

TiCl₄-Mediated Preparation of Thiophthalide Derivatives *via* Formal Thio-Passerini Reactions

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General considerations

All reactions were performed under argon atmosphere. Solvents were distilled or purified with a purification system using activated alumina columns before use. All products were purified by flash chromatography using silica gel (230-400 mesh). ¹H-NMR and ¹³C-NMR were recorded in CDCl₃ and in (CD₃)₂SO with chemical shifts reported for ¹H NMR relative to residual CHCl₃ peak (7.26 ppm) or residual (CD₃)₂SO peak (2.50 ppm). For ¹³C NMR, chemical shifts were reported relative to the central peak of CDCl₃ (77.16 ppm) or that of (CD₃)₂SO (39.52 ppm). HRMS data for new compounds were obtained electrospray ionization method coupled to a LTQ-Orbitrap high resolution detector in positive mode. Unless otherwise noted, all the reagents were ordered and used without further purification. Isocyanide **2e**¹ and substituted 2-formylbenzoic acid **5b**,² **5c**³ were prepared according to literature procedures.

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I. Additional optimization studies

Evaluation of different Lewis acids:

Reaction scheme: 1a $\xrightarrow[\text{CH}_2\text{Cl}_2, 25^\circ\text{C, Time}]{\text{Catalyst (x mol\%), } t\text{BuNC (y equiv)}}$ 3ab

Entry	Catalyst	x mol%	y equiv	Time (h)	Yield (%)
1.	BF ₃ .Et ₂ O	100	1.2	2	0
2.	In(OTf) ₃	100	1.2	2	0
3.	Zn(OTf) ₂	100	1.2	2	0
4.	Cu(OTf) ₂	100	1.2	2	0
5.	La(OTf) ₃	100	1.2	2	0
6.	TfOH	100	1.2	2	0
7.	FeCl ₃	100	1.2	2	0
8.	AlCl ₃	100	1.2	2	13
9.	InCl ₃	100	1.2	2	0
10.	ZnCl ₂	100	1.2	2	0
11.	BiCl ₃	100	1.2	2	0
12.	TiCl ₄	100	1.2	1	76 ^a
13.	Ti(O ⁱ Pr) ₄	100	1.2	2	0
14.	TiCl(O ⁱ Pr) ₃	100	1.2	2	0

Yields are determined from crude ¹H-NMR

^a Isolated yield

Evaluation of different solvents

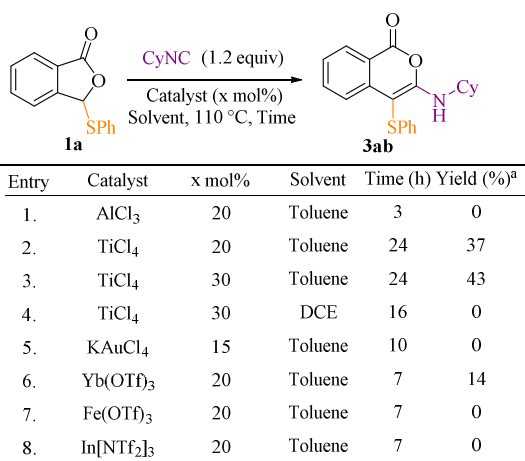
Reaction scheme: 1a $\xrightarrow[\text{Solvent, } 25^\circ\text{C, 1h}]{\text{TiCl}_4 \text{ (x mol\%), } t\text{BuNC (y equiv)}}$ 3ab

Entry	x mol%	y equiv	Solvent	Yield (%)
15.	20	1.2	CH ₂ Cl ₂	0
16.	150	1.2	CH ₂ Cl ₂	34
17.	100	1.2	THF	0
18.	100	1.2	Et ₂ O	18
19.	100	1.2	CH ₃ CN	0
20.	100	1.2	Toluene	39
21.	100	1.2	DCE	16
22.	100	1.2	CHCl ₃	41
23.	100	1.0	CH ₂ Cl ₂	35
24.	100	1.5	CH ₂ Cl ₂	60

Yields are determined from crude ¹H-NMR

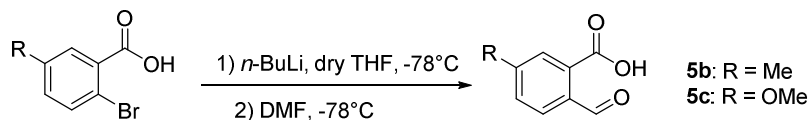
^a Isolated yield

Evaluation of lower catalyst loadings



^a Isolated yield

II. Synthesis of 5-substituted-2-carboxybenzaldehydes



A solution of 2-bromobenzoic acid (2.50 mmol) in anhydrous THF (21 mL) was cooled to -78°C and *n*-butyllithium (2.4 M in hexanes, 2.2 mL, 5.25 mmol) was added dropwise. The solution was stirred at -78°C for 0.5 hour and anhydrous DMF (2.1 mL, 26.50 mmol) was added and the reaction mixture was stirred for a further 2 hours before quenching with saturated aqueous NH_4Cl . The reaction mixture was warmed to room temperature, acidified with aqueous 2 M HCl and extracted with EtOAc. The combined organic extracts are washed with brine and then dried with MgSO_4 . After removing the solvent, the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc/AcOH = 3:1:0.02) to afford the corresponding 2-carboxybenzaldehydes. The analytical data of **5c** matched those previously reported.³

2-Formyl-5-methylbenzoic acid (5b): Starting from 2-bromo-5-methylbenzoic acid (2.15 g, 10 mmol), *n*-butyllithium (2.4 M in hexanes, 8.8 mL, 21 mmol), THF (84 mL), DMF (8.4 mL) and following the general procedure, the crude material was purified by flash column chromatography on silica gel using petroleum ether/EtOAc/AcOH = 3:1:0.02 as eluent. The desired **5b** was obtained as white solid (1.06 g, 65% yield). ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.09 (br s, 1H), 7.75 – 7.35 (m, 3H), 6.62 (br s, 1H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 168.5, 144.9, 140.5, 135.3, 126.8, 124.3, 123.4, 98.2, 20.7; HRMS (ESI+) m/z : $[\text{M}]^+\bullet$ calcd for $\text{C}_9\text{H}_8\text{O}_3$ 164.0473, found: 164.0468.

III. Preparation of 3-sulfanyl-phthalides

General procedure for the synthesis of 3-sulfanyl-phthalides (1): To a stirred solution of 2-formylbenzoic acid (**5a-c**) (1.1 mmol), *p*-toluenesulfonic acid (8 mg) and MgSO_4 (2 g) in dry toluene (5 mL) was added thiol (1.0 mmol). The mixture was heated at reflux for 3h and then cooled to room temperature. The crude reaction mixture was passed through a small pad of silica to remove the excess 2-formylbenzoic acid and washed with toluene (3 x 20 mL). Removal of the solvent under reduced pressure afforded essentially pure 3-sulfanyl-phthalide **1**.

3-(Phenylthio)isobenzofuran-1(3H)-one (1a): Starting from phthalaldehydic acid **5a** (165.4 mg, 1.1 mmol) and thiophenol (103 μL , 1.0 mmol) and following the general procedure, the desired 3-(phenylthio)isobenzofuran-1(3H)-one **1a** was obtained as white solid (213 mg, 88% yield). ^1H NMR (300 MHz, CDCl_3) δ 7.71 (d, J = 7.6 Hz, 1H), 7.66 – 7.54 (m, 2H), 7.47 – 7.37 (m, 3H), 7.22 – 7.14 (m, 3H), 6.64 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 169.2, 146.2, 134.4, 133.9, 130.4, 130.1, 129.2, 129.0, 126.4, 125.5, 123.5, 86.6; HRMS (ESI) m/z : $[\text{M}]^+\bullet$ calcd for $\text{C}_{14}\text{H}_{10}\text{O}_2\text{S}$ 242.0402, found: 242.0397.

3-(Dodecylthio)isobenzofuran-1(3H)-one (1b): Starting from phthalaldehydic acid **5a** (165.4 mg, 1.1 mmol) and dodecane-1-thiol (240 μ L, 1.0 mmol) and following the general procedure, the desired 3-(dodecylthio)isobenzofuran-1(3H)-one **1b** was obtained as white solid (314.8 mg, 94% yield). ^1H NMR (300 MHz, CDCl_3) δ 7.91 (dd, $J = 7.4$, 1.4 Hz, 1H), 7.76 – 7.68 (m, 1H), 7.57 (t, $J = 7.4$ Hz, 2H), 6.58 (s, 1H), 2.77 – 2.50 (m, 2H), 1.72 – 1.54 (m, 2H), 1.25 (s, 18H), 0.88 (t, $J = 6.7$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 169.6, 147.0, 134.5, 130.1, 126.4, 125.7, 123.3, 85.3, 32.0, 30.9, 29.7, 29.6 (4C), 29.5, 29.2, 28.9, 22.8, 14.2; HRMS (ESI) m/z : $[\text{M}]^+\bullet$ calcd for $\text{C}_{20}\text{H}_{30}\text{O}_2\text{S}$ 334.1967, found: 334.1955.

3-(Cyclohexylthio)isobenzofuran-1(3H)-one (1c): Starting from phthalaldehydic acid **5a** (165.4 mg, 1.1 mmol) and cyclohexanethiol (122 μ L, 1.0 mmol) and following the general procedure, the desired 3-(cyclohexylthio)isobenzofuran-1(3H)-one **1c** was obtained as white solid (229 mg, 92% yield). ^1H NMR (300 MHz, CDCl_3) δ 7.89 (dd, $J = 7.0$, 1.5 Hz, 1H), 7.73 – 7.63 (m, 1H), 7.59 – 7.49 (m, 2H), 6.67 (s, 1H), 3.05 (tt, $J = 10.6$, 3.7 Hz, 1H), 2.20 – 2.00 (m, 2H), 1.86 – 1.18 (m, 8H); ^{13}C NMR (75 MHz, CDCl_3) δ 169.6, 147.2, 134.3, 130.0, 126.3, 125.7, 123.3, 84.3, 44.8, 34.1, 26.1, 25.7; HRMS (ESI) m/z : $[\text{M}]^+\bullet$ calcd for $\text{C}_{14}\text{H}_{16}\text{O}_2\text{S}$ 248.0871, found: 248.0865.

3-(4-Methoxybenzylthio)isobenzofuran-1(3H)-one (1d): Starting from phthalaldehydic acid **5a** (165.4 mg, 1.1 mmol) and (4-methoxyphenyl)methanethiol (139 μ L, 1.0 mmol) and following the general procedure, the desired 3-(4-methoxybenzylthio)isobenzofuran-1(3H)-one **1d** was obtained as white solid (237 mg, 83% yield). ^1H NMR (300 MHz, CDCl_3) δ 7.80 (d, $J = 7.6$ Hz, 1H), 7.61 – 7.53 (m, 1H), 7.46 (dd, $J = 10.9$, 4.0 Hz, 1H), 7.38 (dd, $J = 7.6$, 0.8 Hz, 1H), 7.21 – 7.15 (m, 2H), 6.77 (d, $J = 8.7$ Hz, 2H), 6.30 (s, 1H), 3.91 (d, $J = 13.2$ Hz, 1H), 3.75 – 3.66 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 169.5, 159.1, 146.7, 134.4, 130.4, 130.0, 128.3, 126.4, 125.7, 123.1, 114.3, 83.4, 55.4, 34.6; HRMS (ESI) m/z : $[\text{M}]^+\bullet$ calcd for $\text{C}_{16}\text{H}_{14}\text{O}_3\text{S}$ 286.0664, found: 286.0666.

3-(tert-Butylthio)isobenzofuran-1(3H)-one (1e): Starting from phthalaldehydic acid **5a** (165.4 mg, 1.1 mmol) and 2-methylpropane-2-thiol (113 μ L, 1.0 mmol) and following the general procedure, the desired 3-(tert-butylthio)isobenzofuran-1(3H)-one **1e** was obtained as white solid (168 mg, 76% yield). ^1H NMR (300 MHz, CDCl_3) δ 7.88 (d, $J = 7.7$ Hz, 1H), 7.72 – 7.62 (m, 1H), 7.55 – 7.45 (m, 2H), 6.73 (s, 1H), 1.53 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 169.8, 147.2, 134.2, 130.0, 126.4, 125.7, 123.5, 83.3, 45.5, 31.7; HRMS (ESI) m/z : $[\text{M}]^+\bullet$ calcd for $\text{C}_{12}\text{H}_{14}\text{O}_2\text{S}$ 222.0715, found: 222.0726.

3-(tert-Butylthio)-6-methylisobenzofuran-1(3H)-one (1f): Starting from 2-formyl-5-methylbenzoic acid **5b** (270.6 mg, 1.65 mmol) and 2-methylpropane-2-thiol (169 μ L, 1.50 mmol) and following the general procedure, the desired 3-(tert-butylthio)-6-methylisobenzofuran-1(3H)-one **1f** was obtained as white solid (320 mg, 90% yield). ^1H NMR (300 MHz, CDCl_3) δ 7.64 (s, 1H), 7.47 (d, $J = 7.9$ Hz, 1H), 7.39 (d, $J = 7.9$ Hz, 1H), 6.67 (s, 1H), 2.44 (s, 3H), 1.51 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 169.9, 144.5, 140.3, 135.4, 126.5, 125.6, 123.1, 83.2, 45.3, 31.6, 21.4; HRMS (ESI) m/z : $[\text{M}]^+\bullet$ calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2\text{S}$ 236.0871, found: 236.0874.

3-(tert-Butylthio)-6-methoxyisobenzofuran-1(3H)-one (1g): Starting from 2-formyl-5-methoxybenzoic acid **5c** (297 mg, 1.65 mmol) and 2-methylpropane-2-thiol (169 μ L, 1.50 mmol) and following the general procedure, the desired 3-

(*tert*-butylthio)-6-methoxyisobenzofuran-1(3*H*)-one **1g** was obtained as white solid (315 mg, 83% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.33 (d, *J* = 8.4 Hz, 1H), 7.22 (d, *J* = 2.3 Hz, 1H), 7.14 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.60 (s, 1H), 3.78 (s, 3H), 1.44 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 169.8, 161.3, 139.3, 127.7, 124.3, 123.0, 107.5, 83.3, 55.9, 45.3, 31.6; HRMS (APPI) *m/z*: [M]⁺calcd for C₁₃H₁₆O₃S 252.0820, found: 252.0823.

IV. Synthesis of isochromenone derivatives **3**

General procedure for the isocyanide insertion reaction: In a screw cap vial under argon atmosphere were sequentially added the 3-substituted thiophthalide **1** (100 mg, 1 equiv), the substituted isocyanide **2** (1.2 equiv), 1,2-dichloromethane (5 mL) and TiCl₄ (1M in CH₂Cl₂, 1 equiv). The resulting mixture was stirred at room temperature until TLC analysis showed completion of the reaction. The reaction mixture was then quenched by saturated aqueous NaHCO₃ solution dropwise (10 mL) and transferred to a separating funnel. The aqueous phase was extracted with dichloromethane (4 x 15 mL) and the combined organic extracts washed by water (40 mL) and brine (40 mL) before being dried over MgSO₄. After filtration and evaporation of the solvents under reduced pressure, the crude material was purified by flash column chromatography on silica gel to afford the desired isochromenone derivative **3**.

3-(*tert*-Butylamino)-4-(phenylthio)-1*H*-isochromen-1-one (3aa): Starting from 3-(phenylthio)isobenzofuran-1(3*H*)-one **1a** (100 mg, 0.413 mmol), *tert*-butylisocyanide **2a** (54 μL, 0.498 mmol), TiCl₄ (1M in CH₂Cl₂, 413 μL, 0.413 mmol) and following the general procedure, the crude material was purified by flash column chromatography on silica gel using cyclohexane:ethyl acetate (98:2) as eluent. The desired 3-(*tert*-butylamino)-4-(phenylthio)-1*H*-isochromen-1-one **3aa** was obtained as yellow solid (102 mg, 76% yield). ¹H NMR (300 MHz, CDCl₃) δ 8.13 (ddd, *J* = 8.0, 1.4, 0.6 Hz, 1H), 7.64 – 7.48 (m, 2H), 7.29 – 7.19 (m, 2H), 7.18 – 7.07 (m, 4H), 5.83 (s, 1H), 1.45 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 160.6, 160.4, 142.2, 136.1, 135.6, 130.0, 129.3, 125.7, 125.6, 123.4, 122.2, 115.2, 53.5, 30.2; HRMS (APPI) *m/z*: [M]⁺calcd for C₁₉H₁₉NO₂S 325.1136, found: 325.1139.

3-(Cyclohexylamino)-4-(phenylthio)-1*H*-isochromen-1-one (3ab): Starting from 3-(phenylthio)isobenzofuran-1(3*H*)-one **1a** (100 mg, 0.413 mmol), cyclohexylisocyanide **2b** (62 μL, 0.498 mmol), TiCl₄ (1M in CH₂Cl₂, 413 μL, 0.413 mmol) and following the general procedure, the crude material was purified by flash column chromatography on silica gel using cyclohexane:ethyl acetate (98:2) as eluent. The desired 3-(cyclohexylamino)-4-(phenylthio)-1*H*-isochromen-1-one **3ab** was obtained as yellow solid (136.6 mg, 94% yield). ¹H NMR (300 MHz, CDCl₃) δ 8.12 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.62 – 7.47 (m, 2H), 7.28 – 7.18 (m, 2H), 7.15 – 7.05 (m, 4H), 5.68 (d, *J* = 8.5 Hz, 1H), 3.90 – 3.73 (m, 1H), 2.02 – 1.91 (m, 2H), 1.78 – 1.06 (m, 8H); ¹³C NMR (75 MHz, CDCl₃) δ 160.7, 159.3, 142.4, 136.1, 135.7, 130.1, 129.3, 125.7, 125.5, 123.3, 122.1, 115.1, 75.9, 50.8, 33.9, 25.5, 24.7; HRMS (ESI) *m/z*: [M]⁺calcd for C₂₁H₂₁NO₂S 351.1293, found: 351.1282.

3-(Benzylamino)-4-(phenylthio)-1*H*-isochromen-1-one (3ac): Starting from 3-(phenylthio)isobenzofuran-1(3*H*)-one **1a** (100 mg, 0.413 mmol), benzylisocyanide **2c** (61 μ L, 0.498 mmol), TiCl₄ (1M in CH₂Cl₂, 413 μ L, 0.413 mmol) and following the general procedure, the crude material was purified by flash column chromatography on silica gel using cyclohexane:ethyl acetate (98:2) as eluent. The desired 3-(benzylamino)-4-(phenylthio)-1*H*-isochromen-1-one **3ac** was obtained as yellow colored sticky gum (100.6 mg, 68% yield). ¹H NMR (300 MHz, CDCl₃) δ 8.11 – 7.92 (m, 1H), 7.55 – 7.48 (m, 1H), 7.46 – 7.30 (m, 1H), 7.23 – 6.95 (m, 11H), 6.07 (t, *J* = 6.2 Hz, 1H), 4.48 (d, *J* = 6.2 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 160.3, 159.2, 142.0, 137.9, 136.0, 135.7, 130.1, 129.3, 129.1, 128.9, 127.8, 127.5, 125.7, 125.5, 123.6, 122.2, 115.3, 45.8; HRMS (ESI) *m/z*: [M]⁺•calcd for C₂₂H₁₇NO₂S 359.0980, found: 359.0997.

3-(2,6-Dimethylphenylamino)-4-(phenylthio)-1*H*-isochromen-1-one (3ad): Starting from 3-(phenylthio)isobenzofuran-1(3*H*)-one **1a** (100 mg, 0.413 mmol), 2,6-dimethylphenylisocyanide **2d** (65.3 mg, 0.498 mmol), TiCl₄ (1M in CH₂Cl₂, 413 μ L, 0.413 mmol) and following the general procedure, the crude material was purified by flash column chromatography on silica gel using cyclohexane:ethyl acetate (98:2) as eluent. The desired 3-(2,6-dimethylphenylamino)-4-(phenylthio)-1*H*-isochromen-1-one **3ad** was obtained as yellow crystalline solid (132.4 mg, 86% yield). ¹H NMR (300 MHz, CDCl₃) δ 8.13 (ddd, *J* = 8.2, 1.2, 0.6 Hz, 1H), 7.74 (ddd, *J* = 8.2, 1.2, 0.6 Hz, 1H), 7.68 – 7.50 (m, 1H), 7.31 – 7.05 (m, 9H), 2.19 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 160.1, 158.2, 142.0, 136.3, 135.8 (2C), 133.7, 130.2, 129.4, 128.6, 127.7, 125.9, 125.6, 123.9, 122.3, 115.8, 18.5; HRMS (ESI) *m/z*: [M]⁺•calcd for C₂₃H₁₉NO₂S 373.1136, found: 373.1124.

3-(*tert*-Butylamino)-4-(dodecylthio)-1*H*-isochromen-1-one (3ba) and 3-Amino-4-(dodecylthio)-1*H*-isochromen-1-one (3ba'): Starting from 3-(dodecylthio)isobenzofuran-1(3*H*)-one **1b** (100 mg, 0.30 mmol), *tert*-butylisocyanide **2a** (41 μ L, 0.36 mmol), TiCl₄ (1M in CH₂Cl₂, 300 μ L, 0.30 mmol) and following the general procedure, the crude material was purified by flash column chromatography on silica gel using cyclohexane:ethyl acetate (98:2 to 80:20) as eluent. The desired 3-(*tert*-butylamino)-4-(dodecylthio)-1*H*-isochromen-1-one **3ba** was obtained as yellow sticky solid (62.4 mg, 50% yield) and 3-Amino-4-(dodecylthio)-1*H*-isochromen-1-one **3ba'** was obtained as yellow solid (13.4 mg, 12% yield). (**3ba**): ¹H NMR (300 MHz, CDCl₃) δ 8.09 (ddd, *J* = 7.9, 1.4, 0.5 Hz, 1H), 7.77 (ddd, *J* = 8.3, 1.1, 0.6 Hz, 1H), 7.58 (ddd, *J* = 8.4, 7.1, 1.4 Hz, 1H), 7.12 (dd, *J* = 4.5, 3.5 Hz, 1H), 5.99 (br s, 1H), 2.59 – 2.46 (m, 2H), 1.60 – 1.44 (m, 11H), 1.44 – 1.17 (m, 18H), 0.87 (t, *J* = 6.7 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 160.6, 160.0, 142.6, 135.2, 130.0, 122.9, 122.2, 115.2, 80.0, 53.1, 34.8, 32.0, 30.3, 29.8, 29.7 (3C), 29.4 (2C), 29.0, 22.8, 14.2; HRMS (ESI) *m/z*: [M]⁺•calcd for C₂₅H₃₉NO₂S 417.2702, found: 417.2715. (**3ba'**): ¹H NMR (300 MHz, CDCl₃) δ 8.13 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.86 – 7.79 (m, 1H), 7.65 (ddd, *J* = 8.3, 7.2, 1.4 Hz, 1H), 7.24 – 7.17 (m, 1H), 5.14 (br s, 2H), 2.63 – 2.55 (m, 2H), 1.63 – 1.51 (m, 2H), 1.43 – 1.15 (m, 18H), 0.88 (t, *J* = 6.7 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 160.8, 158.4, 141.9, 135.5, 130.2, 124.0, 122.5, 116.5, 81.0, 34.7, 32.0, 30.0, 29.8, 29.7 (2C), 29.5, 29.4, 29.1, 22.8, 14.2; HRMS (ESI) *m/z*: [M]⁺•calcd for C₂₁H₃₁NO₂S 361.2075, found: 361.2082.

3-(Cyclohexylamino)-4-(dodecylthio)-1*H*-isochromen-1-one (3bb): Starting from 3-(dodecylthio)isobenzofuran-1(3*H*)-one **1b** (100 mg, 0.30 mmol), cyclohexylisocyanide **2b** (45 μ L, 0.36 mmol), TiCl₄ (1M in CH₂Cl₂, 300 μ L, 0.30

mmol) and following the general procedure, the crude material was purified by flash column chromatography on silica gel using cyclohexane:ethyl acetate (98:2) as eluent. The desired 3-(cyclohexylamino)-4-(dodecylthio)-1*H*-isochromen-1-one **3bb** was obtained as yellow sticky solid (123 mg, 93% yield). ¹H NMR (300 MHz, CDCl₃) δ 8.12 – 8.05 (m, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.62 – 7.54 (m, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 5.81 (d, *J* = 8.7 Hz, 1H), 3.85 – 3.71 (m, 1H), 2.53 (t, *J* = 7.3 Hz, 2H), 2.10 – 1.85 (m, 2H), 1.82 – 1.15 (m, 28H), 0.86 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 160.9, 158.6, 142.8, 135.3, 130.1, 122.8, 122.1, 115.0, 78.9, 50.6, 34.8, 34.0, 32.0, 29.9, 29.7(4C), 29.4 (2C), 29.1, 25.6, 24.8, 22.8, 14.2; HRMS (ESI) *m/z*: [M]⁺calcd for C₂₇H₄₁NO₂S 443.2858, found: 443.2861.

3-(Cyclohexylamino)-4-(cyclohexylthio)-1*H*-isochromen-1-one (3cb): Starting from 3-(cyclohexylthio)isobenzofuran-1(3*H*)-one **1c** (100 mg, 0.40 mmol), cyclohexylisocyanide **2b** (60 μL, 0.48 mmol), TiCl₄ (1M in CH₂Cl₂, 400 μL, 0.40 mmol) and following the general procedure, the crude material was purified by flash column chromatography on silica gel using cyclohexane:ethyl acetate (98:2 to 80:20) as eluent. The desired 3-(cyclohexylamino)-4-(cyclohexylthio)-1*H*-isochromen-1-one **3cb** was obtained as yellow amorphous solid (97.8 mg, 68% yield) and thiophthalide **4b** was obtained as a white solid (35 mg, 32% yield). (**3cb**): ¹H NMR (300 MHz, CDCl₃) δ 8.07 (ddd, *J* = 8.0, 1.4, 0.5 Hz, 1H), 7.76 (ddd, *J* = 8.3, 1.0, 0.6 Hz, 1H), 7.56 (ddd, *J* = 8.3, 7.1, 1.4 Hz, 1H), 7.09 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 5.84 (d, *J* = 8.6 Hz, 1H), 3.85 – 3.68 (m, 1H), 2.75 (tt, *J* = 10.7, 3.6 Hz, 1H), 2.06 – 1.86 (m, 4H), 1.81 – 1.14 (m, 16H); ¹³C NMR (75 MHz, CDCl₃) δ 160.8, 159.0, 143.2, 135.1, 129.9, 122.6, 122.3, 114.9, 78.0, 50.5, 47.1, 33.9, 33.6, 26.1, 25.7, 25.5, 24.8; HRMS (ESI) *m/z*: [M]⁺calcd for C₂₁H₂₇NO₂S 357.1762, found: 357.1753. (**4b**): ¹H NMR (300 MHz, CDCl₃) δ 7.89 (dd, *J* = 7.7, 0.7 Hz, 1H), 7.79 (d, *J* = 7.7 Hz, 1H), 7.66 (td, *J* = 7.7, 1.3 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 1H), 6.18 (d, *J* = 6.3 Hz, 1H), 5.37 (s, 1H), 3.80 – 3.3.55 (m, 1H), 1.96 – 1.84 (m, 1H), 1.77 – 1.51 (m, 4H), 1.42 – 0.92 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 195.5, 166.2, 146.2, 134.3, 134.1, 129.3, 126.5, 124.2, 53.9, 49.3, 32.7, 32.6, 25.4, 24.8, 24.7; HRMS (ESI) *m/z*: [M]⁺calcd for C₁₅H₁₇NO₂S 275.0980, found: 275.0814.

V. Synthesis of thiophthalides 4

Thiophthalides **4** were synthesized by either one of the two general procedures given below.

General Procedure A:

Starting from S-(*t*-butyl)-substituted phthalides: In a screw cap vial under argon atmosphere were sequentially added the 3-(*tert*-butylthio)isobenzofuran-1(3*H*)-one **1e** (100 mg, 0.45 mmol, 1.0 equiv), the isocyanide **2** (0.54 mmol, 1.2 equiv), dichloromethane (5 mL) and TiCl₄ (1M in CH₂Cl₂, 900 μL, 2.0 equiv). The resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was then quenched by saturated aqueous NaHCO₃ solution (20 mL) and transferred to a separating funnel. The aqueous phase was extracted with dichloromethane (4 x 15 mL) and the combined organic extracts washed by water (40 mL) and brine (40 mL) before being dried over MgSO₄. After

filtration and evaporation of the solvents under reduced pressure, the crude material was purified by flash column chromatography on silica gel to afford the desired benzothiophenone derivatives **4**.

General Procedure B:

Starting from 2-carboxy benzaldehydes (5a-c) and 2-methylpropane-2-thiol by one-pot sequential three-component reaction: In a screw cap vial under argon atmosphere were sequentially added the substituted 2-carboxy benzaldehyde (1.10 mmol, 1.1 equiv) **5**, 2-methylpropane-2-thiol (1.00 mmol, 1 equiv), dichloromethane (5 mL), molecular sieves (4Å, 2.00 g) and TiCl₄ (1M in CH₂Cl₂, 200 µL, 0.2 equiv). After stirring the resulting mixture at room temperature for 1h, isocyanide **2** (1.50 mmol, 1.5 equiv), TiCl₄ (1 M in CH₂Cl₂, 2.00 mL, 2 equiv) were added to the reaction mixture which was then stirred for further 2 hours. The reaction mixture was then poured to a saturated aqueous NaHCO₃ solution (40 mL) and transferred to a separating funnel. The aqueous phase was extracted with dichloromethane (4 x 40 mL) and the combined organic extracts washed by water (100 mL) and brine (100 mL) before being dried over MgSO₄. After filtration and evaporation of the solvents under reduced pressure, the crude material was purified by flash column chromatography on silica gel to afford the desired thiophthalide derivative **4**.

***N*-tert-butyl-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide (4a):** Starting from 3-(*tert*-butylthio)isobenzofuran-1(3*H*)-one **1e** (100 mg, 0.45 mmol), *tert*-butylisocyanide **2a** (61 µL, 0.54 mmol), TiCl₄ (1M in CH₂Cl₂, 900 µL, 0.90 mmol) and following the general procedure A, the crude material was purified by flash column chromatography on silica gel using cyclohexane:ethyl acetate (8:2) as eluent. The desired *N*-*tert*-butyl-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide **4a** was obtained as white solid (80.6 mg, 72% yield). Starting from 2-methylpropane-2-thiol (1.0 mmol) and following general procedure B, **4a** was obtained as white solid (172.3 mg, 69% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.86 (dd, *J* = 7.8, 0.7 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.65 (td, *J* = 7.8, 1.3 Hz, 1H), 7.54 - 7.47 (m, 1H), 6.12 (br s, 1H), 5.27 (s, 1H), 1.27 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 195.5, 166.1, 146.4, 134.2, 134.1, 129.2, 126.3, 124.1, 54.5, 52.1, 28.4; HRMS (ESI) *m/z*: [M]⁺ calcd for C₁₃H₁₅NO₂S 249.0823, found: 149.9861 [M-(CONH^tBu)]⁺; MS (CI-NH₃) *m/z* 250 (100) [MH]⁺.

