SUPPLEMENTARY INFORMATION

Small molecule inhibitors of the BfrB-Bfd interaction decrease *Pseudomonas aeruginosa* fitness and potentiate fluoroquinolone activity

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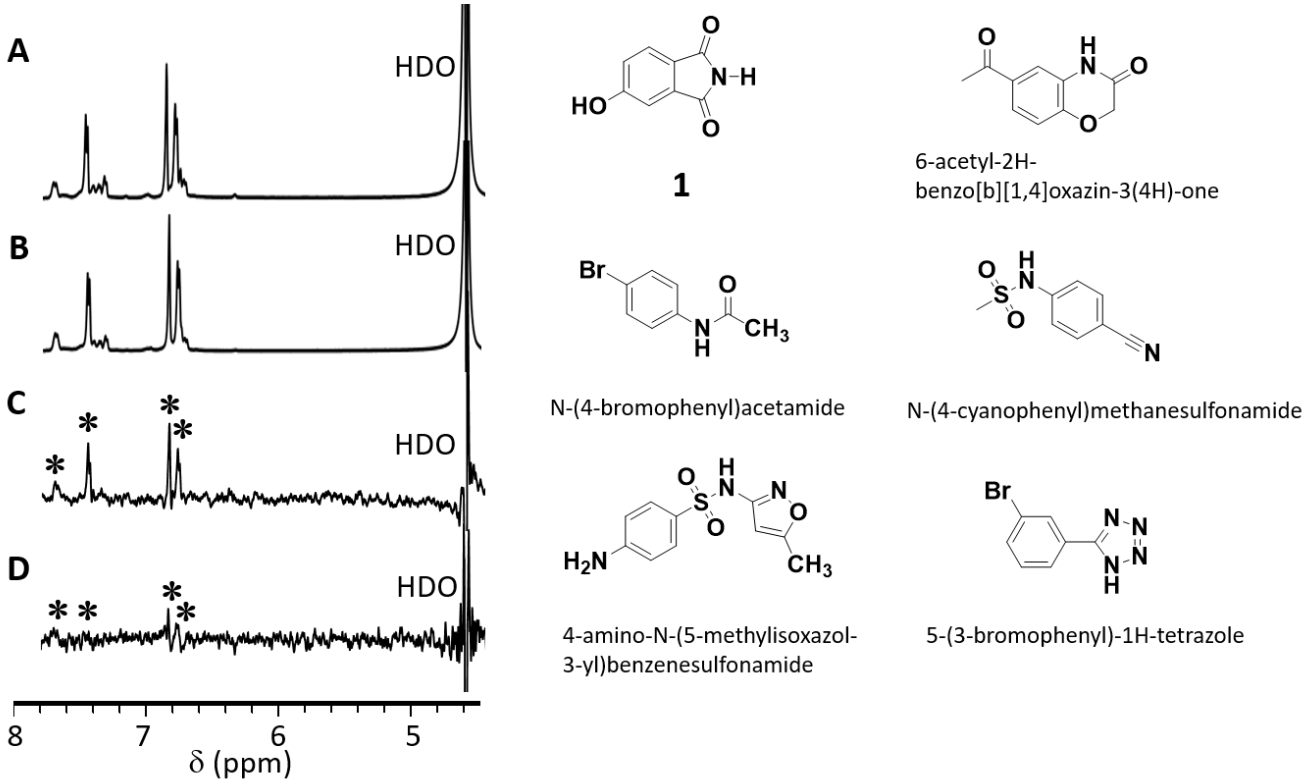

Figure S1. Saturation transfer difference (STD) NMR is well suited to screen fragments that bind to the large 24-mer BfrB (~440 kDa). The screening protocol is illustrated with the NMR spectra obtained for fragment **1** (5-hydroxyisoindoline-1,3-dione): (**A**) ^{1}H spectrum of fragment **1** alone, used to assess purity and solubility of the fragment. (**B**) ^{1}H spectrum of fragment **1** in the presence of BfrB, used to determine that the fragment integrity and solubility are not affected by the presence of protein. (**C**) The STD spectrum of the solution containing fragment **1** and BfrB indicates that the fragment binds to BfrB. (**D**) The STD spectrum of a solution containing fragment **1**, BfrB and Bfd shows that the intensity of the STD signals is largely decreased relative to the spectrum in panel C, which indicates that Bfd displaces fragment **1** from BfrB, and strongly suggests that the fragment binds BfrB at the Bfd-binding site. The structures of fragments identified to bind at the Bfd-binding site of BfrB using this strategy are shown above. Soaking experiments described in the text allowed the determination of fragment **1** bound to the Bfd-binding site on BfrB.

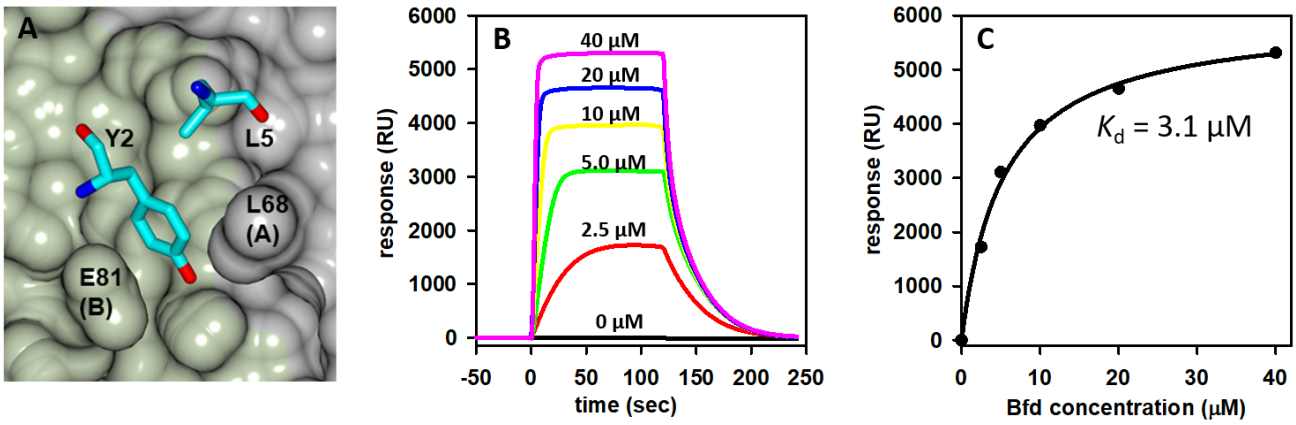

Figure S2. The absence of heme in BfrB does not influence its structure, or the strength of its interaction with Bfd. (**A**) The structure of the Bfd-binding site in apo-BfrB is identical to its counterpart in BfrB: The view shows a subunit dimer from the BfrB-Bfd complex (PDB 4E6K) superimposed onto a subunit dimer of apo-BfrB (surface rendering, green and gray), which results in an RMSD deviation of 0.18 Å, between Cα atoms (155 residues). Amino acids Y2/L5 from Bfd in the BfrB-Bfd complex (4E6K), which are positioned in the Bfd-binding site of BfrB, are rendered as cyan cylinders. (**B**) Overlay of reference- and baseline-subtracted sensograms obtained by passing solutions of Bfd over immobilized apo-BfrB. (**C**) Black circles are the responses at steady state concentrations in panel B plotted as a function of the Bfd concentration and fitted as described in the Experimental Section. The K_d measured for the interaction between apo-BfrB and Bfd is nearly identical to that measured for the interaction between BfrB and Bfd.

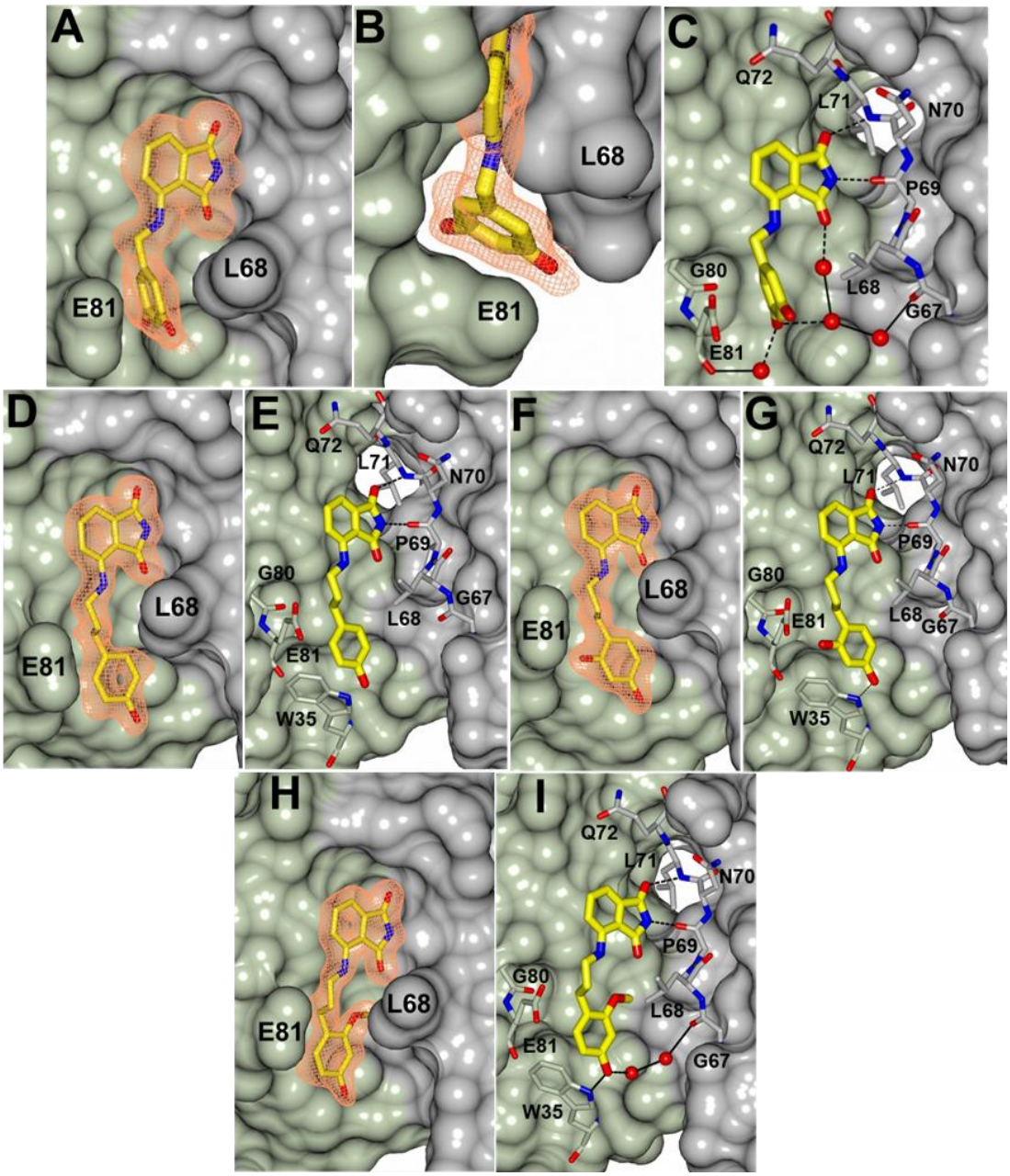

Figure S3. Binding modes of four additional analogs bound to the Bfd-binding site of BfrB. Subunits A and B of a BfrB subunit dimer are colored gray and green, respectively. The Fo-Fc omit map (orange mesh) contoured at 3σ and hydrogen bond interactions (dashed lines) are shown for each analog. Water mediated contacts are indicated by the solid lines. (**A-C**) analog **12** with panel B showing the two orientations modeled for the m-hydroxyphenyl ring, (**D-E**) analog **13**, (**F-G**) analog **14** and (**H-I**) analog **15**.

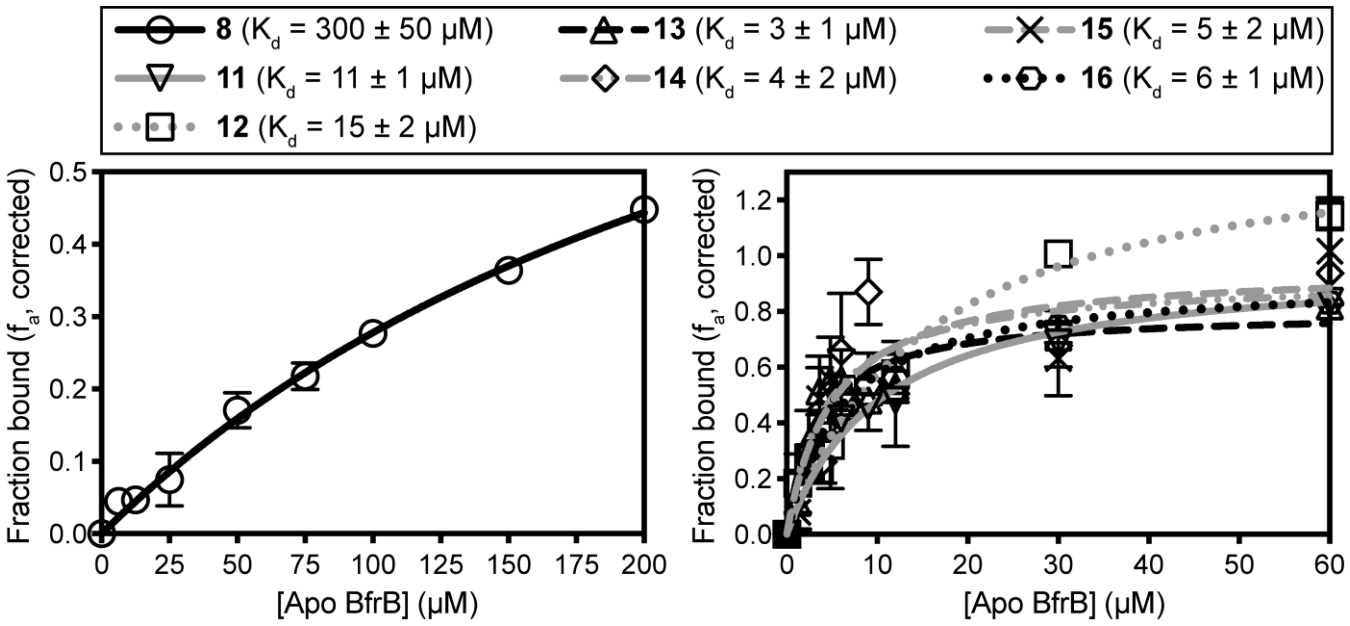

Figure S4. Quantification of the affinity (K_d) of apo-BfrB for fragment **8** and analogs **11**–**16** evaluated by fluorescence polarization, corrected to account for changes in fluorescence intensity upon binding. Values were obtained in 100 mM potassium phosphate buffer (pH 7.6) containing 1 mM TCEP and 0.5% DMSO. The initial concentration of analog titrated with apo-BfrB is: 50 μM (**8**), 2 μM (**12**, **13**), and 5 μM (**11**, **14**, **15**, **16**).

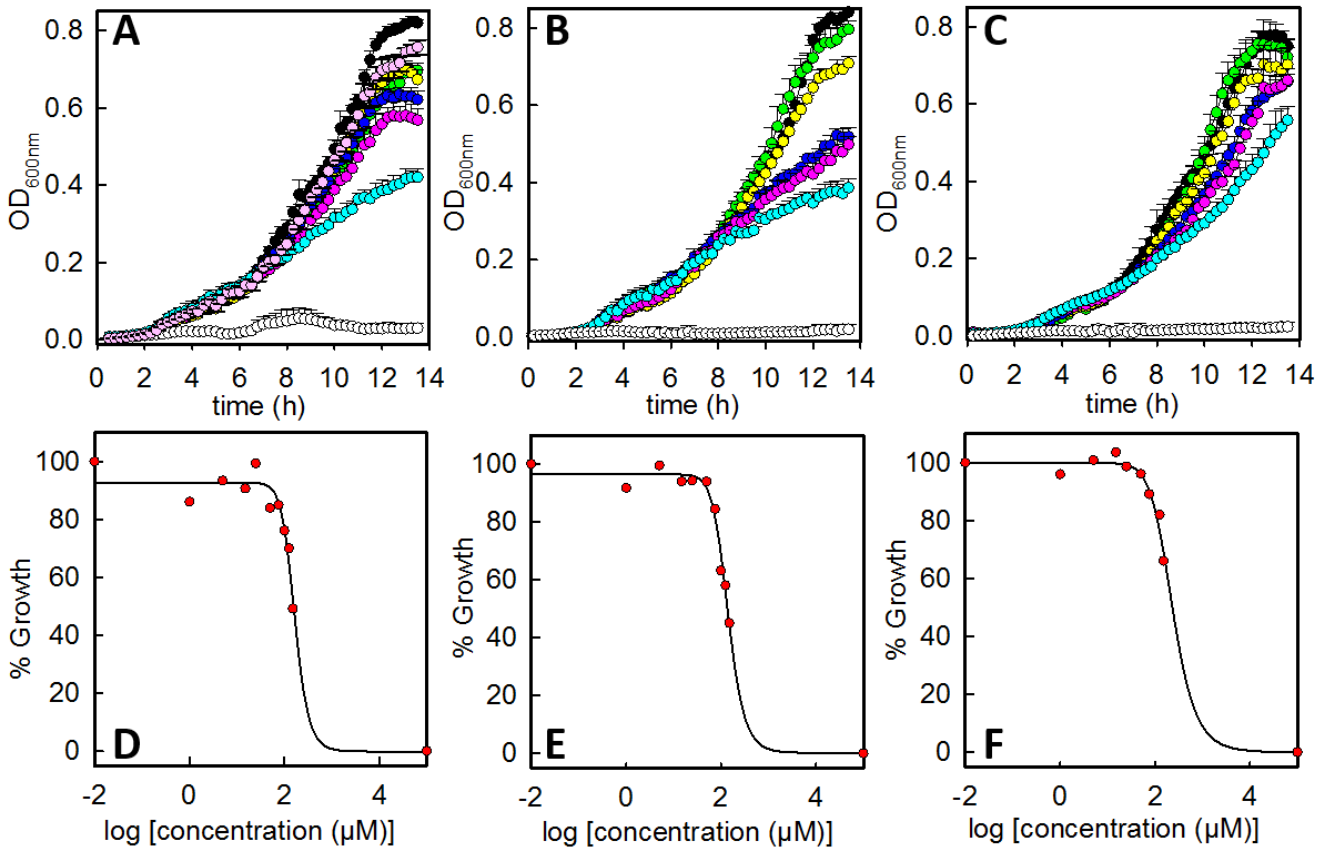

Figure S5. Three other analogs cause a growth defect in *P. aeruginosa*. Panels (**A**), (**B**) and (**C**) show the time-dependent growth of *P. aeruginosa* cultures treated with analog **13**, **14**, and **15**, respectively. The black circles correspond to untreated cells (DMSO control), and the open circles correspond to cells treated with ciprofloxacin (0.75 μg/mL). The concentrations of analog are: 15 μM (pink, analog **13**), 50 μM (green), 75 μM (yellow), 100 μM (blue), 125 μM (magenta), 150 μM (cyan). The corresponding IC_{50} values (**D, E** and **F**) were obtained by calculating the % growth using OD_{600} values at 13 h and fitting to equation 2, as indicated in the Experimental Section. The IC_{50} values (see Table 1) are the average and standard deviation from three independent experiments.

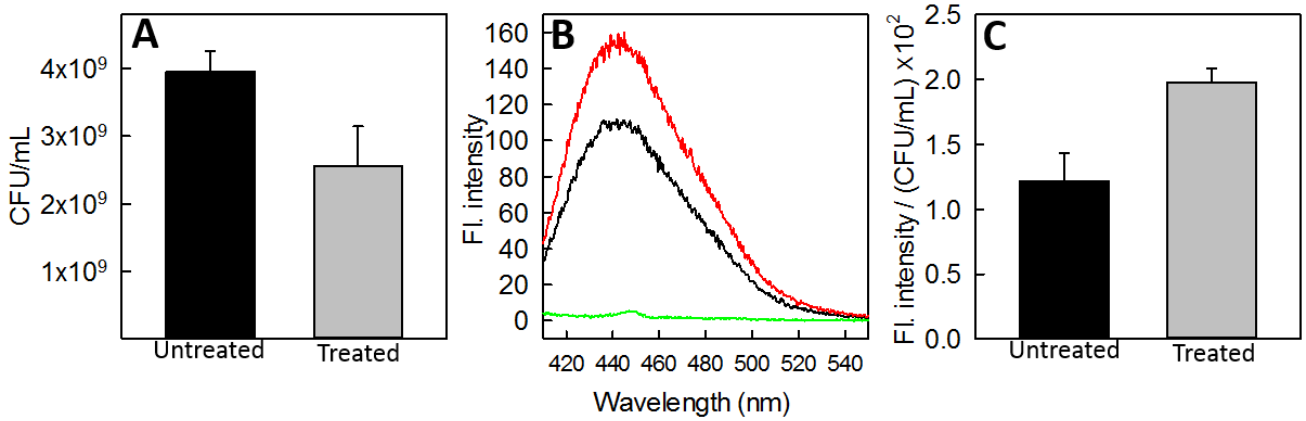

Figure S6. *P. aeruginosa* cells treated with analog **11** overproduce pyoverdin. (**A**) *P. aeruginosa* cultures treated with analog **11** (125 µM) for 13 h exhibit approximately 70% of the viable cells in the untreated control (DMSO). (**B**) Fluorescence spectra obtained from cell free supernatants (13 h post-inoculation) after a 500-fold dilution in PBS buffer, pH 7.4. The black trace is the spectrum from pyoverdin present in cell-free supernatant from untreated cells, and the red trace is the spectrum from pyoverdin in cell-free supernatant from samples treated with analog **11** (125 µM). The green trace was obtained after a 125 µM solution of analog **11** in M63 media was diluted 500-fold in PBS buffer, to show that the relatively weak intrinsic fluorescence of the analog does not interfere with the strong fluorescence response from pyoverdin. (**C**) Fluorescence intensity normalized to the number of viable cells (CFU/mL) show that the cells treated with with analog **11** secrete ~1.8-fold more pyoverdin than cells in the DMSO control. Error bars represent standard deviations from three independent experiments.

Table S1. Crystallographic data for apo-BfrB and the BfrB-Inhibitor complexes.

	Apo BfrB	**Fragment 1**	**Analog 11**	**Analog 12**	**Analog 13**	**Analog 14**	**Analog 15**	**Analog 16**
PDB ID	6NLF	6NLG	6NLI	6NLJ	6NLK	6NLL	6NLM	6NLN
Data Collection								
Unit-cell parameters (Å, º)	*a*=129.73 *b*=197.77 *c*=204.24	*a*=153.81 *c*=153.41	*a*=129.55 *b*=194.23 *c*=202.76	*a*=129.29 *b*=195.01 *c*=203.22	*a*=129.82 *b*=194.56 *c*=203.50	*a*=129.60 *b*=194.39 *c*=202.60	*a*=130.25 *b*=194.97 *c*=203.03	*a*=129.91 *b*=194.88 *c*=203.81
Space group	$C222_1$	$P6_322$	$C222_1$	$C222_1$	$C222_1$	$C222_1$	$C222_1$	$C222_1$
Resolution (Å)[1]	47.90-1.45 (1.47-1.45)	47.84-1.50 (1.53-1.50)	48.56-1.90 (1.93-1.90)	47.60-1.50 (1.68-1.65)	48.64-1.85 (1.88-1.85)	48.60-1.80 (1.83-1.80)	48.74-1.90 (1.93-1.90)	48.72-1.60 (1.63-1.60)
Wavelength (Å)	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
Temperature (K)	100	100	100	100	100	100	100	100
Observed reflns	2,993,762	3,362,221	1,337,641	2,058,004	1,479,771	1,563,475	1,362,877	2,249,402
Unique reflns	458,281	168,538	199,628	305,152	216,954	232,865	201,747	336,765
$\langle I/\sigma(I)\rangle$[1]	11.8 (2.0)	19.2 (2.2)	13.8 (2.2)	15.7 (1.7)	13.3 (2.0)	12.1 (1.7)	9.8 (1.9)	13.0 (1.9)
Completeness (%)[1]	99.9 (100)	99.6 (98.9)	100 (100)	100 (99.9)	99.7 (99.3)	99.3 (99.9)	100 (100)	100 (100)
Multiplicity[1]	6.5 (6.4)	19.9 (20.1)	6.7 (6.9)	6.7 (6.8)	6.8 (6.7)	6.7 (6.5)	6.8 (6.8)	6.7 (6.8)
R_{merge} (%)[1, 2]	9.4 (90.1)	10.6 (185.0)	10.6 (110.2)	7.1 (113.1)	9.2 (95.6)	9.5 (112.3)	16.3 (115.4)	9.1 (107.0)
R_{meas} (%)[1, 4]	10.3 (98.1)	10.9 (189.0)	11.5 (119.1)	7.7 (122.4)	10.0 (103.6)	10.5 (123.6)	17.6 (125.1)	9.8 (115.8)
R_{pim} (%)[1, 4]	4.1 (38.4)	2.4 (41.7)	4.5 (45.0)	3.0 (46.7)	3.8 (39.6)	4.0 (48.0)	6.8 (47.8)	3.8 (44.0)
$CC_{1/2}$ [1, 5]	0.998 (0.700)	0.999 (0.768)	0.998 (0.757)	0.999 (0.637)	0.998 (0.779)	0.998 (0.646)	0.995 (0.610)	0.999 (0.699)
Refinement								
Resolution (Å)	37.18-1.45	38.35-1.50	47.22-1.90	44.09-1.65	47.31-1.85	46.76-1.80	46.92-1.90	48.72-1.60
Reflections (working/test)	435,260/22,924	159,985/8,506	189,601/9,934	289,938/15,131	206,061/10,818	221,176/11,583	191,506/10,141	319,879/16,762
R_{factor} / R_{free} (%)[3]	14.7 / 16.5	15.0/15.8	16.6/20.5	15.5/17.8	16.2/19.5	15.2/17.9	15.2/18.4	14.7/16.9
No. of atoms (Protein/Ligand/Water)	15,816/0/2,448	5,196/36/547	15,301/300/1,299	15,230/80/1,797	15,291/239/1,520	15,174/241/1,523	15,130/288/1,332	15,248/265/1,796
Model Quality								
R.m.s deviations								
Bond lengths (Å)	0.007	0.010	0.009	0.008	0.009	0.009	0.009	0.008
Bond angles (º)	0.876	1.039	0.941	0.869	0.961	0.956	0.993	0.992
Average *B*-factor (Å^2)								
All Atoms	17.4	21.0	29.9	24.7	26.5	26.2	20.0	21.3
Protein	15.3	19.2	28.5	23.2	25.1	24.4	18.5	19.4
Ligand	-	36.0	51.1	36.8	42.6	40.0	34.2	34.8
Water	30.9	33.5	40.7	36.9	35.8	38.6	32.3	32.9
Coordinate error (maximum likelihood) (Å)	0.11	0.11	0.19	0.16	0.20	0.20	0.18	0.15
Ramachandran Plot								
Most favored (%)	99.0	99.8	99.5	99.6	99.7	99.6	99.6	99.8
Additionally allowed (%)	1.0	0.2	0.5	0.4	0.3	0.4	0.4	0.2

1) Values in parenthesis are for the highest resolution shell.
2) $R_{merge} = \Sigma_{hkl}\Sigma_i |I_i(hkl) - \langle I(hkl)\rangle| / \Sigma_{hkl}\Sigma_i I_i(hkl)$, where $I_i(hkl)$ is the intensity measured for the *i*th reflection and $\langle I(hkl)\rangle$ is the average intensity of all reflections with indices hkl.

3) $R_{factor} = \Sigma_{hkl} ||F_{obs}(hkl)| - |F_{calc}(hkl)|| / \Sigma_{hkl} |F_{obs}(hkl)|$; Rfree is calculated in an identical manner using 5% of randomly selected reflections that were not included in the refinement.
4) $CC_{1/2}$ is the correlation coefficient of the mean intensities between two random half-sets of data[1-2]
5) R_{meas} = redundancy-independent (multiplicity-weighted) R_{merge}.[3-4] R_{pim} = precision-indicating (multiplicity-weighted) R_{merge}.[5-6]

Fragment library screening using saturation transfer difference (STD) NMR spectroscopy

Structural information obtained from the BfrB-Bfd complex[7] was used to compile a library of 210 fragments. Each of the 210 fragments was dissolved in DMSO-d_6 to yield a 100 mM stock, which was used to prepare the solutions to be probed by STD-NMR. For each fragment, two solutions were prepared in phosphate buffer (100 mM potassium phosphate buffer, 2.5% DMSO-d_6, 1 mM TCEP, pH 7.6): (1) a 1.2 mM solution of the fragment alone, and (2) a solution 1.2 mM in fragment and 1 μM in BfrB. Because there are 12 Bfd-binding sites in a 24-mer BfrB, the concentration of binding sites in this solution is 12 μM. All NMR experiments were performed in 5 mm NMR tubes at 25 °C using a Bruker 600 MHz spectrometer equipped with a triple resonance probe. The following steps were taken to identify fragment binders: *i*) acquisition of ^{1}H NMR spectra of the fragment alone, *ii*) acquisition of ^{1}H NMR spectra of the fragment in the presence of BfrB, and (*iii*), acquisition of STD NMR spectra. STD spectra were acquired with 512 scans over 32 k data points, with a 1.8 s acquisition time and a 2 s relaxation delay. Spin lock time for protein background suppression was 45 ms, and the saturation time was 2 s; the on- and off-resonance frequencies were set at -2 ppm and 40 ppm, respectively. To differentiate non-specific binders from those that bind at the Bfd-binding site, a displacement strategy with Bfd was implemented: For each of the fragment binders, STD spectra were collected using the above-described parameters, in the absence and in the presence of 24 μM Bfd. Cases where the presence of Bfd caused a >50% decrease in the NMR signal were interpreted to indicate that the fragment binds at the Bfd-binding site on BfrB.

Measurement of dissociation constants (K_d)

Optical spectroscopy and protein binding assays used potassium phosphate buffer (100 mM, pH 7.6) containing TCEP (1 mM), unless otherwise noted. Absorbance spectra were obtained in semimicro (1.4 mL) UV quartz cuvettes (Sigma-Aldrich, Z27667-7) on an Agilent 8452A diode array spectrophotometer. Fluorescence emission spectra were acquired on a Perkin-Elmer LS55 Fluorescence Spectrophotometer (10 nm slit width) in a SUPRASIL ultra-micro quartz cuvette (PerkinElmer, B0631079). To calculate dissociation constants (K_d), fluorescence polarization (FP) and fluorescence intensity (I) values were measured in triplicate and analyzed with a previously reported[8] method. Fixed concentrations of analogs in potassium phosphate buffer were incubated with increasing concentrations of apo-BfrB (based on the subunit dimer) at room temperature (22 °C) with shaking for 1 h, followed by excitation near the absorbance λ_{max} of the small molecule analogs (**8**, 380 nm; **11**, **12**, 400 nm; **13**, **16**, 410 nm; **14**, 415 nm), with analysis of fluorescence polarization near the emission λ_{max} (**8**, 565 nm; **11**, **15**, 540 nm; **12**, 525 nm; **13**, **16**, 550 nm). The small molecule ligands were maintained in buffer for a maximum of 5 min prior to incubation with the protein to minimize any potential for degradation. Fixed ligand concentrations were chosen to be near or below predicted K_d values to assure equilibrium binding measurements. Measurements of both fluorescence intensity (I) and polarization (P) were recorded for each sample to allow

correction for fluorescence enhancement or quenching during binding. The change in polarization of each sample was calculated by subtracting the polarization of the free analog (P_f). This change was plotted against the concentration of apo-BfrB, and the maximum polarization of the fully bound complex was estimated (B_{max}) based on a one-site specific binding model (GraphPad Prism 6.0). This polarization of the complex (P_b) was used in equation 3 to calculate the apparent fraction bound (F_a):

$$F_a = \frac{P - P_f}{P_b - P_f} \qquad (3)$$

Background-subtracted fluorescence intensity (I) signals were calculated with equation 4, where I_{BfrB} is

$$I = I_{ex} - I_{BfrB} \qquad (4)$$

the background fluorescence intensity of the protein alone at each concentration measured, excited under the same conditions as the protein with the analog. To correct for fluorescence enhancement or quenching, a fluorescence enhancement factor (Q) was calculated using equation 5, where I and I_0 are the fluorescence intensity of the sample and free ligand, respectively. To incorporate fluorescence enhancement/quenching

$$Q = \frac{I - I_0}{I_0} \qquad (5)$$

$$f_a = \frac{F_a}{1 + Q(1 - F_a)} \qquad (6)$$

into the measurements, the corrected fraction bound (f_a) was calculated using equation 6. To calculate K_d, the corrected fraction bound (f_a) was plotted against the concentration of the apo-BfrB subunit dimer, and a one site-specific binding equation of GraphPad Prism 6 was used for curve fitting.

Measurement of K_d by Surface Plasmon Resonance

SPR experiments were performed to measure the K_d for the association between Bfd and apo-BfrB. These experiments were carried out at 25 °C using a Biacore X100 instrument (GE Healthcare) using a previously reported protocol.[9-10]

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Synthetic Procedures

General comments. Commercial anhydrous *N*,*N*-dimethylformamide (DMF) was stored under dry N_2 and transferred by syringe into reactions when needed. Tetrahydrofuran (THF) was dried over KOH pellets and distilled from $LiAlH_4$ prior to use. Pyridine was dried over KOH pellets and distilled under nitrogen prior to use. Most chemicals used for the syntheses were purchased from Combi Blocks (San Diego, CA, USA); 4-aminophthalimide (5-aminoisoindoline-1,3-dione) was purchased from TCI (Portland, OR, USA); 3-aminophthalimide (4-aminoisoindoline-1,3-dione) was purchased from Oxchem Corporation (Wood Dale, IL, USA). *Note*: Phthalimide is also known as isoindoline-1,3-dione, which uses a different numbering scheme than phthalimide; we have used isoindoline-1,3-dione in our compound nomenclature. All commercial chemicals were used as received. Unless otherwise specified, all reactions were run under dry N_2 in oven-dried glassware. The $NaHCO_3$, NaCl, NH_4Cl and HCl used in workup procedures were saturated aqueous solutions. Reactions were monitored by thin layer chromatography (TLC) on silica gel GF plates (Analtech, 21521). Preparative separations were performed by chromatography on silica gel (Davisil®, grade 62, 60-200 mesh, pre-treated with a methanol solution of 3-hydroxy-2-methyl-4-pyrone and then dried at room temperature and at 90 °C) mixed with UV-active phosphor (Sorbent Technologies, No UV-05). Band elution for all chromatographic separations was monitored using a hand-held UV lamp. Melting points were uncorrected. FT-IR spectra were run as thin films on NaCl disks. ^{1}H- and ^{13}C-NMR spectra were measured at 400 MHz (^{1}H) and 101 MHz (^{13}C). Chemical shifts (δ) are referenced to internal $(CH_3)_4Si$ and coupling constants (*J*) are given in Hz. Low-resolution mass spectra (ES/DI) were obtained at 30 eV.

Procedure A: Reductive Amination. To a solution of the aldehyde (1.0 mmol) in DMF (1 mL) was added AcOH (0.8 mL) and the solution was stirred for 10 min. To this reaction mixture, 4-aminoisoindoline-1,3-dione (0.5 mmol) was added and stirring was continued at 23 °C for 1 h. An additional 1 mL of DMF was added bringing the volume to 2 mL. The reaction was cooled to 0 °C and $NaBH(OAc)_3$ (3.0 mmol) was added portion-wise to the reaction. Stirring continued at this temperature for 30 min and the reaction was gradually warmed to 23 °C for 18 h. The crude reaction mixture was poured into de-ionized water, extracted with EtOAc (3 × 75 mL) and the combined organic layers were washed with $NaHCO_3$ (2 × 50 mL) and NaCl (50 mL). The organic layer was dried (Na_2SO_4) and concentrated under vacuum. The residue was dissolved in 1 mL of EtOH and the solution was heated at 50 °C for 10 minutes under N_2. The resulting solid was filtered and washed with EtOH (2 x 10 mL). The filtrate was concentrated under vacuum and subjected to silica-gel chromatography (pre-treated with 3-hydroxy-2-methyl-4-pyrone) eluted with 20% EtOAc in hexane to afford the pure product.

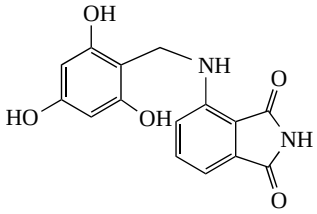
Procedure B: Phenol protection by silyl chlorides. A stirred solution of the phenol (3.00 mmol, 1.0 equiv) in DMF (10 mL) was cooled to 0 °C under nitrogen atmosphere and imidazole (6.00 mmol, 2.0 equiv) was added. The resulting solution was stirred for 20 min and the silyl chloride

(3.60 mmol, 1.2 equiv) as a solution in DMF (10 mL) was added drop-wise over a period of 15 min. The reaction mixture was warmed to 23 °C and stirred until TLC analysis indicated the absence of the starting phenol. The crude reaction was poured into water (50 mL), extracted with ether (3 × 40 mL), and the combined organic layers were washed with NaCl (50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under vacuum. The crude product was purified by column chromatography to afford the silyl ether.

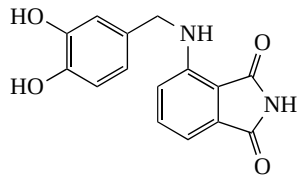
Procedure C: Silyl deprotection. A solution of the silyl ether (1.00 mmol) in 10 mL of THF was stirred under nitrogen at 23 °C and 1.0 M TBAF (2.00 mmol) solution in THF was added. When TLC analysis indicated complete consumption of the silyl ether, water (5.00 mL) was added and the THF was evaporated under vacuum. The product was extracted with ethyl acetate (3 × 40 mL) and the combined organic layers were washed with NaCl (50 mL), dried (Na_2SO_4), concentrated under vacuum and purified by column chromatography using pre-treated silica gel.

4-(Benzylamino)isoindoline-1,3-dione series

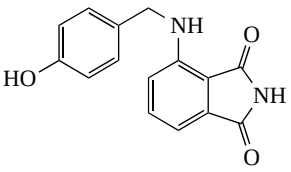
4-((2,4,6-Trihydroxybenzyl)amino)isoindoline-1,3-dione: BN-XIV-069. Procedure A. Orange solid (212 mg, 59%), mp >300 °C (darkened, but did not melt); ^{1}H NMR (DMSO-d_6): δ 10.9 (s, 1H), 9.56 (2, 1H), 7.49 (t, J = 7.8 Hz, 1H), 7.05 (d, J = 8.1 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H), 6.91 (d, J = 7.1 Hz, 1H), 6.78 (br t, J = 6.1 Hz, 1H), 6.32 (s, 1H), 6.16 (d, J = 8.0 Hz, 1H), 4.29 (d, J = 6.0 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 170.8. 168.7, 157.0, 155.5, 145.6, 135.1, 132.9, 129.1, 116.2, 114.4, 110.2, 109.2, 105.4, 101.9, 40.4; MS: *m/z* 300 ($C_{15}H_{12}N_2O_5$, $M^{+\cdot}$).



4-((3,4-Dihydroxybenzyl)amino)isoindoline-1,3-dione: BN-XIV-055. Procedure A. Yellow solid (228 mg, 67%), mp 213-214 °C; ^{1}H NMR (DMSO-d_6): δ 11.0 (s, 1H), 8.86 (s, 1H), 8.81 (s, 1H), 7.47 (t, J = 7.8 Hz, 1H), 6.92 (m, 3H), 6.73 (d, J = 1.8 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 6.61 (dd, J = 8.0, 1.8 Hz, 1H), 4.43 (d, J = 6.0 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 171.8, 169.8, 146.5, 145.8, 144.8, 136.2, 134.0, 130.1, 118.5, 117.5, 116.0, 114.9, 111.4, 110.4, 45.7; MS: *m/z* 284 ($C_{15}H_{12}N_2O_4$, $M^{+\cdot}$).



