Multistep continuous flow synthesis of condensed benzothiazoles

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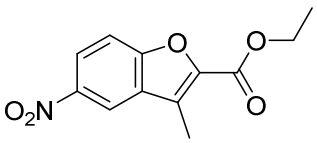
Supporting Information

1. Characterisation data for benzofurans 5a-c.

*1.1. Ethyl 3-methyl-5-nitro-1-benzofuran-2-carboxylate (**5a**)*



Utilizing the general flow procedure for the synthesis of benzofurans, compound **5a** was isolated with 47% overall yield as pale yellow solid.

Mp. 146-148 °C (146-147 °C lit.[1]).

^{1}H NMR: δ 1.36 (t, 3H, CH_3), 2.62 (s, 3H, $ArCH_3$) 4.39 (q, 2H, CH_2), 7.94 (d, 1H), 8.38 (dd, 1H), 8.79 (d, 1H) ppm.

HPLC purity: 99.9%.

Spectral data for **5a** was consistent with that reported for this compound in the literature[1].

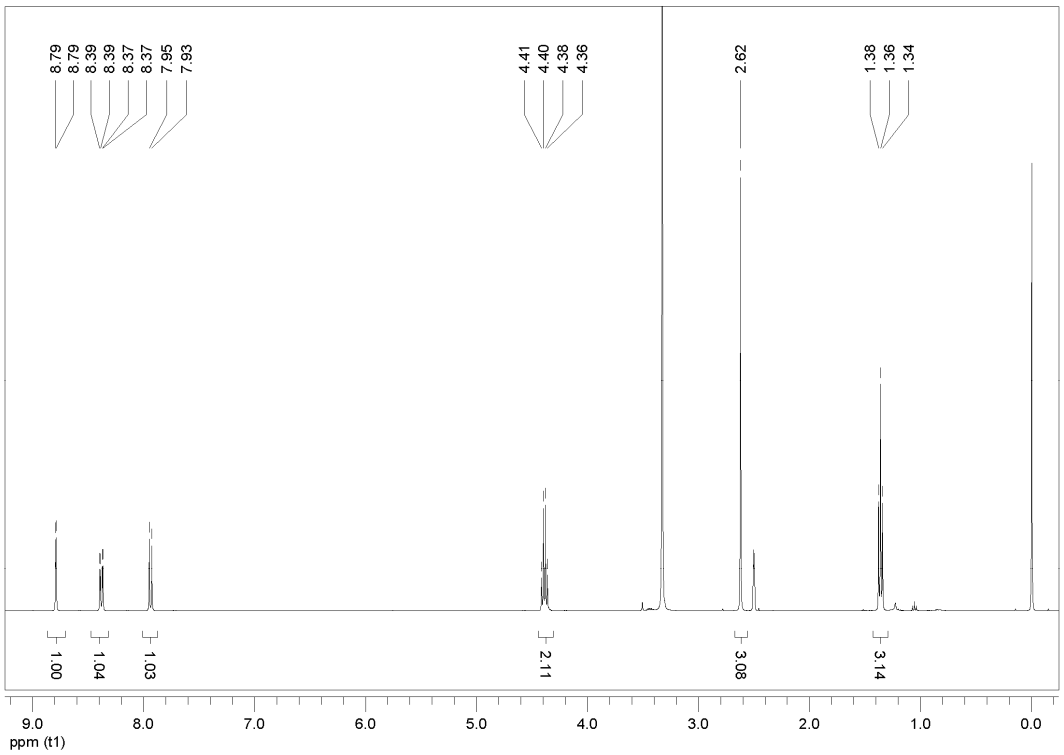
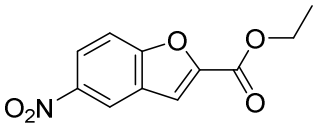


Figure 1. ^{1}H NMR spectral data of **5a**

*1.2. Ethyl 5-nitro-1-benzofuran-2-carboxylate (**5b**)*



Utilizing the general flow procedure for the synthesis of benzofurans, compound **5b** was isolated with 69% overall yield as pale yellow solid.

Mp. 154-155 °C (153-154 °C lit.[2]).

^{1}H NMR: δ 1.35 (t, 3H, CH_3), 4.40 (q, 2H, CH_2), 7.94 (s, 1H), 8.00 (d, 1H), 8.38 (dd, 1H), 8.78 (d, 1H) ppm.

HPLC purity: 99.7%.

Spectral data for **5b** was consistent with that reported for this compound in the literature[3].

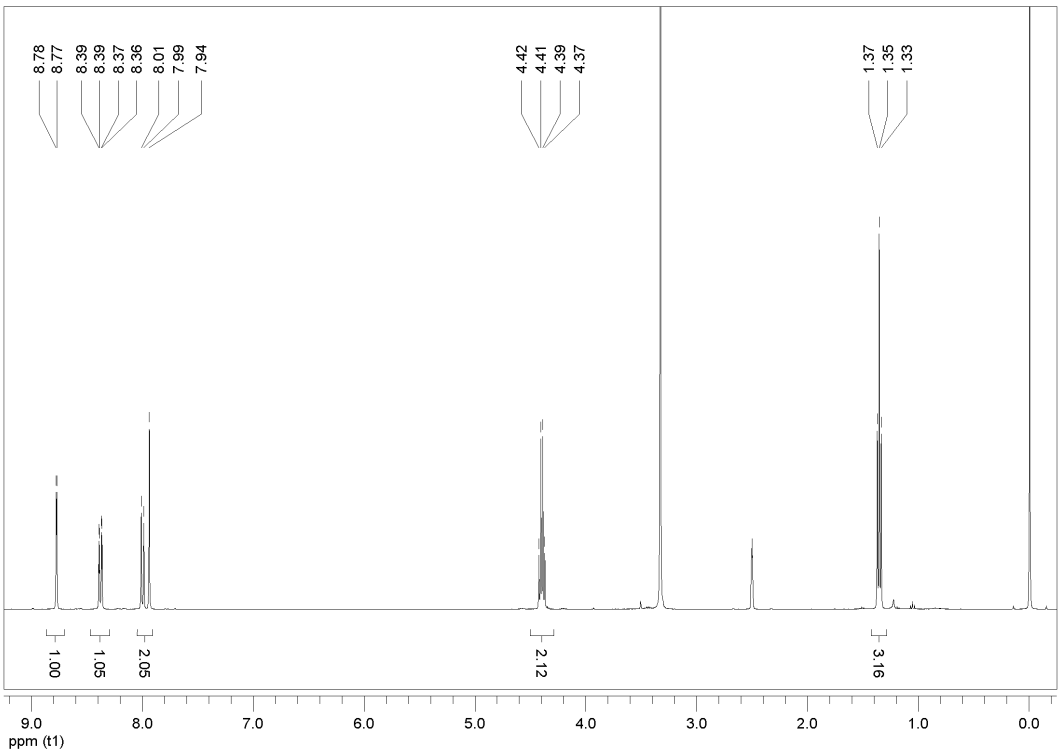
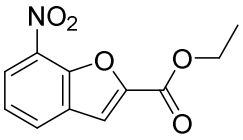


Figure 2. ^{1}H NMR spectral data of **5b**

*1.3 Ethyl 7-nitro-1-benzofuran-2-carboxylate (**5c**)*



Utilizing the general flow procedure for the synthesis of benzofurans, compound **5c** was isolated with 4% overall yield as yellow solid.

