

# A facile protocol for the preparation of 2-carboxylated thieno [2,3-*b*] indoles: a de novo access to alkaloid thienodolin

Giacomo Mari,<sup>a\*</sup> Lucia De Crescentini,<sup>a</sup> Gianfranco Favi,<sup>a</sup> Stefania Santeusano,<sup>a</sup> and Fabio Mantellini<sup>a\*</sup>

<sup>a</sup>*Department of Biomolecular Sciences, University of Urbino “Carlo Bo”, Via I Maggetti 24, 61029 Urbino (PU), Italy*

*e-mail: fabio.mantellini@uniurb.it*

## SUPPORTING INFORMATION

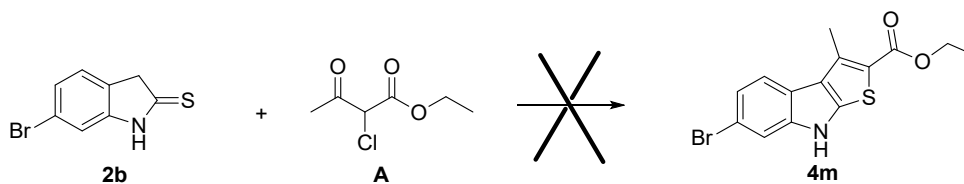
### Table of Contents

<b>1</b>	<b>General experimental details</b>	<b>2</b>
<b>2</b>	<b>Investigations of the reaction between 6-bromoindoline-2-thione 2d and ethyl 2-chloro acetoacetate A</b>	<b>3</b>
<b>3</b>	<b>Starting materials: Table S2: Substituted 1,2-diaza-1,3-dienes (DDs) 1a–p employed.</b>	<b>4</b>
<b>4</b>	<b>Starting materials: Table S3: Substituted-indoline-2-thiones 2a–h employed.</b>	<b>4</b>
<b>5</b>	<b>General procedures</b>	<b>5</b>
<b>6</b>	<b>NMR data for compounds 2b–h, 3a–c, and 4a–v.</b>	<b>7</b>
<b>7</b>	<b>NMR spectra of compounds 2b–h, 3a–c, 4a–v.</b>	<b>17</b>
<b>8</b>	<b>References</b>	<b>55</b>

## 1 General experimental details.

All the commercially available reagents and solvents were used without further purification. 1,2-Diaza-1,3-dienes **1a–p** were synthesized as a mixture of *E/Z* isomers as previously reported.<sup>[1]</sup> Indoline-2-thione **2a–h** were prepared according to the reported method.<sup>[2]</sup> Chromatographic purification of compounds was carried out on silica gel (60–200  $\mu\text{m}$ ). TLC analysis was performed on pre-loaded (0.25 mm) glass supported silica gel plates (Kieselgel 60); compounds were visualized by exposure to UV light and by dipping the plates in 1%  $\text{Ce}(\text{SO}_4)\cdot 4\text{H}_2\text{O}$ , 2.5%  $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O}$  in 10% sulphuric acid followed by heating on a hot plate. All  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded at 400 and 100 MHz, respectively, using  $[\text{D}_6]\text{DMSO}$  or  $\text{CDCl}_3$  as solvent. Chemical shift ( $\delta$  scale) are reported in parts per million (ppm) relative to the central peak of the solvent and are sorted in ascending order within each group. The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, q = quartet, sex = sextet, sept = septet, m = multiplet and br = broad signal. All coupling constants (J value) are given in Hertz [Hz]. High- and low-resolution mass spectroscopy was performed on a Micromass Q-ToF Micro mass spectrometer (Micromass, Manchester, UK) using an ESI source. Melting points were determined in open capillary tubes and are uncorrected. Elemental analyses were within  $\pm 0.4$  of the theoretical values (C, H, N).

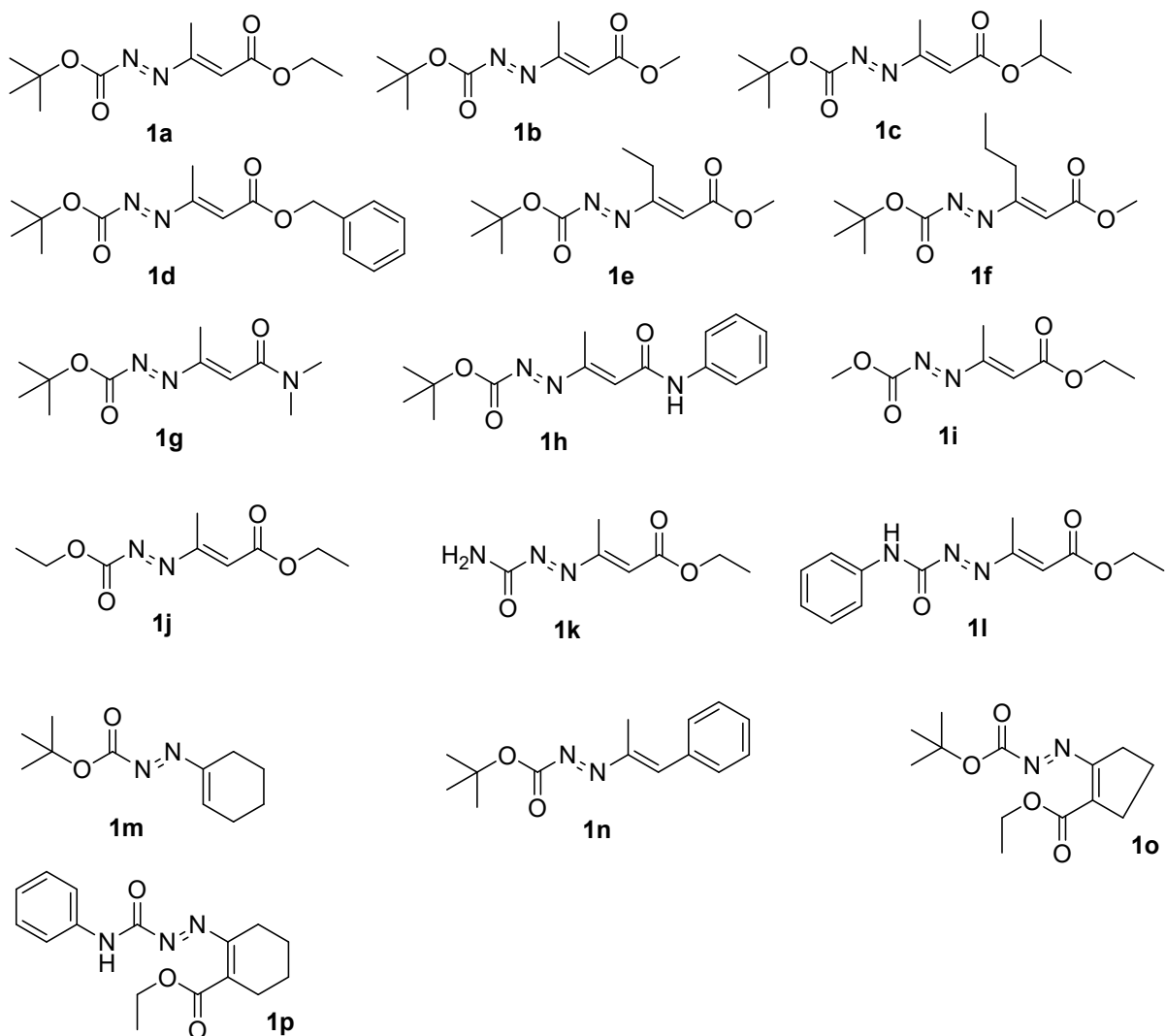
## 2 Investigations of the reaction between 6-bromoindoline-2-thione **2b** and ethyl 2-chloroacetoacetate **A**



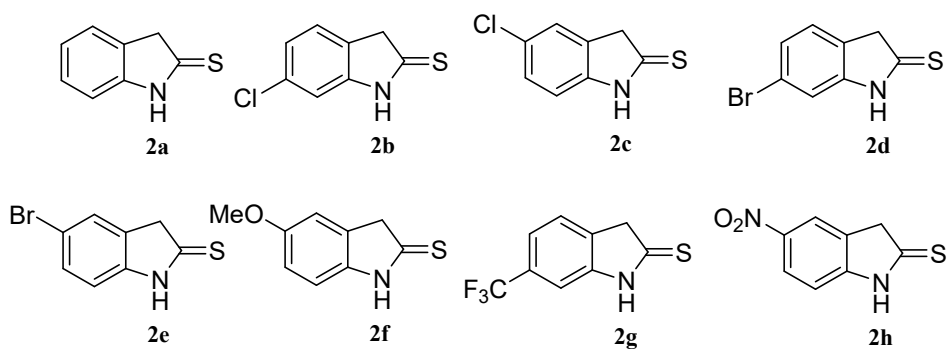
Reaction scale (referred to <b>2b</b> )	<b>A</b> molar ratio	Solvent (mL)	Catalyst	Amount of catalyst (mmol)	Time (h)	Temp.	Yield of <b>4m</b> (%)	<b>2b</b> unreacted (%)
1.0 mmol	1.1 mmol	DMF (1.0)	-	-	48.0	r.t.	0	0 <sup>(a)</sup>
0.5 mmol	0.5 mmol	ACN (	-	-	48.0	r.t.	0	94 <sup>(b)</sup>
0.5 mmol	0.5 mmol	ACN	Amberlyst 15H	1.0	48.0	r.t.	0	88 <sup>(b)</sup>
0.5 mmol	0.5 mmol	ACN	Amberlyst 15H	1.0	5.0	reflux	0	0 <sup>(a)</sup>
0.5 mmol	0.5 mmol	THF	-	-	48.0	r.t.	0	63
0.5 mmol	0.5 mmol	THF	-	-	5.0	reflux	0	0 <sup>(a)</sup>
0.5 mmol	0.5 mmol	MeOH	Amberlyst 15H	1.0	48.0	r.t.	0	83 <sup>(b)</sup>

(a) The profile of the reaction is complicated, and no trace of compound **4m** was never obtained. (b) Amount of isolated compound **2b**.

### 3 Starting materials: Table S2: Substituted 1,2-diaza-1,3-dienes (DDs) 1a–p employed.<sup>[1]</sup>



### 4 Starting materials: Table S3: Substituted-indoline-2-thiones 2a–h employed.<sup>[2]</sup>



## 5 General procedures.

*General procedure for the synthesis of tert-butyl 2-(3-((1H-indol-2-yl)thio)-4-ethoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate 3a, tert-butyl 2-(2-((6-chloro-1H-indol-2-yl)thio)-2-(ethoxycarbonyl)cyclopentylidene)hydrazinecarboxylate 3b and ethyl 1-((1H-indol-2-yl)thio)-2-(2-(phenylcarbamoyl)hydrazono)cyclohexanecarboxylate 3c.*

To a solution of 1,2-diaza-1,3-dienes **1a,o,p** (1.0 mmol) in methanol (6.0 mL) at room temperature indoline-2-thiones **2a,b** (1.0 mmol) were added and the reaction mixture was stirred at room temperature until the disappearance of the reagents (TLC monitoring 0.10–0.50 h) as also evidenced by the color change from red, typical of DDs, to pale yellow. and the solvent was evaporated under reduced pressure. The *a*-thio-functionalized hydrazones **3a–c** were purified by column chromatography on silica gel (elution mixture: cyclohexane : ethyl acetate, 80 : 20 for compounds **3a,b** and cyclohexane : ethyl acetate, 65 : 35 for compound **3c**) and the pure products were precipitated in ethyl acetate/petroleum ether. In the case of compounds **3b,c**, the addition of 1.0 equiv. of Amberlyst 15H (dry form) to the reaction medium does not cause the cyclization process to the corresponding thieno[2,3-*b*]indoles.

*One pot procedure for the synthesis of 2-carbonyl thieno[2,3-*b*]indoles 4a–r, 3-methyl-2-phenyl-8H-thieno[2,3-*b*]indole 4s, 2,3,4,6-tetrahydro-1H-benzo[4,5]thieno[2,3-*b*]indole 4t.*

To a solution of 1,2-diaza-1,3-dienes **1a–n** (1.0 mmol) in methanol (6.0 mL) at room temperature, indoline-2-thiones **2a–h** (1.0 mmol) were added and the reaction mixture was stirred at room temperature until the disappearance of the reagents (TLC monitoring 0.10–0.50 h) as also evidenced by the color change from red, typical of DDs, to pale yellow. Directly to the reaction medium, 1.0 equiv. of Amberlyst 15H (dry form) was then added, and the reaction was softly magnetically stirred. After 2.0–5.0 h (TLC monitoring), the corresponding thieno[2,3-*b*]indoles **4a–p,s,t** were formed. In the case of strong electron withdrawing substituted thieno[2,3-*b*]indoles **4q,r** the reaction times required to reach the completion at room temperature are 48.0 h and 120.0 h, respectively. By heating the reactions at 50°C, the times required are respectively 12.0 h for **4q**, and 18.0 h for **4r**. The Amberlyst 15H was removed by filtration, and the solvent was evaporated under reduced pressure. Thieno[2,3-*b*]indoles **4a–t** were purified by column chromatography on silica gel (elution mixture: cyclohexane : ethyl acetate, 80 : 20) and the pure products were precipitated from ethyl ether/petroleum ether.

*One pot procedure for the synthesis of 3-phenyl-8H-thieno[2,3-*b*]indole 4u.*

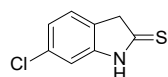
To a solution of ethyl 2-(2-bromo-1-phenylethylidene)hydrazinecarboxylate **5a** (1.0 mmol) in methanol (6.0 mL) at room temperature, indoline-2-thione **2a** (1.0 mmol) and potassium carbonate (2.0 mmol) were added and the reaction mixture was stirred at room temperature until the disappearance of the reagents (TLC monitoring 0.50 h). The crude was filtered to remove the excess of potassium carbonate, and then to the reaction medium 1.0 equiv. of Amberlyst 15H (dry form) was added. The reaction mixture was softly stirred at room temperature until the disappearance of the reagents (TLC monitoring, 3.0 hrs). The Amberlyst 15H was removed by filtration, and the solvent was evaporated under reduced pressure. Thieno[2,3-*b*]indole **4u** was purified by column chromatography on silica gel (elution mixture: cyclohexane : ethyl acetate, 90 : 10) and the pure product was precipitated from ethyl ether/petroleum ether.

*One pot procedure for the synthesis of ethyl 6-chloro-8H-thieno[2,3-*b*]indole-2-carboxylate 4v.*

To a solution of 2-chloro-3-oxopropanoate **6a** (1.0 mmol) in methanol (6.0 mL) at room temperature, *tert*-butyl hydrazinecarboxylate **7a** (1.0 mmol) was added. At the disappearance of **6a** (TLC monitoring, 4.50 hrs), to the crude, potassium carbonate (2.0 mmol) was added and the reaction mixture was stirred

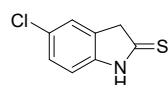
at room temperature until the disappearance of the reagents (TLC monitoring 0.50 h). The crude was filtered to remove the excess of potassium carbonate, and then to the reaction medium 2.0 equiv. of Amberlyst 15H (dry form) was added and the reaction mixture was softly stirred at room temperature until the disappearance of the reagents (TLC monitoring, 5.0 hrs). The Amberlyst 15H was removed by filtration, and the solvent was evaporated under reduced pressure. Thieno[2,3-*b*]indole **4v** was purified by column chromatography on silica gel (elution mixture: cyclohexane : ethyl acetate, 80 : 20) and the pure product was precipitated from ethyl ether/petroleum ether.

## 6 NMR data for compounds 2b–h, 3a–c and 4a–v.



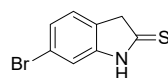
### 6-chloroindoline-2-thione 2b.<sup>[3]</sup>

**2b** was isolated by column chromatography on silica gel (acetate/cyclohexane, 70/30) in 92% yield. Pale green powder; mp: 160–163 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C): δ = 4.05 (s, 2H, CH<sub>2</sub>), 7.00 (d, 1H, *J* = 1.6 Hz), 7.11 (dd, 1H, *J* = 8.0 Hz, *J* = 1.6 Hz, Ar), 7.18 (d, 1H, *J* = 8.0 Hz, Ar), 10.14 (brs, 1H, NH); <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>, 25 °C): δ = 48.7, 110.3, 124.0, 125.0, 128.6, 134.0, 145.1, 204.4; MS *m/z* (ESI): 184 (M + H<sup>+</sup>); anal. calcd. for C<sub>8</sub>H<sub>6</sub>ClNS (183.66): C 52.32, H 3.29, N 7.63; found: C 52.43, H 3.18, N 7.48.



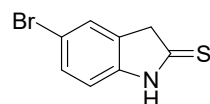
### 5-chloroindoline-2-thione 2c.<sup>[3]</sup>

**2c** was isolated by column chromatography on silica gel (acetate/cyclohexane, 70/30) in 95% yield. Pale green powder; mp: 149–151 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, 25 °C): δ = 4.06 (s, 2H, CH<sub>2</sub>), 6.95 (d, 1H, *J* = 7.6 Hz), 7.30 (dd, 1H, *J* = 7.6 Hz, *J* = 2.0 Hz, Ar), 7.34 (brs, 1H, Ar), 11.65 (brs, 1H, NH); <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, DMSO-*d*<sub>6</sub>, 25 °C): δ = 49.0, 111.0, 124.2, 127.5, 127.6, 133.1, 144.1, 203.2; MS *m/z* (ESI): 184 (M + H<sup>+</sup>); anal. calcd. for C<sub>8</sub>H<sub>6</sub>ClNS (183.66): C 52.32, H 3.29, N 7.63; found: C 52.18, H 3.37, N 7.75.



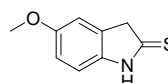
### 6-bromoindoline-2-thione 2d.<sup>[3]</sup>

**2d** was isolated by column chromatography on silica gel (acetate/cyclohexane, 70/30) in 76% yield. Pale green powder; mp: 166–168 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, 25 °C): δ = 3.45 (s, 2H, CH<sub>2</sub>), 6.94 (d, 1H, *J* = 1.6 Hz), 7.10 (dd, 1H, *J* = 7.6 Hz, *J* = 2.0 Hz, Ar), 7.16 (d, 1H, *J* = 7.6 Hz, Ar), 10.48 (brs, 1H, NH); <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, DMSO-*d*<sub>6</sub>, 25 °C): δ = 48.8, 112.6, 120.1, 125.6, 125.7, 130.3, 146.8, 204.1; MS *m/z* (ESI): 229 (M + H<sup>+</sup>); anal. calcd. for C<sub>8</sub>H<sub>6</sub>BrNS (228.11): C 42.12, H 2.65, N 6.14; found: C 42.28, H 2.52, N 6.07.



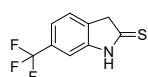
### 5-bromoindoline-2-thione 2e.<sup>[3]</sup>

**2e** was isolated by column chromatography on silica gel (acetate/cyclohexane, 70/30) in 81% yield. Pale green powder; mp: 157–160 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, 25 °C): δ = 4.07 (s, 2H, CH<sub>2</sub>), 6.91 (d, 1H, *J* = 8.4 Hz), 7.43 (dd, 1H, *J* = 8.4 Hz, *J* = 2.0 Hz, Ar), 7.46 (brs, 1H, Ar), 12.66 (brs, 1H, NH); <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, DMSO-*d*<sub>6</sub>, 25 °C): δ = 49.0, 111.5, 115.5, 126.9, 130.4, 133.5, 144.5, 203.2; MS *m/z* (ESI): 229 (M + H<sup>+</sup>); anal. calcd. for C<sub>8</sub>H<sub>6</sub>BrNS (228.11): C 42.12, H 2.65, N 6.14; found: C 42.27, H 2.54, N 6.23.



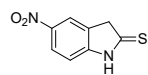
### 5-methoxyindoline-2-thione 2f.<sup>[3]</sup>

**2f** was isolated by column chromatography on silica gel (acetate/cyclohexane, 70/30) in 82% yield. Pale green powder; mp: 159–161 °C; <sup>1</sup>H NMR (400 MHz, DMSO<sub>d6</sub>, 25 °C): δ = 3.71 (s, 3H, OCH<sub>3</sub>), 3.98 (s, 2H, CH<sub>2</sub>), 6.80 (dd, 1H, *J* = 8.8 Hz, *J* = 2.0 Hz, Ar), 6.87 (d, 1H, *J* = 8.4 Hz), 6.91 (brs, 1H, Ar), 12.48 (brs, 1H, NH); <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, DMSO<sub>d6</sub>, 25 °C): δ = 49.2, 55.4, 110.3, 110.7, 112.6, 132.4, 138.7, 156.2, 201.6; MS *m/z* (ESI): 180 (M + H<sup>+</sup>); anal. calcd. for C<sub>9</sub>H<sub>9</sub>NOS (179.24): C 60.31, H 5.06, N 7.81; found: C 60.12, H 5.21, N 7.65.



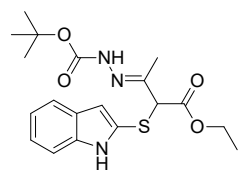
**6-(trifluoromethyl)indoline-2-thione 2g.**<sup>[3]</sup>

**2g** was isolated by column chromatography on silica gel (acetate/cyclohexane, 70/30) in 82% yield. Pale yellow powder; mp: 164–167 °C; <sup>1</sup>H NMR (400 MHz, DMSO<sub>d6</sub>, 25 °C): δ = 4.17 (s, 2H, CH<sub>2</sub>), 7.16 (s, 1H, Ar), 7.44 (d, 1H, *J* = 7.2 Hz, Ar), 7.49 (d, 1H, *J* = 7.6 Hz, Ar), 12.78 (s, 1H, NH); <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, DMSO<sub>d6</sub>, 25 °C): δ = 49.6, 106.4, 120.5, 124.6 (*J*<sub>1CF</sub> = 270 Hz), 125.5, 128.9 (*J*<sub>2CF</sub> = 32 Hz), 136.2, 146.4, 204.6; MS *m/z* (ESI): 218 (M + H<sup>+</sup>); anal. calcd. for C<sub>9</sub>H<sub>6</sub>F<sub>3</sub>NS (217.21): C 49.77, H 2.78, N 6.45; found: C 49.95, H 2.69, N 6.64.



**5-nitroindoline-2-thione 2h.**<sup>[3]</sup>

In this case the reaction does not reach the completion and **2h** is not separable from its precursor 5-nitroindoline-2-one **A** by chromatography. **2h** was precipitated in ice-cold water and washed 3 times with 10.0 mL of methanol obtaining a mixture with the corresponding starting 5-nitroindoline-2-one **A** (molar ratio **2h/A** 86/14, determined by <sup>1</sup>H NMR); **2h** was obtained in 63% yield (calculated for **2h**). <sup>1</sup>H NMR (400 MHz, DMSO<sub>d6</sub>, 25 °C): δ = 4.18 (s, 2H, CH<sub>2</sub>), 7.11 (d, 1H, *J* = 8.4 Hz, Ar), 8.09-8.21 (m, 2H, Ar), 13.02 (s, 1H, NH).

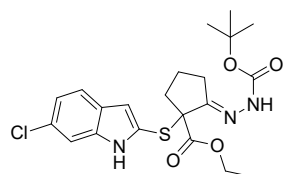


**Tert-butyl 2-(3-((1H-indol-2-yl)thio)-4-ethoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate 3a (unknown product).**<sup>[4]</sup>

**3a** was isolated by column chromatography on silica gel (cyclohexane/acetate, 80/20) and the pure product was precipitated from ethyl acetate/petroleum ether in 98% yield. White solid; mp: 138–140 °C with decomposition; <sup>1</sup>H NMR (400 MHz, DMSO<sub>d6</sub>, 25 °C): δ = 1.11 (t, 3H, *J* = 7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 1.45 (s, 9H, OC(CH<sub>3</sub>)<sub>3</sub>), 1.91 (s, 3H, CH<sub>3</sub>), 4.09 (q, 2H, *J* = 7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 4.79 (s, 1H, CH), 6.58 (dd, 1H, *J* = 1.6 Hz, *J* = 0.8 Hz, Ar), 6.98 (dt, 1H, *J* = 8.0 Hz, *J* = 0.8 Hz, Ar), 7.12 (dt, 1H, *J* = 7.2 Hz, *J* = 1.2 Hz, Ar), 7.33 (dd, 1H, *J* = 8.0 Hz, *J* = 0.8 Hz, Ar), 7.47 (d, 1H, *J* = 8.0 Hz, Ar), 9.92 (brs, 1H, NH), 11.58 (brs, 1H, NH); <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, DMSO<sub>d6</sub>, 25 °C): δ = 13.8, 14.6, 28.0, 58.3, 61.5, 79.8, 109.6, 111.0, 119.2, 119.9, 122.2, 124.6, 127.5, 137.7, 146.8, 153.4,

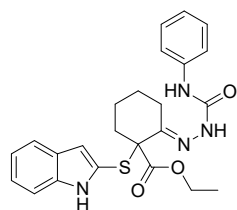


167.9; MS  $m/z$  (ESI): 392 ( $M + H^+$ ); anal. calcd. for  $C_{19}H_{25}N_3O_4S$  (391.48): C 58.29, H 6.44, N 10.73; found: C 58.45, H 6.31, N 10.56.



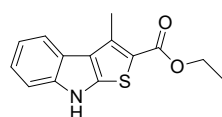
**Tert-butyl** **2-(2-((6-chloro-1H-indol-2-yl)thio)-2-(ethoxycarbonyl)cyclopentylidene)hydrazinecarboxylate** **3b(unknown product).**<sup>[4]</sup>

**3b** was isolated by column chromatography on silica gel (cyclohexane/acetate, 80/20) and the pure product was precipitated from ethyl acetate/petroleum ether in 62% yield. White solid; mp: 195–197 °C with decomposition;  $^1H$  NMR (400 MHz,  $DMSO_{d6}$ , 25 °C):  $\delta$  = 0.90 (t, 3H,  $J$  = 7.2 Hz,  $OCH_2CH_3$ ), 1.16–1.23 (m, 1H, Cycloalk), 1.43 and 1.54 (2s, 9H,  $OC(CH_3)_3$ ), 1.65–1.74 (m, 1H, Cycloalk), 1.82–1.97 (m, 2H, Cycloalk), 2.45 (t, 2H,  $J$  = 7.2 Hz, Cycloalk), 3.83 (q, 2H,  $J$  = 7.2 Hz,  $OCH_2CH_3$ ), 6.64 (s, 1H, Ar), 7.00 (dd, 1H,  $J$  = 7.6 Hz,  $J$  = 2.0 Hz, Ar), 7.39 (d, 1H,  $J$  = 2.0 Hz, Ar), 7.51 (d, 1H,  $J$  = 7.6 Hz, Ar), 10.30 (brs, 1H, NH), 12.03 (brs, 1H, NH);  $^{13}C$   $\{^1H\}$  NMR (100 MHz,  $DMSO_{d6}$ , 25 °C):  $\delta$  = 13.6, 21.4, 27.7, 28.1, 35.6, 61.5, 64.1, 80.3, 110.4, 110.7, 119.5, 121.5, 126.0, 126.2, 127.1, 138.1, 154.1, 158.6, 169.2; MS  $m/z$  (ESI): 452 ( $M + H^+$ ); anal. calcd. for  $C_{21}H_{26}ClN_3O_4S$  (451.97): C 55.81, H 5.80, N 9.30; found: C 55.66, H 5.88, N 9.43.



**Ethyl** **1-((1H-indol-2-yl)thio)-2-(2-(phenylcarbamoyl)hydrazono)cyclohexanecarboxylate** **3c (unknown product).**<sup>[4]</sup>

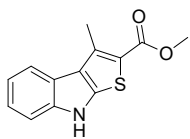
**3c** was isolated by column chromatography on silica gel (cyclohexane/acetate, 65/35) and the pure product was precipitated from ethyl acetate/petroleum ether in 59% yield. White solid; mp: 214–216 °C with decomposition;  $^1H$  NMR (400 MHz,  $DMSO_{d6}$ , 25 °C):  $\delta$  = 1.00 (t, 3H,  $J$  = 7.6 Hz,  $OCH_2CH_3$ ), 1.37–1.46 (m, 2H, Cycloalk), 1.78–1.90 (m, 4H, Cycloalk), 2.43 (d, 1H,  $J$  = 12.4 Hz, Cycloalk), 3.00 (d, 1H,  $J$  = 15.2 Hz, Cycloalk), 4.06 (q, 2H,  $J$  = 7.6 Hz,  $OCH_2CH_3$ ), 6.63 (d, 1H,  $J$  = 0.8 Hz, Ar), 6.99 (dt, 1H,  $J$  = 7.2 Hz,  $J$  = 0.8 Hz, Ar), 7.04 (t, 1H,  $J$  = 7.6 Hz, Ar), 7.14 (dt, 1H,  $J$  = 7.2 Hz,  $J$  = 0.8 Hz, Ar), 7.32–7.38 (m, 3H, Ar), 7.51–7.54 (m, 3H, Ar), 8.57 (s, 1H, NH), 10.18 (s, 1H, NH), 11.68 (brs, 1H, NH);  $^{13}C$   $\{^1H\}$  NMR (100 MHz,  $DMSO_{d6}$ , 25 °C):  $\delta$  = 13.7, 23.0, 24.6, 26.0, 36.1, 61.3, 63.0, 111.8, 112.1, 118.4, 119.1, 120.0, 122.4, 122.5, 123.6, 127.3, 129.0, 137.8, 138.6, 149.2, 153.5, 169.2; HRMS (ESI) calcd for  $C_{24}H_{27}N_4O_3S$  [ $M + H$ ] $^+$ : 451.1804; found: 451.1813.



**Ethyl 3-methyl-8H-thieno[2,3-b]indole-2-carboxylate** **4a (unknown product).**

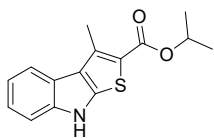
**4a** was isolated by column chromatography on silica gel (cyclohexane/acetate, 80/20) and the pure product was precipitated from ethyl ether/petroleum ether in 84% yield. Brown-red powder; mp: 188–190 °C;  $^1H$  NMR (400 MHz,  $DMSO_{d6}$ , 25 °C):  $\delta$  = 1.31 (t, 3H,  $J$  = 7.2 Hz,  $OCH_2CH_3$ ), 2.88 (s, 3H,  $CH_3$ ), 4.26 (q, 1H,  $J$  = 7.2 Hz,  $OCH_2CH_3$ ), 7.17 (dt, 1H,  $J$  = 7.6 Hz,  $J$  = 0.8 Hz, Ar), 7.27 (dt, 1H,  $J$  = 8.0 Hz,  $J$  = 1.2 Hz, Ar), 7.51 (d, 1H,  $J$  = 8.0 Hz, Ar), 7.91 (d, 1H,  $J$  =

7.6 Hz, Ar), 11.91 (s, 1H, NH);  $^{13}\text{C}$  NMR  $\{^1\text{H}\}$  (100 MHz,  $\text{DMSO}_{d6}$ , 25 °C):  $\delta$  = 14.3, 14.6, 60.0, 111.9, 116.7, 118.7, 119.8, 122.0, 122.9, 125.3, 139.2, 142.2, 143.5, 163.0; HRMS (ESI) calcd for  $\text{C}_{14}\text{H}_{14}\text{NO}_2\text{S}$   $[\text{M} + \text{H}]^+$ : 260.0745; found: 260.0747.



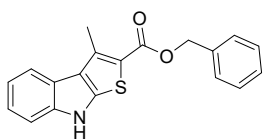
**Methyl 3-methyl-8H-thieno[2,3-b]indole-2-carboxylate 4b (unknown product).**

**4b** was isolated by column chromatography on silica gel (cyclohexane/acetate, 80/20) and the pure product was precipitated from ethyl ether/petroleum ether in 72% yield. Pale brown powder; mp: 194–196 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  = 2.97 (s, 3H,  $\text{CH}_3$ ), 3.90 (s, 3H,  $\text{OCH}_3$ ), 7.25 (dt, 1H,  $J$  = 7.2 Hz,  $J$  = 0.8 Hz, Ar), 7.31 (dt, 1H,  $J$  = 8.0 Hz,  $J$  = 1.2 Hz, Ar), 7.43 (d, 1H,  $J$  = 8.0 Hz, Ar), 7.93 (d, 1H,  $J$  = 7.6 Hz, Ar), 8.56 (brs, 1H, NH);  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta$  = 15.0, 51.6, 111.4, 118.0, 119.1, 120.7, 122.9, 123.3, 126.9, 140.2, 142.2, 143.5, 164.4; MS  $m/z$  (ESI): 246 ( $\text{M} + \text{H}^+$ ); anal. calcd. for  $\text{C}_{13}\text{H}_{11}\text{NO}_2\text{S}$  (245.27): C 63.65, H 4.52, N 5.71; found: C 63.49, H 4.59, N 5.83.



