

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:

Entry	Catalyst	x mol%	y equiv	Time (h)	Yield (%)
					3ab
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>i</i> Pr) ₄	100	1.2	2	0
14.	TiCl(O <i>i</i> Pr) ₃	100	1.2	2	0

Yields are determined from crude ¹H-NMR

^a Isolated yield

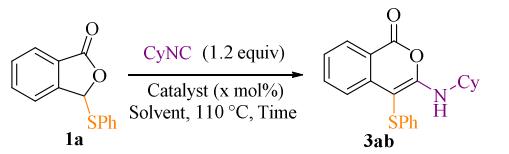
Evaluation of different solvents

Entry	x mol%	y equiv	Solvent	Yield (%)
				3ab
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

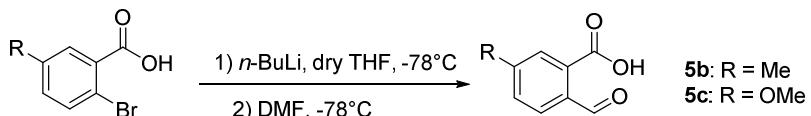
Evaluation of lower catalyst loadings



Entry	Catalyst	x mol%	Solvent	Time (h)	Yield (%) ^a
1.	AlCl ₃	20	Toluene	3	0
2.	TiCl ₄	20	Toluene	24	37
3.	TiCl ₄	30	Toluene	24	43
4.	TiCl ₄	30	DCE	16	0
5.	KAuCl ₄	15	Toluene	10	0
6.	Yb(OTf) ₃	20	Toluene	7	14
7.	Fe(OTf) ₃	20	Toluene	7	0
8.	In[NTf ₂] ₃	20	Toluene	7	0

^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 NH₄Cl. 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 MgSO₄. 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, DMSO-D₆) δ 8.09 (br s, 1H), 7.75 – 7.35 (m, 3H), 6.62 (br s, 1H), 2.42 (s, 3H); ¹³C NMR (75 MHz, DMSO-D₆) δ 168.5, 144.9, 140.5, 135.3, 126.8, 124.3, 123.4, 98.2, 20.7; HRMS (ESI+) *m/z*: [M]⁺ calcd for C₉H₈O₃ 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 MgSO₄ (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, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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*: [M]⁺ calcd for C₁₄H₁₀O₂S 242.0402, found: 242.0397.

3-(Dodecylthio)isobenzofuran-1(3*H*)-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(3*H*)-one **1b** was obtained as white solid (314.8 mg, 94% yield). 1 H NMR (300 MHz, CDCl₃) 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, CDCl₃) 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*: [M]⁺ calcd for C₂₀H₃₀O₂S 334.1967, found: 334.1955.

3-(Cyclohexylthio)isobenzofuran-1(3*H*)-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(3*H*)-one **1c** was obtained as white solid (229 mg, 92% yield). 1 H NMR (300 MHz, CDCl₃) 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, CDCl₃) 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*: [M]⁺ calcd for C₁₄H₁₆O₂S 248.0871, found: 248.0865.

3-(4-Methoxybenzylthio)isobenzofuran-1(3*H*)-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(3*H*)-one **1d** was obtained as white solid (237 mg, 83% yield). 1 H NMR (300 MHz, CDCl₃) 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, CDCl₃) 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*: [M]⁺ calcd for C₁₆H₁₄O₃S 286.0664, found: 286.0666.

3-(*tert*-Butylthio)isobenzofuran-1(3*H*)-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(3*H*)-one **1e** was obtained as white solid (168 mg, 76% yield). 1 H NMR (300 MHz, CDCl₃) 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, CDCl₃) 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*: [M]⁺ calcd for C₁₂H₁₄O₂S 222.0715, found: 222.0726.

3-(*tert*-Butylthio)-6-methylisobenzofuran-1(3*H*)-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(3*H*)-one **1f** was obtained as white solid (320 mg, 90% yield). 1 H NMR (300 MHz, CDCl₃) 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, CDCl₃) 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*: [M]⁺ calcd for C₁₃H₁₆O₂S 236.0871, found: 236.0874.

3-(*tert*-Butylthio)-6-methoxyisobenzofuran-1(3*H*)-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(*H*)-one **1a** (100 mg, 0.413 mmol), benzylisocyanide **2c** (61 μ L, 0.498 mmol), TiCl_4 (1M in CH_2Cl_2 , 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, CDCl_3) 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); ^{13}C NMR (75 MHz, CDCl_3) 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 $\text{C}_{22}\text{H}_{17}\text{NO}_2\text{S}$ 359.0980, found: 359.0997.

3-(2,6-Dimethylphenylamino)-4-(phenylthio)-1*H*-isochromen-1-one (3ad): Starting from 3-(phenylthio)isobenzofuran-1(*H*)-one **1a** (100 mg, 0.413 mmol), 2,6-dimethylphenylisocyanide **2d** (65.3 mg, 0.498 mmol), TiCl_4 (1M in CH_2Cl_2 , 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, CDCl_3) 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); ^{13}C NMR (75 MHz, CDCl_3) 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 $\text{C}_{23}\text{H}_{19}\text{NO}_2\text{S}$ 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(*H*)-one **1b** (100 mg, 0.30 mmol), *tert*-butylisocyanide **2a** (41 μ L, 0.36 mmol), TiCl_4 (1M in CH_2Cl_2 , 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, CDCl_3) 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); ^{13}C NMR (75 MHz, CDCl_3) 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 $\text{C}_{25}\text{H}_{39}\text{NO}_2\text{S}$ 417.2702, found: 417.2715. (**3ba'**): ^1H NMR (300 MHz, CDCl_3) 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); ^{13}C NMR (75 MHz, CDCl_3) 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 $\text{C}_{21}\text{H}_{31}\text{NO}_2\text{S}$ 361.2075, found: 361.2082.

3-(Cyclohexylamino)-4-(dodecylthio)-1*H*-isochromen-1-one (3bb): Starting from 3-(dodecylthio)isobenzofuran-1(*H*)-one **1b** (100 mg, 0.30 mmol), cyclohexylisocyanide **2b** (45 μ L, 0.36 mmol), TiCl_4 (1M in CH_2Cl_2 , 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 μ L, 0.48 mmol), TiCl₄ (1M in CH₂Cl₂, 400 μ L, 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 – 3.355 (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 μ L, 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 TiCl_4 (1M in CH_2Cl_2 , 200 μL , 0.2 equiv). After stirring the resulting mixture at room temperature for 1h, isocyanide **2** (1.50 mmol, 1.5 equiv), TiCl_4 (1 M in CH_2Cl_2 , 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 NaHCO_3 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 MgSO_4 . 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), TiCl_4 (1M in CH_2Cl_2 , 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, CDCl_3) 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). ^{13}C NMR (75 MHz, CDCl_3) 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 $\text{C}_{13}\text{H}_{15}\text{NO}_2\text{S}$ 249.0823, found: 149.9861 [M-(CONH'Bu)] $^{+•}$; 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), TiCl_4 (1M in CH_2Cl_2 , 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, CDCl_3) 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); ^{13}C NMR (75 MHz, CDCl_3) 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.

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), TiCl₄ (1M in CH₂Cl₂, 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-D₆) 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); ¹³C NMR (101 MHz, DMSO-D₆) 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]⁺calcd for C₁₆H₁₃NO₂S 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), TiCl₄ (1M in CH₂Cl₂, 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-D₆) 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); ¹³C NMR (101 MHz, DMSO-D₆) 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]⁺calcd for C₁₇H₁₅NO₂S 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), TiCl₄ (1M in CH₂Cl₂, 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-D₆) 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); ¹³C NMR (75 MHz, DMSO-D₆) 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]⁺calcd for C₁₅H₁₀ClNO₂S 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), TiCl₄ (1M in CH₂Cl₂, 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 μ L, 0.54 mmol), TiCl₄ (1M in CH₂Cl₂, 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 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 μ L, 0.54 mmol), TiCl₄ (1M in CH₂Cl₂, 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: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 (Cl-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 μ L, 0.54 mmol), TiCl₄ (1M in CH₂Cl₂, 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 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] $^{+•}$ calcd for $C_{17}H_{23}NO_2S$ 305.1449, found: 150.0184 [M-CONHMe $_2$ CH $_2$ 'Bu] $^{+•}$; MS (Cl-NH $_3$) 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), TiCl $_4$ (1M in CH $_2$ Cl $_2$, 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). 1 H NMR (300 MHz, CDCl $_3$) 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); 13 C NMR (75 MHz, CDCl $_3$) 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] $^{+•}$ calcd for $C_{16}H_{19}NO_2S$ 289.1136, found: 164.0295 [M-CONHCy] $^{+•}$; MS (Cl-NH $_3$) 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), TiCl $_4$ (1M in CH $_2$ Cl $_2$, 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). 1 H NMR (300 MHz, CDCl $_3$) 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); 13 C NMR (75 MHz, CDCl $_3$) 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] $^{+•}$ calcd for $C_{16}H_{19}NO_3S$ 305.1086, found: 180.0246 [M-CONHCy] $^{+•}$; MS (Cl-NH $_3$) m/z 306 (100) [MH] $^+$.

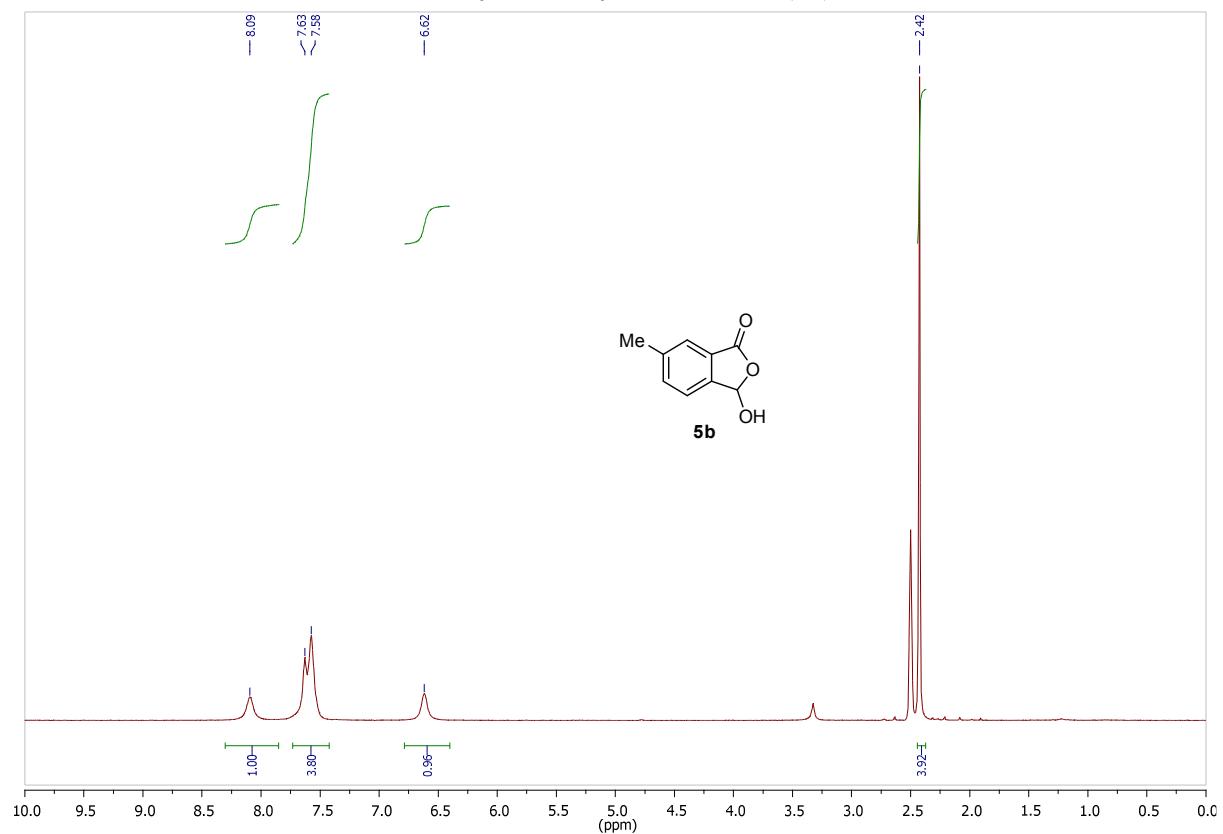
N-(3,4-dimethoxyphenethyl)-3-oxo-1,3-dihydrobenzo[c]thiophene-1-carboxamide (4j): Starting from 2-carboxybenzaldehyde **5a** (165 mg, 1.10 mmol), 2-methylpropane-2-thiol (113 μ L, 1.00 mmol), 4-(2-isocyanoethyl)-1,2-dimethoxybenzene **2j** (287 mg, 1.50 mmol), TiCl $_4$ (1M in CH $_2$ Cl $_2$, 2.20 mL, 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). 1 H NMR (300 MHz, CDCl $_3$) 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); 13 C NMR (75 MHz, CDCl $_3$) 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] $^{+•}$ calcd for $C_{19}H_{19}NO_4S$ 357.1035, found: 357.1049.

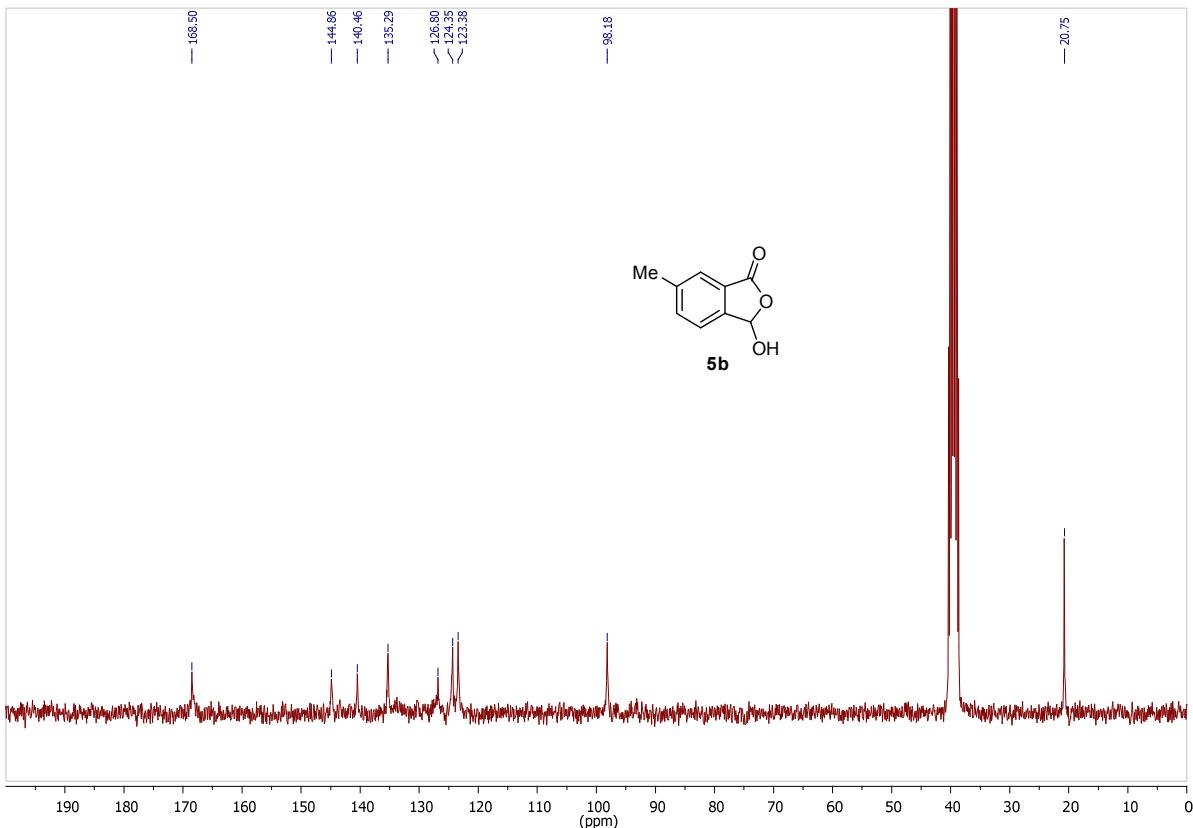
N-tert-butyl-5-methoxy-3-oxo-1,3-dihydrobenzo[c]thiophene-1-carboxamide (4a''): Starting from 2-formyl-5-methoxybenzoic acid **5c** (100 mg, 0.55 mmol), 2-methylpropane-2-thiol (56 μ L, 0.50 mmol), *tert*-butylisocyanide **2a** (85 μ L, 0.75 mmol), $TiCl_4$ (1M in CH_2Cl_2 , 1.10 mL, 1.10 mmol) in 10 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, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{14}H_{17}NO_3S$ 279.0929, found: 180.0246 [M-CONH $'$ Bu] $^{+•}$; MS (CI-NH $_3$) 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(3H)-one **1d** (100 mg, 0.35 mmol), cyclohexylisocyanide **2b** (52 μ L, 0.42 mmol), $TiCl_4$ (1M in CH_2Cl_2 , 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, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{23}H_{25}NO_3S$ 395.1555, found: 149.9808 [M-(CONHCy + CH_2 -4-OMePh)] $^{+•}$; MS (CI-NH $_3$) m/z 396 (100) [MH] $^+$.

