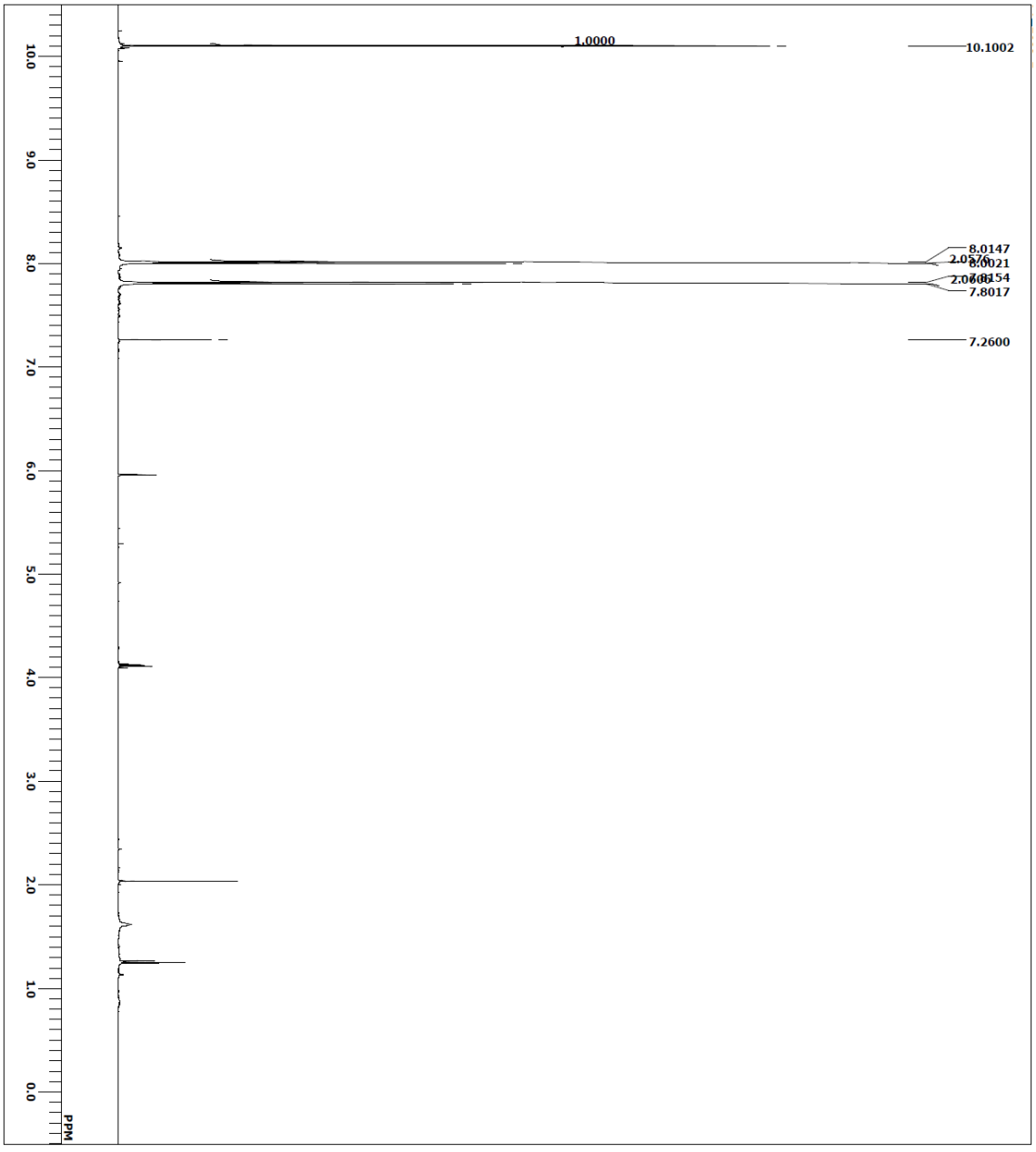

1.0000
10.1586
2.0206
2.0658
8.3995
8.3858
8.0834
8.0685
7.2600
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

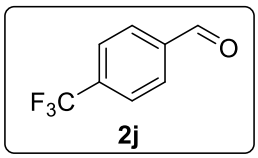

O2N
O
2i


190.2503
151.0991
140.0211
130.4559
124.2802
77.2106
77.0000
76.8372
76.7894
PPM

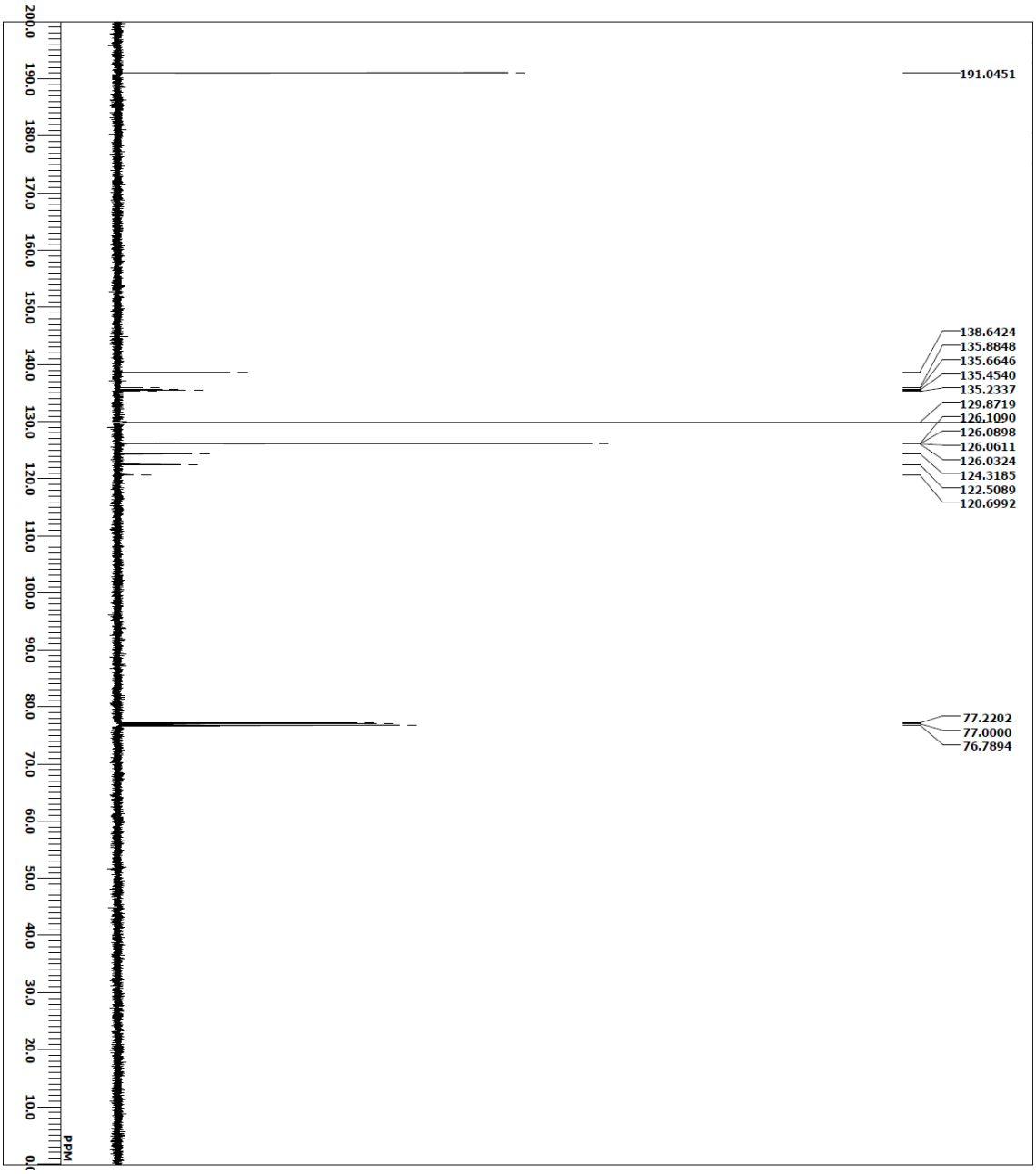

O
F3C

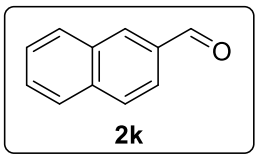
2j

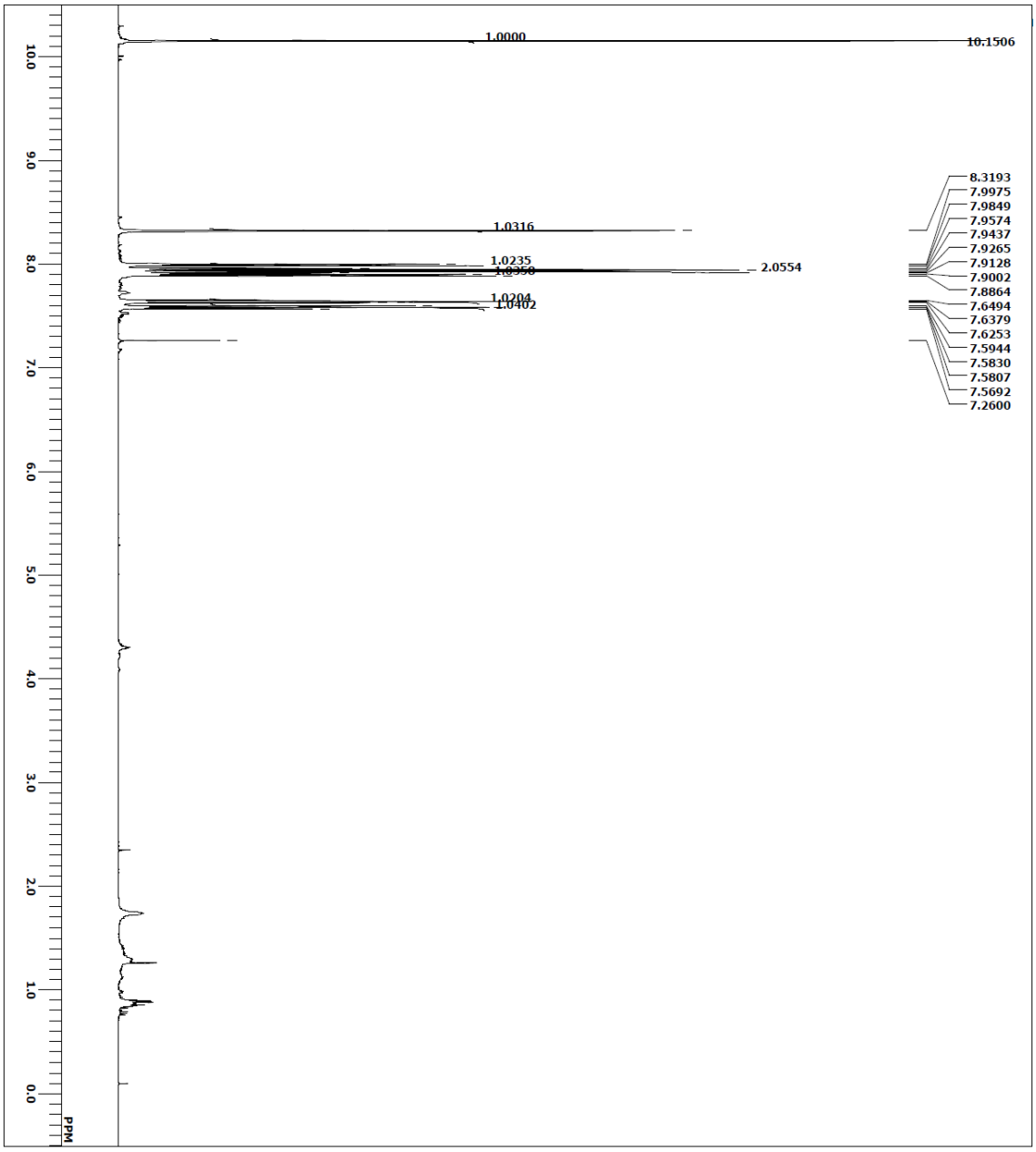

1.0000
10.1002
8.0147
2.0576
8.0021
2.0783
7.8154
7.8017
7.2600
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