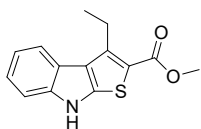
**Isopropyl 3-methyl-8H-thieno[2,3-b]indole-2-carboxylate 4c (unknown product).**

**4c** was isolated by column chromatography on silica gel (cyclohexane/acetate, 80/20) and the pure product was precipitated from ethyl ether/petroleum ether in 70% yield. White powder; mp: 170–172 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}_{d6}$ , 25 °C):  $\delta$  = 1.31 (d, 6H,  $J$  = 6.4 Hz,  $\text{OCH}(\text{CH}_3)_2$ ), 2.86 (s, 3H,  $\text{CH}_3$ ), 5.09 (sep, 1H,  $J$  = 6.4 Hz,  $\text{OCH}(\text{CH}_3)_2$ ), 7.16 (dt, 1H,  $J$  = 7.6 Hz,  $J$  = 0.8 Hz, Ar), 7.26 (dt, 1H,  $J$  = 8.0 Hz,  $J$  = 1.2 Hz, Ar), 7.51 (d, 1H,  $J$  = 8.0 Hz, Ar), 7.89 (d, 1H,  $J$  = 7.6 Hz, Ar), 11.91 (s, 1H, NH);  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR (100 MHz,  $\text{DMSO}_{d6}$ , 25 °C):  $\delta$  = 14.6, 21.8, 67.4, 111.9, 117.3, 118.6, 119.8, 122.1, 122.8, 125.3, 138.9, 142.2, 143.5, 162.6; MS  $m/z$  (ESI): 274 ( $\text{M} + \text{H}^+$ ); anal. calcd. for  $\text{C}_{15}\text{H}_{15}\text{N}_2\text{O}$  (273.35): C 65.91, H 5.53, N 5.12; found: C 66.07, H 5.43, N 5.00.



**Benzyl 3-methyl-8H-thieno[2,3-b]indole-2-carboxylate 4d (unknown product).**

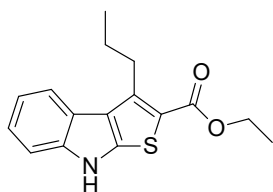
**4d** was isolated by column chromatography on silica gel (cyclohexane/acetate, 80/20) and the pure product was precipitated from ethyl ether/petroleum ether in 54% yield. Brown-red powder; mp: 198–201 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}_{d6}$ , 25 °C):  $\delta$  = 2.89 (s, 3H,  $\text{CH}_3$ ), 5.32 (s, 2H,  $\text{OCH}_2\text{Ar}$ ), 7.17 (t, 1H,  $J$  = 7.6 Hz, Ar), 7.27 (dt, 1H,  $J$  = 8.4 Hz,  $J$  = 1.2 Hz, Ar), 7.33–7.48 (m, 5H, Ar), 7.52 (d, 1H,  $J$  = 8.4 Hz, Ar), 7.92 (d, 1H,  $J$  = 7.6 Hz, Ar), 11.91 (s, 1H, NH);  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR (100 MHz,  $\text{DMSO}_{d6}$ , 25 °C):  $\delta$  = 14.6, 65.4, 111.9, 116.2, 118.7, 119.9, 122.0, 122.9, 125.4, 127.7, 127.9, 128.4, 136.4, 139.7, 142.3, 143.8, 162.8; MS  $m/z$  (ESI): 322 ( $\text{M} + \text{H}^+$ ); anal. calcd. for  $\text{C}_{19}\text{H}_{15}\text{N}_2\text{OS}$  (321.39): C 71.00, H 4.70, N 4.36; found: C 70.86, H 4.78, N 4.51.



**Methyl 3-ethyl-8H-thieno[2,3-b]indole-2-carboxylate 4e (unknown product).**

**4e** was isolated by column chromatography on silica gel (cyclohexane/acetate, 80/20) and the pure product was precipitated from ethyl ether/petroleum ether in 72% yield.

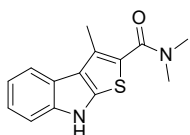
White powder mp: 195–197 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}_{d6}$ , 25 °C):  $\delta$  = 1.30 (t, 3H,  $J$  = 7.2 Hz,  $\text{CH}_2\text{CH}_3$ ), 3.39 (q, 2H,  $J$  = 7.2 Hz,  $\text{CH}_2\text{CH}_3$ ), 3.80 (s, 3H, OCH<sub>3</sub>), 7.18 (dt, 1H,  $J$  = 7.6 Hz,  $J$  = 1.2 Hz, Ar), 7.27 (dt, 1H,  $J$  = 8.4 Hz,  $J$  = 1.2 Hz, Ar), 7.52 (d, 1H,  $J$  = 8.0 Hz, Ar), 7.85 (d, 1H,  $J$  = 8.0 Hz, Ar), 11.94 (s, 1H, NH);  $^{13}\text{C}$  { $^1\text{H}$ } NMR (100 MHz,  $\text{DMSO}_{d6}$ , 25 °C):  $\delta$  = 14.0, 21.5, 51.4, 112.0, 115.7, 118.7, 120.0, 121.6, 122.9, 124.4, 142.3, 144.0, 145.9, 163.1; MS  $m/z$  (ESI): 260 ( $\text{M} + \text{H}^+$ ); anal. calcd. for  $\text{C}_{14}\text{H}_{13}\text{NOS}$  (259.32): C 64.84, H 5.05, N 5.40; found: C 64.96, H 4.96, N 5.34.



**Ethyl 3-propyl-8H-thieno[2,3-b]indole-2-carboxylate 4f (unknown product).**

**4f** was isolated by column chromatography on silica gel (cyclohexane/acetate, 80/20) and the pure product was precipitated from ethyl ether/petroleum ether in 38% yield. Pale brown powder; mp: 201–203 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}_{d6}$ ,

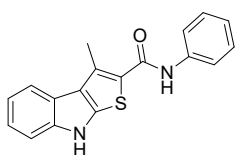
25 °C):  $\delta$  = 1.00 (t, 3H,  $J$  = 7.2 Hz,  $(\text{CH}_2)_2\text{CH}_3$ ), 1.30 (t, 3H,  $J$  = 7.2 Hz,  $\text{OCH}_2\text{CH}_3$ ), 1.72 (sex, 2H,  $J$  = 7.6 Hz,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 3.36 (t, 2H,  $J$  = 7.6 Hz,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 4.26 (q, 2H,  $J$  = 7.6 Hz,  $\text{OCH}_2\text{CH}_3$ ), 7.18 (dt, 1H,  $J$  = 7.6 Hz,  $J$  = 1.2 Hz, Ar), 7.26 (dt, 1H,  $J$  = 7.6 Hz,  $J$  = 0.8 Hz, Ar), 7.52 (d, 1H,  $J$  = 8.0 Hz, Ar), 7.82 (d, 1H,  $J$  = 7.6 Hz, Ar), 11.94 (s, 1H, NH);  $^{13}\text{C}$  { $^1\text{H}$ } NMR (100 MHz,  $\text{DMSO}_{d6}$ , 25 °C):  $\delta$  = 14.0, 14.5, 23.0, 30.2, 60.3, 112.2, 117.1, 119.0, 120.3, 121.9, 123.2, 125.1, 142.5, 144.0, 144.3, 163.1; MS  $m/z$  (ESI): 288 ( $\text{M} + \text{H}^+$ ); anal. calcd. for  $\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}$  (287.38): C 66.87, H 5.96, N 4.87; found: C 66.98, H 5.75, N 4.92.



***N,N*,3-Trimethyl-8H-thieno[2,3-b]indole-2-carboxamide 4g (unknown product).**

**4g** was isolated by column chromatography on silica gel (acetate/cyclohexane) in 52% yield. Beige powder; mp: 206–208 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}_{d6}$ , 25 °C):  $\delta$  = 2.54

(s, 3H, CH<sub>3</sub>), 3.03 (s, 6H, N(CH<sub>3</sub>)<sub>2</sub>), 7.13 (dt, 1H,  $J$  = 8.0 Hz,  $J$  = 1.2 Hz, Ar), 7.22 (dt, 1H,  $J$  = 8.0 Hz,  $J$  = 1.2 Hz, Ar), 7.49 (d, 1H,  $J$  = 8.0 Hz, Ar), 7.83 (d, 1H,  $J$  = 7.6 Hz, Ar), 11.68 (brs, 1H, NH);  $^{13}\text{C}$  { $^1\text{H}$ } NMR (100 MHz,  $\text{DMSO}_{d6}$ , 25 °C):  $\delta$  = 14.4, 37.0, 111.7, 118.2, 119.3, 122.0, 122.0, 122.1, 123.8, 129.5, 140.6, 141.7, 164.8; HRMS (ESI) calcd for  $\text{C}_{14}\text{H}_{15}\text{N}_2\text{OS}$  [ $\text{M} + \text{H}$ ]<sup>+</sup>: 259.0905; found: 259.0911.

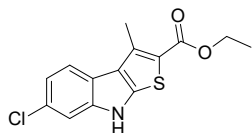


**3-Methyl-*N*-phenyl-8H-thieno[2,3-b]indole-2-carboxamide 4h (unknown product).**

**4h** was isolated by column chromatography on silica gel (cyclohexane/acetate, 80/20) and the pure product was precipitated from ethyl ether/petroleum ether in

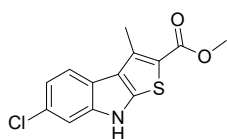
58% yield. White solid; mp: 214–217 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}_{d6}$ , 25 °C):  $\delta$  = 2.85 (s, 3H, CH<sub>3</sub>), 7.08 (t, 1H,  $J$  = 7.2 Hz, Ar), 7.16 (dt, 1H,  $J$  = 8.0 Hz,  $J$  = 1.2 Hz, Ar), 7.25 (dt, 1H,  $J$  = 8.4 Hz,  $J$  = 1.2 Hz, Ar), 7.34 (t, 2H,  $J$  = 7.2 Hz, Ar), 7.51 (d, 1H,  $J$  = 8.0 Hz, Ar), 7.68 (dd, 2H,  $J$  = 8.4 Hz,  $J$  = 1.2 Hz,

Ar), 7.92 (d, 1H,  $J = 8.0$  Hz, Ar), 9.98 (s, 1H, NH), 11.84 (s, 1H, NH);  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR (100 MHz,  $\text{DMSO}_{d6}$ , 25 °C):  $\delta = 15.0, 99.5, 111.9, 118.5, 119.6, 120.2, 122.2, 122.5, 123.1, 123.4, 125.1, 128.6, 133.7, 139.2, 141.4, 142.0, 162.0$ ; HRMS (ESI) calcd for  $\text{C}_{18}\text{H}_{15}\text{N}_2\text{OS}$   $[\text{M} + \text{H}]^+$ : 307.0905; found: 307.0905.



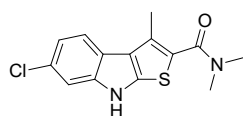
**Ethyl 6-chloro-3-methyl-8H-thieno[2,3-b]indole-2-carboxylate 4i (unknown product).**

**4i** was isolated by column chromatography on silica gel (cyclohexane/acetate, 80/20) and the pure product was precipitated from ethyl ether/petroleum ether in 57% yield. Yellow solid; mp: 218–220 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}_{d6}$ , 25 °C):  $\delta = 1.31$  (t, 3H,  $J = 7.2$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.86 (s, 3H,  $\text{CH}_3$ ), 4.27 (q, 2H,  $J = 7.2$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 7.19 (dd, 1H,  $J = 8.4$  Hz,  $J = 2.0$  Hz, Ar), 7.60 (d, 1H,  $J = 2.0$  Hz, Ar), 7.91 (d, 1H,  $J = 8.4$  Hz, Ar), 11.99 (s, 1H, NH);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}_{d6}$ , 25 °C):  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR (100 MHz,  $\text{DMSO}_{d6}$ , 25 °C):  $\delta = 14.3, 14.5, 60.1, 111.8, 117.6, 119.9, 120.0, 120.8, 124.9, 127.4, 138.9, 142.6, 144.2, 163.0$ ; MS  $m/z$  (ESI): 294 ( $\text{M} + \text{H}^+$ ); anal. calcd. for  $\text{C}_{14}\text{H}_{12}\text{ClNO}_2\text{S}$  (293.77): C 57.24, H 4.12, N 4.77; found: C 57.39, H 4.03, N 4.71.



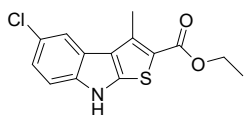
**Methyl 6-chloro-3-methyl-8H-thieno[2,3-b]indole-2-carboxylate 4j (unknown product).**

**4j** was isolated by column chromatography on silica gel (cyclohexane/acetate, 80/20) and the pure product was precipitated from ethyl ether/petroleum ether in 65% yield. Yellow solid; mp: 258–260 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}_{d6}$ , 25 °C):  $\delta = 2.85$  (s, 3H,  $\text{CH}_3$ ), 3.79 (s, 3H,  $\text{OCH}_3$ ), 7.18 (dd, 1H,  $J = 8.8$  Hz,  $J = 2.0$  Hz, Ar), 7.60 (d, 1H,  $J = 1.6$  Hz, Ar), 7.84 (d, 1H,  $J = 8.8$  Hz, Ar), 11.98 (s, 1H, NH);  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR (100 MHz,  $\text{DMSO}_{d6}$ , 25 °C):  $\delta = 14.5, 51.5, 111.8, 117.1, 119.8, 120.0, 120.8, 124.9, 127.4, 139.1, 142.6, 144.2, 163.3$ ; MS  $m/z$  (ESI): 280 ( $\text{M} + \text{H}^+$ ); anal. calcd. for  $\text{C}_{13}\text{H}_{10}\text{ClNO}_2\text{S}$  (279.74): C 55.82, H 3.60, N 5.01; found: C 55.70, H 3.68, N 5.10.



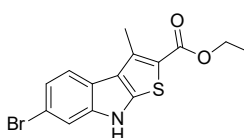
**6-chloro-N,N,3-trimethyl-8H-thieno[2,3-b]indole-2-carboxamide 4k (unknown product).**

**4k** was isolated by column chromatography on silica gel (cyclohexane/acetate, 80/20) and the pure product was precipitated from ethyl ether/petroleum ether in 61% yield. Pale green powder; mp: 220–223 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}_{d6}$ , 25 °C):  $\delta = 2.52$  (s, 3H,  $\text{CH}_3$ ), 3.03 (s, 6H,  $\text{N}(\text{CH}_3)_2$ ), 7.15 (dd, 1H,  $J = 8.4$  Hz,  $J = 2.0$  Hz, Ar), 7.56 (d, 1H,  $J = 1.6$  Hz, Ar), 7.82 (d, 1H,  $J = 8.4$  Hz, Ar), 11.76 (s, 1H, NH);  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR (100 MHz,  $\text{DMSO}_{d6}$ , 25 °C):  $\delta = 14.3, 37.0, 111.5, 119.4, 119.4, 120.7, 122.8, 123.4, 126.6, 129.1, 141.3, 142.0, 164.6$ ; MS  $m/z$  (ESI): 293 ( $\text{M} + \text{H}^+$ ); anal. calcd. for  $\text{C}_{14}\text{H}_{13}\text{ClN}_2\text{OS}$  (292.04): C 57.43, H 4.48, N 9.57; found: C 57.56, H 4.41, N 9.65.



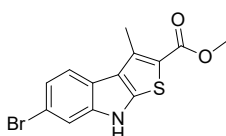
**Ethyl 5-chloro-3-methyl-8H-thieno[2,3-b]indole-2-carboxylate 4l (unknown product).**

**4l** was isolated by column chromatography on silica gel (cyclohexane/acetate, 80/20) and the pure product was precipitated from ethyl ether/petroleum ether in 71% yield. White solid; mp: 216–218 °C; <sup>1</sup>H NMR (400 MHz, DMSO<sub>d6</sub>, 25 °C): δ = 1.31 (t, 3H, *J* = 7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 2.87 (s, 3H, CH<sub>3</sub>), 4.27 (q, 2H, *J* = 7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 7.28 (dd, 1H, *J* = 8.8 Hz, *J* = 2.0 Hz, Ar), 7.54 (d, 1H, *J* = 8.8 Hz, Ar), 7.93 (d, 1H, *J* = 2.0 Hz, Ar), 12.05 (s, 1H, NH); <sup>13</sup>C NMR (100 MHz, DMSO<sub>d6</sub>, 25 °C): <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, DMSO<sub>d6</sub>, 25 °C): δ = 14.3, 14.5, 60.2, 113.4, 117.5, 118.1, 122.7, 123.0, 124.4, 124.6, 139.1, 140.6, 144.6, 163.0; HRMS (ESI) calcd for C<sub>14</sub>H<sub>13</sub>ClNO<sub>2</sub>S [M + H]<sup>+</sup>: 294.0356, found: 294.0356.



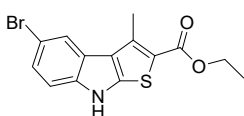
**Ethyl 6-bromo-3-methyl-8H-thieno[2,3-b]indole-2-carboxylate 4m (unknown product).**

**4m** was isolated by column chromatography on silica gel (cyclohexane/acetate, 80/20) and the pure product was precipitated from ethyl ether/petroleum ether in 54% yield. Pale green solid; mp: 259–261 °C; <sup>1</sup>H NMR (400 MHz, DMSO<sub>d6</sub>, 25 °C): δ = 1.30 (t, 3H, *J* = 7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 2.85 (s, 3H, CH<sub>3</sub>), 4.27 (q, 2H, *J* = 7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 7.31 (dd, 1H, *J* = 8.4 Hz, *J* = 1.6 Hz, Ar), 7.74 (d, 1H, *J* = 1.6 Hz, Ar), 7.86 (d, 1H, *J* = 8.4 Hz, Ar), 11.99 (s, 1H, NH); <sup>13</sup>C NMR (100 MHz, DMSO<sub>d6</sub>, 25 °C): <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, DMSO<sub>d6</sub>, 25 °C): δ = 14.3, 14.5, 60.1, 114.6, 115.4, 117.6, 120.2, 121.0, 122.6, 124.9, 138.9, 142.9, 144.1, 162.9; MS *m/z* (ESI): 339 (M + H<sup>+</sup>); anal. calcd. for C<sub>14</sub>H<sub>12</sub>BrNO<sub>2</sub>S (338.22): C 49.72, H 3.58, N 4.14; found: C 49.88, H 3.51, N 4.06.



**Methyl 6-bromo-3-methyl-8H-thieno[2,3-b]indole-2-carboxylate 4n (unknown product).**

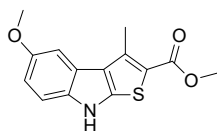
**4n** was isolated by column chromatography on silica gel (cyclohexane/acetate, 80/20) and the pure product was precipitated from ethyl ether/petroleum ether in 63% yield. Yellow solid; mp: 260–262 °C; <sup>1</sup>H NMR (400 MHz, DMSO<sub>d6</sub>, 25 °C): δ = 2.85 (s, 3H, CH<sub>3</sub>), 3.79 (s, 3H, OCH<sub>3</sub>), 7.30 (dd, 1H, *J* = 8.4 Hz, *J* = 0.8 Hz, Ar), 7.74 (d, 1H, *J* = 0.4 Hz, Ar), 7.85 (d, 1H, *J* = 8.4 Hz, Ar), 11.98 (s, 1H, NH); <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, DMSO<sub>d6</sub>, 25 °C): δ = 14.5, 51.5, 114.7, 115.5, 117.2, 120.2, 121.0, 122.6, 124.9, 139.1, 142.9, 144.2, 163.3; HRMS (ESI) calcd for C<sub>13</sub>H<sub>11</sub>BrNO<sub>2</sub>S [M + H]<sup>+</sup>: 323.9694; found: 323.9694.



**Ethyl 5-bromo-3-methyl-8H-thieno[2,3-b]indole-2-carboxylate 4o (unknown product).**

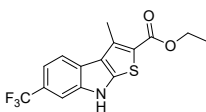
**4o** was isolated by column chromatography on silica gel (cyclohexane/acetate, 80/20) and the pure product was precipitated from ethyl ether/petroleum ether in 48% yield. Pale green solid; mp: 216–218 °C; <sup>1</sup>H NMR (400 MHz, DMSO<sub>d6</sub>, 25 °C): δ = 1.31 (t, 3H, *J* = 7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>),

2.86 (s, 3H,CH<sub>3</sub>), 4.26 (q, 2H,  $J = 7.2$  Hz, OCH<sub>2</sub>CH<sub>3</sub>), 7.39 (dd, 1H,  $J = 8.8$  Hz,  $J = 2.0$  Hz, Ar), 7.49 (d, 1H,  $J = 8.4$  Hz, Ar), 8.04 (d, 1H,  $J = 2.0$  Hz, Ar), 12.06 (s, 1H, NH); <sup>13</sup>C NMR (100 MHz, DMSO<sub>d6</sub>, 25 °C): <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, DMSO<sub>d6</sub>, 25 °C):  $\delta = 14.3, 14.5, 60.1, 112.3, 113.8, 117.5, 121.0, 123.6, 124.5, 125.3, 139.1, 140.9, 144.4, 162.9$ ; MS  $m/z$  (ESI): 339 (M + H<sup>+</sup>); anal. calcd. for C<sub>14</sub>H<sub>12</sub>BrNO<sub>2</sub>S (338.22): C 49.72, H 3.58, N 4.14; found: C 49.86, H 3.67, N 4.19.



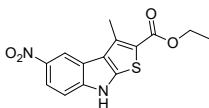
**Methyl 5-methoxy-3-methyl-8H-thieno[2,3-b]indole-2-carboxylate 4p (unknown product).**

**4p** was isolated by column chromatography on silica gel (cyclohexane/acetate, 80/20) and the pure product was precipitated from ethyl ether/petroleum ether in 21% yield. White solid; mp: 186–188 °C; <sup>1</sup>H NMR (400 MHz, DMSO<sub>d6</sub>, 25 °C):  $\delta = 2.87$  (s, 3H, CH<sub>3</sub>), 3.78 (s, 3H, OCH<sub>3</sub>), 3.82 (s, 3H, OCH<sub>3</sub>), 6.90 (dd, 1H,  $J = 8.4$  Hz,  $J = 2.4$  Hz, Ar), 7.39 (d, 1H,  $J = 2.0$  Hz, Ar), 7.40 (d, 1H,  $J = 8.8$  Hz, Ar), 11.73 (s, 1H, NH); <sup>13</sup>C NMR (100 MHz, DMSO<sub>d6</sub>, 25 °C): <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, DMSO<sub>d6</sub>, 25 °C):  $\delta = 14.6, 51.4, 55.5, 102.0, 111.8, 112.5, 115.8, 122.5, 125.1, 137.1, 139.6, 144.1, 153.8, 164.4$ ; HRMS (ESI) calcd for C<sub>14</sub>H<sub>14</sub>NO<sub>3</sub>S [M + H]<sup>+</sup>: 276.0694; found: 276.0704.



**Ethyl 3-methyl-6-(trifluoromethyl)-8H-thieno[2,3-b]indole-2-carboxylate 4q (unknown product).**

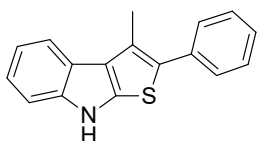
**4q** was isolated by column chromatography on silica gel (cyclohexane/acetate, 80/20) and the pure product was precipitated from ethyl ether/petroleum ether in 34% yield. White solid; mp: 200-201 °C with decomposition; <sup>1</sup>H NMR (400 MHz, DMSO<sub>d6</sub>, 25 °C):  $\delta = 1.31$  (t, 3H,  $J = 7.2$  Hz, OCH<sub>2</sub>CH<sub>3</sub>), 2.90 (s, 3H, CH<sub>3</sub>), 4.28 (q, 2H,  $J = 7.2$  Hz, OCH<sub>2</sub>CH<sub>3</sub>), 7.47 (d, 1H,  $J = 8.4$  Hz, Ar), 7.90 (brs, 1H, Ar), 8.10 (d, 1H,  $J = 8.0$  Hz, Ar), 12.21 (s, 1H, NH); <sup>13</sup>C NMR (100 MHz, DMSO<sub>d6</sub>, 25 °C): <sup>13</sup>C NMR (100 MHz, DMSO<sub>d6</sub>, 25 °C):  $\delta = 14.3, 14.6, 60.3, 109.2$  (<sup>3</sup> $J_{CF} = 4.4$  Hz), 116.2 (<sup>3</sup> $J_{CF} = 3.4$  Hz), 118.3, 119.4, 123.0 (<sup>2</sup> $J_{CF} = 31.3$  Hz), 124.6, 124.9, 125.0 (<sup>1</sup> $J_{CF} = 269.8$  Hz), 139.1, 141.1, 145.7, 162.9; MS  $m/z$  (ESI): 328 (M + H<sup>+</sup>); anal. calcd. for C<sub>15</sub>H<sub>12</sub>F<sub>3</sub>NO<sub>2</sub>S (327.32): C 55.04, H 3.70, N 4.28; found: C 54.85, H 3.57, N 4.42.



**Ethyl 3-methyl-5-nitro-8H-thieno[2,3-b]indole-2-carboxylate 4r (unknown product).**

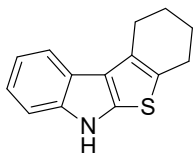
**4r** was isolated by column chromatography on silica gel (cyclohexane/acetate, 80/20) and the pure product was precipitated from ethyl ether/petroleum ether in 39% yield. Pale yellow solid; mp: 218–221 °C with decomposition; <sup>1</sup>H NMR (400 MHz, DMSO<sub>d6</sub>, 25 °C):  $\delta = 1.32$  (t, 3H,  $J = 7.2$  Hz, OCH<sub>2</sub>CH<sub>3</sub>), 2.93 (s, 3H, CH<sub>3</sub>), 4.29 (q, 2H,  $J = 7.2$  Hz, OCH<sub>2</sub>CH<sub>3</sub>), 7.72 (d, 1H,  $J = 8.8$  Hz, Ar), 8.18 (dd, 1H,  $J = 9.2$  Hz,  $J = 2.4$  Hz, Ar), 8.74 (brs, 1H, Ar), 12.58 (s, 1H, NH); <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz,

DMSO<sub>d6</sub>, 25 °C): <sup>13</sup>C NMR (100 MHz, DMSO<sub>d6</sub>, 25 °C): δ = 14.3, 14.4, 60.4, 112.3, 114.9, 118.3, 119.2, 121.2, 125.7, 138.8, 140.8, 145.3, 145.8, 162.8; MS *m/z* (ESI): 305 (M + H<sup>+</sup>); anal. calcd. for C<sub>14</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub>S (304.32): C 55.25, H 3.97, N 9.21; found: C 55.51, H 3.82, N 9.39.



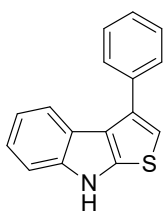
**3-methyl-2-phenyl-8H-thieno[2,3-b]indole- 4s (unknown product).**

**4s** was isolated by column chromatography on silica gel (cyclohexane/acetate, 80/20) and the pure product was precipitated from ethyl ether/petroleum ether in 86% yield. White solid; mp: 134–136 °C; <sup>1</sup>H NMR (400 MHz, DMSO<sub>d6</sub>, 25 °C): δ = 2.63 (s, 3H, CH<sub>3</sub>), 7.11 (dt, 1H, *J* = 8.0 Hz, *J* = 1.2 Hz, Ar), 7.20 (dt, 1H, *J* = 7.6 Hz, *J* = 1.2 Hz, Ar), 7.33 (tt, 1H, *J* = 7.2 Hz, *J* = 1.6 Hz, Ar), 7.44–7.53 (m, 5H, Ar), 7.86 (d, 1H, *J* = 8.0 Hz, Ar), 11.64 (s, 1H, NH); <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, DMSO<sub>d6</sub>, 25 °C): δ = 14.0, 111.5, 118.0, 119.0, 119.9, 121.7, 122.2, 124.9, 126.6, 127.9, 128.6, 128.8, 134.9, 138.9, 141.3; MS *m/z* (ESI): 264 (M + H<sup>+</sup>); anal. calcd. for C<sub>17</sub>H<sub>13</sub>NS (263.36): C 77.53, H 4.98, N 5.32; found: C 77.71, H 5.06, N 5.22.



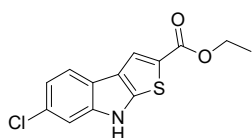
**2,3,4,6-tetrahydro-1H-benzo[4,5]thieno[2,3-b]indole 4t.<sup>[5]</sup>**

**4t** was isolated by column chromatography on silica gel (cyclohexane/acetate, 80/20) and the pure product was precipitated from ethyl ether/petroleum ether in 51% yield. White solid; mp: 260–263 °C; <sup>1</sup>H NMR (400 MHz, DMSO<sub>d6</sub>, 25 °C): δ = 1.83–1.89 (m, 4H, Cyclohex.), 2.74–2.80 (m, 2H, Cyclohex.), 2.88–2.94 (m, 2H, Cyclohex.), 7.04 (dt, 1H, *J* = 7.6 Hz, *J* = 1.2 Hz, Ar), 7.12 (dt, 1H, *J* = 7.6 Hz, *J* = 1.2 Hz, Ar), 7.40 (d, 1H, *J* = 8.0 Hz, Ar), 7.67 (d, 1H, *J* = 8.0 Hz, Ar), 11.44 (s, 1H, NH); <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, DMSO<sub>d6</sub>, 25 °C): δ = 22.4, 23.4, 24.6, 25.2, 111.4, 118.0, 118.7, 121.0, 121.7, 122.6, 126.4, 126.5, 137.8, 141.1; MS *m/z* (ESI): 228 (M + H<sup>+</sup>); anal. calcd. for C<sub>14</sub>H<sub>13</sub>NS (227.07): C 73.97, H 5.76, N 6.16; found: C 73.84, H 5.88, N 6.12.