Mp. 80-81 °C (87-88 °C lit.[4])

^{1}H NMR: δ 1.36 (t, 3H, CH_3), 4.42 (q, 2H, CH_2), 7.61 (t, 1H), 7.99 (s, 1H), 8.27 (dd, 1H), 8.37 (dd, 1H) ppm.

HPLC purity: 96.2%

Spectral data for **5c** was consistent with that reported for this compound in the literature[5].

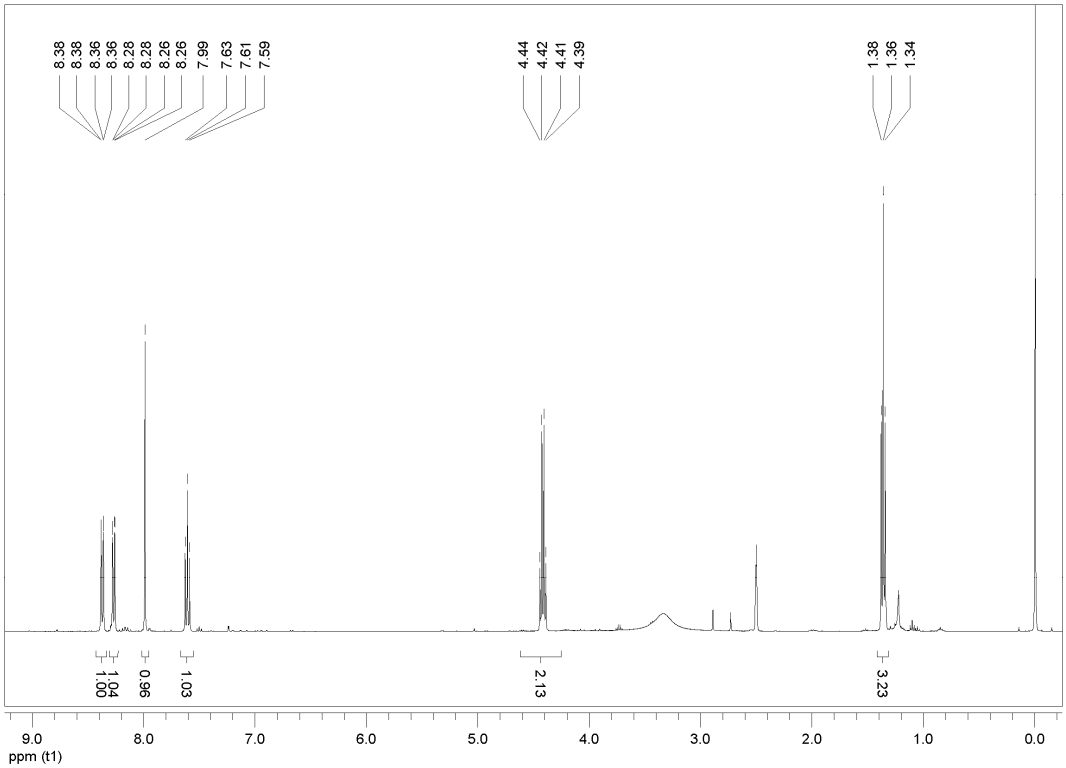
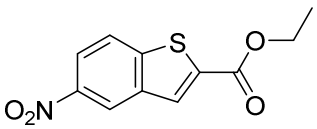


Figure 3. ^{1}H NMR spectral data of **5c**

2. Characterisation data for benzothiophenes 9a-c.

*2.1. Ethyl 5-nitro-1-benzothiophene-2-carboxylate (**9a**)*



Utilizing the general flow procedure for the synthesis of benzothiophenes, compound **9a** was isolated with 35% yield as pale yellow solid.

Mp. 167-168 °C (164-165 °C lit.[6])

^{1}H NMR: δ 1.35 (t, 3H, CH_3), 4.39 (q, 2H, CH_2), 8.30 (dd, 1H), 8.36 (d, 1H), 8.43 (s, 1H), 8.99 (dd, 1H) ppm.

HPLC purity: 99.9%

Spectral data for **9a** was consistent with that reported for this compound in the literature[7].

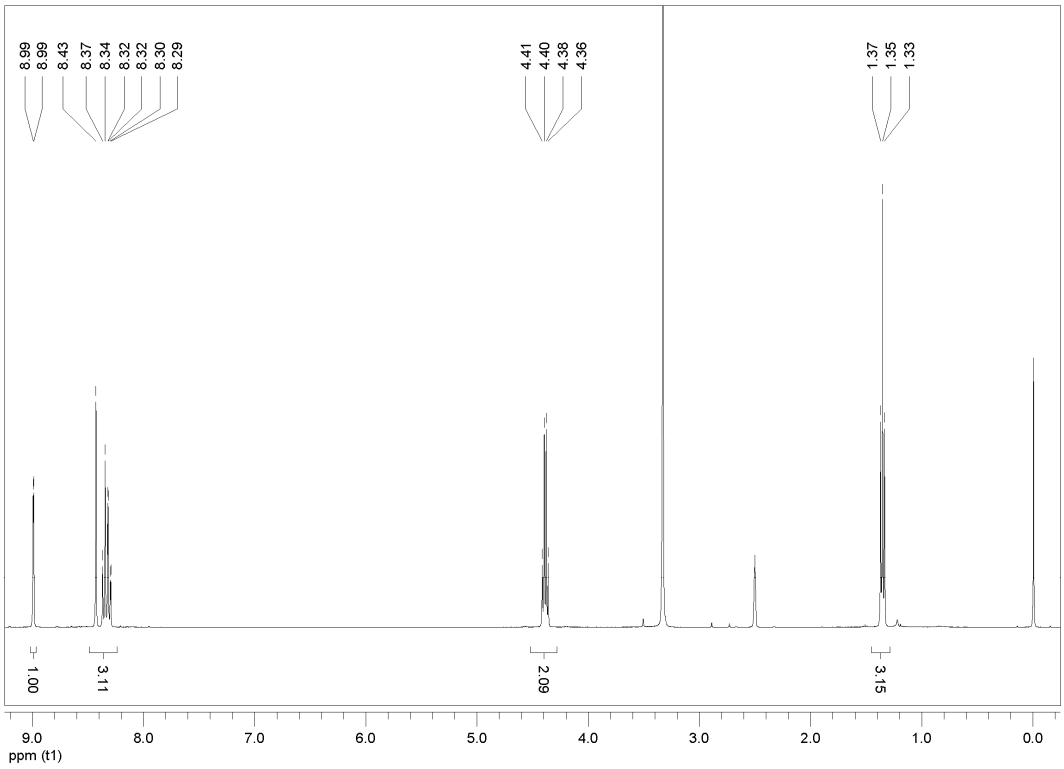
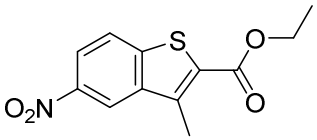


Figure 4. ^{1}H NMR spectral data of **9a**

*2.2. Ethyl 3-methyl-5-nitro-1-benzothiophene-2-carboxylate (**9b**)*



Utilizing the general flow procedure for the synthesis of benzothiophenes, compound **9b** was isolated with 66% yield as pale brown solid.

