

Design, Synthesis and Exploration of Cyclic Imides as PDE4 Inhibitors in Psoriasis

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Molecular Docking Studies

Molecular docking studies of three selected molecules were performed with both PDE4B and PDE4D. The targets used were PDE4B (3W5E, 3KKT, 3HMV, 4MYQ), PDE4D (3G58, 6BOJ, 6NJH). The RMSD values for the corresponding native ligands were estimated by redocking them against the prepared proteins. The resolution coordinates of site sphere RMSD values are recorded in **Table S1**.

Table S1. Key metrics for the proteins of interest; PDB ID, resolution (Å), site sphere coordinates, radius and RMSD

PDB ID	Subtype	Resolution (Å)	Site sphere	Radius	RMSD
3W5E	PDE4B	2.30	24.56, 17.94, -18.98	8.18	0.45- 0.96
3KKT	PDE4B	2.48	35.55, -8.22, -34.10	6.79	0.63-0.1.00
3HMV	PDE4B	2.23	-12.69, -28.65,-6.67	7.93	0.24-0.59
3G58	PDE4D	2.05	21.82, -4.95, 31.99	7.88	0.24-1.94
6BOJ	PDE4D	1.70	3.42, -13.13, 49.44	7.49	0.19-1.44
6NJH	PDE4D	2.15	3.68, -13.20, 49.67	7.59	0.61-2.96
4MYQ	PDE4B	1.90	-15.80, 33.67,-6.86	6.65	0.36-0.98

NMR spectra of cyclic imide derivatives

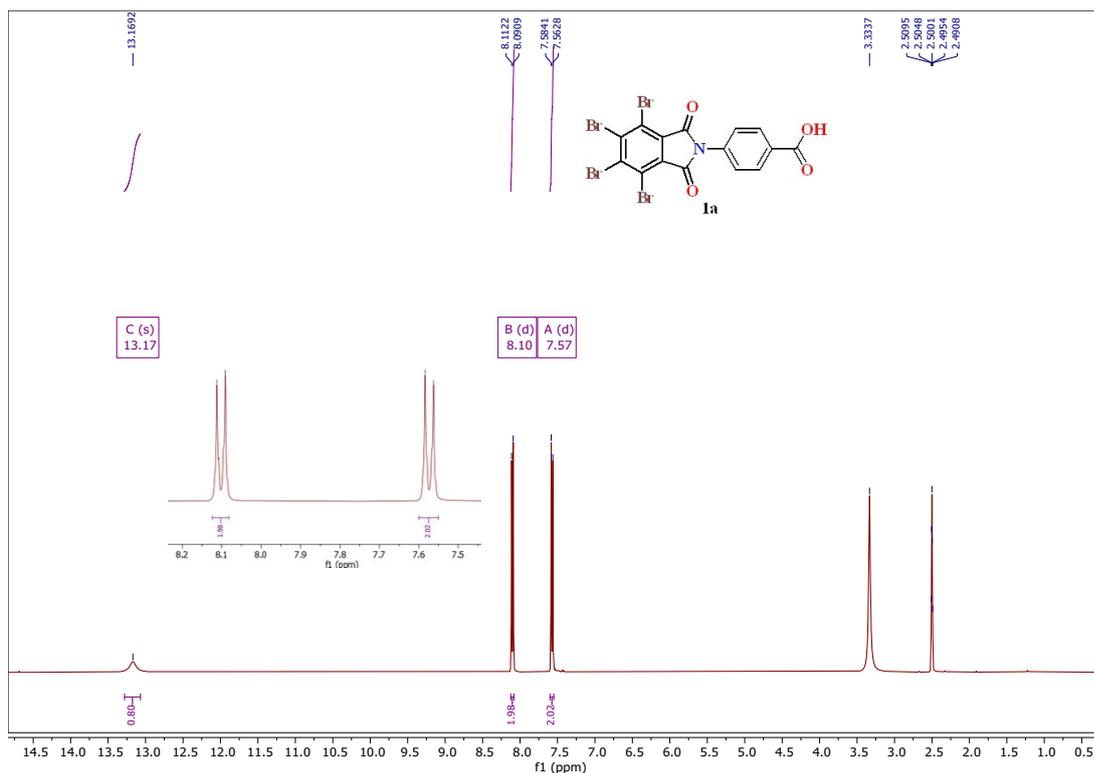


Figure S1: ^1H NMR spectrum of 4-(4,5,6,7-tetrabromo-1,3-dioxisoindolin-2-yl)benzoic acid (**1a**).

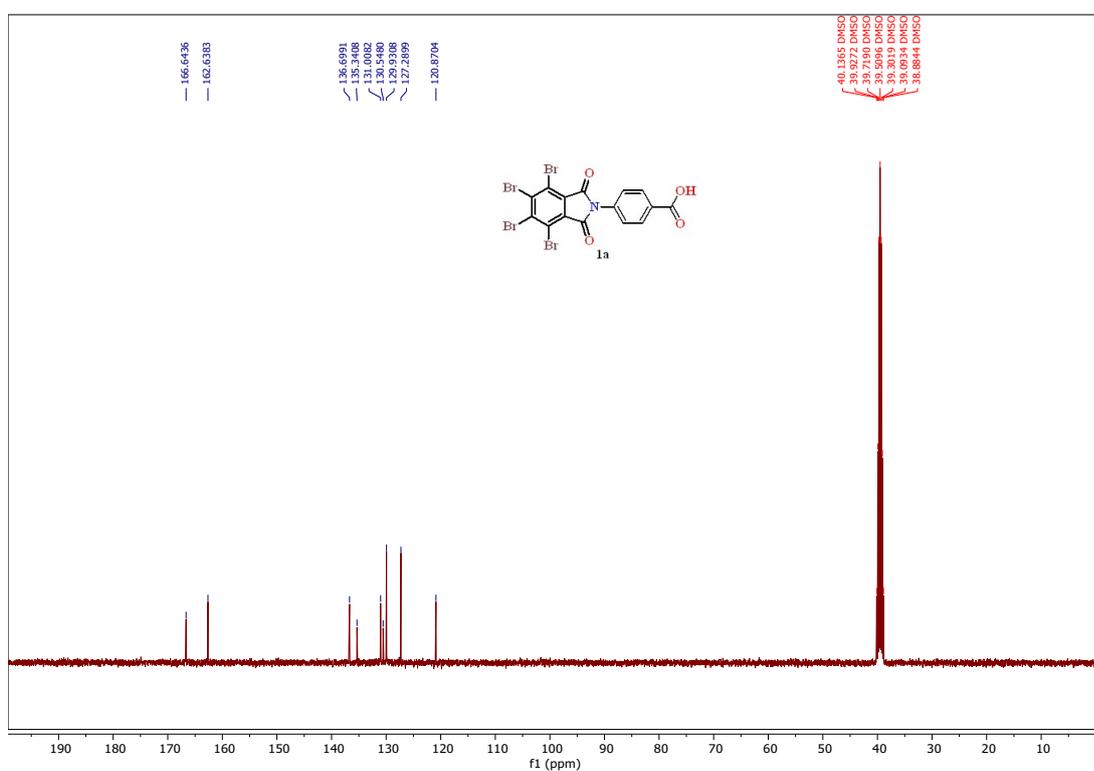


Figure S2: ^{13}C NMR spectrum of 4-(4,5,6,7-tetrabromo-1,3-dioxisoindolin-2-yl)benzoic acid (**1a**).

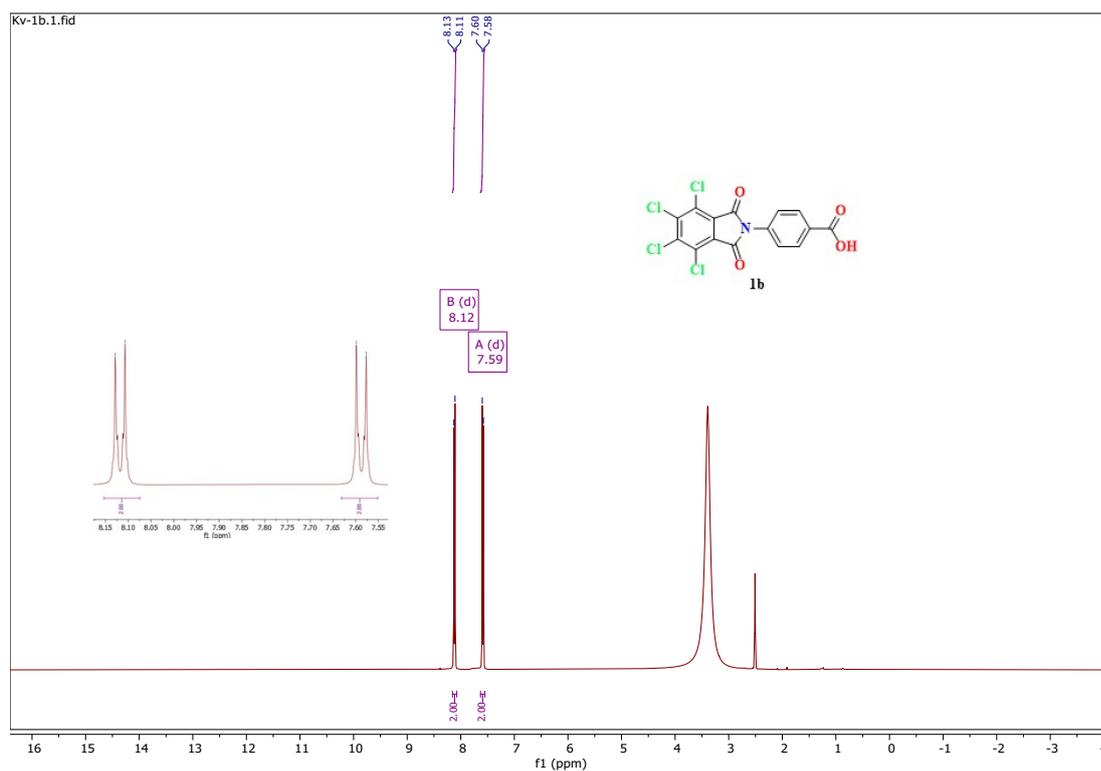


Figure S3: ^1H NMR spectrum of 4-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)benzoic acid (**1b**).

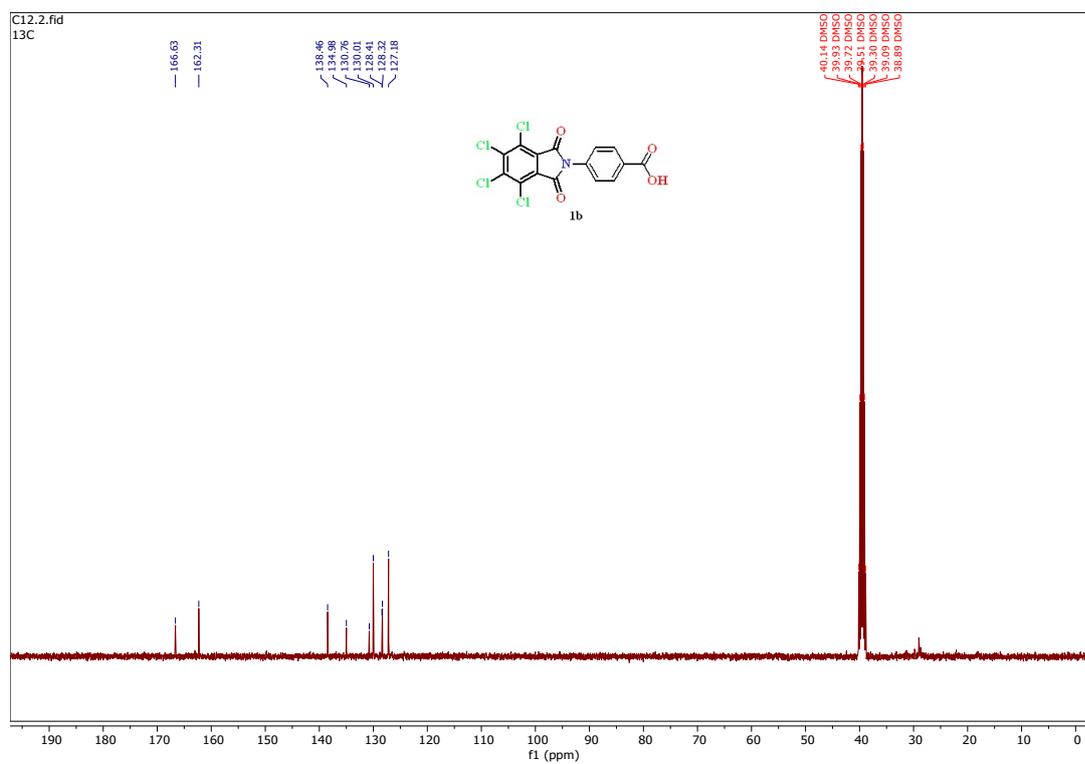


Figure S4: ^{13}C NMR spectrum of 4-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)benzoic acid (**1b**).

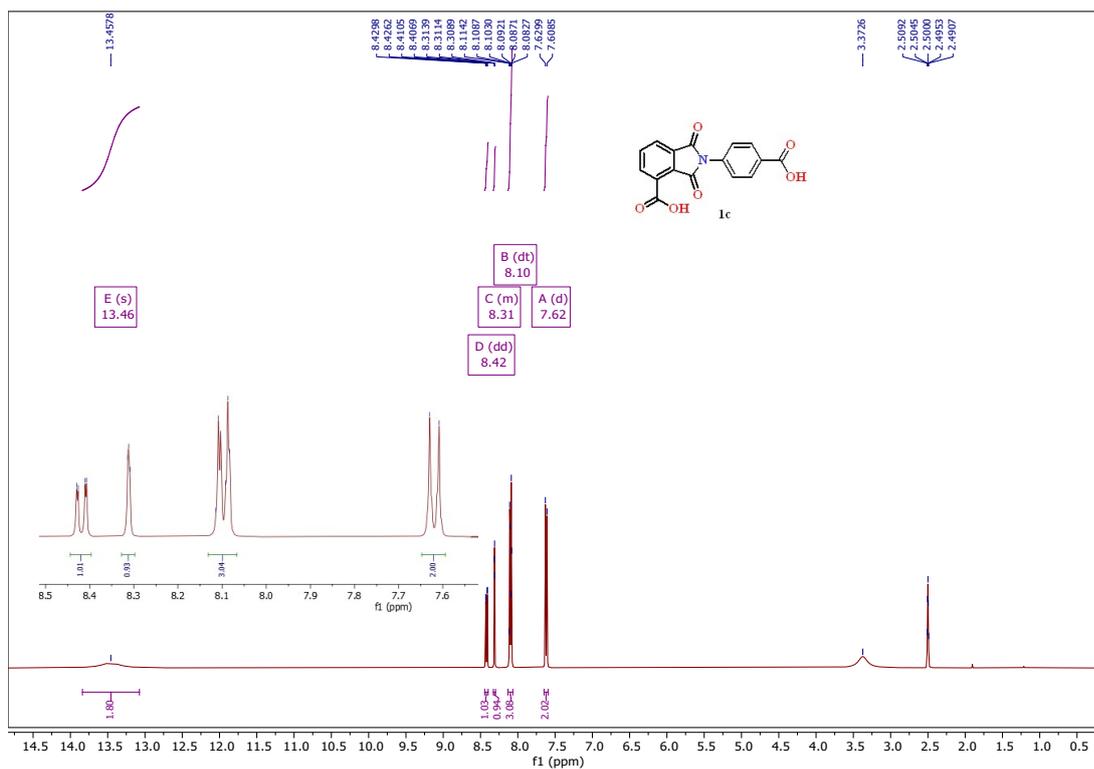


Figure S5: ¹H NMR spectrum of 2-(4-carboxyphenyl)-1,3-dioxisoindoline-4-carboxylic acid (1c).

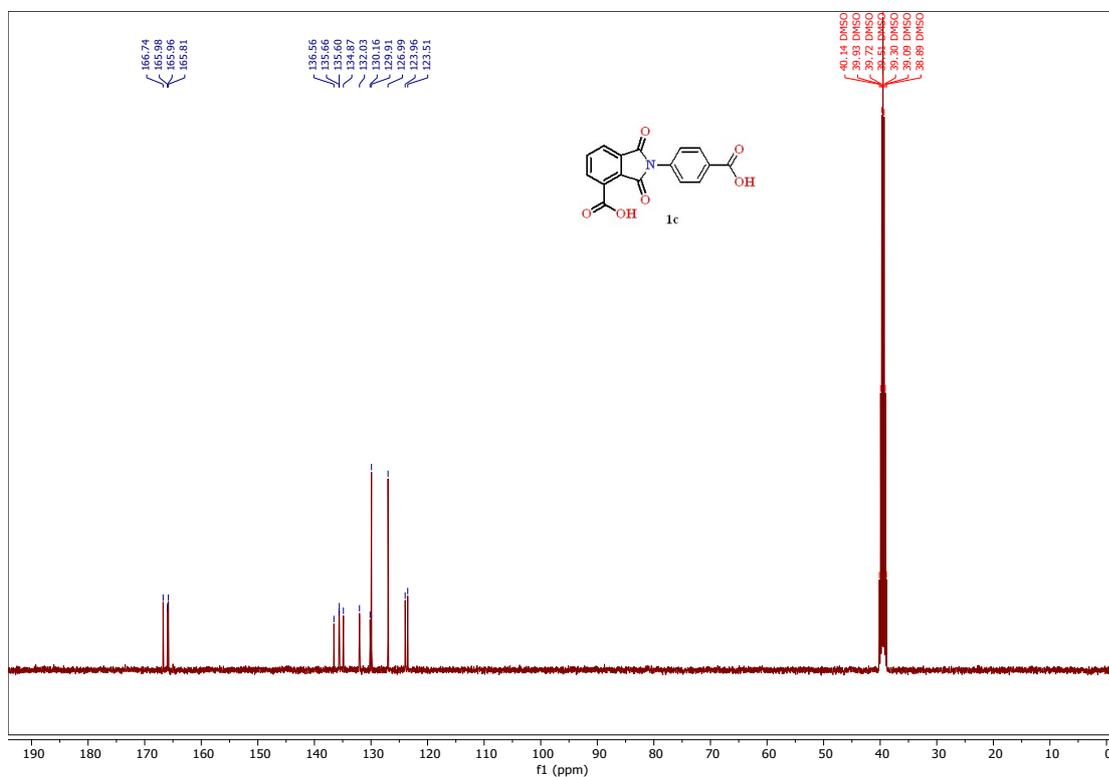


Figure S6: ¹³C NMR spectrum of 2-(4-carboxyphenyl)-1,3-dioxisoindoline-4-carboxylic acid (1c).

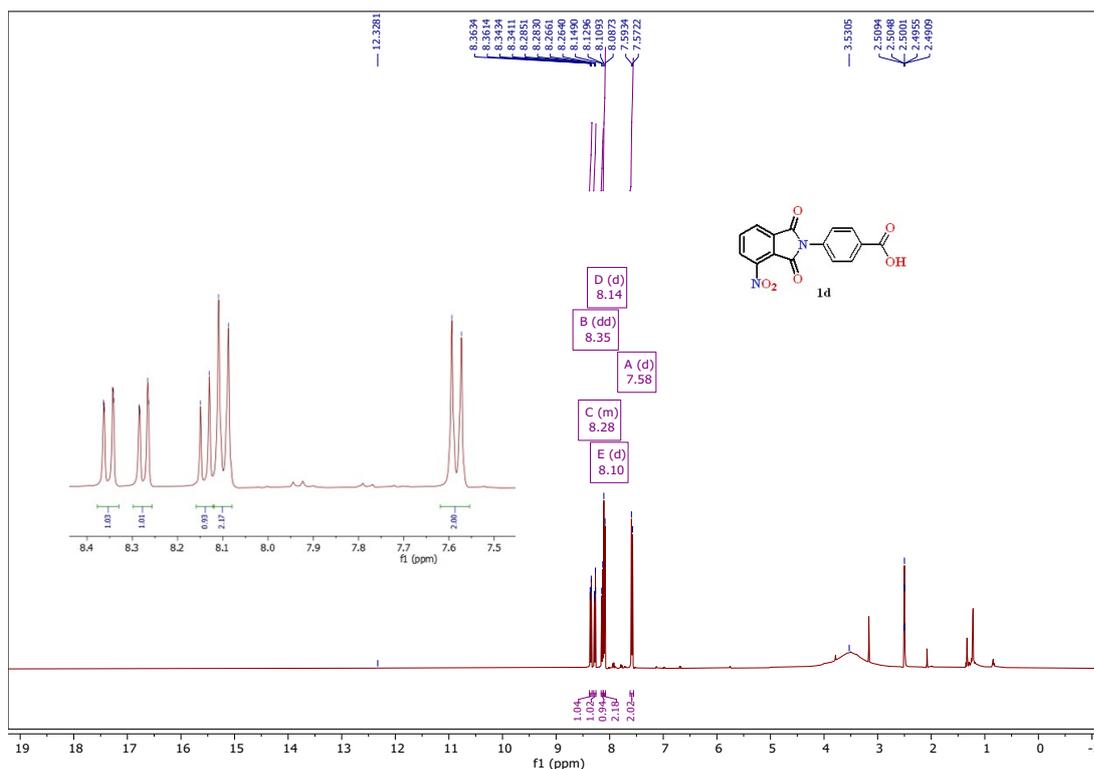


Figure S7: ¹H NMR spectrum of 4-(4-nitro-1,3-dioxisoindolin-2-yl)benzoic acid (1d).

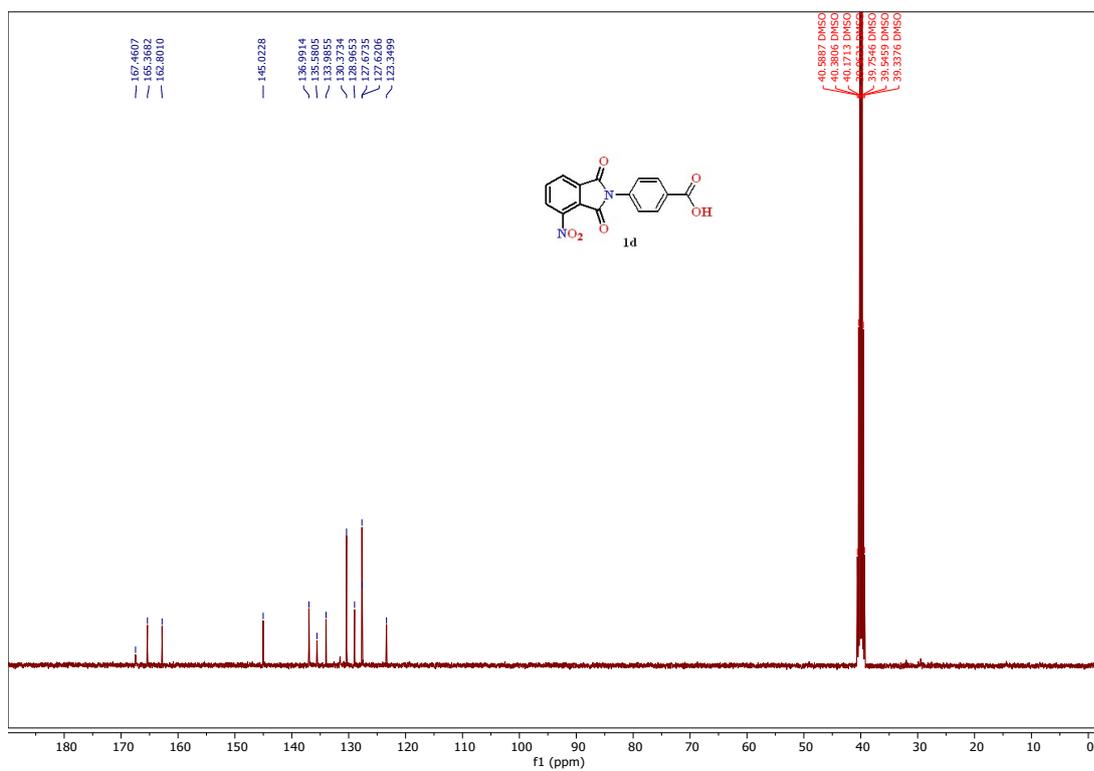


Figure S8: ¹³C NMR spectrum of 4-(4-nitro-1,3-dioxisoindolin-2-yl)benzoic acid (1d).

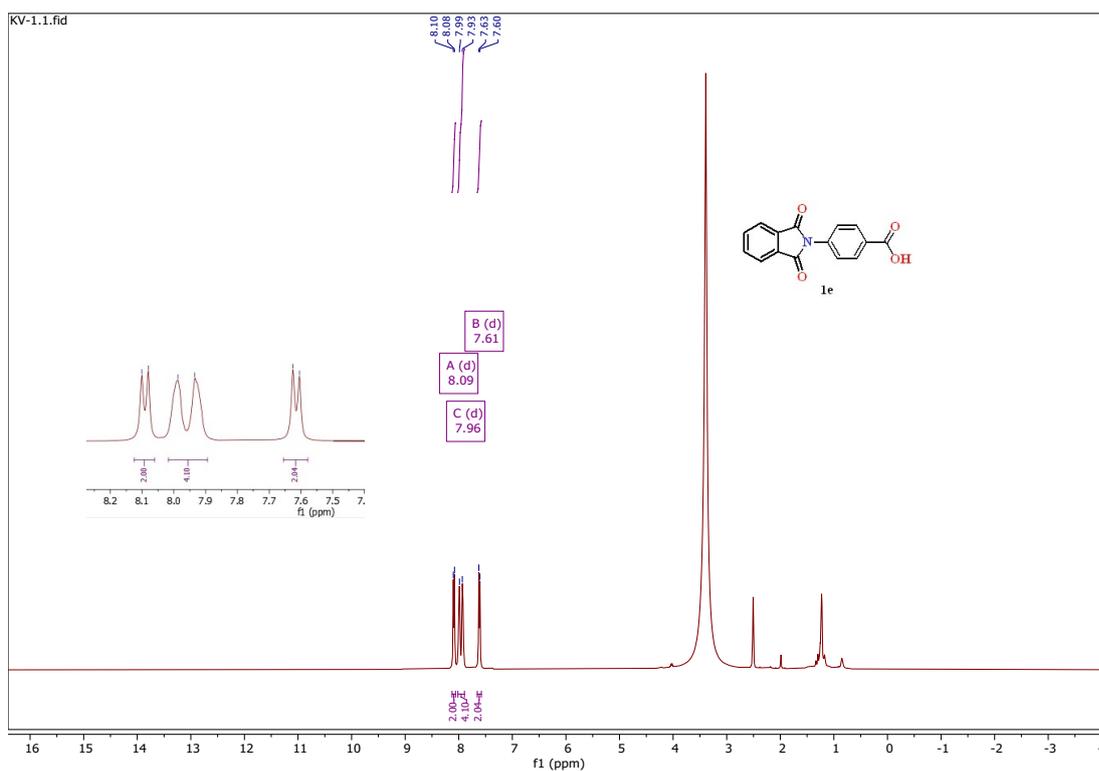


Figure S9: ^1H NMR spectrum of 4-(1,3-dioxisoindolin-2-yl)benzoic acid (**1e**).

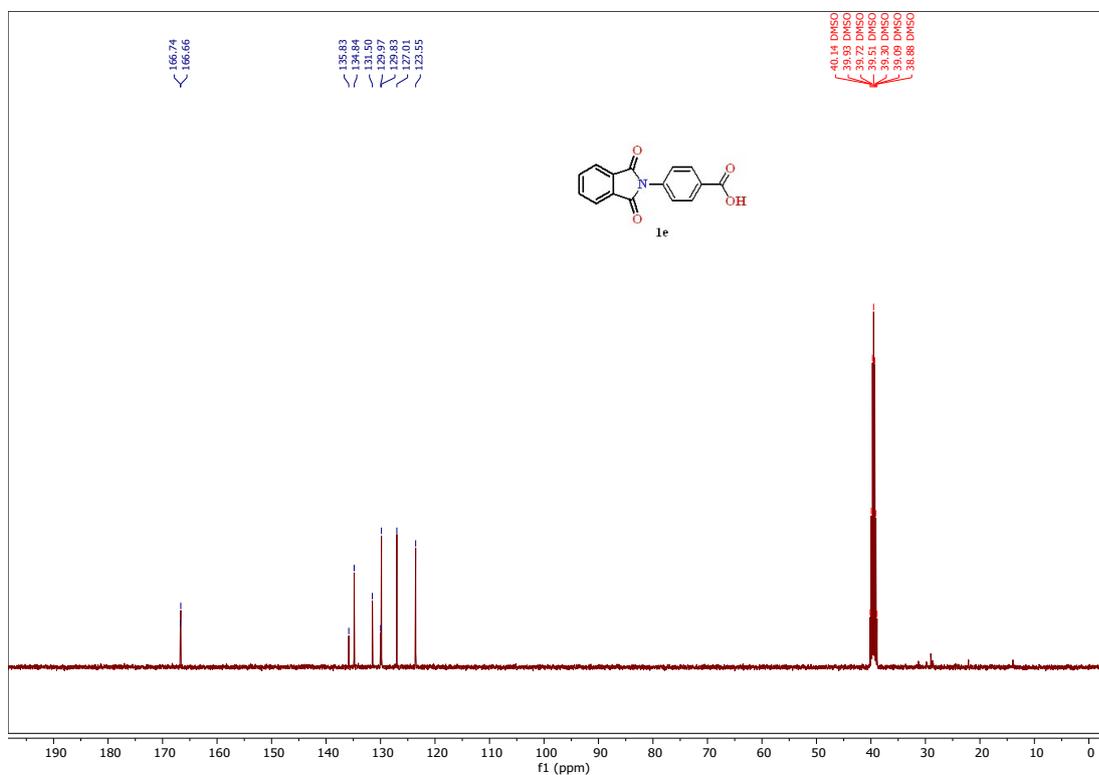


Figure S10: ^{13}C NMR spectrum of 4-(1,3-dioxisoindolin-2-yl)benzoic acid (**1e**).

