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Facile, efficient and green phthalimide synthesis in supercritical carbon dioxide

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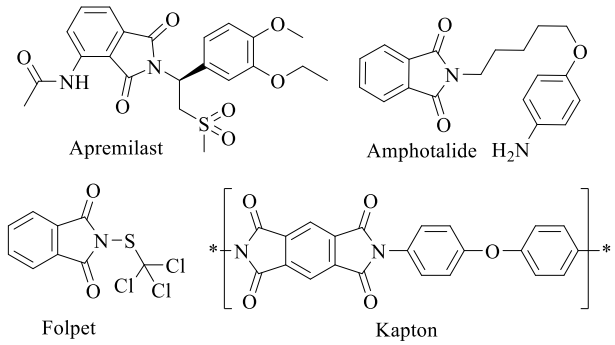


Figure S1. Examples of valuable phtalimide derivatives.[S1-S4.]

General information

All reagents were obtained from Sigma Aldrich and used without further purification. NMR measurements were carried out on Bruker-Avance 400 MHz spectrometer in $CDCl_3$ and DMSO-d6 using TMS as an internal reference.

Electrospray ionization high-resolution mass spectra were recorded in positive ion mode on a TripleTOF 5600+ quadrupole time-of-flight mass spectrometer (ABSciex, Concord, Canada) equipped with DuoSpray ion source. The following MS parameters were applied: capillary voltage 5.5 kV; nebulizing and curtain gas pressure – 15 and 25 psi, respectively; ion source temperature – ambient; declustering potential 20 V; m/z range 100–1200. Elemental compositions of the detected ions were determined based on accurate masses and isotopic distributions using Formula Finder software (ABSciex, Concord, Canada).

Experimental procedures

Scheme of equipment for reactions in supercritical CO_2

All reactions in supercritical carbon dioxide were carried out in the high-pressure experimental setup shown in Figure S2. Stirring and heating was carried out using a laboratory magnetic stirrer.

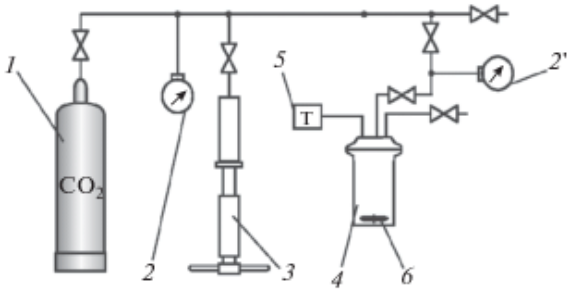
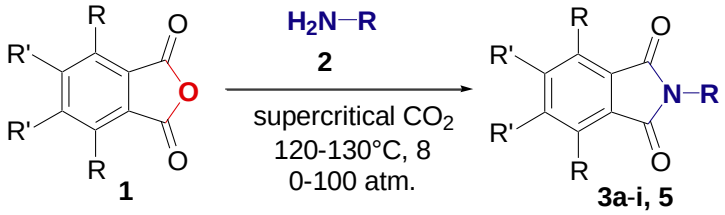


Figure S2. Installation for high pressure: (1) CO_2 tank, (2, 2 ') manometers, (3) hand screw press, (4) reactor, (5) thermocouple, (6) magnetic stir bar anchor.

General procedure of synthesis of phthalimides 3a-i and 5

Scheme S1.



A substituted phthalic anhydride and the corresponding amine are placed in a reaction chamber. The reaction chamber is sealed and filled with liquid CO_2 at room temperature. After pressure inside the reaction chamber reaches 52-60 bar, the reactor is cut from liquid CO_2 source. The reactor is heated to a temperature range of 125-140°C (260-280°C for electron deficient substrates), causing the pressure of carbon dioxide inside the reaction chamber to increase to 80-110 atmospheres. The reaction is carried out at these parameters for a specified duration. The reactor is then cooled down to room temperature and CO_2 is removed via outlet pipeline to a low pressure chamber. The product is removed from the reaction vessel. The conversion of reagents to the final product is monitored by analyzing samples at regular intervals using ^{1}H NMR.

It is important to note that the reduced yield is the result of mechanical losses occurring during the unsealing of the reaction chamber and the product take-out.

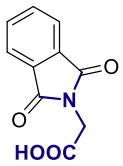
Table S1 Conversion rate of carbamoylbenzamide **3′ f** into imide **3f** at 120 °C and 90 bar CO_2.

Entry	*t*/h	**3′ f**, mol%*	**3f**, mol%*
1	2	92	8
2	4.5	69	31
3	7.5	44	56
4	10.5	27	73
5	18.5	6	94

* Measured by ^{1}H NMR spectroscopy.

2-(1,3-Dioxoisoindolin-2-yl)acetic acid (3a). [S5]

The reaction of phthalic anhydride (148 mg, 1 mmol) and glycine (75 mg, 1 mmol) at 130°C, 90 bar yields 174 mg (85%) of **3a** as a white solid.

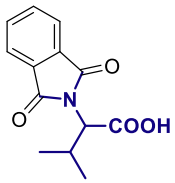


^{1}H NMR (400 MHz, DMSO) δ 13.29 (br.s, 1H), 8.01 – 7.79 (m, 4H), 4.31 (s, 2H). Consistent with lit. [S6]

HRMS calc. for $C_{10}H_6NO_4^{(-)}$(M-H$^{(+)}$): 204.0302, found 204.0301.

2-(1,3-Dioxoisoindolin-2-yl)-3-methylbutanoic acid (3b). [S7]

The reaction of phthalic anhydride (148 mg, 1 mmol) and valine (117 mg, 1 mmol) at 130°C, 95 bar yields 185 mg (75%) of **3b** as a white solid.



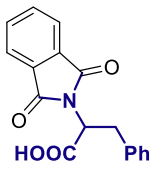
^{1}H NMR (400 MHz, DMSO) δ 7.97 – 7.84 (m, 4H), 4.45 (d, J = 7.8 Hz, 1H), 2.61 – 2.53 (m, 1H), 1.07 (d, J = 6.5 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, DMSO) δ 169.8, 167.6, 135.0, 131.0, 123.5, 57.0, 28.0, 20.9, 19.3.

HRMS calc. for $C_{12}H_{14}NO_2^{(+)}$(M-CO_2+H$^{(+)}$): 204.1019, found 204.1012.

2-(1,3-Dioxoisoindolin-2-yl)-3-phenylpropanoic acid (3c). [S8]

The reaction of phthalic anhydride (148 mg, 1 mmol) and phenylalanine (165 mg, 1 mmol) at 132°C, 94 bar yields 202 mg (69%) of **3c** as a white solid.



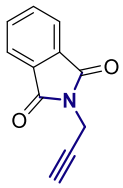
^{1}H NMR (400 MHz, DMSO) δ 7.83 (s, 4H), 7.20 – 7.06 (m, 5H), 5.10 (dd, J = 11.7, 4.7 Hz, 1H), 3.48 (dd, J = 14.1, 4.8 Hz, 1H), 3.38 – 3.29 (m, 1H).

^{13}C NMR (101 MHz, DMSO) δ 170.1, 167.2, 137.5, 135.0, 130.8, 128.7, 128.3, 126.6, 123.4, 53.1, 34.0.

HRMS calc. for $C_{17}H_{12}NO_4^{(-)}$(M-H$^{(+)}$): 294.0772, found 294.0775.

2-(Prop-2-yn-1-yl)isoindoline-1,3-dione (3d). [S9]

The reaction of phthalic anhydride (148 mg, 1 mmol) and propargylamine (66 mg, 1,2 mmol) at 130°C, 92 bar yields 133 mg (72%) of **3d** as a dark gray solid.



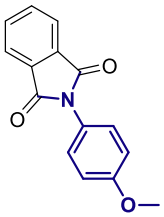
^{1}H NMR (400 MHz, DMSO) δ 7.88 (d, J = 16.3 Hz, 4H), 4.36 (s, 2H), 3.27 (s, 1H).

^{13}C NMR (101 MHz, DMSO) δ 166.7, 134.8, 131.4, 123.4, 78.2, 73.9, 26.7.

HRMS calc. for $C_{11}H_8NO_2^{(+)}$(M+H$^{(+)}$): 186.0550, found 186.0553.

2-(4-Methoxyphenyl)isoindoline-1,3-dione (3e). [S10]

The reaction of phthalic anhydride (148 mg, 1 mmol) and p-anisidine (123 mg, 1 mmol) at 275°C, 80 bar yields 218 mg (86%) of **3e** as a white solid.



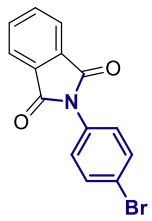
^{1}H NMR (400 MHz, DMSO) δ 9.17 (s, 1H), 7.84 (s, 4H), 6.91 (d, J = 7.9 Hz, 2H), 6.53 (d, J = 8.0 Hz, 2H), 5.01 (dd, J = 11.7, 4.8 Hz, 1H), 3.22 (t, J = 12.9 Hz, 1H).

^{13}C NMR (101 MHz, DMSO) δ 167.3, 158.9, 134.6, 131.6, 128.8, 124.4, 123.3, 114.1, 55.4.

HRMS calc. for $C_{15}H_{11}NNaO_3^{(+)}$ (M+Na$^{(+)}$): 276.0631, found 276.0637.

2-(4-Bromophenyl)isoindoline-1,3-dione (3f). [S10]

The reaction of phthalic anhydride (148 mg, 1 mmol) and 4-bromoaniline (172 mg, 1 mmol) at 265°C, 98 bar yields 233 mg (77%) of **3f** as a dark gray solid.



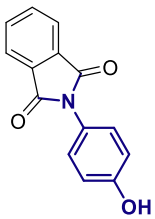
^{1}H NMR (400 MHz, DMSO) δ 8.03 – 7.84 (m, 4H), 7.74 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H).

^{13}C NMR (101 MHz, CDCl3) δ 166.8, 134.8, 131.9, 131.6, 131.3, 129.4, 123.5, 121.0.

HRMS calc. for $C_{14}H_8BrNNaO_2^{(+)}$(M+Na$^{(+)}$): 323,9631, found 323,9632.