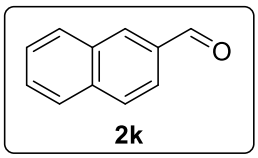

O
F3C

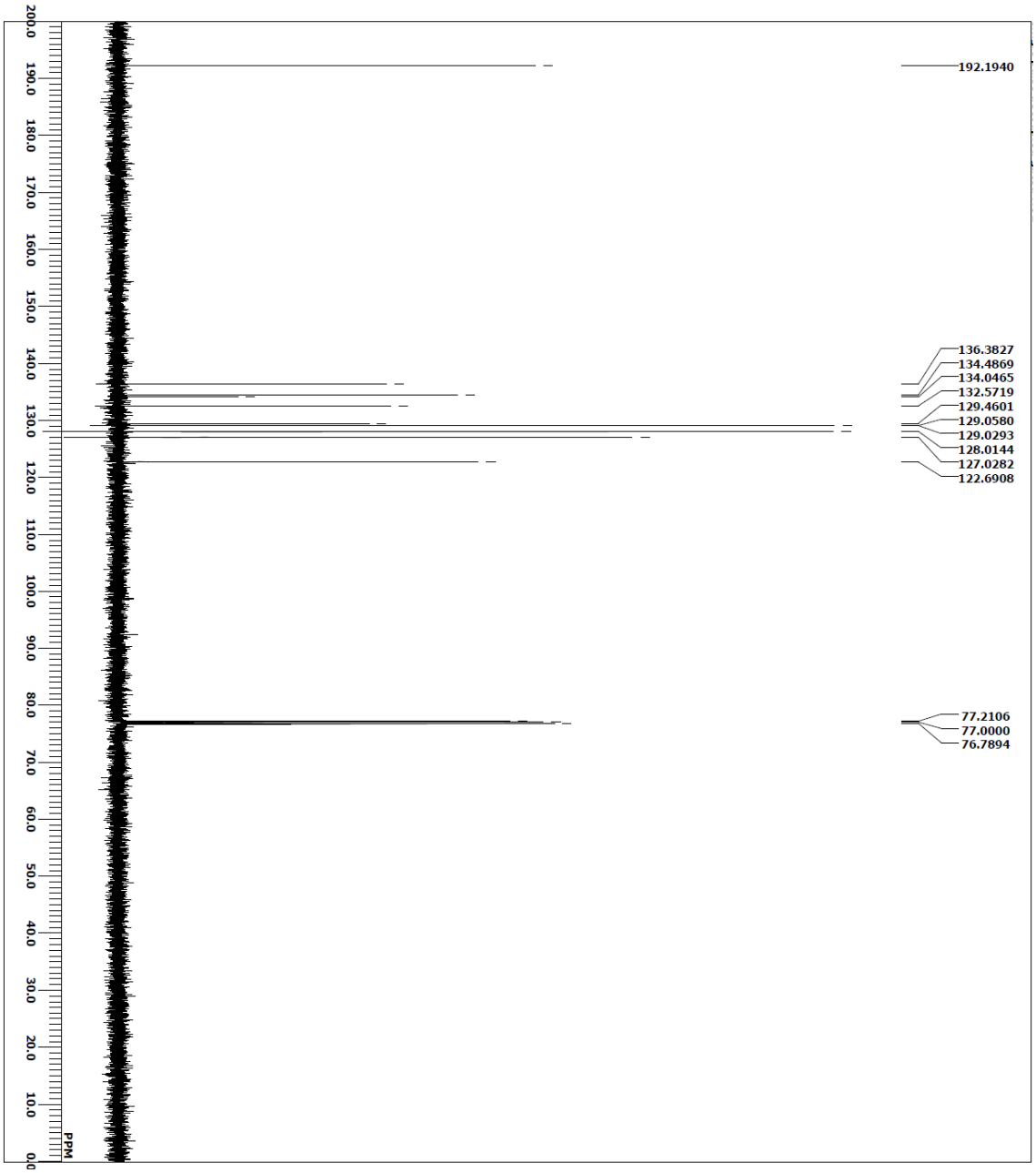
2j

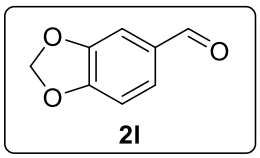

191.0451
138.6424
135.8848
135.6646
135.4540
135.2337
129.8719
126.1090
126.0898
126.0611
126.0324
124.3185
122.5089
120.6992
77.2202
77.0000
76.7894
PPM


O
2k

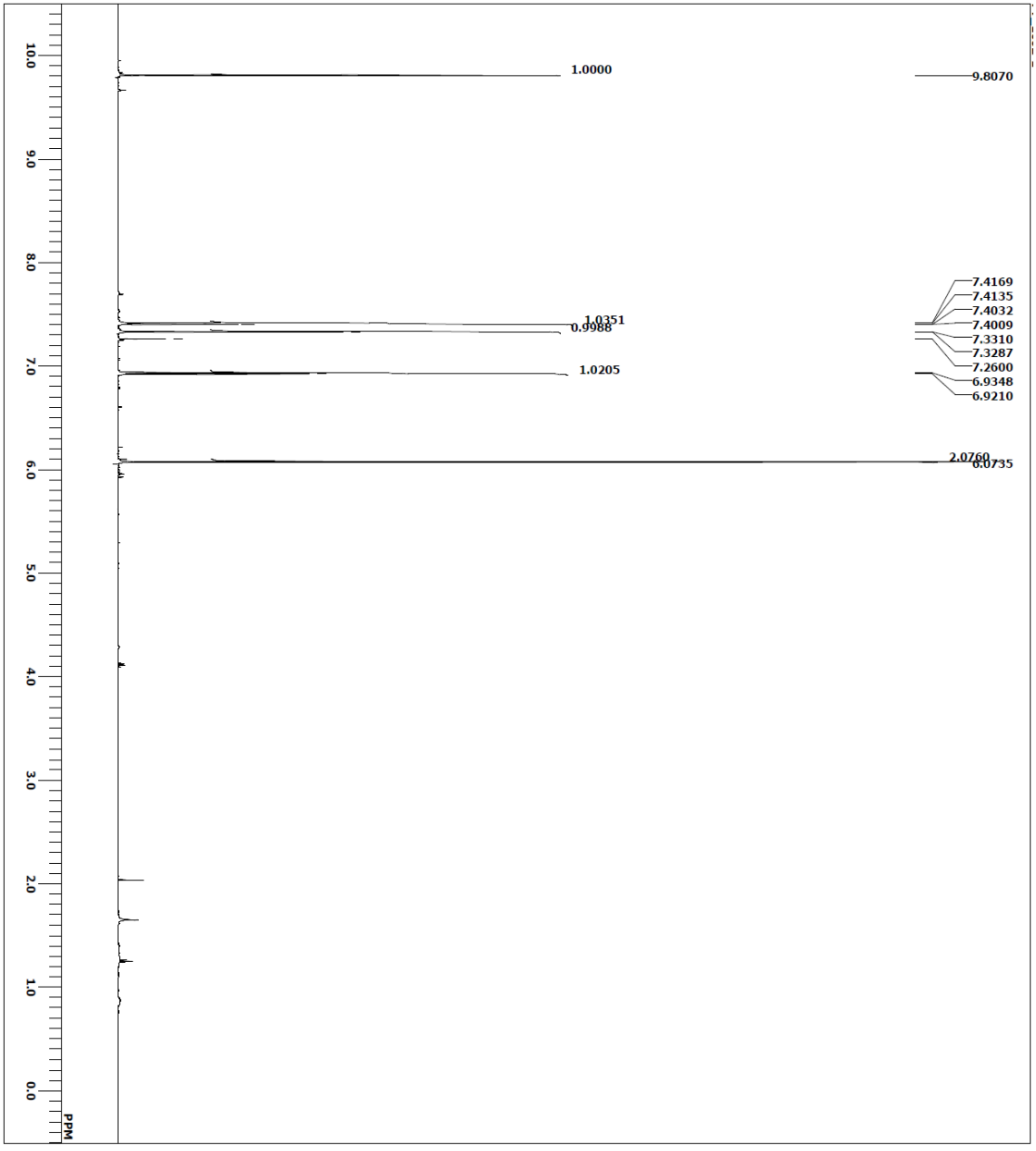

1.0000
10.1506
1.0316
1.0235
2.0554
1.0204
1.0402
8.3193
7.9975
7.9849
7.9574
7.9437
7.9265
7.9128
7.9002
7.8864
7.6494
7.6379
7.6253
7.5944
7.5830
7.5807
7.5692
7.2600
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

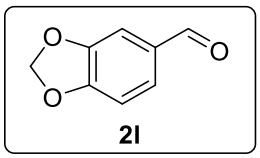

O
2k


192.1940
136.3827
134.4869
134.0465
132.5719
129.4601
129.0580
129.0293
128.0144
127.0282
122.6908
77.2106
77.0000
76.7894
PPM