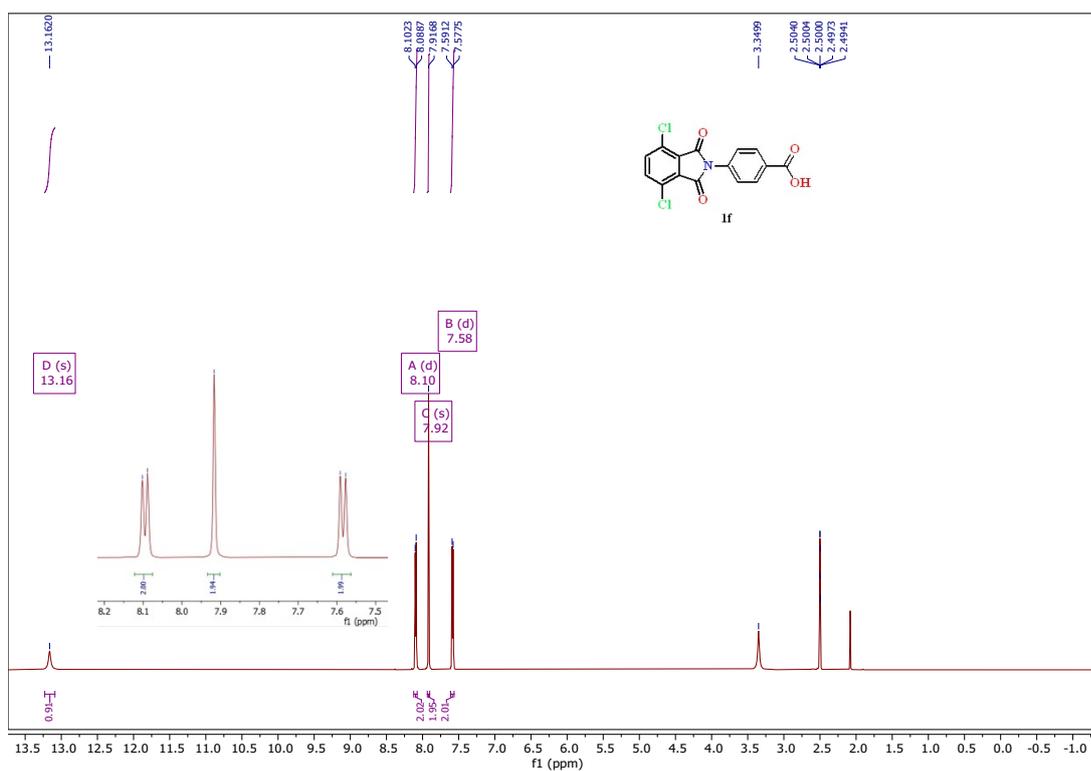


Figure S11: ^1H NMR spectrum of 4-(4,7-dichloro-1,3-dioxisoindolin-2-yl)benzoic acid (**1f**).

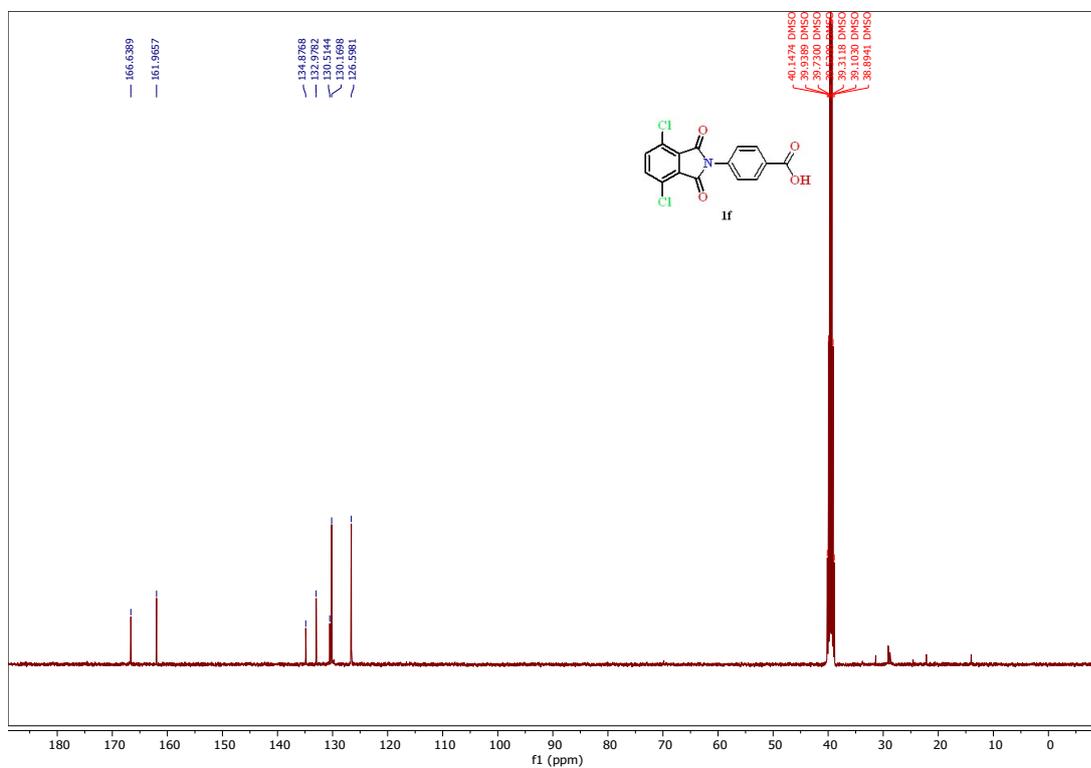


Figure S12: ^{13}C NMR spectrum of 4-(4,7-dichloro-1,3-dioxisoindolin-2-yl)benzoic acid (**1f**).

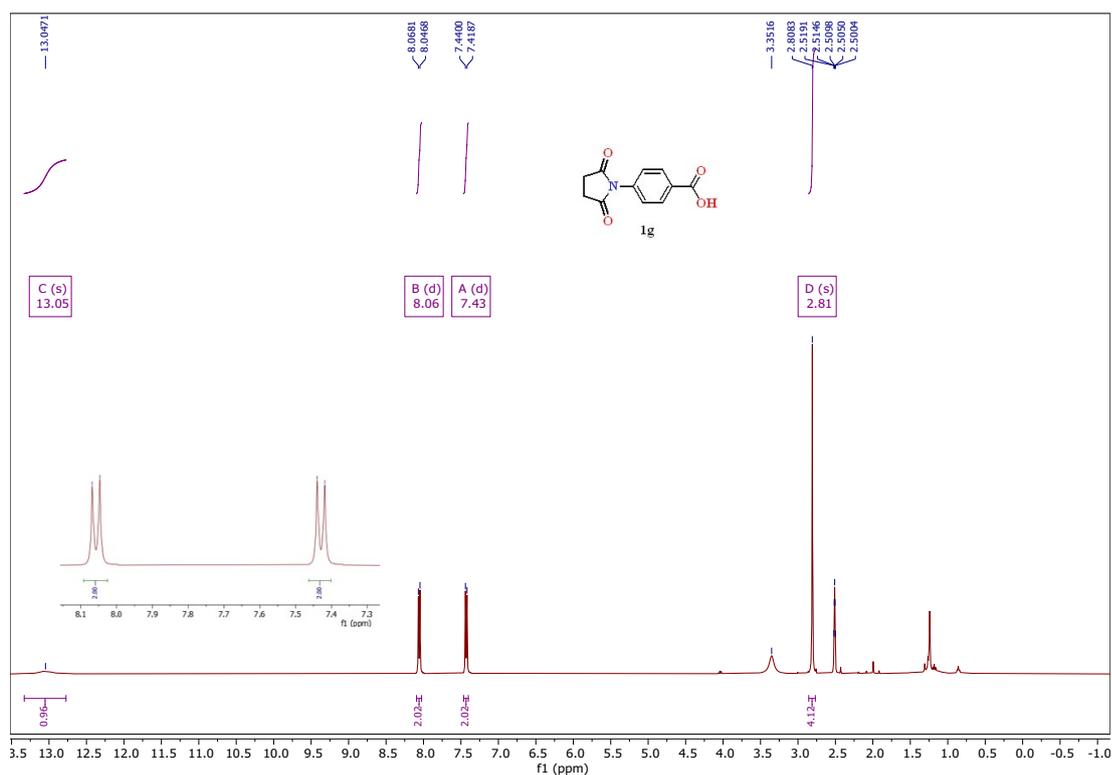


Figure S13: ¹H NMR spectrum of 4-(2,5-dioxopyrrolidin-1-yl)benzoic acid (**1g**).

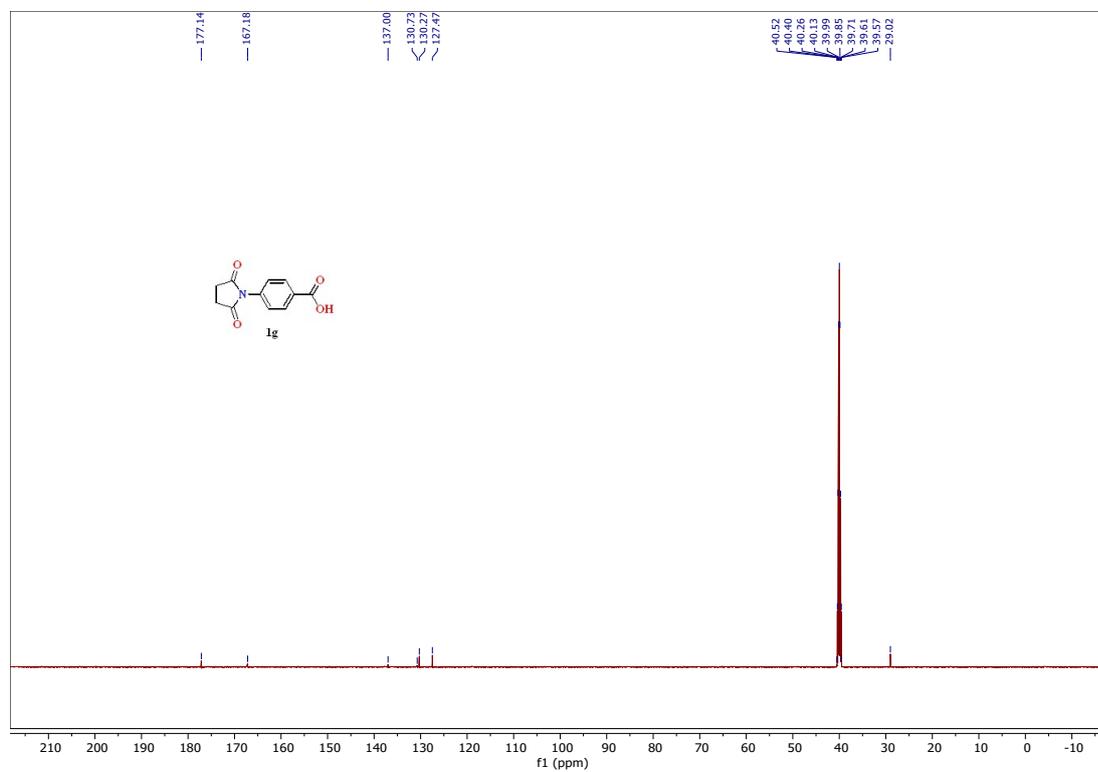


Figure S14: ¹³C NMR spectrum of 4-(2,5-dioxopyrrolidin-1-yl)benzoic acid (**1g**).

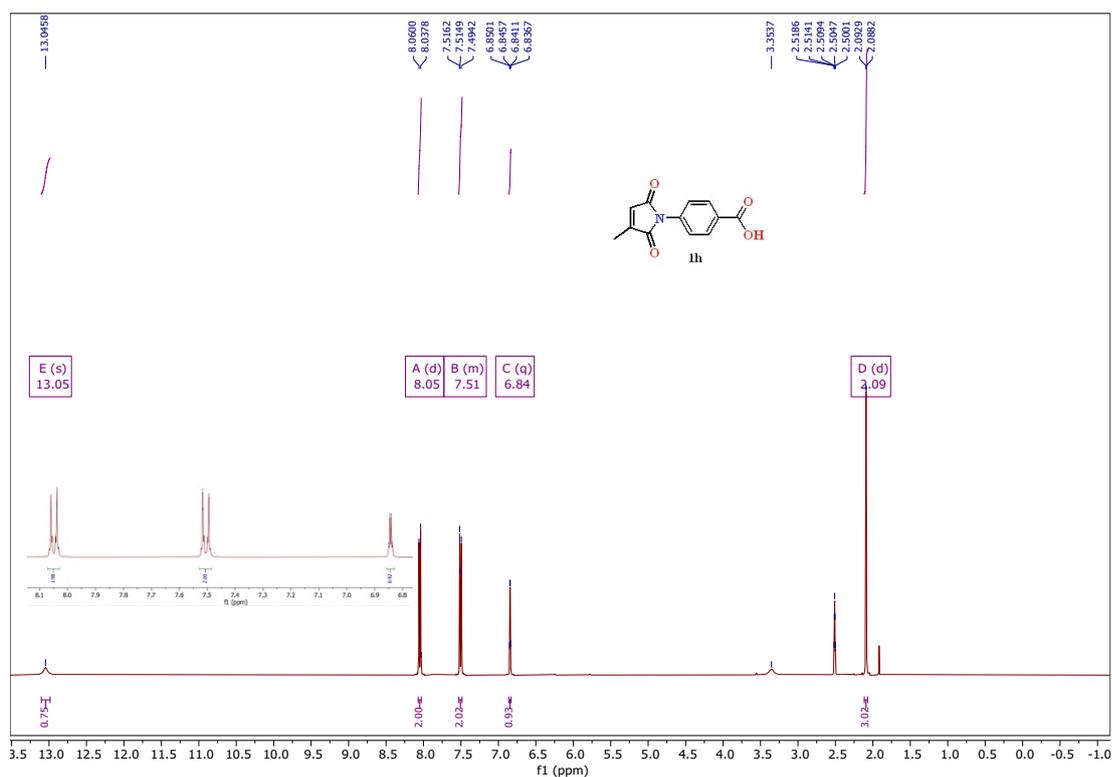


Figure S15: ¹H NMR spectrum of 4-(3-methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic acid (**1h**).

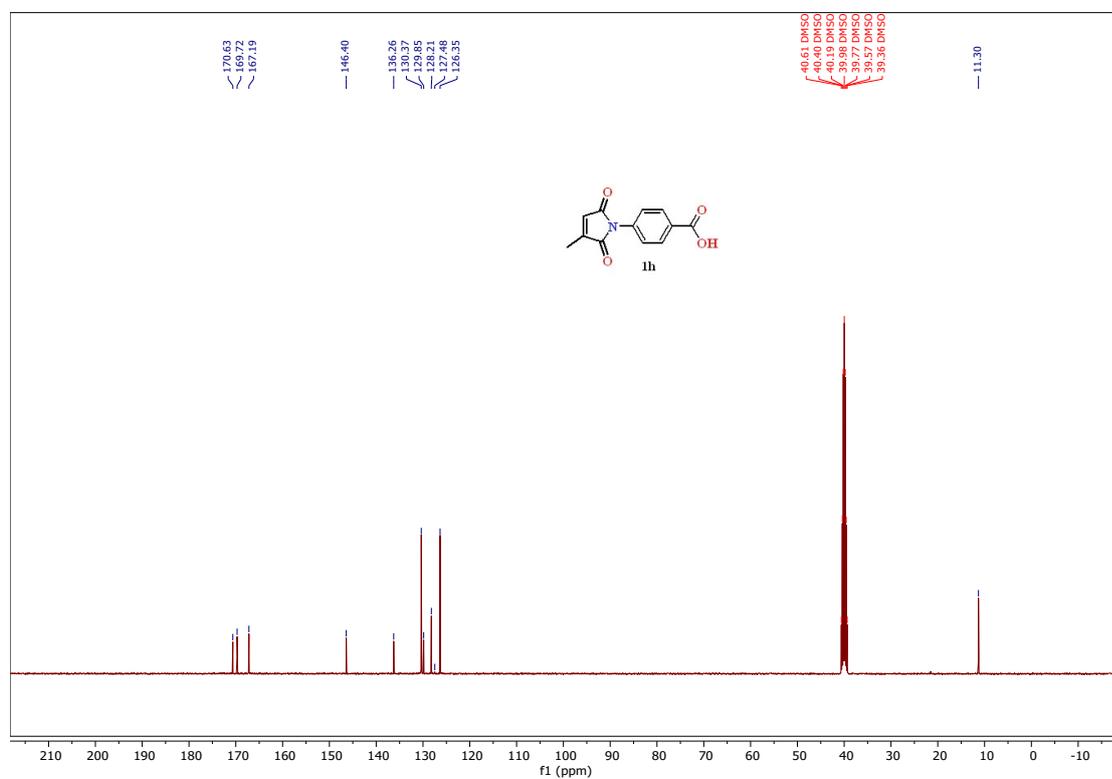


Figure S16: ¹³C NMR spectrum of 4-(3-methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic acid (**1h**).

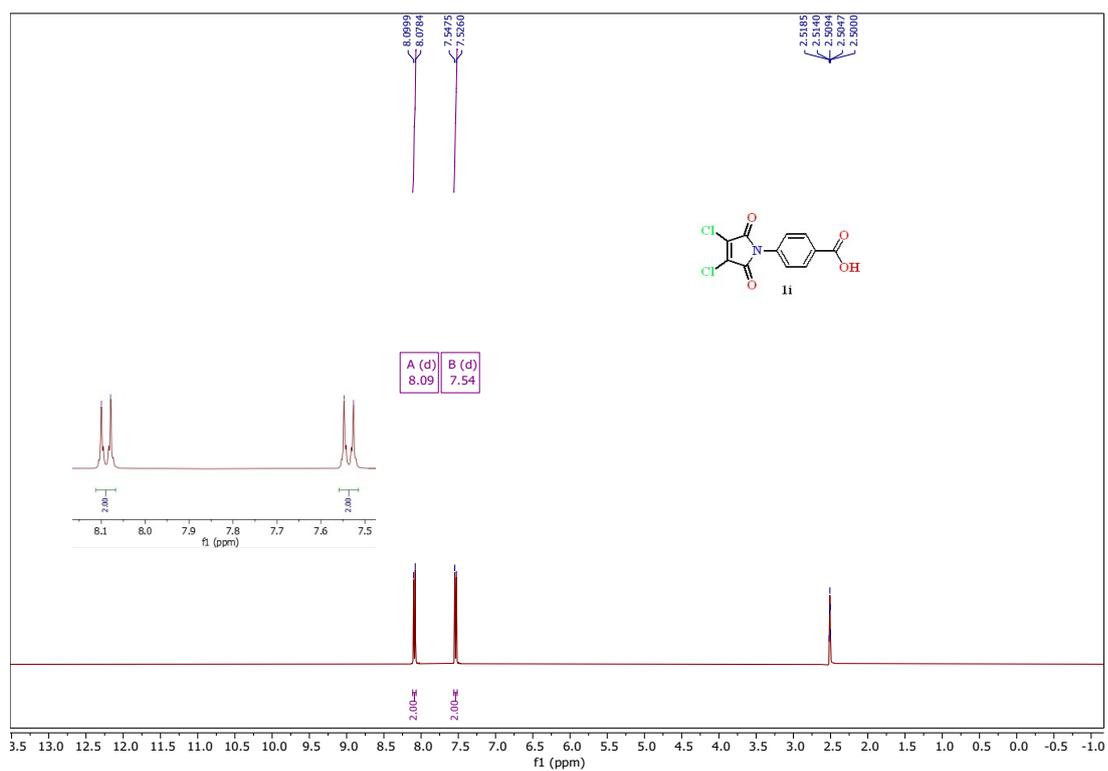


Figure S17: ¹H NMR spectrum of 4-(3,4-dichloro-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic acid (**1i**).

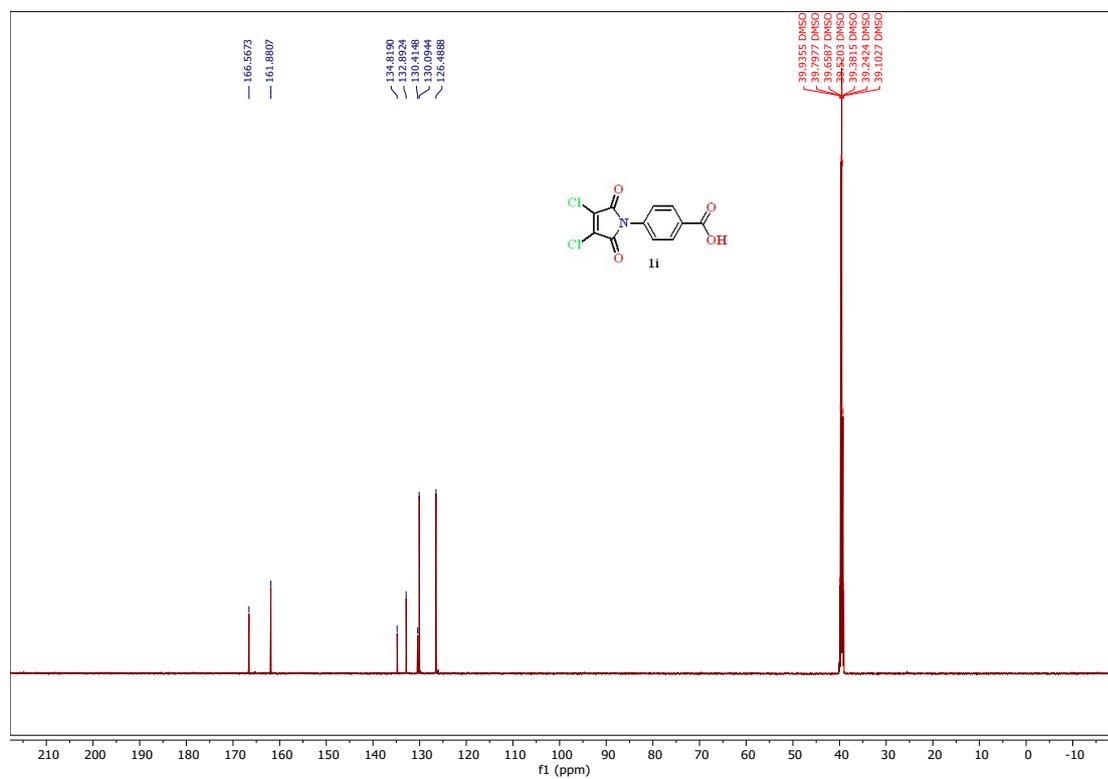


Figure S18: ¹³C NMR spectrum of 4-(3,4-dichloro-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic acid (**1i**).

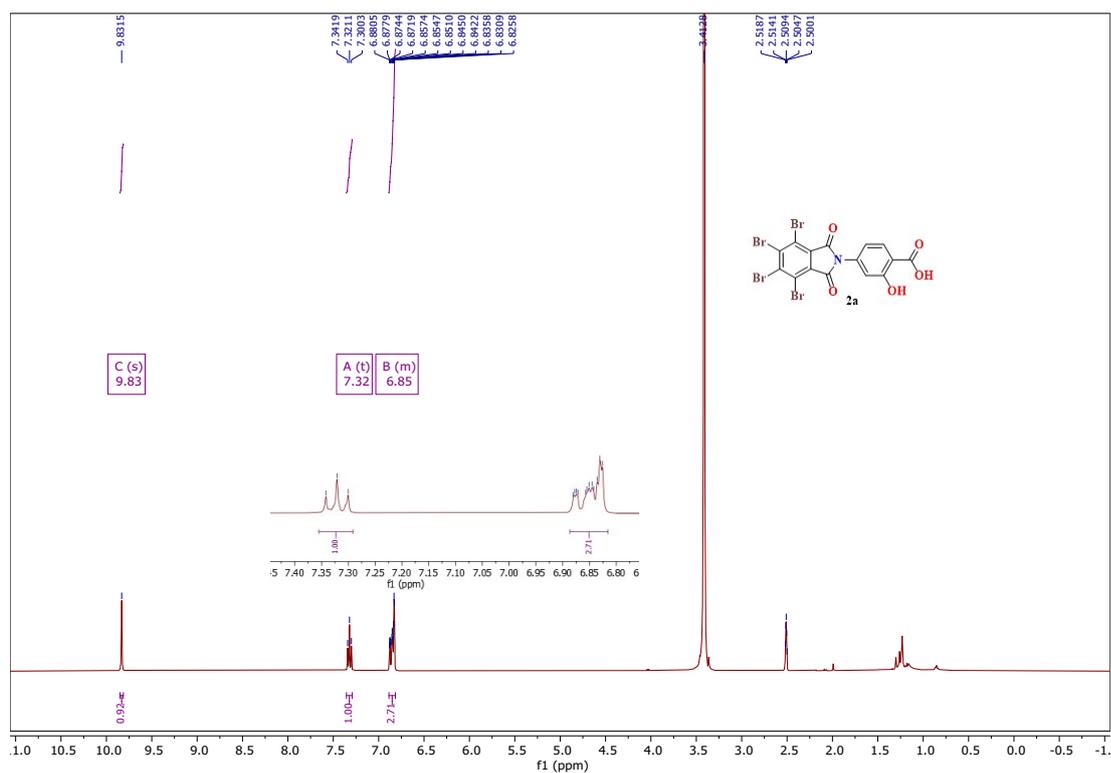


Figure S19: ^1H NMR spectrum of 2-hydroxy-4-(4,5,6,7-tetrabromo-1,3-dioxisoindolin-2-yl)benzoic acid (**2a**).

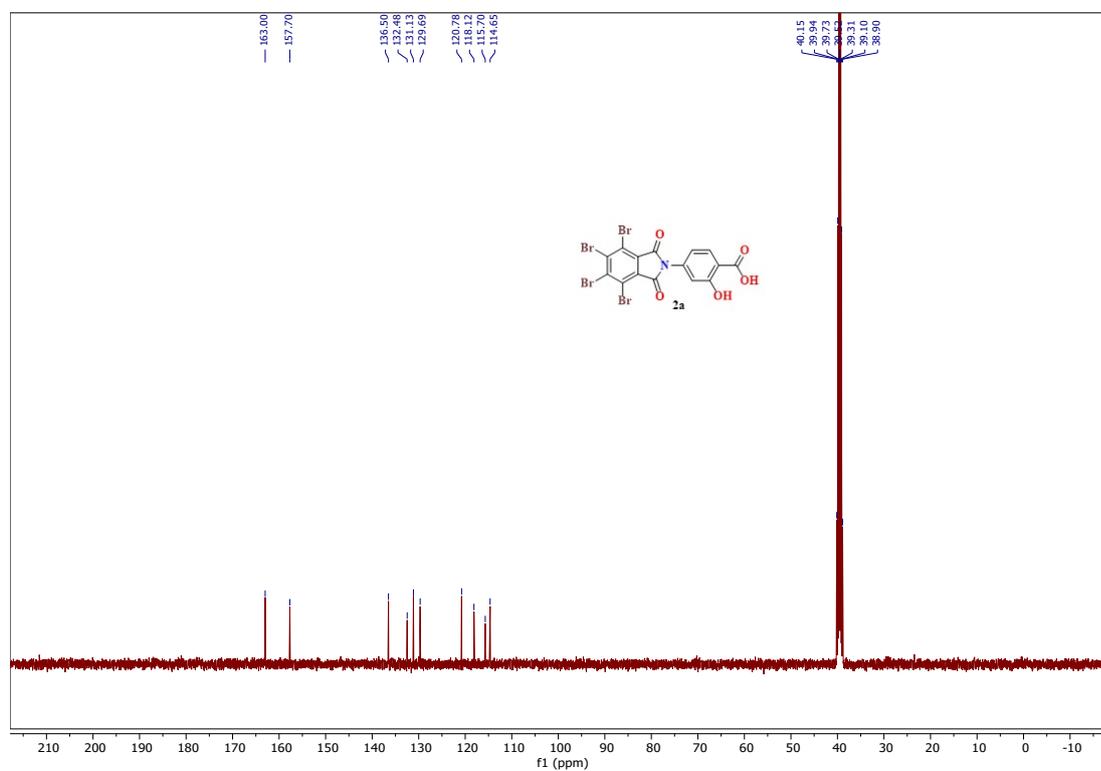


Figure S20: ^{13}C NMR spectrum of 2-hydroxy-4-(4,5,6,7-tetrabromo-1,3-dioxisoindolin-2-yl)benzoic acid (**2a**).