2-(4-Hydroxyphenyl)isoindoline-1,3-dione (3g). [S11]

The reaction of phthalic anhydride (148 mg, 1 mmol) and 4-hydroxyaniline (109 mg, 1 mmol) at 280°C, 82 bar yields 146 mg (61%) of **3g** as a gray solid.



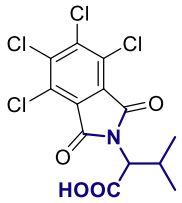
^{1}H NMR (400 MHz, DMSO) δ 9.77 (s, 1H), 7.96 – 7.85 (m, 4H), 7.24 – 7.17 (m, 2H), 6.90 – 6.84 (m, 2H).

^{13}C NMR (101 MHz, DMSO) δ 167.4, 157.3, 134.6, 131.6, 128.8, 123.3, 122.9, 115.4.

HRMS calc. for $C_{14}H_8NO_3^{(-)}$(M-H$^{(+)}$): 238.0510, found 238.0511.

3-Methyl-2-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)butanoic acid (3h). [S12]

The reaction of tetrachlorophthalic anhydride (286 mg, 1 mmol) and valine (117 mg, 1 mmol) at 260°C, 110 bar yields 293 mg (76%) of **3h** as a white solid.



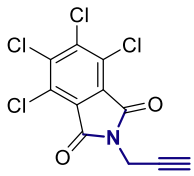
^{1}H NMR (400 MHz, DMSO) δ 4.48 (d, J = 7.7 Hz, 1H), 2.59 – 2.51 (m, 1H), 1.07 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, DMSO) δ 169.2, 163.1, 138.8, 128.6, 127.6, 57.8, 28.1, 20.7, 19.2.

HRMS calc. for $C_{13}H_8Cl_4NO_4^{(-)}$(M-H$^{(+)}$):381.9213, found 381.9216.

4,5,6,7-Tetrachloro-2-(prop-2-yn-1-yl)isoindoline-1,3-dione (3i)

The reaction of tetrachlorophthalic anhydride (286 mg, 1 mmol) and propargylamine (66 mg, 1,2 mmol) at 135°C, 101 bar yields 203 mg (63%) of **3i** as a gray solid.



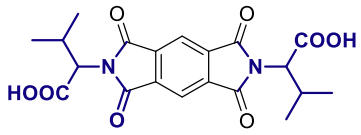
^{1}H NMR (400 MHz, DMSO) δ 4.38 (d, J = 2.5 Hz, 2H), 3.32 (t, J = 2.5 Hz, 1H).

^{13}C NMR (101 MHz, DMSO) δ 162.4, 138.4, 128.3, 128.3, 77.5, 74.5, 27.5.

HRMS calc. for $C_{11}H_4Cl_4NO_2^{(+)}$ (M+H$^{(+)}$): 321.8991, found 321.8986.

2,2'-(1,3,5,7-Tetraoxo-5,7-dihydropyrrolo[3,4-*f*]isoindole-2,6(1*H*,3*H*)-diyl)-bis(3-methylbutanoic acid) (5). [S13]

The reaction of pyromellitic dianhydride (218 mg, 1 mmol) and valine (234 mg, 2 mmol) at 260°C, 108 bar yields 276 mg (66%) of **5** as a white solid. M.p. 277-279 (lit. [S14] 276-278).



^{1}H NMR (400 MHz, DMSO) δ 13.26 (br.s, 2H), 8.34 (s, 2H), 4.54 (d, J = 7.5 Hz, 2H), 2.58 (s, 2H), 1.08 (s, 6H), 0.85 (s, 6H).

^{13}C NMR (101 MHz, DMSO) δ 169.4, 165.8, 136.6, 118.5, 57.6, 28.1, 20.8, 19.3.

HRMS calc. for $C_{20}H_{19}N_2O_8^{(-)}$(M-H$^{(+)}$):415.1147, found 415.1148.

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^{1}H and ^{13}C NMR spectra

2-(1,3-Dioxoisoindolin-2-yl)acetic acid (3a)

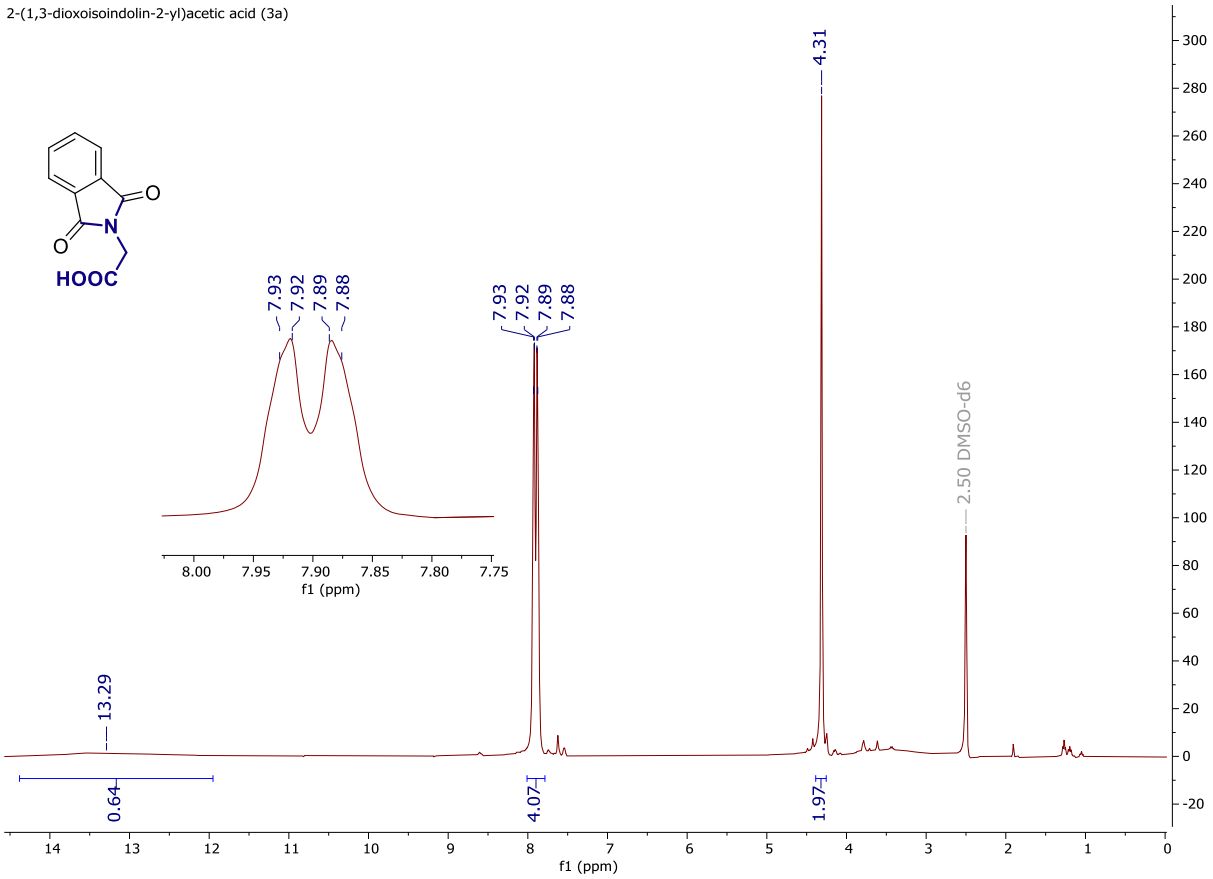

Figure S3. ^{1}H NMR spectrum of compound **3a**.

2-(1,3-Dioxoisoindolin-2-yl)-3-methylbutanoic acid (3b)

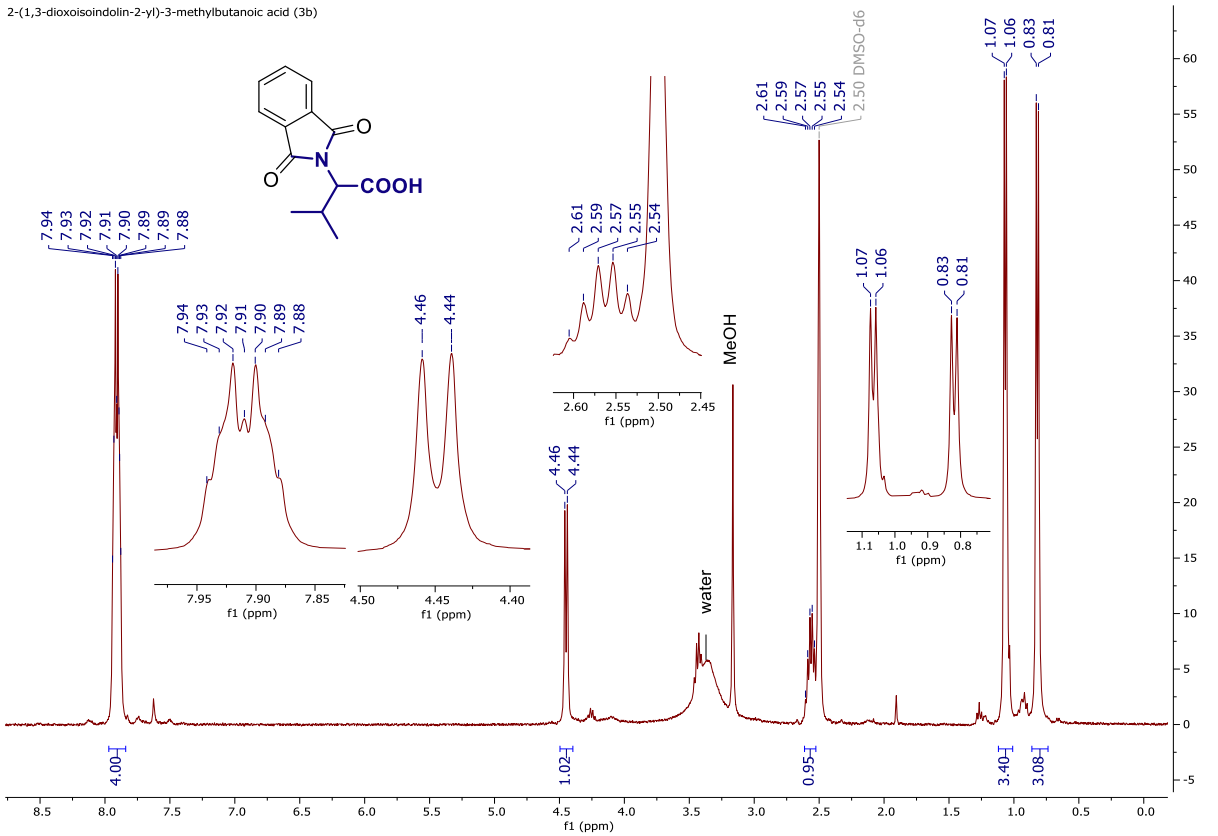

Figure S4. ^{1}H NMR spectrum of compound **3b**.

