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Supporting Information

Evaluation of 3- and 4-Phenoxybenzamides as Selective Inhibitors of the Mono-ADP-Ribosyltransferase PARP10

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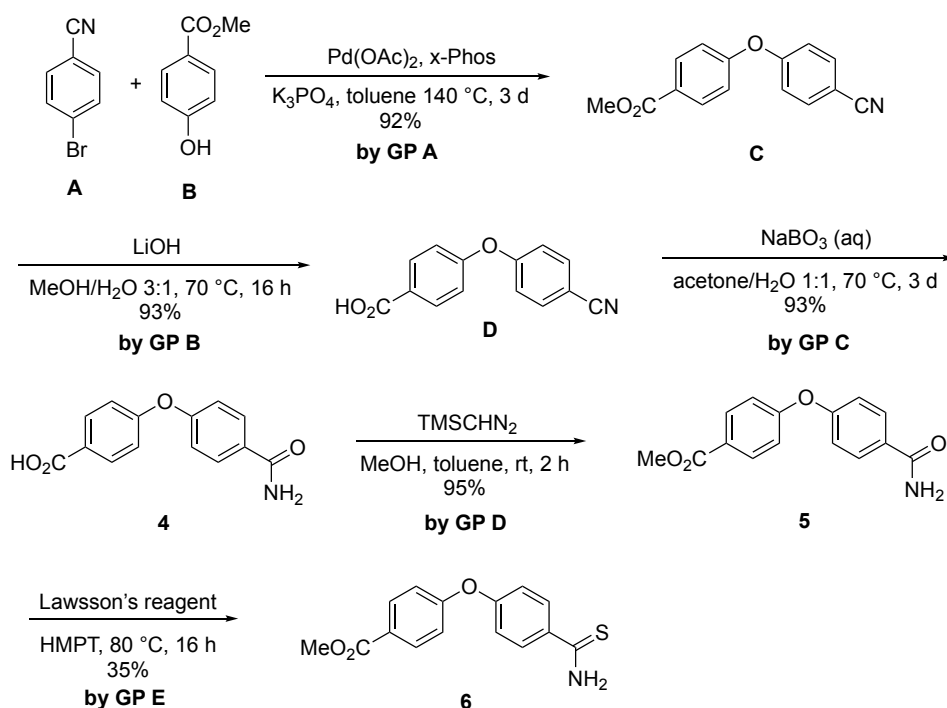
1. Chemistry

1.1. General information

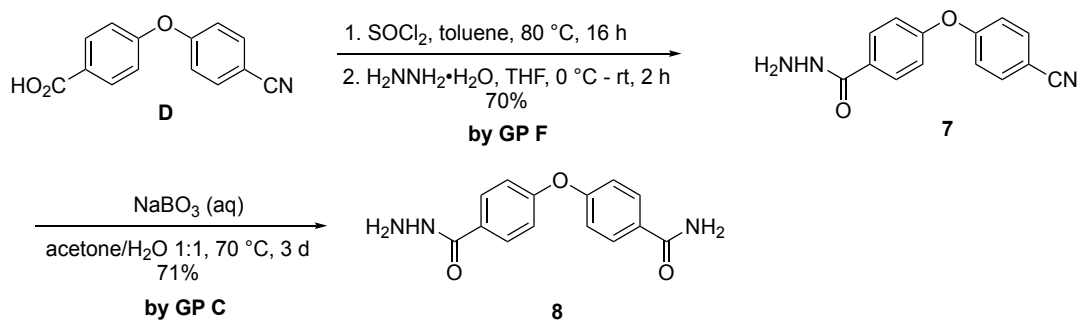
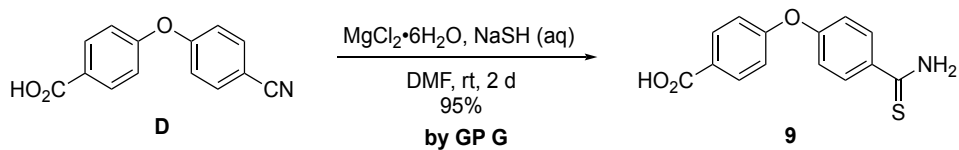
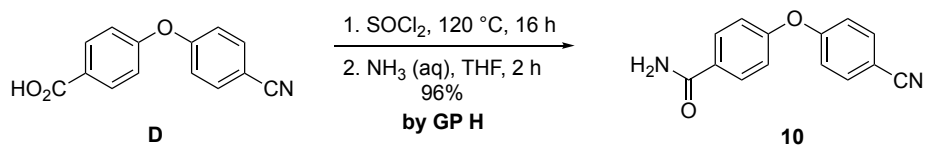
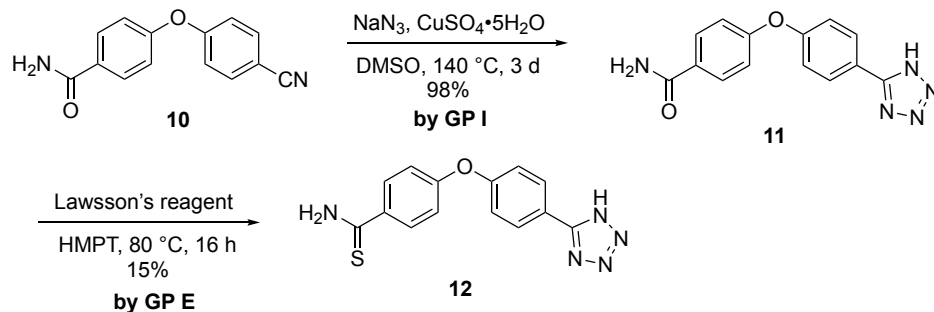
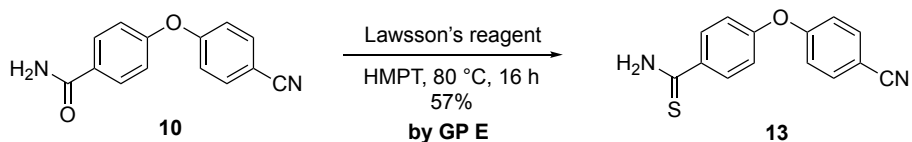
^1H NMR and ^{13}C NMR were recorded on a Varian VNMR 400 or VNMR 600 spectrometer in CDCl_3 or DMSO-d_6 . Chemical shifts (δ) were given in ppm relative to TMS ($\delta = 0$). Coupling constants J were reported in Hz and coupling patterns were described as br = broad, s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Mass spectra (MS) were recorded on a Finnigan SSQ 7000 spectrometer (EI, 70 eV). The atomic mass of the molecular ion and the fragments per elementary charge were reported as dimensionless quantities. The intensities were given in percent relative to the base peak. HRMS was recorded on a ThermoFisher Scientific LTQ-Orbitap XL spectrometer. IR spectra were acquired on a Perkin-Elmer Spectrum FT-IR 100 spectrometer with the wavenumbers in cm^{-1} . Melting points were measured with a Büchi Melting Point B-540 apparatus.

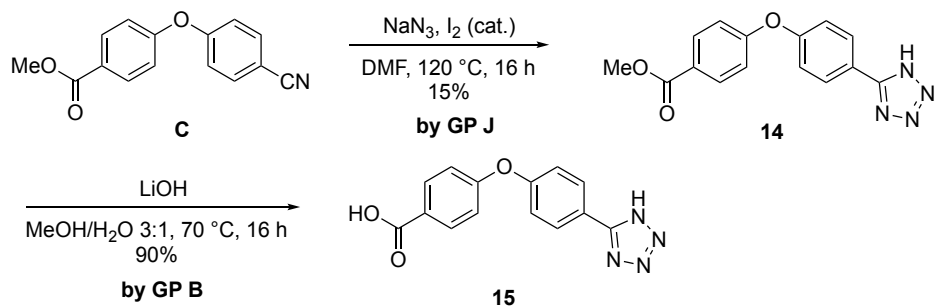
1.2. Reaction schemes

1.2.1. Syntheses of *para,para*-disubstituted diarylethers

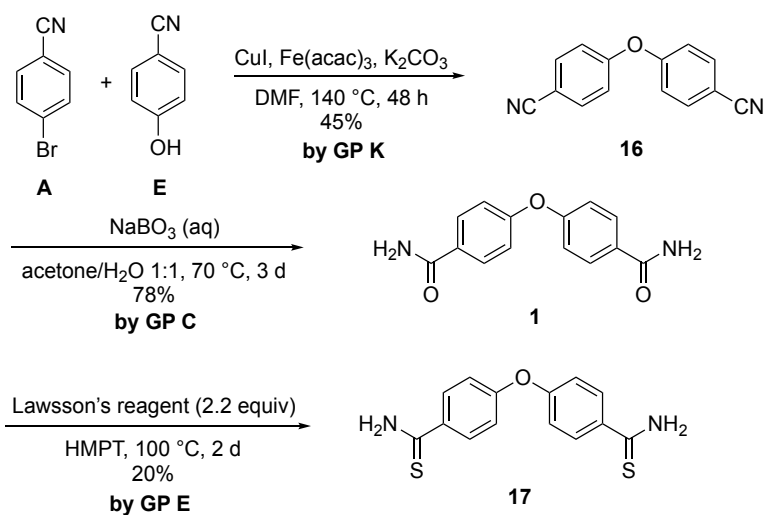


Scheme S1. Syntheses of **4-6** starting from compounds **A** and **B**.

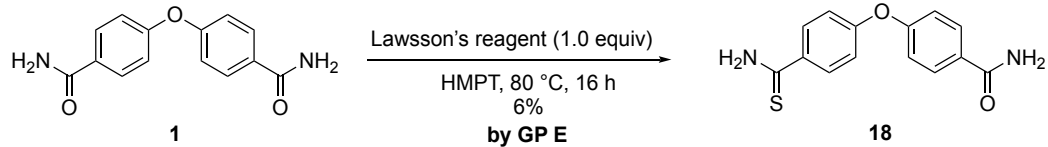
Scheme S2. Syntheses of **7** and **8** starting from compound **D**Scheme S3. Synthesis of **9** starting from compound **D**Scheme S4. Synthesis of **10** starting from compound **D**Scheme S5. Syntheses of **11** and **12** starting from compound **10**Scheme S6. Synthesis of **13** starting from compound **10**



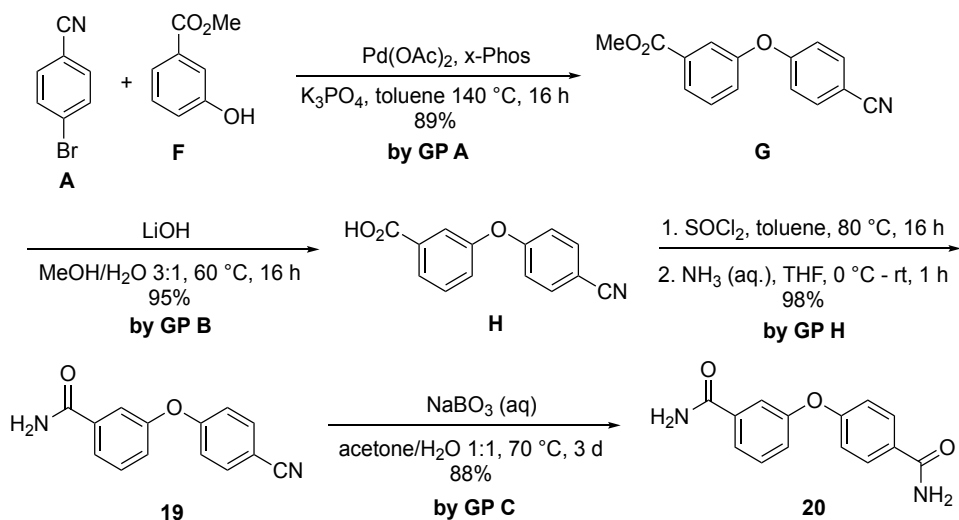
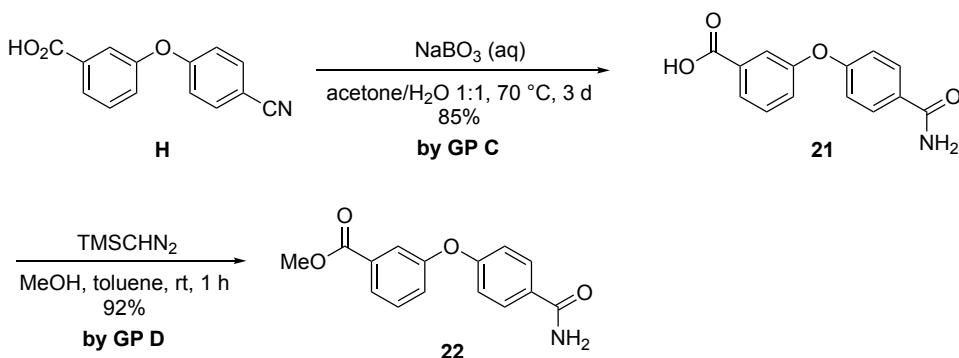
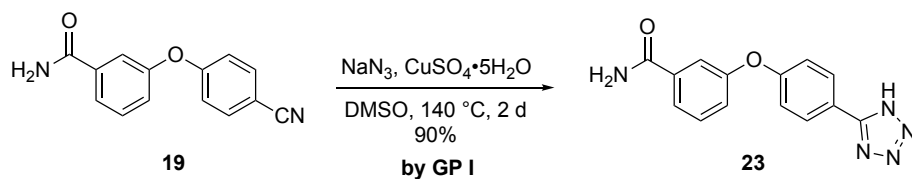
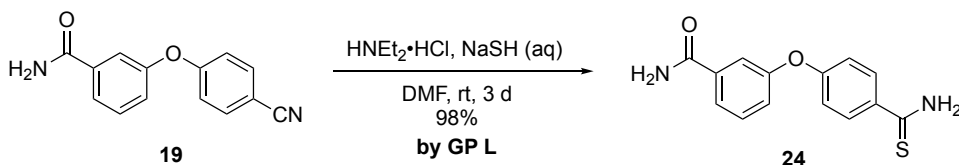
Scheme S7. Syntheses of **14** and **15** starting from compound **C**

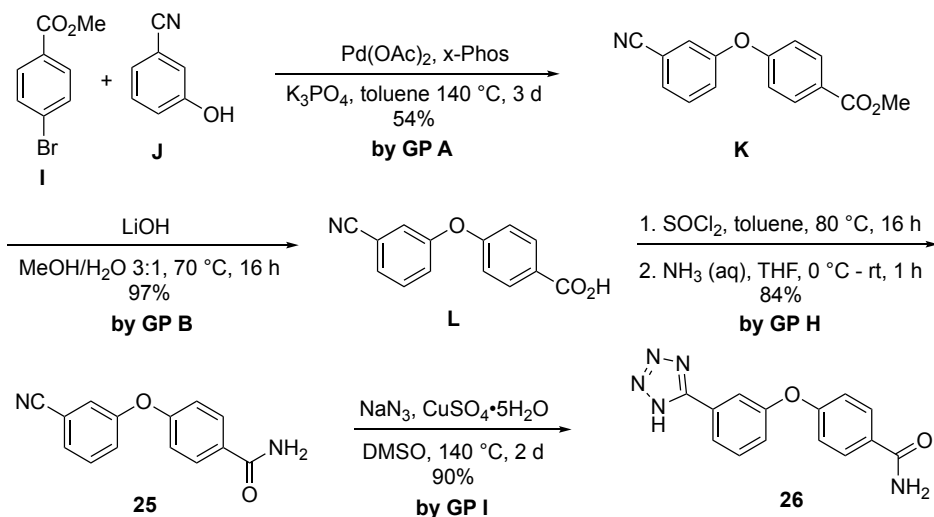


Scheme S8. Syntheses of **1**, **16** and **17** starting from compounds **A** and **E**

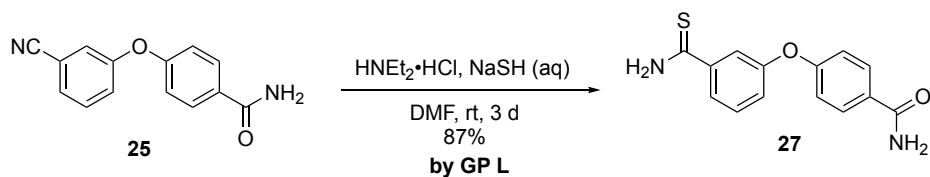


Scheme S9. Synthesis of **18** starting from compound **1**

1.2.2. Syntheses of *para,meta*-disubstituted diarylethersScheme S10. Syntheses of **19** and **20** starting from compounds **A** and **F**Scheme S11. Syntheses of **21** and **22** starting from compound **H**Scheme S12. Synthesis of **23** starting from compound **19**Scheme S13. Synthesis of **24** starting from compound **19**

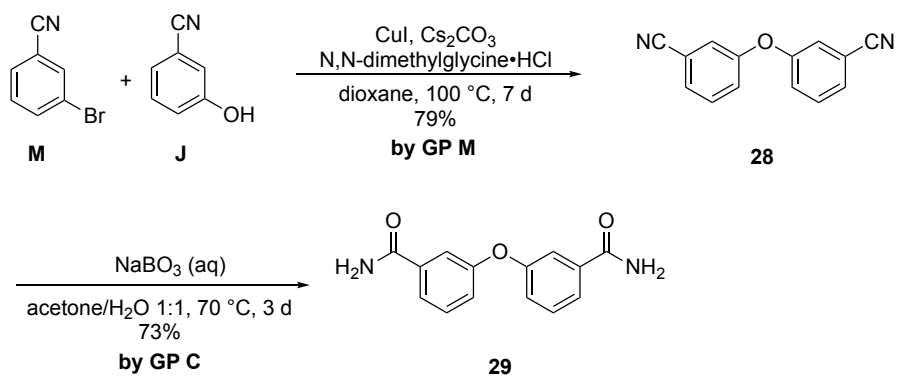


Scheme S14. Syntheses of **25** and **26** starting from compounds **I** and **J**

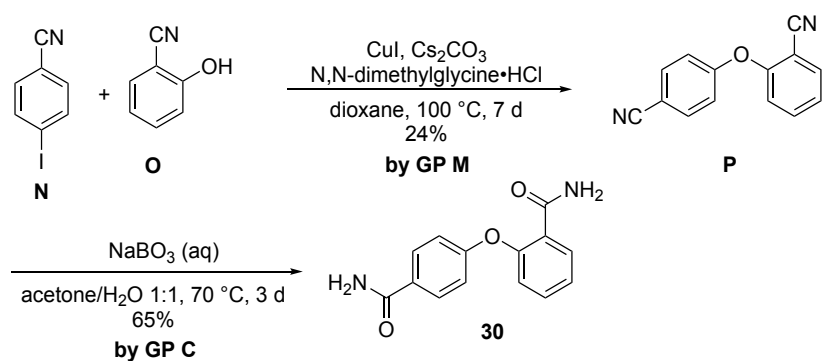
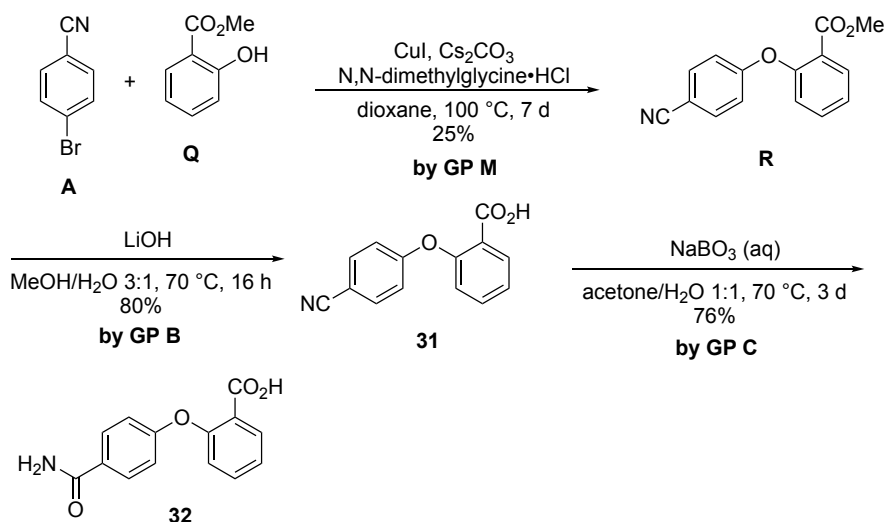
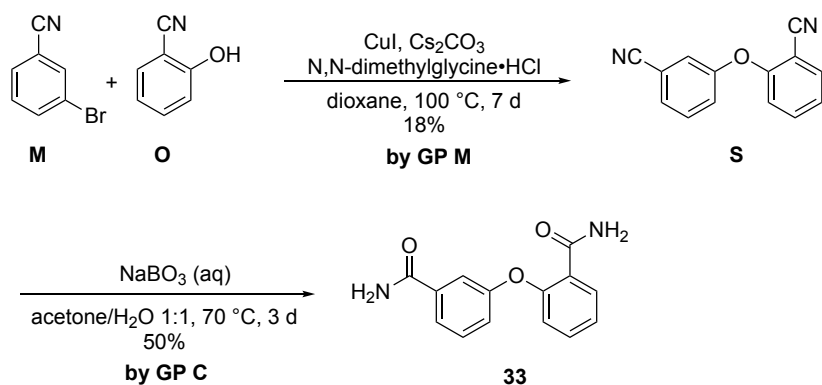


Scheme S15. Synthesis of **27** starting from compound **25**

1.2.3. Syntheses of *meta,meta*-disubstituted diarylethers



Scheme S16. Syntheses of **28** and **29** starting from compounds **M** and **J**

1.2.4. Syntheses of *para,ortho*-disubstituted diarylethersScheme S17. Synthesis of **30** starting from compounds **N** and **O**Scheme S18. Syntheses of **31** and **32** starting from compounds **A** and **Q**1.2.5. Syntheses of *meta,ortho*-disubstituted diarylethersScheme S19. Synthesis of **33** starting from compounds **M** and **O**

1.3. General procedures

General Procedure A (GP A) - for the syntheses of compounds C, G, and K:^[S1]

In a sealed Schlenk tube, the 4-bromo-substituted arene (10 mmol) and the respective phenole derivative (10 mmol) were mixed with palladium-(II)-acetate (44 mg, 0.2 mmol, 2 mol %) and 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-Phos, 143 mg, 0.3 mmol, 3 mol %) under an atmosphere of argon. Then, dry tripotassium phosphate (20 mmol, generated from 4.6 g of tripotassium phosphate monohydrate by heating at 160 °C under vacuum for 16 h) followed by dry toluene (30 mL) were added. The mixture was heated to 140 °C for the described time under an atmosphere of argon. Cooling to room temperature, adding water (25 mL) and extracting with ethyl acetate (3 x 30 mL) led to a mixture, which was washed with water and dried over magnesium sulfate. After filtration, evaporation of the organic components gave a crude product mixture, and the product was purified by column chromatography using the described mixture of cyclohexane and ethyl acetate.

General Procedure B (GP B) - for the syntheses of compounds D, H, L, 15, and 31:

The ester (3 mmol) resulting from GP A and lithium hydroxide monohydrate (157.3 mg, 3.75 mmol) were kept in 36 mL of a mixture of methanol/water (v/v = 3:1) at 70 °C for 16 h. After evaporation, the residue was treated with water (5 mL), and the mixture was set to pH 3 with hydrochloric acid (2 M). Suction, washing with water, and drying at 40 °C for 16 h gave a colorless solid of the corresponding benzoic acid.

General Procedure C (GP C) - for the syntheses of compounds 1, 4, 8, 20, 21, 29, 30, 32, and 33:^[S2]

The benzonitrile (1.1 mmol) was stirred with sodium perborate tetrahydrate (520 mg, 3.4 mmol) in 10 mL of a mixture of acetone and water (v/v=1:1) in a sealed tube at 70 °C for 3 days. Then, the reaction mixture was cooled, evaporated in vacuum, and the residue was boiled up in water (10 mL). The suspension was filtered through a G3 glass frit, and the filter cake was washed with boiling water (3 x 5 mL). Drying at 40 °C for 16 h yielded colorless phenoxy benzamides.

General Procedure D (GP D) - for the syntheses of compounds 5 and 22:

The respective benzoic acid (1 mmol) was suspended in a mixture of 2 mL of methanol and 5 mL of dry toluene and cooled to 0 °C. After dropwise addition of 2.17 mL of a 0.6 M solution of trimethylsilyl diazomethane in hexane the reaction was allowed to come to room temperature during 2 hours. Evaporation and column chromatography with ethyl acetate/cyclohexane (6:1) gave the colorless solids of the corresponding methyl esters.

General Procedure E (GP E) - for the syntheses of compounds 6, 12, 13, 17, and 18:^[S3,S4]

The respective benzamide (0.6 mmol) was heated with Lawsson's reagent (1.32 mmol, 2.2 equiv) in hexamethyl phosphoric acid triamide (2 mL) at 80 °C (except for **17** where the temperature was 100 °C) for the specified period of time. (Note: In the preparation of **18**, only 1 equiv of Lawsson's reagent was used.) Each product was isolated by direct column chromatography of the resulted reaction solution with the described mixtures of eluents to yield the corresponding thiobenzamide.

General Procedure F (GP F) - for the synthesis of compound 7:

Benzoic acid **D** (1.67 mmol) was suspended in dry toluene (15 mL). After dropwise addition of thionyl chloride (0.4 mL, 5.5 mmol) the mixture was heated at 120 °C for 16 h. Evaporation of the reaction solution and drying in vacuum gave the crude acid chloride that was reacted further directly. A solution of the acid chloride in dry THF (5 mL) was cooled to 0 °C, and hydrazine hydrate (2 mL) was carefully dropped in with stirring while the reaction mixture was allowed to come to room temperature during 2 h. After extraction with ethyl acetate (3 x 20 mL), washing with water and drying over magnesium sulfate, the organic extract was filtered and evaporated in vacuum to yield benzoic acid hydrazide **7**.

General Procedure G (GP G) - for the synthesis of compound 9:^[S5]

A mixture of benzoic acid **D** (0.5 mmol), magnesium chloride hexahydrate (0.5 mmol), and sodium hydrosulfide hydrate (0.5 mmol) in dimethyl formamide (5 mL) was stirred at room temperature for 3 days. After diluting with water (10 mL), the reaction mixture was set to pH 3 with 2M hydrochloric acid. Extraction with ethyl acetate (3 x 15 mL) was followed by drying over magnesium sulfate, filtration and evaporation. The product was then purified by column chromatography (ethyl acetate/cyclohexane = 2:1) to yield **9** as a bright yellowish solid.

General Procedure H (GP H) - for the syntheses of compounds 10, 19, and 25:

The respective benzoic acid (1.67 mmol) resulting from GP B was suspended in dry toluene (15 mL). After dropwise addition of thionyl chloride (0.4 mL, 5.5 mmol) the mixture was heated at 120 °C for 16 h. Evaporation and drying in vacuum gave a crude acid chloride that was dissolved in dry THF (5 mL). While cooling in an ice bath, ammonia (3 mL, 25% water solution) was carefully dropped into the solution followed by stirring for up to 2 h at room temperature. After extraction with ethyl acetate (3 x 20 mL), washing with water, and drying over magnesium sulfate the organic extract was filtered and evaporated in vacuum to yield the corresponding amide as a colorless solid.

General Procedure I (GP I) - for the syntheses of compounds 11, 23, and 26:^[S6]

A mixture of the respective aryl nitrile (0.5 mmol), sodium azide (0.75 mmol) and a catalytic amount of copper sulfate pentahydrate (5 mg) in dimethyl sulfoxide (3 mL) was heated at 140 °C for 2 days. After cooling, the reaction mixture was acidified with 1 mL of 2 M hydrochloric acid, extracted with ethyl acetate (3 x 10 mL) and washed with water to neutrality. The product was purified by column chromatography (ethyl acetate/ethanol = 3:1) to yield the colorless solid tetrazoles.

General Procedure J (GP J) - for the synthesis of compound 14:^[S7]

Aryl nitrile **C** (0.5 mmol), sodium azide (0.75 mmol) and a catalytic amount of iodine (10 mg, 8 mol %) in dry dimethyl formamide (5 mL) were heated at 120 °C for 16 h. Then, the reaction mixture was cooled to room temperature, acidified with 1 mL of 2 M hydrochloric acid and extracted with ethyl acetate (3 x 10 mL). Decolorization of the organic phase was achieved by washing with a diluted solution of sodium thiosulfate. Drying over magnesium sulfate, filtration and evaporation led to a crude product mixture, and the product was purified by column chromatography (ethyl acetate/ethanol = 3:1) to yield **14** as a colorless solid.

General Procedure K (GP K) - for the synthesis of compound 16:^[S8]

A mixture of 4-cyano bromobenzene (**A**, 15 mmol), 4-cyanophenol (**E**, 15 mmol), potassium carbonate (15.5 mmol), copper(I) iodide (57.3 mg, 2 mol %), and ferrum-III-acetylacetonate (212.1 mg, 4 mol %) in dry dimethyl formamide (10 mL) was heated to 140 °C under an atmosphere of argon for 2 days. After cooling, the reaction mixture was treated with 10 mL of a 2.5 M sodium hydroxide solution and extracted with dichloromethane (3 x 30 mL). Drying over magnesium sulfate, filtration and evaporation gave a crude product mixture that was further evaporated in high vacuum at 60 °C to get rid of most of the dimethyl formamide. For crystallization the crude product was dissolved in ethyl acetate (15 mL) under reflux and cyclohexane was dropped in (about 24 mL) until a bright cloudiness occurred. Then, the mixture was slowly cooled to room temperature and put into the fridge at 2 °C for 16 h. The crystallized product was filtered off and dried at 40 °C for 16 h to yield **16** as a colorless solid.

General Procedure L (GP L) - for the syntheses of compounds 24 and 27:^[S9]

A mixture of the respective aryl nitrile (0.5 mmol), diethyl ammonium hydrochloride (1.75 mmol), and sodium hydrogensulfide hydrate (1.75 mmol) was stirred in dimethyl formamide

(5 mL) at room temperature for 3 days. Dilution with water (10 mL), acidification with 2 M hydrochloric acid to pH 3 and extraction with ethyl acetate (3 x 10 mL) led to an extract that was dried over magnesium sulfate, filtered and evaporated to give a crude product. Purification by column chromatography (ethyl acetate/cyclohexane = 3:1) yielded the products as yellowish solids.

General Procedure M (GP M) - for the syntheses of compounds P, R, S, and 28:^[S10]

A mixture of the respective halo benzene (2 mmol), the substituted phenol (2.2 mmol), copper(I) iodide (0.2 mmol), cesium carbonate (4 mmol), and N,N-dimethyl glycine hydrochloride (0.6 mmol) in 1,4-dioxane (5 mL) was heated to 100 °C for 7 days. After cooling to room temperature, the reaction mixture was treated with water (10 mL), extracted with ethyl acetate (3 x 10 mL), dried over magnesium sulfate, filtered and finally evaporated to give a crude product. Purification by column chromatography (cyclohexane/ethyl acetate = 3:1) yielded the products as colorless solids.

1.4. Analytical data

The presentation follows the sequence of depicted products shown in Schemes S1-S19 (under section 1.2.).

4-Methyl-(4-cyanophenoxy)benzoate (C)

Following GP A, 4-bromobenzonitrile (**A**, 1.82 g, 10 mmol) and methyl-4-hydroxy benzoate (**B**, 1.52 g, 10 mmol) were reacted with heating for 3 days, and then the product was purified by column chromatography (cyclohexane/ethyl acetate = 6:1) to yield 2.32 g (92%) of **C** as a colorless solid. The analytical data are in accord with those from literature.^[S11-S14] Mp. 104-105 °C. IR (KBr): ν = 3408, 3050, 2998, 2950, 2328, 2229, 2080, 1918, 1797, 1708, 1992, 1496, 1431, 1321, 1279, 1239, 1170, 1105, 1013, 960, 863, 760, 688. EI (MS, 70 eV): m/z = 255.3 ($[M+2]^+$, 3), 254.3 ($[M+1]^+$, 17), 253.3 ($[M]^+$, 83), 223.3 (15), 222.3 (100), 166.2 (21), 140.2 (21), 139.1 (10), 102.0 (10), 76.1 (10), 75.1 (8), 64.2 (8), 63.1 (9). ¹H NMR (400 MHz, CDCl₃): δ = 8.05 (d, J = 8.8 Hz, 2H), 7.63 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 8.8 Hz, 2H), 3.90 (s, 3H). ¹³C NMR (100.6 MHz, CDCl₃): δ = 166.2, 160.1, 159.2, 134.3, 132.0, 126.5, 119.1, 118.5, 107.1, 52.2.

4-(4-Cyanophenoxy)benzoic acid (D)^[S15-S18]

Following GP B, 4-methyl-(4-cyanophenoxy)benzoate (**C**, 760 mg, 3 mmol) yielded 667 mg (93%) of benzoic acid **D** as a colorless solid. Mp. 200-201 °C. IR (KBr): ν = 3743, 3325, 3187, 3093, 2992, 2823, 2663, 2547, 2223, 2064, 1971, 1920, 1796, 1670, 1589, 1496,

1423, 1294, 1240, 1161, 1104, 1010, 931, 844, 772, 733, 688. EI (MS, 70 eV): m/z = 241.0 ($[M+2]^+$, 4), 240.0 ($[M+1]^+$, 16), 239.0 ($[M]^+$, 100), 223.0 (7), 222.0 (43), 194.0 (7), 166.0 (10), 140.0 (7), 65.1 (9), 51.1 (8), 50.1 (7). ^1H NMR (400 MHz, CDCl_3): δ = 8.14 (d, J = 8.8 Hz, 2H), 7.66 (d; J = 8.8 Hz, 2H), 7.10 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100.6 MHz, CDCl_3): δ = 170.9, 160.1, 159.9, 134.4, 132.7, 125.4, 119.4, 119.1, 118.4, 107.5.

4-(4-Carbamoylphenoxy)benzoic acid (4)^[S14]

Following GP C, the yield was 238 mg (93%) as a colorless solid. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.80 (brs, 1H), 7.94 (d, J = 8.8 Hz, 2H), 7.93 (s, 1H), 7.91 (d, J = 8.8 Hz, 2H), 7.31 (s, 1H), 7.10 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 167.0, 167.1, 160.5, 158.3, 132.2, 130.6, 130.3, 126.4, 119.2, 118.6.

Methyl 4-(4-carbamoylphenoxy)benzoate (5)

Following GP D, the yield was 258 mg (95%) as a colorless solid. ^1H NMR (600 MHz, CDCl_3): δ = 8.05 (d, J = 8.8 Hz, 2H), 7.84 (d, J = 8.7 Hz, 2H), 7.09 (d, J = 8.7 Hz, 2H), 7.05 (d, J = 8.8 Hz, 2H), 6.02 (brs, 1H), 5.71 (brs, 1H), 3.92 (s, 3H). ^{13}C NMR (150.8 MHz, CDCl_3): δ = 168.3, 166.3, 160.3, 159.3, 131.8, 129.6, 128.9, 125.7, 119.1, 118.4, 52.1.

Methyl 4-(4-carbamothioylphenoxy)benzoate (6)

Following GP E, the reaction was performed at 80 °C for 16 h. Purification by column chromatography (cyclohexane/ethyl acetate = 1:1) gave 60 mg (35%) of **6** as a bright yellowish solid. ^1H NMR (400 MHz, CDCl_3): δ = 8.03 (d, J = 8.5 Hz, 2H), 7.91 (d, J = 8.5 Hz, 2H), 7.63 (brs, 1H), 7.15 (brs, 1H), 7.03 (d, J = 8.3 Hz, 2H), 7.02 (d, J = 8.3 Hz, 2H) 3.90 (s, 3H). ^{13}C NMR (100.6 MHz, CDCl_3): δ = 201.4, 166.4, 160.2, 159.5, 134.6, 131.9, 129.2, 125.7, 118.7, 118.5, 52.1.

4-(4-Cyanophenoxy)benzohydrazide (7)

Following GP F, the yield of **7** was 317 mg (70%) as a colorless solid. ^1H NMR (600 MHz, DMSO-d_6): δ = 10.55 (s, 1H), 8.01 (d, J = 7.9 Hz, 2H), 7.89 (d, J = 7.8 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 7.18-7.11 (m, 2H). ^{13}C NMR (150.8 MHz, DMSO-d_6): δ = 165.6, 160.5, 158.2, 135.3, 130.4, 129.2, 119.9, 119.6, 118.9, 106.5.

4-[4-(Hydrazinecarbonyl)phenoxy]benzamide (8)

Following GP C, the yield of **8** was 193 mg (71%) as a colorless solid. ^1H NMR (600 MHz, DMSO-d_6): δ = 12.82 (brs, 1H), 7.97 (s, 1H), 7.96 (d, J = 8.7 Hz, 2H), 7.93 (d, J = 8.7 Hz, 2H), 7.34 (s, 1H), 7.13 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H), 6.50 (brs, 1H). ^{13}C NMR

(150.8 MHz, DMSO- d_6): δ = 167.5, 167.1, 160.5, 158.3, 132.3, 132.2, 130.6, 130.3, 126.4, 119.3, 118.6.

4-(4-Carbamothioylphenoxy)benzoic acid (9)

Following GP G, the yield of **9** was 120 mg (95%) as a bright yellowish solid. ^1H NMR (600 MHz, DMSO- d_6): δ = 12.86 (brs, 1H), 9.83 (s, 1H), 9.47 (s, 1H), 7.98 (d, J = 8.8 Hz, 2H), 7.96 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H). ^{13}C NMR (150.8 MHz, DMSO- d_6): δ = 199.1, 167.1, 160.4, 158.5, 135.6, 132.2, 130.2, 126.5, 118.8, 118.6.

4-(4-Cyanophenoxy)benzamide (10)

Following GP H, 4-(4-cyanophenoxy)benzoic acid (**D**, 400 mg, 1.67 mmol) yielded 384.9 mg (96%) of benzamide **10** as a colorless solid. Mp. 196-197 °C. IR (KBr): ν = 3362, 3171, 2225, 1652, 1617, 1589, 1495, 1411, 1389, 1240, 1165, 1012, 867, 831, 798, 677. EI (MS, 70 eV): m/z = 239.3 ($[\text{M}+1]^+$, 12), 238.2 ($[\text{M}]^+$, 79), 223.3 (13), 222.2 (100), 166.1 (12), 140.0 (17), 76.2 (8), 64.3 (8), 63.3 (8), 50.2 (8). ^1H NMR (400 MHz, CDCl_3): δ = 7.85 (d, J = 8.8 Hz, 2H), 7.63 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 8.8 Hz, 2H), 6.00 (brs, 1H), 5.94 (brs, 1H). ^{13}C NMR (100.6 MHz, CDCl_3): δ = 168.2, 160.3, 158.4, 134.3, 129.7, 129.6, 119.6, 118.9, 118.5, 107.1. HRMS (ESI): m/z = calc. for $\text{C}_{14}\text{H}_{11}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 239.0815, found 239.0815.

4-[4-(1H-Tetrazol-5-yl)phenoxy]benzamide (11)

Following GP I, the yield of **11** was 137,8 mg (98%) as a colorless solid. ^1H NMR (600 MHz, DMSO- d_6): δ = 8.07 (d, J = 8.8 Hz, 2H), 7.97 (s, 1H), 7.95 (d, J = 8.8 Hz, 2H), 7.35 (s, 1H), 7.26 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.8 Hz, 2H). ^{13}C NMR (150.8 MHz, DMSO- d_6): δ = 167.5, 158.7, 155.5, 130.4, 130.3, 130.3, 129.6, 129.5, 120.5, 118.9, 120.0, 119.9.

4-[4-(1H-Tetrazol-5-yl)phenoxy]benzothioamide (12)

Following GP E, the reaction was performed at 80 °C for 16 h. Purification by column chromatography (ethyl acetate/ethanol = 4:1) gave 27 mg (15%) of **12** as a bright yellowish solid. ^1H NMR (600 MHz, DMSO- d_6): δ = 9.74 (s, 1H), 9.39 (s, 1H), 7.99 (d, J = 8.8 Hz, 2H), 7.91 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H). ^{13}C NMR (150.8 MHz, DMSO- d_6): δ = 199.2, 159.0, 158.8, 135.4, 130.4, 129.7, 120.5, 120.2, 118.6.

4-(4-Cyanophenoxy)benzothioamide (13)

Following GP E, the yield of **13** was 97.7 mg (57%) as a bright yellowish solid. ^1H NMR (400 MHz, CDCl_3): δ = 7.93 (d, J = 8.8 Hz, 2H), 7.63 (s, 1H), 7.63 (d, J = 8.8 Hz, 2H), 7.15 (brs,

1H), 7.06 (d, $J = 8.8$ Hz, 2H), 7.04 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR (100.6 MHz, CDCl_3): $\delta = 201.1, 160.2, 158.5, 135.4, 134.3, 129.3, 119.3, 119.0, 118.5, 107.1$.

Methyl 4-[4-(1H-tetrazol-5-yl)phenoxy]benzoate (14)

Following GP J, the yield of **14** was 22.2 mg (15%) as a colorless solid. ^1H NMR (600 MHz, DMSO-d_6): $\delta = 8.10$ (d, $J = 8.8$ Hz, 2H), 8.00 (d, $J = 8.8$ Hz, 2H), 7.32 (d, $J = 8.8$ Hz, 2H), 7.17 (d, $J = 8.8$ Hz, 2H), 3.83 (s, 3H). ^{13}C NMR (150.8 MHz, DMSO-d_6): $\delta = 166.1, 160.7, 158.1, 155.3, 132.2, 129.7, 125.4, 120.7, 118.8, 52.6$.

4-[4-(1H-Tetrazol-5-yl)phenoxy]benzoic acid (15)

Following GP B, the yield of **15** was 762 mg (90%) as a colorless solid. ^1H NMR (600 MHz, DMSO-d_6): $\delta = 8.09$ (d, $J = 8.8$ Hz, 2H), 7.99 (d, $J = 8.8$ Hz, 2H), 7.30 (d, $J = 8.8$ Hz, 2H), 7.15 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR (150.8 MHz, DMSO-d_6): $\delta = 167.1, 160.3, 158.2, 155.5, 132.3, 132.2, 129.6, 129.6, 126.6, 120.9, 120.5, 120.5, 118.7$.

4,4'-Oxybenzotrile (16)^[S19]

Following GP K, the yield of **16** was 1.49 g (45%) as a colorless solid. Mp. 182-185 °C. ^1H NMR (600 MHz, CDCl_3): $\delta = 7.68$ (d, $J = 8.9$ Hz, 4H), 7.10 (d, $J = 8.9$ Hz, 4H). ^{13}C NMR (150.8 MHz, CDCl_3): $\delta = 159.2, 134.5, 119.7, 118.3, 108.0$.

4,4'-Oxybenzamide (1)^[S14, S20-S22]

Following GP C, the yield of **1** was 200 mg (78%) as a colorless solid. ^1H NMR (400 MHz, DMSO-d_6): $\delta = 7.92$ (brs, 2H), 7.89 (d, $J = 8.8$ Hz, 4H), 7.30 (brs, 2H), 7.06 (d, $J = 8.8$ Hz, 4H). ^{13}C NMR (100.6 MHz, DMSO-d_6): $\delta = 167.5, 158.9, 130.2, 130.2, 118.7$.