Mp. 131-132 °C (132-133 °C lit.[8])

^{1}H NMR: δ 1.35 (t, 3H, CH_3), 2.79 (s, 3H, $ArCH_3$), 4.36 (q, 2H, CH_2), 8.29 (d, 1H), 8.32 (dd, 1H), 8.78 (dd, 1H) ppm.

HPLC purity: 96.8%

For compound **9b**, only less detailed ^{1}H NMR spectral data are available in the literature[8].

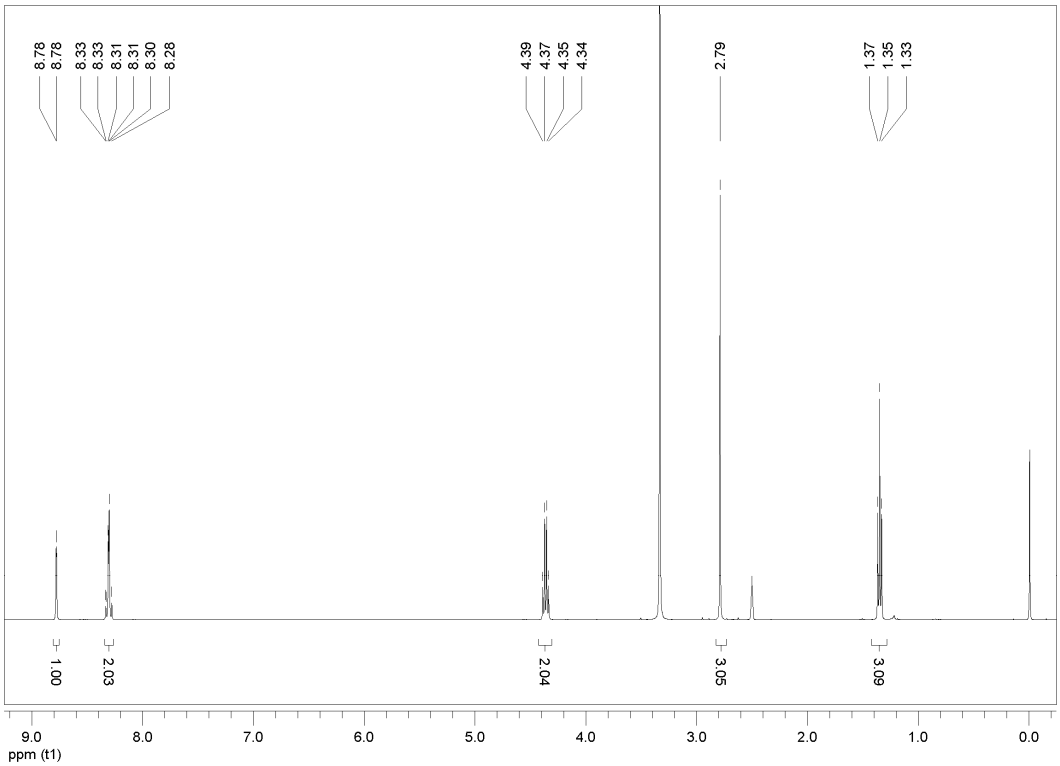
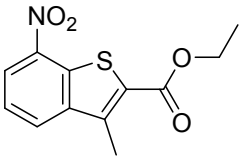


Figure 5. 1H NMR spectral data of **9b**

*2.3. Ethyl 3-methyl-7-nitro-1-benzothiophene-2-carboxylate (**9c**)*



Utilizing the general flow procedure for the synthesis of benzothiophenes, compound **9c** was isolated with 56% yield as yellow solid.

Mp. 172-173 °C (179-180 °C lit.[9])

^{1}H NMR: δ 1.37 (t, 3H, CH_3), 2.77 (s, 3H, $ArCH_3$), 4.38 (q, 2H, CH_2), 7.78 (t, 1H), 8.48 (dd, 1H), 8.58 (dd, 1H) ppm.

HPLC purity: 97.3%

For compound **9c**, no ^{1}H NMR spectral data are available in the literature[9].

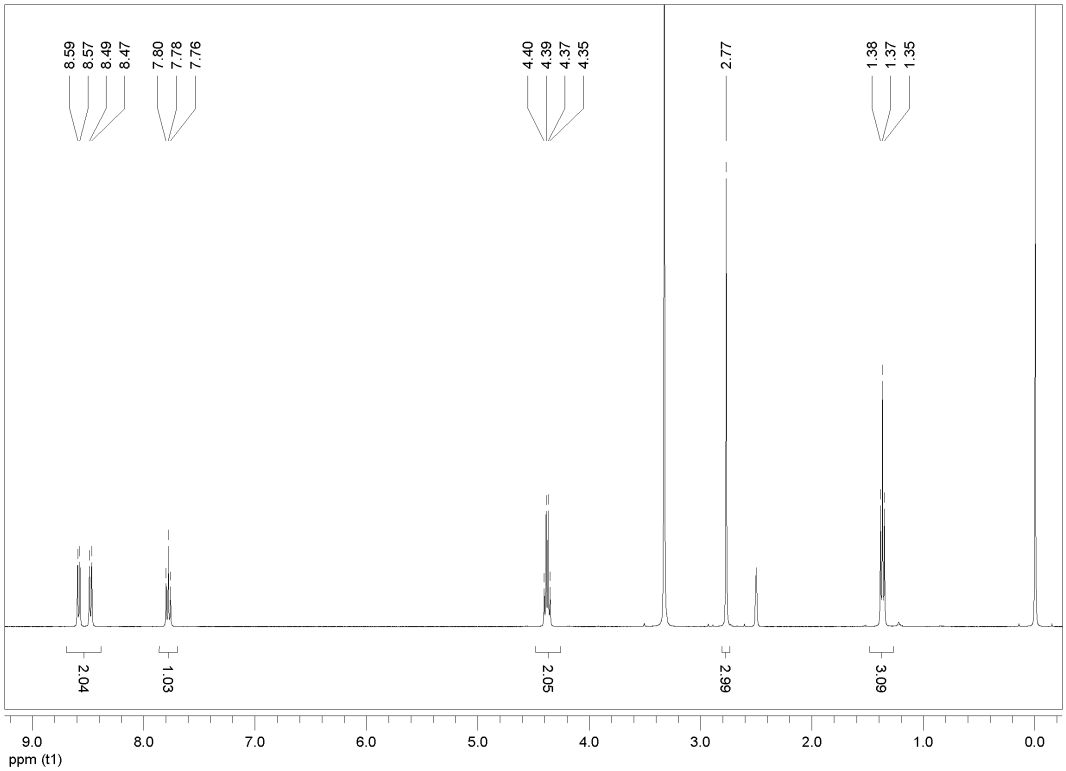
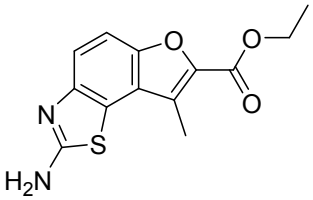


Figure 6. ^{1}H NMR spectral data for **9c**

3. Characterisation data for compounds I-V.

*3.1. Ethyl 2-amino-8-methylfuro[2,3-g][1,3]benzothiazole-7-carboxylate (**I**).*



Utilizing the general flow procedure, compound **I** was isolated with 55% yield as pale yellow powder.