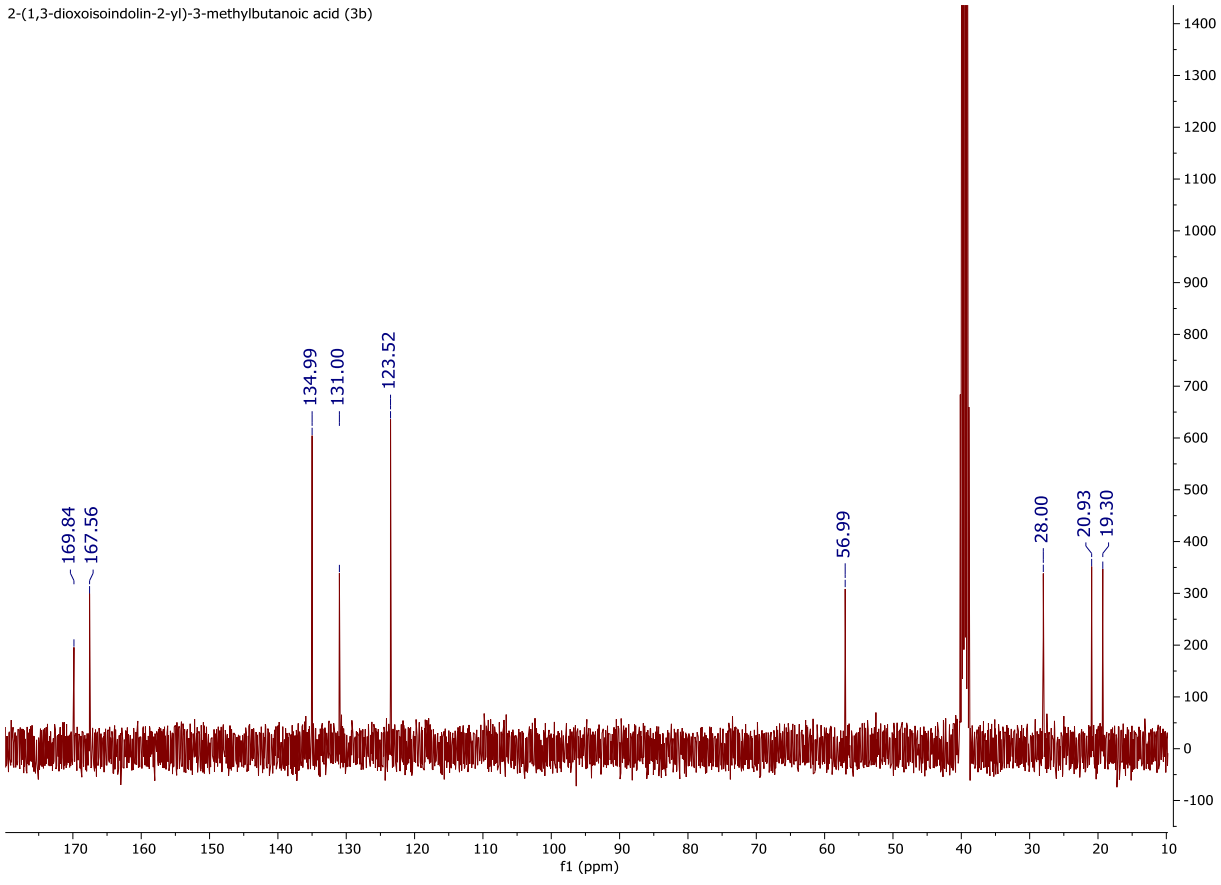

Figure S5. ^{13}C NMR spectrum of compound **3b**.

2-(1,3-Dioxoisoindolin-2-yl)-3-phenylpropanoic acid (3c)

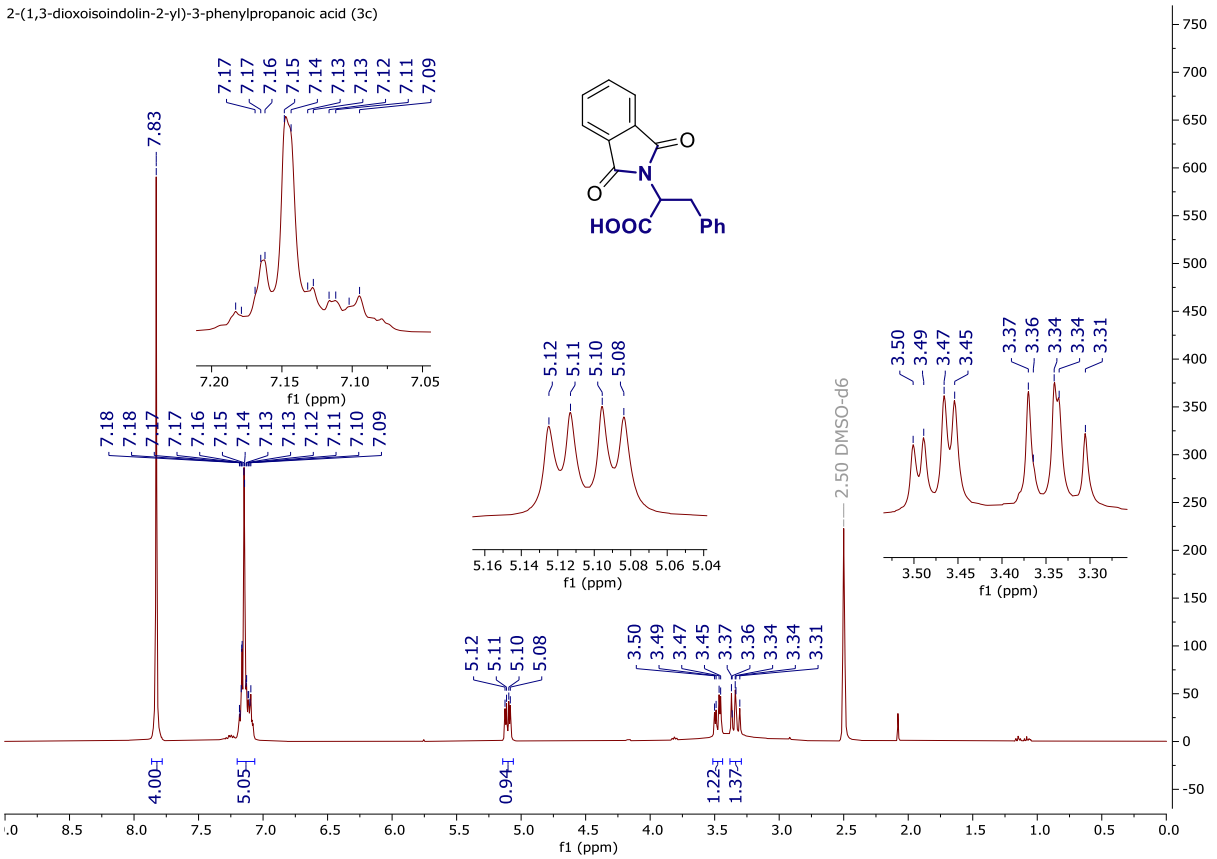

Figure S6. ^{1}H NMR spectrum of compound **3c**.