***N*-cyclohexyl-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide (4b):** Starting from 3-(*tert*-butylthio)isobenzofuran-1(3*H*)-one **1e** (100 mg, 0.45 mmol), cyclohexylisocyanide **2b** (67 µL, 0.54 mmol), TiCl₄ (1M in CH₂Cl₂, 900 µL, 0.90 mmol) and following the general procedure A, the crude material was purified by flash column chromatography on silica gel using cyclohexane:ethyl acetate (8:2) as eluent. The desired *N*-cyclohexyl-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide **4b** was obtained as a white solid (93.5 mg, 76% yield). Starting from 2-methylpropane-2-thiol (1.0 mmol) and following general procedure B, **4b** was obtained as a white solid (213.6 mg, 78% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.89 (dd, *J* = 7.8, 0.7 Hz, 1H), 7.79 (d, *J* = 7.7 Hz, 1H), 7.66 (td, *J* = 7.6, 1.3 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 6.18 (d, *J* = 6.3 Hz, 1H), 5.37 (s, 1H), 3.80 – 3.55 (m, 1H), 1.96 – 1.84 (m, 1H), 1.77 – 1.51 (m, 4H), 1.42 – 0.92 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 195.5, 166.2, 146.2, 134.3, 134.1, 129.3,

126.5, 124.2, 53.9, 49.3, 32.7, 32.6, 25.4, 24.8, 24.7; HRMS (ESI) m/z : $[M]^+\bullet$ calcd for $C_{15}H_{17}NO_2S$ 275.0980, found: 275.0814.

***N*-benzyl-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide (4c):** Starting from 3-(*tert*-butylthio)isobenzofuran-1(3*H*)-one **1e** (100 mg, 0.45 mmol), benzylisocyanide **2c** (66 μ L, 0.54 mmol), $TiCl_4$ (1M in CH_2Cl_2 , 900 μ L, 0.90 mmol) and following the general procedure A, the crude material was purified by flash column chromatography on silica gel using cyclohexane:ethyl acetate (8:2) as eluent. The desired *N*-benzyl-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide **4c** was obtained as pale yellow solid (89.5 mg, 70% yield). Starting from 2-methylpropane-2-thiol (1.0 mmol) and following general procedure B, **4c** was obtained as pale yellow solid (164.0 mg, 58% yield). 1H NMR (300 MHz, $DMSO-D_6$) δ 9.14 (t, J = 5.6 Hz, 1H), 7.87 – 7.49 (m, 4H), 7.40 – 7.20 (m, 5H), 5.74 (s, 1H), 4.34 (d, J = 5.6 Hz, 2H); ^{13}C NMR (101 MHz, $DMSO-D_6$) δ 196.4, 167.1, 147.0, 138.7, 134.6, 134.1, 129.0, 128.4, 127.3, 127.0, 126.4, 123.3, 52.5, 42.9; HRMS (ESI) m/z : $[M]^+\bullet$ calcd for $C_{16}H_{13}NO_2S$ 283.0667, found: 283.0677.

***N*-(2,6-dimethylphenyl)-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide (4d):** Starting from 3-(*tert*-butylthio)isobenzofuran-1(3*H*)-one **1e** (100 mg, 0.45 mmol), 2,6-dimethylphenylisocyanide **2d** (71 mg, 0.54 mmol), $TiCl_4$ (1M in CH_2Cl_2 , 900 μ L, 0.90 mmol) and following the general procedure A, the crude material was purified by flash column chromatography on silica gel using cyclohexane:ethyl acetate (8:2) as eluent. The desired *N*-(2,6-dimethylphenyl)-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide **4d** was obtained as white solid (101.2 mg, 76% yield). Starting from 2-methylpropane-2-thiol (1.0 mmol) and following general procedure B, **4d** was obtained as white solid (224.0 mg, 75% yield). 1H NMR (400 MHz, $DMSO-D_6$) δ 10.00 (s, 1H), 7.88 – 7.73 (m, 3H), 7.63 (t, J = 7.4 Hz, 1H), 7.20 – 7.00 (m, 3H), 5.94 (s, 1H), 2.16 (s, 6H); ^{13}C NMR (101 MHz, $DMSO-D_6$) δ 196.3, 165.8, 146.9, 135.1, 134.7, 134.3, 134.2, 129.1, 127.8, 126.9, 126.7, 123.4, 52.4, 18.0; HRMS (ESI) m/z : $[M]^+\bullet$ calcd for $C_{17}H_{15}NO_2S$ 297.0823, found: 297.0814.

***N*-(4-chlorophenyl)-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide (4e):** Starting from 3-(*tert*-butylthio)isobenzofuran-1(3*H*)-one **1e** (100 mg, 0.45 mmol), 4-chlorophenylisocyanide **2e** (74.3 mg, 0.54 mmol), $TiCl_4$ (1M in CH_2Cl_2 , 900 μ L, 0.90 mmol) and following the general procedure A, the crude material was purified by flash column chromatography on silica gel using cyclohexane:ethyl acetate (8:2) as eluent. The desired *N*-(4-chlorophenyl)-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide **4e** was obtained as white amorphous solid (109.6 mg, 80% yield). 1H NMR (300 MHz, $DMSO-D_6$) δ 10.91 (s, 1H), 7.85 – 7.75 (m, 3H), 7.75 – 7.55 (m, 3H), 7.48 – 7.39 (m, 2H), 5.90 (s, 1H); ^{13}C NMR (75 MHz, $DMSO-D_6$) δ 196.2, 166.0, 146.5, 137.4, 134.7, 134.1, 129.1, 128.8, 127.7, 126.7, 123.3, 121.1, 53.2; HRMS (ESI) m/z : $[M]^+\bullet$ calcd for $C_{15}H_{10}ClNO_2S$ 303.0121, found: 303.0109.

***N*-(naphthalen-2-yl)-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide (4f):** Starting from 3-(*tert*-butylthio)isobenzofuran-1(3*H*)-one **1e** (100 mg, 0.45 mmol), 2-isocyanonaphthalene **2f** (82.7 mg, 0.54 mmol), $TiCl_4$ (1M in CH_2Cl_2 , 900 μ L, 0.90 mmol) and following the general procedure A, the crude material was purified by flash column chromatography on silica gel using cyclohexane:ethyl acetate (9:1) as eluent. The desired *N*-(naphthalen-2-yl)-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide **4f** was obtained as grey solid (93.8 mg, 65% yield). Starting from

2-methylpropane-2-thiol (1 mmol) and following general procedure B, **4f** was obtained as grey solid (204.0 mg, 64% yield). ¹H NMR (300 MHz, DMSO-D₆) δ 8.28 (s, 1H), 8.00 – 7.70 (m, 7H), 7.69 – 7.58 (m, 2H), 7.52 – 7.38 (m, 2H), 5.95 (s, 1H); ¹³C NMR (75 MHz, DMSO-D₆) δ 197.3, 167.0, 147.7, 137.0, 135.7, 135.1, 134.2, 131.0, 130.0, 129.5, 128.4, 128.3, 127.7, 127.5, 125.9, 124.2, 120.8, 116.9, 54.2; HRMS (ESI) *m/z*: [M]⁺calcd for C₁₉H₁₃NO₂S 319.0667, found: 319.0668.

Methyl 2-(3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamido)acetate (4g): Starting from 3-(*tert*-butylthio)isobenzofuran-1(3*H*)-one **1e** (100 mg, 0.45 mmol), methyl 2-isocyanoacetate **2g** (49 μL, 0.54 mmol), TiCl₄ (1M in CH₂Cl₂, 900 μL, 0.90 mmol) and following the general procedure A, the crude material was purified by flash column chromatography on silica gel using cyclohexane:ethyl acetate (8:2) as eluent. The desired methyl 2-(3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamido)acetate **4g** was obtained as yellow solid (52 mg, 44% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.91 – 7.76 (m, 2H), 7.68 (td, *J* = 7.6, 1.3 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 6.80 (s, 1H), 5.45 (s, 1H), 4.15 – 3.80 (m, 2H), 3.72 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 195.2, 169.6, 167.7, 145.4, 134.3, 129.5, 126.6, 124.3, 53.3, 52.6, 41.8; HRMS (ESI) *m/z*: [M]⁺calcd for C₁₂H₁₁NO₄S 265.0409, found: 265.0409.

3-Oxo-*N*-pentyl-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide (4h): Starting from 3-(*tert*-butylthio)isobenzofuran-1(3*H*)-one **1e** (100 mg, 0.45 mmol), pentylisocyanide **2h** (68 μL, 0.54 mmol), TiCl₄ (1M in CH₂Cl₂, 900 μL, 0.90 mmol) and following the general procedure A, the crude material was purified by flash column chromatography on silica gel using cyclohexane:ethylacetate (8:2) as eluent. The desired 3-oxo-*N*-pentyl-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide **4h** was obtained as pale grey solid (91 mg, 77% yield). Starting from 2-methylpropane-2-thiol (1.0 mmol) and following general procedure B, **4h** was obtained as pale grey solid (207 mg, 79% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.89 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 7.7 Hz, 1H), 7.66 (td, *J* = 7.7, 1.2 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 6.33 (s, 1H), 5.40 (s, 1H), 3.31 – 3.09 (m, 2H), 1.48 – 1.38 (m, 2H), 1.31 – 1.13 (m, 4H), 0.83 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 195.4, 167.0, 146.1, 134.3, 134.0, 129.3 (2C), 126.6, 124.2, 53.8, 40.4, 28.9, 22.3, 14.0; HRMS (ESI) *m/z*: [M]⁺calcd for C₁₄H₁₇NO₂S 263.0980, found: 150.0131 [M-CONHC₅H₁₁]⁺; MS (CI-NH₃) *m/z* 264 (100) [MH]⁺.

3-Oxo-*N*-(2,4,4-trimethylpentan-2-yl)-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide (4i): Starting from 3-(*tert*-butylthio)isobenzofuran-1(3*H*)-one **1e** (100 mg, 0.45 mmol), 2-isocyano-2,4,4-trimethylpentane **2i** (95 μL, 0.54 mmol), TiCl₄ (1M in CH₂Cl₂, 900 μL, 0.90 mmol) and following the general procedure A, the crude material was purified by flash column chromatography on silica gel using cyclohexane:ethyl acetate (9:1) as eluent. The desired 3-oxo-*N*-(2,4,4-trimethylpentan-2-yl)-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide **4i** was obtained as white solid (60.3 mg, 44% yield). Starting from 2-methylpropane-2-thiol (1.0 mmol) and following general procedure B, **4i** was obtained as white solid (137.3 mg, 45% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.94 – 7.88 (m, 1H), 7.80 (d, *J* = 7.7 Hz, 1H), 7.71 – 7.63 (m, 1H), 7.56 – 7.48 (m, 1H), 6.14 (br s, 1H), 5.28 (s, 1H), 1.62 (d, *J* = 1.2 Hz, 2H), 1.35 (s, 3H), 1.33 (s, 3H), 0.83 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 195.3, 165.6, 146.2, 134.2, 134.0, 129.2, 126.4, 124.1, 56.0, 54.7,

51.9, 31.6, 31.4, 28.7; HRMS (ESI) m/z : $[M]^+\bullet$ calcd for $C_{17}H_{23}NO_2S$ 305.1449, found: 150.0184 $[M-CONHCMe_2CH_2^tBu]^+\bullet$; MS (CI-NH₃) m/z 306 (100) $[MH]^+$.

***N*-cyclohexyl-5-methyl-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide (4b')**: Starting from 3-(*tert*-butylthio)-6-methylisobenzofuran-1(3*H*)-one **1f** (100 mg, 0.423 mmol), cyclohexylisocyanide **2b** (63 μ L, 0.507 mmol), TiCl₄ (1M in CH₂Cl₂, 826 μ L, 0.826 mmol) and following the general procedure A, the crude material was purified by flash column chromatography on silica gel using cyclohexane:ethyl acetate (85:15) as eluent. The desired *N*-cyclohexyl-5-methyl-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide **4b'** was obtained as pale yellow solid (90.2 mg, 74% yield). Starting from 2-methylpropane-2-thiol (1.0 mmol) and following general procedure B, **4b'** was obtained as pale yellow solid (185.0 mg, 64% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.72 (d, J = 8.0 Hz, 1H), 7.55 (s, 1H), 7.45 (d, J = 8.0 Hz, 1H), 6.19 (d, J = 7.1 Hz, 1H), 5.31 (s, 1H), 3.75 – 3.60 (m, 1H), 2.42 (s, 3H), 1.90 – 1.77 (m, 1H), 1.77 – 1.49 (m, 4H), 1.38 – 0.81 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 195.6, 166.4, 143.6, 139.6, 135.4, 134.3, 126.0, 124.1, 53.6, 49.2, 32.7, 32.6, 25.4, 24.8, 24.7, 21.1; HRMS (ESI) m/z : $[M]^+\bullet$ calcd for $C_{16}H_{19}NO_2S$ 289.1136, found: 164.0295 $[M-CONHCy]^+\bullet$; MS (CI-NH₃) m/z 290 (100) $[MH]^+$.

***N*-cyclohexyl-5-methoxy-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide (4b'')**: Starting from 3-(*tert*-butylthio)-6-methoxyisobenzofuran-1(3*H*)-one **1g** (100 mg, 0.396 mmol), cyclohexylisocyanide **2b** (59 μ L, 0.476 mmol), TiCl₄ (1M in CH₂Cl₂, 792 μ L, 0.729 mmol) and following the general procedure, the crude material was purified by flash column chromatography on silica gel using cyclohexane:ethyl acetate (85:15) as eluent. The desired *N*-cyclohexyl-5-methoxy-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide **4b''** was obtained as pale grey solid (97 mg, 80% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.74 (d, J = 9.5 Hz, 1H), 7.27 – 7.15 (m, 2H), 6.09 (d, J = 7.1 Hz, 1H), 5.29 (s, 1H), 3.86 (s, 3H), 3.76 – 3.61 (m, 1H), 1.95 – 1.82 (m, 1H), 1.78 – 1.51 (m, 4H), 1.44 – 0.81 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 195.4, 166.4, 160.9, 138.7, 135.7, 127.0, 122.8, 106.1, 55.9, 53.3, 49.2, 32.8, 32.7, 25.5, 24.8 (2C); HRMS (ESI) m/z : $[M]^+\bullet$ calcd for $C_{16}H_{19}NO_3S$ 305.1086, found: 180.0246 $[M-CONHCy]^+\bullet$; MS (CI-NH₃) m/z 306 (100) $[MH]^+$.

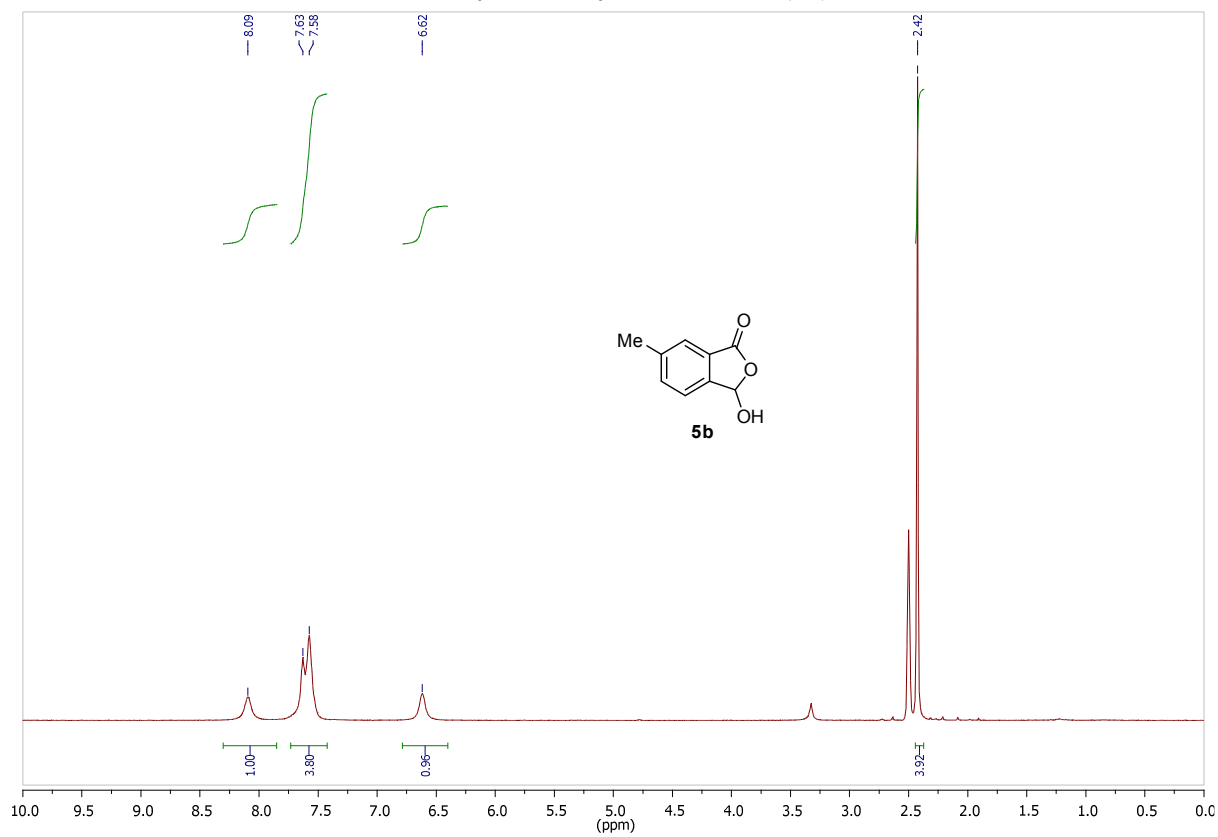
***N*-(3,4-dimethoxyphenethyl)-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide (4j)**: Starting from 2-carboxybenzaldehyde **5a** (165 mg, 1.10 mmol), 2-methylpropane-2-thiol (113 μ L, 1.00 mmol), 4-(2-isocyanoethyl)-1,2-dimethoxybenzene **2j** (287 mg, 1.50 mmol), TiCl₄ (1M in CH₂Cl₂, 2.20 mL, 2.20 mmol) and following the general procedure B, the crude material was purified by flash column chromatography on silica gel using cyclohexane:ethyl acetate (1:1) as eluent. The desired *N*-(3,4-dimethoxyphenethyl)-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide **4j** was obtained as white solid (206 mg, 58% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.80 – 7.71 (m, 2H), 7.65 – 7.59 (m, 1H), 7.50 (t, J = 7.4 Hz, 1H), 6.72 – 6.64 (m, 1H), 6.60 – 6.45 (m, 2H), 6.40 (s, 1H), 5.34 (s, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.49 – 3.39 (m, 2H), 2.67 (t, J = 6.8 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 195.0, 166.9, 149.0, 147.8, 145.8, 134.2, 133.9, 130.5, 129.2, 126.4, 124.0, 120.6, 111.6, 111.3, 55.9, 55.8, 53.7, 41.3, 34.9; HRMS (ESI) m/z : $[M]^+\bullet$ calcd for $C_{19}H_{19}NO_4S$ 357.1035, found: 357.1049.

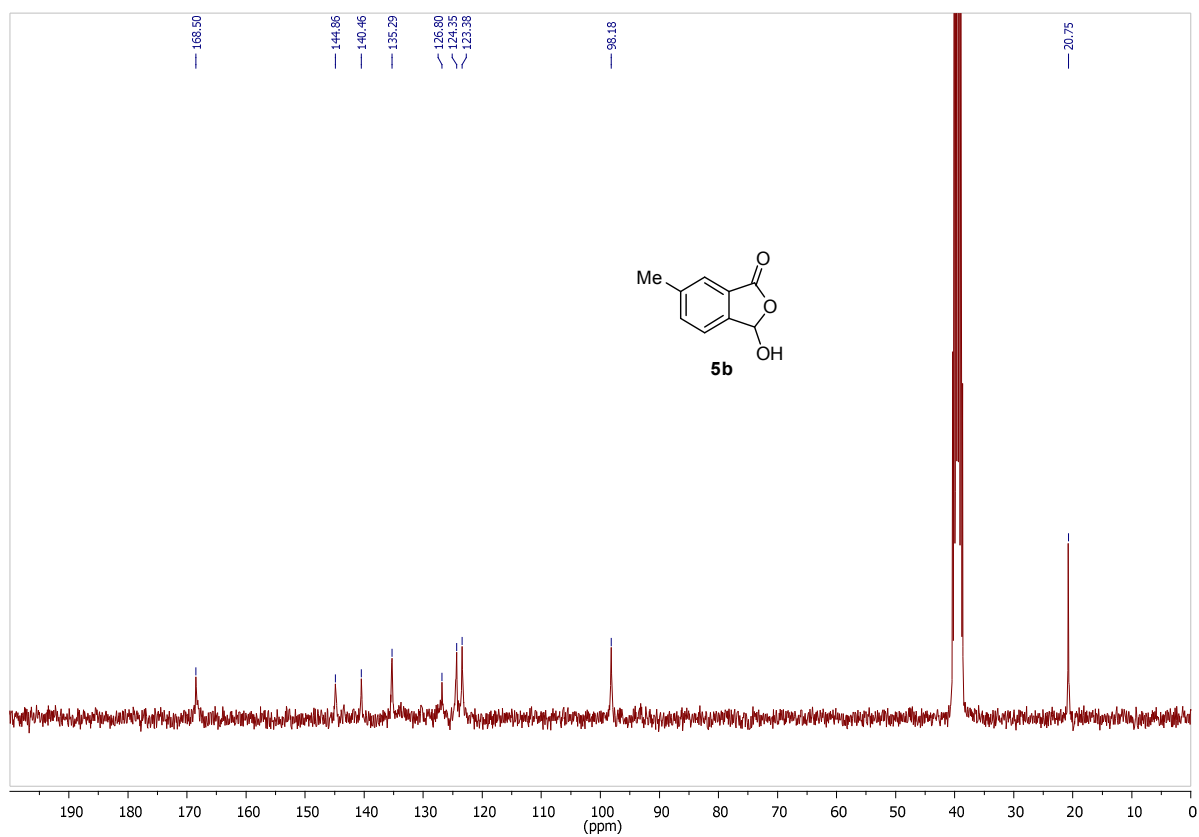
***N*-tert-butyl-5-methoxy-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide (4a'')**: Starting from 2-formyl-5-methoxybenzoic acid **5c** (100 mg, 0.55 mmol), 2-methylpropane-2-thiol (56 μ L, 0.50 mmol), *tert*-butylisocyanide **2a** (85 μ L, 0.75 mmol), TiCl₄ (1M in CH₂Cl₂, 1.10 mL, 1.10 mmol) in 10 mL dichloromethane and following the general procedure B, the crude material was purified by flash column chromatography on silica gel using cyclohexane:ethyl acetate (85:15) as eluent. The desired *N*-tert-butyl-5-methoxy-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide **4a''** was obtained as white solid (101 mg, 72% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.72 (d, *J* = 8.3 Hz, 1H), 7.27 – 7.17 (m, 2H), 6.03 (br s, 1H), 5.20 (s, 1H), 3.85 (s, 3H), 1.27 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 195.4, 166.4, 160.8, 138.8, 135.7, 126.8, 122.8, 106.0, 55.9, 53.9, 52.0, 28.5; HRMS (ESI) *m/z*: [M]⁺•calcd for C₁₄H₁₇NO₃S 279.0929, found: 180.0246 [M-CONH^tBu]⁺•; MS (CI-NH₃) *m/z* 280 (100) [MH]⁺.

***N*-cyclohexyl-1-(4-methoxybenzyl)-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide (6)**: Starting from 3-(4-methoxybenzyl)benzo[*c*]thiophen-1(3*H*)-one **1d** (100 mg, 0.35 mmol), cyclohexylisocyanide **2b** (52 μ L, 0.42 mmol), TiCl₄ (1M in CH₂Cl₂, 700 μ L, 0.70 mmol) and following the general procedure A, the crude material was purified by flash column chromatography on silica gel using cyclohexane:ethyl acetate (9:1) as eluent. The desired *N*-cyclohexyl-1-(4-methoxybenzyl)-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide **6** was obtained as colorless sticky solid (33.2 mg, 24% yield). ¹H NMR (300 MHz, CDCl₃) δ 8.08 (d, *J* = 7.8 Hz, 1H), 7.77 – 7.60 (m, 2H), 7.50 (t, *J* = 7.3 Hz, 1H), 7.14 (d, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 8.6 Hz, 2H), 6.47 (d, *J* = 7.8 Hz, 1H), 4.17 (d, *J* = 13.5 Hz, 1H), 3.77 (s, 3H), 3.75 – 3.57 (m, 1H), 3.08 (d, *J* = 13.5 Hz, 1H), 1.90 – 1.72 (m, 1H), 1.69 – 1.47 (m, 4H), 1.39 – 0.85 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 194.6, 168.0, 159.0, 150.7, 134.2, 134.0, 131.5, 129.3, 128.7, 126.3, 123.9, 113.6, 69.7, 55.3, 49.6, 45.4, 32.6, 32.4, 25.5, 24.7; HRMS (ESI) *m/z*: [M]⁺•calcd for C₂₃H₂₅NO₃S 395.1555, found: 149.9808 [M-(CONHCy + CH₂-4-OMePh)]⁺•; MS (CI-NH₃) *m/z* 396 (100) [MH]⁺.

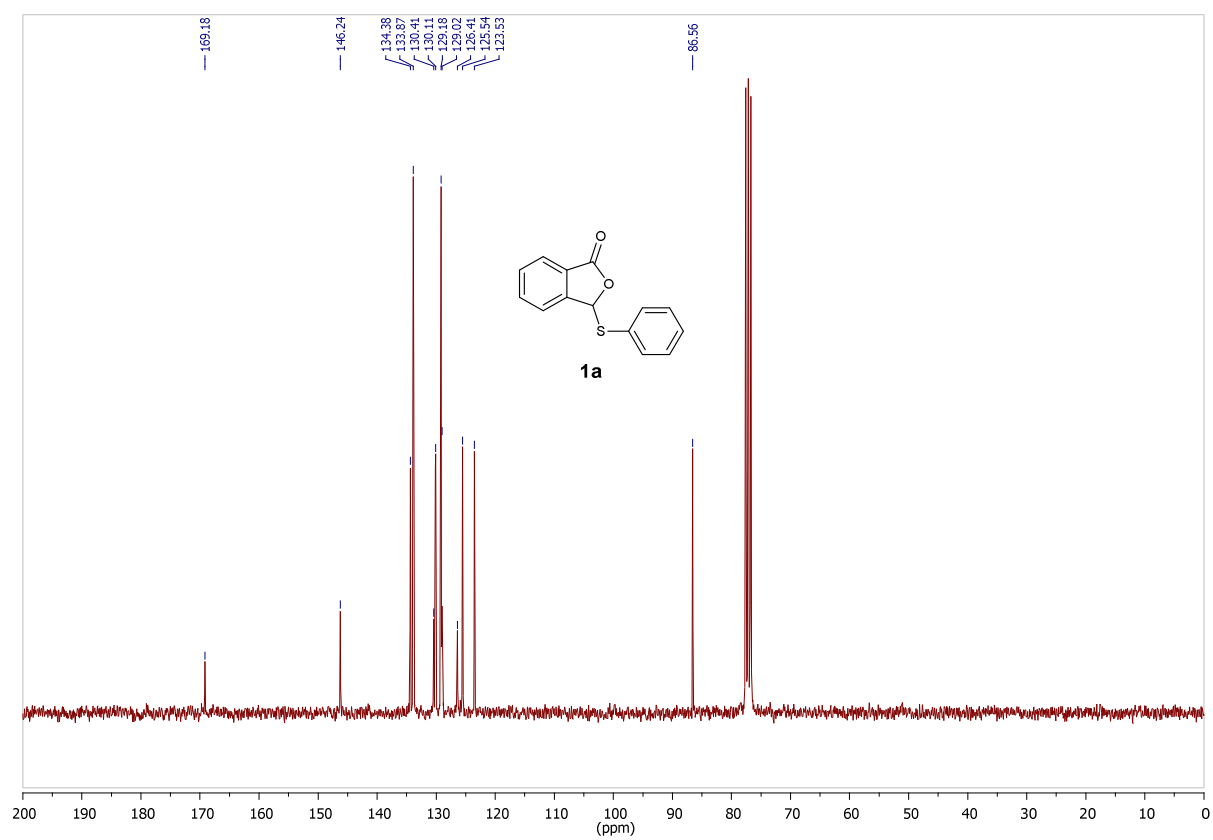
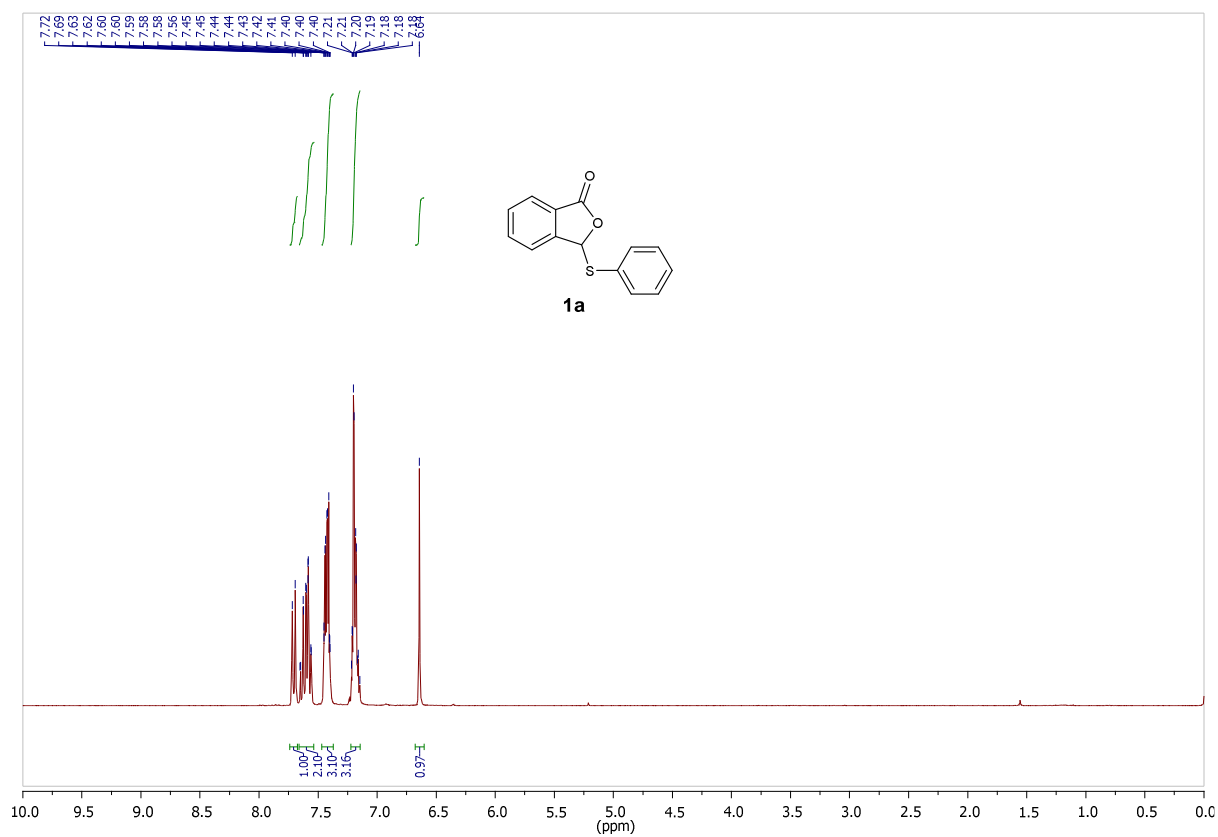
VI. Copies of ¹H & ¹³C NMR spectra