4,4'-Oxybenzothioamide (17)

Following GP E, the reaction was performed at 100 °C for 2 d. Purification by column chromatography (cyclohexane/ethyl acetate = 1:1) gave 35 mg (20%) of **17** as a bright yellowish solid. ^1H NMR (600 MHz, DMSO-d_6): $\delta = 10.08$ (s, 2H), 9.70 (s, 2H), 7.98 (d, $J = 8.4$ Hz, 4H), 7.75 (d, $J = 8.4$ Hz, 4H). ^{13}C NMR (150.8 MHz, DMSO-d_6): $\delta = 199.7, 195.3, 143.5, 138.8, 129.7, 127.8$.

4-(4-Carbamothioylphenoxy)benzamide (18)

Following GP E, the reaction was performed with 1.0 equiv of Lawsson's reagent at 80 °C for 16 h. Purification by column chromatography (cyclohexane/ethyl acetate 2:1) gave 10 mg (6%) of **18** as a bright yellowish solid. Mp. 223-224 °C, IR (KBr): $\nu = 3385, 3325, 3190, 1643, 1595, 1503, 1388, 1254, 1166, 1132, 1105, 1011, 954, 885, 836, 779, 724$. EI (MS,

70 eV): m/z = 273.3 ($[M + H]^+$, 2), 272.0 ($[M]^+$, 14), 256.1 (5), 239.4 (13), 238.2 (82), 223.2 (13), 222.2 (100), 166.2 (9), 140.2 (7), 111.2 (5), 48.6 (8). ^1H NMR (400 MHz, DMSO- d_6): δ = 9.77 (s, 1H), 9.42 (s, 1H), 7.92 (s, 1H), 7.92 (d, J = 8.8 Hz, 2H), 7.90 (d, J = 8.8 Hz, 2H), 7.29 (s, 1H), 7.07 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100.6 MHz, DMSO- d_6): δ = 199.1, 167.5, 159.1, 158.7, 135.1, 130.3, 130.3, 130.1, 118.8, 118.2. HRMS (ESI): m/z = calc. for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_2\text{SNa}$ $[M+\text{Na}]^+$ 295.0512, found 295.0512.

Methyl 3-(4-cyanophenoxy)benzoate (G)

Following GP A, 4-bromobenzonitrile (**A**, 1.82 g, 10 mmol) and methyl-3-hydroxy benzoate (**F**, 1.52 g, 10 mmol) were reacted by heating for 3 days. Then, the product was purified by column chromatography (cyclohexane/ethyl acetate = 7:1) to yield 2.26 g (89%) of product **G** as a colorless solid. The analytical data were in agreement to those reported in the literature [S14, S23, S24]. Mp. 93-94 °C. IR (KBr): ν = 3417, 3097, 3001, 2950, 2323, 2842, 2226, 2088, 1930, 1719, 1580, 1500, 1480, 1434, 1291, 1237, 1196, 1100, 1071, 973, 919, 887, 848, 818, 754, 680, 659. EI (MS, 70 eV): m/z = 255.3 ($[M+2]^+$, 2), 254.3 ($[M+1]^+$, 15), 253.3 ($[M]^+$, 100), 223.3 (14), 222.3 (81), 194.3 (14), 166.2 (31), 140.2 (22), 139.1 (11), 102.1 (11), 76.2 (16), 75.1 (11), 64.2 (11), 63.1 (12), 50.1 (10). ^1H NMR (600 MHz, CDCl_3): δ = 7.89 (d, J = 7.8 Hz, 1H), 7.71 (s, 1H), 7.61 (d, J = 8.8 Hz, 2H), 7.48 (t, J = 8.0 Hz, 1H), 7.26 (dd, J = 7.8/7.6 Hz, 1H), 7.10 (d, J = 8.9 Hz, 2H), 3.90 (s, 3H). ^{13}C NMR (150.8 MHz, CDCl_3): δ = 166.1, 161.1, 155.0, 134.3, 132.4, 130.3, 126.2, 124.8, 121.2, 118.7, 118.2, 106.4, 52.4.

3-(4-Cyanophenoxy)benzoic acid (H)^[S24]

Following GP B, 3-methyl-(4-cyanophenoxy)benzoate (**G**, 760 mg, 3 mmol) yielded 683 mg (95%) of benzoic acid **H** as a colorless solid. Mp. 165-166 °C. IR (KBr): ν = 2985, 2828, 2668, 2554, 2222, 1916, 1689, 1578, 1495, 1422, 1305, 1269, 1245, 1202, 1165, 1112, 932, 901, 836, 759, 674. EI (MS, 70 eV): m/z = 241.3 ($[M+2]^+$, 6), 240.2 ($[M+1]^+$, 24), 239.3 ($[M]^+$, 100), 222.3 (13), 221.2 (10), 194.3 (27), 193.2 (19), 167.2 (11), 166.2 (22), 140.2 (12), 76.1 (9), 65.2 (17). ^1H NMR (600 MHz, CDCl_3): δ = 7.97 (d, J = 7.8 Hz, 1H), 7.78 (s, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.53 (t, J = 7.9 Hz, 1H), 7.33 (d, J = 8.3 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.04 (d, J = 8.8 Hz, 2H). ^{13}C NMR (150.8 MHz, CDCl_3): δ = 171.0, 160.9, 155.2, 134.3, 131.5, 130.5, 126.7, 125.7, 121.6, 118.6, 118.3, 106.6.

3-(4-Cyanophenoxy)benzamide (19)

Following GP H, 3-(4-cyanophenoxy)benzoic acid (**H**, 400 mg, 1.67 mmol) yielded 390.5 mg (98%) of benzamide **19** as a colorless solid. Mp. 149-150 °C. IR (KBr): ν = 3420, 3201, 2223, 1683, 1608, 1574, 1494, 1388, 1240, 1165, 892, 835, 808, 678. EI (MS, 70 eV): m/z

= 239.4 ($[M+1]^+$, 27), 238.2 ($[M]^+$, 100), 237.2 (50), 223.3 (14), 222.0 (90), 220.2 (14), 194.0 (53), 166.2 (45), 140.2 (28), 139.1 (16), 76.3 (12), 63.3 (11), 50.4 (13). ^1H NMR (600 MHz, DMSO- d_6): δ = 8.05 (s, 1H), 7.84 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 7.8 Hz, 1H), 7.60 (dd, J = 2.1/1.9 Hz, 1H), 7.53 (t, J = 8.0 Hz, 1H), 7.49 (s, 1H), 7.30 (dd, J = 8.0/2.1 Hz, 1H), 7.12 (d, J = 8.6 Hz, 2H). ^{13}C NMR (150.8 MHz, DMSO- d_6): δ = 167.2, 161.2, 155.0, 137.0, 135.2, 130.9, 124.6, 123.5, 119.5, 119.1, 118.8, 105.9. HRMS (ESI): m/z calc. for $\text{C}_{14}\text{H}_{11}\text{N}_2\text{O}_2$ $[M+H]^+$ 239.0815, found 239.0815.

3-(4-Carbamoylphenoxy)benzamide (20)

Following GP C, 288.1 mg of **19** (1.1 mmol) yielded 254 mg (88%) of diamide **20** as a colorless solid. The analytical data were in agreement to those reported in the literature.^{S8d} Mp. 258-259 °C. IR (KBr): ν = 3391, 3190, 1639, 1610, 1506, 1446, 1389, 1247, 1162, 1126, 932, 905, 852, 776, 737, 679. EI (MS, 70 eV); m/z = 257.2 ($[M+1]^+$, 10), 255.9 ($[M]^+$, 100), 255.0 (5), 241.2(10), 241.1(77), 238.1(14), 141.1(9), 139.1(6), 112.1(6). ^1H NMR (400 MHz, DMSO- d_6): δ = 7.99 (s, 1H), 7.89 (brs, 1H), 7.88 (d, J = 8.6 Hz, 2H), 7.68 (d, J = 7.5 Hz, 1H), 7.51 (s, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.41 (s, 1H), 7.27 (brs, 1H), 7.21 (dd, J = 8.0/1.0 Hz, 1H), 7.01 (d, J = 8.6 Hz, 2H). ^{13}C NMR (100.6 MHz, DMSO- d_6): δ = 167.6, 167.3, 159.5, 156.2, 136.8, 130.6, 130.2, 129.8, 123.6, 122.6, 118.6, 118.1. HRMS (ESI): m/z calc. for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_3\text{Na}$ $[M+\text{Na}]^+$ 279.0740, found 279.0735.

3-(4-Carbamoylphenoxy)benzoic acid (21)^[S14]

Following GP C, the yield of **21** was 219 mg (85%) as a colorless solid. ^1H NMR (600 MHz, DMSO- d_6): δ = 7.94 (brs, 1H), 7.91 (d, J = 8.7 Hz, 2H), 7.74 (d, J = 7.7 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.47 (s, 1H), 7.35 (dd, J = 8.1/2.0 Hz, 1H), 7.32 (brs, 1H), 7.07 (d, J = 8.7 Hz, 2H). ^{13}C NMR (150.8 MHz, DMSO- d_6): δ = 167.6, 167.0, 159.2, 156.6, 133.3, 131.1, 130.3, 130.2, 125.3, 124.1, 119.5, 118.5.

Methyl 3-(4-carbamoylphenoxy)benzoate (22)

Following GP D, the yield of **22** was 250 mg (92%) as a colorless solid. Mp. 154-155 °C. IR (KBr): ν = 3372, 3171, 1710, 1652, 1619, 1585, 1445, 1411, 1390, 1274, 1236, 1202, 1158, 1095, 989, 900, 859, 799, 755, 666. EI (MS, 70 eV): m/z = 272.2 ($[M+H]^+$, 26), 271.1 ($[M]^+$, 92), 256.2 (22), 255.2 (100), 240.2 (30), 168.1 (26), 139.1 (15), 112.1 (12). ^1H NMR (400 MHz, CDCl_3): δ = 7.83 (dt, J = 7.8/1.3 Hz, 1H), 7.80 (d, J = 9.0 Hz, 2H), 7.67 (dd, J = 2.6/1.6 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.24 (ddd, J = 8.0/2.6/1.1 Hz, 1H), 7.00 (d, J = 8.9 Hz, 2H), 6.05 (brs, 2H), 3.88 (s, 3H). ^{13}C NMR (100.6 MHz, CDCl_3): δ = 168.7, 166.3, 160.3, 156.1, 132.2, 130.1, 129.5, 128.2, 125.4, 124.3, 120.5, 118.0, 52.3. HRMS calc. for $\text{C}_{15}\text{H}_{13}\text{NO}_4\text{Na}$ $[M+\text{Na}]^+$ 294.0737, found 294.0737.

3-[4-(1*H*-Tetrazol-5-yl)phenoxy]benzamide (23)

Following GP I, the yield of **23** was 126.8 mg (90%) as a colorless solid. ¹H NMR (600 MHz, DMSO-*d*₆): δ = 8.05 (s, 1H), 8.05 (d, *J* = 8.8 Hz, 2H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.58 (dd, *J* = 2.1/1.9 Hz, 1H), 7.51 (t, *J* = 7.9 Hz, 1H), 7.46 (s, 1H), 7.27 (dd, *J* = 8.0/2.2 Hz, 1H), 7.20 (d, *J* = 8.8 Hz, 1H). ¹³C NMR (150.8 MHz, DMSO-*d*₆): δ = 167.4, 159.2, 156.1, 155.6, 136.9, 130.7, 123.8, 122.8, 120.3, 119.4, 118.7.

3-(4-Carbamothioylphenoxy)benzamide (24)

Following GP L, the yield of **24** was 133.4 mg (98%) as a bright yellowish solid. Mp 205-206 °C. IR (KBr): ν = 3437, 3337, 3281, 3168, 1654, 1611, 1578, 1504, 1435, 1383, 1244, 1169, 1108, 891, 824, 773, 693. EI (MS, 70 eV): *m/z* = 273.2 ([*M*+*H*]⁺, 14), 272.1 ([*M*]⁺, 88), 256.0 (11), 239.3 (25), 238.2 (100), 237.2 (38), 221.1 (64), 196.2 (15), 194.0 (33), 166.1 (27), 140.1 (20), 139.1 (16), 102.2 (11), 92.1 (18), 77.3 (16), 76.3 (28), 75.2 (20), 65.3 (19), 64.3 (25), 63.1 (26), 60.1 (14), 51.3 (18), 50.2 (24). ¹H NMR (400 MHz, DMSO-*d*₆): δ = 9.76 (s, 1H), 9.42 (s, 1H), 8.01 (s, 1H), 7.94 (d, *J* = 8.8 Hz, 2H), 7.69 (ddd, *J* = 7.8/1.2/1.1 Hz, 1H), 7.53 (dd, *J* = 2.1/1.9 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.42 (s, 1H), 7.22 (ddd, *J* = 8.1/2.4/1.0 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 2H). ¹³C NMR (100.6 MHz, DMSO-*d*₆): δ = 199.1, 167.4, 159.7, 156.1, 136.8, 132.8, 130.6, 130.1, 123.7, 122.7, 118.7, 117.7. HRMS (ESI): *m/z* calc. for C₁₄H₁₃N₂O₂S [*M*+*H*]⁺ 273.0692, found 273.0692.

Methyl 4-(3-cyanophenoxy)benzoate (K)^[S25]

Following GP A, the reaction time was 3 d, and the product was purified by column chromatography (cyclohexane/ ethyl acetate = 7:1) to yield 1.36 g (54%) of **K** as a colorless solid. ¹H NMR (600 MHz, CDCl₃): δ = 8.04 (d, *J* = 8.7 Hz, 2H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.44 (dt, *J* = 7.7/1.4 Hz, 1H), 7.29 (s, 1H), 7.28-7.26 (m, 1H), 7.01 (d, *J* = 8.1 Hz, 2H), 3.90 (s, 3H). ¹³C NMR (150.8 MHz, CDCl₃): δ = 166.3, 160.0, 156.5, 132.0, 131.0, 127.7, 126.0, 124.0, 122.6, 118.3, 117.9, 113.9, 52.2.

4-(3-Cyanophenoxy)benzoic acid (L)^[S14]

Following GP B, the yield of **L** was 697 mg (97%) as a colorless solid. ¹H NMR (600 MHz, DMSO-*d*₆): δ = 7.96 (d, *J* = 9.2 Hz, 2H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.62 (s, 1H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.43 (dd, *J* = 8.4/2.4 Hz, 1H), 7.08 (d, *J* = 8.7 Hz, 2H). ¹³C NMR (150.8 MHz, DMSO-*d*₆): δ = 167.2, 160.2, 156.3, 132.2, 132.1, 128.7, 127.0, 125.1, 123.5, 118.5, 118.4, 113.4.

4-(3-Cyanophenoxy)benzamide (25)

Following GP H, the yield of **25** was 334 mg (84%) as a colorless solid. Mp. 176-177 °C. IR (KBr): ν = 3317, 3143, 3064, 2230, 1669, 1614, 1577, 1507, 1479, 1397, 1250, 1221, 1169, 944, 910, 850, 826, 795, 686. EI (MS, 70 eV): m/z = 239.3 ($[M+H]^+$, 11), 238.2 ($[M]^+$, 62), 223.3 (14), 222.2 (100), 166.2 (19), 140.2 (19), 139.2 (11), 102.1 (11), 92.1 (10), 63.2 (11), 50.2 (11). 1H NMR (400 MHz, DMSO- d_6): δ = 7.93 (s, 1H), 7.90(d, J = 8.8 Hz, 2H), 7.62 (dt, J = 7.7/1.4 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.56 (dd, J = 2.1/1.5 Hz, 1H), 7.37 (ddd, J = 8.0/2.5/1.3 Hz, 1H), 7.32 (s, 1H), 7.07 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100.6 MHz, DMSO- d_6): δ = 167.5, 158.7, 156.7, 132.0, 130.4, 130.3, 128.3, 124.6, 122.9, 118.6, 118.5, 113.3. HRMS (ESI): m/z calc. for $C_{14}H_{11}N_2O_2$ $[M+H]^+$ 239.0815, found 239.0814.

4-[3-(1H-Tetrazol-5-yl)phenoxy]benzamide (26)

Following GP I, the yield of **26** was 126.5 mg (90%) as a colorless solid. 1H NMR (600 MHz, DMSO- d_6): δ = 7.98 (s, 1H), 7.93 (d, J = 8.6 Hz, 2H), 7.88 (d, J = 7.8 Hz, 1H), 7.69 (dd, J = 1.9/1.8 Hz, 1H), 7.58 (t, J = 7.9 Hz, 1H), 7.33 (s, 1H), 7.21 (dd, J = 8.2/1.8 Hz, 1H), 7.10 (d, J = 8.7 Hz, 2H). ^{13}C NMR (150.8 MHz, DMSO- d_6): δ = 176.6, 159.3, 156.9, 155.6, 131.6, 130.3, 130.0, 122.8, 121.3, 118.4, 117.4.

4-(3-Carbamothioylphenoxy)benzamide (27)

Following GP L, the yield of **27** was 118.5 mg (87%) as a bright yellowish solid. 1H NMR (600 MHz, DMSO- d_6): δ = 9.95 (s, 1H), 9.94 (s, 1H), 7.93 (s, 1H), 7.90 (d, J = 8.7 Hz, 2H), 7.70 (d, J = 7.9 Hz, 1H), 7.59 (s, 1H), 7.58 (dd, J = 2.1/2.0 Hz, 1H), 7.45 (t, J = 7.9 Hz, 1H), 7.31 (s, 1H), 7.21 (dd, J = 8.0/2.0 Hz, 1H), 7.04 (d, J = 8.7 Hz, 2H). ^{13}C NMR (150.8 MHz, DMSO- d_6): δ = 199.3, 167.6, 159.5, 155.7, 141.7, 130.3, 130.2, 129.8, 123.4, 122.4, 118.7, 118.1.

3,3'-Oxybenzotrile (28)^[S26]

Following GP M, the yield of **28** was 348 mg (79%) as a colorless solid. 1H NMR (600 MHz, $CDCl_3$): δ = 7.51-7.45 (m, 4H), 7.28-7.24 (m, 4H). ^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 156.5, 131.2, 127.9, 123.7, 122.2, 117.8, 114.1.

3,3'-Oxybenzamide (29)

Following GP C, the yield of **29** was 187 mg (73%) as a colorless solid. Mp. 260-261 °C. IR (KBr): ν = 3416, 3385, 3185, 1659, 1621, 1576, 1445, 1393, 1246, 1121, 951, 909, 759, 686. EI (MS, 70 eV): m/z = 257.3 ($[M+H]^+$, 14), 256.1 ($[M]^+$, 100), 240.1 (37), 238.2 (23), 211.2 (22), 195.1 (31), 169.0 (32), 141.0 (25), 139.1 (17), 115.1 (12), 92.1 (11), 76.3 (12), 70.1 (10), 65.3 (10). 1H NMR (600 MHz, DMSO- d_6): δ = 8.03 (s, 2H), 7.67 (d, J = 8.0 Hz,

2H), 7.52-7.43 (m, 6H), 7.19 (dd, $J = 8.0/2.1$ Hz, 2H). ^{13}C NMR (150.8 MHz, DMSO- d_6): $\delta = 167.5, 156.9, 136.7, 130.6, 123.2, 122.1, 118.1$. HRMS (ESI): m/z calc. for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 279.0740, found 279.0742.

2-(4-Cyanophenoxy)benzonitrile (P)^[S27-S30]

Following GP M, the yield of **P** was 414 mg (94%) as a colorless solid. ^1H NMR (600 MHz, CDCl_3): $\delta = 7.71$ (dd, $J = 7.8/1.8$ Hz, 1H), 7.66 (d, $J = 8.9$ Hz, 2H), 7.60 (d, $J = 8.0/1.5$ Hz, 1H), 7.29 (t, $J = 7.7$ Hz, 1H), 7.09 (d, $J = 8.9$ Hz, 2H), 7.04 (d, $J = 8.4$ Hz, 1H). ^{13}C NMR (150.8 MHz, CDCl_3): $\delta = 159.5, 157.0, 134.7, 134.3, 125.1, 119.6, 119.1, 118.3, 115.2, 107.9, 105.6$.

2-(4-Carbamoylphenoxy)benzamide (30)^[S31]

Following GP C, the yield of **30** was 167 mg (65%) as a colorless solid. ^1H NMR (600 MHz, DMSO- d_6): $\delta = 7.91$ (s, 1H), 7.87 (d, $J = 8.0$ Hz, 2H), 7.69 (dd, $J = 7.7/2.2$ Hz, 1H), 7.63 (s, 1H), 7.51–7.45 (m, 2H), 7.29 (s, 1H), 7.27 (t, $J = 7.6$ Hz, 1H), 7.00 (s, 1H), 6.98 (s, $J = 8.4$ Hz, 2H). ^{13}C NMR (150.8 MHz, DMSO- d_6): $\delta = 167.6, 167.1, 159.8, 153.0, 132.4, 130.6, 130.0, 129.5, 129.1, 124.9, 120.8, 117.7$.

Methyl 2-(4-cyanophenoxy)benzoate (R)

Following GP M, the yield of **R** was 110 mg (25%) as a colorless solid. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.98$ (dd, $J = 7.9/1.8$ Hz, 1H), 7.59-7.54 (m, 1H), 7.56 (d, $J = 8.9$ Hz, 2H), 7.32 (t, $J = 7.7$ Hz, 1H), 7.09 (d, $J = 8.4$ Hz, 1H), 6.90 (d, $J = 8.9$ Hz, 2H), 3.73 (s, 3H). ^{13}C NMR (100.6 MHz, CDCl_3): $\delta = 165.2, 162.0, 153.7, 134.2, 134.1, 132.3, 125.6, 124.0, 123.0, 118.8, 117.0, 105.6, 52.3$.

2-(4-Cyanophenoxy)benzoic acid (31)^[S32]

Following GP B, the yield of **31** was 575 mg (80%) as a colorless solid. ^1H NMR (600 MHz, CDCl_3): $\delta = 8.10$ (d, $J = 7.8$ Hz, 1H), 7.63 (d, $J = 7.7$ Hz, 1H), 7.60 (d, $J = 8.7$ Hz, 2H), 7.35 (t, $J = 7.7$ Hz, 1H), 7.26 (s, 1H), 7.09 (d, $J = 8.2$ Hz, 1H), 6.96 (d, $J = 8.7$ Hz, 2H). ^{13}C NMR (150.8 MHz, CDCl_3): $\delta = 169.4, 161.4, 154.6, 135.2, 134.2, 133.2, 125.6, 122.5, 122.5, 118.7, 117.7, 106.1$.

2-(4-Carbamoylphenoxy)benzoic acid (32)

Following GP C, the yield of **32** was 195 mg (76%) as a colorless solid. ^1H NMR (600 MHz, DMSO- d_6): $\delta = 7.89$ (s, 1H), 7.87 (s, 1H), 7.84 (d, $J = 8.6$ Hz, 2H), 7.69 (t, $J = 7.7$ Hz, 1H), 7.32 (t, $J = 7.6$ Hz, 1H), 7.26 (s, 1H), 7.11 (d, $J = 8.5$ Hz, 1H), 6.87 (d, $J = 8.6$ Hz, 2H). ^{13}C

NMR (150.8 MHz, DMSO- d_6): δ = 167.7, 166.8, 160.8, 154.2, 134.2, 132.0, 132.0, 130.0, 128.8, 125.6, 125.4, 122.7, 116.6.

2-(3-Cyanophenoxy)benzonitrile (S)^[S28]

Following GP M, the yield of **S** was 79.3 mg (18%) as a colorless solid. ¹H NMR (600 MHz, CDCl₃): δ = 7.71 (d, J = 7.9 Hz, 1H), 7.58 (t, J = 8.1 Hz, 1H), 7.53-7.44 (m, 2H), 7.32 (d, J = 8.9 Hz, 1H), 7.30 (s, 1H), 7.26 (t, J = 7.8 Hz, 1H), 6.96 (d, J = 8.6 Hz, 1H). ¹³C NMR (150.8 MHz, CDCl₃): δ = 157.8, 156.0, 134.7, 134.3, 131.2, 128.3, 124.6, 123.9, 122.2, 118.5, 117.8, 115.4, 114.0, 105.0.

2-(3-Carbamoylphenoxy)benzamide (33)^[S31]

Following GP C, the yield of **33** was 128 mg (50%) as a colorless solid. ¹H NMR (400 MHz, DMSO- d_6): δ = 7.97 (s, 1H), 7.70 (dd, J = 7.8/1.8 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.60 (br. s, 1H), 7.50-7.37 (m, 5H), 7.21 (t, J = 7.6 Hz, 1H), 7.14 (dd, J = 8.2/2.6 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H). ¹³C NMR (100.6 MHz, DMSO- d_6): δ = 167.5, 167.0, 157.0, 153.9, 136.6, 132.4, 130.7, 130.3, 128.3, 124.3, 124.9, 122.9, 121.8, 119.8, 118.0.

2. Biochemistry and biology

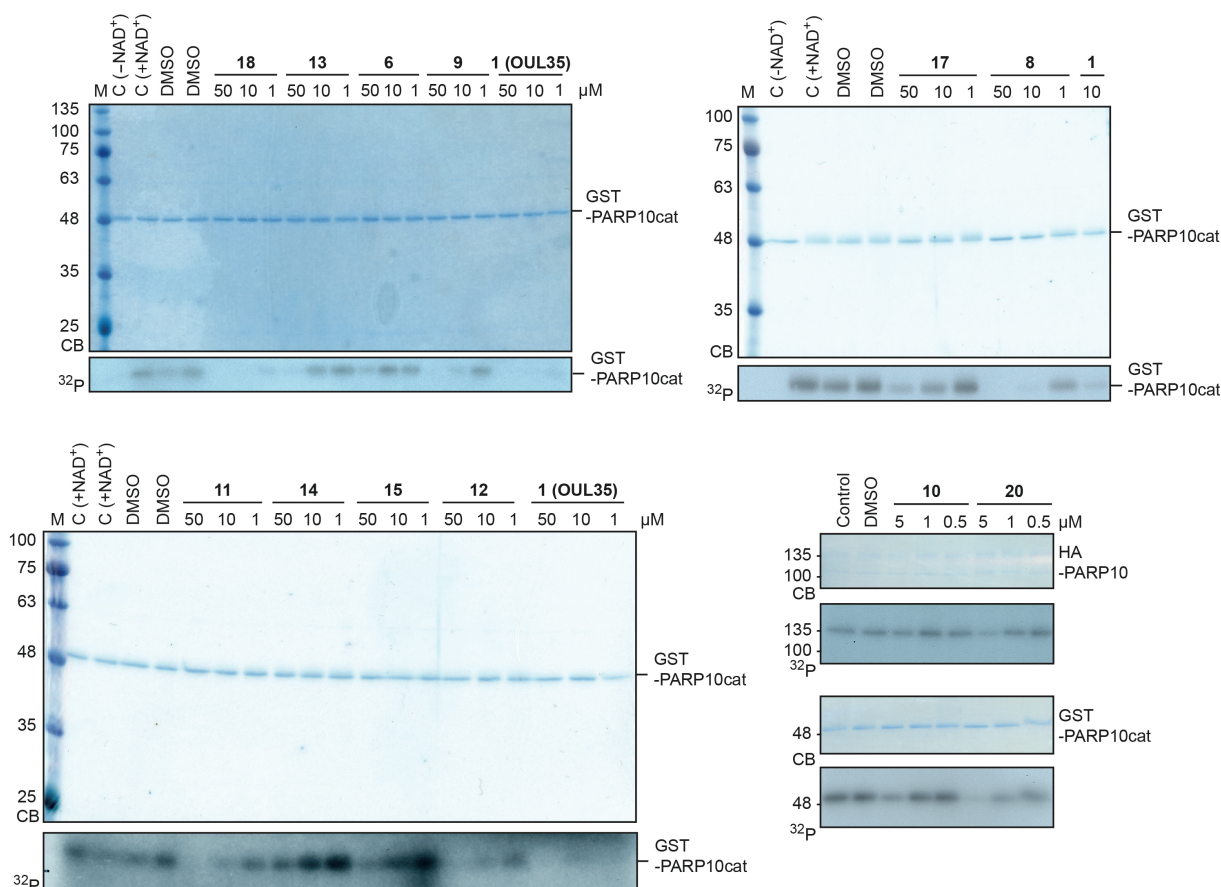


Figure S1. *In vitro* ADP-ribosylation with the catalytic domain of PARP10 and with full-length HA-tagged PARP10 (related to Fig. 3).

The bacterially expressed, catalytic domain of GST-PARP10 (PARP10cat) was incubated with ^{32}P -labelled NAD^+ . The indicated compounds were solubilized in DMSO with the final concentration of the solvent being 0.05%. The concentration of the compounds (in μM) are indicated. Displayed are Coomassie blue stained SDS-gels (CB) and the corresponding autoradiograms (^{32}P).

For the analyzing full-length HA-PARP10 (bottom right panel), the proteins were expressed transiently in HEK293 cells. The immunoprecipitated HA-PARP10 was assayed using ^{32}P -labelled NAD^+ . The indicated compounds were used as for the other panels. The comparison of HA-PARP10 and GST-PARP10cat were analyzed on the same gel.

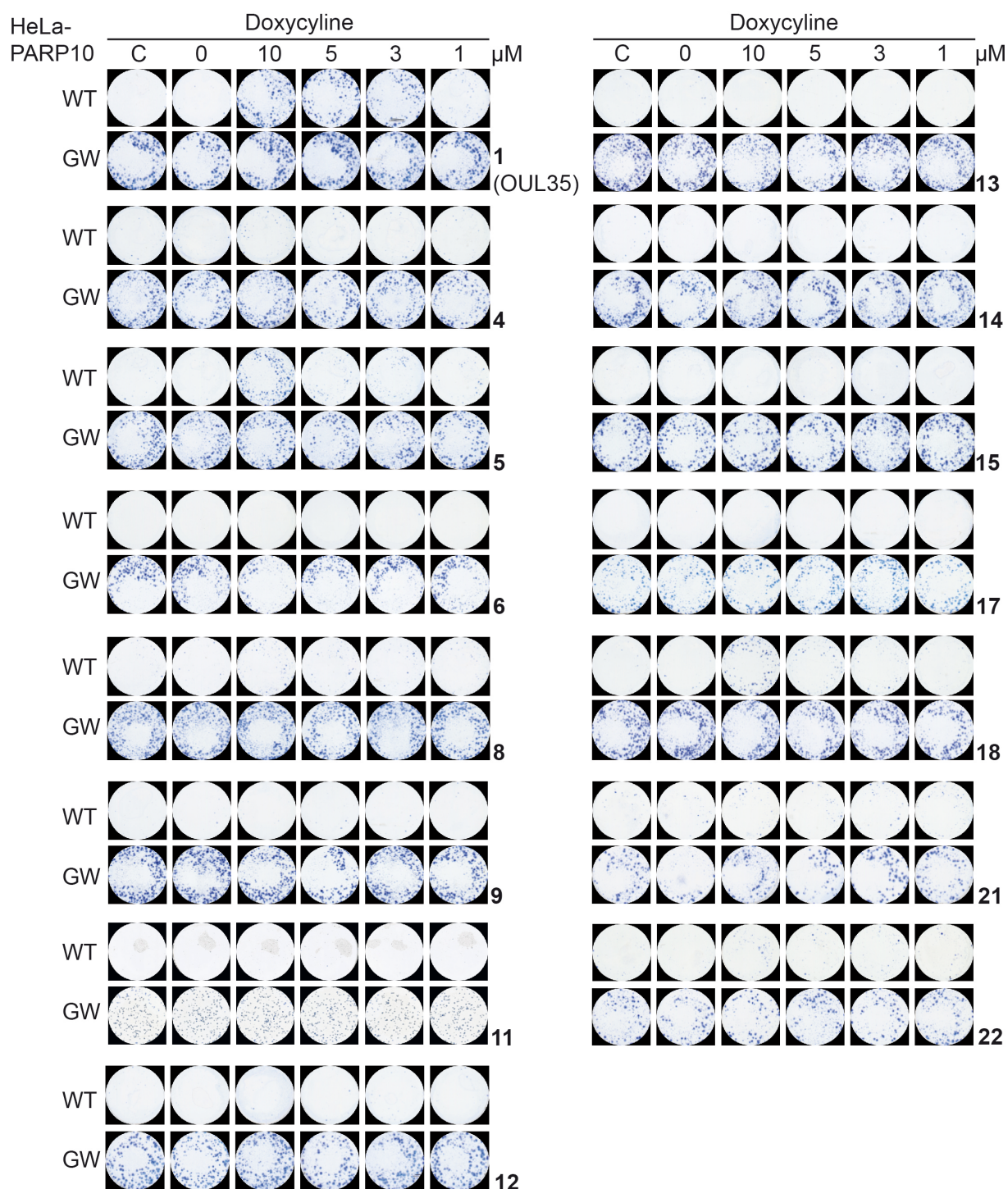


Figure S2. HeLa cell proliferation assays (related to Fig. 3).

Five hundred HeLa-PARP10 or HeLa-PARP10-G888W cells were plated per well of a 6-well plate and the expression of PARP10 or PARP10-G888W, which is catalytically inactive, induced with doxycycline. The indicated compounds were added at the given concentrations. The cells were grown for 10-12 days with doxycycline and compounds replenished every three days and then fixed and stained with ethylene blue. Examples of individual wells are shown.

3. Selectivity

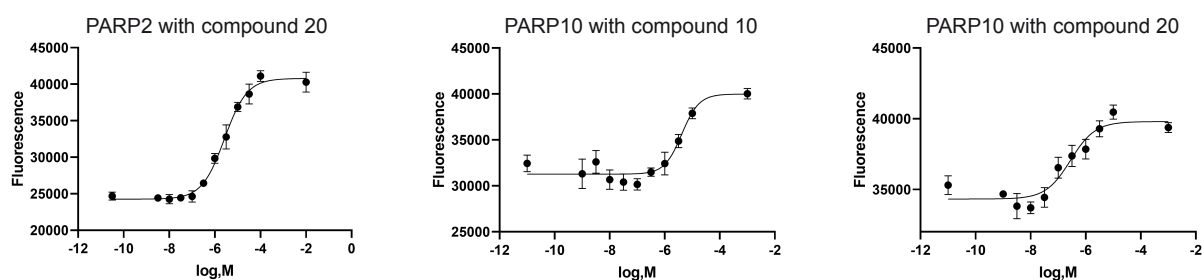


Figure S3. Titrations of the compounds **10** and **20** on PARP2 and PARP10 as indicated (related to Table 2). Example curves are shown with data as means \pm standard deviations of four replicates. Lowest and highest compound concentrations are controls without an inhibitor and without enzyme, respectively.

4. *In silico* modeling and structural analyses

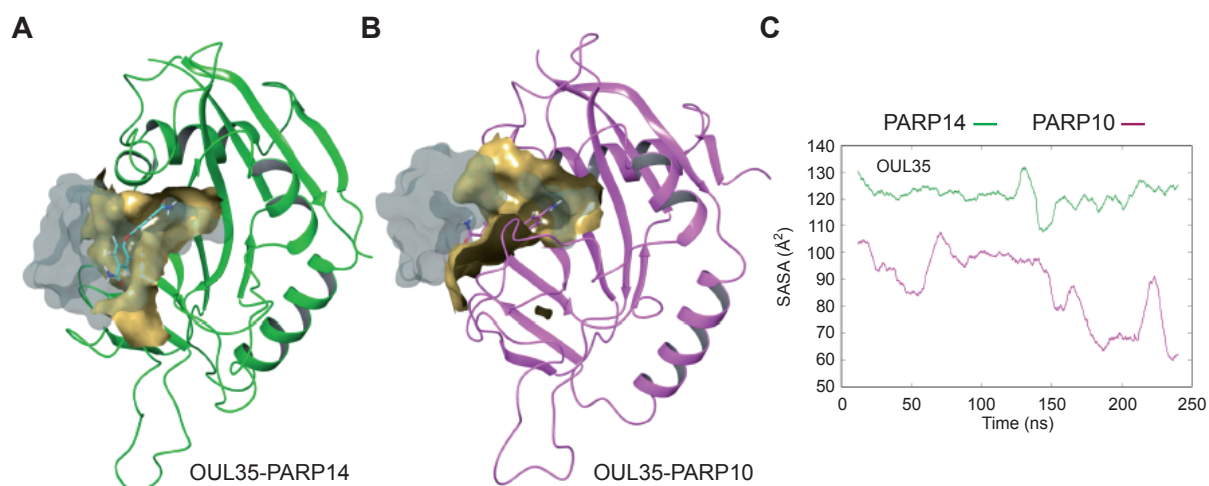


Figure S4. Solvent accessible surface areas of compound **1** (OUL35) in complex with PARP14 and PARP10 (related to Fig. 4).

A. and B. The **1**-PARP14 and **1**-PARP10 complexes, as indicated, were analyzed by molecular dynamics and the solvent accessible surface areas (SASA) of compound **1** are shown as grey volumes. The part of the protein that contains the catalytic domain and more specifically interacts with the buried part of the ligand are shown as yellow volumes. PARP14 and PARP10 are in green and pink cartoon, while the ligand is in stick following the same color code.

C. SASA as a function of time is shown obtained from molecular dynamics simulations.

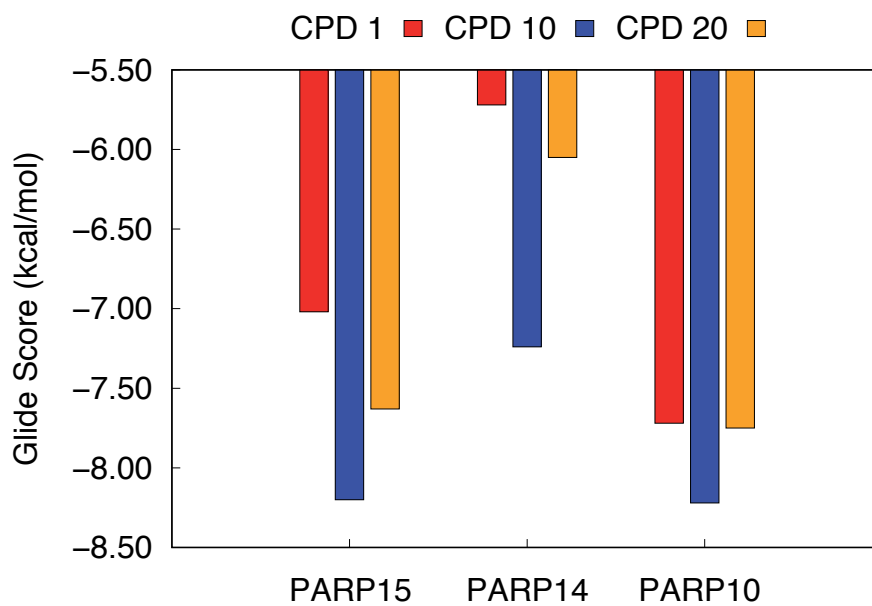


Figure S5: Glide score of compounds **1**, **10** and **20** in PARP10, PARP14 and PARP15 (related to Fig. 5).^[S33, S34]

Table S1. Data collection and refinement statistics of the PARP15-20 complex (related to Fig. 6).