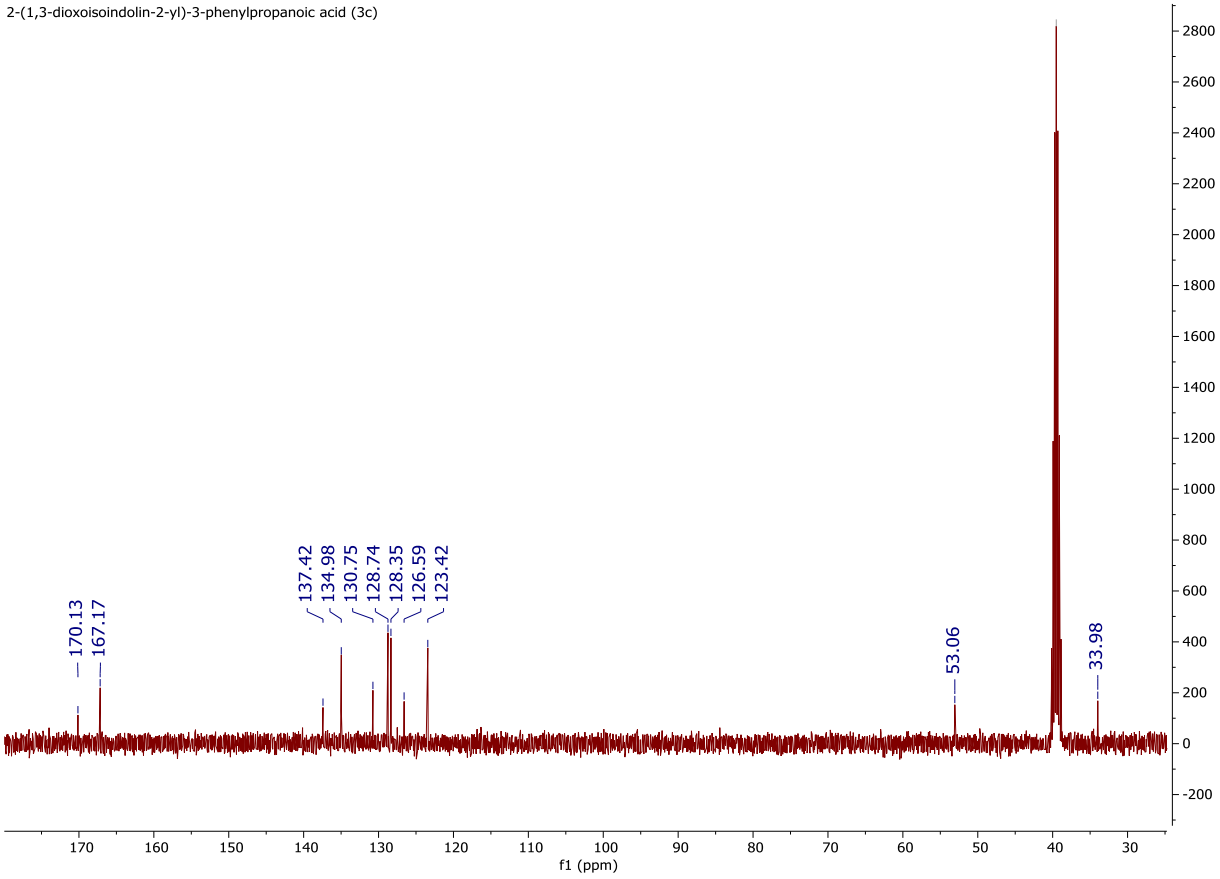

Figure S7. ^{13}C NMR spectrum of compound **3c**.

2-(Prop-2-yn-1-yl)isoindoline-1,3-dione (3d)

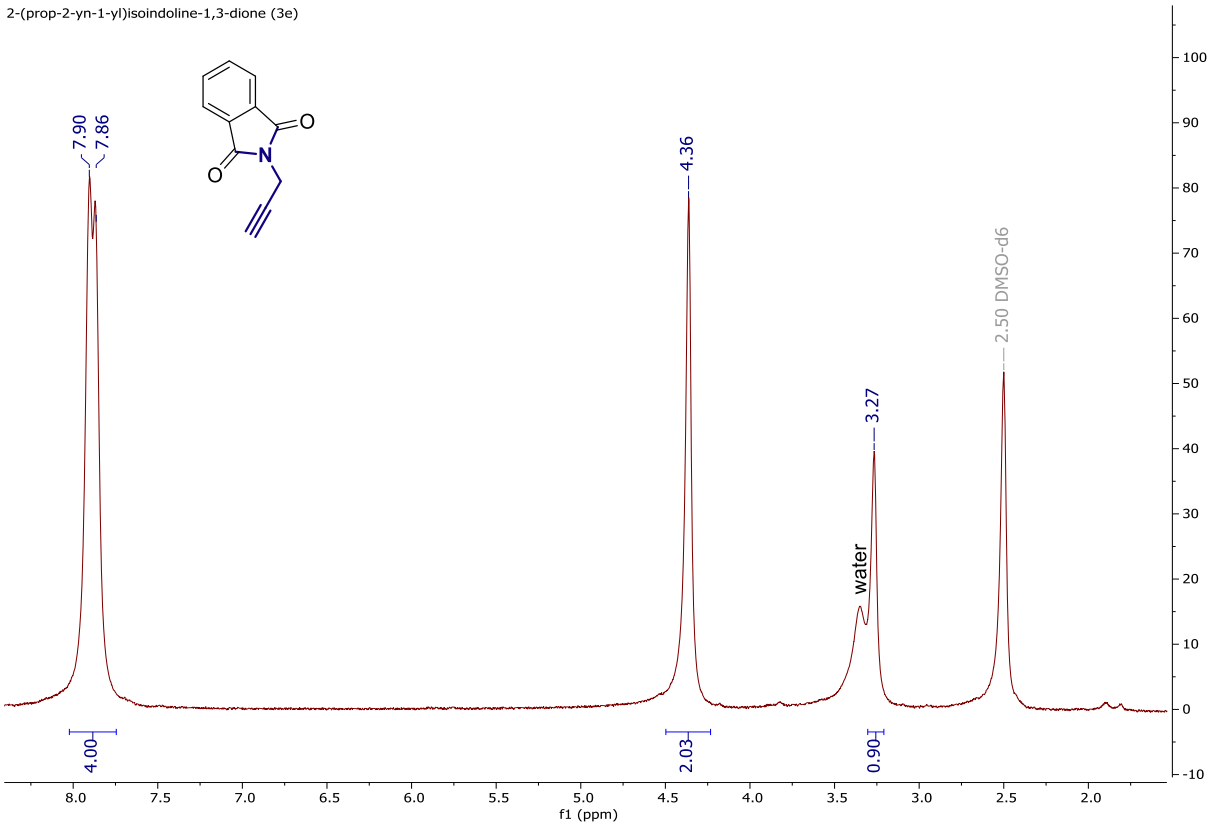

Figure S8. ^{1}H NMR spectrum of compound **3d**.

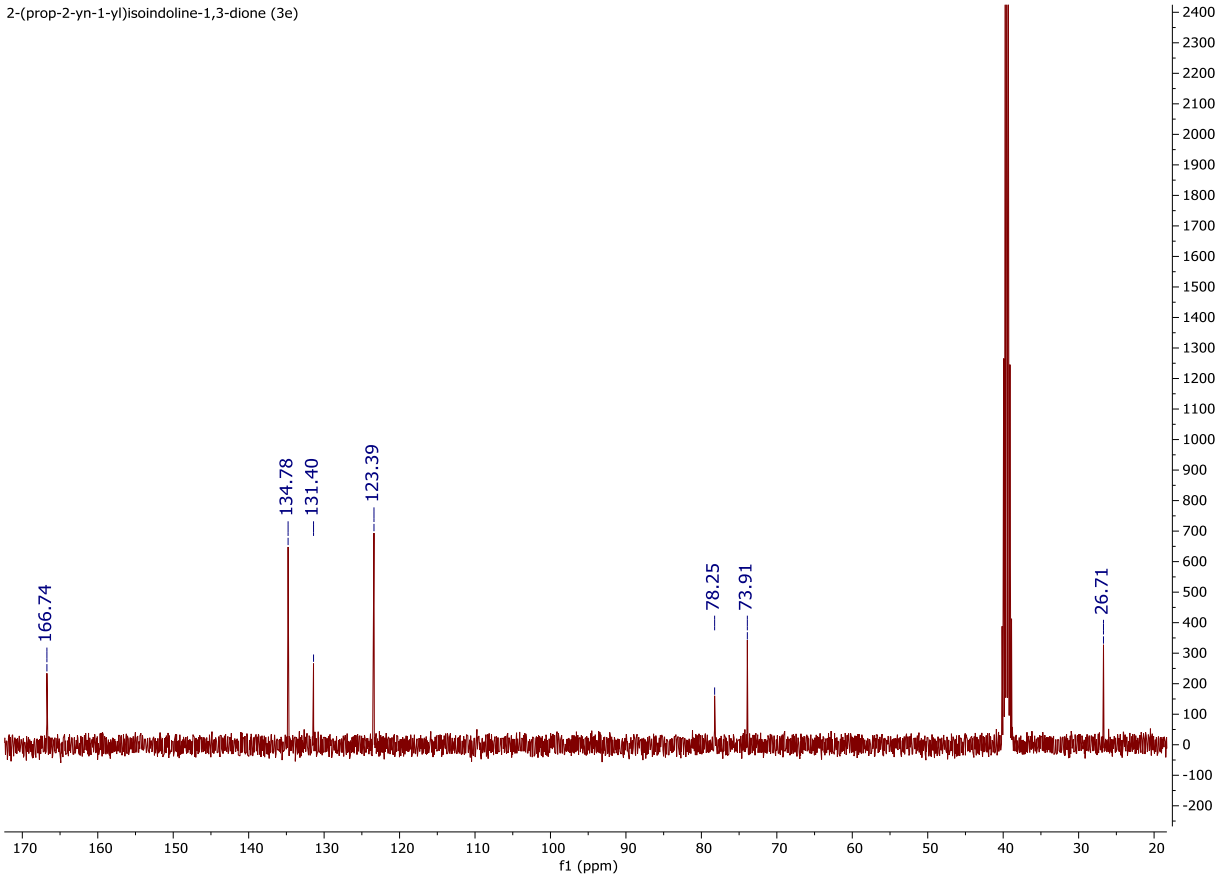

Figure S9. ^{13}C NMR spectrum of compound **3d**.

2-(4-Methoxyphenyl)isoindoline-1,3-dione (3e)