4-((4-Hydroxybenzyl)amino)isoindoline-1,3-dione: BN-XIV-052. Procedure A. Off-white solid (232 mg, 72%), mp 194-195 °C; ^{1}H NMR (DMSO-d_6): δ 11.0 (s, 1H), 9.31 (s, 1H), 7.47 (t, J = 7.8 Hz, 1H), 7.17 (d, J = 8.2 Hz, 2H), 6.94 (m, 3H), 6.72 (d, J = 8.2 Hz, 2H), 4.38 (d, J = 6.1 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 171.8, 169.8, 156.9, 146.5, 136.2, 134.0, 129.4, 128.9, 117.4, 115.7, 111.5 110.5, 45.6; MS: *m/z* 268 ($C_{15}H_{12}N_2O_3$, $M^{+\cdot}$).

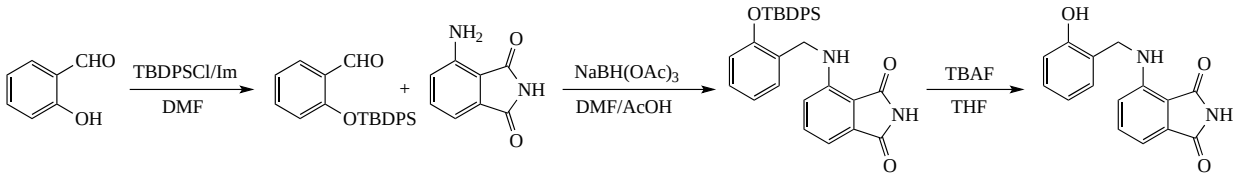


4-((3,5-Dihydroxybenzyl)amino)isoindoline-1,3-dione: BN-XVI-071. Procedure A. Yellow solid (245 mg, 70%), mp 253-254 °C; ^{1}H NMR (DMSO-d_6): δ 10.9 (br s, 1H), 9.31 (s, 2H), 7.47 (t, J = 7.8 Hz, 1H), 7.01 (br t, J = 6.1 Hz, 1H), 6.93 (d, J = 7.1 Hz, 1H), 6.86 (d, J = 8.8 Hz, 1H), 6.18 (s, 2H), 6.05 (s, 1H), 4.35 (d, J = 6.1 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 171.9, 169.9, 159.0 (2C), 146.6, 141.6, 136.2, 134.0, 117.5, 111.5, 105.1, 101.6, 46.0; MS: *m/z* 284 ($C_{15}H_{12}N_2O_4$, $M^{+\cdot}$).

4-((2-Chloro-4-hydroxybenzyl)amino)isoindoline-1,3-dione: GKK-007-100. Procedure A. Yellow solid (163 mg, 54%), mp 238-240 °C; ^{1}H NMR (DMSO-d_6): δ 11.0 (s, 1H), 9.84 (s, 1H), 7.49 (t, J = 7.8 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 6.95 (coincident t, J = 6.4 Hz, 1H and d, J = 7.1 Hz, 1H), 6.90 (d, J = 8.5 Hz, 1H), 6.86 (d, J = 2.5 Hz, 1H), 6.70 (dd, J = 8.4, 2.5 Hz, 1H), 4.47 (d, J = 6.2 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 171.8, 169.7, 157.9, 146.2, 136.3, 134.0, 133.0, 130.4, 126.1, 117.2, 116.5, 114.9, 111.8, 110.8, 43.5; MS: *m/z* 302 ($C_{15}H_{11}{}^{35}ClN_2O_3$, $M^{+\cdot}$).

4-((2-Hydroxybenzyl)amino)isoindoline-1,3-dione: GKK-011-017 (Analog 11).

Reaction Scheme:



GKK-011-017

2-((*tert*-Butyldiphenylsilyl)oxy)benzaldehyde. This compound was prepared from salicylaldehyde (2.0 g, 16.4 mmol) and TBDPSCl (5.40 g, 19.7 mmol) according to Procedure B to provide the TBDPS-protected salicylaldehyde (3.81 g, 10.6 mmol, 65%) as a white solid. This compound was used without further purification.

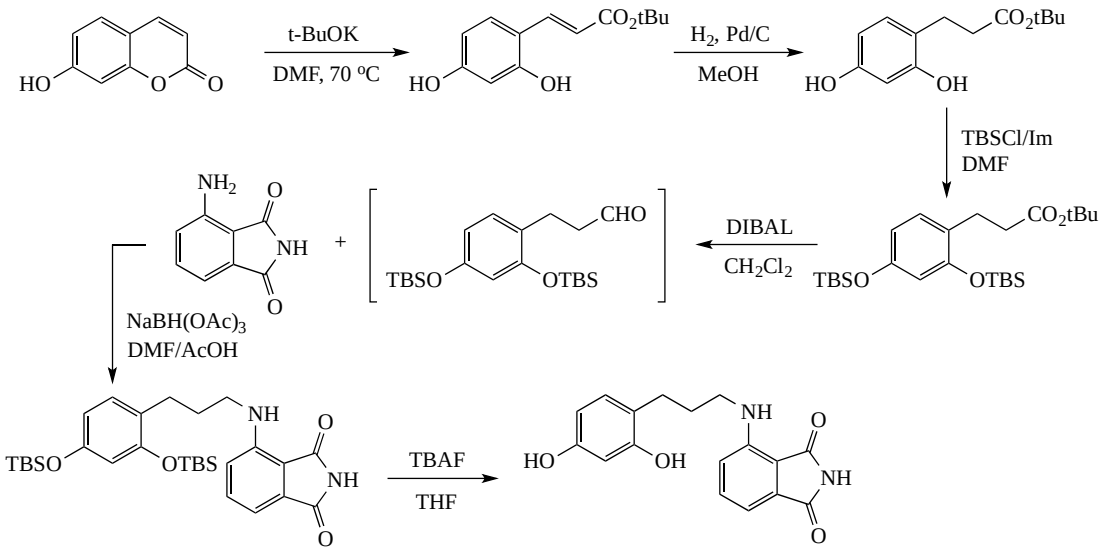
4-((2-((*tert*-Butyldiphenylsilyl)oxy)benzyl)amino)isoindoline-1,3-dione. The reductive amination was performed using Procedure A starting from the silyl ether of salicylaldehyde (720 mg, 2.0 mmol) and 4-aminoisoindoline-1,3-dione (162 mg, 1.0 mmol) to give the silyl-protected 4-((2-hydroxybenzyl)amino)isoindoline-1,3-dione (306 mg, 0.60 mmol, 60%), mp 175-178 °C. This compound was used directly in the next step without further purification.

4-((2-Hydroxybenzyl)amino)isoindoline-1,3-dione: GKK-011-017. Using Procedure C, the silyl ether (252 mg, 0.50 mmol) was cleaved to generate the hydroxyl compound (107 mg, 0.40 mmol, 80%) as a yellow solid, mp 192-194 °C; ^{1}H NMR (DMSO-d_6): δ 11.0 (s, 1H), 9.73 (s, 1H),

7.48 (t, *J* = 7.8 Hz, 1H), 7.20 (d, *J* = 7.4 Hz, 1H), 7.08 (td, *J* = 7.2, 1.4 Hz, 1H), 6.96 (overlapping d, *J* = 8.5 Hz, 1H and br t, *J* = 6.1 Hz, 1H), 6.92 (d, *J* = 7.1 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.74 (t, *J* = 7.4 Hz, 1H), 4.43 (d, *J* = 6.1 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 171.8, 169.8, 155.6, 146.6, 136.2, 134.0, 129.0, 128.7, 124.9, 119.4, 117.2, 115.5, 111.4, 110.4, 41.6; MS: *m/z* 268 ($C_{15}H_{12}N_2O_2$, $M^{+\cdot}$).

4-((3-(2-Hydroxyphenyl)propyl)amino)isoindoline-1,3-dione: GKK-007-047 (Analog 14).

Reaction Scheme:



GKK-007-047

***tert*-Butyl 3-(2,4-dihydroxyphenyl)propionate**. To a stirred solution of 7-hydroxycoumarin (3.00 g, 18.5 mmol) in DMF (15 mL) was added *t*-BuOK (6.30 g, 56.0 mmol) under nitrogen atmosphere. The reaction flask was immersed in a pre-heated oil bath (80 °C) and stirred for 4 h. The reaction mixture was poured into ice-cold water and acidified using citric acid. The product was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were dried (Na_2SO_4). The organic layer was concentrated under vacuum to give a brown oil that was used without further purification. A solution of the crude *tert*-butyl (*E*)-3-(2,4-dihydroxyphenyl)cinnamate in MeOH (250 mL) was flushed twice with nitrogen and commercial 10% Pd/C (200 mg, 50% wet, 10% w/w) was added. The reaction mixture was stirred at room temperature under hydrogen (1 atm) for 18 h. The reaction was filtered through Celite® and washed with methanol (2 × 25 mL). The filtrate was concentrated under vacuum to provide *tert*-butyl 3-(2,4-dihydroxyphenyl)propionate (2.80 g 11.9 mmol, 64% after two steps) as a yellow oil. This compound was used without further purification.

***tert*-Butyl 3-(2,4-bis((*tert*-butyldimethylsilyl)oxy)phenyl)propionate**. Procedure B was followed to protect both phenols. To a solution of *tert*-butyl 3-(2,4-dihydroxyphenyl)propionate (2.80 g, 11.9 mmol) in DMF (14 mL) was added imidazole (4.00 g, 59.0 mmol) and the mixture

was stirred for 20 min. A solution of TBSCl (4.42 g, 29.0 mmol) in DMF (14 mL) was then added drop-wise over a period of 30 min. The reaction was stirred at 0 ^{o}C for 2 h and monitored by TLC. The reaction mixture was added to water, extracted with ether (3 × 50 mL), dried (Na_2SO_4) and concentrated under vacuum to afford the bis-TBS-protected ester (4.98 g, 10.7 mmol, 90%) as a colorless oil.

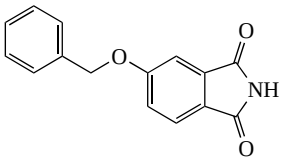
4-((3-(2-Hydroxyphenyl)propyl)amino)isoindoline-1,3-dione: GKK-007-047. A stirred solution of the bis-TBS-protected ester (2.50 g, 5.36 mmol) in CH_2Cl_2 (100 mL) was cooled to -78 ^{o}C, 1.5 M DIBAL-H in toluene (4.50 mL, 6.43 mmol) was added, and stirring was continued at this temperature for 3 h or until TLC analysis indicated the complete consumption of the ester. The reaction was quenched by drop-wise addition of MeOH (10 mL), followed by addition of 1 M HCl (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to provide the aldehyde as a colorless oil, which was used for the next step without further purification. This aldehyde was subjected to reductive amination with 4-aminoisoindoline-1,3-dione according to Procedure A and was used without further purification. Finally, the TBS group was cleaved according to Procedure C to afford 4-((3-(2-hydroxyphenyl)propyl)-amino)isoindoline-1,3-dione (125 mg, 0.40 mmol, 7.5% for 3 steps) as a yellow solid, mp 207-208 ^{o}C. ^{1}H NMR (DMSO-d_6): δ 10.9 (br s, 1H), 9.12 (s, 1H), 8.94 (s, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.92 (d, *J* = 7.2 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 6.54 (br t, *J* = 6.3 Hz, 1H), 6.27 (s, 1H), 6.13 (d, *J* = 8. 2 Hz, 1H), 3.24 (q, *J* = 6.8 Hz, 2H), 2.48 (t, *J* = 7.0 Hz, 2H), 1.76 (quintet, *J* = 7.2 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 171.9, 169.8, 156.8, 156.3, 146.8, 136.3, 134.1, 130.4, 118.3, 116.8, 111.2, 110.1, 106.4, 102.8, 41.8, 29.6, 26.6; MS: *m/z* 312 ($C_{17}H_{16}N_2O_4$, $M^{+\cdot}$).

5-(Benzyloxy)isoindoline-1,3-dione series

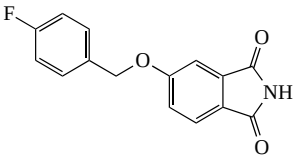
Procedure D: General procedure for the synthesis of substituted ether derivatives. To a stirred solution of dimethyl 4-hydroxyphthalate (500 mg, 2.38 mmol) in acetone (15 mL) was added K_2CO_3 (490 mg, 3.6 mmol), followed by the corresponding benzyl bromide (2.50 mmol). The reaction was refluxed for a period of 3-4 h, concentrated under vacuum and the product was extracted into EtOAc (3 × 35 mL). The organic layer was washed with 1 M HCl (25 mL), water (25 mL), and NaCl (25 mL). The organic solution was dried (Na_2SO_4) and concentrated to dryness. The product was obtained in 92-95% yield and was taken to the next step without purification.
To a stirred solution of the diester (1.50 mmol) in THF (10 mL), NaOH (2.40 mmol, 4.0 equiv) dissolved in MeOH/H_2O (10 mL) was added and stirred for a period of 3 h. After completion, the reaction mixture was concentrated to dryness. The residue was dissolved in water, the pH was adjusted to pH 3-4 with 6 M HCl, and the mixture was extracted with EtOAc (3 × 35 mL). The organic layer was washed with NaCl (30 mL), dried (Na_2SO_4) and concentrated to give the diacid. The compounds, obtained in yields of 90-95%, were spectroscopically pure and used directly in the next reaction.

A stirred solution of the diacid (1.47 mmol) in AcOH (3.0 mL), was placed in a pre-heated oil bath at 140 °C and stirred for 2 min. To the reaction mixture $(NH_4)_2CO_3$ (7.50 mmol, 5.0 equiv) was added and stirring was continued for 1 h. [*Note*: If the reaction was not complete at this time, an additional portion of $(NH_4)_2CO_3$ (1.0 equiv) was added and heating was continued until the reaction was complete]. The reaction mixture was cooled and extracted with EtOAc (3 × 30 mL). The organic layer was washed with 0.5 M HCl (20 mL), followed by $NaHCO_3$ (30 mL) and NaCl (25 mL), dried (Na_2SO_4), and concentrated under vacuum to give the pure 5-benzyloxyisoindoline-1,3-dione. These compounds were further purified by recrystallization from hot EtOH.

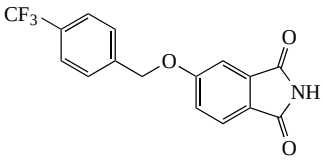
5-(Benzyloxy)isoindoline-1,3-dione: BN-XIII-007. Procedure D. White solid (325 mg, 87%), mp 154-155 °C; ^{1}H NMR (DMSO-d_6): δ 11.2 (s, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.48 (d, J = 7.2 Hz, 2H), 7.45-7.33 (complex, 5H), 5.30 (s, 2H); ^{13}C NMR (DMSO-d_6): δ 169.30, 169.27, 163.8, 136.6, 135.7, 129.0, 128.6, 128.3, 125.3, 125.1, 121.2, 109.1, 70.6; MS: *m/z* 253 ($C_{15}H_{10}FNO_3$, $M^{+\cdot}$).



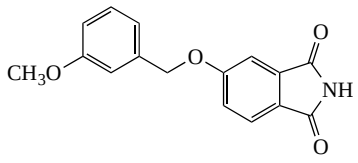
5-((4-Fluorobenzyl)oxy)isoindoline-1,3-dione: BN-XIII-013. Procedure D. White solid (275 mg, 74%), mp 204-205 °C; ^{1}H NMR (DMSO-d_6): δ 11.2 (s, 1H), 7.75 (d, J = 8.2, 1H), 7.54 (dd, J = 9.0, 5.5 Hz, 2H), 7.41 (d, J = 2.4 Hz, 1H), 7.38 (dd, J = 8.2, 2.3 Hz, 1H), 7.25 (t, J = 8.9 Hz, 2H), 5.28 (s, 2H); ^{13}C NMR (DMSO-d_6): δ 169.29, 169.26, 163.7, 162.4 (d, J = 244.1 Hz), 135.7, 132.9, 130.6 (d, J = 8.4 Hz), 125.24, 125.18, 121.2, 115.8 (d, J = 21.4 Hz), 109.1, 69.9; MS: *m/z* 271 ($C_{15}H_{10}F_3NO_3$, $M^{+\cdot}$).



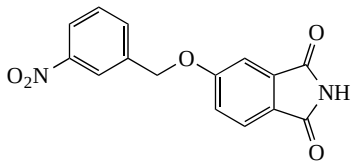
5-((4-(Trifluoromethyl)benzyl)oxy)isoindoline-1,3-dione: BN-XIII-016. Procedure D. Off-white solid (272 mg, 72%), mp 243-244 °C; ^{1}H NMR (DMSO-d_6): δ 11.2 (s, 1H), 7.85-7.67 (complex, 5H), 7.44 (s, 1H), 7.41 (d, J = 8.2 Hz, 1H), 5.43 (s, 2H); ^{13}C NMR (DMSO-d_6): δ 169.23, 169.20, 163.4, 141.5, 135.7, 129.0 (q, J = 31.8 Hz), 128.5, 126.0, 125.9, 125.8, 124.6 (q, J = 272.7 Hz), 121.1, 109.1, 69.6; MS: *m/z* 321 ($C_{16}H_{10}F_3NO_3$, $M^{+\cdot}$).



5-((3-Methoxybenzyl)oxy)isoindoline-1,3-dione: BN-XII-046. Procedure D. Off-white solid (330 mg, 90%), mp 154-155 °C; ^{1}H NMR (DMSO-d_6): δ 11.2 (s, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.40 (d, J = 2.3 Hz, 1H), 7.30 (dd, J = 8.1, 2.3 Hz, 1H), 7.32 (t, J = 8.1 Hz, 1H), 7.05 (s, 1H), 7.04 (obscured, 1H), 6.92 (dd, J = 8.1, 2.3 Hz, 1H), 5.07 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 169.29, 169.28, 163.7, 159.8, 138.2, 135.7, 130.2, 125.3, 125.1, 121.2, 120.3, 114.0, 113.8, 109.1, 70.4, 55.5; MS: *m/z* 283 ($C_{16}H_{13}NO_4$, $M^{+\cdot}$).



5-((3-Nitrobenzyl)oxy)isoindoline-1,3-dione: BN-XII-044. Procedure D. Yellow solid (250 mg, 67%), mp 275-276 °C; ^{1}H NMR (DMSO-d_6): δ 11.2 (s, 1H), 8.36 (t, *J* = 1.9 Hz, 1H), 8.23 (ddd, *J* = 8.2, 2.3, 0.9 Hz, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.74 (t, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 2.3 Hz, 1H), 7.42 (dd, *J* = 8.2, 2.3 Hz, 1H), 5.46 (s, 2H); ^{13}C NMR (DMSO-d_6): δ 169.3, 169.2, 163.4, 148.3, 139.0, 135.7, 134.7, 130.7, 125.5, 125.3, 123.5, 122.7, 121.2, 109.1, 69.2; MS: *m/z* 298 ($C_{15}H_{10}N_2O_5$, $M^{+\cdot}$).

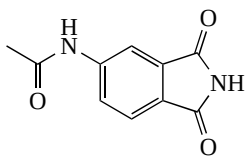


5-Amidoisoindoline-1,3-dione series

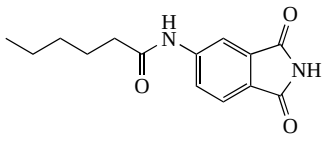
Procedure E1: N-Amidation of amino substituted 5-aminoisoindoline-1,3-diones using the acid chloride/sulfonyl chloride. To a stirred solution of 5-aminoisoindoline-1,3-dione (200 mg, 1.25 mmol) in pyridine (5 mL) at 0 °C, the acid chloride / sulfonyl chloride (1.15 mmol) was added drop-wise and stirring was continued for 2 h. The reaction mixture was quenched with cold 6 M HCl to pH 2-3 and the crude product was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with 2% $NaHCO_3$ (15 mL) and NaCl (15 mL). The resulting organic layer was dried (Na_2SO_4) and concentrated under vacuum to afford a yellow solid. As the product obtained contained traces of 5-aminoisoindoline-1,3-dione and pyridine, it was purified by recrystallization from EtOH (5 mL). The solid was collected and dried to afford the product as a pale yellow solid.

Procedure E2: N-Amidation of amino substituted 4-aminoisoindoline-1,3-dione from the acid. To a stirred solution of the carboxylic acid (1.20 mmol) in benzene was added DMF (2 drops) and $SOCl_2$ (3.00 mmol). The mixture was heated at reflux for 1 h and cooled to room temperature (23 °C). The solvent and excess $SOCl_2$ were removed under vacuum and the resulting crude acid chloride was dissolved in 10 mL of pyridine. To this solution was added 4-aminoisoindoline-1,3-dione (1.00 mmol) and the mixture was heated at reflux for 2 h. The reaction mixture was allowed to slowly cool to 23 °C, and then further cool in an ice-bath for 15 min. The resulting solid was collected and recrystallized from ethanol/ether (2:1) to give the corresponding amide.

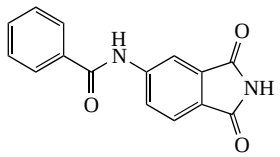
***N*-(1,3-Dioxoisoindolin-5-yl)acetamide: BN-XII-078**. Procedure E1. White solid (216 mg, 86%), mp 333-334 °C; ^{1}H NMR (DMSO-d_6): δ 11.2 (s, 1H), 10.5 (s, 1H), 8.15 (d, *J* = 1.8 Hz, 1H), 7.84 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 2.12 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 168.6, 168.4, 168.3, 144.1, 133.5, 125.7, 123.5, 122.5, 111.8, 23.6; MS: *m/z* 204 ($C_{10}H_8N_2O_3$, $M^{+\cdot}$).



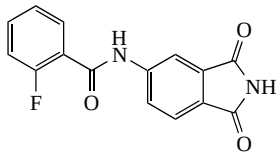
***N*-(1,3-Dioxoisoindolin-5-yl)hexanamide: BN-XII-079**. Procedure E1. White solid (295 mg, 92%), mp 209-210 °C; ^{1}H NMR (DMSO-d_6): δ 11.2 (s, 1H), 10.5 (s, 1H), 8.17 (d, *J* = 1.8 Hz, 1H), 7.86 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 2.37 (t, *J* = 7.4 Hz, 2H), 1.61 (quintet, *J* = 7.4 Hz, 2H), 1.30 (m, 4H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6): δ 171.6, 168.4, 168.3, 144.1, 133.5, 125.6, 123.5, 122.5, 111.8, 35.9, 30.2, 24.0, 21.3, 13.3; MS: *m/z* 260 ($C_{14}H_{16}N_2O_3$, $M^{+\cdot}$).



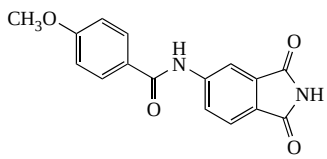
***N*-(1,3-Dioxoisoindolin-5-yl)benzamide: BN-XII-061**. Procedure E1. White solid (282 mg, 86%), mp 312-313 °C; ^{1}H NMR (DMSO-*d*$_6$): δ 11.3 (s, 1H), 10.8 (s, 1H), 8.34 (d, *J* = 1.6 Hz, 1H), 8.15 (dd, *J* = 8.2, 1.9 Hz, 1H), 8.00-7.98 (complex, 2H), 7.83 (d, *J* = 1.9 Hz, 1H), 7.67-7.62 (complex, 1H), 7.60-7.55 (complex, 2H); ^{13}C NMR (DMSO-*d*$_6$): δ 169.5, 169.3, 166.7, 145.1, 134.7, 134.4, 132.6, 129.0, 128.3, 127.3, 124.9, 124.4, 114.2; MS: *m/z* 266 ($C_{13}H_{10}N_2O_3$, $M^{+\cdot}$).



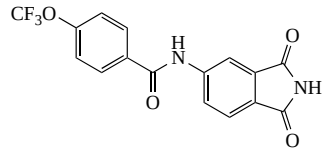
***N*-(1,3-Dioxoisoindolin-5-yl)-2-fluorobenzamide: BN-XII-060**. Procedure E1. Off-white solid (276 mg, 79%), mp 272-273 °C; ^{1}H NMR (DMSO-*d*$_6$): δ 11.1 (s, 2H), 8.15 (s, 1H), 7.96 (d, *J* = 8.1 Hz, 1H), 7.72 (t, *J* = 8.4 Hz, 2H), 7.61 (q, *J* = 7.5 Hz, 1H), 7.42-7.32 (complex, 2H); ^{13}C NMR (DMSO-*d*$_6$): δ 172.5, 163.2 (2C), 158.8 (d, *J* = 246.8 Hz), 143.3, 135.7, 133.0 (d, *J* = 8.3 Hz), 130.0 (d, *J* = 2.6 Hz), 128.9, 124.7 (d, *J* = 3.4 Hz), 124.6, 124.4, 123.6 (d, *J* = 13.7 Hz), 116.3 (d, *J* = 21.4 Hz), 112.7; MS: *m/z* 284 ($C_{15}H_9FN_2O_3$, $M^{+\cdot}$).



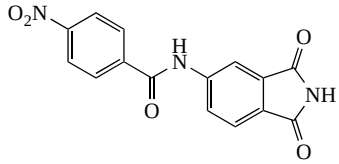
***N*-(1,3-Dioxoisoindolin-5-yl)-4-methoxybenzamide: BN-XII-064**. Procedure E1. Pale yellow solid (320 mg, 88%), mp 342-343 °C; ^{1}H NMR (DMSO-*d*$_6$): δ 11.2 (s, 1H), 10.6 (s, 1H), 8.33 (d, *J* = 1.8 Hz, 1H), 8.14 (dd, *J* = 8.2, 1.9 Hz, 1H), 8.00 (d, *J* = 8.8 Hz, 2H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.10 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (DMSO-*d*$_6$): δ 169.5, 169.4, 165.9, 162.8, 145.4, 134.4, 130.4, 127.0, 126.7, 124.8, 124.3, 114.2, 114.1, 56.0; MS: *m/z* 296 ($C_{16}H_{12}N_2O_4$, $M^{+\cdot}$).



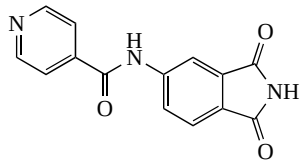
***N*-(1,3-Dioxoisoindolin-5-yl)-4-(trifluoromethoxy)benzamide: BN-XII-059**. Procedure E1. Off-white solid (390 mg, 90%), mp 345-346 °C; ^{1}H NMR (DMSO-*d*$_6$): δ 11.1 (br s, 2H), 8.30 (d, *J* = 1.5 Hz, 1H), 8.15-8.09 (complex, 3H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.56 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (DMSO-*d*$_6$): δ 170.0, 169.8, 165.4, 151.2, 144.8, 134.6, 133.9, 130.8, 127.7, 124.8, 124.3, 121.2, 120.4 (q, *J* = 257.3 Hz), 114.1; MS: *m/z* 350 ($C_{16}H_9F_3N_2O_4$, $M^{+\cdot}$).



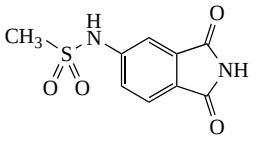
***N*-(1,3-Dioxoisoindolin-5-yl)-4-nitrobenzamide: BN-XII-063**. Procedure E1. Yellow solid (290 mg, 76%), mp 355-356 °C; ^{1}H NMR (DMSO-*d*$_6$): δ 11.3 (s, 1H), 11.1 (s, 1H), 8.40 (d, *J* = 8.4 Hz, 2H), 8.32 (d, *J* = 1.5 Hz, 1H), 8.24 (d, *J* = 8.4 Hz, 2H), 8.13 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR: δ 168.3, 168.2, 164.0, 148.8, 143.5, 139.3, 133.4, 128.8, 126.7, 124.1, 123.4, 123.0, 113.3; MS: *m/z* 311 ($C_{15}H_9N_3O_5$, $M^{+\cdot}$).



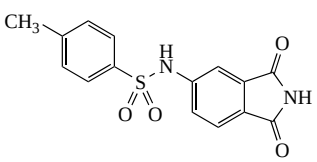
***N*-(1,3-Dioxoisoindolin-5-yl)isonicotinamide: BN-XII-070**. Procedure E1. Off-white solid (215 mg, 65%), mp 322-323 °C; ^{1}H NMR (DMSO-*d*$_6$): δ 11.3 (s, 1H), 11.0 (s, 1H), 8.84 (d, *J* = 6.0 Hz, 2H), 8.31 (d, *J* = 1.6 Hz, 1H), 8.13 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.91 (d, *J* = 6.0 Hz, 2H), 7.84 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (DMSO-*d*$_6$): δ 168.3, 168.2, 164.1, 149.8, 143.4, 140.7, 133.4, 126.8, 124.0, 123.4, 121.1, 113.3; MS: *m/z* 267 ($C_{14}H_9N_3O_3$, $M^{+\cdot}$).



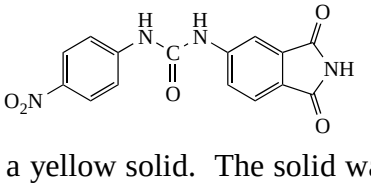
***N*-(1,3-Dioxoisoindolin-5-yl)methanesulfonamide: BN-XII-065**. Procedure E1. White solid (280 mg, 95%), mp 275-276 °C; ^{1}H NMR (DMSO-*d*$_6$): δ 11.3 (s, 1H), 10.6 (s, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.56 (d, *J* = 2.1 Hz, 1H), 7.53 (dd, *J* = 8.1, 2.1 Hz, 1H), 2.17 (s, 3H); ^{13}C NMR (DMSO-*d*$_6$): δ 168.2, 168.1, 143.6, 134.0, 125.9, 124.0, 122.1, 111.1, 39.4; MS: *m/z* 240 ($C_9H_8N_2O_4S$, $M^{+\cdot}$).



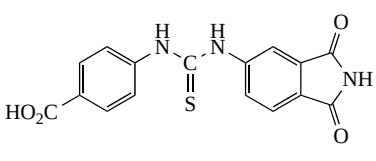
***N*-(1,3-Dioxoisoindolin-5-yl)-4-methylbenzenesulfonamide: BN-XII-062**. Procedure E1. White solid (280 mg, 95%), mp 278-279 °C; ^{1}H NMR (DMSO-*d*$_6$): δ 11.2 (s, 1H), 11.1 (s, 1H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.72 (obscured, 1H), 7.46 (dd, *J* = 6.9, 1.9 Hz, 1H), 7.45 (s, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (DMSO-*d*$_6$): δ 169.1, 169.0, 144.5, 144.0, 136.6, 134.9, 130.5, 127.3, 127.2, 125.0, 123.4, 112.3, 21.4; MS: *m/z* 316 ($C_{15}H_{12}N_2O_4S$, $M^{+\cdot}$).



1-(1,3-Dioxoisoindolin-5-yl)-3-(4-nitrophenyl)urea: BN-XII-071. Procedure E1. To a stirred solution of 5-aminoisoindoline-1,3-dione (200 mg, 1.25 mmol) in DMF (5 mL) was added 4-nitrophenylisocyanate (215 mg, 1.29 mmol) and the mixture was stirred for a period of 18 h. The reaction mixture was poured into ice-cold water and stirred for 3 h to obtain a yellow solid. The solid was filtered, dried and recrystallized using hot EtOH (7 mL) to obtain the desired compound as a yellow solid (300 mg, 72%), mp 335-336 °C; ^{1}H NMR (DMSO-*d*$_6$): δ 11.2 (s, 1H), 9.65 (s, 1H), 9.59 (s, 1H), 8.21 (d, *J* = 9.3 Hz, 2H), 8.05 (d, *J* = 1.8 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.72 (d, *J* = 9.3 Hz, 2H), 7.72 (obscured dd, *J* = 8.2, 1.8 Hz, 1H); ^{13}C NMR (DMSO-*d*$_6$): δ 169.5, 169.3, 152.3, 146.2, 145.3, 141.9, 134.8, 126.1, 125.6, 124.6, 123.2, 118.4, 112.3; MS: *m/z* 326 ($C_{15}H_{10}N_4O_5$, $M^{+\cdot}$).



4-(3-(1,3-Dioxoisoindolin-5-yl)thioureido)benzoic acid: BN-XII-072. Procedure E1. A similar method was used for the preparation of the thiourea compound. In this case, 4-carboxyphenyl-isothiocyanate (225 mg, 1.05 mmol) gave the desired product as an off-white solid (220 mg, 62%), mp 337-339 °C; ^{1}H NMR (DMSO-*d*$_6$): δ 12.8 (br s, 1H), 10.6 (s, 1H), 10.5 (s, 1H), 8.14 (d, *J* = 1.6 Hz, 1H), 7.93 (d, *J* = 8.3 Hz, 2H), 7.86 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 2H), acid proton not observed; ^{13}C NMR (DMSO-*d*$_6$): δ

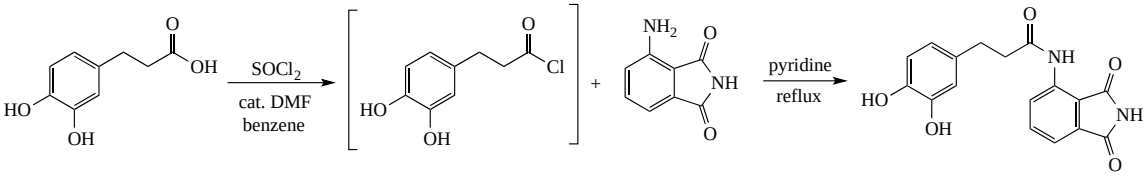


179.8, 169.3, 169.2, 167.3, 145.6, 143.7, 133.8, 130.5, 127.7, 127.6, 126.8, 124.1, 122.6, 116.8; MS: *m/z* 341 ($C_{16}H_{11}N_3O_4S$, $M^{+\cdot}$).

4-Amidoisoindoline-1,3-dione series

3-(3,4-Dihydroxyphenyl)-*N*-(1,3-dioxoisoindolin-4-yl)propanamide: GKK-006-090.

Reaction Scheme:

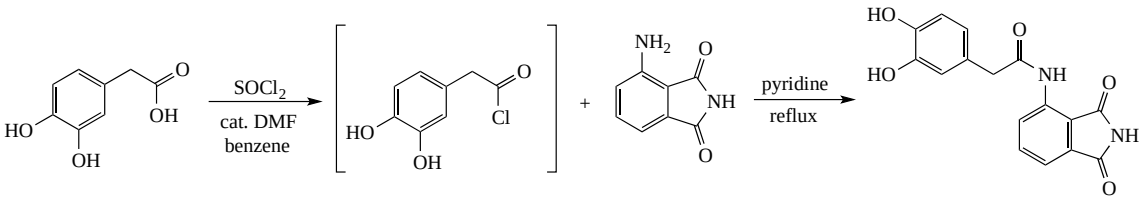


GKK-006-090

Procedure E2. Yellow solid (49 mg, yield 15%), mp 235-236 ºC; ^{1}H NMR (DMSO-d_6): δ 11.4 (s, 1H), 9.67 (s, 1H), 8.76 (s, 1H), 8.68 (s, 1H), 8.48 (d, *J* = 8.4 Hz, 1H), 7.76 (t, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 7.3 Hz, 1H), 6.64 (s, 1H), 6.63 (d, *J* = 8.4 Hz, 1H), 6.50 (d, *J* = 8.0 Hz, 1H), 2.77 (t, *J* = 7.1 Hz, 2H), 2.69 (t, *J* = 7.1 Hz, 2H) ^{13}C NMR (DMSO-d_6): δ 171.8, 170.8, 169.2, 145.5, 143.9, 136.9, 136.2, 133.3, 131.8, 125.5, 119.3, 118.3, 118.1, 116.2, 115.9, 39.1, 30.4; MS: *m/z* 326 ($C_{17}H_{14}N_2O_5$, $M^{+\cdot}$).

2-(3,4-Dihydroxyphenyl)-*N*-(1,3-dioxoisoindolin-4-yl)acetamide: GKK-006-082.

Reaction Scheme:

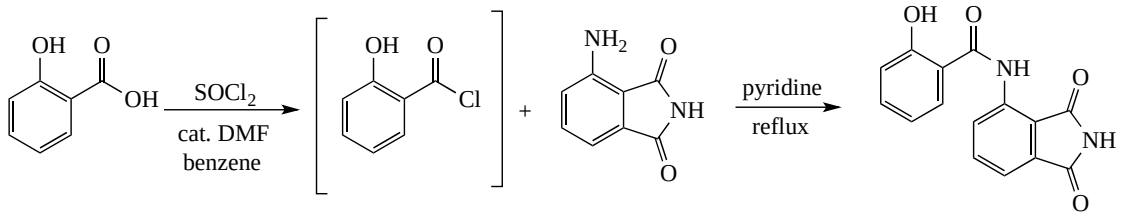


GKK-006-082

Procedure E2. Yellow solid (65 mg, 21%), mp 230-231 ºC; ^{1}H NMR (DMSO-d_6): δ 11.4 (s, 1H), 9.64 (s, 1H), 8.90 (s, 1H), 8.84 (s, 1H), 8.54 (d, *J* = 8.5 Hz, 1H), 7.75 (t, *J* = 7.9 Hz, 1H), 7.47 (d, *J* = 7.3 Hz, 1H), 6.74 (s, 1H), 6.72 (d, *J* = 8.5 Hz, 1H), 6.62 (d, *J* = 7.3 Hz, 1H), 3.62 (s, 2H); ^{13}C NMR (DMSO-d_6): δ 170.1, 169.7, 168.1, 144.8, 143.9, 135.9, 135.2, 132.1, 129.4, 123.5, 119.7, 116.9, 116.8, 116.1, 115.2, 42.8; MS: *m/z* 312 ($C_{16}H_{12}N_2O_5$, $M^{+\cdot}$).

***N*-(1,3-Dioxoisoindolin-4-yl)-2-hydroxybenzamide: GKK-010-075**.

Reaction Scheme:

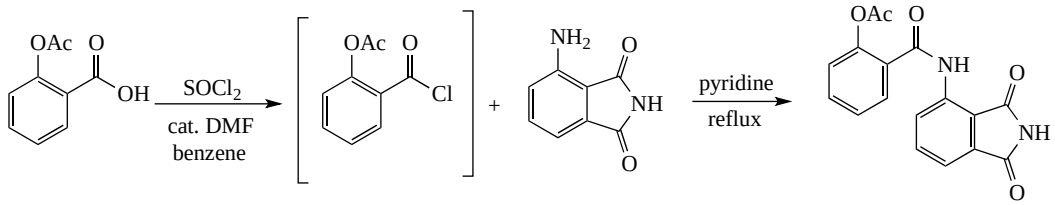


GKK-010-075

Procedure E2. Yellow solid (163 mg, 58%), mp 282-284 °C; ^{1}H NMR (DMSO-d_6): δ 11.9 (s, 1H), 11.8 (s, 1H), 11.4 (s, 1H), 8.96 (d, *J* = 8.5 Hz, 1H), 8.01 (d, *J* = 7.7 Hz, 1H), 7.81 (t, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 7.7 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.98 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 169.4, 168.2, 163.9, 155.9, 136.1, 135.1, 133.5, 132.4, 130.6, 124.5, 119.0, 117.7, 117.0, 116.8, 116.2; MS: *m/z* 282 ($C_{15}H_{10}N_2O_4$, $M^{+\cdot}$).

2-((1,3-Dioxoisoindolin-4-yl)carbamoyl)phenyl acetate: GKK-010-070.

Reaction Scheme:

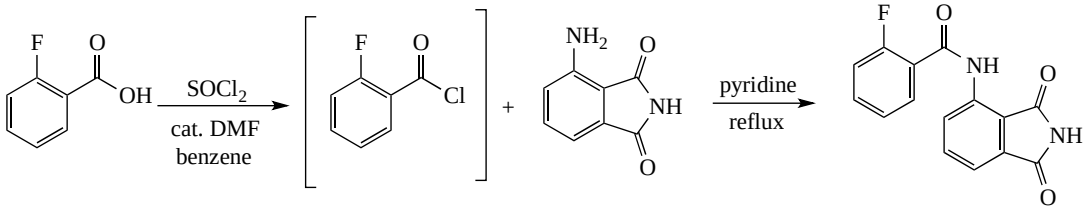


GKK-010-070

Procedure E2. Yellow solid (55 mg, 20%), mp 212-214 °C; ^{1}H NMR (DMSO-d_6): δ 11.5 (s, 1H), 10.4 (s, 1H), 8.7 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 7.7 Hz, 1H), 7.84 (t, *J* = 7.9 Hz, 1H), 7.69 (t, *J* = 7.7 Hz, 1H), 7.57 (d, *J* = 7.3 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 170.0, 168.5, 168.1, 163.0, 147.4, 135.5, 135.3, 132.6, 132.2, 129.2, 126.6, 125.9, 124.3, 123.3, 117.8, 117.6, 20.3; MS: *m/z* 324 ($C_{17}H_{12}N_2O_5$, $M^{+\cdot}$).