Mp. 284-285 °C.

^{1}H NMR: δ 1.35 (t, 3H, *J* 7.1 Hz, CH_3), 2.60 (s, 3H, $ArCH_3$), 4.35 (q, 2H, *J* 7.1 Hz, CH_2), 7.50 (s, 2H, NH_2), 7.52 (s, 2H, ArH) ppm.

^{13}C NMR: δ 10.1 ($ArCH_3$), 14.1 (CH_3), 60.8 (CH_2), 109.3 (C-5), 118.7 (C-4), 121.2 & 122.4 (C-8a, C-8b), 123.8 (C-8), 140.5 (C-7), 149.4 & 149.5 (C-3a, C-5a), 159.4 (COO), 166.0 (CNH_2) ppm.

HRMS: 277.06396 ($C_{13}H_{13}O_3N_2S$; calc. 277.06414). ESI-MS-MS (rel. int. %): 249(100).

HPLC purity: 98.1%.

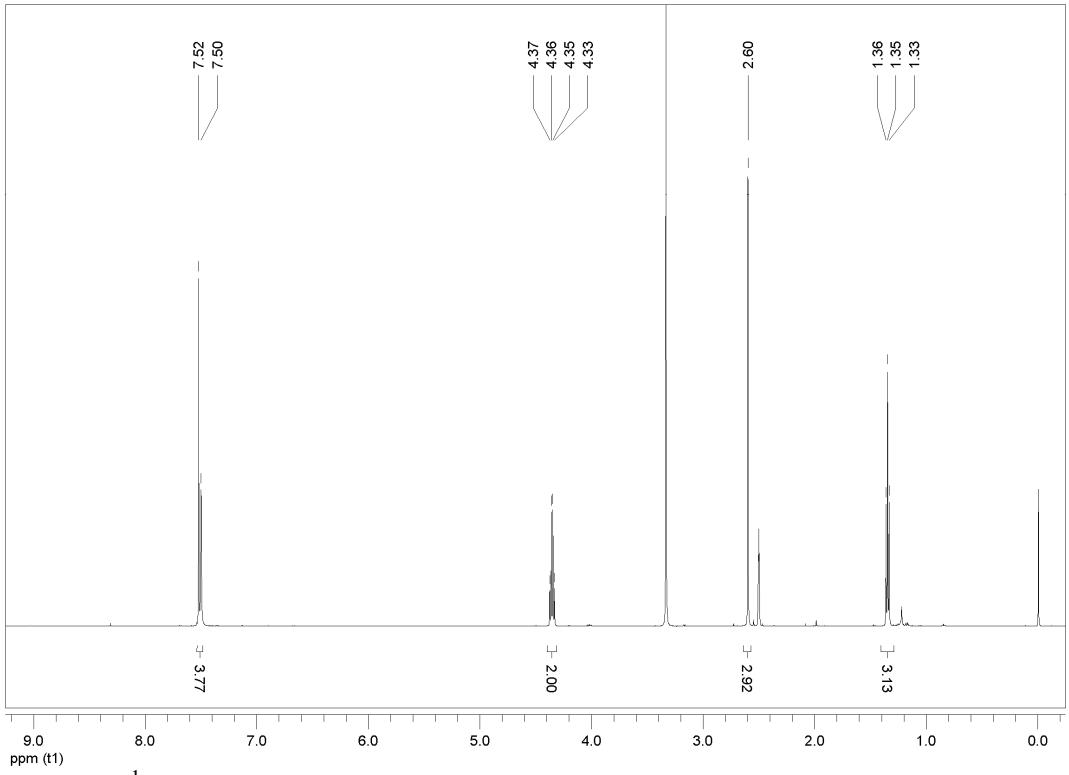


Figure 7. ^{1}H NMR spectral data for **I**

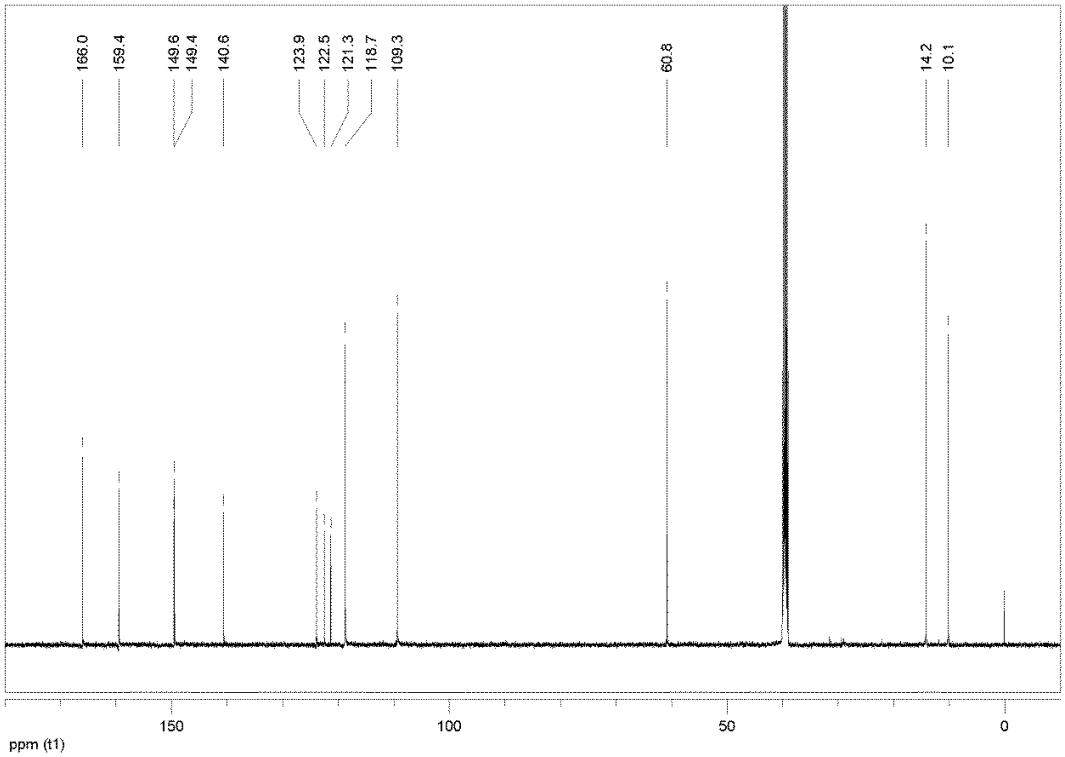
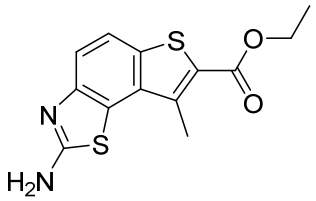


Figure 8. ^{13}C NMR spectral data for **I**

*3.2. Ethyl 2-amino-8-methylthieno[2,3-g][1,3]benzothiazole-7-carboxylate (**II**)*



Utilizing the general flow procedure, compound **II** was isolated with 62% yield as pale yellow powder.