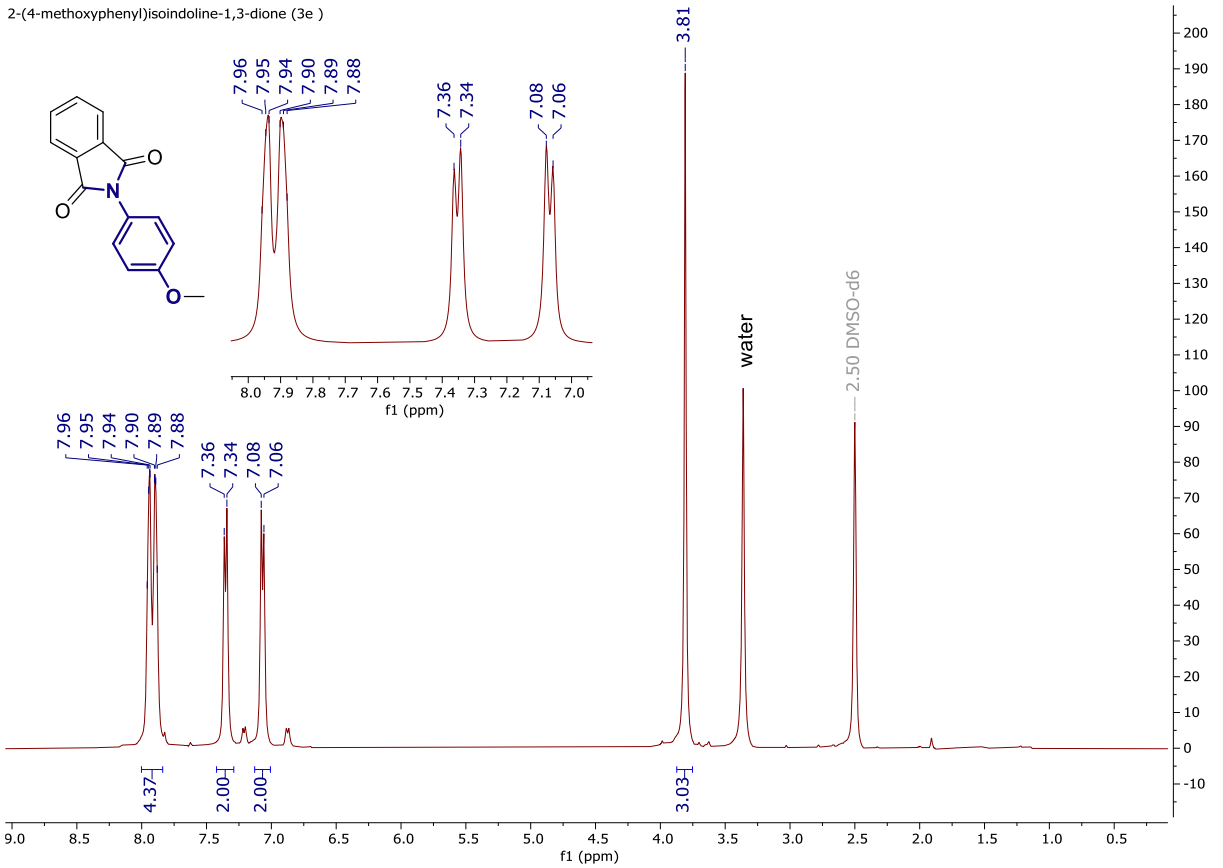

Figure S10. ^{1}H NMR spectrum of compound **3e**.

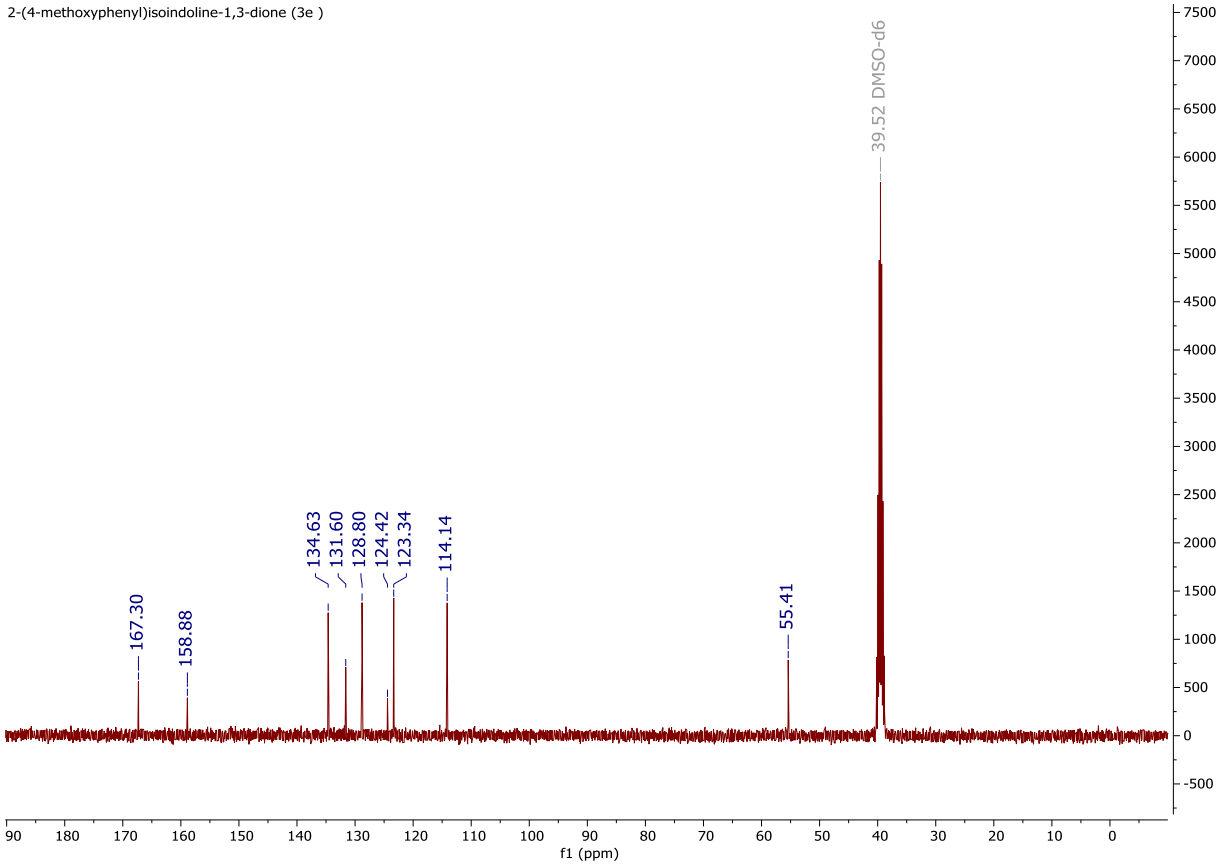

Figure S11. ^{13}C NMR spectrum of compound **3e**.

2-(4-Bromophenyl)isoindoline-1,3-dione (3f)

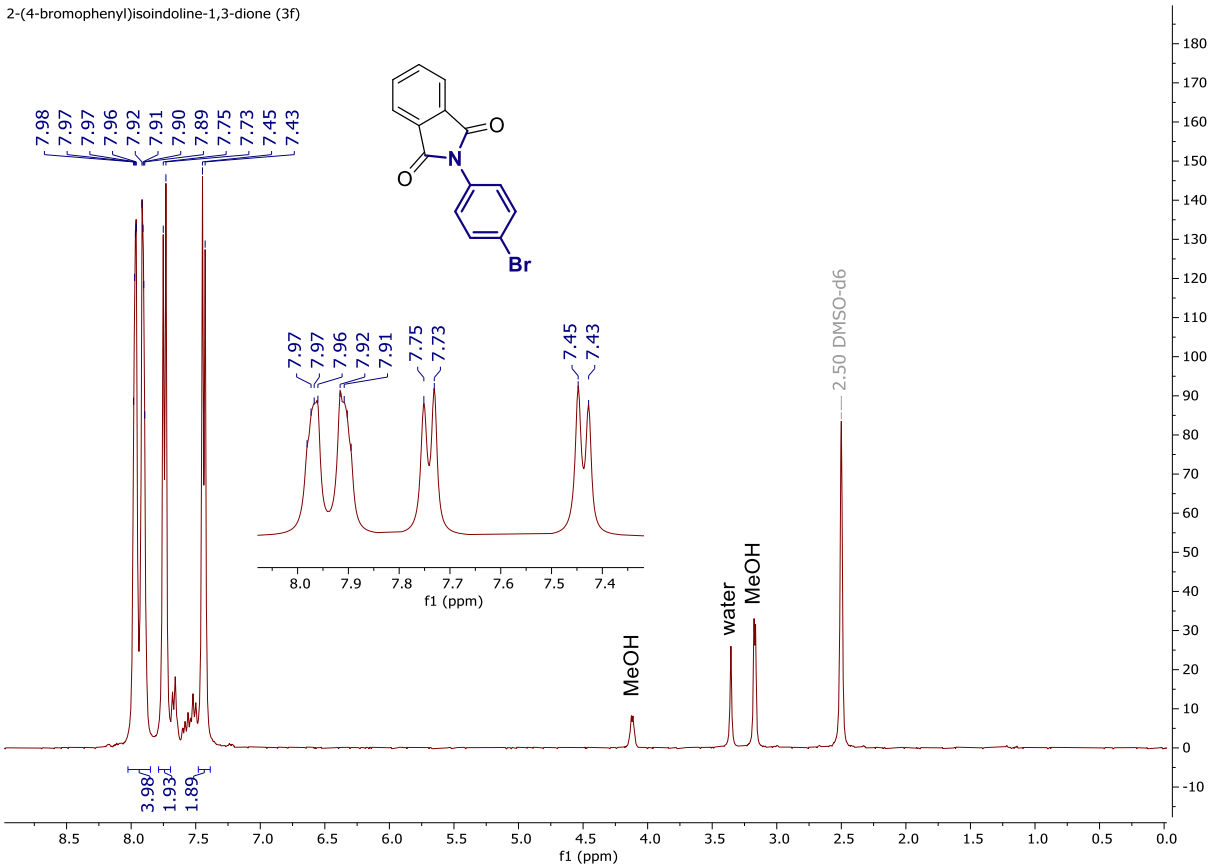

Figure S12. ^{1}H NMR spectrum of compound **3f**.