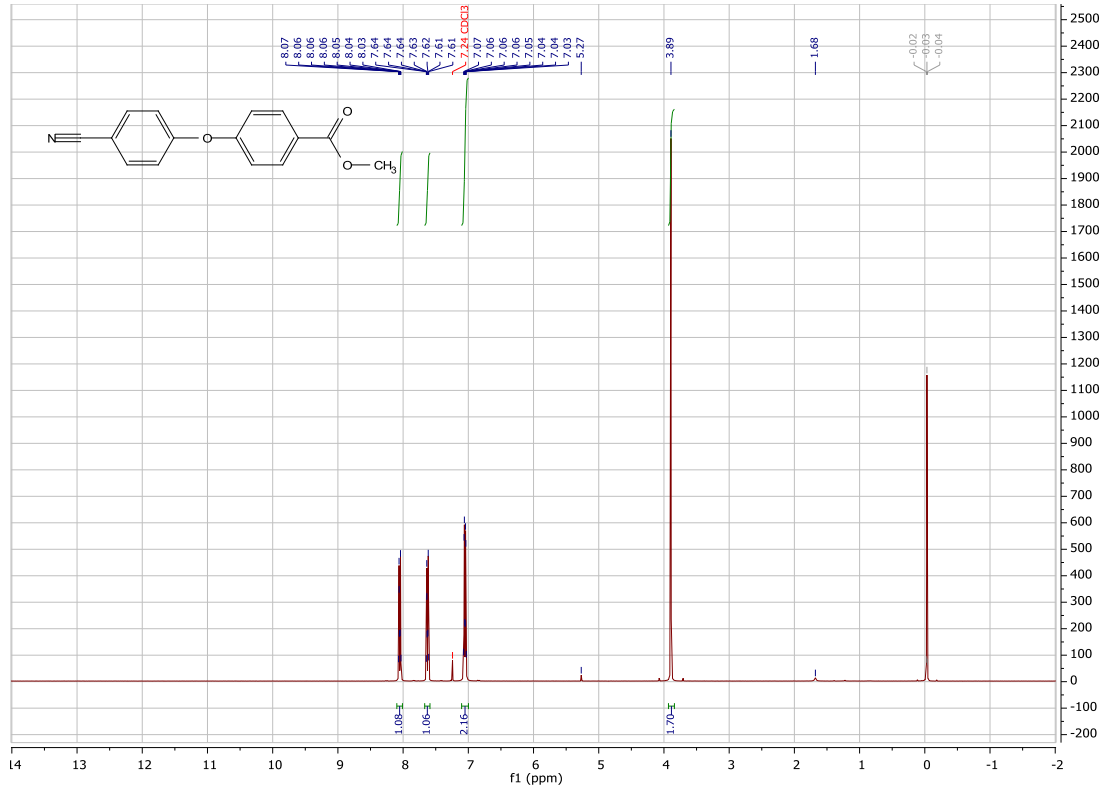
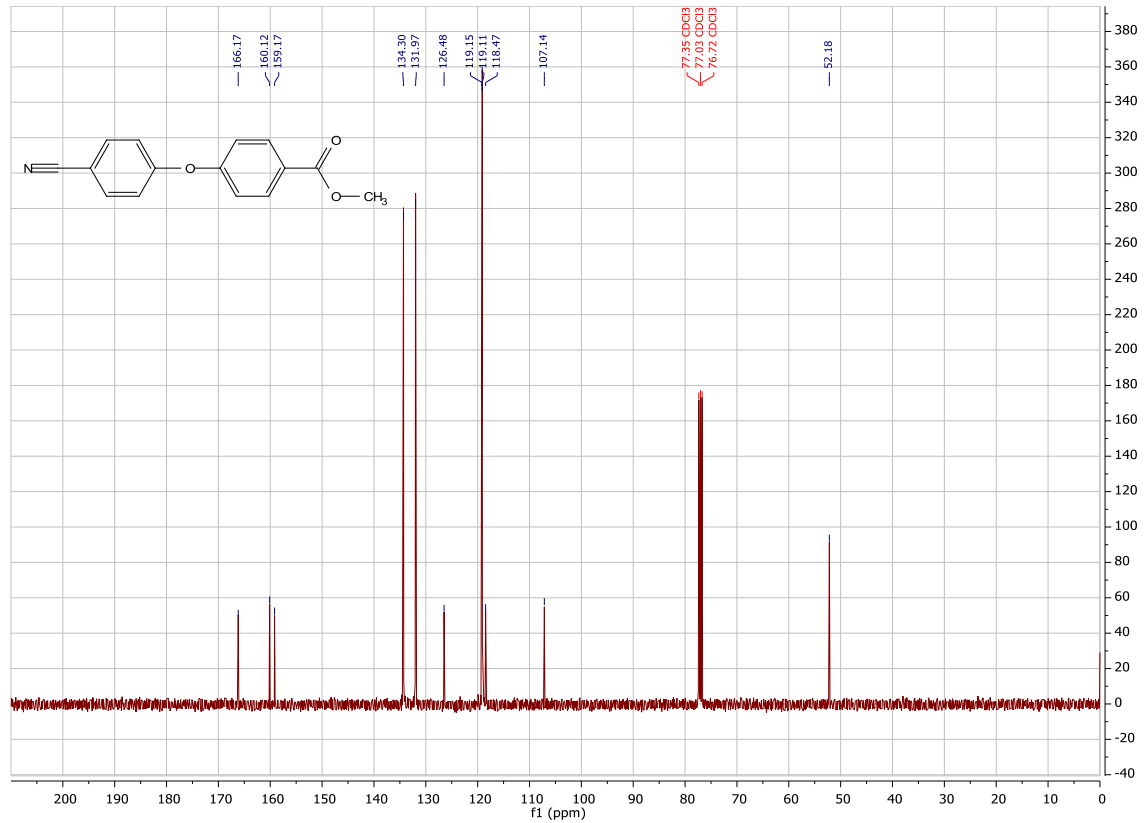
Data processing		Refinement	
Resolution (Å)	40.31 – 1.95	R-factor	18.08
(Outer shell)	2.02 – 1.95	R-free	21.93
Wavelength (Å)	0.97950	Number of atoms	3477
Beamline	I04, DLS	Protein atoms	3229
Temperature (K)	100	Ligand atoms	19
Space group	P2 ₁ 2 ₁ 2 ₁	Waters	229
Unit cell parameters (Å)	a = 45.5	rmsd bond lengths (Å)	0.007
	b = 69.0	rmsd bond angles (°)	1.46
	c = 161.3	Average B-factors (Å ²)	
	$\alpha, \beta, \gamma = 90.0^\circ$	Protein atoms	28.59
Total no. of reflections	245829 (16733)	Ligand atoms	44.44
No. of unique reflections	37918 (2756)	Waters	31.7
Multiplicity	6.4 (6.07)	Ramachandran plot (%)	
I/ σ	10.64 (2.05)	favored	97.7
R-meas (%)	12.2 (74.2)	allowed	1.68
Completeness (%)	100 (100)	outliers	0.62

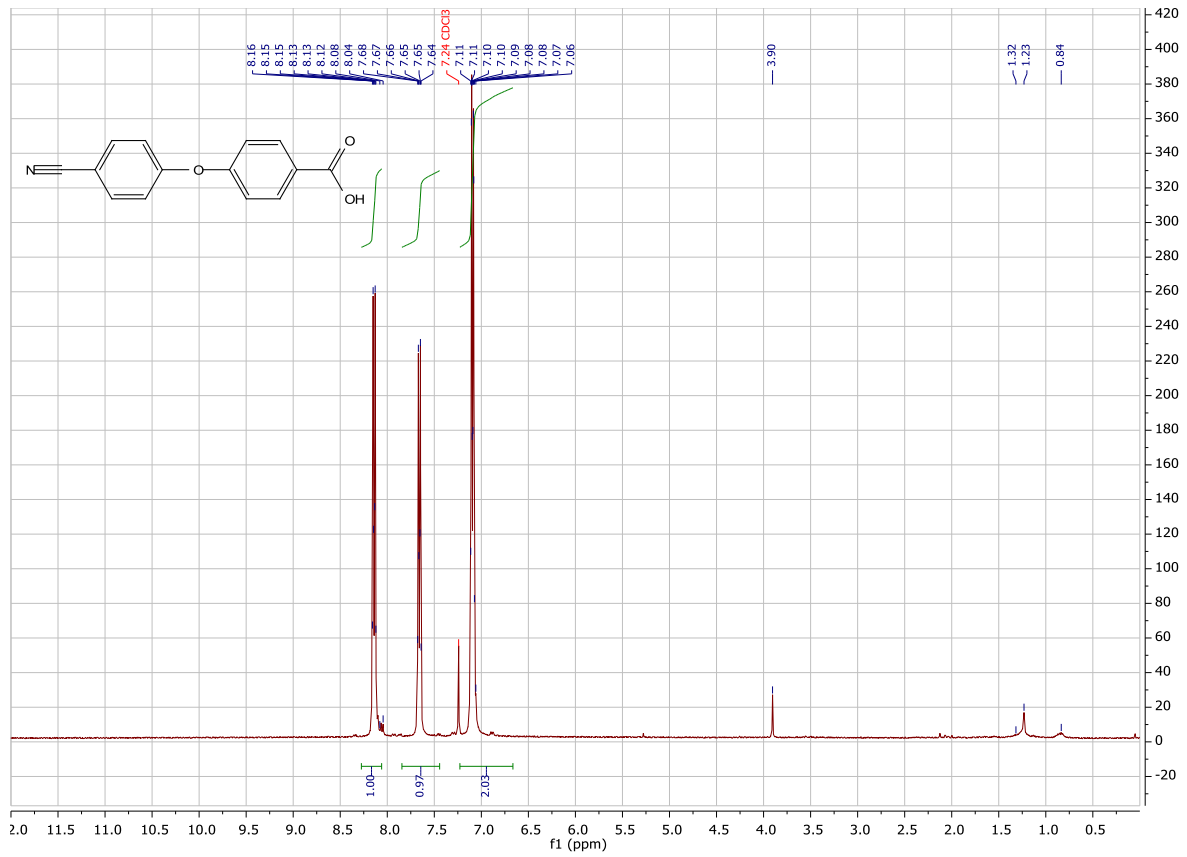
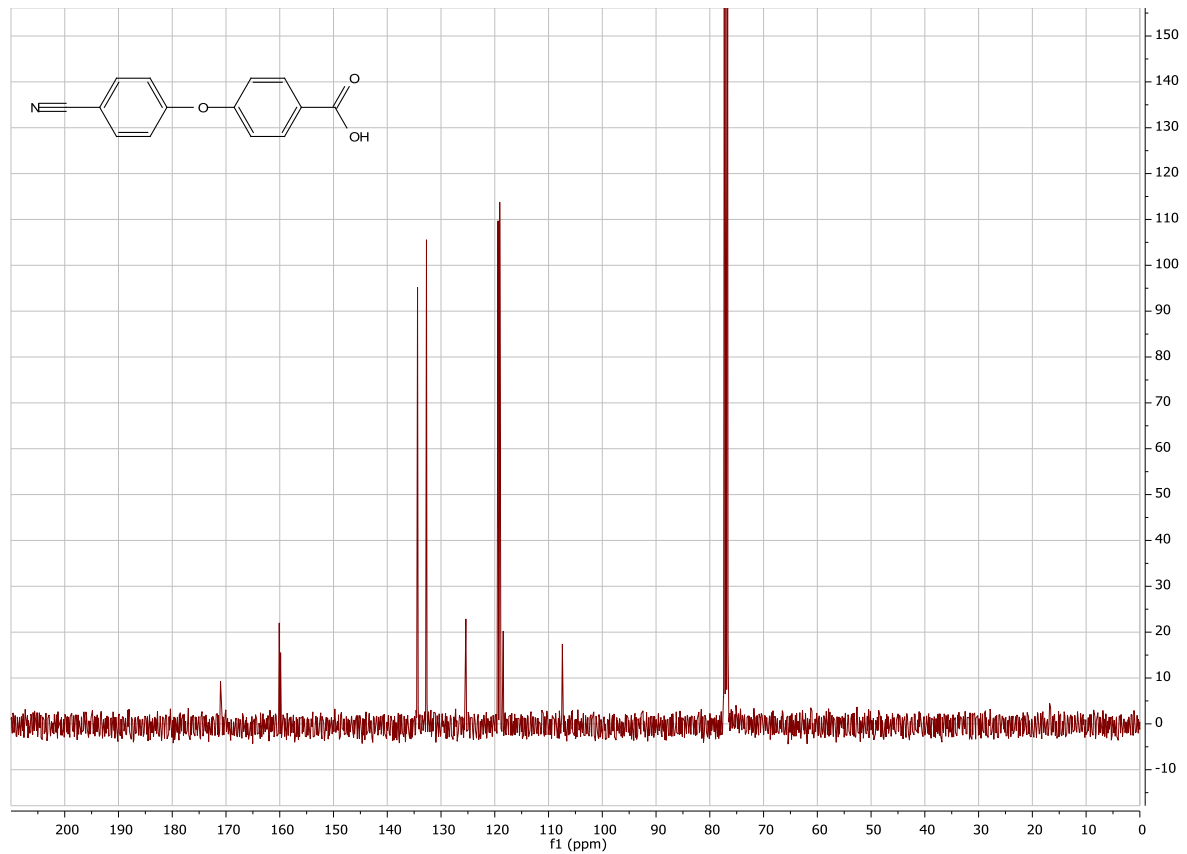
5. References

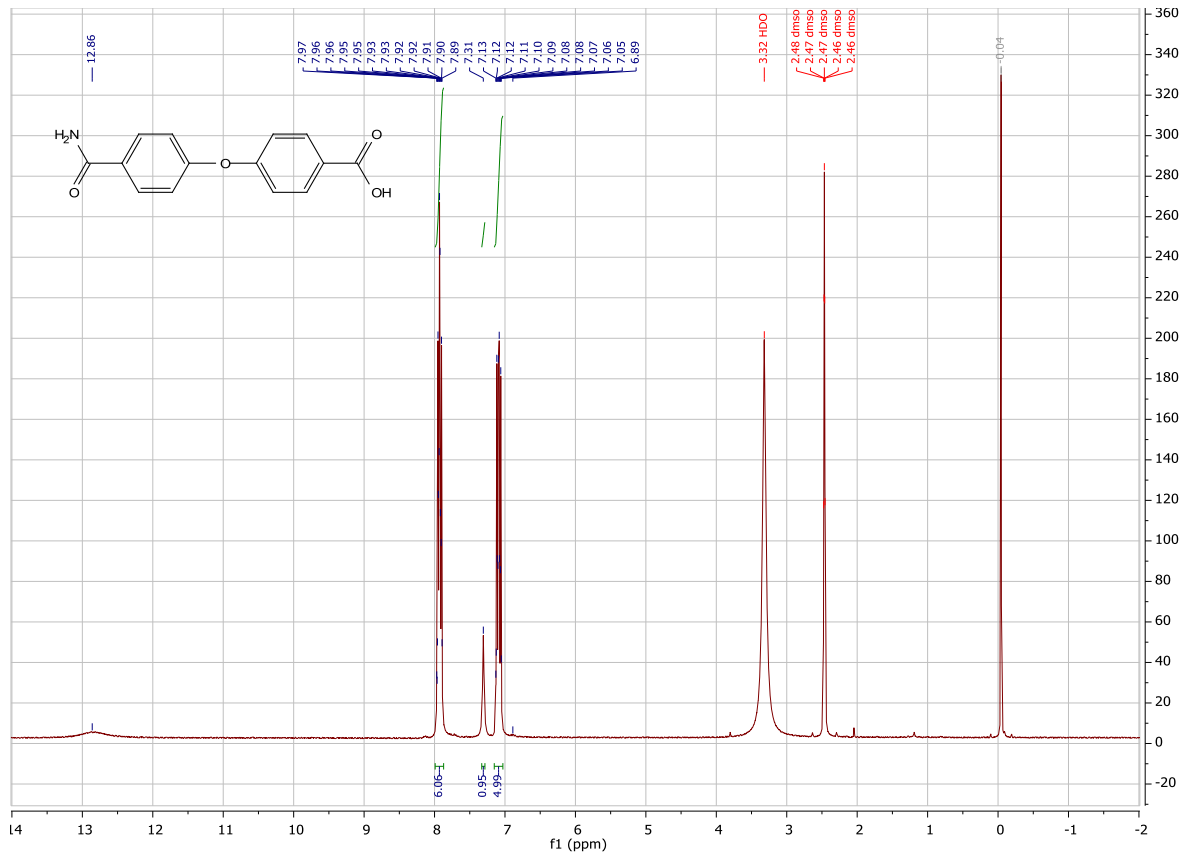
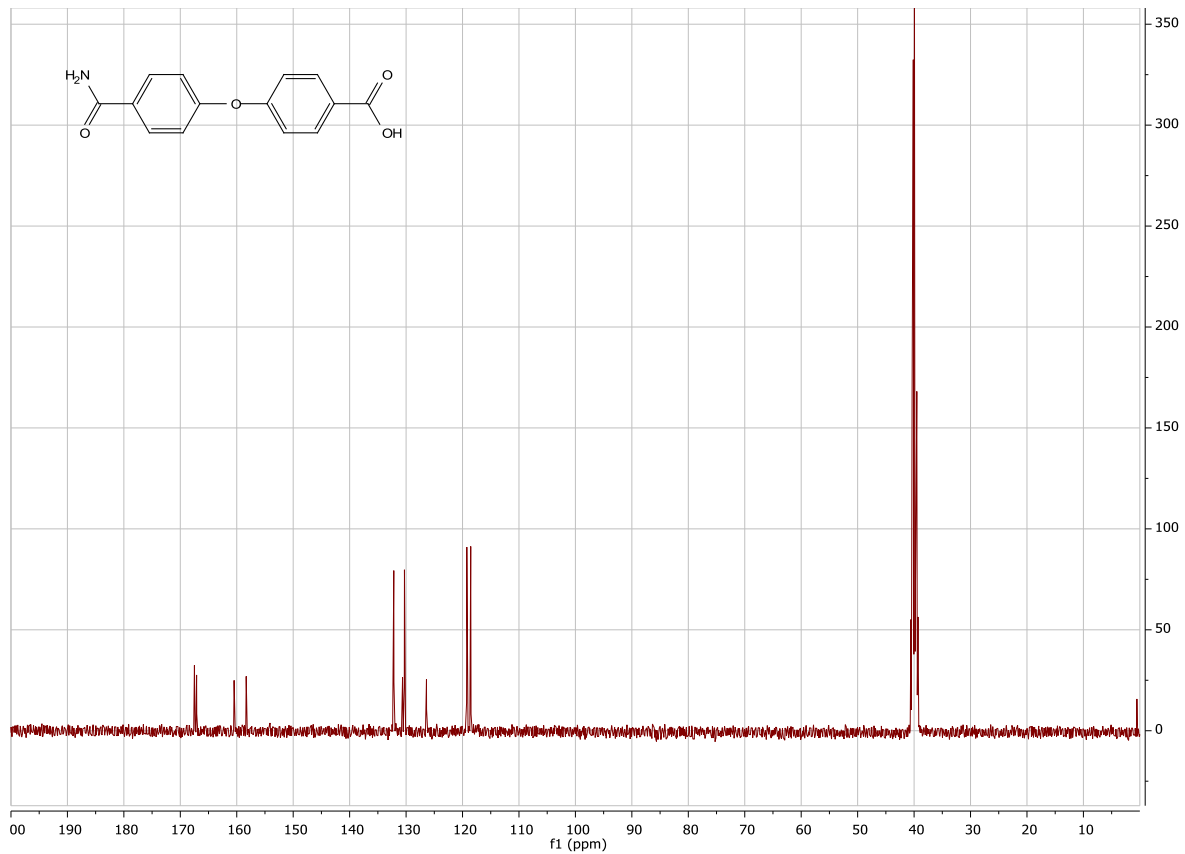
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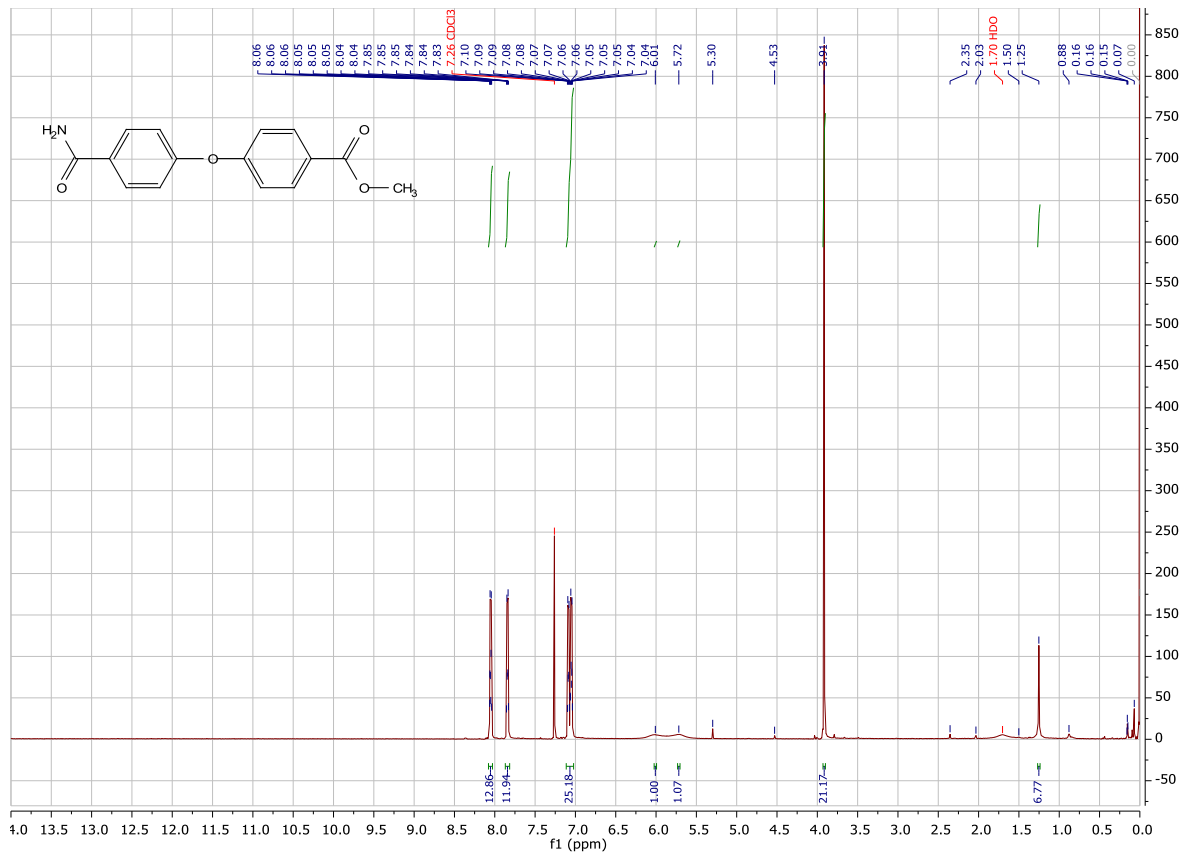
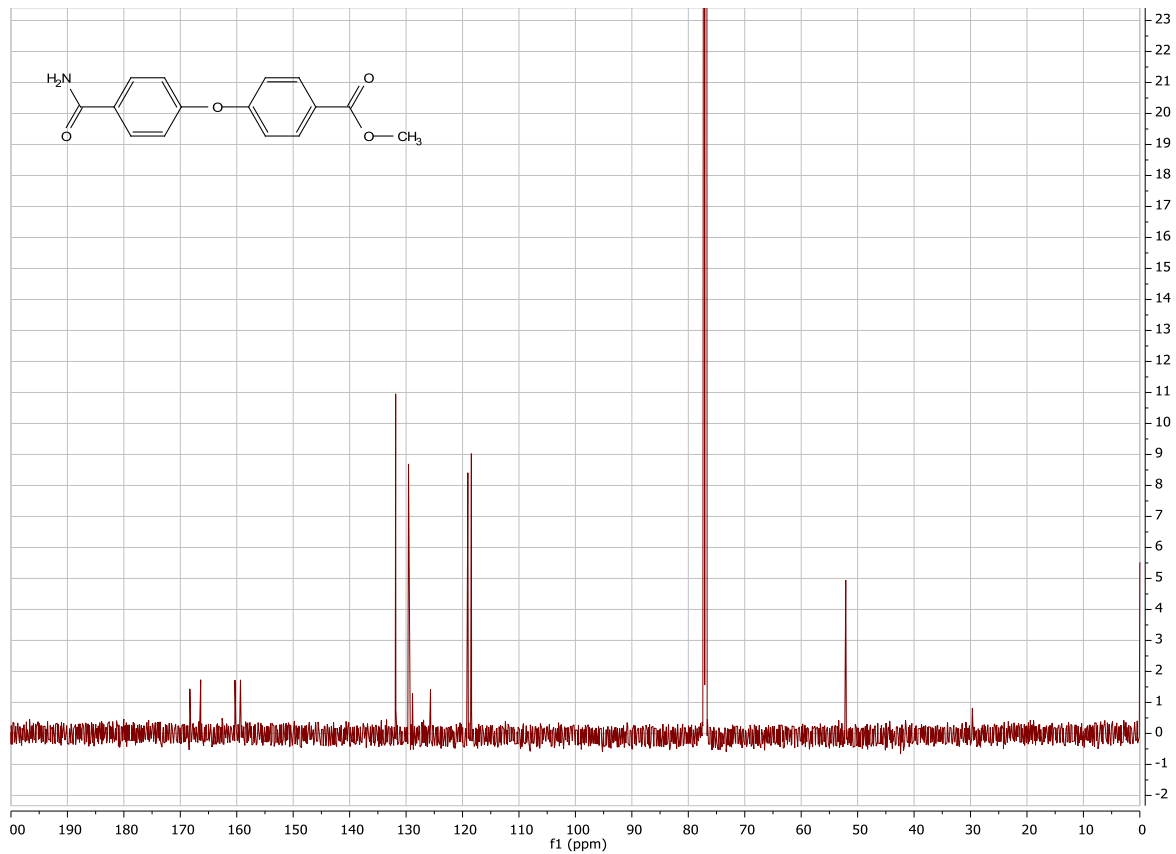
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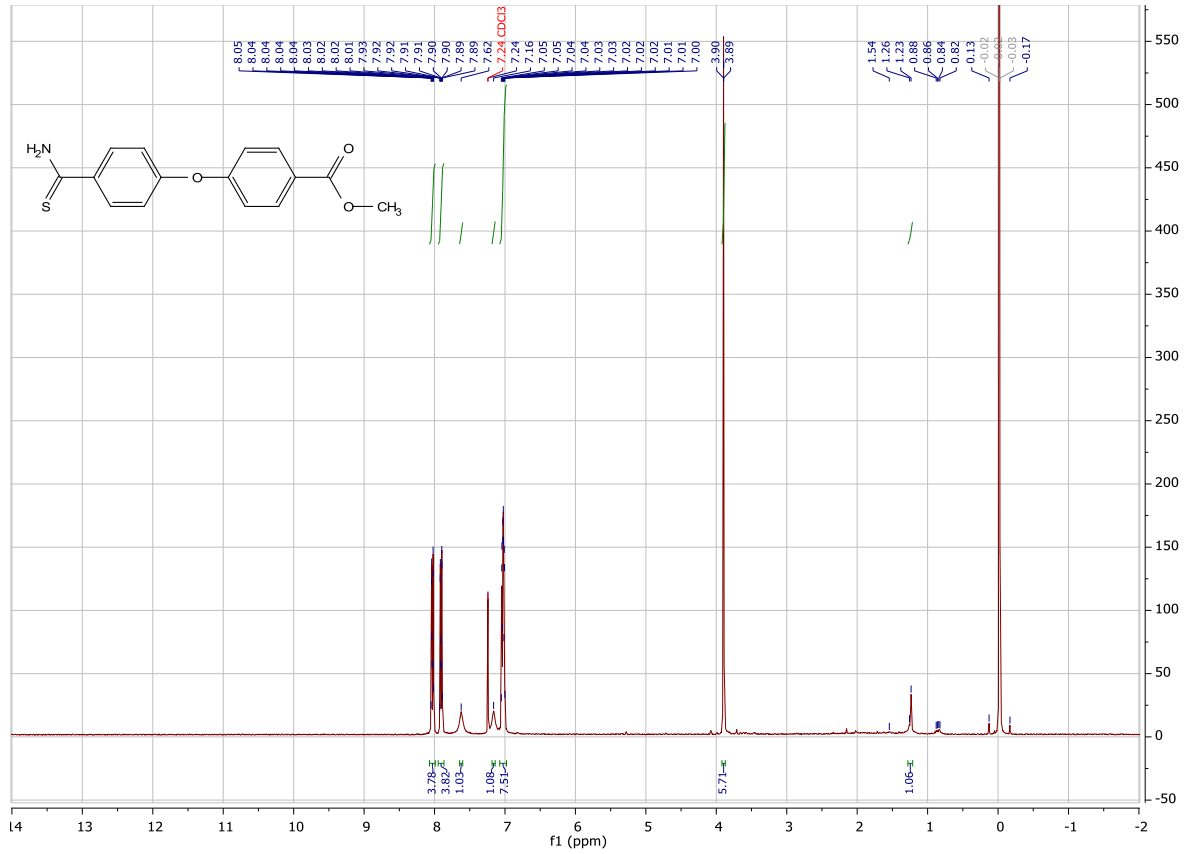
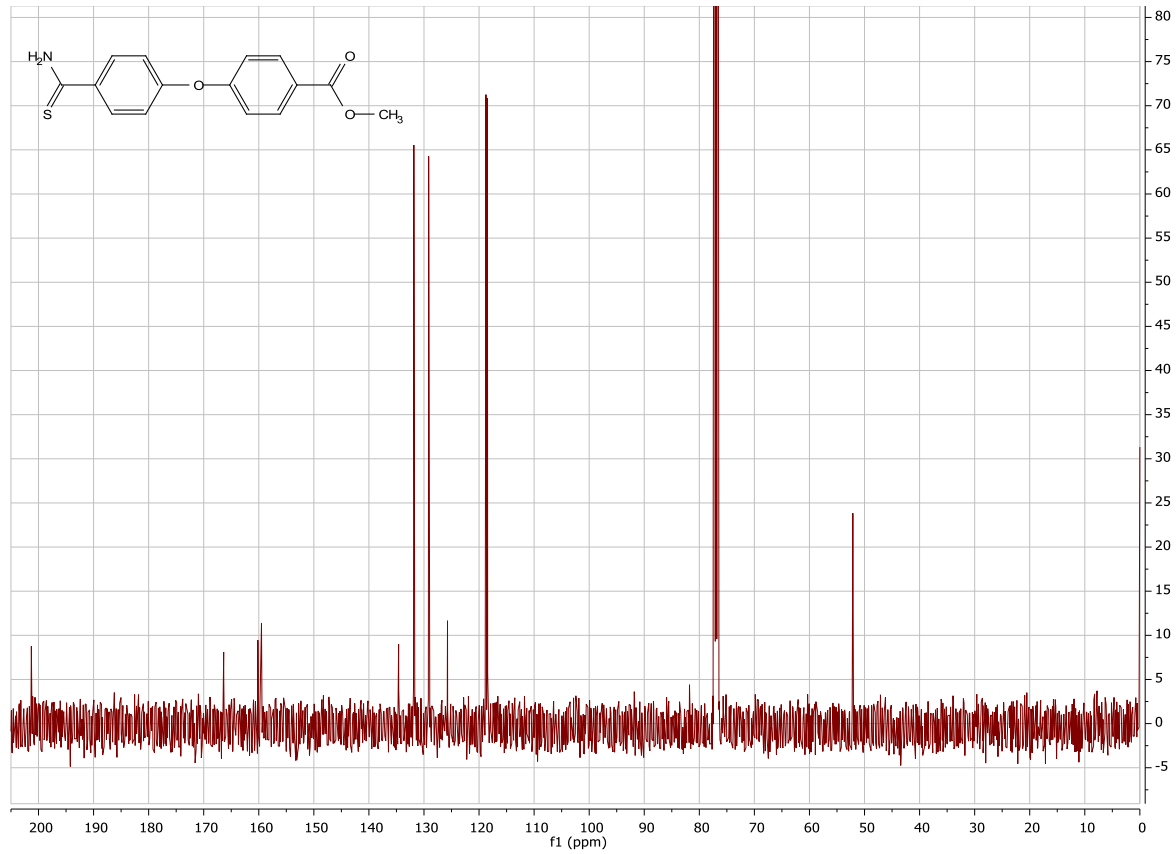
6. NMR spectra