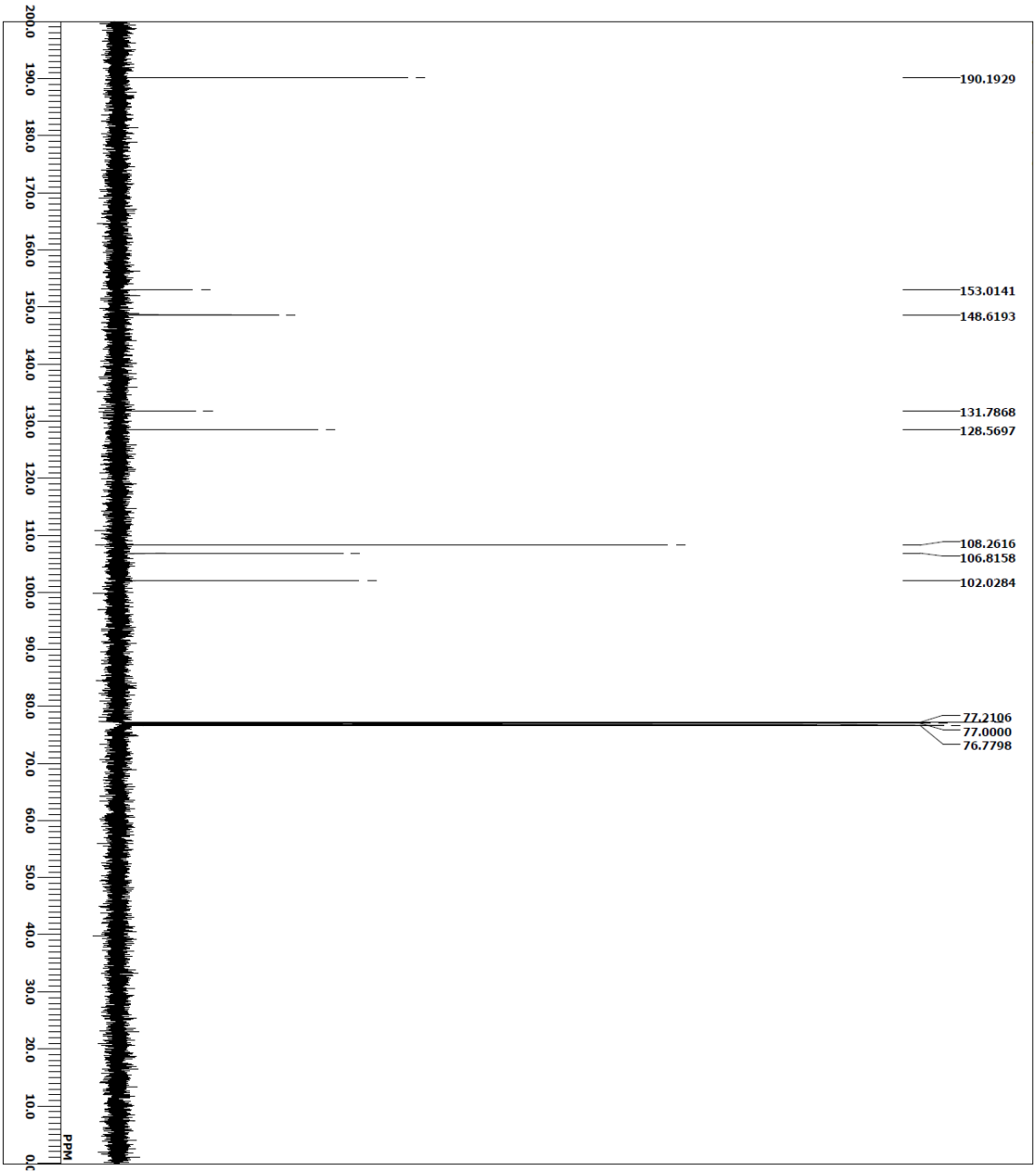

O
O
O

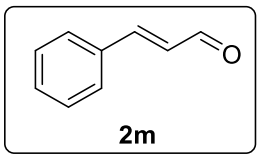
2l

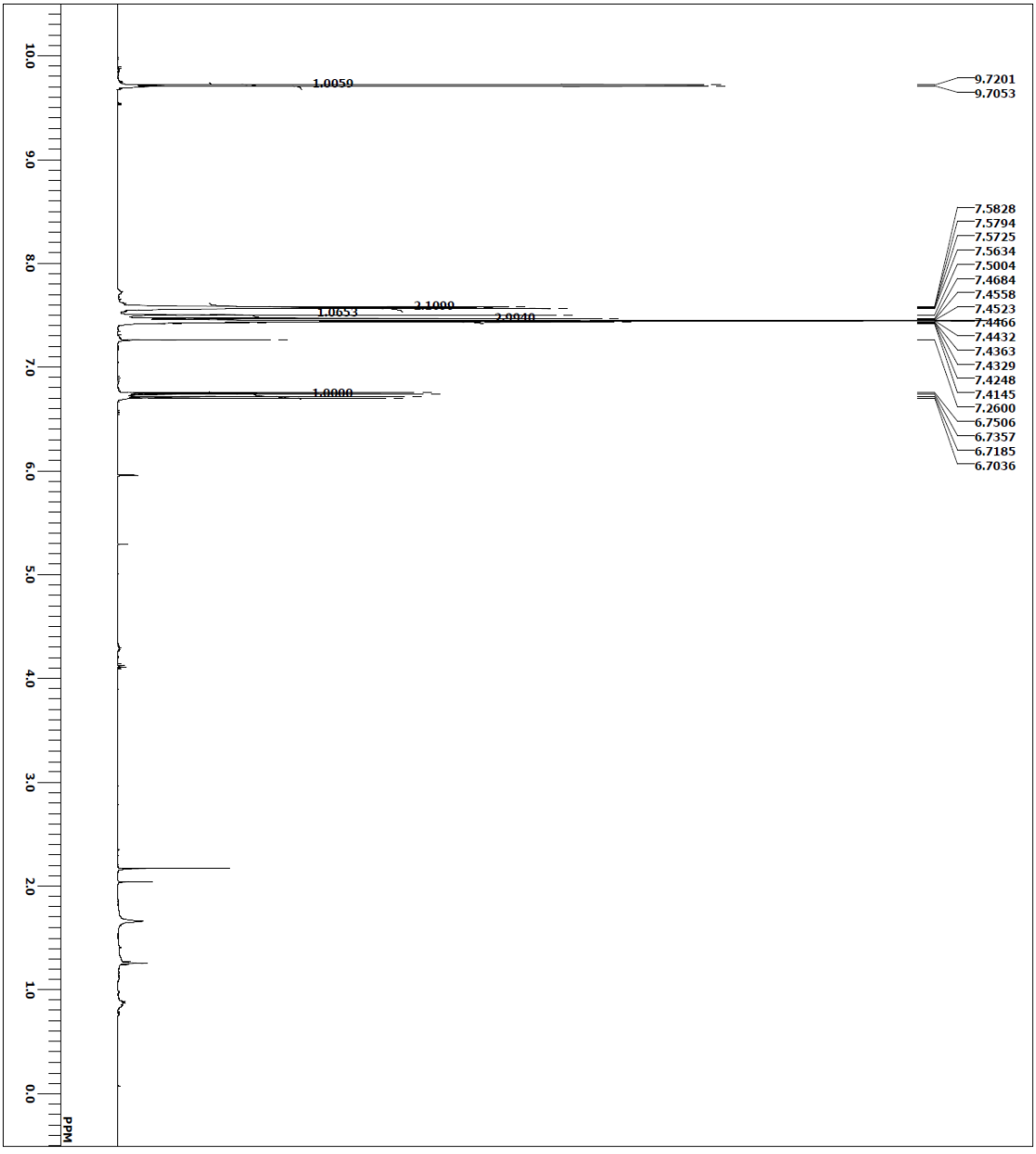

1.0000
9.8070
7.4169
7.4135
7.4032
7.4009
7.3310
7.3287
7.2600
6.9348
6.9210
1.0351
0.9988
1.0205
2.0760
6.0735
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