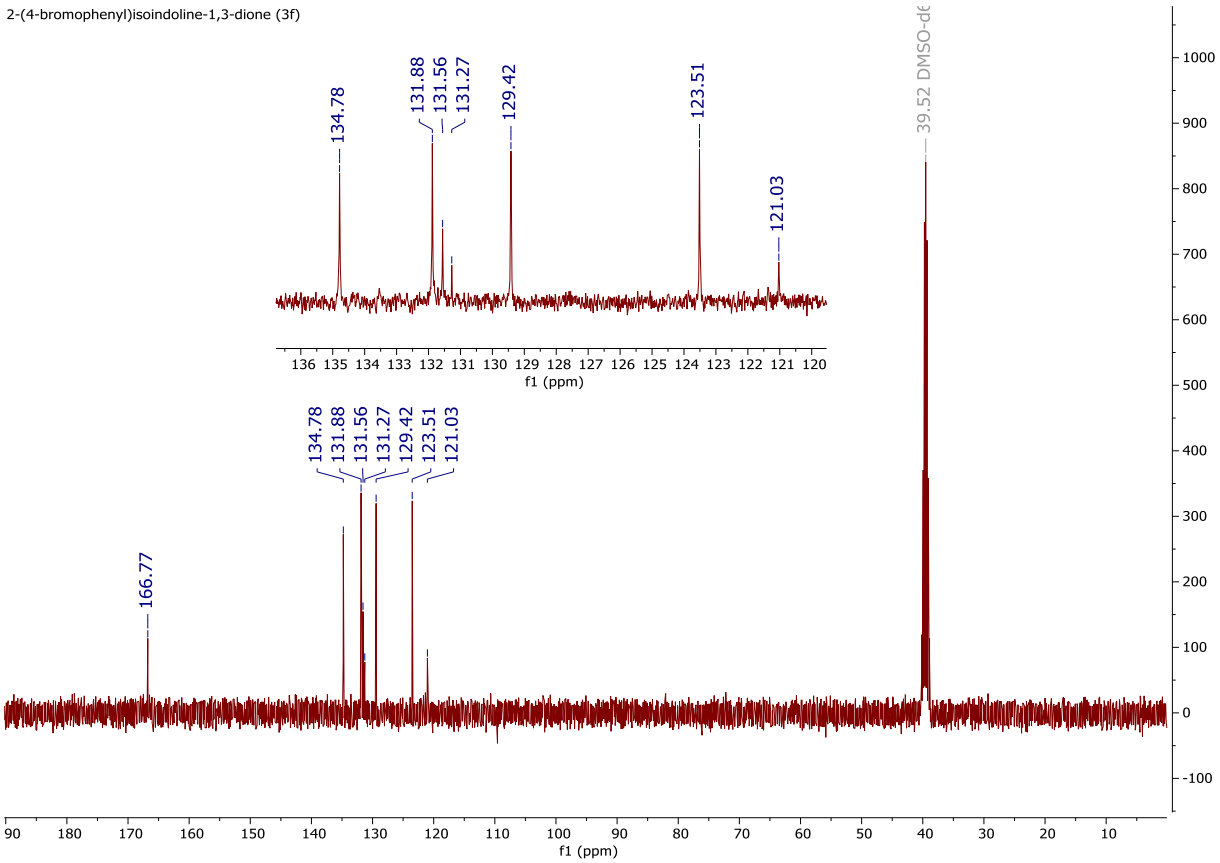

Figure S13. ^{13}C NMR spectrum of compound **3f**.

2-(4-Hydroxyphenyl)isoindoline-1,3-dione (3g)

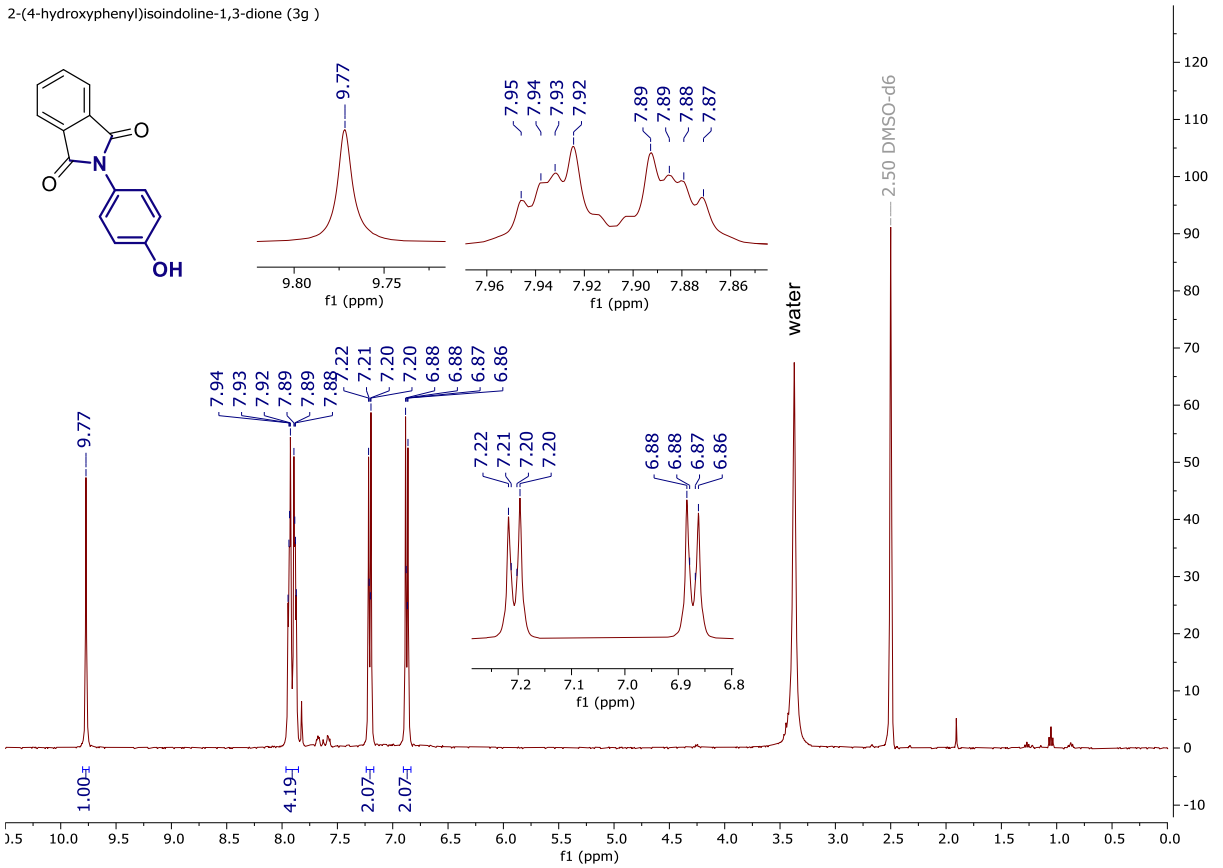

Figure S14. ^{1}H NMR spectrum of compound **3g**.

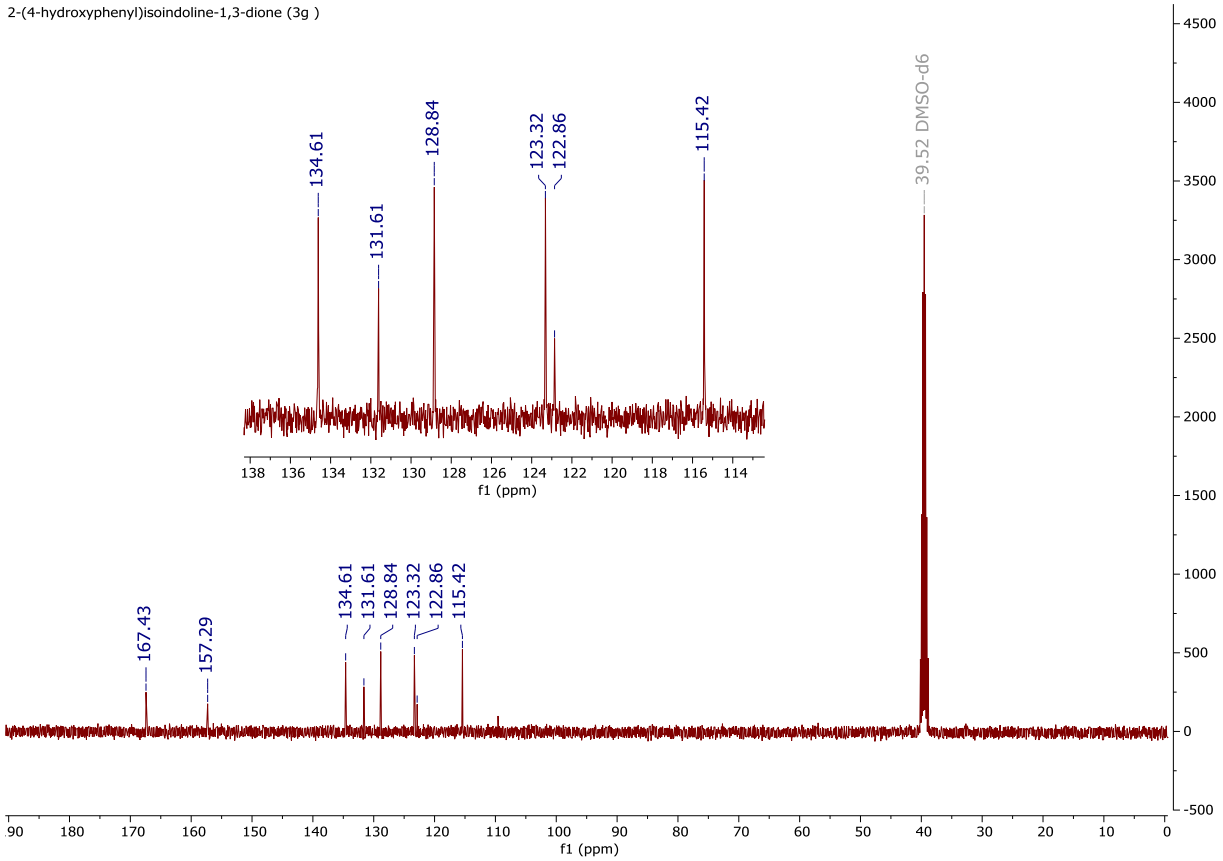

Figure S15. ^{13}C NMR spectrum of compound **3g**.