2-Formyl-5-methylbenzoic acid (5b):

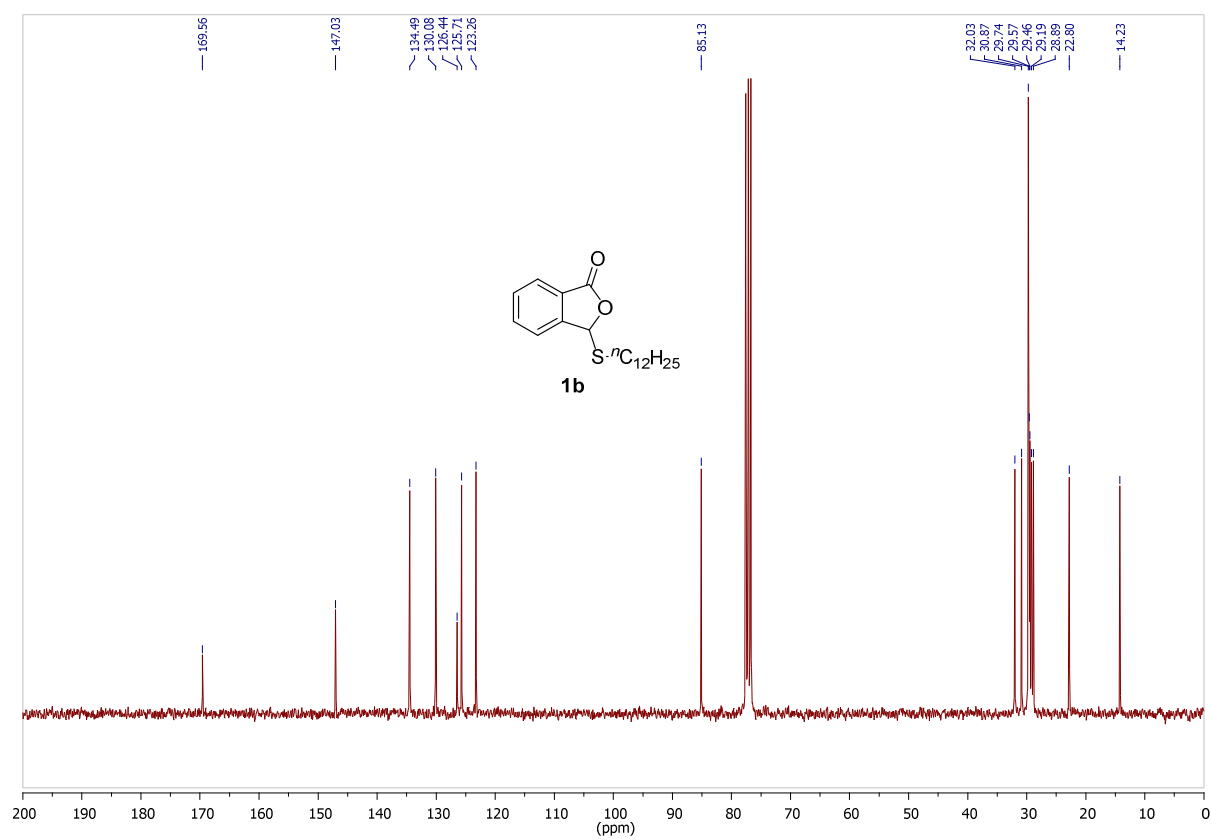
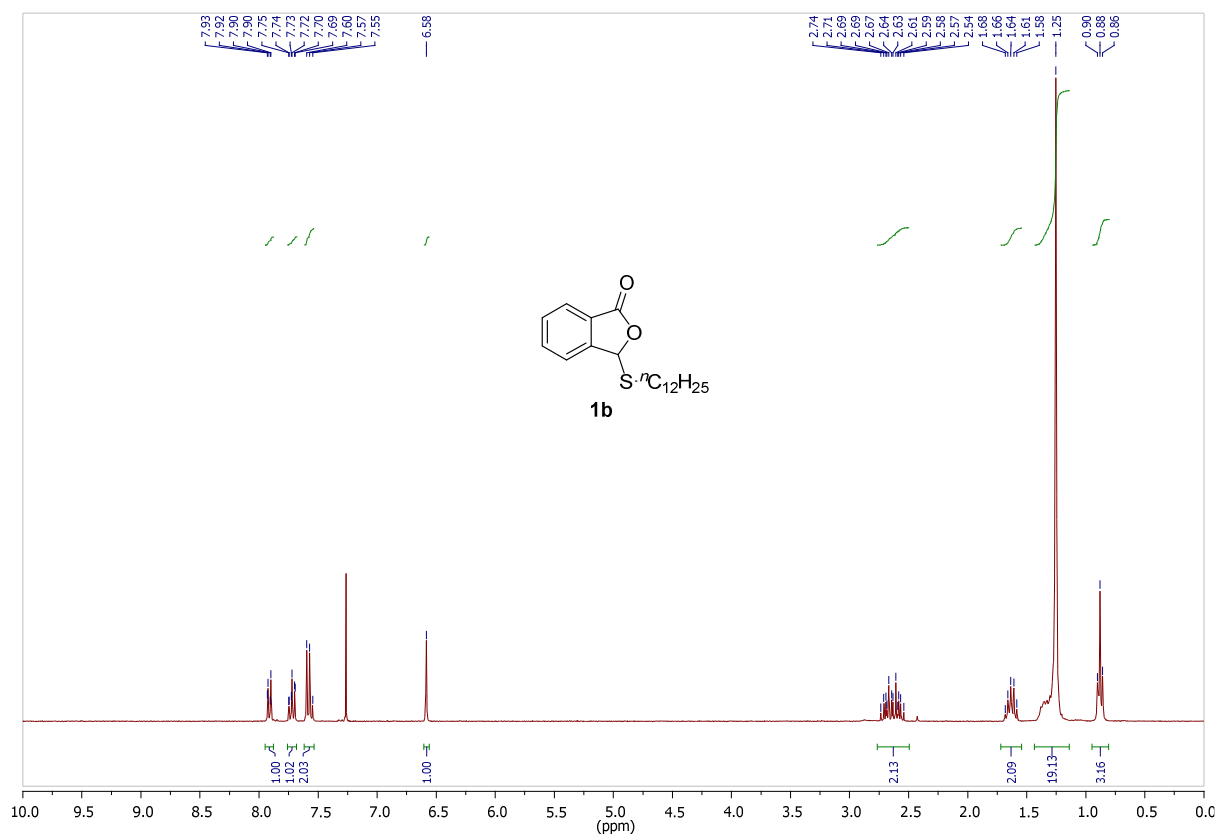




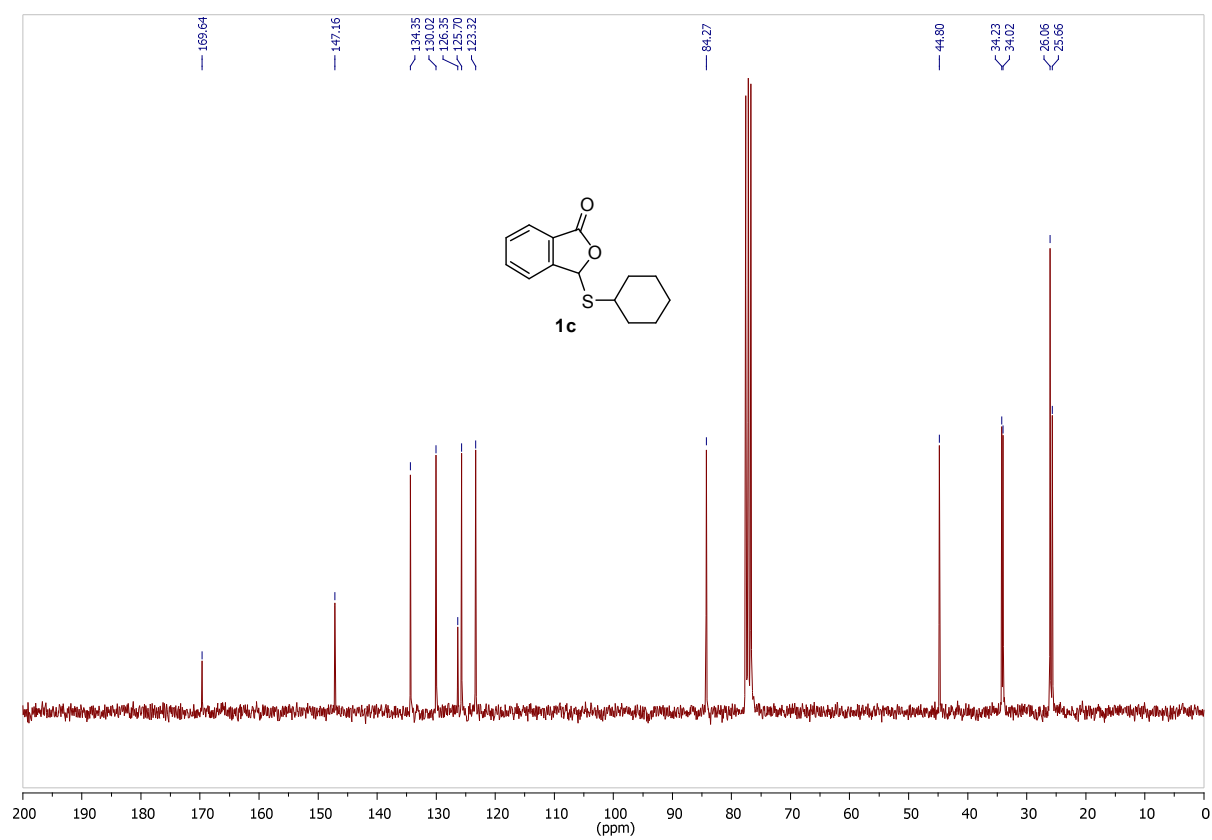
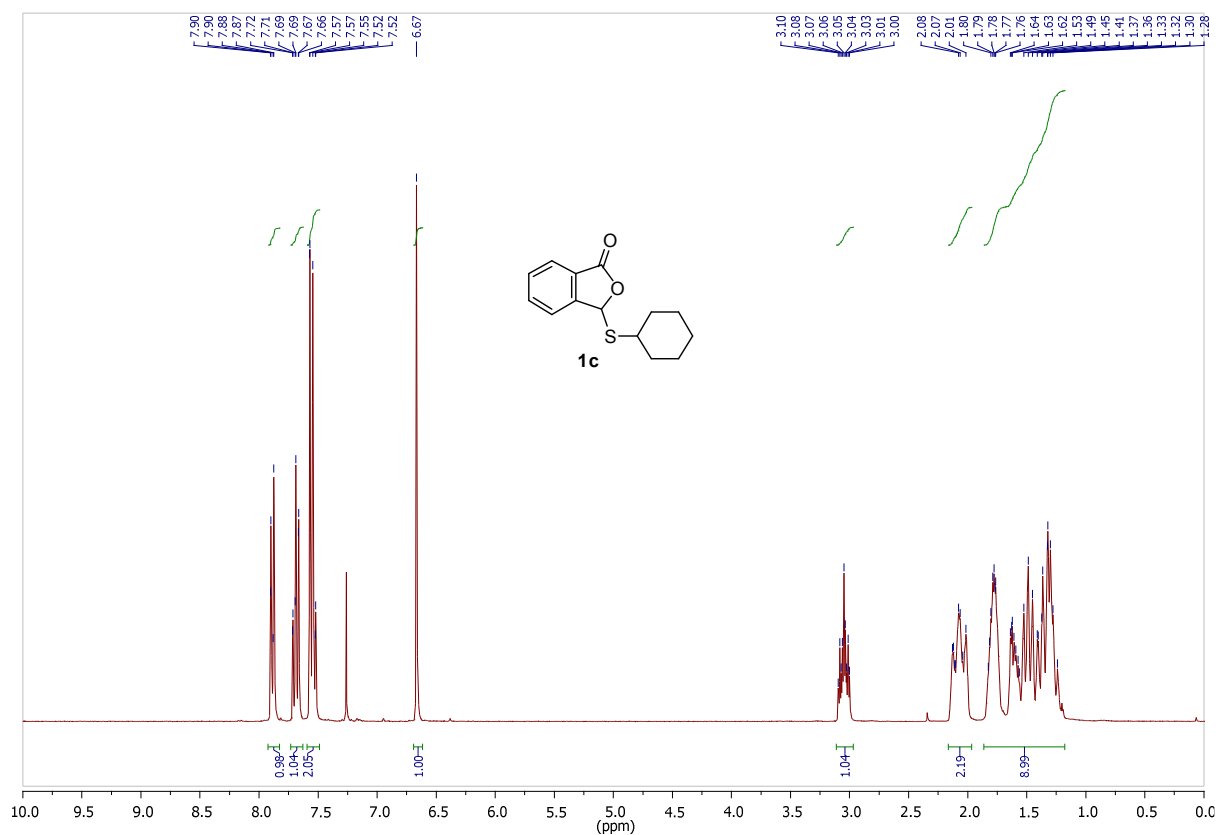
3-(Phenylthio)isobenzofuran-1(3*H*)-one(1a):



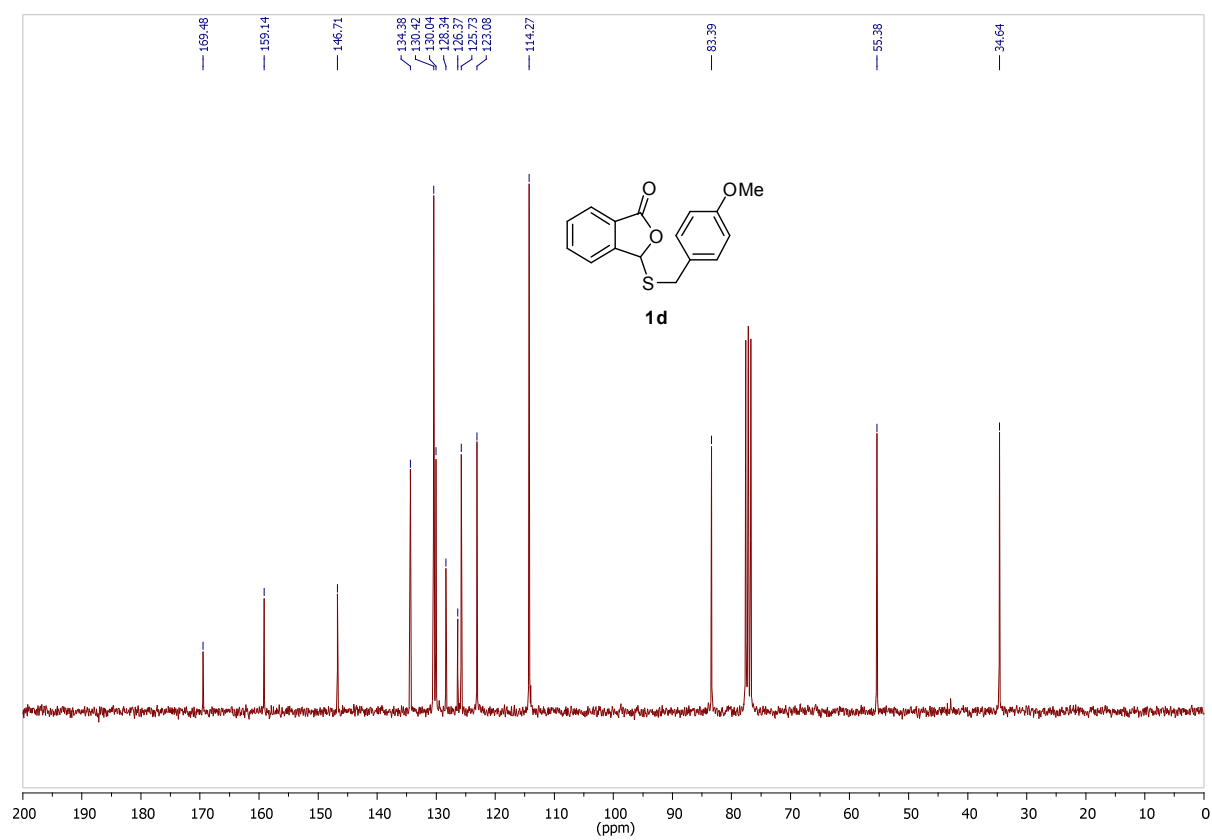
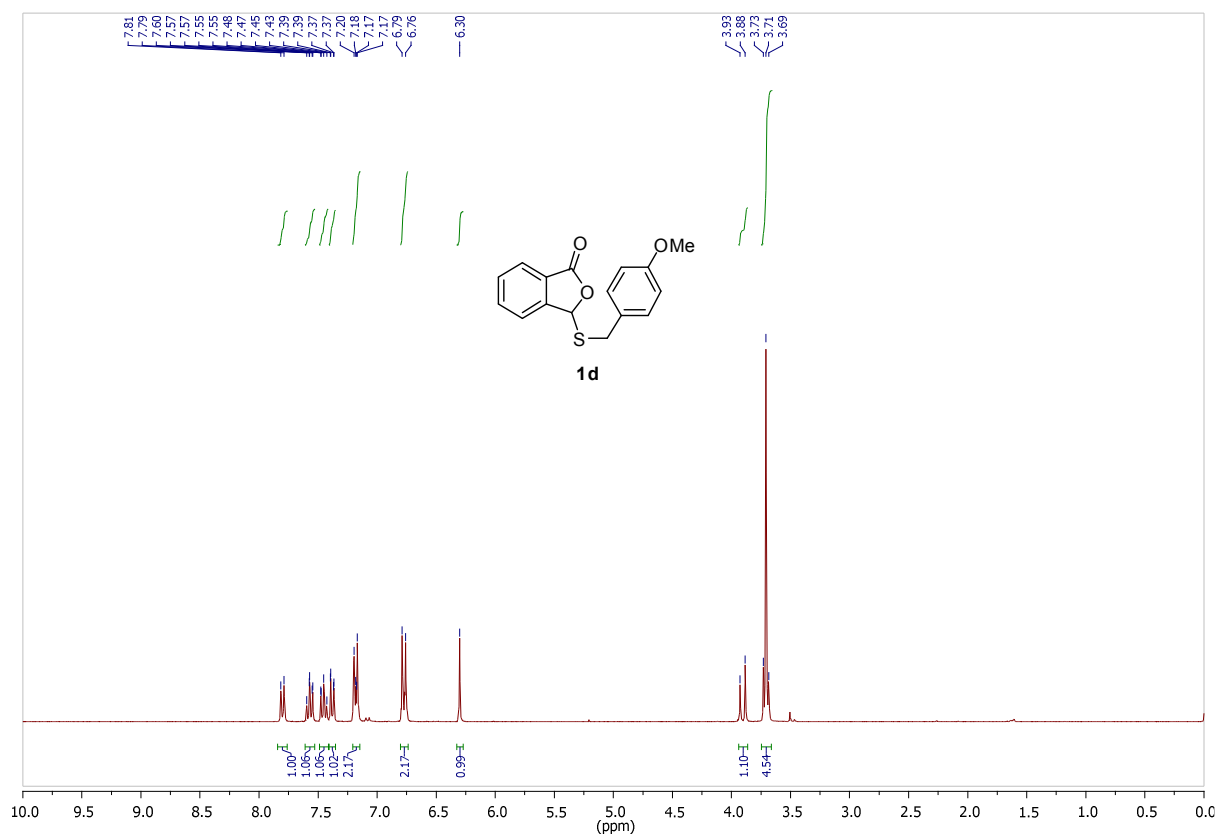
3-(Dodecylthio)isobenzofuran-1(3*H*)-one(1b):



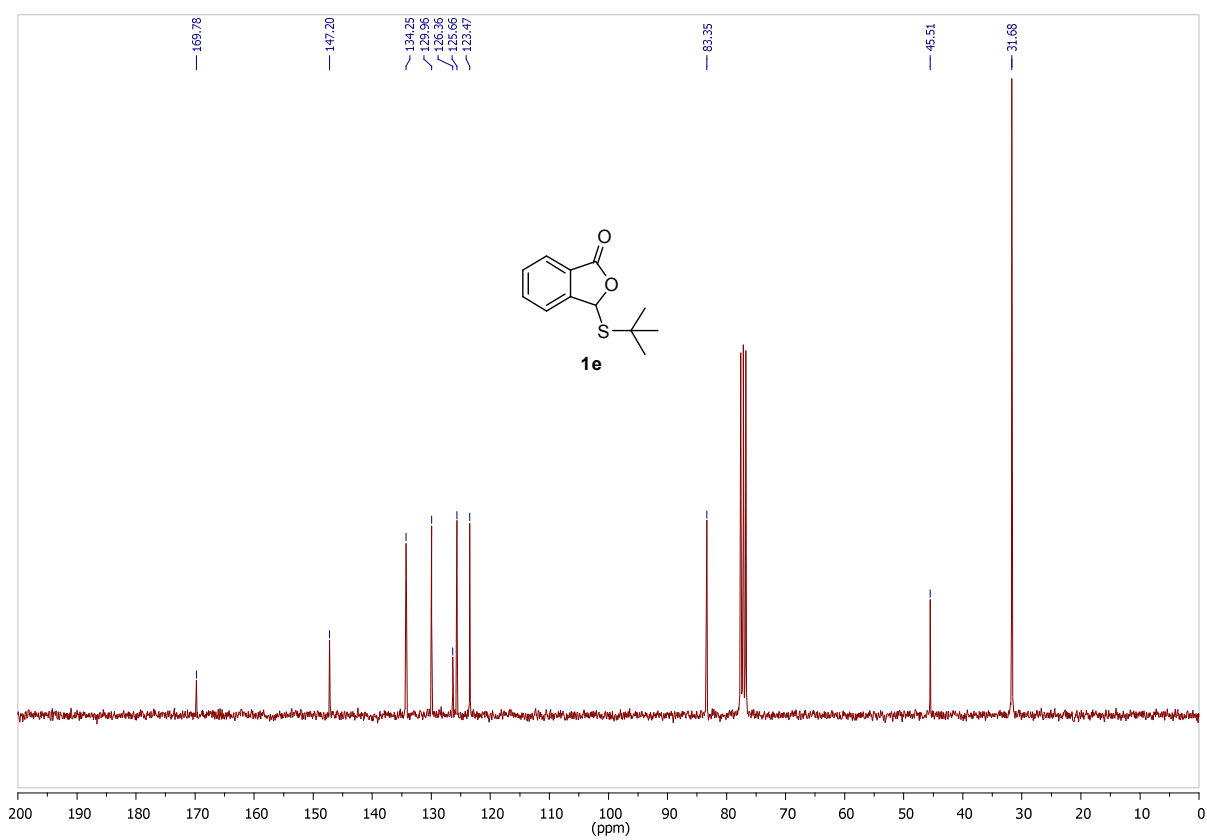
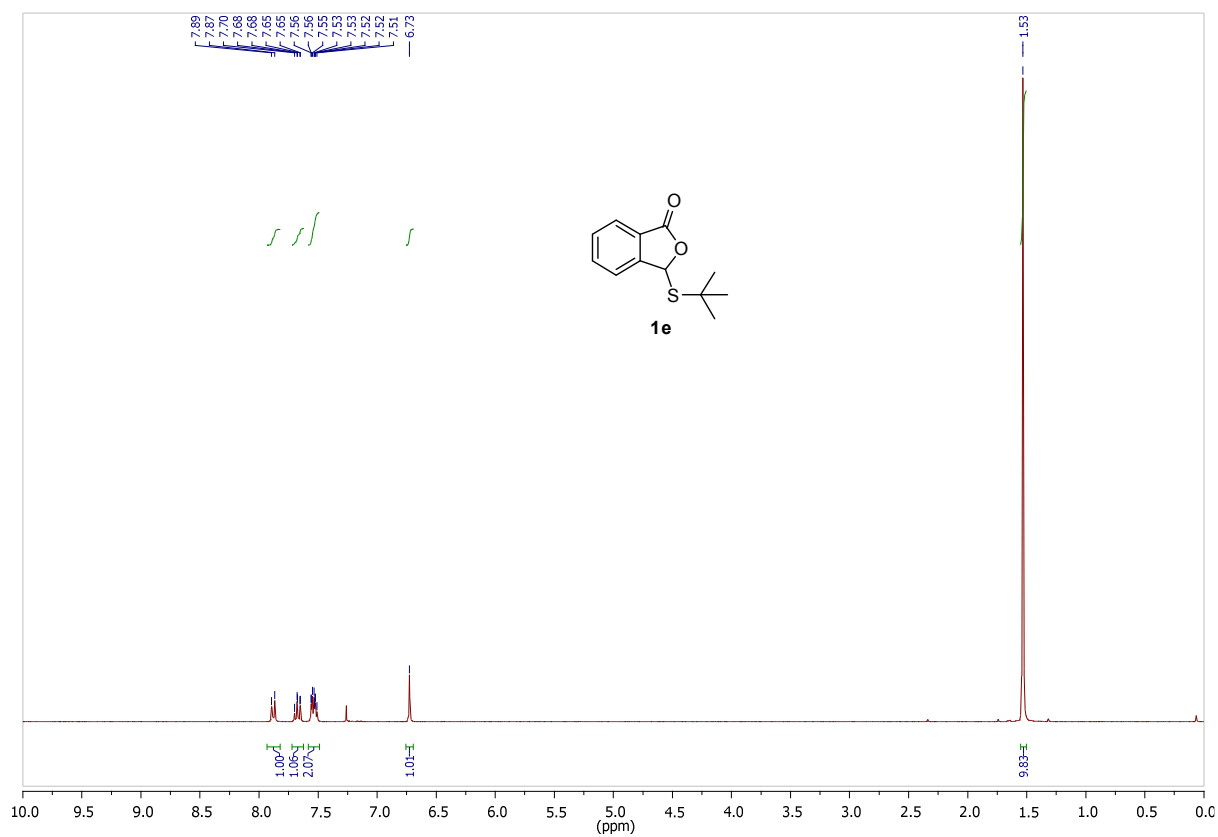
3-(Cyclohexylthio)isobenzofuran-1(3*H*)-one(1c):