Mp. 255-258 °C.

^{1}H NMR: δ 1.33 (t, 3H, J 7.1 Hz, CH_3), 2.84 (s, 3H, $ArCH_3$), 4.33 (q, 2H, J 7.1 Hz, CH_2), 7.55 (s, 2H, NH_2), 7.59 (d, 1H, J_{orto} 8.6 Hz, H-4), 7.82 (d, 1H, J_{orto} 8.6 Hz, H-5) ppm.

^{13}C NMR: δ 14.1 (CH_3), 14.5 ($ArCH_3$), 61.0 (CH_2), 119.2 (C-4), 119.9 (C-5), 124.1 (C-5a), 126.7 (C-8), 132.9 (C-8b), 133.7 (C-8a), 138.8 (C-7), 150.8 (C-3a), 162.5 (COO), 166.3 (CNH_2) ppm.

HRMS: 293.04154 ($C_{13}H_{13}O_2N_2S_2$; calc. 293.04130). ESI-MS-MS (rel. int. %): 265(100).

HPLC purity: 99.6%.

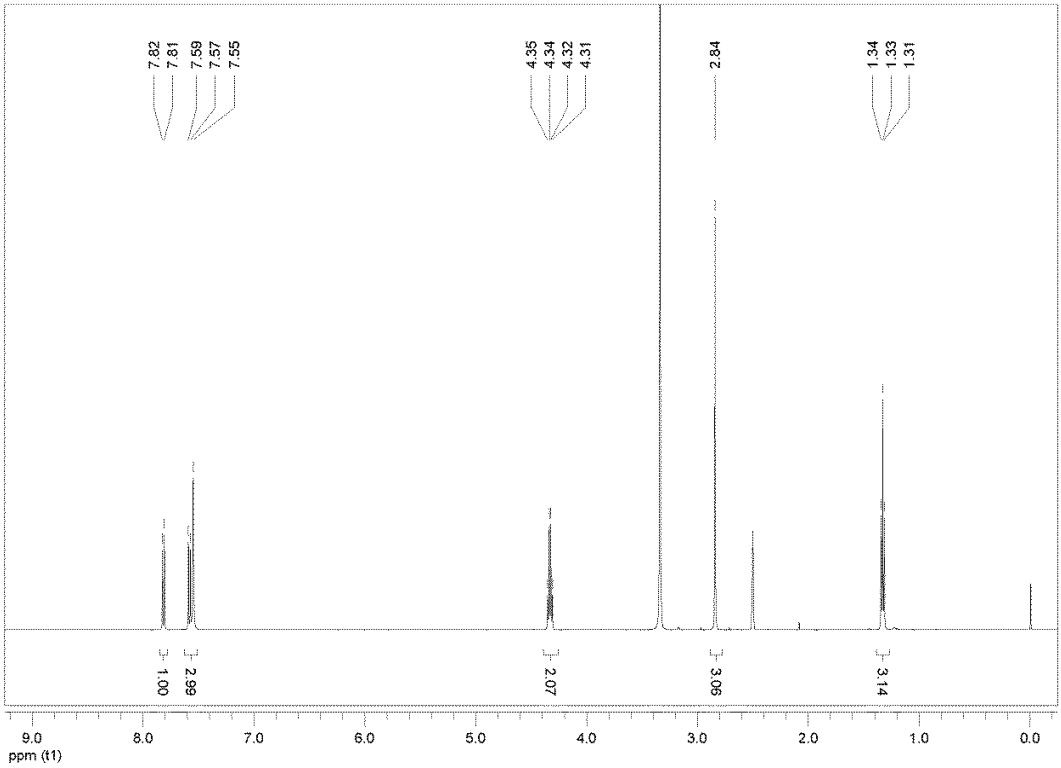


Figure 9. ^{1}H NMR spectral data for **II**

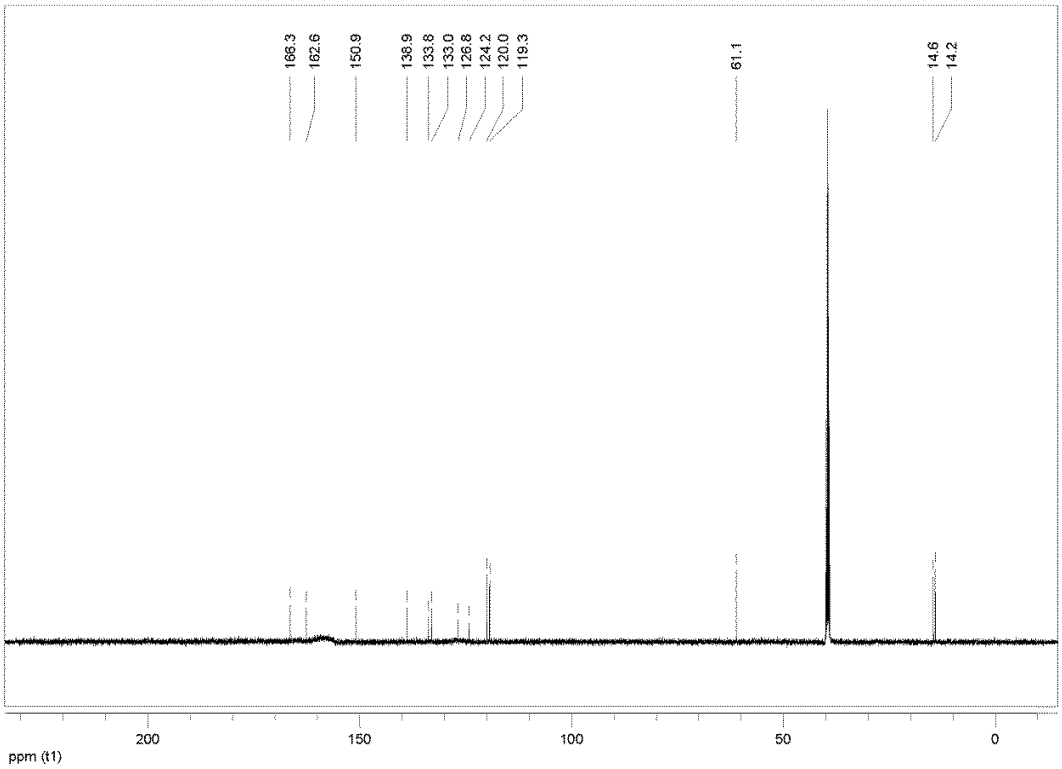
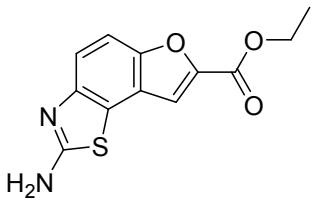


Figure 10. ^{13}C NMR spectral data for **II**

*3.3. Ethyl 2-aminofuro[2,3-g][1,3]benzothiazole-7-carboxylate (**III**)*



Utilizing the general flow procedure, compound **III** was isolated with 33% yield as yellow powder.