3-Methyl-2-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)butanoic acid (3h)

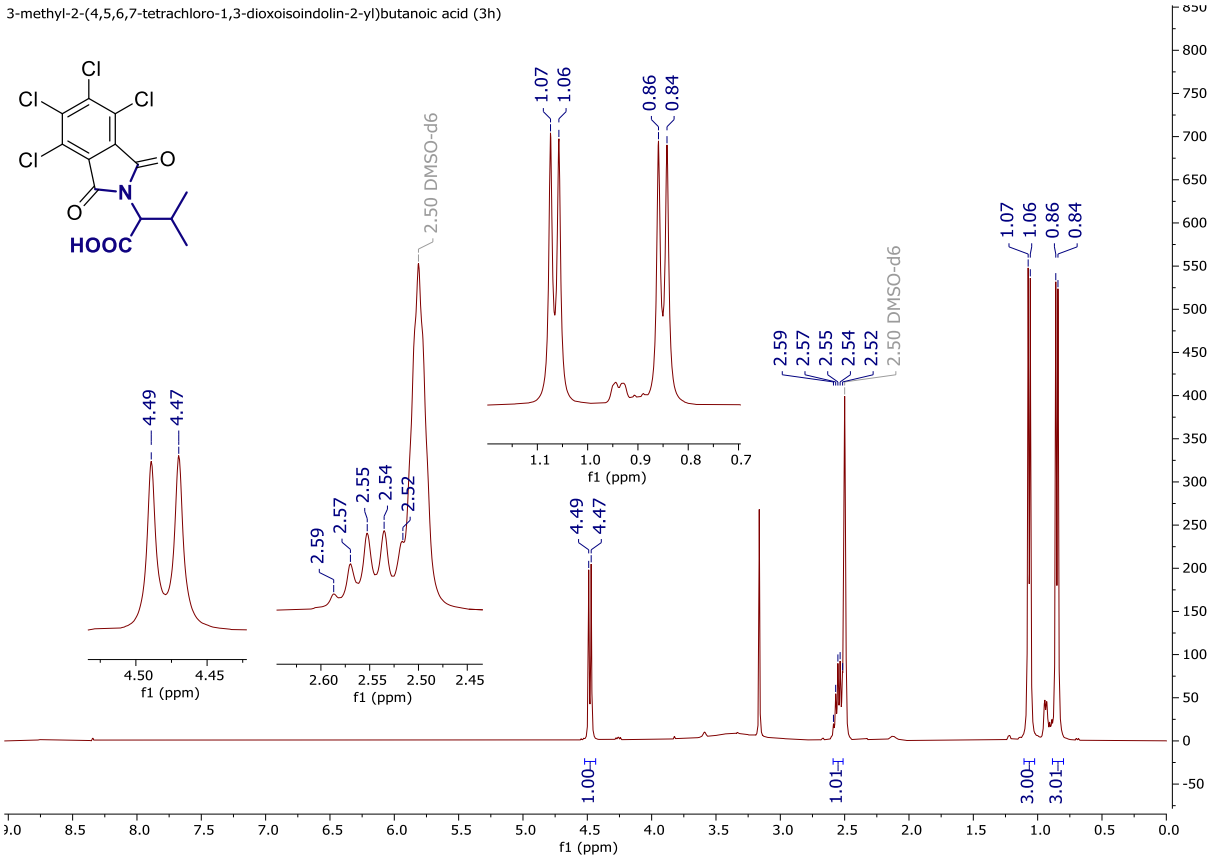

Figure S16. ^{1}H NMR spectrum of compound **3h**.

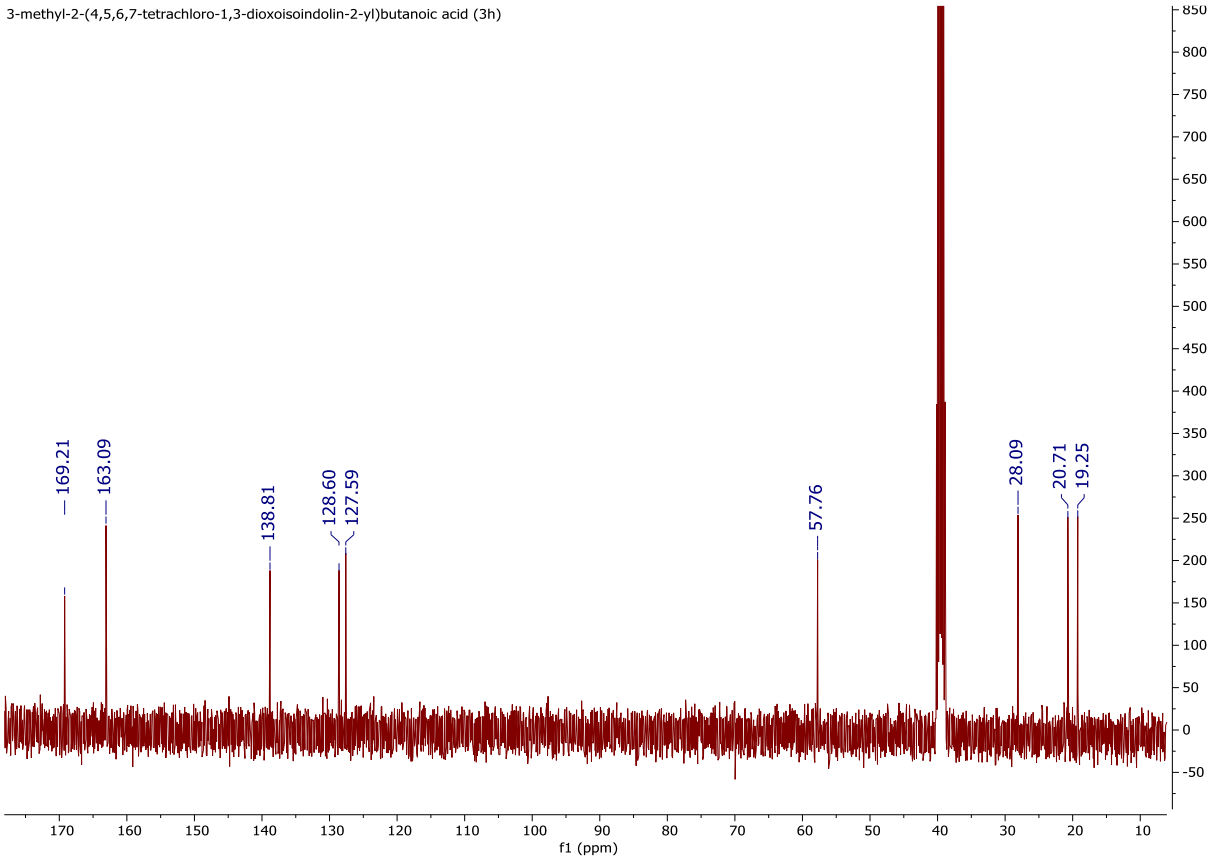

Figure S17. ^{13}C NMR spectrum of compound **3h**.

4,5,6,7-Tetrachloro-2-(prop-2-yn-1-yl)isoindoline-1,3-dione (3i)

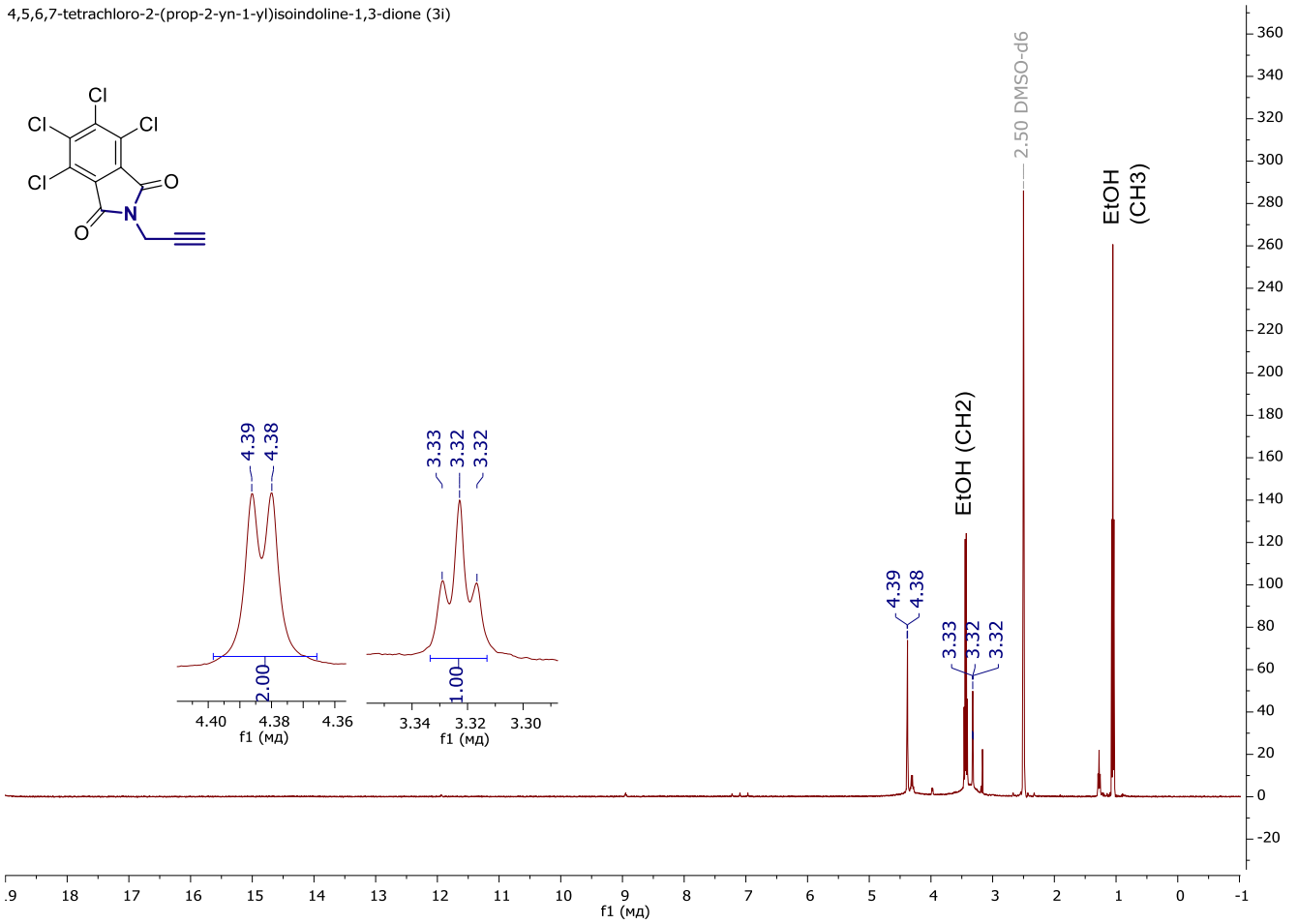

Figure S18. ^{1}H NMR spectrum of compound **3i**.