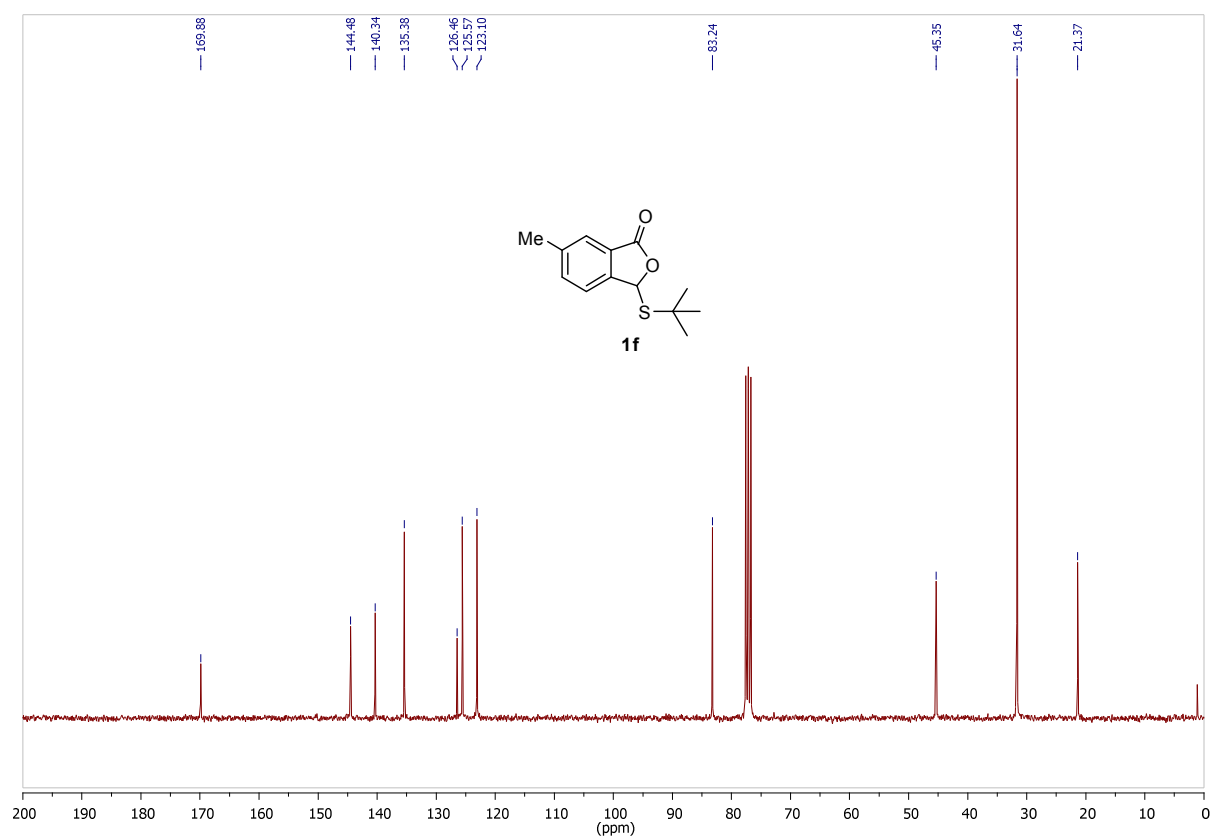
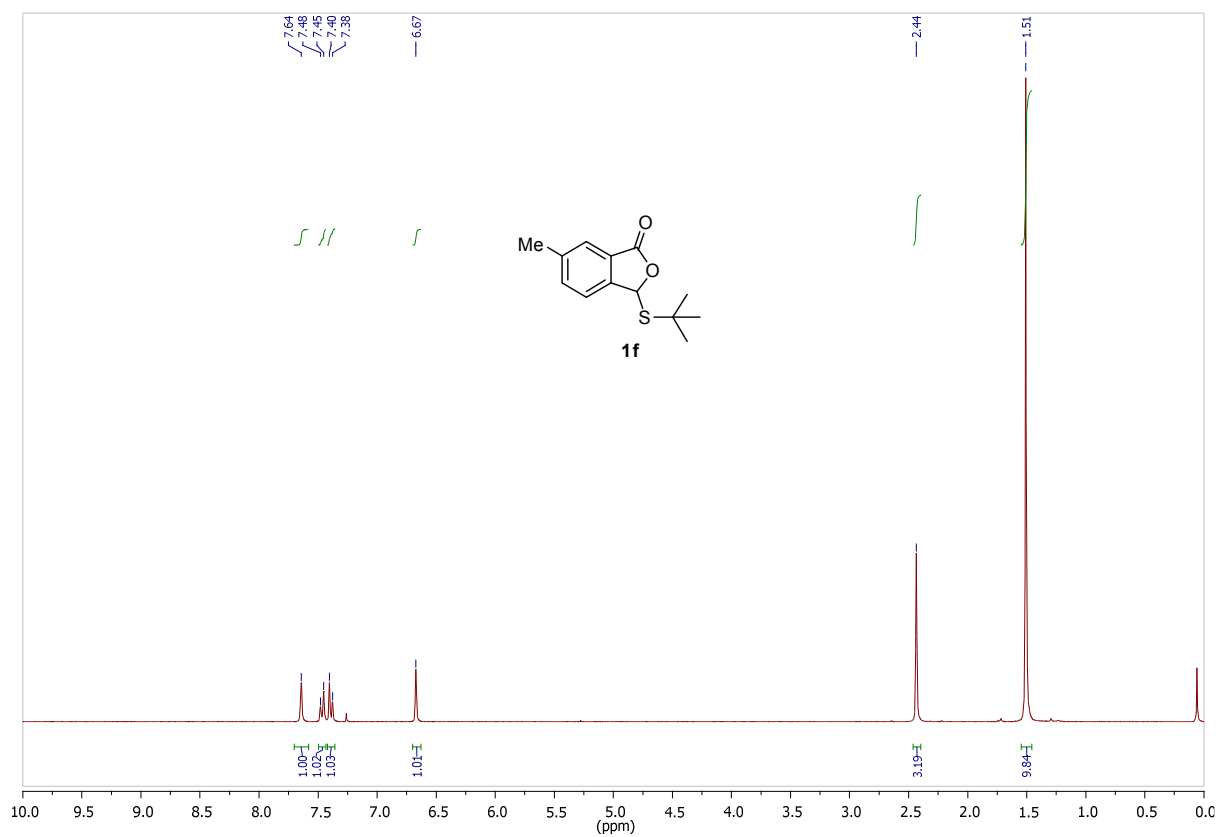
3-(4-Methoxybenzylthio)isobenzofuran-1(3*H*)-one(1d):



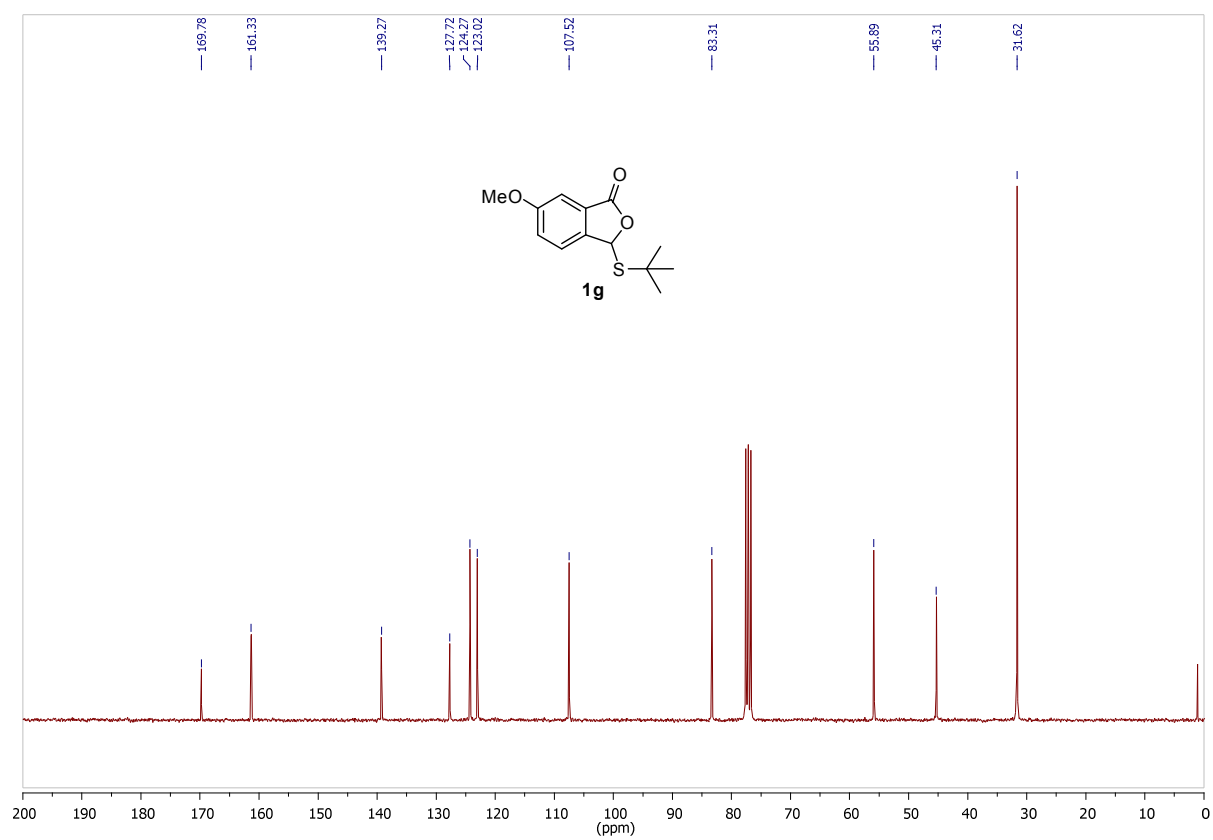
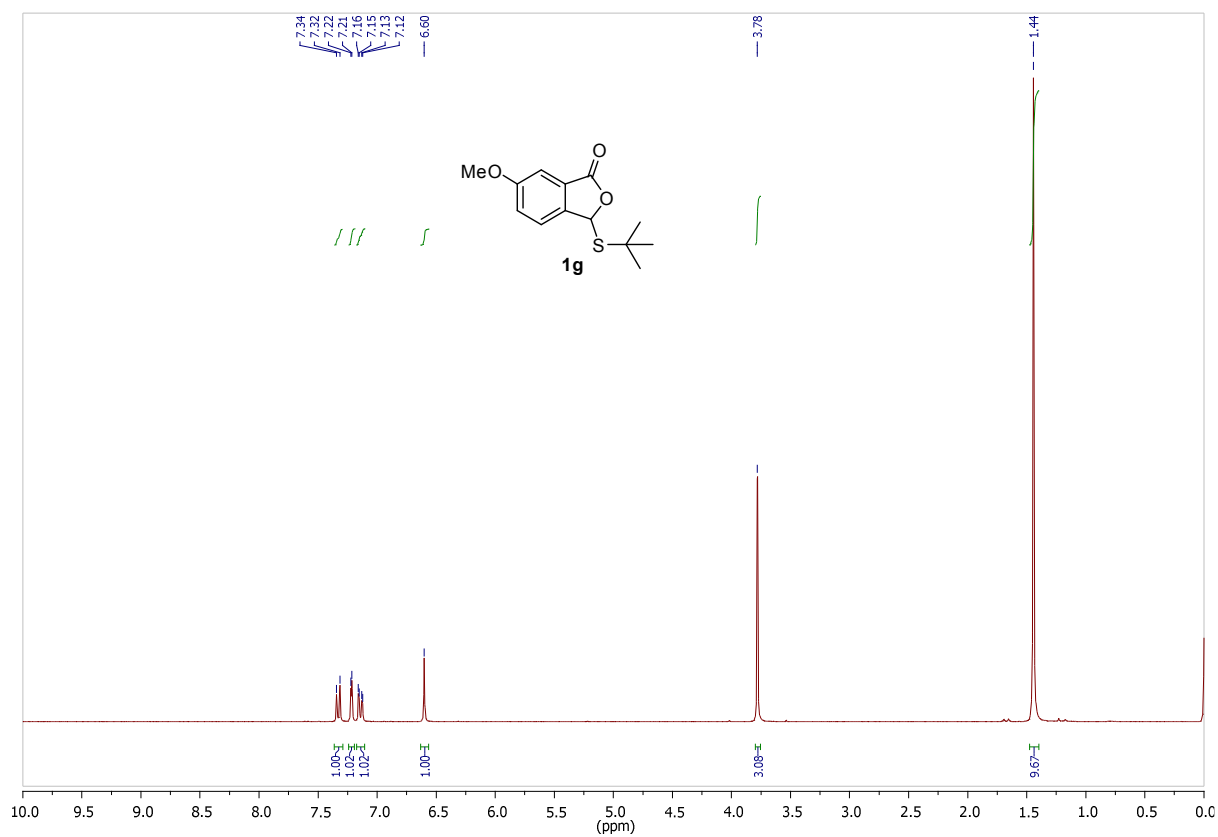
3-(*tert*-Butylthio)isobenzofuran-1(3*H*)-one(1e):



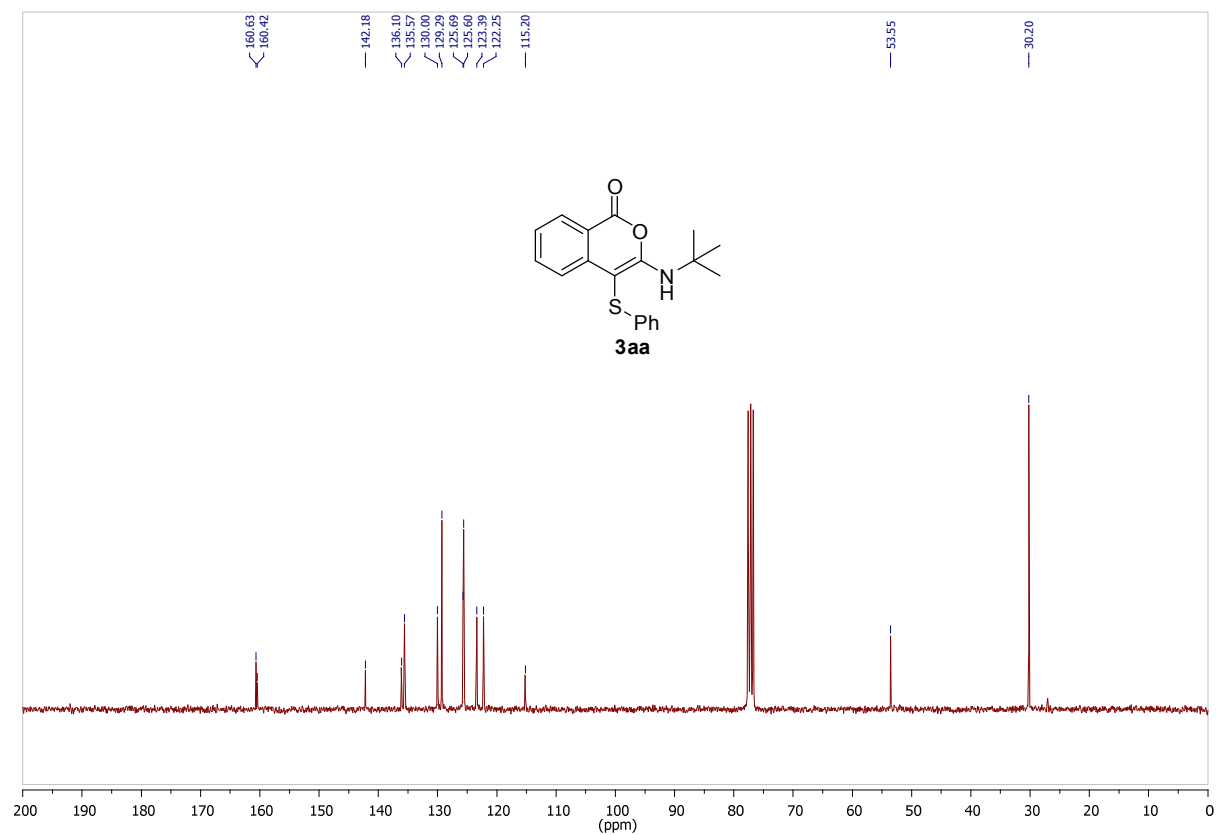
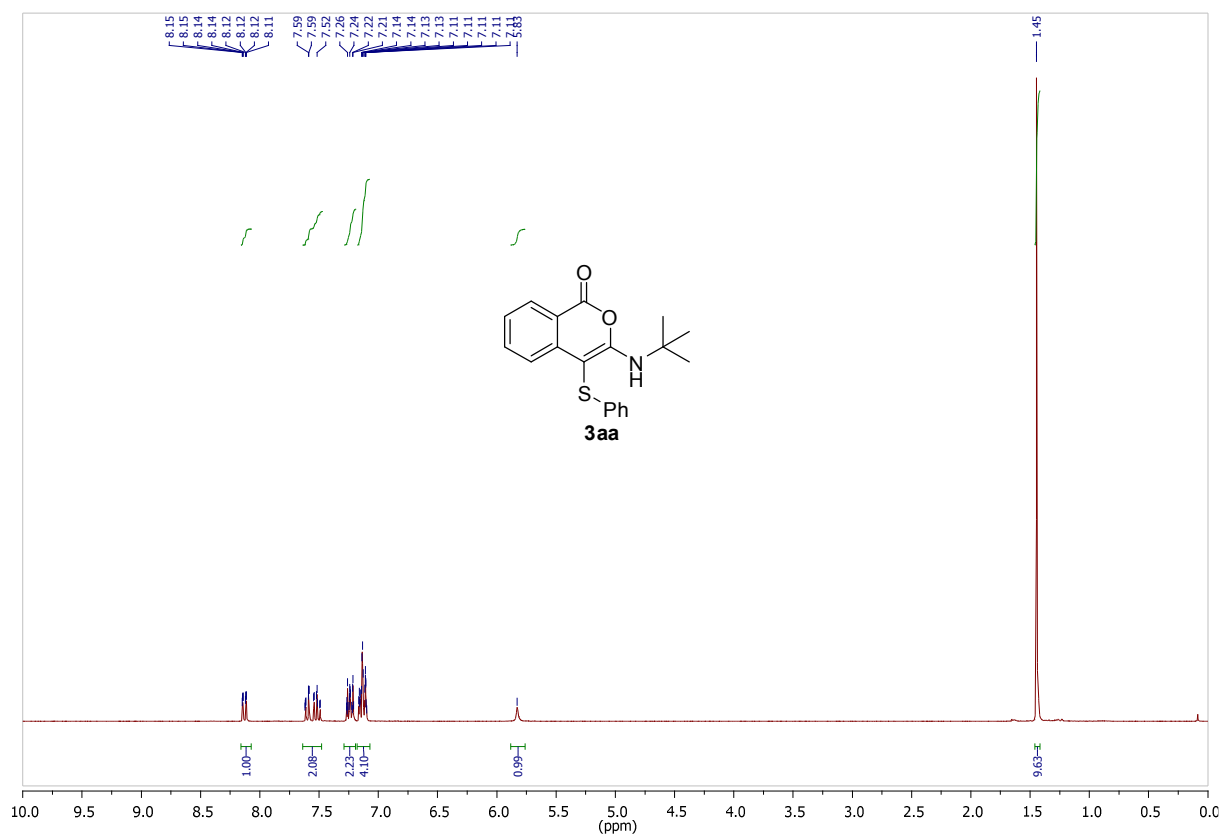
3-(*tert*-Butylthio)-6-methylisobenzofuran-1(3*H*)-one(1f):



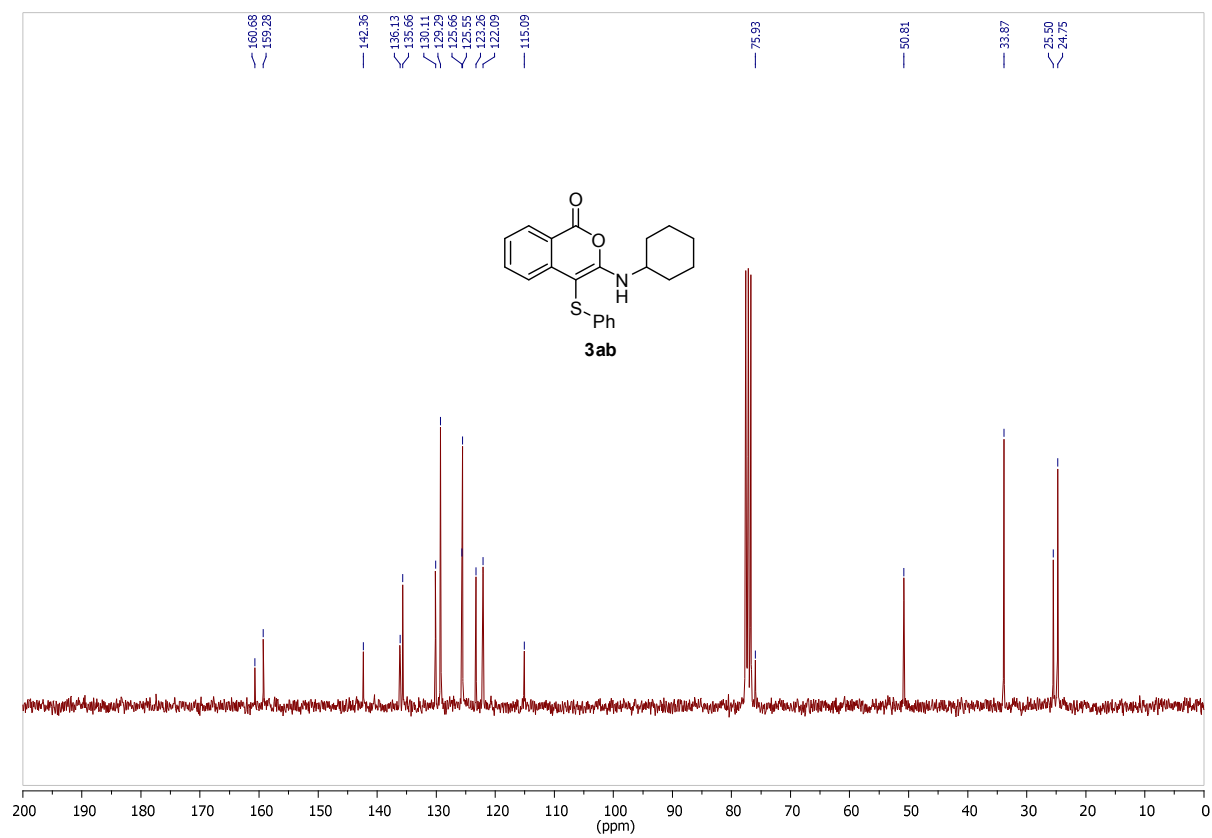
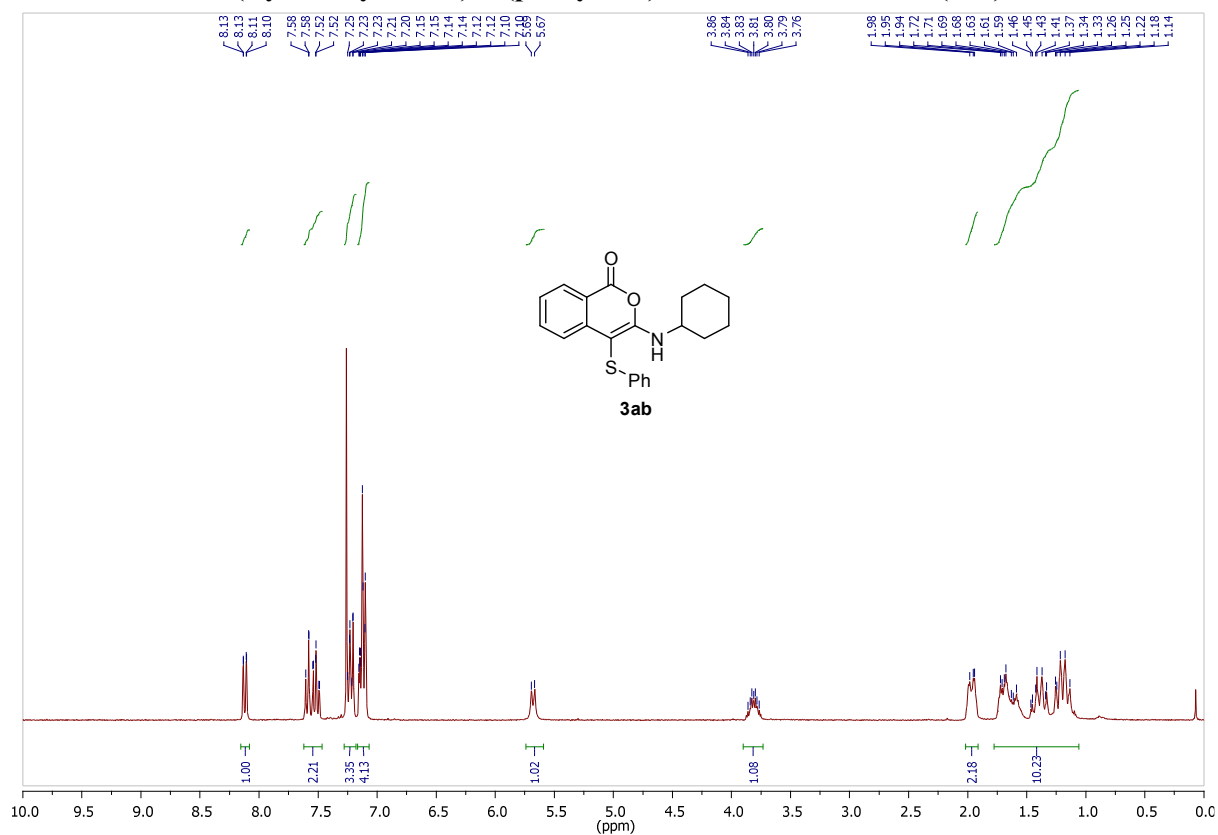
3-(*tert*-Butylthio)-6-methoxyisobenzofuran-1(3*H*)-one(1g**):**



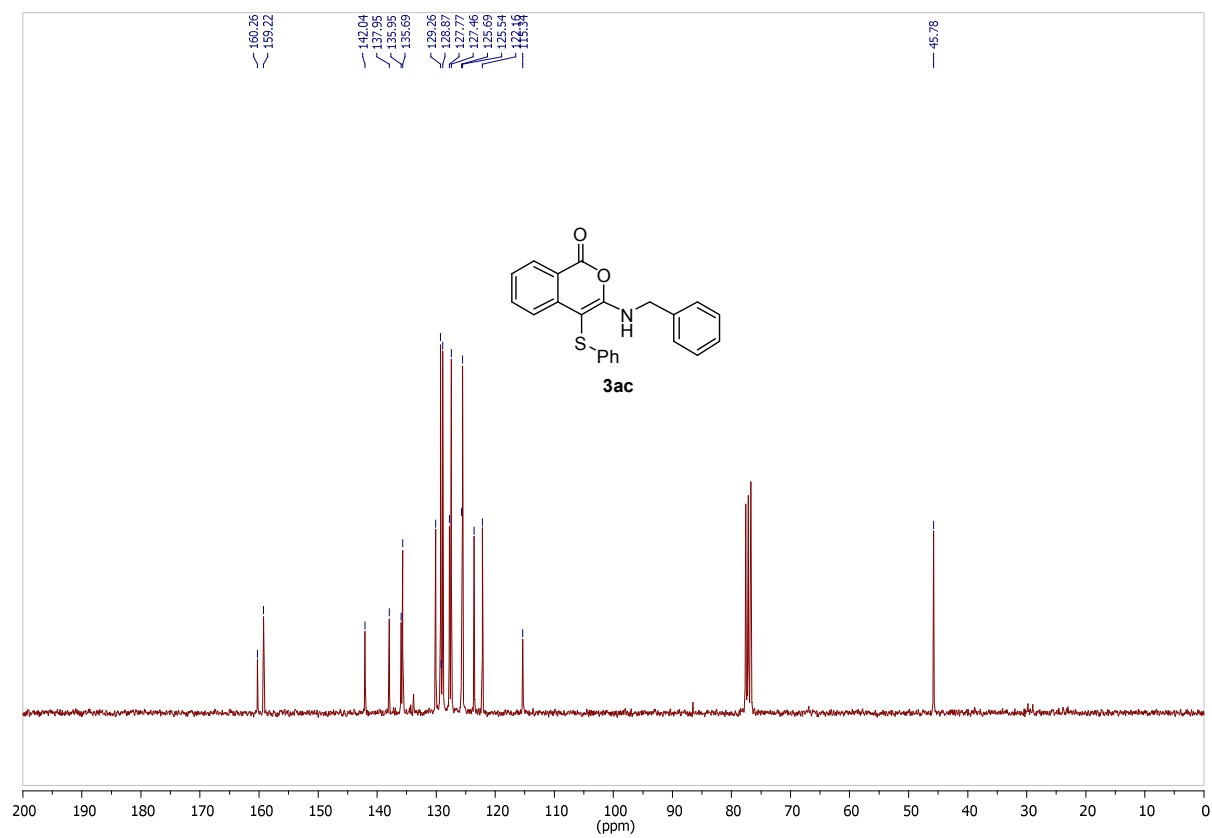
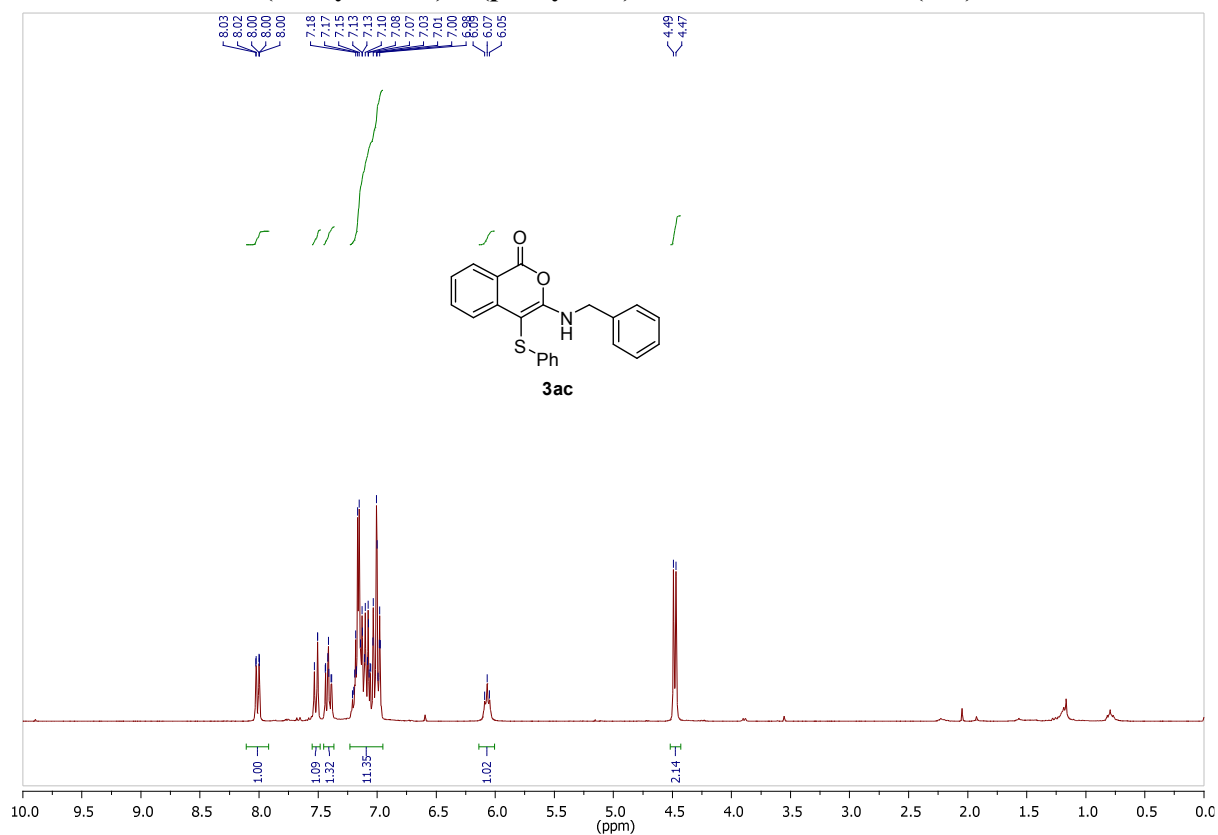
3-(*tert*-Butylamino)-4-(phenylthio)-1*H*-isochromen-1-one (3aa):