**3-phenyl-8H-thieno[2,3-b]indole 4u.<sup>[6]</sup>**

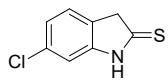
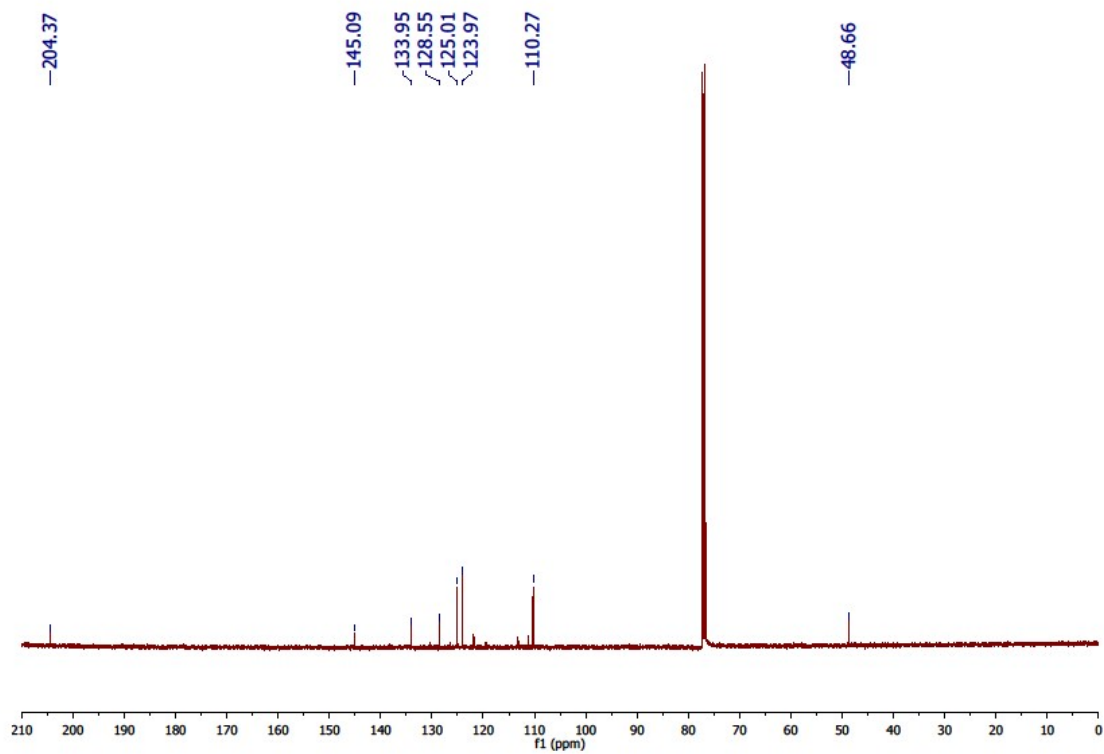
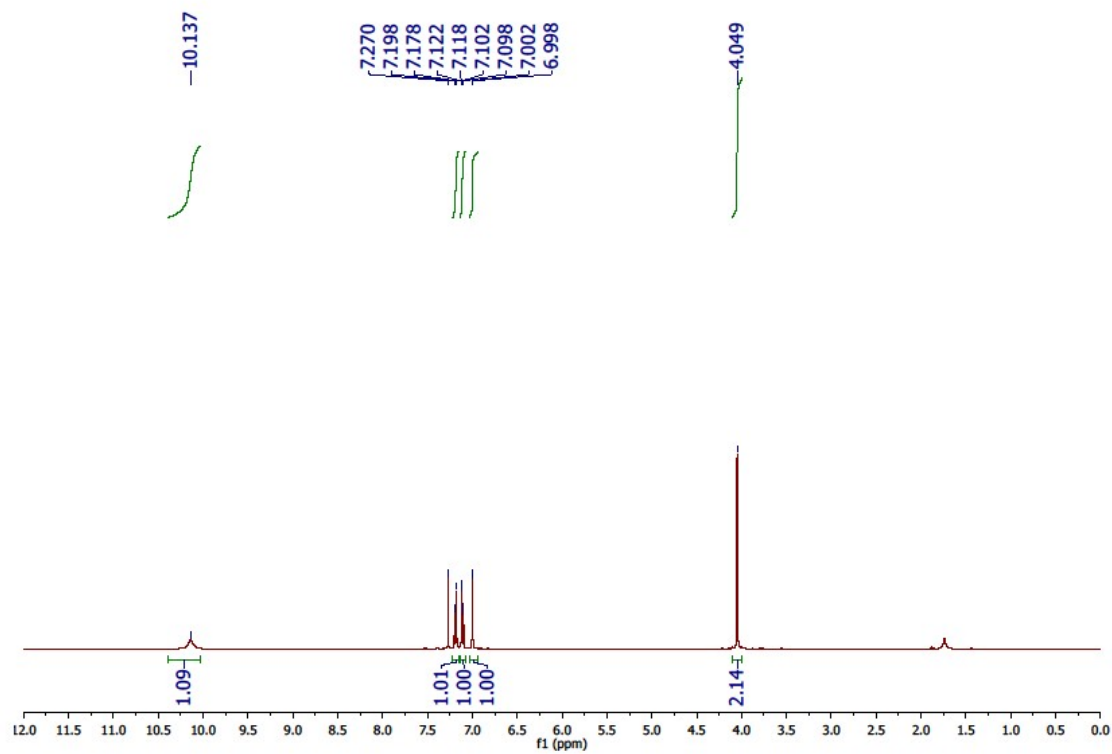
**4u** was isolated by column chromatography on silica gel (cyclohexane/acetate, 90/10) and the pure product was precipitated from ethyl ether/petroleum ether in 83% yield. Yellow solid; mp: 153–155 °C; <sup>1</sup>H NMR (400 MHz, DMSO<sub>d6</sub>, 25 °C): δ = 7.06 (dt, 1H, *J* = 7.6 Hz, *J* = 1.2 Hz, Ar), 7.06 (s, 1H, Ar), 7.21 (dt, 1H, *J* = 7.2 Hz, *J* = 1.2 Hz, Ar), 7.42 (tt, 1H, *J* = 6.8 Hz, *J* = 1.2 Hz, Ar), 7.49–7.57 (m, 3H, Ar), 7.72 (d, 1H, *J* = 8.0 Hz, Ar), 7.77 (dd, 2H, *J* = 7.6 Hz, *J* = 1.6 Hz, Ar), 11.74 (s, 1H, NH); <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, DMSO<sub>d6</sub>, 25 °C): δ = 111.8, 113.5, 118.4, 118.8, 121.2, 121.2, 121.9, 127.5, 127.6, 128.8, 134.3, 136.2, 142.0, 142.2; HRMS (ESI) calcd for C<sub>16</sub>H<sub>12</sub>NS [M + H]<sup>+</sup>: 250.0690; found: 250.0688.

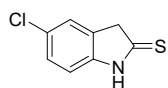


**Ethyl 6-chloro-8H-thieno[2,3-b]indole-2-carboxylate 4v.**<sup>[7]</sup>

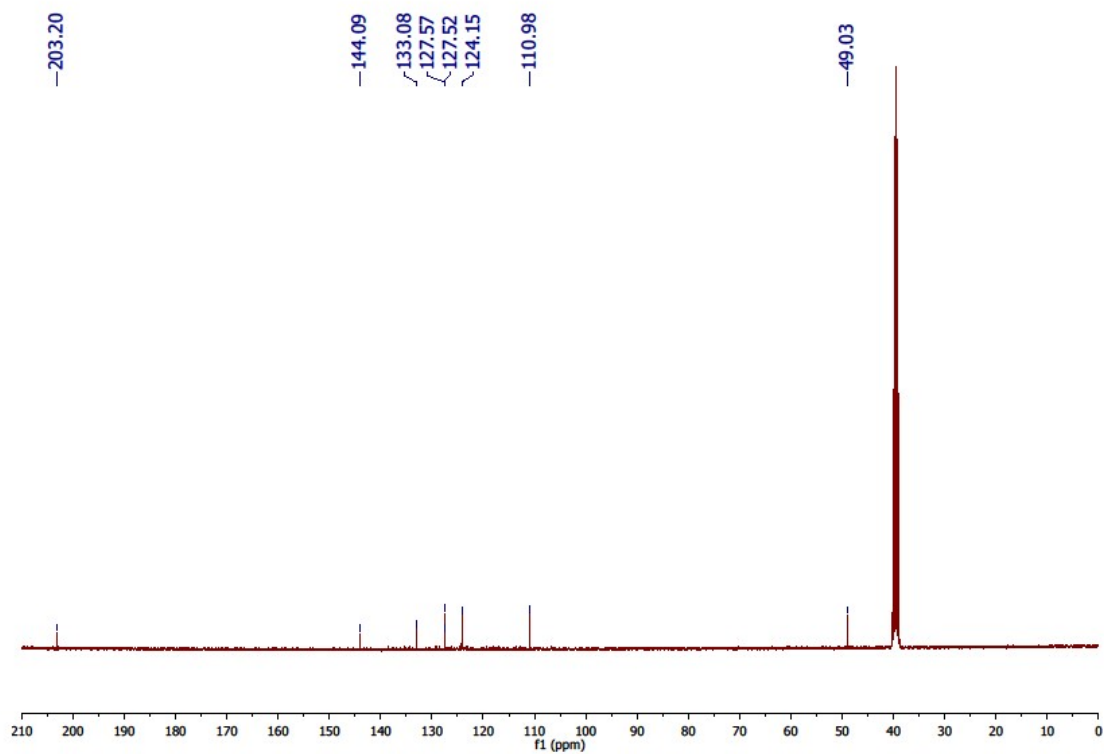
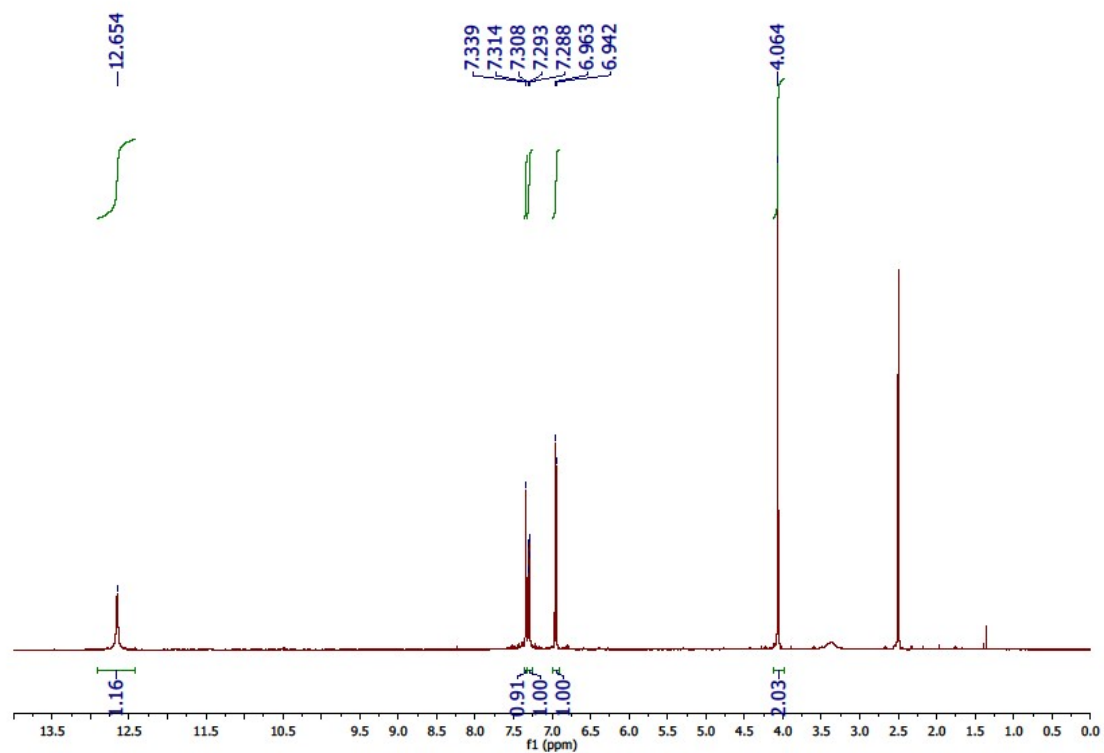
**4v** was isolated by column chromatography on silica gel (cyclohexane/acetate, 80/20) and the pure product was precipitated from ethyl ether/petroleum ether in 14% yield (referred to the starting ethyl 2-chloro-3-oxopropanoate **6a**). Pale green solid; mp: 187–189 °C; <sup>1</sup>H NMR (400 MHz, DMSO<sub>d6</sub>, 25 °C): δ = 1.32 (t, 3H, *J* = 7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 4.30 (q, 2H, *J* = 7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 7.19 (dd, 1H, *J* = 8.4 Hz, *J* = 1.6 Hz, Ar), 7.61 (d, 1H, *J* = 2.0 Hz, Ar), 7.92 (d, 1H, *J* = 8.4 Hz, Ar), 8.25 (s, 1H, CH), 12.02 (brs, 1H, NH); <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, DMSO<sub>d6</sub>, 25 °C): <sup>13</sup>C NMR (100 MHz, DMSO<sub>d6</sub>, 25 °C): δ = 14.3, 60.6, 111.8, 120.1, 120.3, 120.9, 123.6, 124.2, 125.4, 127.7, 142.6, 146.5, 162.5; MS *m/z* (ESI): 280 (M + H<sup>+</sup>); anal. calcd. for C<sub>13</sub>H<sub>10</sub>ClNO<sub>2</sub>S (279.74): C 55.82, H 3.60, N 5.01; found: C 55.98, H 3.71, N 5.14.

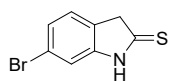


6-chloroindoline-2-thione 2b.<sup>[3]</sup>

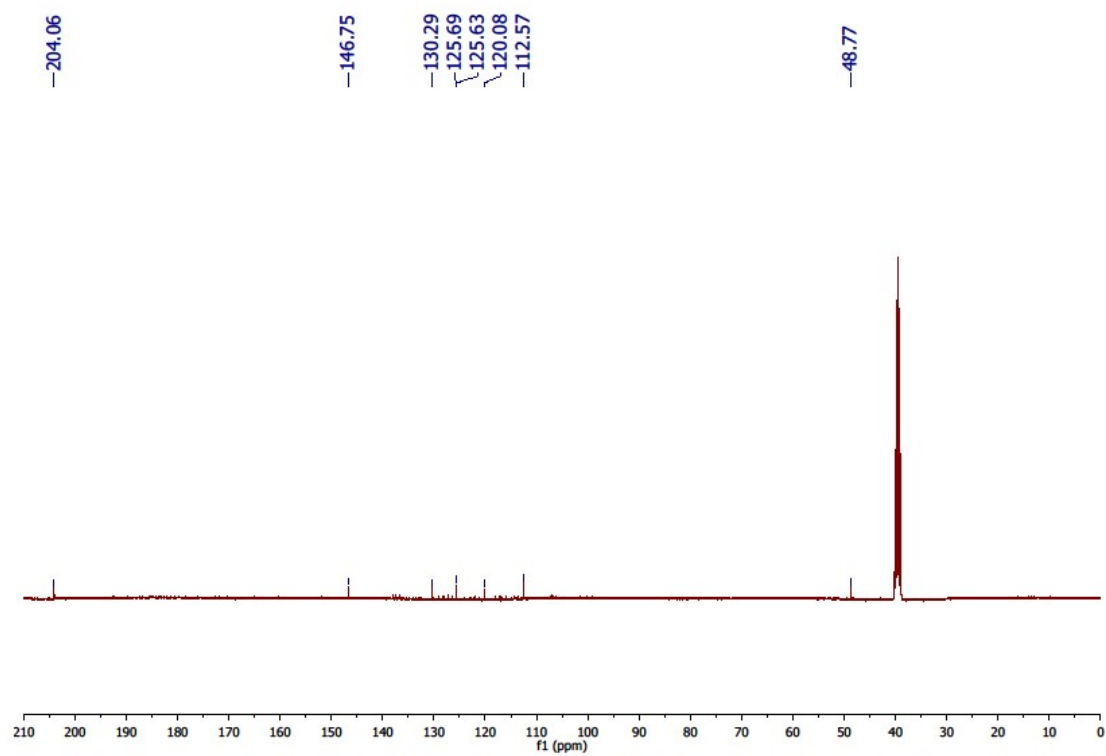
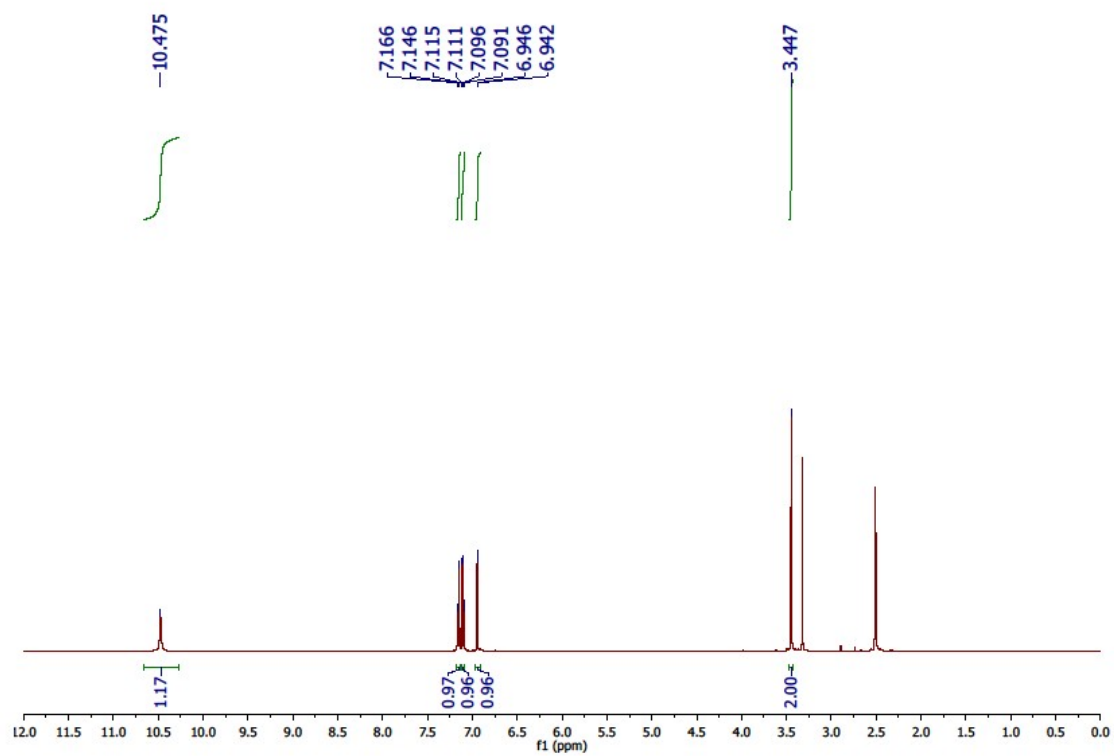


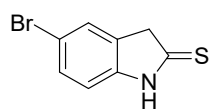
5-chloroindoline-2-thione 2c.<sup>[3]</sup>



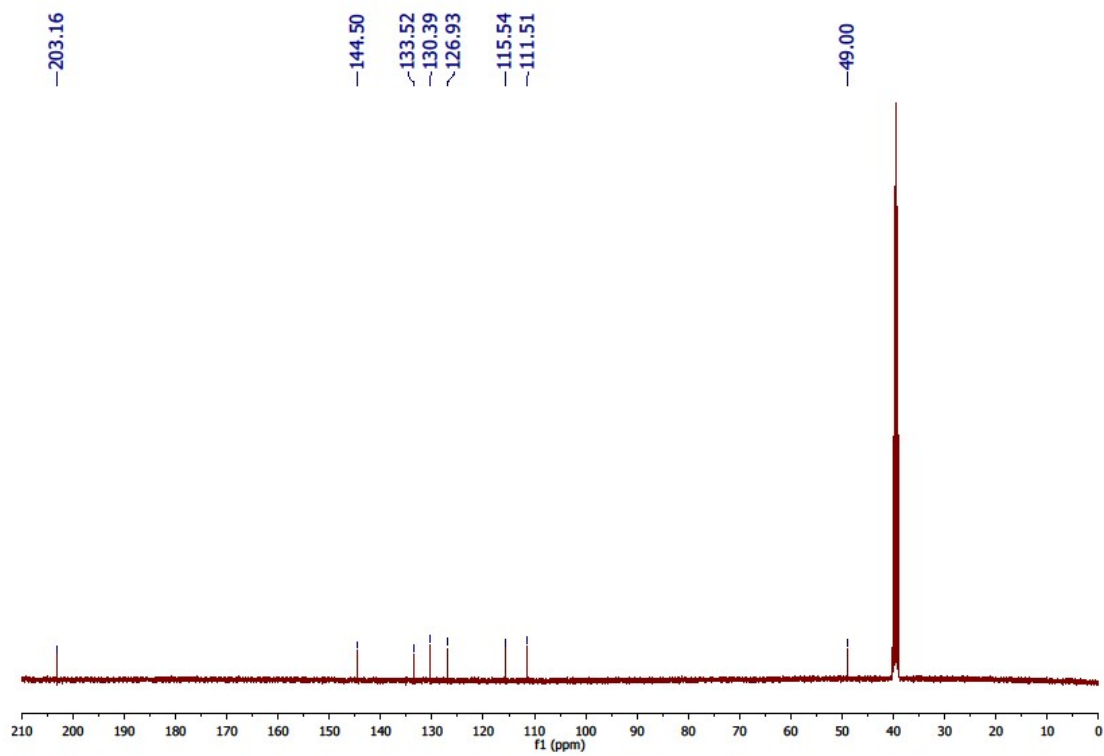
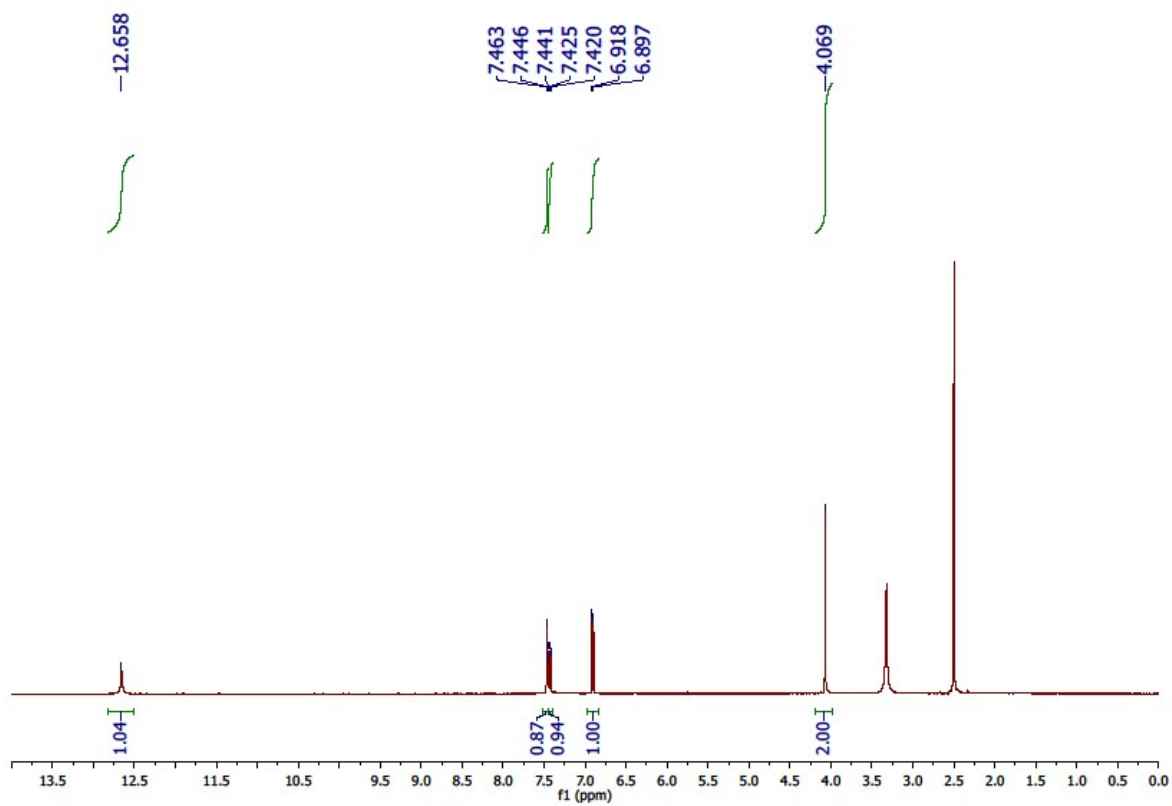


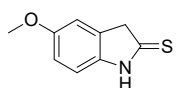
6-bromoindoline-2-thione 2d.<sup>[3]</sup>



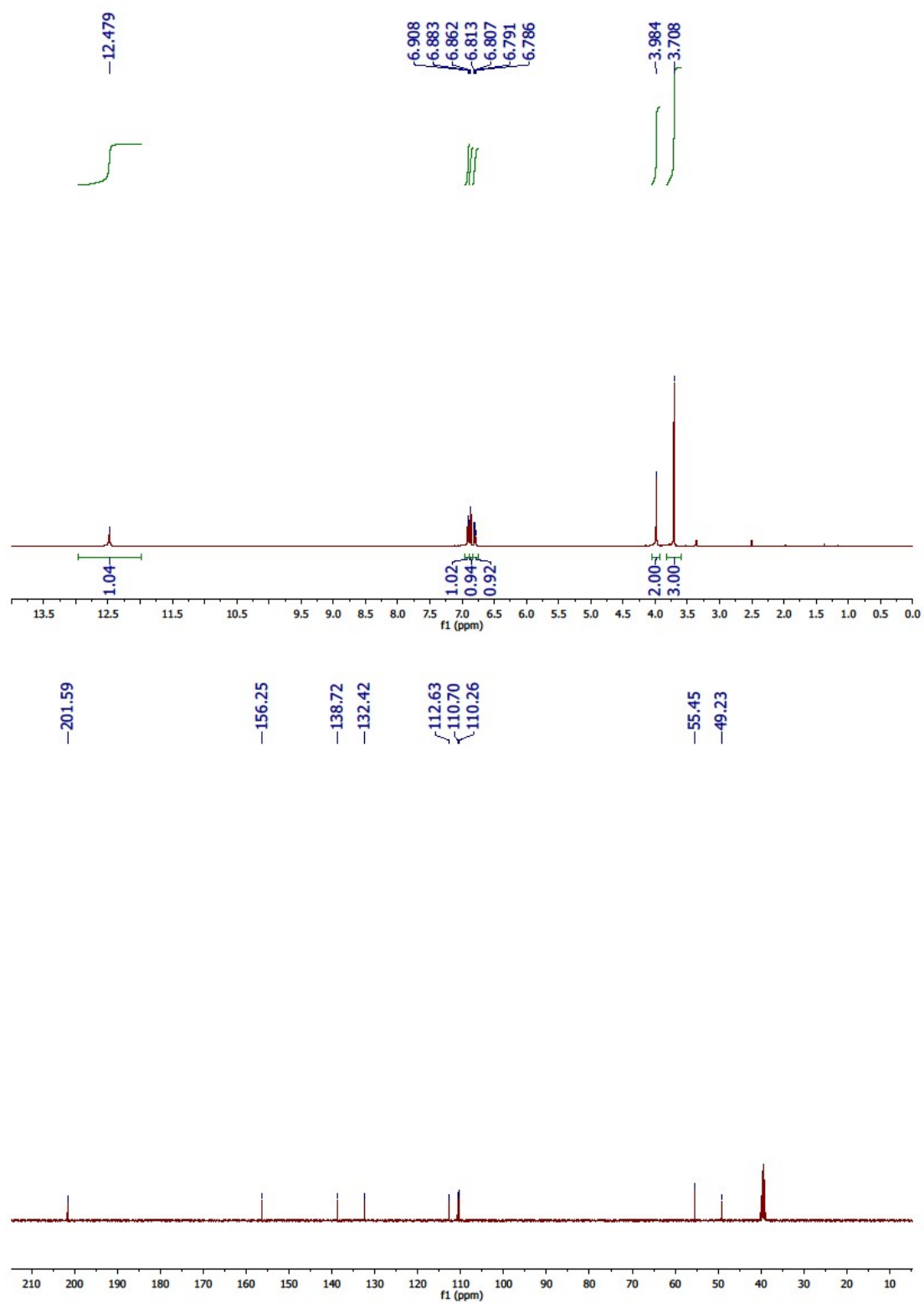


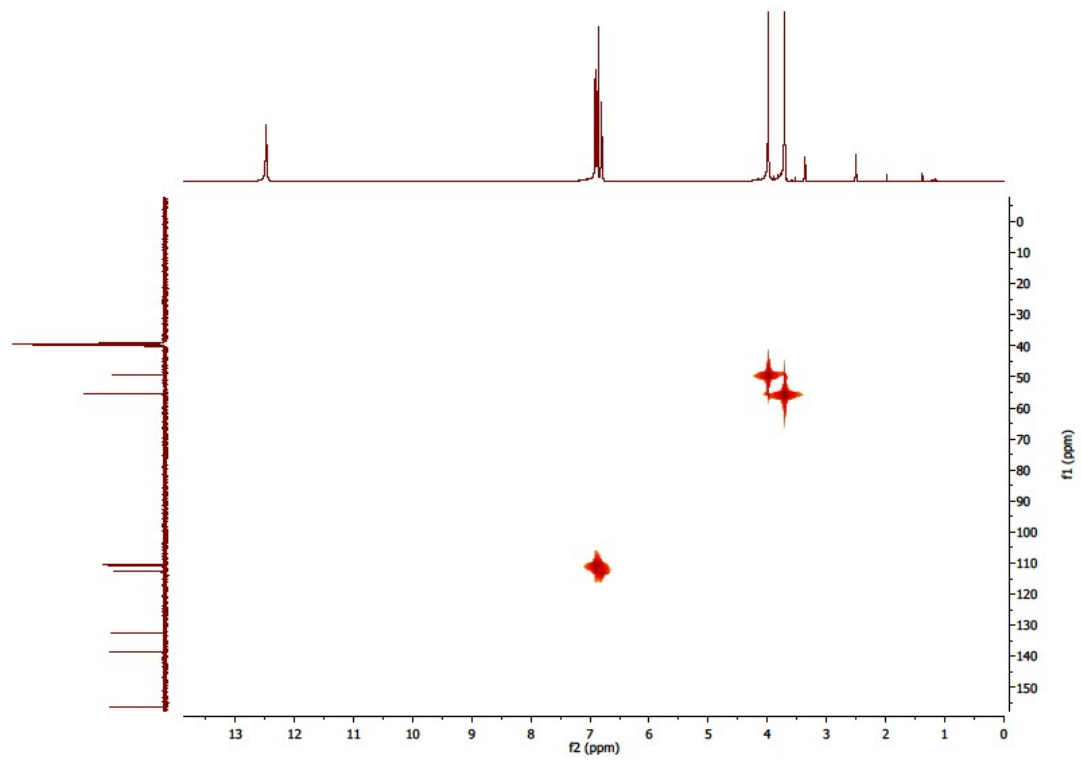
5-bromoindoline-2-thione 2e.<sup>[3]</sup>

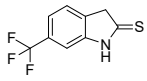




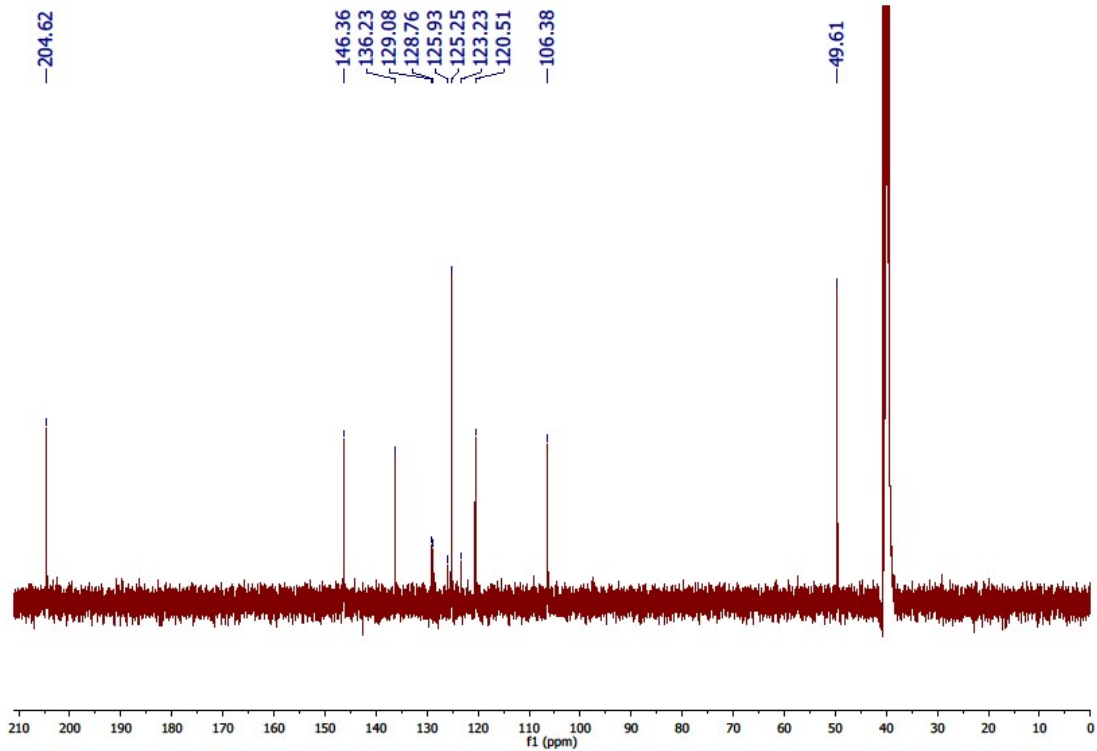
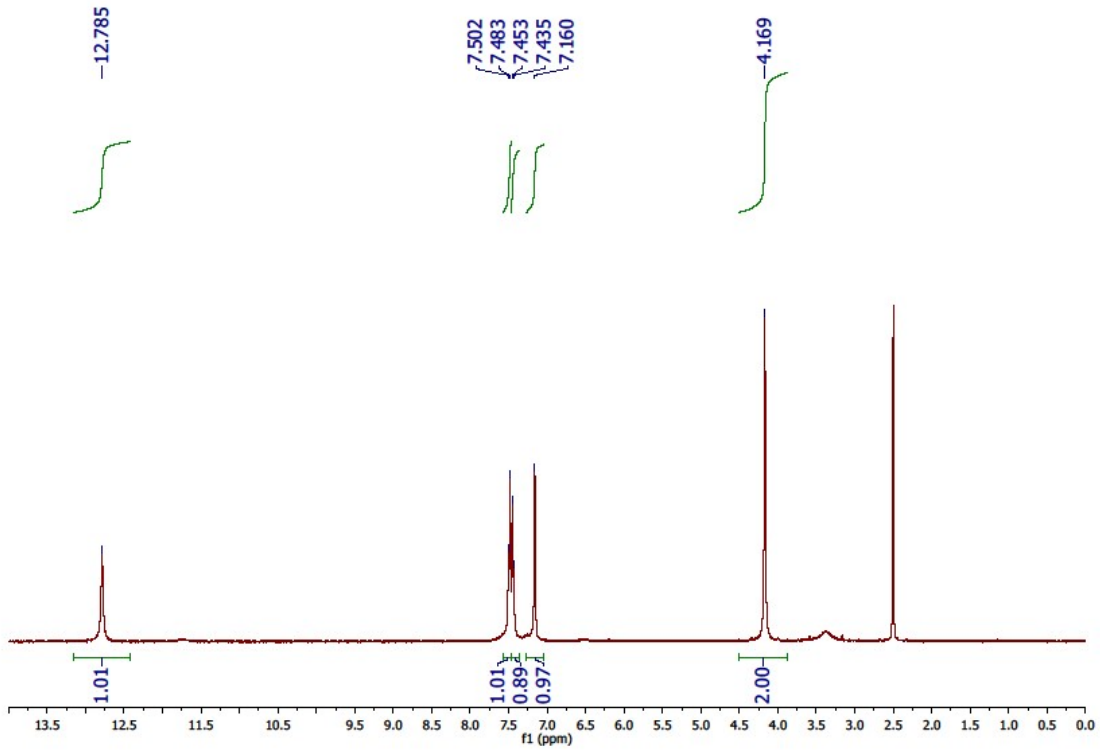
5-methoxyindoline-2-thione 2f.<sup>[3]</sup>