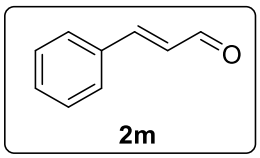

O
O
O

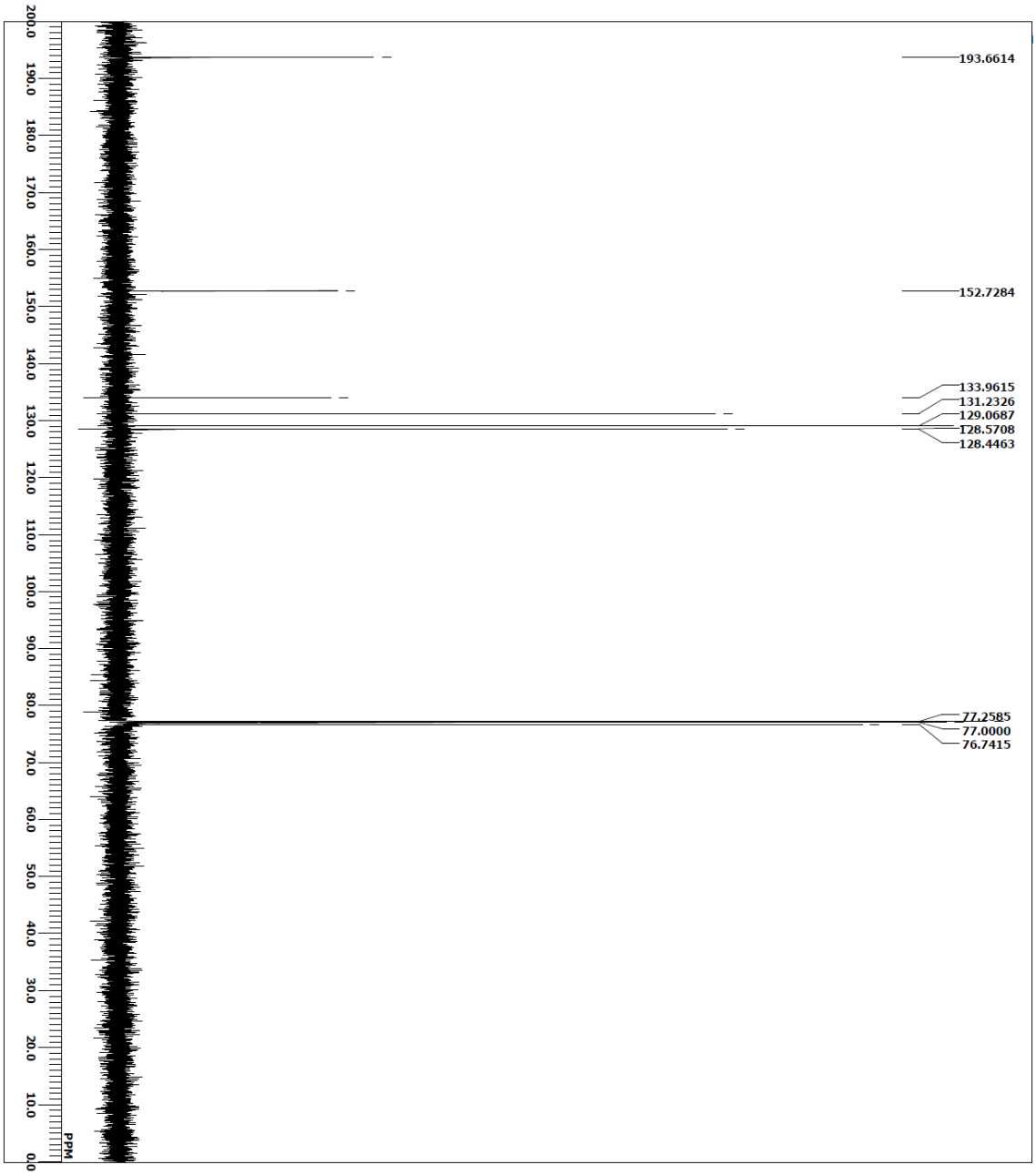
2l

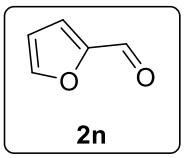

190.1929
153.0141
148.6193
131.7868
128.5697
108.2616
106.8158
102.0284
77.2106
77.0000
76.7798
PPM

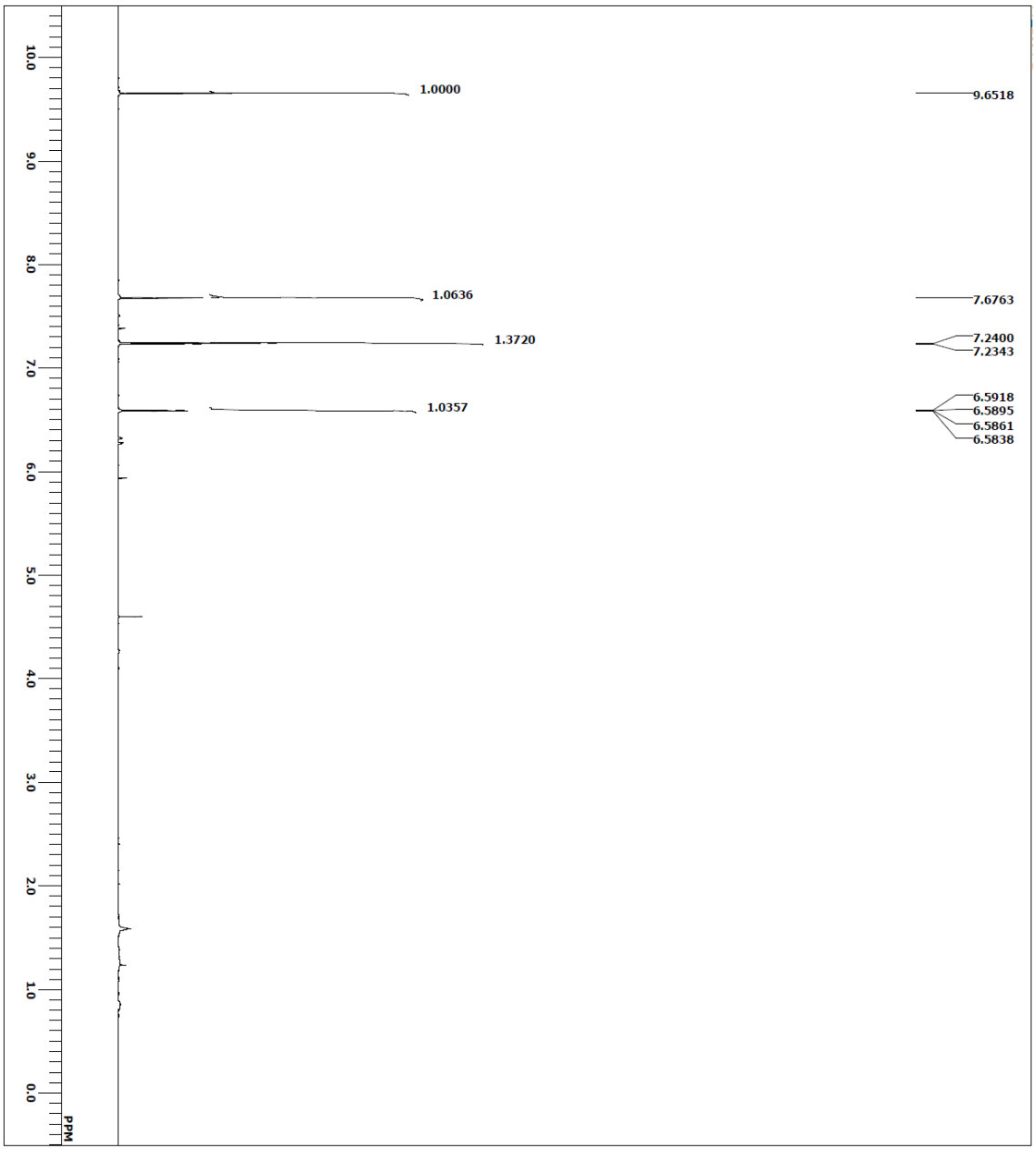

O
2m

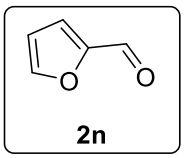

1.0059
1.0653
2.1000
2.9940
1.0000
9.7201
9.7053
7.5828
7.5794
7.5725
7.5634
7.5004
7.4684
7.4558
7.4523
7.4466
7.4432
7.4363
7.4329
7.4248
7.4145
7.2600
6.7506
6.7357
6.7185
6.7036
PPM


O
2m

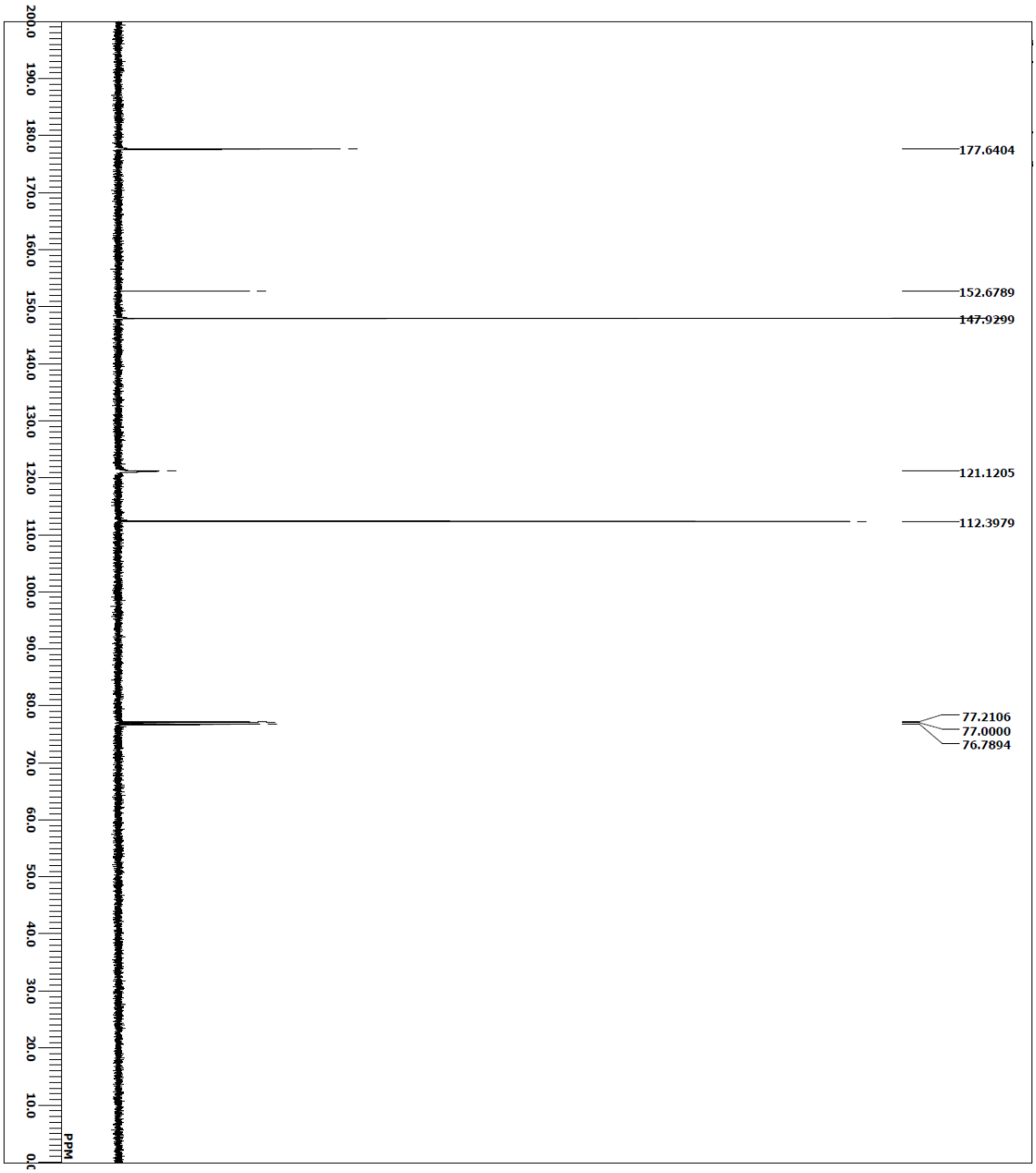

193.6614
152.7284
133.9615
131.2326
129.0687
128.5708
128.4463
77.2585
77.0000
76.7415
PPM

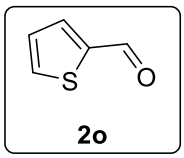

2n


10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM
1.0000
1.0636
1.3720
1.0357
9.6518
7.6763
7.2400
7.2343
6.5918
6.5895
6.5861
6.5838