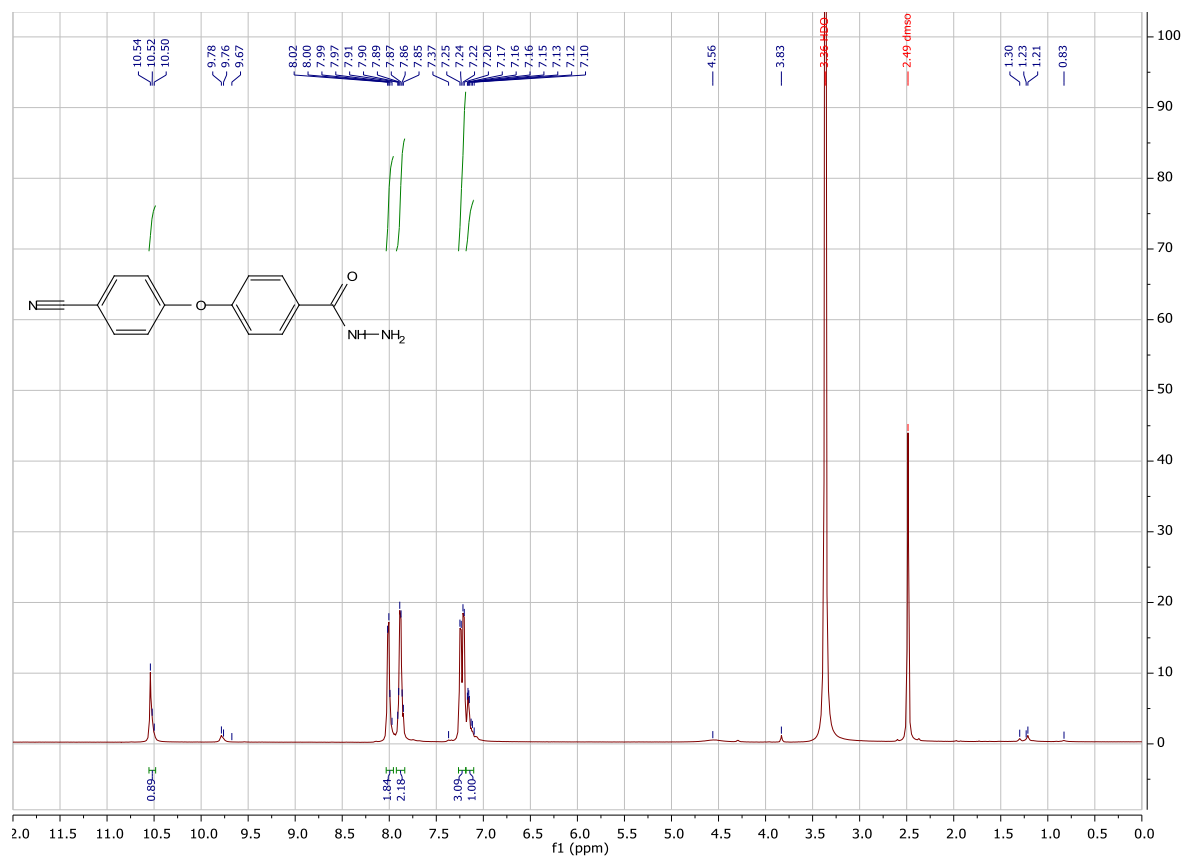
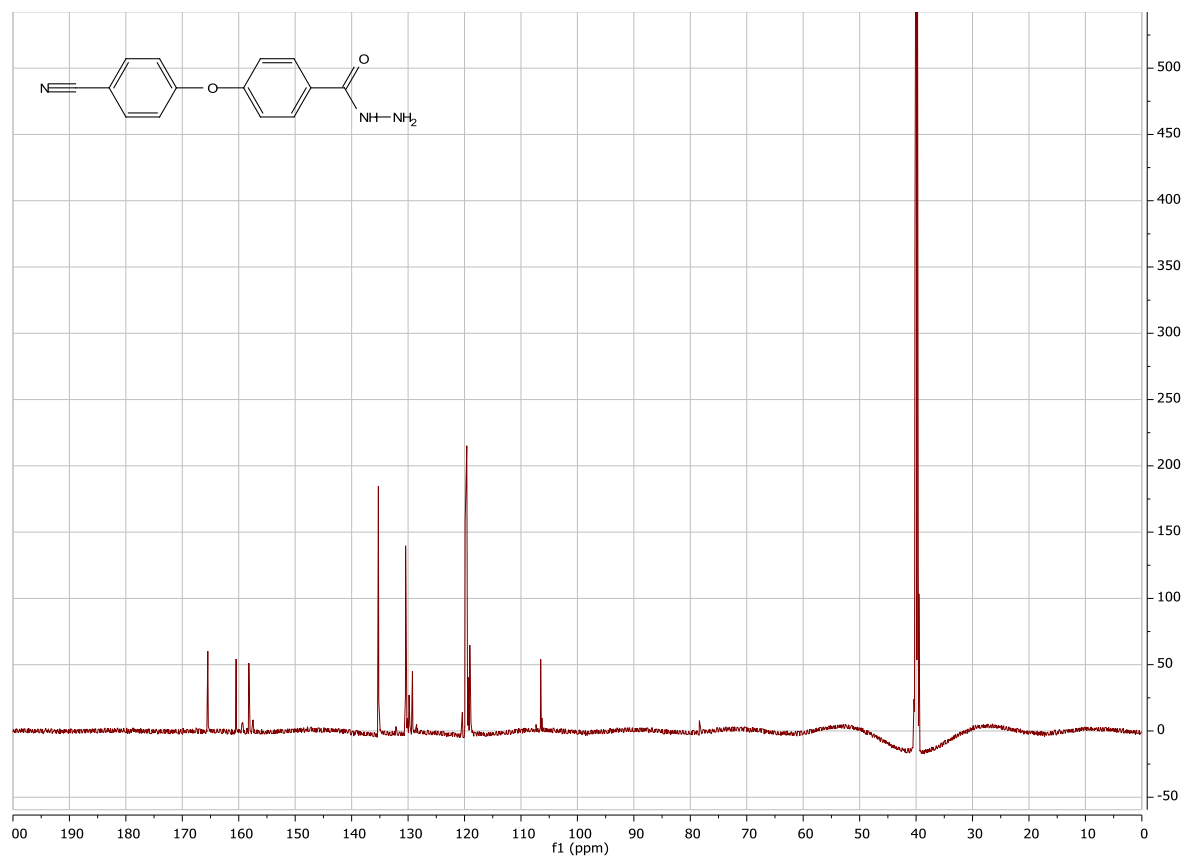
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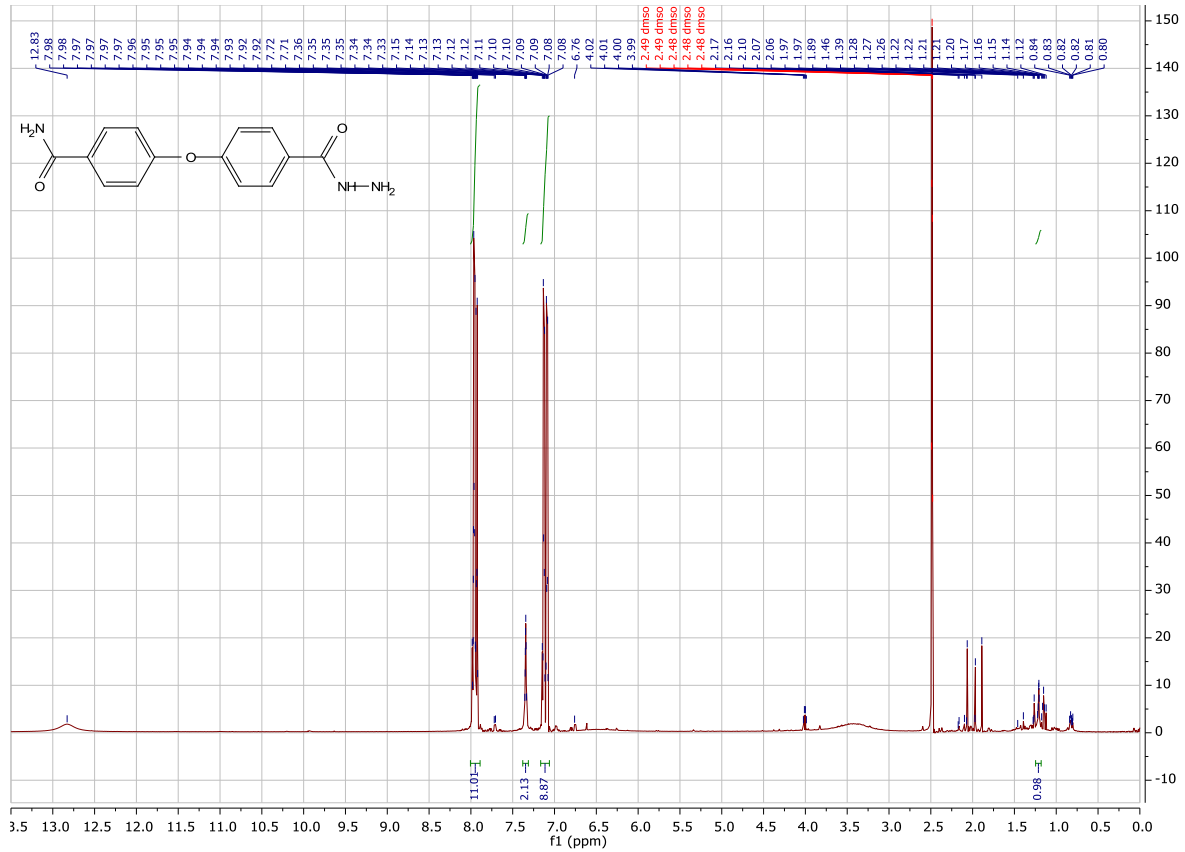
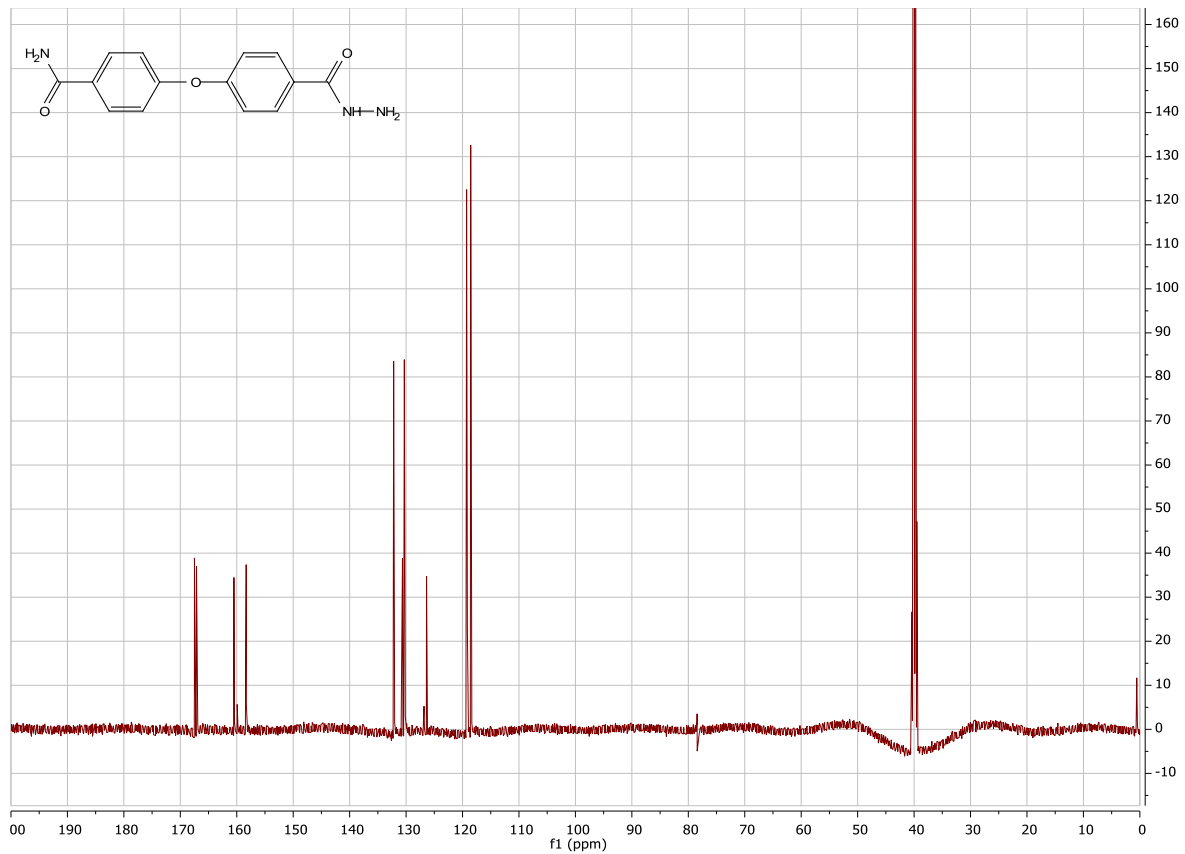
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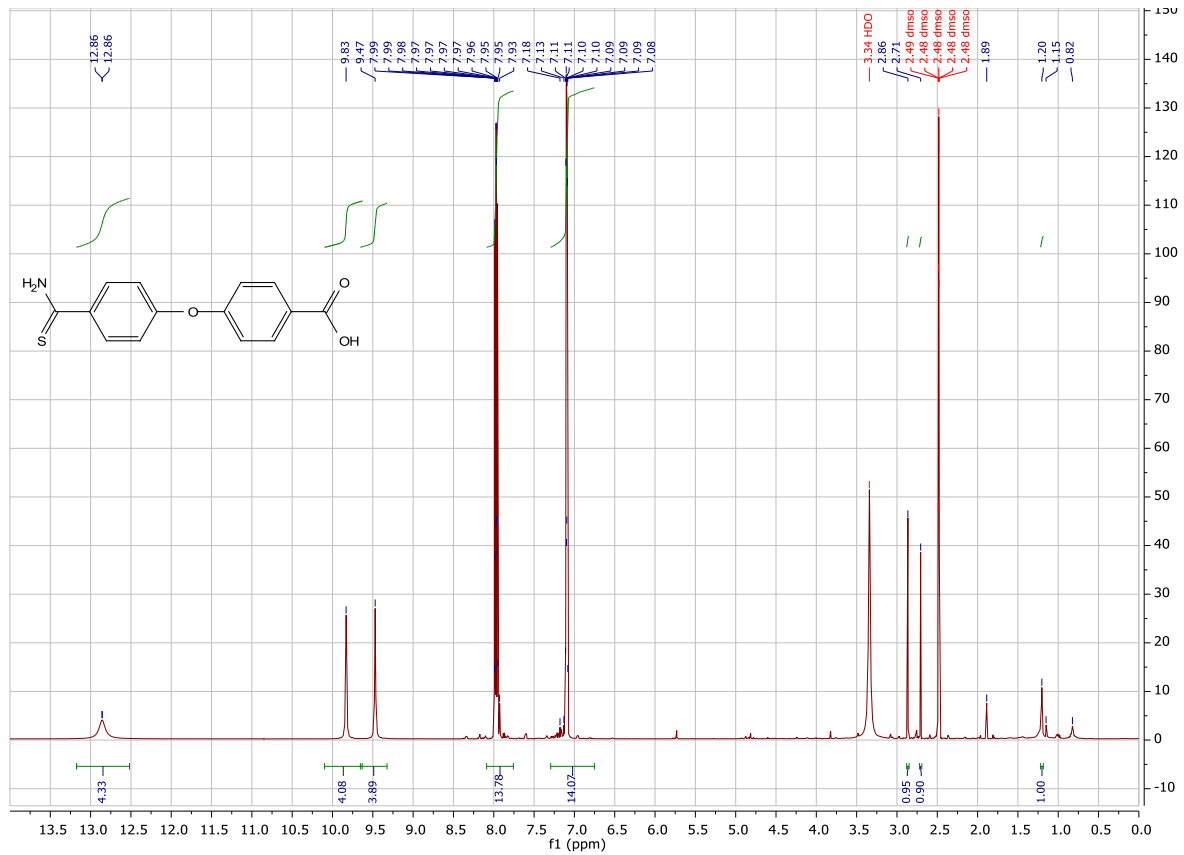
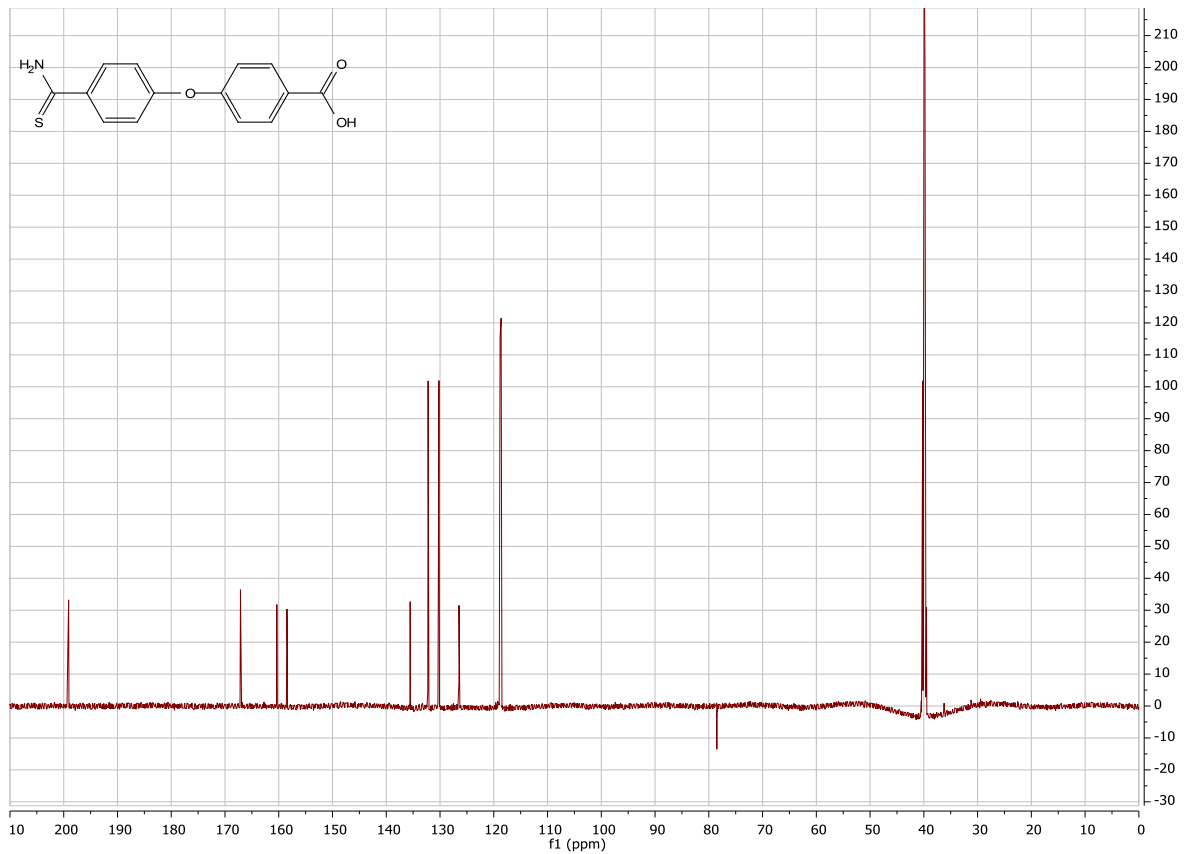
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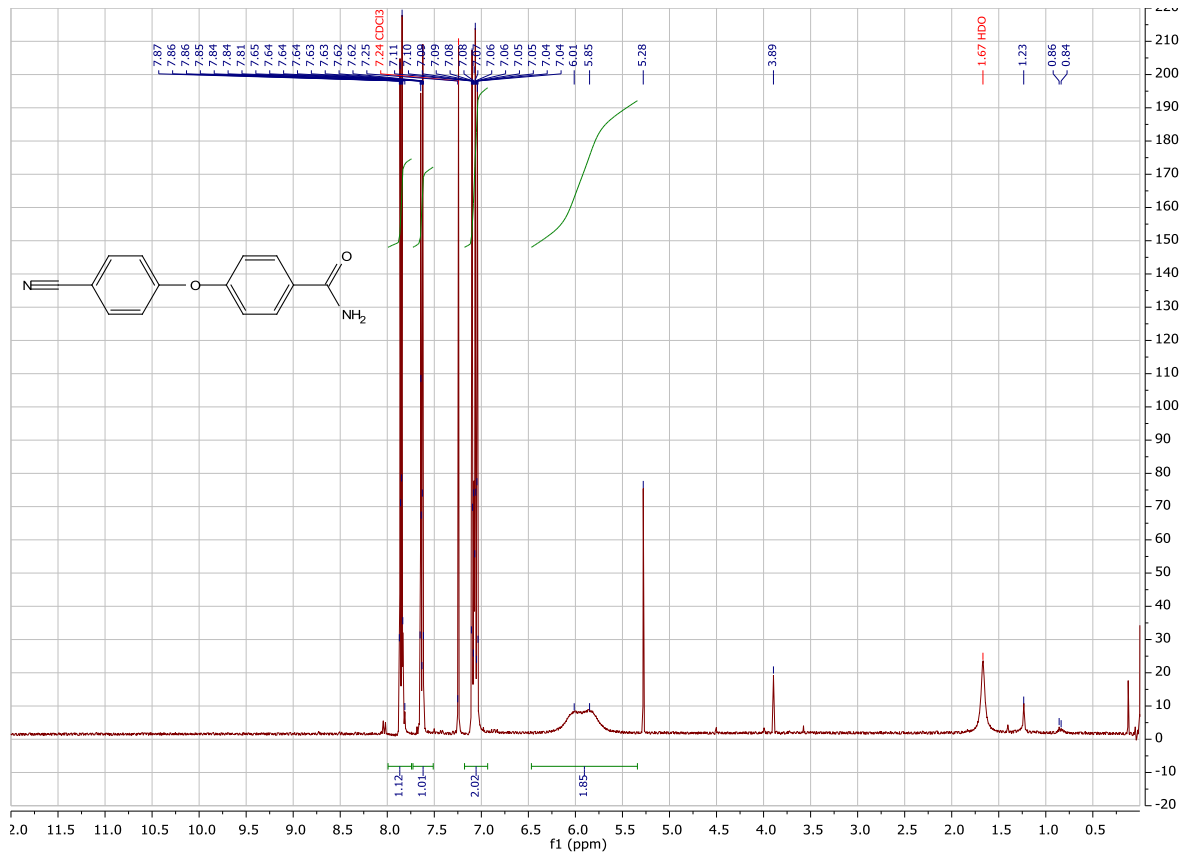
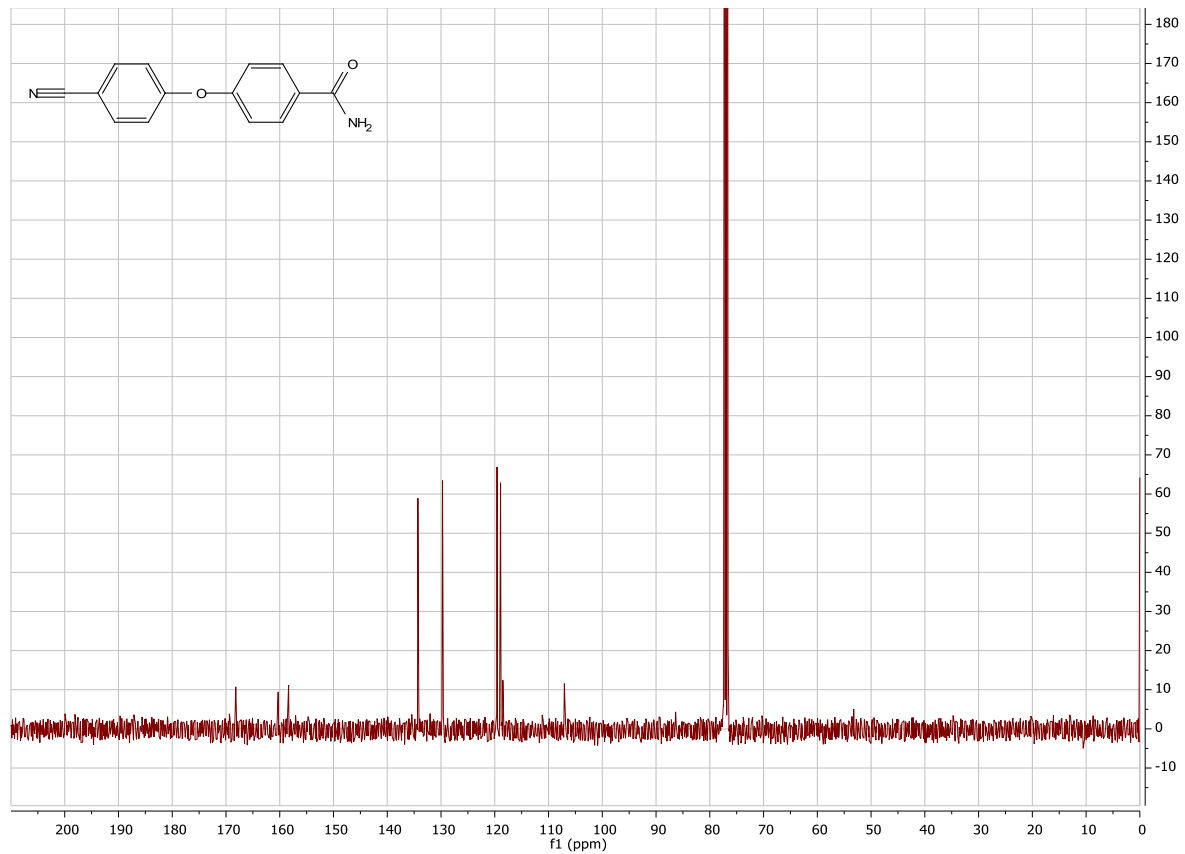
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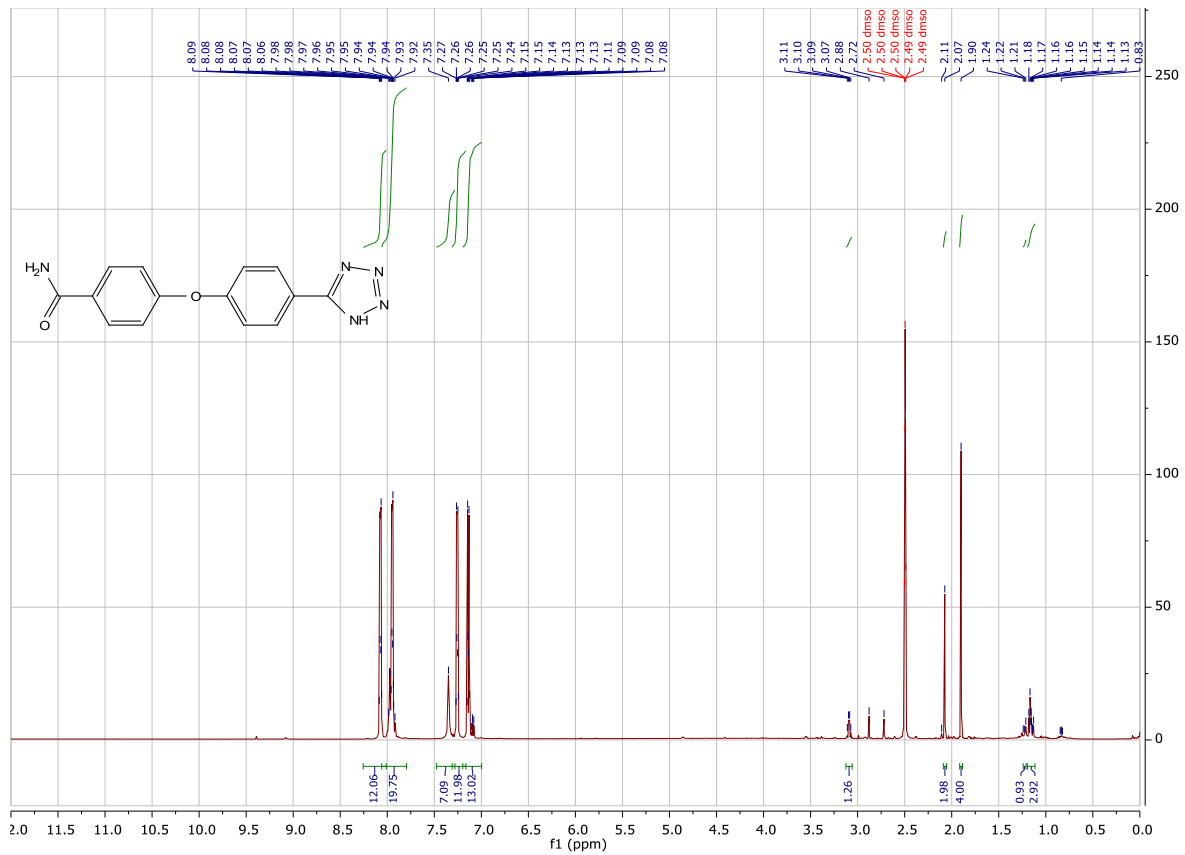
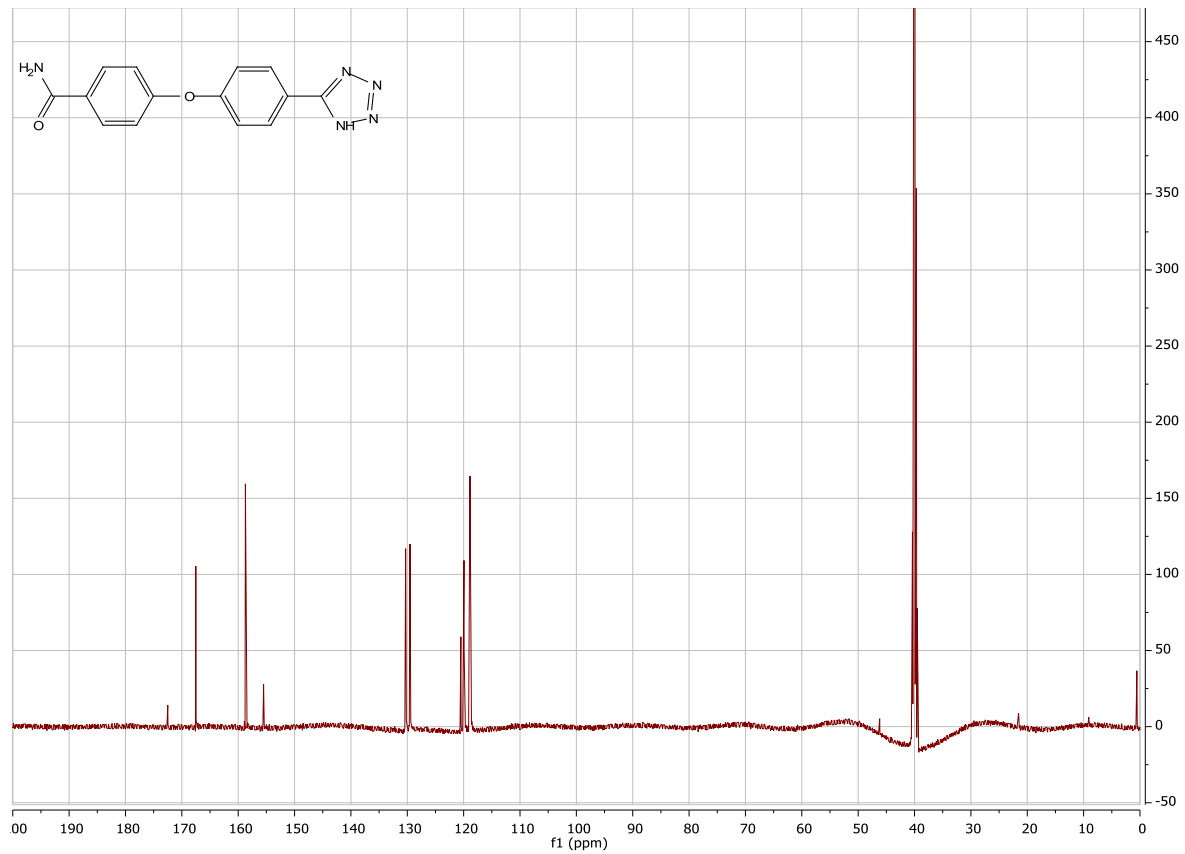
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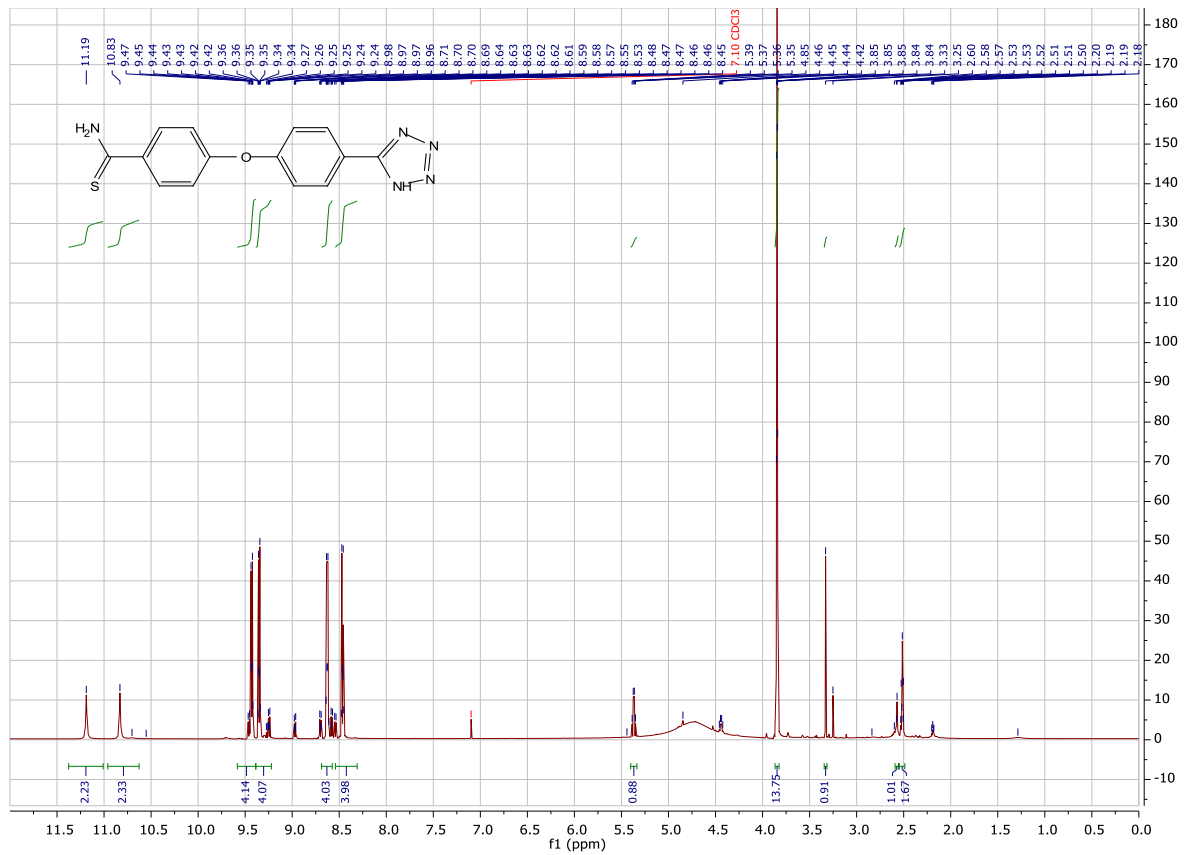
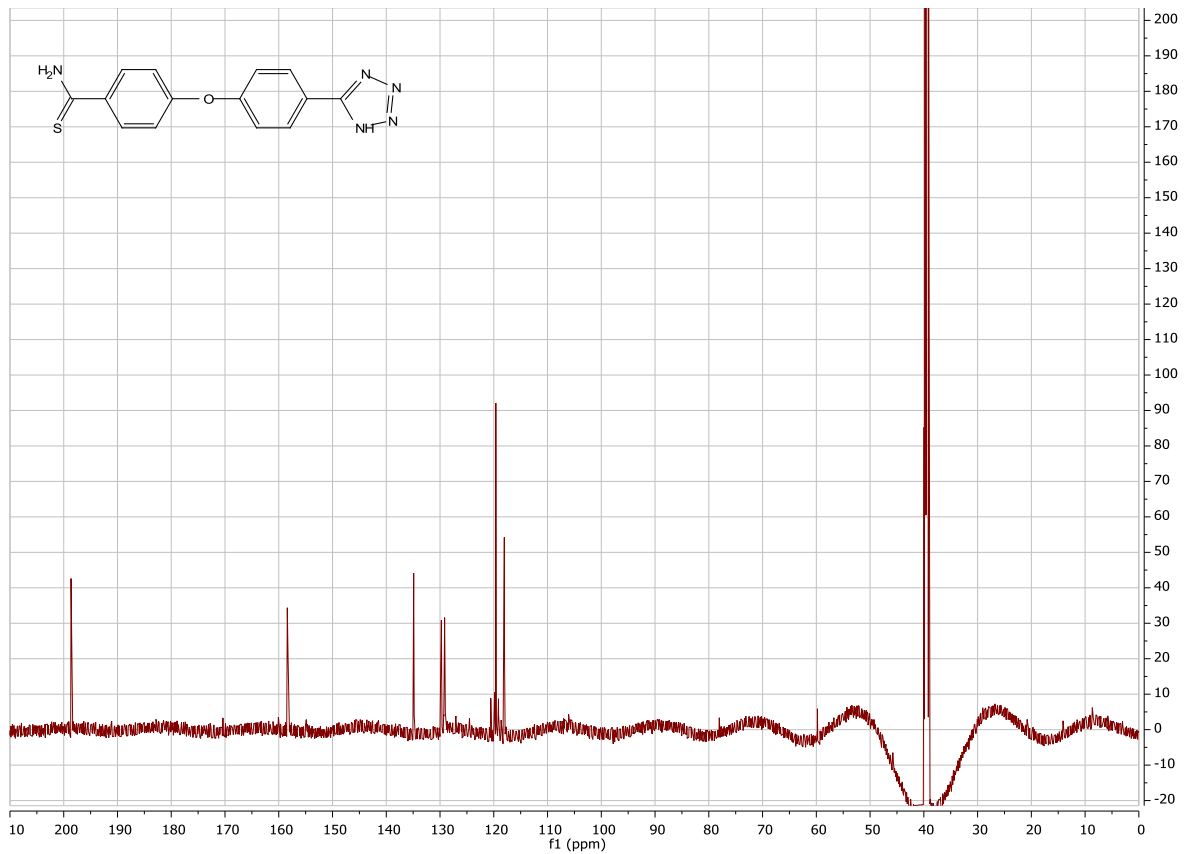
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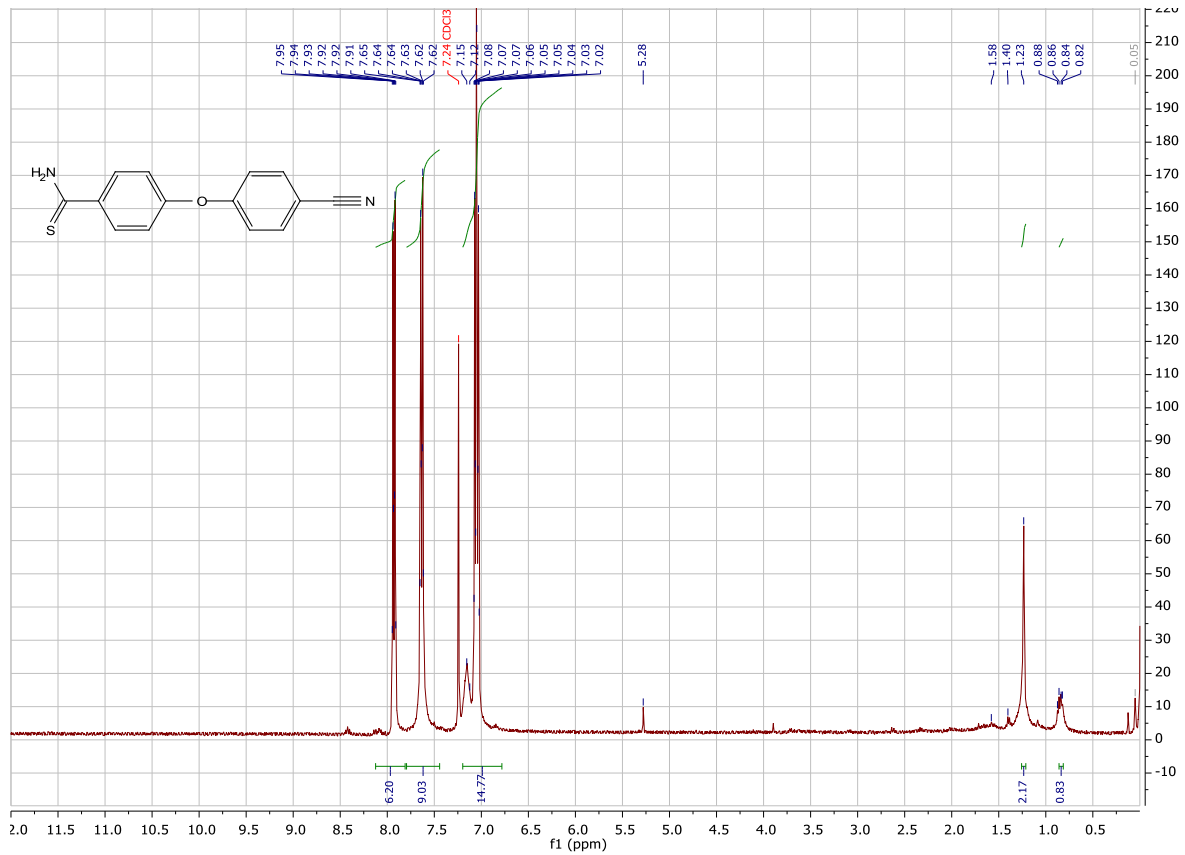
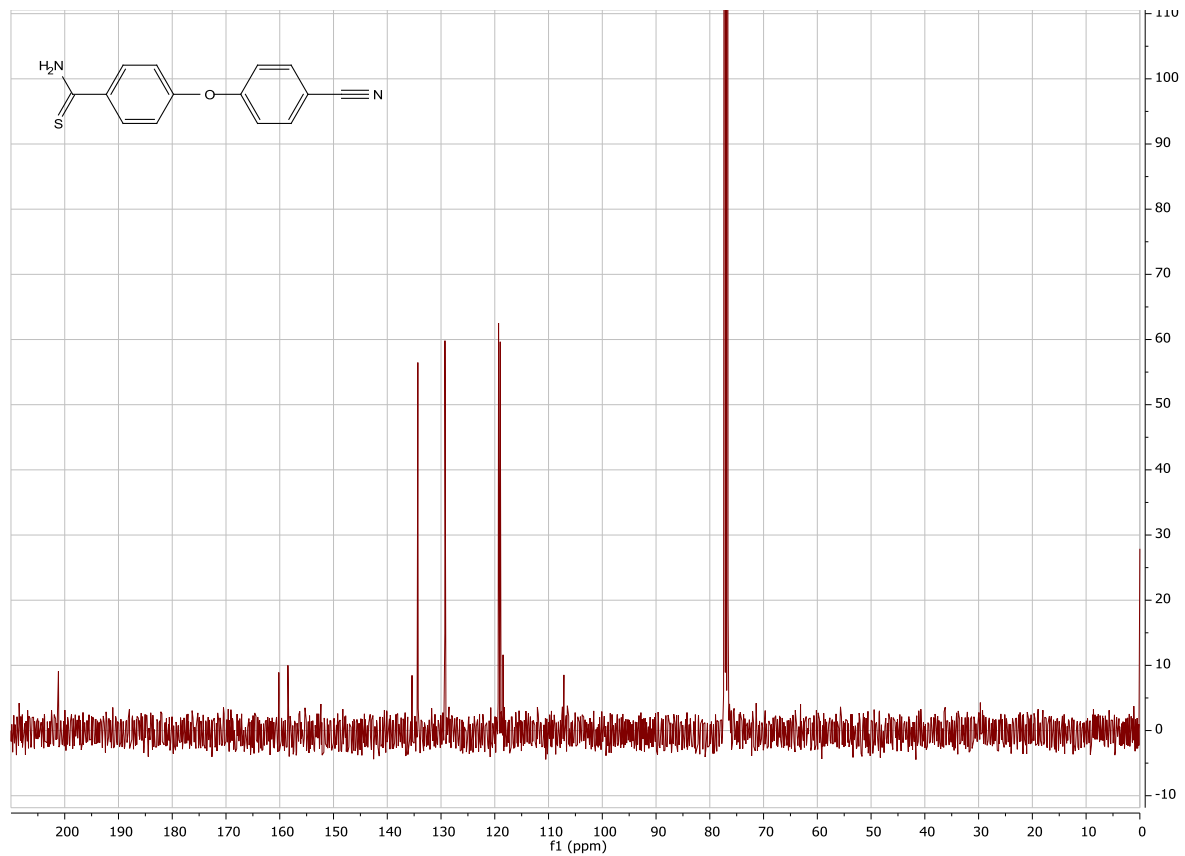
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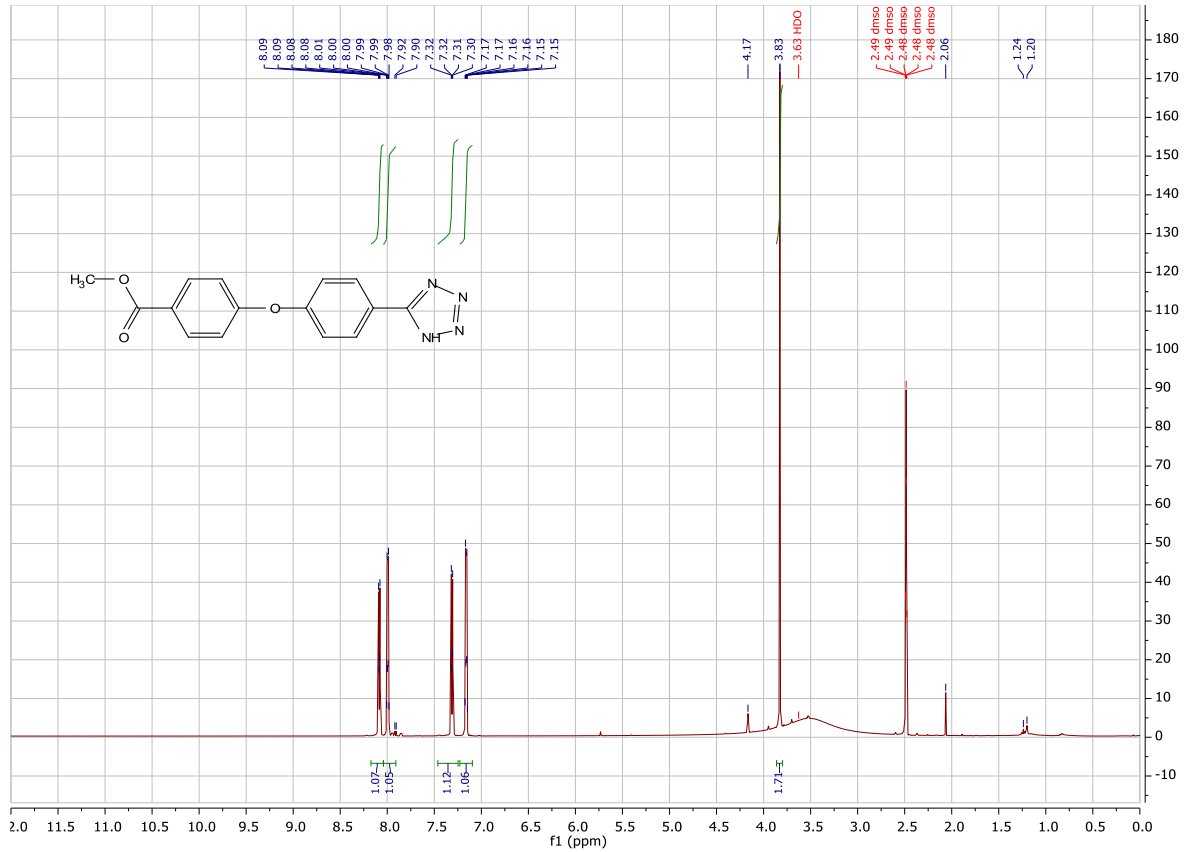
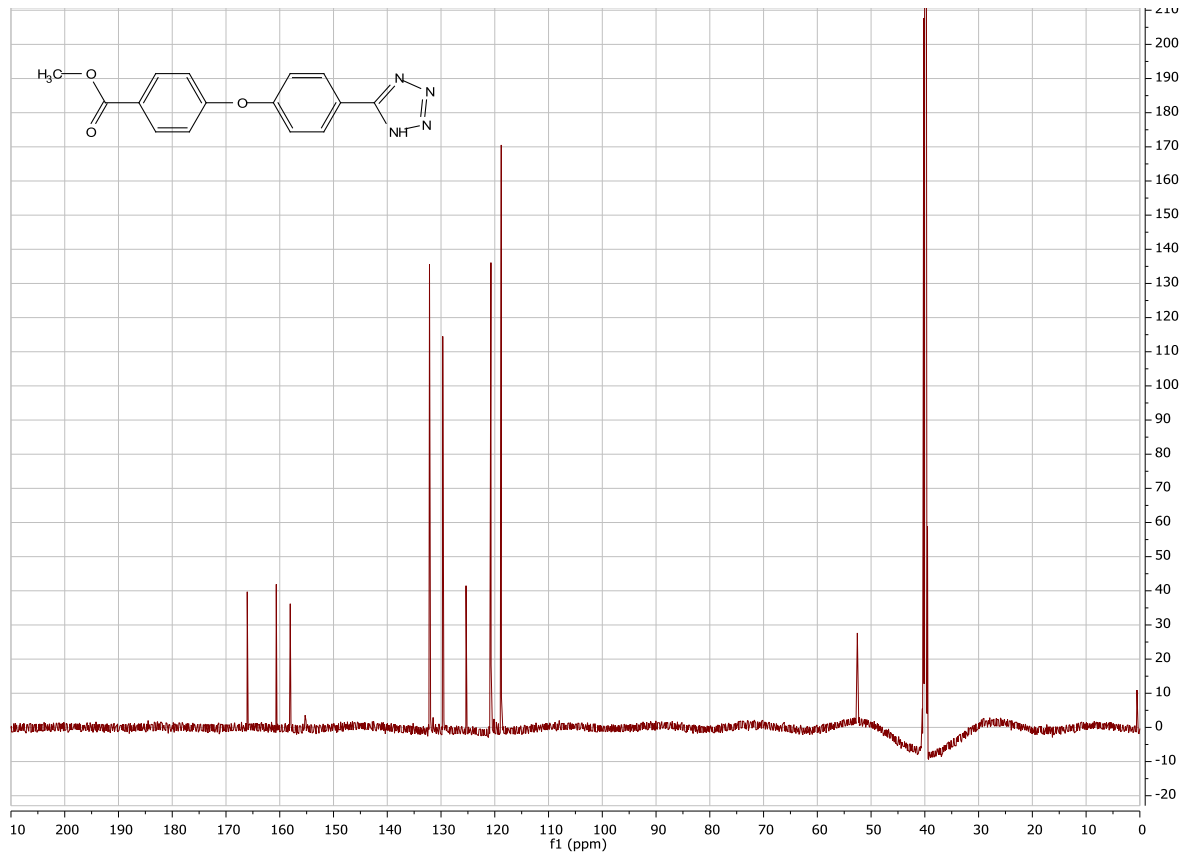
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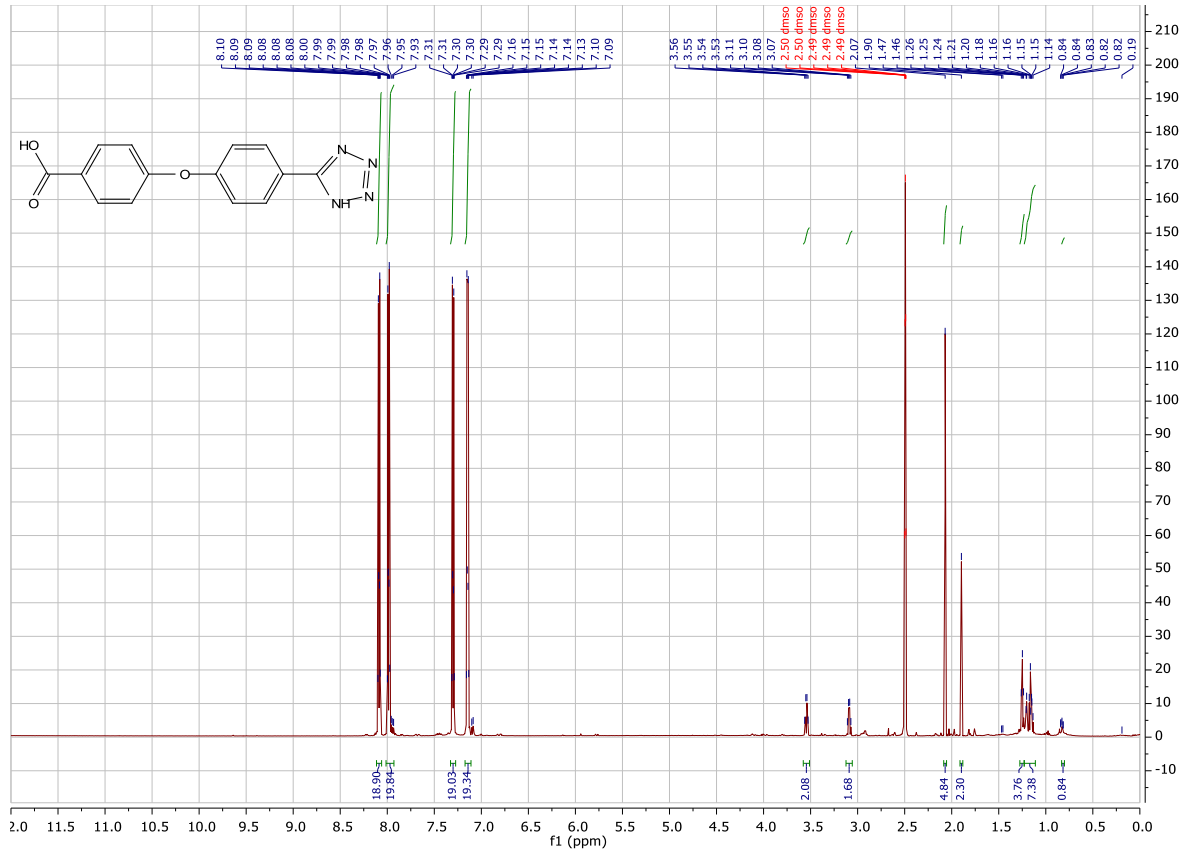
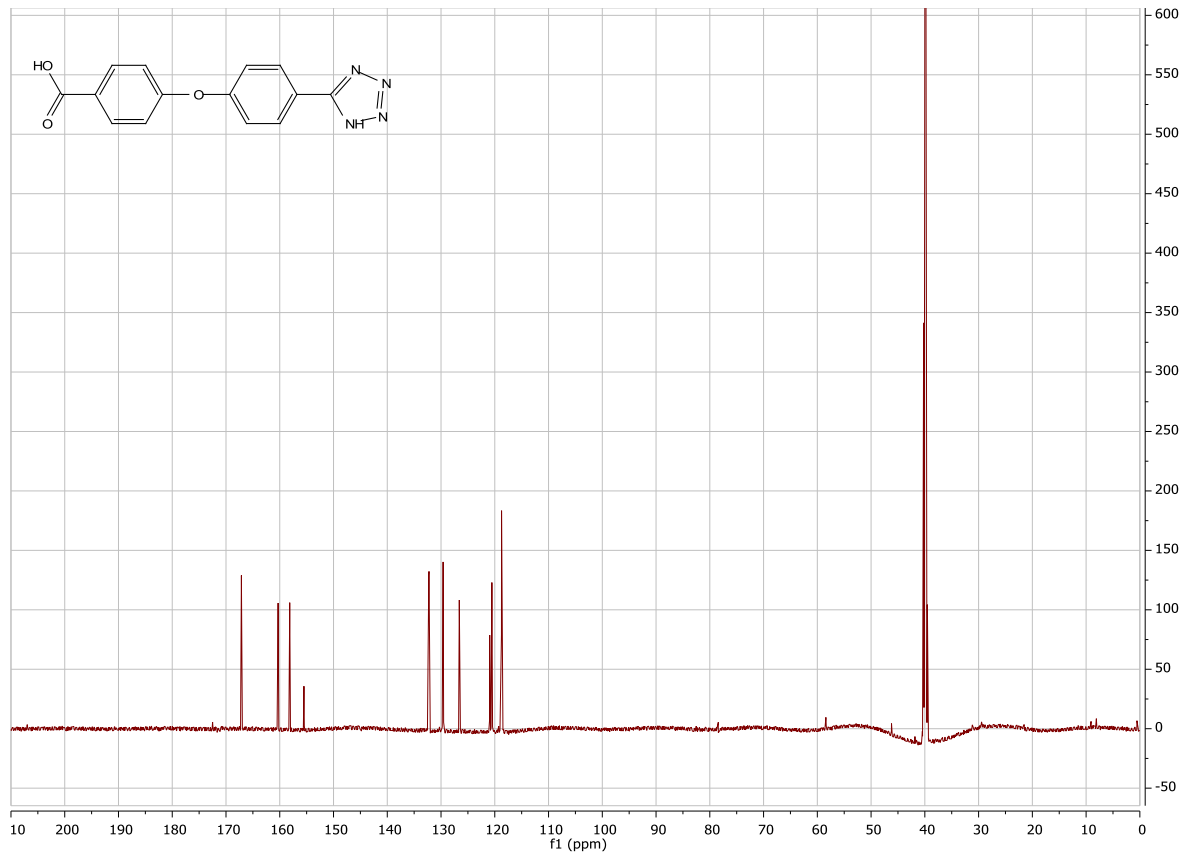
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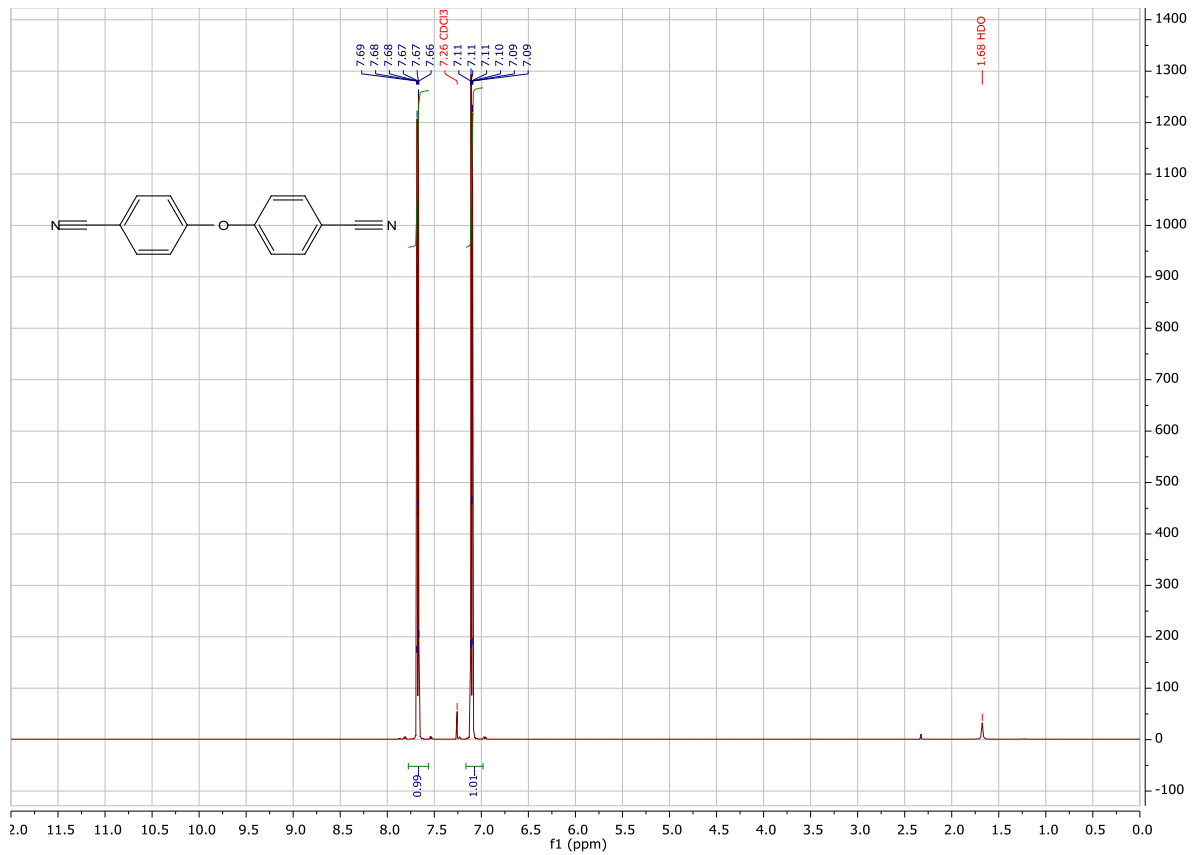
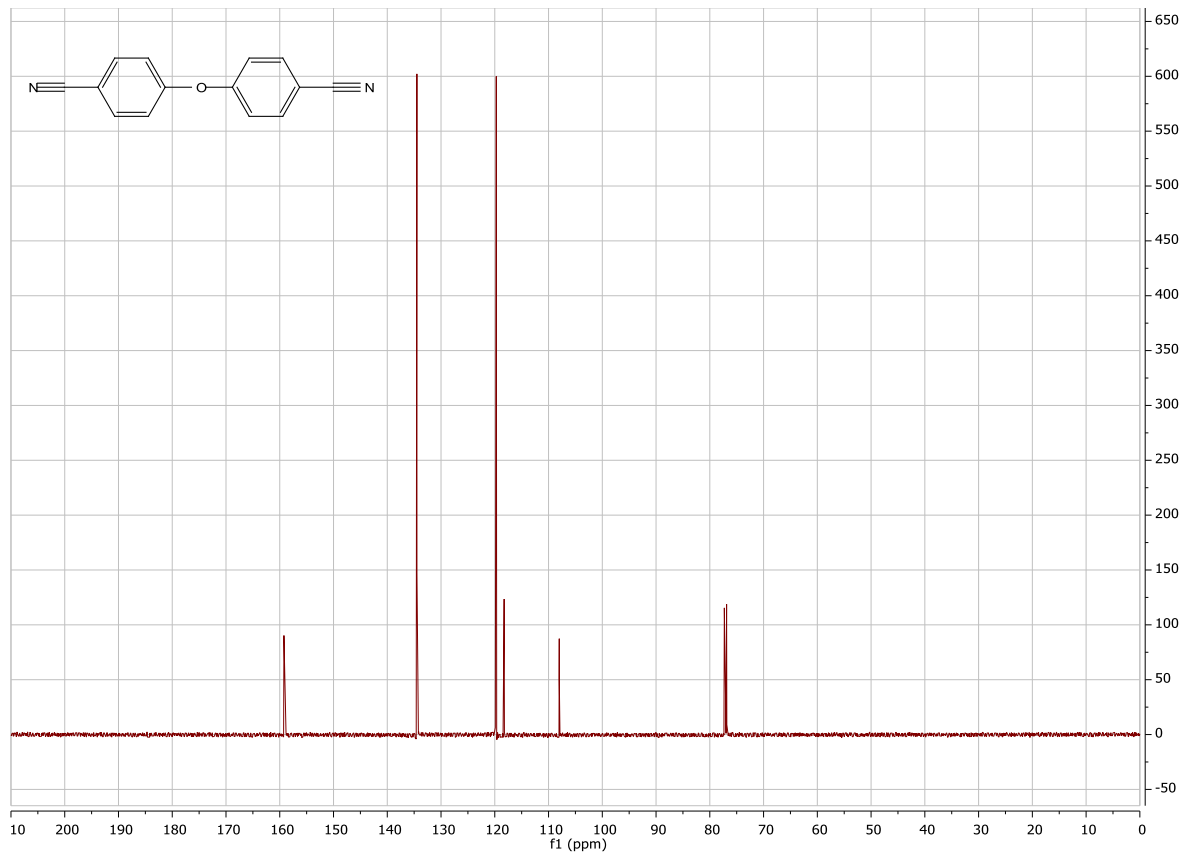
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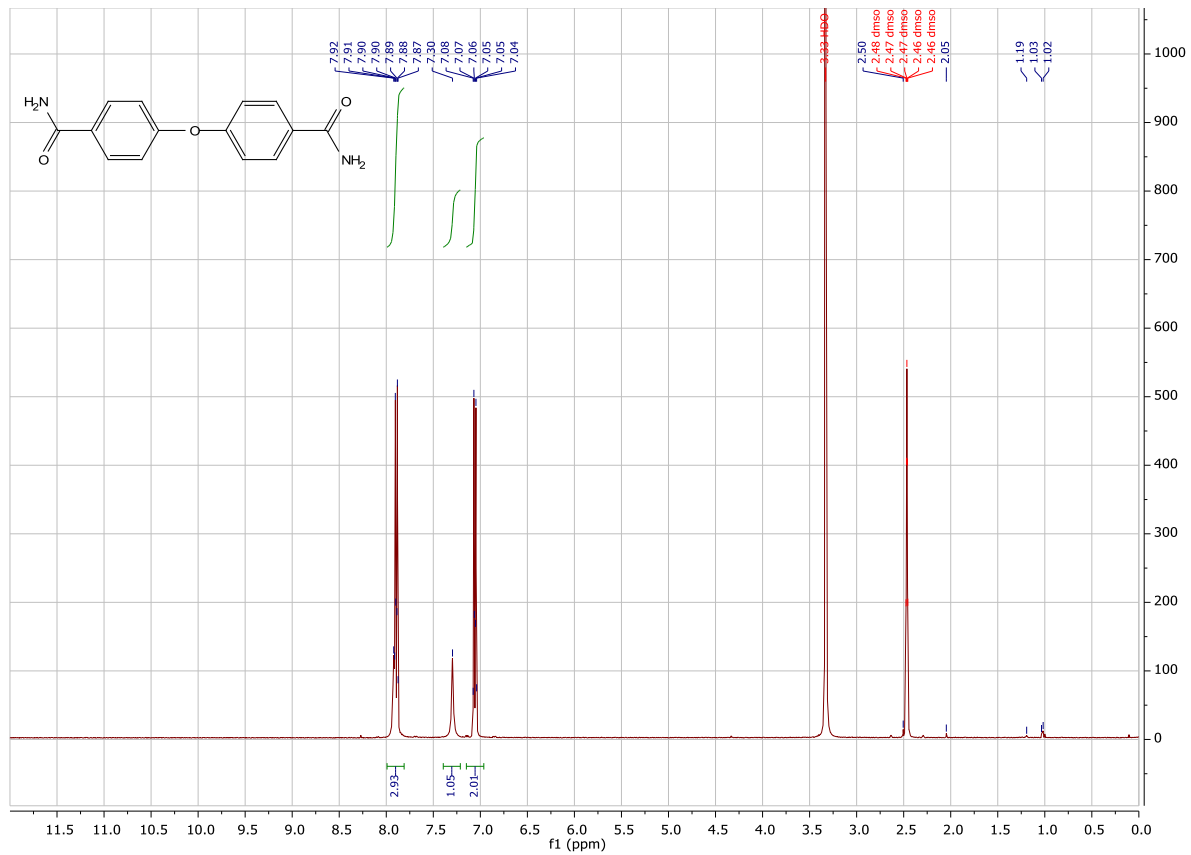
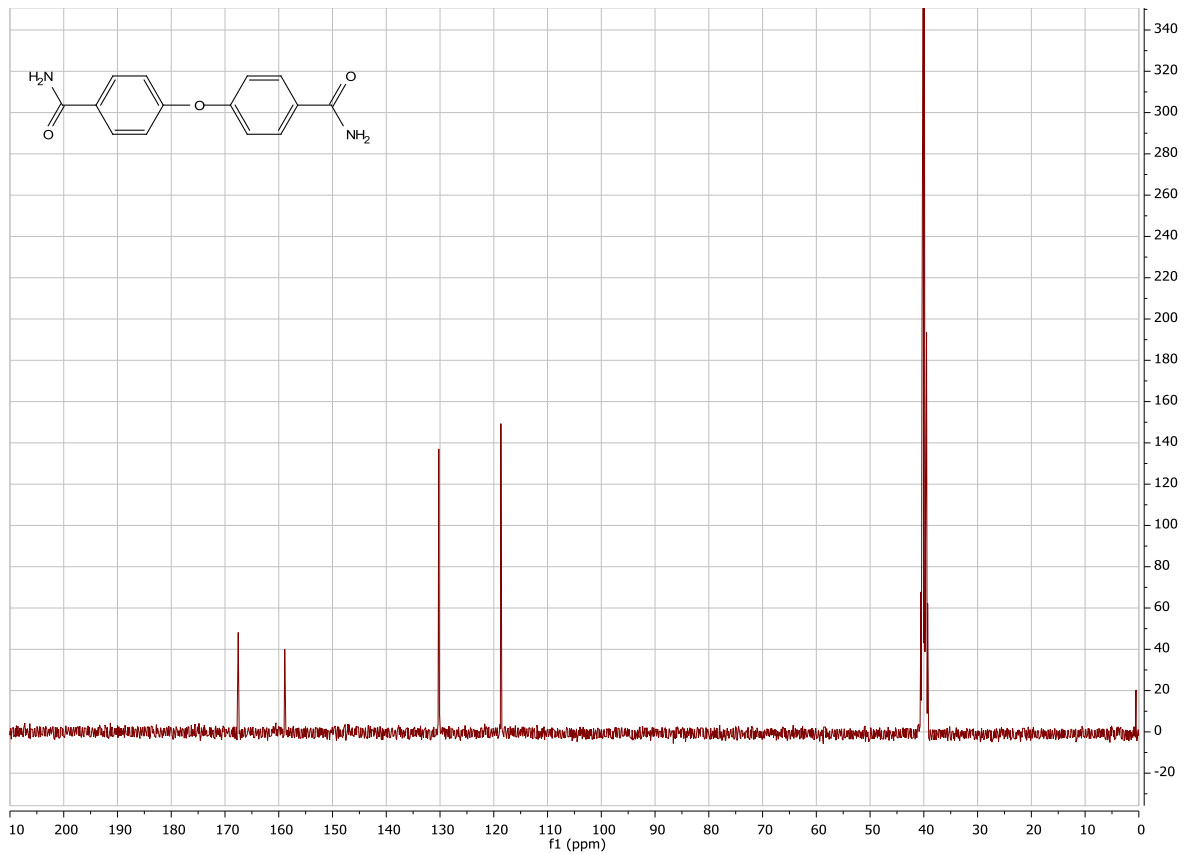
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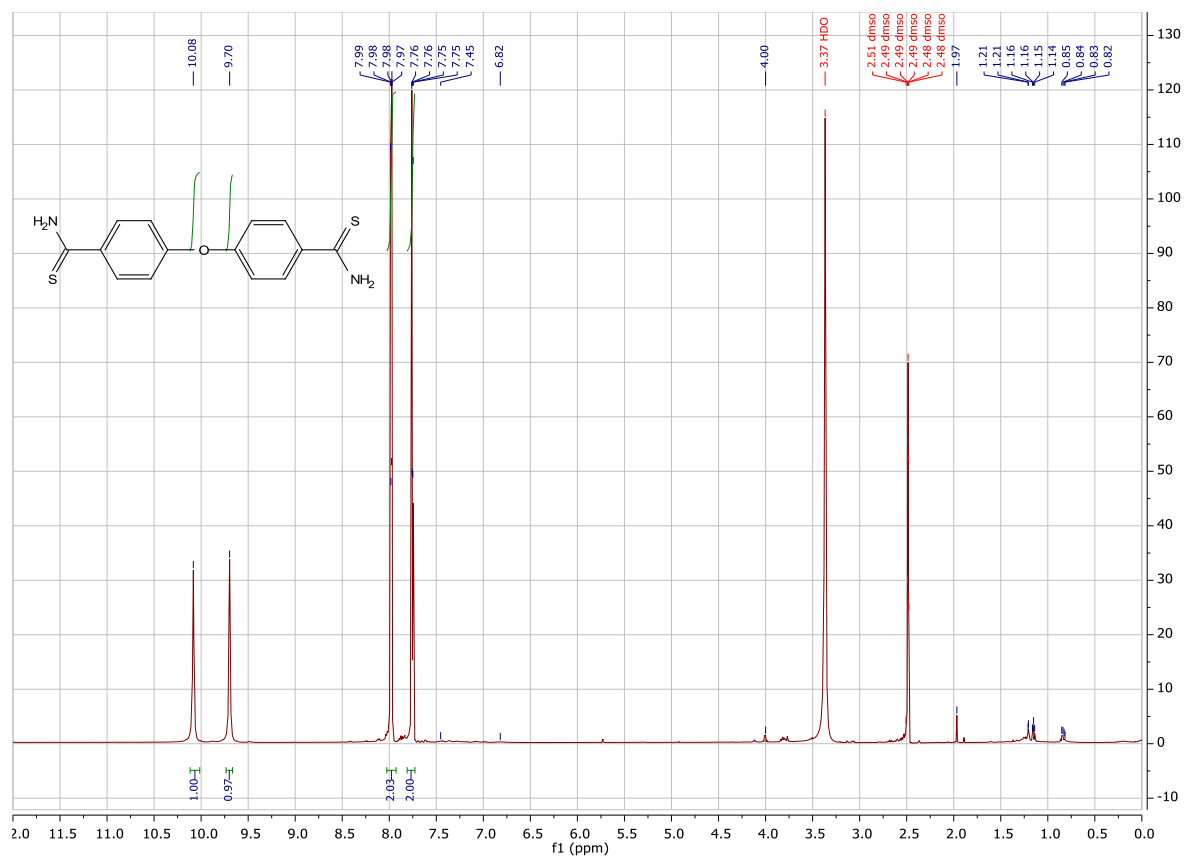
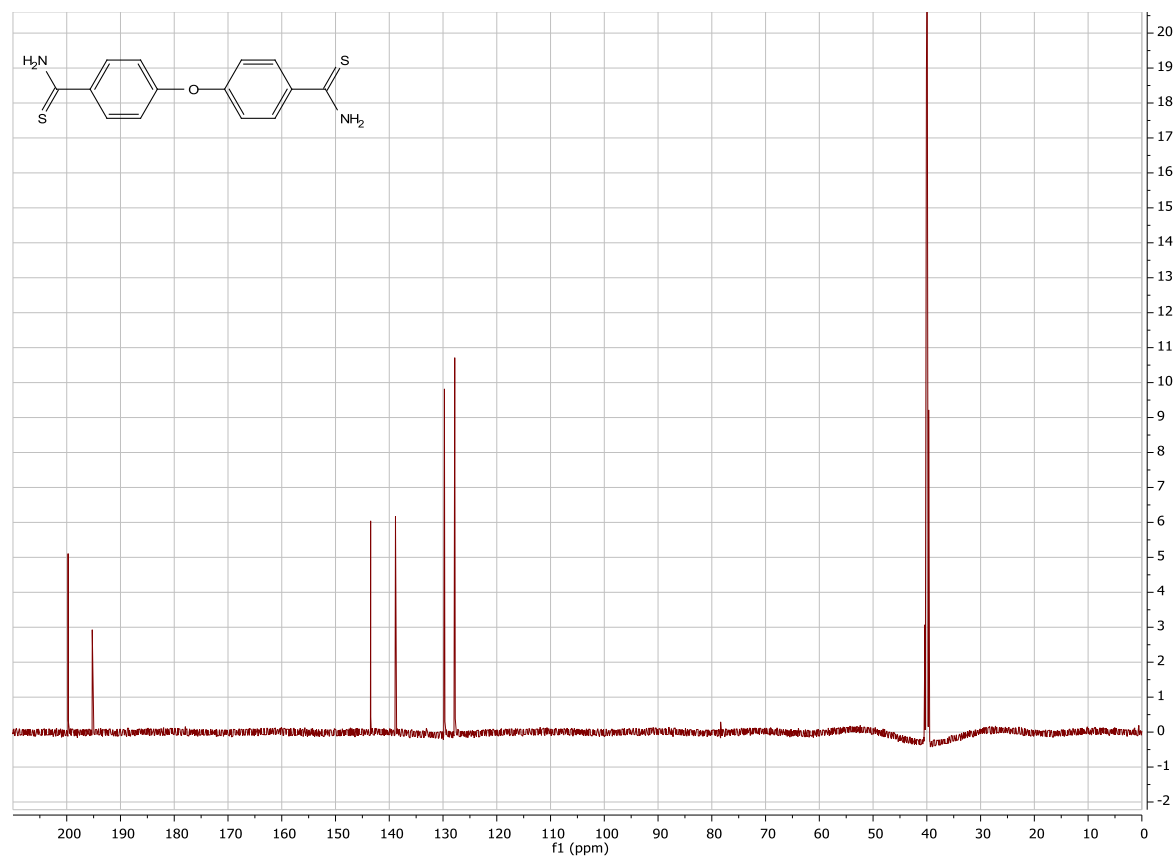
^1H NMR (400 MHz, CDCl_3) 4-(4-Cyanophenoxy)benzothioamide (13) ^{13}C { ^1H } NMR (100.6 MHz, CDCl_3) 4-(4-Cyanophenoxy)benzothioamide (13)