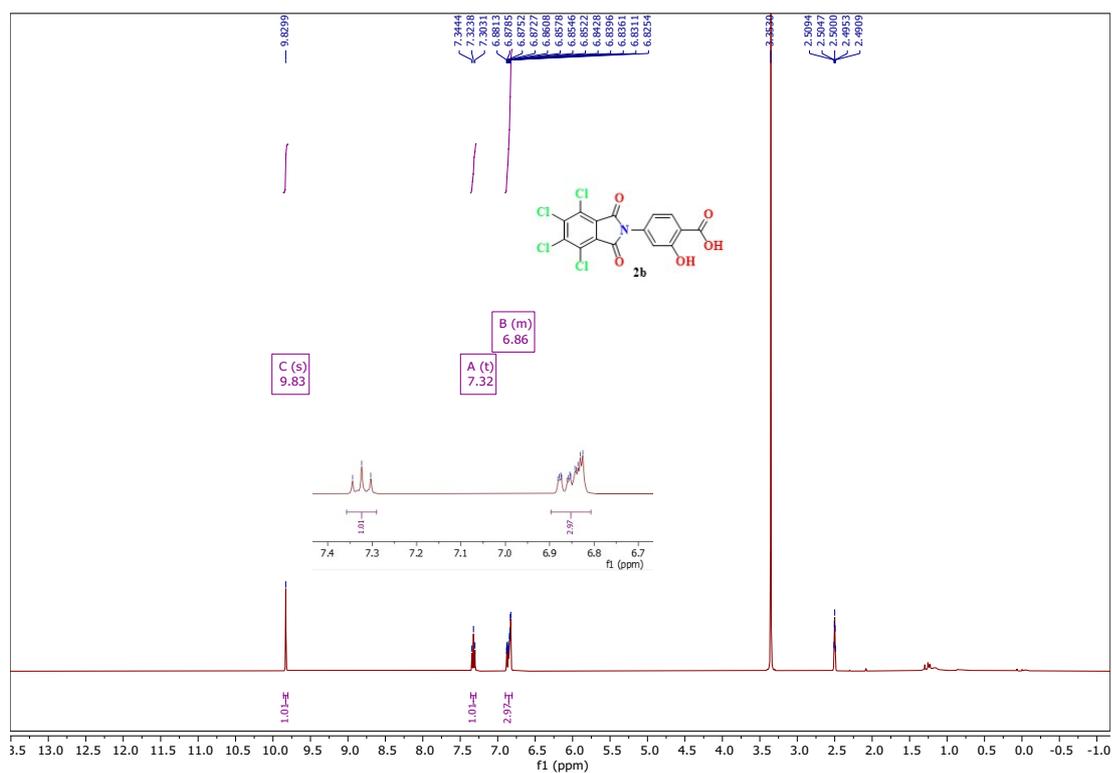


Figure S21: ¹H NMR spectrum of 2-hydroxy-4-(4,5,6,7-tetrachloro-1,3-dioxisoindolin-2-yl)benzoic acid (2b).

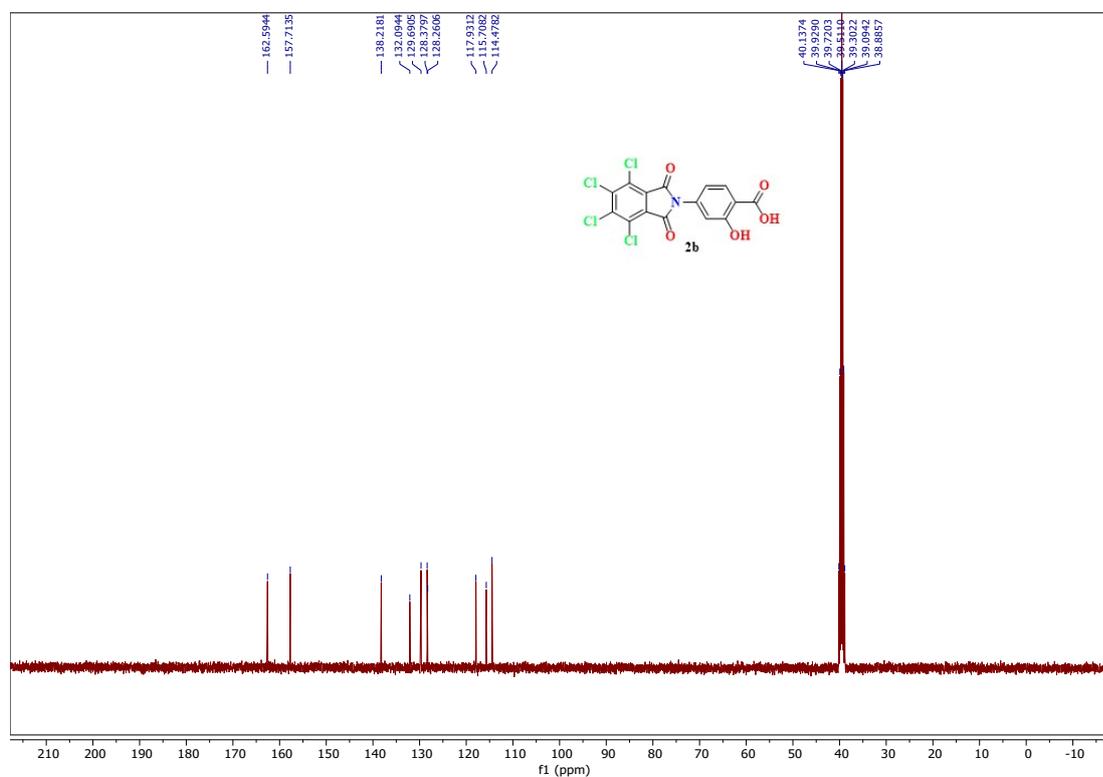


Figure S22: ¹³C NMR spectrum of 2-hydroxy-4-(4,5,6,7-tetrachloro-1,3-dioxisoindolin-2-yl)benzoic acid (2b).

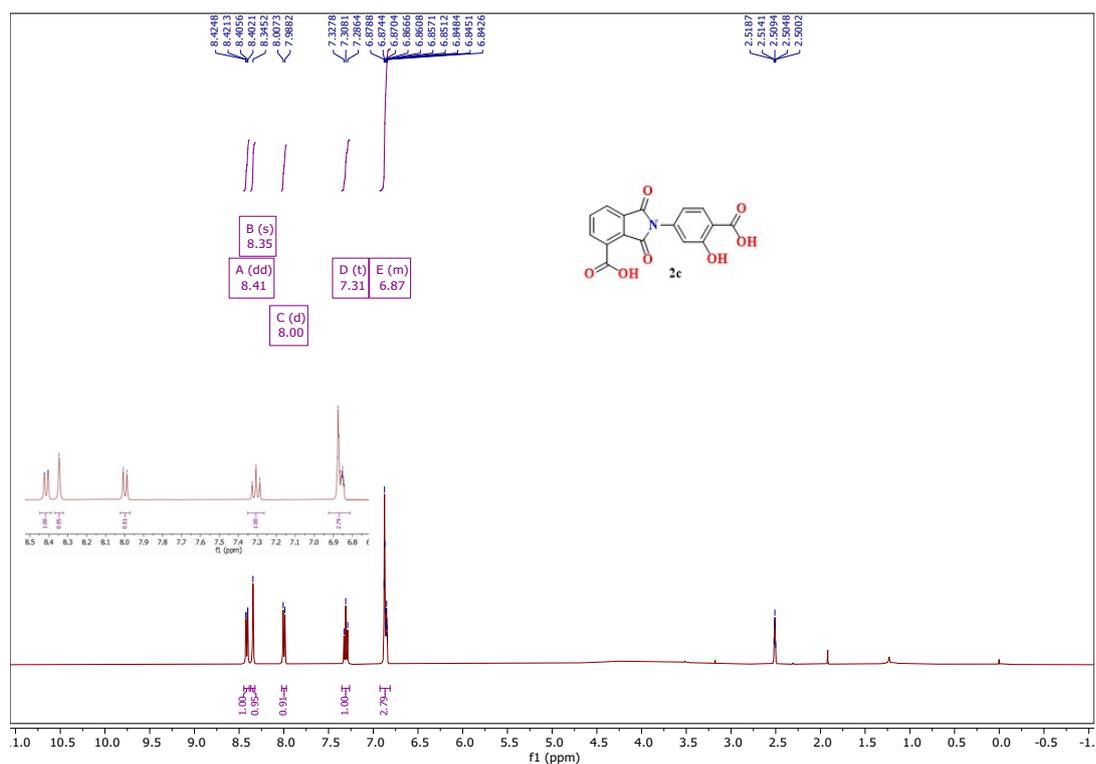


Figure S23: ¹H NMR spectrum of 2-(4-carboxy-3-hydroxyphenyl)-1,3-dioxoisindoline-4-carboxylic acid (**2c**).

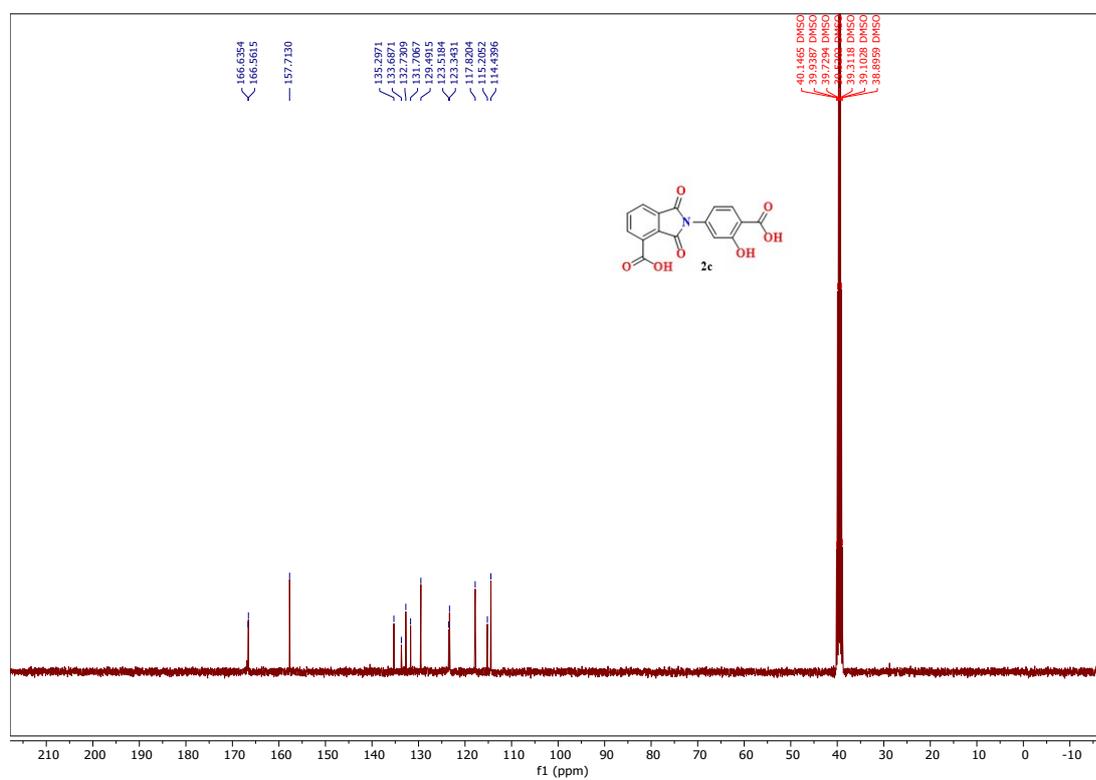


Figure S24: ¹³C NMR spectrum of 2-(4-carboxy-3-hydroxyphenyl)-1,3-dioxoisindoline-4-carboxylic acid (**2c**).

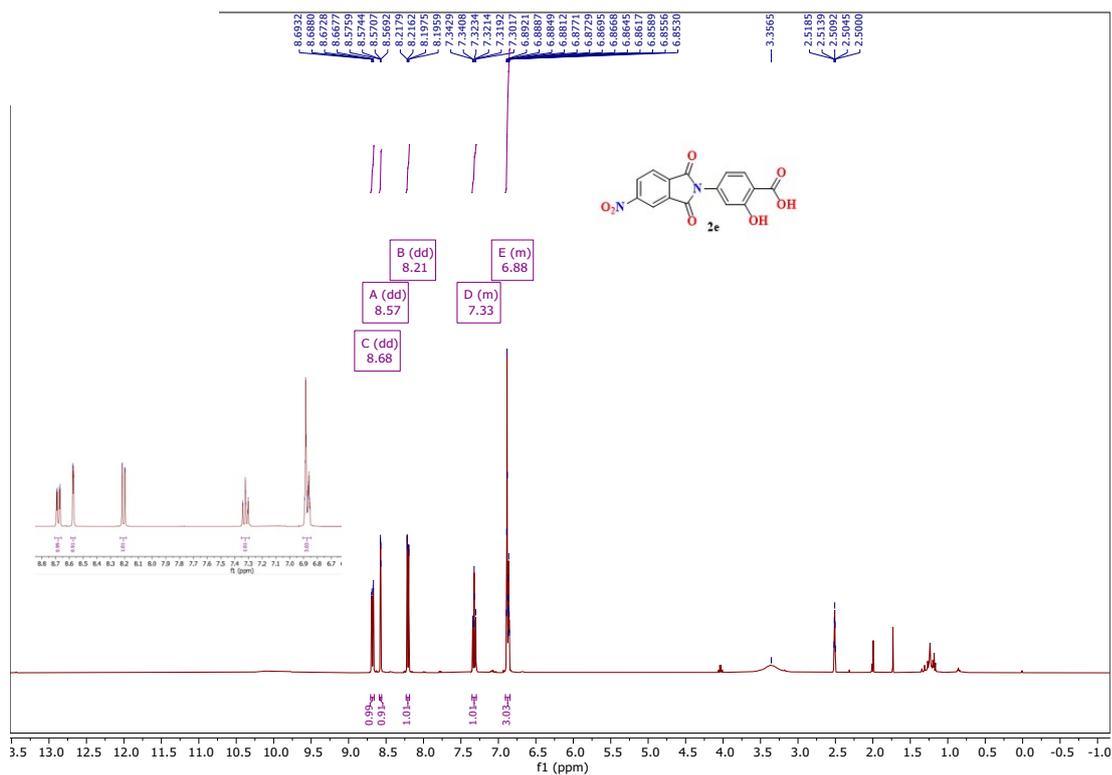


Figure S27: ¹H NMR spectrum of 2-hydroxy-4-(5-nitro-1,3-dioxoisindolin-2-yl)benzoic acid (2e).

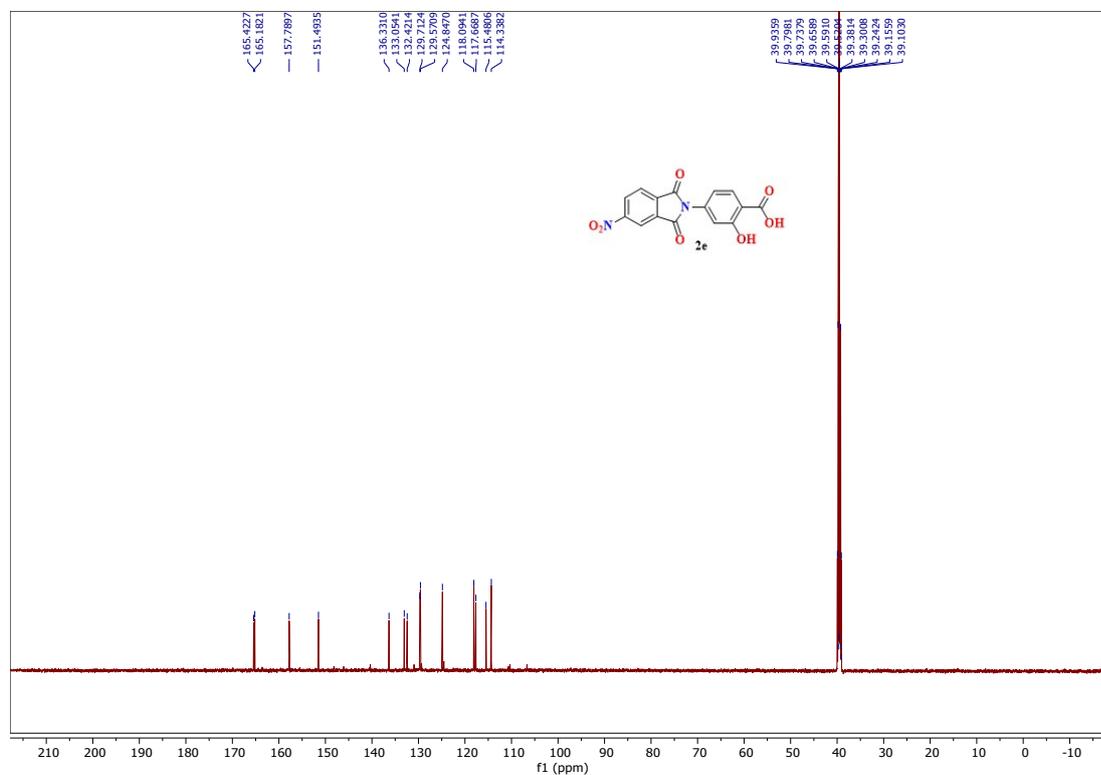


Figure S28: ¹³C NMR spectrum of 2-hydroxy-4-(5-nitro-1,3-dioxoisindolin-2-yl)benzoic acid (2e).

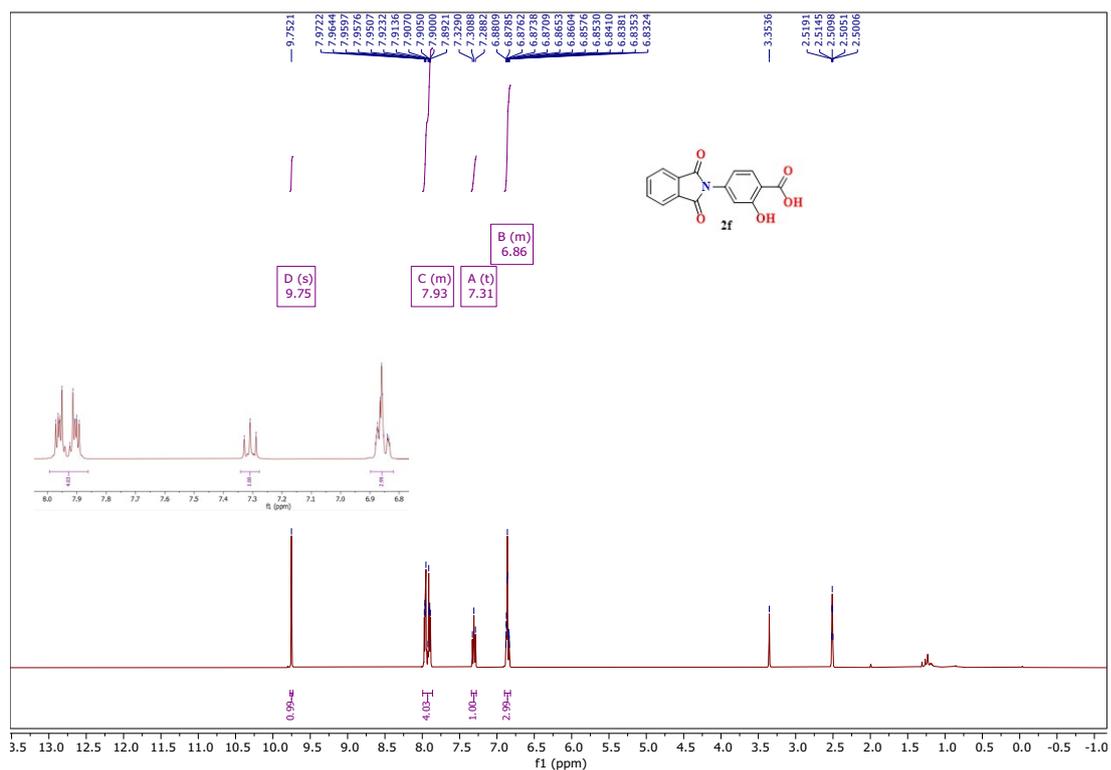


Figure S29: ¹H NMR spectrum of 4-(1,3-dioxisoindolin-2-yl)-2-hydroxybenzoic acid (**2f**).

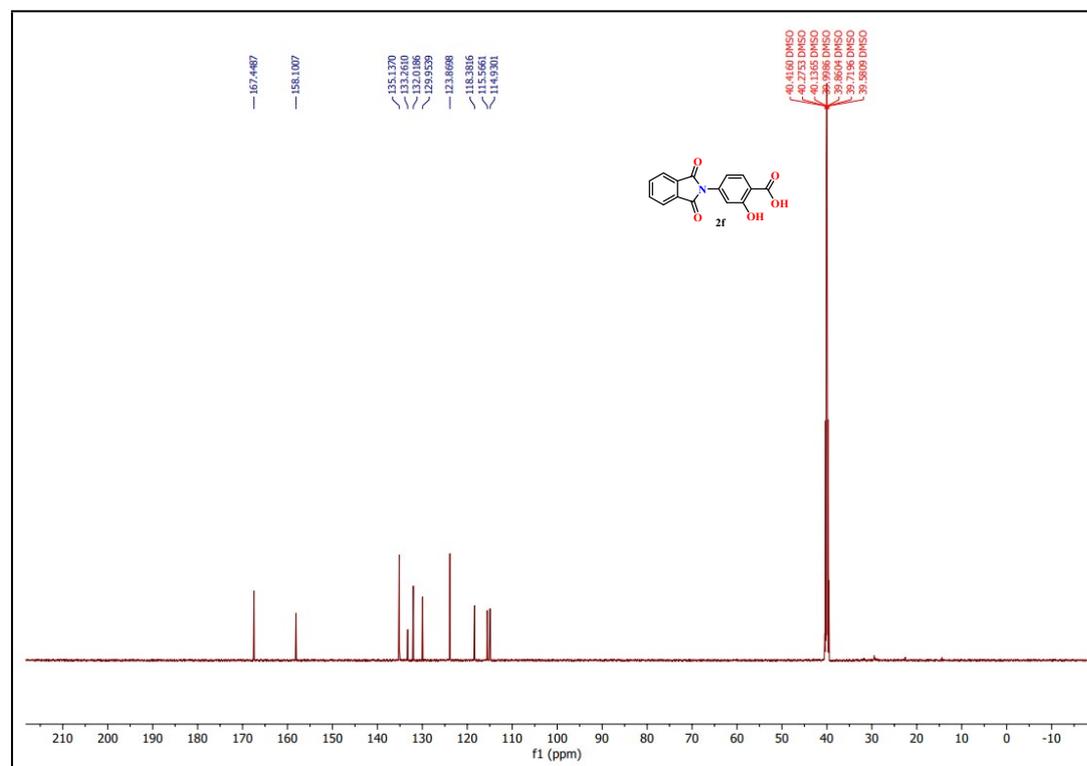


Figure S30: ¹³C NMR spectrum of 4-(1,3-dioxisoindolin-2-yl)-2-hydroxybenzoic acid (**2f**).

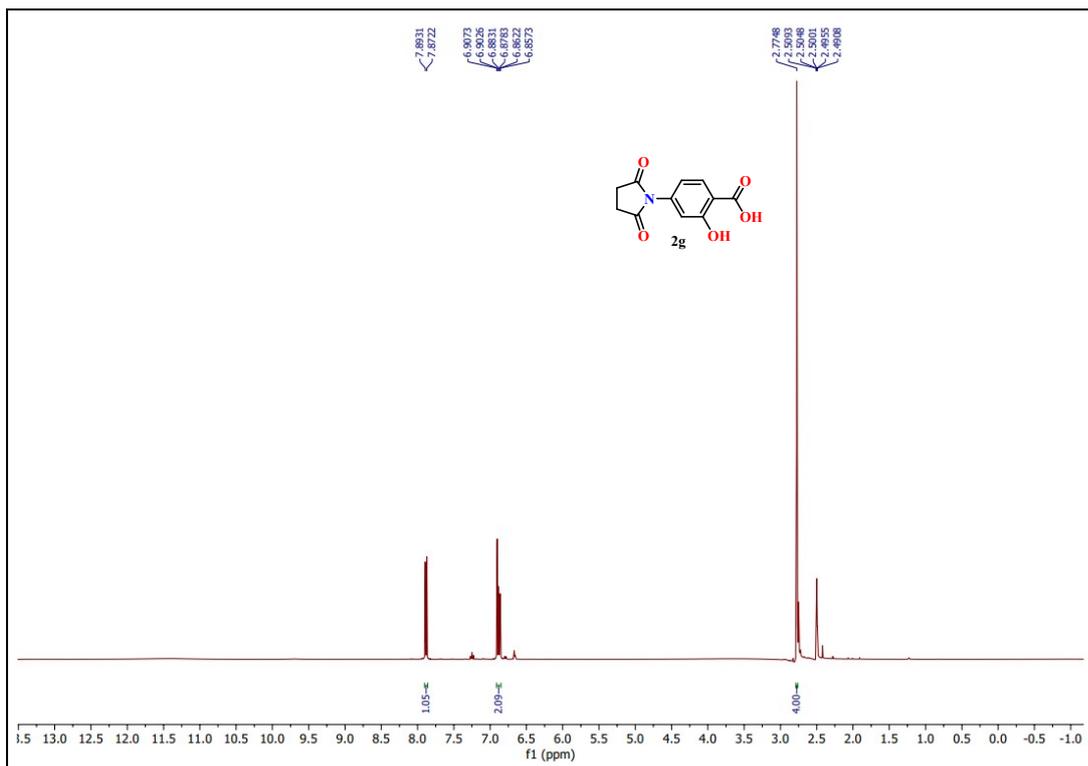


Figure S31: ¹H NMR spectrum of 4-(2,5-dioxypyrrolidin-1-yl)-2-hydroxybenzoic acid (2g).

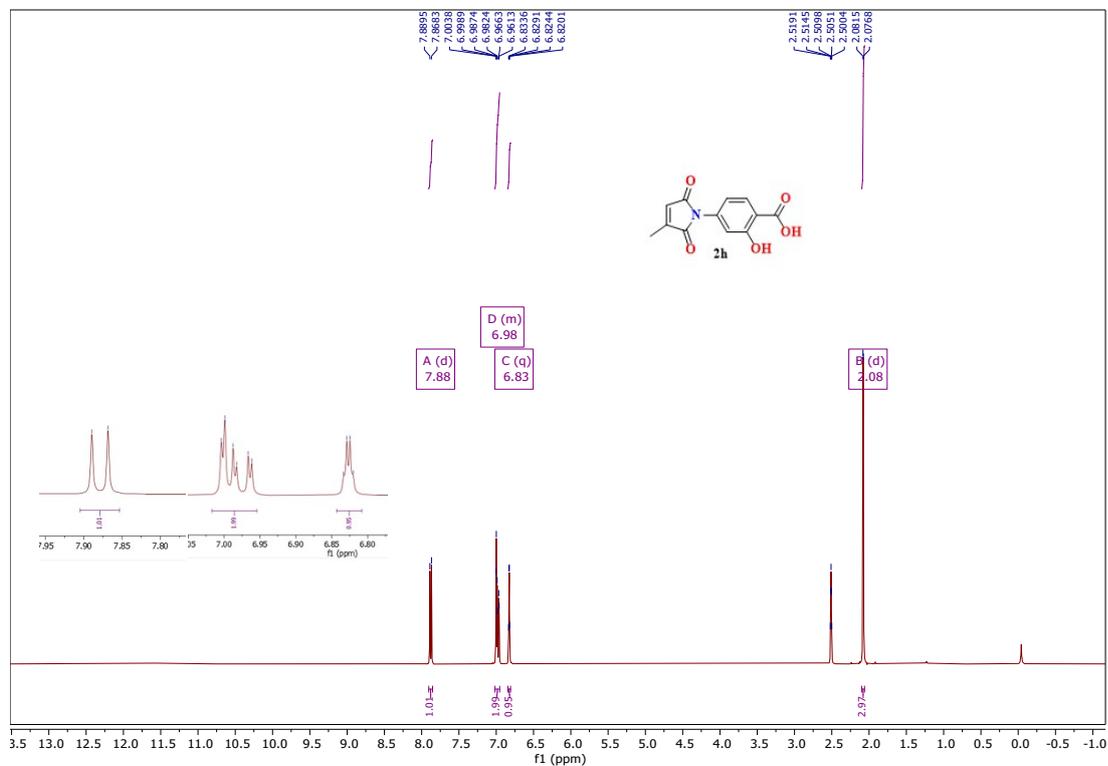


Figure S32: ¹H NMR spectrum of 2-hydroxy-4-(3-methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic acid (2h).