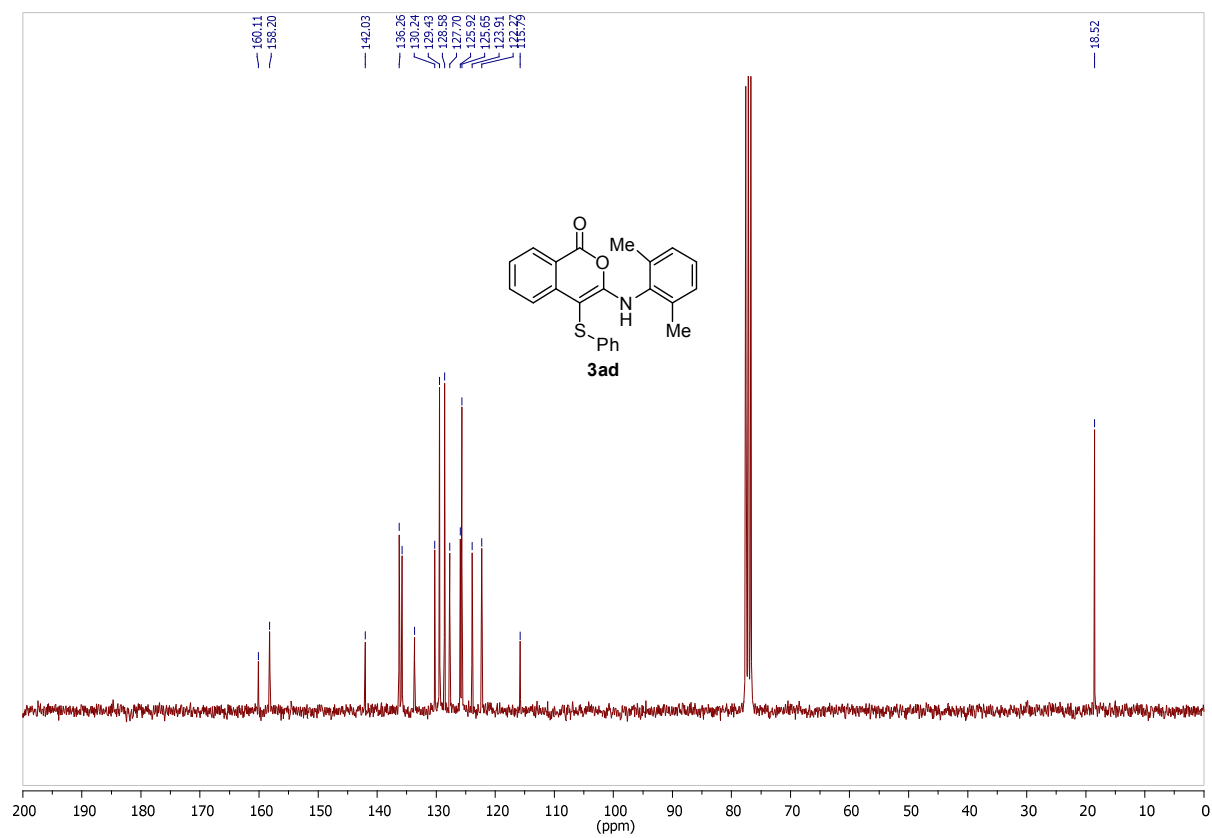
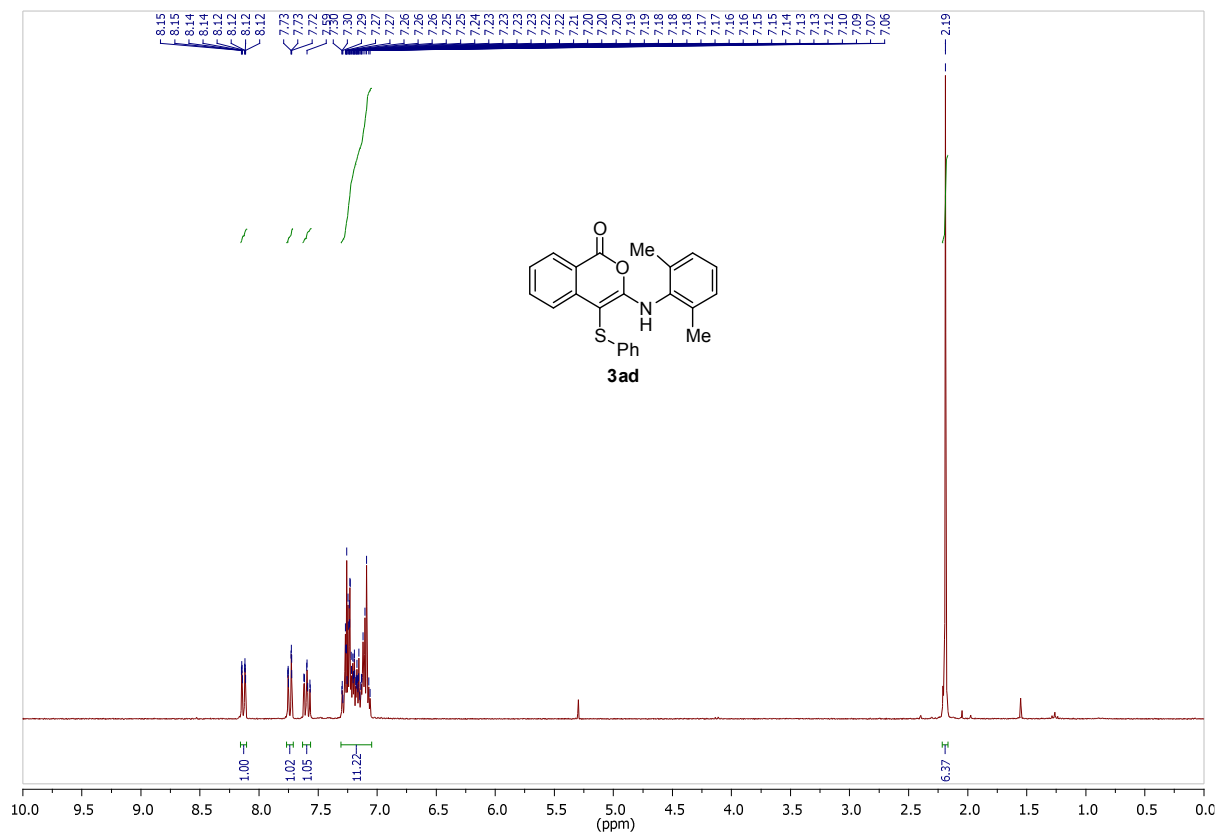
3-(Cyclohexylamino)-4-(phenylthio)-1H-isochromen-1-one(3ab):



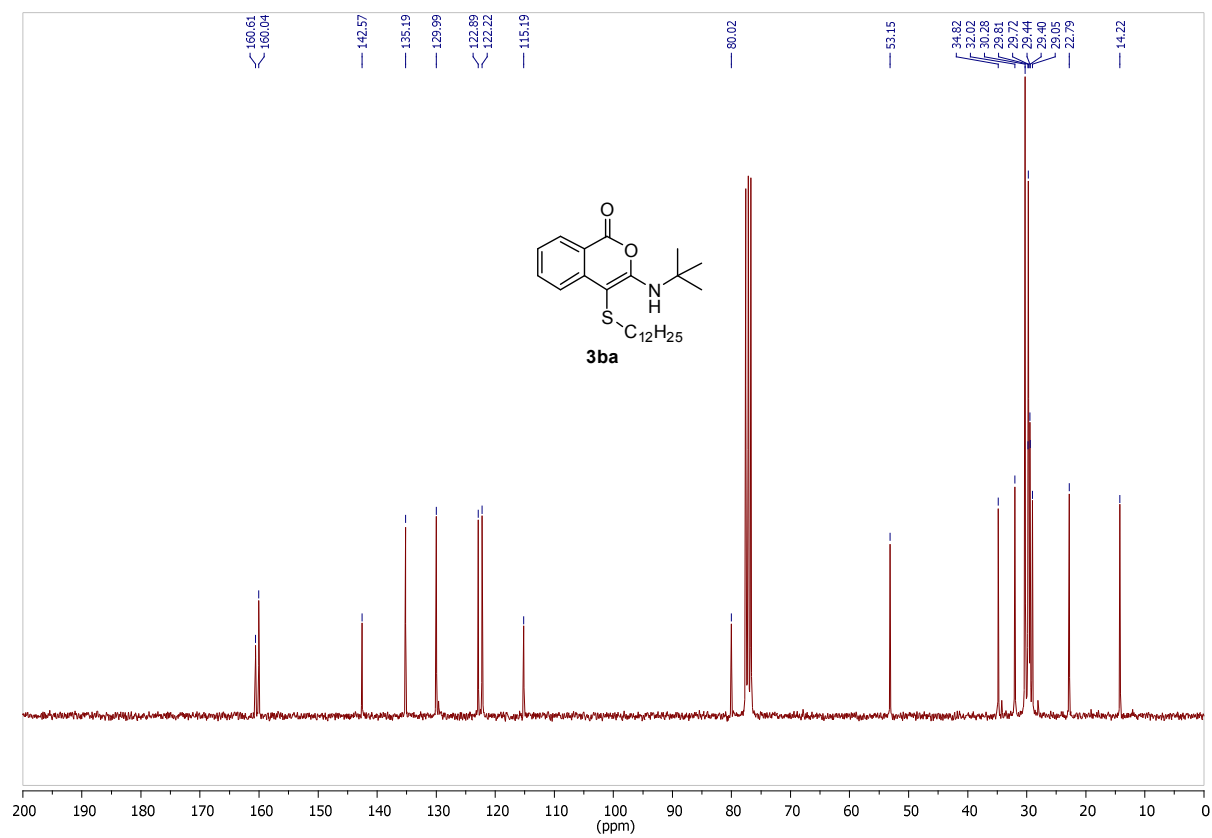
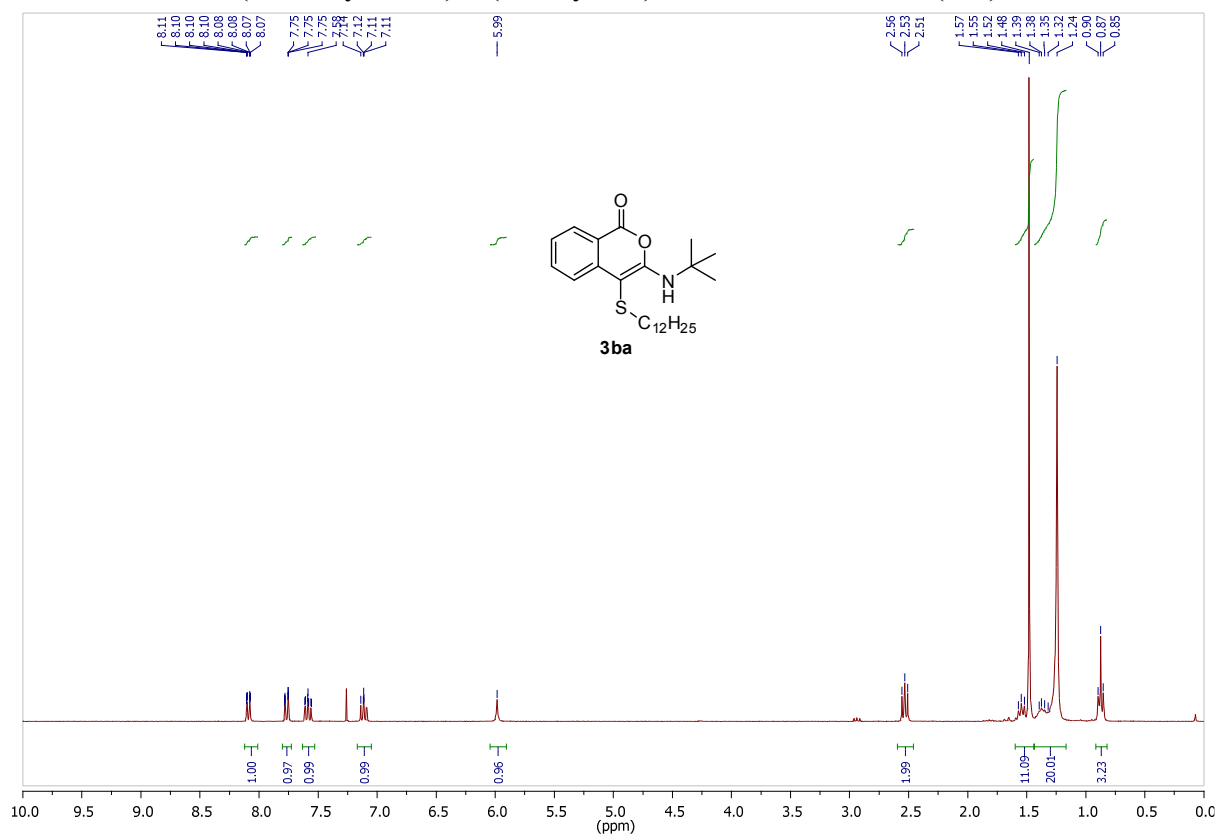
3-(Benzylamino)-4-(phenylthio)-1*H*-isochromen-1-one(3ac):



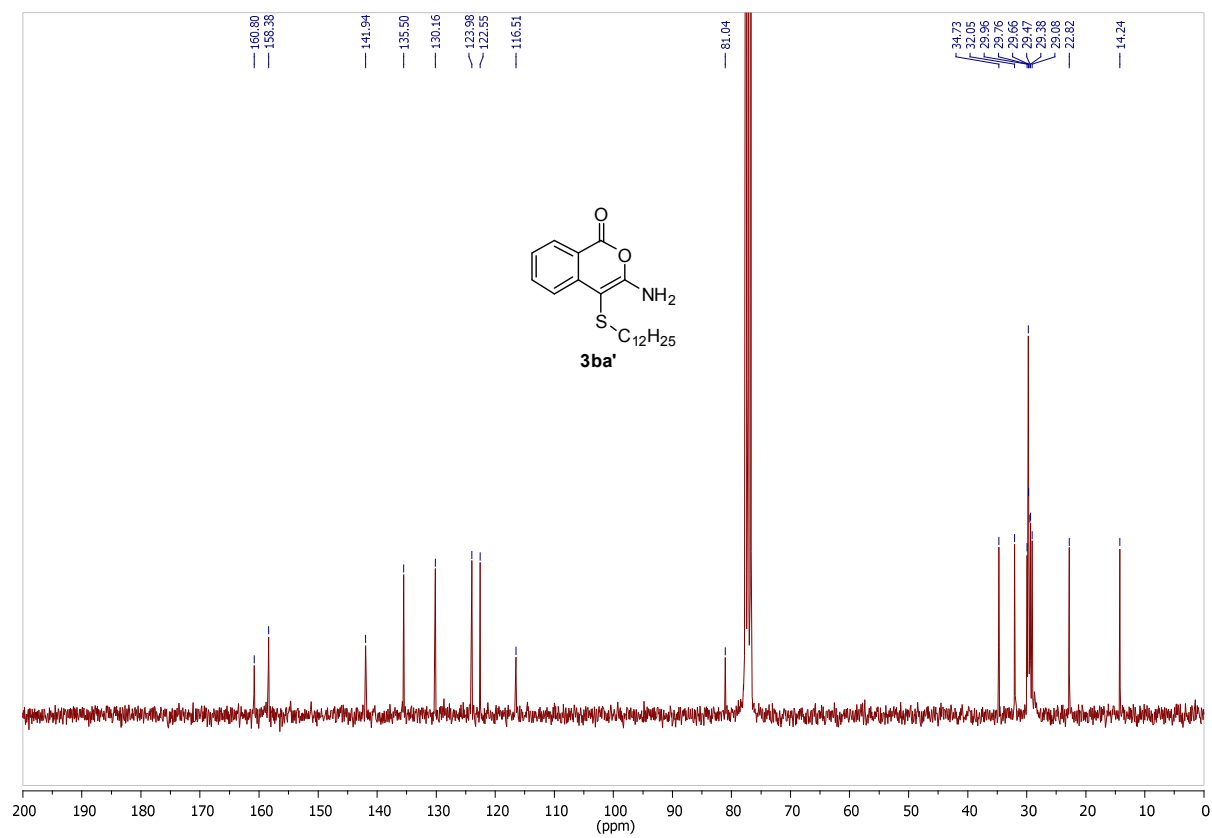
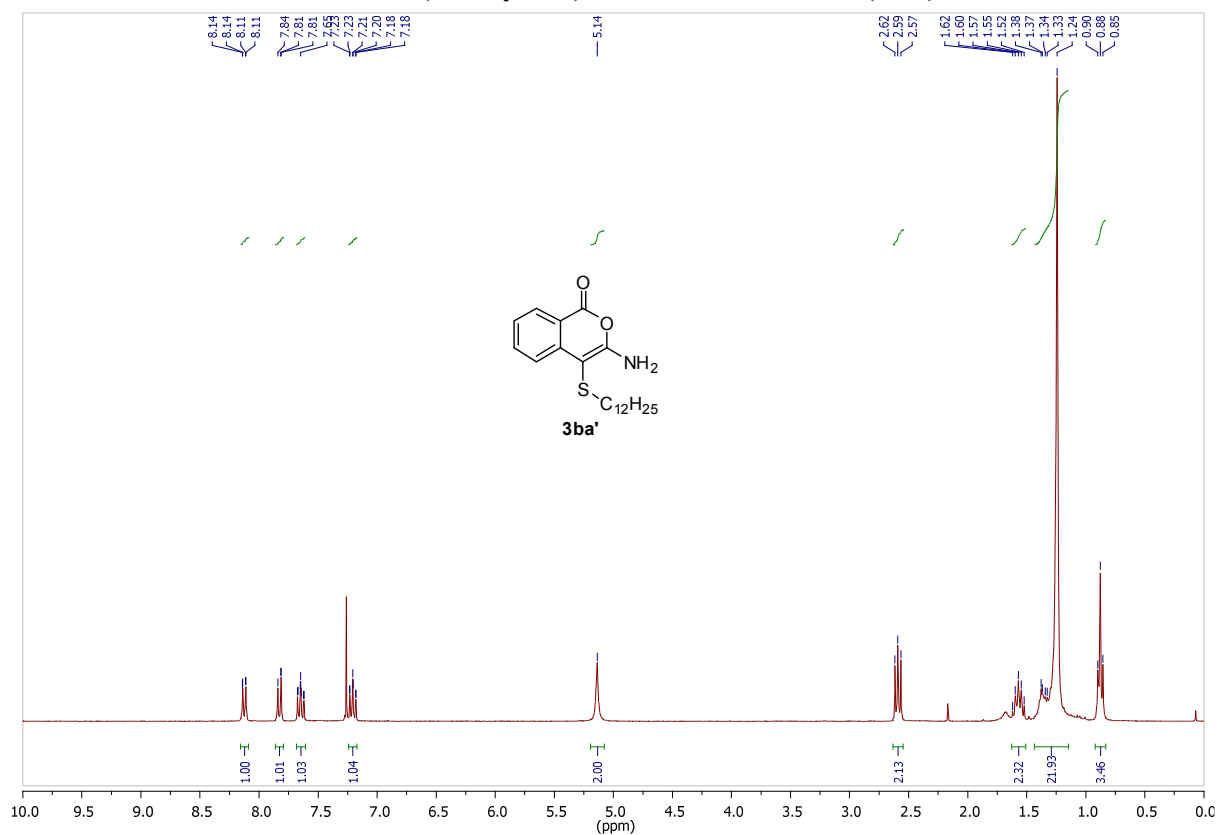
3-(2,6-Dimethylphenylamino)-4-(phenylthio)-1*H*-isochromen-1-one(3ad):



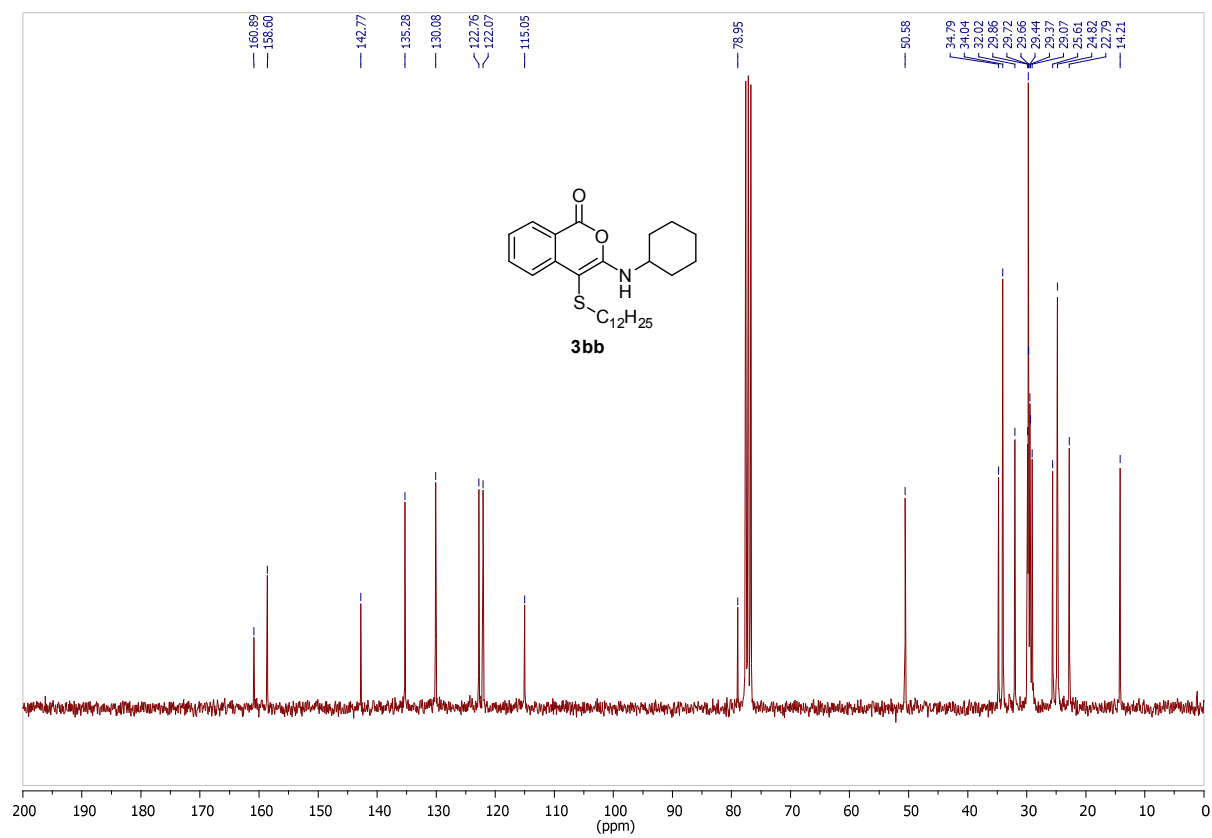
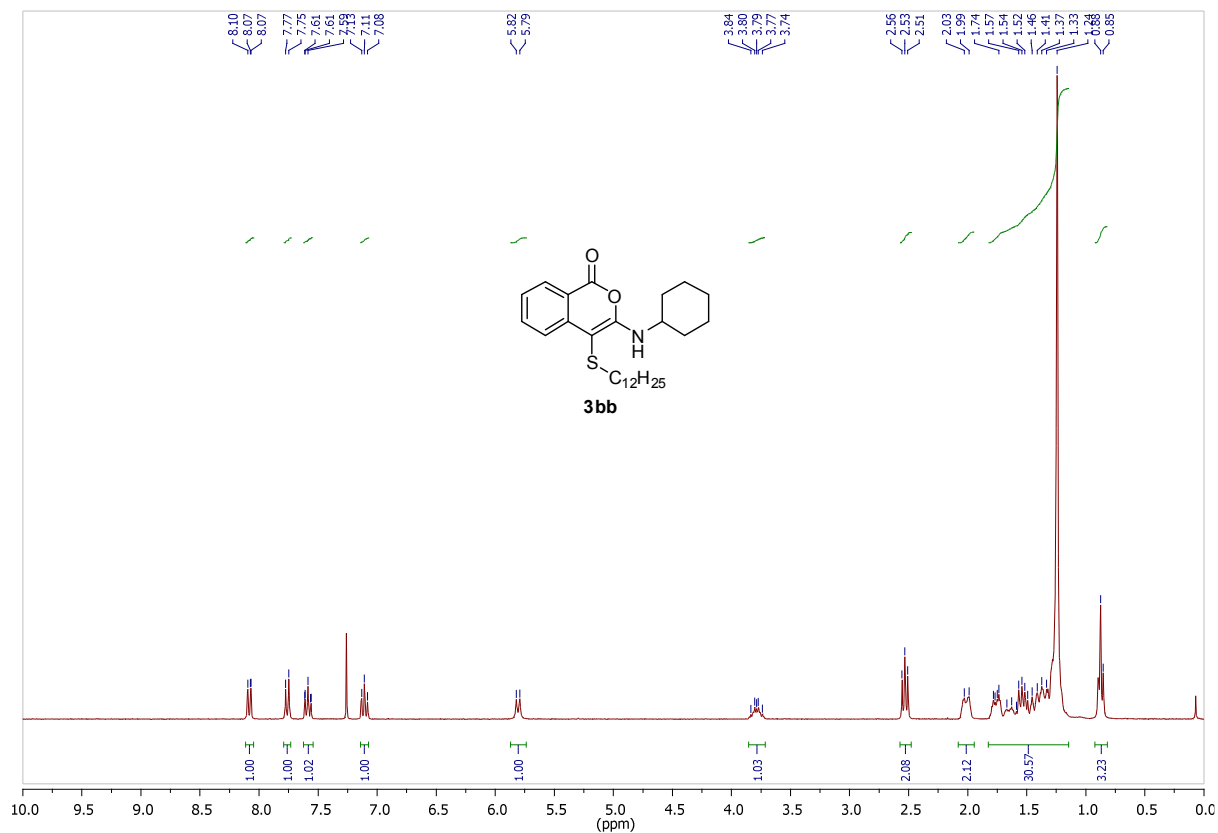
3-(*tert*-Butylamino)-4-(dodecylthio)-1*H*-isochromen-1-one(3ba):



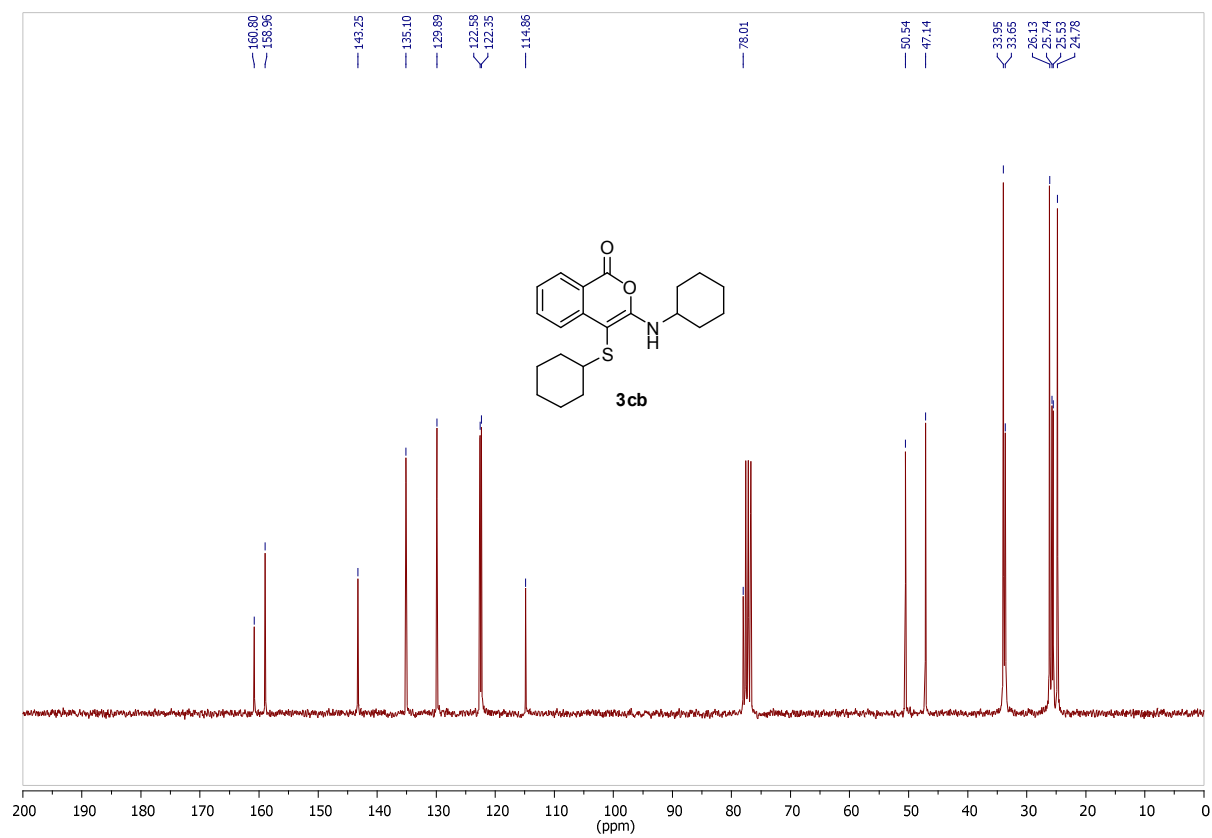
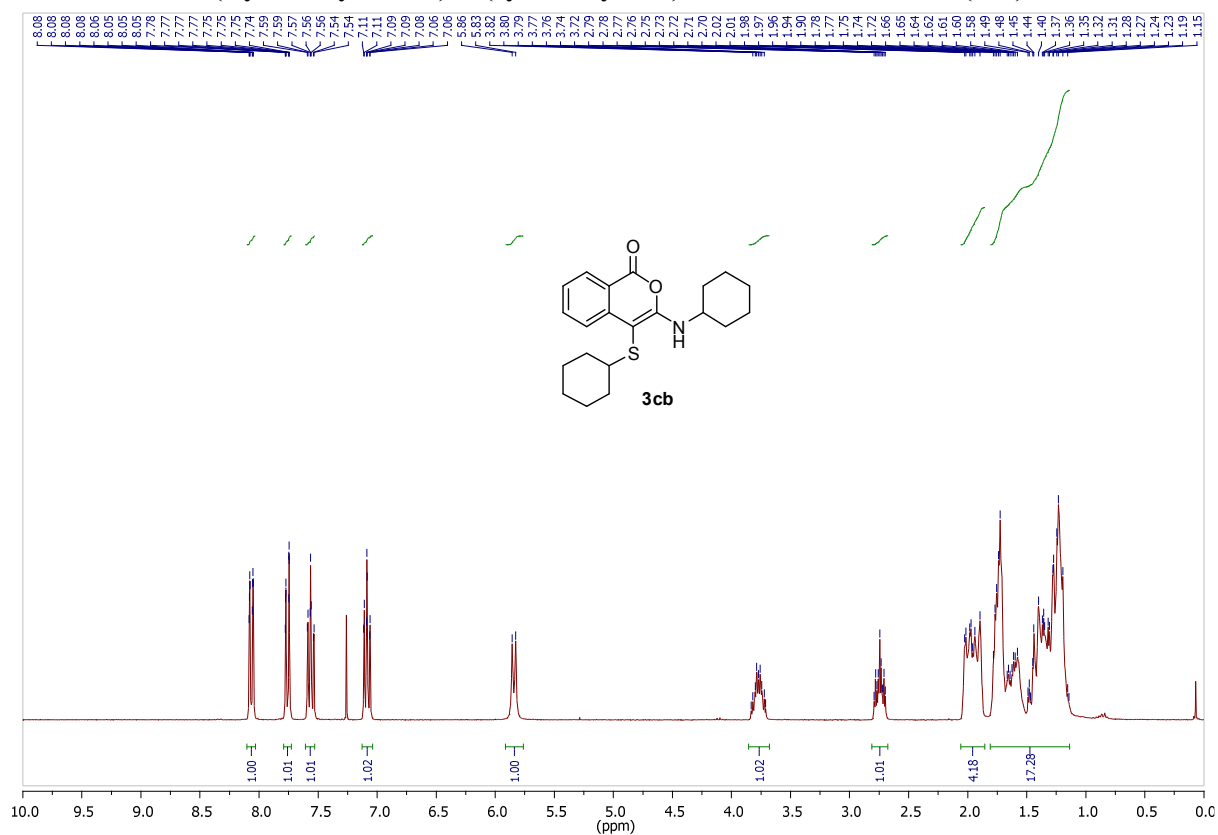
3-Amino-4-(dodecylthio)-1*H*-isochromen-1-one(3ba'):