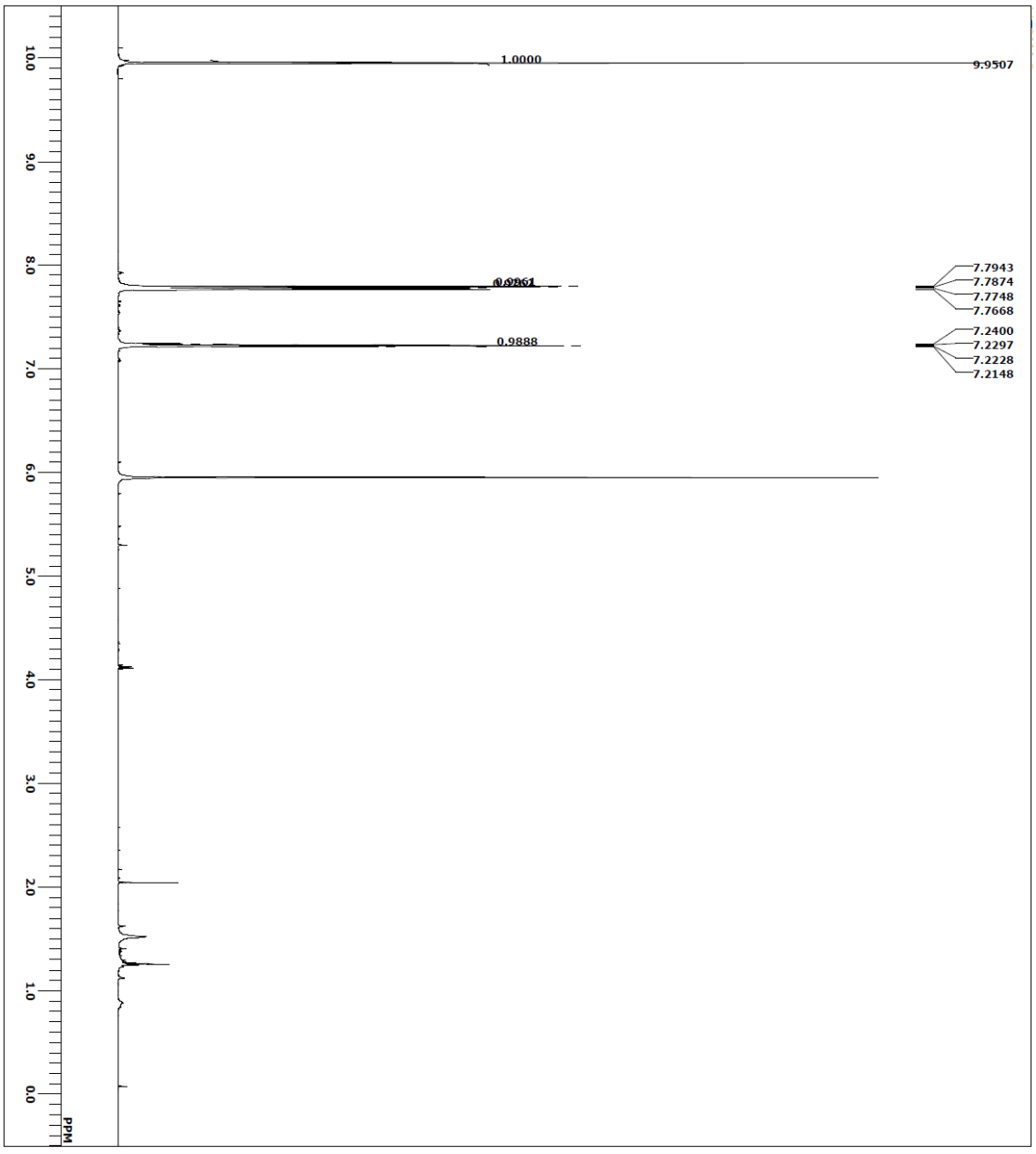

O
O

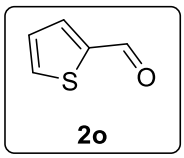
2n


177.6404
152.6789
147.9299
121.1205
112.3979
77.2106
77.0000
76.7894
PPM

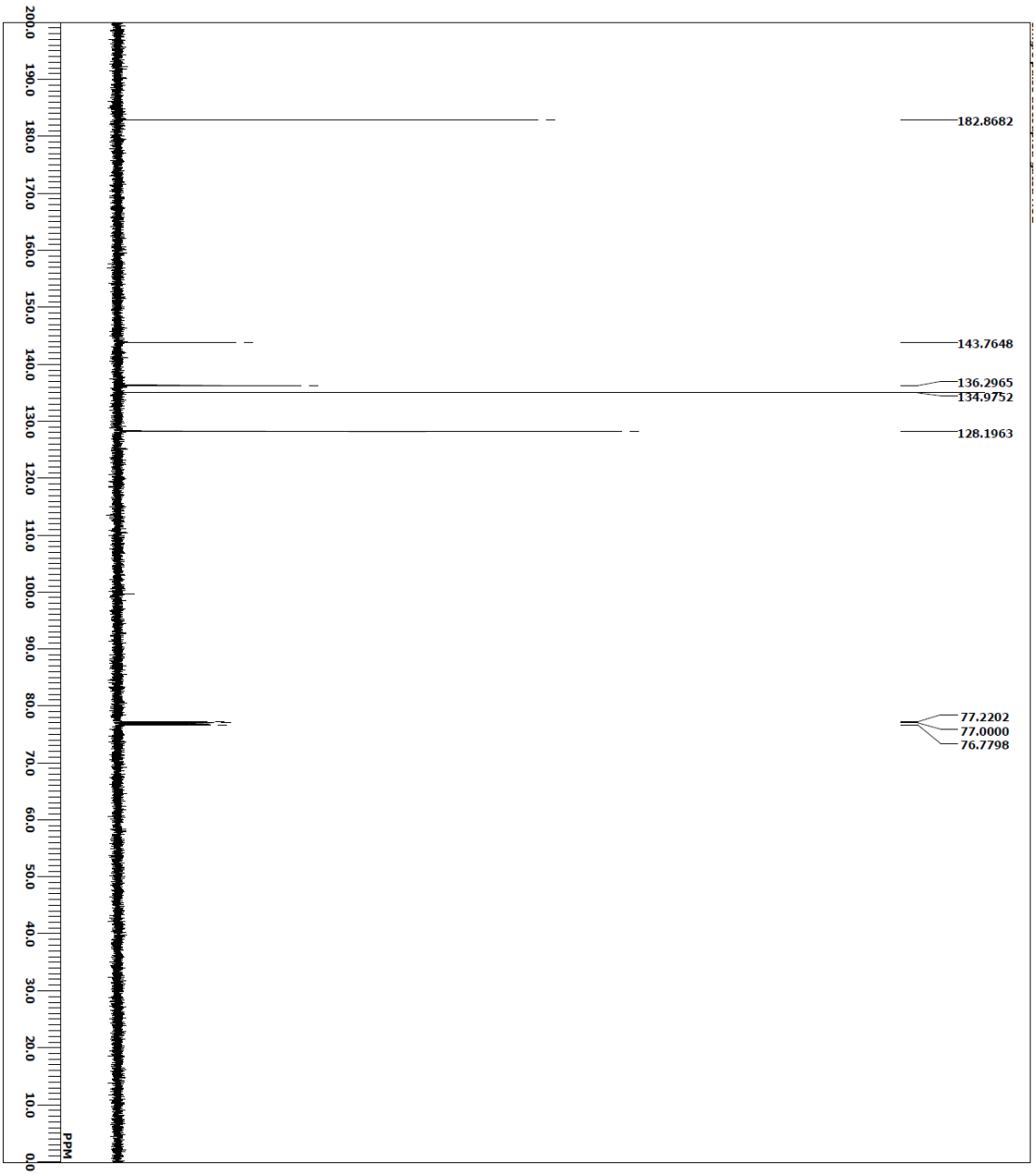

S
O

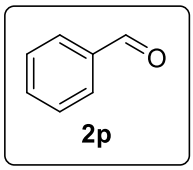
2o

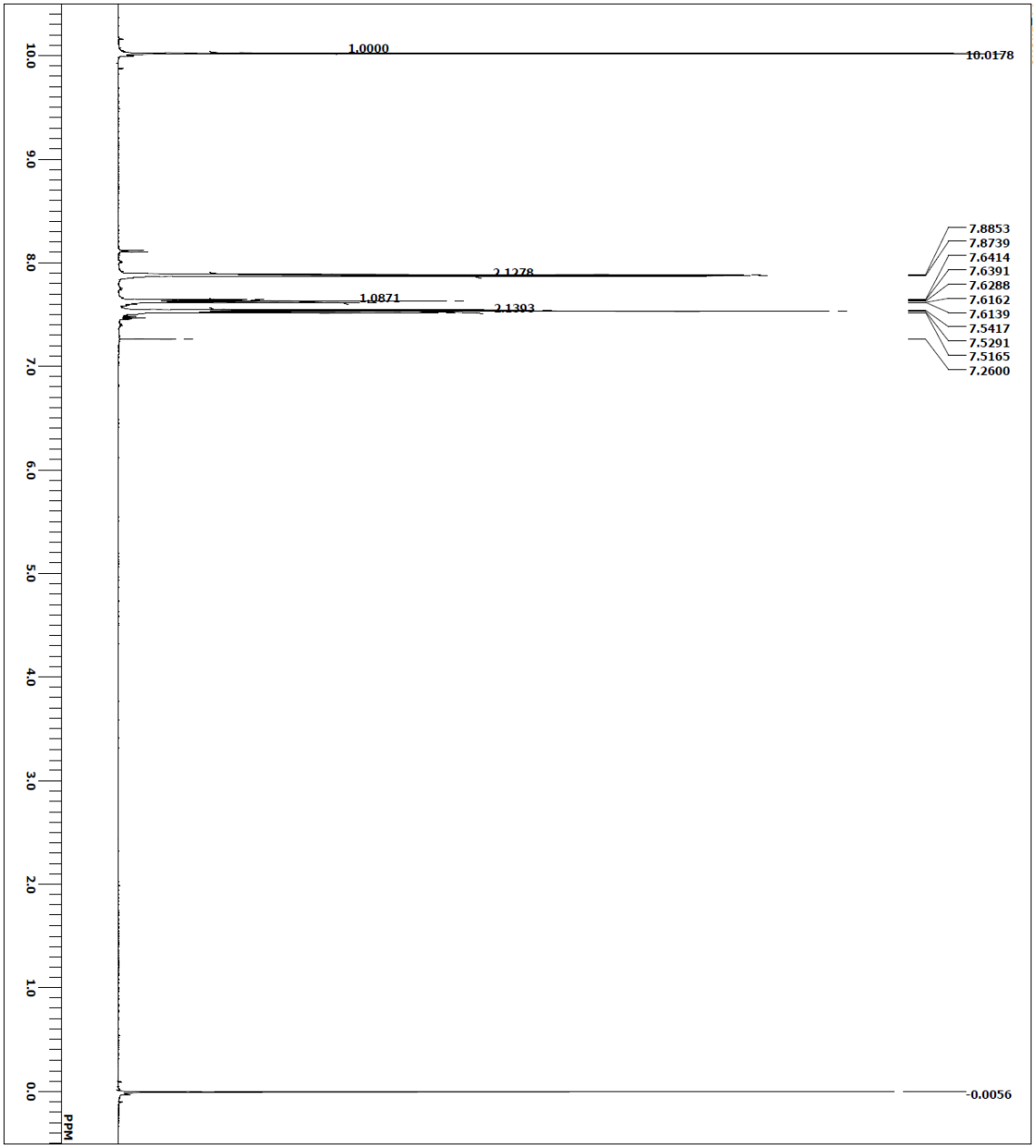

1.0000
9.9507
0.9861
0.9888
7.7943
7.7874
7.7748
7.7668
7.2400
7.2297
7.2228
7.2148
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