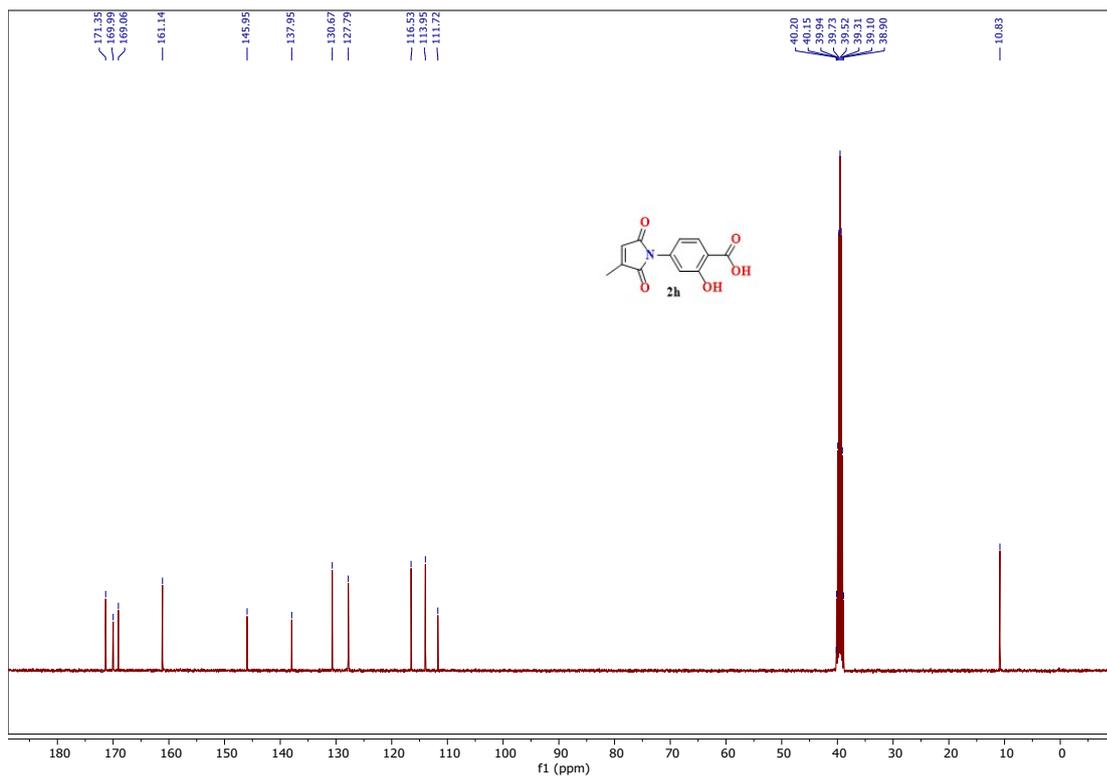


Figure S33: ¹³C NMR spectrum of 2-hydroxy-4-(3-methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic acid (2h).

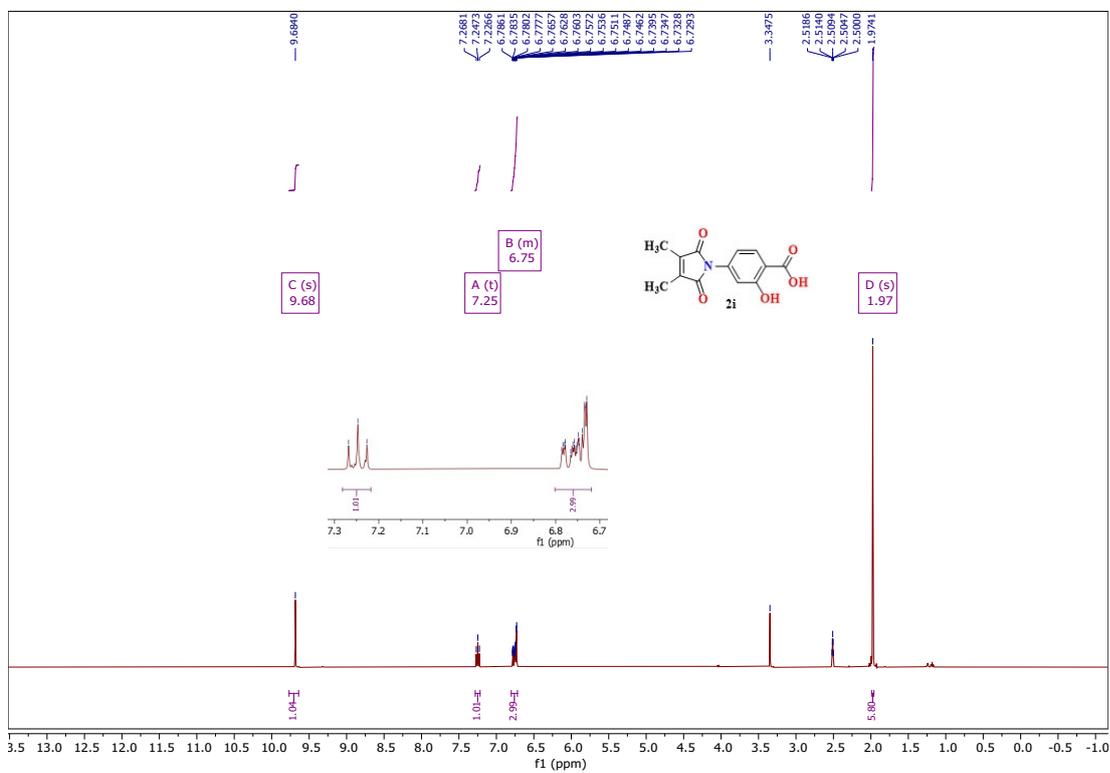


Figure S34: ¹H NMR spectrum of 4-(3,4-dimethyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2-hydroxybenzoic acid (2i).

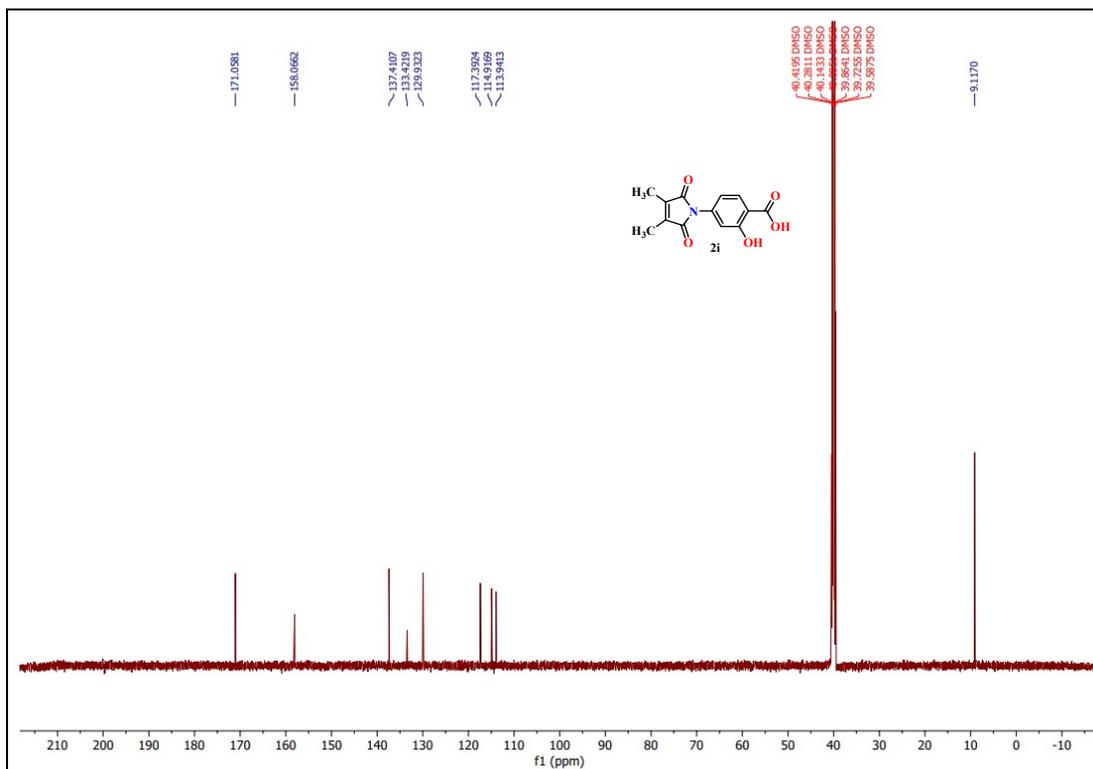


Figure S35: ¹³C NMR spectrum of 4-(3,4-dimethyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2-hydroxybenzoic acid (2i).

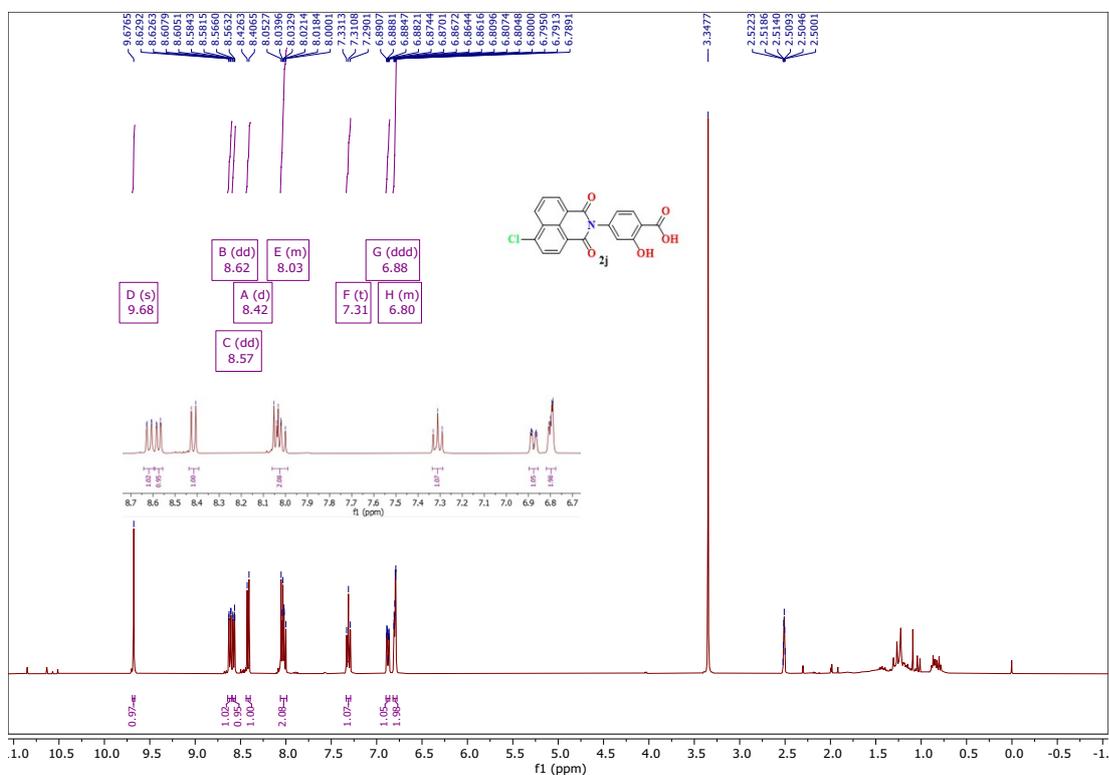


Figure S36: ¹H NMR spectrum of 4-(6-chloro-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)-2-hydroxybenzoic acid (2j).

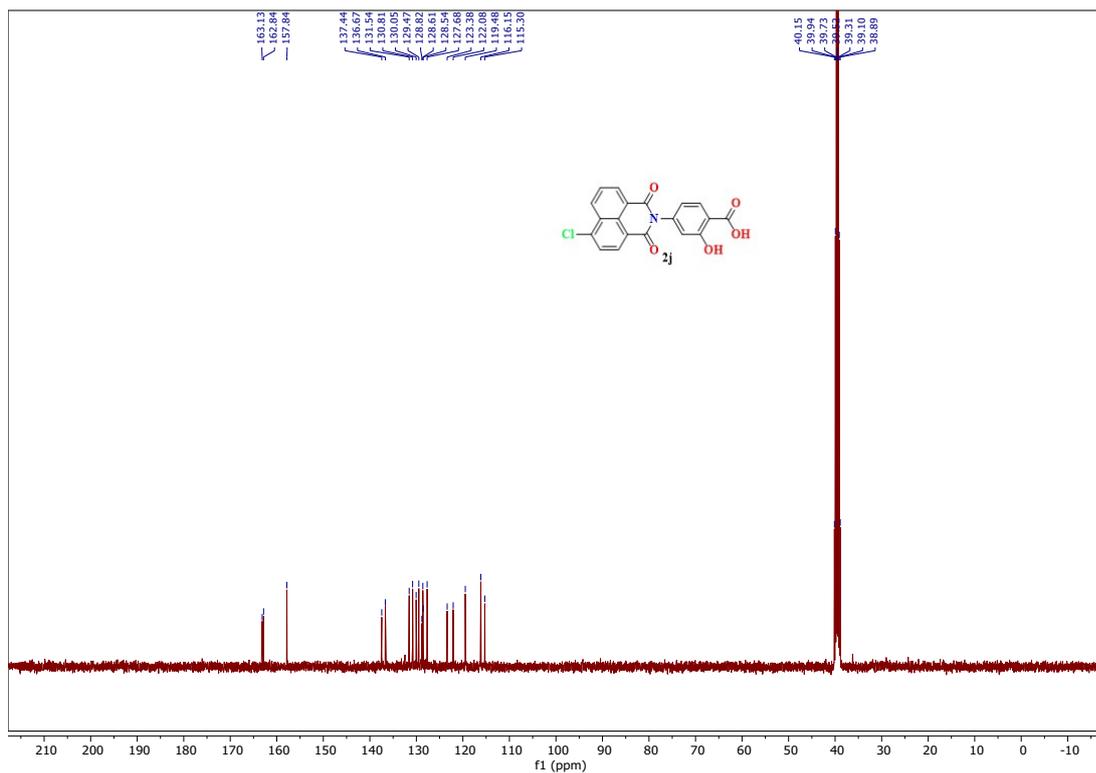


Figure S37: ^{13}C NMR spectrum of 4-(6-chloro-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)-2-hydroxybenzoic acid (**2j**).

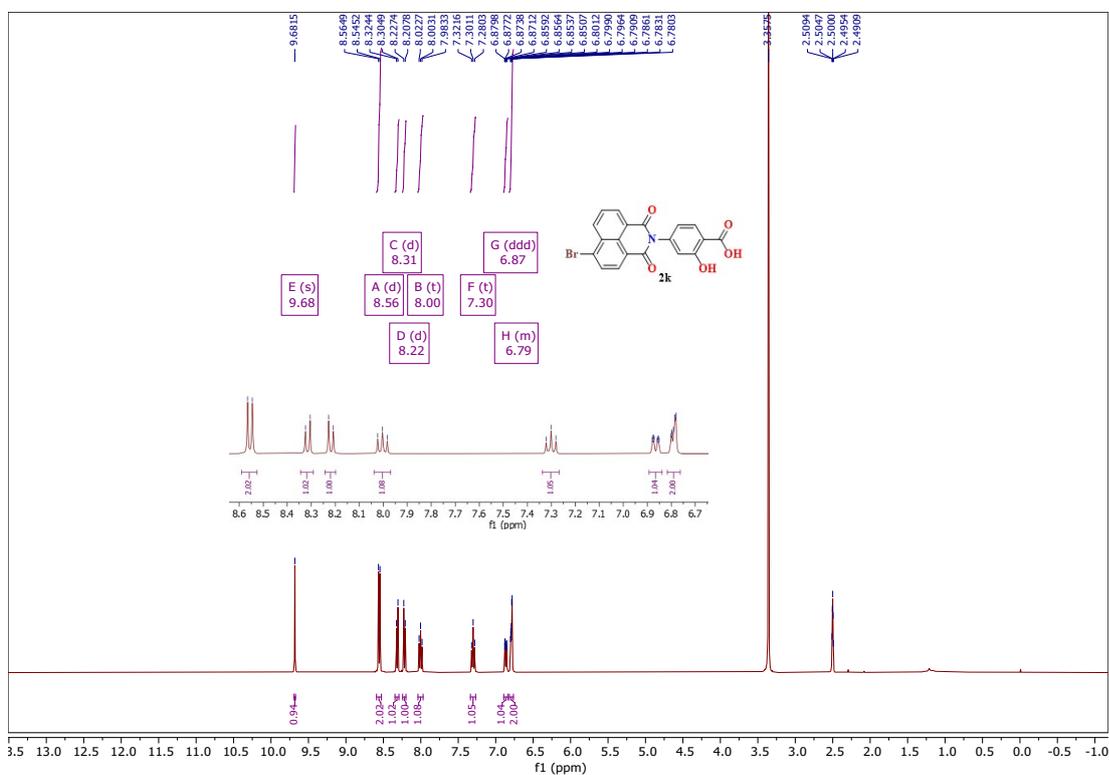


Figure S38: ^1H NMR spectrum of 4-(6-bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)-2-hydroxybenzoic acid (**2k**).

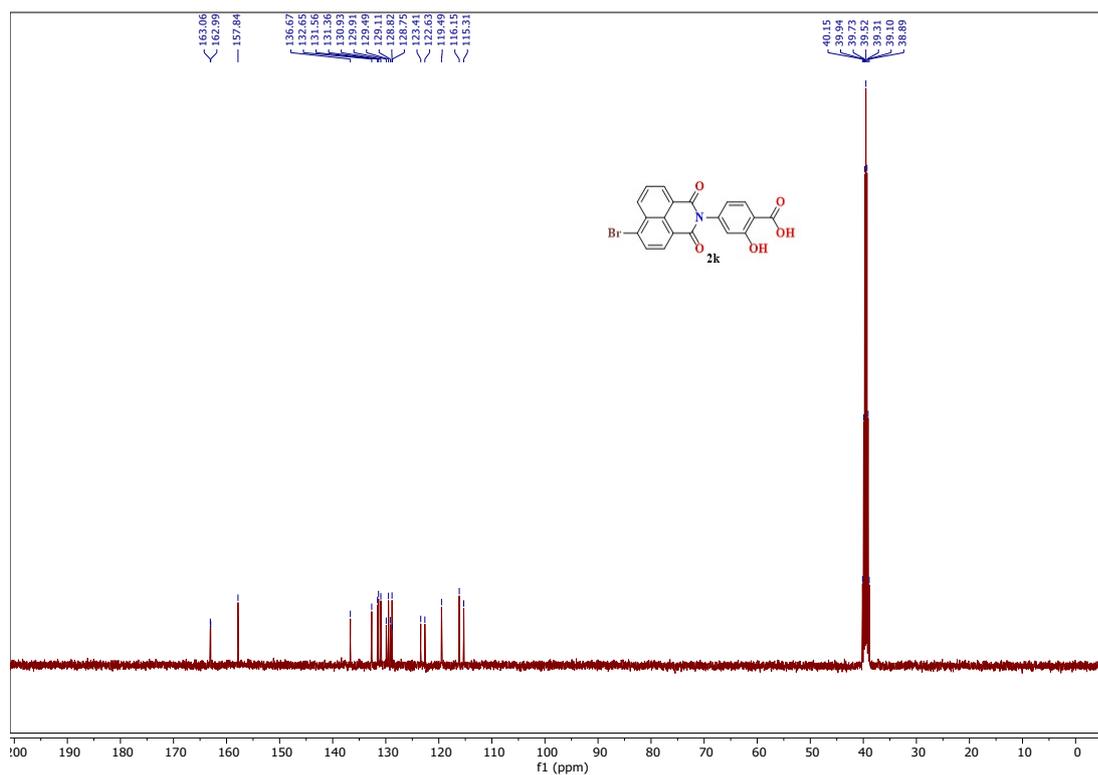


Figure S39: ¹³C NMR spectrum of 4-(6-bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)-2-hydroxybenzoic acid (**2k**).

HRMS spectra of cyclic imide derivatives

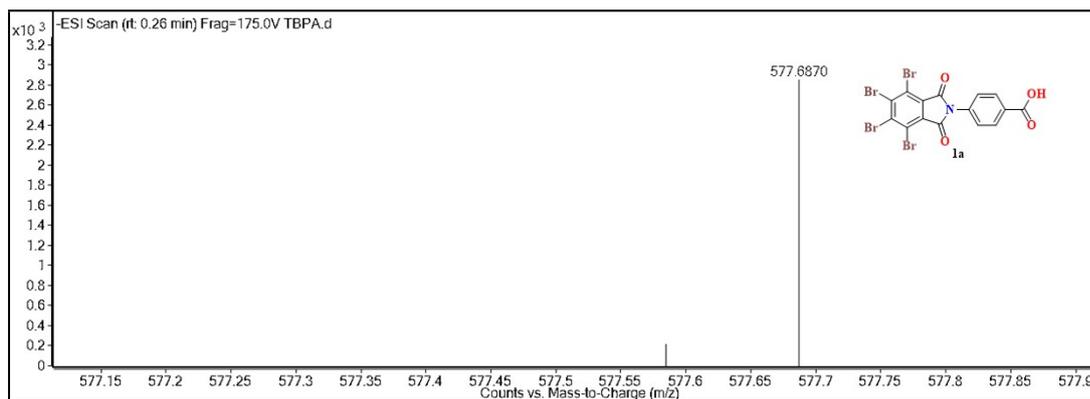


Figure S40. HRMS spectrum of 4-(4,5,6,7-tetrabromo-1,3-dioxoisindolin-2-yl)benzoic acid (**1a**).

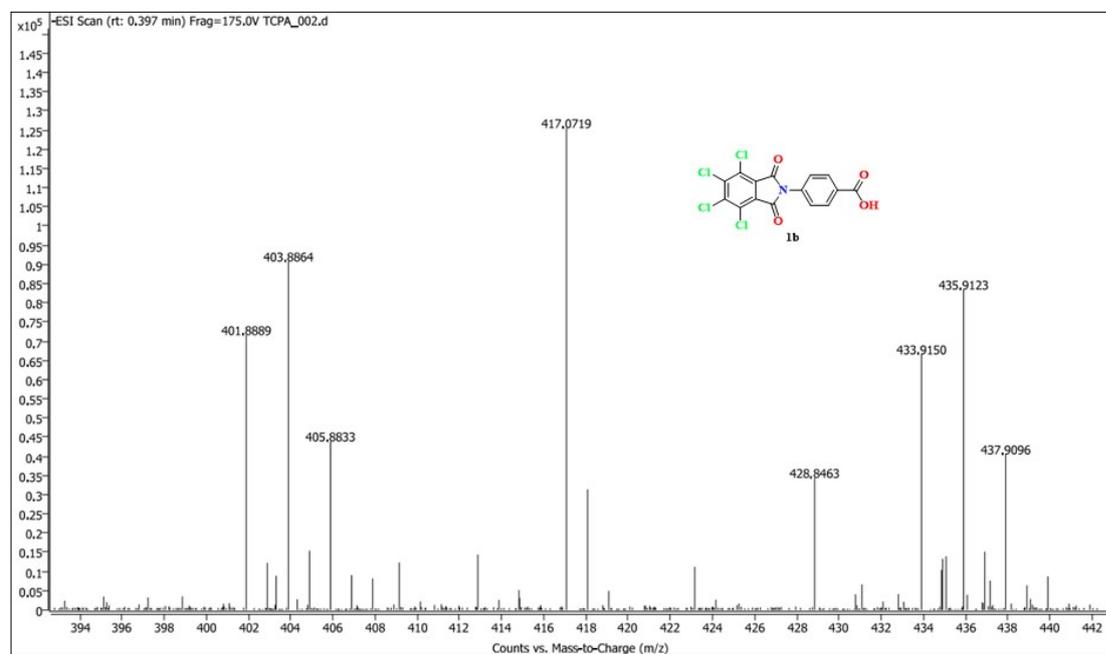


Figure S41. HRMS spectrum of 4-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)benzoic acid (**1b**).

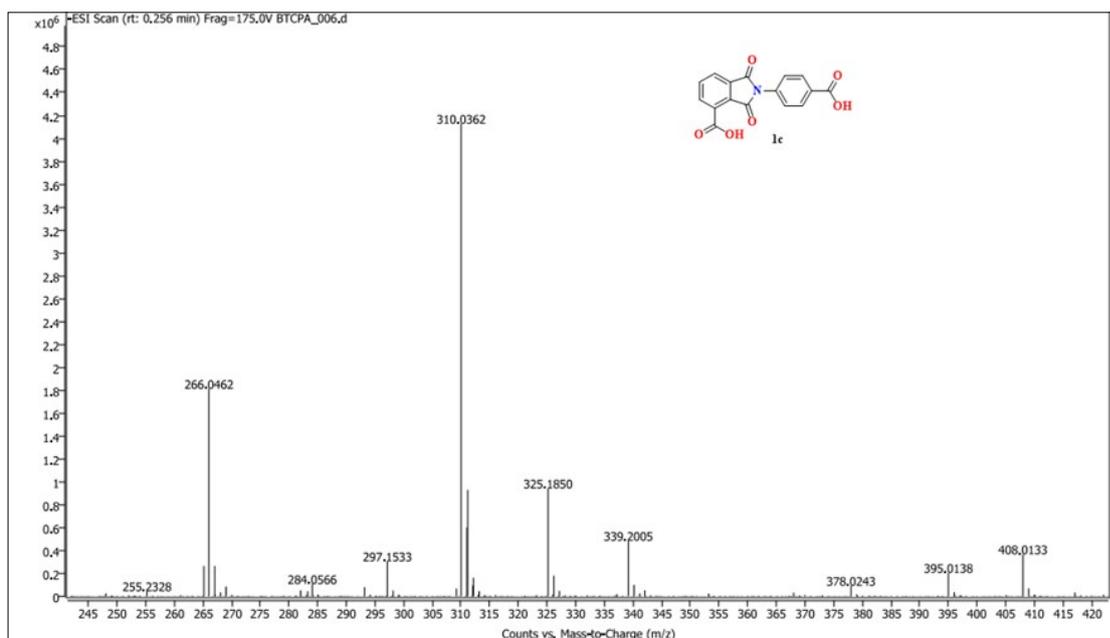


Figure S42. HRMS spectrum of 2-(4-carboxyphenyl)-1,3-dioxisoindoline-4-carboxylic acid (**1c**).