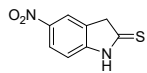




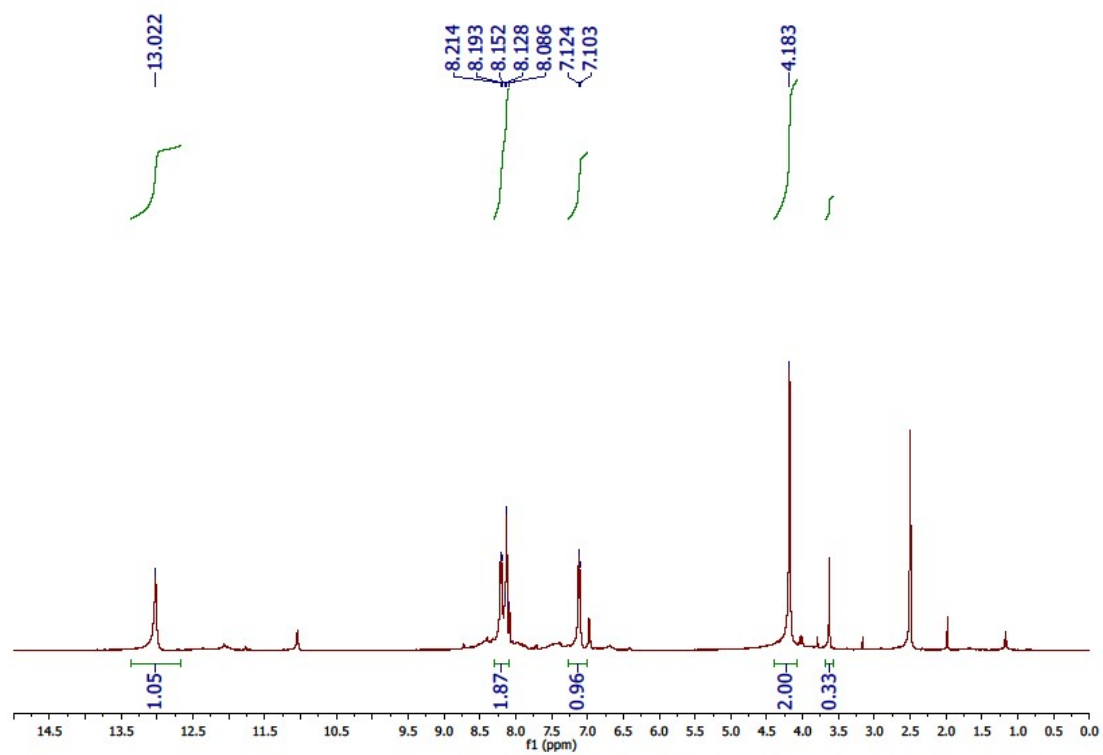


6-(Trifluoromethyl)indoline-2-thione 2g.<sup>[3]</sup>

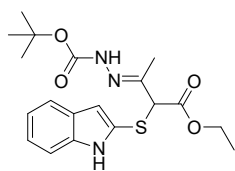




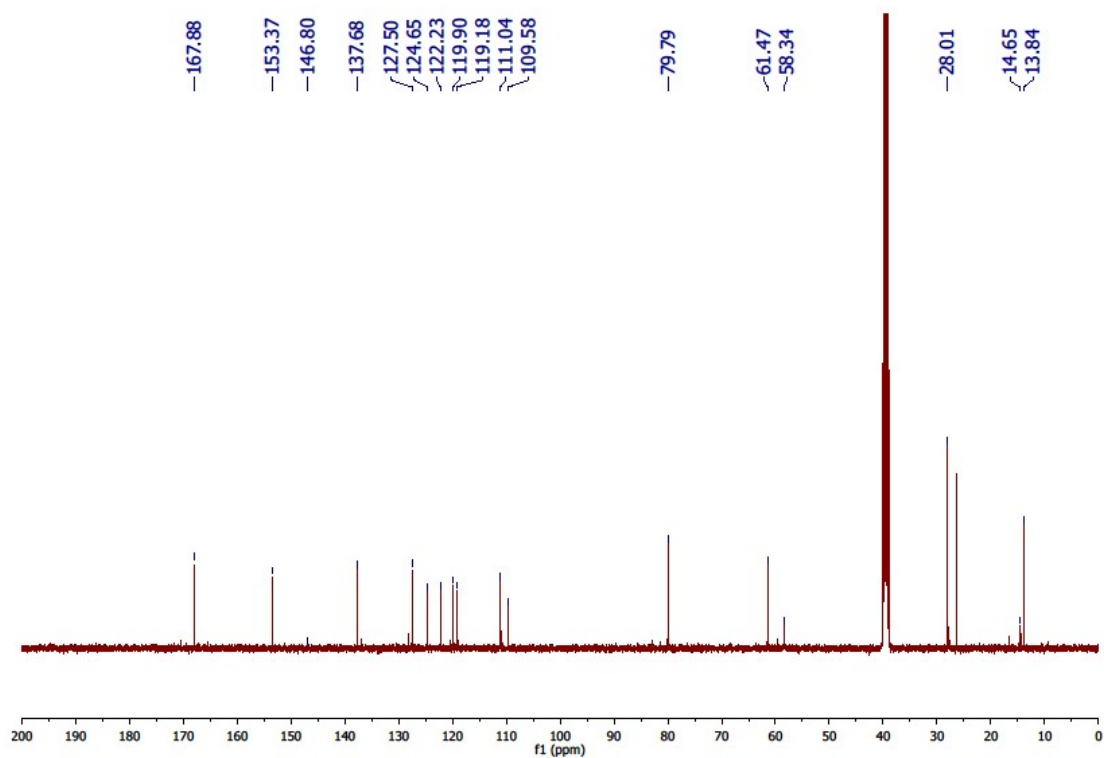
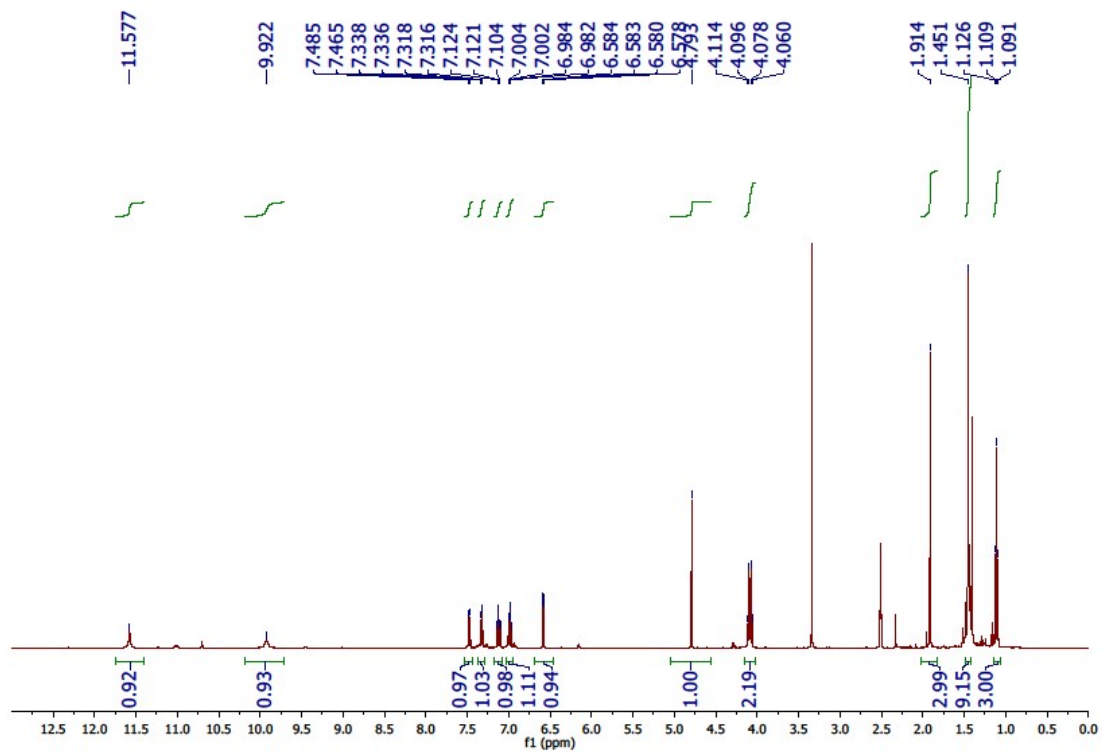
5-Nitroindoline-2-thione 2h.<sup>[3]</sup>

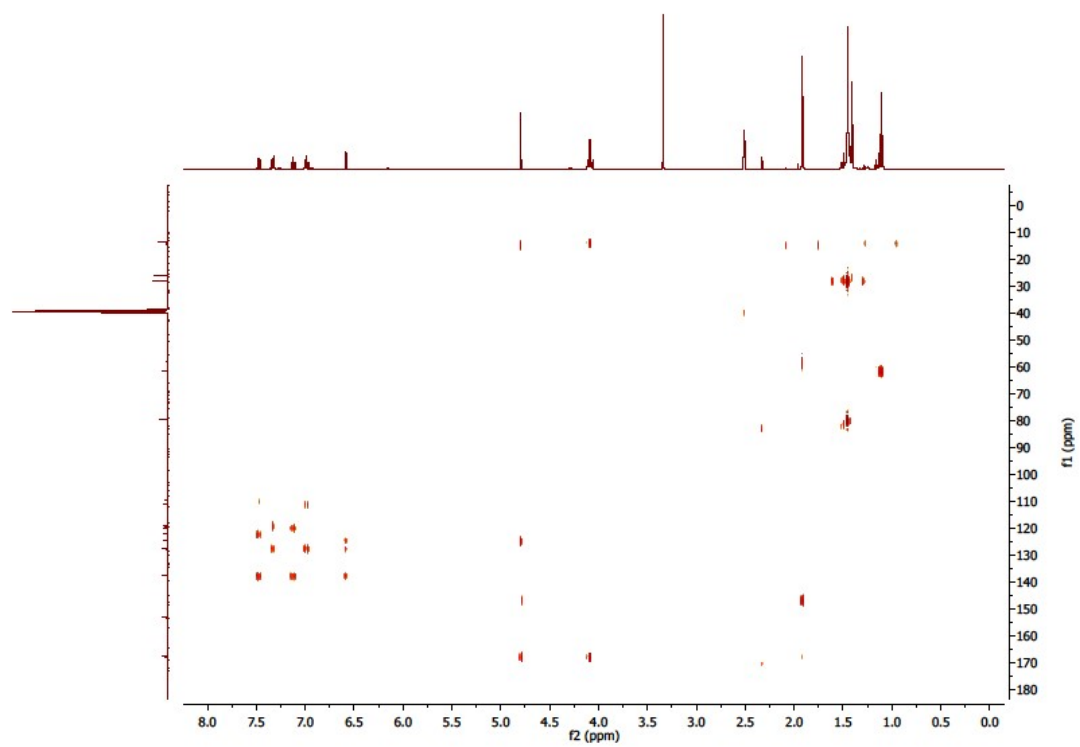
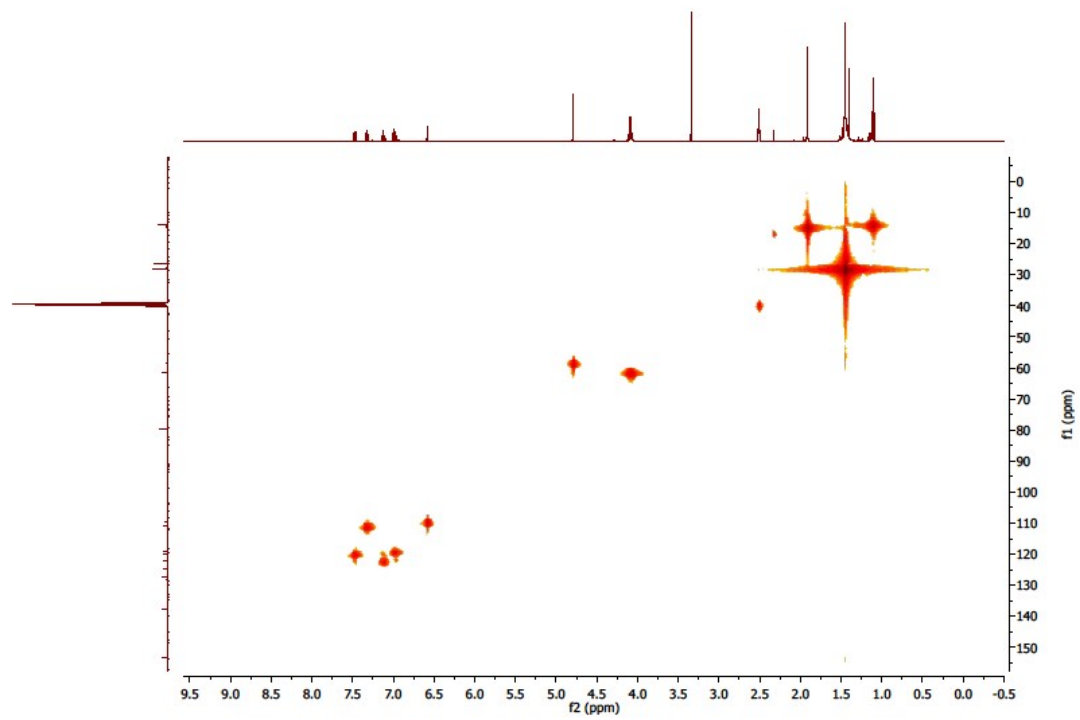


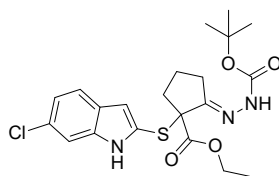




**Tert-butyl 2-(3-((1*H*-indol-2-yl)thio)-4-ethoxy-4-oxobutan-2-ylidene)hydrazinecarboxylate 3a.**<sup>[4]</sup>

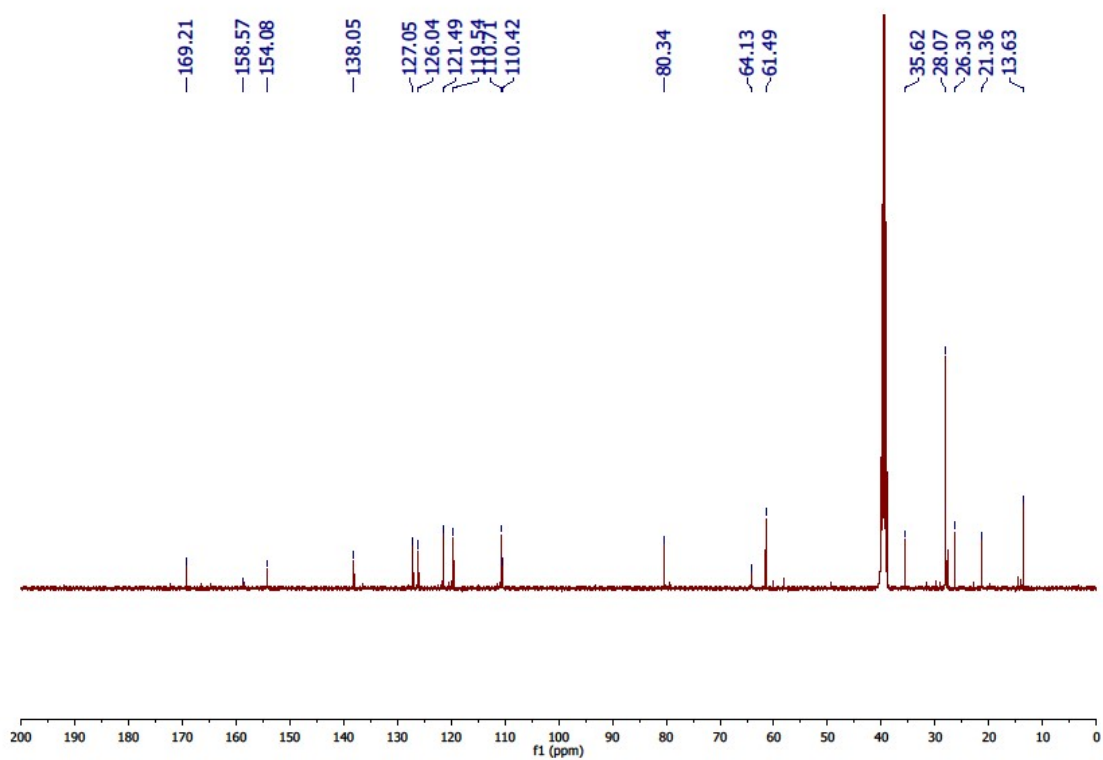
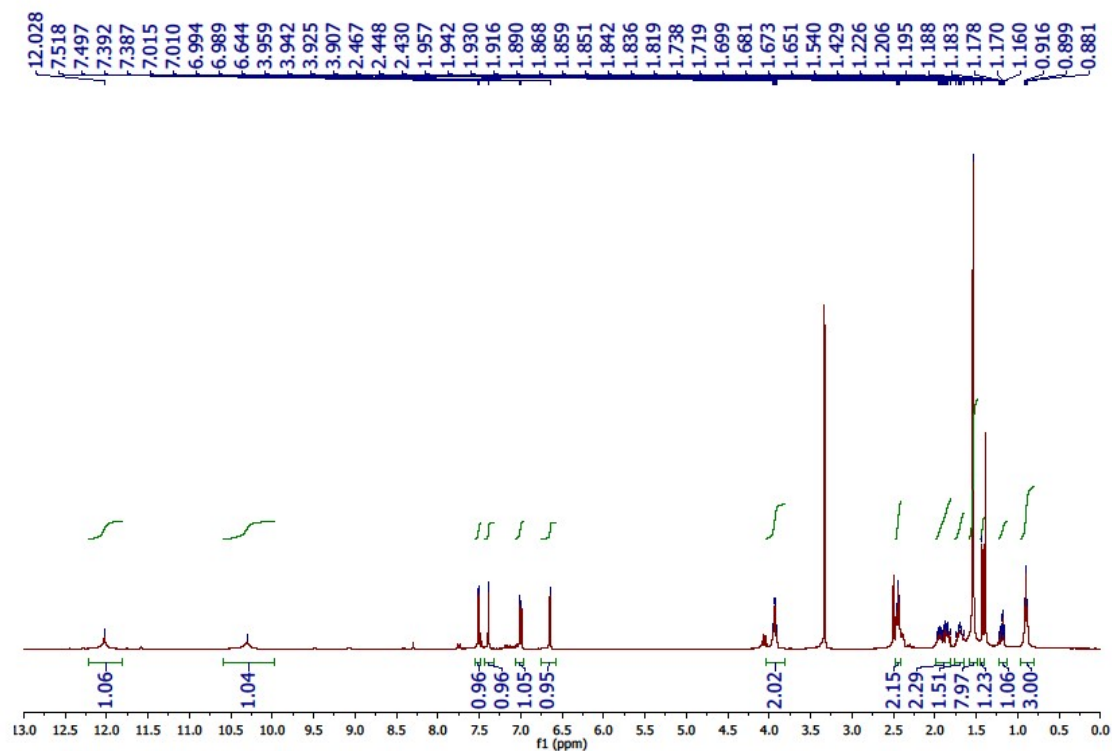


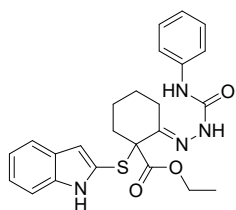




**Tert-butyl**

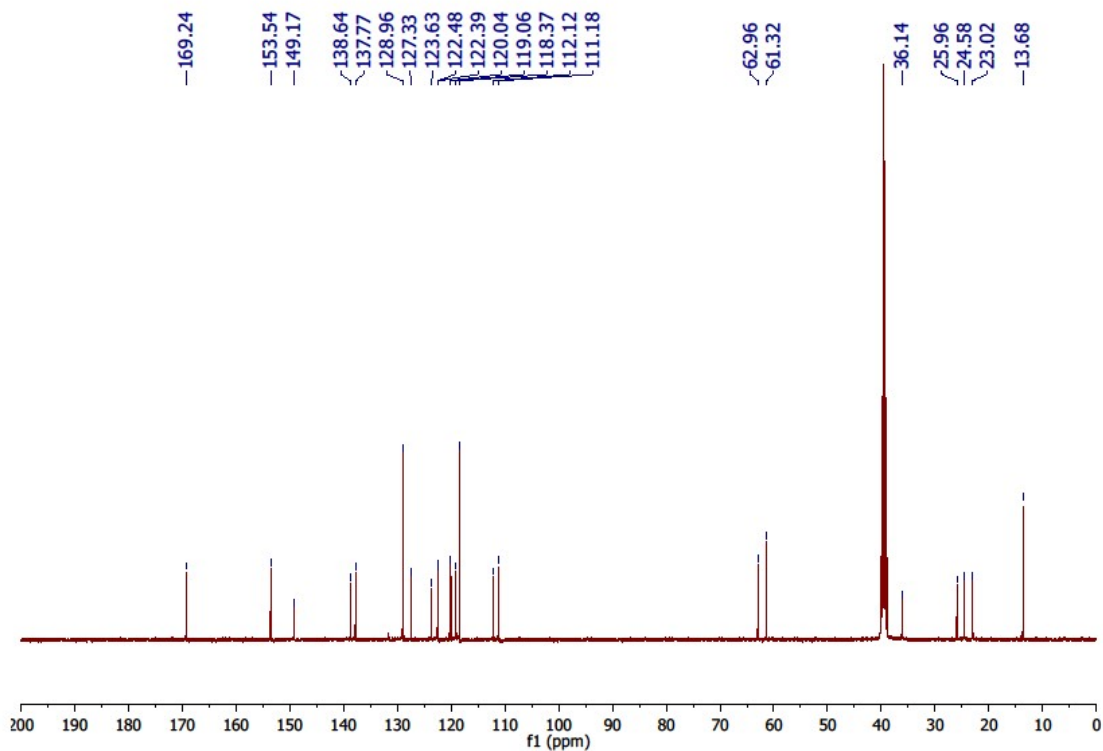
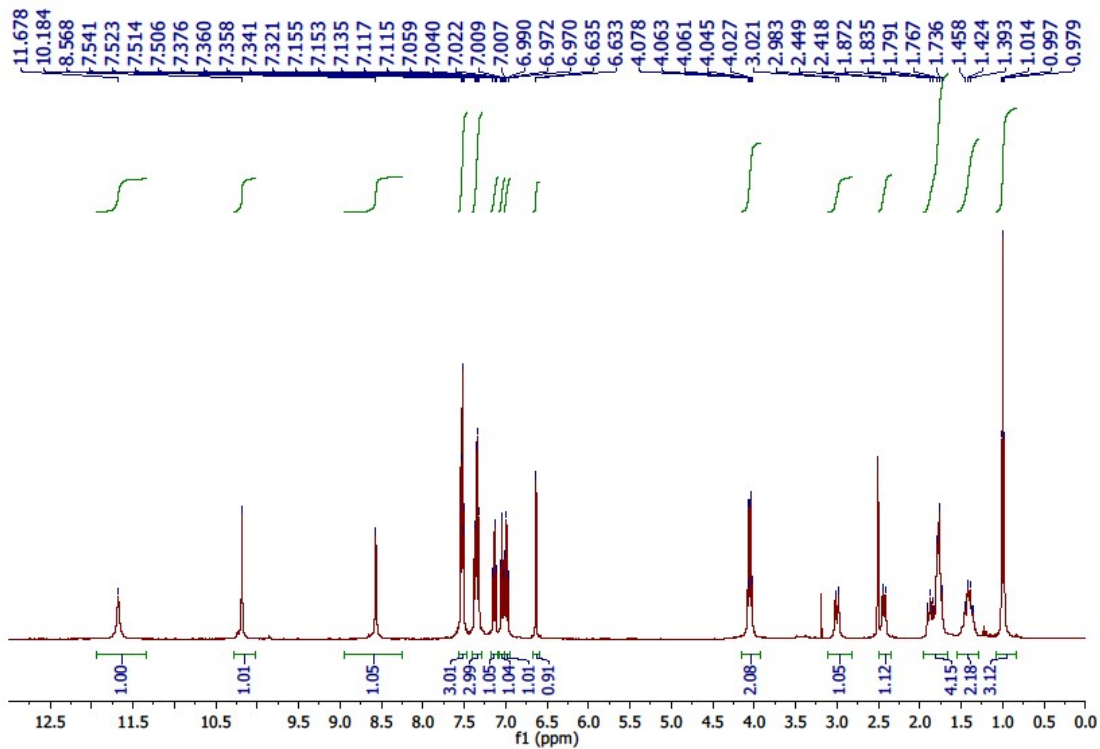
**2-(2-((6-chloro-1H-indol-2-yl)thio)-2-(ethoxycarbonyl)cyclopentylidene)hydrazinecarboxylate 3b.<sup>[4]</sup>**

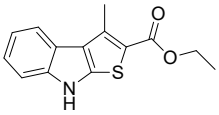




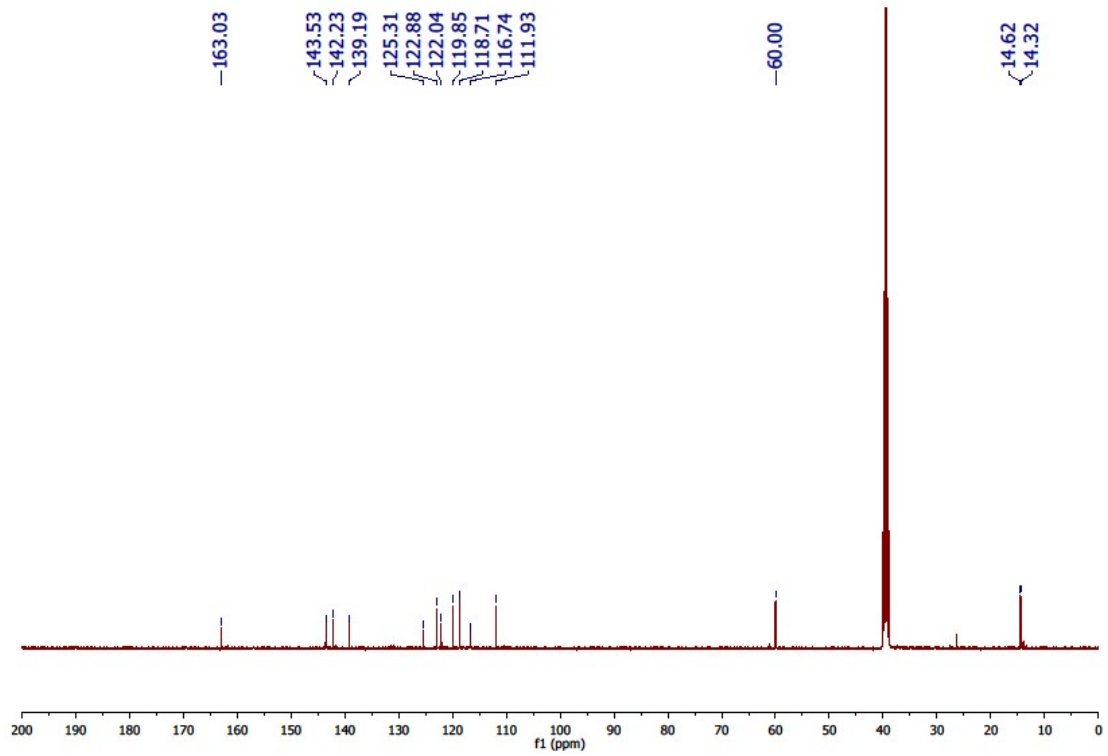
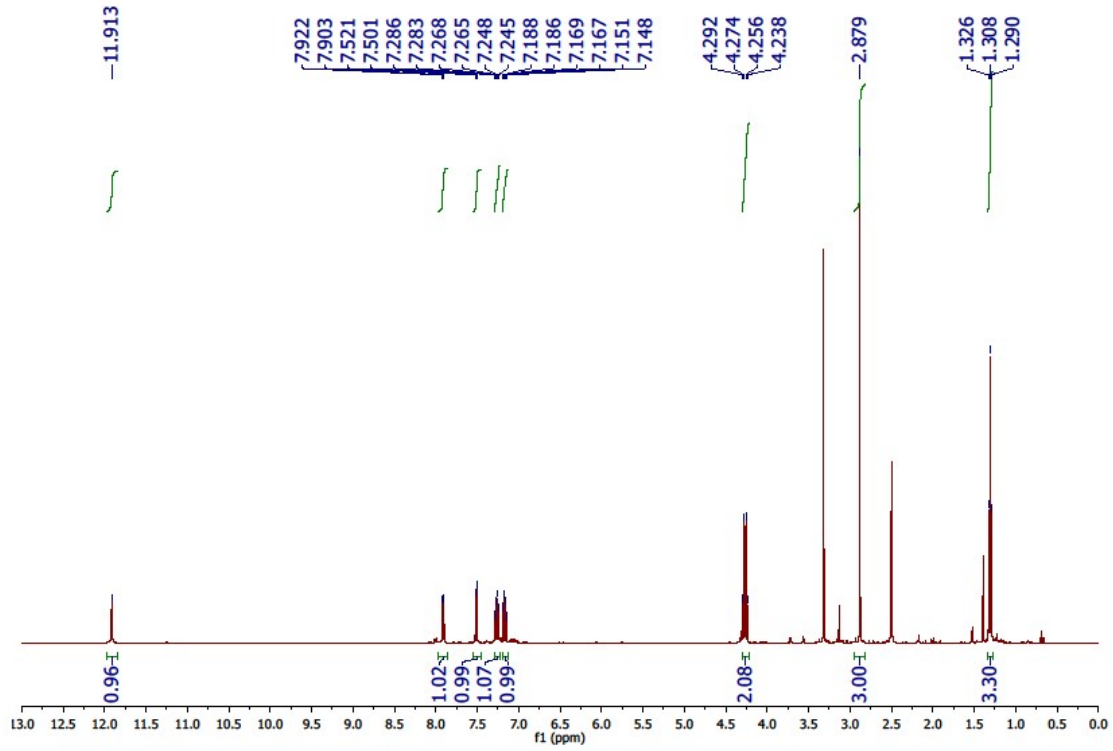
**Ethyl**