Mp. 234-236 °C.

^{1}H NMR: δ 1.34 (t, 3H, J 7.1 Hz, CH_3), 4.36 (q, 2H, J 7.1 Hz, CH_2), 7.47 (s, 2H, NH_2), 7.52 (d, 1H, J_{orto} 8.9 Hz, H-4), 7.57 (dd, 1H, J_{orto} 8.9 Hz, ^{5}J 0.9 Hz, H-5), 7.89 (d, 1H, ^{5}J 0.9 Hz, H-8) ppm.

^{13}C NMR: δ 14.1 (CH_3), 61.2 (CH_2), 109.2 (C-5), 112.7 (C-8), 118.4 (C-4), 120.3 (C-8a), 122.1 (C-8b), 145.2 (C-7), 149.5 (C-3a), 151.0 (C-5a), 158.5 (COO), 166.1 (CNH_2) ppm.

HRMS: 263.04836 ($C_{12}H_{11}O_3N_2S$; calc. 263.04849). ESI-MS-MS (rel. int. %): 235(100).

HPLC purity: 95.8%.

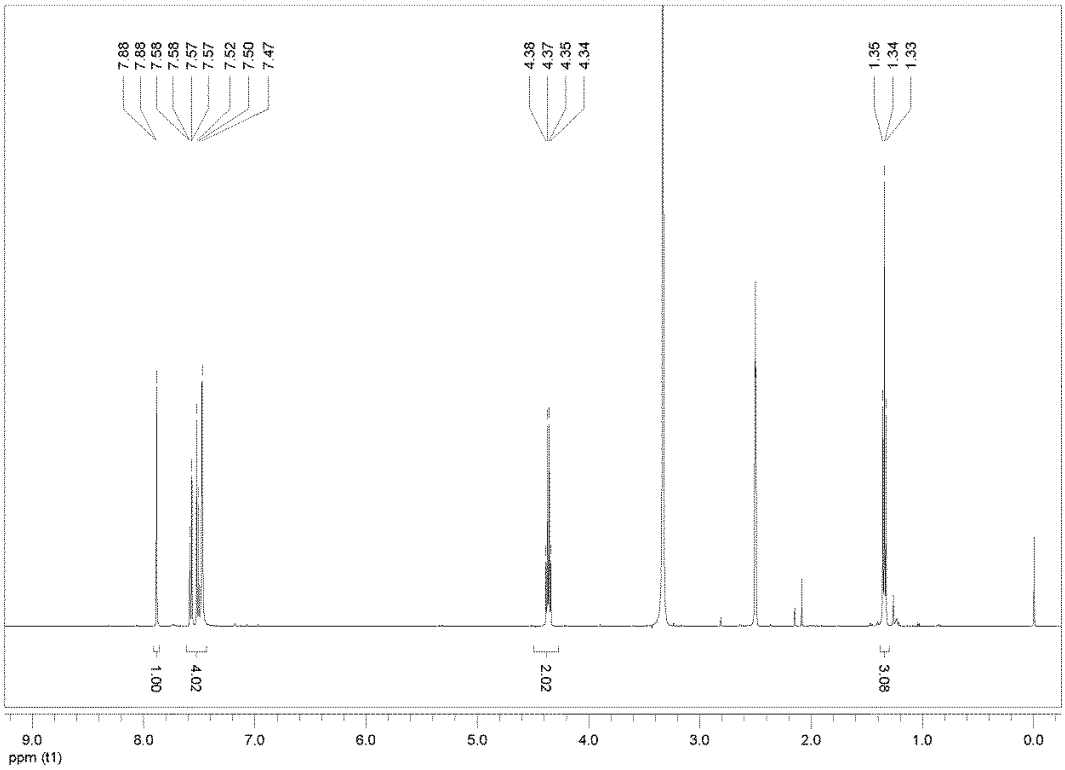


Figure 11. ^{1}H NMR spectral data for **III**

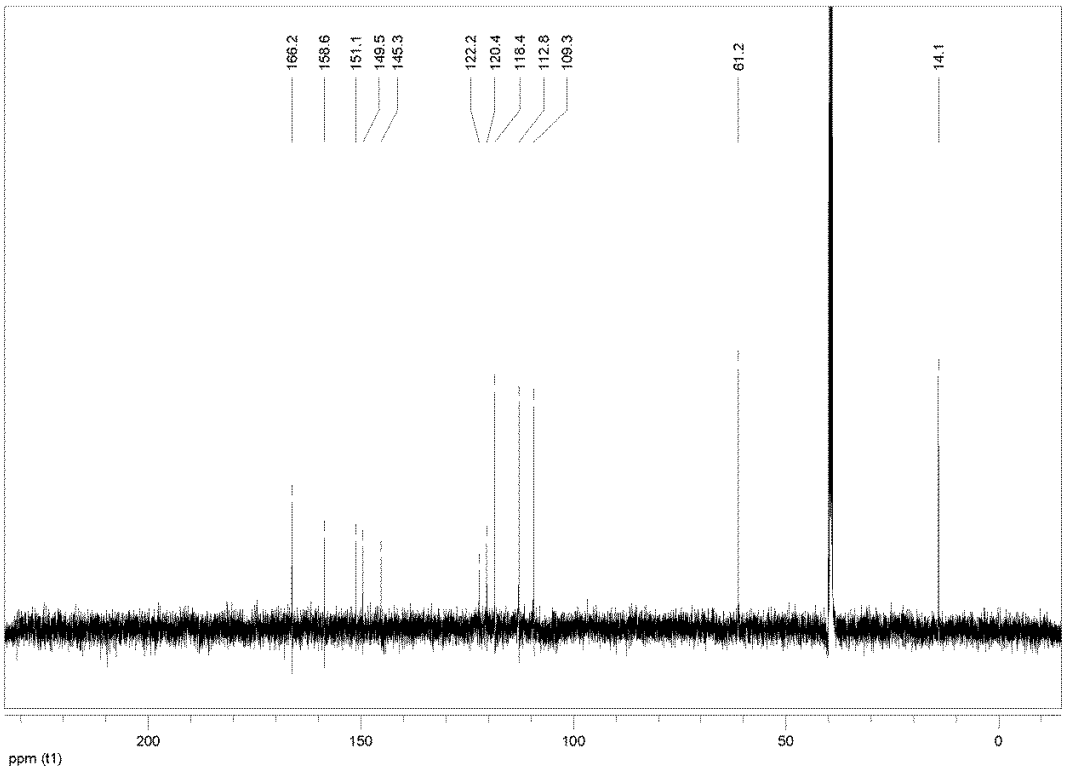
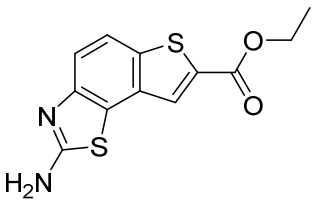


Figure 12. ^{13}C NMR spectral data for **III**

*3.4. Ethyl 2-aminothieno[2,3-g][1,3]benzothiazole-7-carboxylate (**IV**)*



Utilizing the general flow procedure, compound **IV** was isolated with 82% yield as pale yellow powder.