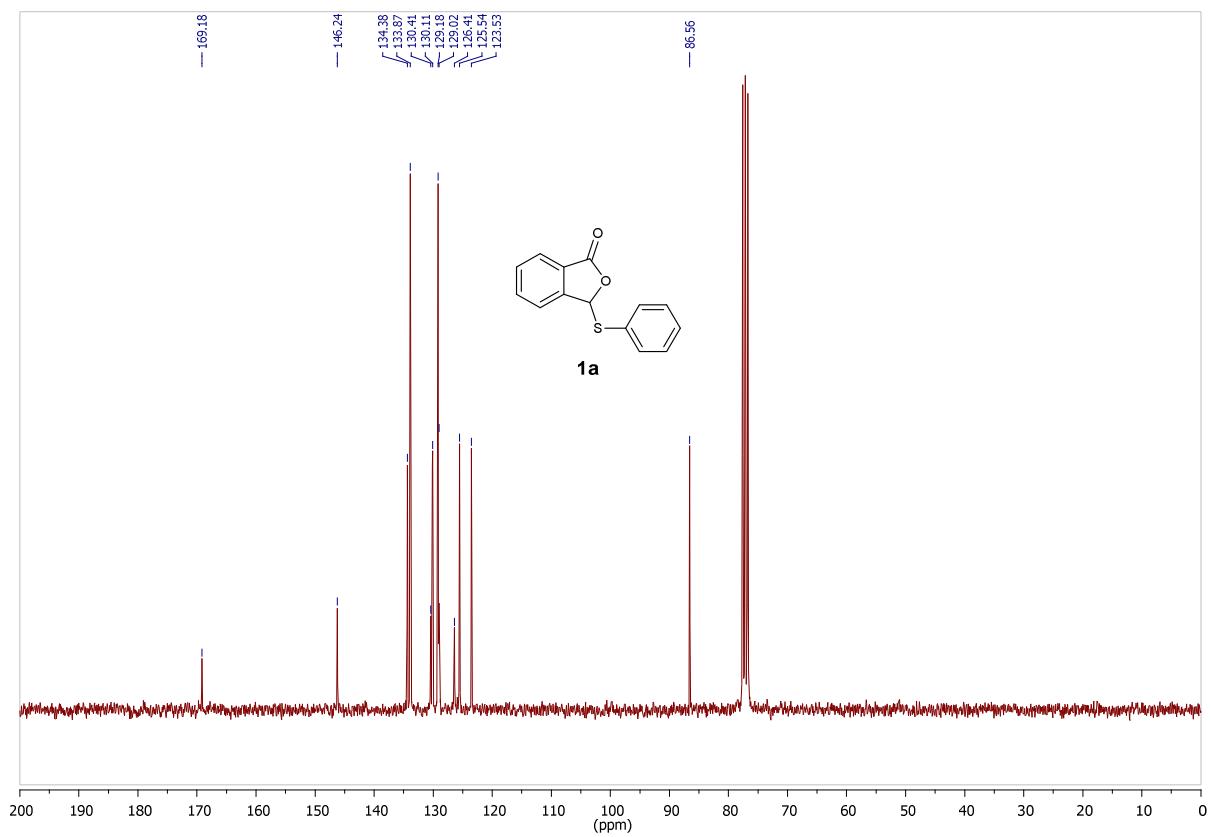
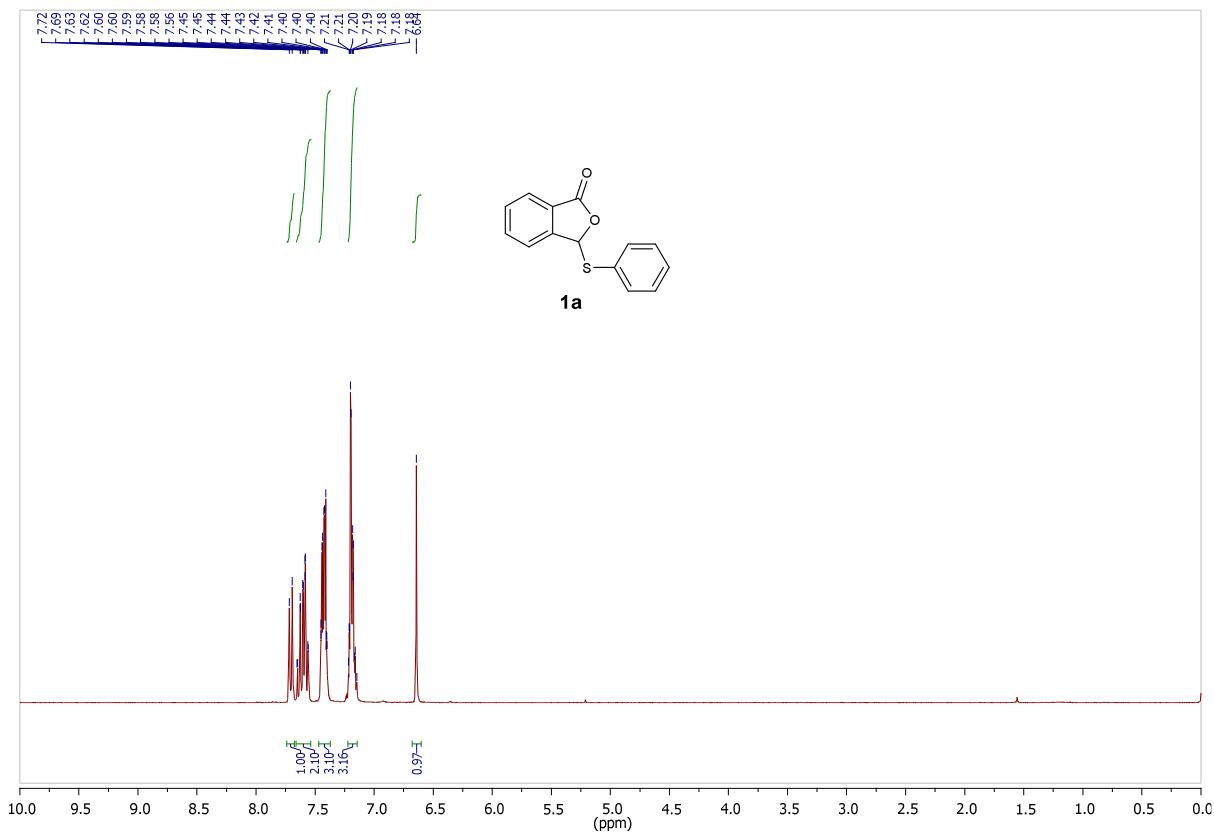
VI. Copies of 1H & ^{13}C NMR spectra

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

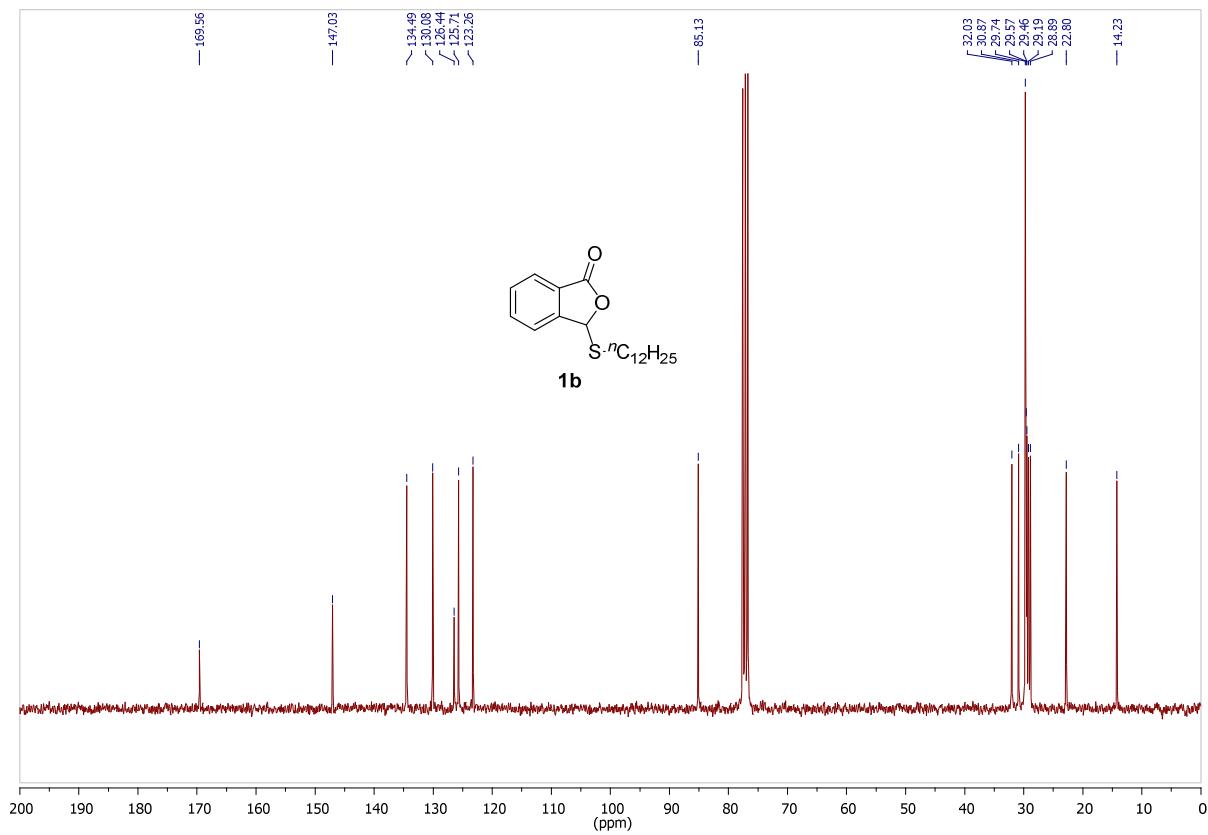
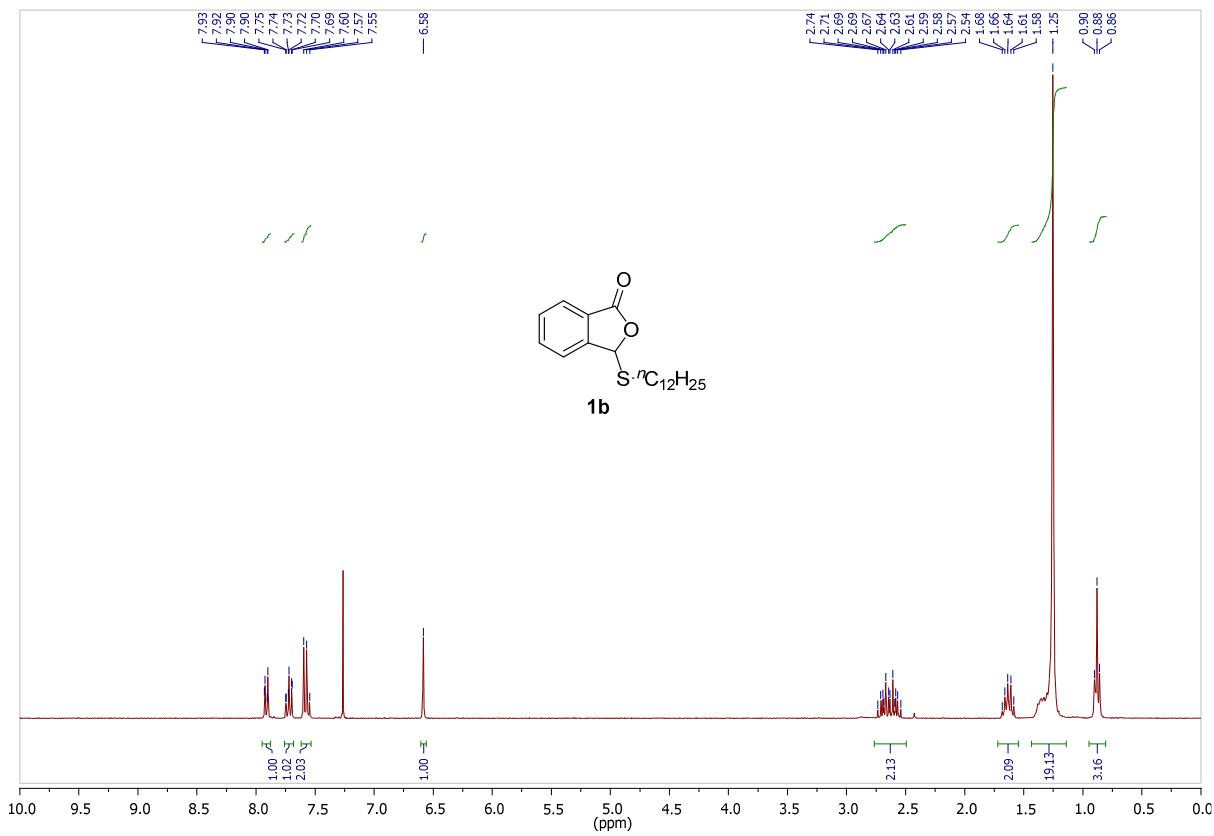




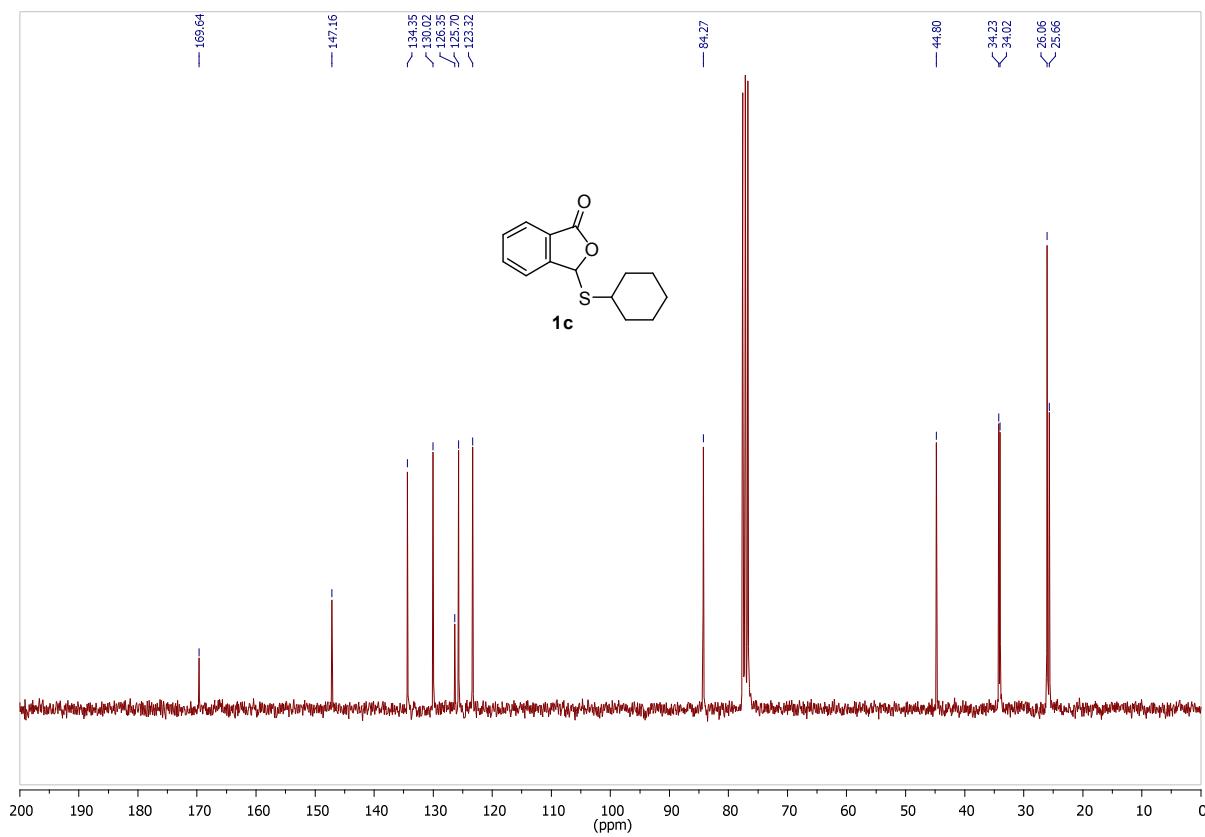
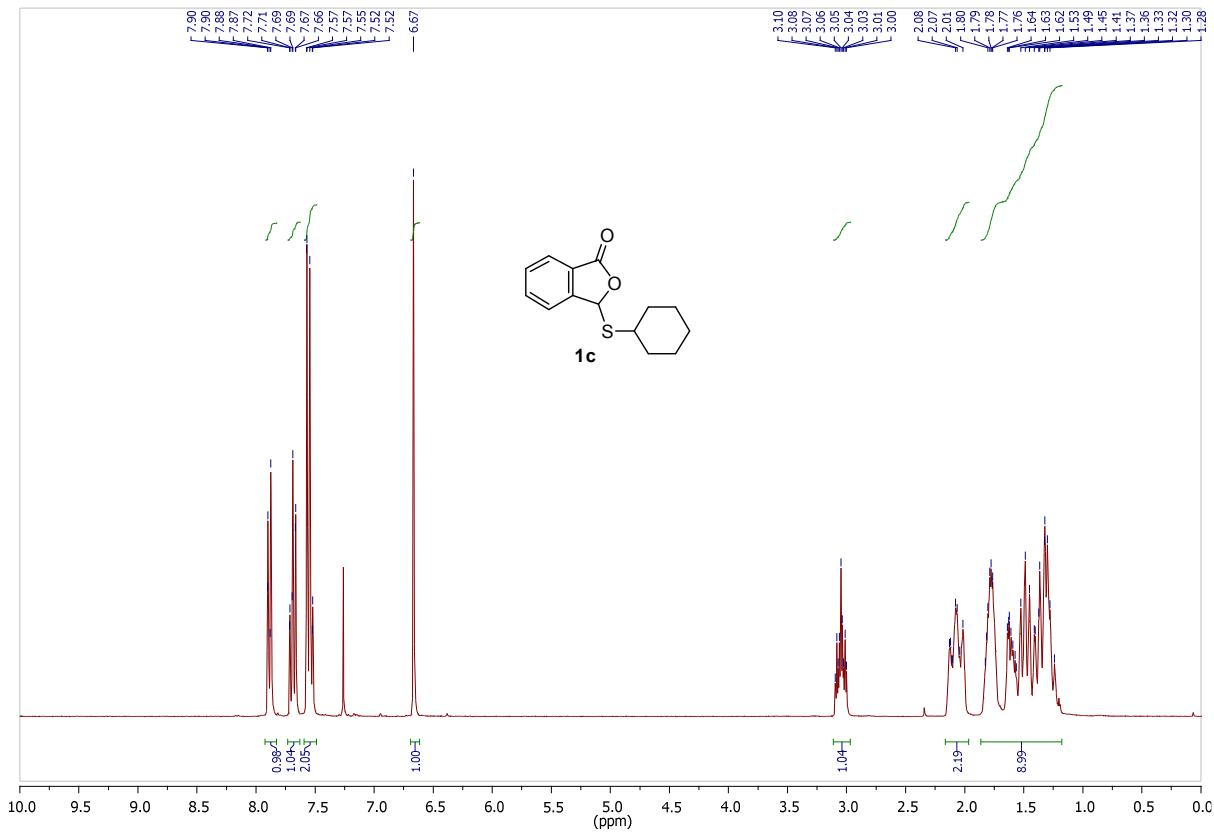
3-(Phenylthio)isobenzofuran-1(3H)-one(1a):