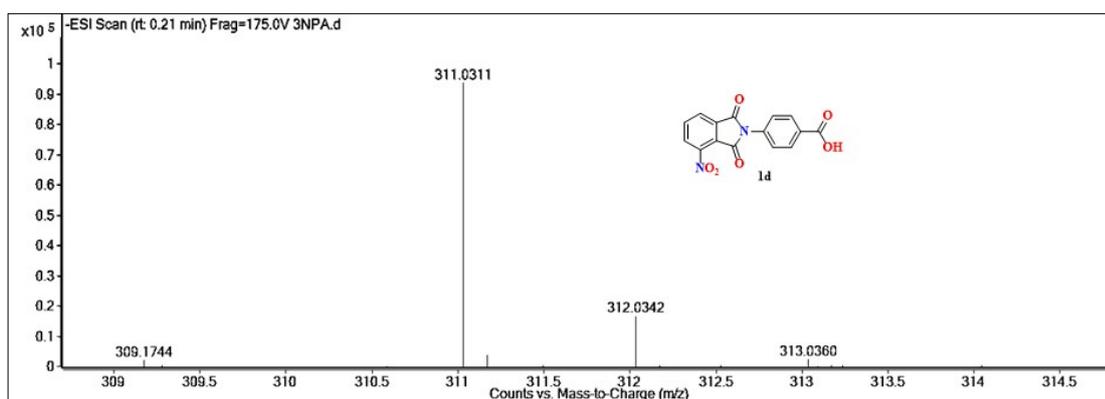
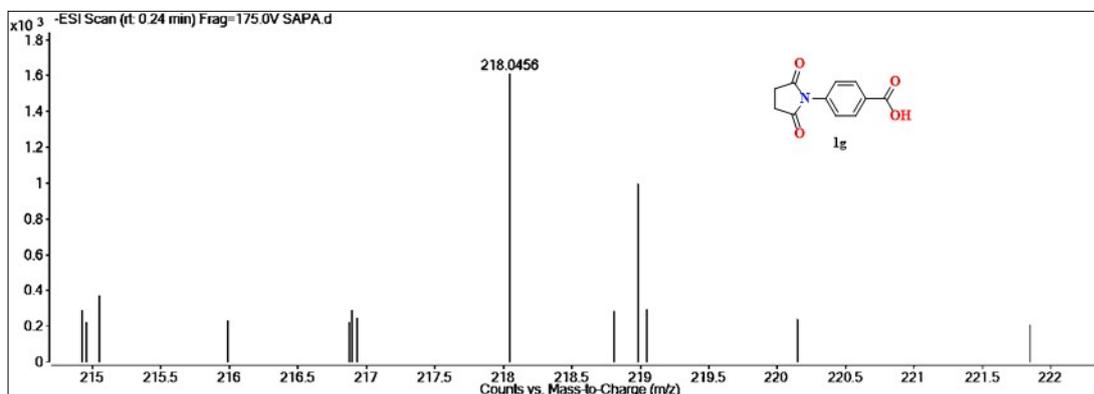
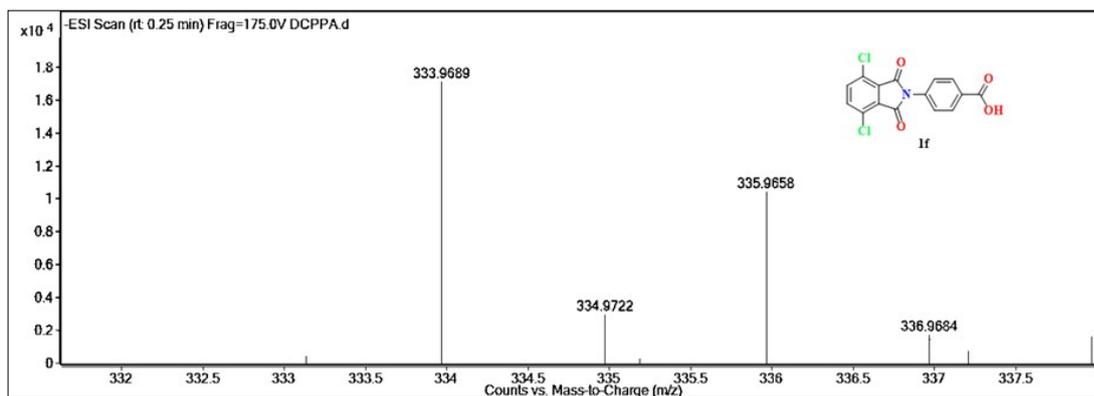
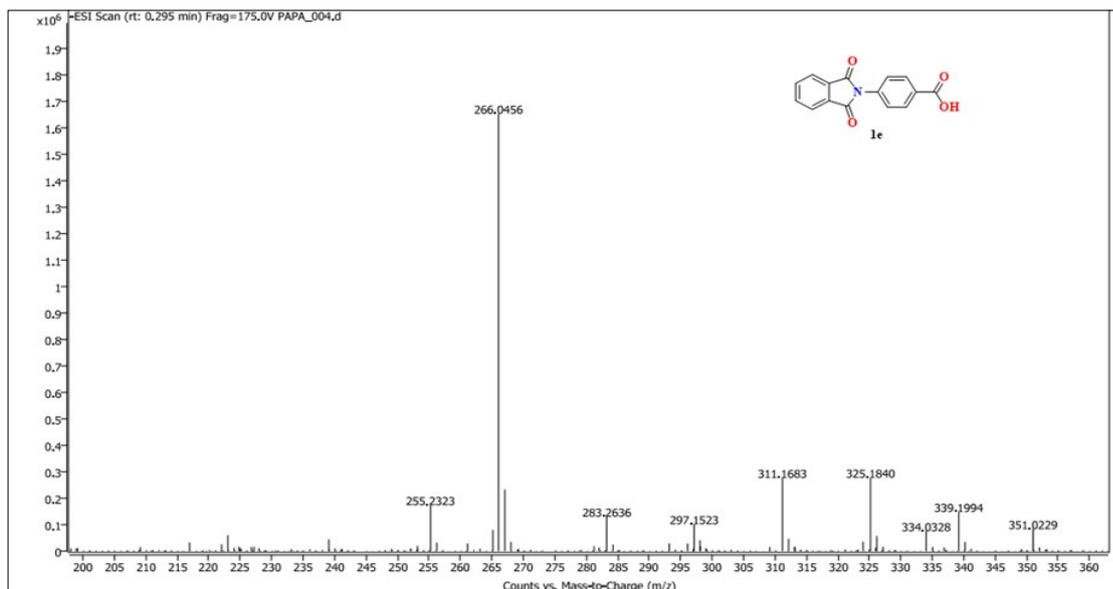
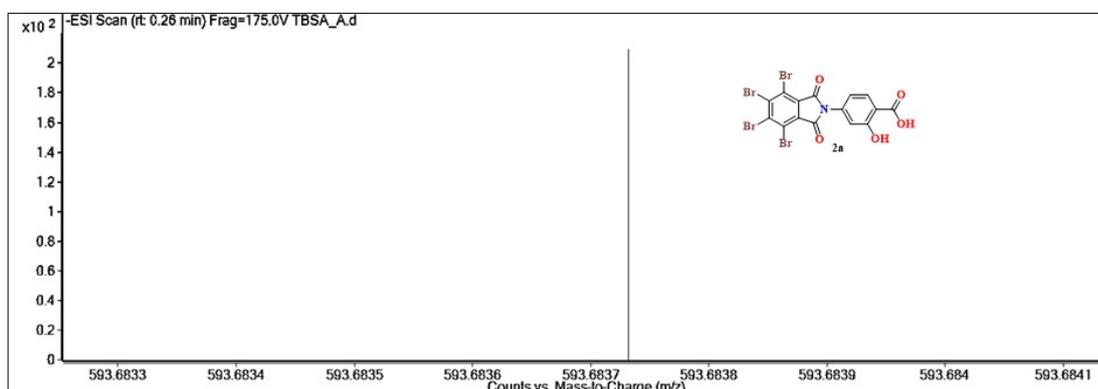
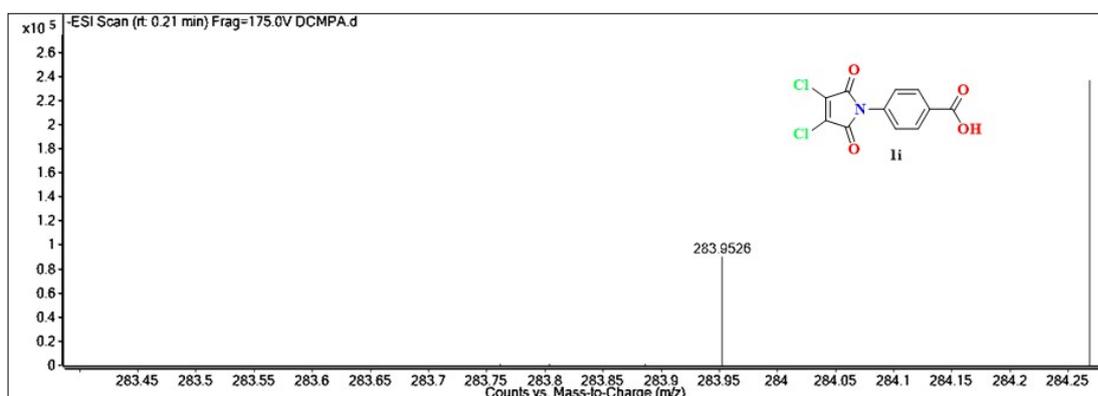
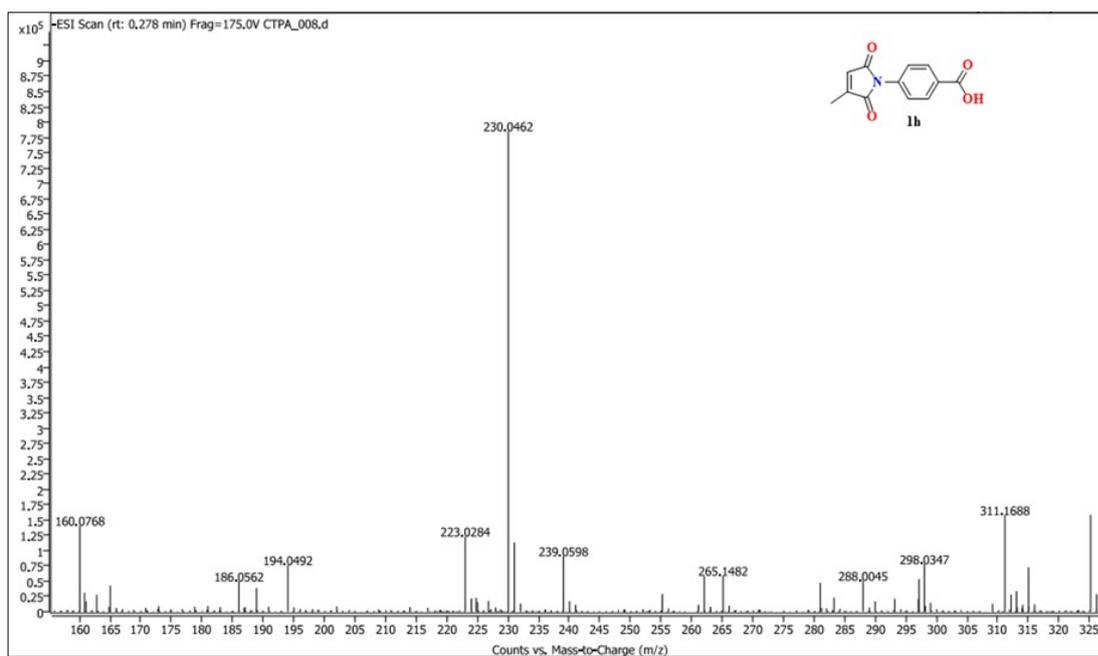


Figure S43. HRMS spectrum of 4-(4-nitro-1,3-dioxisoindolin-2-yl)benzoic acid (**1d**).





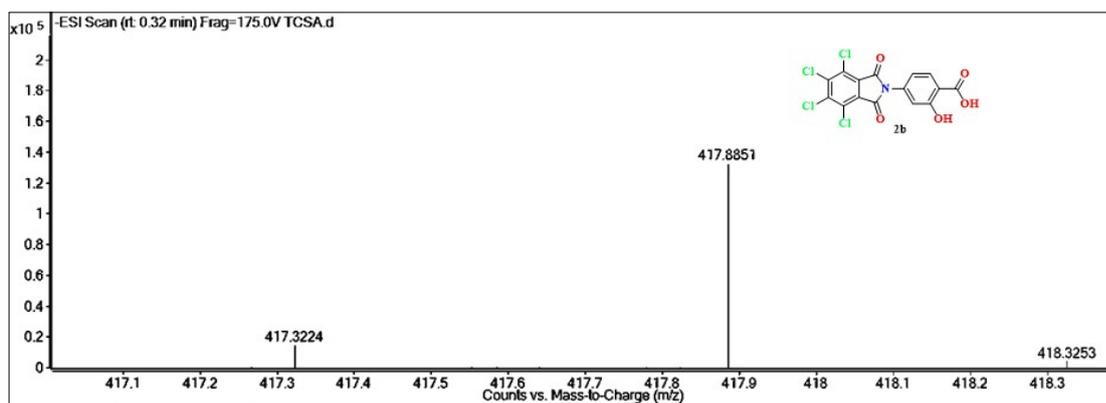


Figure S50. HRMS spectrum of 2-hydroxy-4-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)benzoic acid (**2b**).

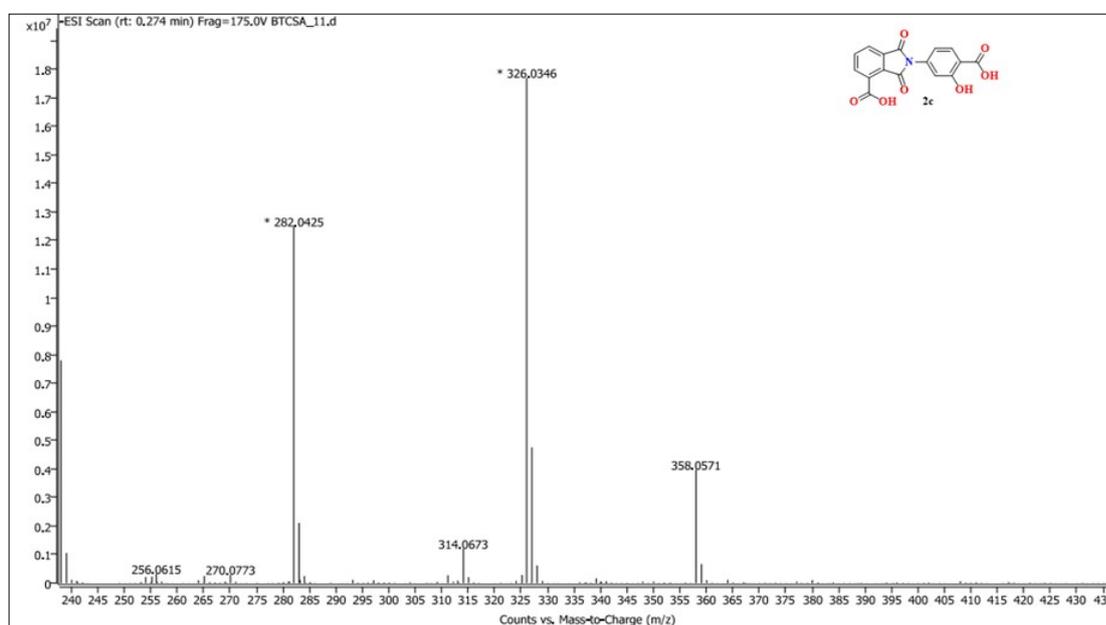


Figure S51. HRMS spectrum of 2-(4-carboxy-3-hydroxyphenyl)-1,3-dioxoisindoline-4-carboxylic acid (**2c**).

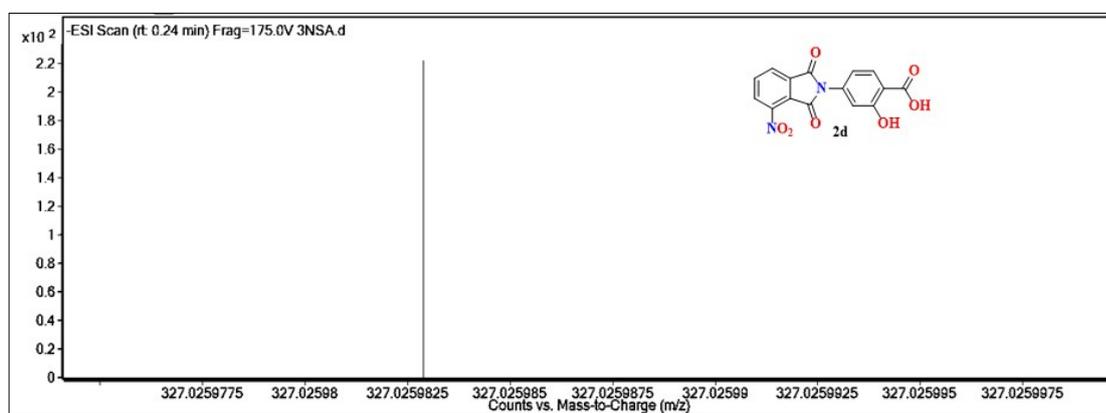
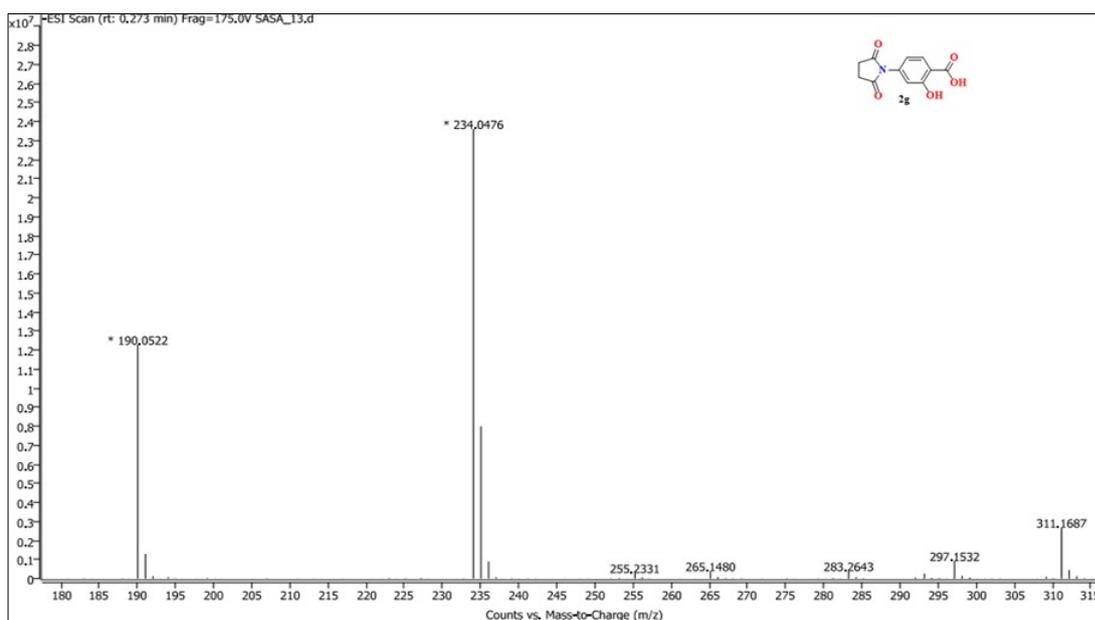
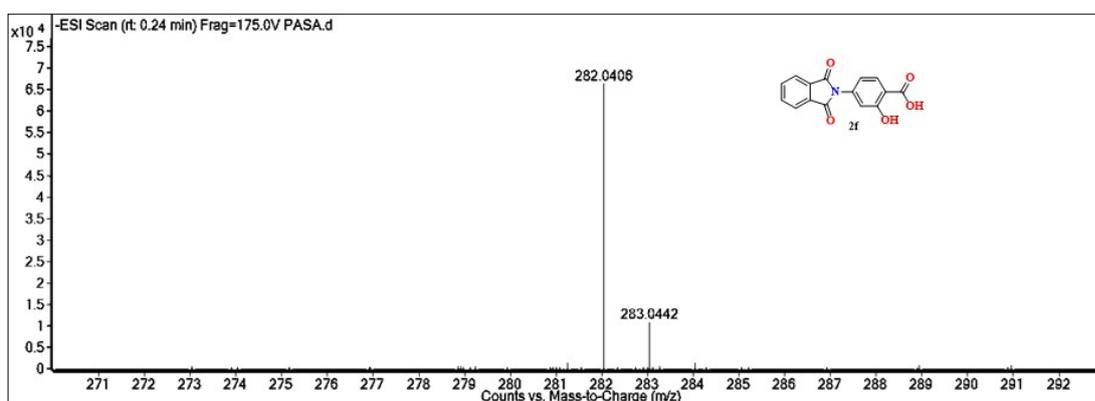
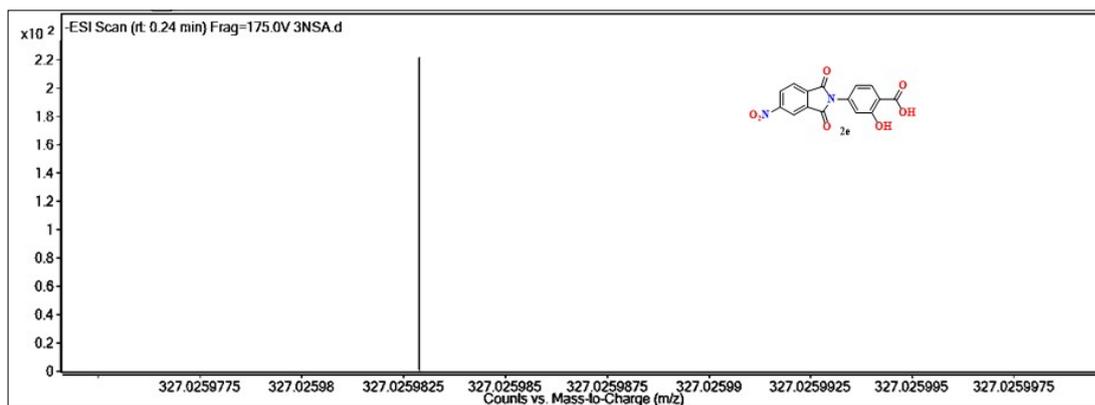


Figure S52. HRMS spectrum of 2-hydroxy-4-(4-nitro-1,3-dioxoisindolin-2-yl)benzoic acid (**2d**).



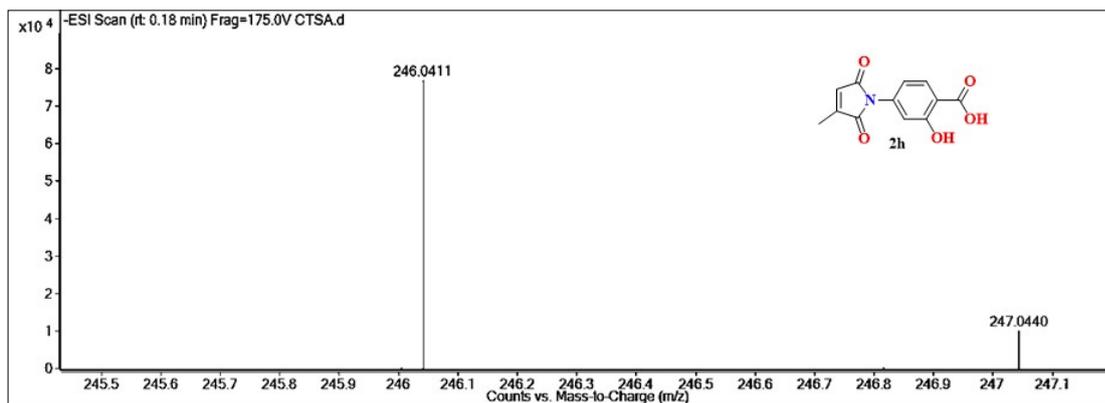


Figure S56. HRMS spectrum of 2-hydroxy-4-(3-methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic acid (2h).

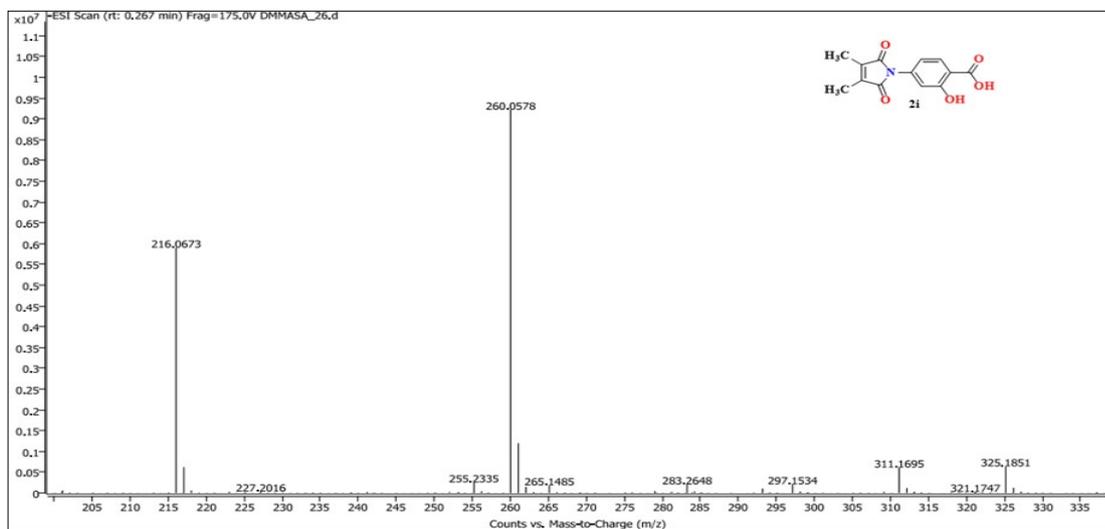


Figure S57. HRMS spectrum of 4-(3,4-dimethyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2-hydroxybenzoic acid (2i).

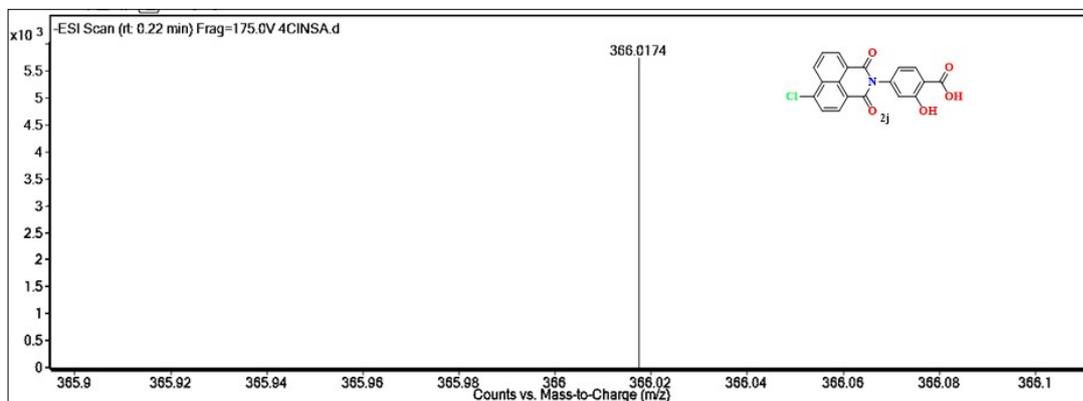


Figure S58. HRMS spectrum of 4-(6-chloro-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)-2-hydroxybenzoic acid (2j).

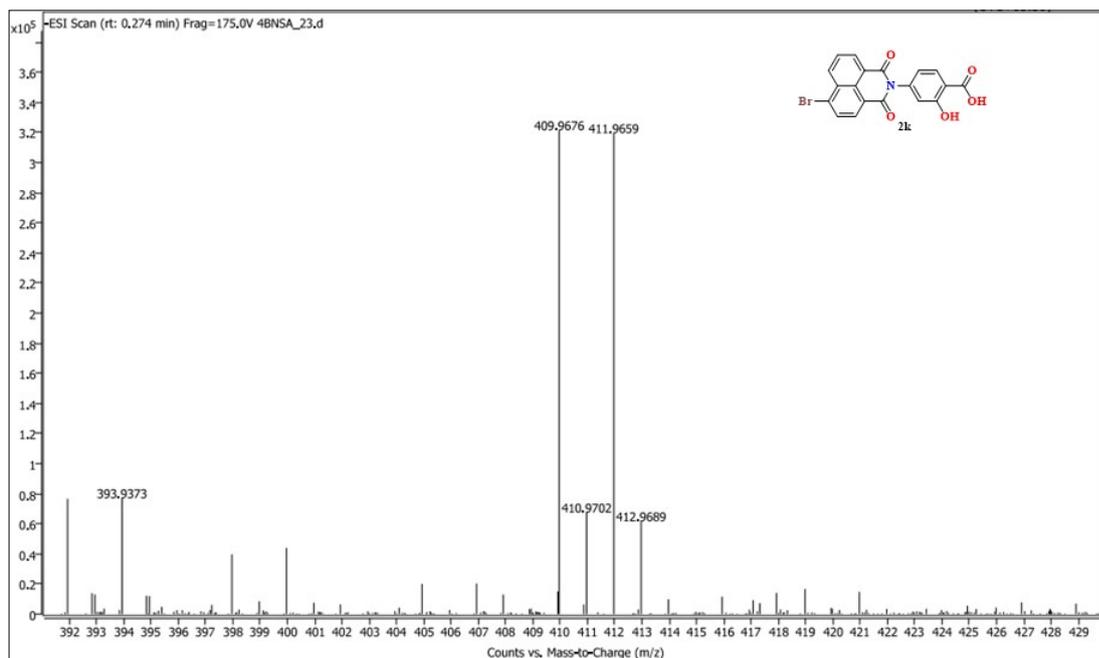


Figure S59. HRMS spectrum of 4-(6-bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)-2-hydroxybenzoic acid (**2k**).