Mp. 255-257 °C.

^{1}H NMR: δ 1.34 (t, 3H, J 7.1 Hz, CH_3), 4.36 (q, 2H, J 7.1 Hz, CH_2), 7.58 (s, 2H, NH_2), 7.57 (d, 1H, J_{orto} 8.7 Hz, H-4), 7.87 (d, 1H, J_{orto} 8.7 Hz, H-5), 8.12 (s, 1H, H-8) ppm.

^{13}C NMR: δ 14.1 (CH_3), 61.4 (CH_2), 118.8 (C-4), 119.9 (C-5), 125.1 (C-5a), 128.0 (C-8), 131.5 (C-8a), 134.0 (C-7), 134.8 (C-8b), 150.7 (C-3a), 161.8 (COO), 166.4 (CNH_2) ppm.

HRMS: 279.02553 ($C_{12}H_{11}O_2N_2S_2$; calc. 279.02565). ESI-MS-MS (rel. int. %): 251(100).

HPLC purity: 95.6%.

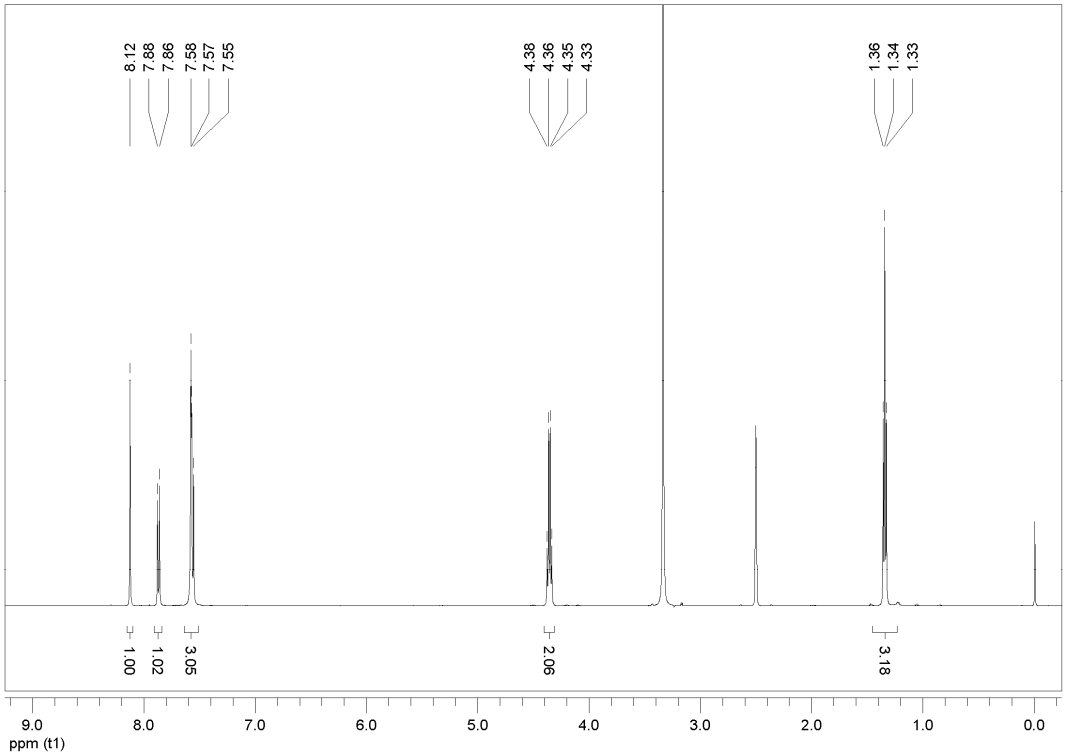


Figure 13. ^{1}H NMR spectral data for **IV**

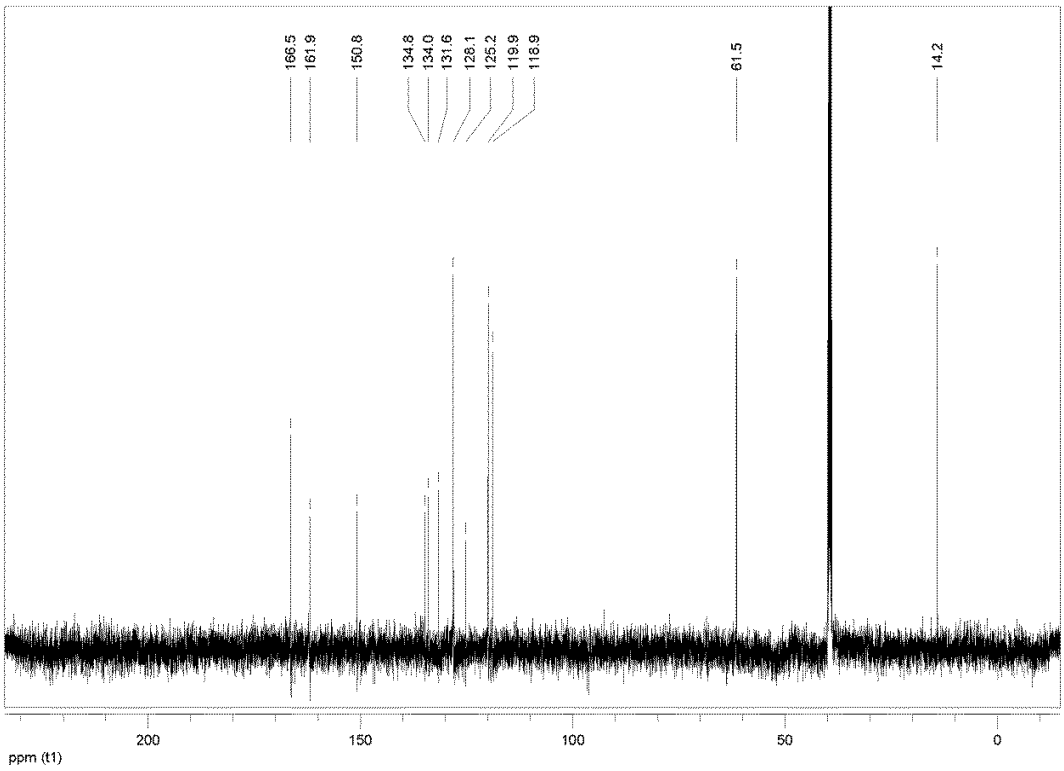
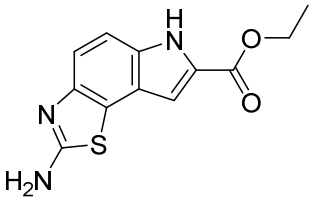


Figure 14. ^{13}C NMR spectral data for **IV**

*3.5. Ethyl 2-amino-6H-[1,3]thiazolo[5,4-e]indole-7-carboxylate (**V**)*



Utilizing the general flow procedure, compound **V** was isolated with 45% yield as pale brown powder.