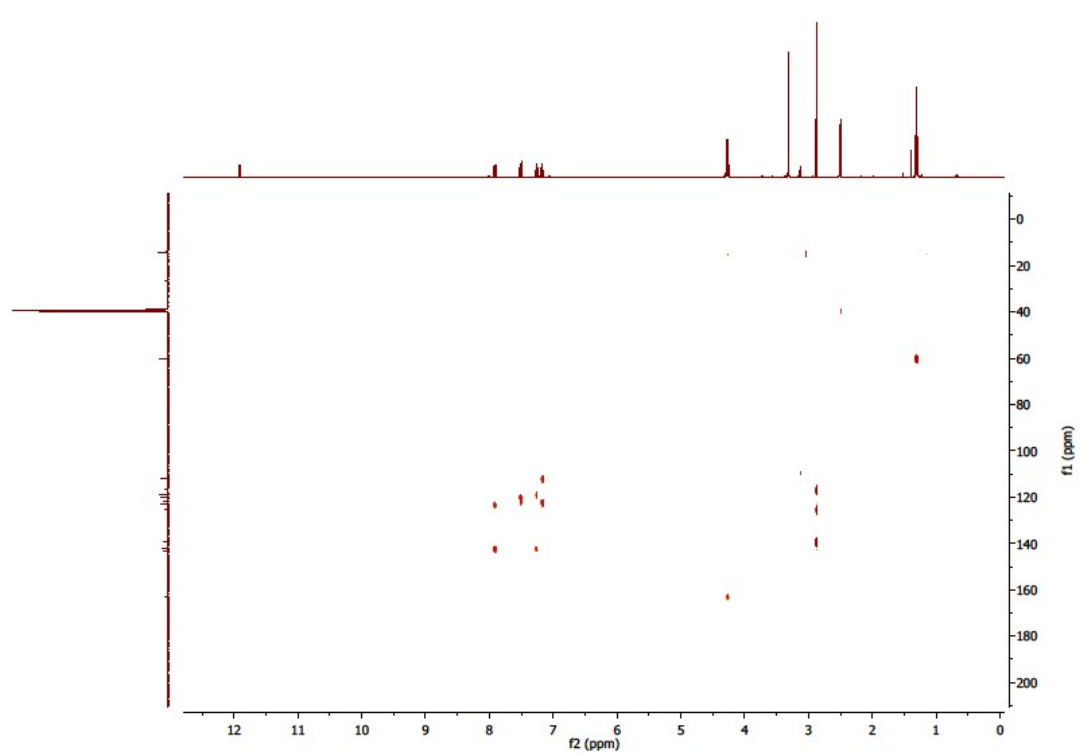
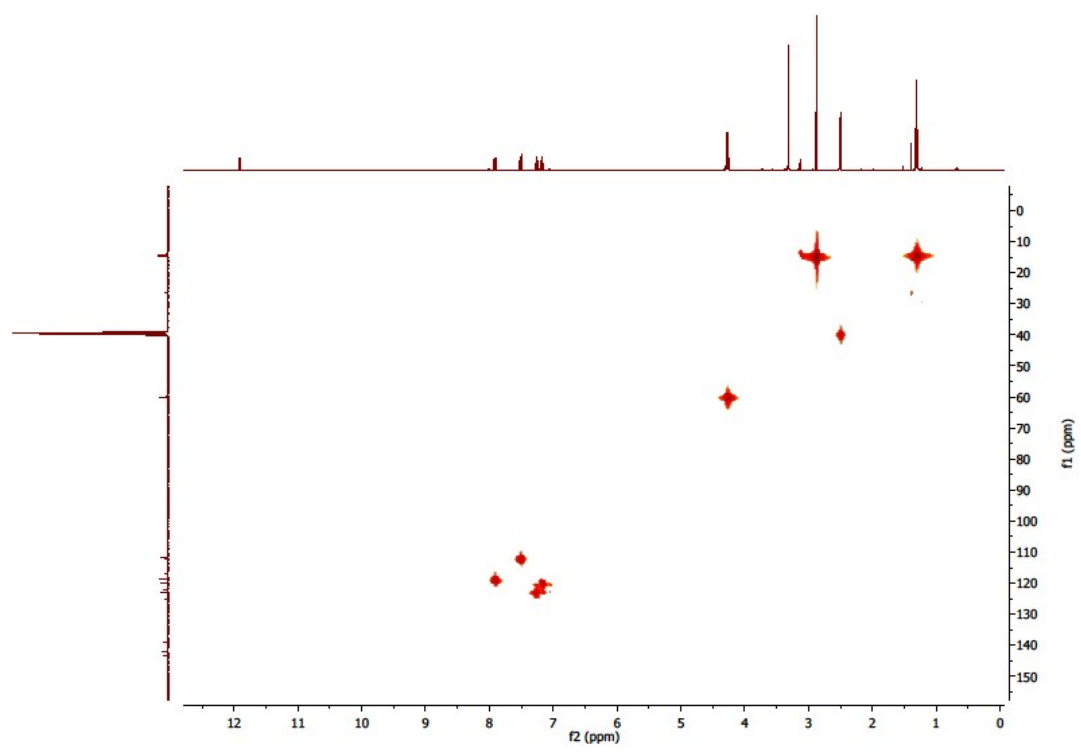
**1-((1H-indol-2-yl)thio)-2-(2-(phenylcarbamoyl)hydrazono)cyclohexanecarboxylate 3c.<sup>[4]</sup>**

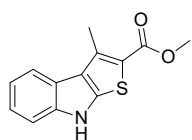




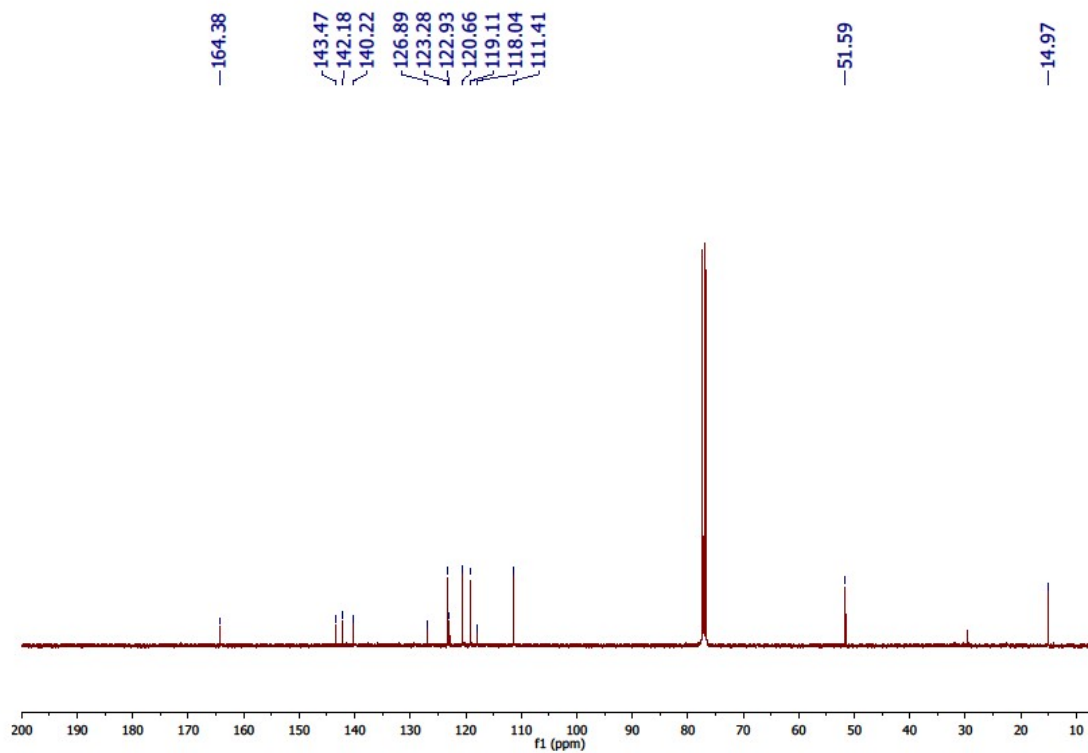
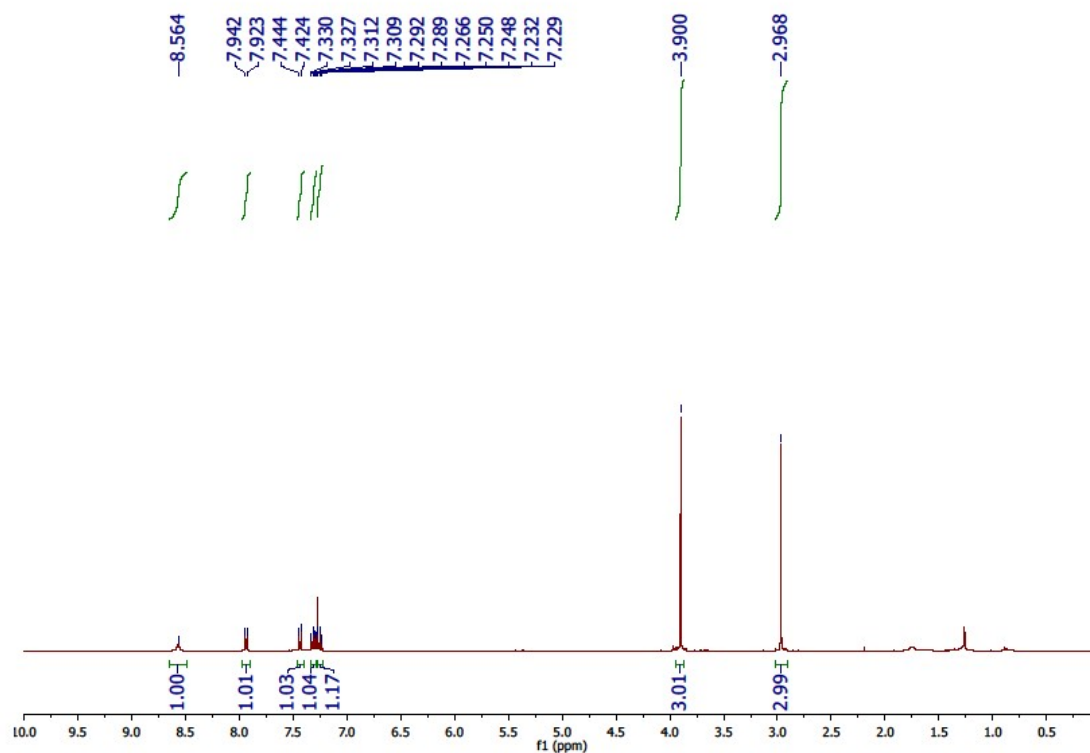
Ethyl 3-methyl-8*H*-thieno[2,3-*b*]indole-2-carboxylate 4a.

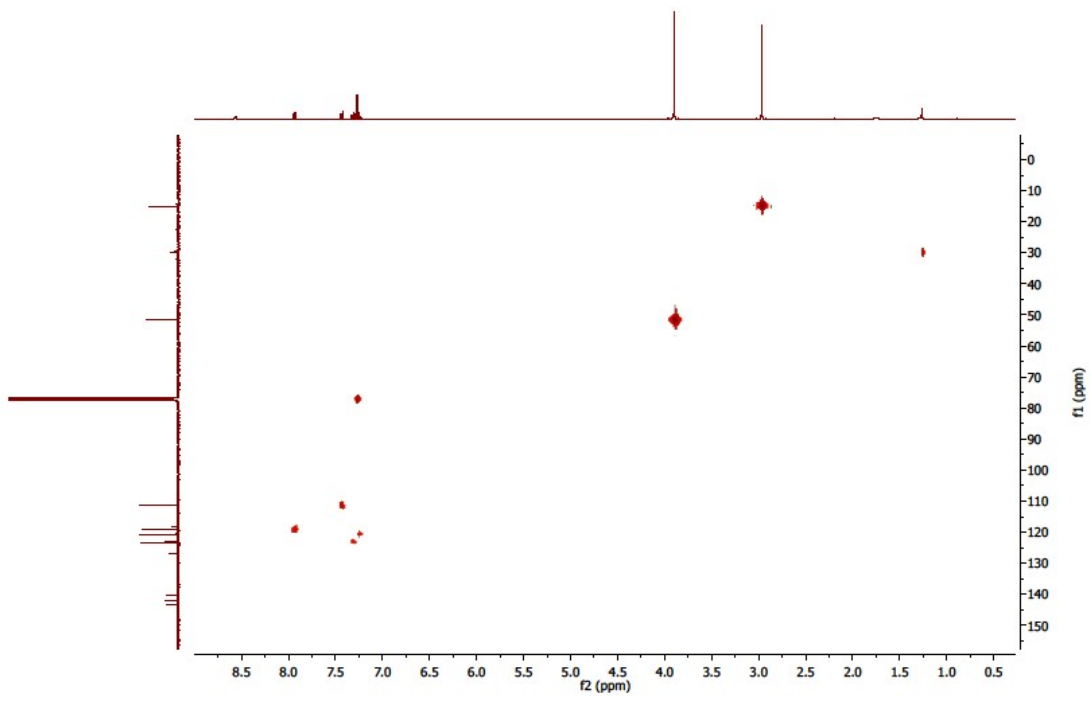




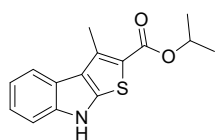


Methyl 3-methyl-8*H*-thieno[2,3-*b*]indole-2-carboxylate 4b.

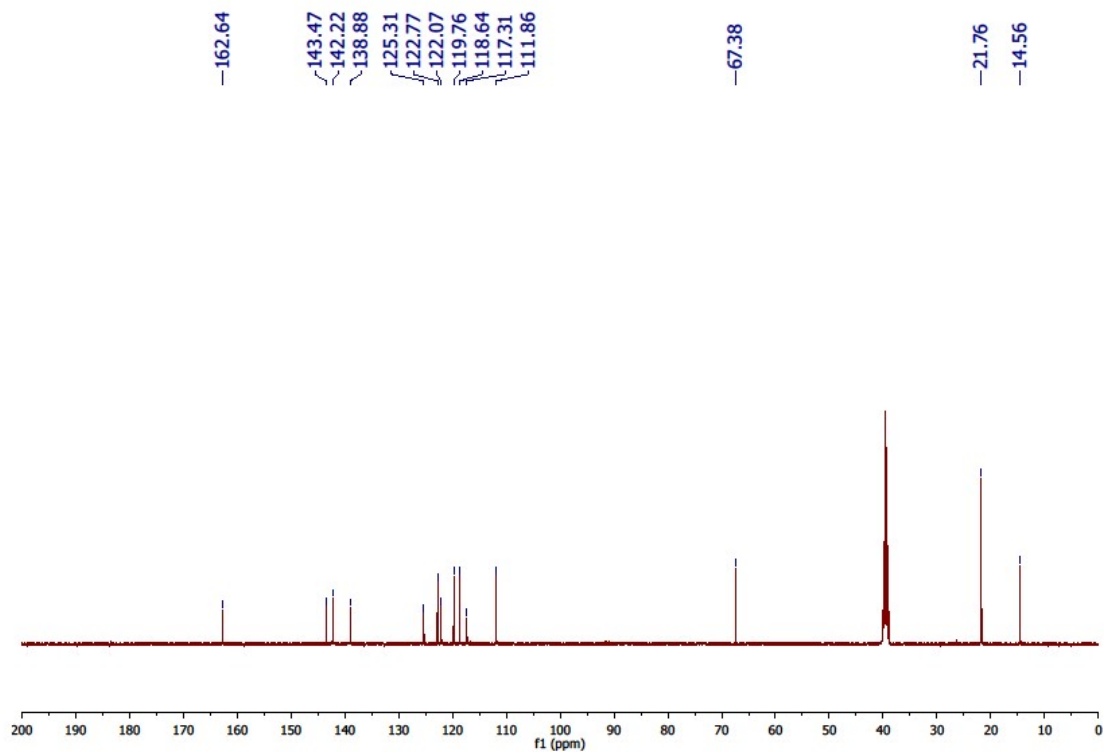
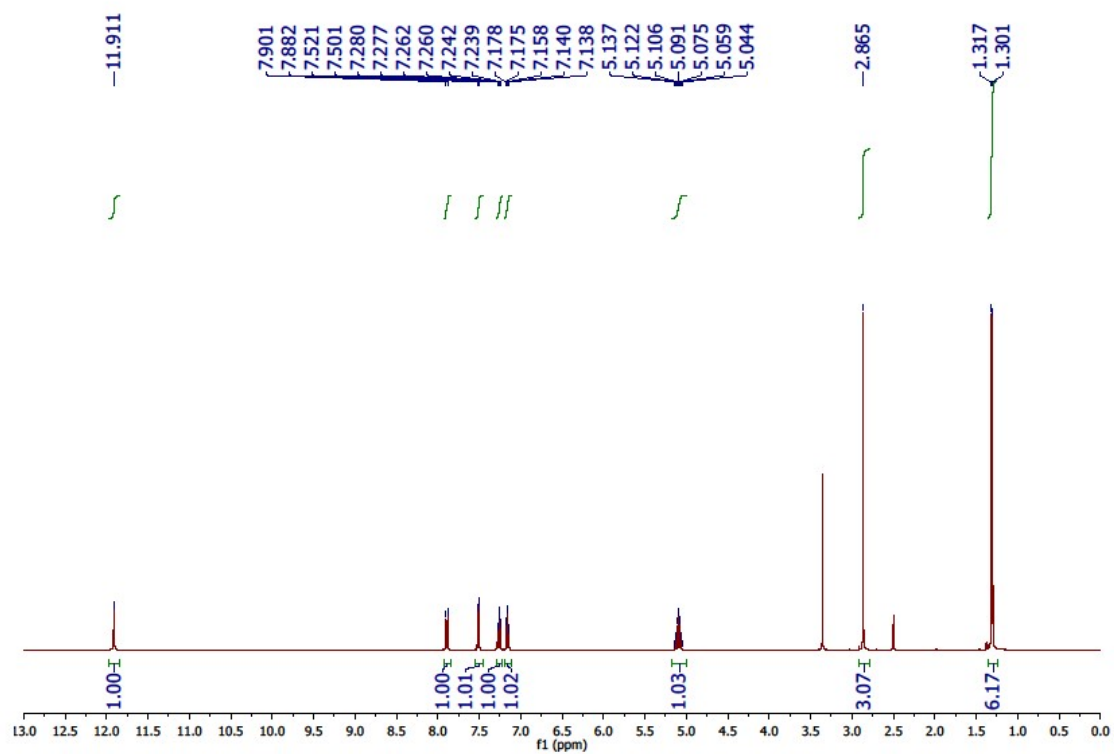


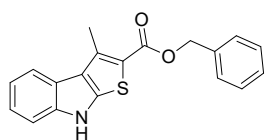




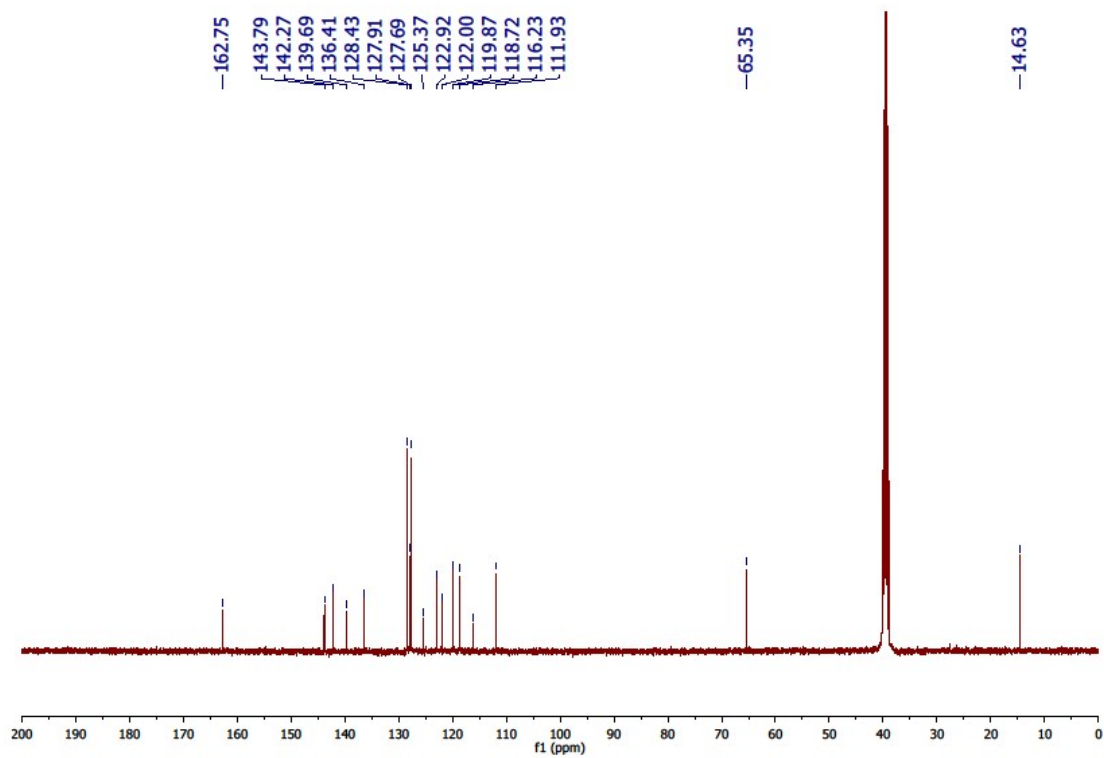
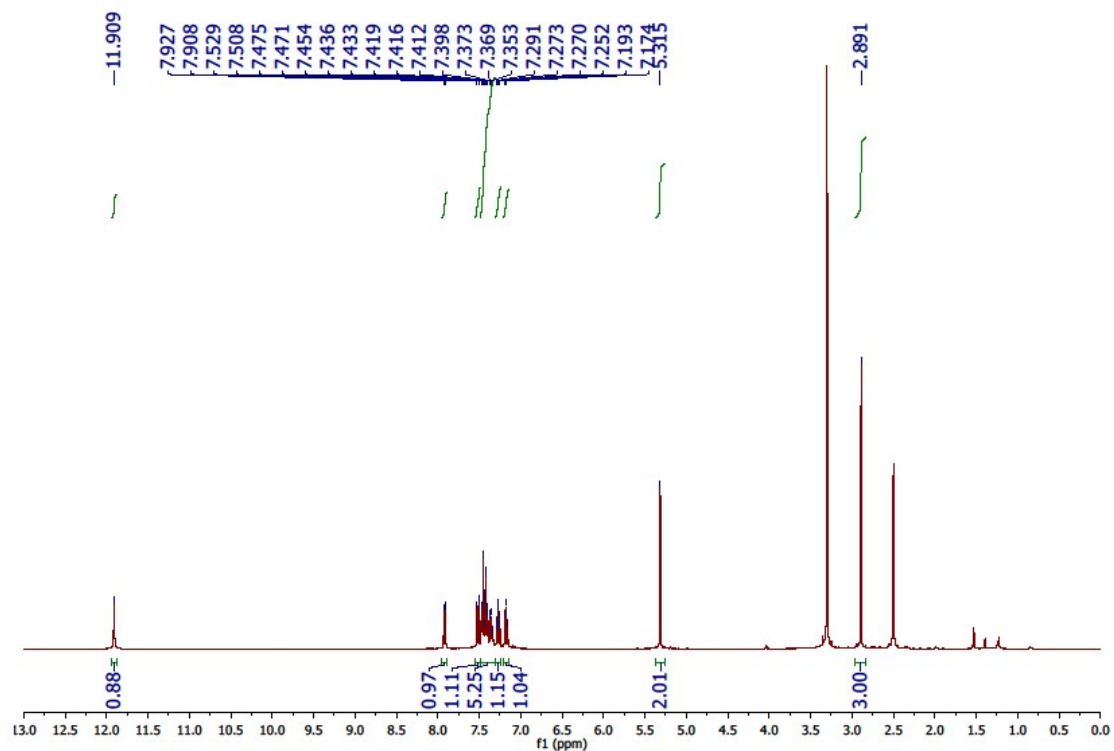


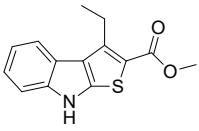
Isopropyl 3-methyl-8*H*-thieno[2,3-*b*]indole-2-carboxylate 4c.



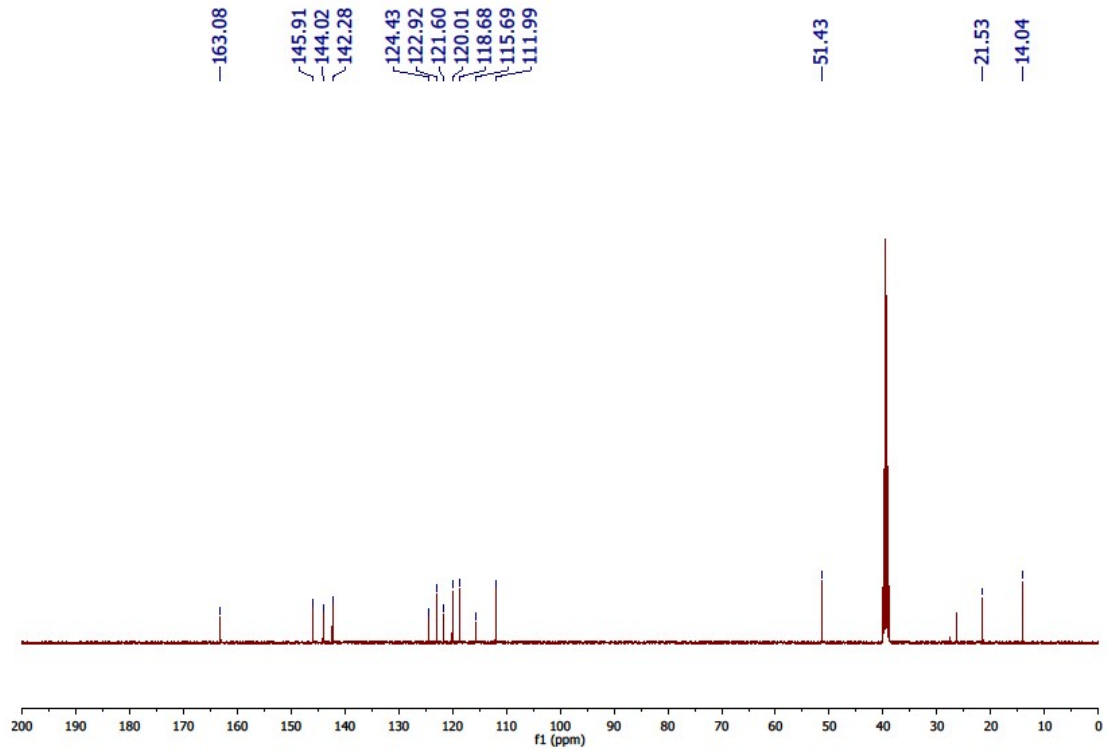
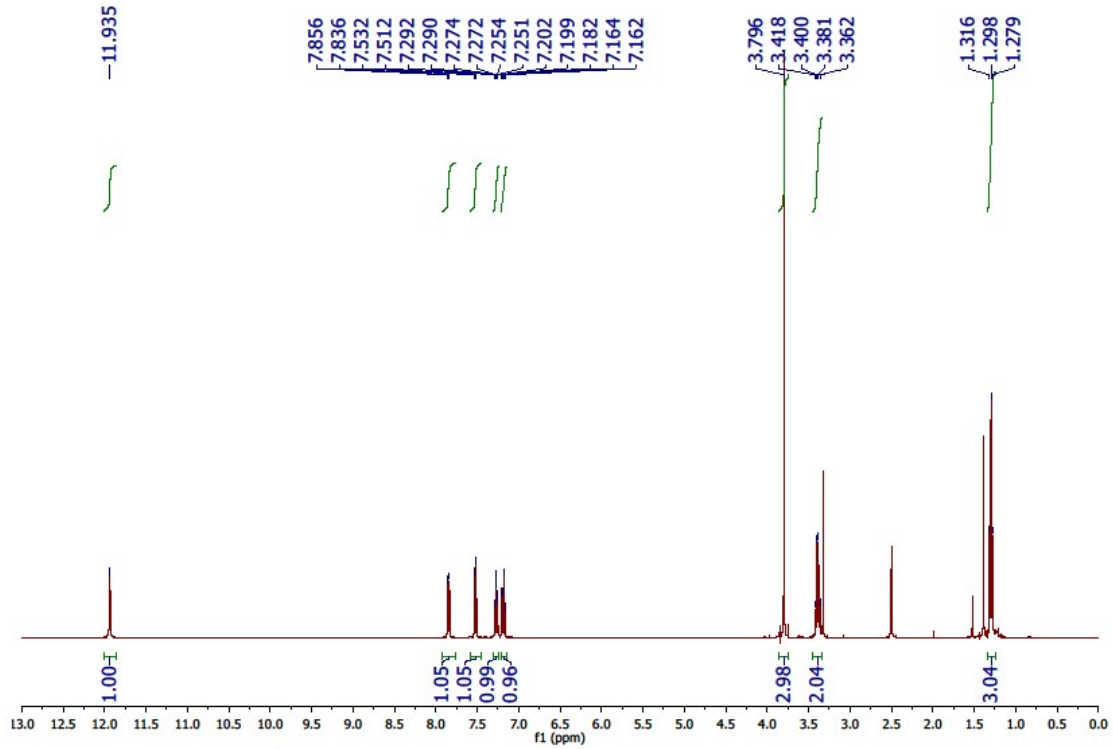


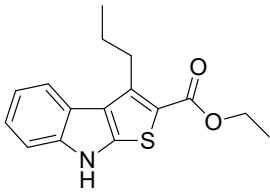
Benzyl 3-methyl-8*H*-thieno[2,3-*b*]indole-2-carboxylate 4d.



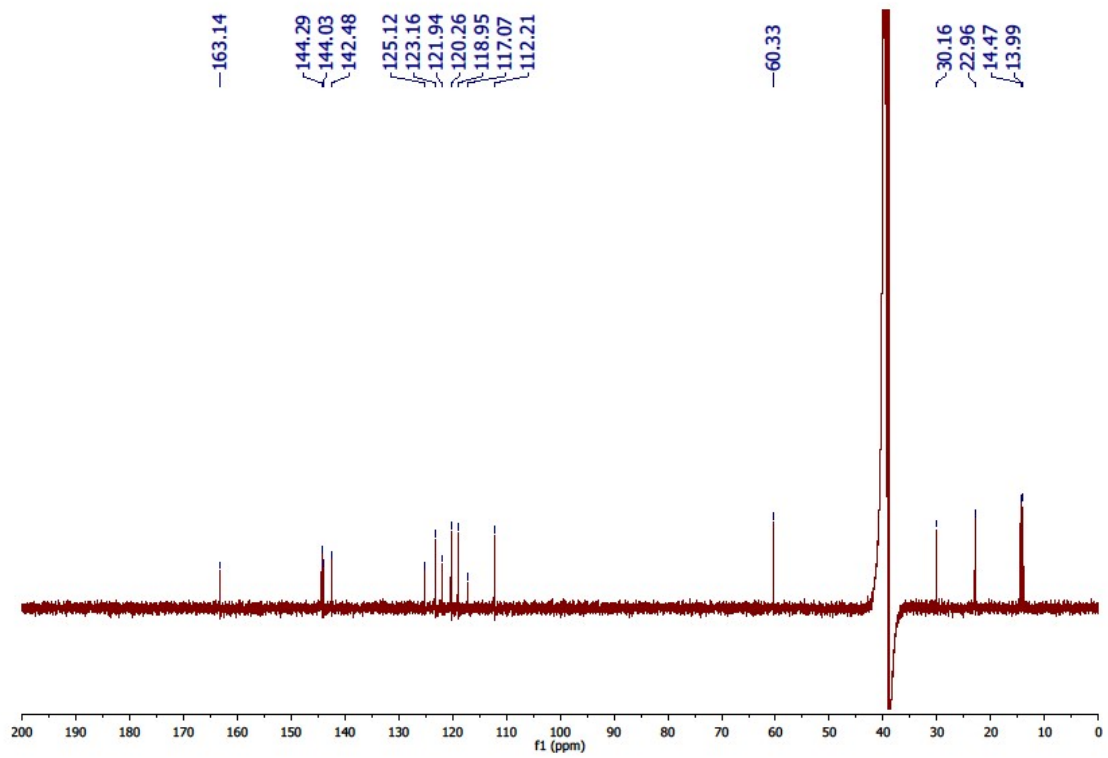
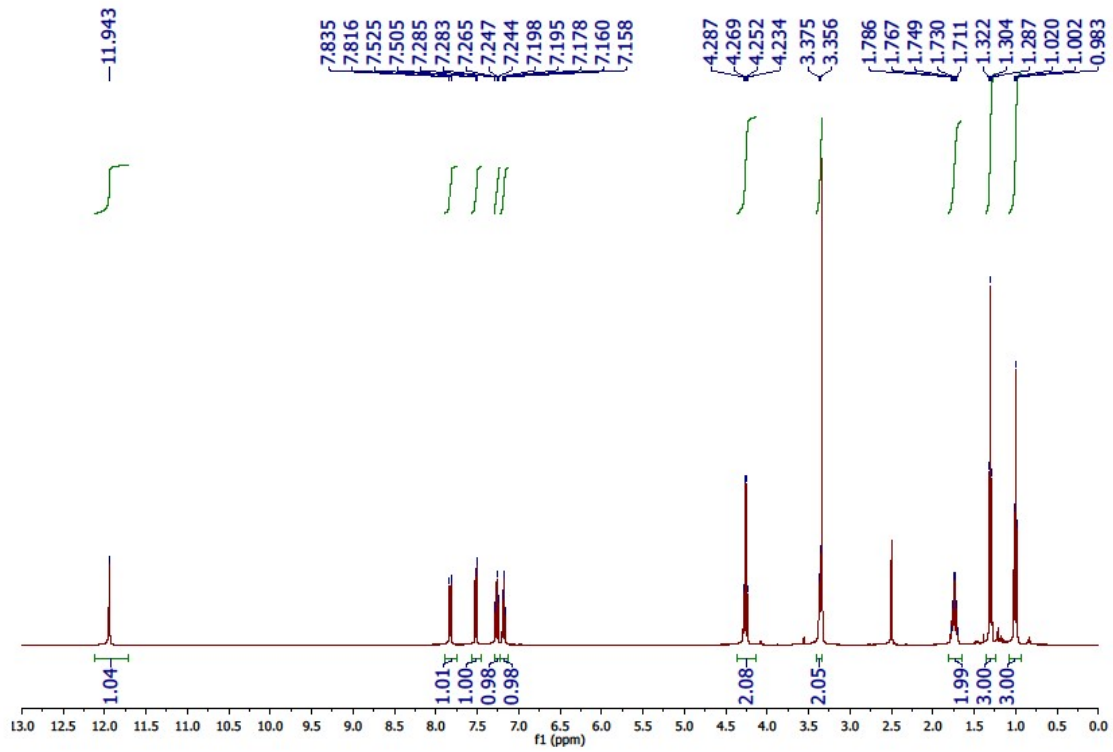


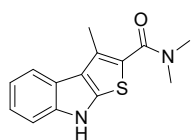
Methyl 3-ethyl-8*H*-thieno[2,3-*b*]indole-2-carboxylate 4e.