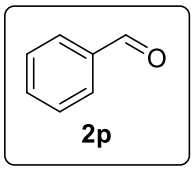

S
O

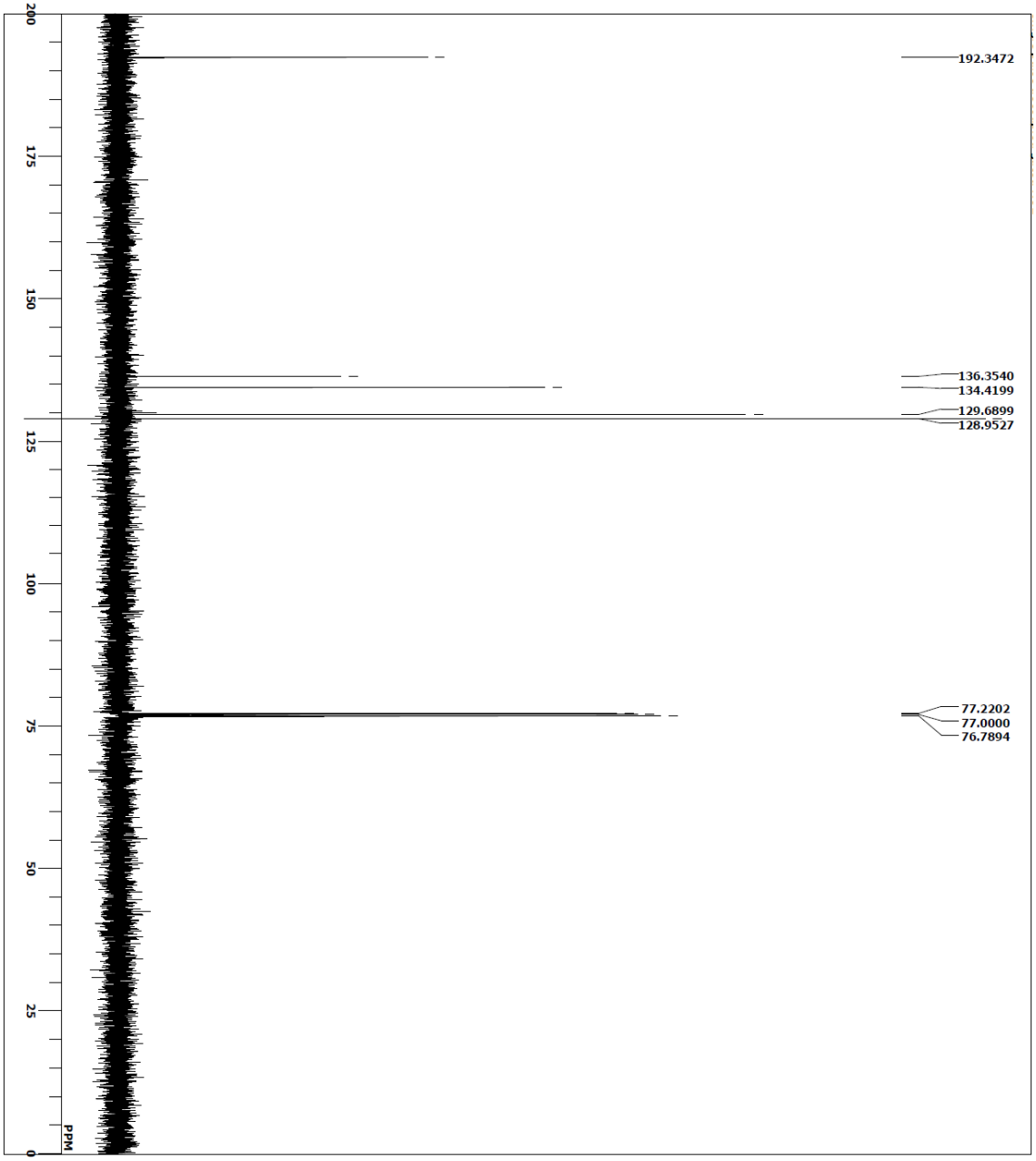
2o

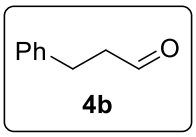

182.8682
143.7648
136.2965
134.9752
128.1963
77.2202
77.0000
76.7798
PPM


O
2p

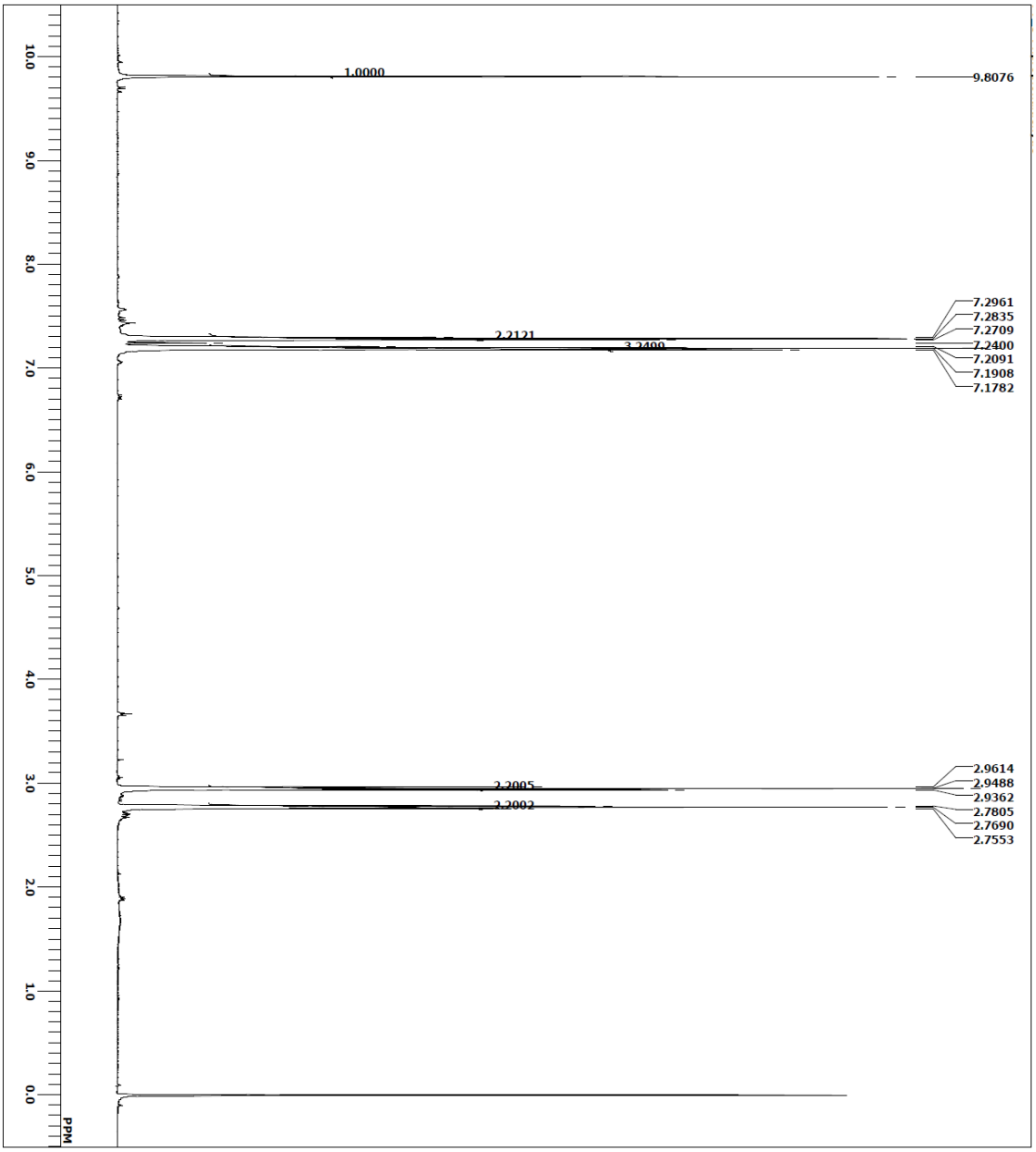

1.0000
10.0178
2.1278
1.0871
2.1393
7.8853
7.8739
7.6414
7.6391
7.6288
7.6162
7.6139
7.5417
7.5291
7.5165
7.2600
0.0056
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