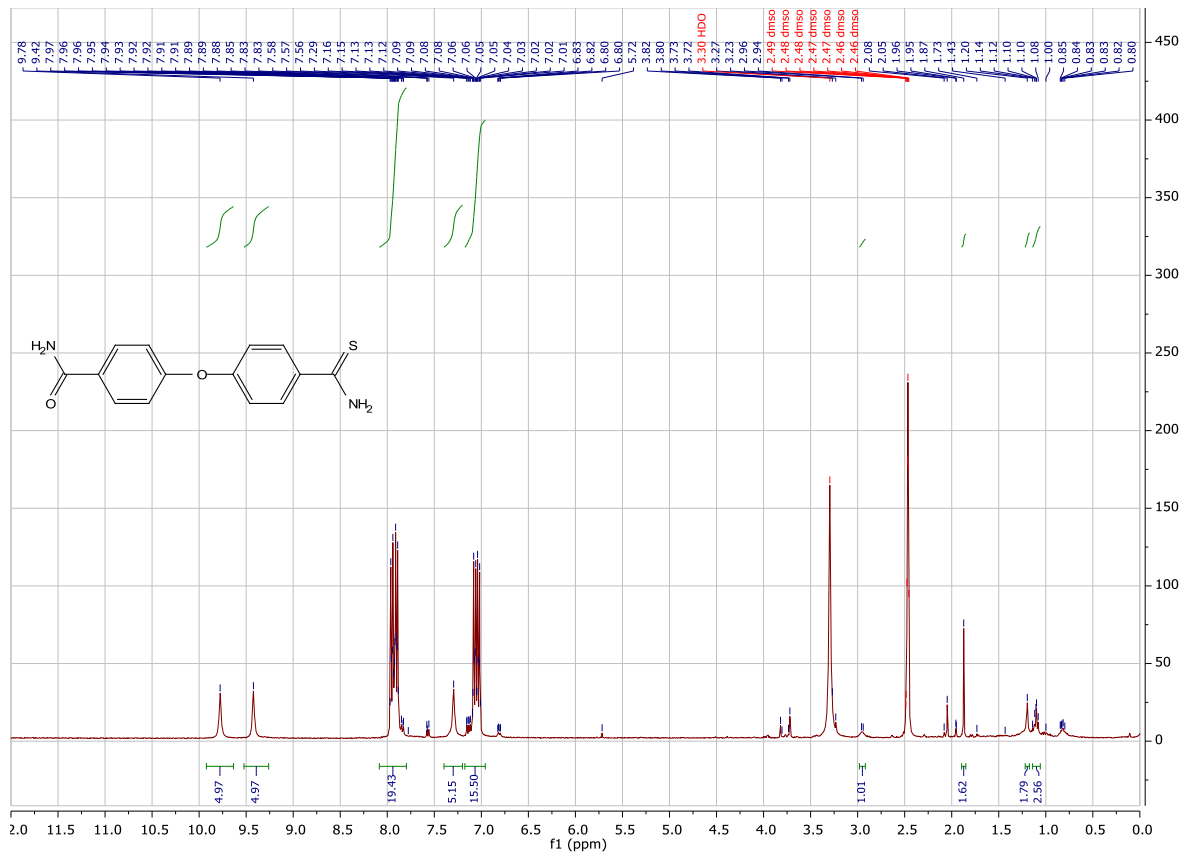
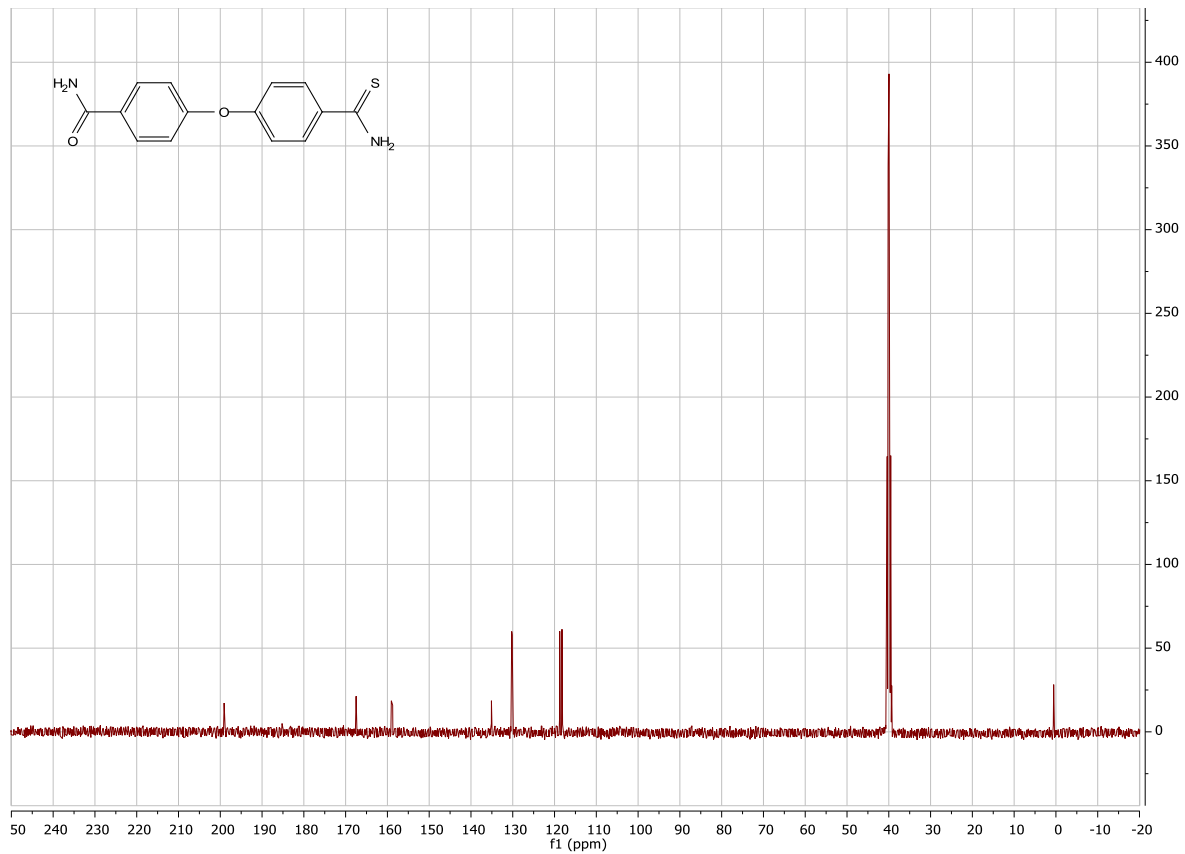
^1H NMR (600 MHz, DMSO- d_6) **Methyl 4-[4-(1H-Tetrazol-5-yl)phenoxy]benzoate (14)** ^{13}C { ^1H } NMR (150.8 MHz, DMSO- d_6) **Methyl 4-[4-(1H-Tetrazol-5-yl)phenoxy]benzoate (14)**

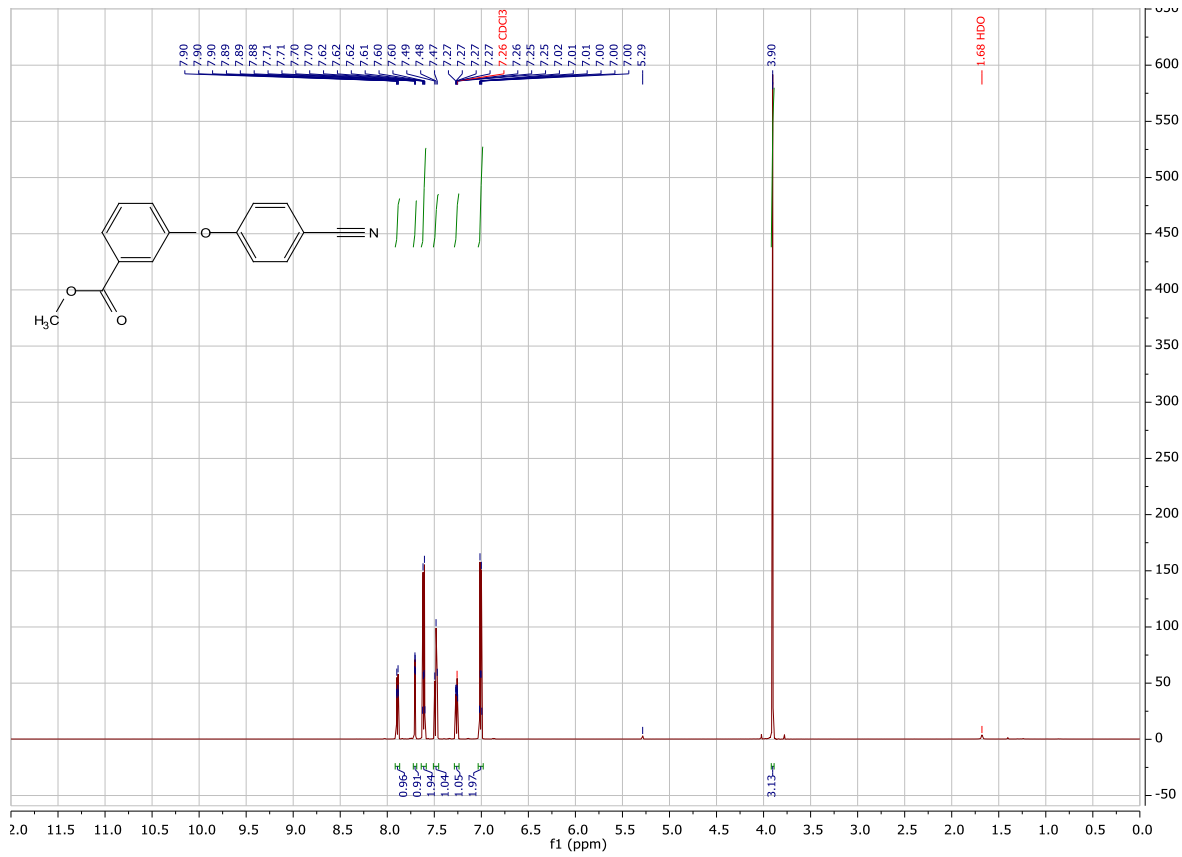
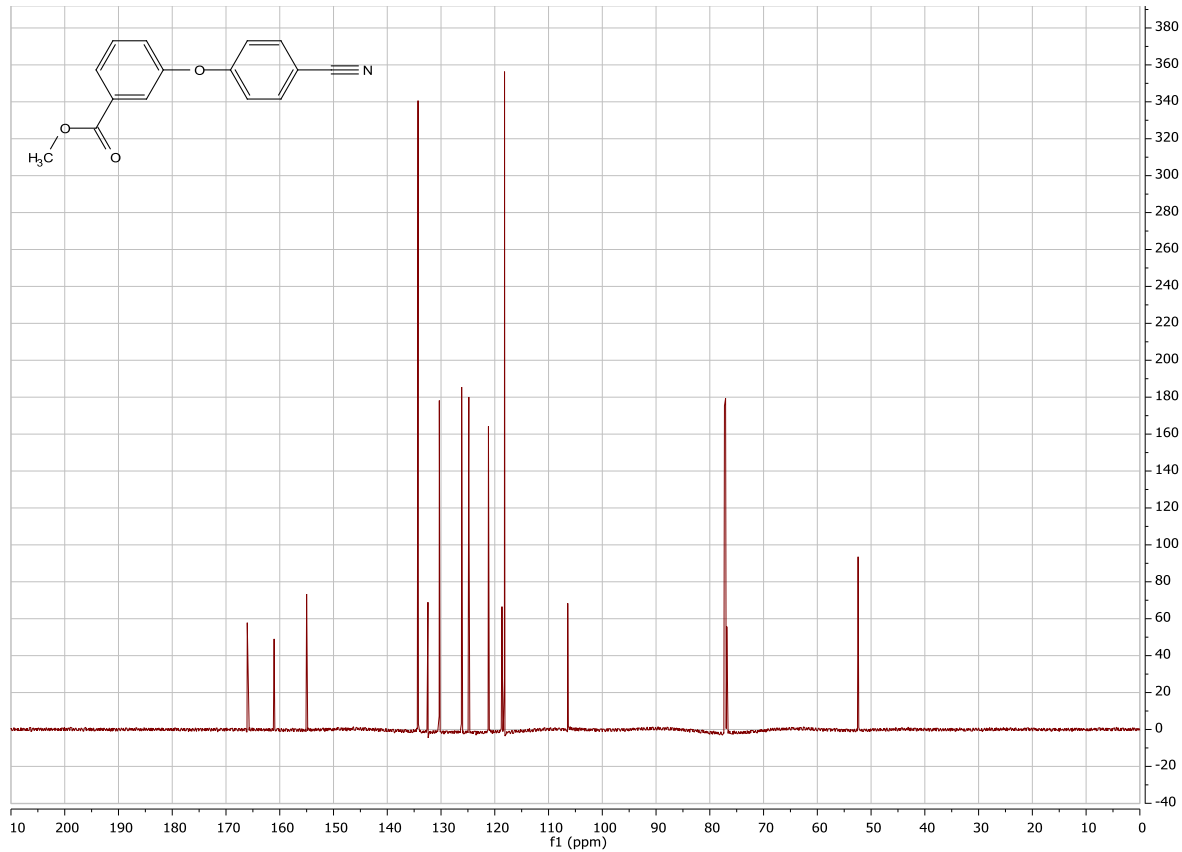
¹H NMR (600 MHz, DMSO-d₆) 4-[4-(1H-Tetrazol-5-yl)phenoxy]benzoate (15)¹³C {¹H} NMR (150.8 MHz, DMSO-d₆) 4-[4-(1H-Tetrazol-5-yl)phenoxy]benzoate (15)

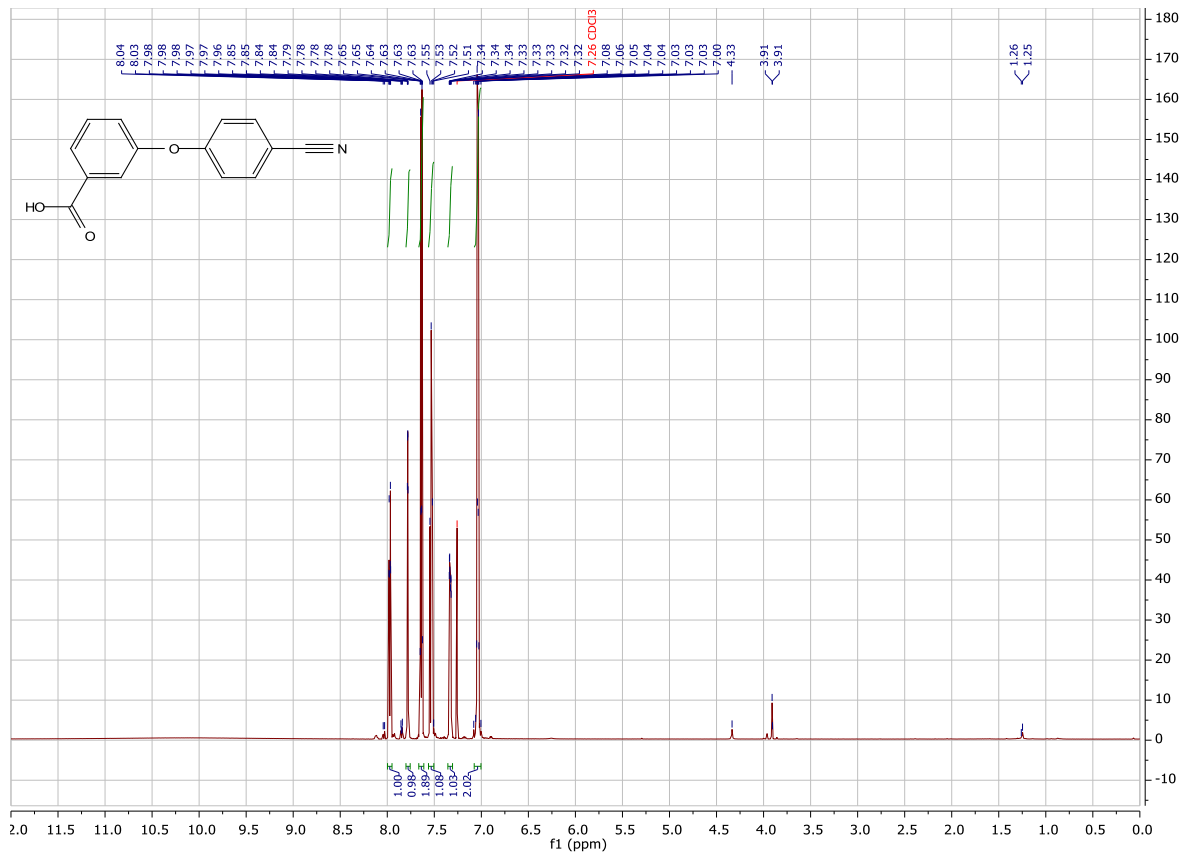
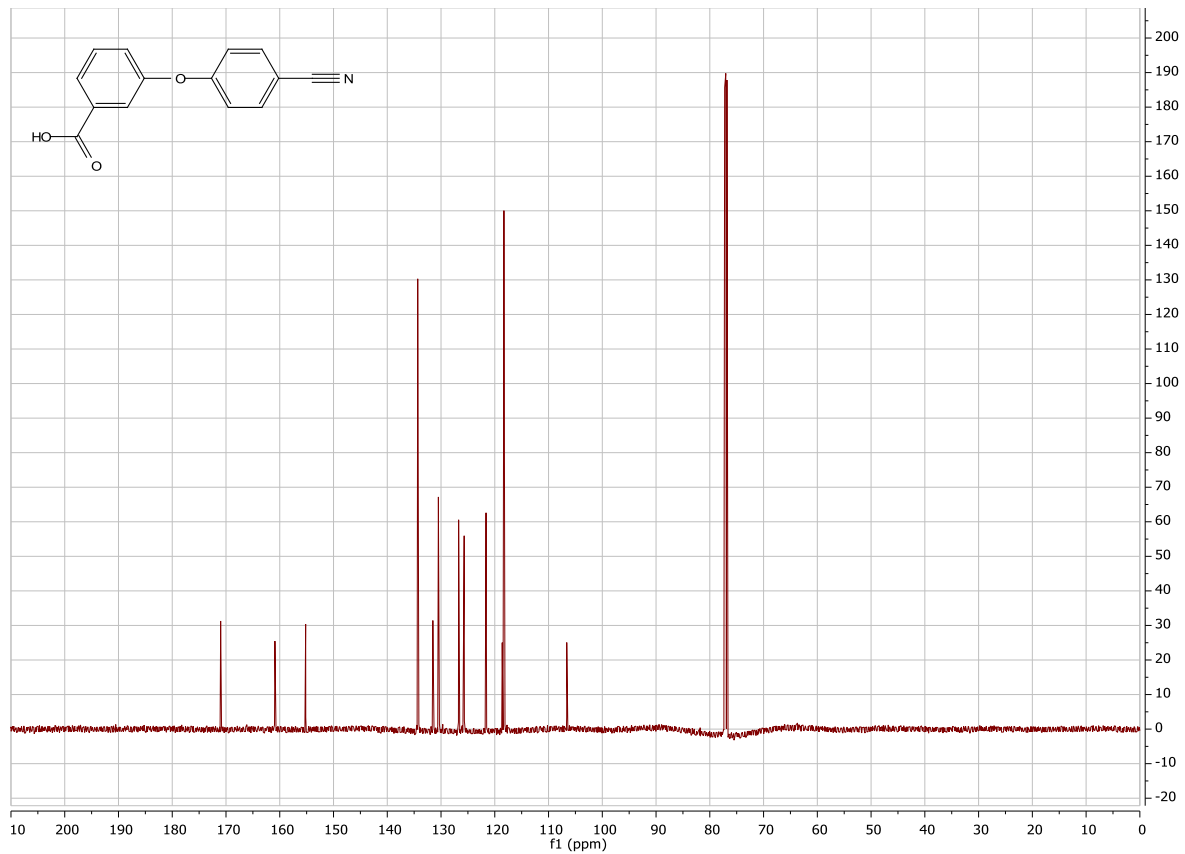
^1H NMR (600 MHz, CDCl_3) 4,4'-Oxybenzodinitrile (16) ^{13}C $\{^1\text{H}\}$ NMR (150.8 MHz, CDCl_3) 4,4'-Oxybenzodinitrile (16)