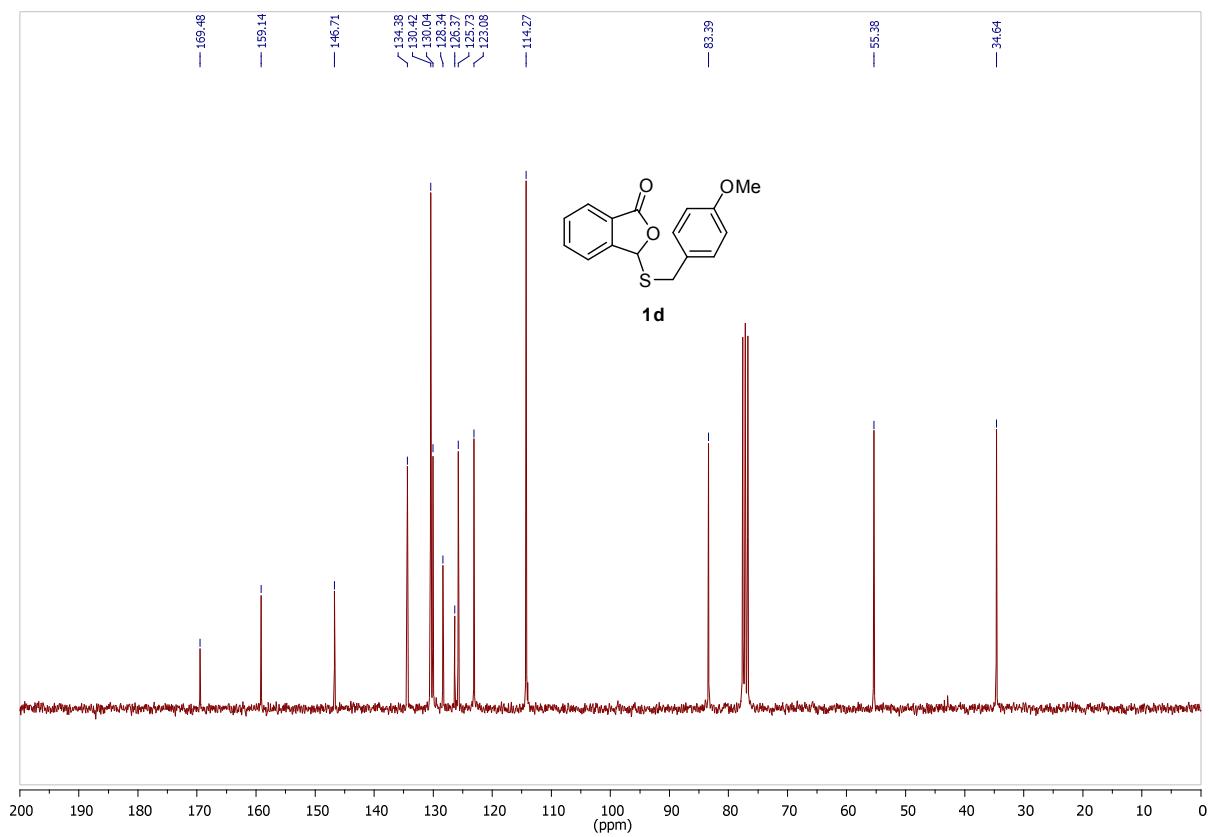
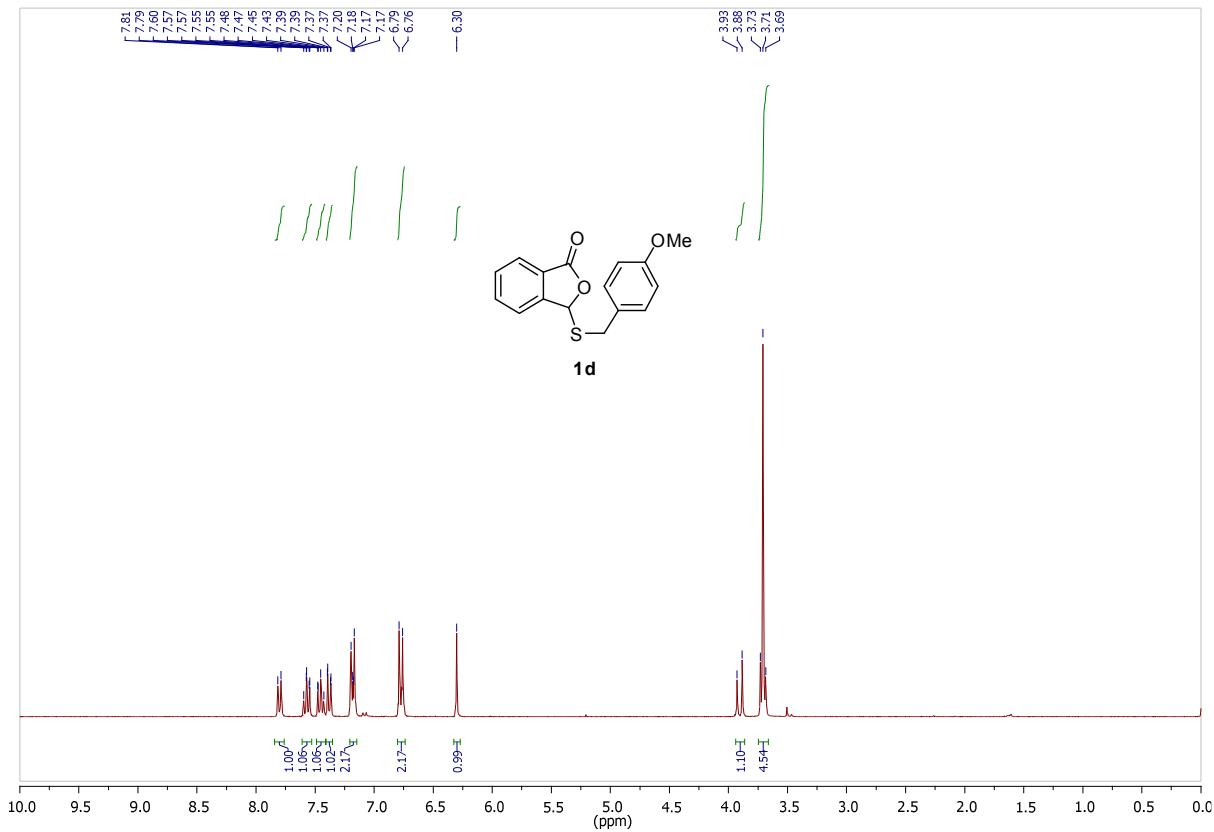
3-(Dodecylthio)isobenzofuran-1(3H)-one(1b):



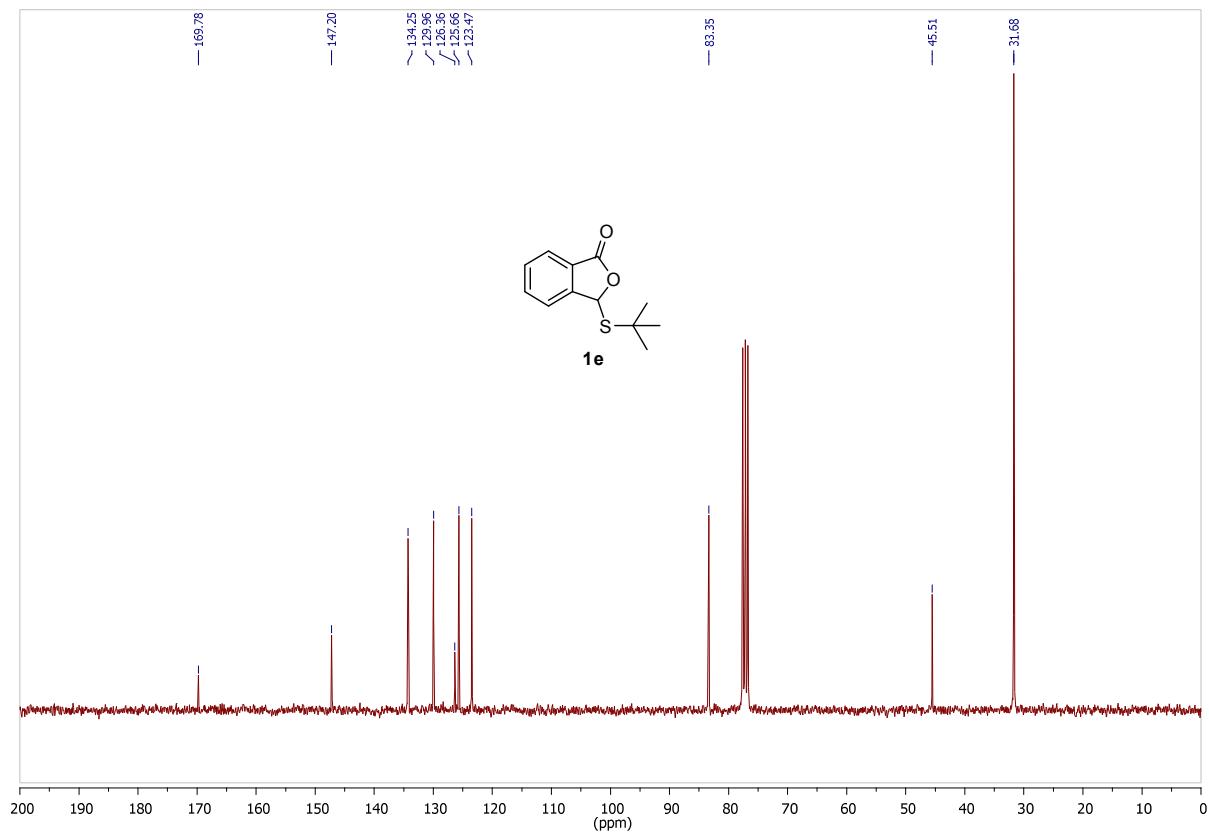
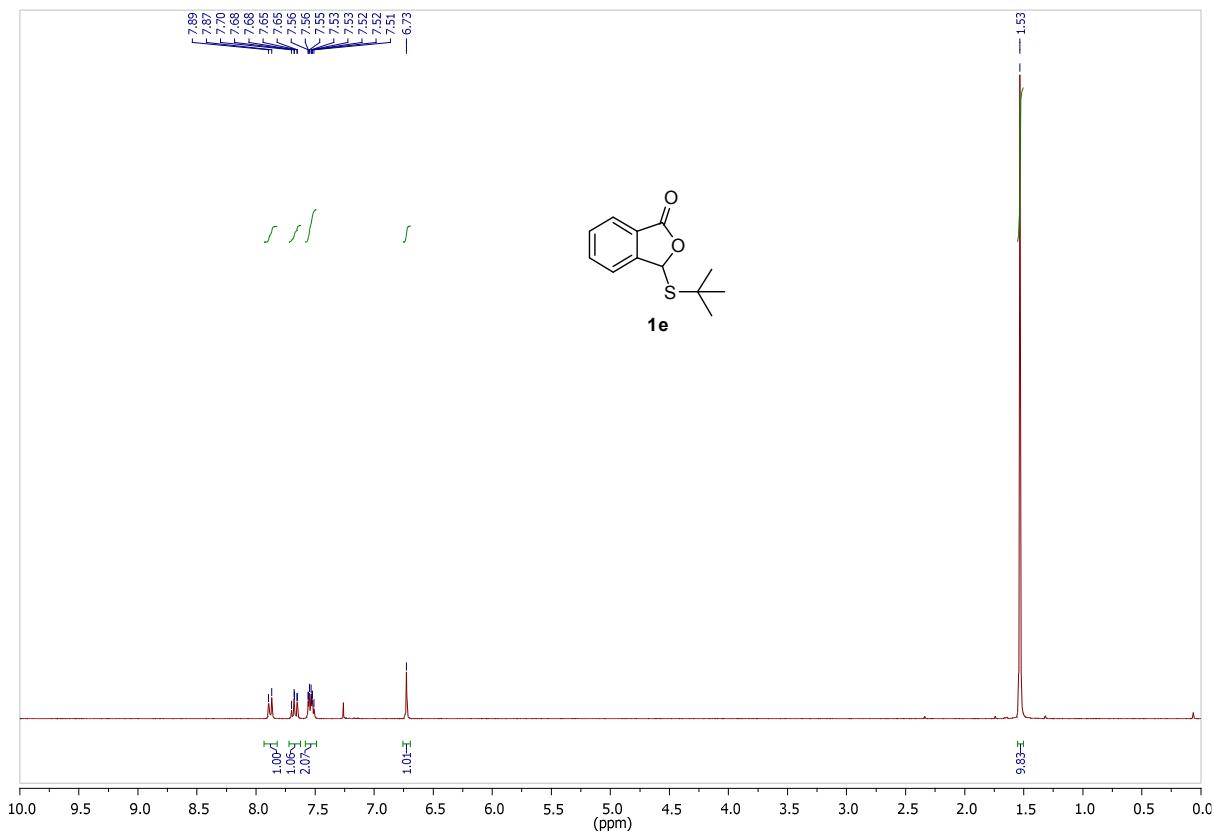
3-(Cyclohexylthio)isobenzofuran-1(3H)-one(1c):



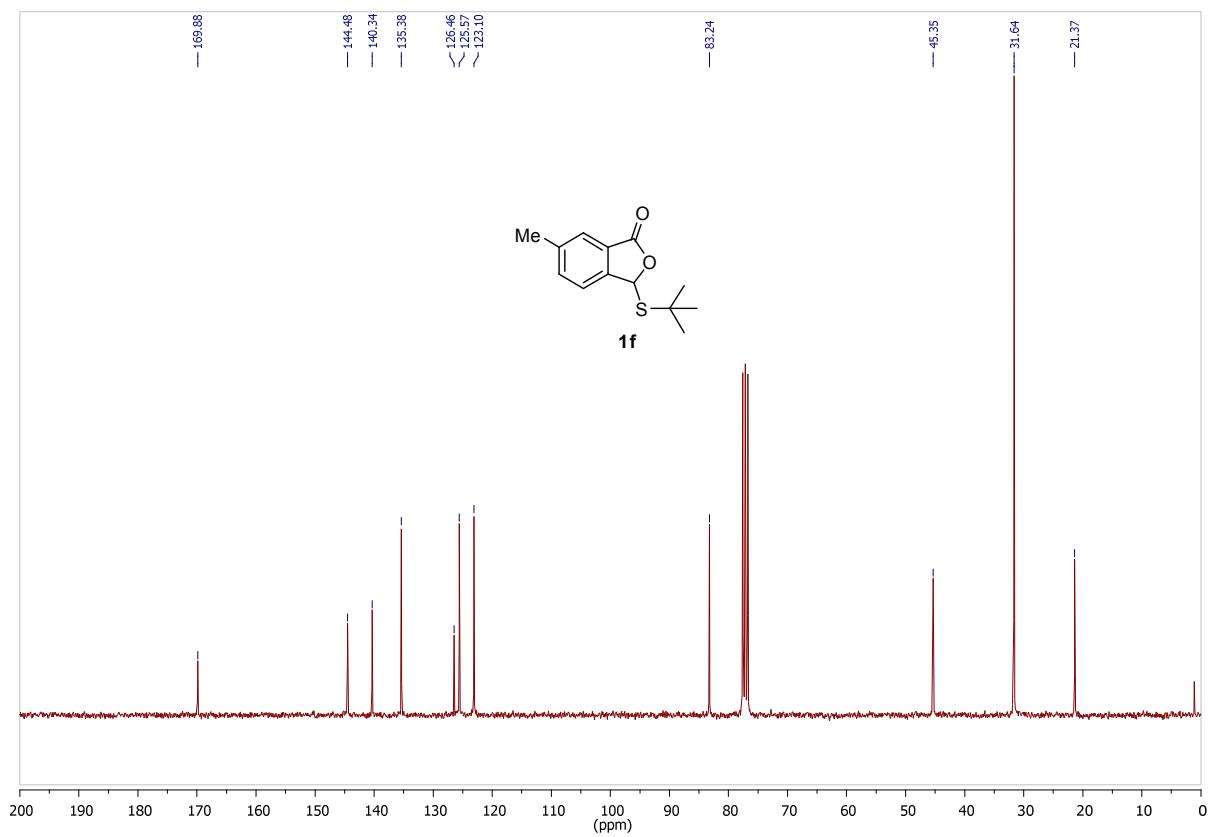
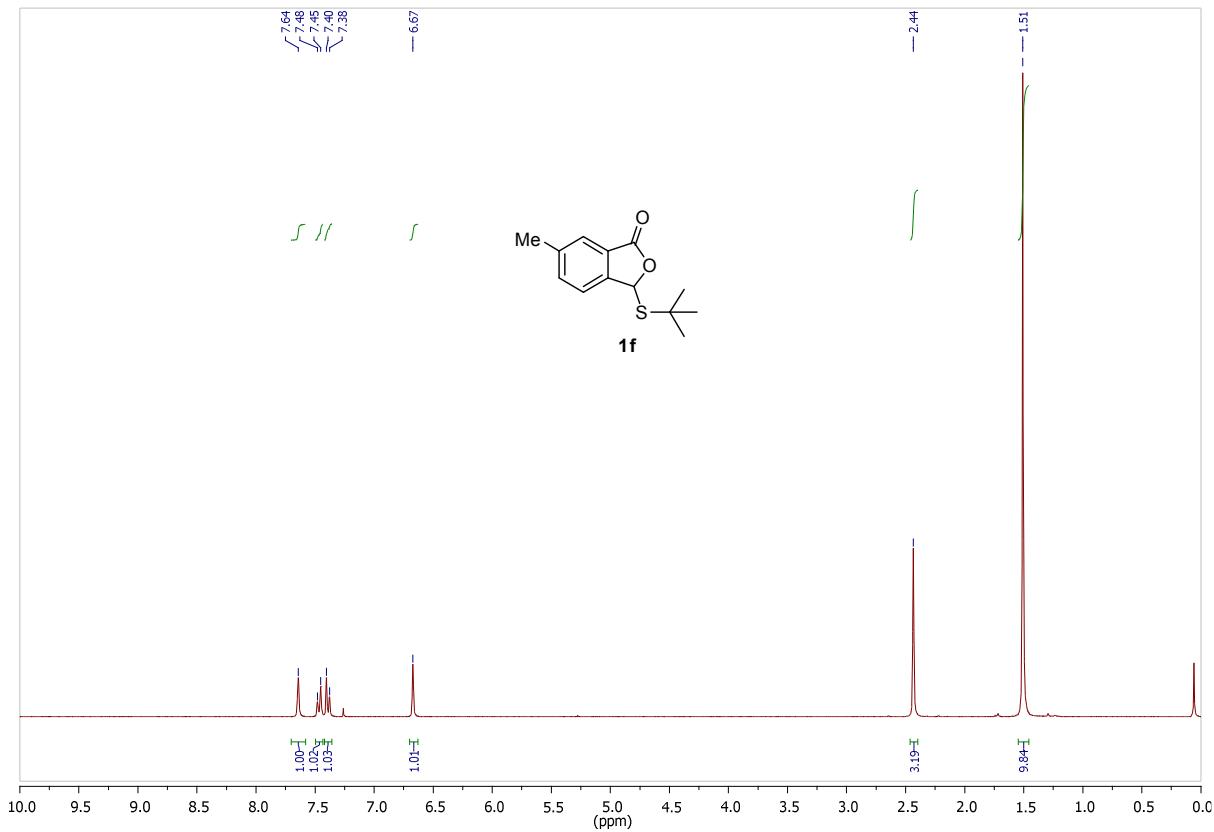
3-(4-Methoxybenzylthio)isobenzofuran-1(3H)-one(1d):