Mp. 197 °C, with decomposition.

^{1}H NMR: δ 1.34 (t, 3H, J 7.1 Hz, CH_3), 4.34 (q, 2H, J 7.1 Hz, CH_2), 7.08 (dd, 1H, ^{5}J 0.9 Hz, $J_{H\text{-}8,NH}$ 2.3 Hz, H-8), 7.19 (s, 2H, NH_2), 7.32 (dd, 1H, J_{orto} 8.7 Hz, ^{5}J 0.9 Hz, H-5), 7.35 (d, 1H, J_{orto} 8.7 Hz, H-4), 11.99 (brm, 1H, NH) ppm.

^{13}C NMR: δ 14.2 (CH_3), 60.3 (CH_2), 105.1 (C-8), 110.2 (C-5), 116.9 (C-4), 120.2 (C-8a), 120.6 (C-8b), 127.2 (C-7), 133.6 (C-5a), 146.6 (C-3a), 161.0 (COO), 164.4 (CNH_2) ppm.

HRMS: 262.06429 ($C_{12}H_{12}O_2N_3S$; calc. 262.06447). ESI-MS-MS (rel. int. %): 234(16); 216(100).

HPLC purity: 87.7%.

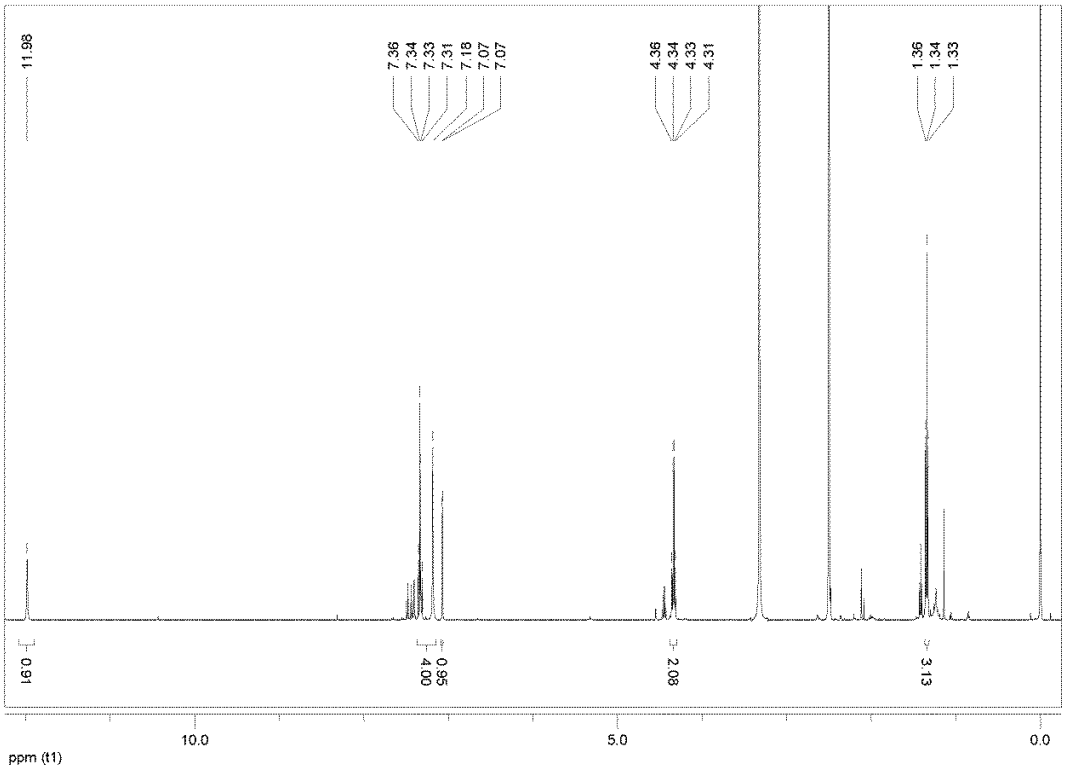


Figure 15. ^{1}H NMR spectral data for **V**

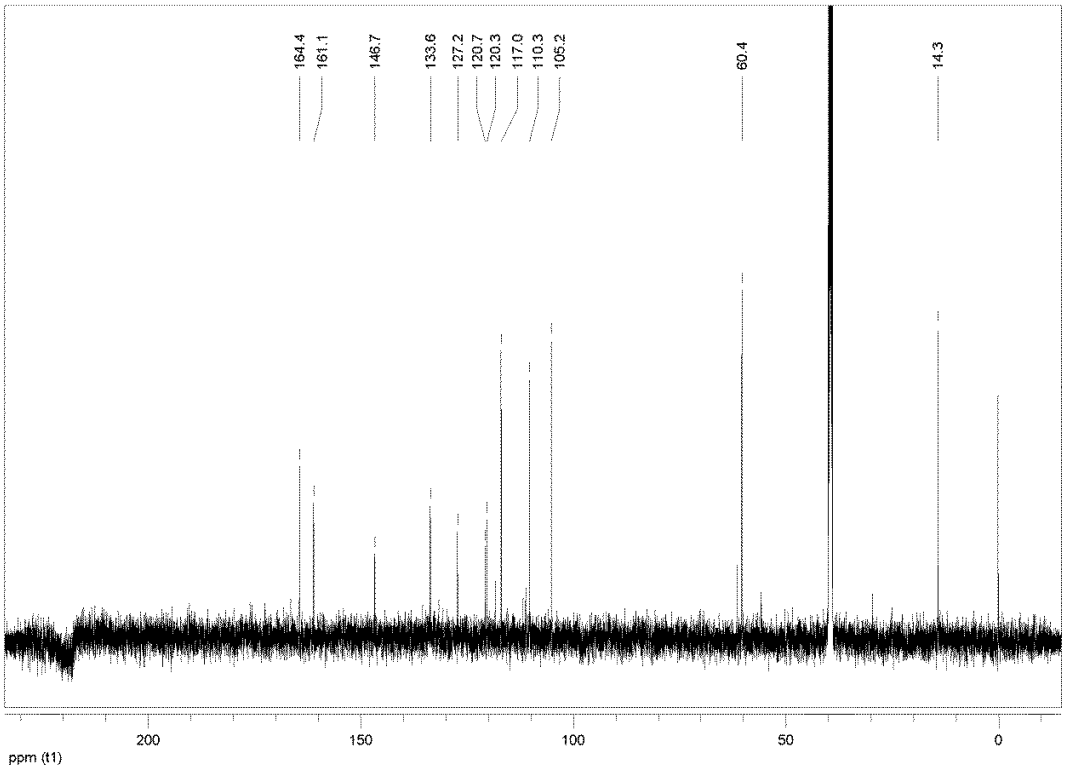


Figure 16. ^{13}C NMR spectral data for **V**

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