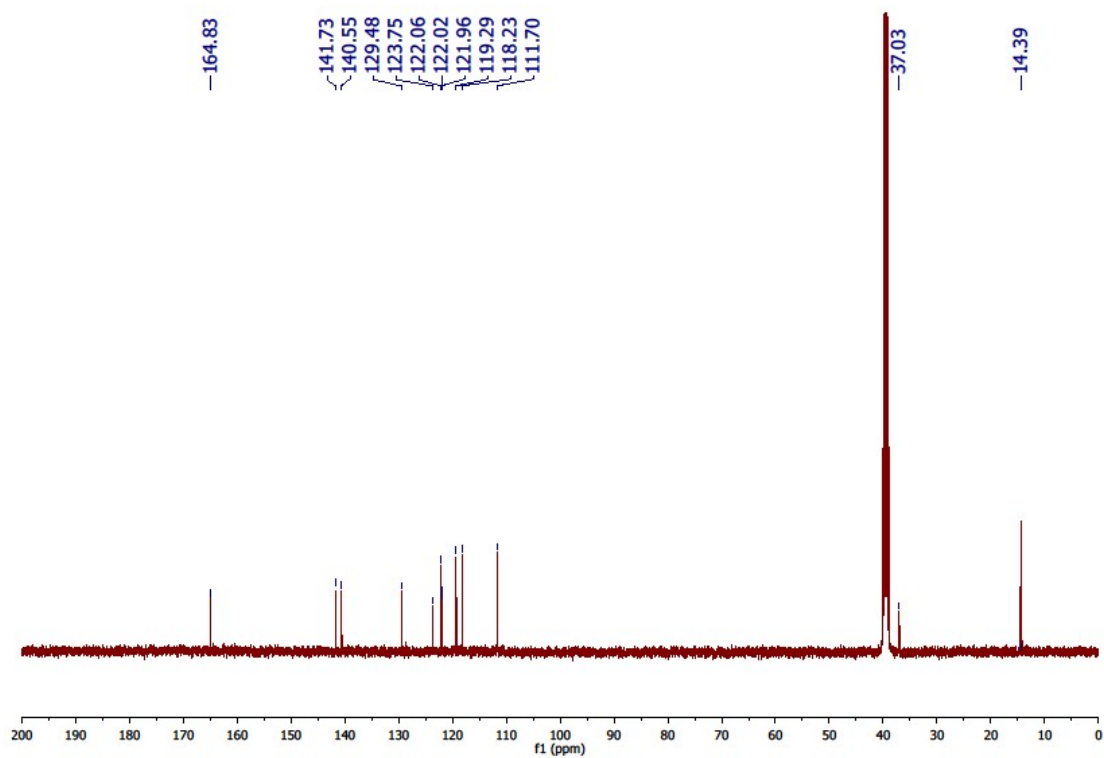
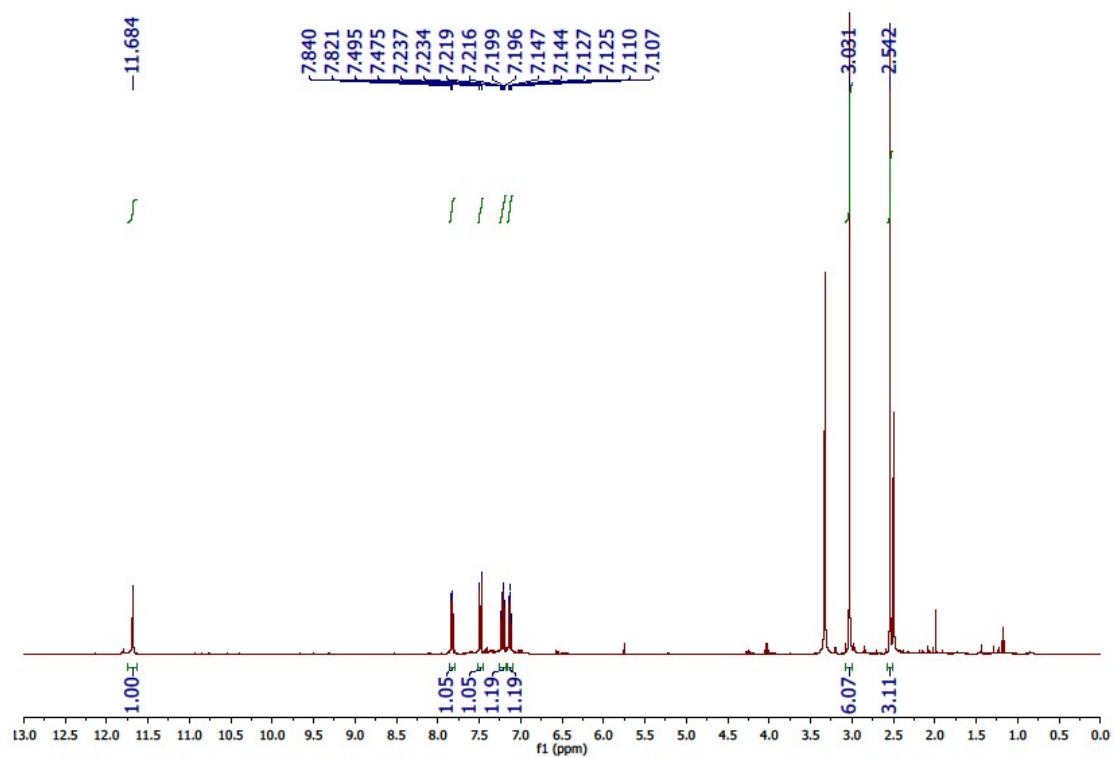


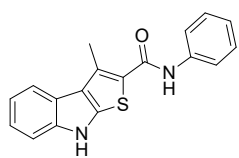
Ethyl 3-propyl-8*H*-thieno[2,3-*b*]indole-2-carboxylate 4f.



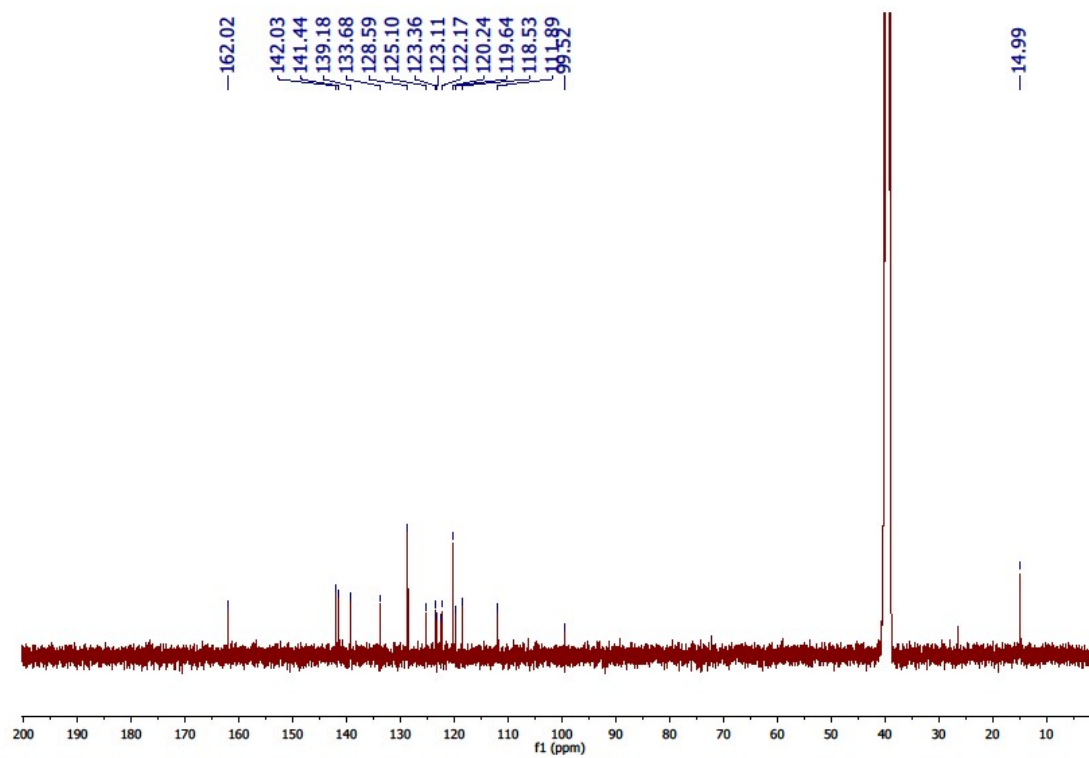
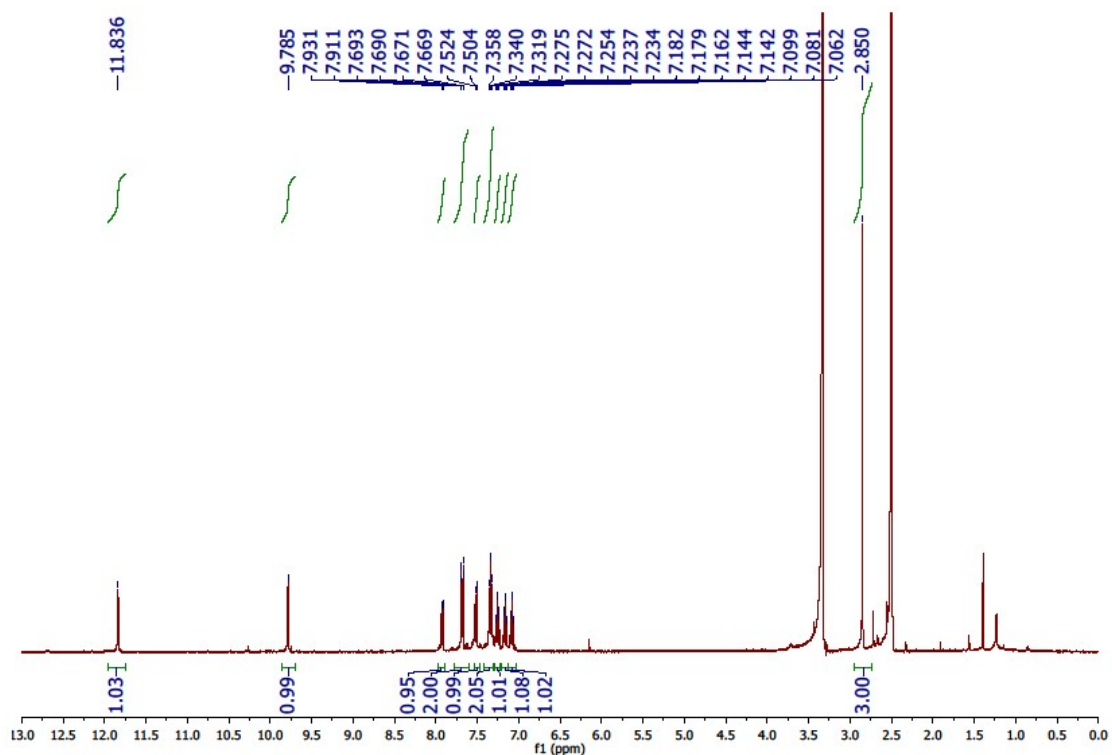


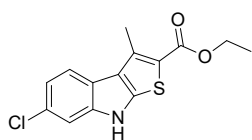
*N,N,3*-Trimethyl-8*H*-thieno[2,3-*b*]indole-2-carboxamide 4g.



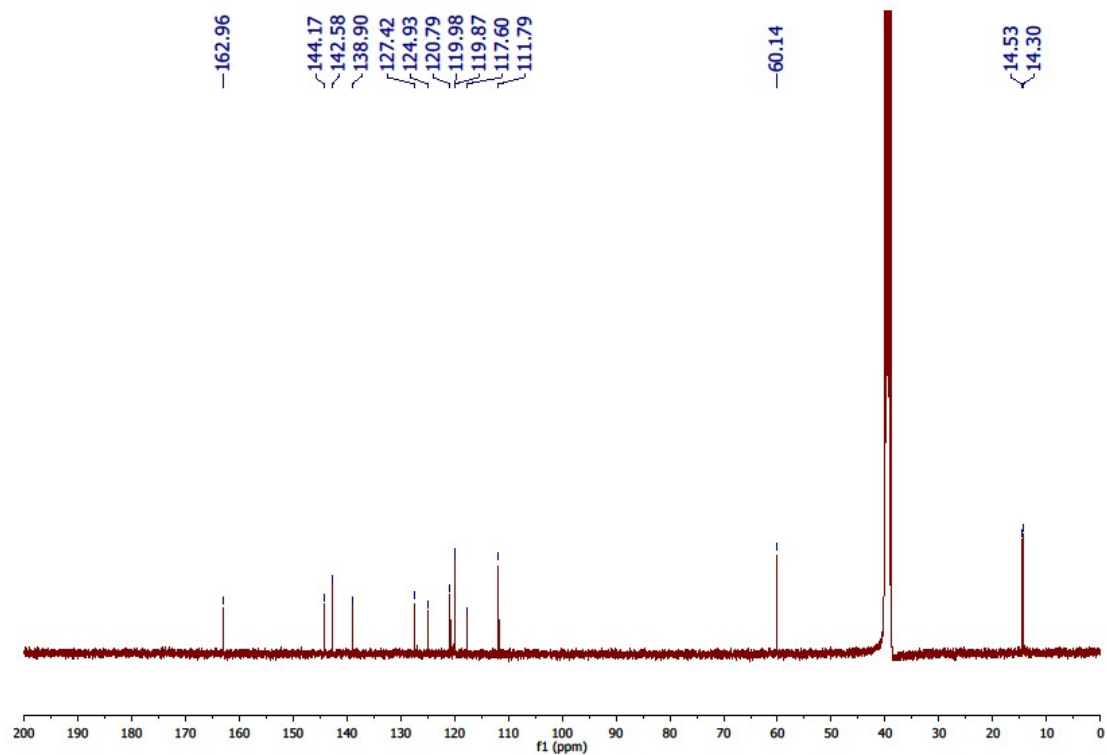
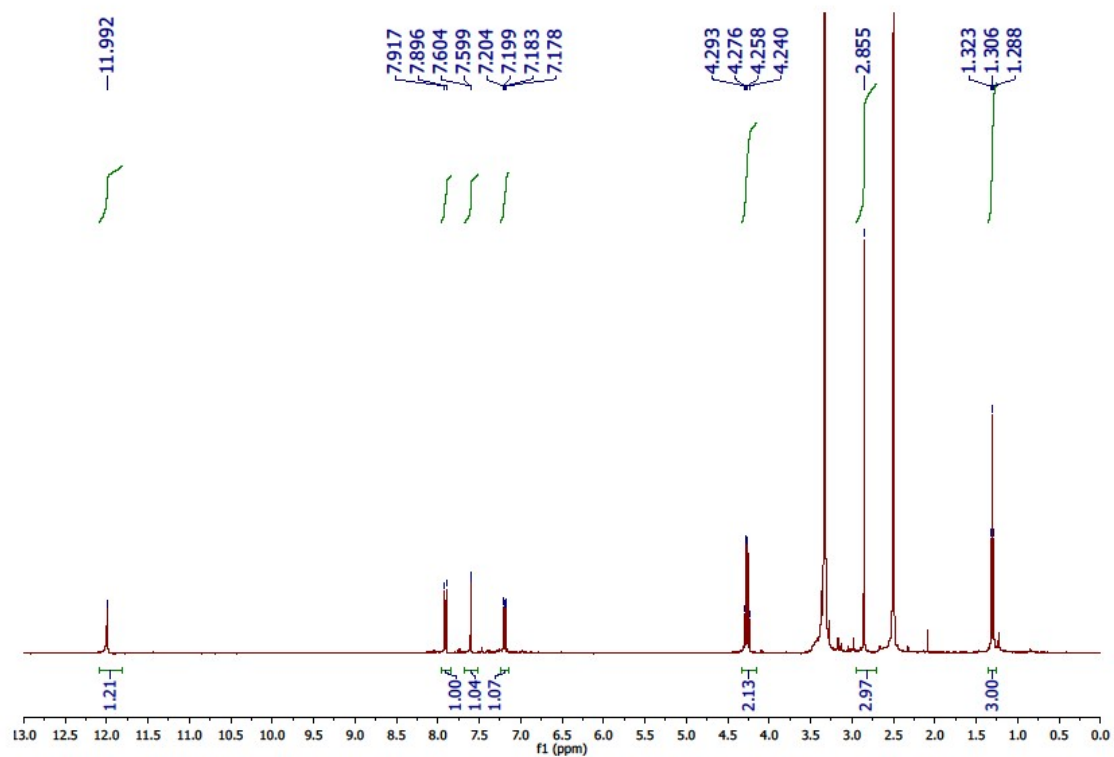


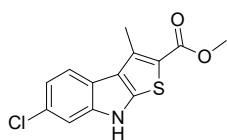
3-Methyl-N-phenyl-8H-thieno[2,3-b]indole-2-carboxamide 4h.



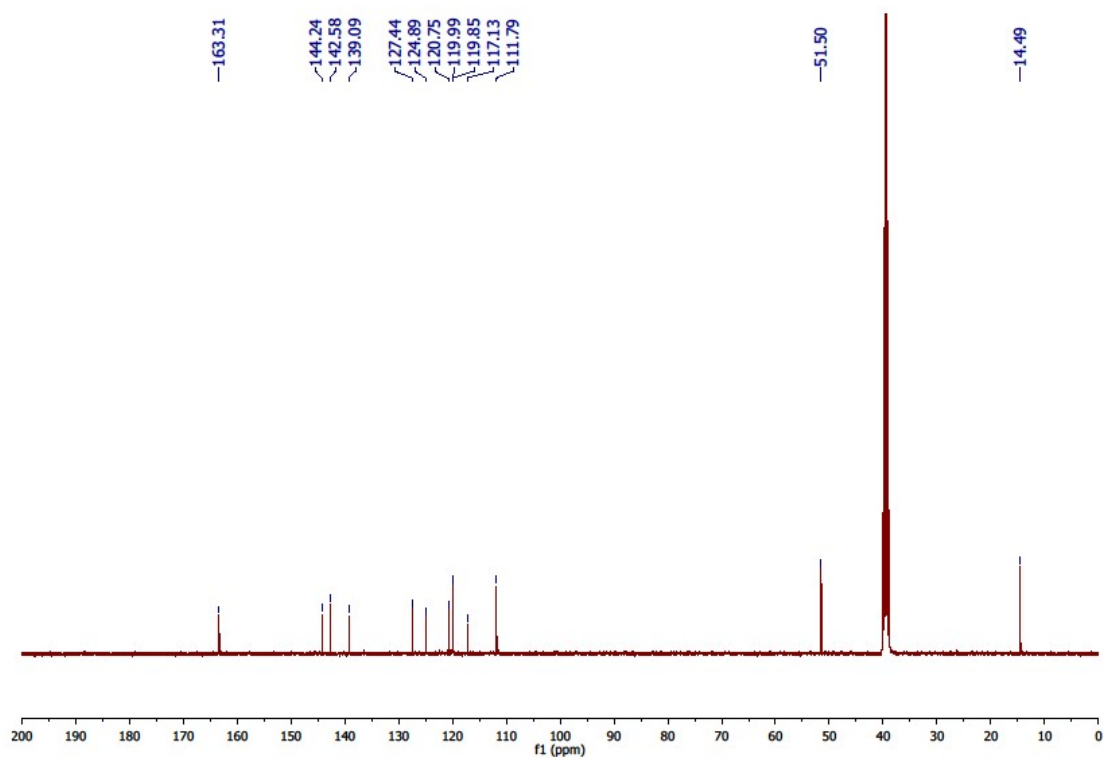
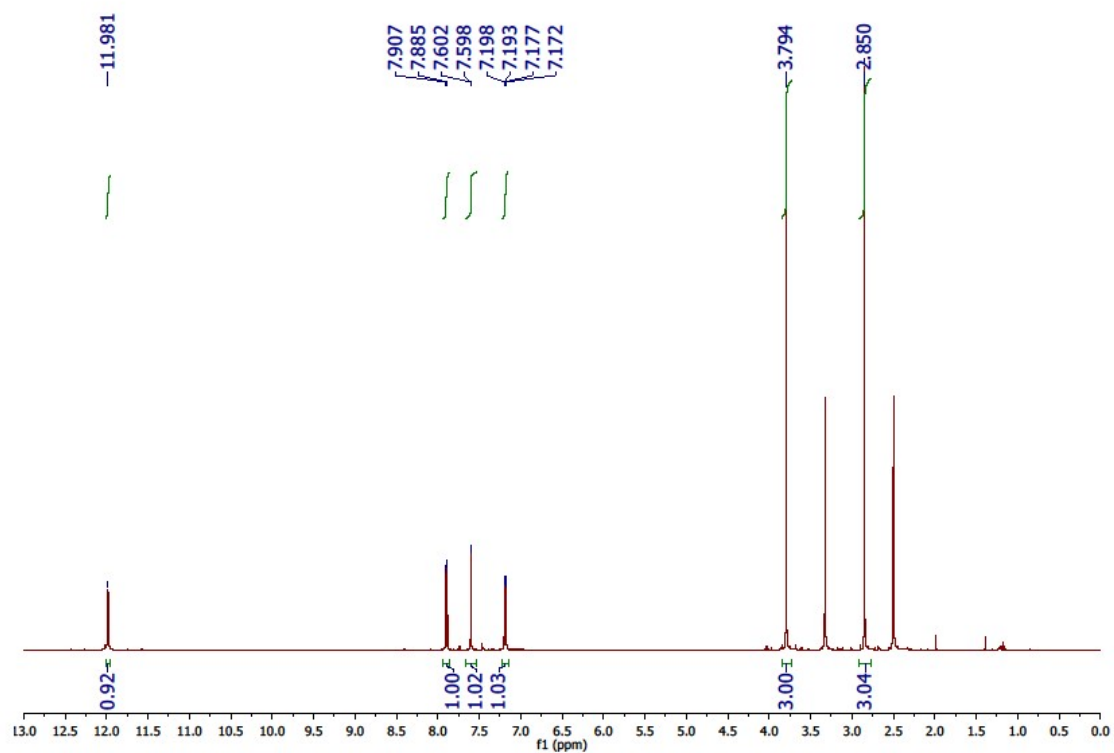


Ethyl 6-chloro-3-methyl-8*H*-thieno[2,3-*b*]indole-2-carboxylate 4i.

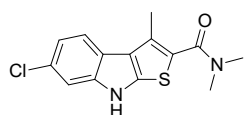




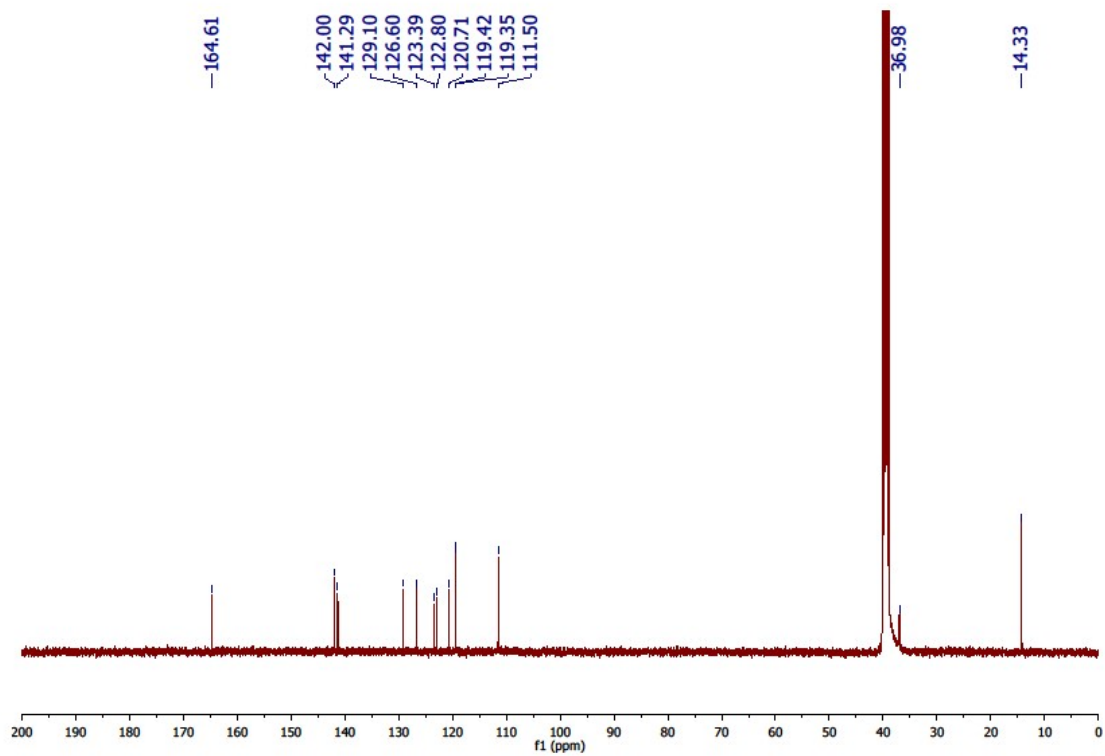
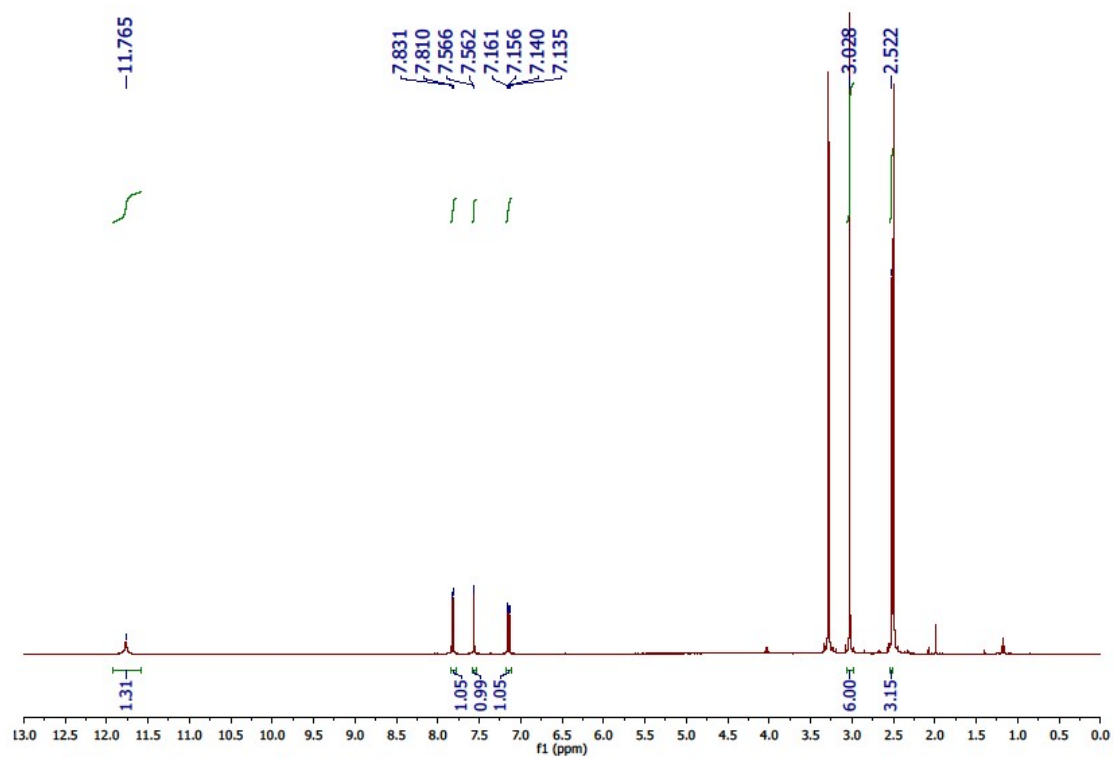
Methyl 6-chloro-3-methyl-8*H*-thieno[2,3-*b*]indole-2-carboxylate 4j.

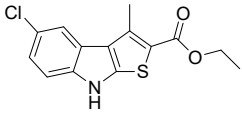




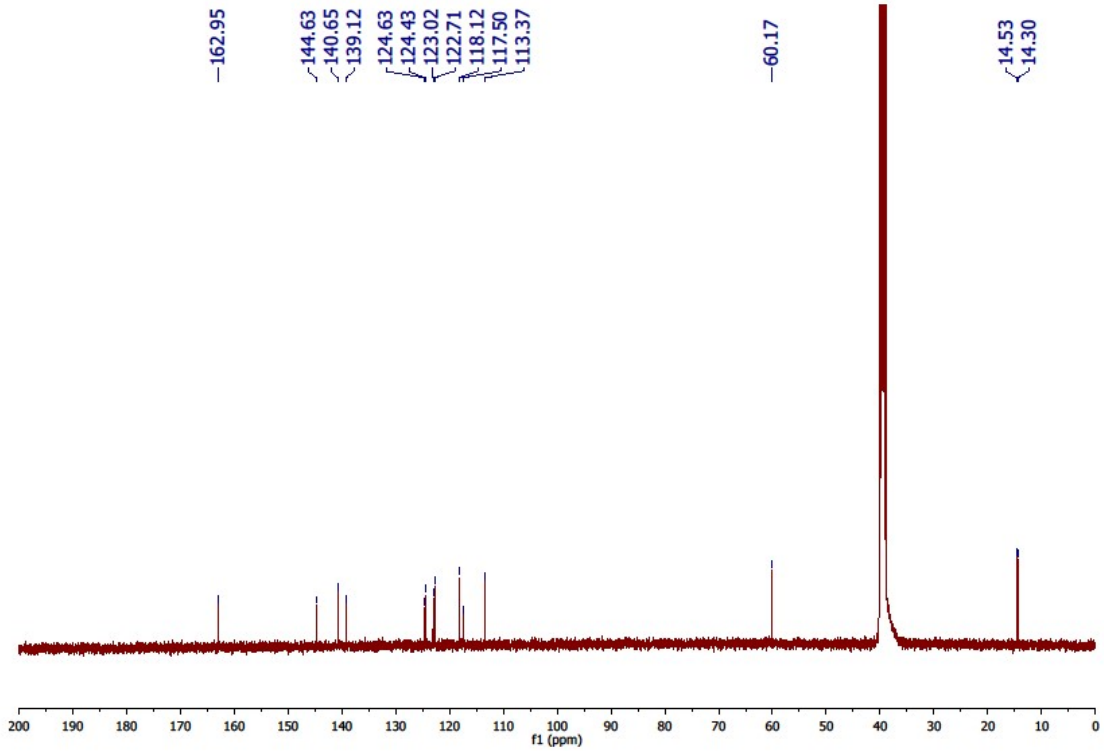
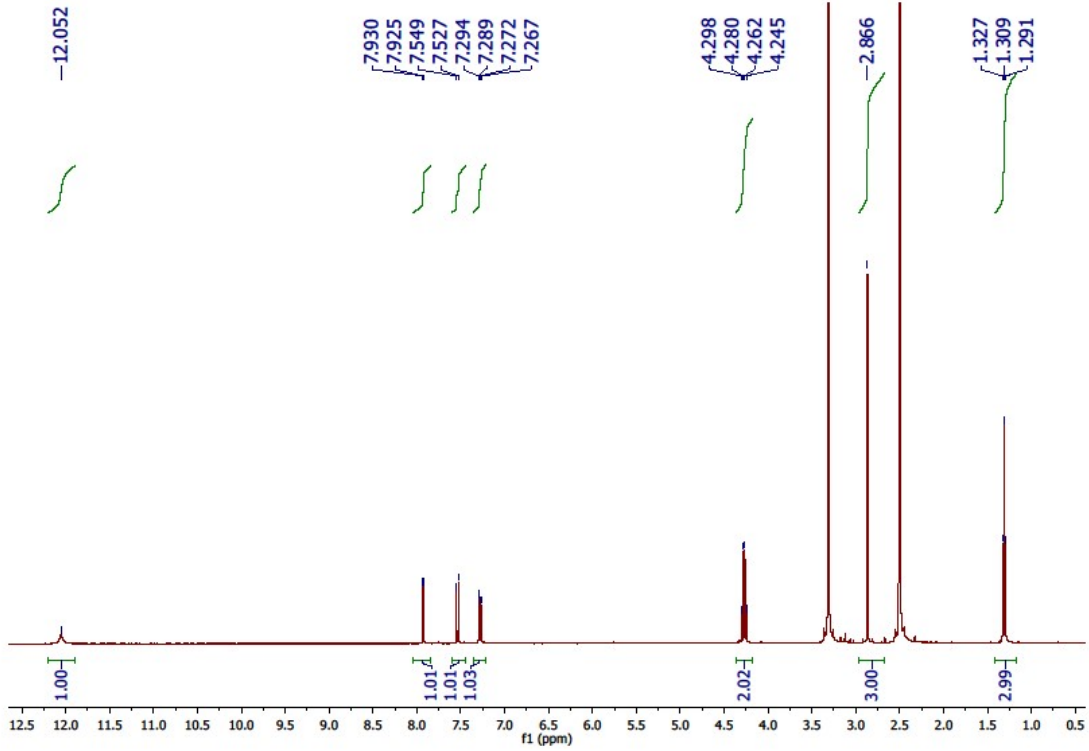


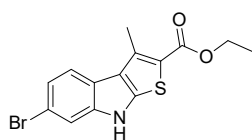
6-chloro-*N,N*,3-trimethyl-8*H*-thieno[2,3-*b*]indole-2-carboxamide 4k.