***N*-(1,3-Dioxoisoindolin-4-yl)-2-fluorobenzamide: GKK-010-069**.

Reaction Scheme:

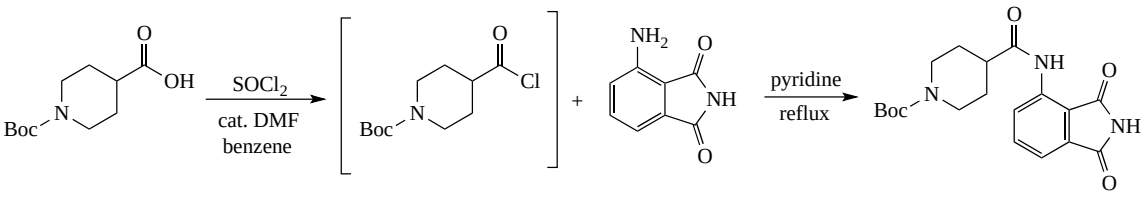


GKK-010-069

Procedure E2. Yellow solid (181 mg, 64%), mp 272-273 °C; ^{1}H NMR (DMSO-d_6): δ 11.5 (s, 1H), 10.6 (d, *J* = 9.7 Hz, 1H), 8.76 (d, *J* = 8.4 Hz, 1H), 8.02 (td, *J* = 7.8, 1.7 Hz, 1H), 7.85 (t, *J* = 7.8 Hz, 1H), 7.76-7.68 (m, 1H), 7.57 (d, *J* = 7.3 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.43 (q, *J* = 7.8 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 171.0, 169.1, 162.1, 160.2 (d, *J* = 247.0 Hz), 136.5, 136.4, 135.3 (d, *J* = 10.0 Hz), 133.2, 131.8, 125.8, 125.2, 121.3 (d, *J* = 8.0 Hz), 118.6, 118.5, 117.2 (d, *J* = 23.0 Hz); MS: *m/z* 284 ($C_{15}H_9FN_2O_3$, $M^{+\cdot}$).

***tert*-Butyl 4-((1,3-dioxoisoindolin-4-yl)carbamoyl)piperidine-1-carboxylate: GKK-010-072**.

Reaction Scheme:

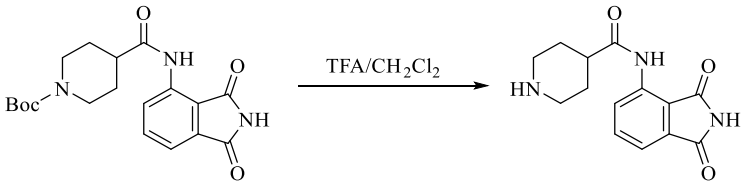


GKK-010-072

Procedure E2. Yellow solid (186 mg, 50%), mp 201-202 °C; ^{1}H NMR (DMSO-d_6): δ 11.5 (s, 1H), 9.76 (s, 1H), 8.46 (d, *J* = 8.4 Hz, 1H), 7.77 (t, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 7.3 Hz, 1H), 3.99 (d, *J* = 13.0 Hz, 1H), 2.84 (br s, 2H), 2.68 (tt, *J* = 11.5, 4.1 Hz, 1H), 1.88 (d, *J* = 10.5 Hz, 2H), 1.59-1.35 (complex, 3H), 1.41 (s, 9H); ^{13}C NMR (DMSO-d_6): δ 173.9, 170.9, 169.2, 154.3, 136.8, 136.2, 133.2, 125.7, 118.7, 118.3, 79.2, 43.2, 28.5, two aliphatic carbons coincident with solvent peaks; MS: *m/z* 373 ($C_{19}H_{23}N_3O_5$, $M^{+\cdot}$).

***N*-(1,3-Dioxoisoindolin-4-yl)piperidine-4-carboxamide: GKK-010-073.**

Reaction Scheme:

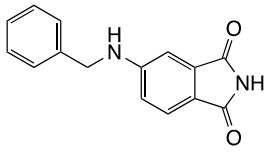


GKK-010-072 **GKK-010-073**

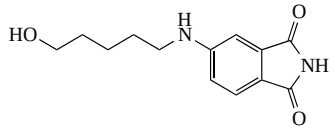
Boc-protected amide GKK-010-072 was treated with trifluoroacetic acid in dichloromethane at room temperature until TLC indicated that the reaction was complete. Extractive workup with $NaHCO_3$ and NaCl, followed by drying (Na_2SO_4), filtration and concentration yielded amide GKK-010-073 as a white solid (139 mg, 51%), mp 234-236 °C; ^{1}H NMR (DMSO-d_6): δ 9.75 (s, 1H), 8.49 (d, *J* = 8.4 Hz, 1H), 7.75 (t, *J* = 7.9 Hz, 1H), 7.48 (d, *J* = 7.3 Hz, 1H), 4.01 (br s, 1H), 3.02 (d, *J* = 11.9 Hz, 2H), 2.83 (br s, 1H), 2.55 (obscured, 3H), 1.83 (d, *J* = 12.6 Hz, 2H), 1.53 (apparent q, *J* = 12.3 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 174.2, 171.8, 170.0, 136.9, 136.0, 133.5, 125.2, 118.7, 118.0, 45.5, 43.7, 29.0; MS: *m/z* 273 ($C_{14}H_{15}N_3O_3$, $M^{+\cdot}$).

5-Aminoisoindoline-1,3-dione series

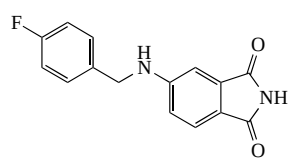
5-(Benzylamino)isoindoline-1,3-dione: BN-XIII-063. Procedure A. Off-white solid (265 mg, 85%), mp 263-264 °C; ^{1}H NMR (DMSO-d_6): δ 10.8 (s, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.36 (m, 5H), 7.26 (s, 1H), 6.87 (s, 1H), 6.85 (obscured, 1H), 4.42 (d, J = 3.4 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 170.1, 169.7, 154.4, 139.3, 135.8, 129.0, 127.6, 127.5, 124.9, 118.7, 116.2, 105.6, 46.5; MS: *m/z* 252 ($C_{15}H_{12}N_2O_2$, $M^{+\cdot}$).



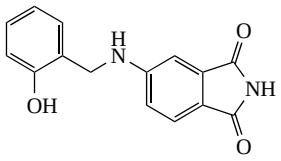
5-((5-Hydroxypentyl)amino)isoindoline-1,3-dione: BN-XIV-035. Procedure A. Pale yellow solid (260 mg, 86%), mp 197-198 °C; ^{1}H NMR (DMSO-d_6): δ 10.7 (br s, 1H), 7.54 (d, J = 8.3 Hz, 1H), 6.96 (br t, J = 4.5 Hz, 1H), 6.86 (s, 1H), 6.80 (d, J = 8.3 Hz, 1H), 4.38 (br s, 1H), 3.41 (t, J = 6.3 Hz, 2H), 3.14 (q, J = 6.3 Hz, 2H), 1.58 (quintet, J = 7.2 Hz, 2H), 1.52-1.34 (complex, 4H); ^{13}C NMR (DMSO-d_6): δ 170.2, 169.8, 154.6, 135.9, 125.0, 117.9, 115.5, 105.1, 61.1, 43.0, 32.7, 28.7, 23.6; MS: *m/z* 248 ($C_{13}H_{16}N_2O_3$, $M^{+\cdot}$).



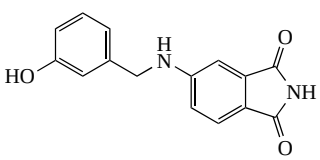
5-((4-Fluorobenzyl)amino)isoindoline-1,3-dione: BN-XIII-069. Procedure A. Yellow solid (260 mg, 78%), mp 237-238 °C; ^{1}H NMR (DMSO-d_6): δ 10.8 (s, 1H), 7.55 (br s, 1H), 7.48 (d, J = 8.2 Hz, 1H), 7.40 (br s, 2H), 7.28 (br t, J = 8.8 Hz, 2H), 6.86 (m, 2H), 4.41 (d, J = 4.3 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 170.0, 169.7, 161.7 (d, J = 242.4 Hz), 154.2, 135.8, 135.4, 129.6 (d, J = 8.1 Hz), 125.0, 118.8, 116.3, 115.7 (d, J = 21.3 Hz), 105.7, 45.7; MS: *m/z* 270 ($C_{15}H_{11}FN_2O_2$, $M^{+\cdot}$).



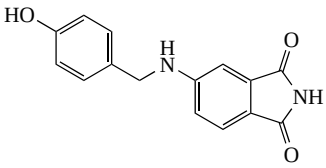
5-((2-Hydroxybenzyl)amino)isoindoline-1,3-dione: BN-XIII-093. Procedure A. Yellow solid (235 mg, 71%), mp 205-206 °C; ^{1}H NMR (DMSO-d_6): δ 10.7 (s, 1H), 9.66 (s, 1H), 7.48 (d, J = 8.3 Hz, 1H), 7.39 (s, 1H), 7.16 (d, J = 7.5 Hz, 1H), 7.09 (br t, J = 7.8, 1H), 6.92-6.83 (complex, 3H), 6.76 (t, J = 7.6 Hz, 1H), 4.32 (d, J = 5.1 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 170.1, 169.8, 155.6, 154.5, 135.8, 128.8, 128.5, 124.9, 124.7, 119.4, 118.3, 115.9, 115.5, 105.4, 41.5; MS: *m/z* 268 ($C_{15}H_{12}N_2O_3$, $M^{+\cdot}$).



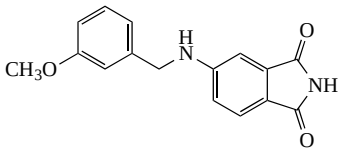
5-((3-Hydroxybenzyl)amino)isoindoline-1,3-dione: BN-XIII-092. Procedure A. Off-white solid (225 mg, 68%), mp 218-219 °C; ^{1}H NMR (DMSO-d_6): δ 10.8 (s, 1H), 9.37 (s, 1H), 7.55 (t, J = 6.0 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H), 7.14 (t, J = 7.2 Hz, 1H), 6.85 (s, 1H), 6.84 (d, J = 7.4 Hz, 1H), 6.77 (d, J = 7.4 Hz, 1H), 6.74 (s, 1H), 6.64 (dd, J = 8.1, 1.8 Hz, 1H), 4.34 (d, J = 5.9 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 170.1, 169.7, 158.0, 154.4, 140.8, 135.8, 130.0, 124.9, 118.6, 118.1, 116.2, 114.4, 114.2, 105.6, 46.4; MS: *m/z* 268 ($C_{15}H_{12}N_2O_3$, $M^{+\cdot}$).



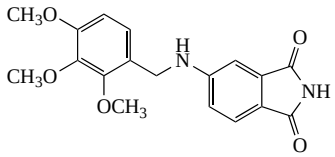
5-((4-Hydroxybenzyl)amino)isoindoline-1,3-dione: BN-XIII-068. Procedure A. Off-white solid (220 mg, 67%), mp 233-234 °C; ^{1}H NMR (DMSO-d_6): δ 10.7 (br s, 1H), 9.33 (br s, 1H), 7.47 (s, 2H), 7.16 (s, 2H), 6.86 (s, 2H), 6.74 (s, 2H), 4.27 (s, 2H); ^{13}C NMR (DMSO-d_6): δ 170.1, 169.8, 156.9, 154.4, 135.8, 129.1, 129.0, 124.9, 118.4, 116.1, 115.7, 105.6, 46.2; MS: *m/z* 268 ($C_{15}H_{12}N_2O_3$, $M^{+\cdot}$).



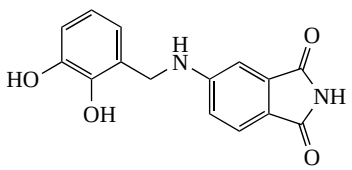
5-((3-Methoxybenzyl)amino)isoindoline-1,3-dione: BN-XIII-070. Procedure A. Yellow solid (300 mg, 86%), mp 147-148 °C; ^{1}H NMR (DMSO-d_6): δ 10.8 (s, 1H), 7.55 (s, 1H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.27 (t, *J* = 8.2 Hz, 1H), 6.93 (s, 2H), 6.90-6.78 (complex, 3H), 4.39 (d, *J* = 4.5 Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 170.1, 169.7, 159.9, 154.4, 141.0, 135.8, 130.0, 124.9, 119.7, 118.7, 116.2, 113.4, 112.7, 105.7, 55.4, 46.4; MS: *m/z* 282 ($C_{16}H_{14}N_2O_3$, $M^{+\cdot}$).



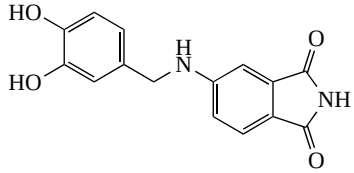
5-((2,3,4-Trimethoxybenzyl)amino)isoindoline-1,3-dione: BN-XIII-067. Procedure A. Off-white solid (375 mg, 89%), mp 202-203 °C; ^{1}H NMR (DMSO-d_6): δ 10.8 (s, 1H), 7.48 (d, *J* = 6.7 Hz, 1H), 7.32 (s, 1H), 7.00-6.73 (complex, 4H), 4.30 (s, 2H), 5.85 (s, 3H), 3.77 (s, 6H); ^{13}C NMR (DMSO-d_6): δ 170.1, 169.8, 154.3, 153.3, 151.8, 142.2, 135.8, 125.0, 124.1, 123.4, 118.4, 115.9, 108.2, 105.5, 61.3, 60.8, 56.3, 41.6; MS: *m/z* 342 ($C_{18}H_{18}N_2O_5$, $M^{+\cdot}$).



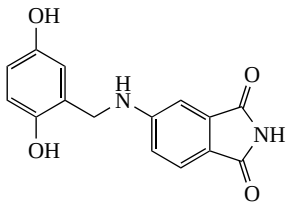
5-((2,3-Dihydroxybenzyl)amino)isoindoline-1,3-dione: BN-XIV-073. Procedure A. White solid (215 mg, 62%), mp 182-184 °C; ^{1}H NMR (DMSO-d_6): δ 10.7 (br s, 1H), 8.96 (br s, 2H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.37 (br t, *J* = 6.0 Hz, 1H), 6.87 (s, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.71 (d, *J* = 7.7 Hz, 1H), 6.65 (d, *J* = 7.5 Hz, 1H), 6.59 (t, *J* = 7.6 Hz, 1H), 4.32 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR: δ 170.1, 169.8, 154.6, 145.5, 143.6, 135.8, 125.6, 124.9, 119.2. 119.1, 118.2, 115.9, 114.7, 105.5, 41.7; MS: *m/z* 284 ($C_{15}H_{12}N_2O_4$, $M^{+\cdot}$).



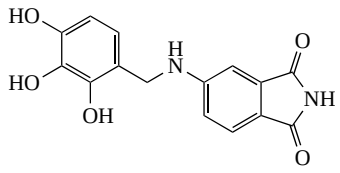
5-((3,4-Dihydroxybenzyl)amino)isoindoline-1,3-dione: BN-XIII-091. Procedure A. Off-white solid (227 mg, 65%), mp 189-190 °C; ^{1}H NMR: δ 10.7 (br s, 1H), 8.83 (br s, 2H), 7.45 (overlapping d, *J* = 8.1 Hz, 1H and br t, *J* = 5.6 Hz, 1H), 6.85 (s, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 6.78 (s, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 4.22 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 169.0, 168.7, 153.4, 144.7, 143.7, 134.7, 128.7, 123.8, 117.5, 117.3, 115.0, 114.9, 114.0, 104.5, 45.7; MS: *m/z* 284 ($C_{15}H_{12}N_2O_4$, $M^{+\cdot}$).



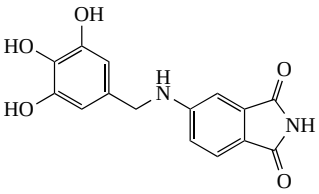
5-((2,5-Dihydroxybenzyl)amino)isoindoline-1,3-dione: BN-XV-062. Procedure A. White solid (200 mg, 62%), mp 154-155 °C; ^{1}H NMR (DMSO-*d*$_6$): δ 10.7 (s, 1H), 8.92 (s, 1H), 8.63 (s, 1H), 7.48 (d, *J* = 8.3 Hz, 1H), 7.42 (br t, *J* = 5.8 Hz, 1H), 6.84 (s, 1H), 6.83 (obscured, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 6.58 (s, 1H), 6.48 (d, *J* = 8.4 Hz, 1H), 4.26 (d, *J* = 5.9 Hz, 2H); ^{13}C NMR (DMSO-*d*$_6$): δ 169.1, 168.7, 153.5, 149.2, 146.7, 134.8, 124.3, 123.9, 117.2, 115.1, 114.9, 113.9, 113.6, 104.3, 40.4; MS: *m/z* 284 ($C_{15}H_{12}N_2O_4$, $M^{+\cdot}$).



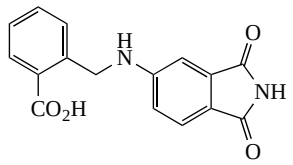
5-((2,3,4-Trihydroxybenzyl)amino)isoindoline-1,3-dione: BN-XVI-031. Procedure A. Pale yellow solid (215 mg, 58%), mp 193-194 °C; ^{1}H NMR (DMSO-*d*$_6$): δ 10.7 (s, 1H), 8.98 (s, 1H), 8.47 (s, 1H), 8.30 (s, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.23 (br t, *J* = 5.6 Hz, 1H), 6.86 (s, 1H), 6.82 (d, *J* = 8.6 Hz, 1H), 6.47 (d, *J* = 8.3 Hz, 1H), 6.25 (d, *J* = 8.2 Hz, 1H), 4.20 (d, *J* = 5.5 Hz, 2H); ^{13}C NMR (DMSO-*d*$_6$): δ 170.2, 169.8, 154.6, 145.7, 144.8, 135.8, 133.5, 124.9, 118.7, 118.0, 116.3, 115.8, 106.9, 105.5, 41.7; MS: *m/z* 300 ($C_{15}H_{12}N_2O_5$, $M^{+\cdot}$).



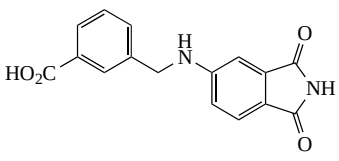
5-((3,4,5-Trihydroxybenzyl)amino)isoindoline-1,3-dione: BN-XVI-037. Procedure A. Yellow solid (230 mg, 62%), mp 215-216 °C; ^{1}H NMR (DMSO-*d*$_6$): δ 10.7 (s, 1H), 8.78 (s, 2H), 7.97 (s, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.44 (obscured, 1H), 6.86-6.78 (complex, 2H), 6.25 (s, 2H), 4.15 (d, *J* = 5.8 Hz, 2H); ^{13}C NMR (DMSO-*d*$_6$): δ 169.0, 168.7, 153.5, 145.5, 134.7, 131.3, 128.0, 123.8, 117.2, 115.1, 105.2, 104.9, 45.3; MS: *m/z* 300 ($C_{15}H_{12}N_2O_5$, $M^{+\cdot}$).



2-(((1,3-Dioxoisoindolin-5-yl)amino)methyl)benzoic acid: BN-XIV-037. Procedure A. Off-white solid (175 mg, 48%), mp 332-333 °C; ^{1}H NMR (DMSO-*d*$_6$): δ 11.3 (s, 1H), 8.44 (d, *J* = 1.8 Hz, 1H), 8.30 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.92 (d, *J* = 8.3 Hz, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.77-7.68 (complex, 2H), 7.59 (t, *J* = 7.2, 1H), 5.18 (s, 2H), acid and amine protons not observed; ^{13}C NMR (DMSO-*d*$_6$): δ 169.4, 169.3, 167.9, 145.1, 141.6, 134.6, 133.5, 132.2, 128.9, 127.4, 124.6, 124.1, 123.9, 123.6, 113.1, 51.2; MS: *m/z* 296 ($C_{16}H_{12}N_2O_4$, $M^{+\cdot}$).



3-(((1,3-Dioxoisoindolin-5-yl)amino)methyl)benzoic acid: BN-XIII-088. Procedure A. Off-white solid (183 mg, 50%), mp 303-304 °C; ^{1}H NMR (DMSO-*d*$_6$): δ 10.8 (br s, 1H), 7.95 (s, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.66 (br t, *J* = 6.0 Hz, 1H), 7.48 (complex, 2H), 7.40 (t, *J* = 7.6 Hz, 1H), 6.89 (s, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 2H), carboxylic acid proton not observed; ^{13}C NMR (DMSO-*d*$_6$): δ 170.1. 169.7, 168.7, 154.3, 139.3, 135.8, 134.9, 130.6, 128.7, 128.4 (2C), 125.0, 118.7, 116.2, 105.7, 46.3; MS: *m/z* 296 ($C_{16}H_{12}N_2O_4$, $M^{+\cdot}$).



4-(((1,3-Dioxoisoindolin-5-yl)amino)methyl)benzoic acid: BN-XVI-041. Procedure A. Off-white solid (170 mg, 47%), mp 351-353 °C; ^{1}H NMR (DMSO-d_6): δ 10.8 (s, 1H), 7.82 (d, J = 7.7 Hz, 2H), 7.63 (br t, J = 5.9 Hz, 1H), 7.46 (s, J = 8.2 Hz, 1H), 7.01 (d, J = 7.8 Hz, 2H) 6.88 (s, 1H), 6.86 (d, J = 8.3 Hz, 1H), 4.41 (d, J = 5.9 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 169.0, 168.7, 167.7, 153.4, 138.6, 138.4, 134.7, 128.6, 125.4, 123.8, 117.5, 115.1, 104.6, 45.4; MS: *m/z* 296 ($C_{16}H_{12}N_2O_4$, $M^{+\cdot}$).

5-((Cyclopent-1-en-1-ylmethyl)amino)isoindoline-1,3-dione: BN-XIV-031. Procedure A. White solid (230 mg, 76%), mp 193-194 °C; ^{1}H NMR (DMSO-d_6): δ 10.8 (s, 1H), 7.48 (d, J = 8.3 Hz, 1H), 7.19 (br t, J = 6.0 Hz, 1H), 6.88 (s, 1H), 6.83 (d, J = 8.7 Hz, 1H), 5.56 (s, 1H), 3.85 (d, J = 6.0 Hz, 2H), 2.28 (t, J = 7.6 Hz, 4H), 1.86 (quintet, J = 7.5 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 170.1, 169.8, 154.6, 141.6, 135.8, 125.6, 124.9, 118.3, 115.2, 105.5, 43.4, 33.5, 32.3, 23.3; MS: *m/z* 242 ($C_{14}H_{14}N_2O_2$, $M^{+\cdot}$).

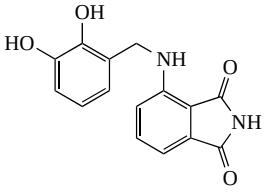
5-(((2-Methylfuran-3-yl)methyl)amino)isoindoline-1,3-dione: BN-XIII-072. Procedure A. Yellow solid (156 mg, 61%), mp 158-159 °C; ^{1}H NMR (DMSO-d_6): δ 10.8 (s, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.38 (s, 1H), 6.96 (s, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.22 (s, 1H), 6.00 (s, 1H), 4.33 (d, J = 4.4 Hz, 2H), 2.23 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 170.1, 169.8, 154.1, 151.4, 150.4, 135.7, 124.9, 118.9, 116.1, 108.8, 106.8, 105.7, 39.9, 13.8; MS: *m/z* 256 ($C_{14}H_{12}N_2O_3$, $M^{+\cdot}$).

5-((2-(Phenylthio)benzyl)amino)isoindoline-1,3-dione: BN-XIV-036. Procedure A. Yellow solid (375 mg, 84%), mp 192-193 °C; ^{1}H NMR (DMSO-d_6): δ 10.8 (s, 1H), 7.54 (br t, J = 6.0 Hz, 1H), 7.46 (d, J = 8.3 Hz, 1H), 7.44-7.26 (complex, 9H), 6.81 (s, 1H), 6.76 (d, J = 8.3 Hz, 1H), 4.46 (d, J = 6.0 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 170.0, 169.7, 154.1, 139.8, 135.8, 135.5, 133.8, 133.2, 130.2, 130.1, 128.9, 128.8, 128.6, 127.6, 125.0, 119.0, 116.0, 105.6, 45.2; MS: *m/z* 360 ($C_{21}H_{16}N_2O_2S$, $M^{+\cdot}$).

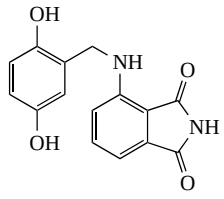
4-Aminoisoindoline-1,3-dione series

4-((3-Hydroxybenzyl)amino)isoindoline-1,3-dione: BN-XIV-053 (Analog 12). Procedure A. Yellow solid (218 mg, 67%), mp 192-193 °C; ^{1}H NMR (DMSO-d_6): δ 10.9 (br s, 1H), 9.60 (br s, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.13 (t, J = 7.8 Hz, 1H), 7.08 (br t, J = 6.3 Hz, 1H), 6.94 (d, J = 7.1 Hz, 1H), 6.89 (d, J = 8.5 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 6.76 (s, 1H), 6.65 (d, J = 8.2 Hz, 1H), 4.46 (d, J = 6.3 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 171.8, 169.8, 158.0, 146.5, 141.0, 136.2, 134.0, 130.0, 117.9, 117.4, 114.4, 114.0, 111.5, 110.6, 45.9; MS: *m/z* 268 ($C_{15}H_{12}N_2O_3$, $M^{+\cdot}$).

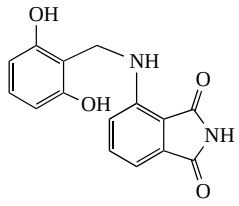
4-((2,3-Dihydroxybenzyl)amino)isoindoline-1,3-dione: BN-XIV-074. Procedure A. Yellow solid (220 mg, 67%), mp 182-184 °C; ^{1}H NMR (DMSO-d_6): δ 10.9 (s, 1H), 9.34 (s, 1H), 8.60 (s, 1H), 7.48 (t, J = 7.8 Hz, 1H), 6.99 (d, J = 8.5 Hz, 1H), 6.90 (overlapping d, J = 7.0 Hz, 1H and br t, J = 6.1 Hz, 1H), 6.69 (t, J = 7.2 Hz, 2H), 6.57 (t, J = 7.7 Hz, 1H), 4.41 (d, J = 6.1 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 170.8, 168.7, 145.6, 144.4, 142.6, 135.1, 132.9, 124.7, 118.3, 118.2, 116.2, 113.8, 110.3, 109.3, 40.6; MS: *m/z* 284 ($C_{15}H_{12}N_2O_4$, $M^{+\cdot}$).



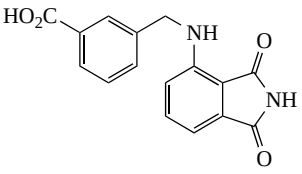
4-((2,5-Dihydroxybenzyl)amino)isoindoline-1,3-dione: **BN-XVI-069**. Procedure A. White solid (247 mg, 71%), mp 178-179 °C; ^{1}H NMR (DMSO-d_6): δ 10.9 (s, 1H), 9.35 (s, 1H), 9.18 (s, 1H), 7.49 (t, J = 7.7 Hz, 1H), 7.05 (d, J = 8.5 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H), 6.91 (d, J = 7.1 Hz, 1H), 6.77 (br t, J = 6.1 Hz, 1H), 6.32 (s, 1H), 6.16 (d, J = 8.0 Hz, 1H), 4.29 (d, J = 6.0 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 170.8, 168.7, 157.0, 155.5, 145.6, 135.1, 132.9, 129.1, 116.2, 114.4, 110.2, 109.2, 105.4, 101.9, 40.4; MS: *m/z* 284 ($C_{15}H_{12}N_2O_4$, $M^{+\cdot}$).



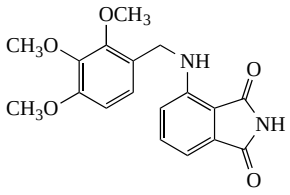
4-((2,6-Dihydroxybenzyl)amino)isoindoline-1,3-dione: BN-XVI-070. Procedure A. White solid (260 mg, 73%), mp 166-167 °C; ^{1}H NMR (DMSO-d_6): δ 10.9 (s, 1H), 9.62 (s, 2H), 7.52 (t, J = 7.9 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 6.92-6.83 (complex, 2H), 6.77 (br t, J = 6.2 Hz, 1H), 6.32 (d, J = 8.1 Hz, 2H), 4.37 (d, J = 6.2 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 170.9, 168.7, 155.9, 145.8, 135.2, 132.9, 127.8, 116.1, 110.6, 110.1, 109.1, 105.7, 34.7; MS: *m/z* 284 ($C_{15}H_{12}N_2O_4$, $M^{+\cdot}$).



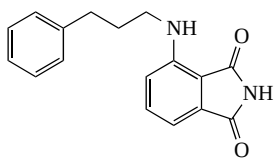
3-(((1,3-Dioxoisoindolin-4-yl)amino)methyl)benzoic acid: BN-XIV-059. Procedure A. Yellow solid (310 mg, 85%), mp 253-254 °C; ^{1}H NMR (DMSO-d_6): δ 13.0 (br s, 1H), 11.0 (s, 1H), 7.97 (s, 1H), 7.82 (d, J = 7.7 Hz, 1H), 7.62 (d, J = 7.7 Hz, 1H), 7.45 (overlapping t, $J \approx$ 7.1 Hz, 2H), 7.26 (br t, J = 6.5 Hz, 1H), 6.94 (d, J = 7.1 Hz, 1H), 6.88 (d, J = 8.5 Hz, 1H), 4.61 (d, J = 6.4 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 171.7, 169.8, 167.7, 146.3, 140.3, 136.2, 134.1, 131.9, 131.5, 129.2, 128.4, 128.2, 117.3, 111.7, 110.7, 45.5; MS *m/z* 296 ($C_{16}H_{12}N_2O_4$, $M^{+\cdot}$).



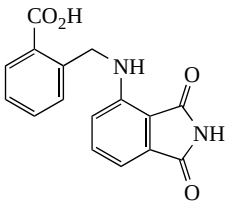
4-((2,3,4-Trimethoxybenzyl)amino)isoindoline-1,3-dione: BN-XIV-060. Procedure A. Yellow solid (395 mg, 94%), mp 138-139 °C; ^{1}H NMR (DMSO-d_6): δ 11.0 (s, 1H), 7.50 (br t, J = 8.2 Hz, 1H), 7.00 (d, J = 8.5 Hz, 1H), 6.98 (obscured, 2H), 6.85 (s, 1H), 6.76 (d, J = 8.7 Hz, 1H), 4.43 (d, J = 4.1 Hz, 2H), 3.86 (s, 3H), 3.77 (s, 6H); ^{13}C NMR (DMSO-d_6): δ 171.9, 169.8, 153.3, 151.7, 146.4, 142.2, 136.2, 134.0, 124.8, 123.3, 117.2, 111.5, 110.5, 108.1, 61.3, 60.8, 56.3, 41.3; MS: *m/z* 342 ($C_{18}H_{18}N_2O_5$, $M^{+\cdot}$).



4-(3-Phenylpropylamino)isoindoline-1,3-dione: BN-XVI-067. Procedure A. Yellow solid (315 mg, 96%), mp 157-158 °C; ^{1}H NMR (DMSO-*d*$_6$): δ 11.0 (s, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.25-7.15 (complex, 3H), 6.95 (d, *J* = 8.5 Hz, 1H), 6.91 (d, *J* = 7.1 Hz, 1H), 6.53 (br t, *J* = 6.2 Hz, 1H), 3.29 (q, *J* = 6.7 Hz, 2H), 2.67 (t, *J* = 7.7 Hz, 2H), 1.88 (quintet, *J* = 7.4 Hz, 2H); ^{13}C NMR (DMSO-*d*$_6$): δ 170.8, 168.7, 145.6, 140.8, 135.3, 133.0, 127.72, 127.65, 125.2, 115.8, 110.2, 109.2, 40.8, 31.8, 29.7; MS: *m/z* 280 ($C_{17}H_{16}N_2O_2$, $M^{+\cdot}$).

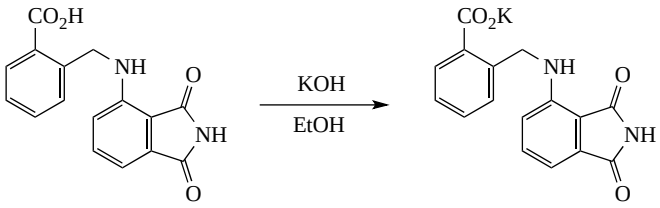


2-(((1,3-Dioxoisoindolin-4-yl)amino)methyl)benzoic acid: GKK-008-060. Procedure A. Yellow solid (261 mg, 88%), mp 310-312 °C; ^{1}H NMR (DMSO-*d*$_6$): δ 11.2 (s, 1H), 7.92 (d, *J* = 7.7 Hz, 1H), 7.88 (t, *J* = 7.4 Hz, 1H), 7.78 (d, *J* = 7.9 Hz, 1H), 7.76-7.68 (complex, 2H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.39 (br s, 2H), 7.27 (t, *J* = 7.7 Hz, 1H), acid and amine protons not observed; ^{13}C NMR (DMSO-*d*$_6$): δ 171.1, 169.4, 169.1, 145.8, 143.6, 136.5, 135.3, 134.0, 131.3, 127.7, 125.4, 124.1, 119.5, 114.7, 114.3, 85.6; MS: *m/z* 296 ($C_{16}H_{12}N_2O_4$, $M^{+\cdot}$).



Potassium 2-(((1,3-dioxoisoindolin-4-yl)amino)methyl)benzoate: GKK-011-011.

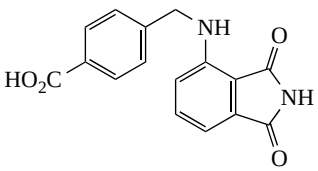
Reaction Scheme:



GKK-011-011

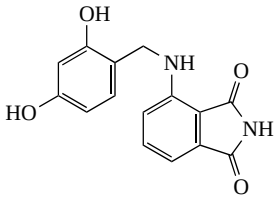
To a stirred solution of the acid (200 mg, 0.68 mmol) in ethanol (10 mL) was added KOH (76 mg, 1.36 mmol) and the mixture was stirred at 23 °C for 2 h. The solid was collected by filtration and washed with ethanol (2 × 2.5 mL) to afford 71 mg (31%) of the potassium carboxylate salt as a yellow solid, mp >300 °C; ^{1}H NMR (DMSO-*d*$_6$): δ 9.24 (s, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.41-7.33 (complex, 2H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 7.1 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), benzylic and amine protons not observed; ^{13}C NMR (DMSO-*d*$_6$): δ 183.8, 170.4, 165.7, 149.2, 146.0, 141.3, 134.2, 131.5, 130.2, 129.4, 127.3, 126.7, 124.8, 116.1, 106.8, 100.0.

4-(((1,3-Dioxoisoindolin-4-yl)amino)methyl)benzoic acid: GKK-008-056. Procedure A. Yellow solid (201 mg, 68%), mp 290-291 °C; ^{1}H NMR (DMSO-*d*$_6$): δ 12.9 (s, 1H), 11.0 (s, 1H), 7.90 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.45 (obscured, 1H), 7.25 (br t, *J* = 6.5 Hz, 1H), 6.93 (d, *J* = 7.1 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 1H), 4.62 (d, *J* = 6.5 Hz, 2H); ^{13}C NMR

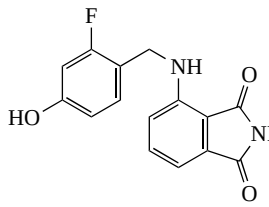


(DMSO-d_6): δ 171.7, 169.8, 167.6, 146.2, 145.0, 136.2, 134.1, 130.04, 129.98, 127.4, 117.3, 111.8, 110.7, 45.7; MS: *m/z* 296 ($C_{16}H_{12}N_2O_4$, $M^{+\cdot}$)

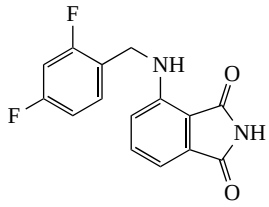
4-((2,4-Dihydroxybenzyl)amino)isoindoline-1,3-dione: GKK-006-092. Yellow solid (71 mg, 25%), mp >300 °C; ^{1}H NMR (DMSO-d_6): δ 10.9 (s, 1H), 9.53 (s, 1H), 9.16 (s, 1H), 7.49 (t, *J* = 7.9 Hz, 1H), 7.04 (d, *J* = 8.5 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 1H), 6.90 (d, *J* = 7.1 Hz, 1H), 6.77 (br t, *J* = 6.1 Hz, 1H), 6.31 (d, *J* = 2.4 Hz, 1H), 6.16 (dd, *J* = 8.1, 2.4 Hz, 1H), 4.28 (d, *J* = 6.1 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 170.8, 168.7, 157.0, 155.5, 145.6, 135.1, 132.9, 129.1, 116.2, 114.4, 110.2, 109.2, 105.4, 101.9, 40.4; MS: *m/z* 284 ($C_{15}H_{12}N_2O_4$, $M^{+\cdot}$).



4-((2-Fluoro-4-hydroxybenzyl)amino)isoindoline-1,3-dione: GKK-010-096A. Yellow solid (206 mg, 72%), mp 215-217 °C; ^{1}H NMR (DMSO-d_6): δ 11.0 (s, 1H), 9.84 (s, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.20 (t, *J* = 8.6 Hz, 1H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.95 (d, *J* = 7.0 Hz, 1H), 6.86 (br t, *J* = 6.3 Hz, 1H), 6.58 (br s, 1H), 6.56 (s, 1H), 4.44 (d, *J* = 6.2 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 170.7, 168.7, 160.2 (d, *J* = 244.4 Hz), 157.6 (d, *J* = 11.1 Hz), 145.2, 135.2, 133.0, 129.5 (d, *J* = 7.1 Hz), 116.0, 114.7 (d, *J* = 15.2 Hz), 110.9, 110.6, 109.7, 102.0 (d, *J* = 23.2 Hz), 38.7; MS: *m/z* 286 ($C_{15}H_{11}FN_2O_3$, $M^{+\cdot}$).

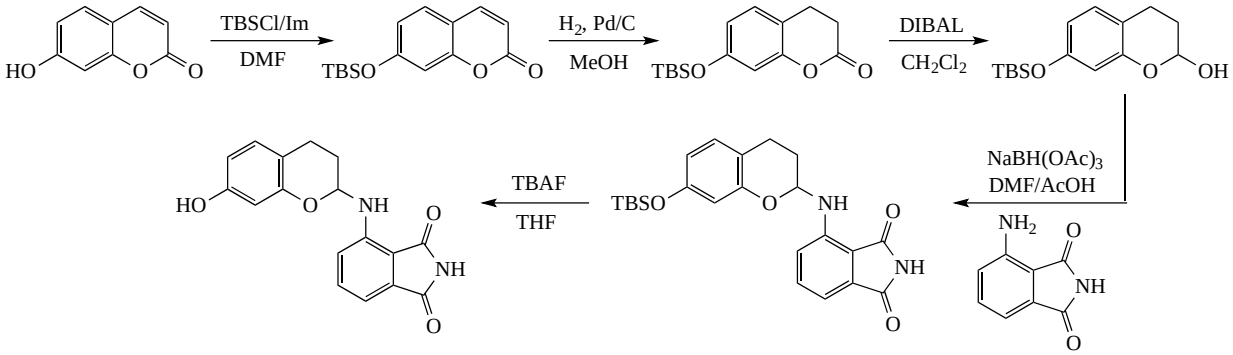


4-((2,4-Difluorobenzyl)amino)isoindoline-1,3-dione: GKK-010-096B. Yellow solid (216 mg, 75%), mp 178-180 °C; ^{1}H NMR (DMSO-d_6): δ 11.0 (s, 1H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.43 (q, *J* = 8.4 Hz, 1H), 7.25 (td, *J* = 9.5, 2.3 Hz, 1H), 7.05 (m, 2H), 6.95 (t, *J* = 8.1 Hz, 2H), 4.57 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 170.6, 168.6, 160.8 (dd, *J* = 245.0, 12.2 Hz), 159.6 (dd, *J* = 247.0, 12.3 Hz), 145.0, 135.3, 133.0, 129.6 (dd, *J* = 9.9, 6.2 Hz), 121.4 (dd, *J* = 15.2, 3.7 Hz), 116.0, 110.9 (dd, *J* = 21.3, 3.4 Hz), 110.8, 109.9, 103.8 (t, *J* = 25.7 Hz), 38.5; MS: *m/z* 288 ($C_{15}H_{10}F_2N_2O_2$, $M^{+\cdot}$).