HPLC spectra of cyclic imide derivatives

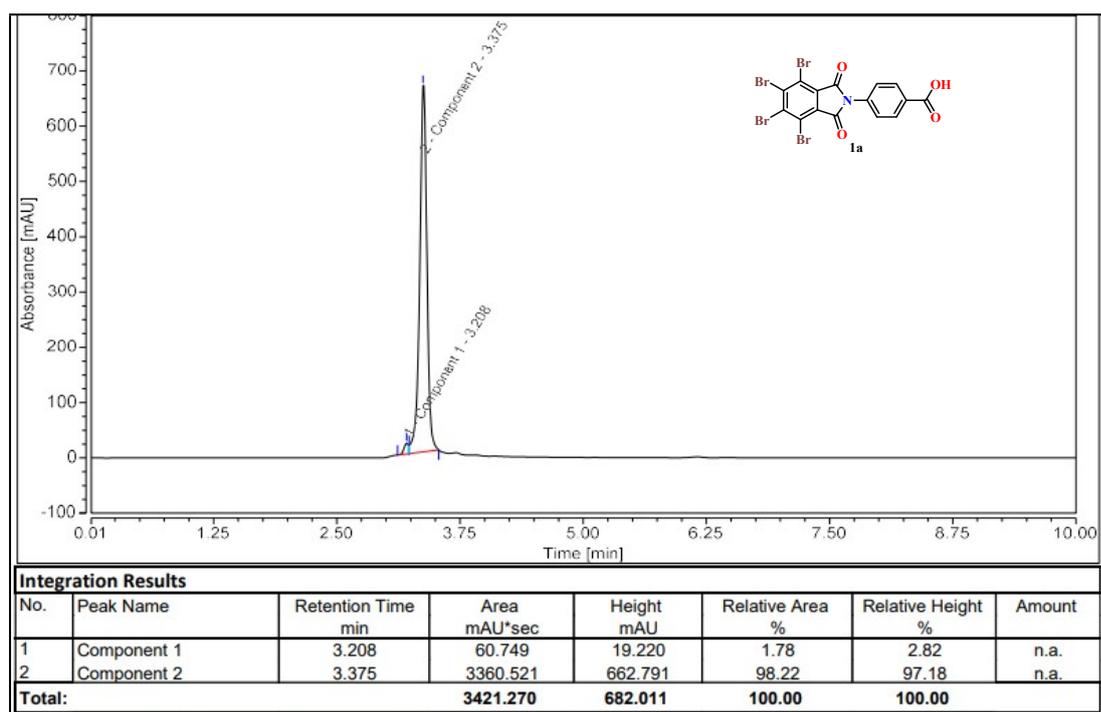


Figure S60. HPLC chromatogram of 4-(4,5,6,7-tetrabromo-1,3-dioxisoindolin-2-yl)benzoic acid (**1a**).

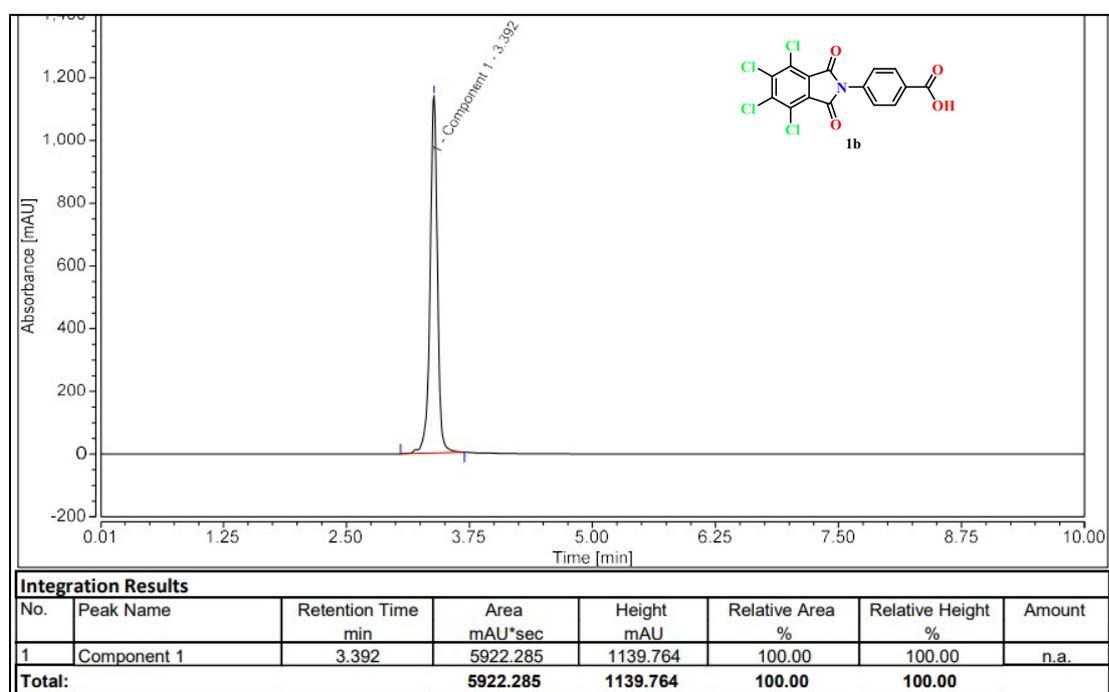


Figure S61. HPLC chromatogram of 4-(4,5,6,7-tetrachloro-1,3-dioxisoindolin-2-yl)benzoic acid (**1b**).

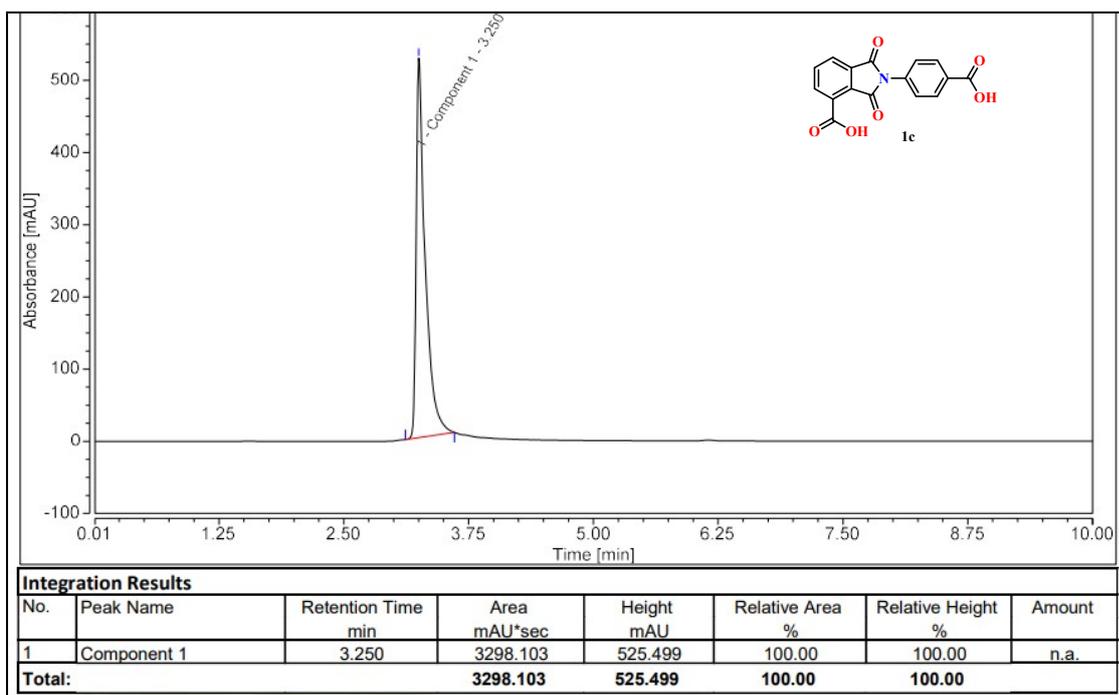


Figure S62. HPLC chromatogram of 2-(4-carboxyphenyl)-1,3-dioxisoindoline-4-carboxylic acid (**1c**).

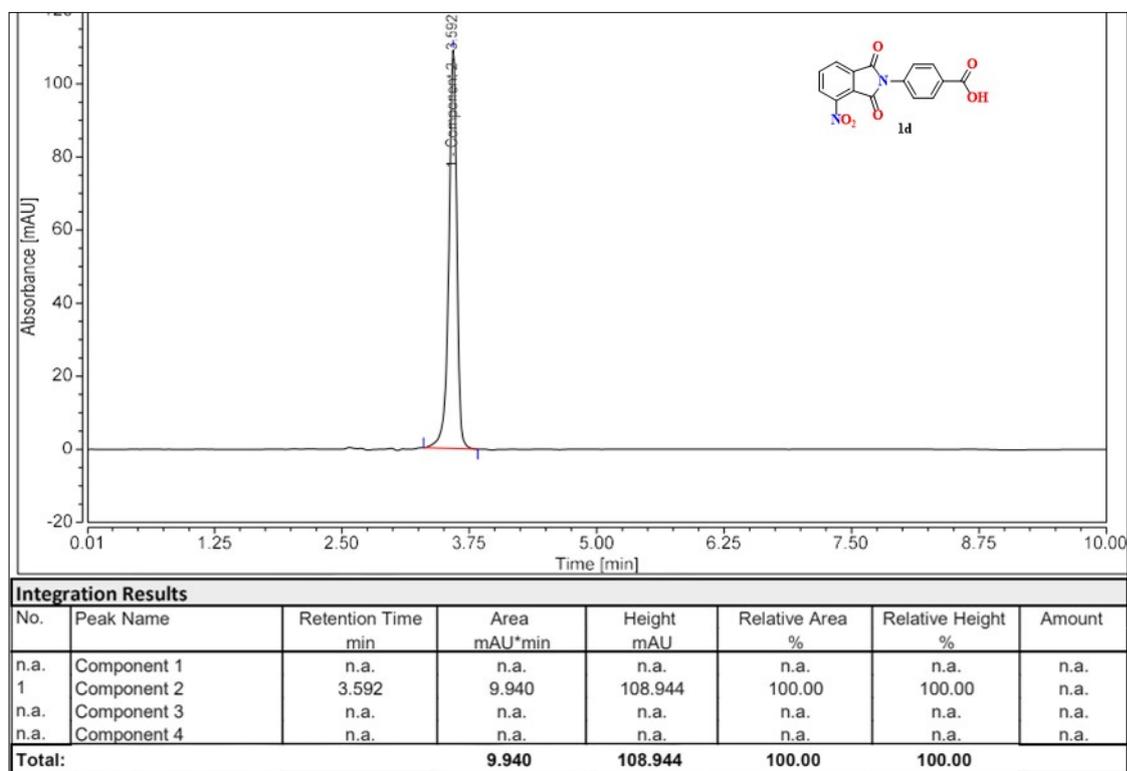


Figure S63. HPLC chromatogram of 4-(4-nitro-1,3-dioxisoindolin-2-yl)benzoic acid (**1d**).

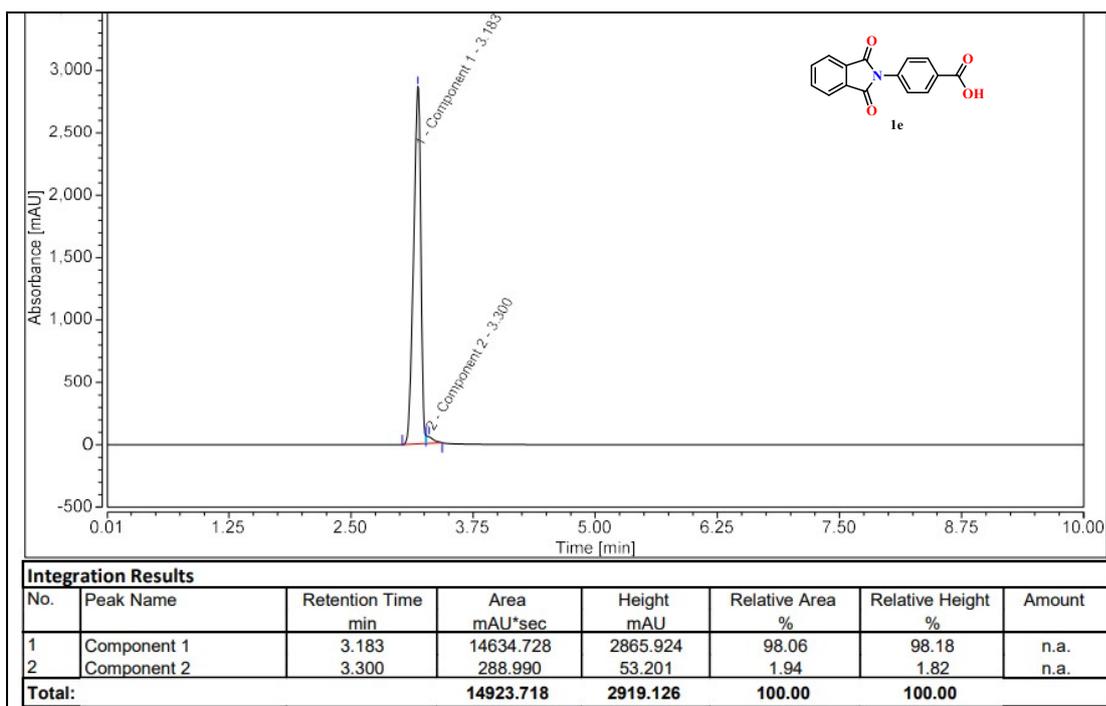


Figure S64. HPLC chromatogram of 4-(1,3-dioxisoindolin-2-yl)benzoic acid (**1e**).

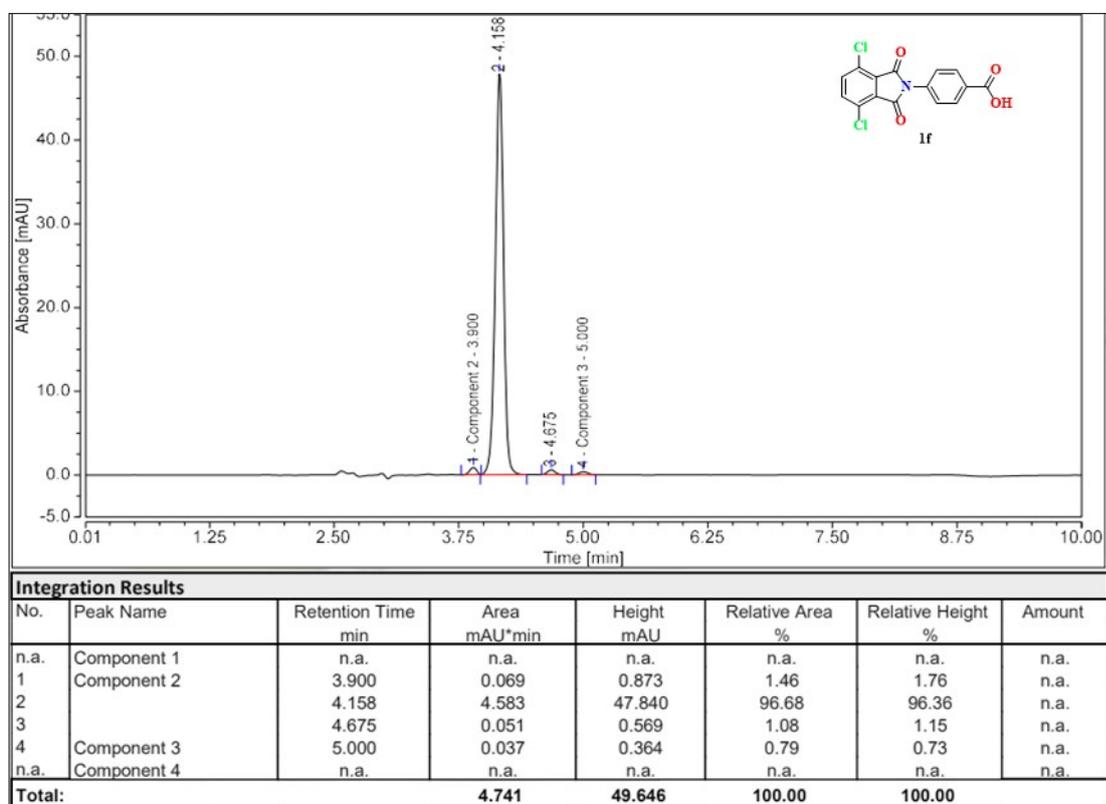


Figure S65. HPLC chromatogram of 4-(4,7-dichloro-1,3-dioxisoindolin-2-yl)benzoic acid (**1f**).

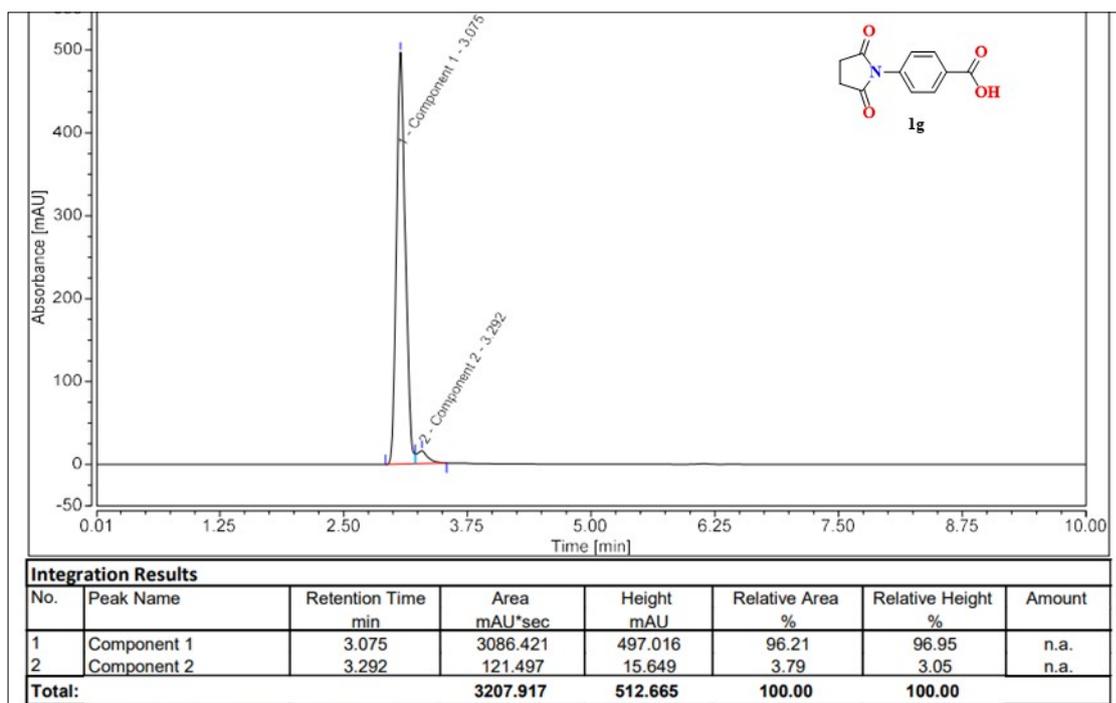


Figure S66. HPLC chromatogram of 4-(2,5-dioxopyrrolidin-1-yl)benzoic acid (**1g**).

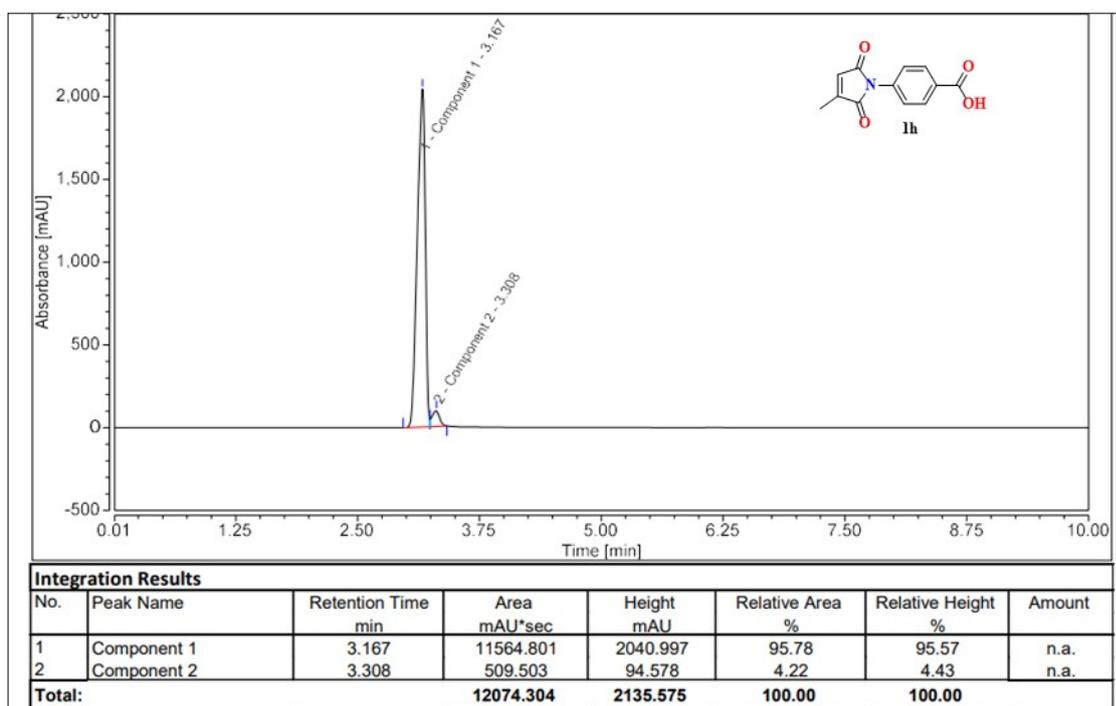


Figure S67. HPLC chromatogram of 4-(3-methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic acid (**1h**).

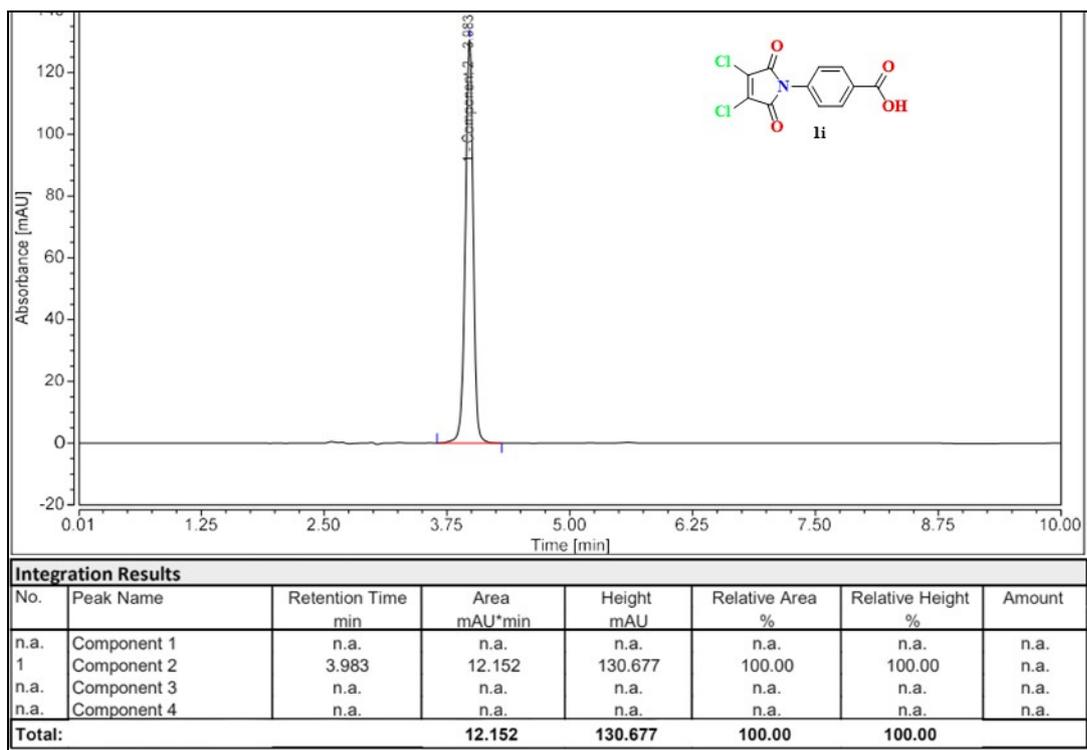


Figure S68. HPLC chromatogram of 4-(3,4-dichloro-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic acid (**1i**).

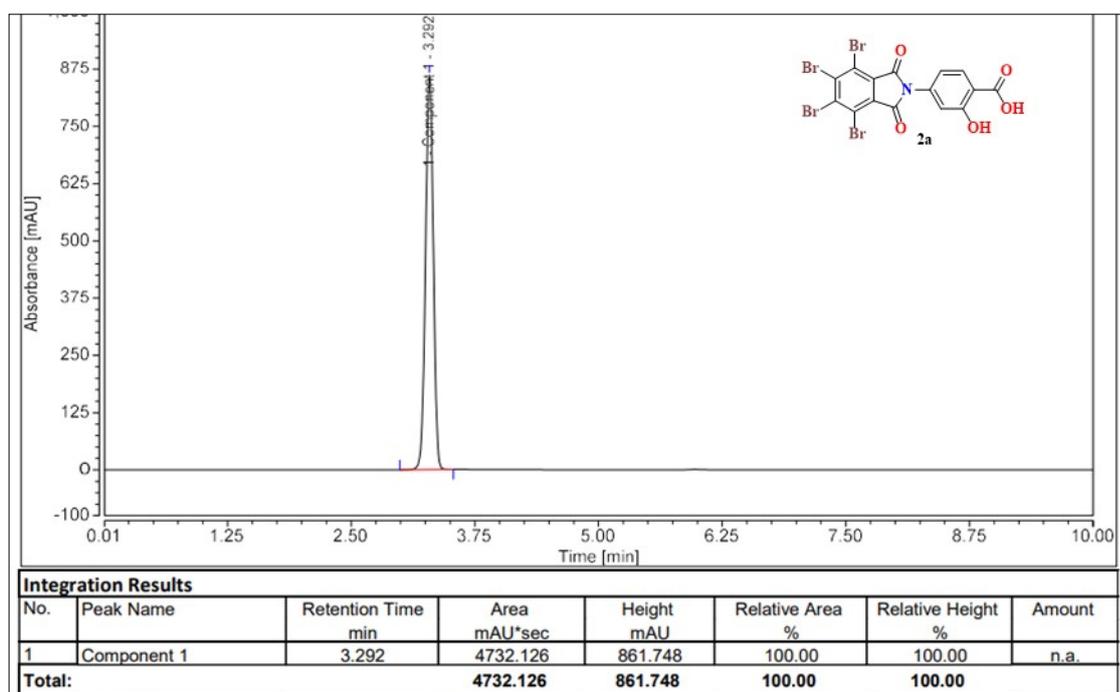


Figure S69. HPLC chromatogram of 2-hydroxy-4-(4,5,6,7-tetrabromo-1,3-dioxoisindolin-2-yl)benzoic acid (**2a**).

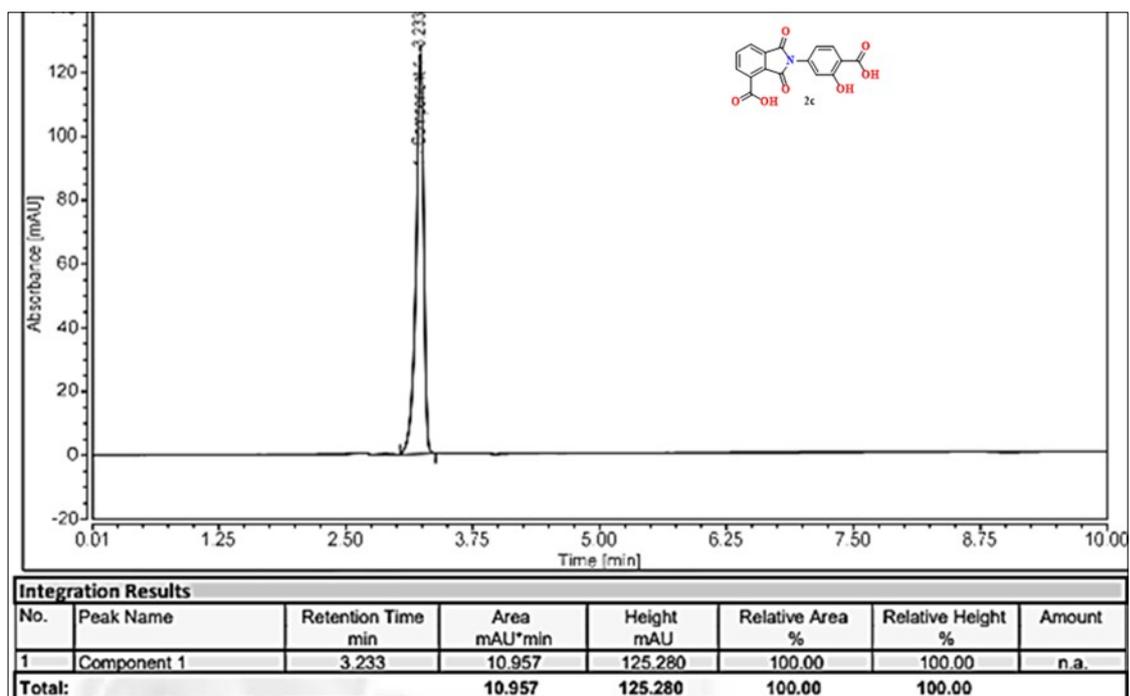


Figure S70. HPLC chromatogram of 2-(4-carboxy-3-hydroxyphenyl)-1,3-dioxisoindoline-4-carboxylic acid (2c).