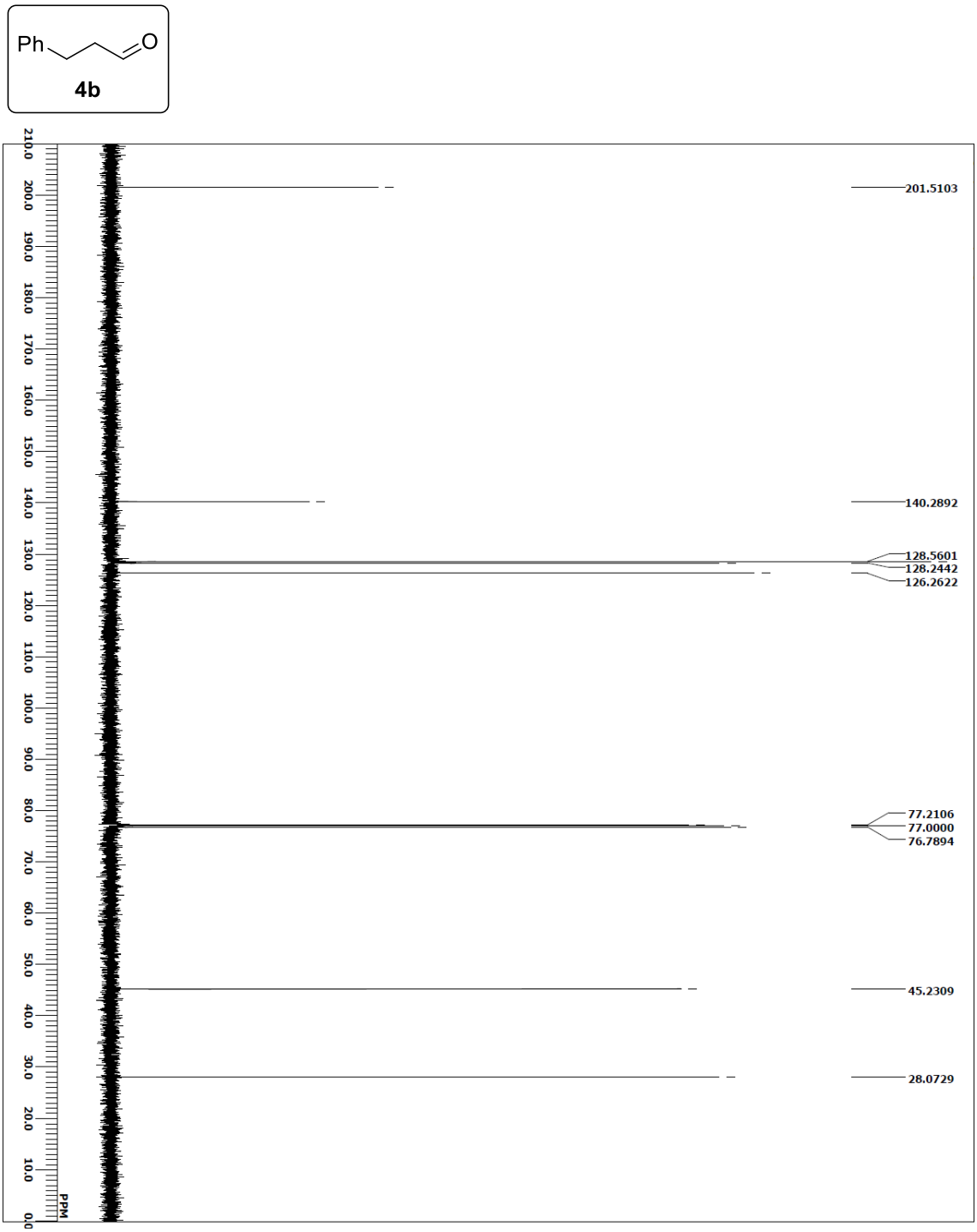

O
2p

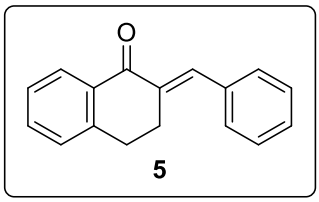

200
175
150
125
100
75
50
25
0
PPM
192.3472
136.3540
134.4199
129.6899
128.9527
77.2202
77.0000
76.7894


Ph
O

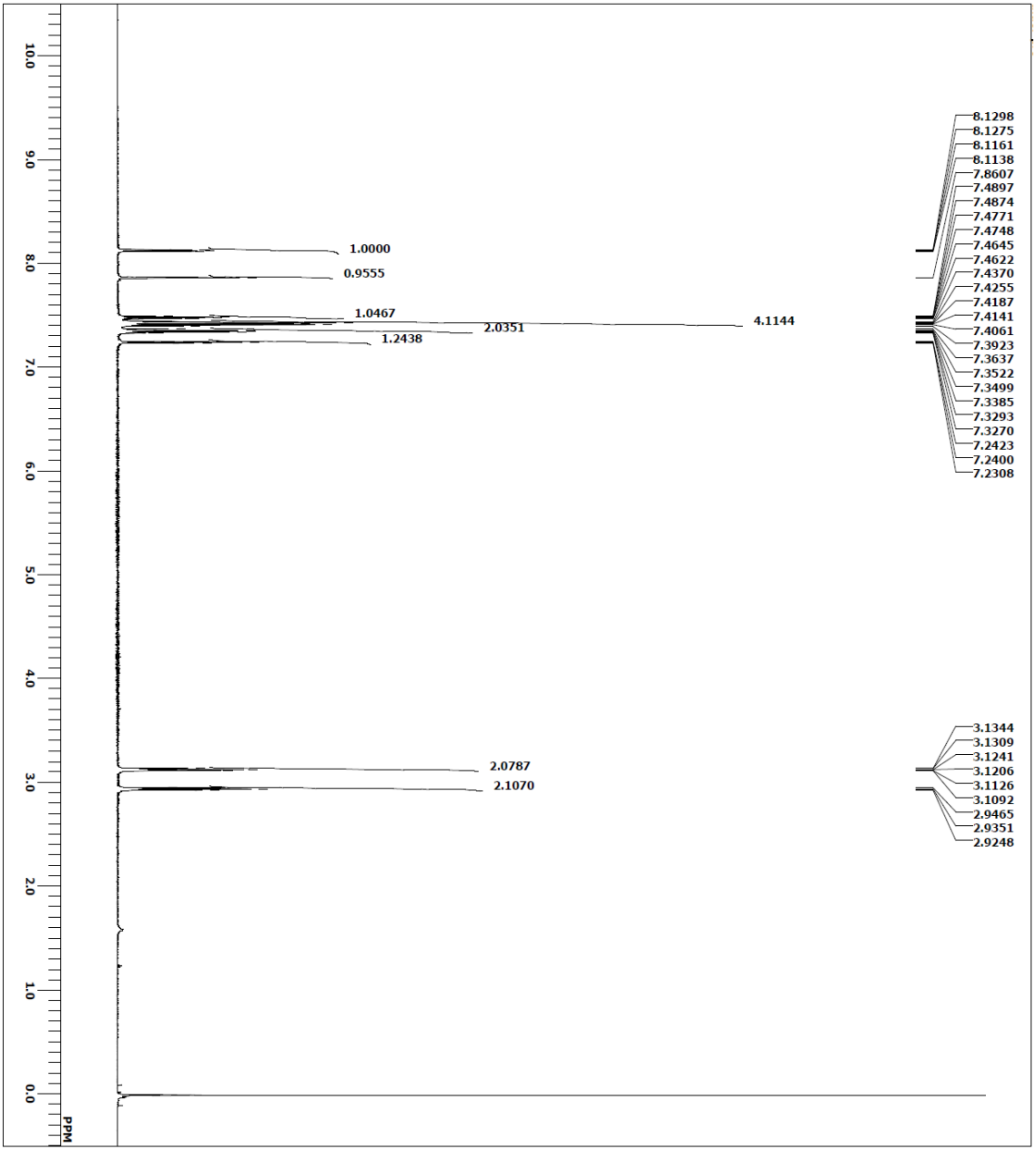
4b

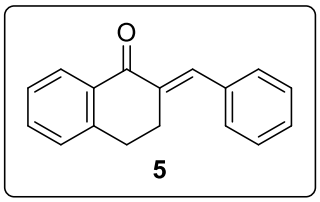

1.0000
9.8076
7.2961
7.2835
7.2709
7.2400
7.2091
7.1908
7.1782
2.2121
3.2409
2.9614
2.9488
2.9362
2.7805
2.7690
2.7553
2.2005
2.2002
PPM


Ph
O
4b
201.5103
140.2892
128.5601
128.2442
126.2622
77.2106
77.0000
76.7894
45.2309
28.0729
PPM

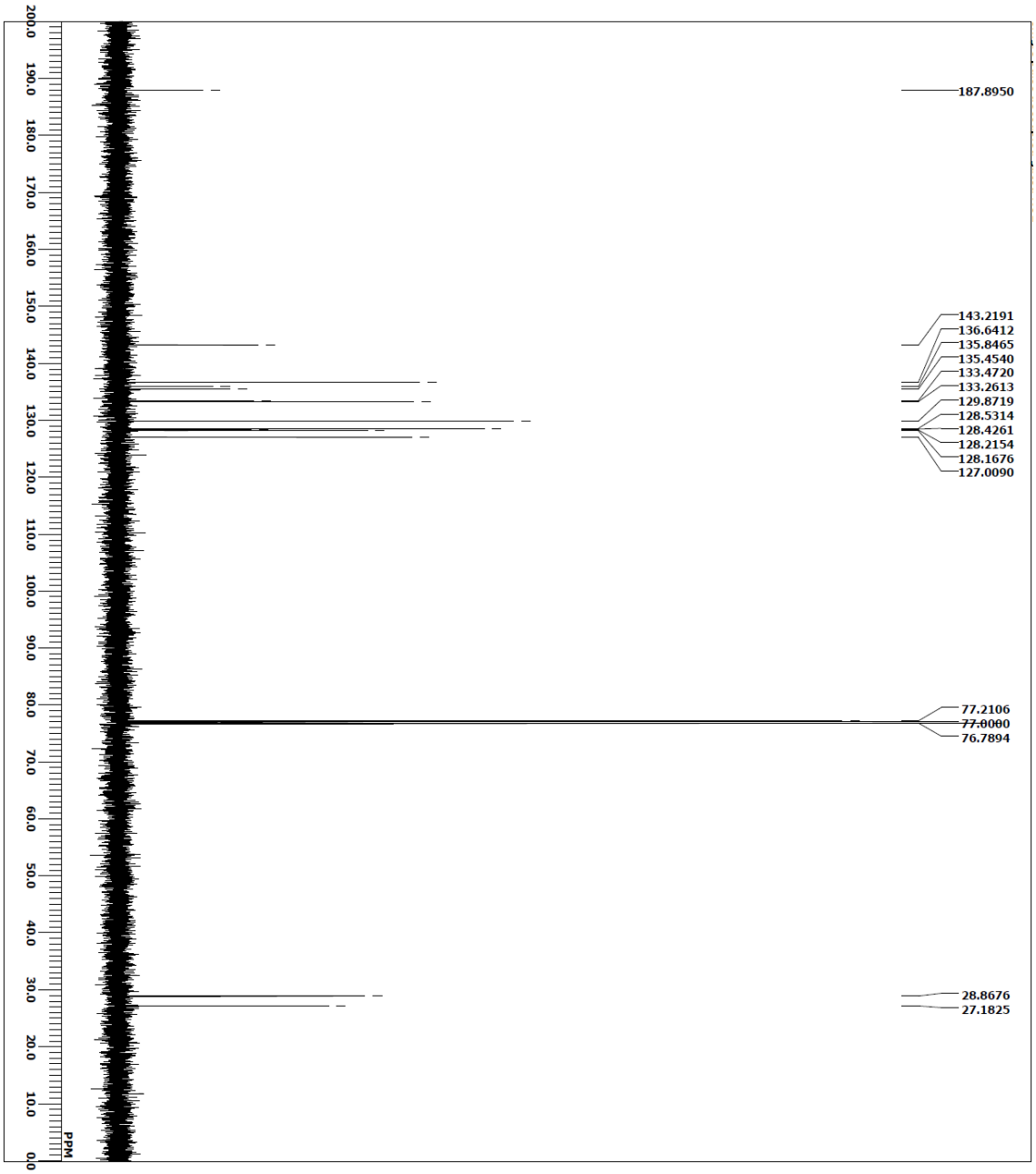

O

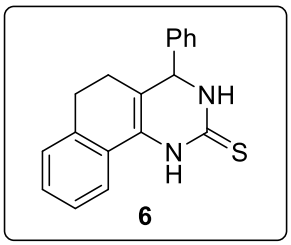
5


10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM
1.0000
0.9555
1.0467
2.0351
4.1144
1.2438
2.0787
2.1070
8.1298
8.1275
8.1161
8.1138
7.8607
7.4897
7.4874
7.4771
7.4748
7.4645
7.4622
7.4370
7.4255
7.4187
7.4141
7.4061
7.3923
7.3637
7.3522
7.3499
7.3385
7.3293
7.3270
7.2423
7.2400
7.2308
3.1344
3.1309
3.1241
3.1206
3.1126
3.1092
2.9465
2.9351
2.9248