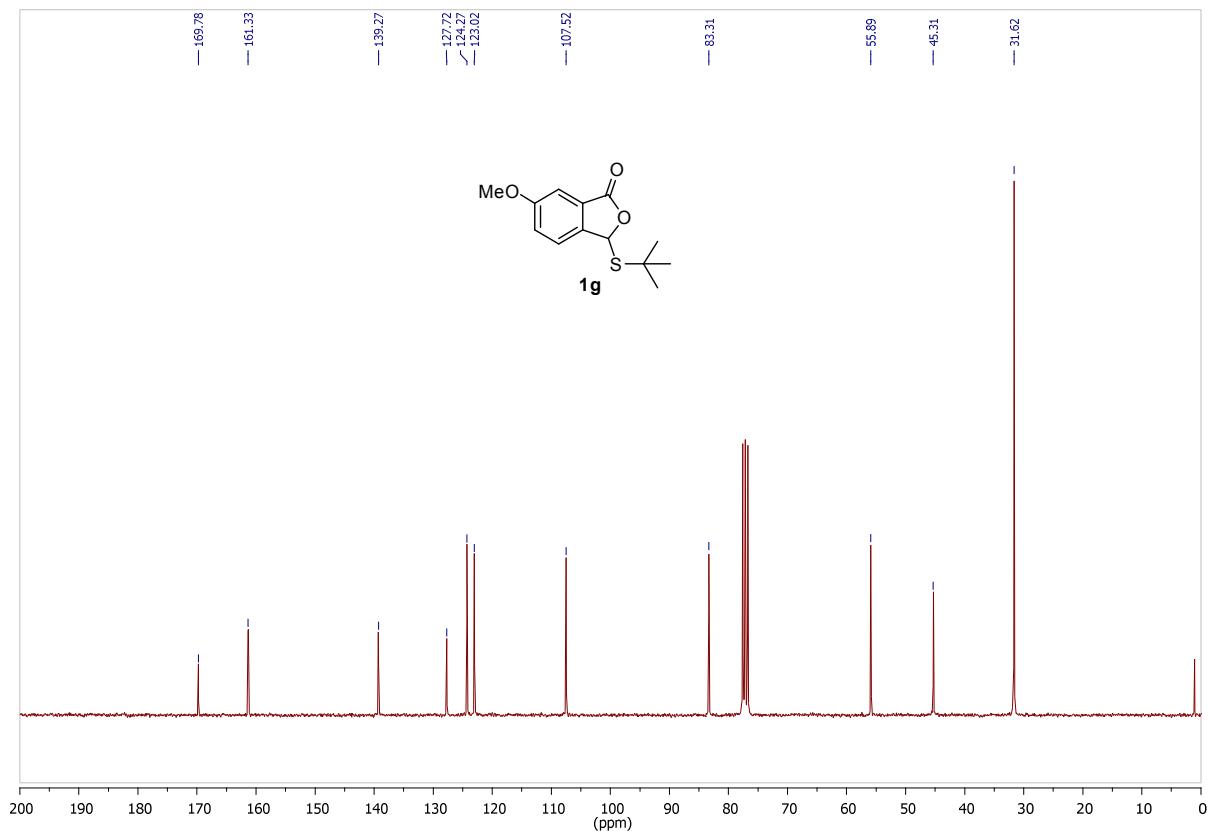
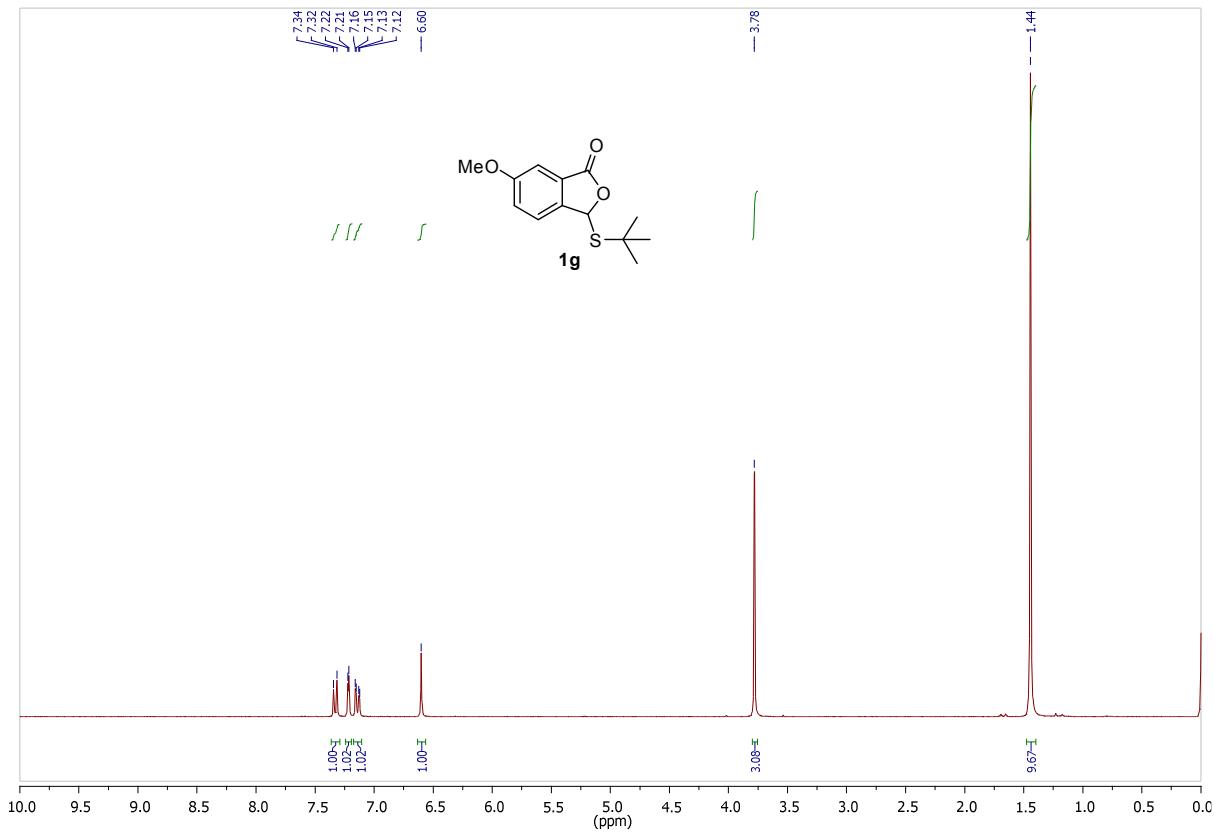
3-(tert-Butylthio)isobenzofuran-1(3H)-one(1e):



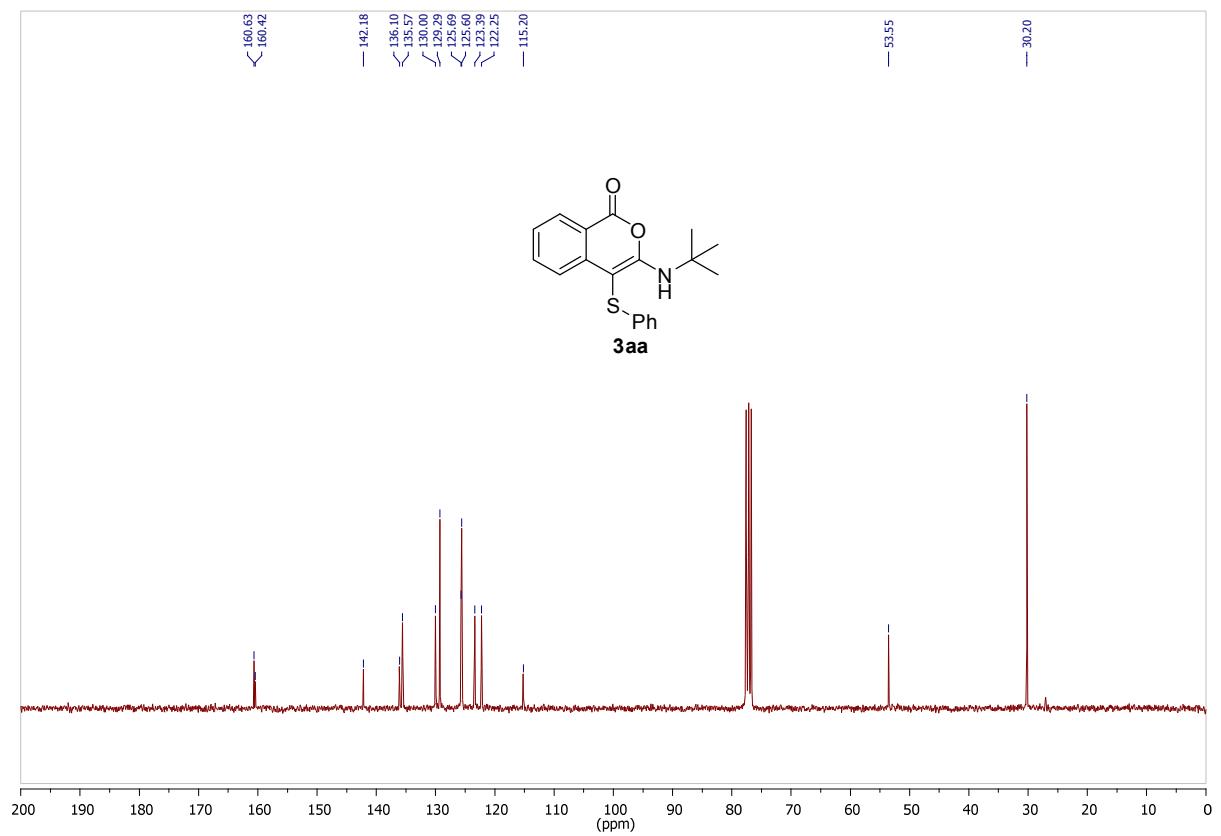
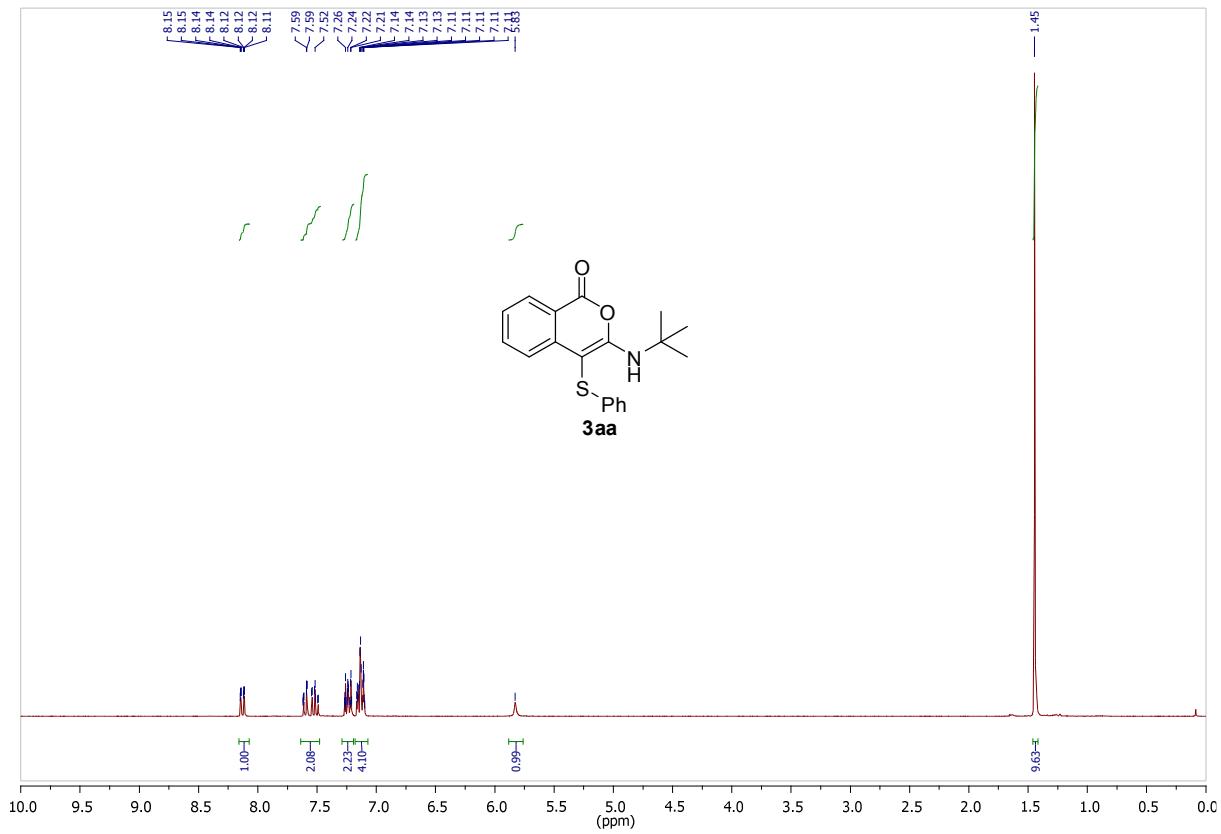
3-(*tert*-Butylthio)-6-methylisobenzofuran-1(3*H*)-one(**1f**):



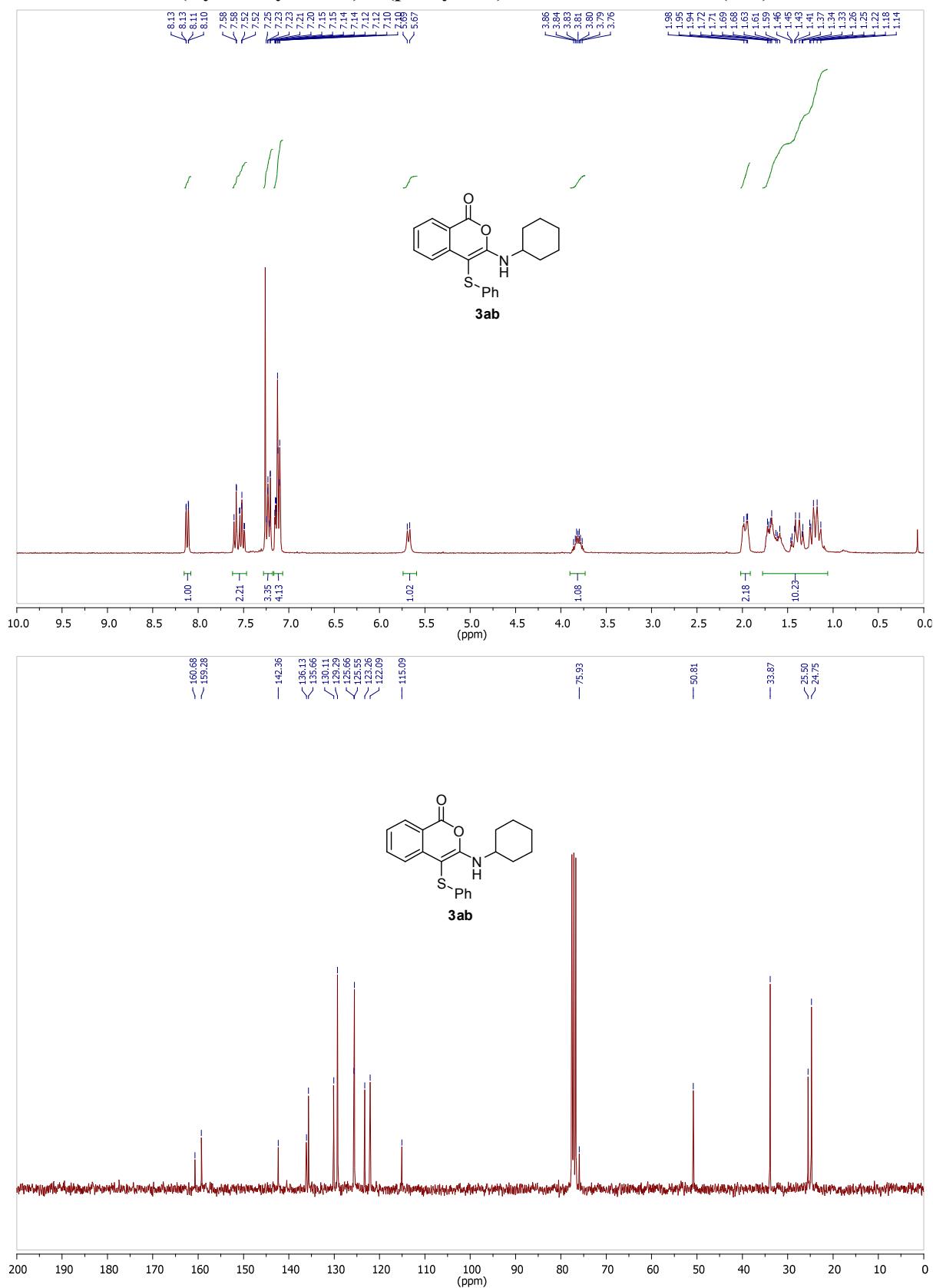
3-(*tert*-Butylthio)-6-methoxyisobenzofuran-1(3*H*)-one(1g):



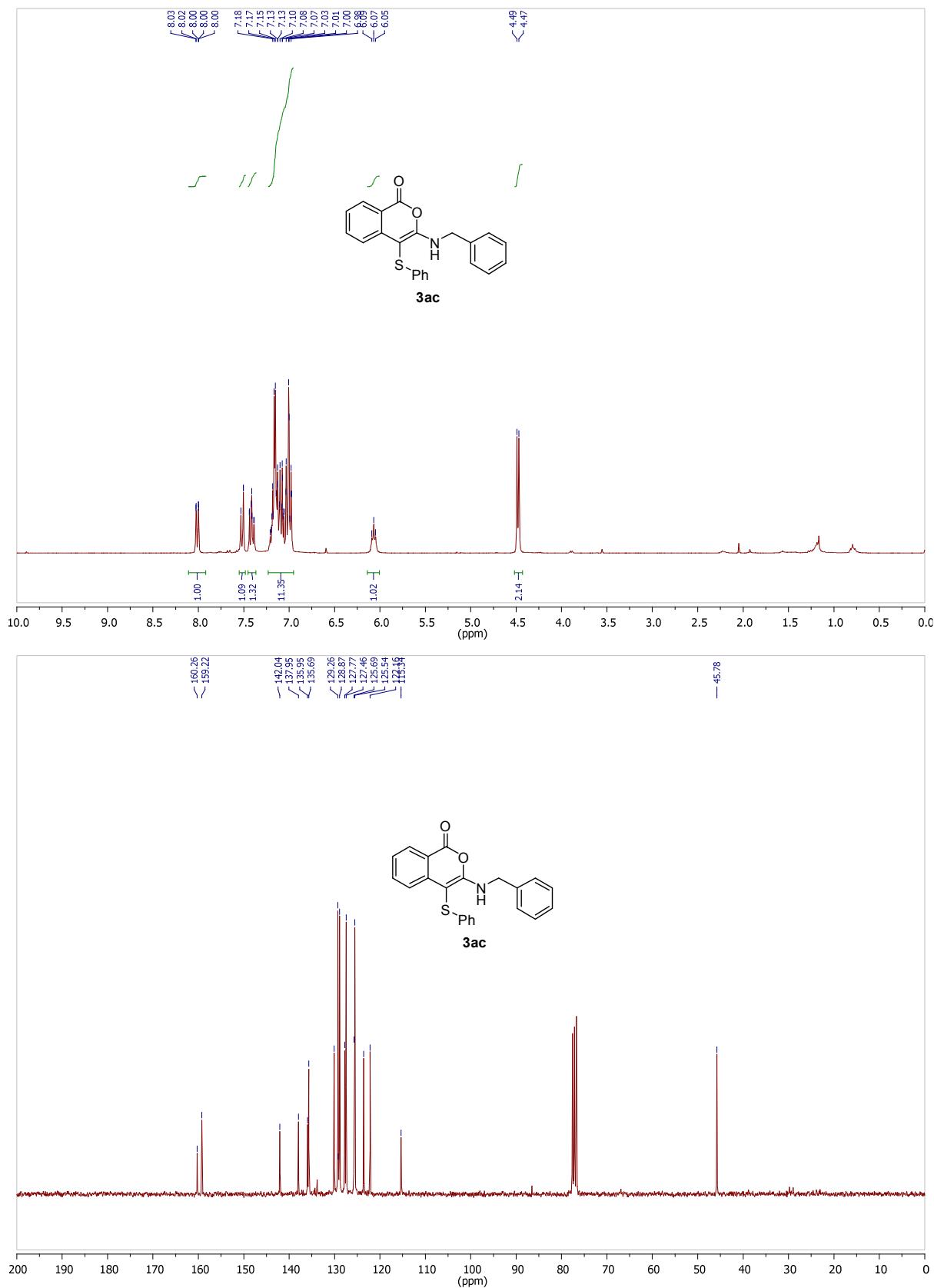
3-(*tert*-Butylamino)-4-(phenylthio)-1*H*-isochromen-1-one (3aa):