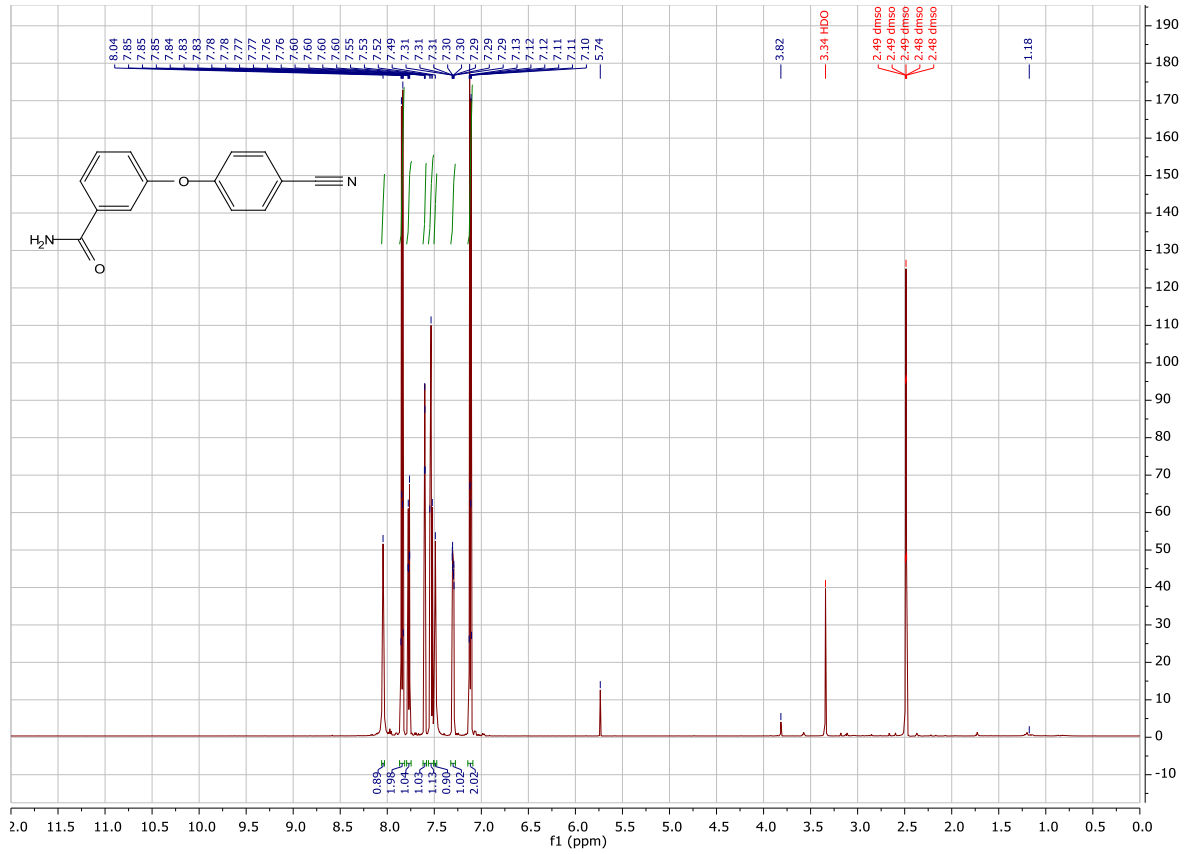
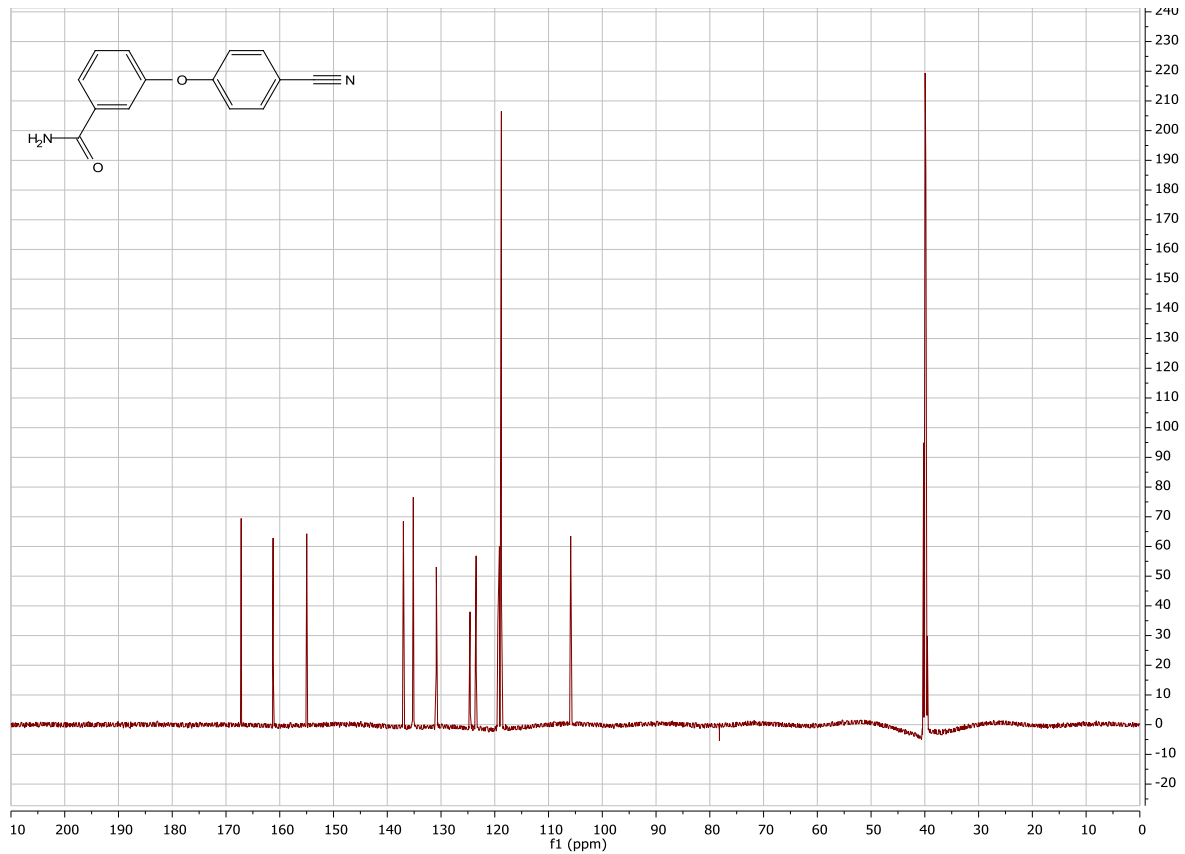
^1H NMR (400 MHz, DMSO- d_6) **4,4'-Oxybenzamide (1)** ^{13}C { ^1H } NMR (100.6 MHz, DMSO- d_6) **4,4'-Oxybenzamide (1)**

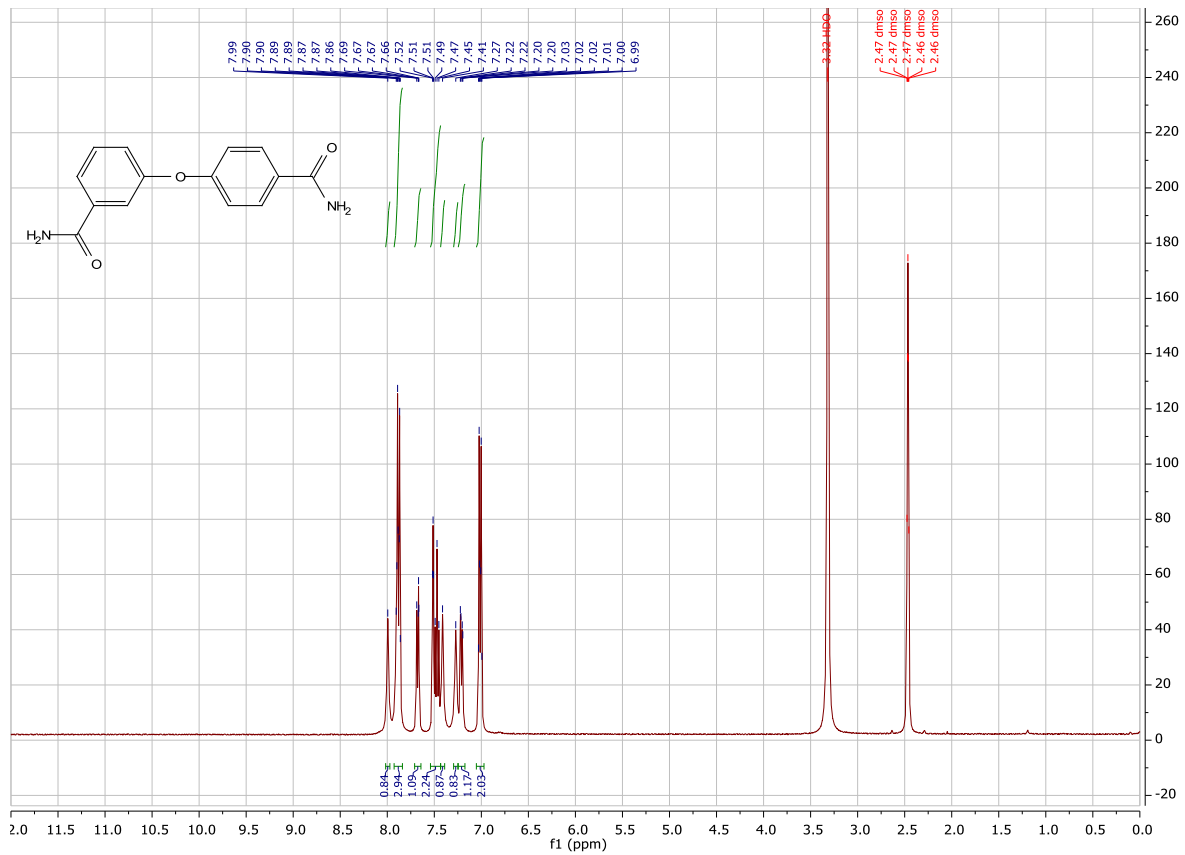
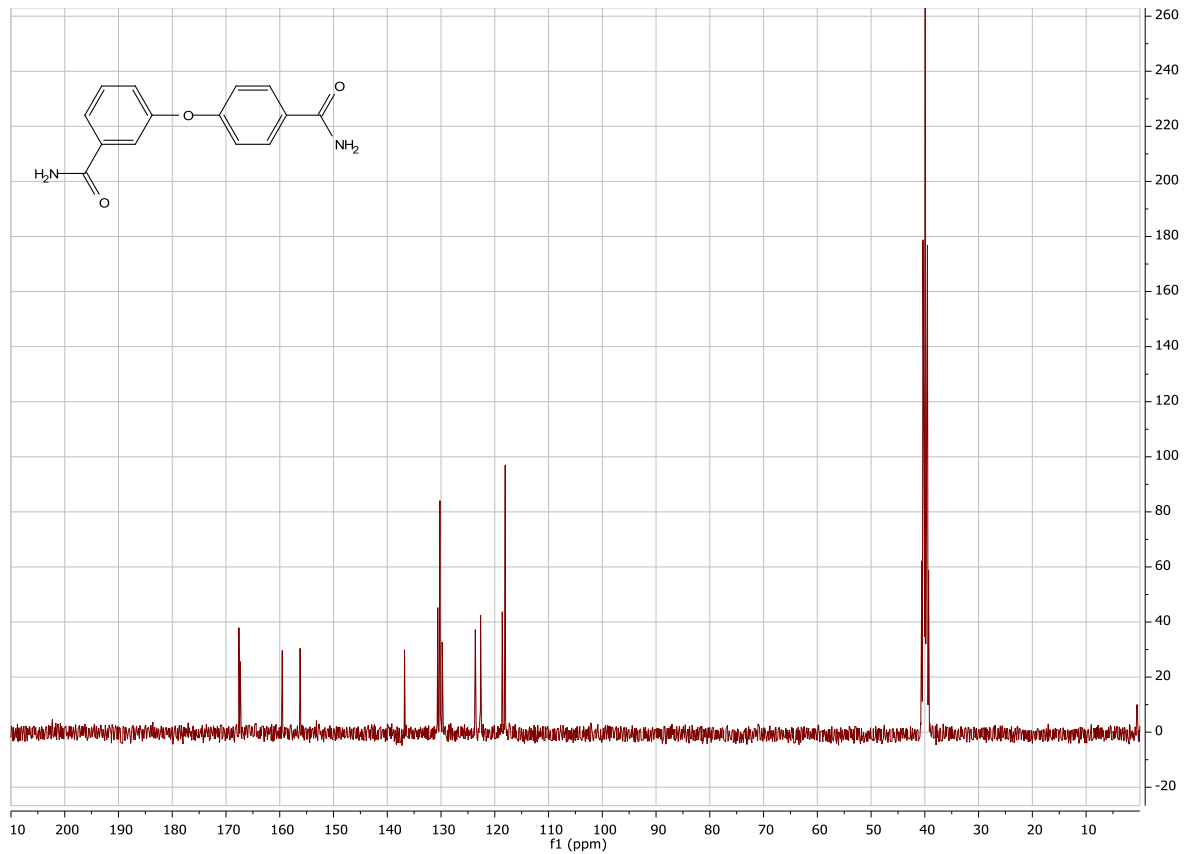
^1H NMR (600 MHz, DMSO-d_6) **4,4'-Oxybenzothioamide (17)** ^{13}C { ^1H } NMR (150.8 MHz, DMSO-d_6) **4,4'-Oxybenzothioamide (17)**

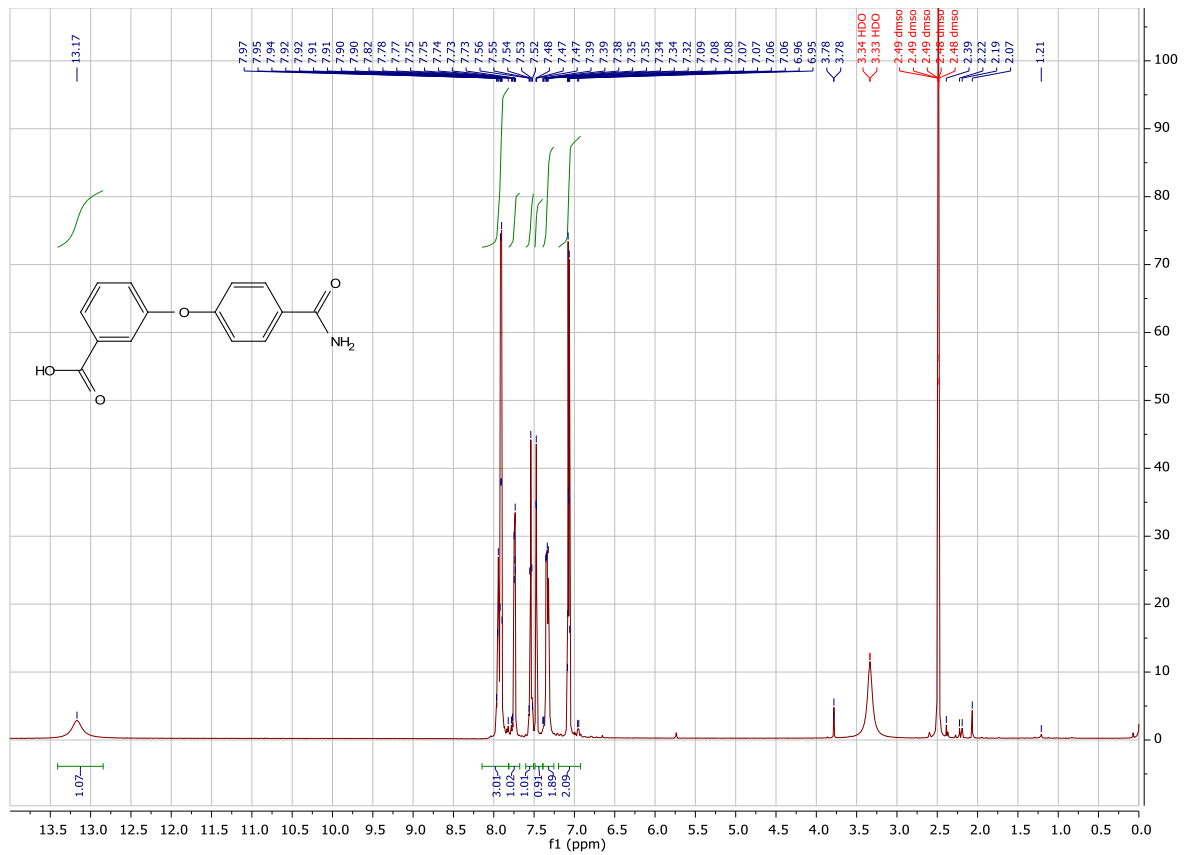
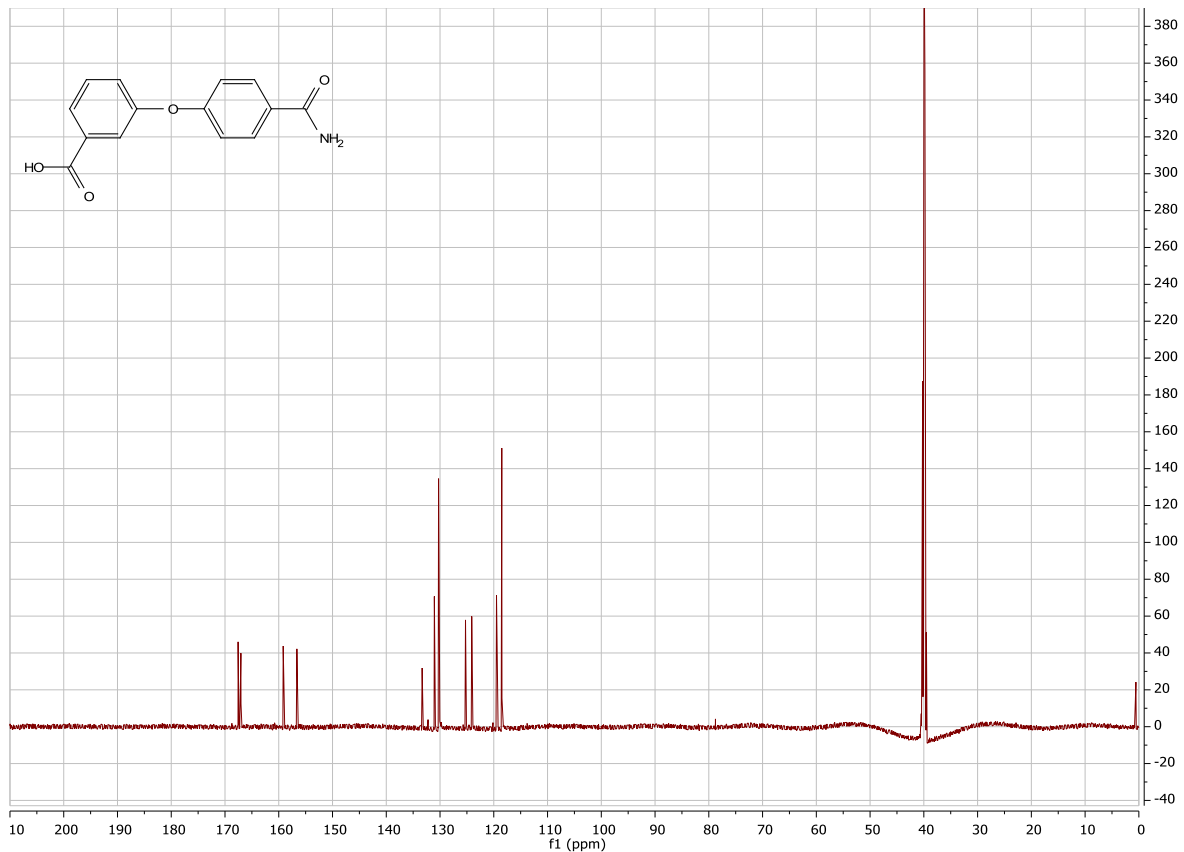
¹H NMR (400 MHz, DMSO-d₆) 4-(4-Carbamothioylphenoxy)benzamide (18)¹³C {¹H} NMR (100.6 MHz, DMSO-d₆) 4-(4-Carbamothioylphenoxy)benzamide (18)

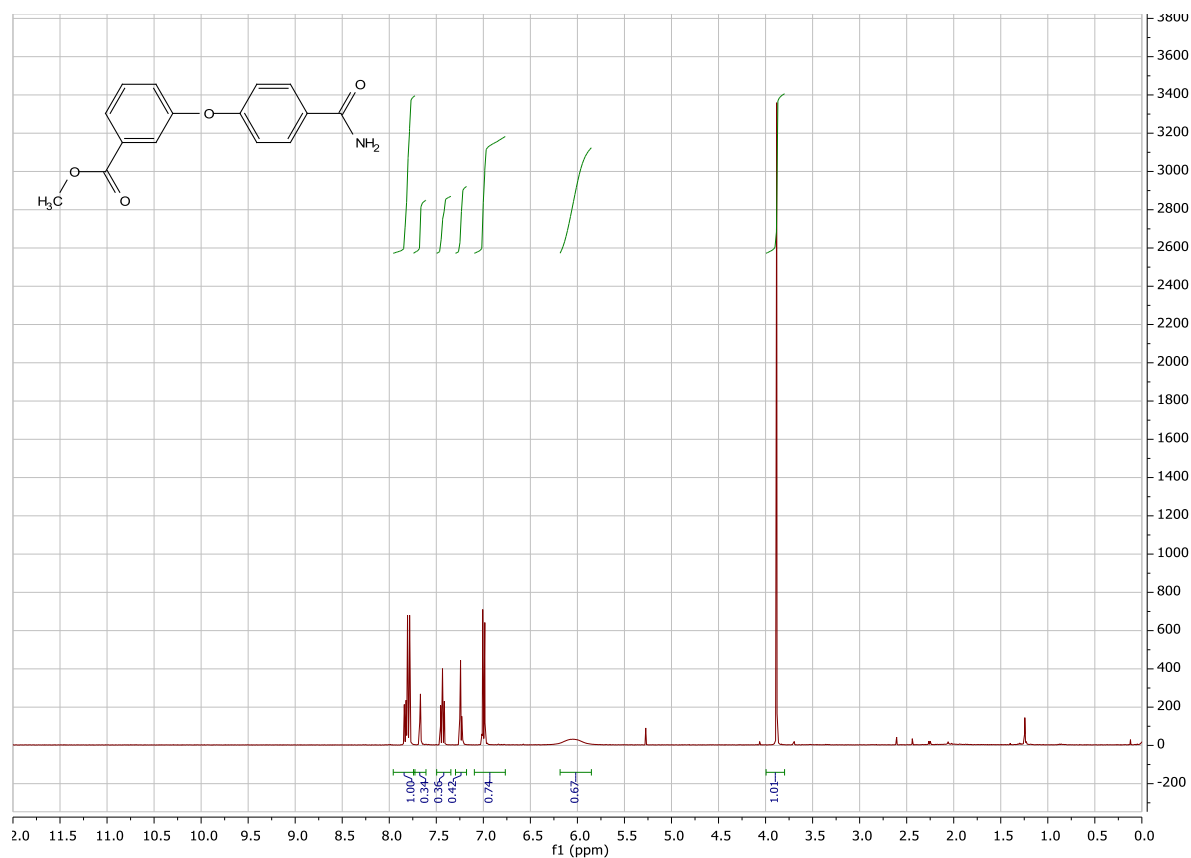
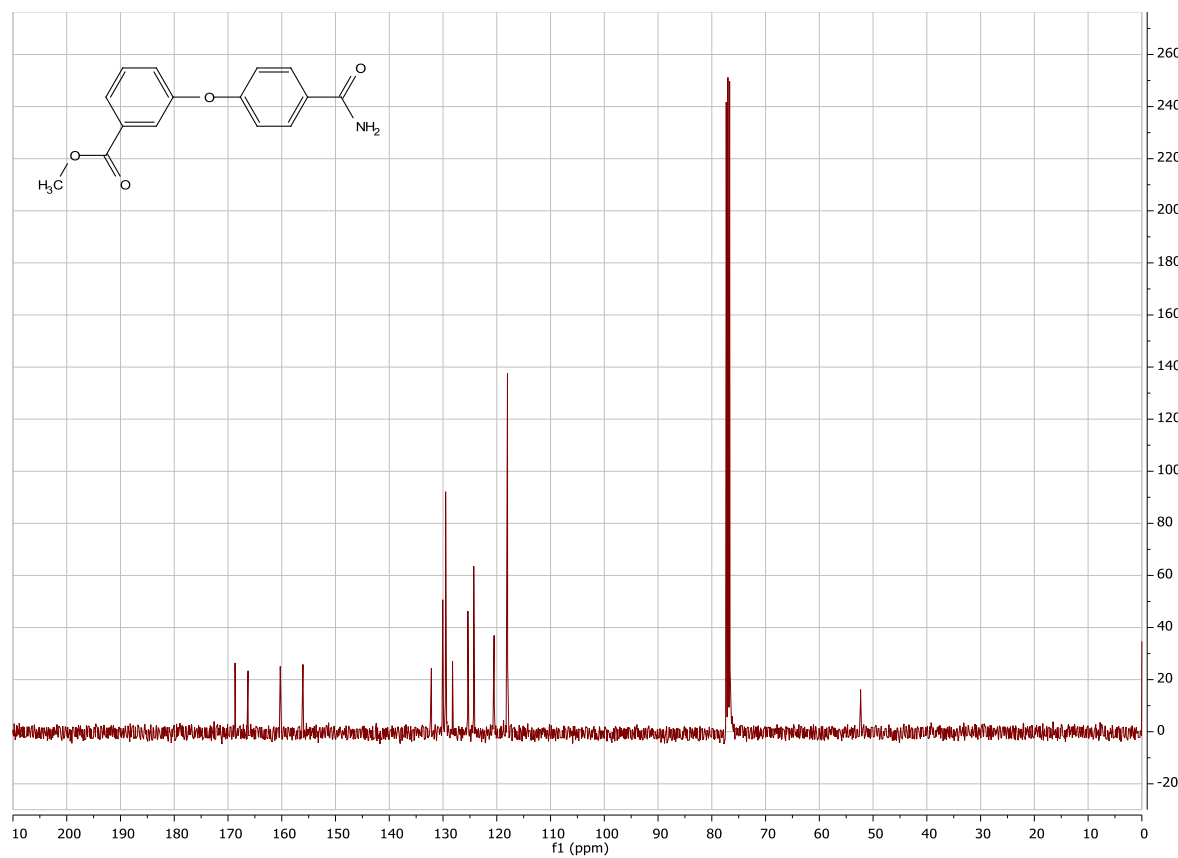
^1H NMR (600 MHz, CDCl_3) **Methyl 3-(4-cyanophenoxy)benzoate (G)** ^{13}C { ^1H } NMR (150.8 MHz, CDCl_3) **Methyl 3-(4-cyanophenoxy)benzoate (G)**

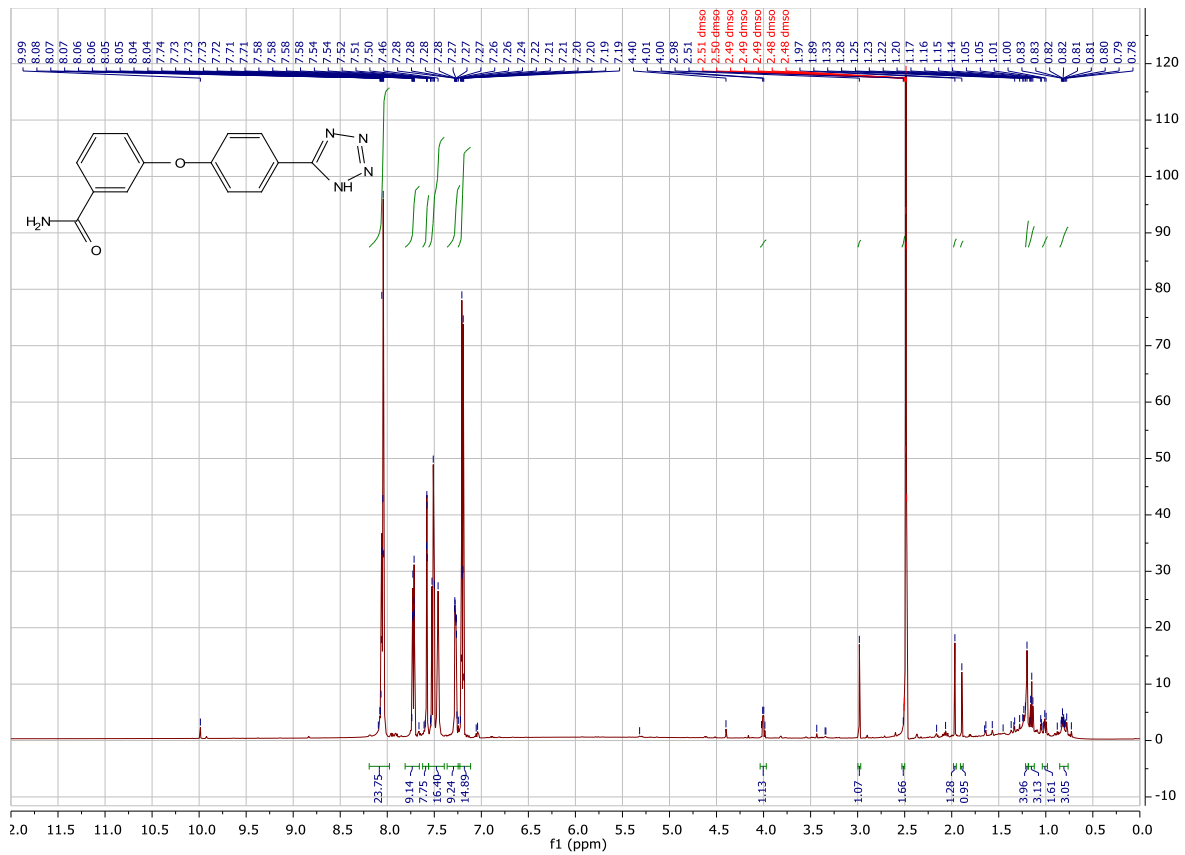
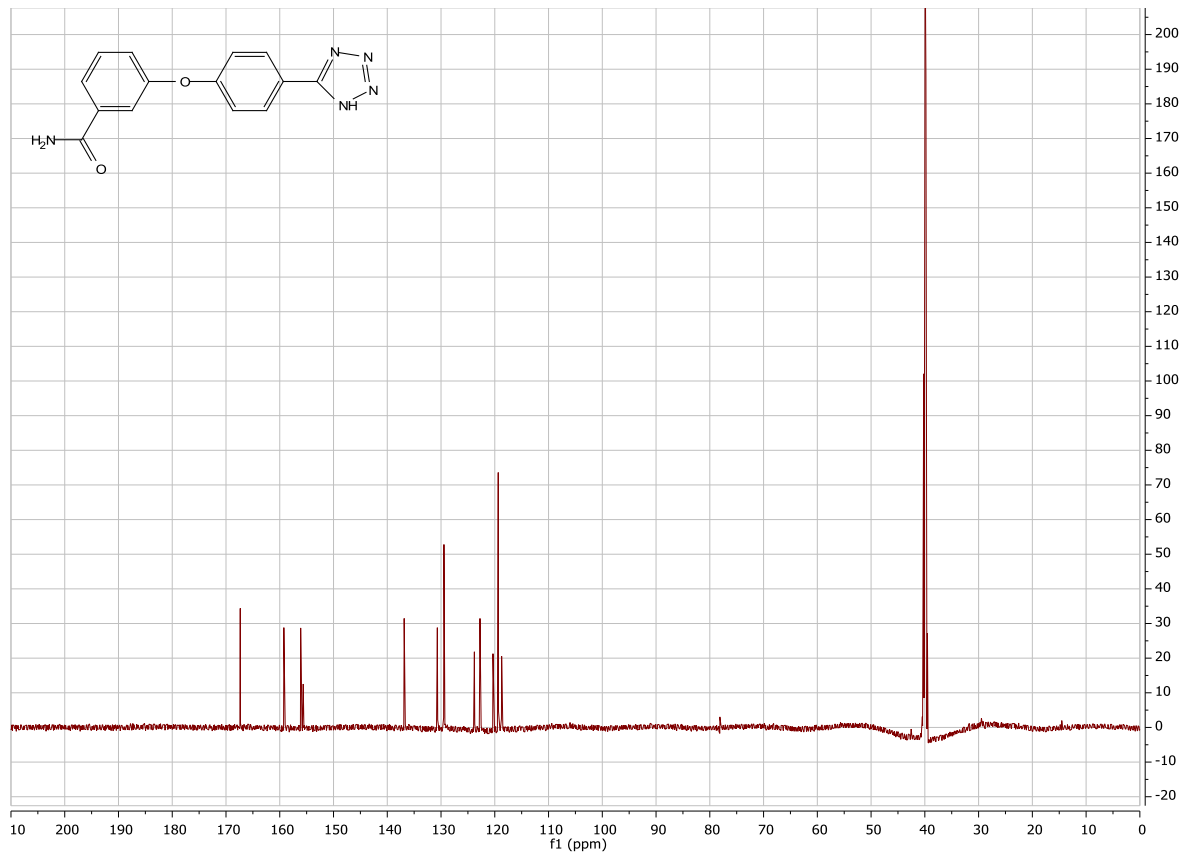
¹H NMR (600 MHz, CDCl₃) 3-(4-Cyanophenoxy)benzoic acid (H)¹³C {¹H} NMR (150.8 MHz, CDCl₃) 3-(4-Cyanophenoxy)benzoic acid (H)

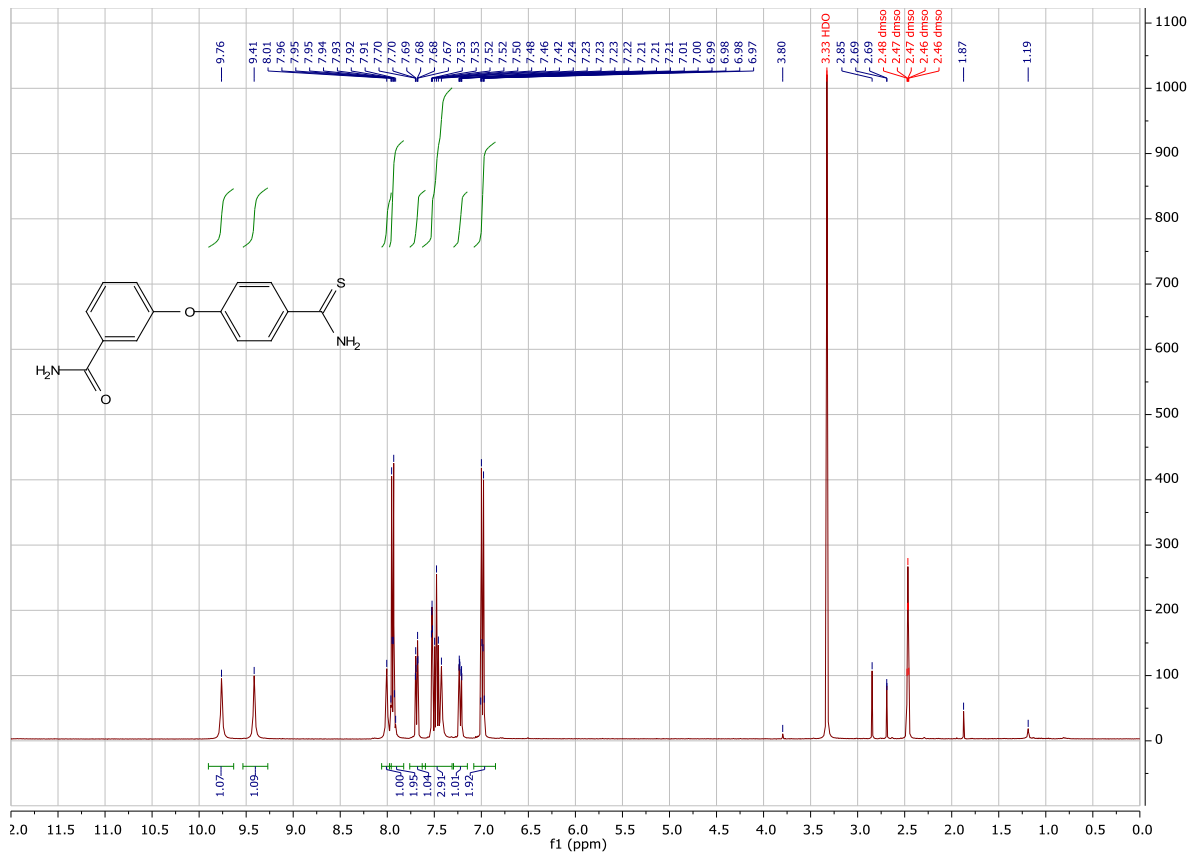
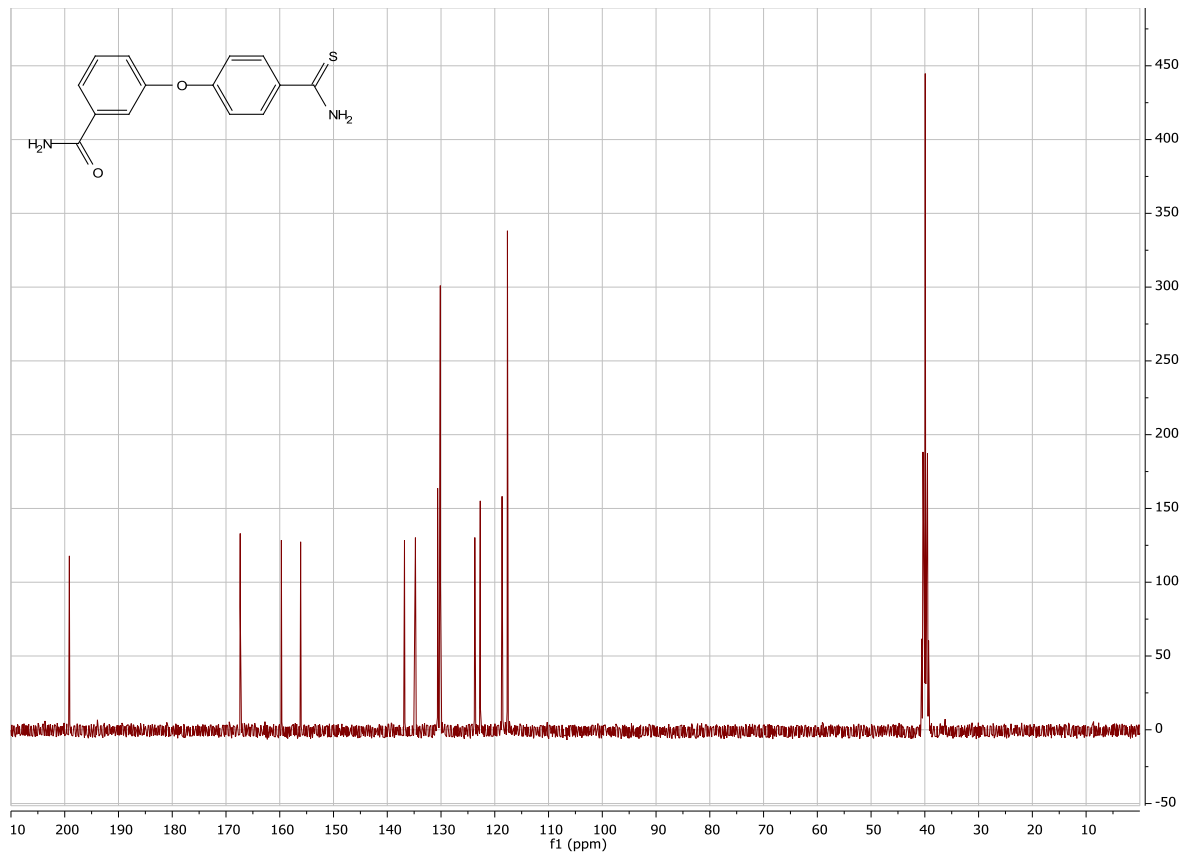
^1H NMR (600 MHz, DMSO- d_6) **3-(4-Cyanophenoxy)benzamide (19)** ^{13}C { ^1H } NMR (150.8 MHz, DMSO- d_6) **3-(4-Cyanophenoxy)benzamide (19)**

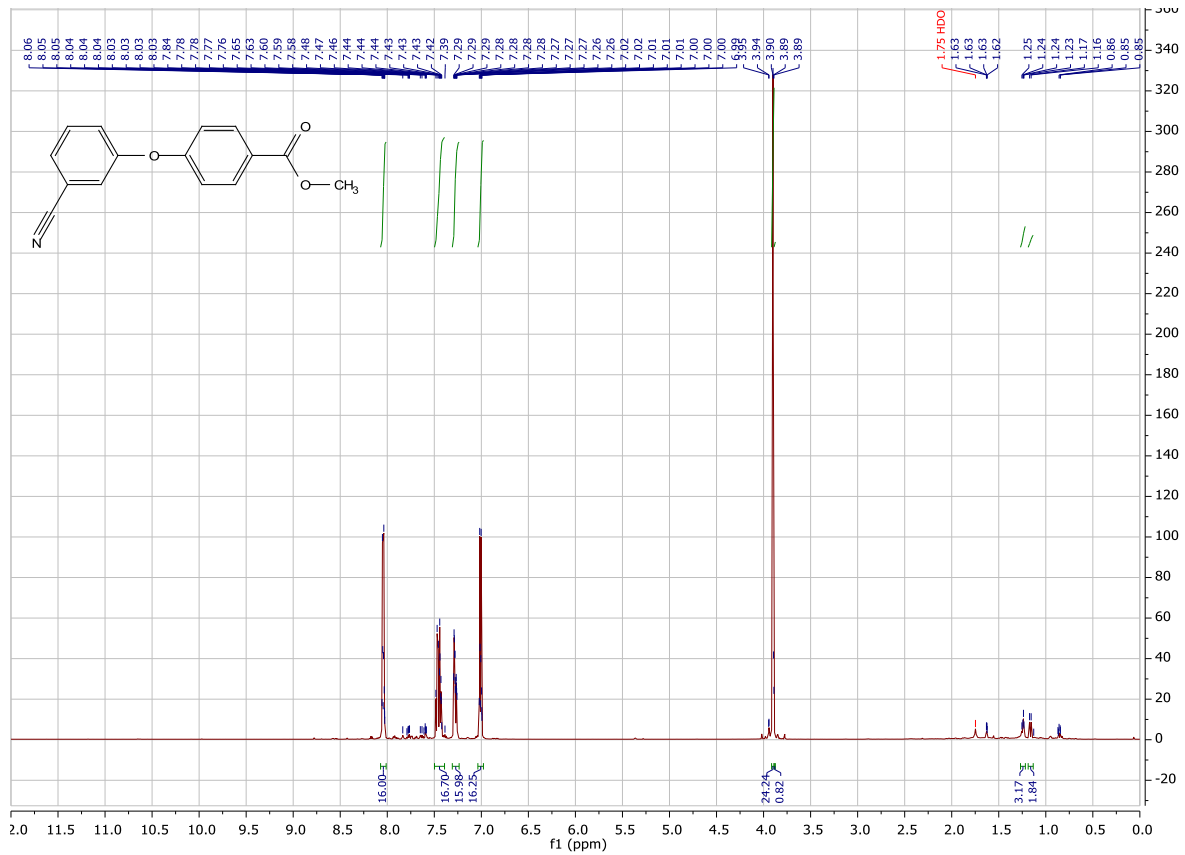
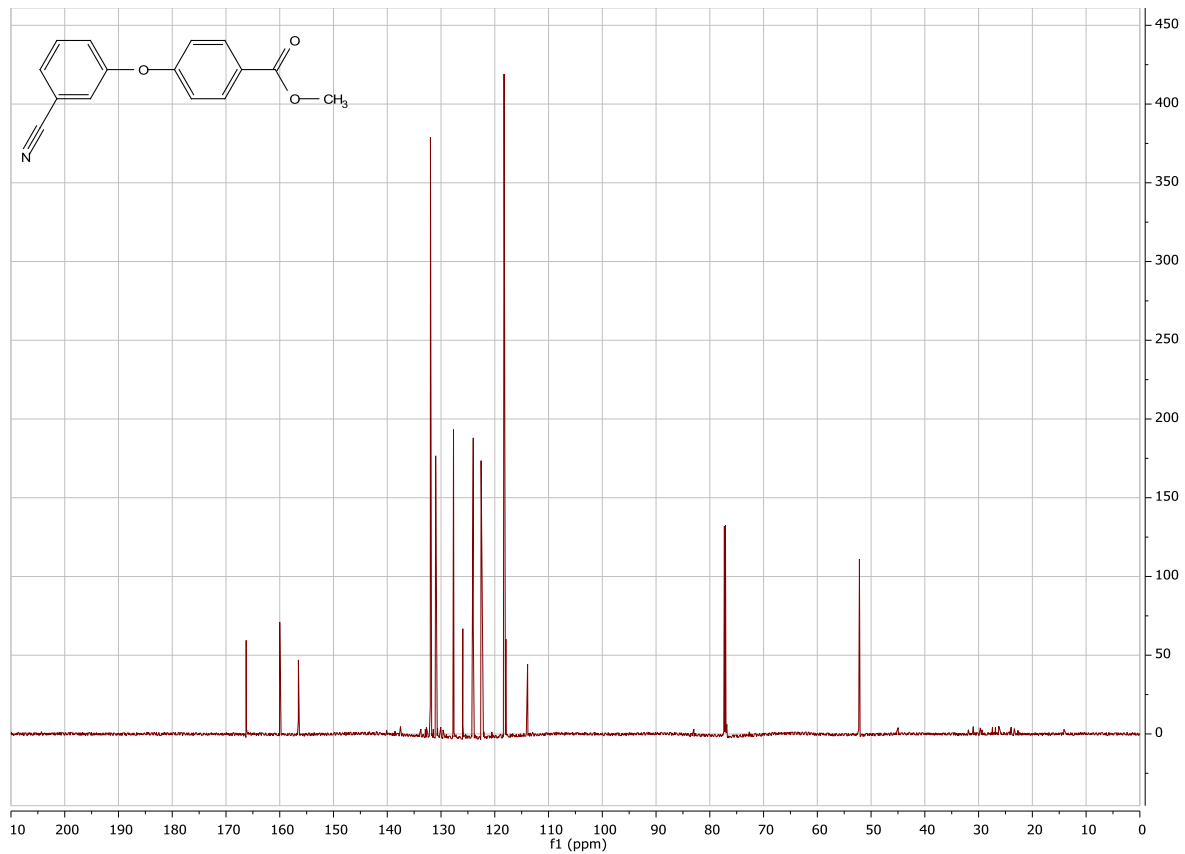
^1H NMR (400 MHz, DMSO- d_6) **3-(4-Carbamoylphenoxy)benzamide (20)** ^{13}C { ^1H } NMR (100.6 MHz, DMSO- d_6) **3-(4-Carbamoylphenoxy)benzamide (20)**