4-((7-Hydroxychroman-2-yl)amino)isoindoline-1,3-dione: GKK-007-019.

Reaction Scheme:



GKK-007-019

7-((*tert*-Butyldimethylsilyl)oxy)-2*H*-chromen-2-one. 7-Hydroxycoumarin (1.80 g, 12.3 mmol) was silylated with TBSCl (2.08 g, 14.8 mmol) according to Procedure B to give the TBS-protected derivative (3.28 g, 11.9 mmol, 97%) as a white solid. This compound was used without further purification.

7-((*tert*-Butyldimethylsilyl)oxy)chroman-2-one. A solution of the TBS-protected coumarin (0.60 g, 2.17 mmol) in absolute EtOH (60 mL) was flushed twice with nitrogen and 10% Pd/C (220 mg, 50% wet, 10% w/w) was added. The reaction was stirred under hydrogen (1 atm) for 5 h. The reaction mixture was filtered through Celite® and washed with EtOH (2 × 25 mL). The filtrate was concentrated under vacuum to provide the 2-chromanone (0.45 g, 1.62 mmol, 74%) as a colorless oil. This compound was used in the next reaction without further purification.

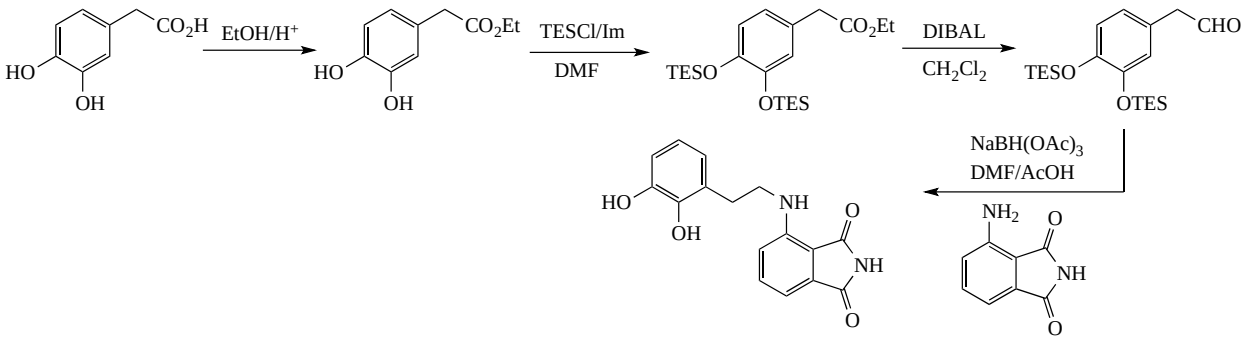
7-((*tert*-Butyldimethylsilyl)oxy)chroman-2-ol. A solution of the (*tert*-butyldimethylsilyl)oxy-chromanone (1.10 g, 3.96 mmol) in CH_2Cl_2 (10 mL) was cooled to –78 °C and 1.5 M DIBAL-H in toluene (3.2 mL, 4.74 mmol) was added drop-wise with stirring. Stirring was continued at this temperature for 2 h or until TLC analysis indicated the complete consumption of starting material. The reaction was quenched by drop-wise addition of MeOH (10 mL), followed by 1 M HCl (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum to provide the crude product, which was purified by column chromatography to give the 2-chromanol (475 mg, 1.70 mmol, 43%) as a colorless oil. This compound existed as a mixture of the open and closed forms and was used without further purification.

4-((7-((tert-Butyldimethylsilyl)oxy)chroman-2-yl)amino)isoindoline-1,3-dione. This compound was prepared by reductive amination of 7-((*tert*-butyldimethylsilyl)oxy)chroman-2-ol (475 mg, 1.70 mmol) with 4-aminoisoindoline-1,3-dione according to Procedure A to afford the TBS protected 4-(7-(hydroxychroman-2-yl)amino)isoindoline-1,3-dione (240 mg, 0.57 mmol, 34%) as a yellow solid, mp 187-189 °C. This compound was used in the next step without further purification.

4-((7-Hydroxychroman-2-yl)amino)isoindoline-1,3-dione: GKK-007-019. The TBS group was cleaved from the TBS-protected isoindoline-1,3-dione (230 mg, 0.54 mmol) according to Procedure C to provide 4-((7-hydroxychroman-2-yl)amino)isoindoline-1,3-dione (93 mg, 0.30 mmol, 53%) as a yellow solid, mp 228-229 °C; ^{1}H NMR (DMSO-d_6): δ 11.1 (s, 1H), 9.18 (s, 1H), 7.64 (t, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.13 (d, *J* = 7.1 Hz, 1H), 7.03 (d, *J* = 8.7 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.29 (d, *J* = 8.2 Hz, 1H), 6.09 (s, 1H), 5.74 (t, *J* = 7.9 Hz, 1H), 2.85 (m, 1H), 2.72 (m, 1H), 2.17 (m, 1H), 2.08 (m, 1H); ^{13}C NMR (DMSO-d_6): δ 171.9, 160.6, 157.1, 153.9, 144.3, 136.4, 133.7, 130.2, 119.0, 112.92, 112.85, 111.9, 108.8, 103.5, 78.6, 26.8, 22.0; MS: *m/z* 310 ($C_{17}H_{14}N_2O_4$, $M^{+\cdot}$).

4-((3,4-Dihydroxyphenethyl)amino)isoindoline-1,3-dione: GKK-007-027B.

Reaction Scheme:



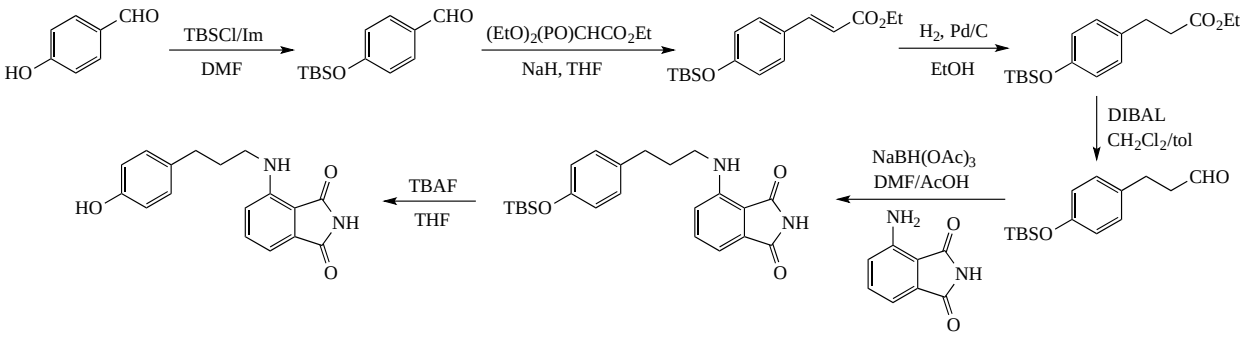
GKK-007-027B

Ethyl 2-(3,4-Dihydroxyphenyl)acetate. To a stirred solution of (3,4-dihydroxyphenyl)acetic acid (2.00 g, 11.9 mmol) in ethanol (10 mL) was added 3 drops of conc. H_2SO_4 and the reaction was heated at reflux for 2 h. The ethanol was removed under vacuum and the resulting residue was diluted with water and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with aqueous $NaHCO_3$ (2 × 50 mL) and water (50 mL), dried (Na_2SO_4) and evaporated under vacuum to afford the ester (2.10 g, 10.7 mmol, 90%) as a colorless oil. This compound was used without further purification.

4-((3,4-Dihydroxyphenethyl)amino)isoindoline-1,3-dione: GKK-007-027B. The hydroxyl groups in ethyl 2-(3,4-dihydroxyphenyl)acetate (2.00 g, 10.2 mmol) were silyl-protected with TESCl (3.93 g, 4.36 mL, 26.0 mmol) according to Procedure B. The crude di-TES-protected product was dissolved in CH_2Cl_2 (100 mL), cooled to –78 °C and 1.5 M DIBAL (9.4 mL, 14.0 mmol) in toluene was added drop-wise over a period of 30 min. Stirring was continued for 2 h or until TLC analysis indicated the complete consumption of starting material. The reaction was quenched by drop-wise addition of MeOH (10 mL), followed by 1 M HCl (20 mL). The organic layer was separated and the aqueous layer was extracted using CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to provide the crude aldehyde. This aldehyde was subjected to reductive amination with 4-aminoisoindoline-1,3-dione according to Procedure A to afford 4-((3,4-dihydroxyphenethyl)amino)isoindoline-1,3-dione (160 mg, 0.54 mmol, 5.3% for 4 steps) as a yellow solid, mp 204-205 °C. (*Note*: The TES groups were cleaved during the reductive amination). ^{1}H NMR (DMSO-d_6): δ 10.9 (s, 1H), 8.74 (s, 1H), 8.69 (s, 1H), 7.53 (t, J = 7.8 Hz, 1H), 7.05 (d, J = 8.5 Hz, 1H), 6.93 (d, J = 7.1 Hz, 1H), 6.65 (d, J = 7.1 Hz, 1H), 6.64 (s, 1H), 6.52 (d, J = 8.2 Hz, 1H), 6.46 (br t, J = 6.5 Hz, 1H), 3.42 (q, J = 6.9 Hz, 2H), 2.69 (t, J = 7.3 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 171.8, 169.8, 146.6, 145.6, 144.1, 136.4, 134.0, 130.1, 119.8, 117.0, 116.6, 116.0, 111.2, 110.3, 44.1, 34.6; MS: *m/z* 298 ($C_{16}H_{14}N_2O_4$, $M^{+\cdot}$).

4-((3-(4-Hydroxyphenyl)propyl)amino)isoindoline-1,3-dione: GKK-006-080 (Analog 13).

Reaction Scheme:



GKK-006-080

4-((*tert*-Butyldimethylsilyl)oxy)benzaldehyde. 4-Hydroxybenzaldehyde (2.00 g, 16.4 mmol) was reacted with TBSCl (2.77 g, 19.7 mmol) according to Procedure B to give the TBS-protected 4-hydroxybenzaldehyde (2.0 g, 10.6 mmol, 65%) as a white solid. This compound was used without further purification.

Ethyl (*E*)-3-(4-(((tert-butyldimethylsilyl)oxy)phenyl)acrylate. To a stirred suspension of NaH (140 mg of a 60% dispersion in mineral oil, 3.50 mmol) in THF at 0 °C was added a solution of triethylphosphonoacetate (785 mg, 0.70 mL, 3.50 mmol) in THF (5.0 mL) and the reaction was stirred for 15 min. To the resulting mixture was added drop-wise TBS-protected 4-hydroxybenzaldehyde (740 mg, 3.13 mmol) in THF (5.0 mL) and the reaction was allowed to warm to 23 °C. At this time, TLC analysis indicated the complete absence of starting material. The reaction was cooled to 0 °C and quenched by drop-wise addition of ice-cold water. The product was extracted into ether (2 × 25 mL), and the combined organic layers were washed with NaCl (15 mL), dried (Na_2SO_4) and evaporated to afford the acrylate (870 mg, 2.84 mmol, 91%) as a colorless oil. This compound was carried forward without further purification.

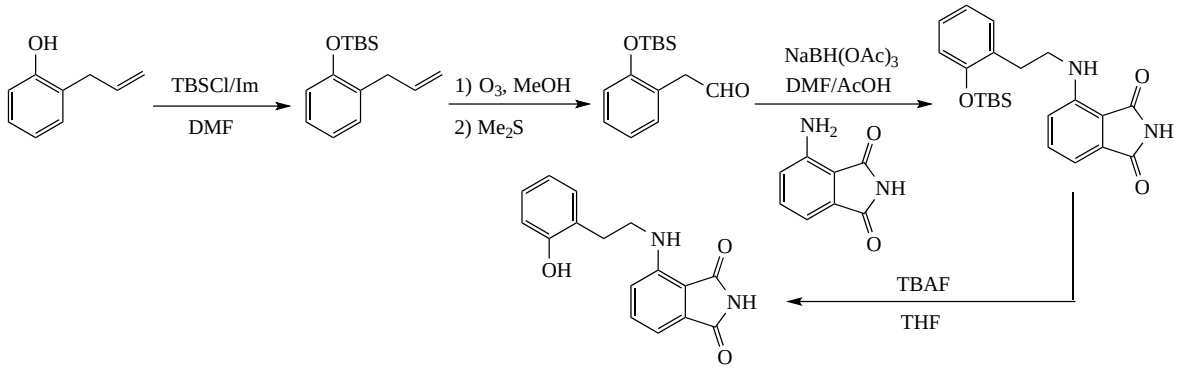
Ethyl 3-(4-((tert-butyldimethylsilyl)oxy)phenyl)propanoate. A solution of the acrylate ester (766 mg, 2.50 mmol) in ethanol (10 mL) was flushed twice with nitrogen and 5% Pd/C (10% w/w) was added. The reaction was stirred at 23 °C under H_2 (1 atm) for 18 h, filtered through Celite® and washed with EtOH (2 × 25 mL). The filtrate was concentrated to provide the propanoate ester (570 mg, 1.85 mmol, 74%) as a colorless oil. This compound was used directly in the next reaction.

4-((3-(4-Hydroxyphenyl)propyl)amino)isoindoline-1,3-dione: GKK-006-080. The above ester (500 mg, 1.62 mmol) prepared above was dissolved in CH_2Cl_2 (10 mL), cooled to –78 °C and a 1.5 M solution of DIBAL (1.3 mL, 1.94 mmol) in toluene was added drop-wise over a period of 30 min. Stirring was continued for 2 h or until TLC analysis indicated the complete absence of starting material. The reaction was quenched by drop-wise addition of MeOH (5 mL), followed by 1 M HCl (10 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were dried (Na_2SO_4) and evaporated to provide the aldehyde as a colorless oil. This crude material was subjected to reductive amination with 4-aminoisoindoline-1,3-dione according to Procedure A, to provide the 4-((3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)propyl)amino)isoindoline-1,3-dione. The TBS groups were

cleaved according to Procedure C to afford 4-((3-(4-hydroxyphenyl)propyl)amino)isoindoline-1,3-dione (100 mg, 0.34 mmol, 21%, 4.2% overall) as a yellow solid, mp 170-171 °C. ^{1}H NMR (DMSO-d_6): δ 10.9 (s, 1H), 9.13 (s, 1H), 7.51 (t, *J* = 7.9 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 2H), 6.96 (d, *J* = 8.6 Hz, 1H), 6.92 (d, *J* = 7.1 Hz, 1H), 6.67 (d, *J* = 8.2 Hz, 2H), 6.50 (br t, *J* = 6.0 Hz, 1H), 3.25 (q, *J* = 6.8 Hz, 2H), 2.54 (t, *J* = 7.7 Hz, 2H), 1.82 (quintet, *J* = 7.5 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 170.8, 168.7, 154.8, 145.6, 135.3, 133.0, 130.7, 128.5, 115.8, 114.5, 110.1, 109.2, 40.7, 30.9, 30.0; MS: *m/z* 296 ($C_{17}H_{16}N_2O_3$, $M^{+\cdot}$).

4-((2-Hydroxyphenethyl)amino)isoindoline-1,3-dione: GKK-010-054.

Reaction Scheme:



GKK-010-054

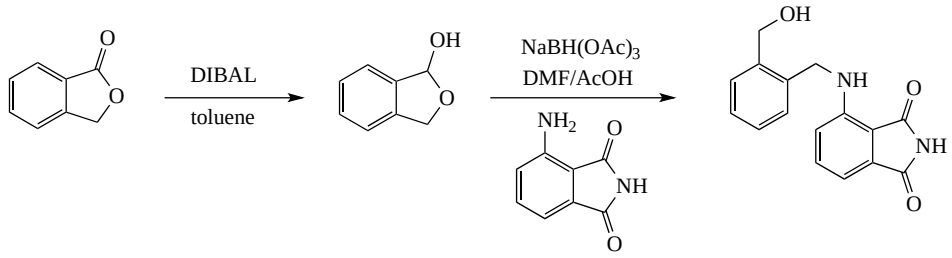
(2-Allylphenoxy)(*tert*-butyl)dimethylsilane. 2-Allylphenol (3.00 g, 22.4 mmol) was silylated with TBSCl (3.77 g, 26.9 mmol) according to Procedure B to provide (2-allylphenoxy)(*tert*-butyl)dimethylsilane (4.59 g, 18.5 mmol, 83%) as a yellow oil. This compound was used without further purification.

4-((2-Hydroxyphenethyl)amino)isoindoline-1,3-dione: GKK-010-054. A stirred solution of TBS-protected 2-allylphenol (4.30 g, 17.3 mmol) in MeOH (50 mL) was treated with ozone gas over a period of 15-20 min at –78 °C. When TLC analysis indicated the absence of starting material, the reaction was quenched at low temperature by drop-wise addition of Me_2S (1.18 g, 1.40 mL, 19.0 mmol) and then slowly warmed to 23 °C. The crude reaction mixture was diluted with water (20 mL), reduced the volume to 20 mL under vacuum (< 35 °C bath temperature) and the product was extracted with ether (2 × 75 mL). The combined organic layers were washed with NaCl (3 × 50 mL) and concentrated under vacuum. The residual oil was dissolved in DMF and reacted with 4-aminoisoindoline-1,3-dione according to Procedure A to provide the crude 5-((2-((*tert*-butyldimethylsilyl)oxy)phenethyl)amino)isoindoline-1,3-dione as a yellow solid. This yellow solid was subjected to silyl deprotection using Procedure C to afford 5-((2-hydroxyphenethyl)amino)isoindoline-1,3-dione (71 mg, 0.25 mmol, 1.4% for 3 steps) as a yellow solid, mp 199-200 °C. ^{1}H NMR (DMSO-d_6): δ 10.9 (s, 1H), 9.50 (s, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.03 (t, *J* = 7.7 Hz, 1H), 6.93 (d, *J* = 7.1 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.72 (t, *J* = 7.4 Hz, 1H), 6.60 (br t, *J* = 5.8 Hz, 1H), 3.45 (q, *J* = 6.9 Hz, 2H), 2.83 (t, *J* = 7.3 Hz,

2H); ^{13}C NMR (DMSO-d_6): δ 171.7, 169.8, 155.9, 146.7, 136.3, 134.0, 130.9, 127.9, 125.5, 119.5, 116.9, 115.4, 111.2, 110.3, 42.7, 30.2; MS: *m/z* 282 ($C_{16}H_{14}N_2O_3$, $M^{+\cdot}$).

4-((2-(Hydroxymethyl)benzyl)amino)isoindoline-1,3-dione: GKK-010-091.

Reaction Scheme:

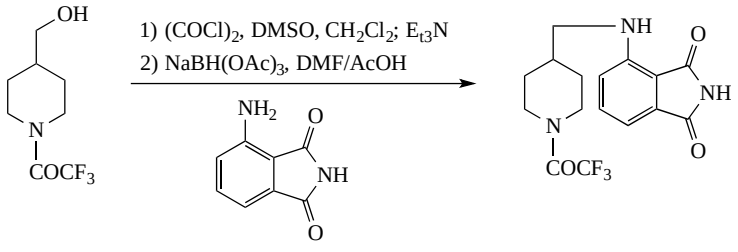


GKK-010-091

A stirred solution of isobenzofuran-1(3*H*)-one (2.00 g, 14.9 mmol) in toluene (30 mL) was cooled to –78 °C and 1.5 M DIBAL (13.0 mL, 22.4 mmol) in toluene (30 mL) was added drop-wise over a period of 30 min. The resulting mixture was stirred for an additional 30 min and quenched with MeOH (10 mL), followed by 1 M HCl (20 mL). The product was extracted into ether (2 × 50 mL) and the combined organic layers were washed with aq NaCl (50 mL), dried (Na_2SO_4) and evaporated to afford the crude lactol as a colorless oil. The lactol was subjected to reductive amination with 4-aminoisoindoline-1,3-dione according to Procedure A to afford 4-((2-(hydroxymethyl)benzyl)amino)isoindoline-1,3-dione (358 mg, 1.27 mmol, 8.5% overall) as a yellow solid, mp 198-200 °C. ^{1}H NMR (DMSO-d_6): δ 11.0 (s, 1H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.91 (d, *J* = 7.2 Hz, 1H), 7.30-7.17 (complex, 3H), 6.98 (br t, *J* = 6.1 Hz, 1H), 6.92 (t, *J* = 7.4 Hz, 2H), 5.23 (t, *J* = 5.3 Hz, 1H), 4.62 (d, *J* = 5.4 Hz, 2H), 4.58 (d, *J* = 6.1 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 171.8, 169.8, 146.5, 140.2, 136.5, 136.2, 134.0, 128.1, 127.5, 127.3, 127.2, 117.4, 111.6, 110.6, 61.3, 43.3; MS: *m/z* 282 ($C_{16}H_{14}N_2O_3$, $M^{+\cdot}$).

4-(((1-(2,2,2-Trifluoroacetyl)piperidin-4-yl)methyl)amino)isoindoline-1,3-dione: GKK-008-031.

Reaction Scheme:

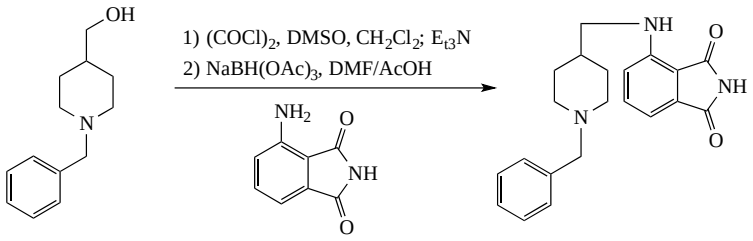


GKK-008-031

A solution of oxalyl chloride (470 mg, 0.31 mL, 3.62 mmol) in CH_2Cl_2 (20 mL) was cooled to -78 ºC, DMSO (510 mg, 0.46 mL, 6.54 mmol) was added drop-wise over a period of 20 min and stirring was continued for an additional 20 min. *N*-Trifluoroacetylpiperidinemethanol (0.38 g, 1.80 mmol) in CH_2Cl_2 (10 mL) was added over a period of 20 min, and the reaction was stirred for 30 min at -78°C. To this mixture was slowly added triethylamine (1.09 g, 1.5 mL, 10.8 mmol) over a period of 30 min. The reaction mixture was warmed to 0 ºC, and quenched by drop-wise addition of water (20 mL). The layers were separated, and the product was extracted into CH_2Cl_2 (2 × 25 mL). The combined organic extracts were washed with aq NaCl (20 mL), dried (Na_2SO_4), and evaporated under vacuum to provide the crude *N*-trifluoroacetylpiperidine-4-carboxaldehyde as a yellow oil. The crude aldehyde was subjected to reductive amination according to Procedure A, which gave 4-(((1-(2,2,2-trifluoroacetyl)piperidin-4-yl)methyl)amino)isoindoline-1,3-dione (135 mg, 0.38 mmol, 21% overall) as a yellow solid, mp 186-187 ºC. ^{1}H NMR (DMSO-d_6): δ 11.0 (s, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.09 (d, *J* = 8.7 Hz, 1H), 6.93 (d, *J* = 7.1 Hz, 1H), 6.61 (br t, *J* = 6.5 Hz, 1H), 4.30 (d, *J* = 13.8 Hz, 1H), 3.87 (d, *J* = 13.8 Hz, 1H), 3.22 (m, 3H), 2.87 (t, *J*= 12.1 Hz, 1H), 1.95 (m, 1H), 1.83 (t, *J* = 11.9 Hz, 2H), 1.19 (quintet of doublets, *J* = 12.0, 4.2 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 171.9, 169.8, 154.2, 146.8, 136.3, 134.1, 117.1, 111,2, 110.3, 47.1, 45.6, 43.5, 35.3, 30.3, 29.3, CF_3 not observed ; MS: *m/z* 355 ($C_{16}H_{16}F_3N_3O_3$, $M^{+\cdot}$).

4-(((1-Benzylpiperidin-4-yl)methyl)amino)isoindoline-1,3-dione: GKK-008-025.

Reaction Scheme:



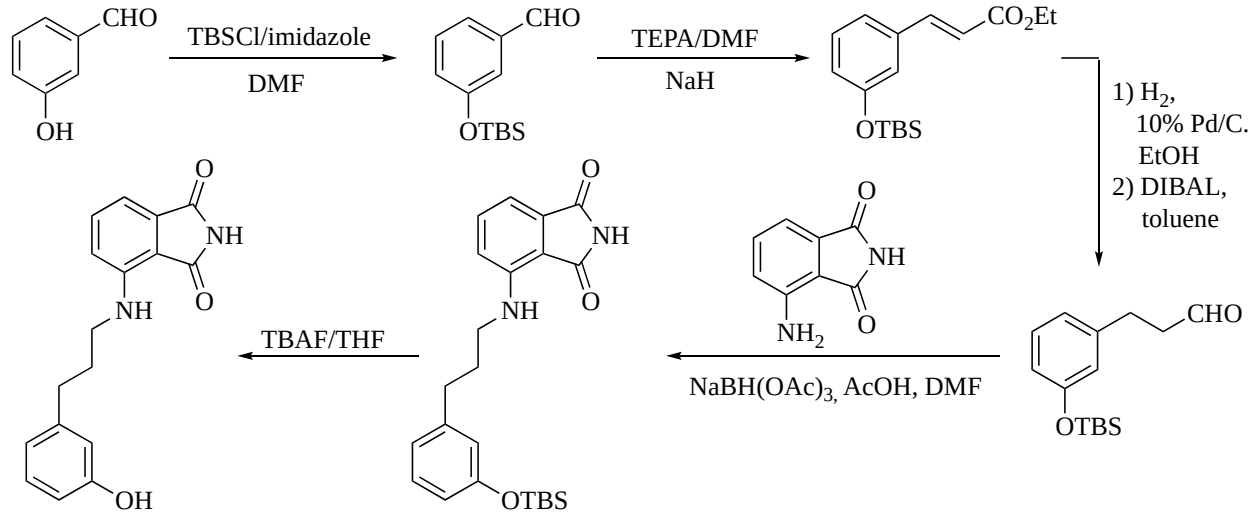
GKK-008-025

A solution of oxalyl chloride (500 mg, 0.33 mL, 3.91 mmol) in CH_2Cl_2 (20 mL) was cooled to -78 ºC, DMSO (550 mg, 0.50 mL, 7.08 mmol) was added drop-wise over a period of 20 min and stirring was continued for an additional 20 min. (1-Benzylpiperidin-4-yl)methanol (400 mg, 1.95 mmol) in CH_2Cl_2 (10 mL) was added over a period of 20 min, and the reaction was stirred for 30 min. To this mixture was slowly added triethylamine (1.18 g, 1.63 mL, 11.7 mmol) over a period of 30 min -78°C. The reaction was warmed to 0 ºC and quenched by drop-wise addition of water (20 mL). The layers were separated and the product was extracted into CH_2Cl_2 (2 × 25 mL). The combined organic extracts were washed with NaCl (20 mL), dried (Na_2SO_4), and evaporated under vacuum to provide the crude 1-benzylpiperidine-4-carbaldehyde as a yellow oil. This aldehyde was subjected to reductive amination with 4-aminoisoindoline-1,3-dione according to Procedure A to afford 4-(((1-benzylpiperidin-4-yl)methyl)amino)isoindoline-1,3-dione (70 mg, 0.20 mmol, 10% overall) as a yellow solid, mp 168-169 ºC. ^{1}H NMR (DMSO-d_6): δ 10.9 (s, 1H), 7.51 (t, *J* =

7.8 Hz, 1H), 7.34-7.20 (complex, 5H), 7.04 (d, *J* = 8.5 Hz, 1H), 6.92 (d, *J* = 7.0 Hz, 1H), 6.52 (br t, *J* = 6.2 Hz, 1H), 3.43 (s, 2H), 3.18 (t, *J* = 6.5 Hz, 2H), 2.81 (d, *J* = 11.0 Hz, 2H), 1.88 (t, *J* = 8.7 Hz, 2H), 1.66 (d, *J* = 11.8 Hz, 2H), 1.57 (m, 1H), 1.23 (qd, *J* = 12.0, 3.7 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 172.0, 169.8, 147.0, 139.1, 136.3, 134.0, 129.2, 128.6, 127.2, 117.1, 111.1, 110.2, 62.9, 53.4, 47.8, 35.9, 30.0; MS: *m/z* 349 ($C_{21}H_{23}N_3O_2$, $M^{+\cdot}$).

4-((3-(3-Hydroxyphenyl)propyl)amino)isoindoline-1,3-dione (GKK-011-045) (Analog 16).

Reaction Scheme:



GKK-011-045

3-((*tert*-Butyldimethylsilyl)oxy)benzaldehyde. The silyl ether of 3-hydroxy-benzaldehyde (1.00 g, 8.20 mmol) was prepared according to Procedure B to provide the TBS-protected benzaldehyde (1.71 g, 7.2 mmol, 88%) as a white solid.

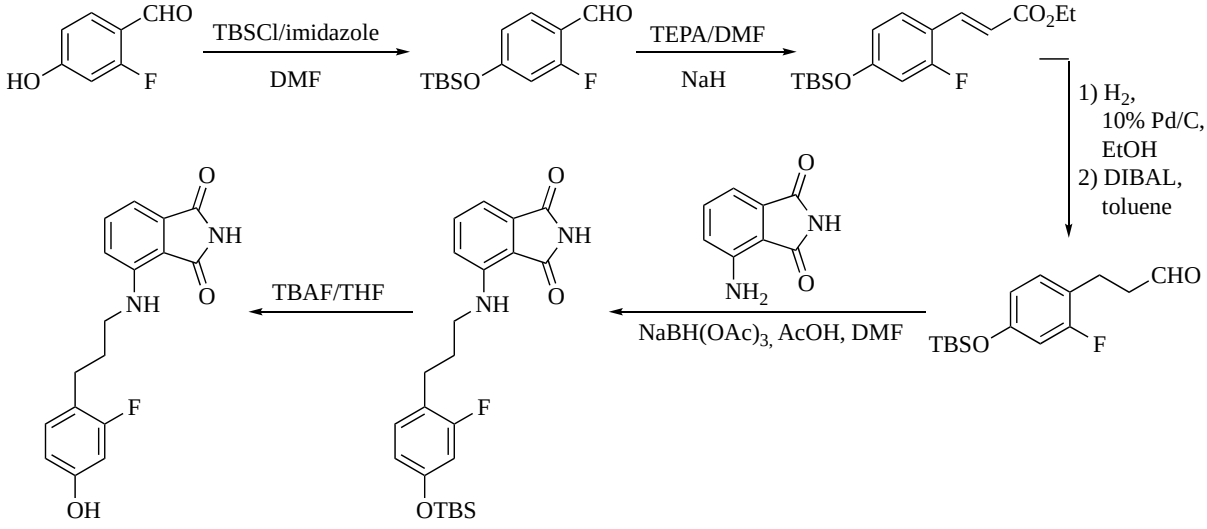
Ethyl 3-(3-((*tert*-butyldimethylsilyl)oxy)phenyl)propanoate. To a stirred, ice-cold solution of triethylphosphonoacetate (1.84 g, 1.63 mL, 8.1 mmol) in DMF (5.0 mL) was added 60% NaH dispersed in mineral oil (324 mg, 8.1 mmol) and the mixture was stirred for 15 min. To the resulting reaction mixture was added dropwise the TBS-protected benzaldehyde (1.60 g, 6.78 mmol) in DMF (5.0 mL) and the reaction was allowed to warm to room temperature. After TLC analysis indicated the complete consumption of the starting material, the reaction was cooled and quenched by dropwise addition of ice-cold water. The product was extracted with ether (2 × 25 mL) and the organic extract was washed with saturated aq NaCl (15 mL), dried (Na_2SO_4), filtered and evaporated to afford the unsaturated ester as a colorless oil. A solution of the ester in ethanol (20 mL) was flushed twice with nitrogen and 10% Pd/C (160 mg, 50% wet, 10% w/w) was added. The reaction was stirred at room temperature under 1 atm of hydrogen for 18 h. The reaction was filtered through Celite® and washed with ethanol (2 × 25 mL). The filtrate was concentrated and

purified by column chromatography to provide the desired ester (1.70 g, 5.51 mmol, 81%) as a colorless oil.

4-((3-(3-Hydroxyphenyl)propyl)amino)isoindoline-1,3-dione (GKK-011-045). The ester (1.70 g, 5.51 mmol) prepared above was dissolved in dichloromethane (17 mL), cooled to –78 °C and 1.5 M DIBAL (4.05 mL, 6.08 mmol) in toluene was added dropwise over a 30-min period. Stirring at this temperature was continued for 2 h at which time TLC analysis indicated complete conversion. The reaction was quenched by dropwise addition of methanol (5 mL), followed by 1.0 M HCl (10 mL) and the two phases were separated. The aqueous layer was extracted with dichloromethane (2 × 50 mL) and the combined organic layers were washed with saturated aq NaCl, dried ($MgSO_4$), filtered and concentrated under vacuum to provide the crude compound as a colorless oil. This crude aldehyde was subjected to reductive amination according to Procedure B, to provide 4-((3-(3-((*tert*-butyldimethylsilyl)oxy)phenyl)propyl)amino)-isoindoline-1,3-dione and this was carried on to the next step without purification. The TBS group was cleaved according to the general procedure for silyl deprotection (Procedure C) to afford the target compound (180 mg, 0.61 mmol, 11% for 3 steps) as a yellow solid, mp 176-178 °C. ^{1}H NMR (DMSO-d_6) δ 10.9 (s, 1H), 9.23 (s, 1H), 7.51 (t, J = 7.8 Hz, 1H), 7.06 (t, J = 7.7 Hz, 1H), 6.97 (d, J = 8.5 Hz, 2H), 6.93 (d, J = 7.1 Hz, 1H), 6.65-6.54 (complex, 3H), 6.52 (br t, J = 6.2 Hz, 1H), 3.27 (q, J = 6.7 Hz, 2H), 2.57 (t, J = 7.7 Hz, 2H), 1.84 (quintet, J = 7.4 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 171.9, 169.8, 157.8, 146.7, 143.3, 136.3, 134.1, 129.7, 119.3, 116.9, 115.6, 113.3, 111.2, 110.3, 41.8, 32.8, 30.7; MS: *m/z* for $C_{17}H_{16}N_2O_3$: 296 ($M^{+\cdot}$).

4-((3-(2-fluoro-4-hydroxyphenyl)propyl)amino)isoindoline-1,3-dione (GKK-011-048).

Reaction Scheme:



GKK-011-048

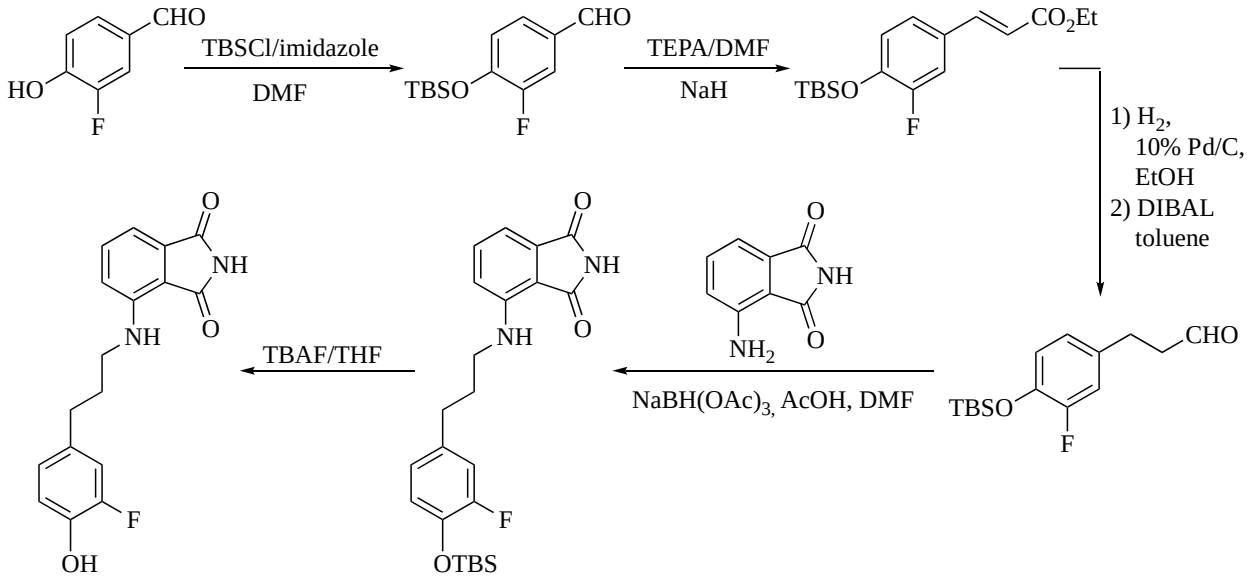
4-((*tert*-Butyldimethylsilyl)oxy)-2-fluorobenzaldehyde (GKK-011-037). The silyl ether of 4-hydroxy-2-fluorobenzaldehyde (2.00 g, 14.3 mmol) was prepared according to Procedure B to provide the TBS-protected benzaldehyde (2.95 g, 11.6 mmol, 81%) as a white solid.

Ethyl 3-(4-((*tert*-butyldimethylsilyl)oxy)-2-fluorophenyl)propanoate (GKK-011-040). To a stirred, ice-cold solution of triethylphosphonoacetate (2.71 g, 2.40 mL, 12.1 mmol) in DMF (5.0 mL) was added 60% NaH dispersed in mineral oil (484 mg, 12.1 mmol) and the mixture was stirred for 15 min. To the resulting reaction mixture was added dropwise the TBS-protected benzaldehyde (2.80 g, 11.0 mmol) in DMF (5.0 mL), and the reaction was warmed to room temperature. When TLC analysis indicated complete consumption of the starting material, the reaction was cooled and quenched by dropwise addition of ice-cold water. The product was extracted with ether (2 × 25 mL) and the combined organic extracts were washed with saturated aq NaCl (15 mL), dried (Na_2SO_4), filtered and evaporated to afford the unsaturated ester as a colorless oil. A solution of the ester in ethanol (20 mL) was flushed twice with nitrogen and 10% Pd/C (280 mg, 50% wet, 10% w/w) was added. The reaction was stirred at room temperature under 1 atm of hydrogen for 18 h. The reaction was filtered through Celite® and washed with ethanol (2 × 25 mL). The filtrate was concentrated and purified by column chromatography to provide the desired ester (2.33 g. 7.15 mmol, 65%) as a colorless oil.