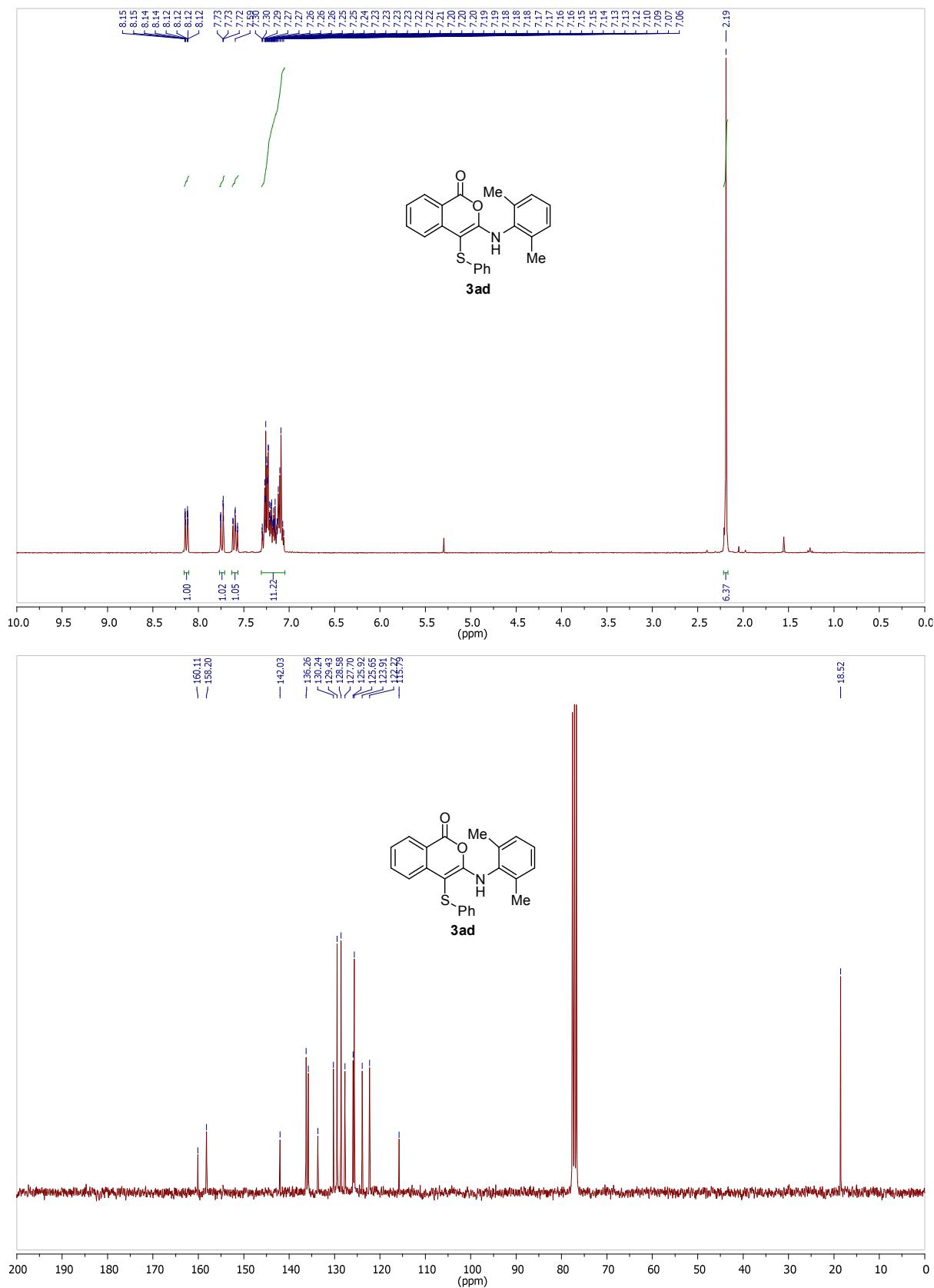
3-(Cyclohexylamino)-4-(phenylthio)-1*H*-isochromen-1-one(3ab):



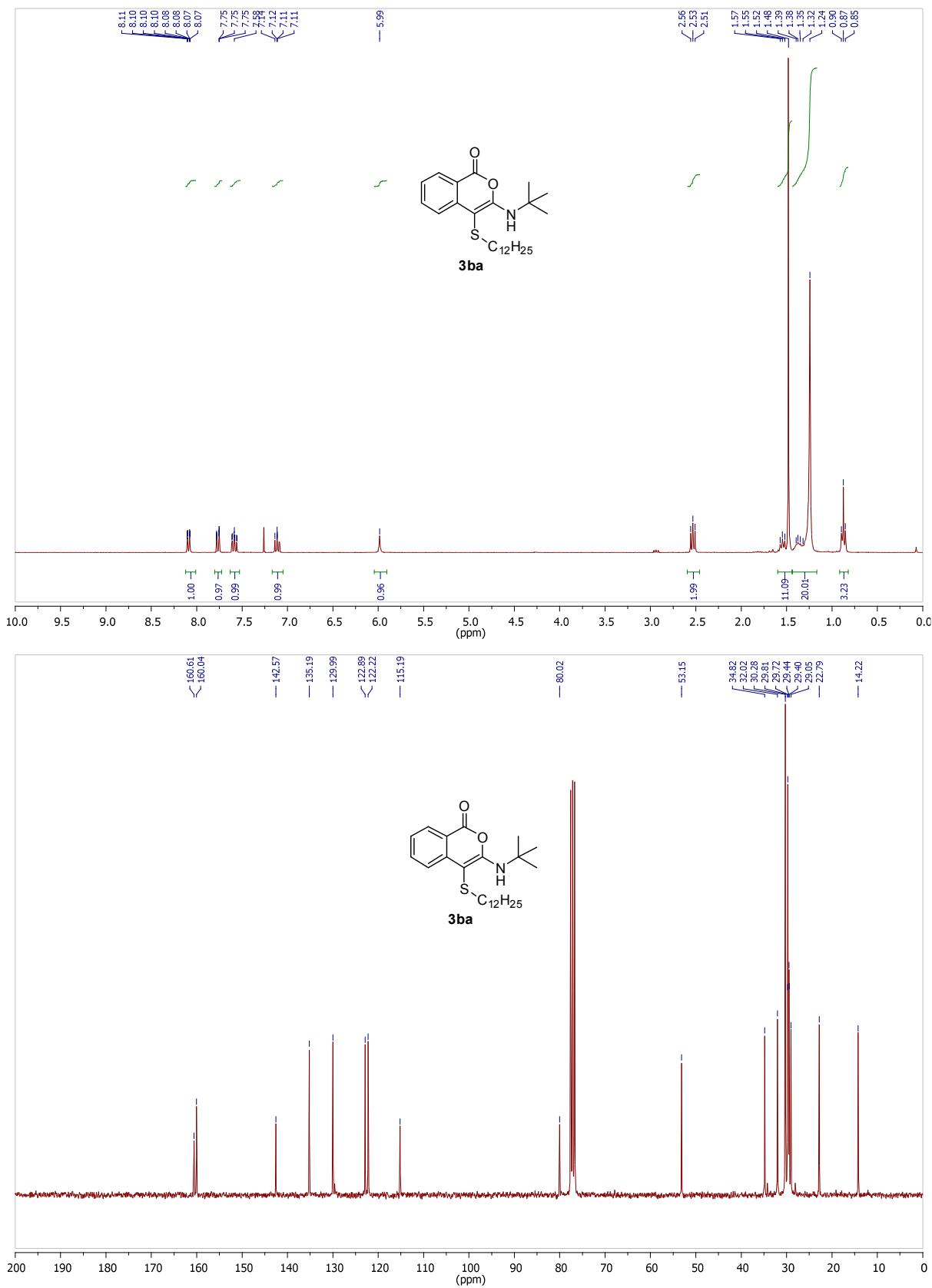
3-(Benzylamino)-4-(phenylthio)-1*H*-isochromen-1-one(3ac):



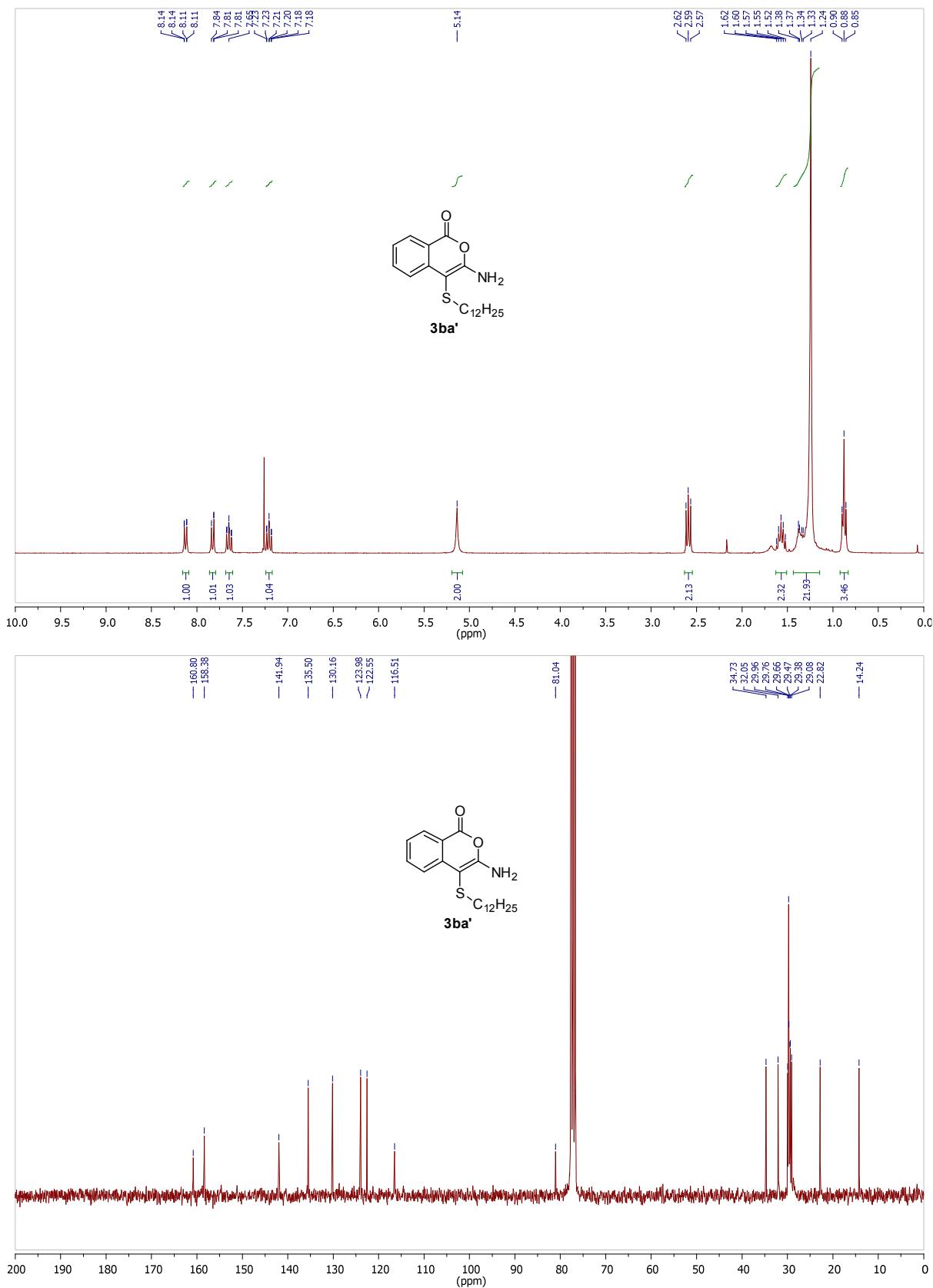
3-(2,6-Dimethylphenylamino)-4-(phenylthio)-1*H*-isochromen-1-one(3ad):



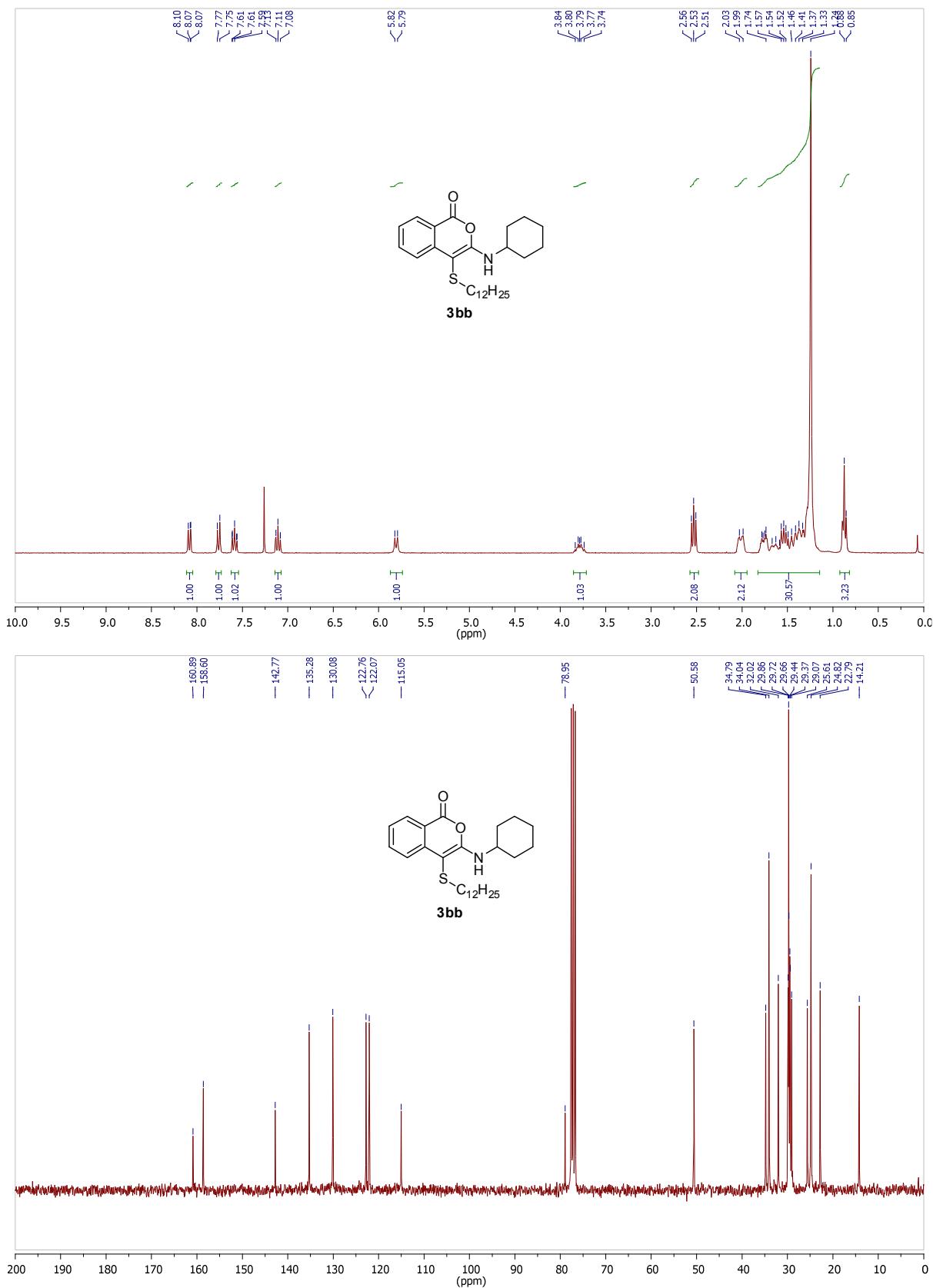
3-(*tert*-Butylamino)-4-(dodecylthio)-1*H*-isochromen-1-one(3ba):



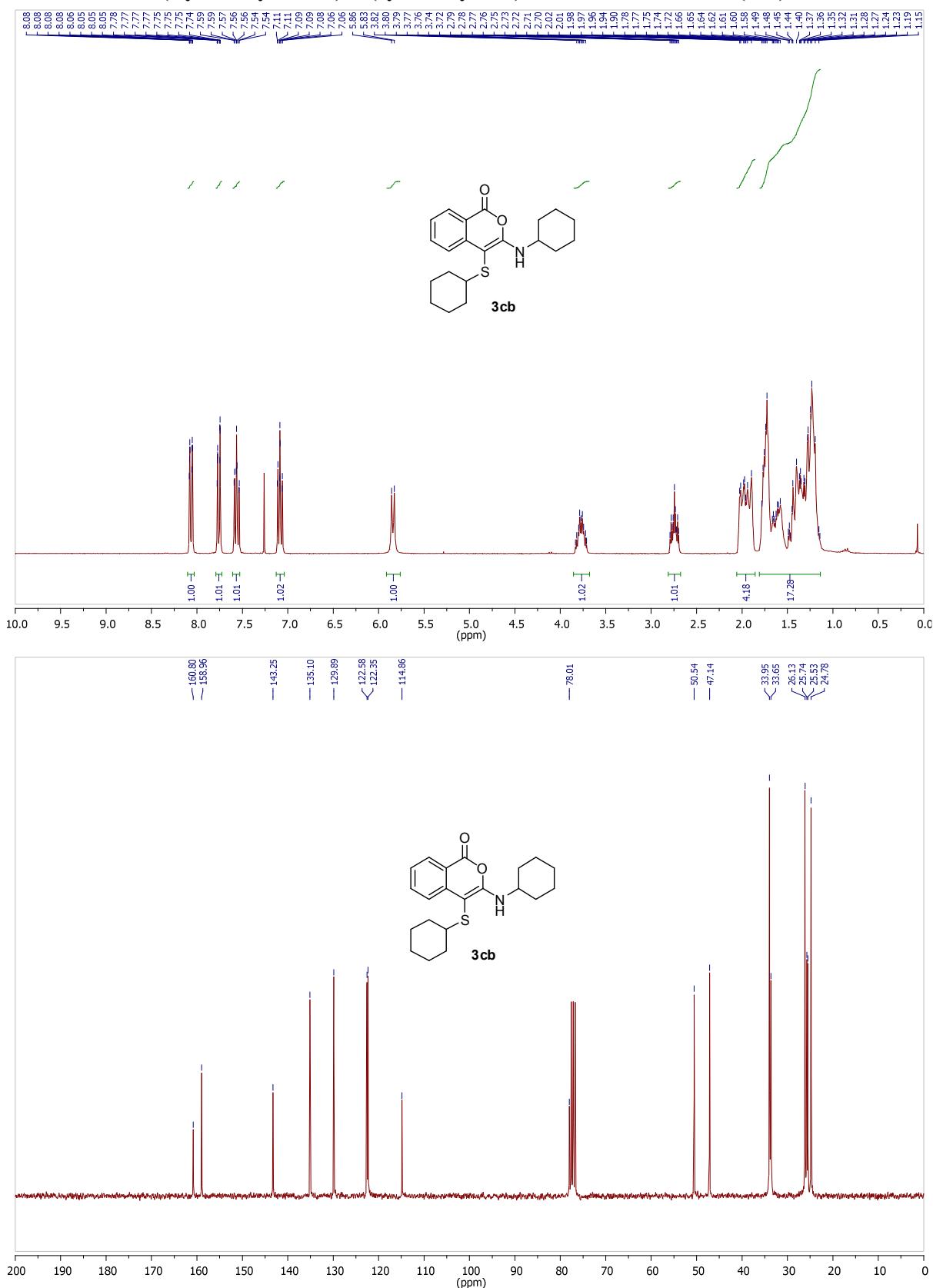
3-Amino-4-(dodecylthio)-1*H*-isochromen-1-one(3ba'):