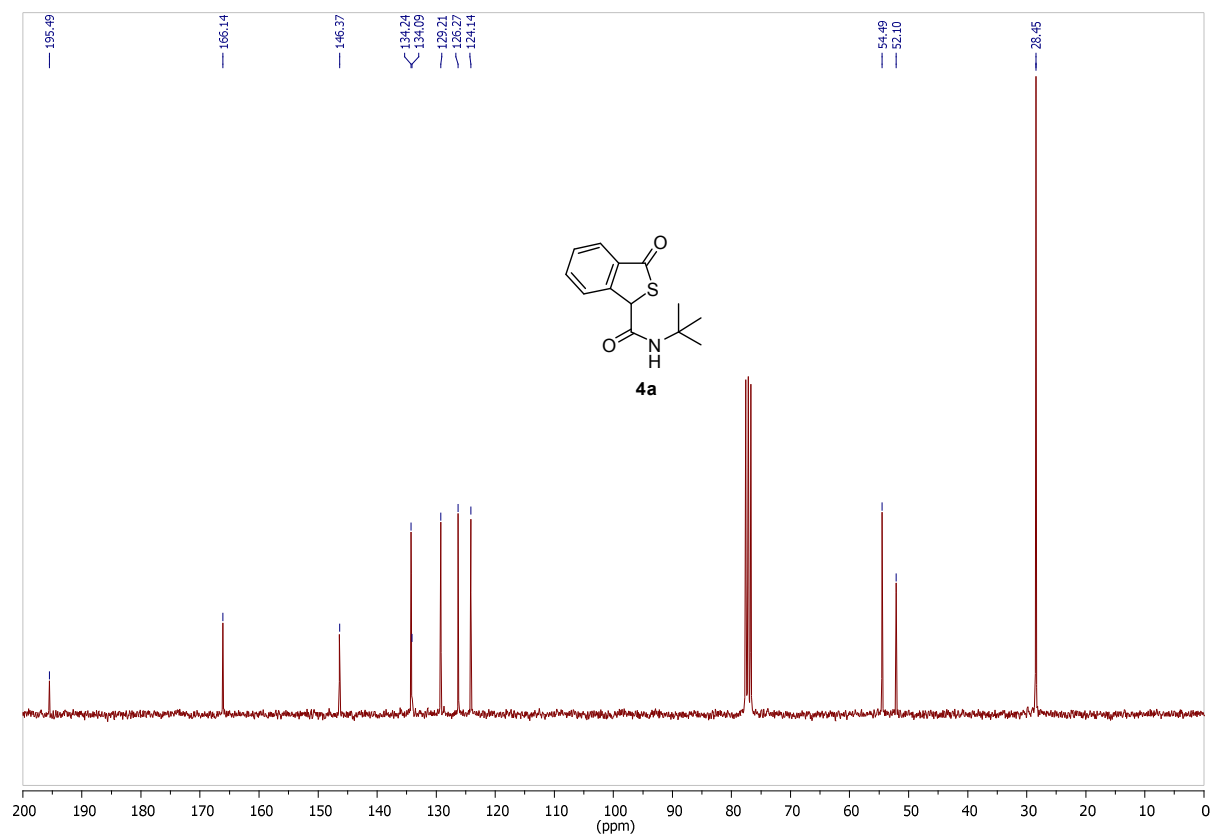
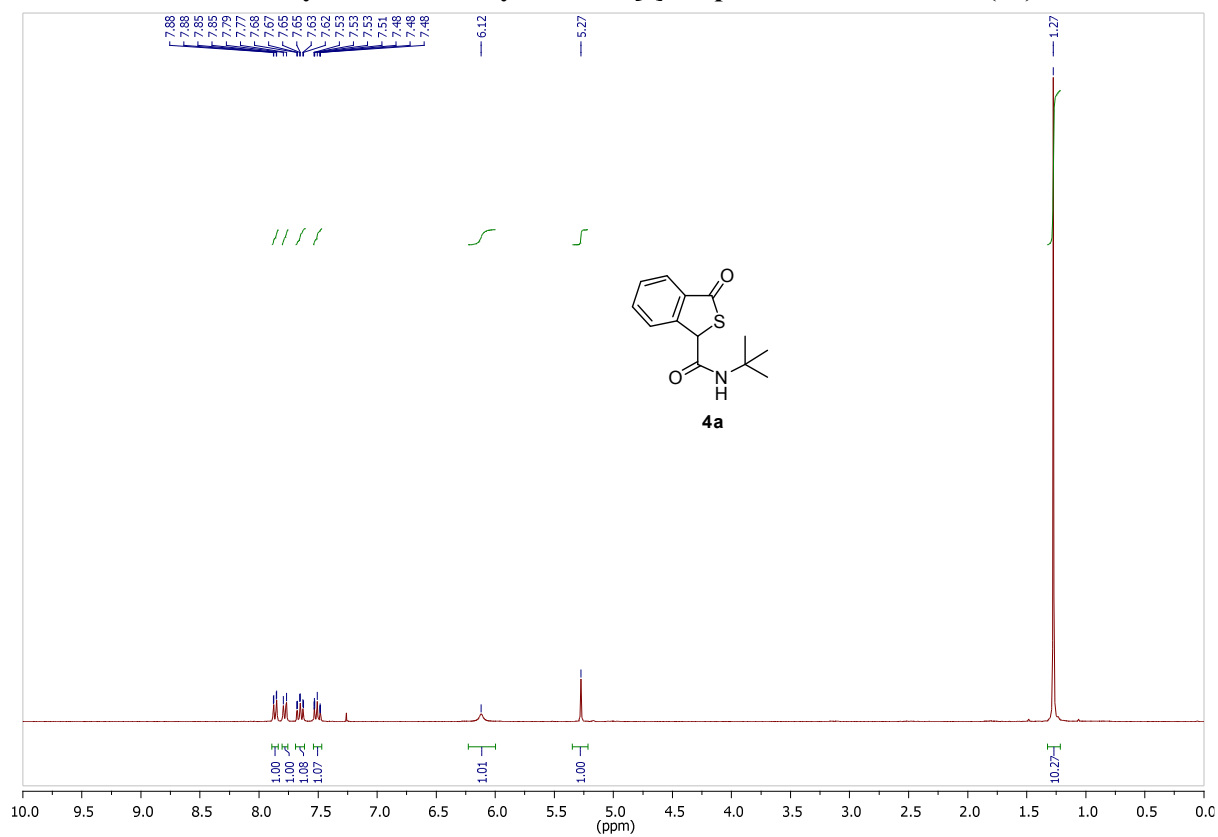
3-(Cyclohexylamino)-4-(dodecylthio)-1*H*-isochromen-1-one(3bb):



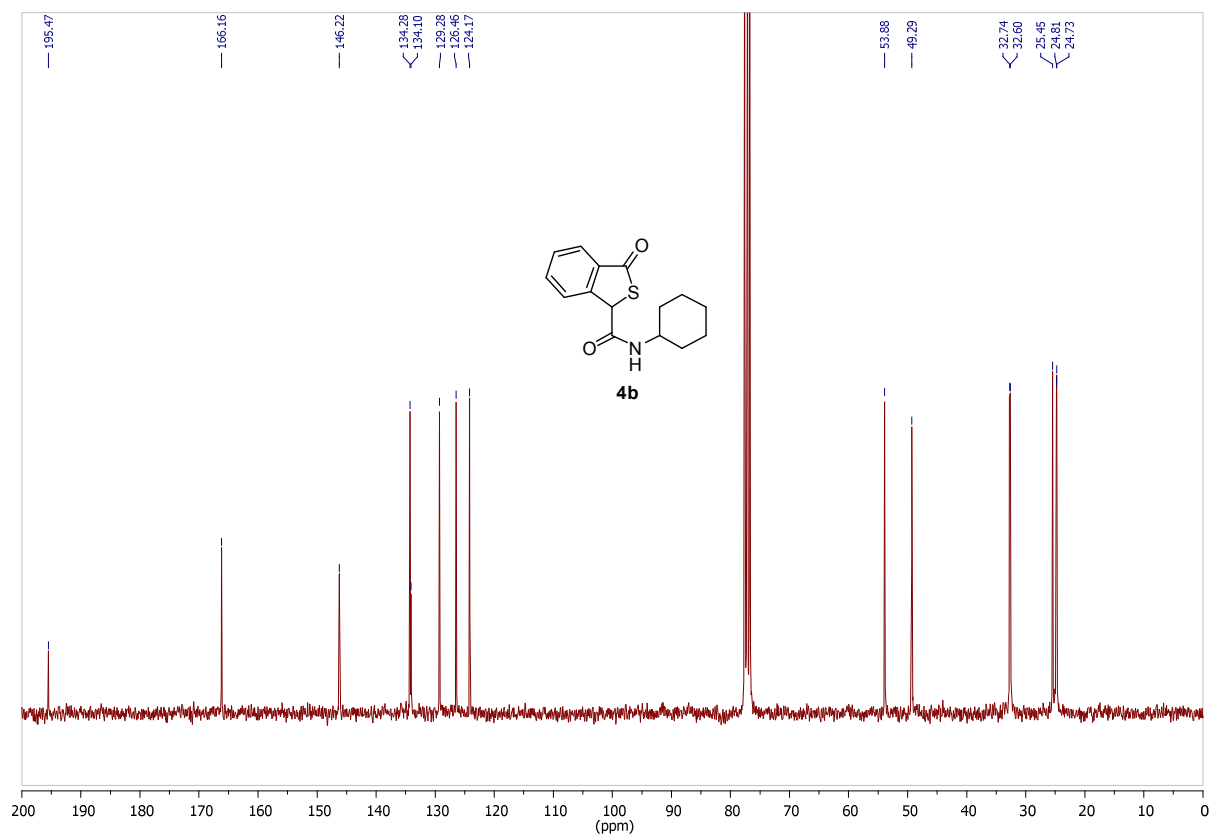
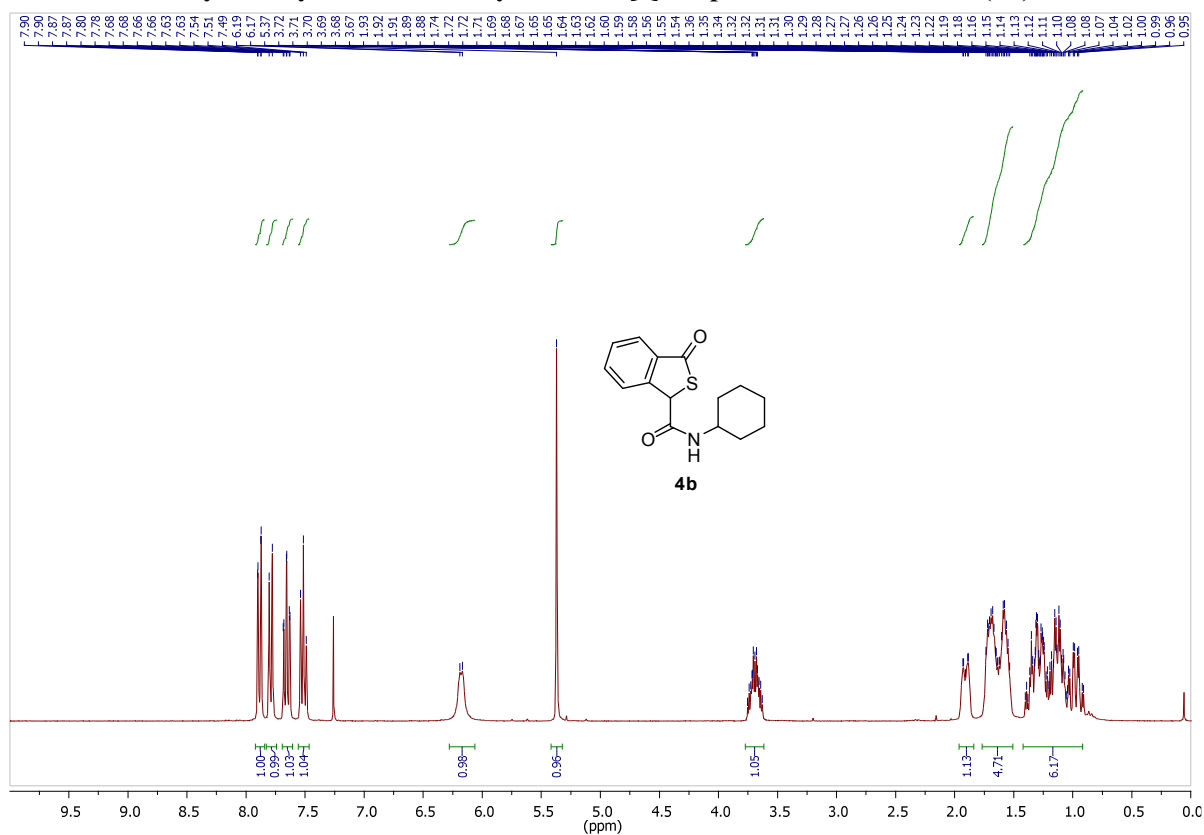
3-(Cyclohexylamino)-4-(cyclohexylthio)-1*H*-isochromen-1-one(3cb):



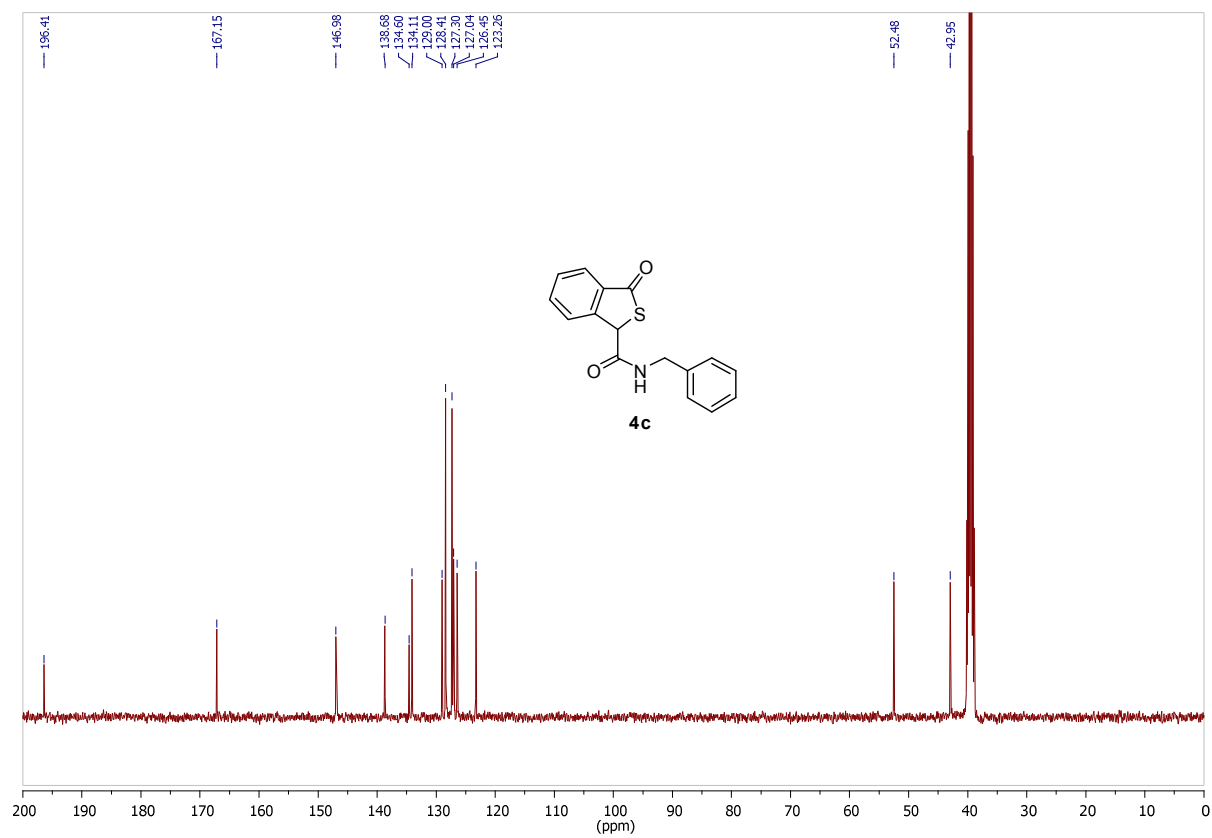
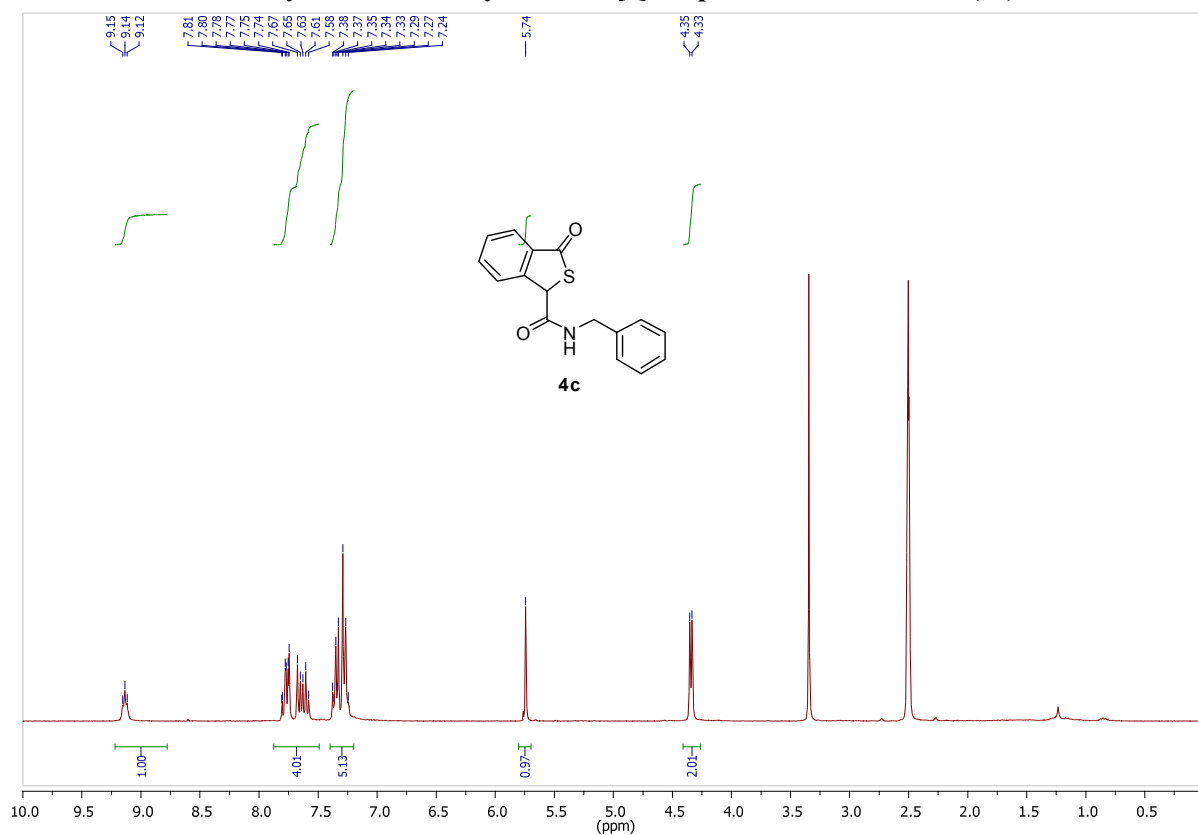
***N*-tert-butyl-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide(4a):**



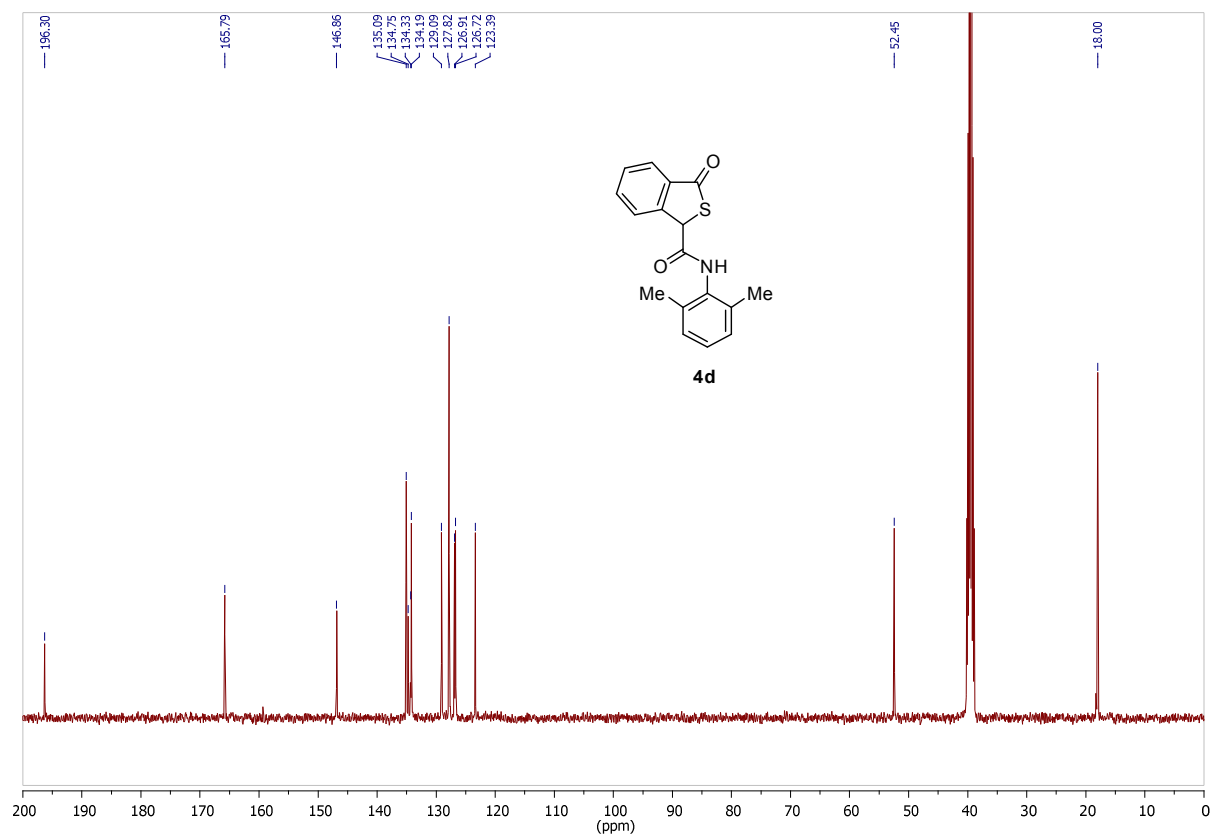
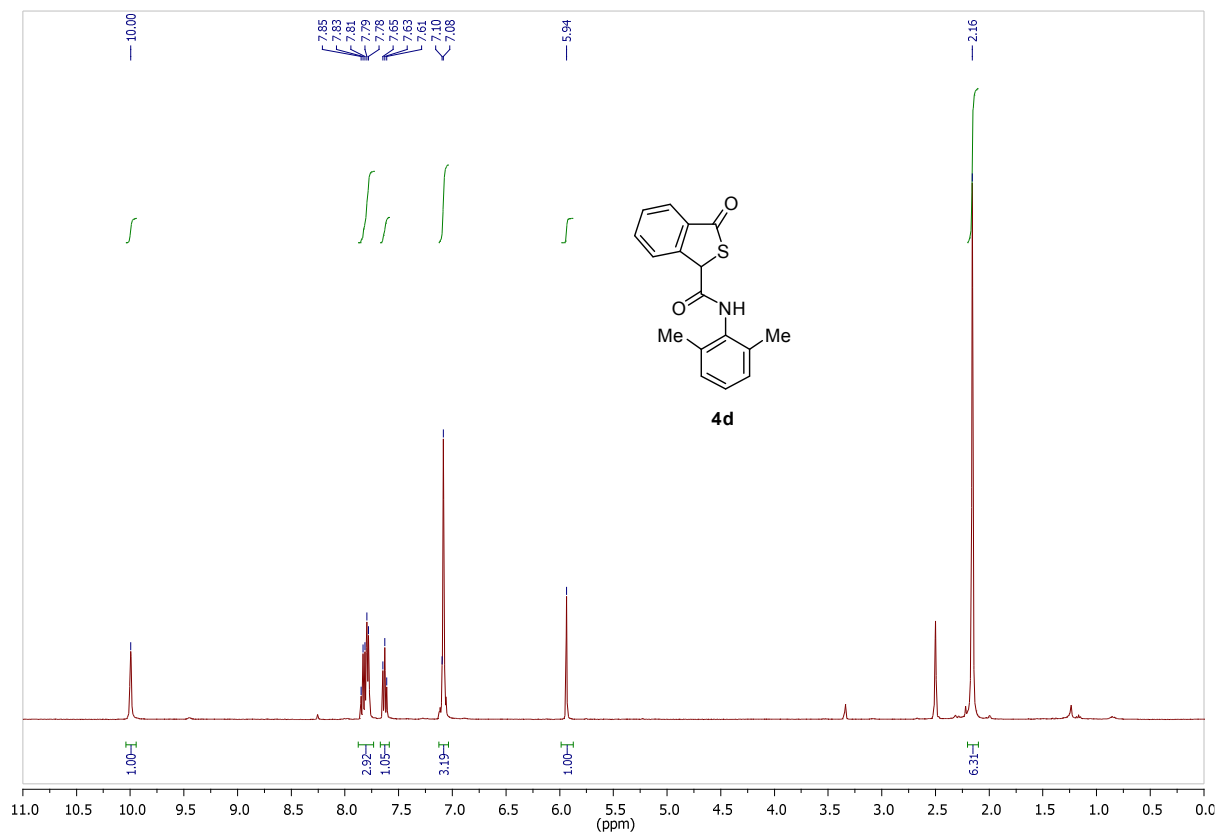
***N*-cyclohexyl-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide(4b):**



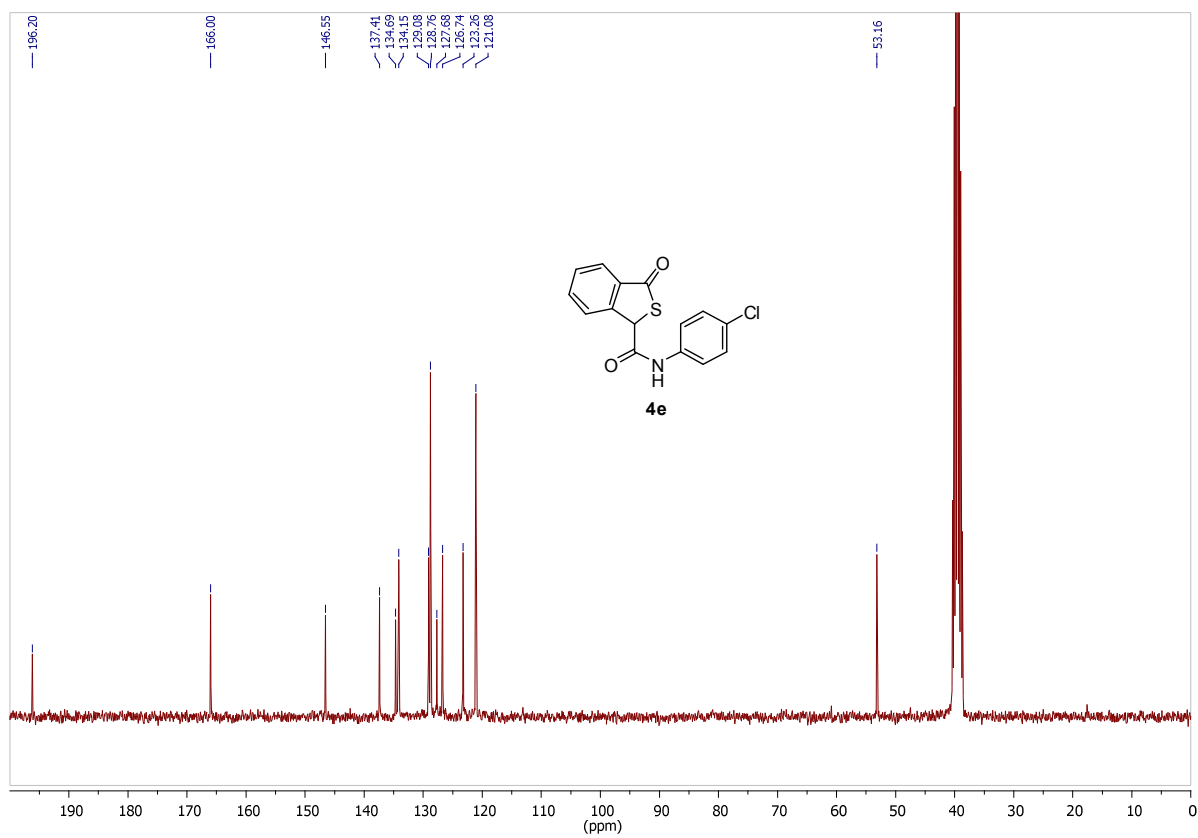
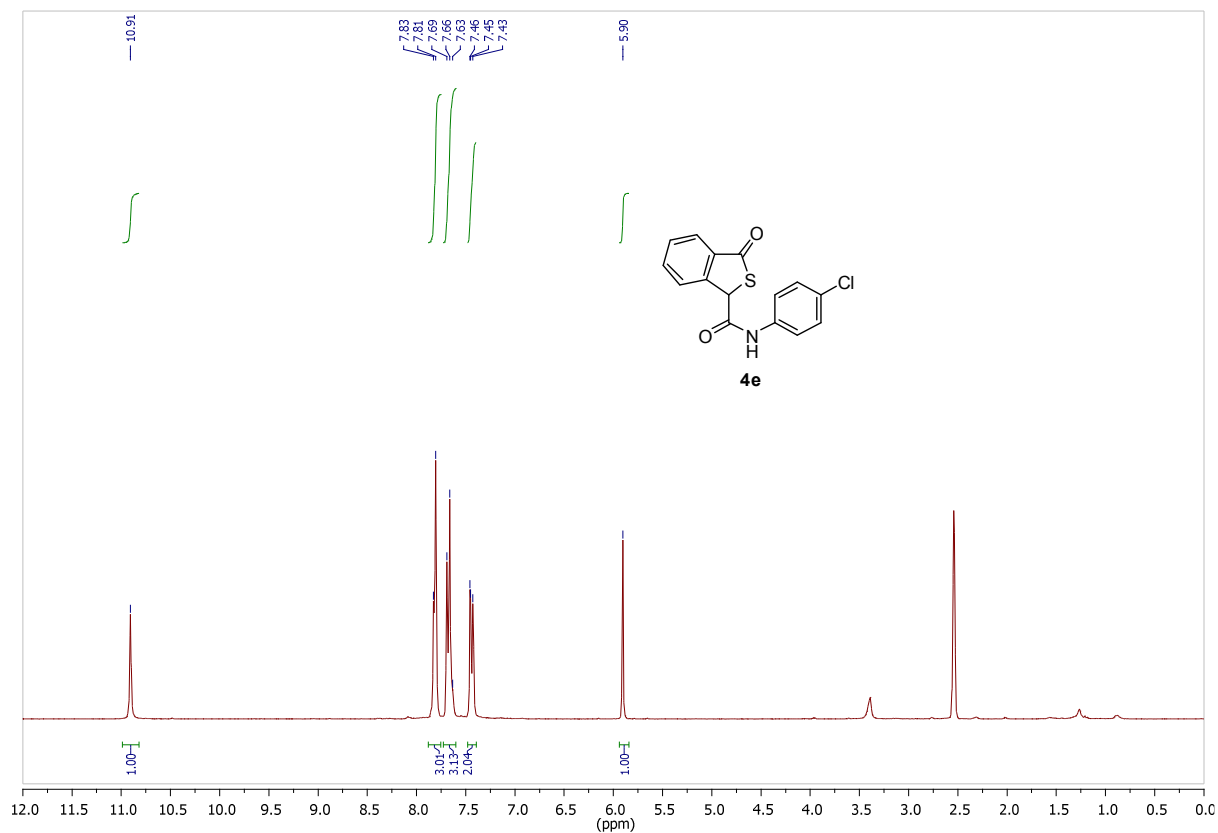
***N*-benzyl-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide(4c):**