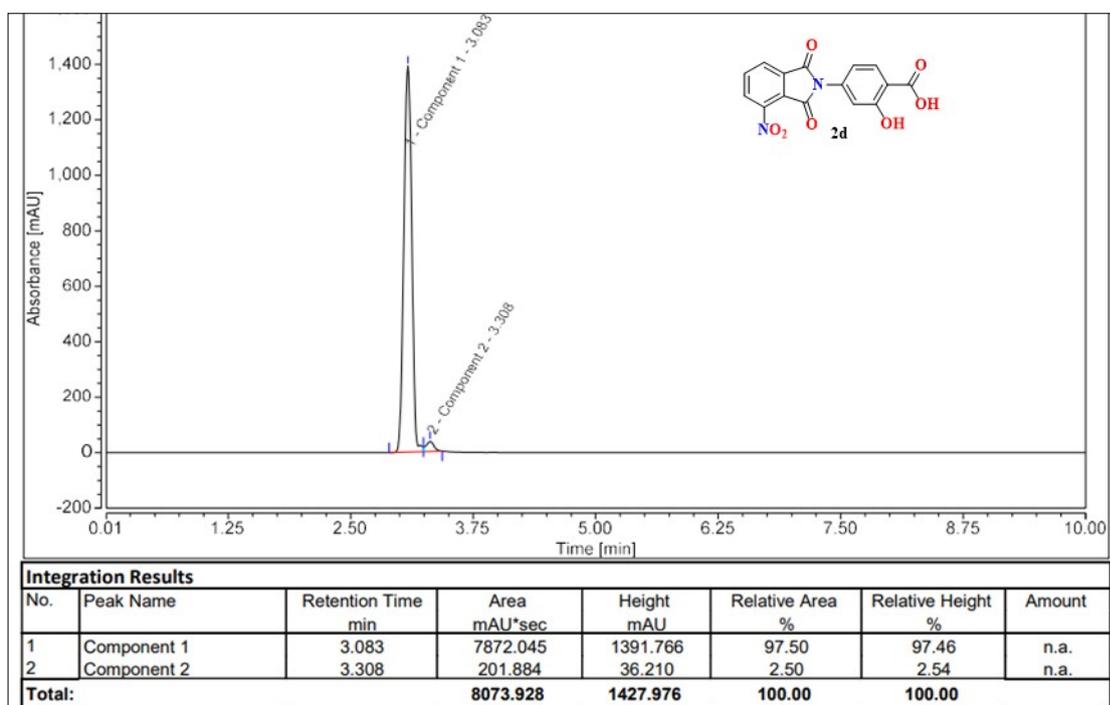


Figure S71. HPLC chromatogram of 2-hydroxy-4-(4-nitro-1,3-dioxisoindolin-2-yl)benzoic acid (2d).

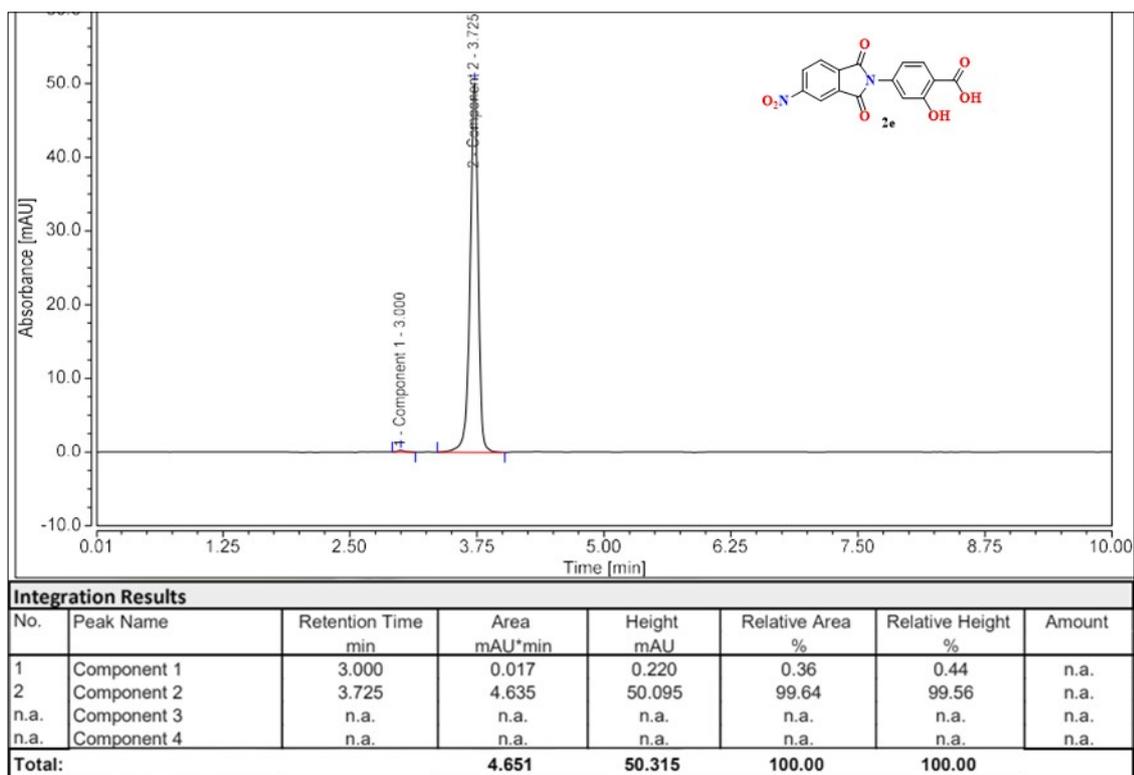


Figure S72. HPLC chromatogram of 2-hydroxy-4-(5-nitro-1,3-dioxoisindolin-2-yl)benzoic acid (**2e**).

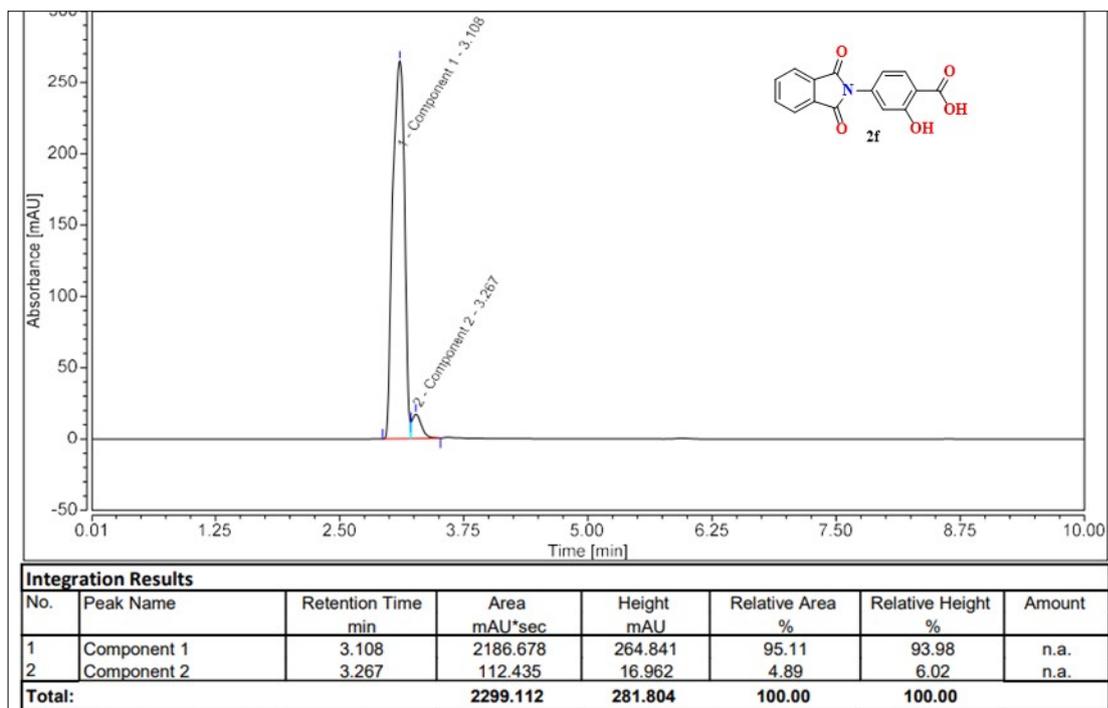


Figure S73. HPLC chromatogram of 4-(1,3-dioxoisindolin-2-yl)-2-hydroxybenzoic acid (**2f**).

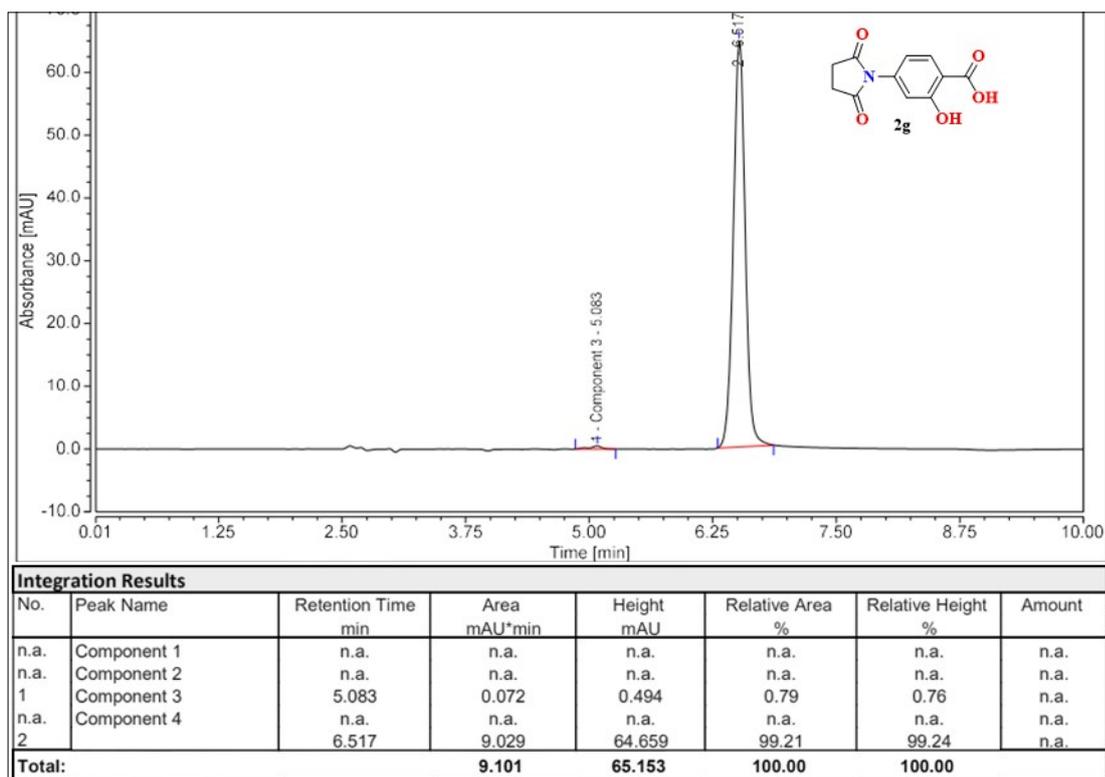


Figure S74. HPLC chromatogram of 4-(2,5-dioxopyrrolidin-1-yl)-2-hydroxybenzoic acid (**2g**).

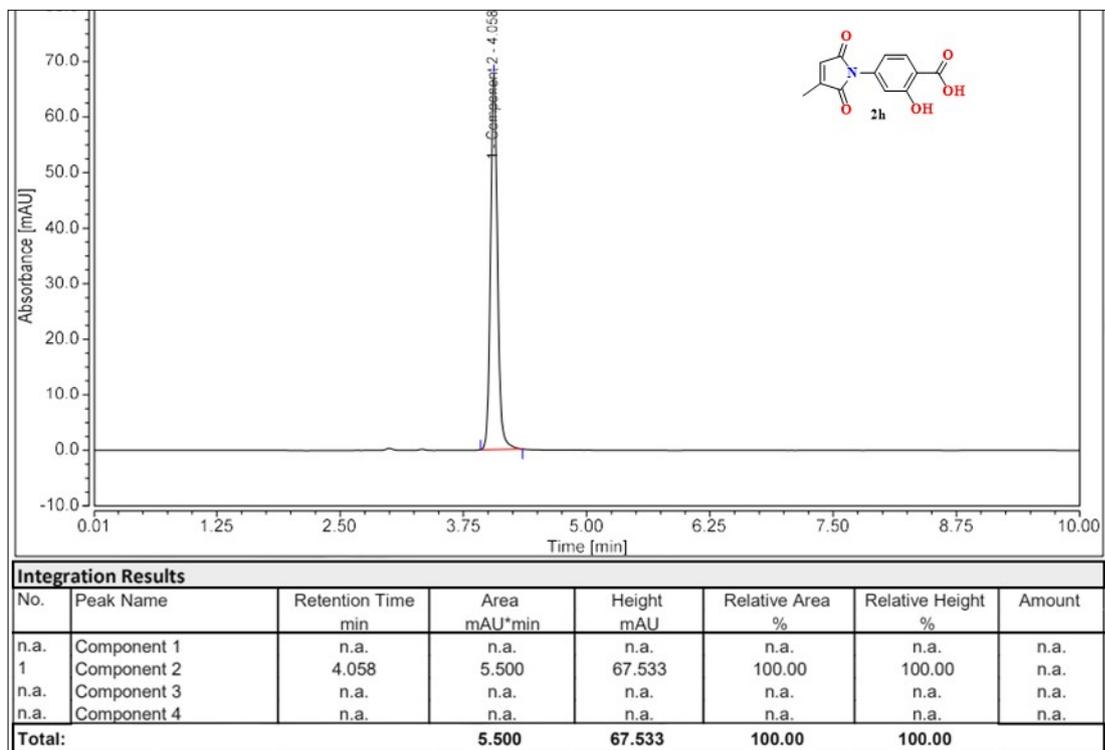


Figure S75. HPLC chromatogram of 2-hydroxy-4-(3-methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic acid (**2h**).

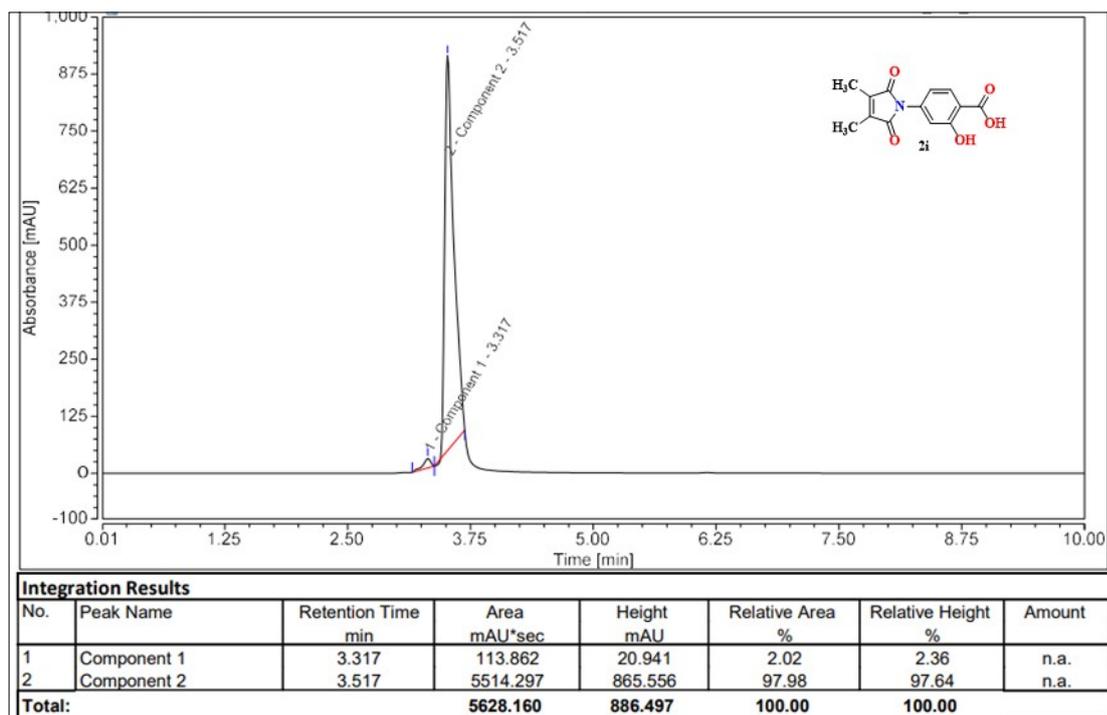


Figure S76. HPLC chromatogram of 4-(3,4-dimethyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2-hydroxybenzoic acid (**2i**).

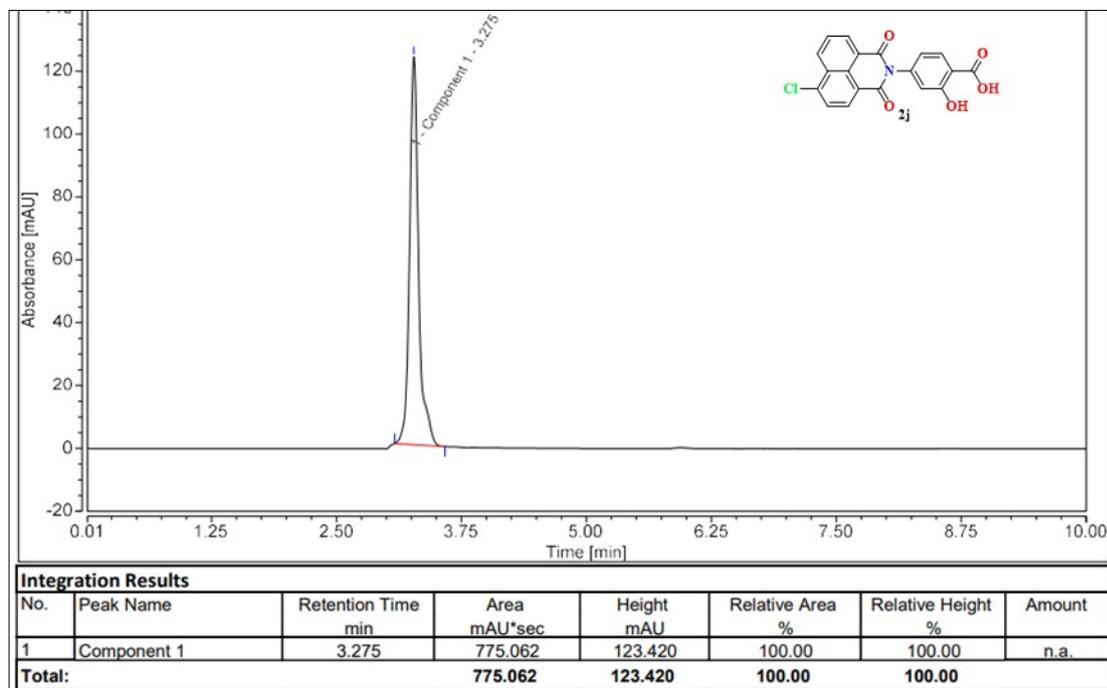


Figure S77. HPLC chromatogram of 4-(6-chloro-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)-2-hydroxybenzoic acid (**2j**).

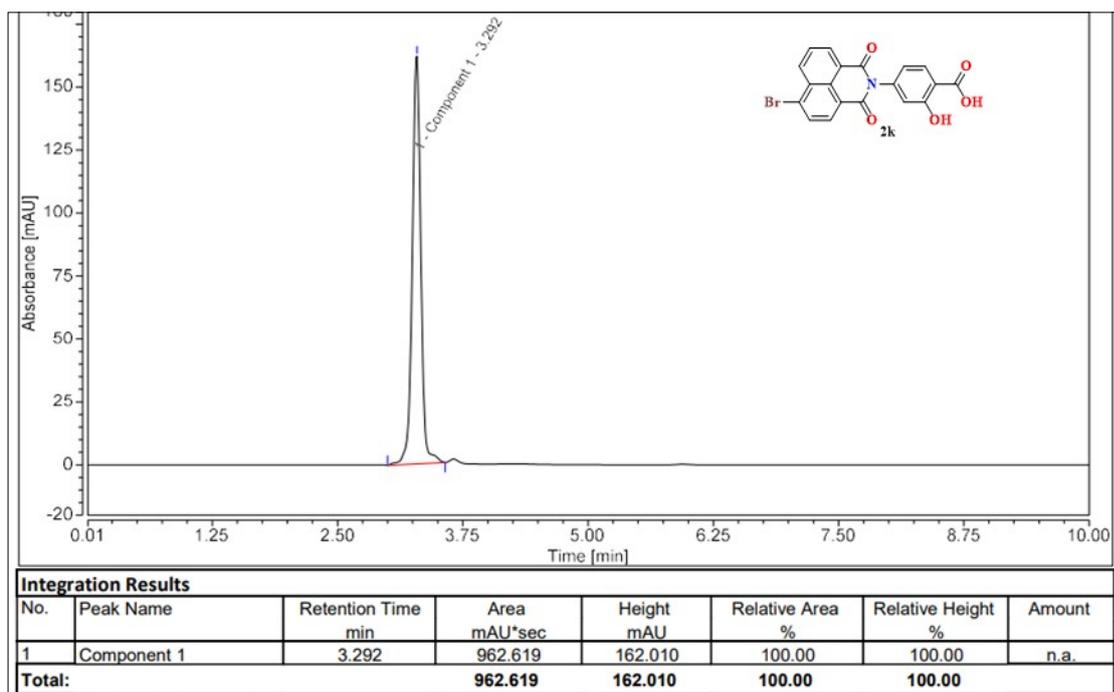


Figure S78. HPLC chromatogram of 4-(6-bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)-2-hydroxybenzoic acid (**2k**).

IR spectra of cyclic imide derivatives

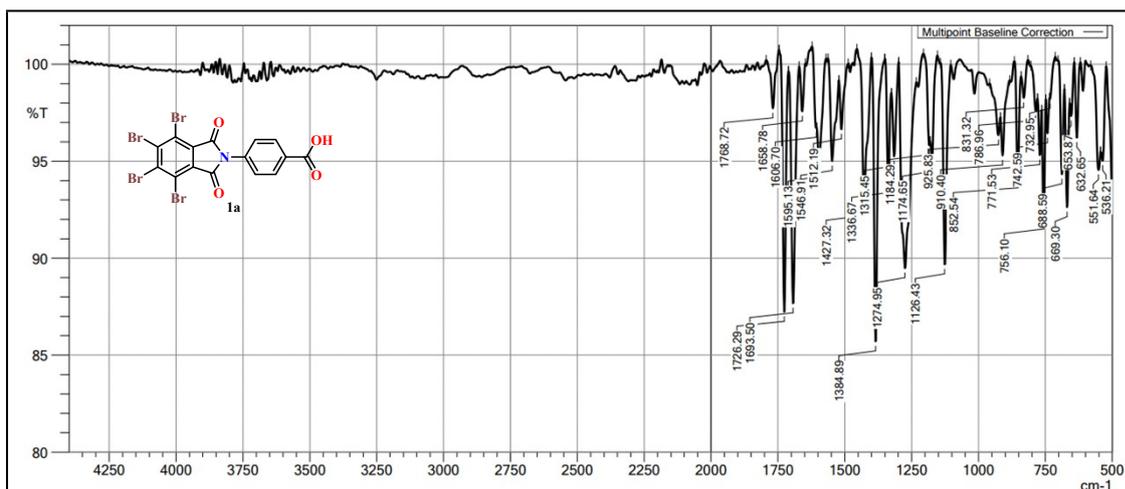


Figure S79. IR spectrum of 4-(4,5,6,7-tetrabromo-1,3-dioxisoindolin-2-yl)benzoic acid (**1a**).

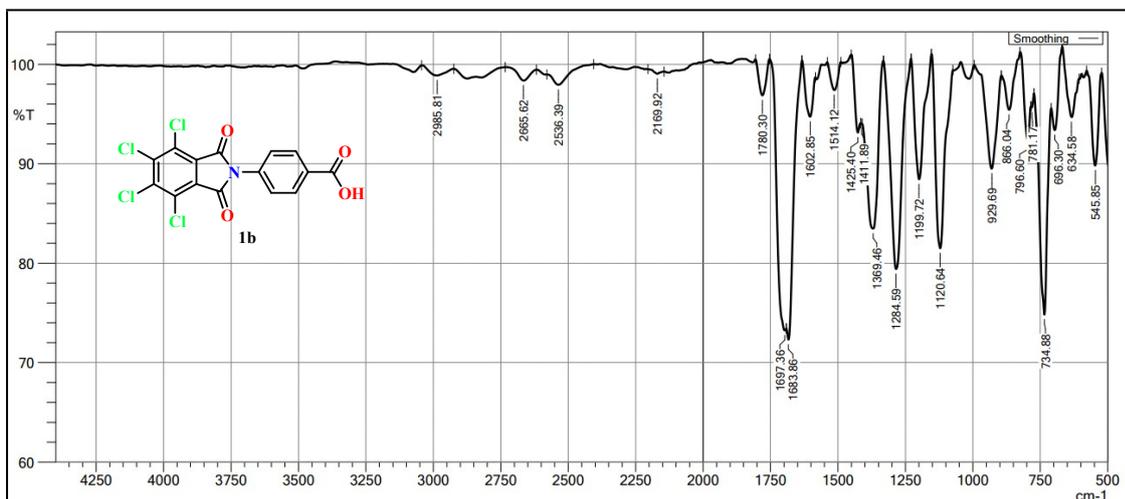


Figure S80. IR spectrum of 4-(4,5,6,7-tetrachloro-1,3-dioxisoindolin-2-yl)benzoic acid (**1b**).

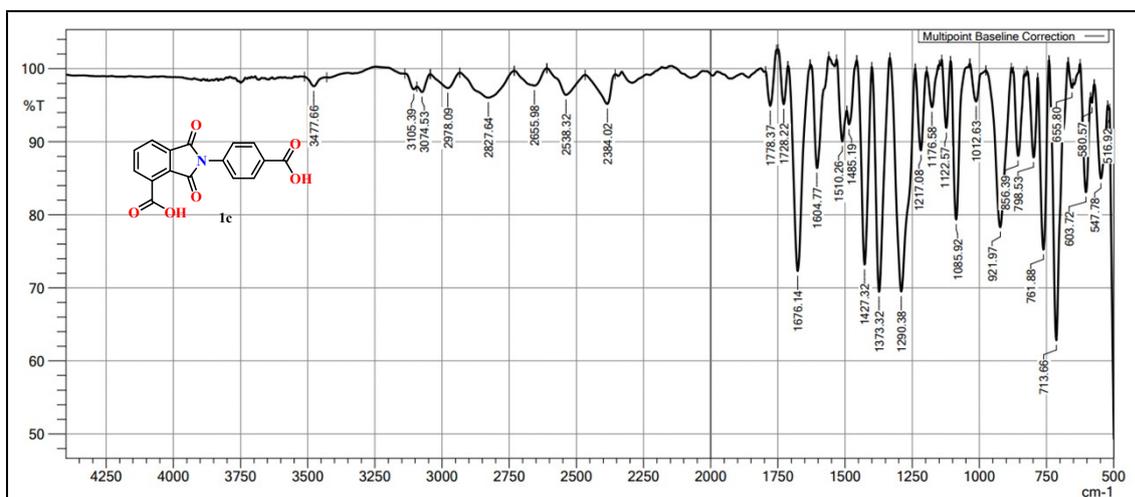


Figure S81. IR spectrum of 2-(4-carboxyphenyl)-1,3-dioxisoindoline-4-carboxylic acid (**1c**).