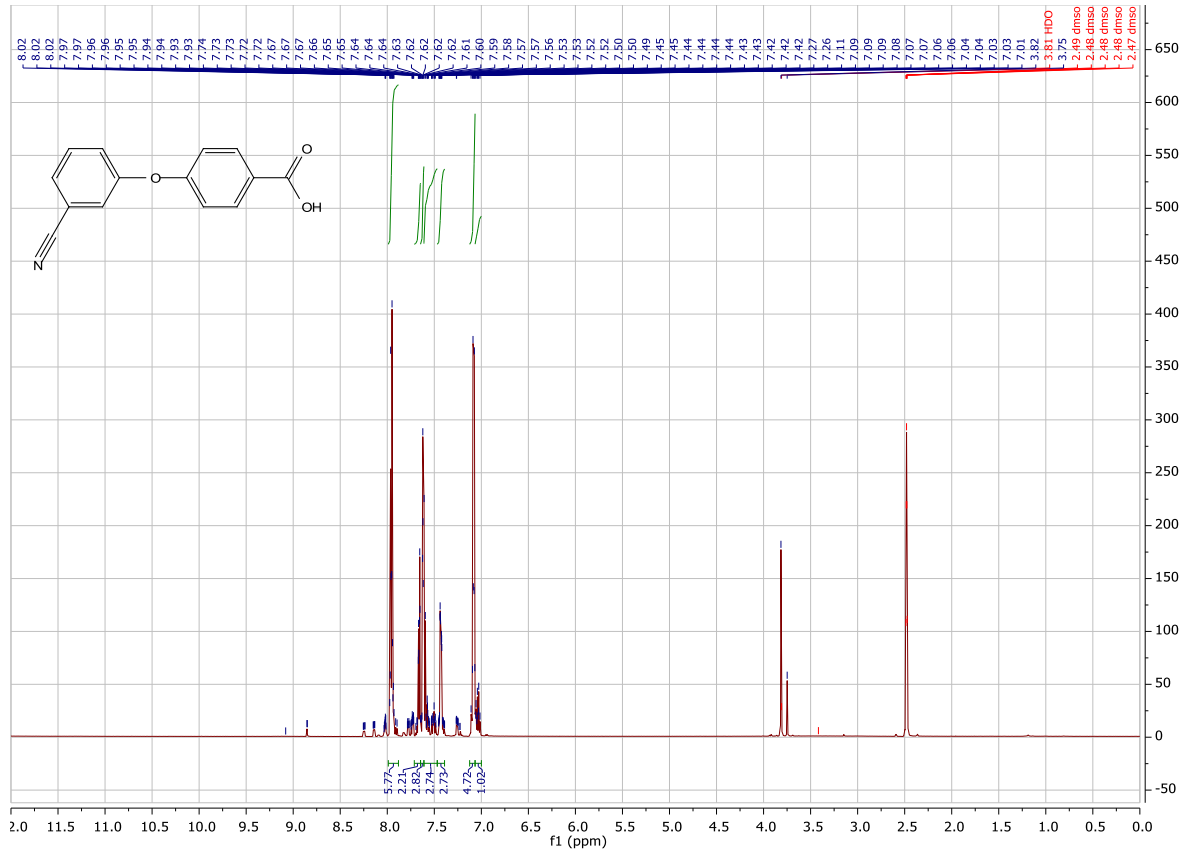
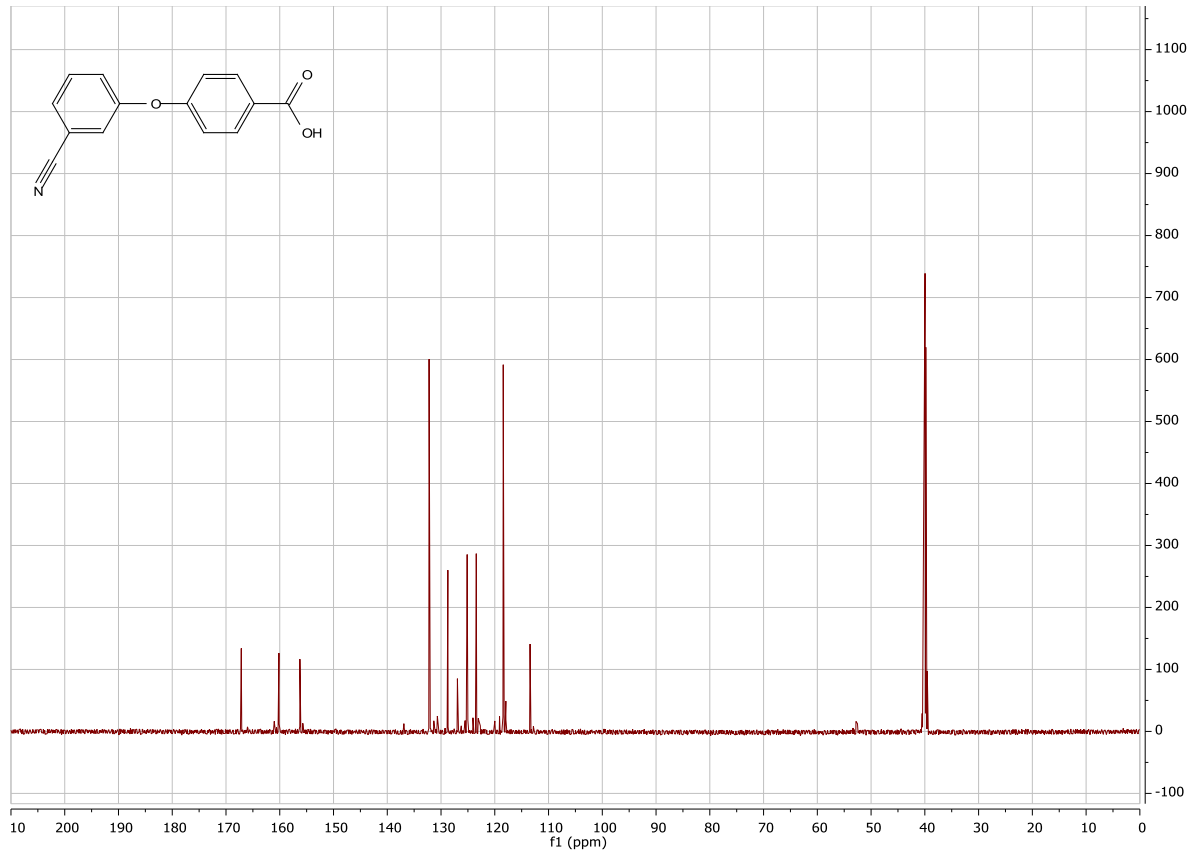
¹H NMR (600 MHz, DMSO-d₆) **3-(4-Carbamoylphenoxy)benzoic acid (21)**¹³C {¹H} NMR (150.8 MHz, DMSO-d₆) **3-(4-Carbamoylphenoxy)benzoic acid (21)**

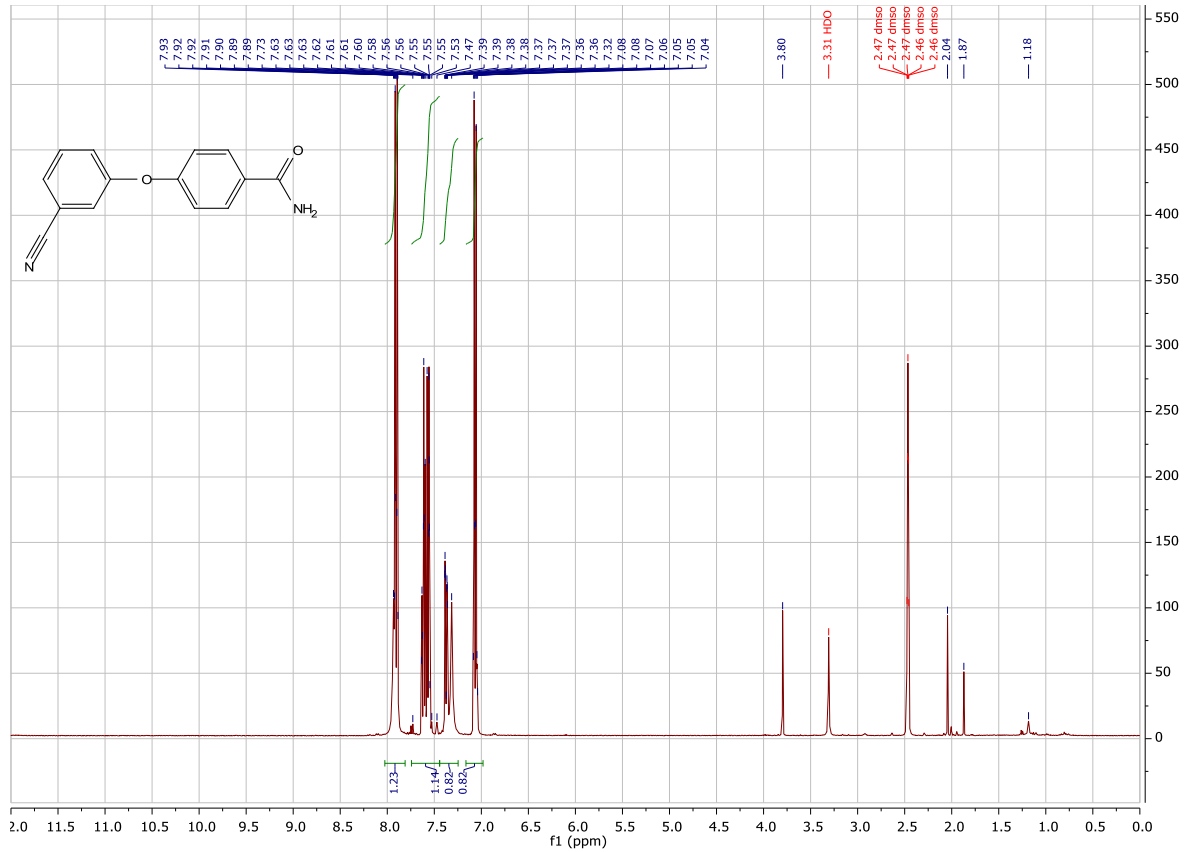
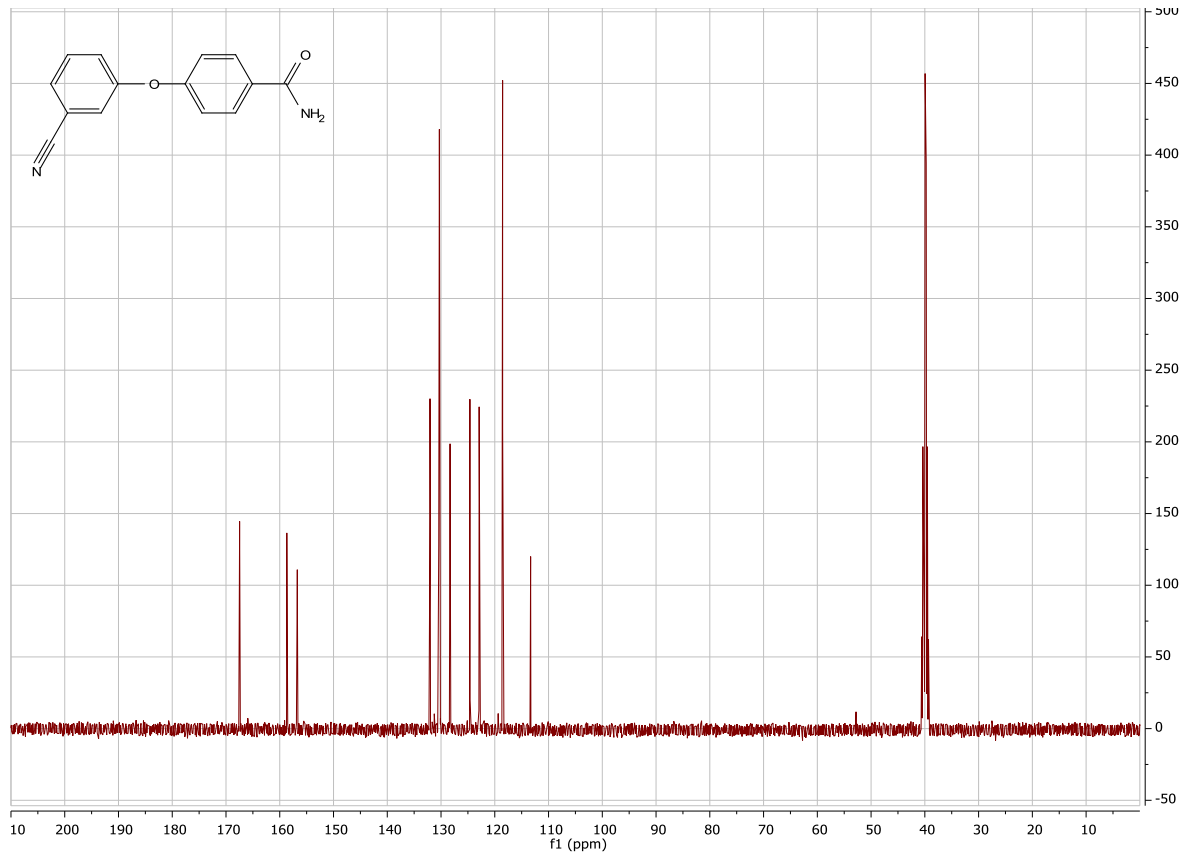
^1H NMR (400 MHz, CDCl_3) **Methyl 3-(4-carbamoylphenoxy)benzoate (22)** ^{13}C { ^1H } NMR (100.6 MHz, CDCl_3) **Methyl 3-(4-carbamoylphenoxy)benzoate (22)**

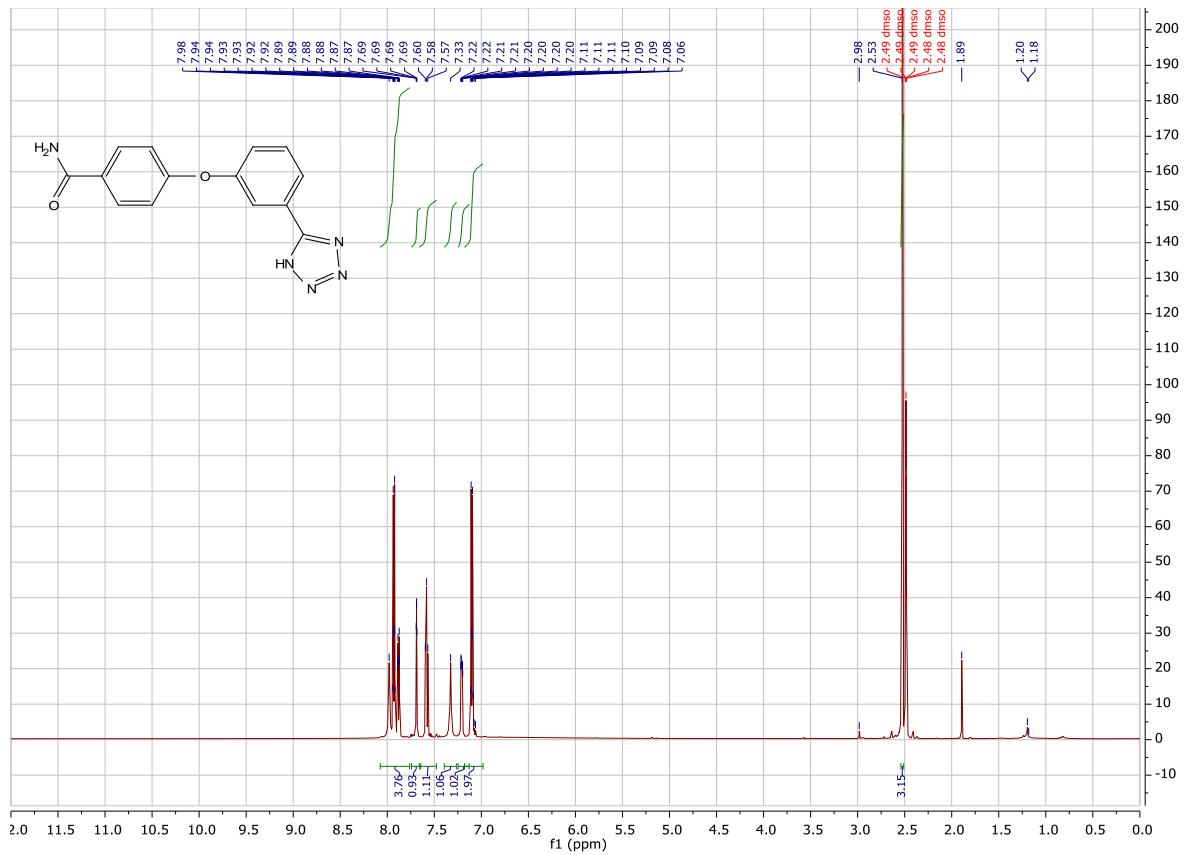
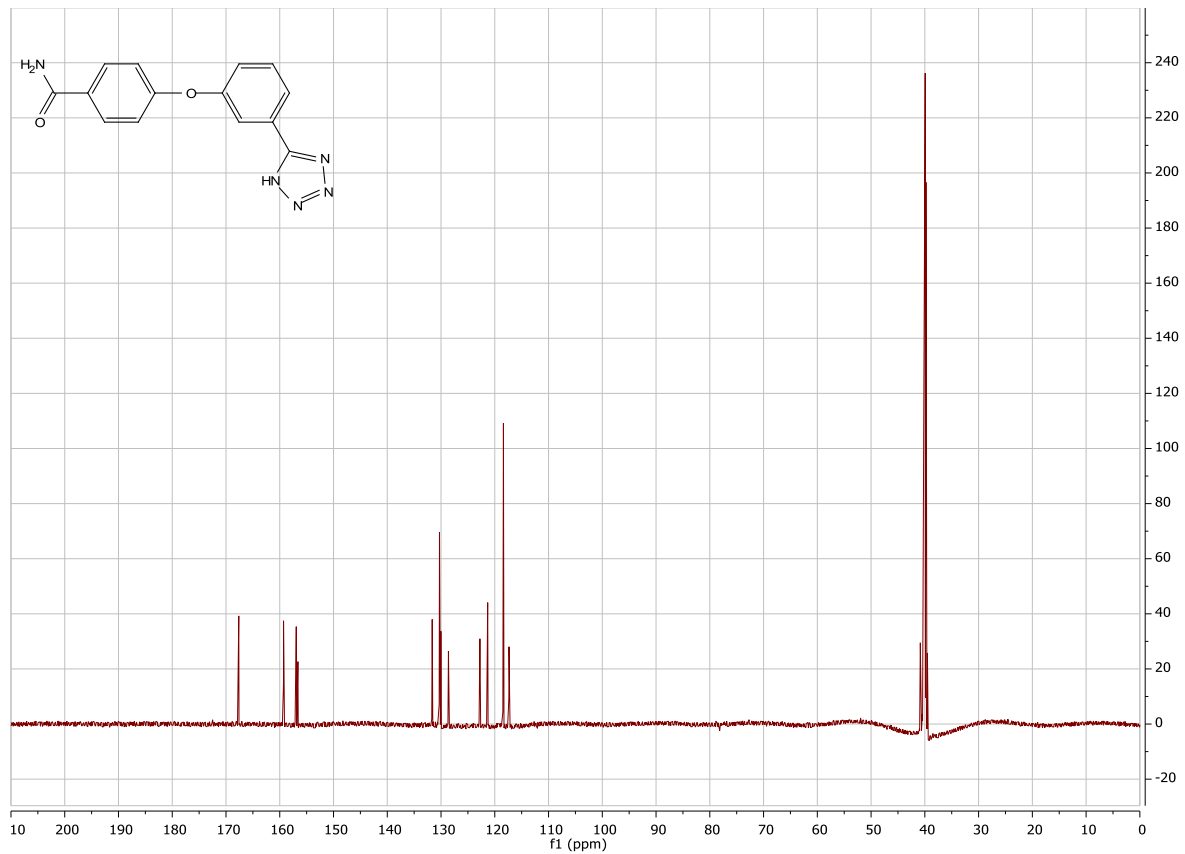
¹H NMR (600 MHz, DMSO-d₆) 3-[4-(1H-Tetrazol-5-yl)phenoxy]benzamide (23)¹³C {¹H} NMR (150.8 MHz, DMSO-d₆) 3-[4-(1H-Tetrazol-5-yl)phenoxy]benzamide (23)

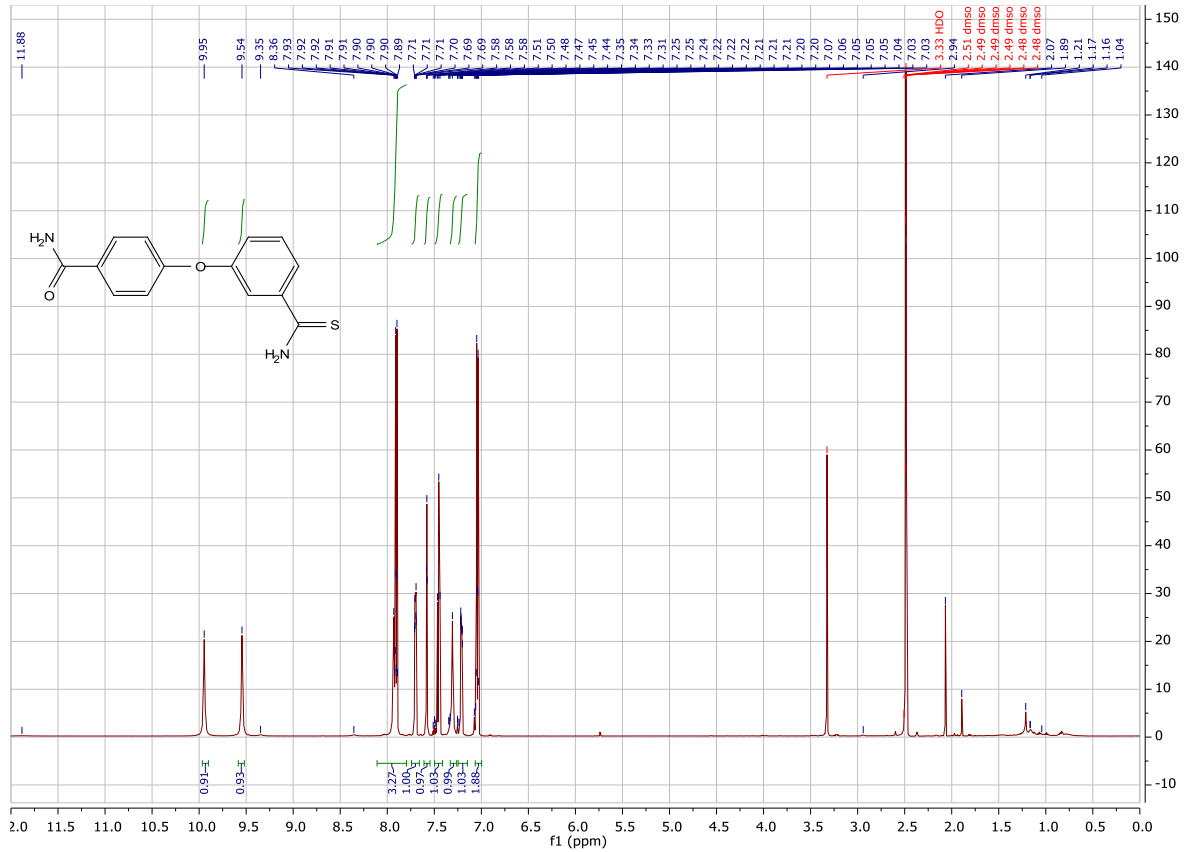
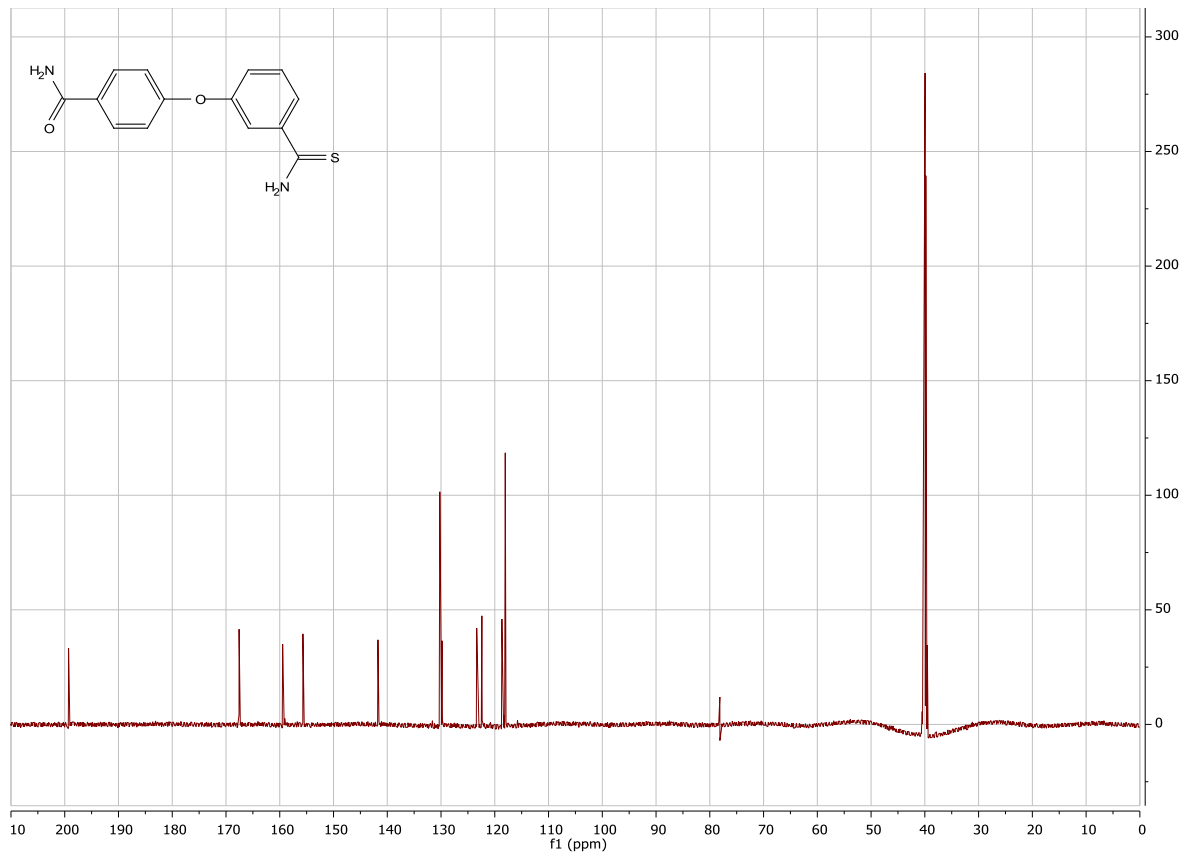
^1H NMR (400 MHz, DMSO- d_6) **3-(4-Carbamothioylphenoxy)benzamide (24)** ^{13}C { ^1H } NMR (100.6 MHz, DMSO- d_6) **3-(4-Carbamothioylphenoxy)benzamide (24)**

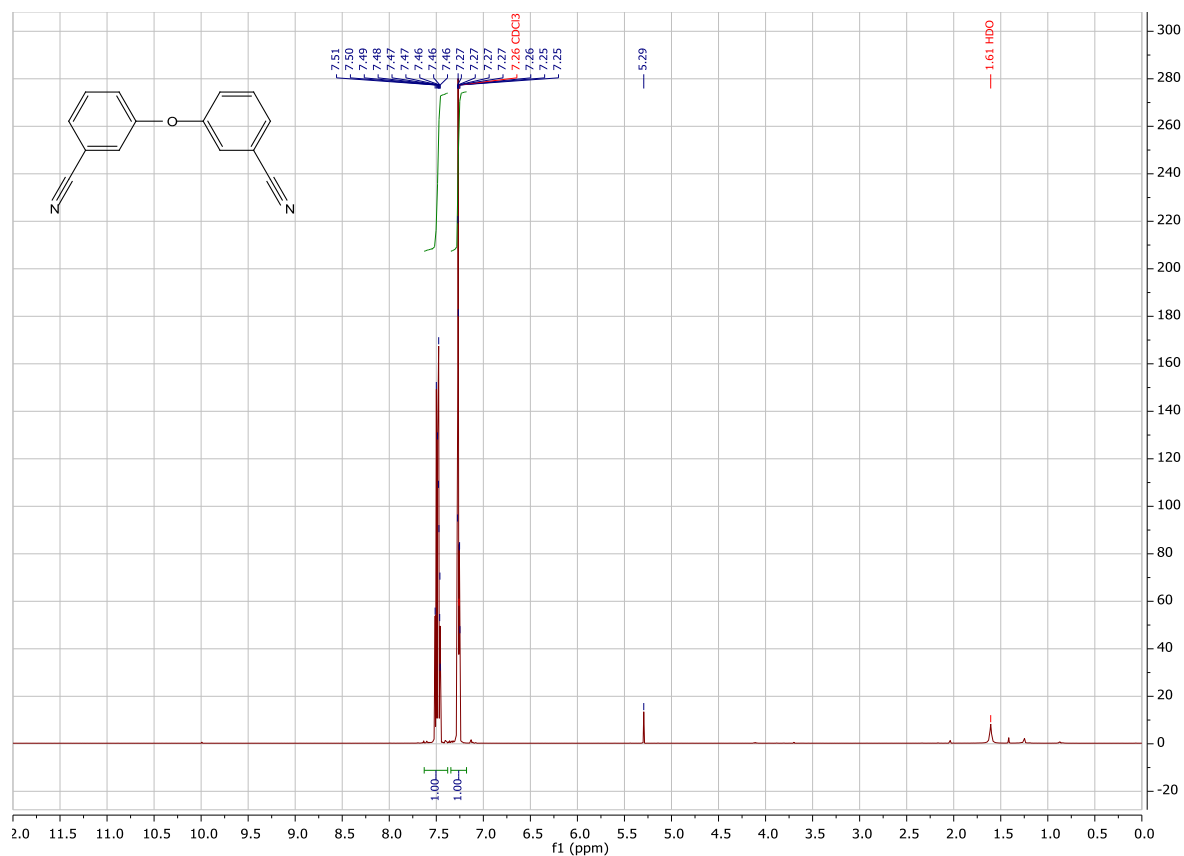
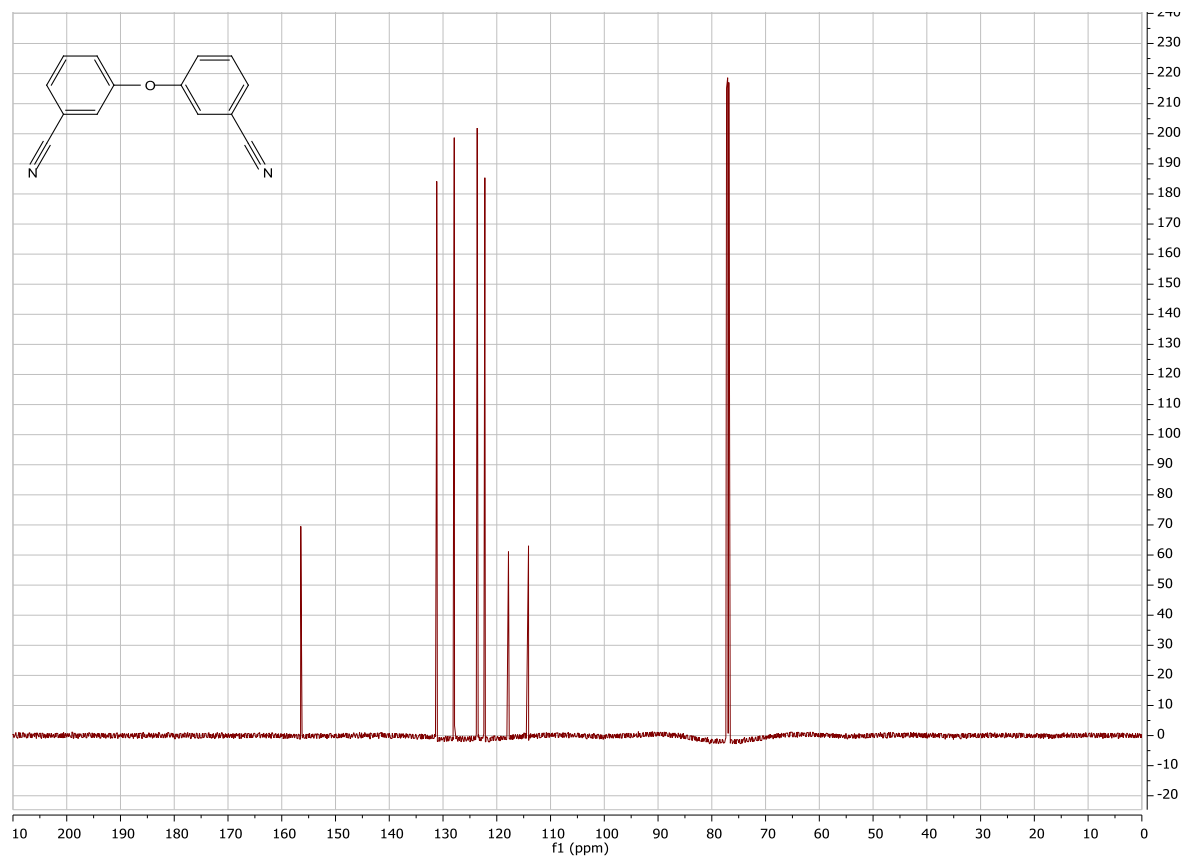
^1H NMR (600 MHz, CDCl_3) Methyl 4-(3-cyanophenoxy)benzoate (K) ^{13}C $\{^1\text{H}\}$ NMR (150.8 MHz, CDCl_3) Methyl 4-(3-cyanophenoxy)benzoate (K)

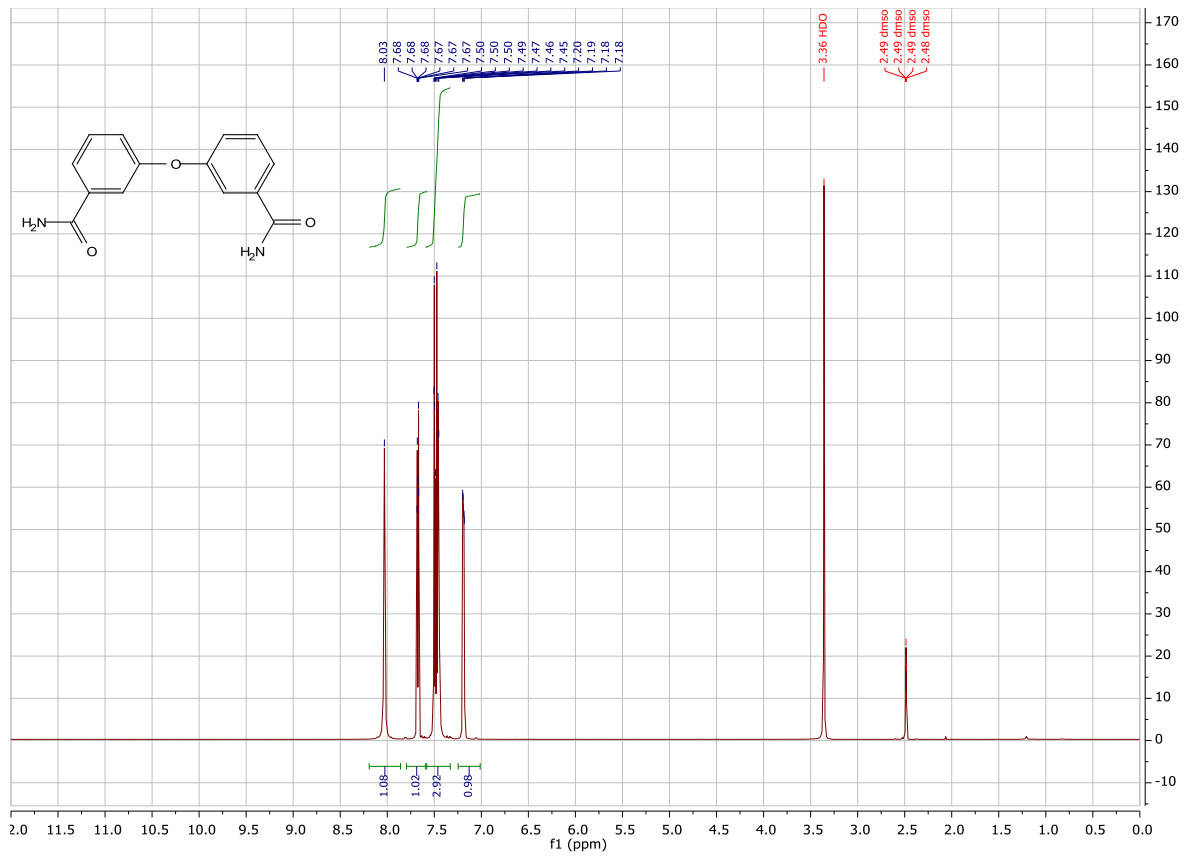
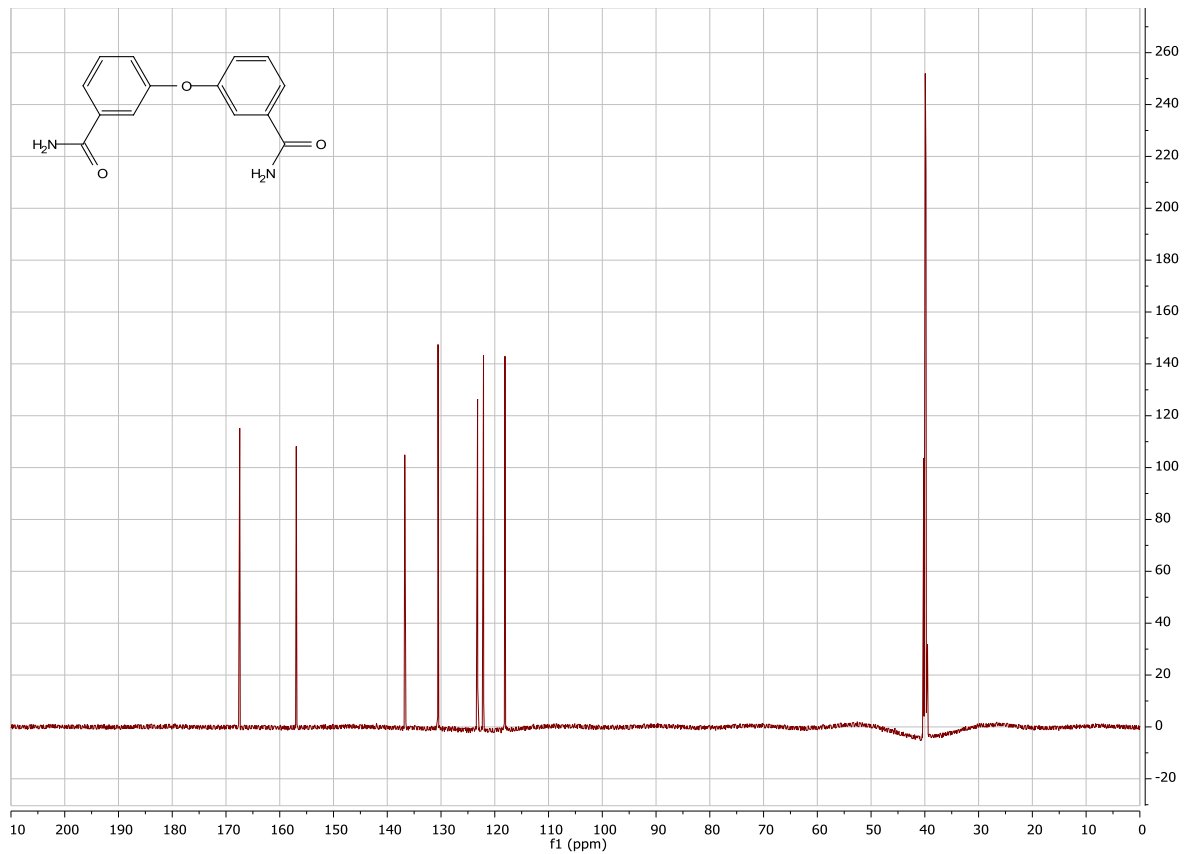
^1H NMR (600 MHz, DMSO- d_6) 4-(3-Cyanophenoxy)benzoic acid (L) ^{13}C { ^1H } NMR (150.8 MHz, DMSO- d_6) 4-(3-Cyanophenoxy)benzoic acid (L)