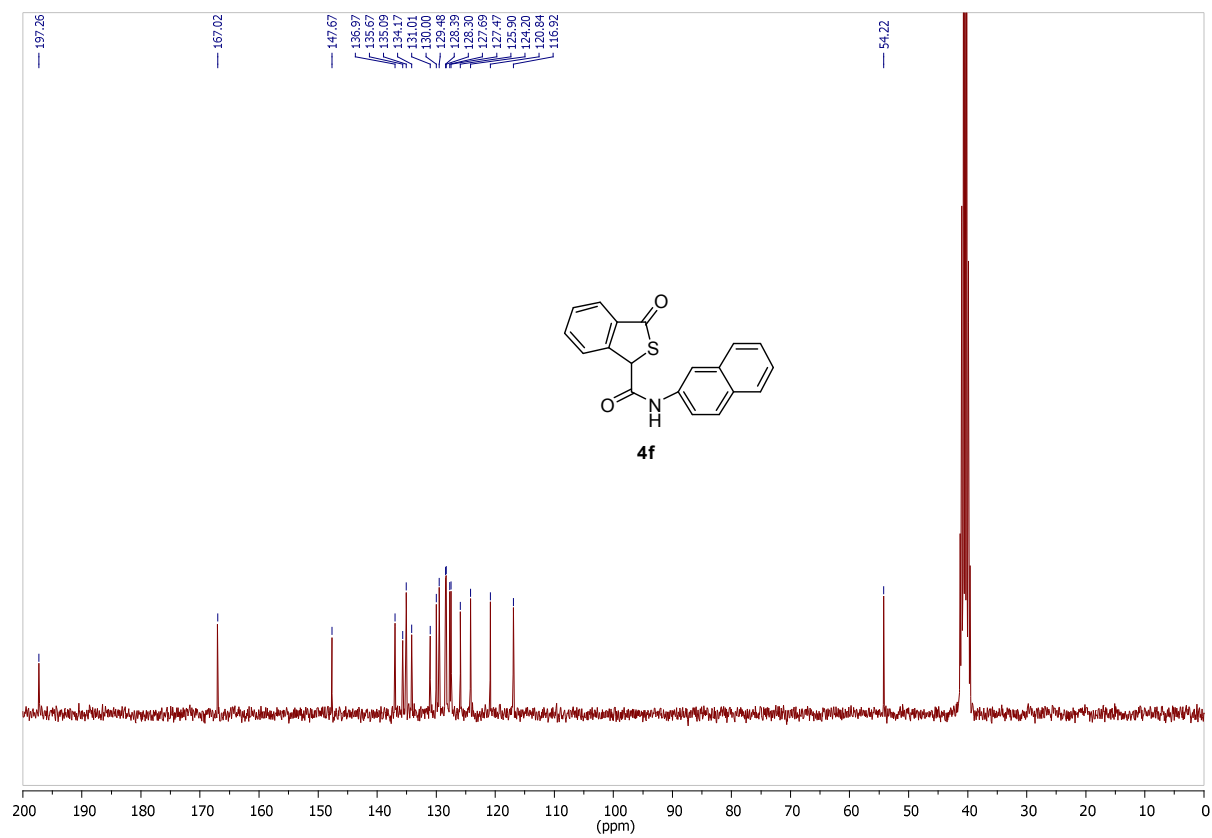
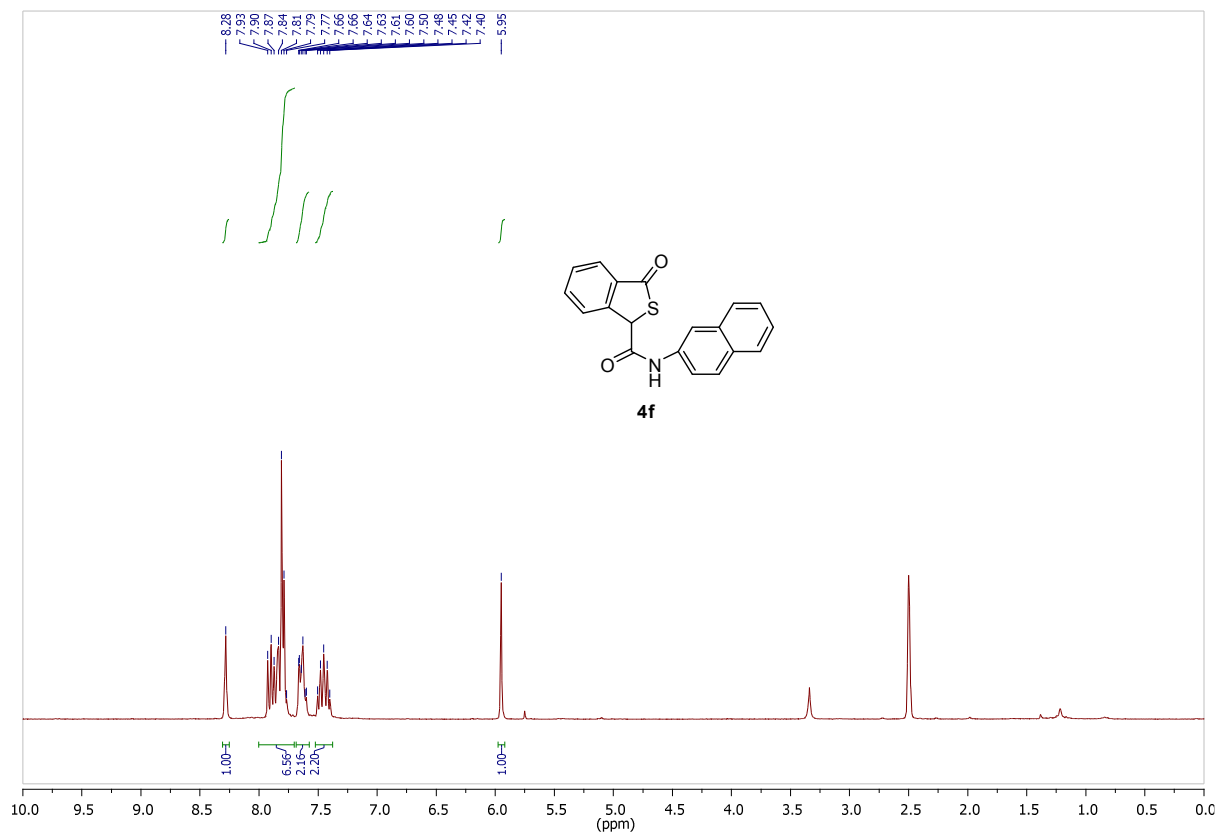
***N*-(2,6-dimethylphenyl)-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide(4d):**



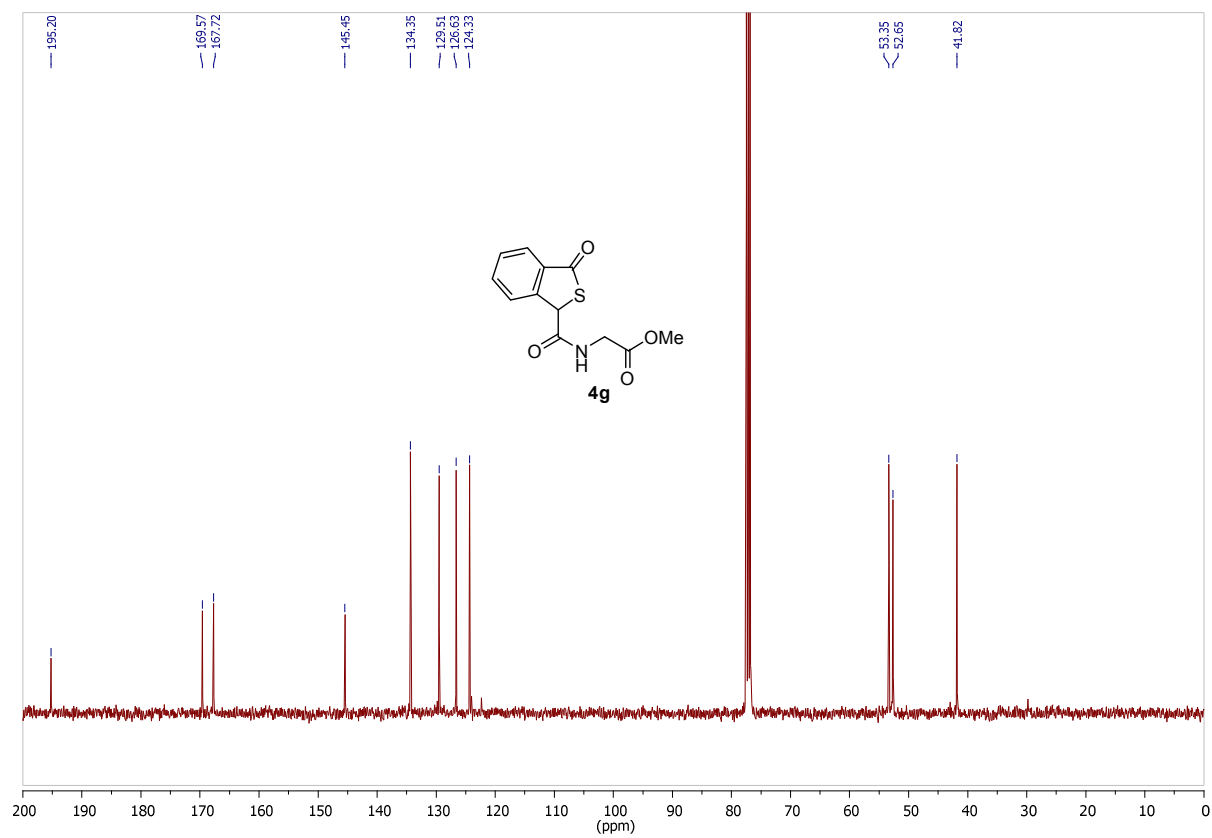
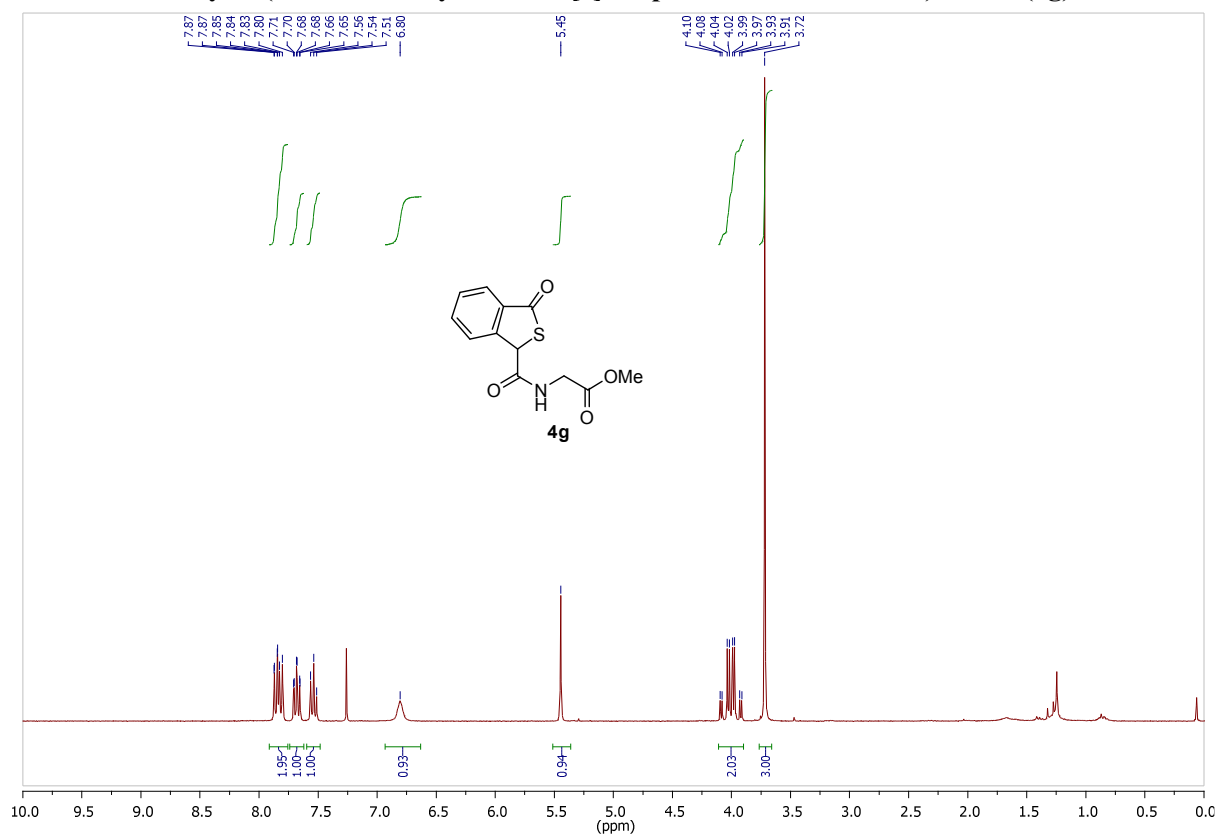
***N*-(4-chlorophenyl)-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide(4e):**



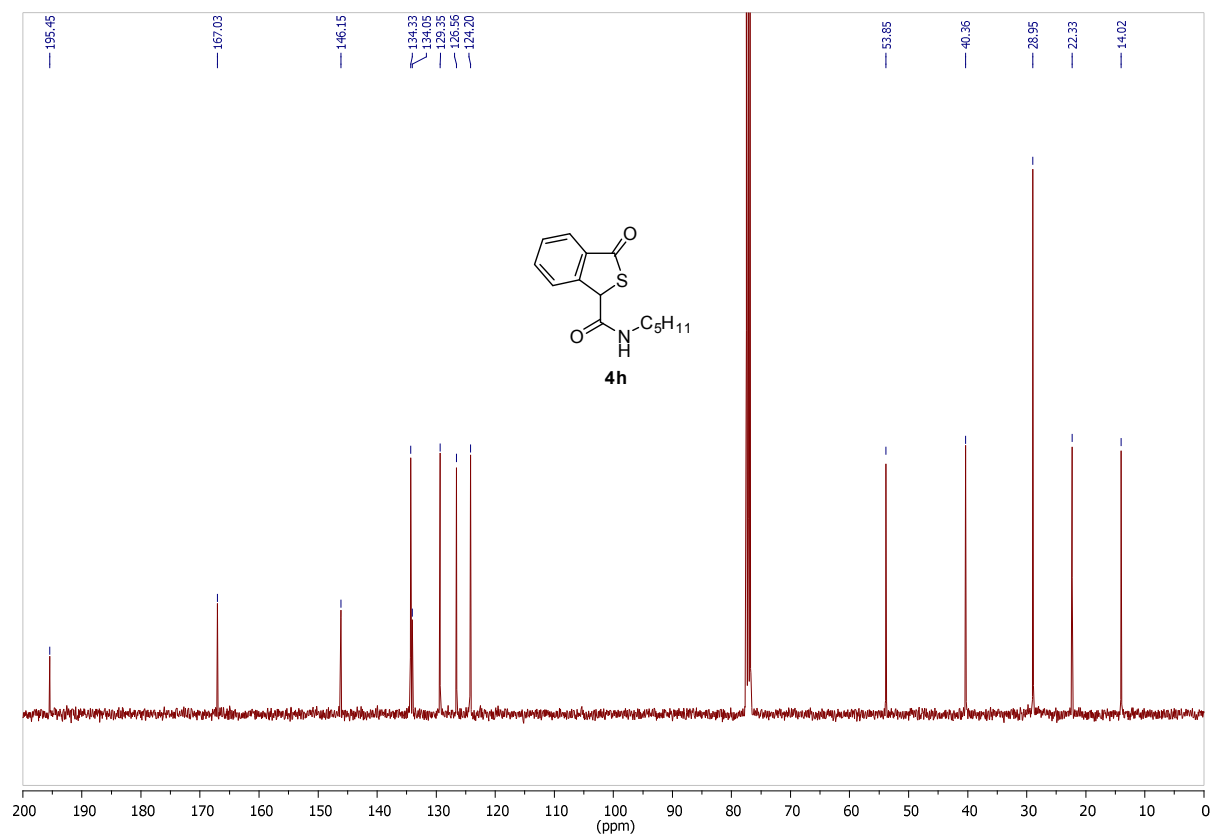
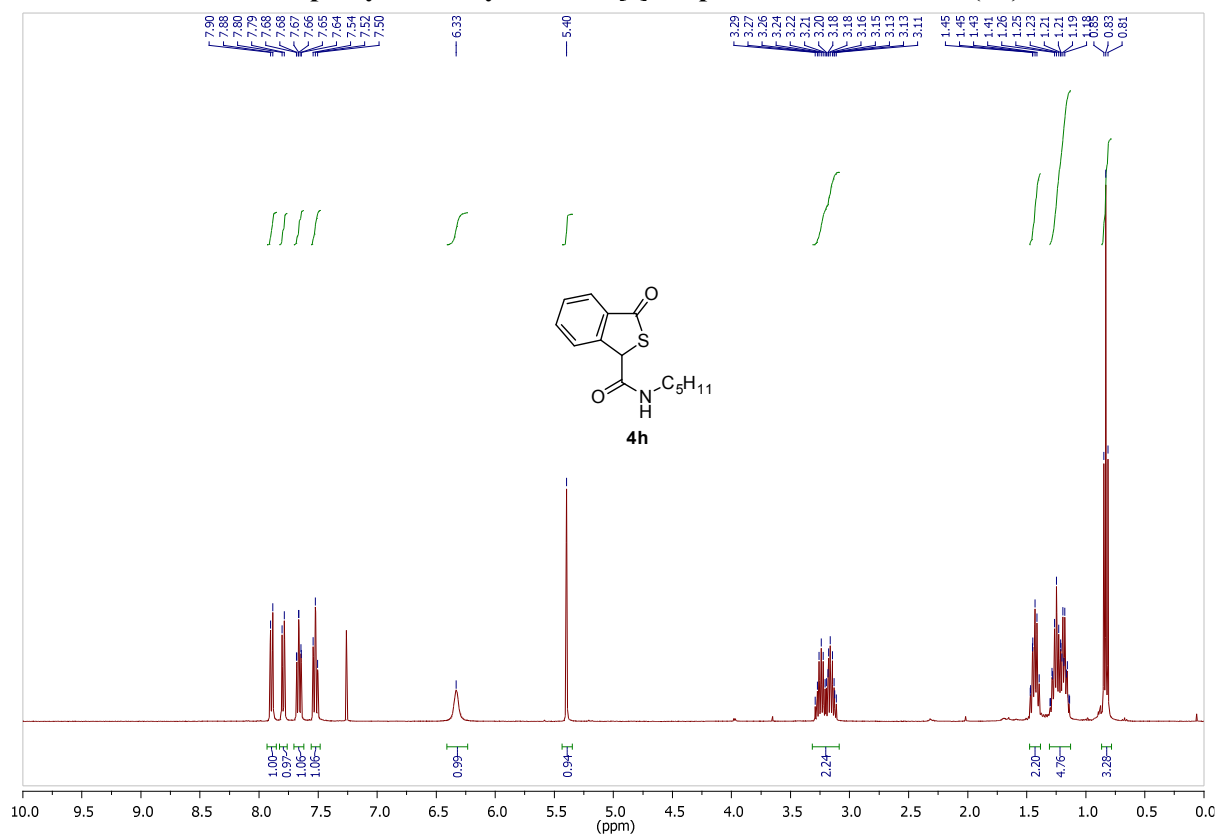
***N*-(naphthalen-2-yl)-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide(4f):**



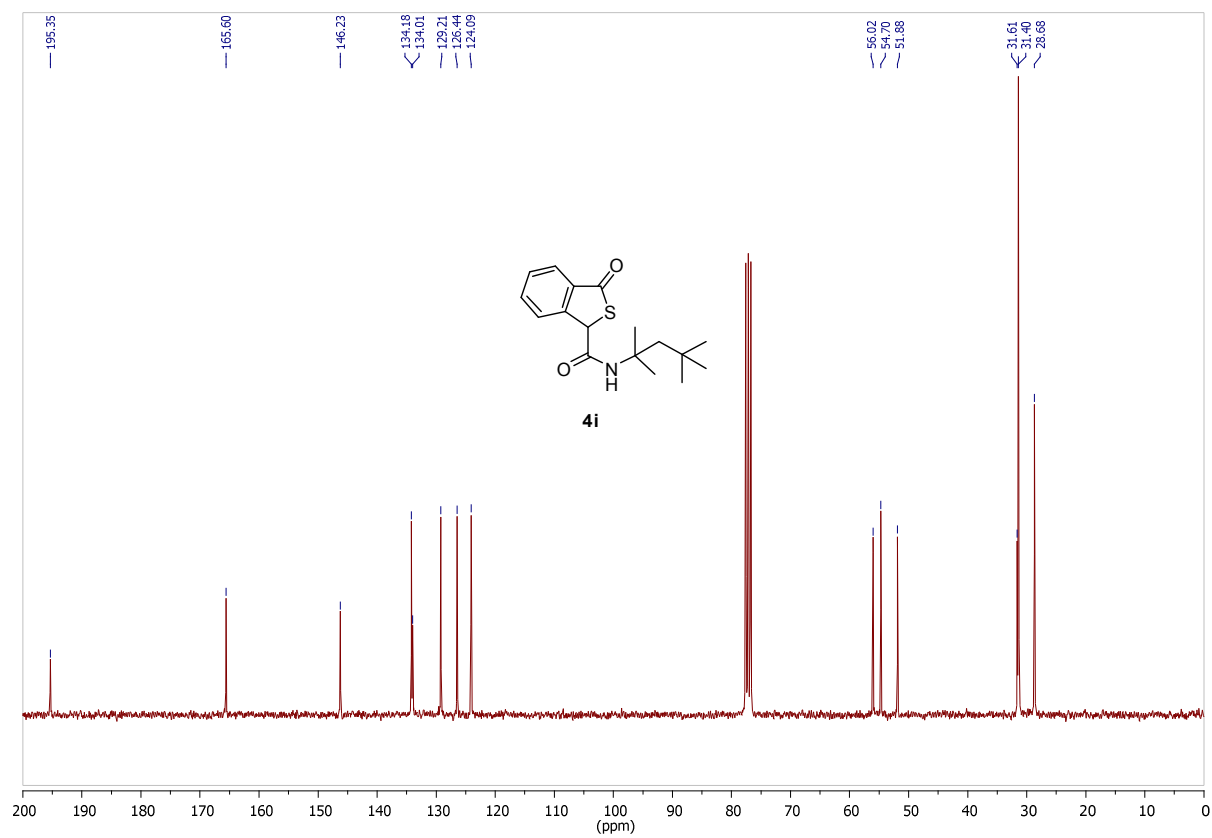
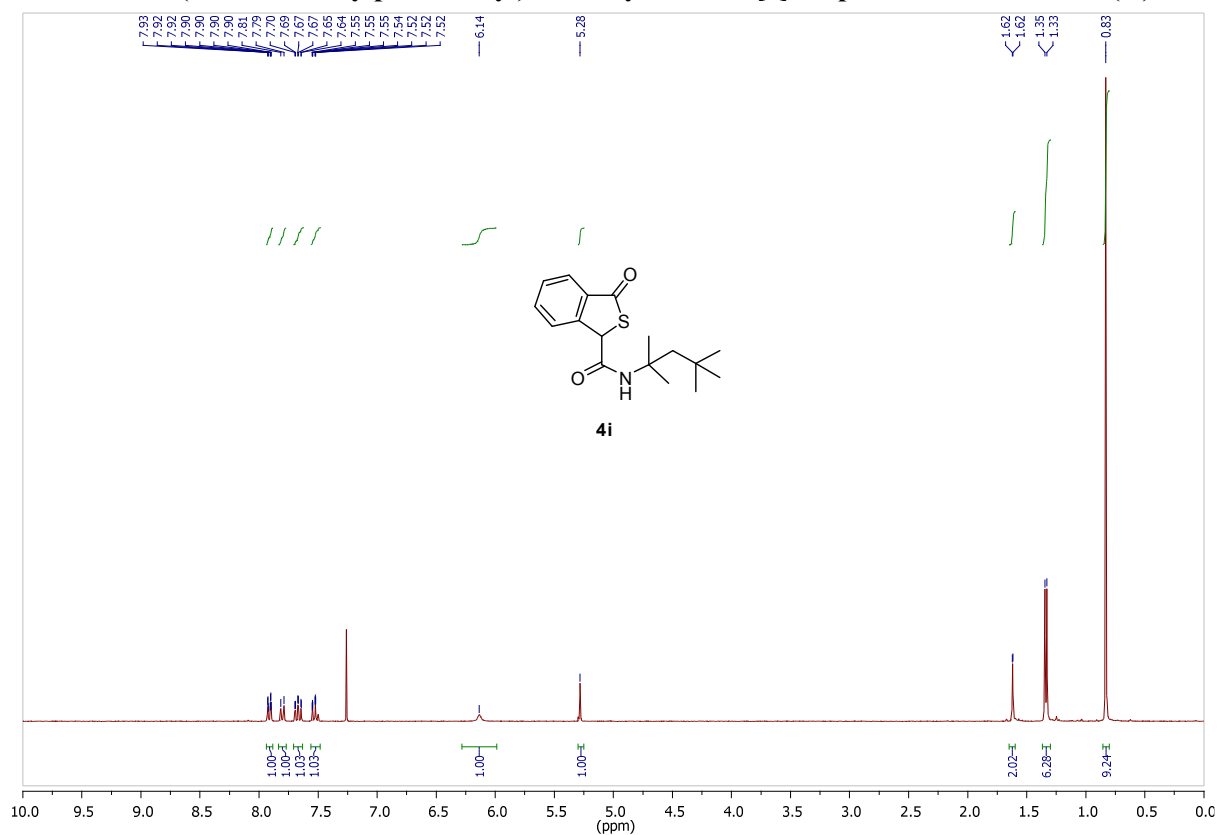
Methyl 2-(3-oxo-1,3-dihydrobenzo[c]thiophene-1-carboxamido)acetate(4g):