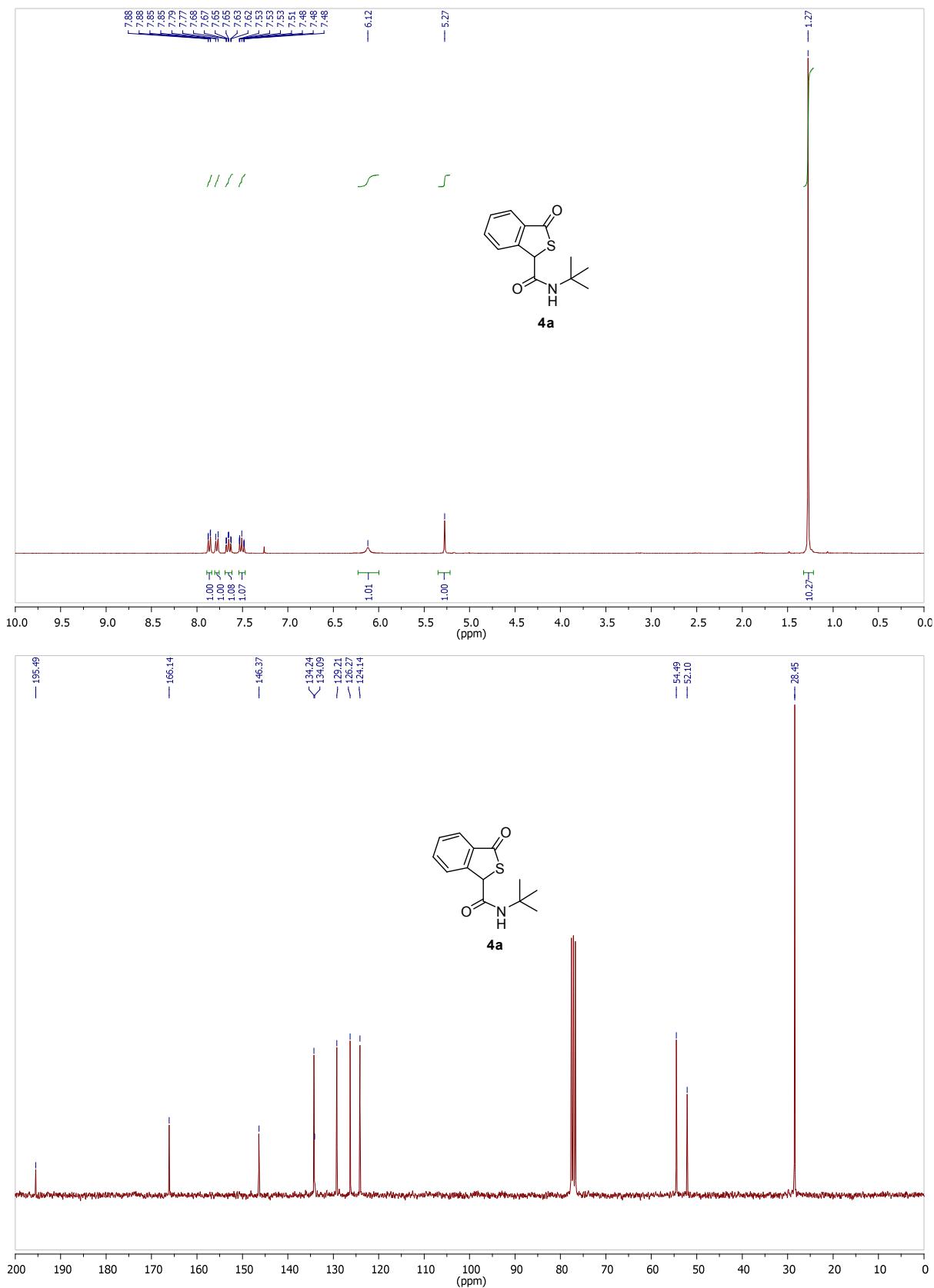
3-(Cyclohexylamino)-4-(dodecylthio)-1*H*-isochromen-1-one(3bb):



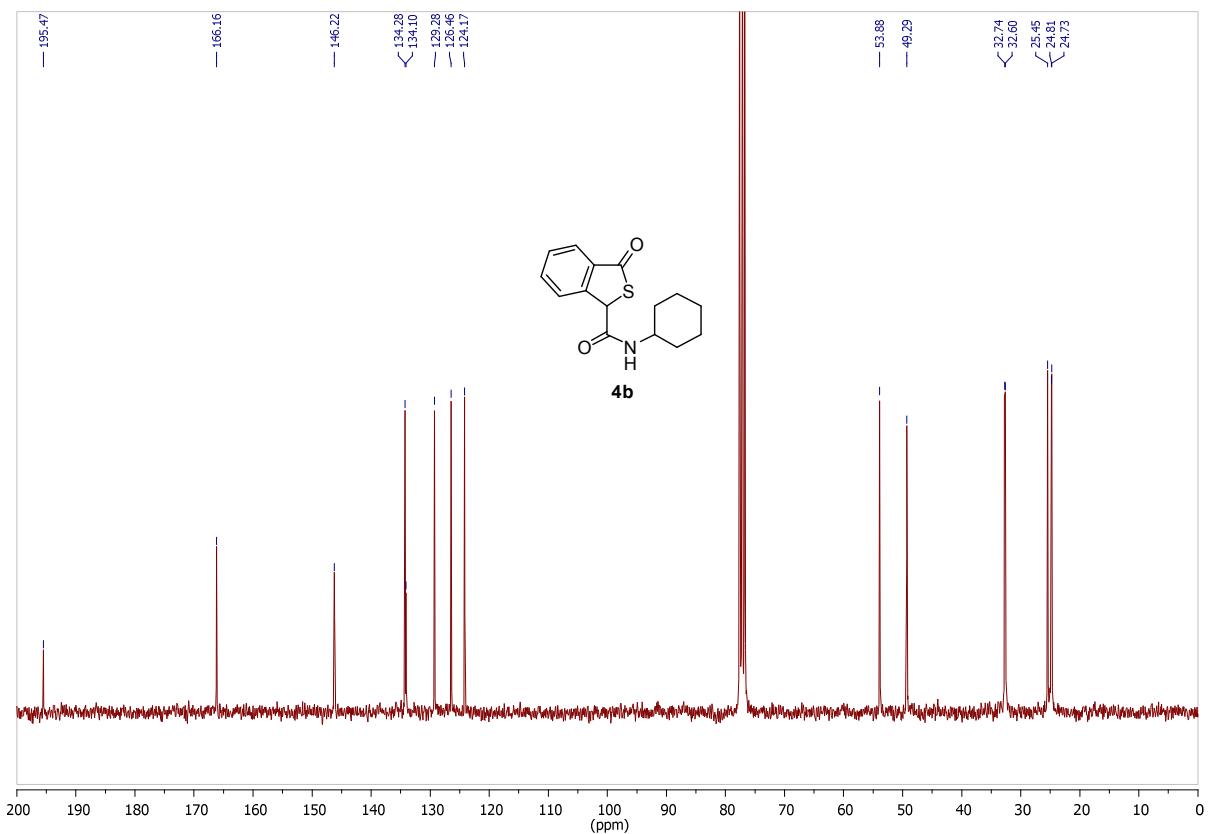
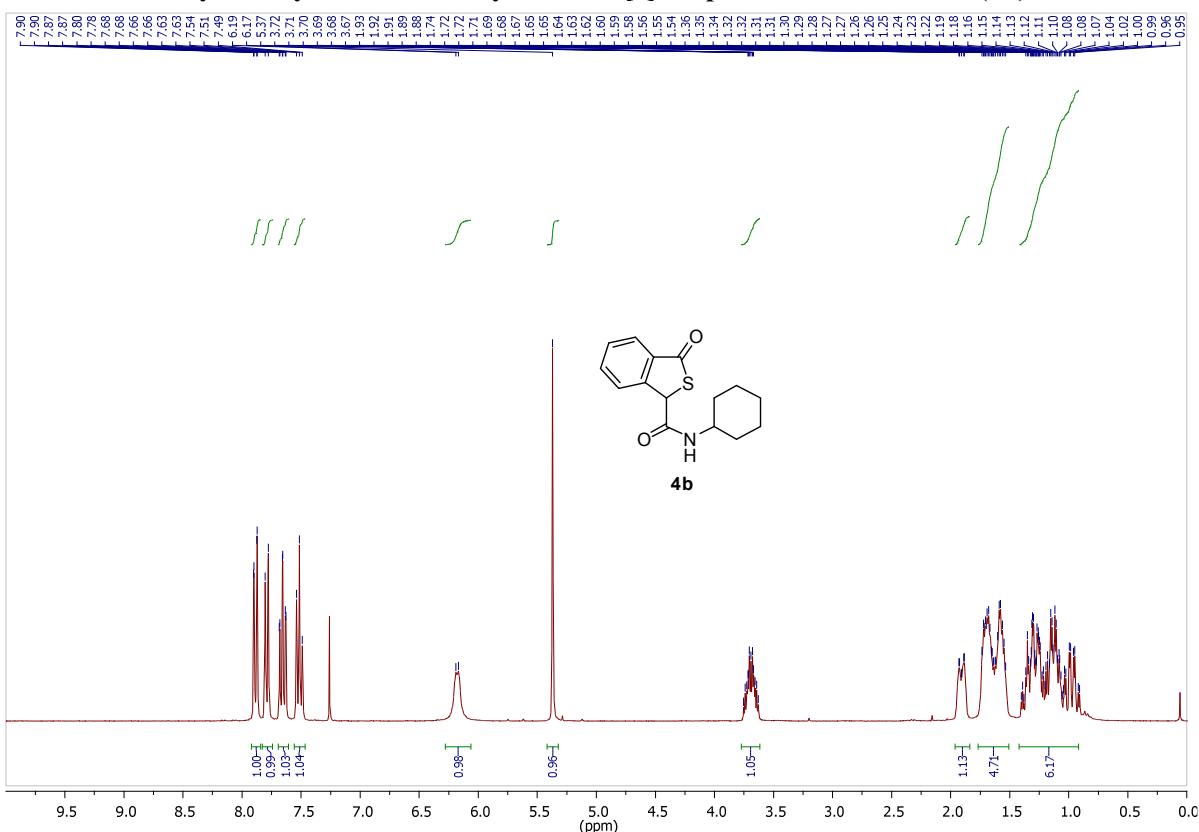
3-(Cyclohexylamino)-4-(cyclohexylthio)-1*H*-isochromen-1-one(3cb):



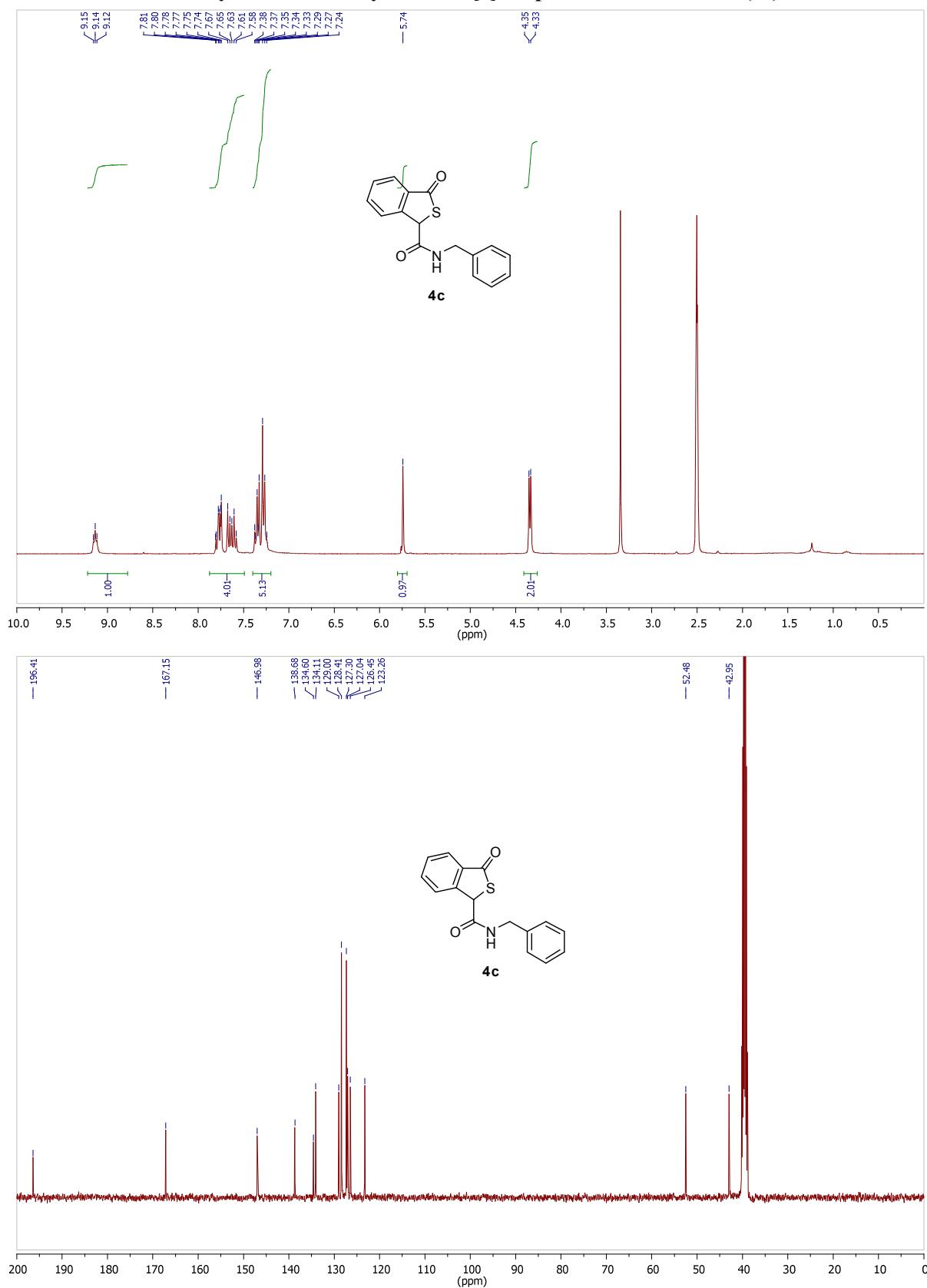
N-tert-butyl-3-oxo-1,3-dihydrobenzo[c]thiophene-1-carboxamide(4a):



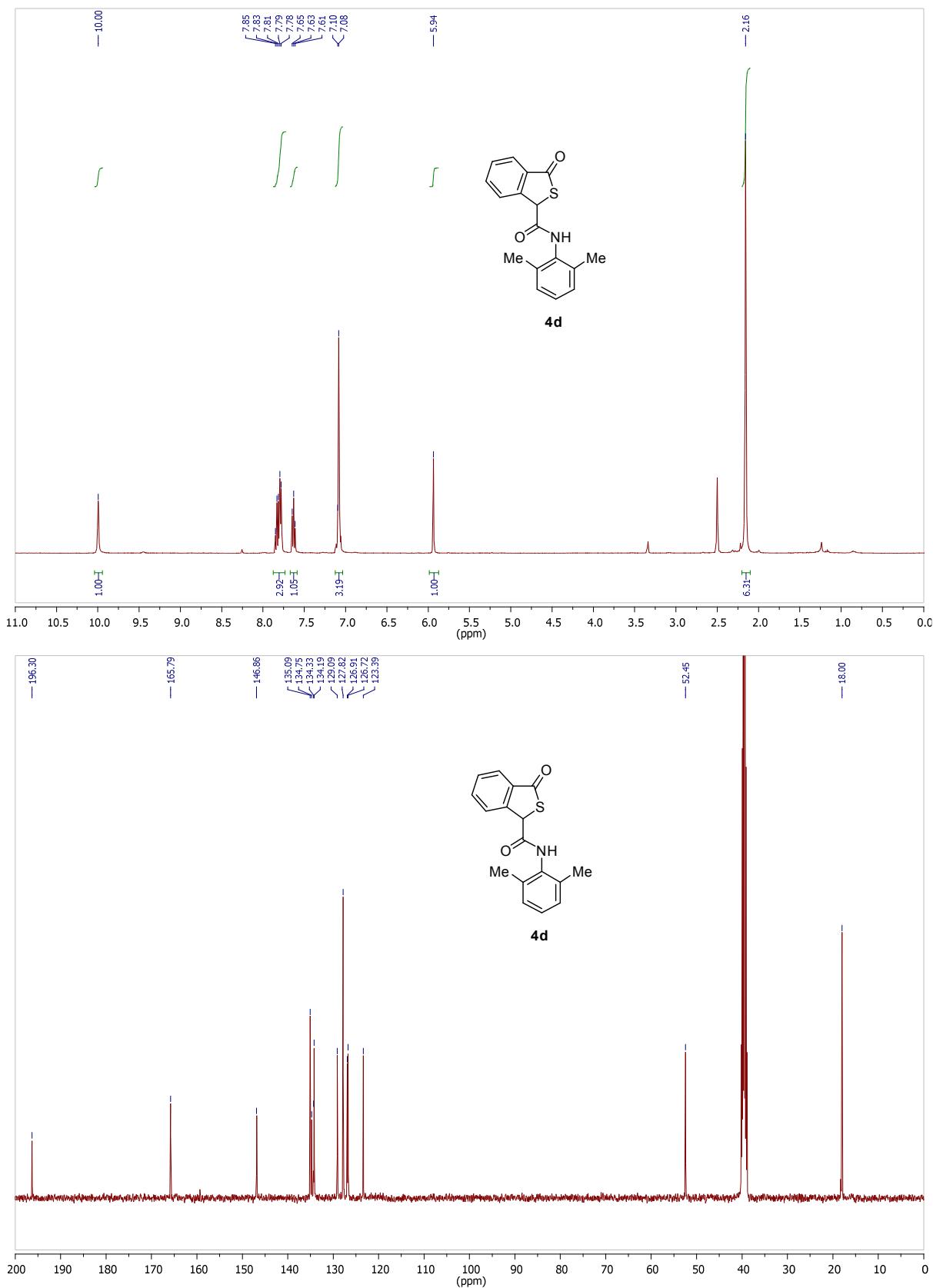
N-cyclohexyl-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide(4b):