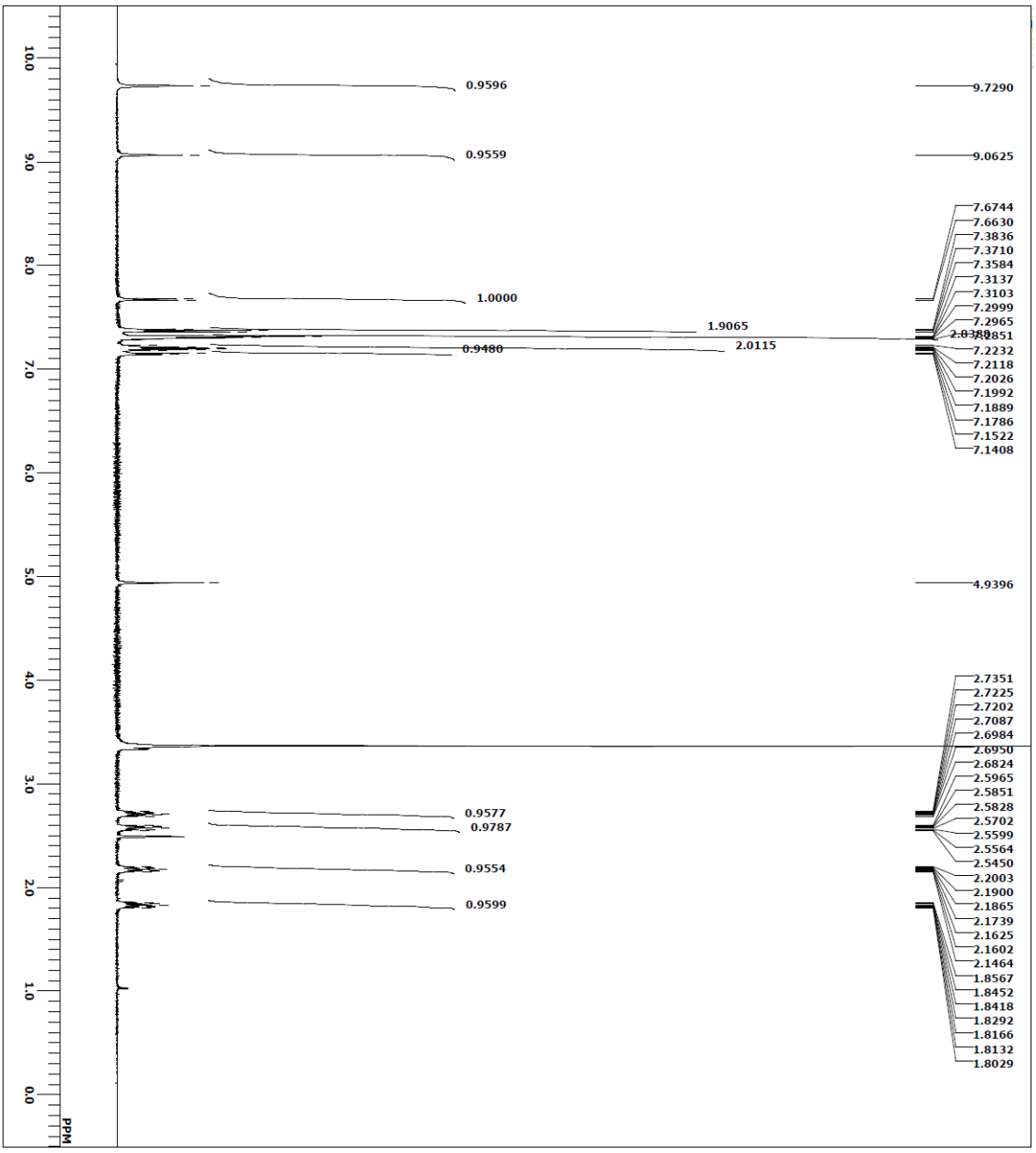

O

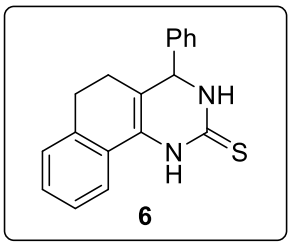
5


187.8950
143.2191
136.6412
135.8465
135.4540
133.4720
133.2613
129.8719
128.5314
128.4261
128.2154
128.1676
127.0090
77.2106
77.0000
76.7894
28.8676
27.1825
PPM

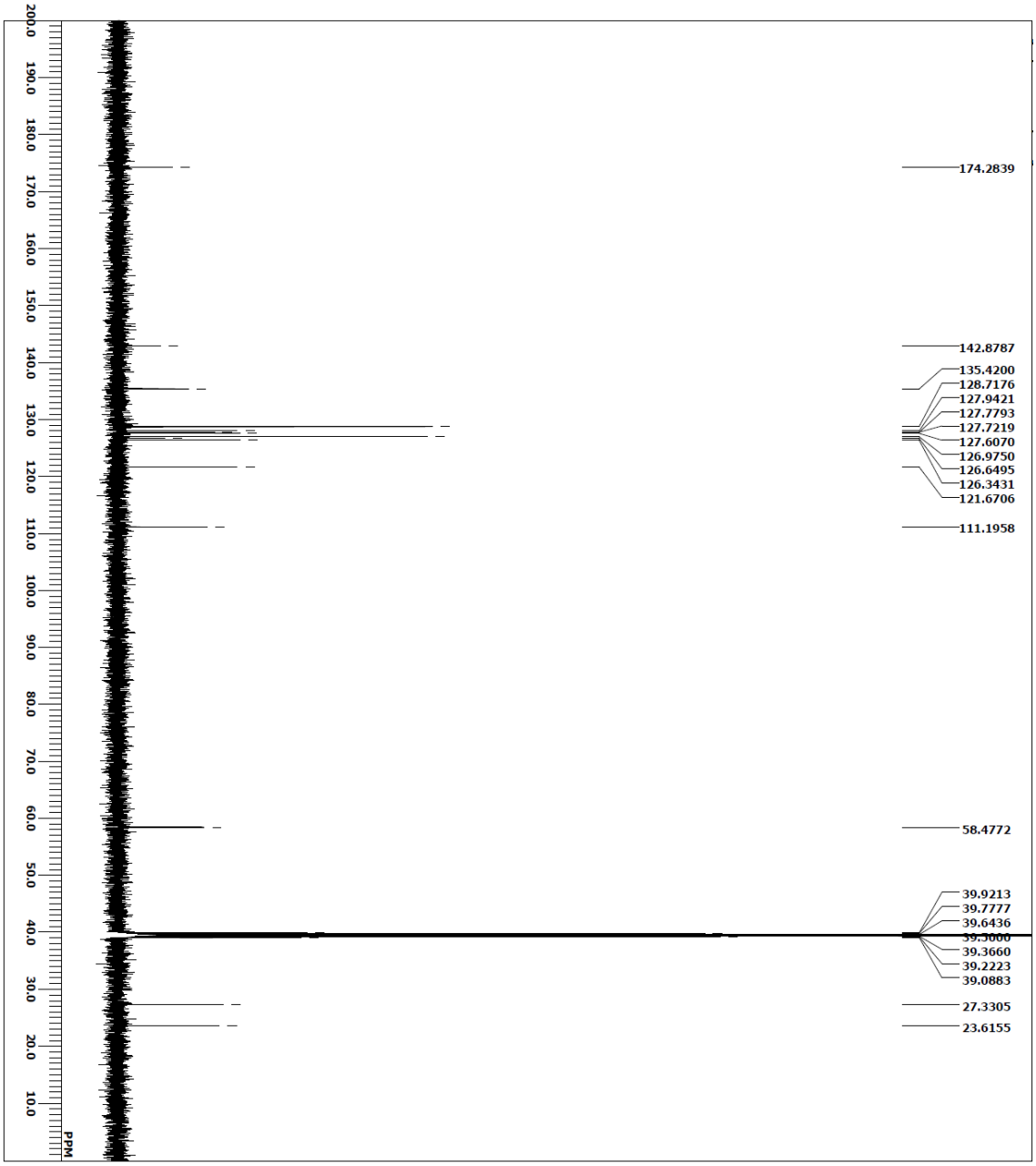

Ph
NH
N
H
S

6


0.9596
0.9559
1.0000
1.9065
0.9480
2.0115
0.9577
0.9787
0.9554
0.9599
9.7290
9.0625
7.6744
7.6630
7.3836
7.3710
7.3584
7.3137
7.3103
7.2999
7.2965
7.2851
7.2232
7.2118
7.2026
7.1992
7.1889
7.1786
7.1522
7.1408
4.9396
2.7351
2.7225
2.7202
2.7087
2.6984
2.6950
2.6824
2.5965
2.5851
2.5828
2.5702
2.5599
2.5564
2.5450
2.2003
2.1900
2.1865
2.1739
2.1625
2.1602
2.1464
1.8567
1.8452
1.8418
1.8292
1.8166
1.8132
1.8029
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM


Ph
NH
N
H
S

6


174.2839
142.8787
135.4200
128.7176
127.9421
127.7793
127.7219
127.6070
126.9750
126.6495
126.3431
121.6706
111.1958
58.4772
39.9213
39.7777
39.6436
39.5060
39.3660
39.2223
39.0883
27.3305
23.6155
PPM

10. References

1. Deng, X.; Chen, K.; Tüysüz, H., Protocol for the Nanocasting Method: Preparation of Ordered Mesoporous Metal Oxides. *Chem. Mater.* **2017**, *29*, 40.
2. Bobbitt, J. M.; Eddy, N. A.; Cady, C. X.; Jin, J.; Gascon, J. A.; Gelpí-Dominguez, S.; Zakrzewski, J.; Morton, M. D., Preparation of Some Homologous TEMPO Nitroxides and Oxoammonium Salts; Notes on the NMR Spectroscopy of Nitroxide Free Radicals; Observed Radical Nature of Oxoammonium Salt Solutions Containing Trace Amounts of Corresponding Nitroxides in an Equilibrium R. *J. Org. Chem.* **2017**, *82*, 9279.
3. Yasukawa, T.; Yang, X.; Kobayashi, S., Development of N-Doped Carbon-Supported Cobalt/Copper Bimetallic Nanoparticle Catalysts for Aerobic Oxidative Esterifications Based on Polymer Incarceration Methods. *Org. Lett.* **2018**, *20*, 5172.
4. Yasukawa, T.; Miyamura, H.; Kobayashi, S., Polymer-incarcerated chiral Rh/Ag nanoparticles for asymmetric 1,4-addition reactions of arylboronic acids to enones: Remarkable effects of bimetallic structure on activity and metal leaching. *J. Am. Chem. Soc.* **2012**, *134*, 16963.
5. Tabata, M.; Moriyama, K.; Togo, H., One-Pot Transformation of Methylarenes into Aromatic Aldehydes under Metal-Free Conditions. *Eur. J. Org. Chem.* **2014**, *2014*, 3402.
6. Han, C.; Buchwald, S. L., Negishi Coupling of Secondary Alkylzinc Halides with Aryl Bromides and Chlorides. *J. Am. Chem. Soc.* **2009**, *131*, 7532.
7. Nicklaus, C. M.; Phua, P. H.; Buntara, T.; Noel, S.; Heeres, H. J.; De Vries, J. G., Ruthenium/1,1′-Bis(diphenylphosphino)ferrocene-Catalysed Oppenauer Oxidation of Alcohols and Lactonisation of α,ω-Diols using Methyl Isobutyl Ketone as Oxidant. *Adv. Synth. Catal.* **2013**, *355*, 2839.
8. Cheng, C.; Brookhart, M., Efficient Reduction of Esters to Aldehydes through Iridium-Catalyzed Hydrosilylation. *Angew. Chem., Int. Ed.* **2012**, *51*, 9422.
9. Laroche, B.; Saito, Y.; Ishitani, H.; Kobayashi, S., Basic Anion-Exchange Resin-Catalyzed Aldol Condensation of Aromatic Ketones with Aldehydes in Continuous Flow. *Org. Process Res. Dev.* **2019**, *23*, 961.
10. Sivakumar, M.; Prabakaran, K.; Seenivasa Perumal, M., Base-mediated one-pot synthesis of 3,4,5,6-tetrahydro-4-substituted benzo[h]quinazoline-2(1H)-thione derivatives and evaluation of their antioxidant activity. *Synth. Commun.* **2018**, *48*, 197.