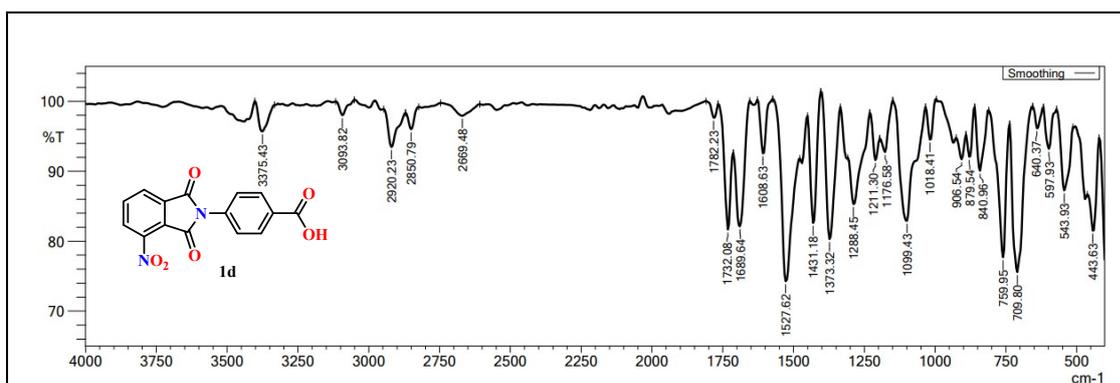


Figure S82. IR spectrum of 4-(4-nitro-1,3-dioxoisindolin-2-yl)benzoic acid (**1d**).

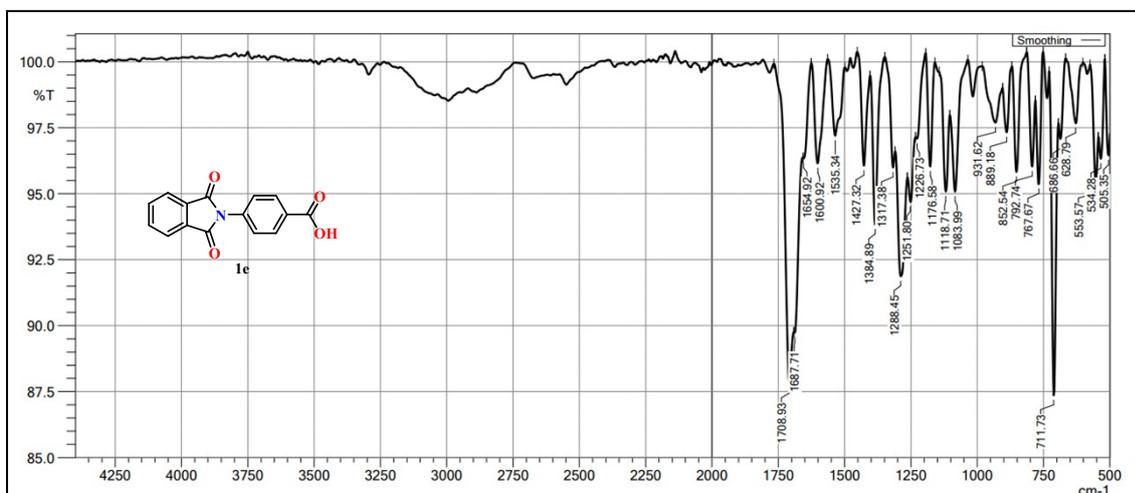


Figure S83. IR spectrum of 4-(1,3-dioxoisindolin-2-yl)benzoic acid (**1e**).

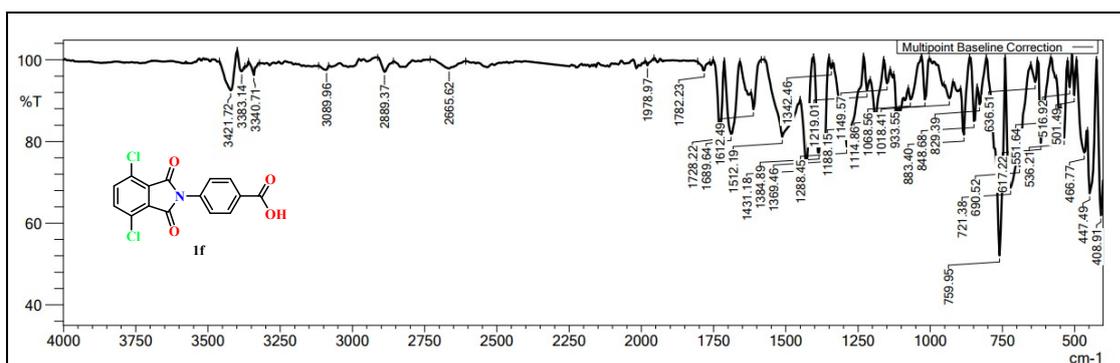
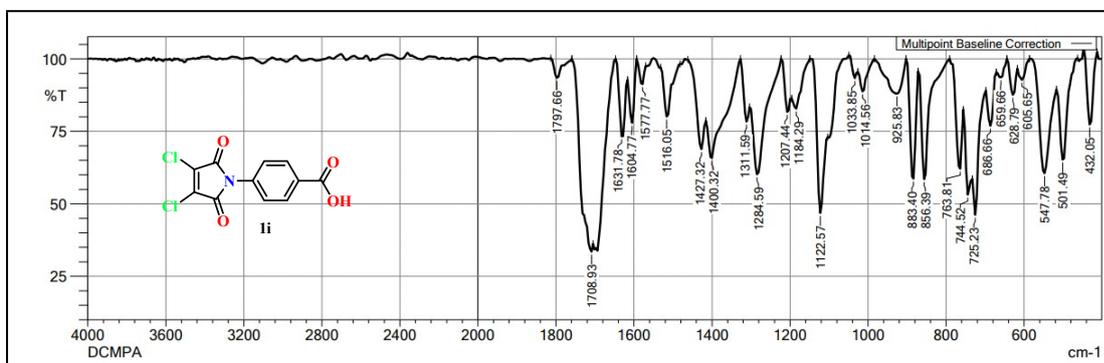
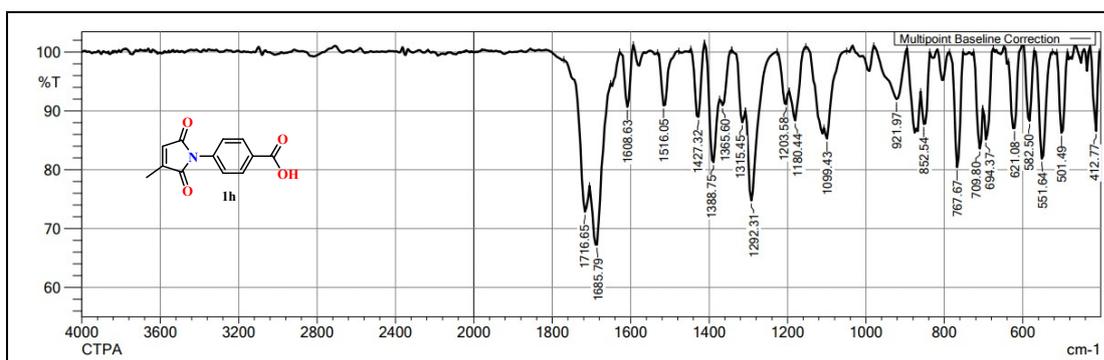
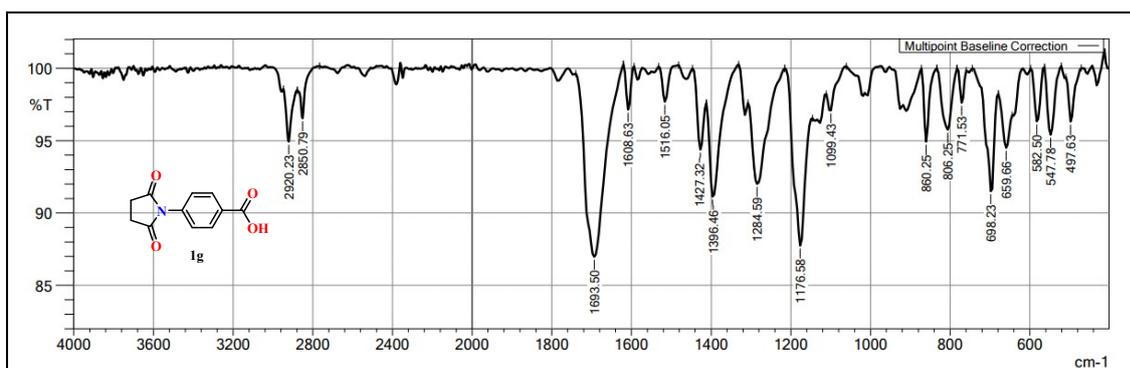


Figure S84. IR spectrum of 4-(4,7-dichloro-1,3-dioxoisindolin-2-yl)benzoic acid (**1f**).



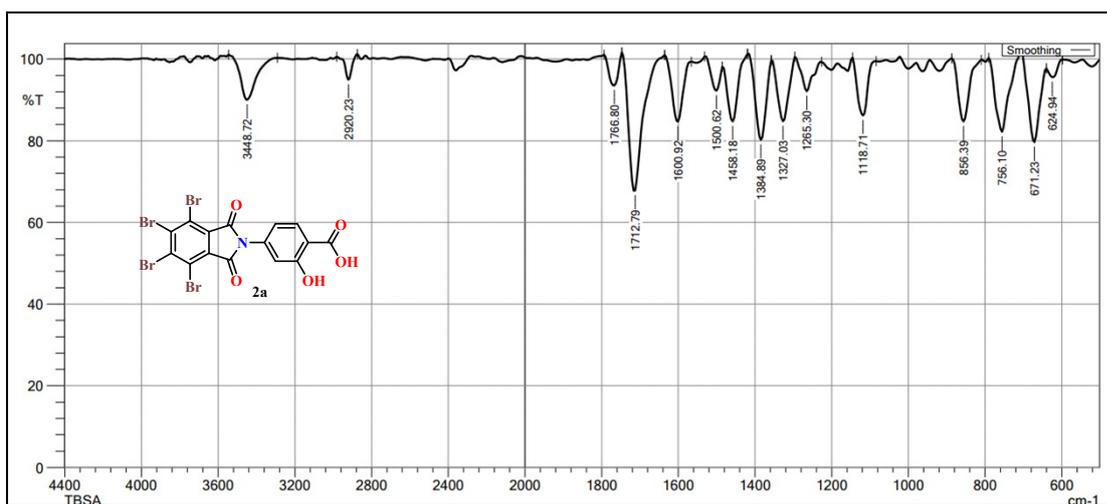


Figure S88. IR spectrum of 2-hydroxy-4-(4,5,6,7-tetrabromo-1,3-dioxoisindolin-2-yl)benzoic acid (**2a**).

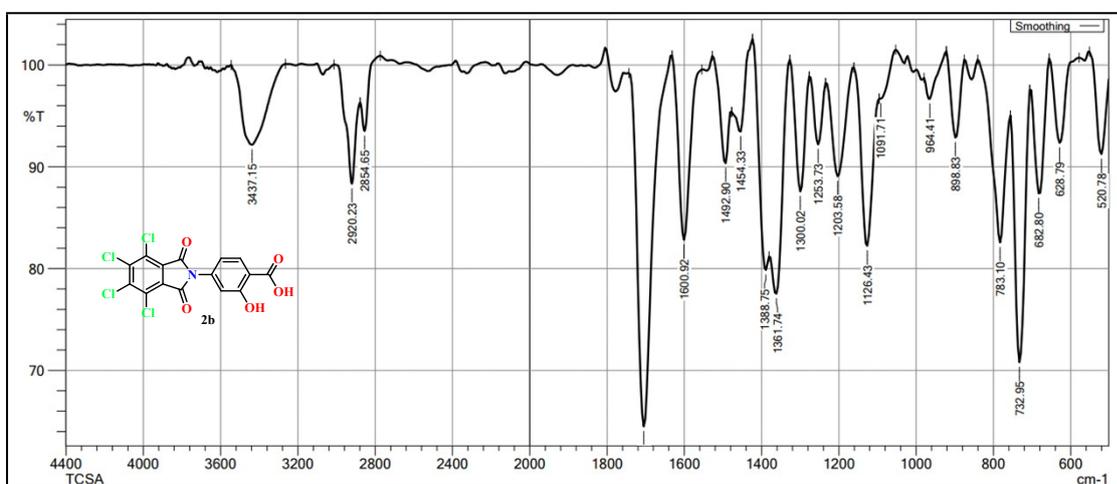


Figure S89. IR spectrum of 2-hydroxy-4-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)benzoic acid (**2b**).

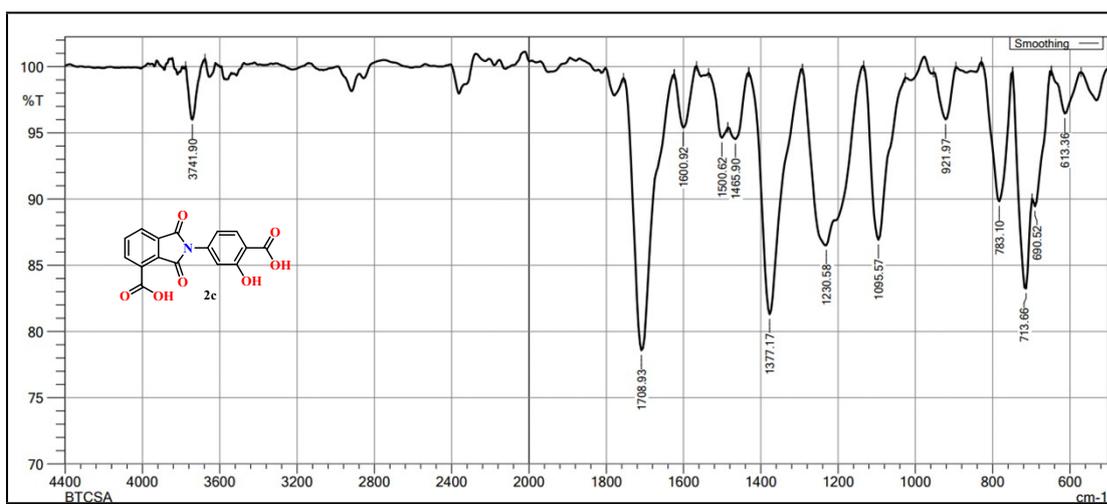


Figure S90. IR spectrum of 2-(4-carboxy-3-hydroxyphenyl)-1,3-dioxoisindoline-4-carboxylic acid (**2c**).

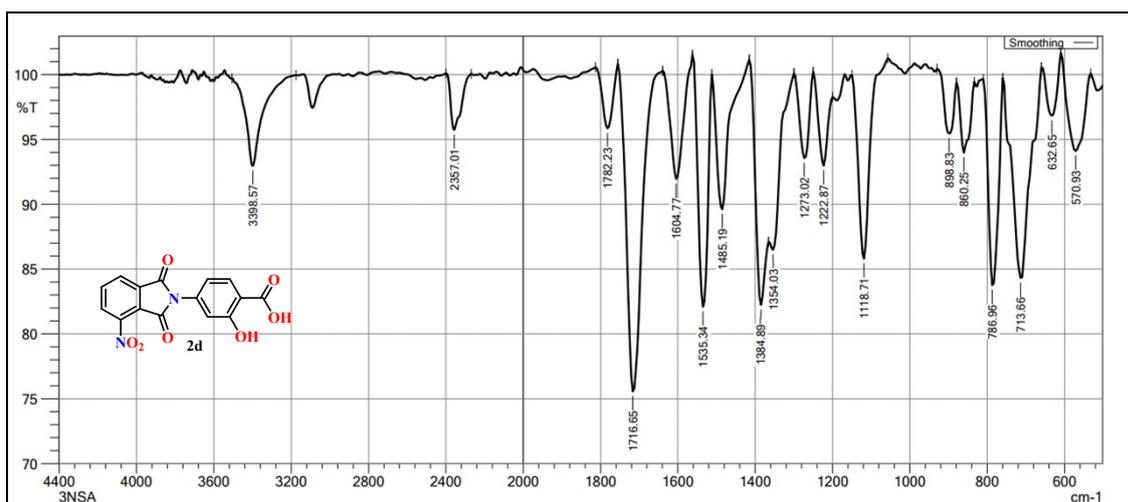


Figure S91. IR spectrum of 2-hydroxy-4-(4-nitro-1,3-dioxisoindolin-2-yl)benzoic acid (**2d**).

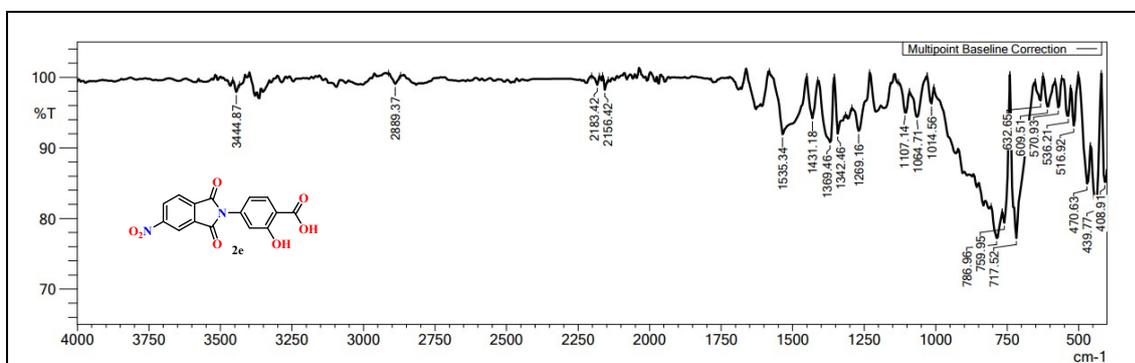


Figure S92. IR spectrum of 2-hydroxy-4-(5-nitro-1,3-dioxisoindolin-2-yl)benzoic acid (**2e**).

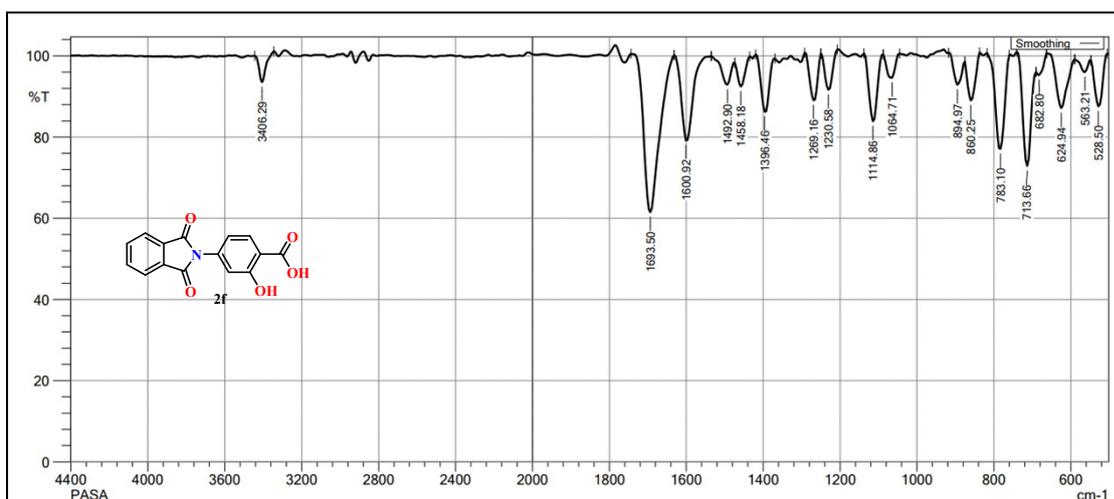


Figure S93. IR spectrum of 4-(1,3-dioxisoindolin-2-yl)-2-hydroxybenzoic acid (**2f**).

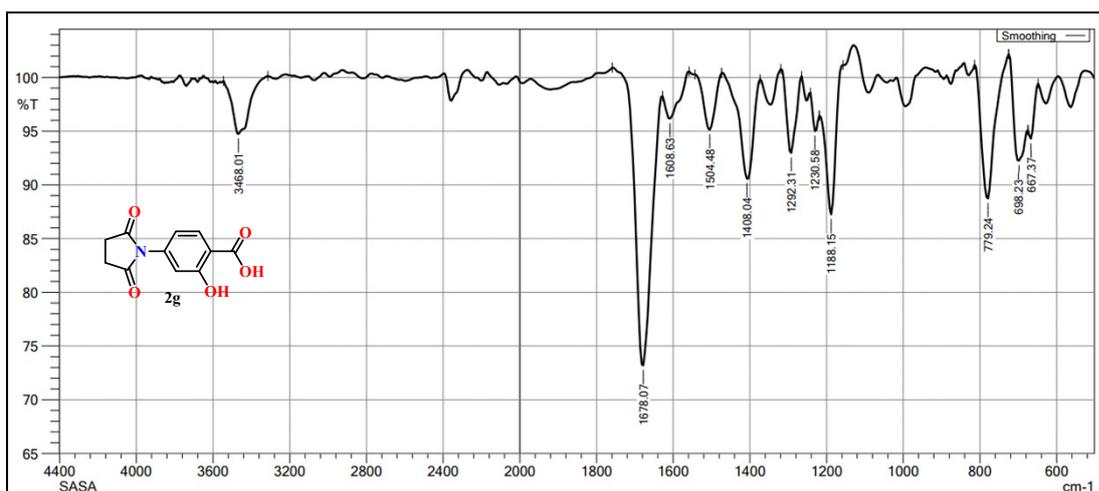


Figure S94. IR spectrum of 4-(2,5-dioxopyrrolidin-1-yl)-2-hydroxybenzoic acid (**2g**).

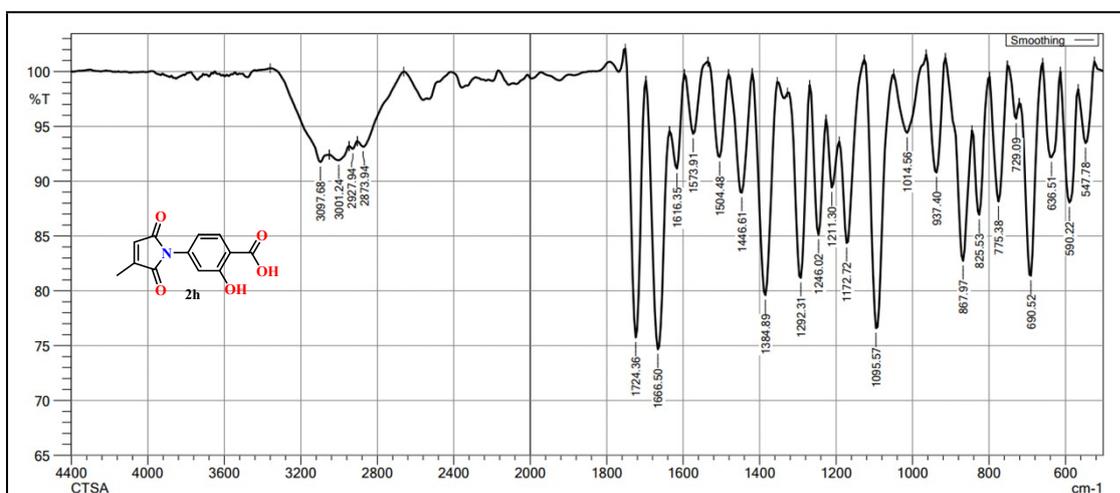


Figure S95. IR spectrum of 2-hydroxy-4-(3-methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoic acid (**2h**).

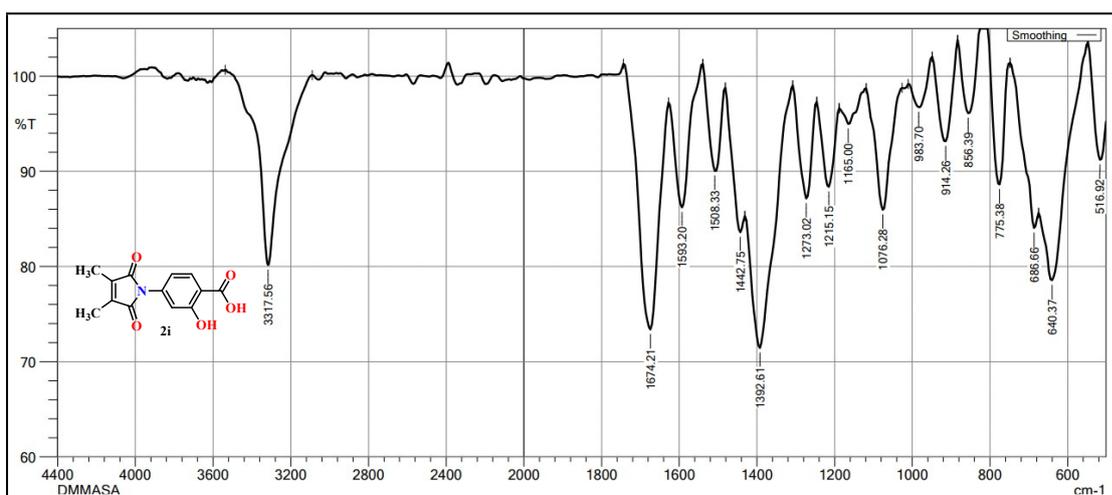


Figure S96. IR spectrum of 4-(3,4-dimethyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2-hydroxybenzoic acid (**2i**).

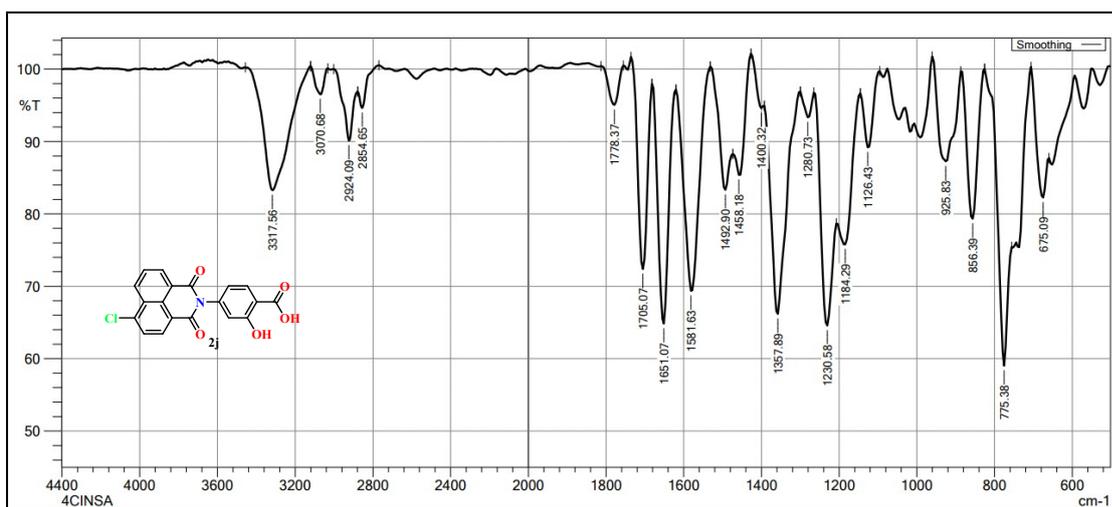


Figure S97. IR spectrum of 4-(6-chloro-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)-2-hydroxybenzoic acid (2j).

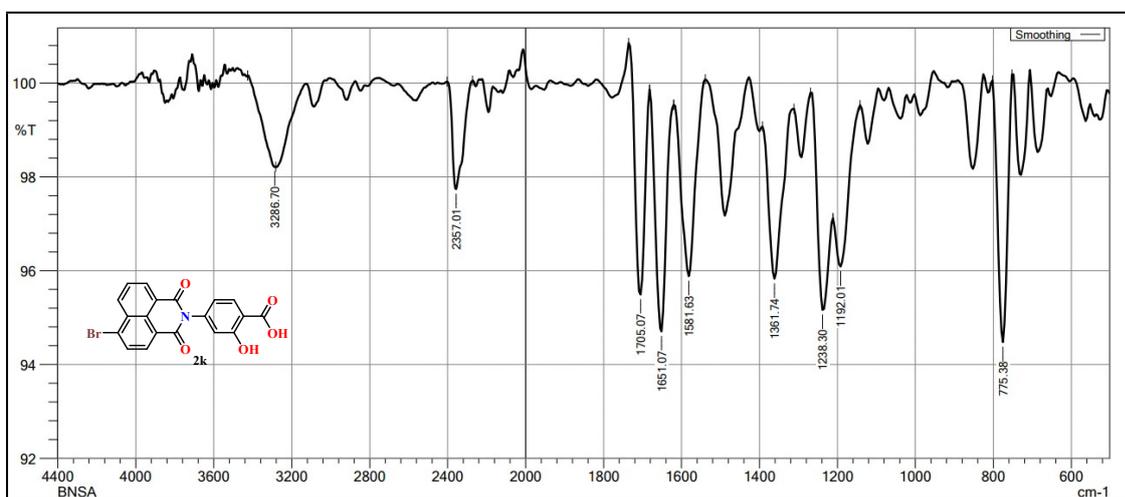


Figure S98. IR spectrum of 4-(6-bromo-1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)-2-hydroxybenzoic acid (2k).