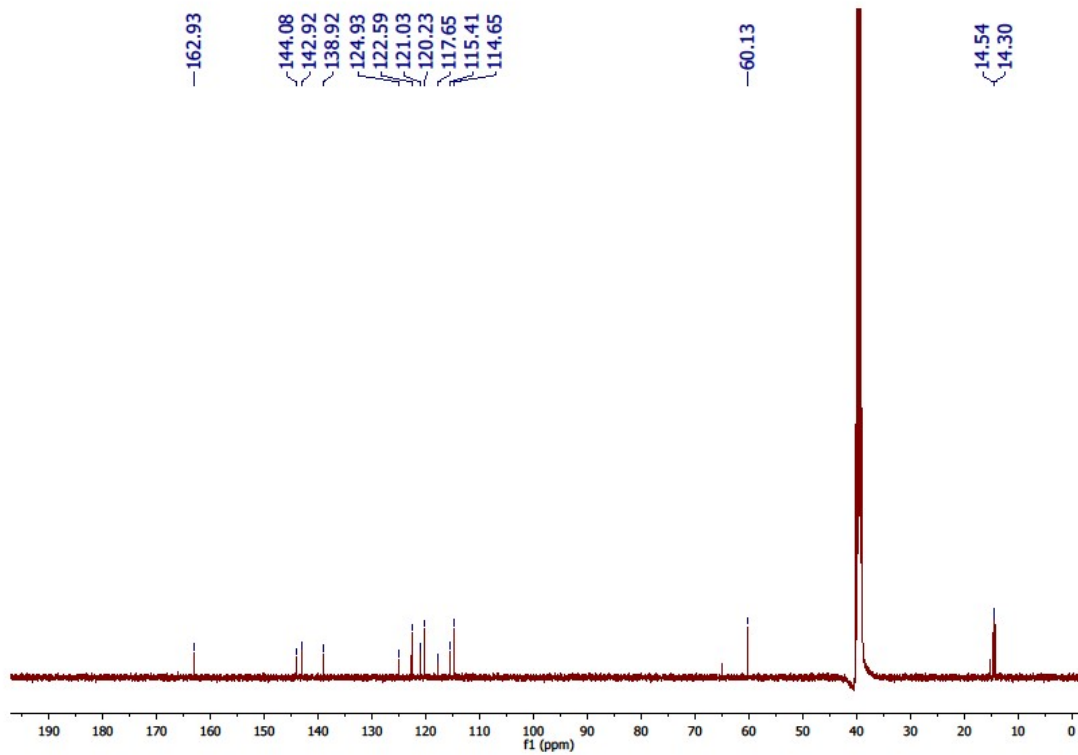
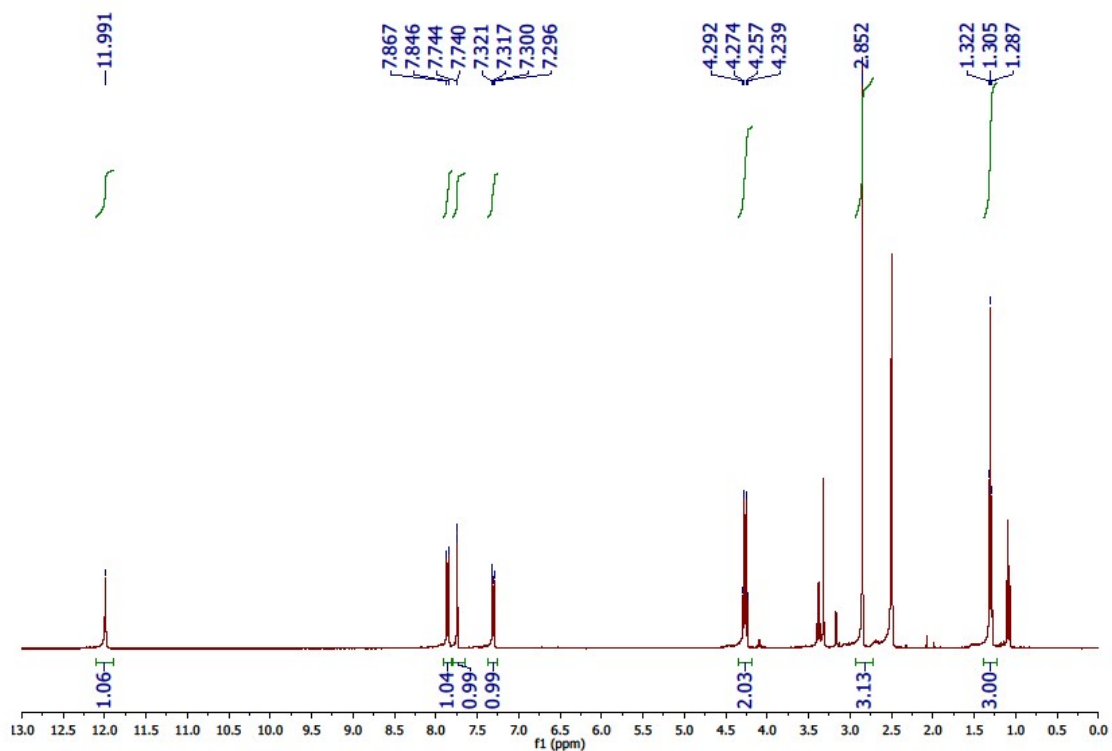


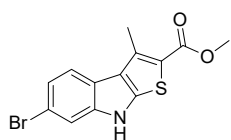
**Ethyl 5-chloro-3-methyl-8*H*-thieno[2,3-*b*]indole-2-carboxylate 4l.**



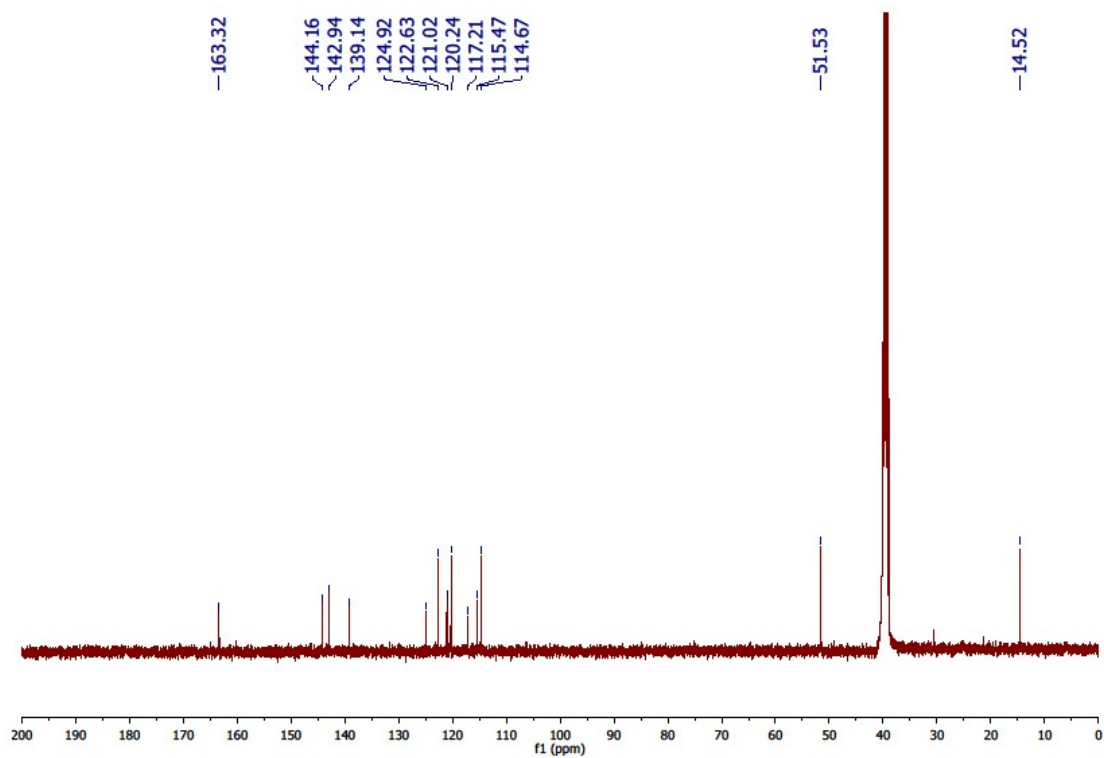
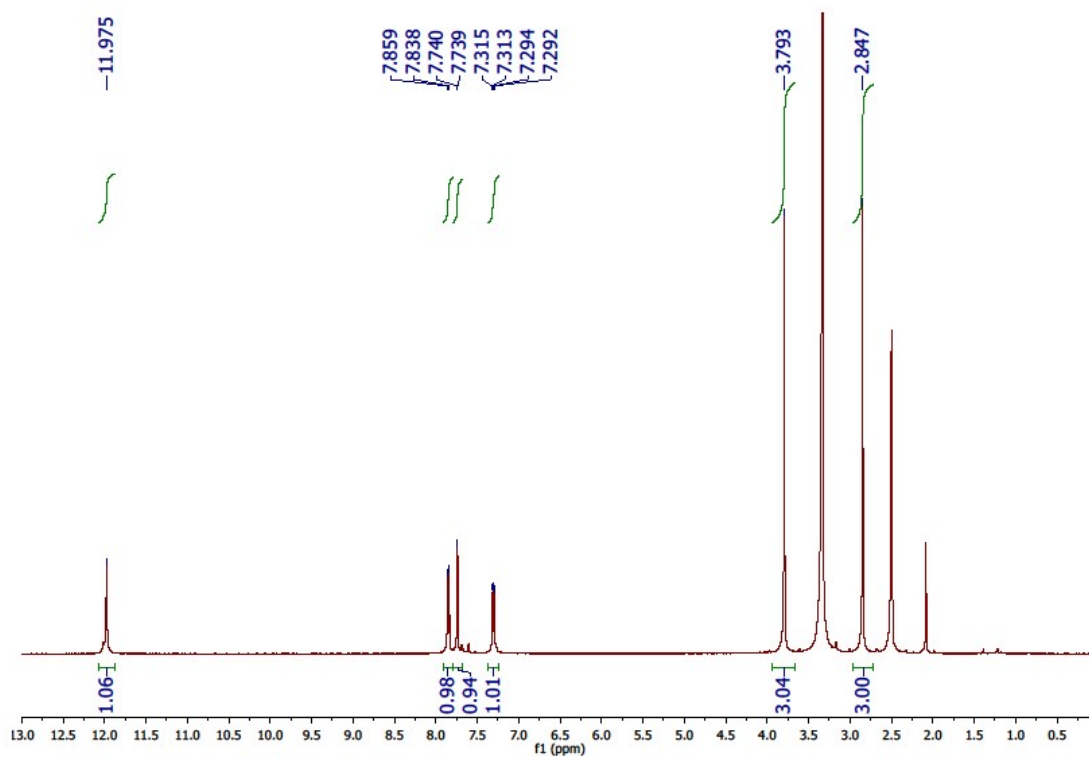


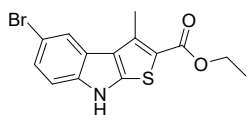
Ethyl 6-bromo-3-methyl-8H-thieno[2,3-b]indole-2-carboxylate 4m.



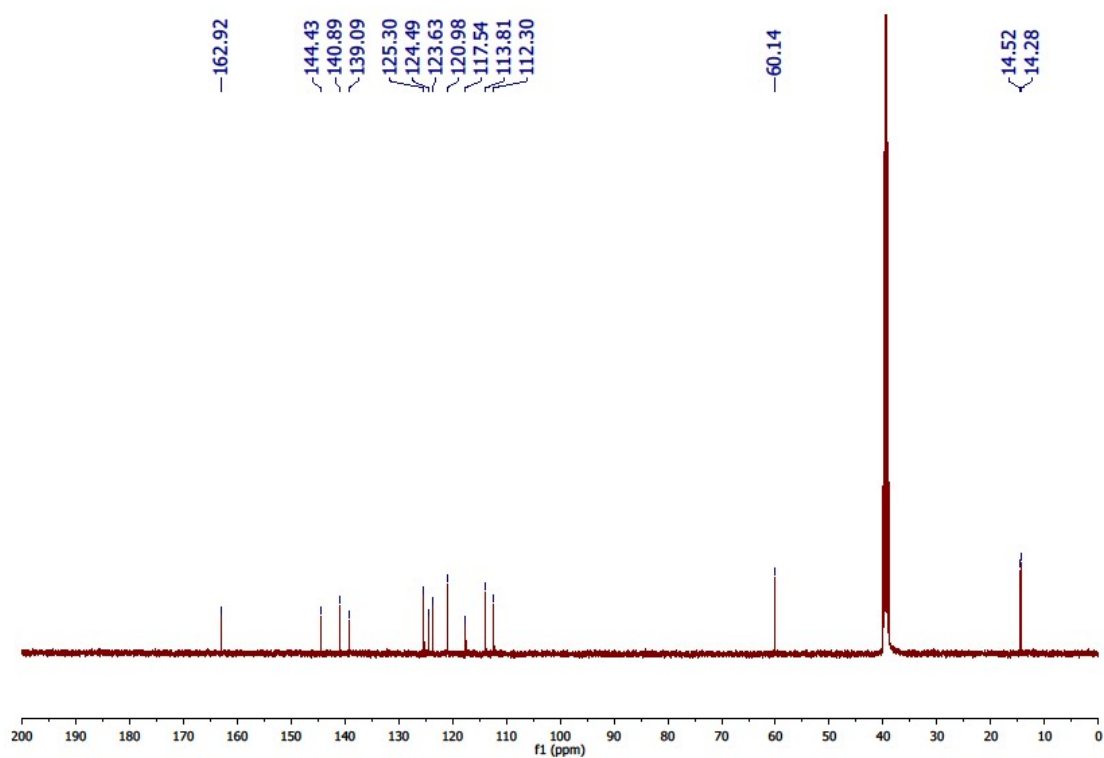
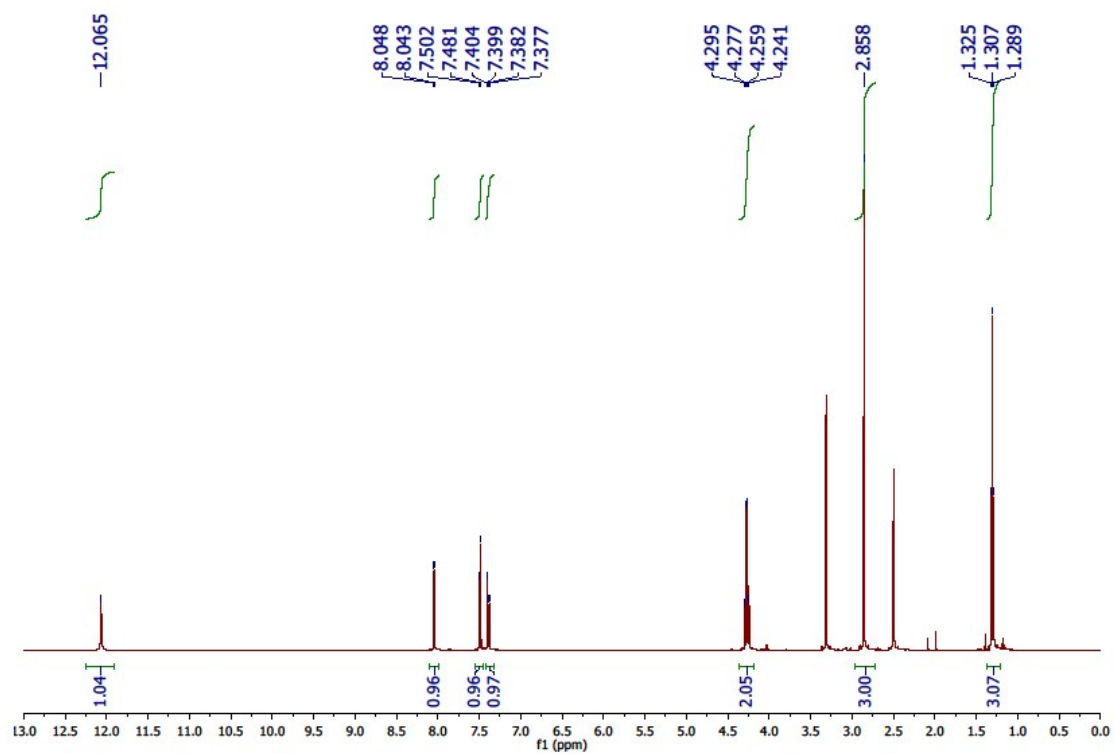


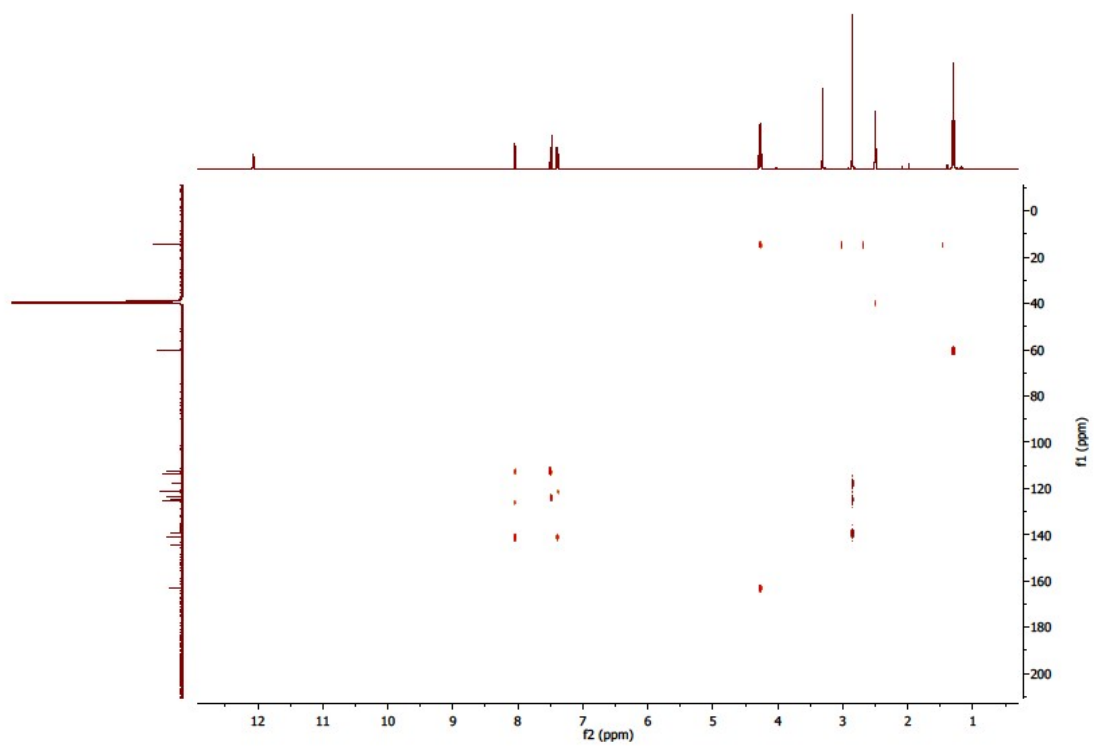
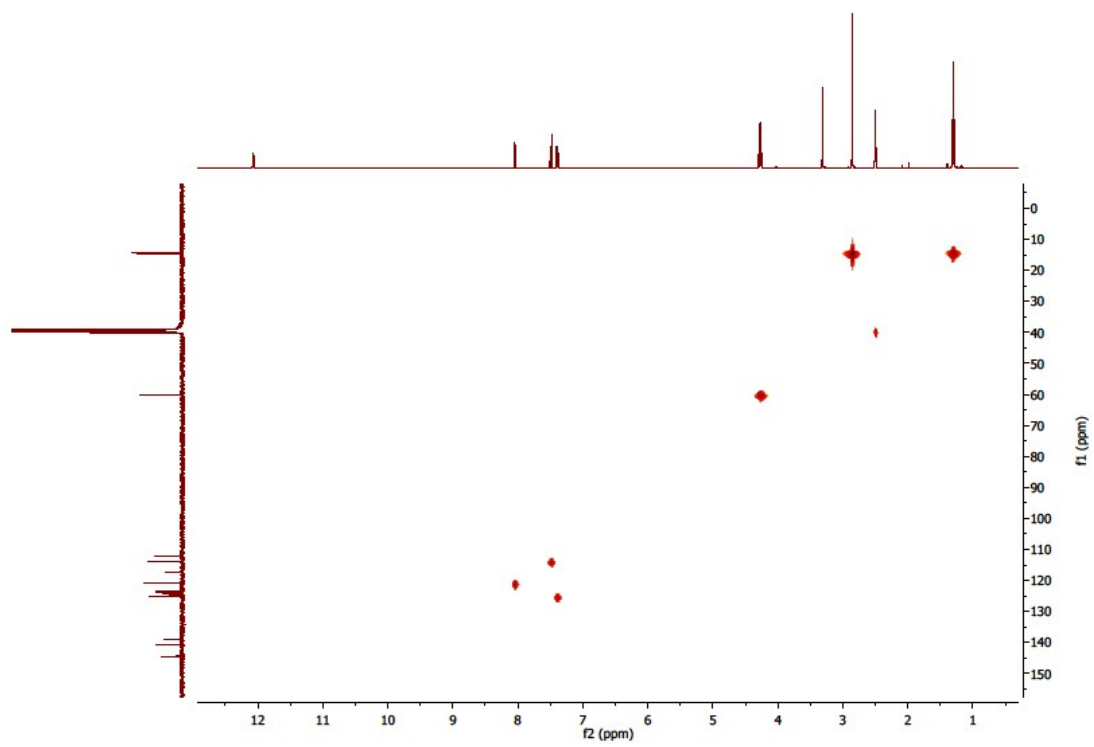
Methyl 6-bromo-3-methyl-8*H*-thieno[2,3-*b*]indole-2-carboxylate 4n.

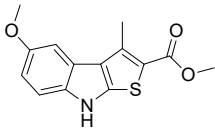




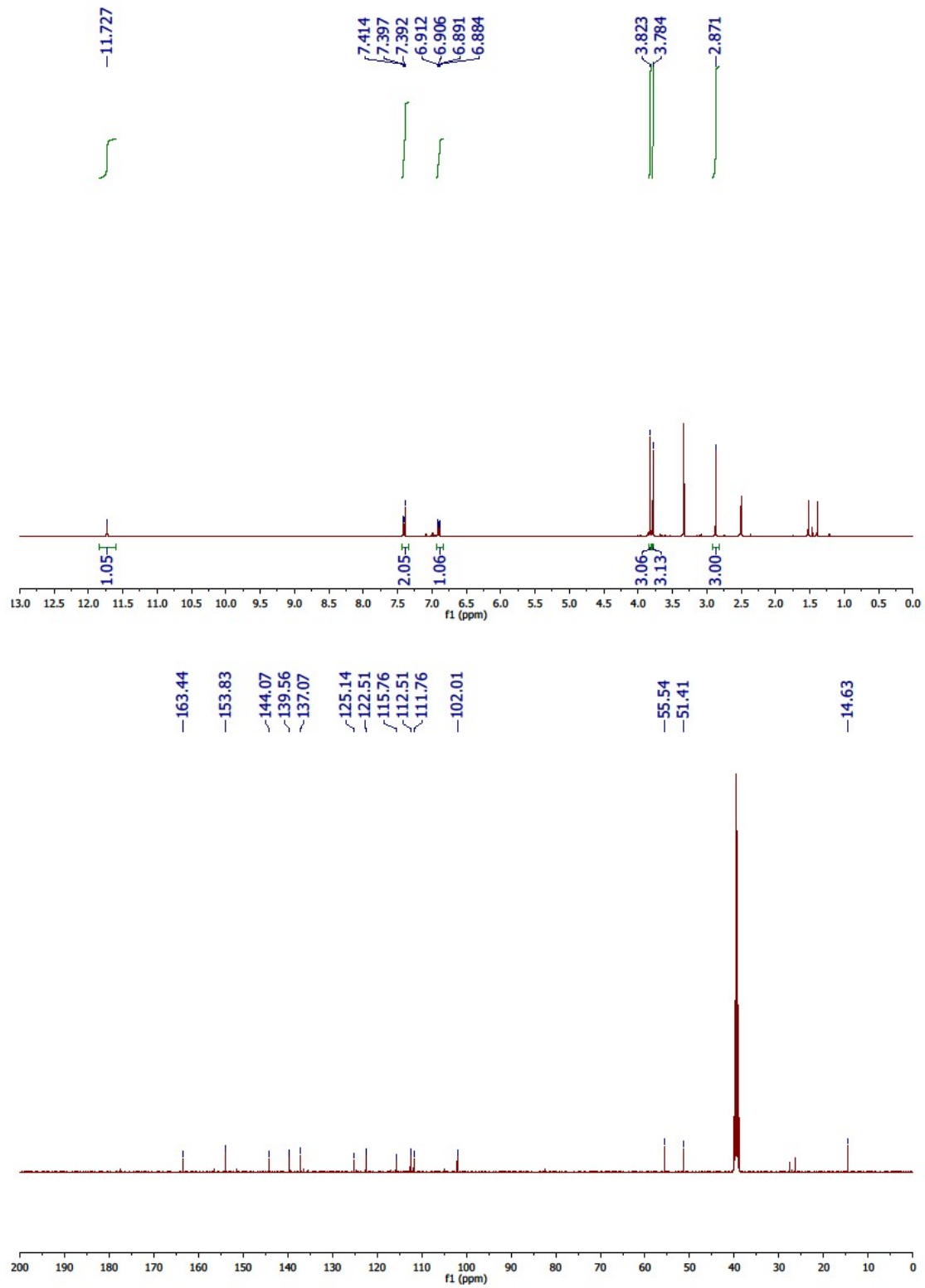
**Ethyl 5-bromo-3-methyl-8*H*-thieno[2,3-*b*]indole-2-carboxylate 4o.**

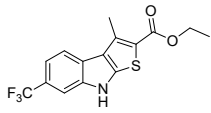




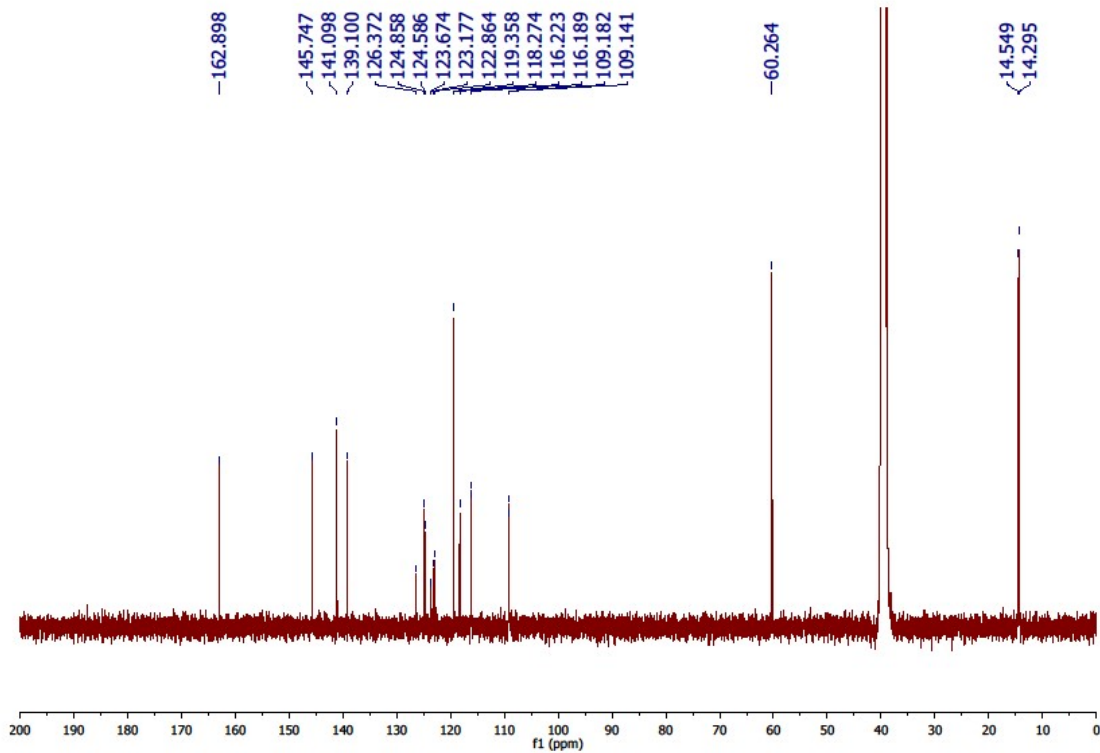
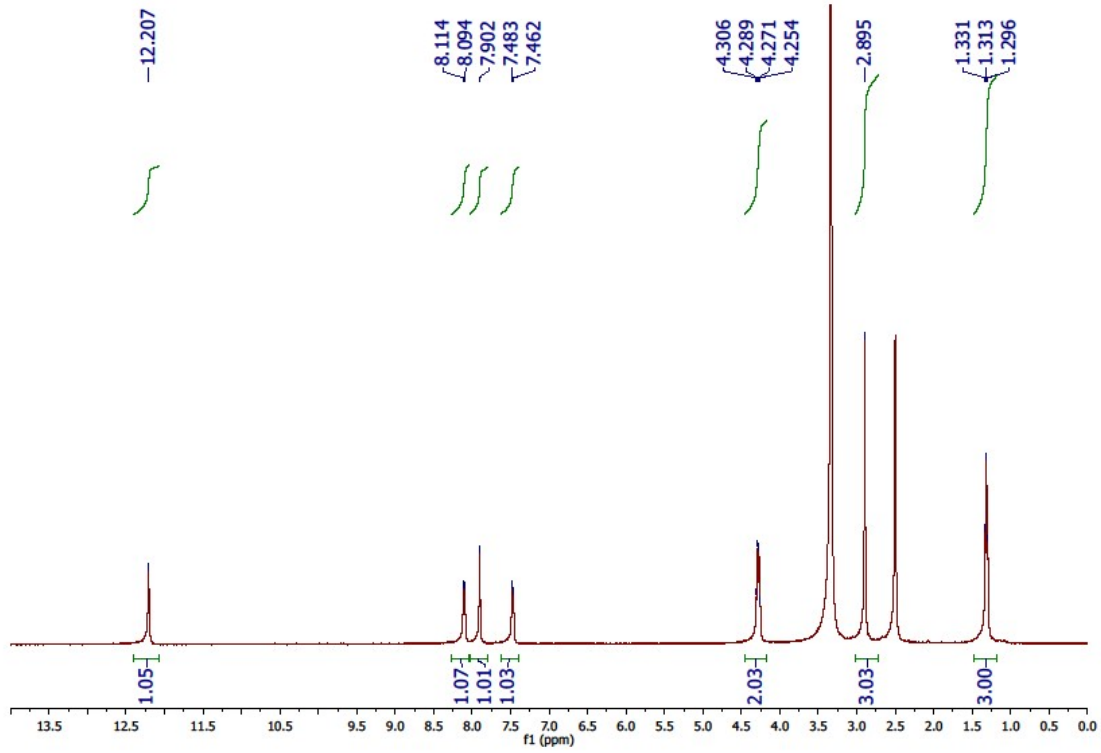


Methyl 5-methoxy-3-methyl-8*H*-thieno[2,3-*b*]indole-2-carboxylate 4p.