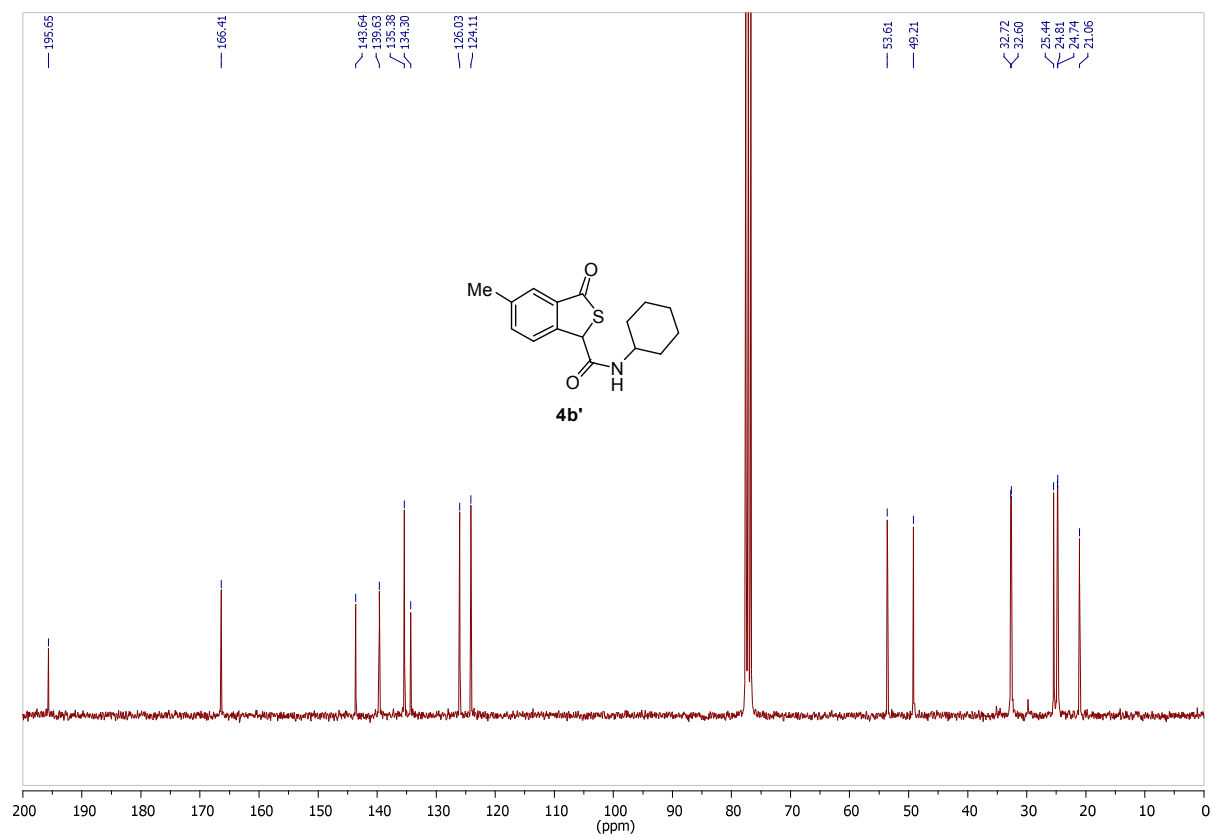
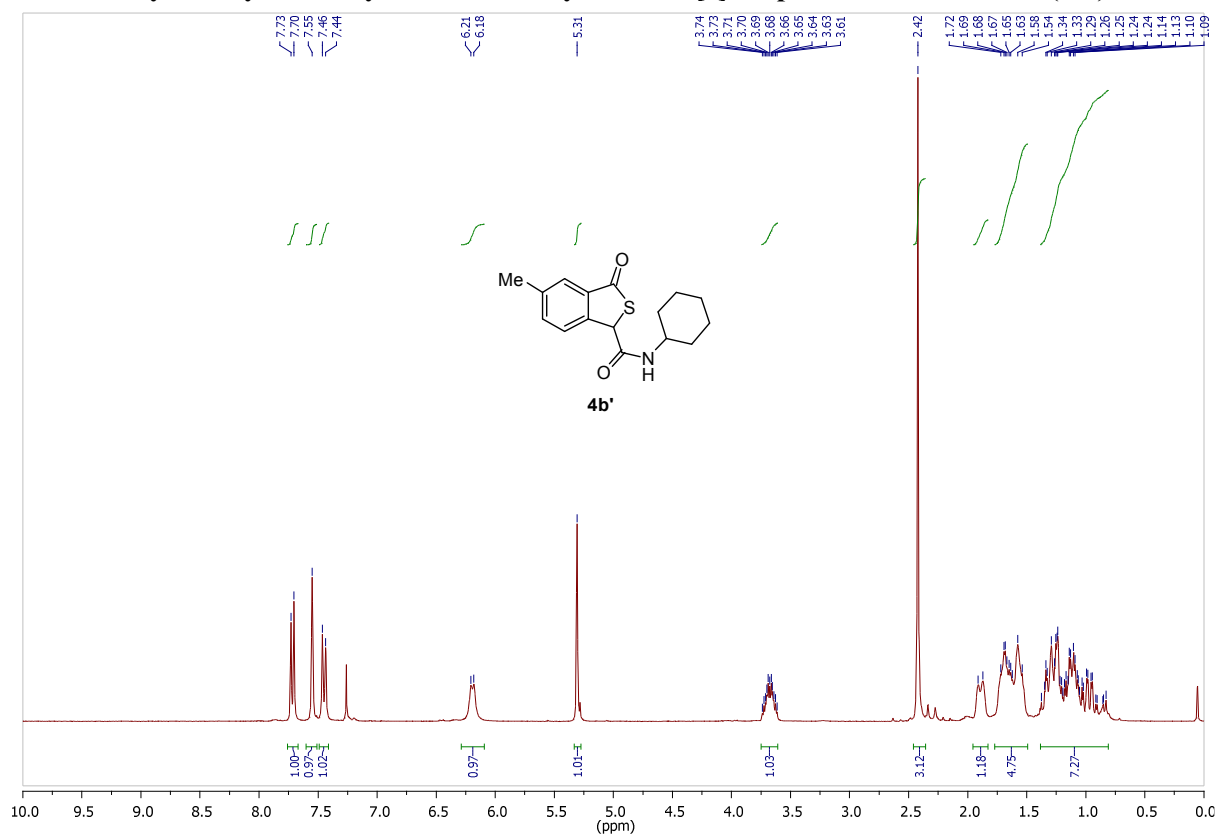
3-Oxo-N-pentyl-1,3-dihydrobenzo[c]thiophene-1-carboxamide(4h):



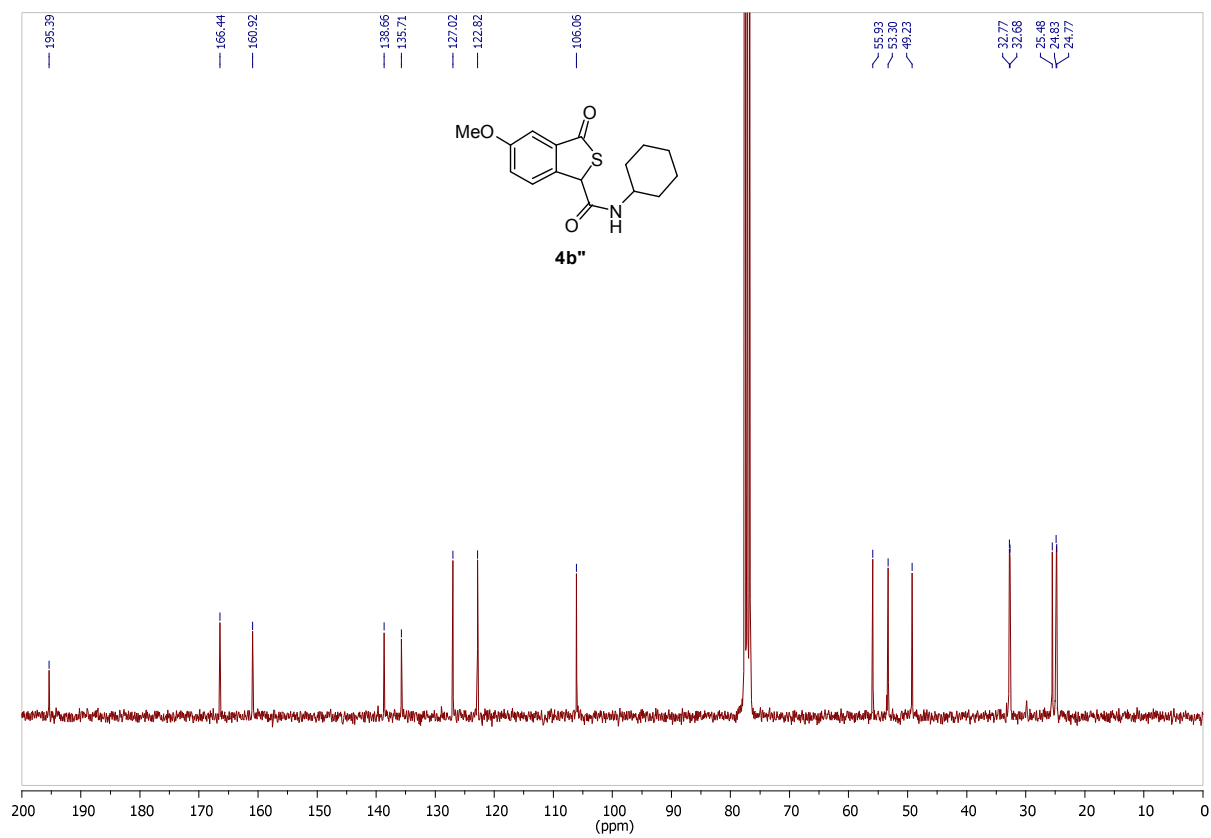
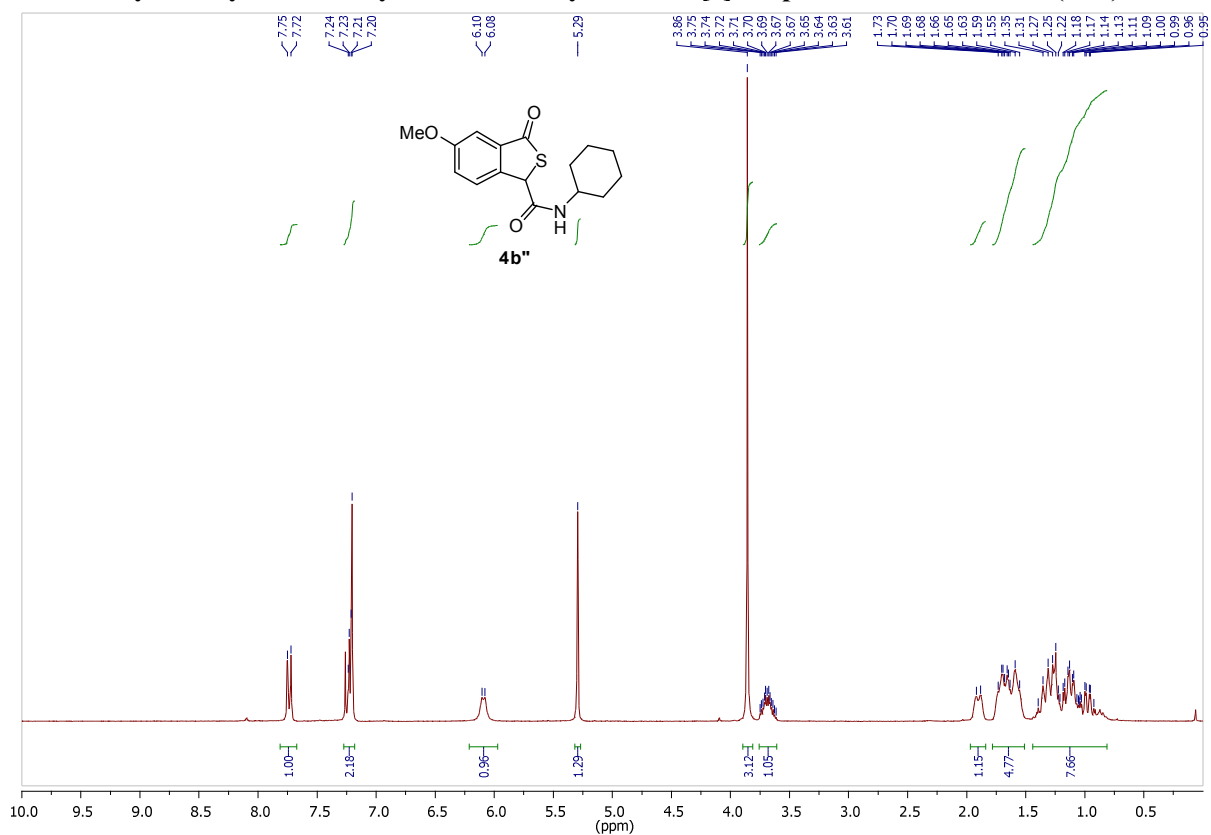
3-Oxo-N-(2,4,4-trimethylpentan-2-yl)-1,3-dihydrobenzo[c]thiophene-1-carboxamide(4i):



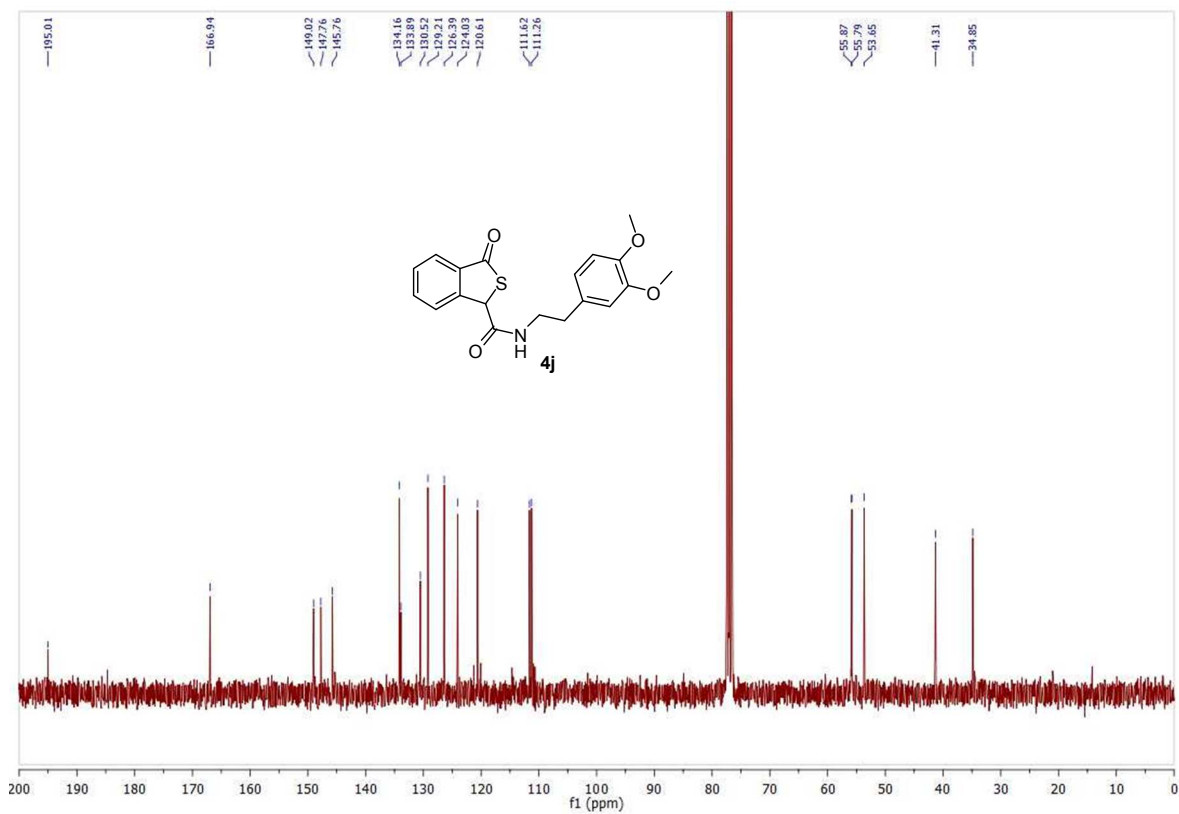
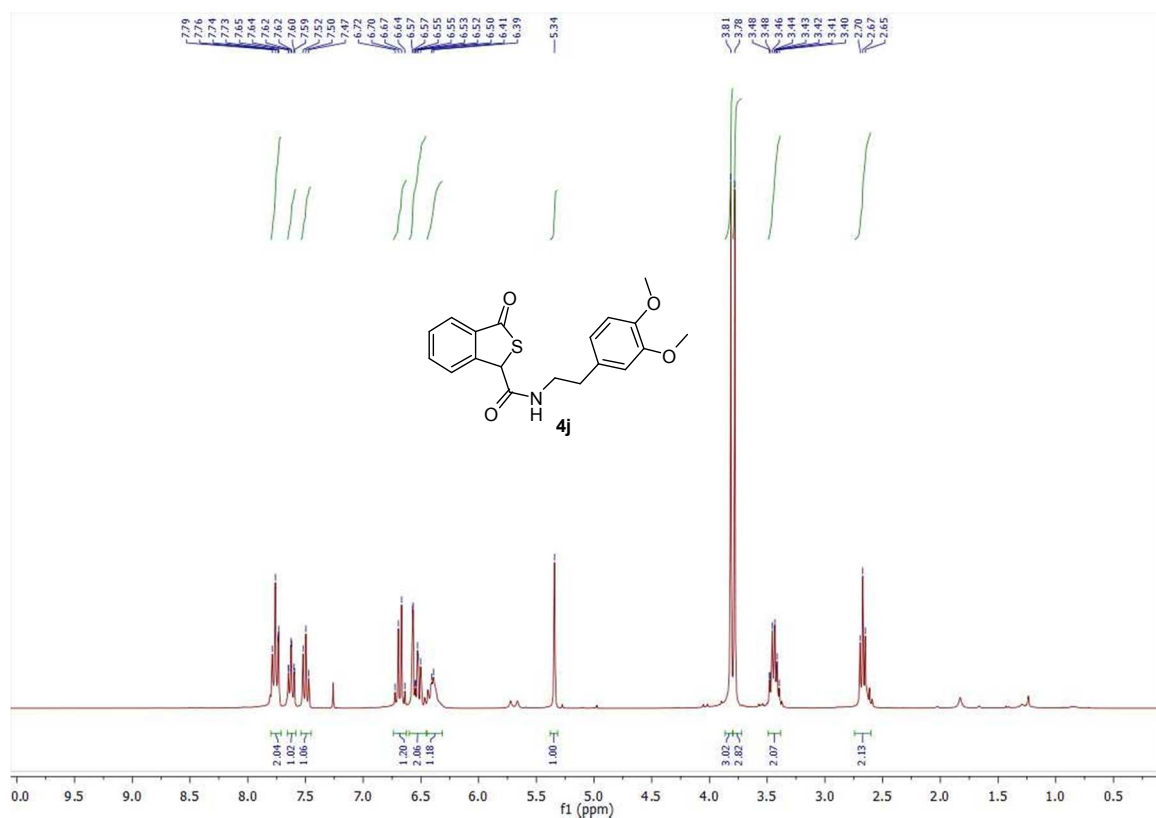
***N*-cyclohexyl-5-methyl-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide(4b'):**



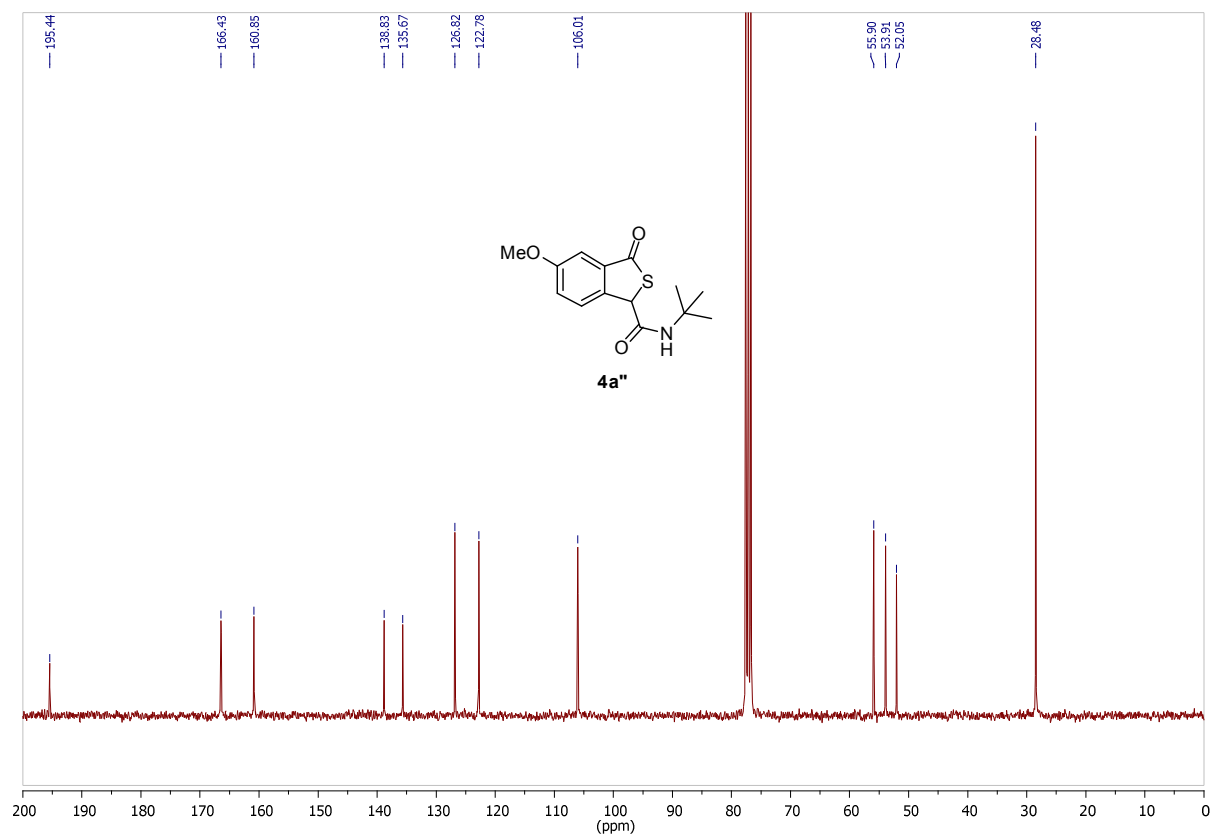
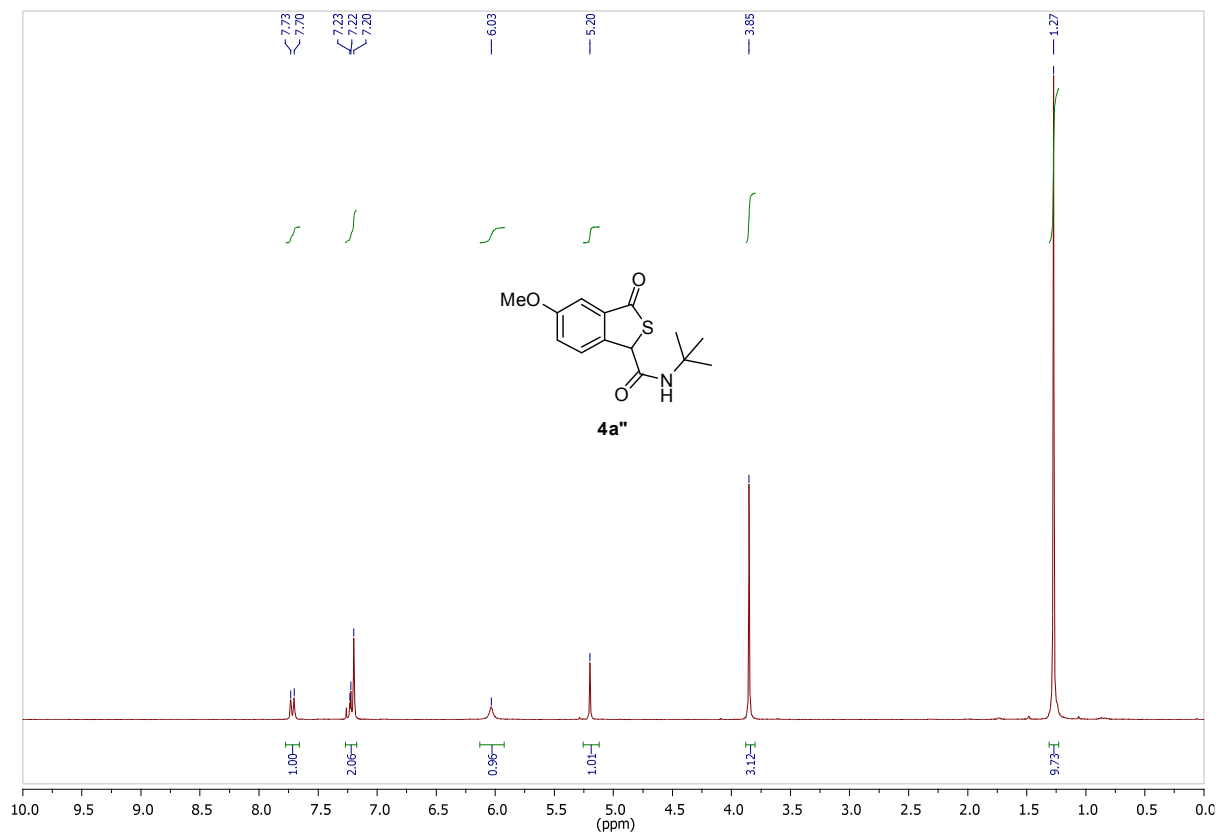
***N*-cyclohexyl-5-methoxy-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide(4b'')**



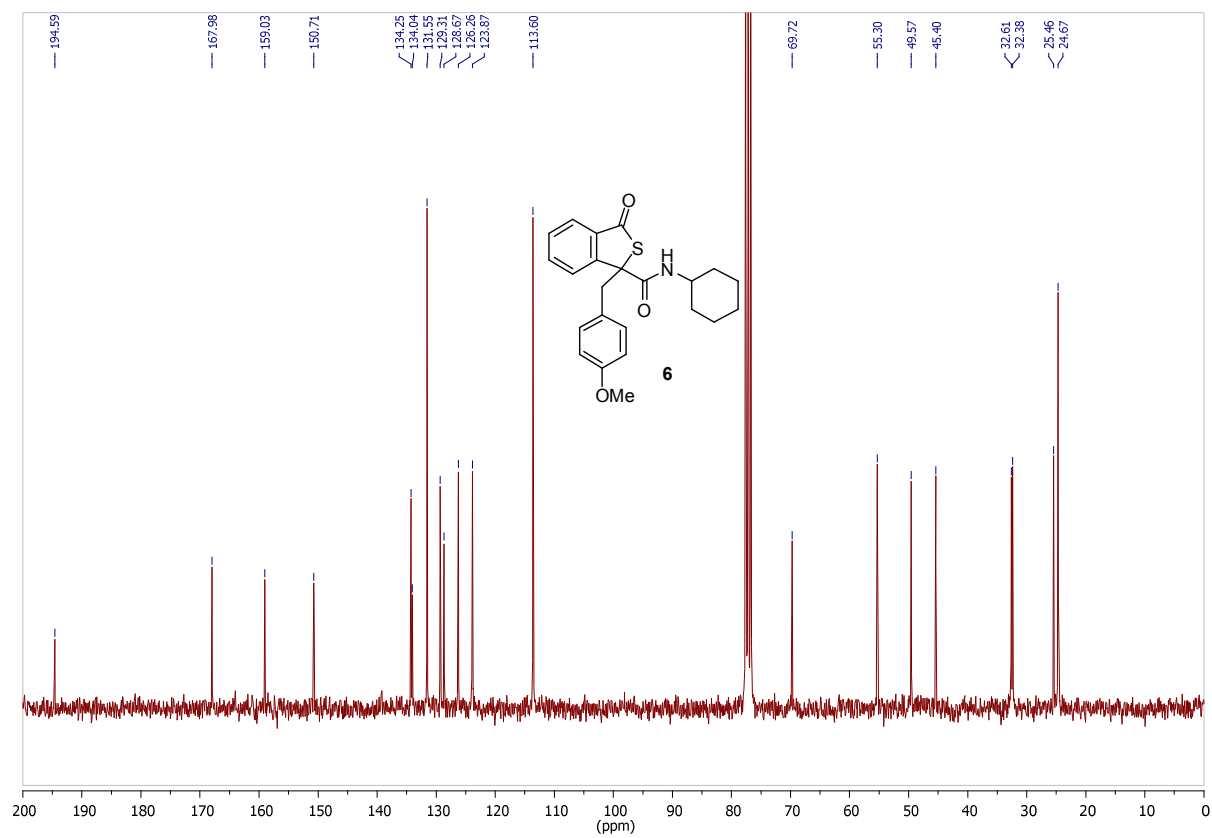
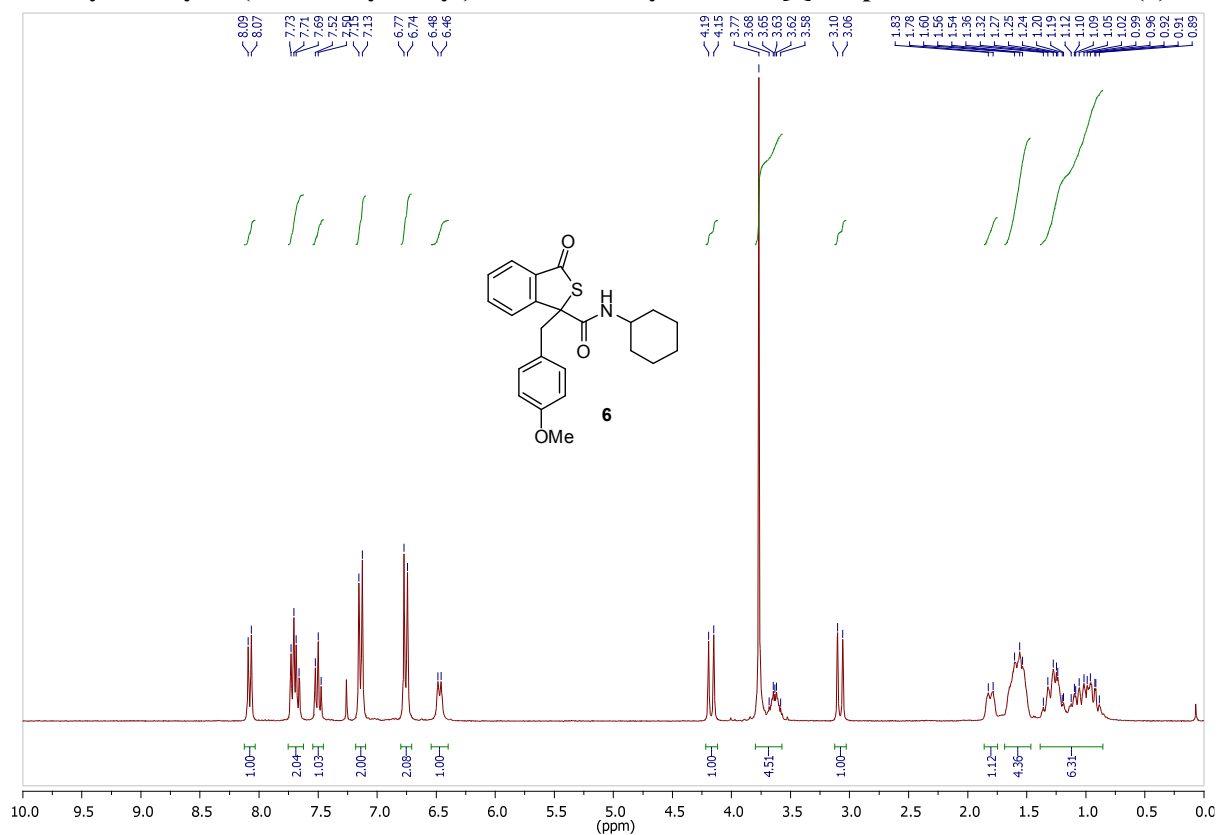
***N*-(3,4-dimethoxyphenethyl)-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide (4j):**



***N*-tert-butyl-5-methoxy-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide(4a'')**



***N*-cyclohexyl-1-(4-methoxybenzyl)-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide(6):**



VII. References

- 1) Dewanji, A.; Mick-Lichtenfeld, C.; Bergander, K.; Daniliuc, C. G.; Studer, A. *Chem. Eur. J.* **2015**, *21*, 12295 - 12298.
- 2) Chen, Z. D.; Stephane, D. L.; Alan, D. J.; et al. Preparation of benzimidazole derivatives for use as leukotriene production inhibitors. WO 2012058254-A1 [P].
- 3) Zhang, Y.; Ao, Y-F.; Huang, Z-T.; Wang, D-X.; Wang, M-X.; Zhu, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 5282-5285.