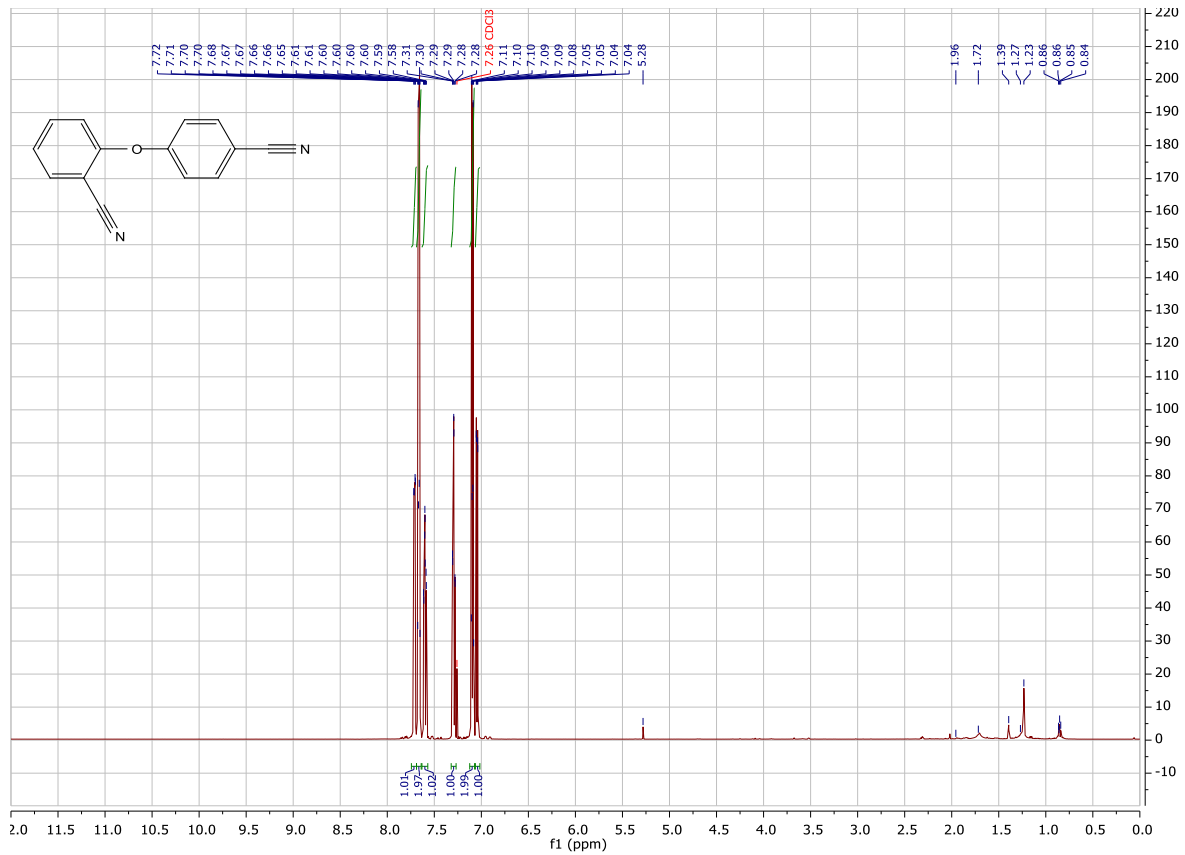
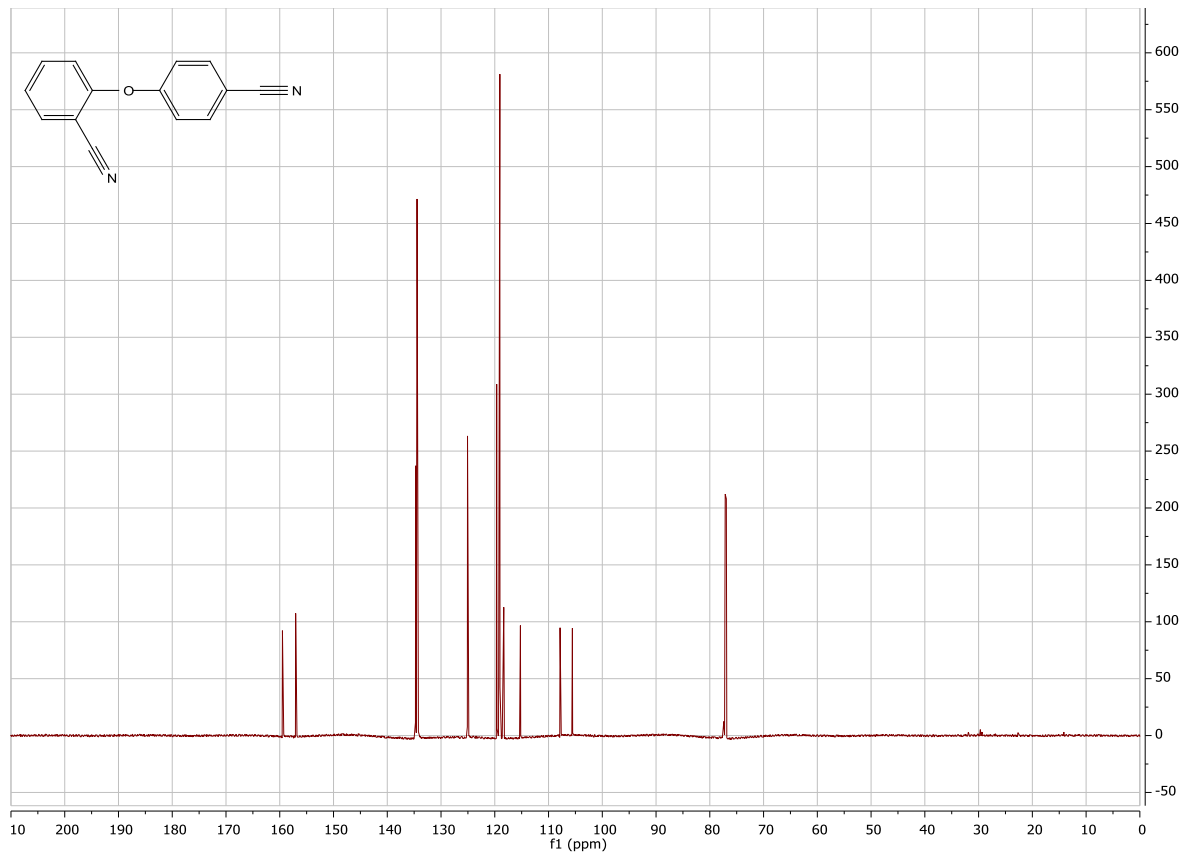
^1H NMR (400 MHz, DMSO- d_6) 4-(3-Cyanophenoxy)benzamide (25) ^{13}C { ^1H } NMR (100.6 MHz, DMSO- d_6) 4-(3-Cyanophenoxy)benzamide (25)

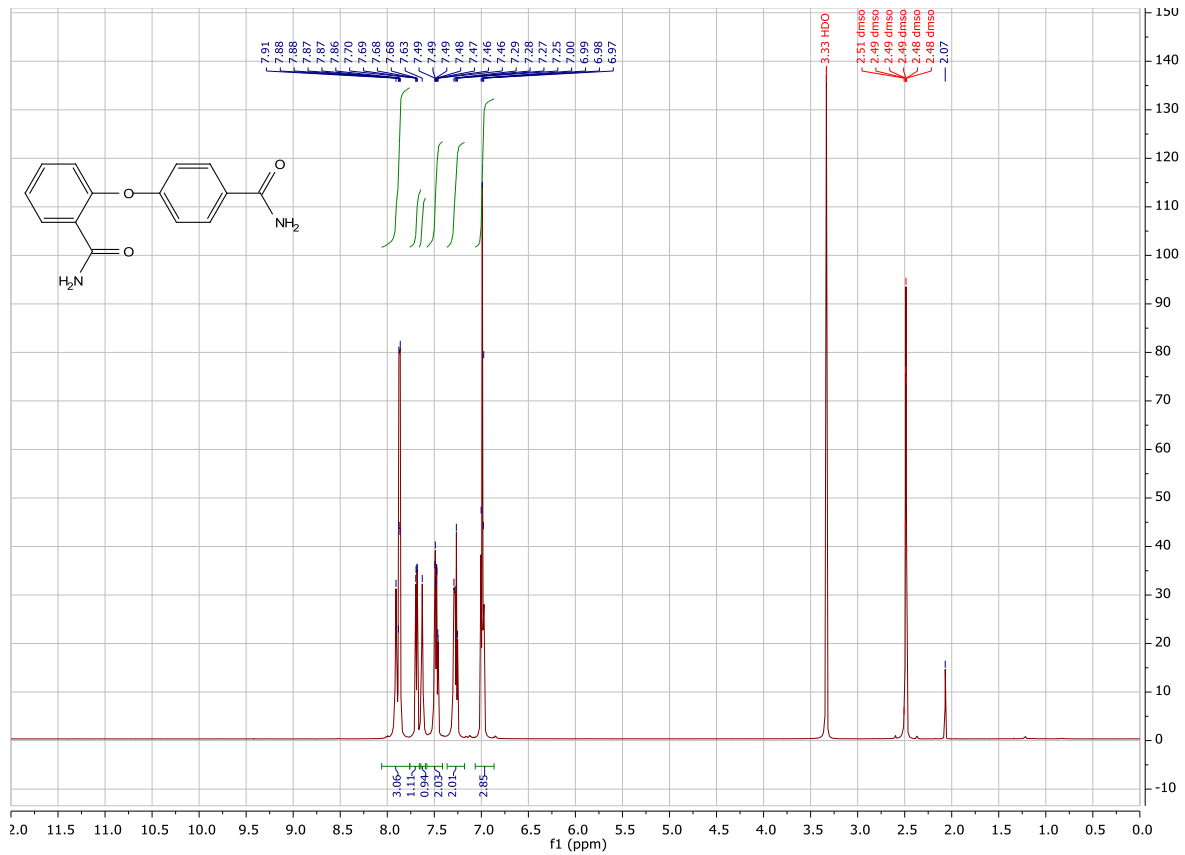
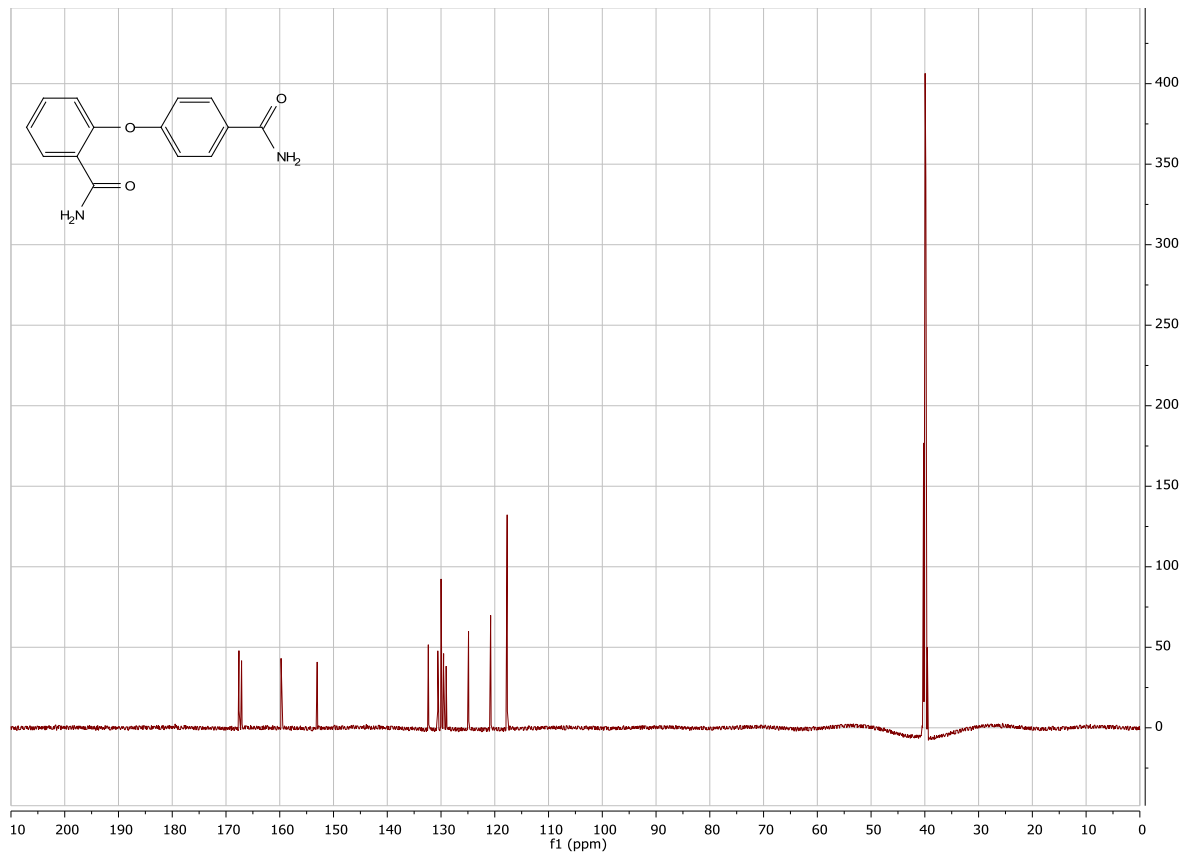
^1H NMR (600 MHz, DMSO- d_6) 4-[3-(1H-Tetrazol-5-yl)phenoxy]benzamide (26) ^{13}C { ^1H } NMR (150.8 MHz, DMSO- d_6) 4-[3-(1H-Tetrazol-5-yl)phenoxy]benzamide (26)

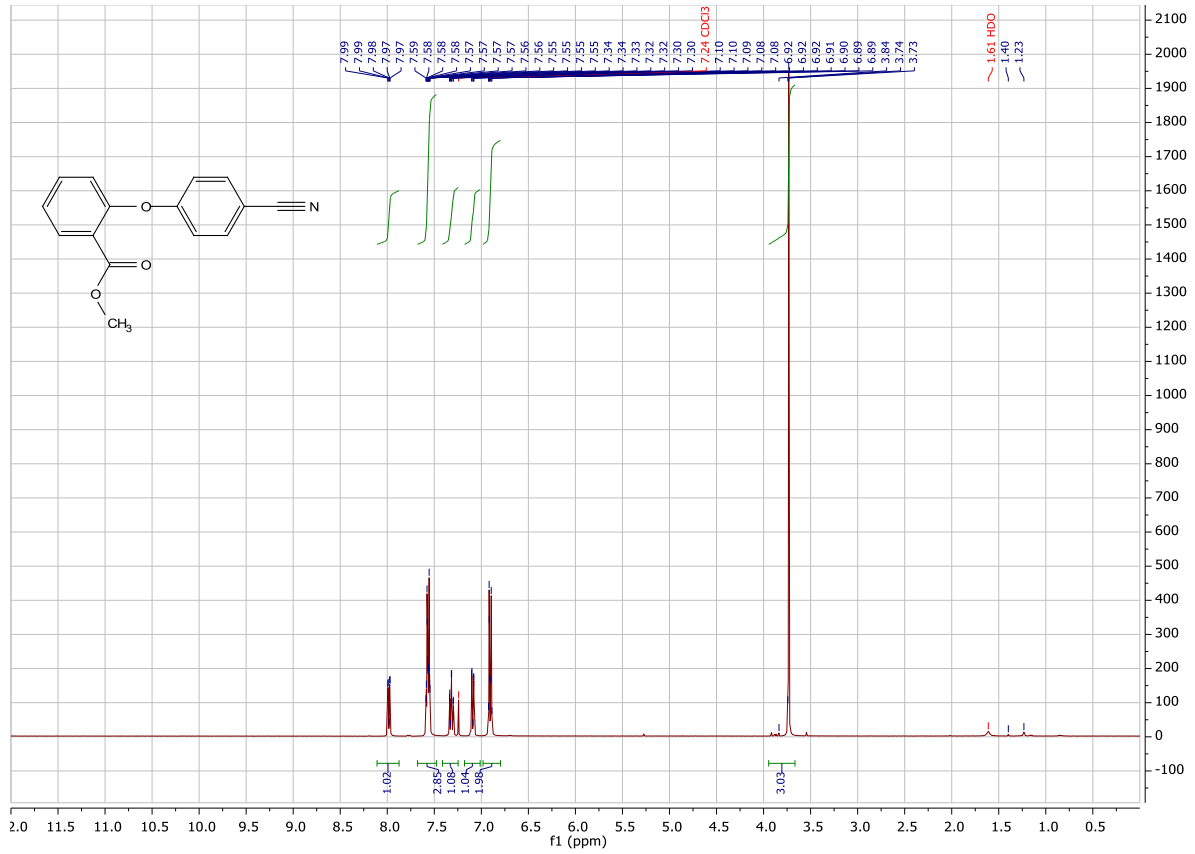
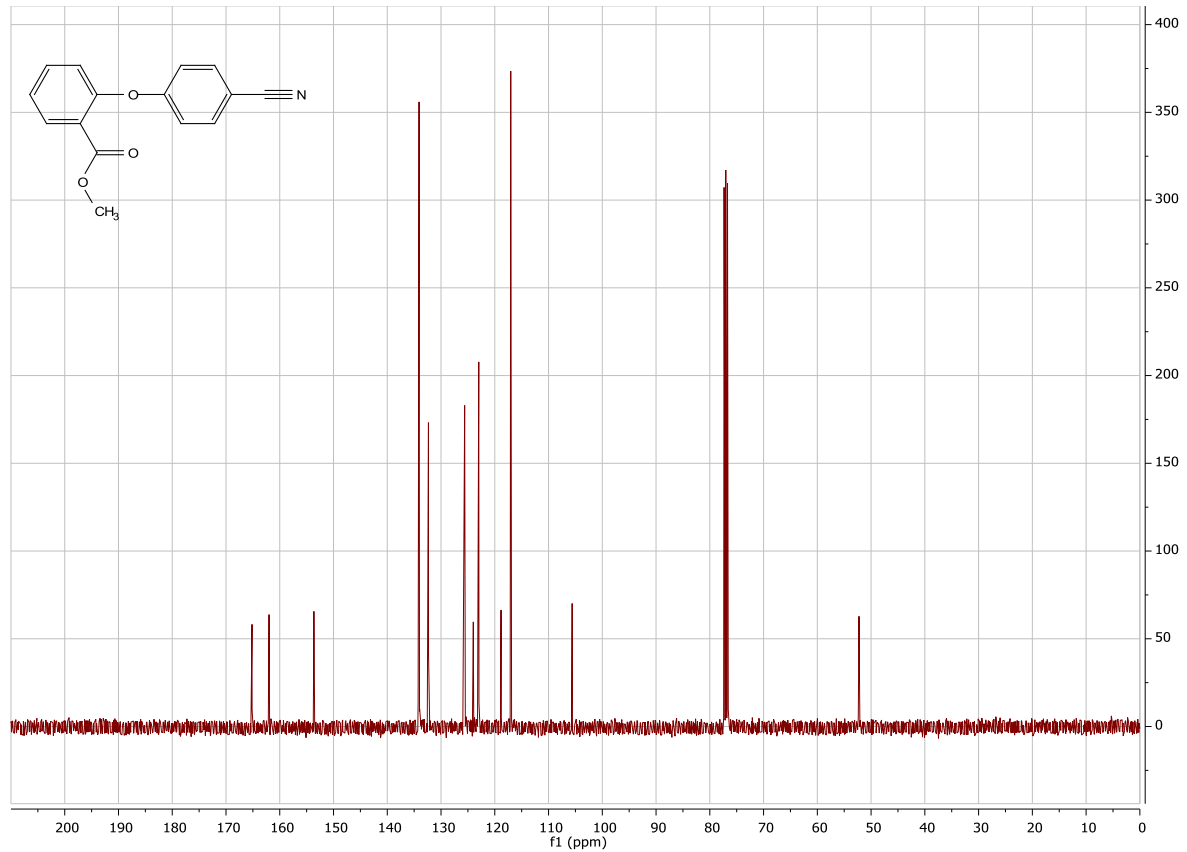
^1H NMR (600 MHz, DMSO- d_6) 4-(3-Carbamothioylphenoxy)benzamide (27) ^{13}C { ^1H } NMR (150.8 MHz, DMSO- d_6) 4-(3-Carbamothioylphenoxy)benzamide (27)

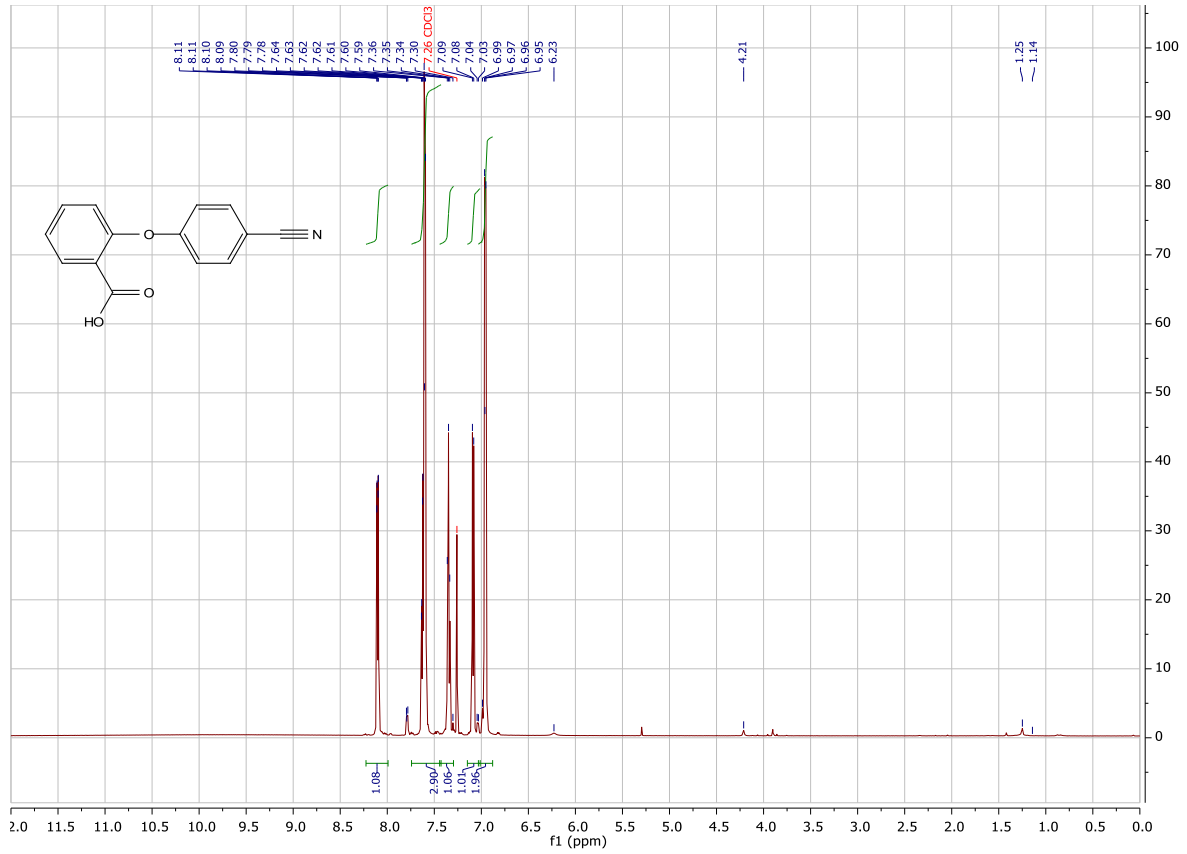
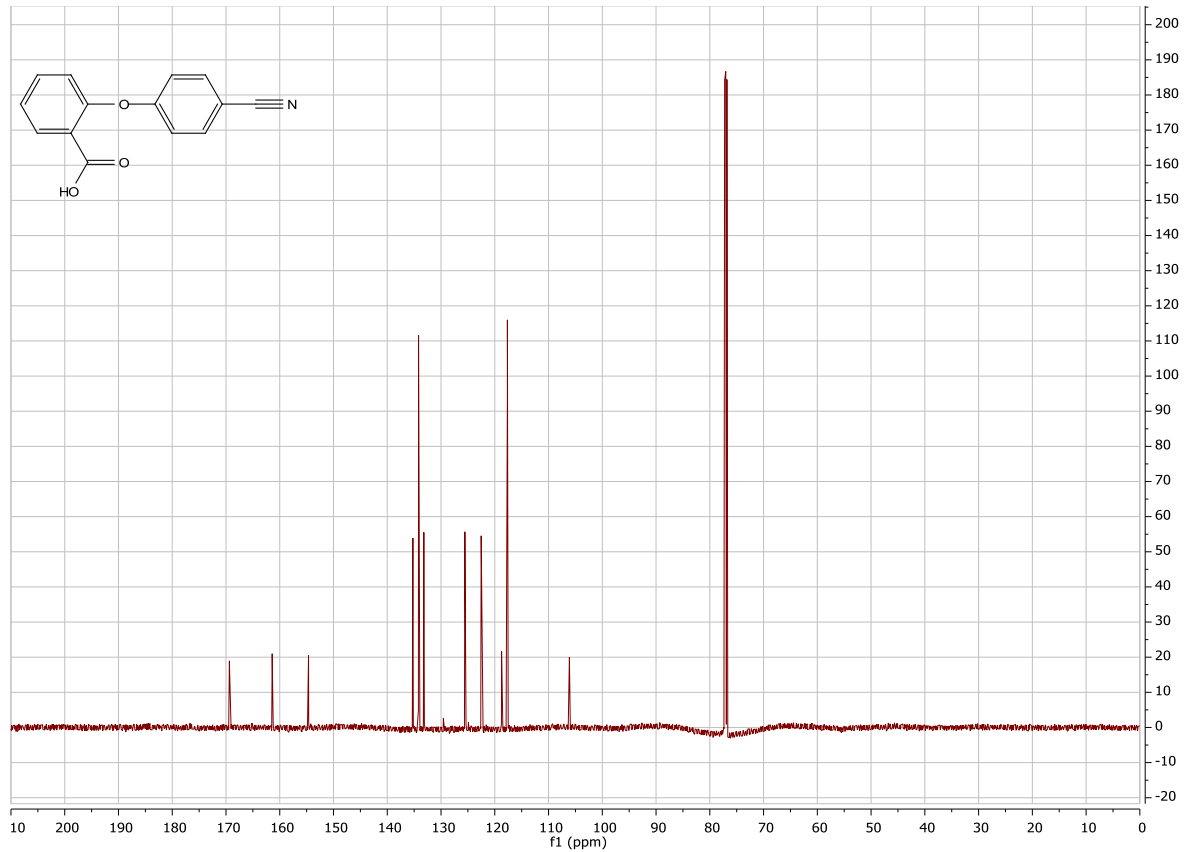
^1H NMR (600 MHz, CDCl_3) **3,3'-Oxybenzodinitrile (28)** ^{13}C { ^1H } NMR (150.8 MHz, CDCl_3) **3,3'-Oxybenzodinitrile (28)**

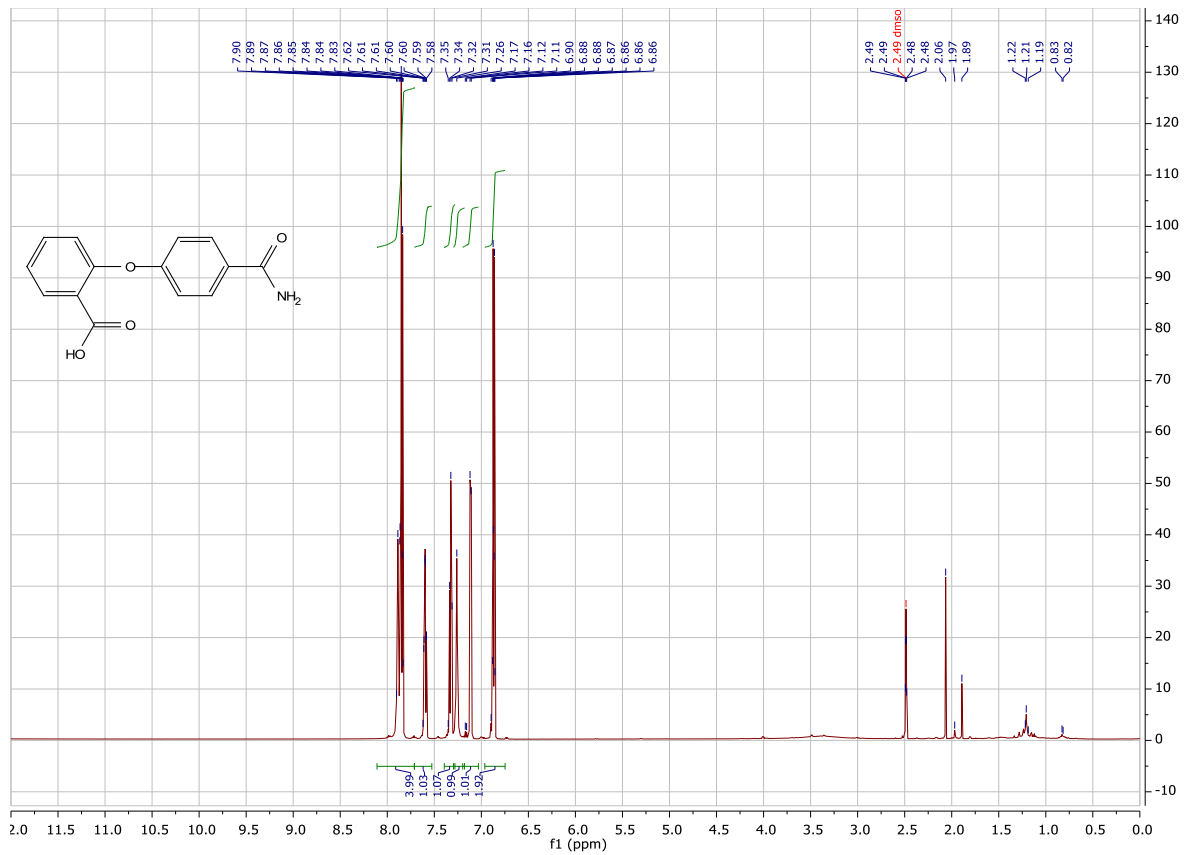
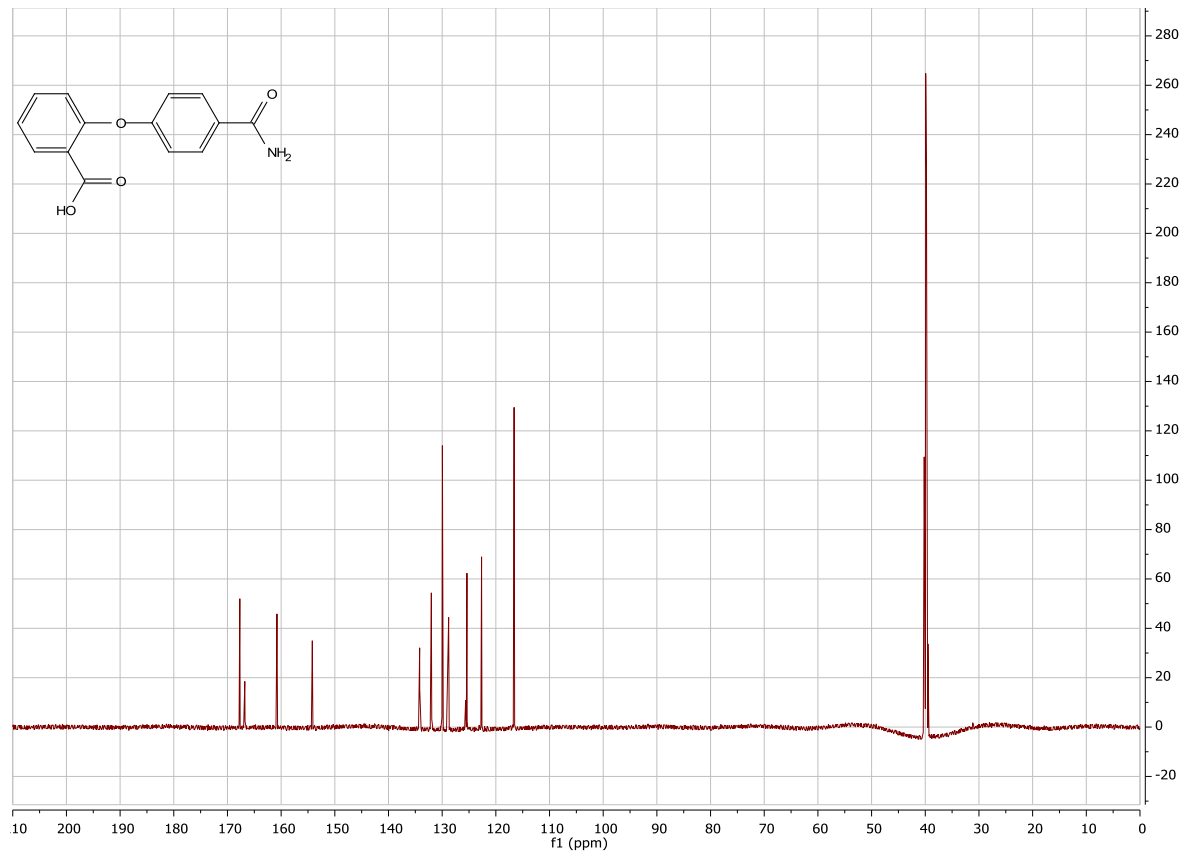
^1H NMR (600 MHz, DMSO- d_6) **3,3'-Oxybenzamide (29)** ^{13}C { ^1H } NMR (150.8 MHz, DMSO- d_6) **3,3'-Oxybenzamide (29)**

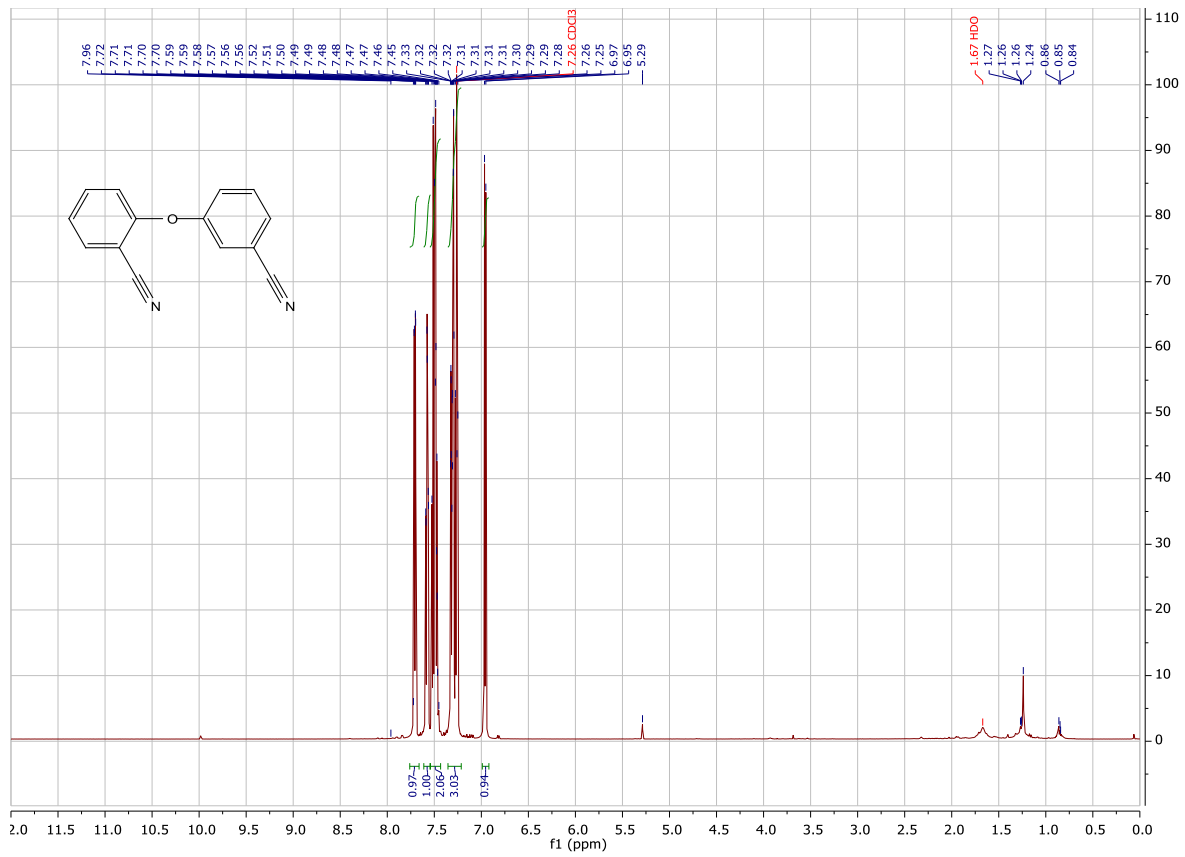
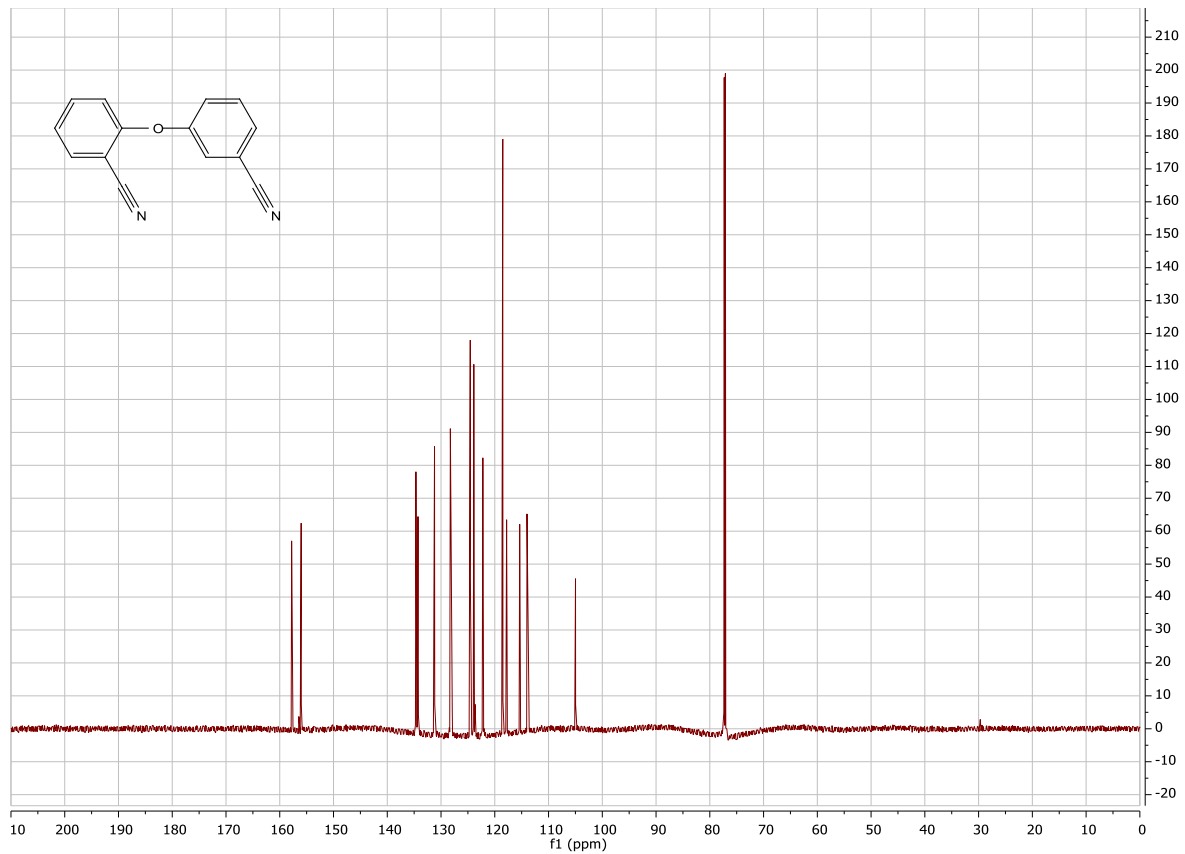
^1H NMR (600 MHz, CDCl_3) 2-(4-Cyanophenoxy)benzonitrile (P) ^{13}C { ^1H } NMR (150.8 MHz, CDCl_3) 2-(4-Cyanophenoxy)benzonitrile (P)

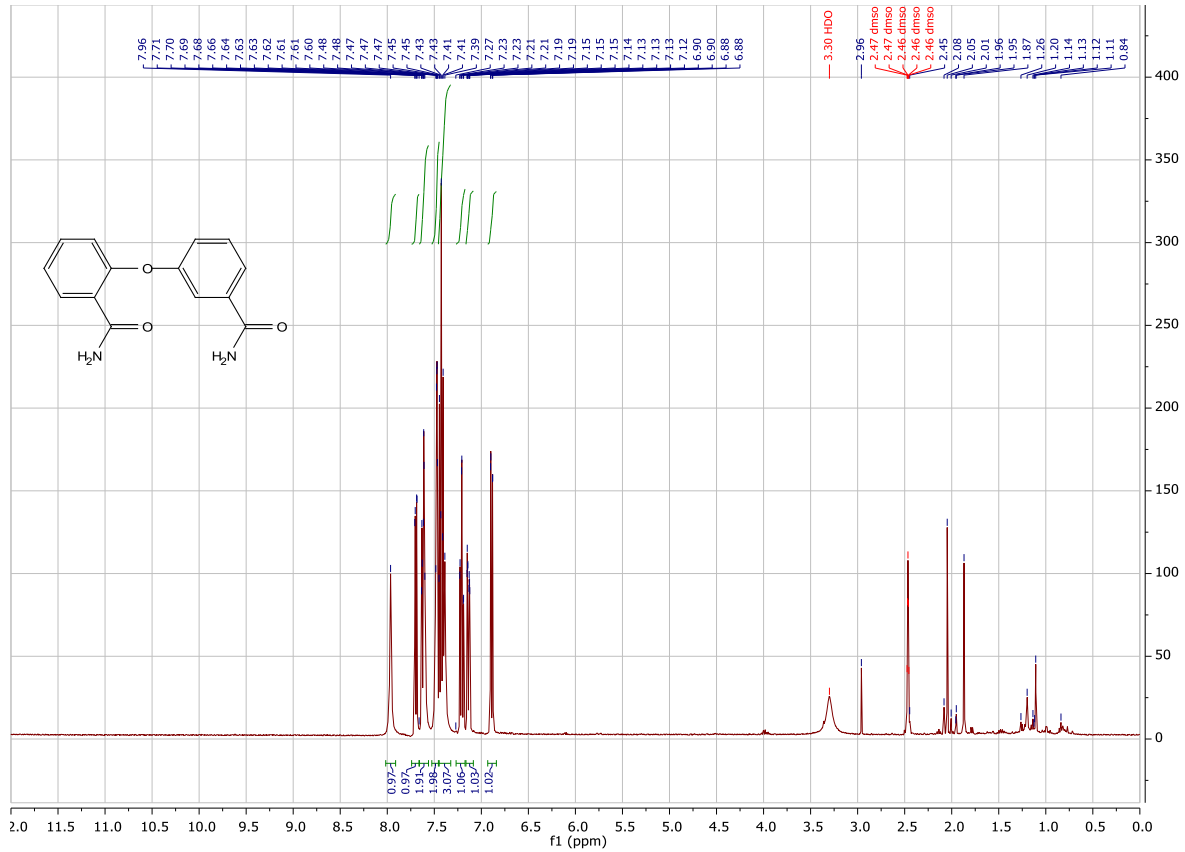
^1H NMR (600 MHz, DMSO- d_6) 2-(4-Carbamoylphenoxy)benzamide (30) ^{13}C { ^1H } NMR 150.8 MHz, DMSO- d_6) 2-(4-Carbamoylphenoxy)benzamide (30)

¹H NMR (400 MHz, CDCl₃) **Methyl 2-(4-cyanophenoxy)benzoate (R)**¹³C {¹H} NMR (100.6 MHz, CDCl₃) **Methyl 2-(4-cyanophenoxy)benzoate (R)**

^1H NMR (600 MHz, CDCl_3) 2-(4-Cyanophenoxy)benzoic acid (31) ^{13}C { ^1H } NMR (150.8 MHz, CDCl_3) 2-(4-Cyanophenoxy)benzoic acid (31)

^1H NMR (600 MHz, DMSO- d_6) **2-(4-Carbamoylphenoxy)benzoic acid (32)** ^{13}C { ^1H } NMR (150.8 MHz, DMSO- d_6) **2-(4-Carbamoylphenoxy)benzoic acid (32)**

^1H NMR (600 MHz, CDCl_3) 2-(3-Cyanophenoxy)benzonitrile (S) ^{13}C $\{^1\text{H}\}$ NMR (150.8 MHz, CDCl_3) 2-(3-Cyanophenoxy)benzonitrile (S)

^1H NMR (400 MHz, DMSO-d_6) **2-(3-Carbamoylphenoxy)benzamide (33)** ^{13}C { ^1H } NMR (100.6 MHz, DMSO-d_6) **2-(3-Carbamoylphenoxy)benzamide (33)**