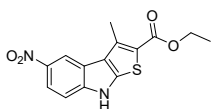




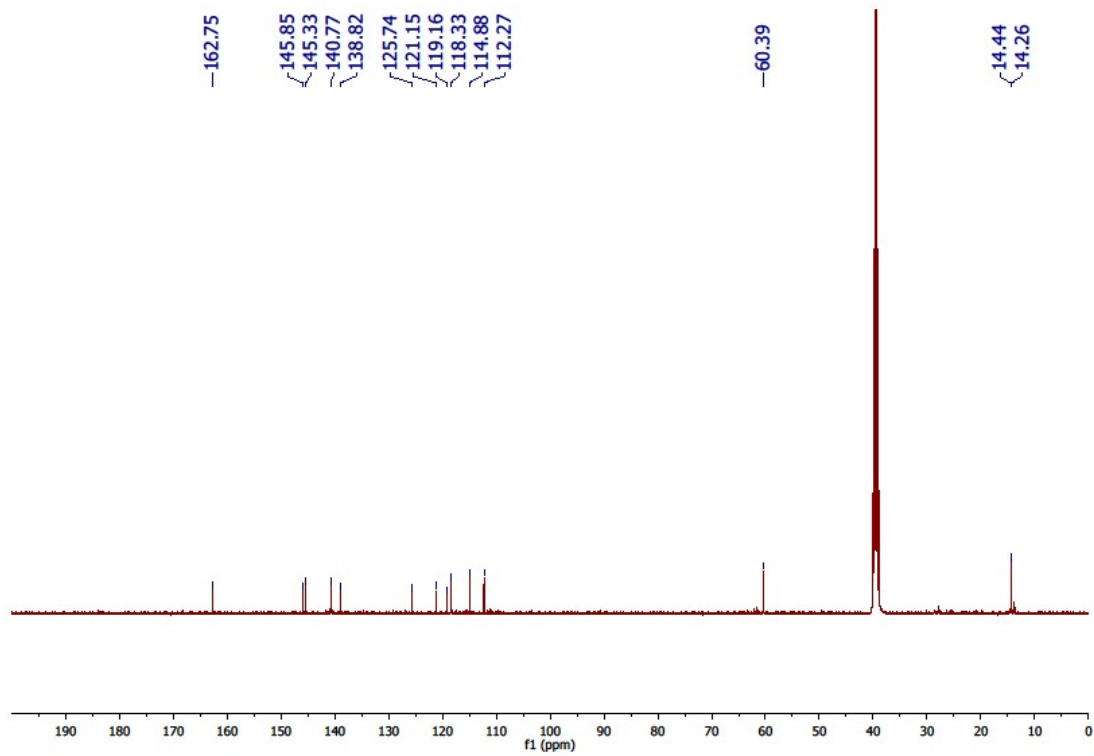
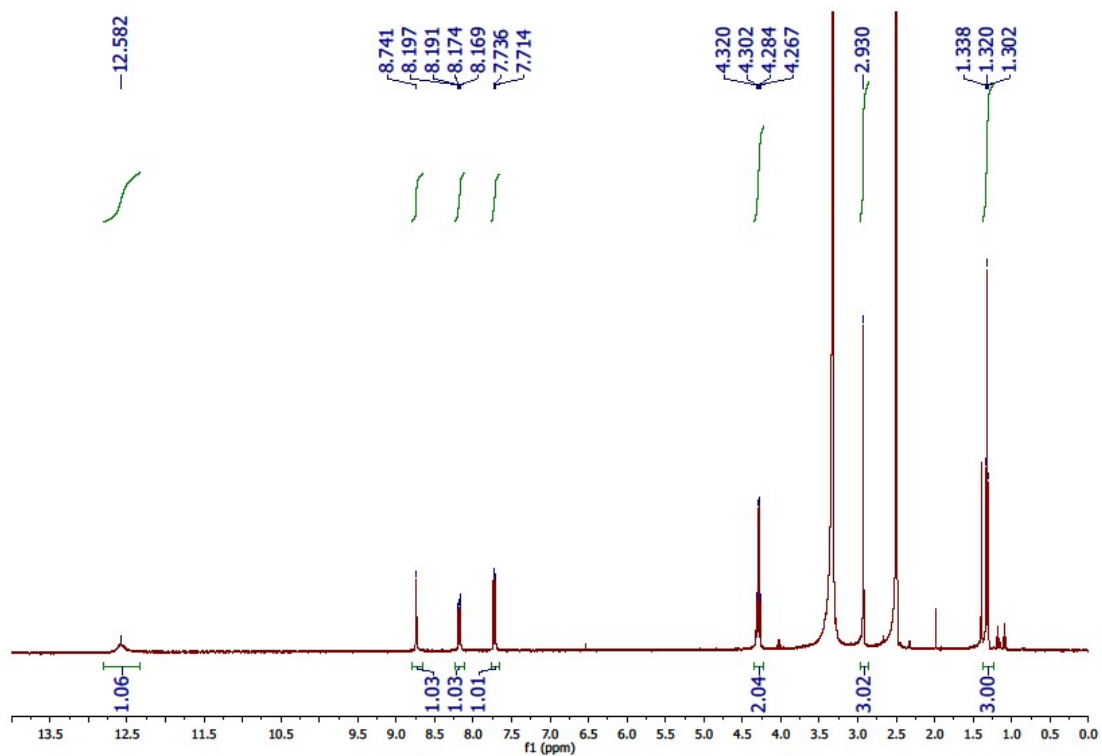
**Ethyl 3-methyl-6-(trifluoromethyl)-8H-thieno[2,3-b]indole-2-carboxylate 4q.**

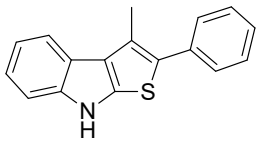




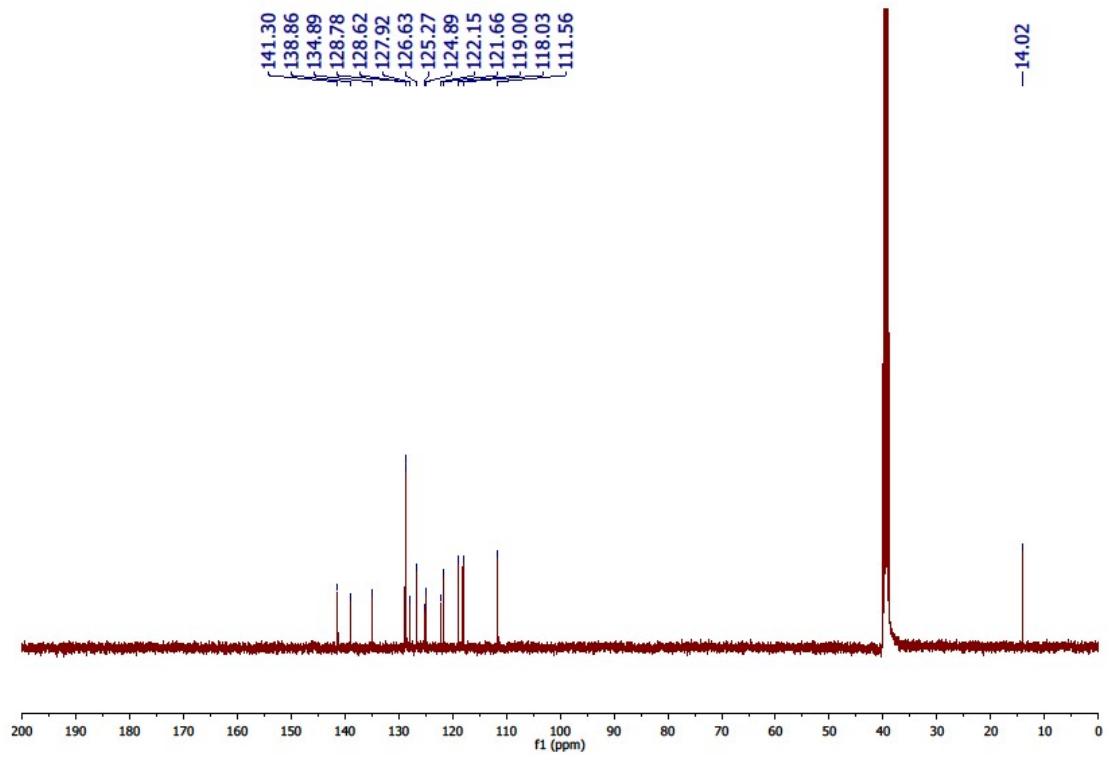
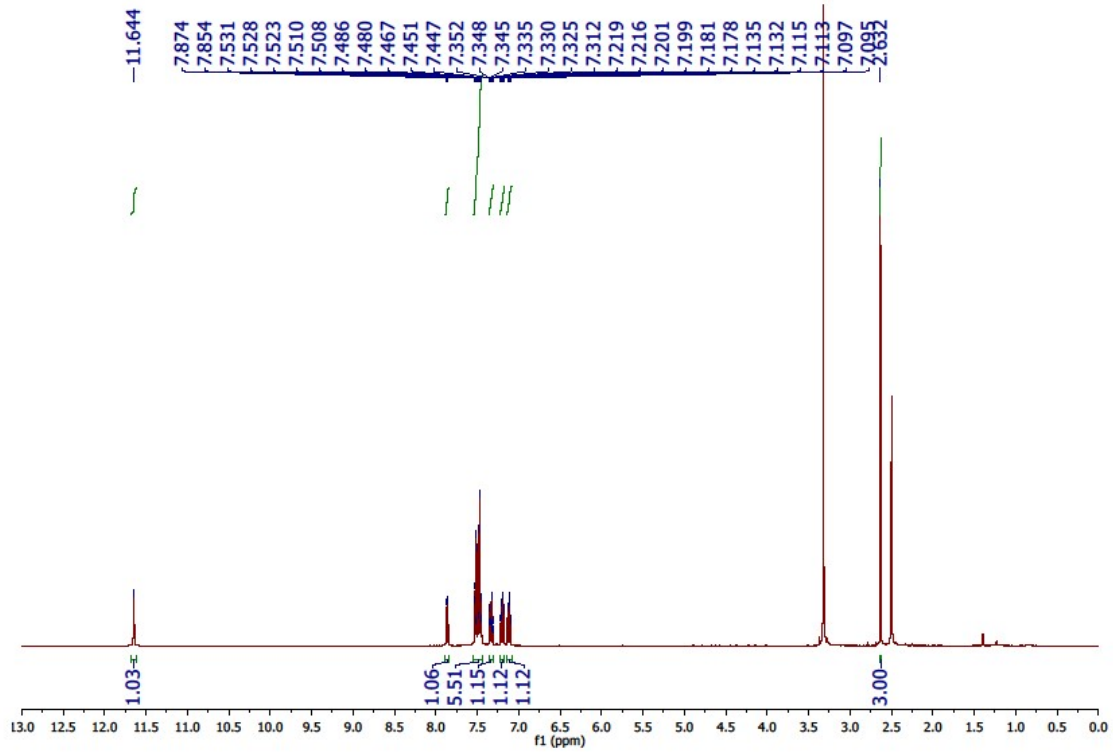


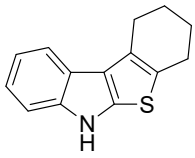
Ethyl 3-methyl-5-nitro-8*H*-thieno[2,3-*b*]indole-2-carboxylate 4r.



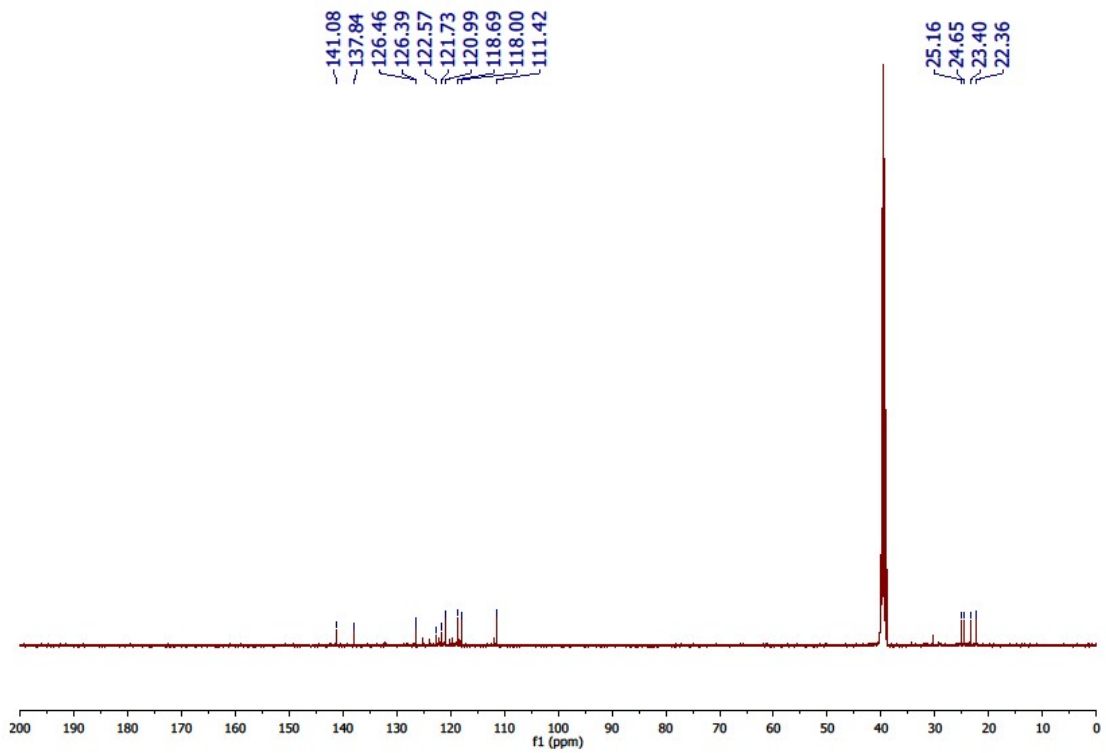
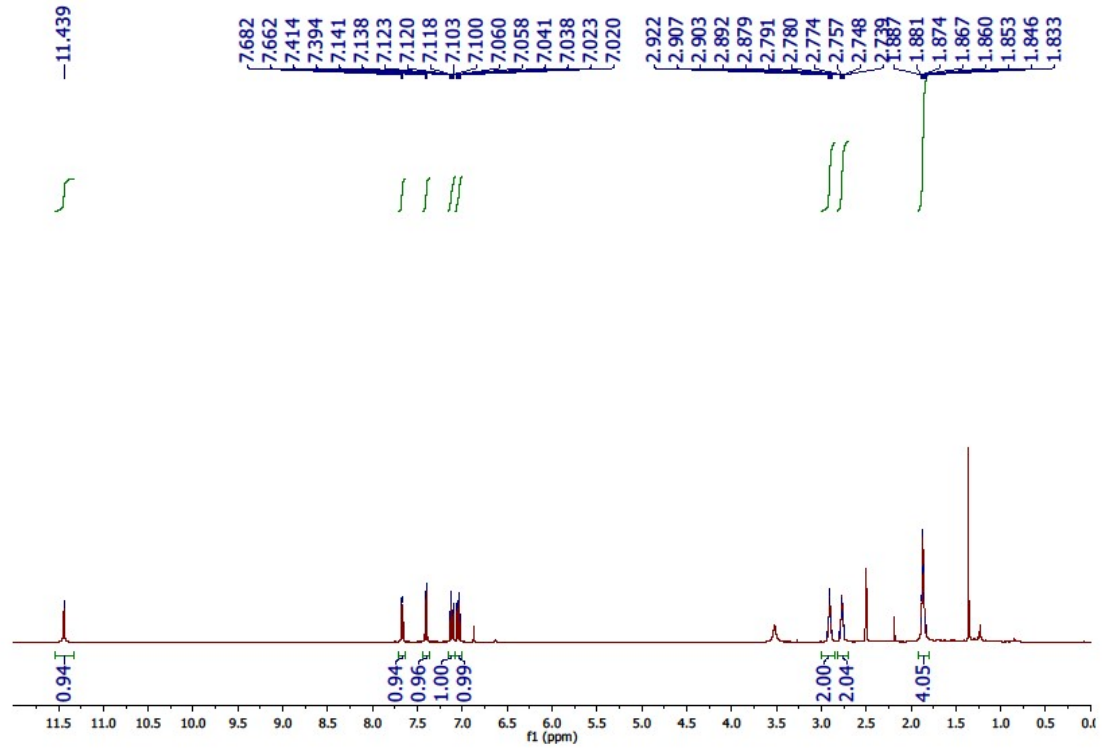


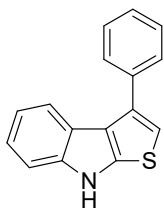
3-methyl-2-phenyl-8*H*-thieno[2,3-*b*]indole- 4s.



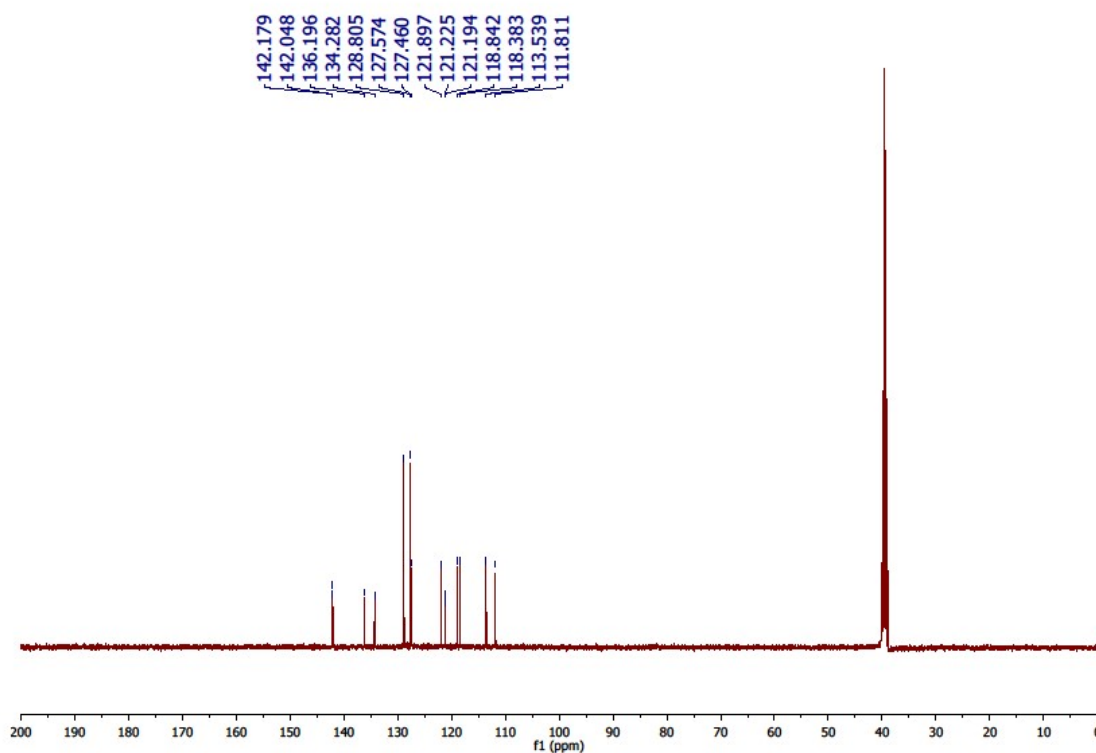
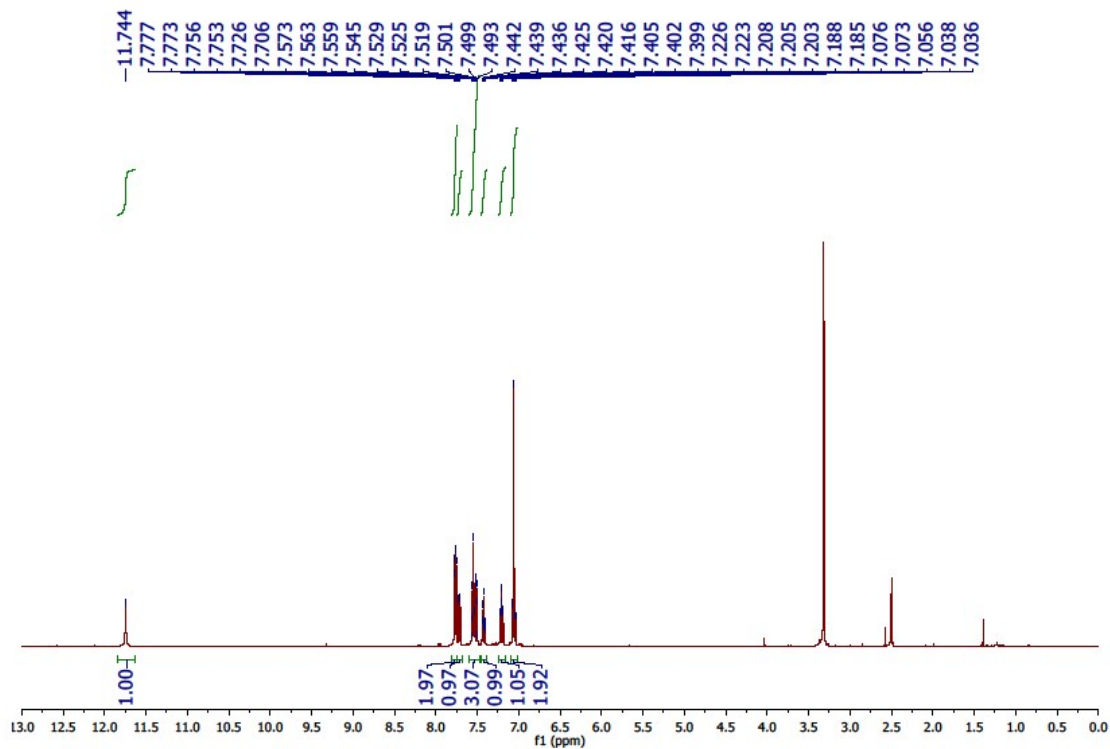


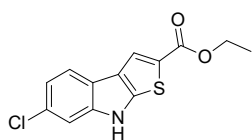
2,3,4,6-tetrahydro-1*H*-benzo[4,5]thieno[2,3-*b*]indole 4t.



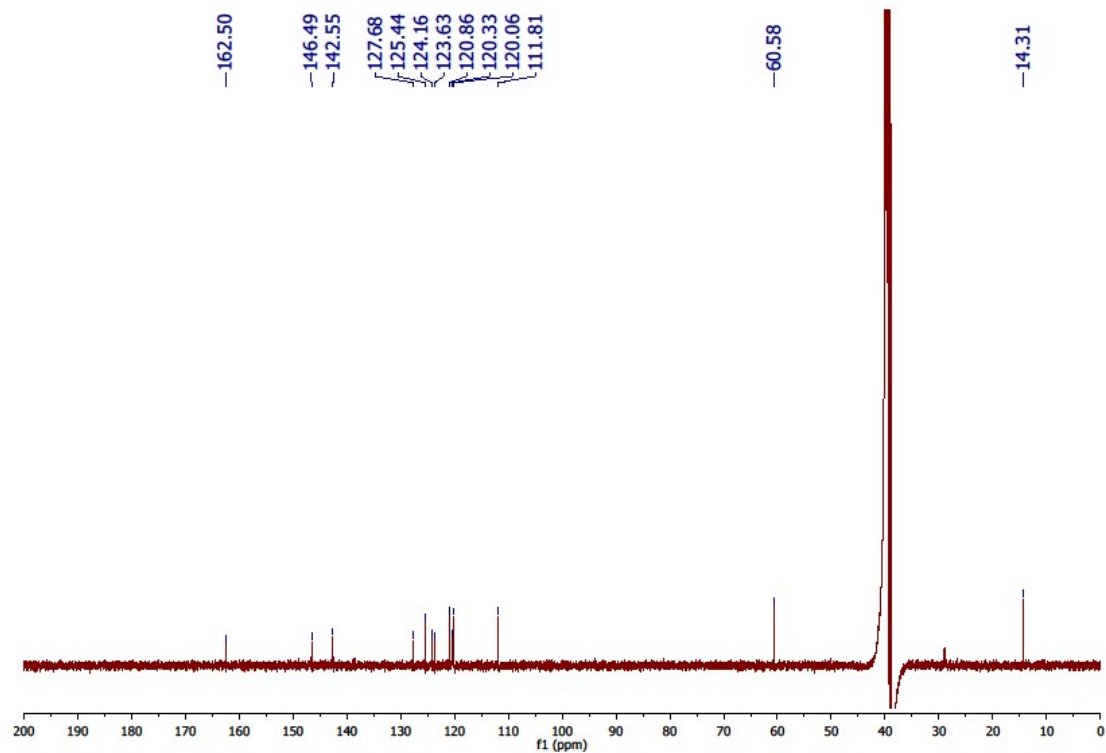
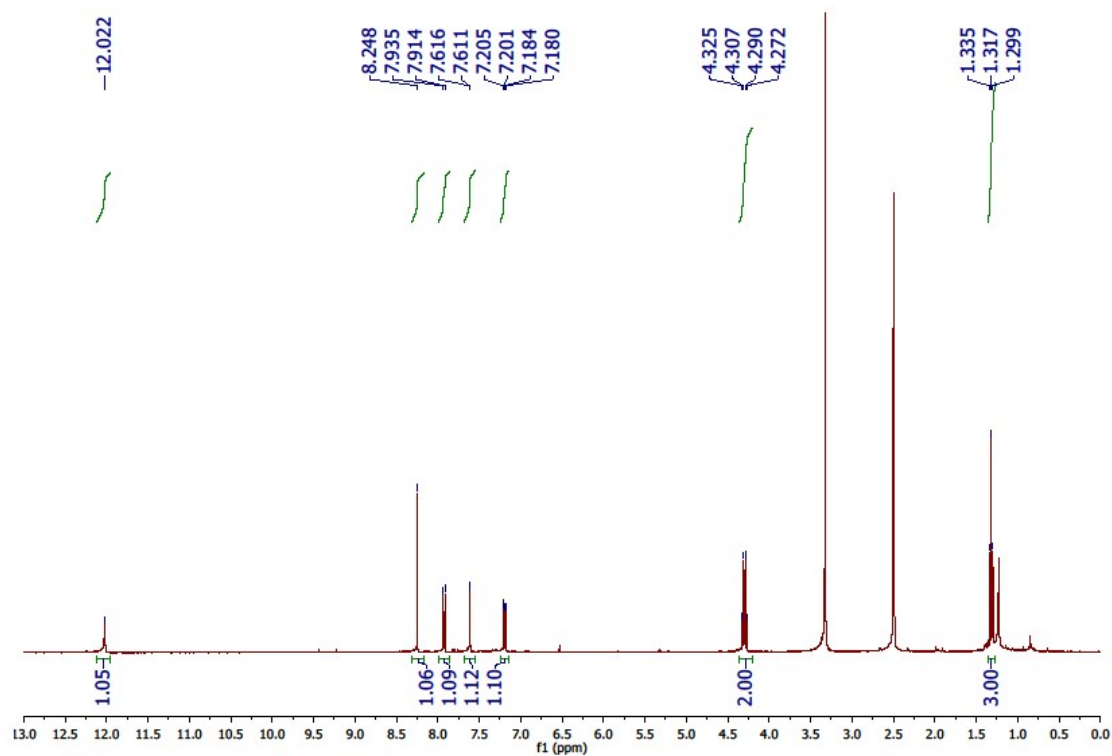


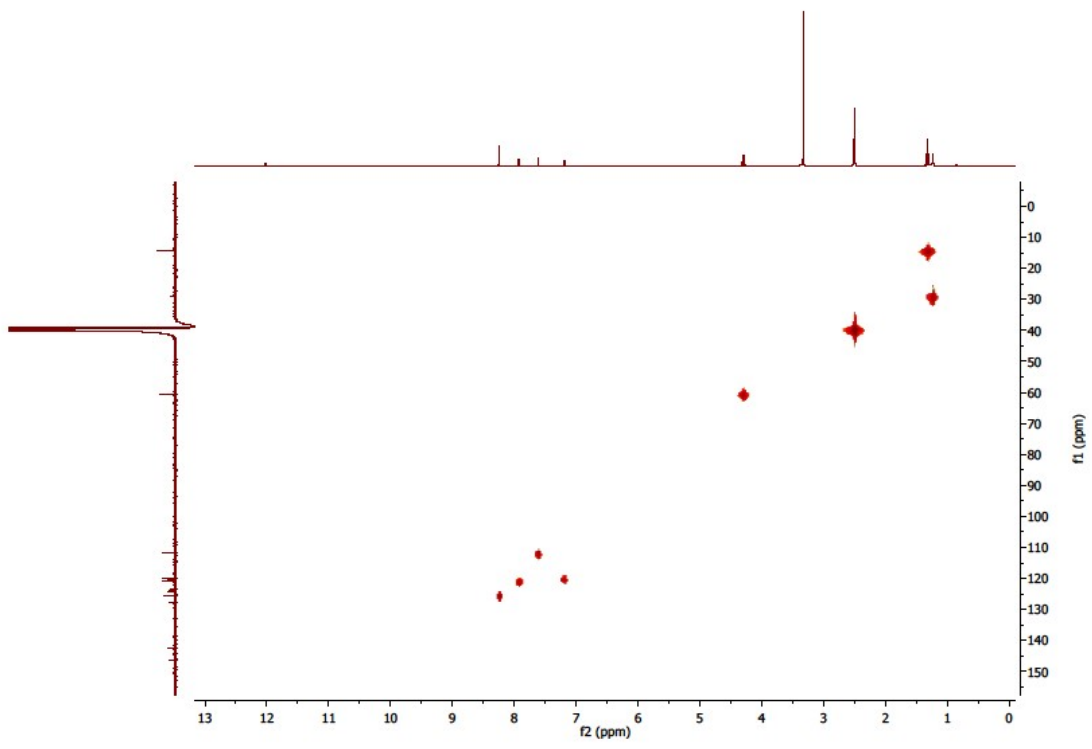
3-phenyl-8H-thieno[2,3-b]indole 4u.





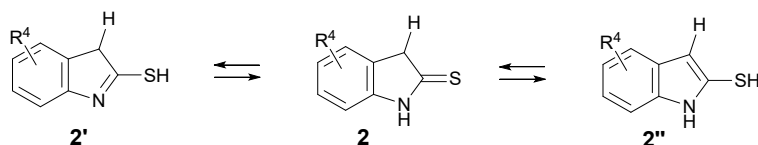
Ethyl 6-chloro-8*H*-thieno[2,3-*b*]indole-2-carboxylate 4v.



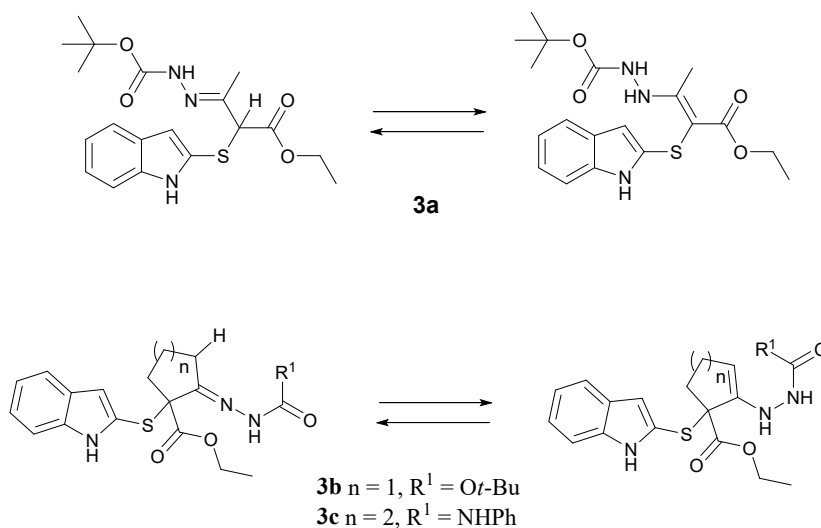


## 8 References

- 1) L. Preti, O. A. Attanasi, E. Caselli, G. Favi, C. Ori, P. Davoli, F. Felluga, F. Prati, *Eur. J. Org. Chem.*, 2010, 4312.
- 2) For a practical procedure to synthesize of the indoline-2-thiones **2** please see: a) T. Hino, K. Tsuneoka, M. Nakagawa, S. Akaboshi, *Chem. Pharm. Bull.*, 1969, **17**, 550. b) J. W. Scheeren, P. H. J. Ooms, R. J. F. Nivard, *Synthesis*, 1973, 149
- 3) In the  $^{13}\text{C}$ -NMR spectra of indoline-2-thiones **2** small signals appear due to the tautomeric processes that in the time necessary for these analyses are established in the deuterated solvent.



- 4) In the NMR spectra of hydrazones **3** the presence of small signals is due to the presence of different tautomeric processes involving both the thiophene ring (similarly to what previously described for the indoline-2-thiones) and the hydrazone portion:



- 5) (a) T. Saito, Y. Sonoki, T. Otani, N. Kutsumura, *Org. Biomol. Chem.*, 2014, **12**, 8398. (b) J. Levy, D. Royer, J. Guilhem, M. Cesario, C. Pascard, *Bull. Soc. Chim. Fr.*, 1987, **1**, 193.
- 6) P. Ni, B. Li, H. Huang, F. Xiao, G.-J. Deng, *Green Chem.*, 2017, **19**, 5553.
- 7) The ethyl ester derivative is an unknown product, while its methyl ester analog was employed in the total synthesis of thienodolin: R. Engqvist, A. Javaid, J. Bergman, *Eur. J. Org. Chem.*, 2004, 2589.