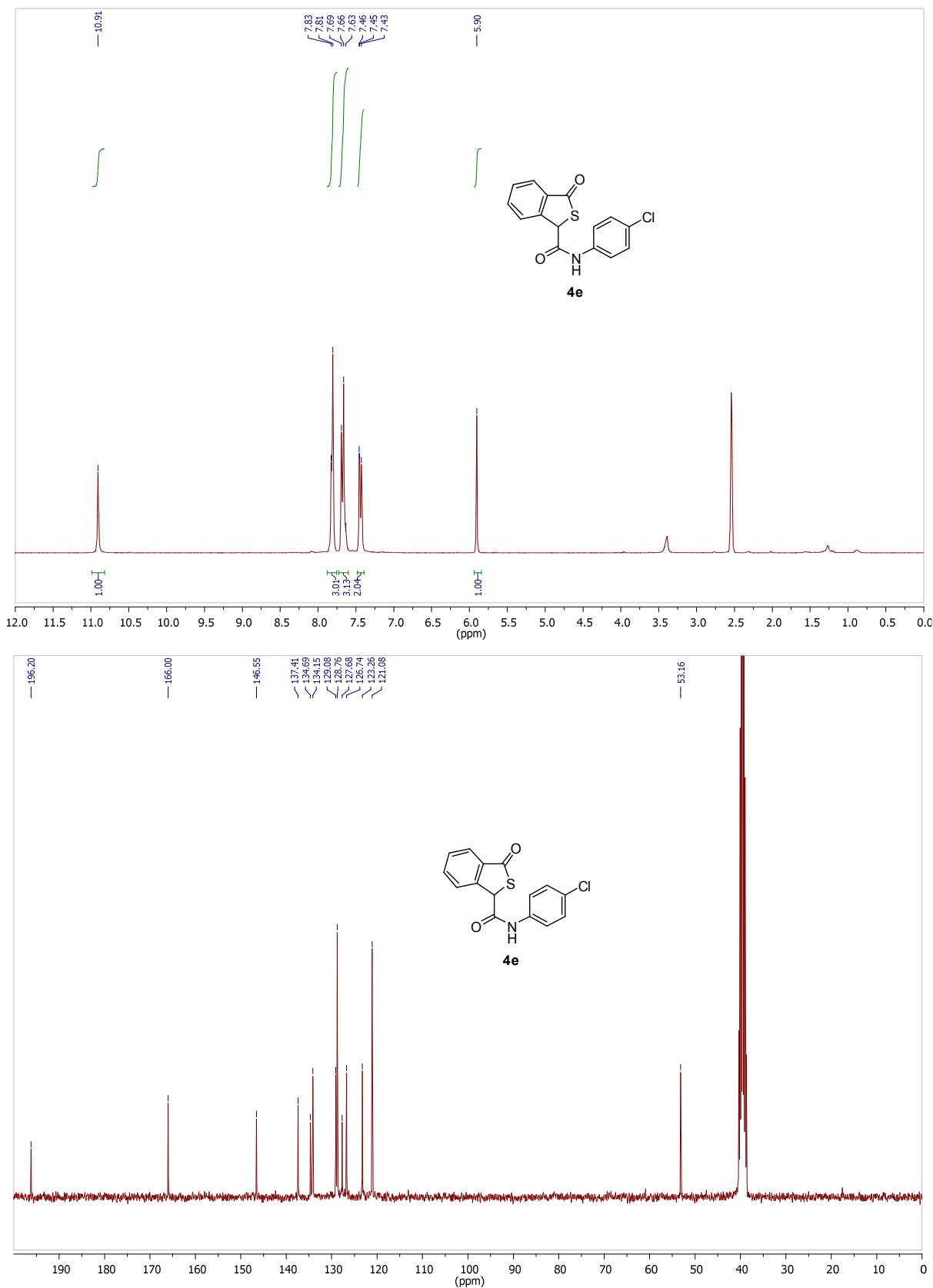
***N*-benzyl-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide(4c):**



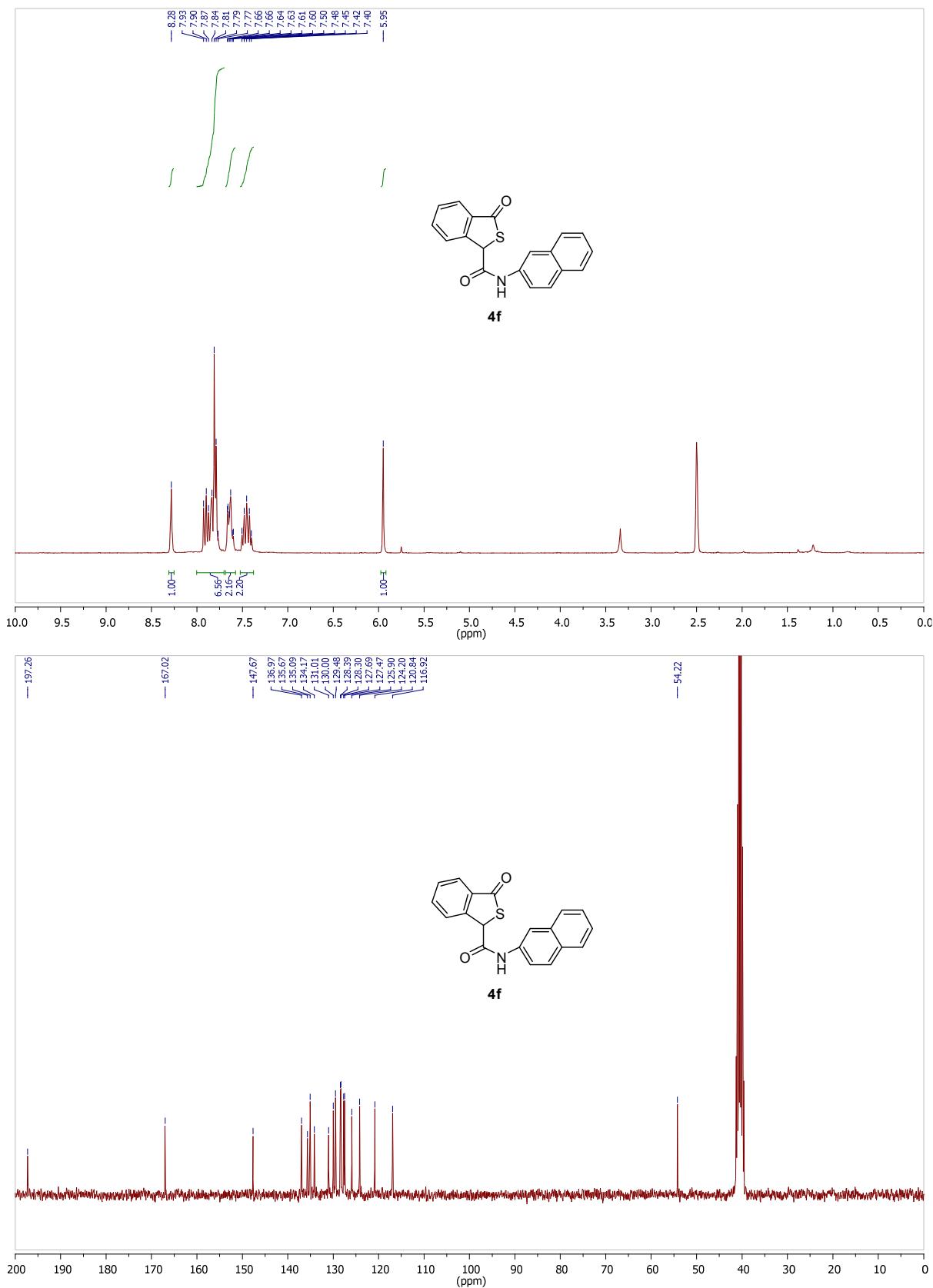
***N*-(2,6-dimethylphenyl)-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide(4d):**



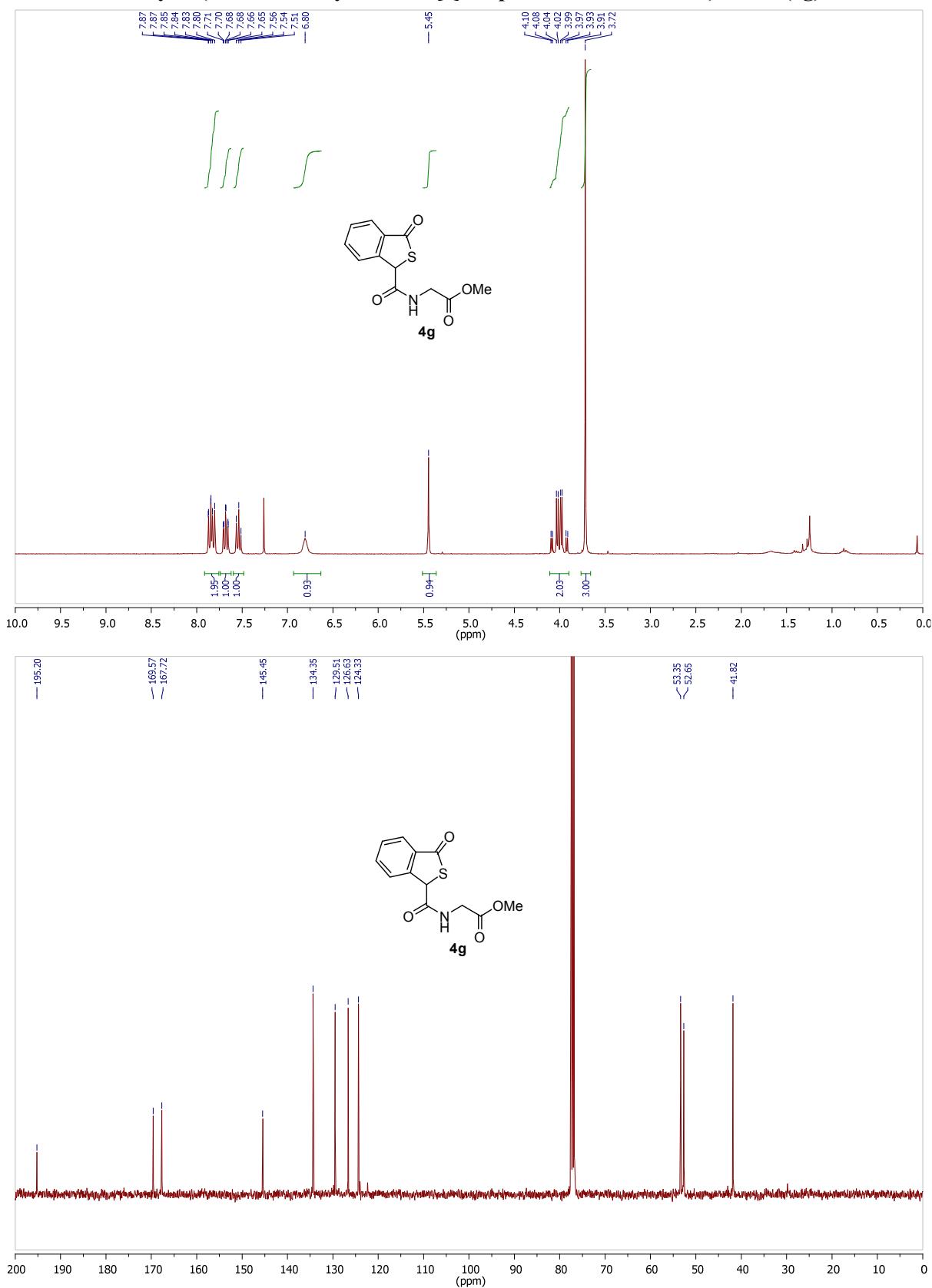
***N*-(4-chlorophenyl)-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide(4e):**



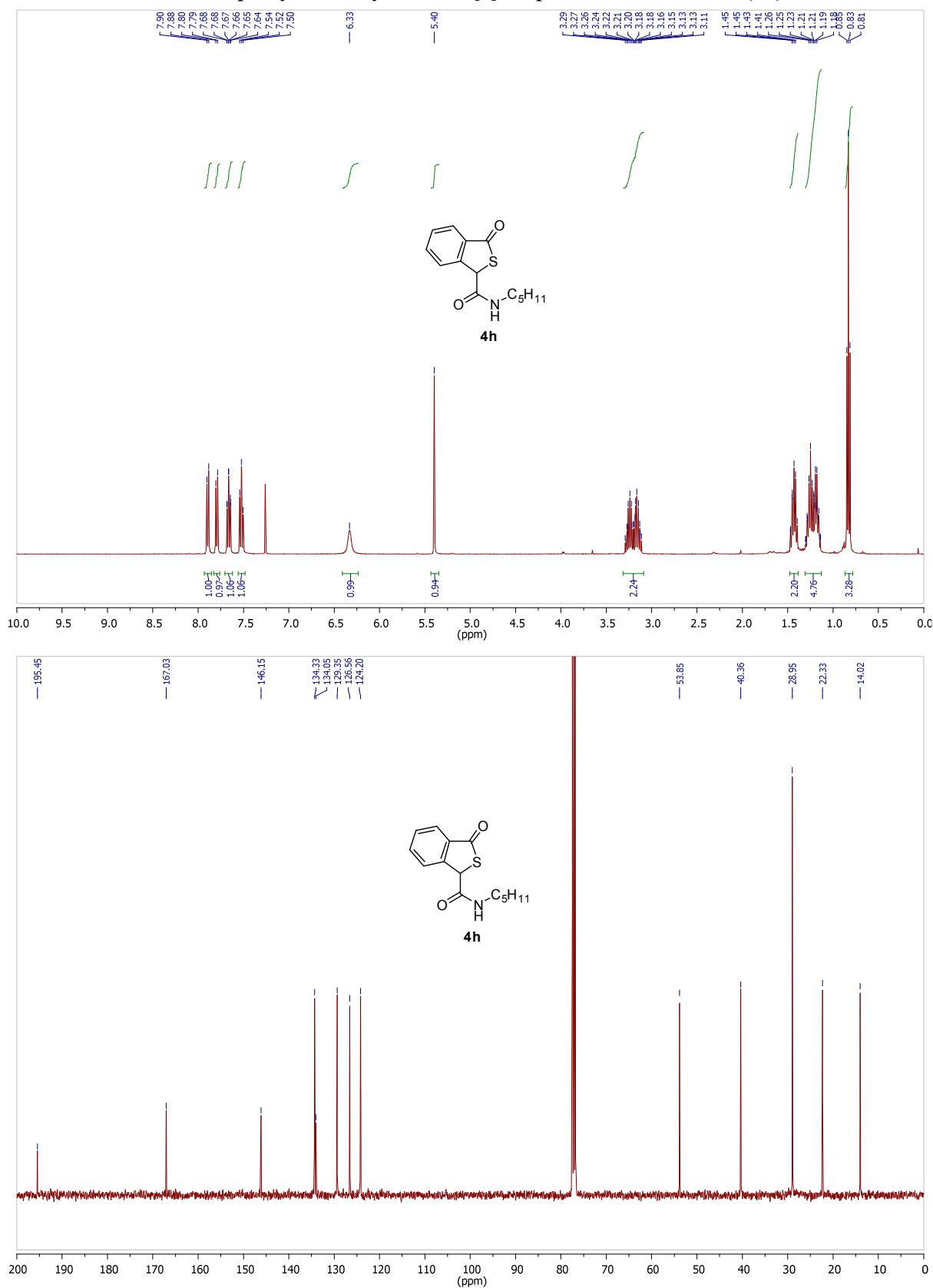
N-(naphthalen-2-yl)-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide(4f):



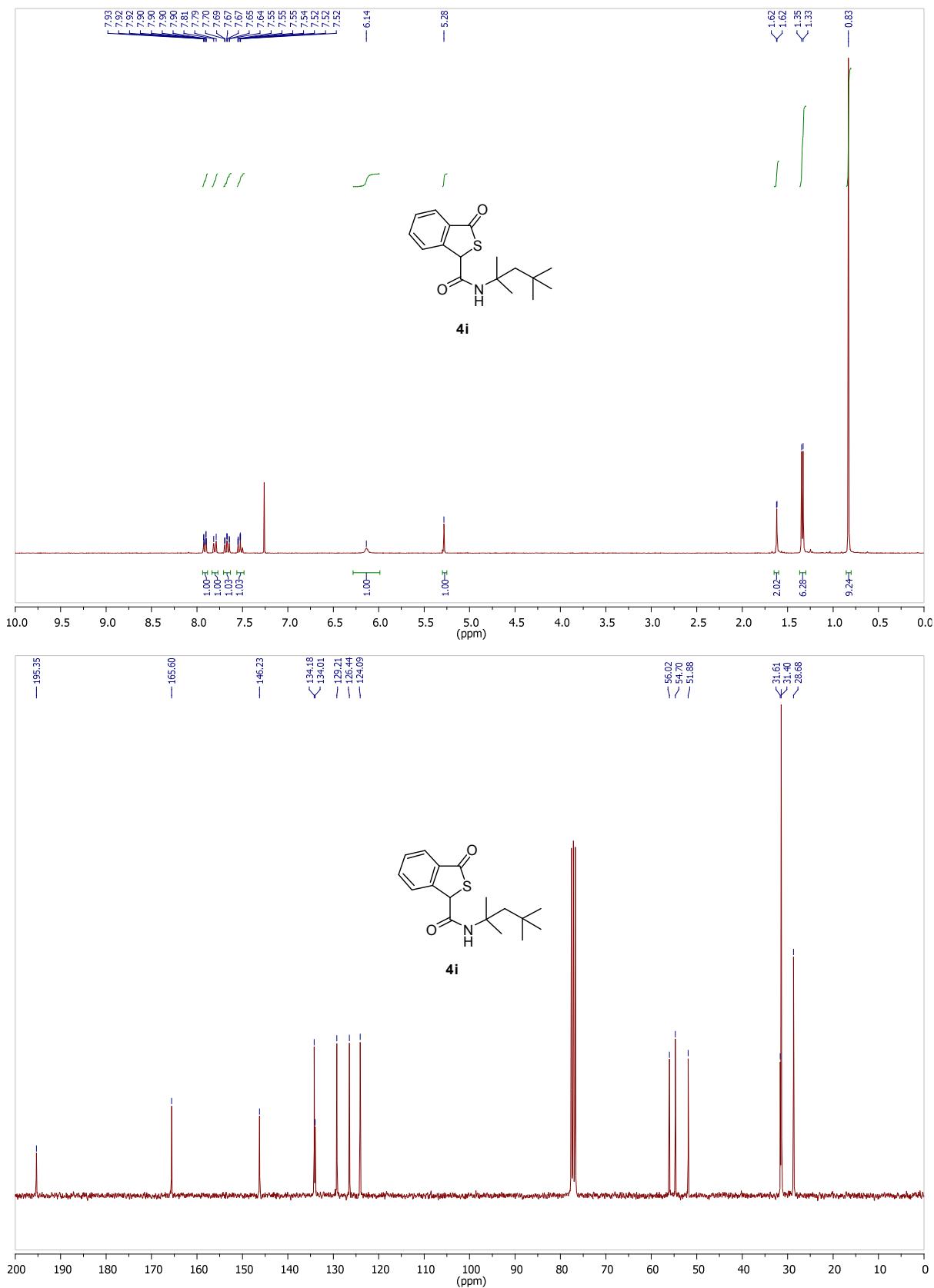
Methyl 2-(3-oxo-1,3-dihydrobenzo[c]thiophene-1-carboxamido)acetate(4g):