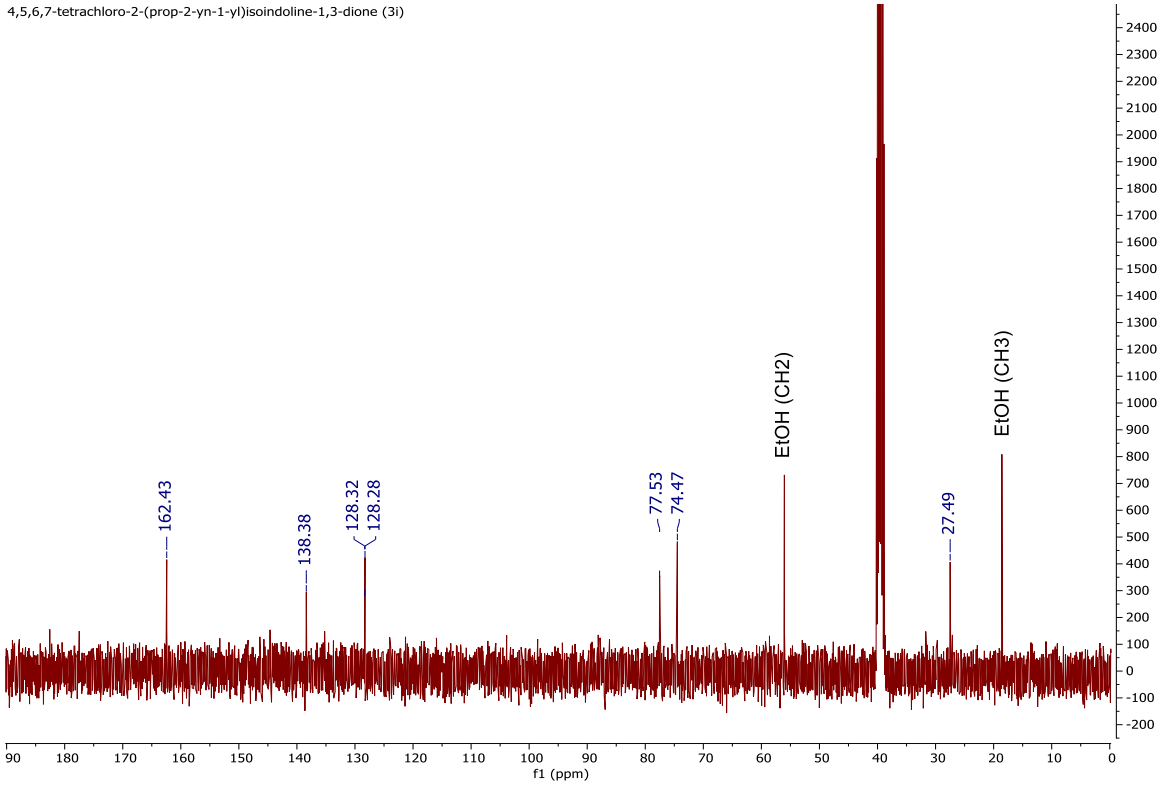

Figure S19. ^{13}C NMR spectrum of compound **3i**.

2,2'-(1,3,5,7-Tetraoxo-5,7-dihydropyrrolo[3,4-*f*]isoindole-2,6(1*H*,3*H*)-diyl)bis(3-methylbutanoic acid) (5)

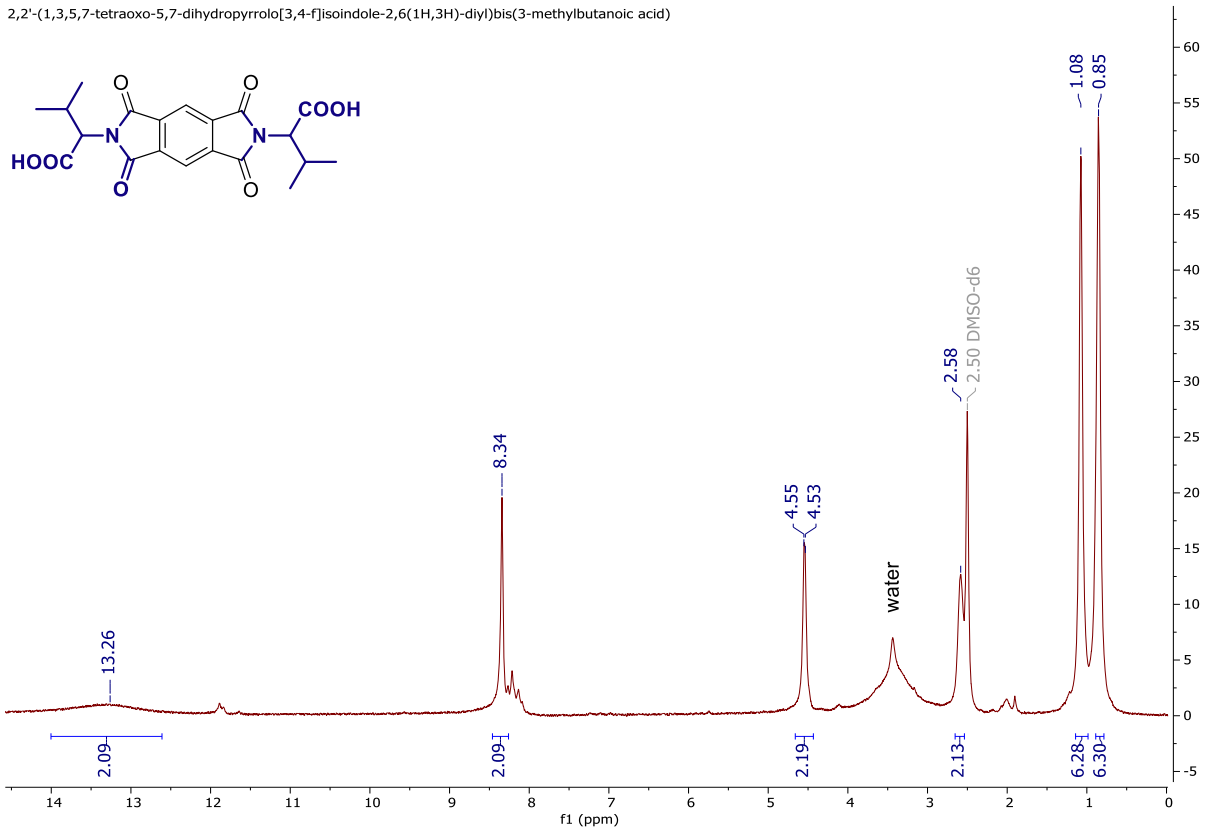

Figure S20. ^{1}H NMR spectrum of compound **5**.

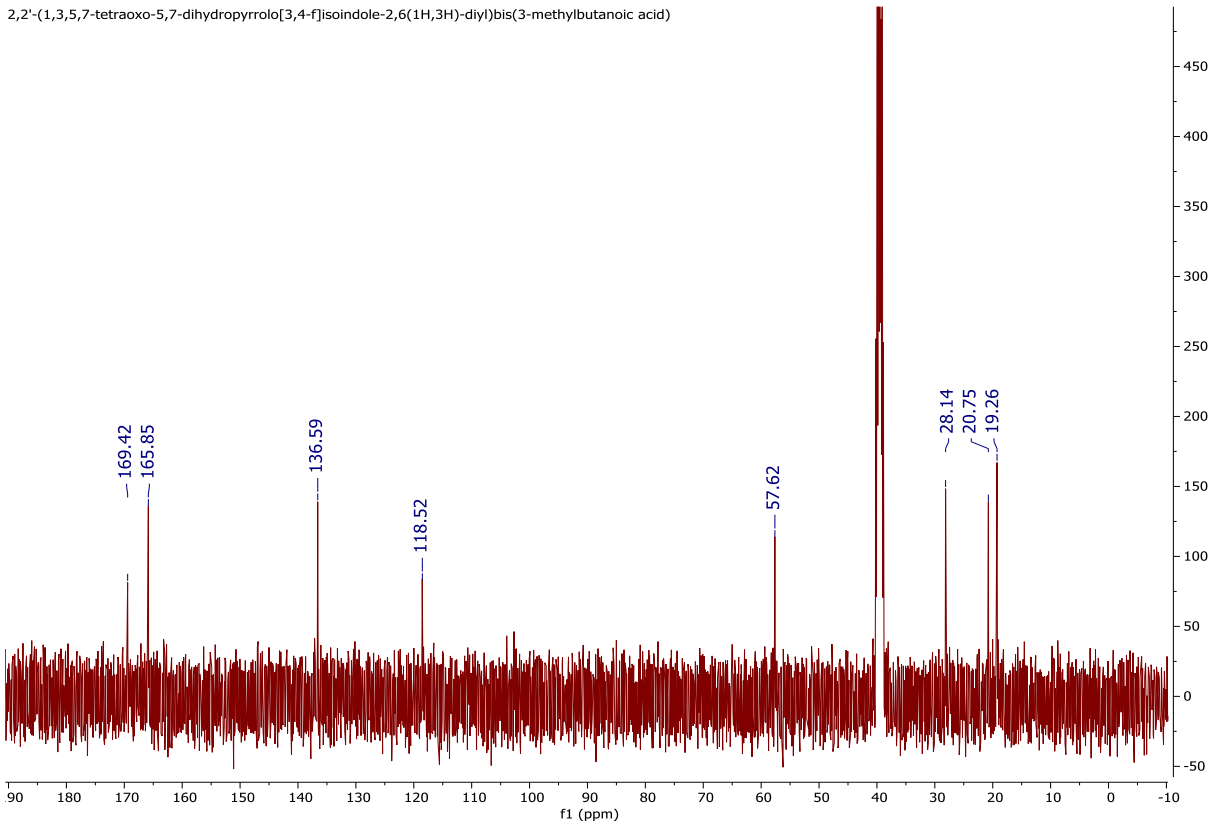

Figure S21. ^{13}C NMR spectrum of compound **5**.