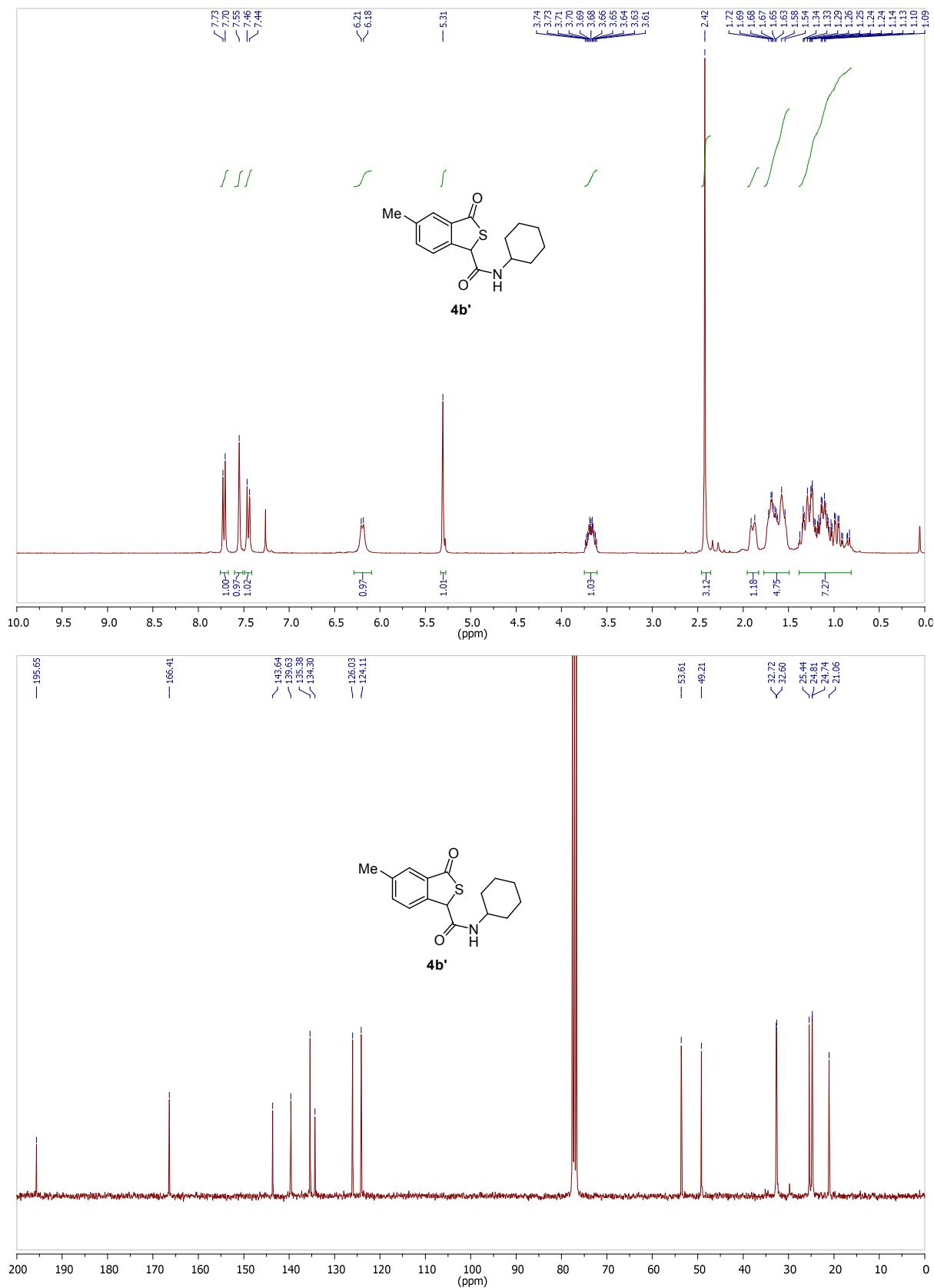
3-Oxo-*N*-pentyl-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide(4h):



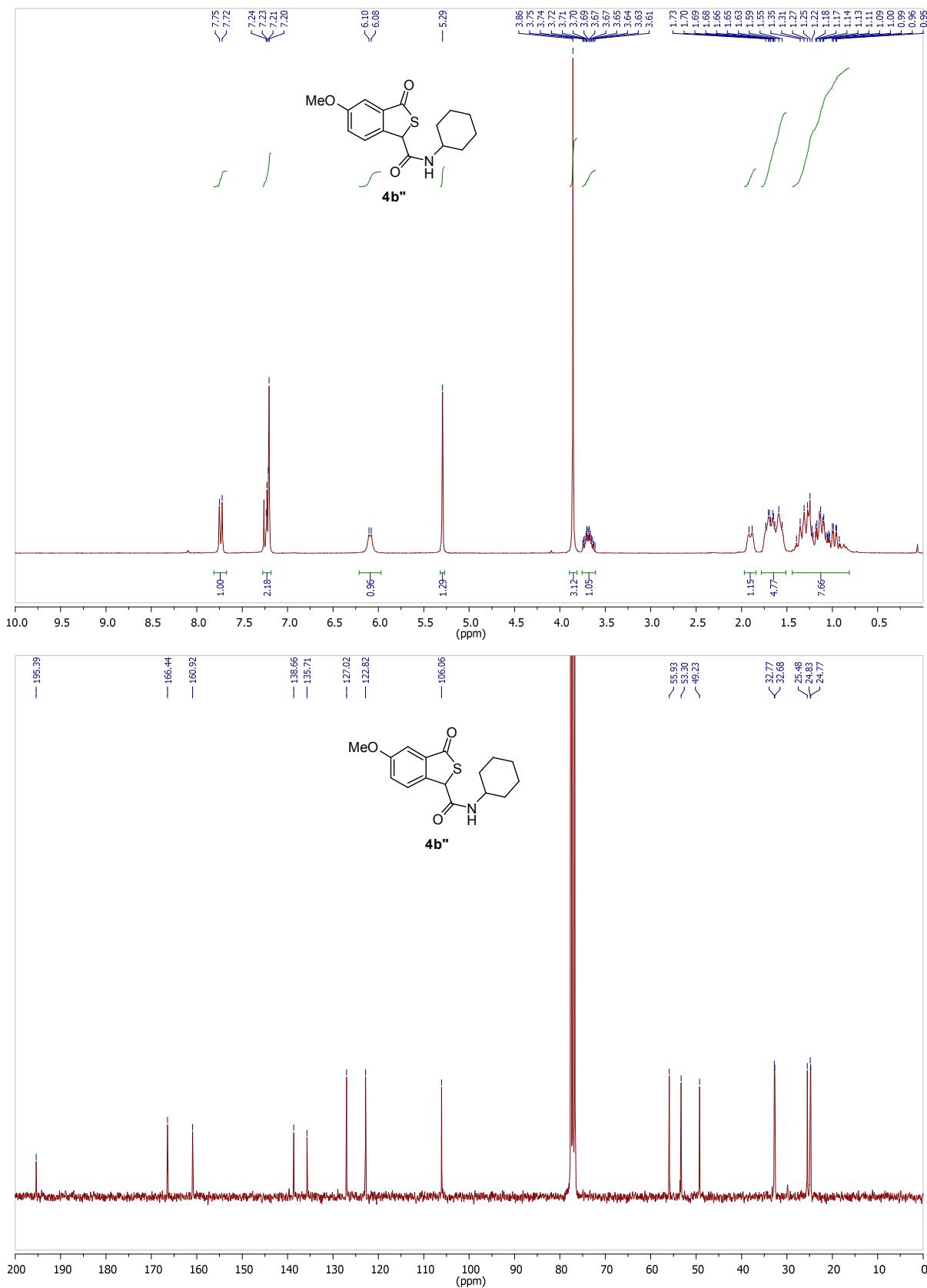
3-Oxo-*N*-(2,4,4-trimethylpentan-2-yl)-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide(4i):



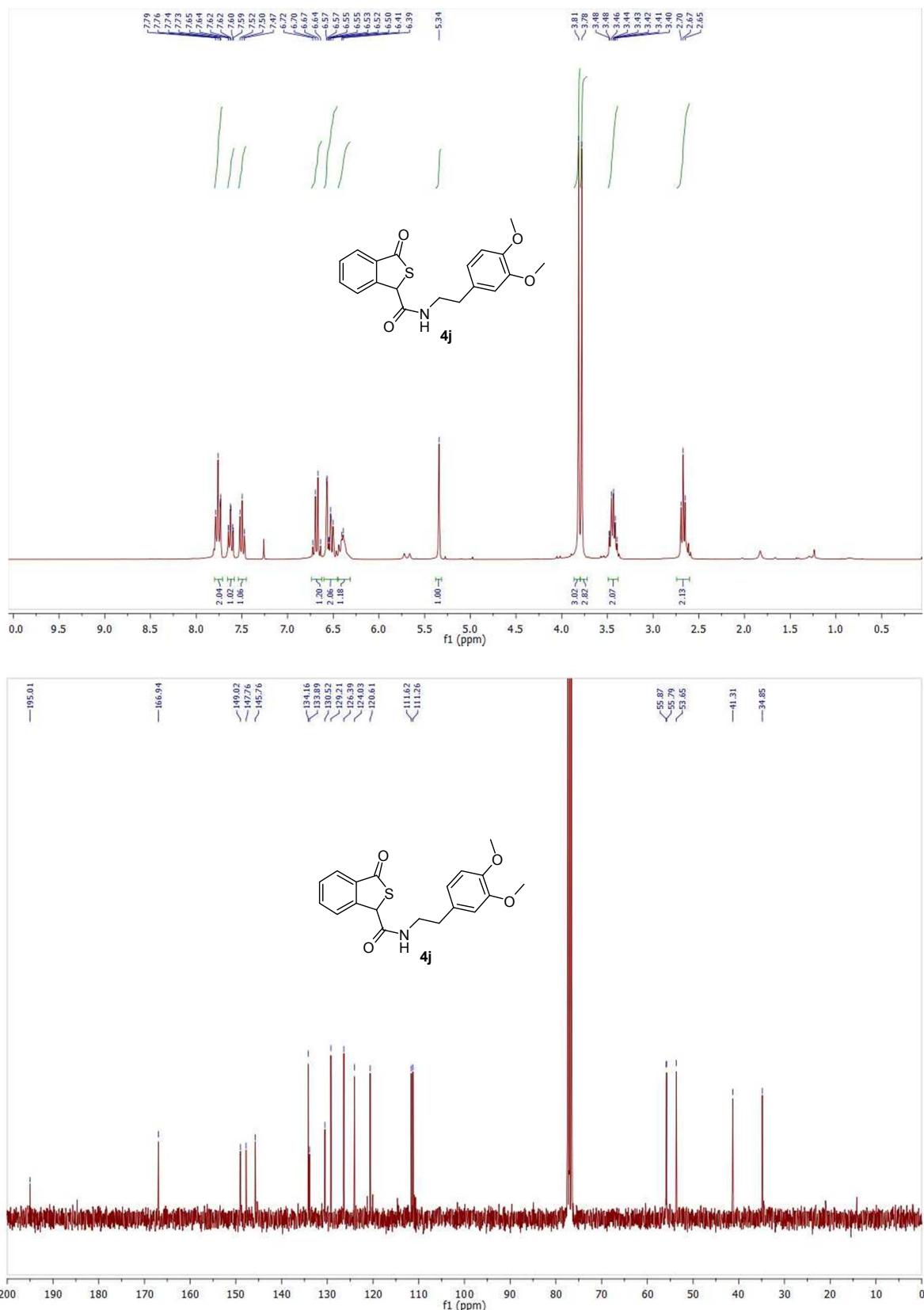
***N*-cyclohexyl-5-methyl-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide(4b'):**



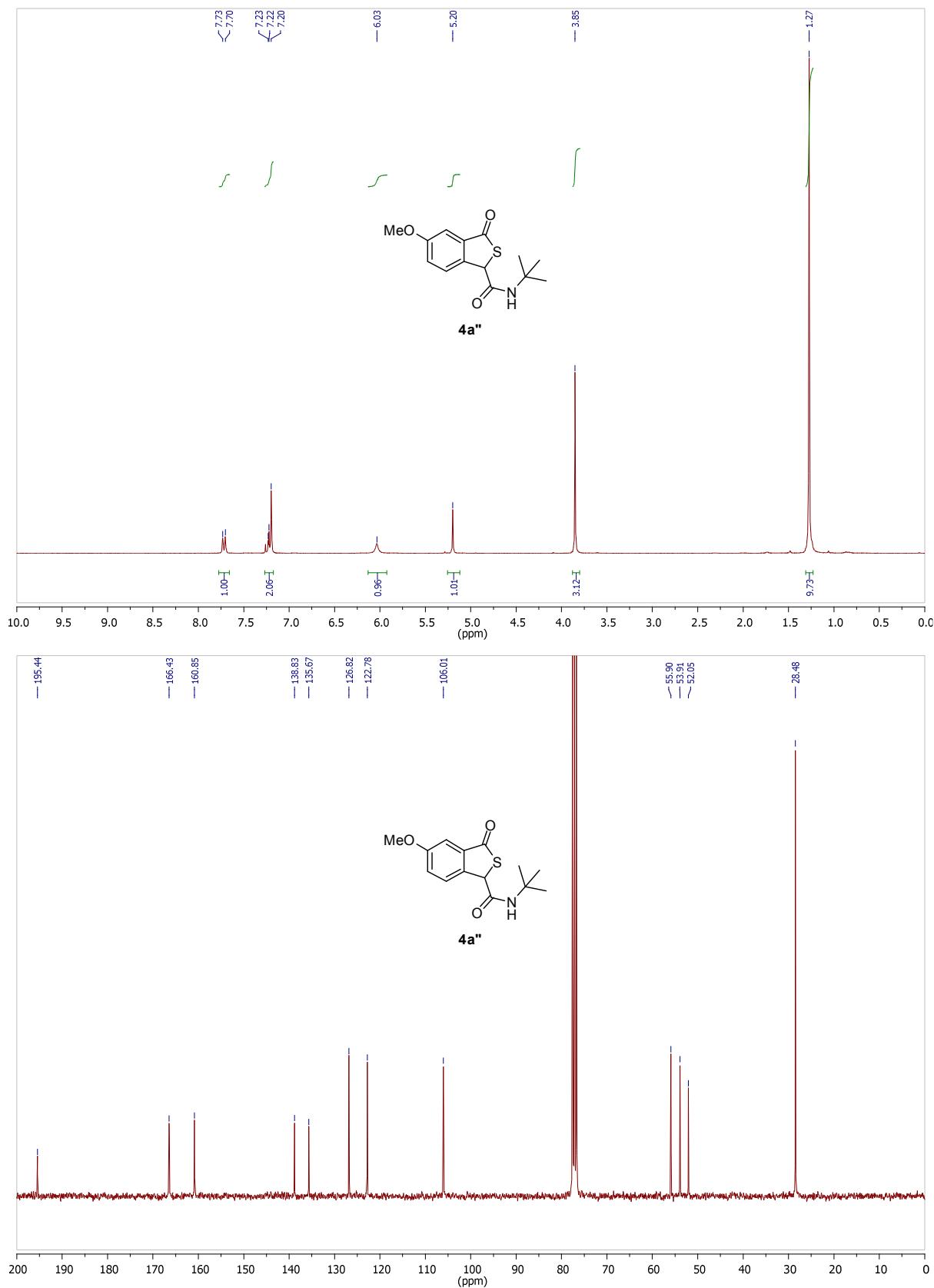
N-cyclohexyl-5-methoxy-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide(4b''):



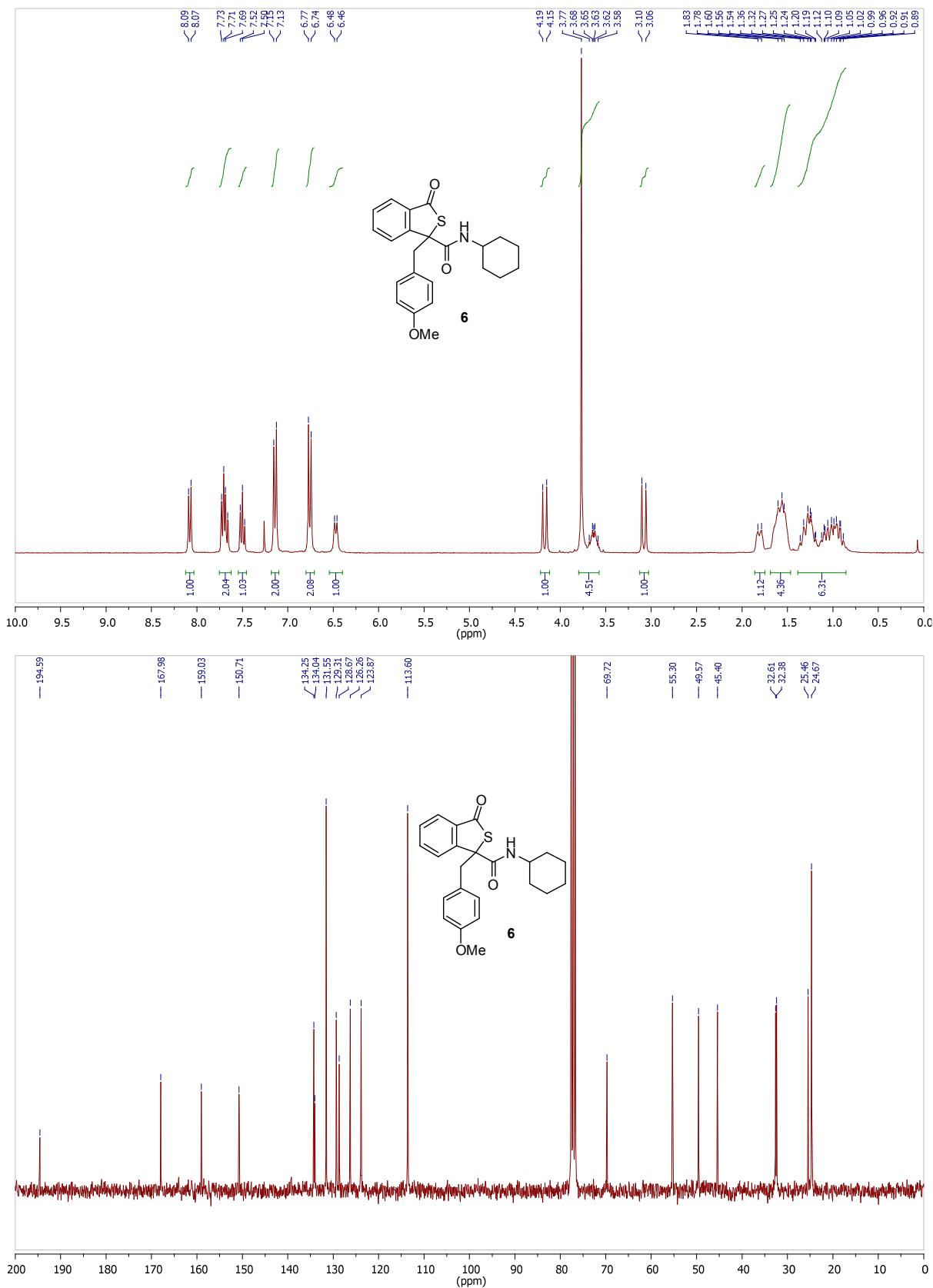
N-(3,4-dimethoxyphenethyl)-3-oxo-1,3-dihydrobenzo[*c*]thiophene-1-carboxamide (**4j**):



***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.