4-((3-(2-Fluoro-4-hydroxyphenyl)propyl)amino)isoindoline-1,3-dione (GKK-011-048). The ester (1.72 g, 5.28 mmol) prepared above was dissolved in dichloromethane (17 mL), cooled to –78 °C and 1.5 M DIBAL (3.88 mL, 5.81 mmol) in toluene was added dropwise over a 30-min period. Stirring was continued at this temperature for 2 h at which time TLC analysis indicated complete conversion. The reaction was quenched by dropwise addition of methanol (5 mL), followed by 1.0 M HCl (10 mL) and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 50 mL), and the combined organic extracts were washed with saturated aq NaCl, dried ($MgSO_4$), filtered and evaporated to provide the crude compound as a colorless oil. This crude aldehyde was subjected to reductive amination according to Procedure A, to provide the 4-((3-(4-((*tert*-butyldimethylsilyl)oxy)-2-fluorophenyl)propyl)amino)-isoindoline-1,3-dione and this was carried forward to the next step without purification. The TBS group was cleaved according to the general procedure for silyl deprotection (Procedure C) to afford the target compound (158 mg, 0.50 mmol, 9.5% for 3 steps) as a yellow solid, mp 182-183 °C. ^{1}H NMR (DMSO-d_6) δ 10.9 (s, 1H), 9.63 (s, 1H), 7.51 (t, J = 7.8 Hz, 1H), 7.07 (t, J = 8.7 Hz, 1H), 6.96 (d, J = 8.5 Hz, 1H), 6.92 (d, J = 7.1 Hz, 1H), 6.56-6.47 (complex, 3H), 3.27 (q, J = 6.7 Hz, 2H), 2.57 (t, J = 7.6 Hz, 2H), 1.80 (quintet, J = 7.4 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 171.9, 169.8, 161.3 (q, J = 244.2 Hz), 157.0 (d, J = 12.1 Hz), 146.7, 136.3, 134.1, 131.3 (d, J = 7.1 Hz), 118.2 (d, J = 17.2 Hz), 116.8, 111.8 (d, J = 2.8 Hz), 111.2, 110.3, 102.8 (d, J = 24.5 Hz), 47.8, 29.8, 25.4; MS: *m/z* for $C_{17}H_{15}FN_2O_3$: 314 ($M^{+\cdot}$).

4-((3-(3-Fluoro-4-hydroxyphenyl)propyl)amino)isoindoline-1,3-dione (GKK-011-054).

Reaction Scheme:



GKK-011-054

The synthesis of **GKK-011-054** was carried out using the same sequence detailed above.

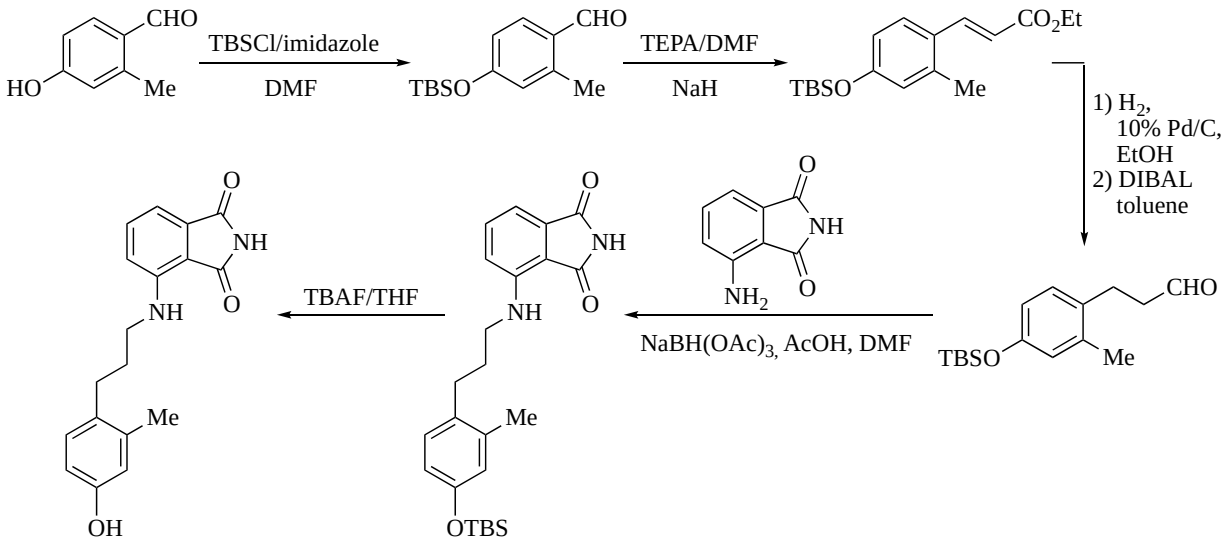
Ethyl 3-(4-((*tert*-butyldimethylsilyl)oxy)-3-fluorophenyl)propanoate. Yield: 2.60 g (7.98 mmol, 56% for 3 steps).

4-((3-(4-((*tert*-Butyldimethylsilyl)oxy)-3-fluorophenyl)propyl)amino)isoindoline-1,3-dione. Yield: 1.16 g (2.71 mmol, 34% for 2 steps).

4-((3-(3-Fluoro-4-hydroxyphenyl)propyl)amino)isoindoline-1,3-dione (GKK-011-054). Yield: 140 mg **(**0.45 mmol, 52%), mp 149-150 ^{o}C. ^{1}H NMR (DMSO-d_6) δ 10.9 (s, 1H), 9.54 (s, 1H), 7.51 (t, J = 8.4 Hz, 1H), 7.03-6.95 (complex, 2H), 6.92 (d, J = 7.1 Hz, 1H), 6.84 (obscured, J = 8.2 Hz, 1H), 6.82 (s, 1H), 67.50 (br t, J = 6.1 Hz, 1H), 3.26 (q, J = 6.7 Hz, 2H), 2.36 (t, J = 7.6 Hz, 2H), 1.83 (quintet, J = 7.5 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 171.9, 169.8, 151.3 (d, J = 243.8 Hz), 146.7, 143.2 (d, J = 12.1 Hz), 136.3, 134.1, 133.2 (d, J = 6.1 Hz), 124.6 (d, J = 4.0 Hz), 18.0 (d, J = 3.0 Hz), 116.9, 116.2 (d, J = 17.2 Hz), 111.2, 110.3, 41.8, 31.7, 30.7; MS: *m/z* for $C_{17}H_{15}FN_2O_3$: 314 ($M^{+\cdot}$).

4-((3-(4-Hydroxy-2-methylphenyl)propyl)amino)isoindoline-1,3-dione (GKK-011-059).

Reaction Scheme:



GKK-011-059

The synthesis of **GKK-011-059** was carried out using the same sequence detailed above.

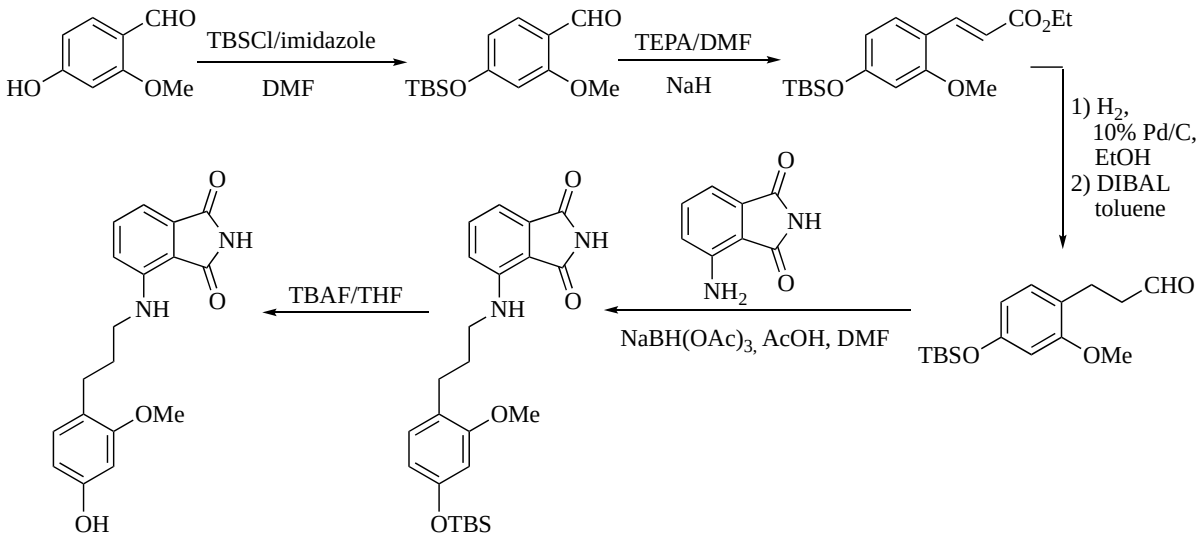
4-((*tert*-Butyldimethylsilyl)oxy)-2-methylbenzaldehyde. Yield: 2.56 g (10.2 mmol, 78%).

Ethyl 3-(4-((*tert*-butyldimethylsilyl)oxy)-2-methylphenyl)propanoate. Yield: 2.06 g (6.43 mmol, 67% for 2 steps).

4-((3-(4-Hydroxy-2-methylphenyl)propyl)amino)isoindoline-1,3-dione (GKK-011-059). Yield: 198 mg (0.64 mmol, 10% for 3 steps), mp 150-152 ^{o}C. ^{1}H NMR (DMSO-d_6) δ 10.9 (s, 1H), 9.00 (s, 1H), 7.52 (t, J = 7.5 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 6.92 (d, J = 7.1 Hz, 1H), 6.91 (d, J = 8.2 Hz, 1H), 6.54 (s, 1H), 6.57-6.47 (complex, 2H), 3.29 (q, J = 6.6 Hz, 2H), 2.53 (t, J = 8.1 Hz, 2H), 2.15 (s, 3H), 1.76 (quintet, J = 7.3 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 171.9, 169.8, 155.7, 146.7, 136.9, 136.3, 134.1, 130.2, 129.9, 117.3, 116.9, 113.1, 111.2, 110.3, 42.0, 30.0, 29.4, 19.5; MS: *m/z* for $C_{18}H_{18}N_2O_3$: 310 ($M^{+\cdot}$).

4-((3-(4-Hydroxy-2-methoxyphenyl)propyl)amino)isoindoline-1,3-dione (GKK-011-067) (Analog 15).

Reaction Scheme:



GKK-011-067

The synthesis of **GKK-011-067** was carried out using the same sequence detailed above.

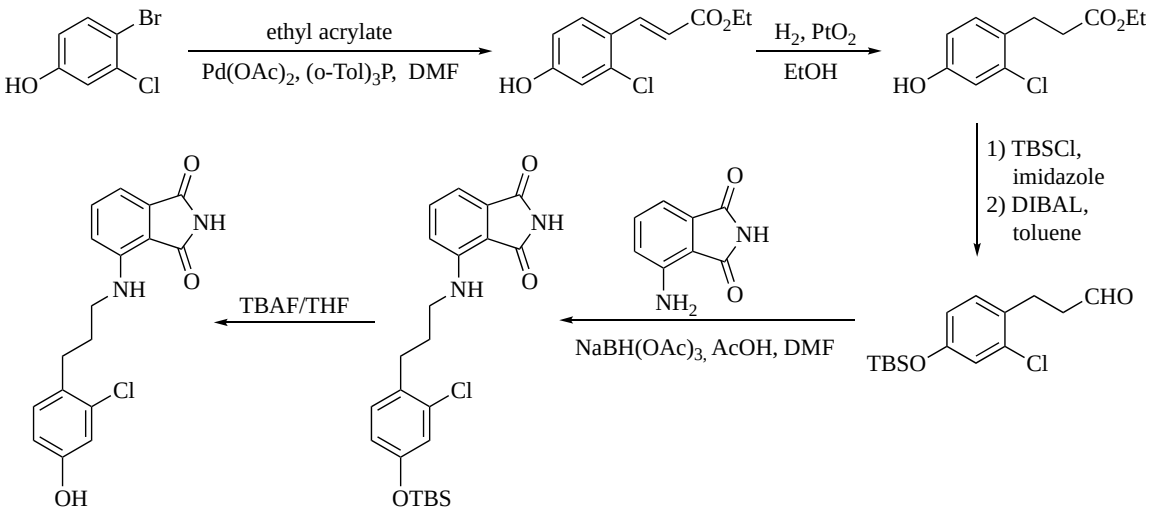
4-((*tert*-Butyldimethylsilyl)oxy)-2-methoxybenzaldehyde. Yield: 2.59 g (9.74 mmol, 74%).

Ethyl 3-(4-((*tert*-butyldimethylsilyl)oxy)-2-methoxyphenyl)propanoate. Yield: 1.98 g (5.86 mmol, 61% for 2 steps).

4-((3-(4-Hydroxy-2-methoxyphenyl)propyl)amino)isoindoline-1,3-dione (GKK-011-067). Yield: 186 mg (0.57 mmol, 28% for 3 steps), mp 166-168 °C. ^{1}H NMR (DMSO-d_6) δ 10.9 (s, 1H), 9.18 (s, 1H), 7.51 (dd, J = 8.5, 7.1 Hz, 1H), 6.94 (t, J = 8.3 Hz, 1H), 6.92 (d, J = 7.1 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 6.53 (br t, J = 6.1 Hz, 1H), 6.37 (d, J = 2.3 Hz, 1H), 6.27 (dd, J = 8.0, 2.3 Hz, 1H), 3.72 (s, 3H), 3.22 (q, J = 6.6 Hz, 2H), 2.52 (obscured, 2H), 1.76 (quintet, J = 7.2 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 171.9, 169.8, 158.3, 157.3, 146.7, 136.3, 134.1, 130.3, 119.7, 116.9, 111.2, 110.2, 107.9, 99.3, 55.5, 41.7, 29.6, 26.5; MS: *m/z* for $C_{18}H_{18}N_2O_4$: 326 ($M^{+\cdot}$).

4-((3-(2-Chloro-4-hydroxyphenyl)propyl)amino)isoindoline-1,3-dione (GKK-011-077).

Reaction Scheme:



GKK-011-077

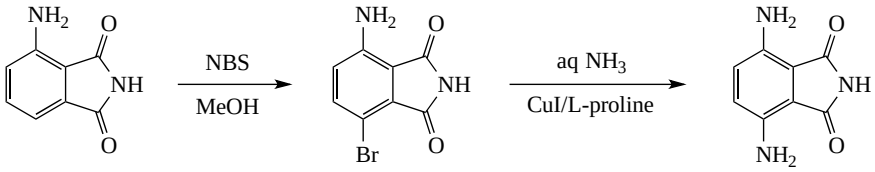
Ethyl (*E*)-3-(2-chloro-4-hydroxyphenyl)acrylate. To a stirred solution of 4-bromo-3-chlorophenol (1.00 g, 4.82 mmol) in DMF (1.0 mL) was added ethyl acrylate (1.00 mL, 9.20 mmol), palladium acetate (0.03 g, 0.14 mmol), tri(o-tolyl)phosphine (73 mg, 0.24 mmol), triethylamine (1.00 mL, 7.26 mmol) and the mixture was heated to 95-100 ^{o}C for 18 h. The reaction was cooled to room temperature, filtered through Celite®, washed the Celite® with ethyl acetate and the product was purified by column chromatography to afford 1.00 g (4.42 mmol, 92%) of a white solid.

4-((3-(2-Chloro-4-hydroxyphenyl)propyl)amino)isoindoline-1,3-dione (GKK-011-077). The above compound (1.00 g, 4.42 mmol) dissolved in ethanol and platinum oxide (100 mg) was added. The resulting solution was stirred under 1 atm of hydrogen for 6 h and then filtered through Celite®. The filtrate was concentrated, dissolved in DMF and cooled to 0 ^{o}C. Imidazole (0.45 g, 6.62 mmol) was added and the solution was stirred for 20 min. TBSCl (723 mg, 4.80 mmol) was then added and the reaction was slowly warmed to room temperature for 2 h, and poured into cold water. The product was extracted with ether (2 × 75 mL) and the combined organic extracts were washed with saturated aq NaCl (50 mL), dried (Na_2SO_4), filtered and concentrated under vacuum. The product was dissolved in dichloromethane (30 mL), cooled to –78 ^{o}C and 1.5 M DIBAL (3.2 mL, 4.8 mmol) in toluene was added. The reaction was stirred for 2.0 h at –78 ^{o}C, and then quenched with NH_4Cl solution (10 mL). The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with distilled water (2 × 20 mL), dried (Na_2SO_4) and concentrated under vacuum to give a colorless oil. The crude aldehyde was subjected to reductive amination according to Procedure A, to provide the 4-((3-(4-((*tert*-butyldimethylsilyl)oxy)-2-fluorophenyl)propyl)amino)isoindoline-1,3-dione. This product was used directly in the next step without purification. The TBS group was cleaved according to the general procedure for silyl deprotection (Procedure C) to afford the target compound (230 mg, 0.70 mmol, 12% for 3 steps) as a yellow solid, mp 182-184 ^{o}C. ^{1}H NMR (DMSO-d_6) δ 10.9 (s,

1H), 9.66 (s, 1H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 1H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.93 (d, *J* = 7.2 Hz, 1H), 6.80 (d, *J* = 2.6 Hz, 1H), 6.68 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.55 (br t, *J* = 6.1 Hz, 1H), 3.30 (q, *J* = 6.6 Hz, 2H), 2.66 (t, *J* = 7.8 Hz, 2H), 1.82 (quintet, *J* = 7.5 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 171.9, 169.8, 156.9, 146.7, 136.3, 134.1, 133.3, 131.5, 129.2, 116.9, 116.2, 115.0, 111.3, 110.3, 41.8, 29.7, 29.6; MS: *m/z* for $C_{17}H_{15}ClN_2O_3$: 330 ($M^{+\cdot}$).

4,7-Diaminoisoindoline-1,3-dione (GKK-011-016).

Reaction Scheme:



GKK-011-016

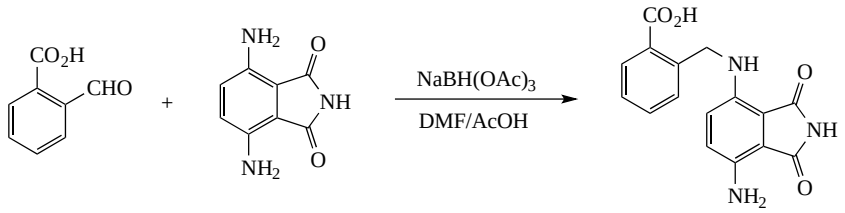
4-Amino-7-bromoisoindoline-1,3-dione. 4-Aminoisoindoline-1,3-dione (2.00 g, 12.3 mmol) was dissolved in MeOH (200 mL), and the solution was treated with *N*-bromosuccinimide (2.19 g, 12.3 mmol). The reaction was stirred at room temperature for 50 min. The solid obtained was collected by filtration and washed with MeOH to give 4-amino-7-bromoisoindoline-1,3-dione (2.21 g, 9.21 mmol, 75%) as a yellow powder, mp 287-289 °C. ^{1}H NMR: δ 11.1 (s, 1H), 7.51 (d, *J* = 8.9 Hz, 1H), 6.90 (d, *J* = 8.9 Hz, 1H), 6.53 (br s, 2H); ^{13}C NMR: δ 170.0, 167.7, 146.5, 139.6, 130.2, 123.6, 112.4, 101.6; MS: *m/z* 240 ($C_8H_5{}^{79}BrN_2O_2$, $M^{+\cdot}$).

4,7-Diaminoisoindoline-1,3-dione (GKK-011-016). A clean, dried 250-mL Chemglass pressure vessel® (CG-1880-R-03) was charged with 4-amino-7-bromoisoindoline-1,3-dione (1.00 g, 4.17 mmol), copper iodide (80 mg, 10 mol%), L-proline (100 mg, 0.86 mmol) and aq NH_3 (5 mL). The reaction vessel was closed and heated to 110 °C for 3 h. The reaction was cooled to 23 °C, filtered, and the resulting solid was loaded onto a column packed with silica gel and eluted with 1:1 hexanes:ethyl acetate. The product fractions were concentrated under vacuum to provide the diamine (300 mg, 1.69 mmol, 41%) as a red solid, mp 294-296 °C. ^{1}H NMR (DMSO-d_6): δ 10.5 (s, 1H), 6.82 (s, 2H), 5.75 (s, 4H); ^{13}C NMR (DMSO-d_6): δ 170.8, 138.5, 125.6, 108.8; MS: *m/z* 177 ($C_8H_7N_3O_2$, $M^{+\cdot}$).

4,7-Diaminoisoindoline-1,3-dione series

2-(((7-Amino-1,3-dioxoisoindolin-4-yl)amino)methyl)benzoic acid (GKK-008-080).

Reaction Scheme:

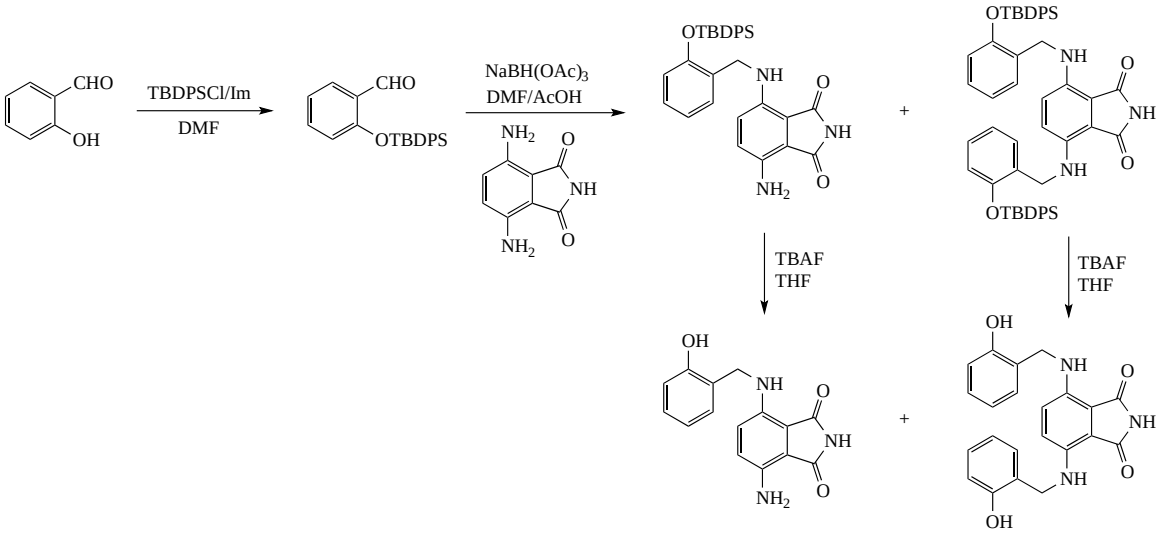


GKK-008-080

The reductive amination, using 4,7-diaminoisoindoline-1,3-dione (177 mg, 1.00 mmol), was performed according to Procedure A to give the mono-reductive amination product (124 mg, 0.40 mmol, 40%) as a yellow solid, mp 279-281 ºC. ^{1}H NMR (DMSO-d_6): δ 11.4 (s, 1H), 7.92 (d, J = 7.9 Hz, 1H), 7.88 (t, J = 7.5 Hz, 1H), 7.80-7.67 (complex, 3H), 7.53-7.45 (complex, 2H), 7.35 (apparent d, J = 10.1 Hz, 1H), acid, amine, and benzylic protons not observed; ^{13}C NMR (DMSO-d_6): δ 168.7, 167.9, 165.9, 144.6, 141.6, 136.5, 134.2, 130.2, 127.7, 126.6, 124.4, 122.3, 120.2, 118.3, 115.1, 84.3; MS: *m/z* 311 ($C_{16}H_{13}N_3O_4$, $M^{+\cdot}$).

4-Amino-7-((2-hydroxybenzyl)amino)isoindoline-1,3-dione (GKK-011-023F2) and 4,7-bis((2-hydroxybenzyl)amino)isoindoline-1,3-dione (GKK-011-023F1).

Reaction Scheme:



GKK-011-023F2 **GKK-011-023F1**

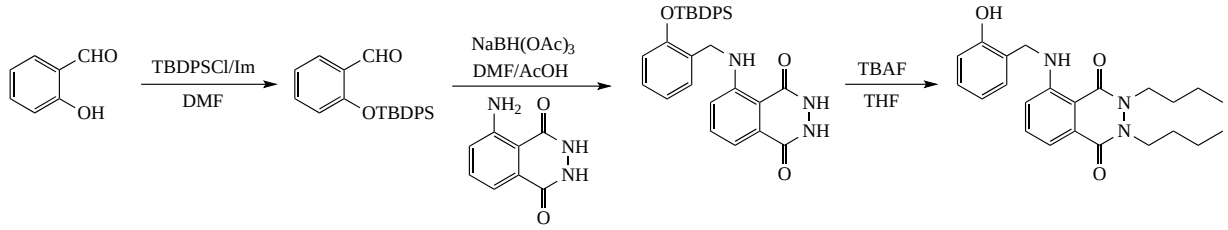
2-((*tert*-Butyldiphenylsilyl)oxy)benzaldehyde. This compound was prepared from salicylaldehyde (1.22 g, 10.0 mmol) and TBDPSCl (3.29 g, 12.0 mmol) according to Procedure B to provide the TBDPS-protected salicylaldehyde (1.80 g, 6.5 mmol, 65%) as a white solid. This compound was used without further purification.

4,7-Bis((2-hydroxybenzyl)amino)isoindoline-1,3-dione (GKK-011-023F1) and 4-amino-7-((2-hydroxybenzyl)amino)isoindoline-1,3-dione (GKK-011-023F2). The reductive amination of 4,7-diaminoisoindoline-1,3-dione (0.40 g, 2.26 mmol) with 2-((*tert*-butyldiphenylsilyl)oxy)-

benzaldehyde (1.60 g, 4.44 mmol) was performed using Procedure A to give a mixture of the mono- and dibenzylamino compounds. The TBDPS groups in these compounds were cleaved using Procedure C and isolated by column chromatography using increasing concentrations of ethyl acetate in hexanes. F1: 120 mg (0.31 mmol, 6.9%) as a red solid; mp 237-239 ºC; F2: 205 mg (0.72 mmol, 16%) as a red solid, mp 200-203 ºC. The spectral data for F1 were: ^{1}H NMR (DMSO-d_6): δ 10.7 (s, 1H), 9.65 (s, 2H), 7.16 (d, *J* = 7.2 Hz, 2H), 7.05 (td, *J* = 7.6, 1.9 Hz, 2H), 6.96 (s, 2H), 6.81 (d, *J* = 8.0 Hz, 2H), 6.71 (t, *J* = 7.4 Hz, 2H), 6.41 (t, *J* = 6.4 Hz, 2H), 4.33 (d, *J* = 6.4 Hz, 4H); ^{13}C NMR (DMSO-d_6): δ 170.9, 155.6, 138.8, 129.1, 128.5, 125.7, 121.5, 119.3, 113.3, 110.3, 42.0; MS: *m/z* 389 ($C_{22}H_{19}N_3O_4$, $M^{+\cdot}$). The spectral data for F2 were: ^{1}H NMR (DMSO-d_6): δ 10.6 (s, 1H), 9.64 (s, 1H), 7.17 (d, *J* = 7.3 Hz, 1H), 7.06 (t, *J* = 7.7 Hz, 1H), 6.95 (d, *J* = 9.3 Hz, 1H), 6.87 (d, *J* = 9.0 Hz, 1H), 6.82 (d, *J* = 7.7 Hz, 1H), 6.73 (t, *J* = 7.4 Hz, 1H), 6.42 (br t, *J* = 6.0 Hz, 1H), 5.72 (s, 2H), 4.34 (d, *J* = 6.1 Hz, 2H) ^{13}C NMR (DMSO-d_6): δ 171.0, 170.7, 155.6, 139.3, 138.5, 129.1, 128.5, 125.8, 125.7, 121.52, 121.46, 119.3, 115.5, 109.6, 42.0; MS: *m/z* 283 ($C_{15}H_{13}N_3O_3$, $M^{+\cdot}$).

2,3-Dibutyl-5-((2-hydroxybenzyl)amino)-2,3-dihydrophthalazine-1,4-dione (GKK-011-022).

Reaction Scheme:



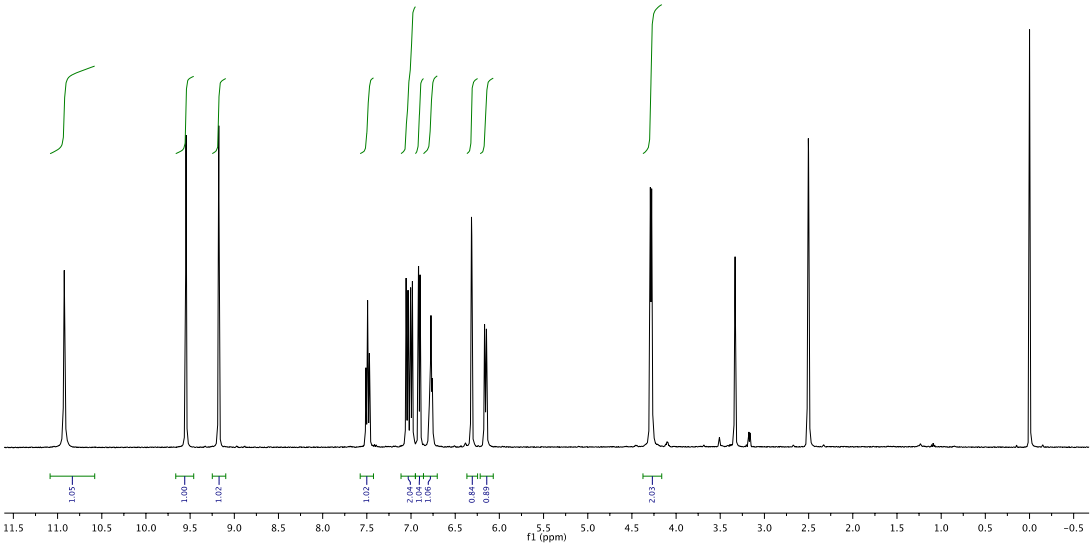
GKK-011-022

The TBDPS-protected salicylaldehyde (2.00 g, 5.55 mmol) was treated with luminol (0.50 g, 2.82 mmol) as per Procedure A to provide the crude 5-((2-((*tert*-butyldiphenylsilyl)oxy)benzyl)-amino)-2,3-dihydrophthalazine-1,4-dione. This material was dissolved in 10 mL of THF and treated with 1.0 M solution of TBAF in THF (0.74 mL, 0.74 mmol) under nitrogen atmosphere for 4 h. The precipitate was collected and the filter cake was washed with water and dried under vacuum to afford the title compound (105 mg, 0.27 mmol, 9.4% overall) as a white solid, mp 193-194 ºC. ^{1}H NMR (DMSO-d_6): δ 9.97 (br s, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 7.04 (apparent t, *J* = 6.5 Hz, 2H), 6.88 (d, *J* = 7.7 Hz, 1H), 6.70 (t, *J* = 7.4 Hz, 1H), 6.65 (d, *J* = 8.2 Hz, 1H), 4.30 (s, 2H), 3.14 (t, *J* = 7.8 Hz, 4H), 1.56 (quintet, *J* = 7.8 Hz, 4H), 1.30 (sextet, *J* = 7.3 Hz, 4H), 0.93 (t, *J* = 7.3 Hz, 6H), amine proton not observed; ^{13}C NMR (DMSO-d_6): δ 161.7, 156.1, 150.3, 133.3, 128.5, 128.2, 125.3, 118.9, 115.6, 112.9, 110.6, 110.4, 58.0, 41.5, 23.5, 19.7, 14.0; MS: *m/z* 395 ($C_{23}H_{29}N_3O_3$, $M^{+\cdot}$).

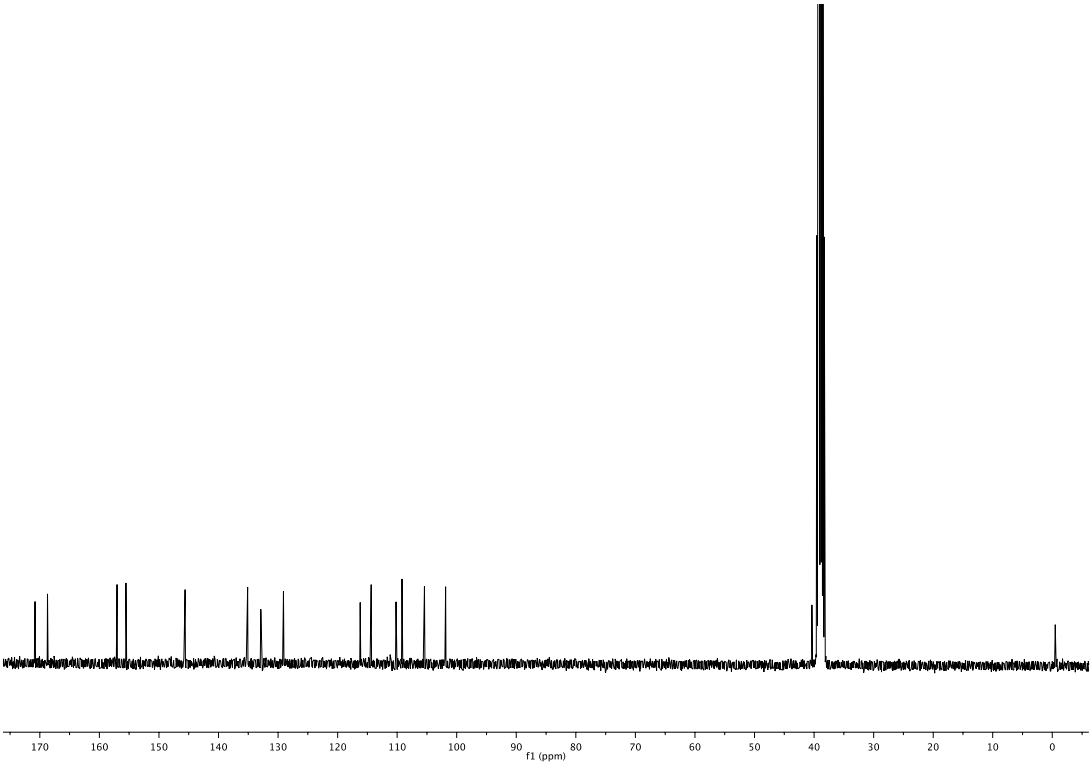
^{1}H and ^{13}C spectra for 4-(benzylamino)isoindoline-1,3-dione series

4-((2,4,6-Trihydroxybenzyl)amino)isoindoline-1,3-dione: BN-XIV-069

^{1}H NMR:

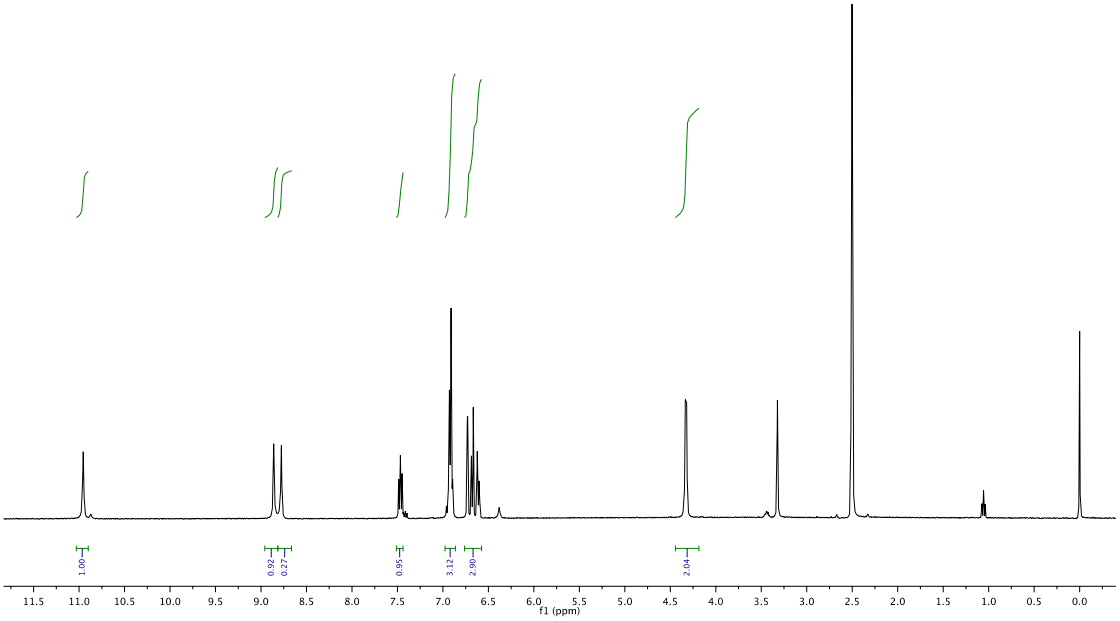


^{13}C NMR:

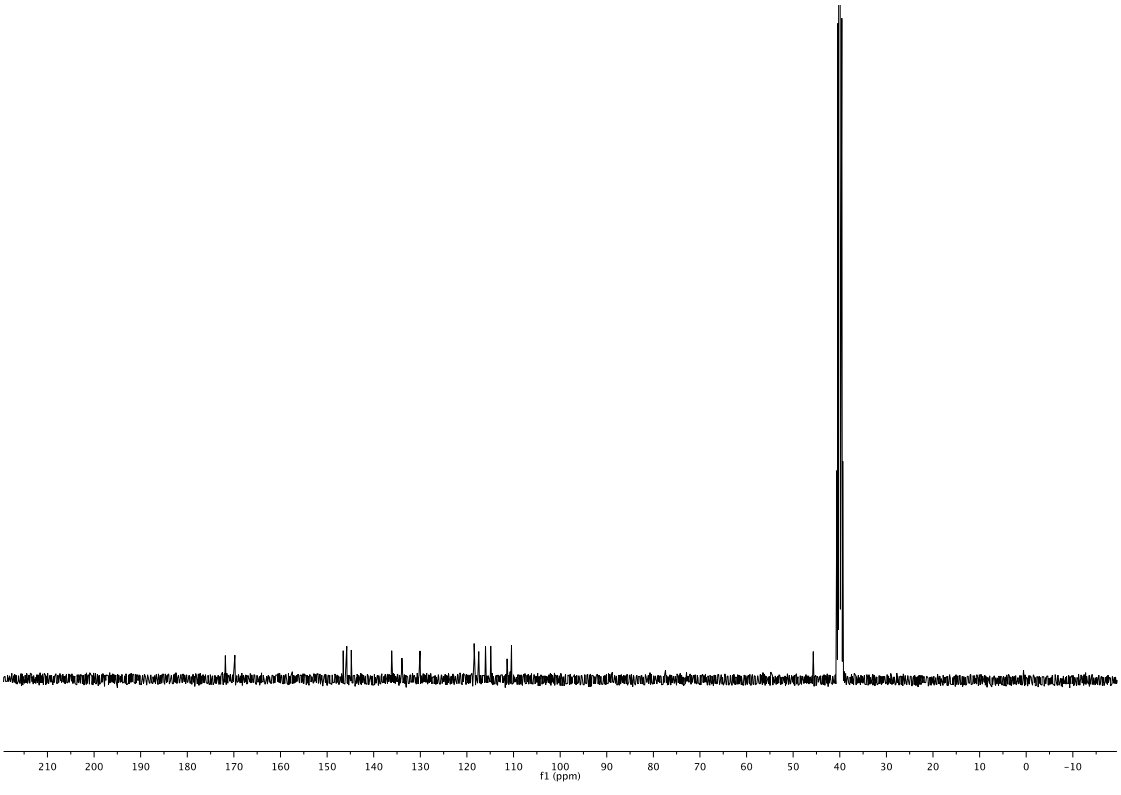


4-((3,4-Dihydroxybenzyl)amino)isoindoline-1,3-dione: BN-XIV-055

^{1}H NMR:

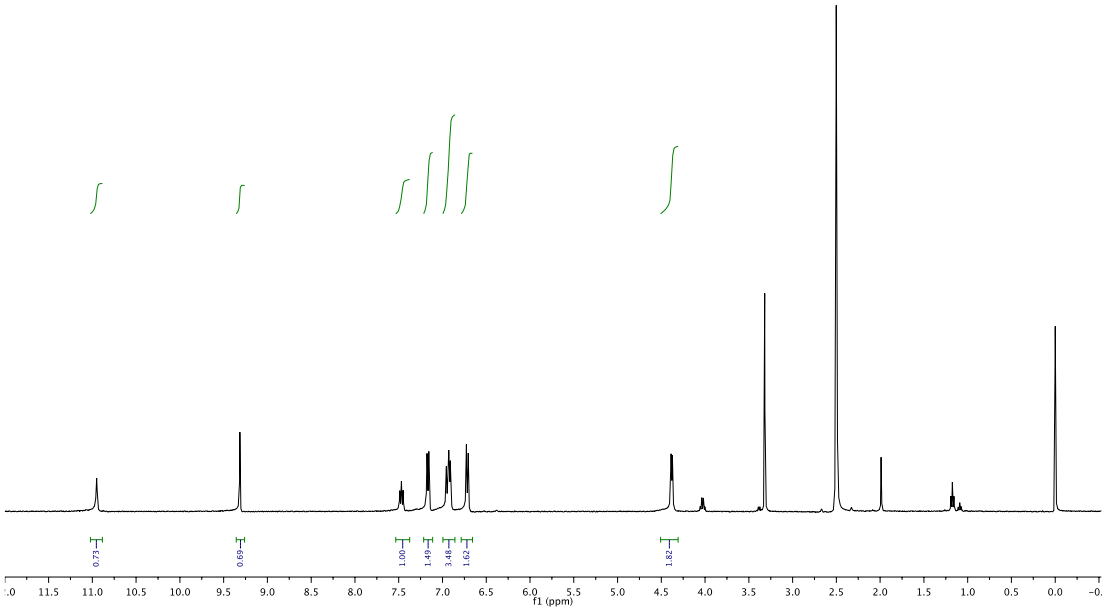


^{13}C NMR

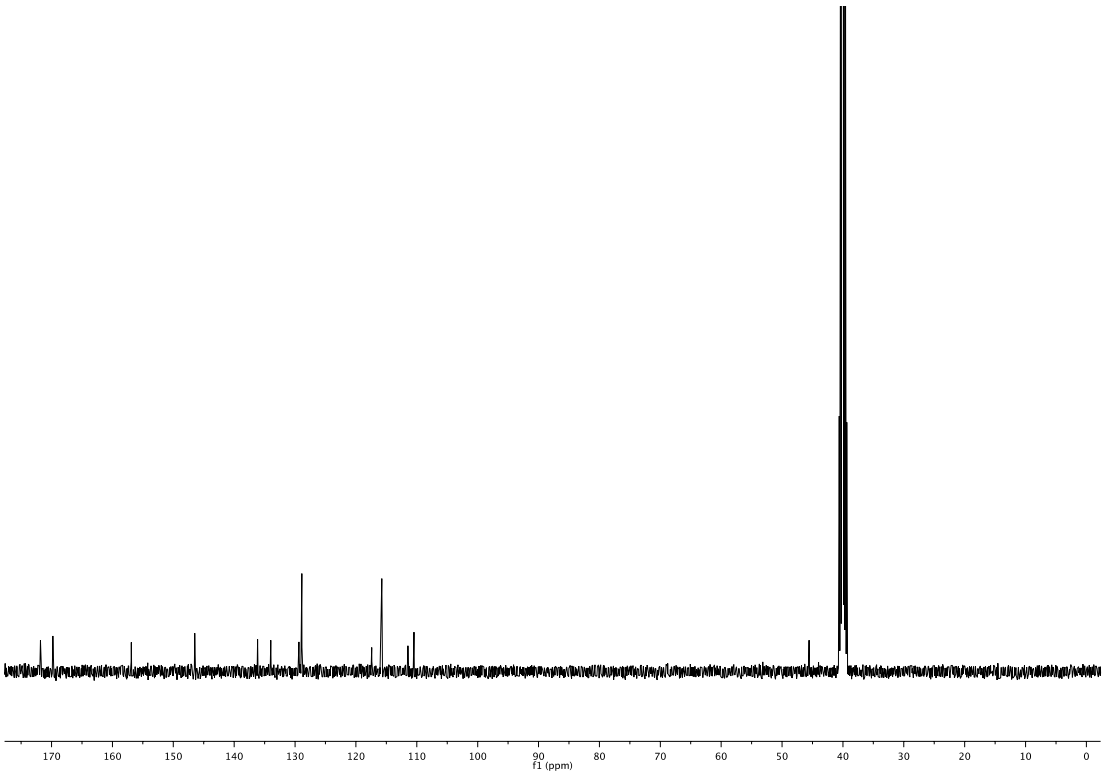


4-((4-Hydroxybenzyl)amino)isoindoline-1,3-dione: BN-XIV-052

^{1}H NMR:

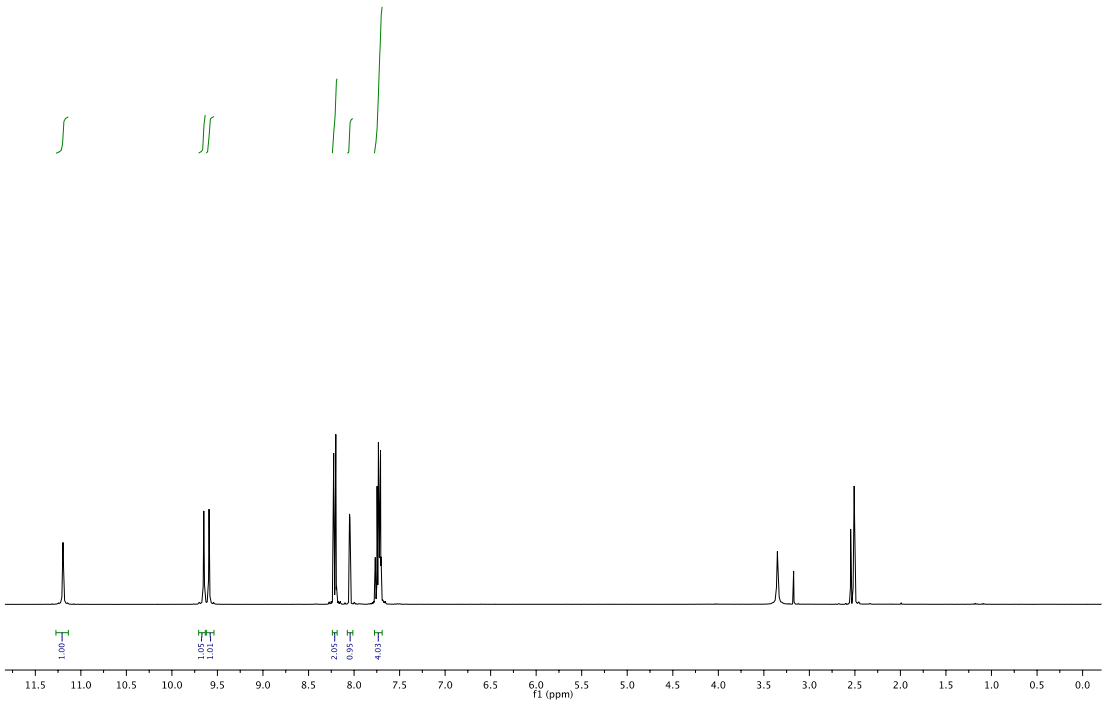


^{13}C NMR:

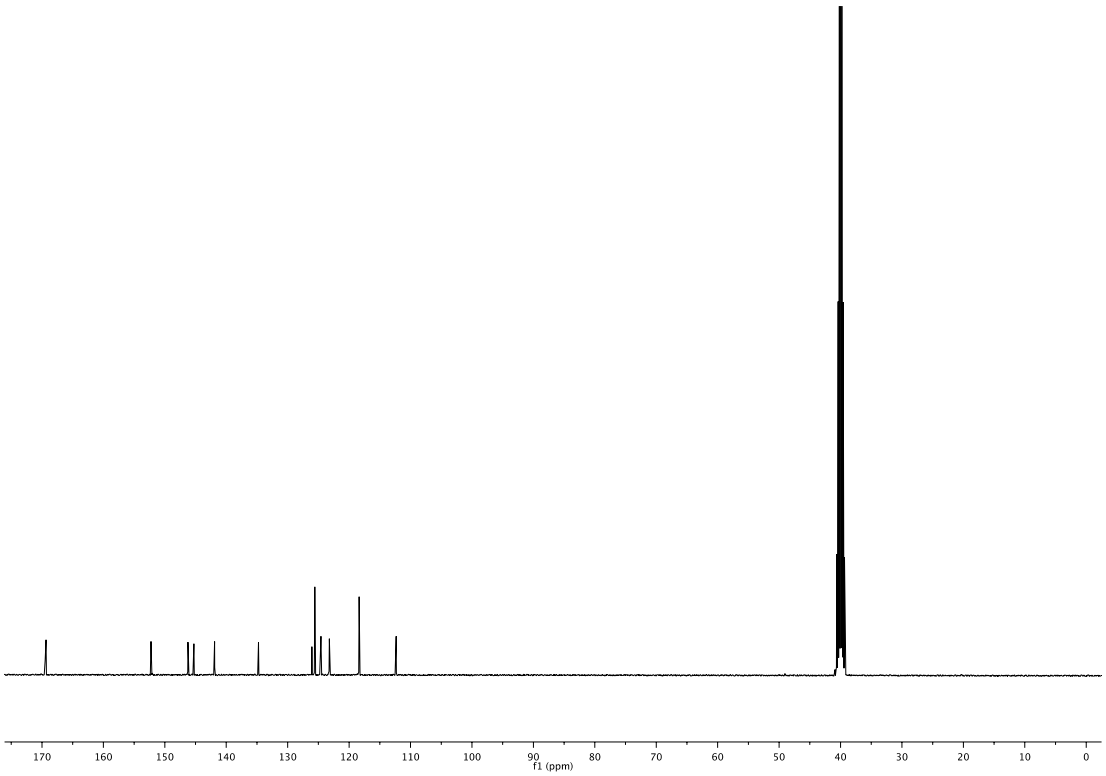


1-(1,3-Dioxoisoindolin-5-yl)-3-(4-nitrophenyl)urea: BN-XII-071

^{1}H NMR:

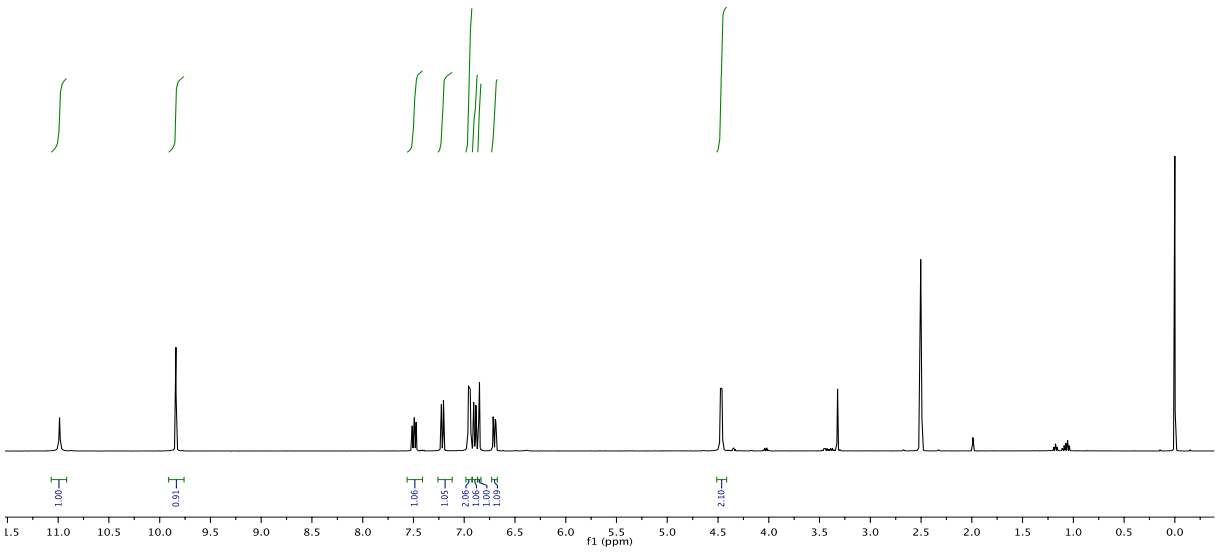


^{13}C NMR:

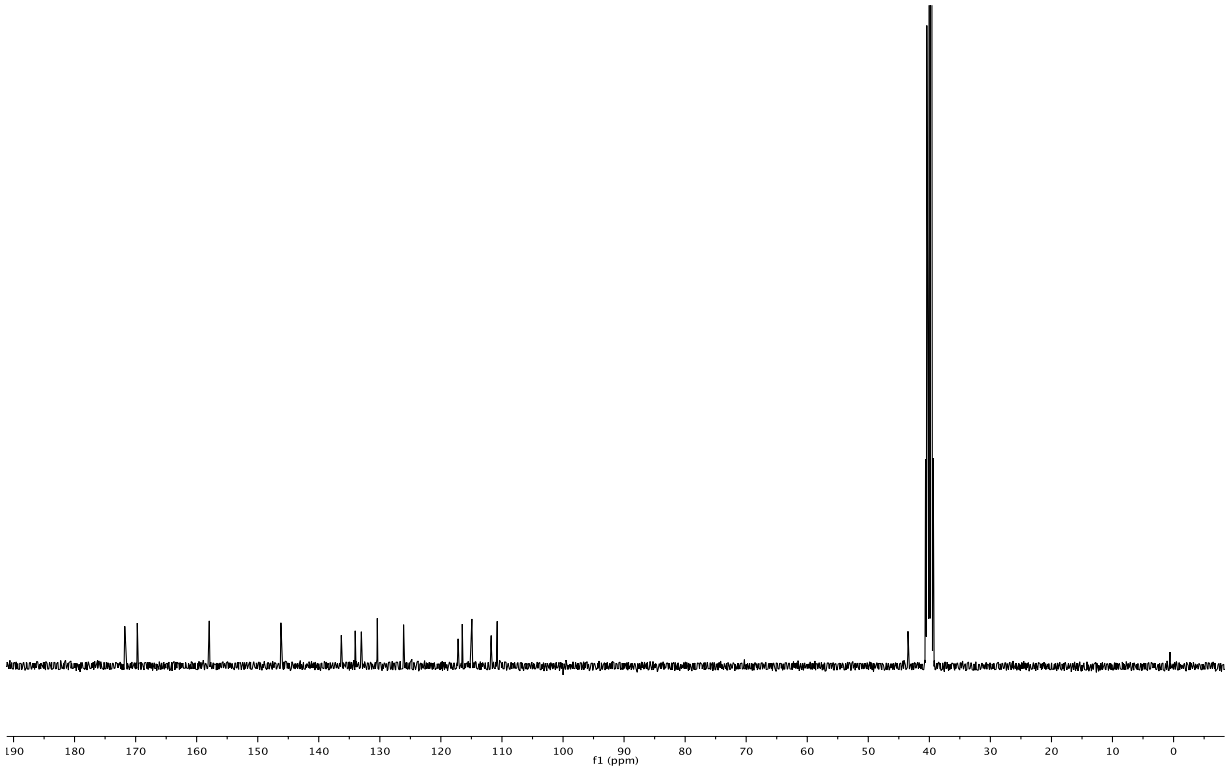


4-((2-Chloro-4-hydroxybenzyl)amino)isoindoline-1,3-dione: GKK-007-100

^{1}H NMR:

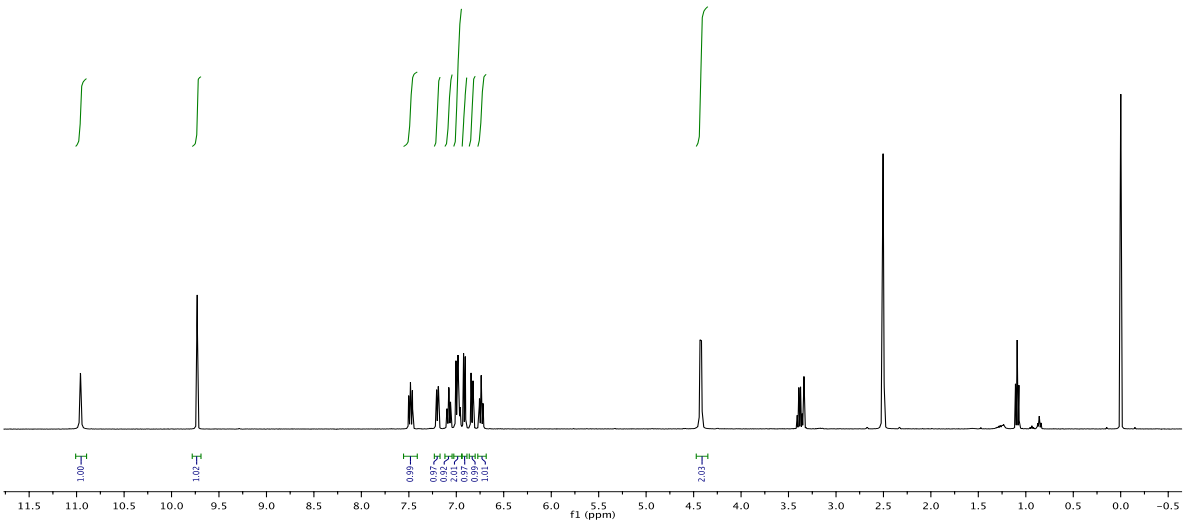


^{13}C NMR:

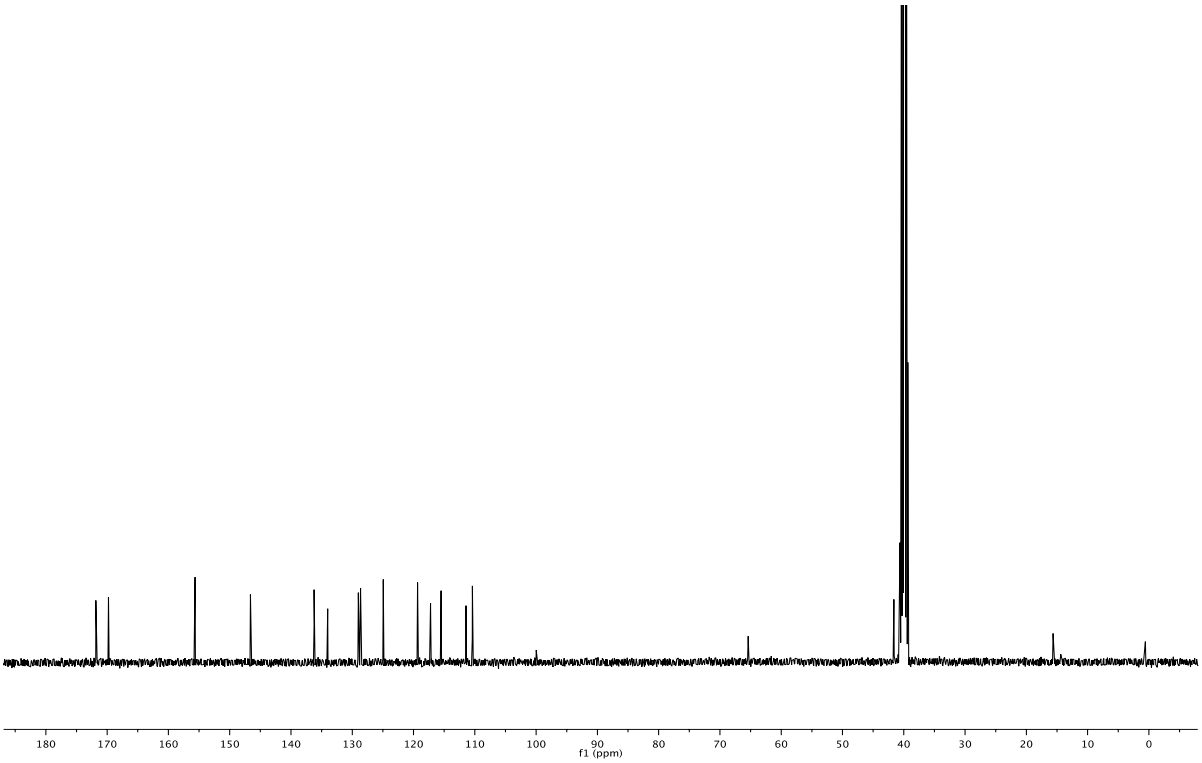


4-((2-Hydroxybenzyl)amino)isoindoline-1,3-dione: GKK-011-017 (**Analog 11**)

^{1}H NMR:

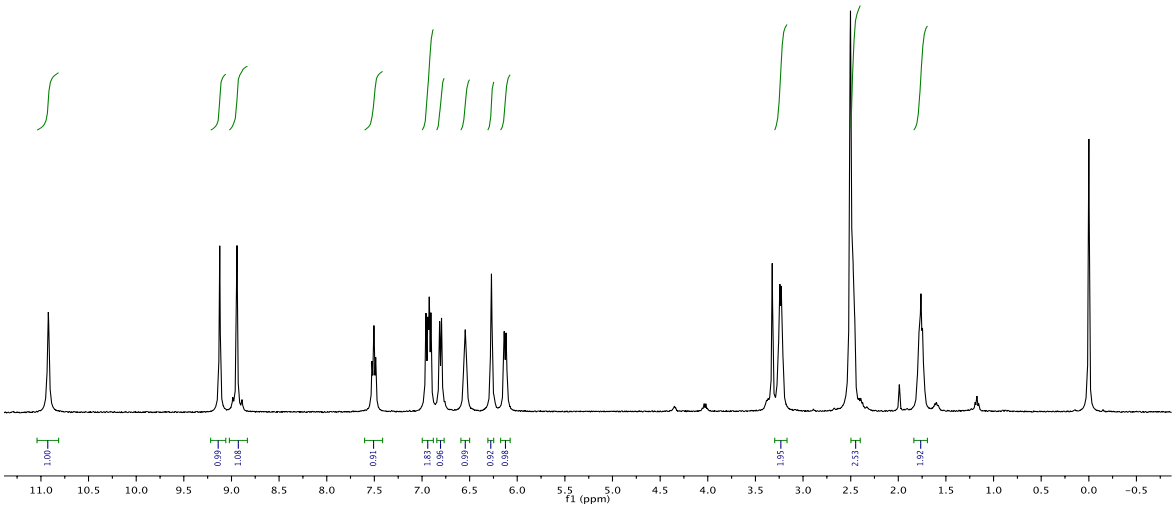


^{13}C NMR:

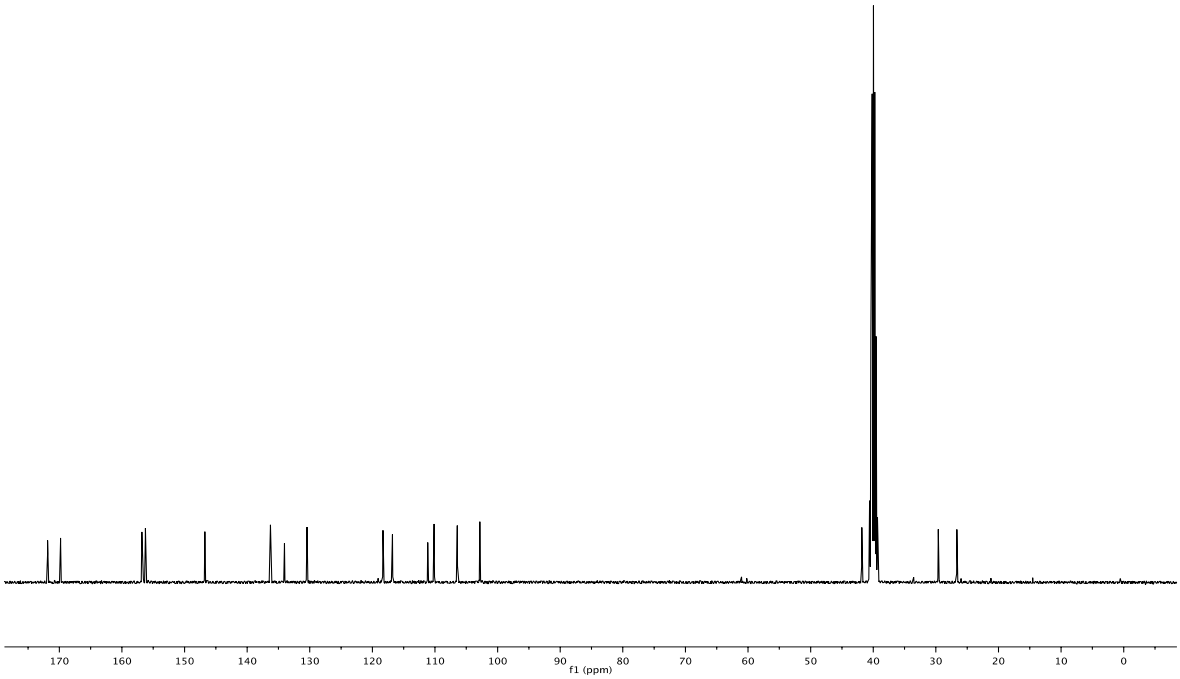


4-((3-(2-Hydroxyphenyl)propyl)amino)isoindoline-1,3-dione: GKK-007-047 (**Analog 14**)

^{1}H NMR:



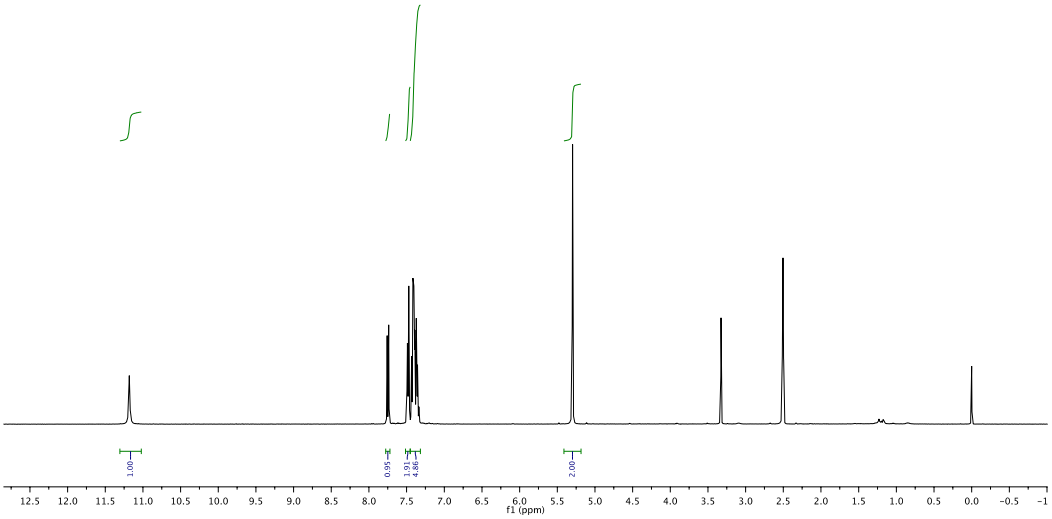
^{13}C NMR:



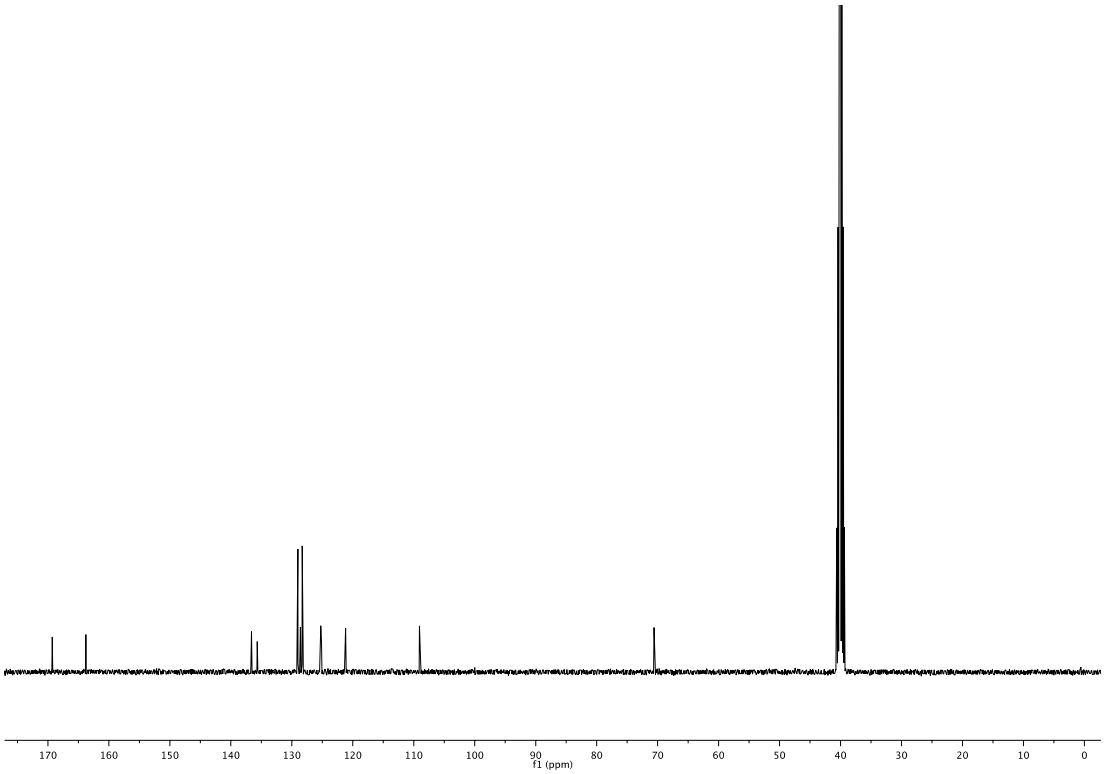
^{1}H and ^{13}C spectra for 5-(benzyloxy)isoindoline-1,3-dione series

5-(Benzyloxy)isoindoline-1,3-dione: BN-XIII-07

^{1}H NMR:

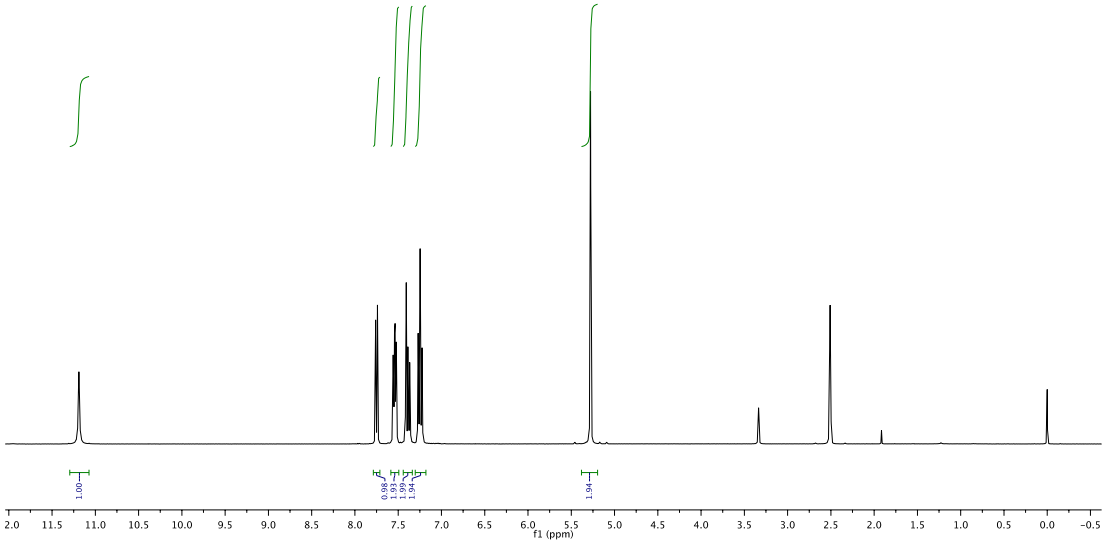


^{13}C NMR:

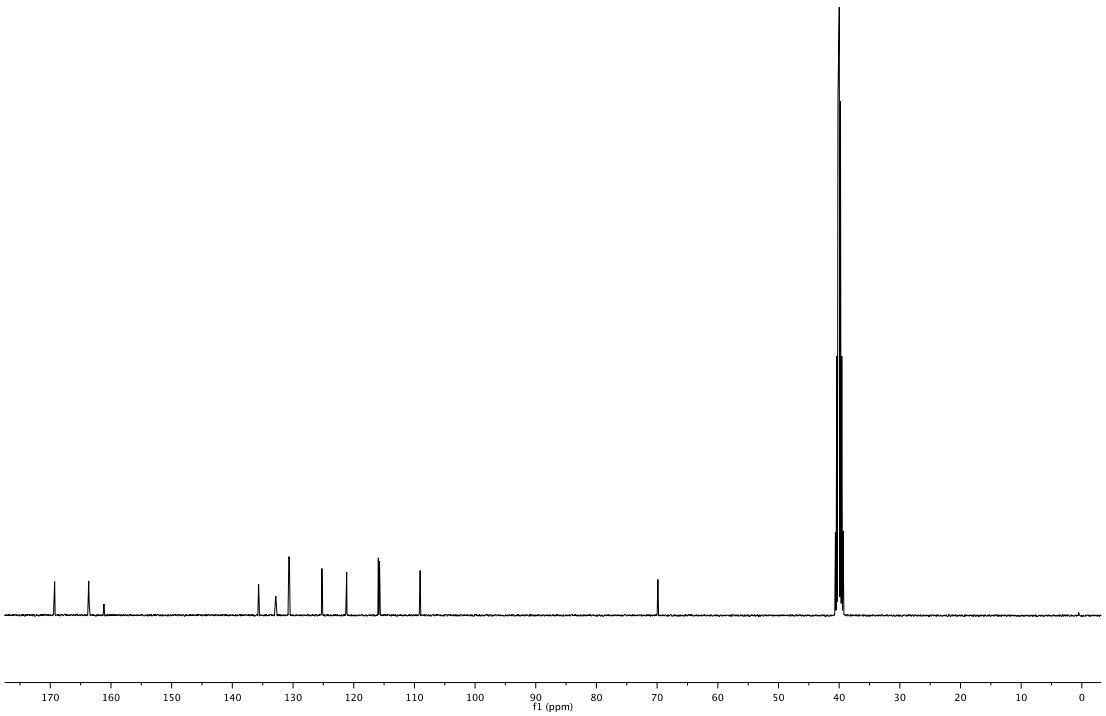


5-((4-Fluorobenzyl)oxy)isoindoline-1,3-dione: BN-XIII-013

^{1}H NMR:

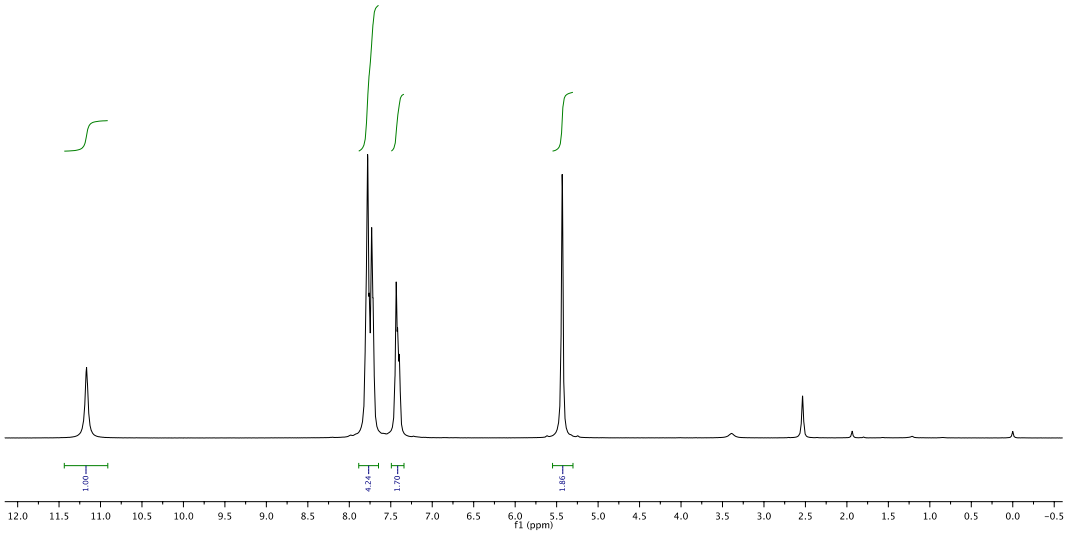


^{13}C NMR:

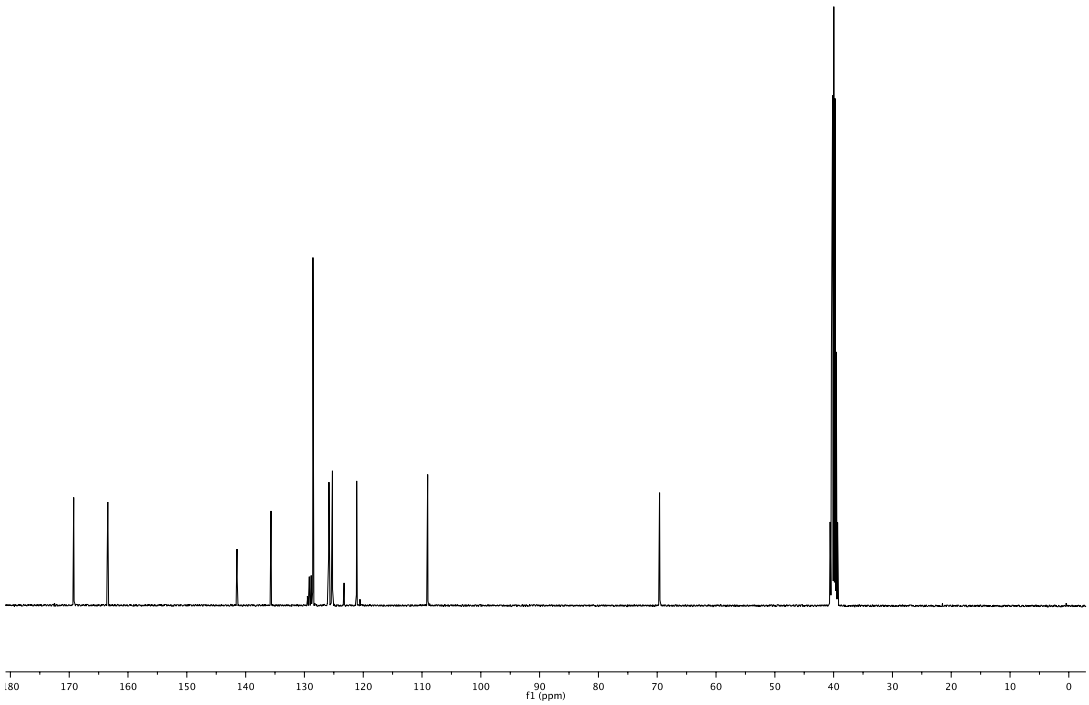


5-((4-(Trifluoromethyl)benzyl)oxy)isoindoline-1,3-dione: BN-XIII-016

^{1}H NMR:

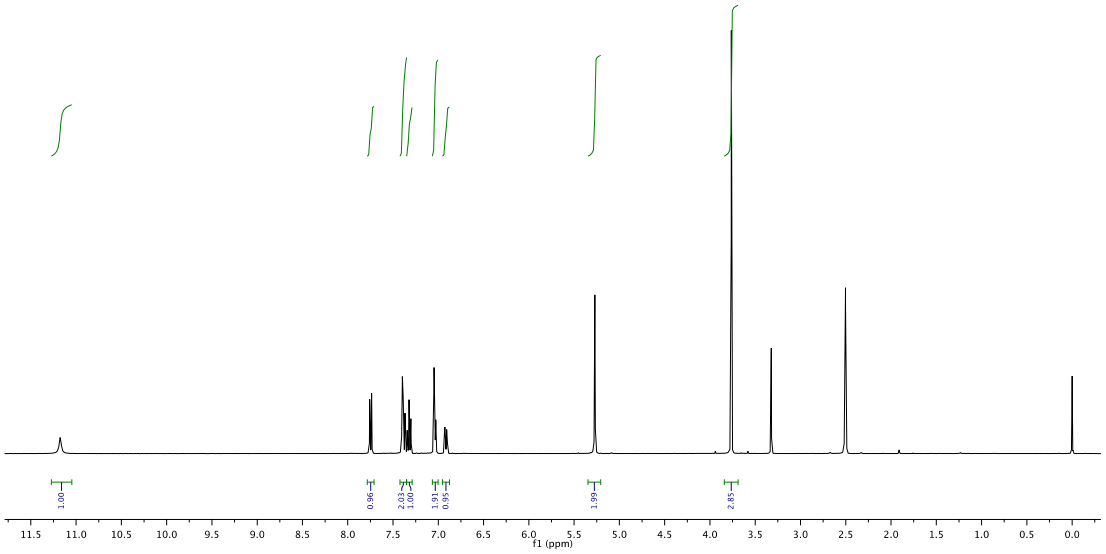


^{13}C NMR:

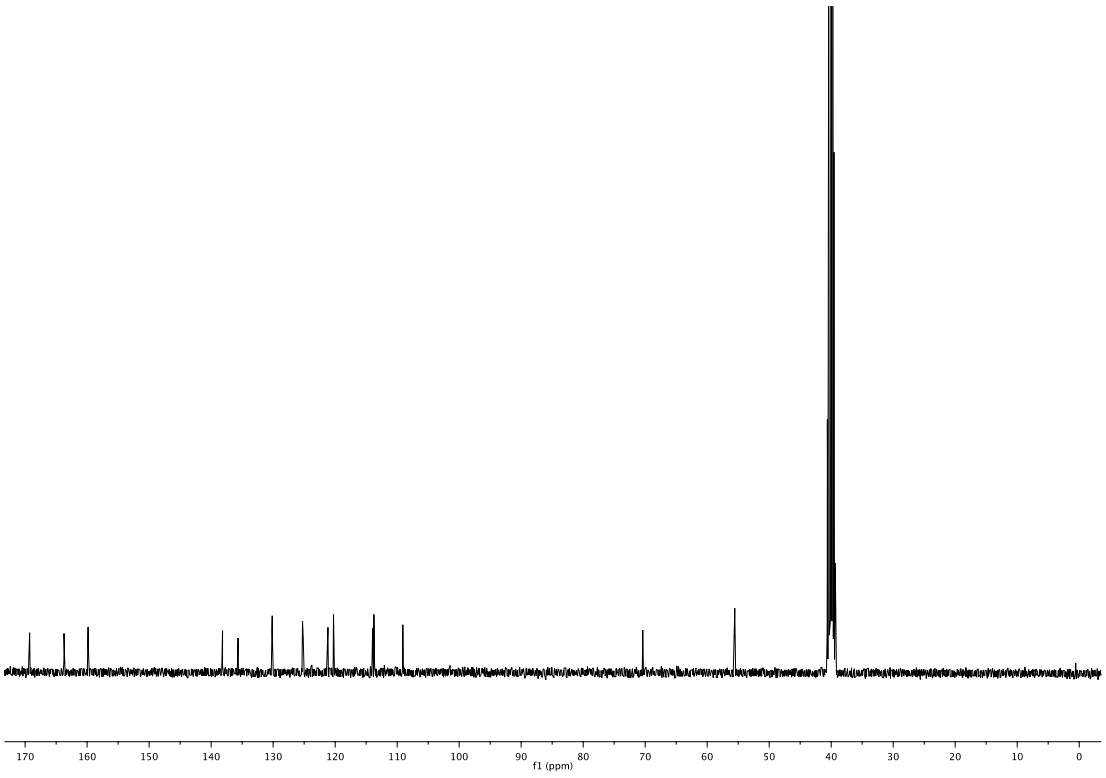


5-((3-Methoxybenzyl)oxy)isoindoline-1,3-dione: BN-XII-046

^{1}H NMR:

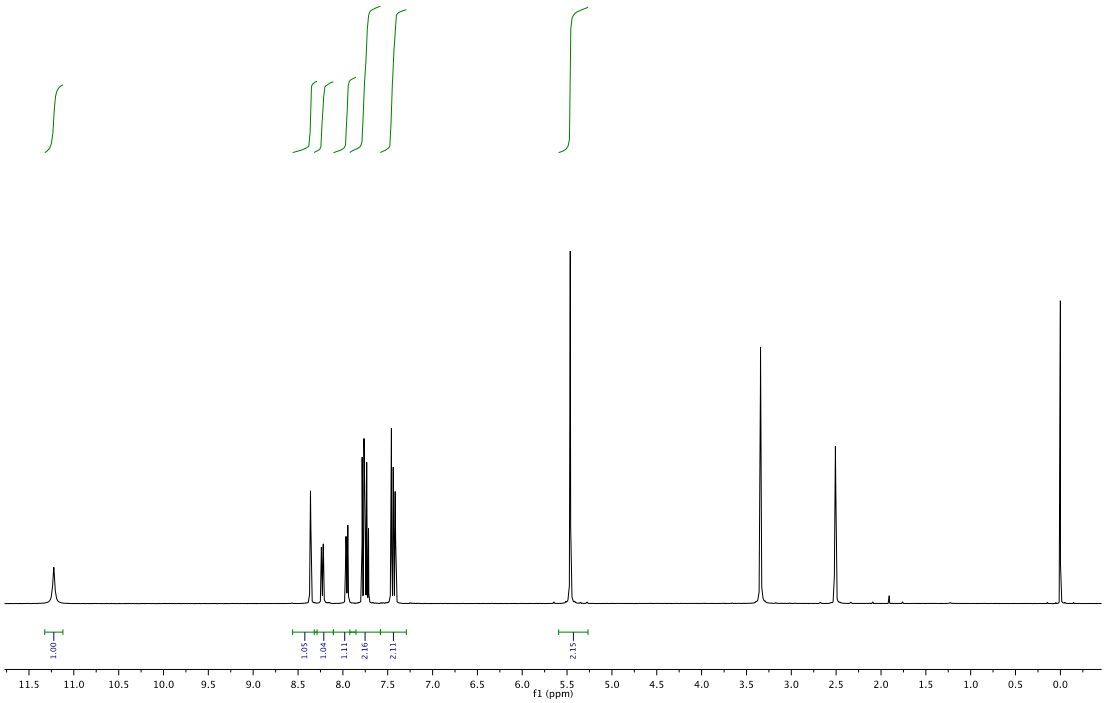


^{13}C NMR:

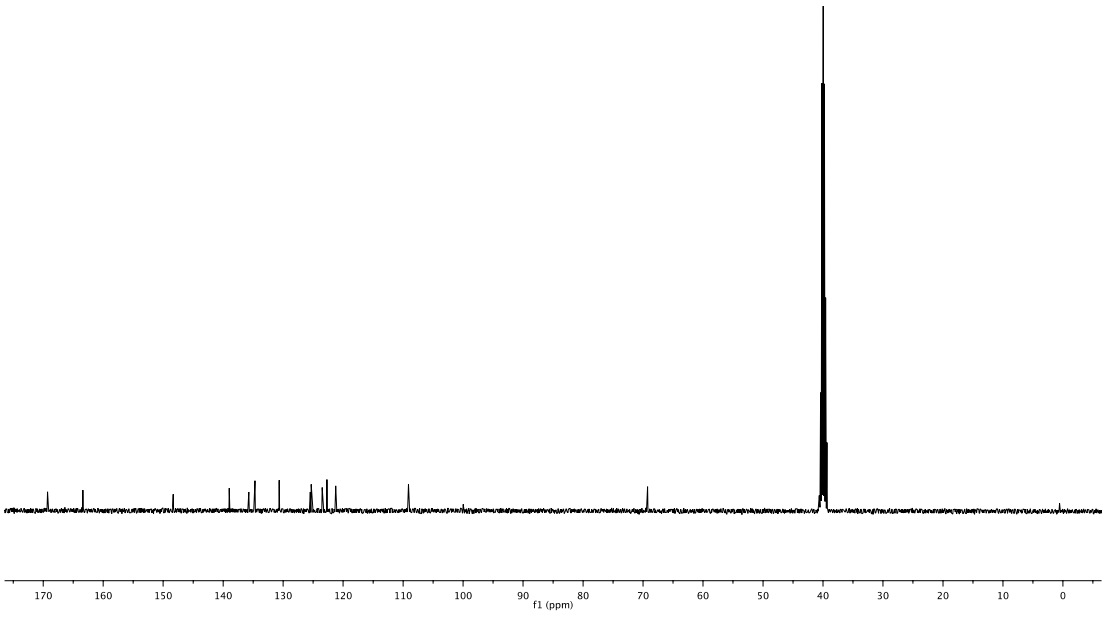


5-((3-Nitrobenzyl)oxy)isoindoline-1,3-dione: BN-XII-044

^{1}H NMR:



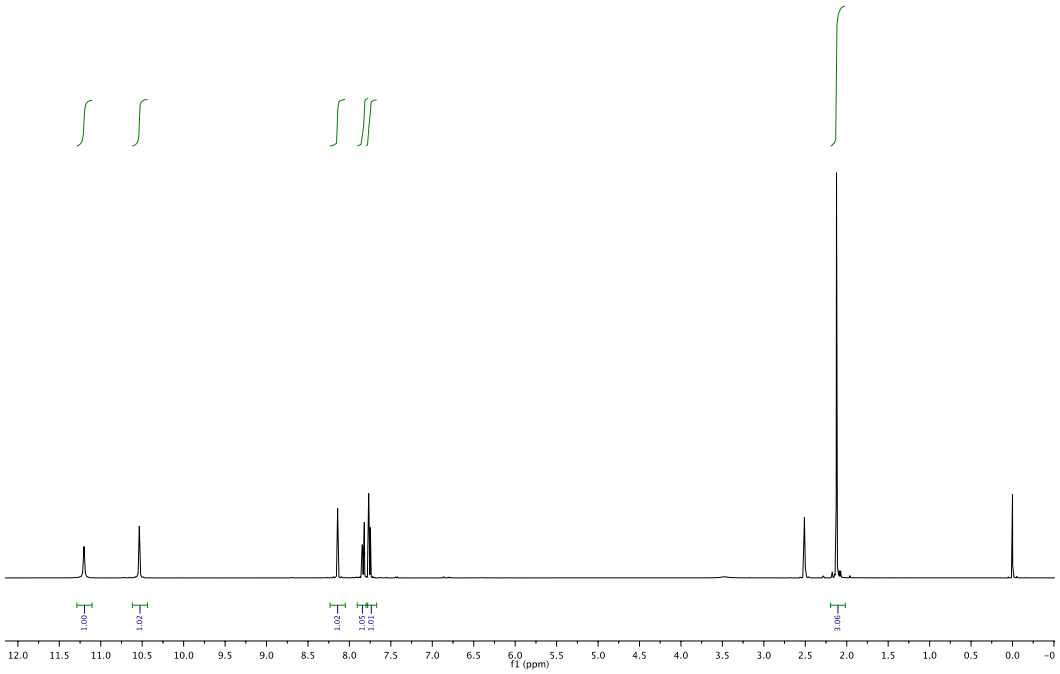
^{13}C NMR:



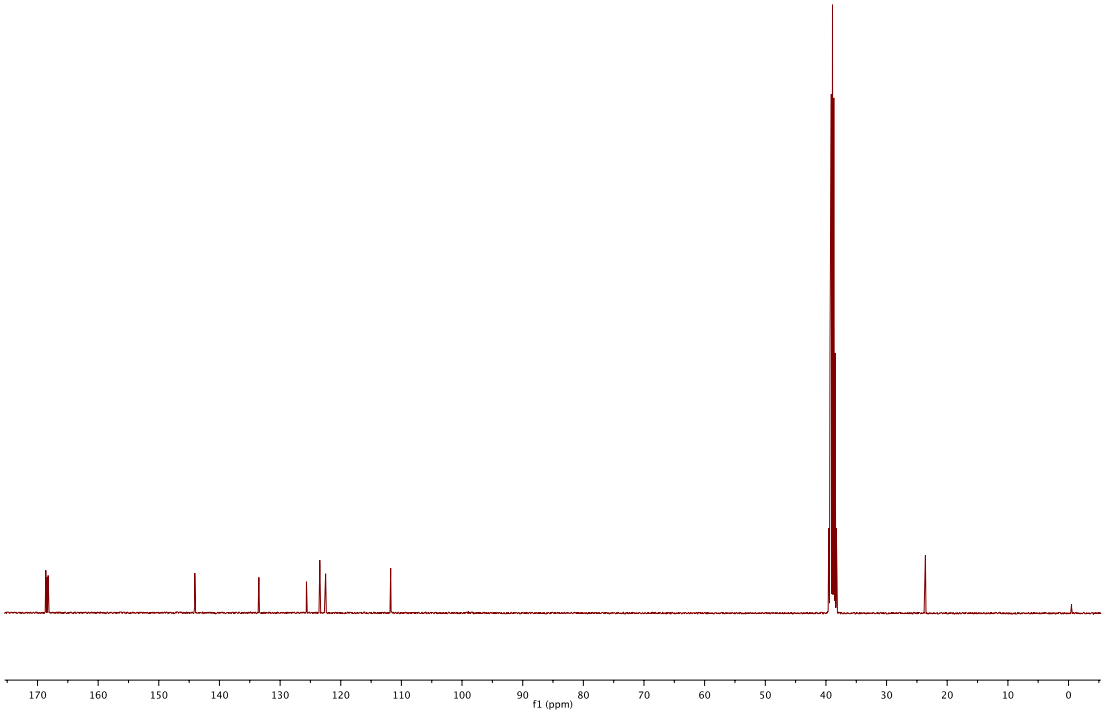
^{1}H and ^{13}C spectra for 5-amidoisoindoline-1,3-dione series

N-(1,3-Dioxoisoindolin-5-yl)acetamide: BN-XII-078

^{1}H NMR:

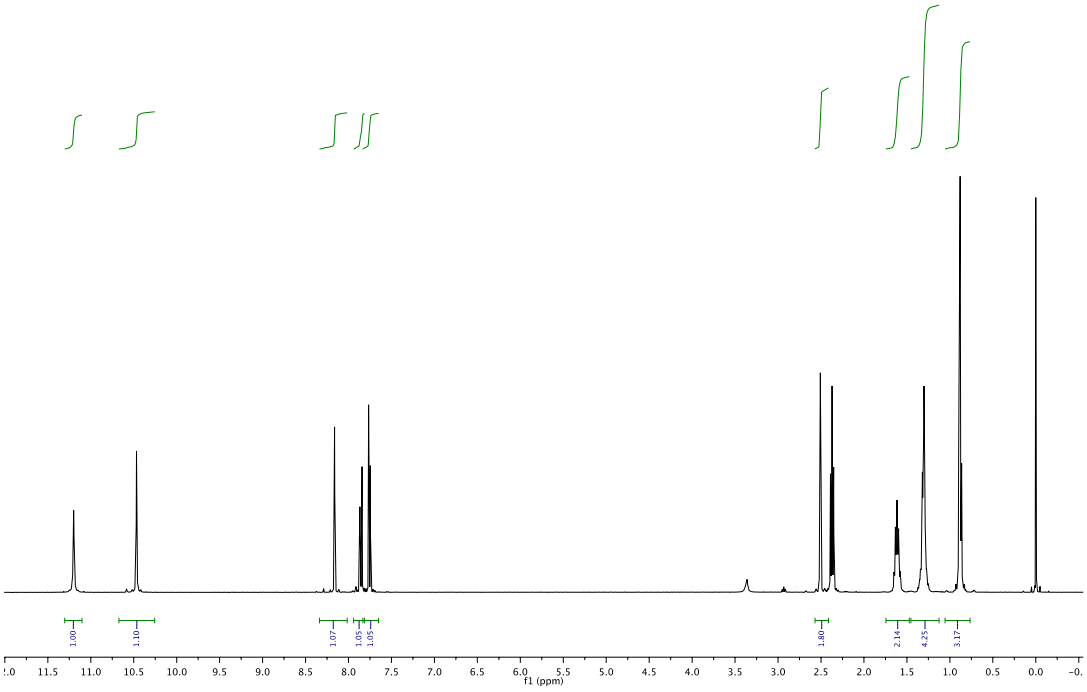


^{13}C NMR:

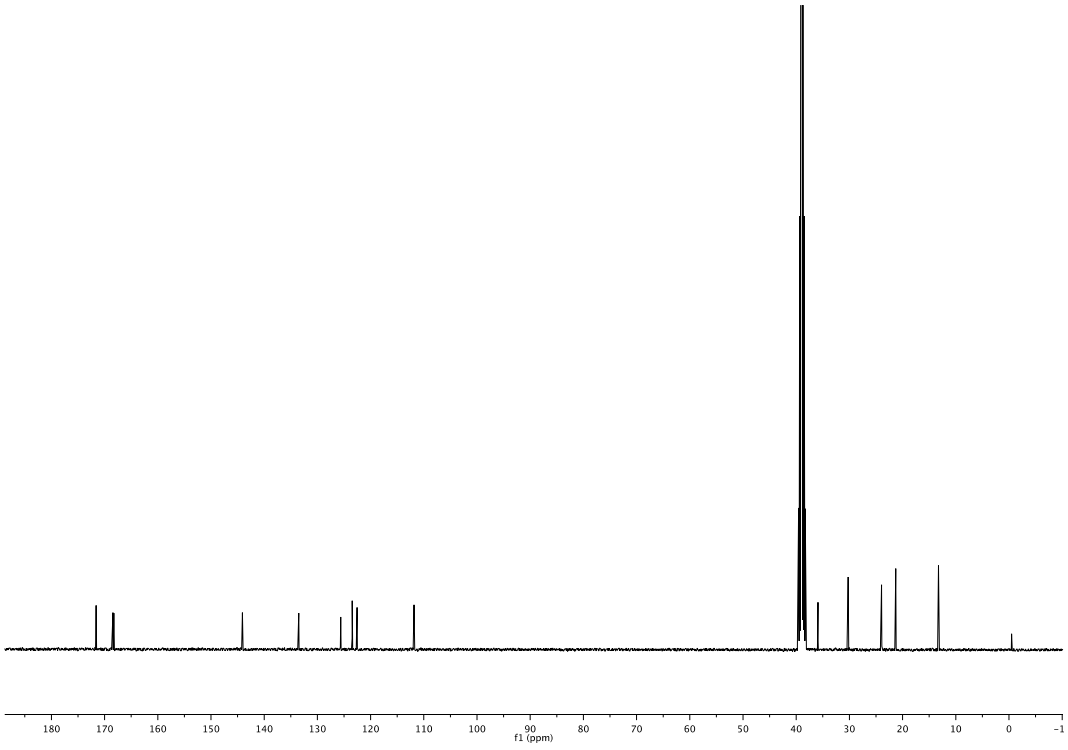


N-(1,3-Dioxoisoindolin-5-yl)hexanamide: BN-XII-079

^{1}H NMR:

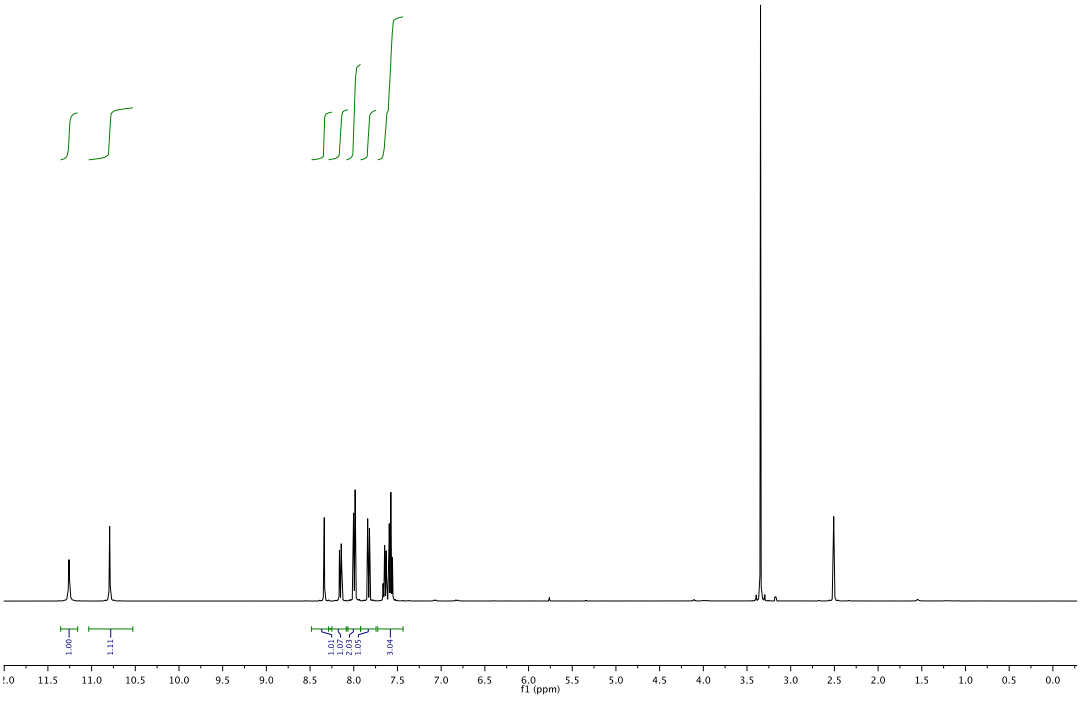


^{13}C NMR:

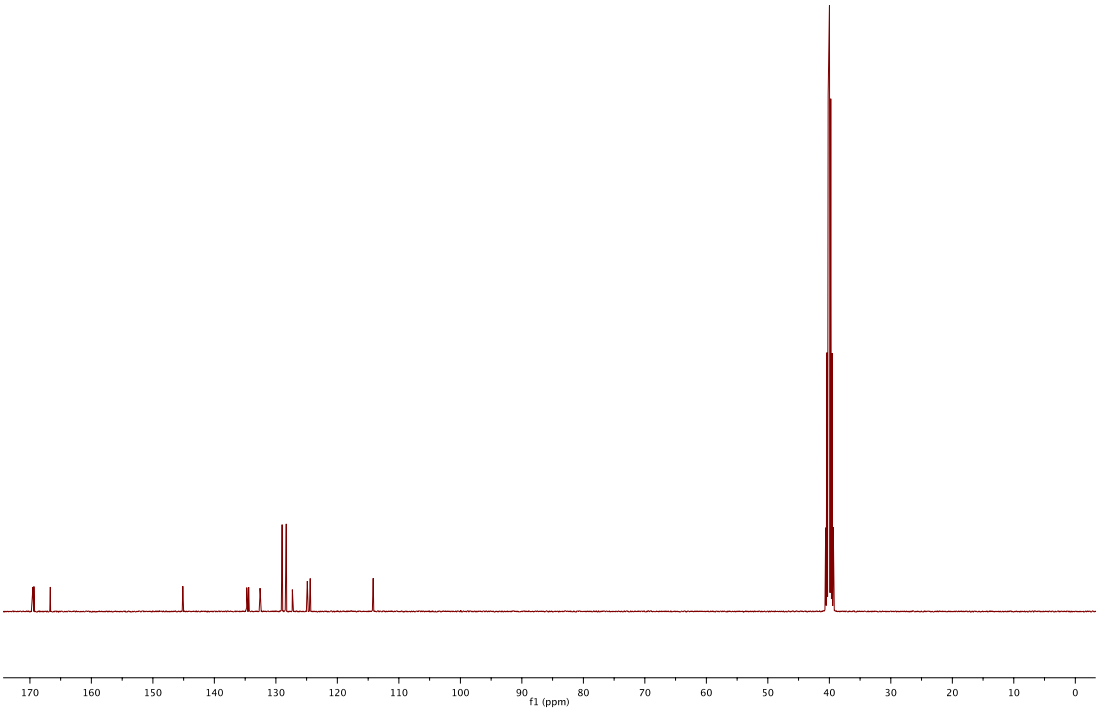


N-(1,3-Dioxoisoindolin-5-yl)benzamide: BN-XII-061

^{1}H NMR:

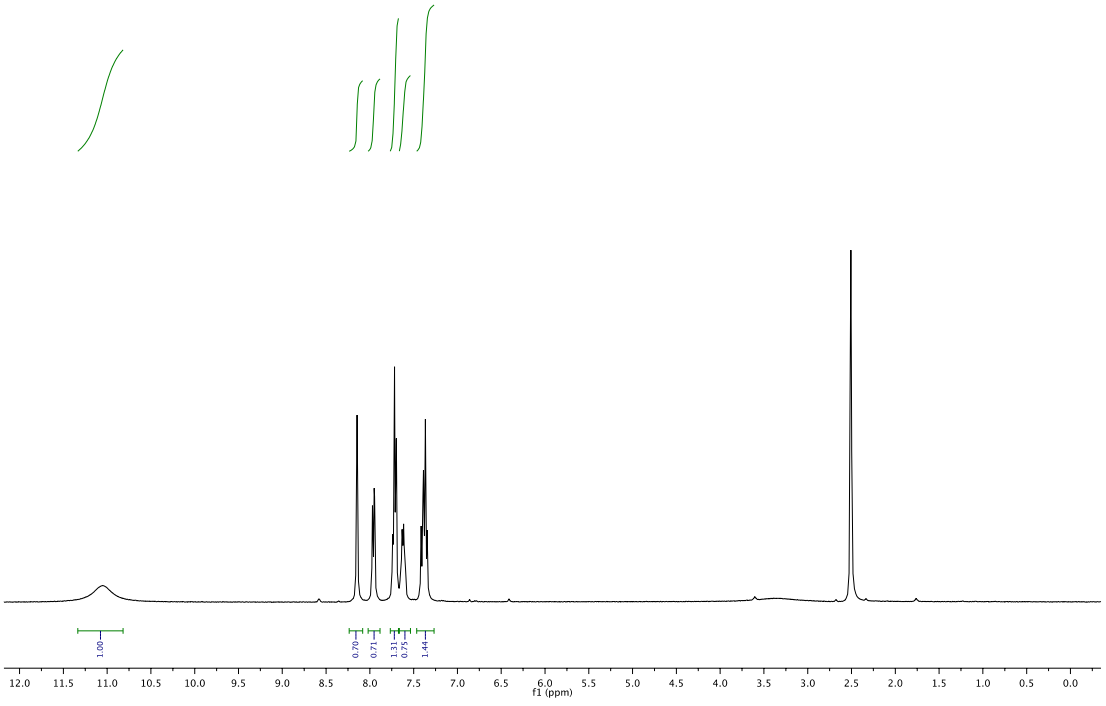


^{13}C NMR:

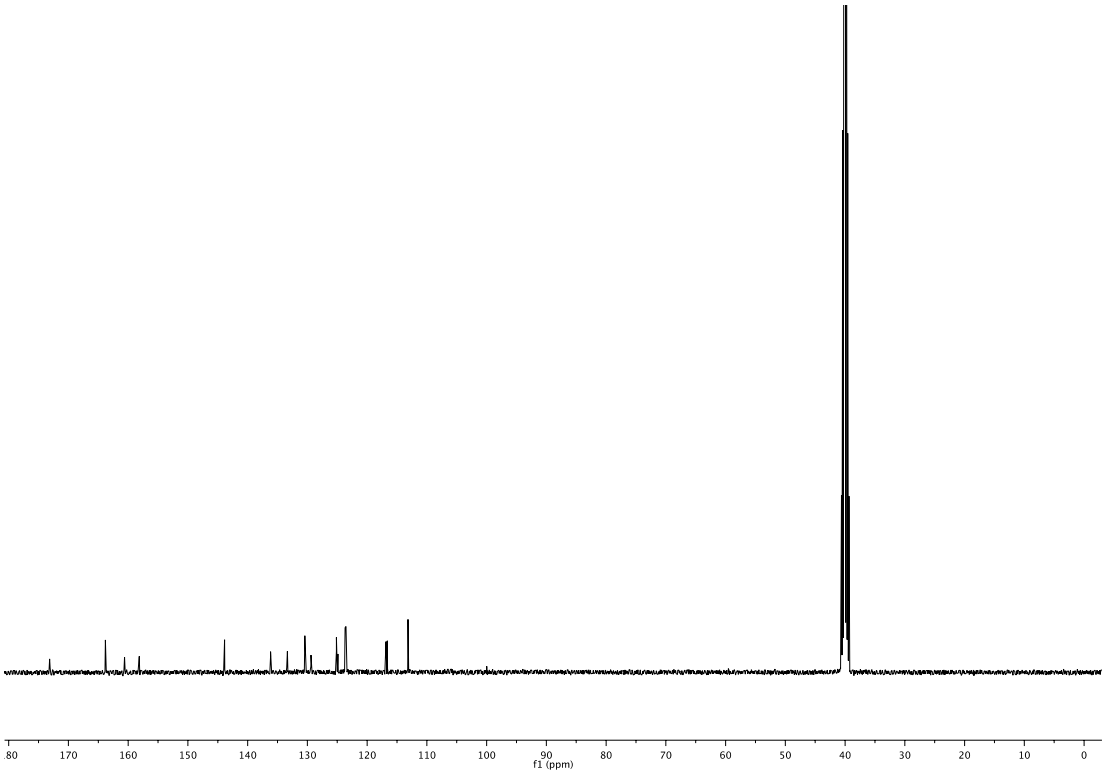


N-(1,3-Dioxoisoindolin-5-yl)-2-fluorobenzamide: BN-XII-060

^{1}H NMR:

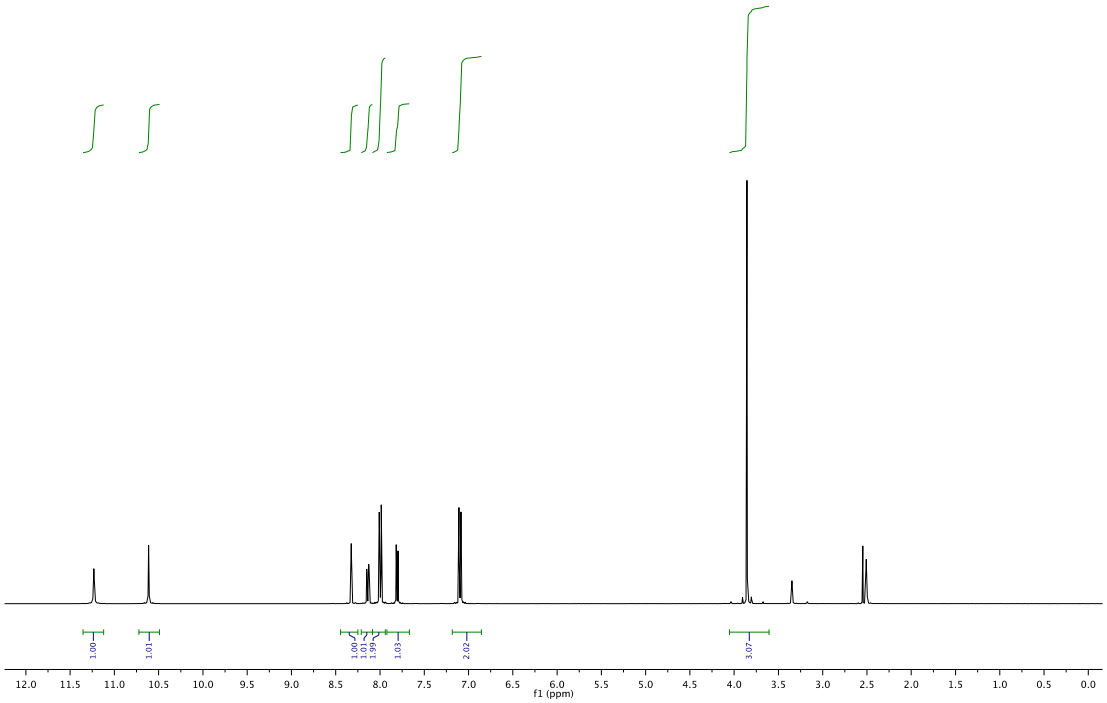


^{13}C NMR:

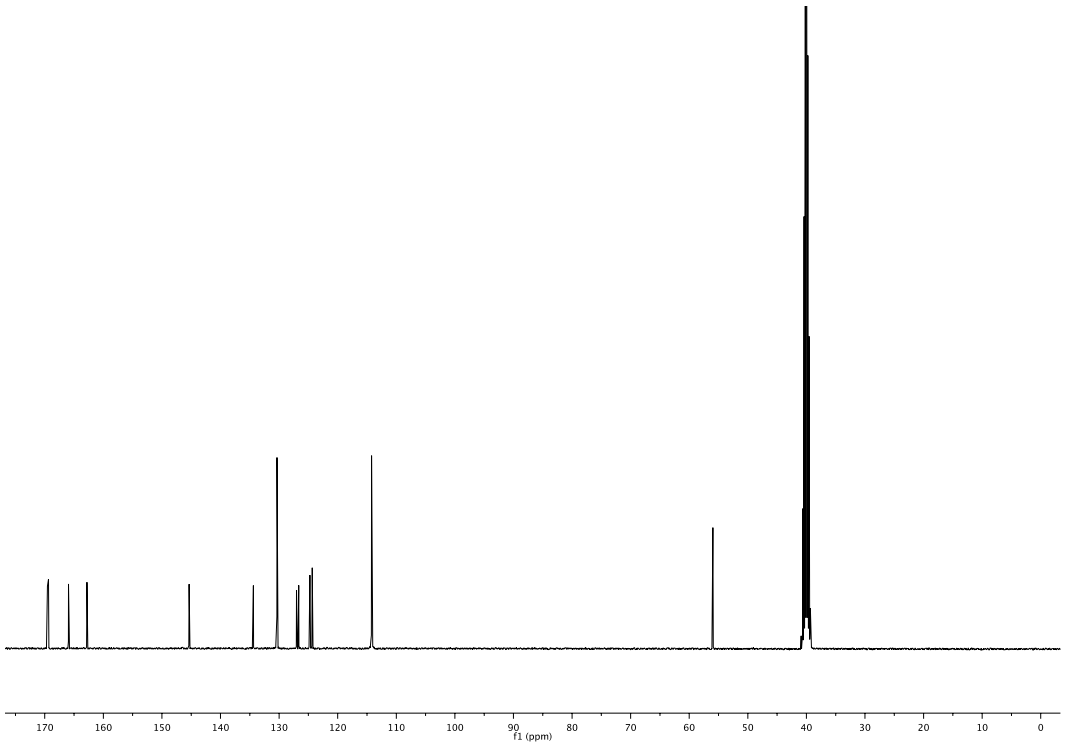


N-(1,3-Dioxoisoindolin-5-yl)-4-methoxybenzamide: BN-XII-064

^{1}H NMR:

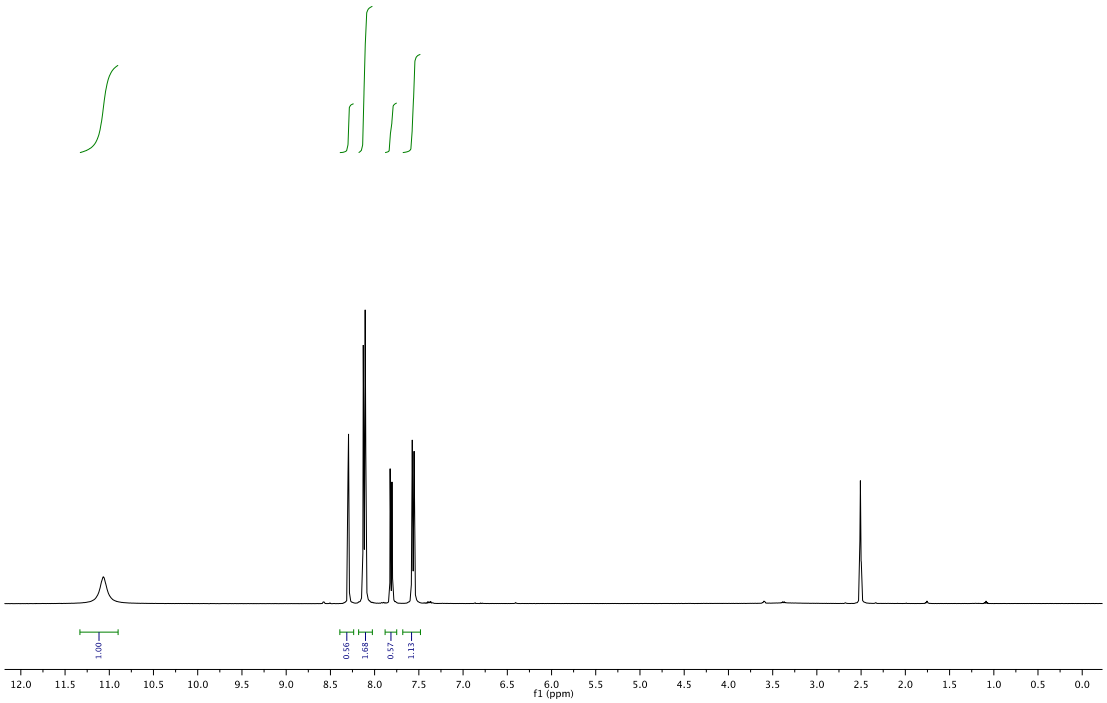


^{13}C NMR:

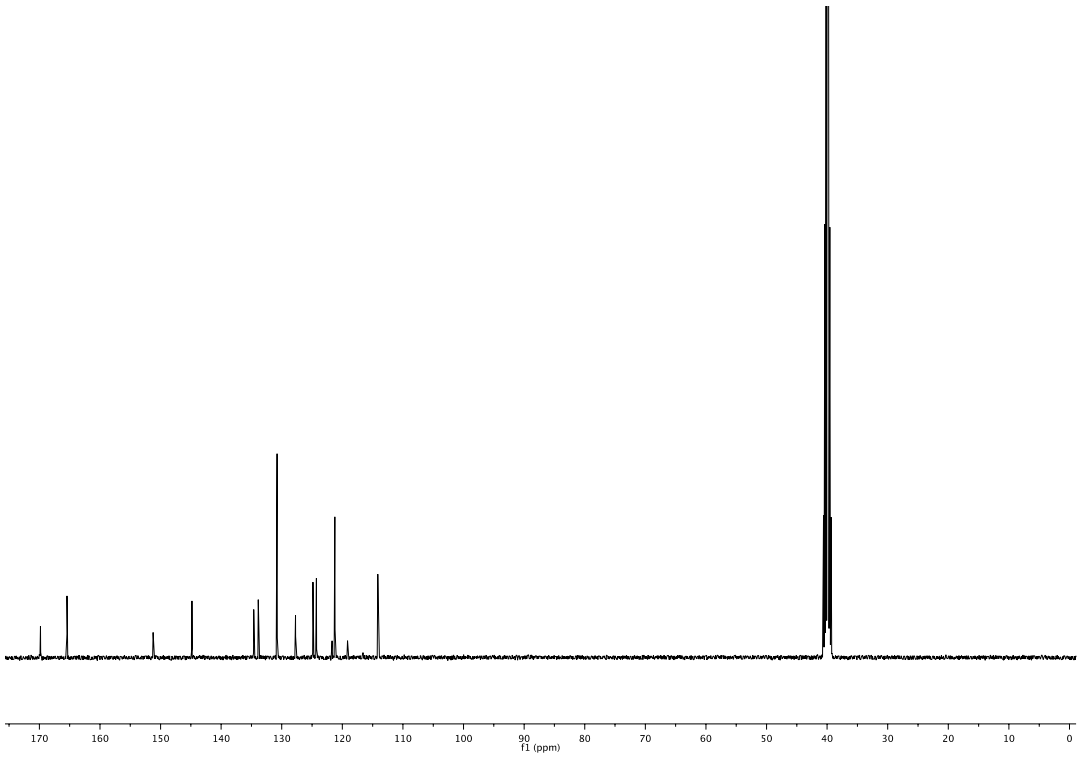


N-(1,3-Dioxoisoindolin-5-yl)-4-(trifluoromethoxy)benzamide: BN-XII-059

^{1}H NMR:

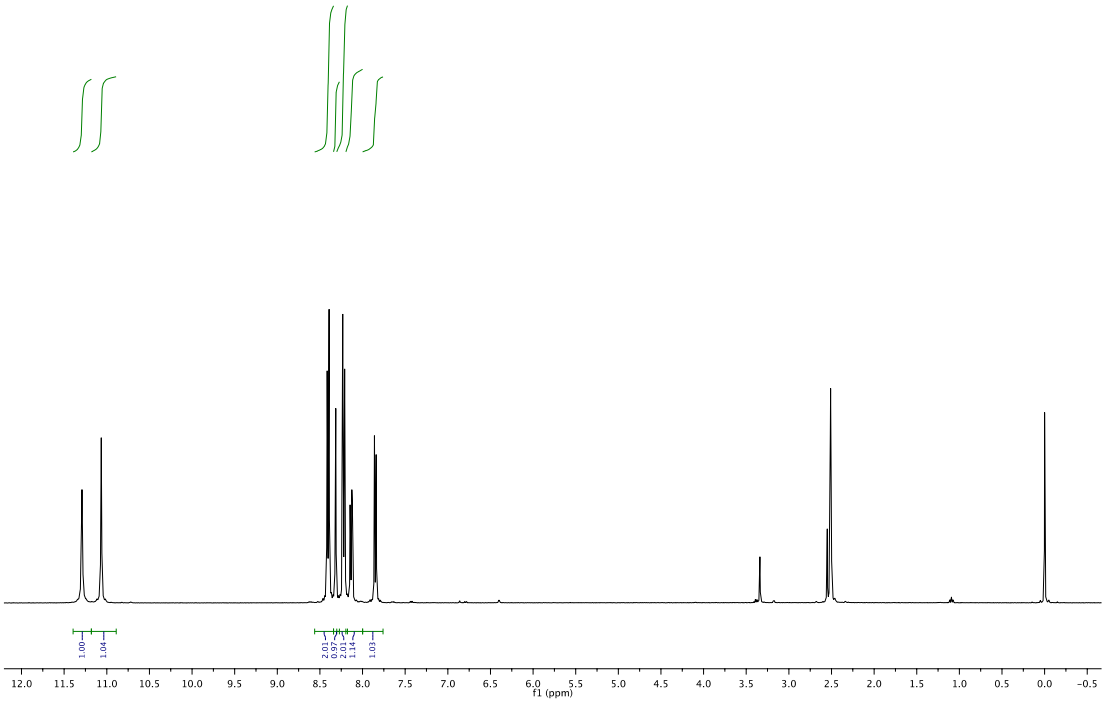


^{13}C NMR:

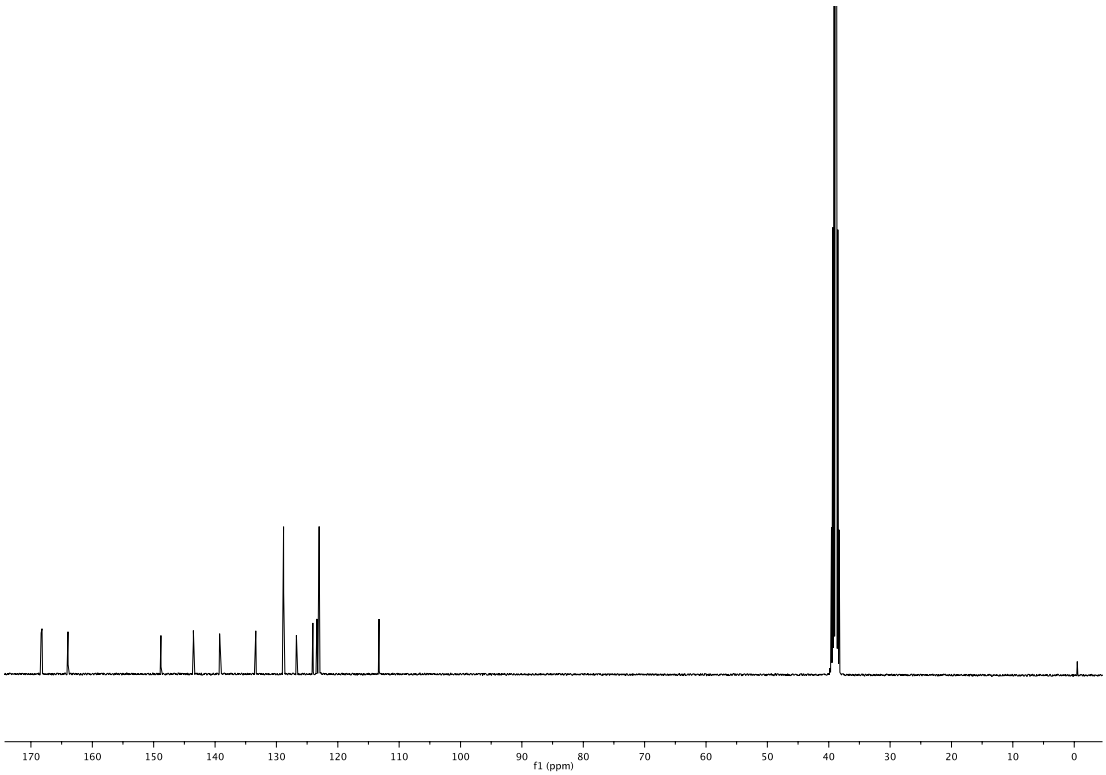


N-(1,3-Dioxoisoindolin-5-yl)-4-nitrobenzamide:BN-XII-063

^{1}H NMR:

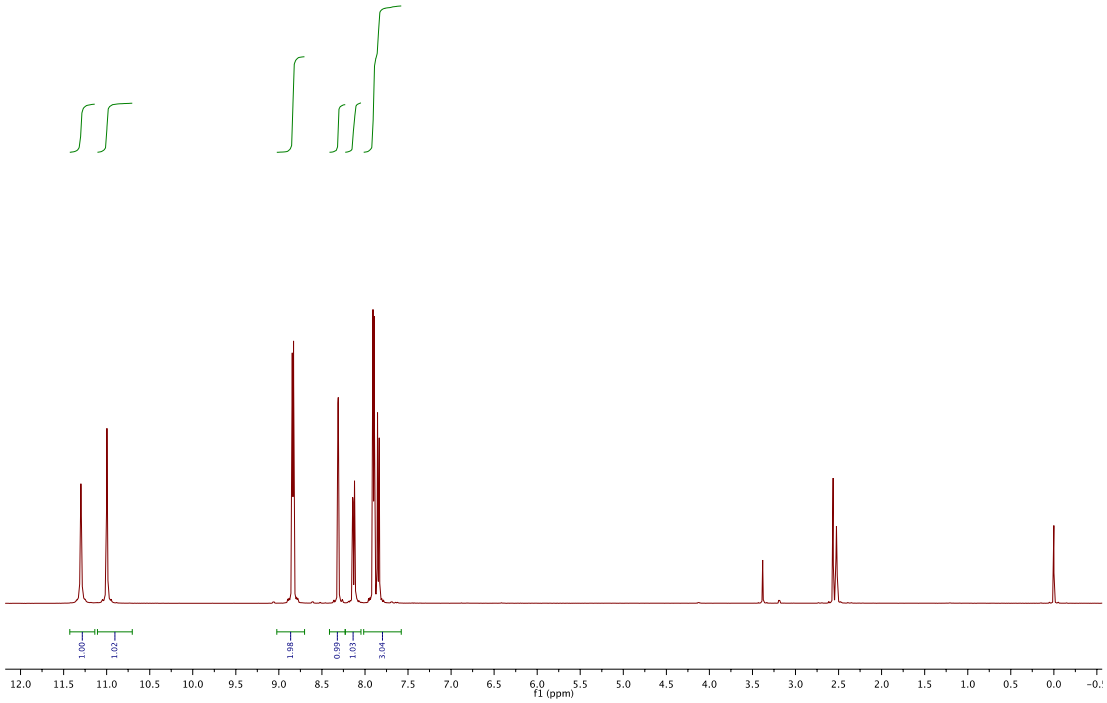


^{13}C NMR:

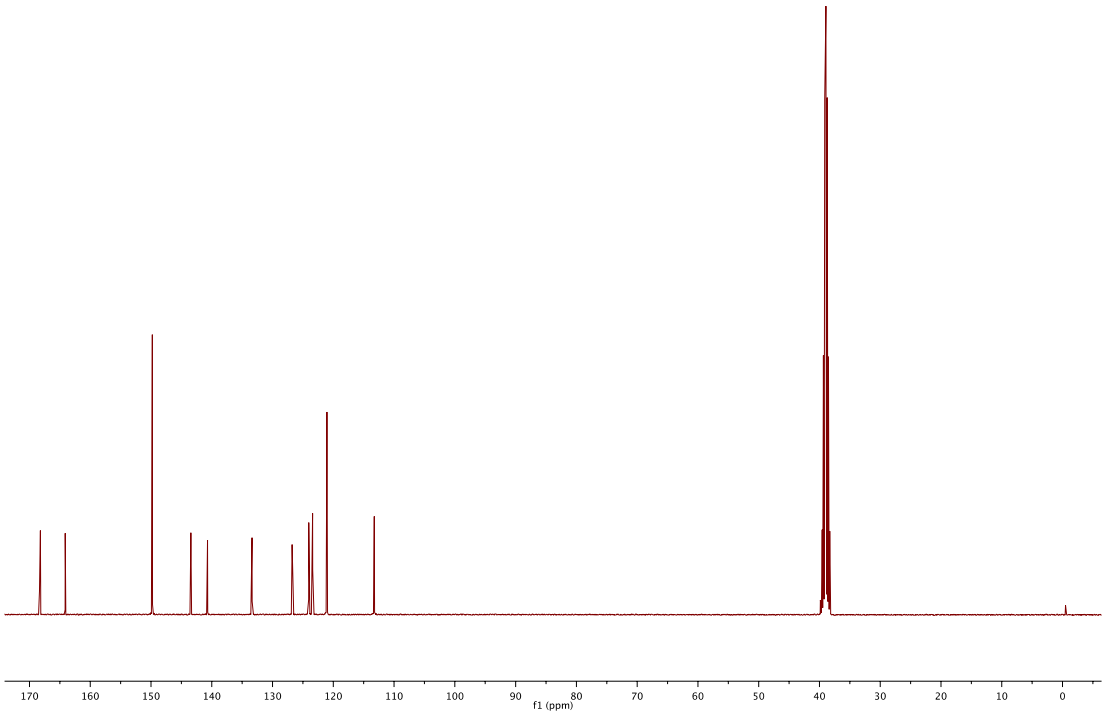


N-(1,3-Dioxoisoindolin-5-yl)isonicotinamide: BN-XII-070

^{1}H NMR:

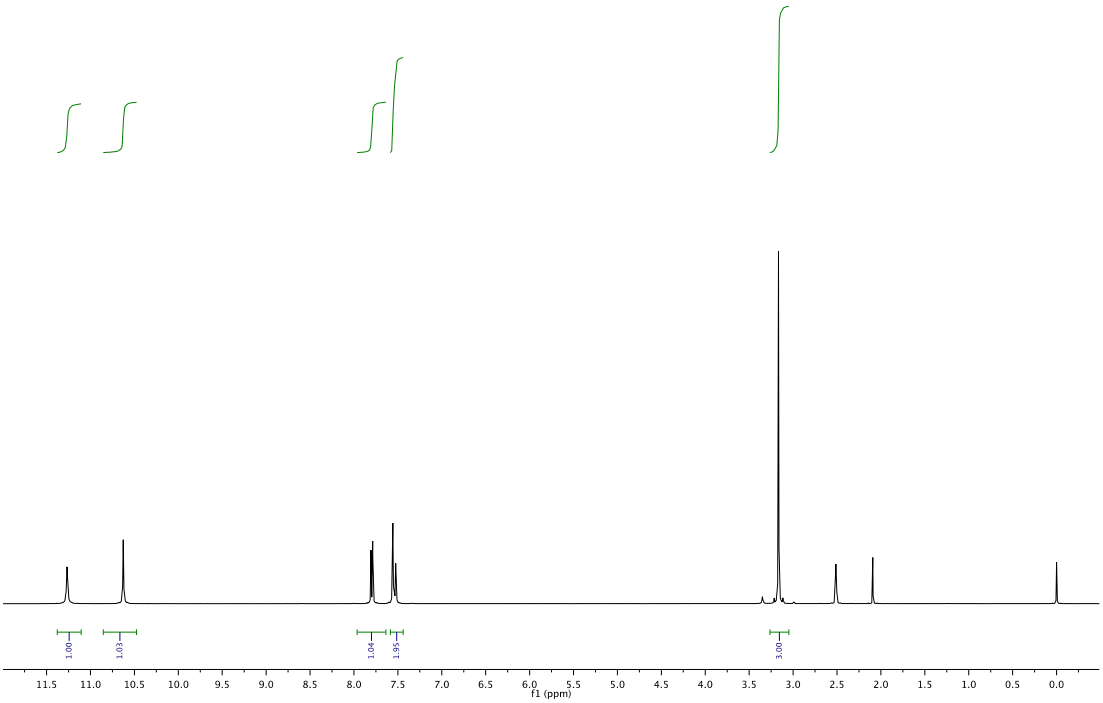


^{13}C NMR:

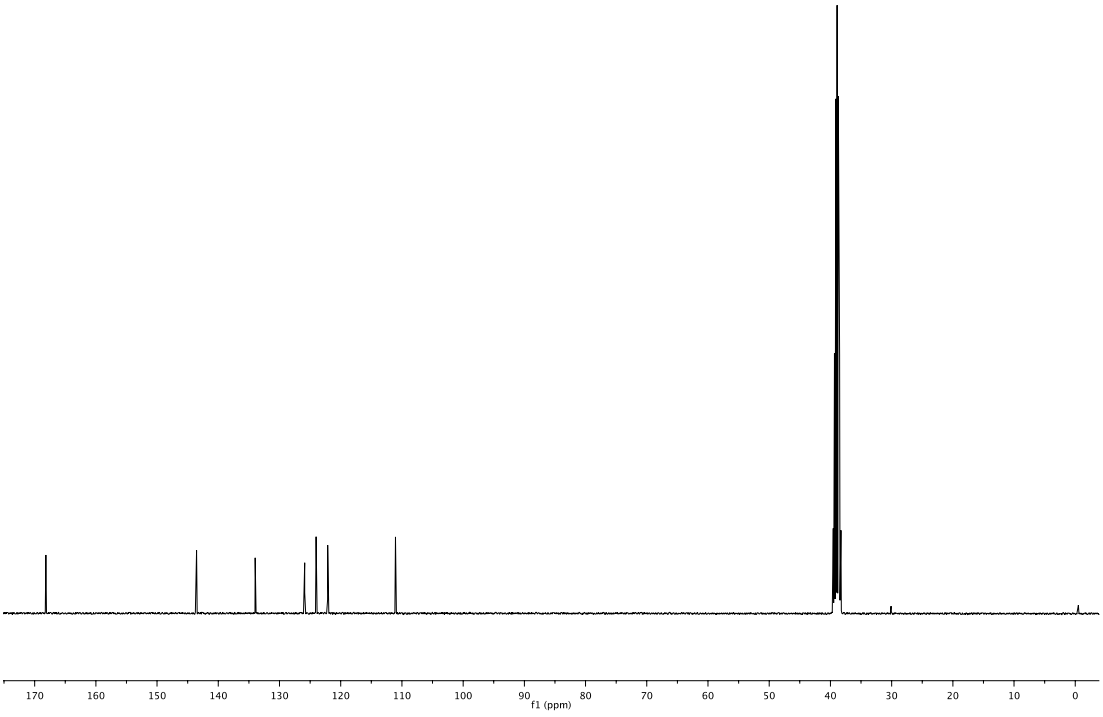


N-(1,3-Dioxoisoindolin-5-yl)methanesulfonamide: BN-XII-065

^{1}H NMR:

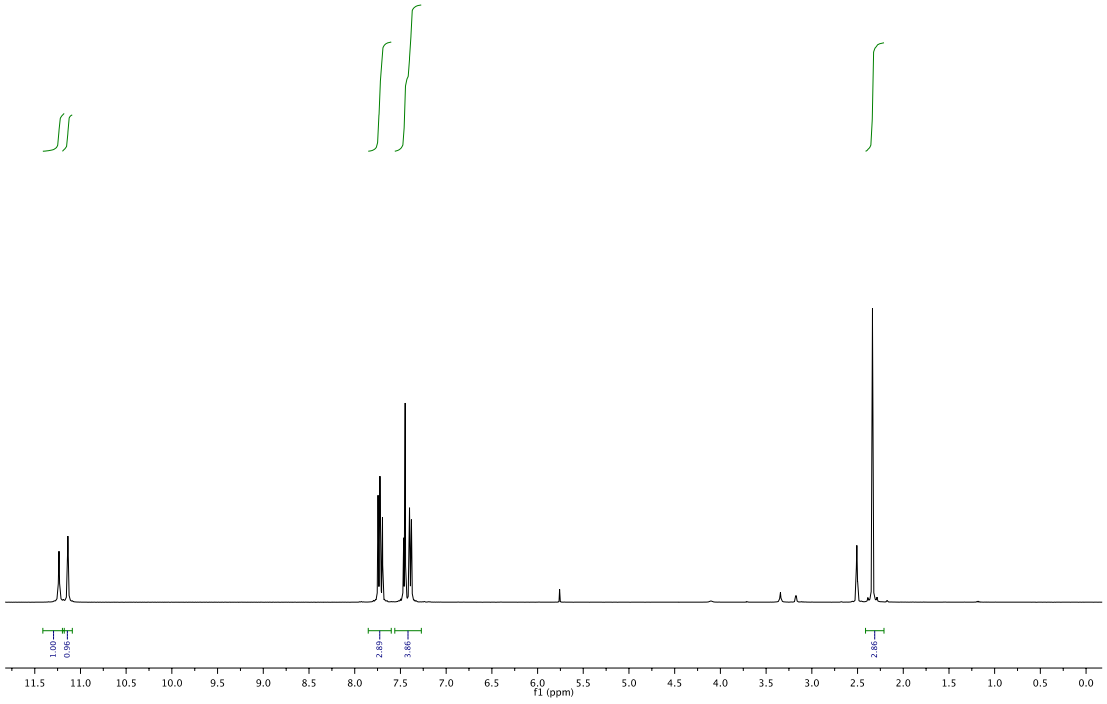


^{13}C NMR:

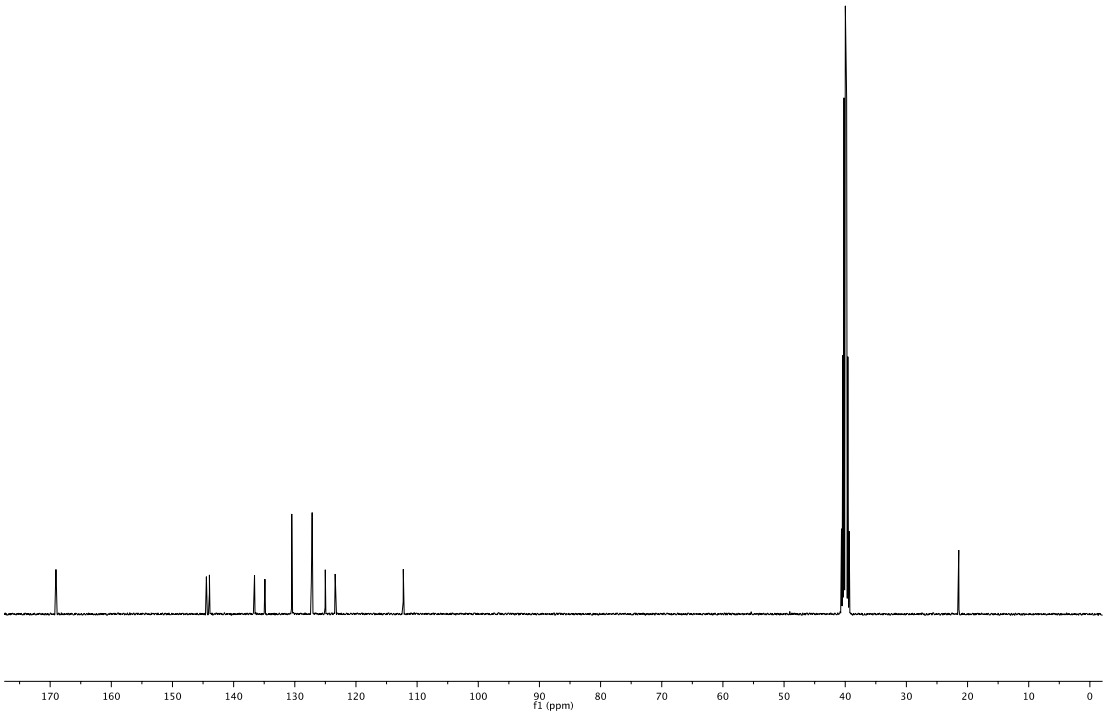


N-(1,3-Dioxoisoindolin-5-yl)-4-methylbenzenesulfonamide: BN-XII-062

^{1}H NMR:

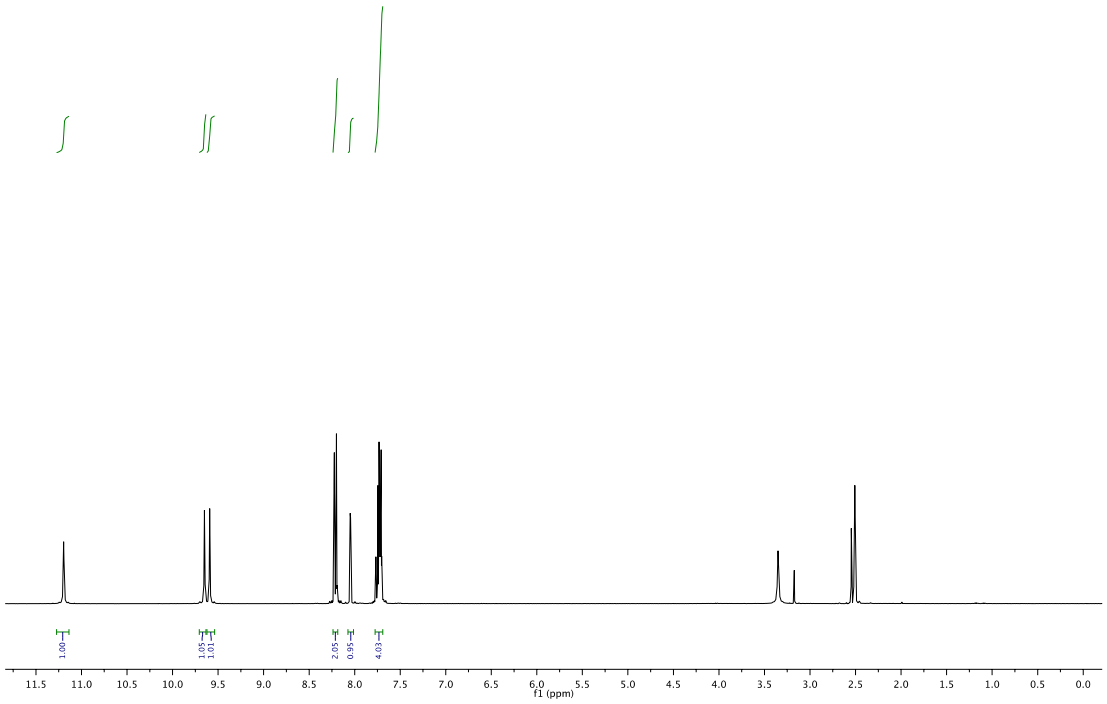


^{13}C NMR:

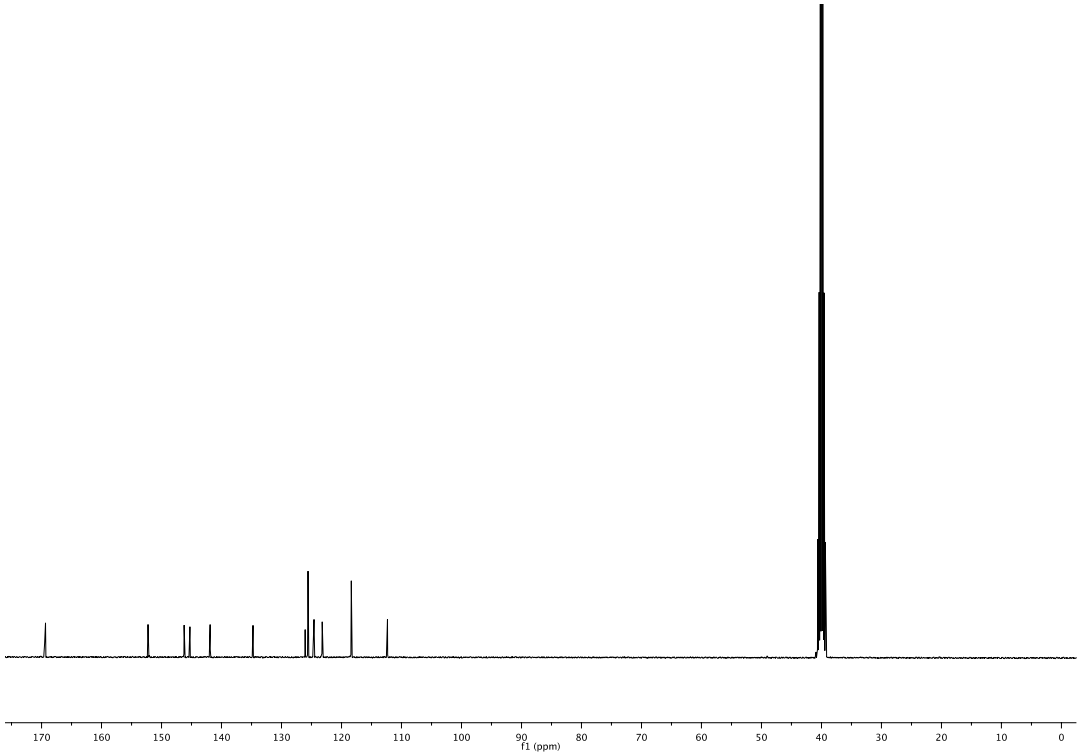


1-(1,3-Dioxoisoindolin-5-yl)-3-(4-nitrophenyl)urea: BN-XII-071

^{1}H NMR:

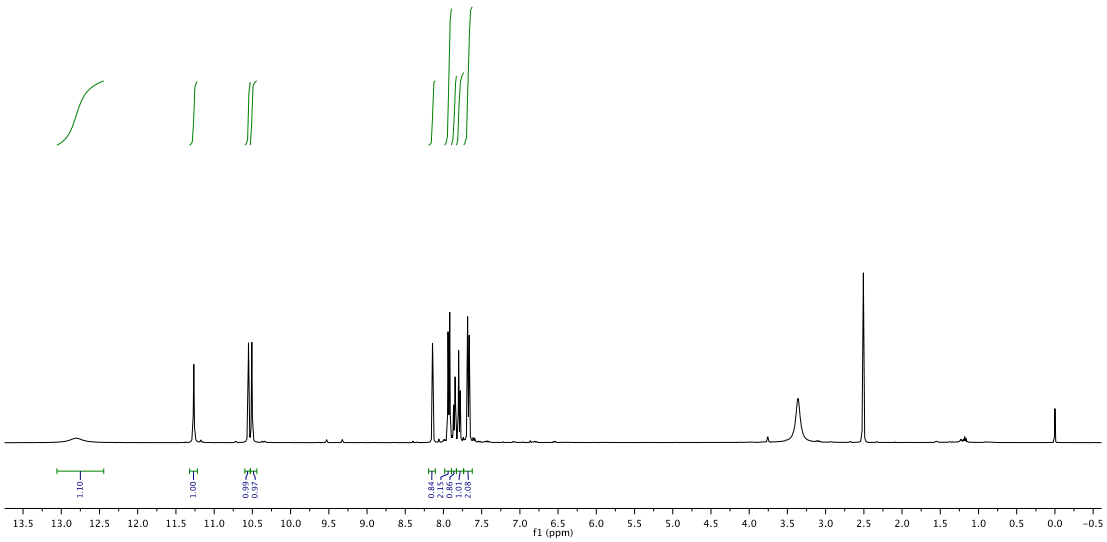


^{13}C NMR:

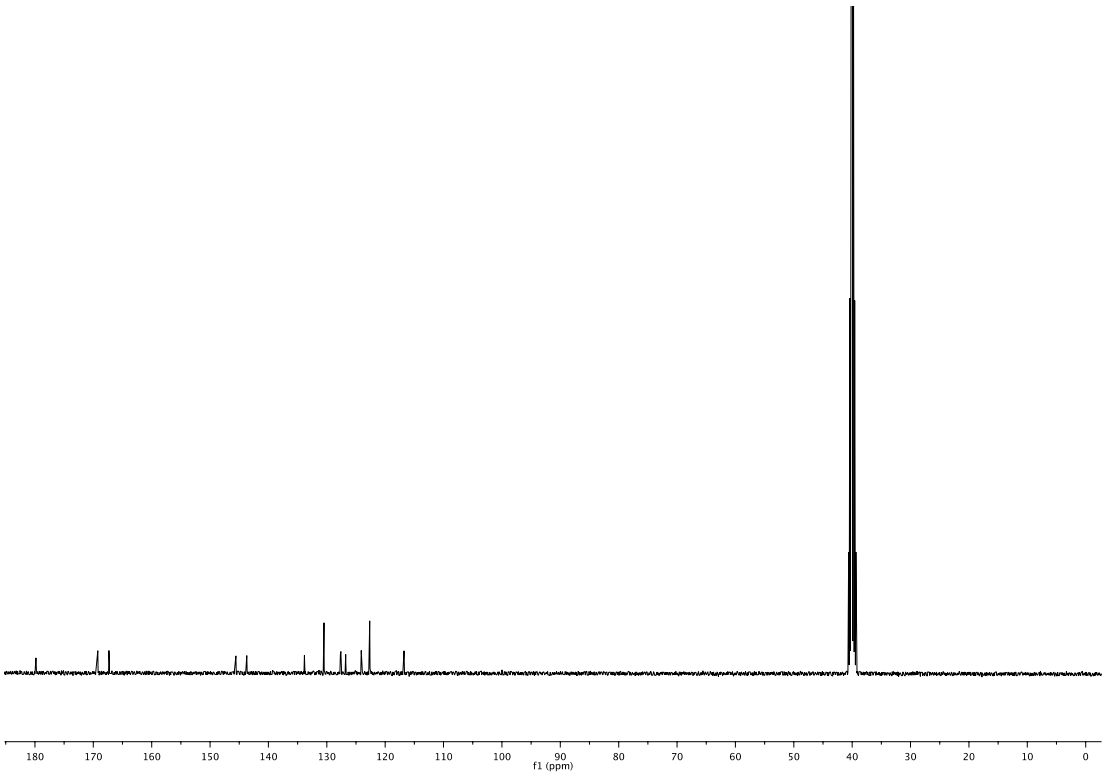


4-(3-(1,3-Dioxoisoindolin-5-yl)thioureido)benzoic acid: BN-XII-072

^{1}H NMR:



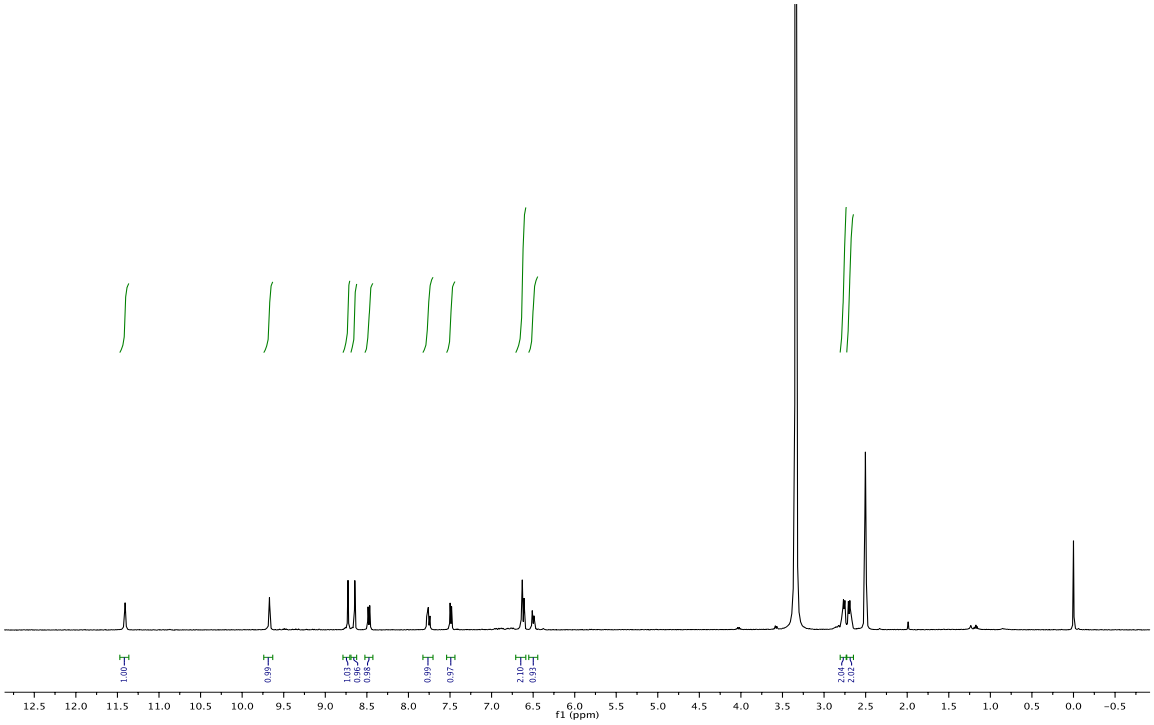
^{13}C NMR:



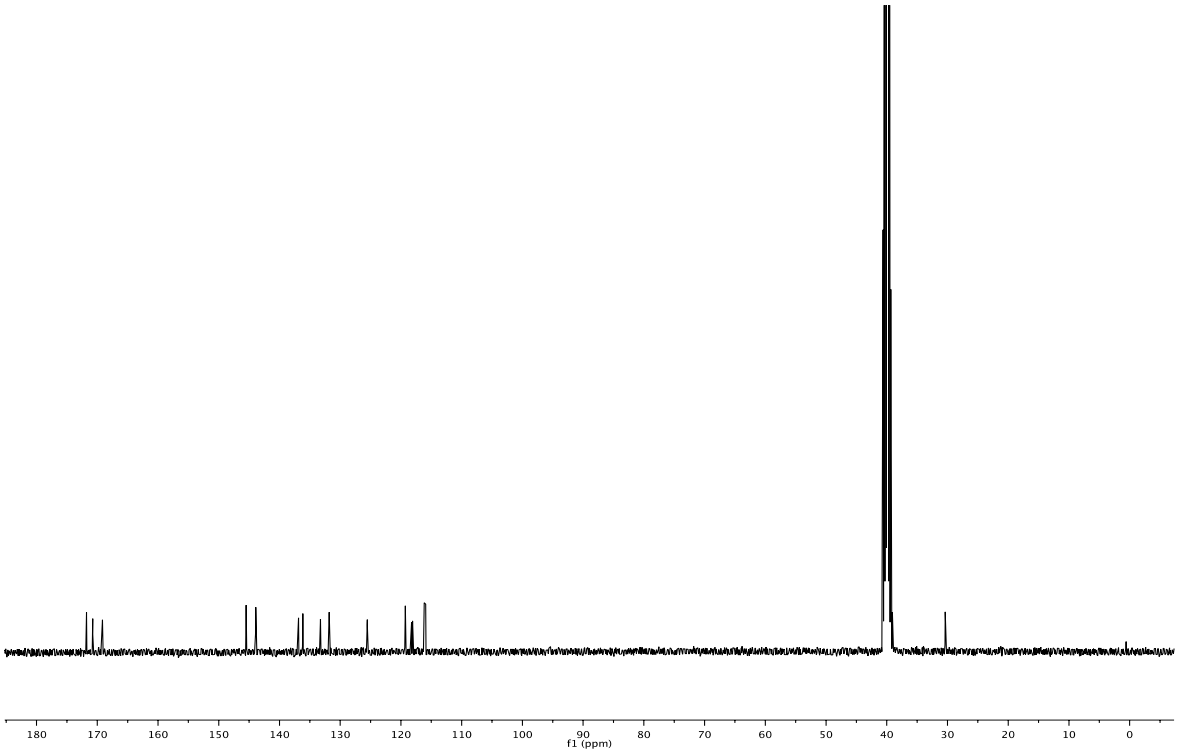
^{1}H and ^{13}C spectra for 4-amidoisoindoline-1,3-dione series

3-(3,4-Dihydroxyphenyl)-*N*-(1,3-dioxoisoindolin-4-yl)propanamide: GKK-006-090

^{1}H NMR:

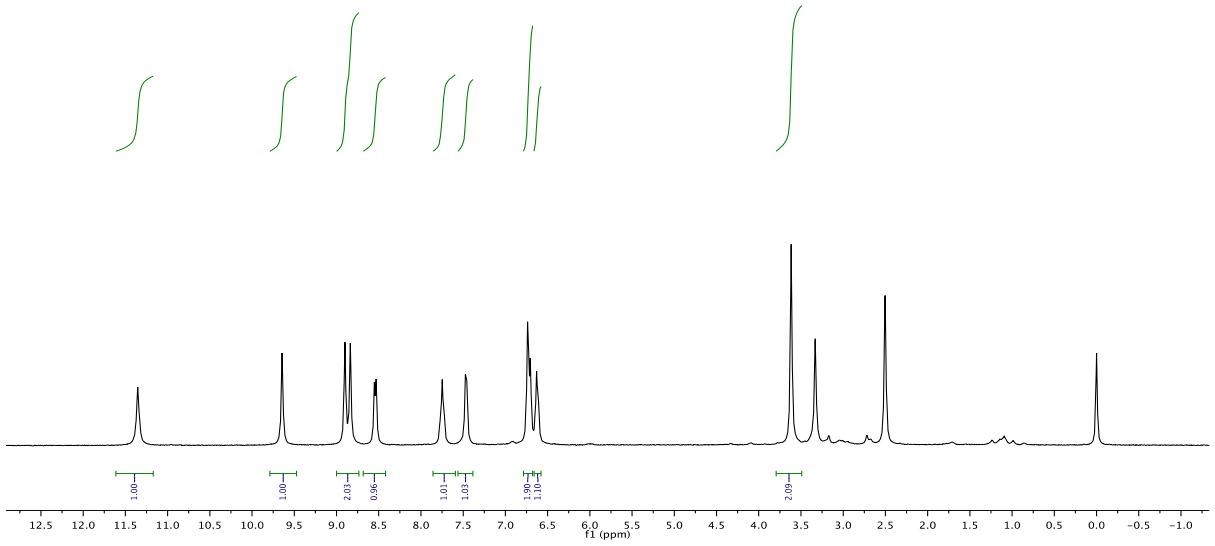


^{13}C NMR:

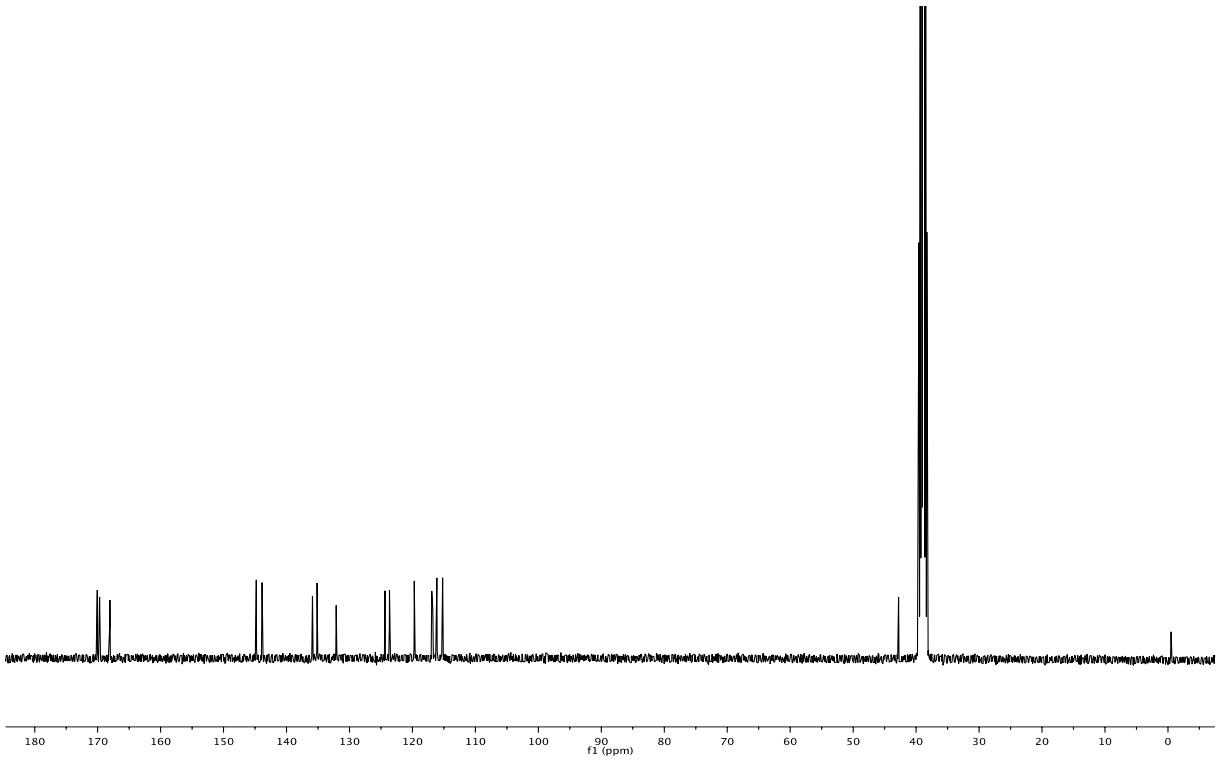


2-(3,4-Dihydroxyphenyl)-*N*-(1,3-dioxoisoindolin-4-yl)acetamide: GKK-006-082

^{1}H NMR:

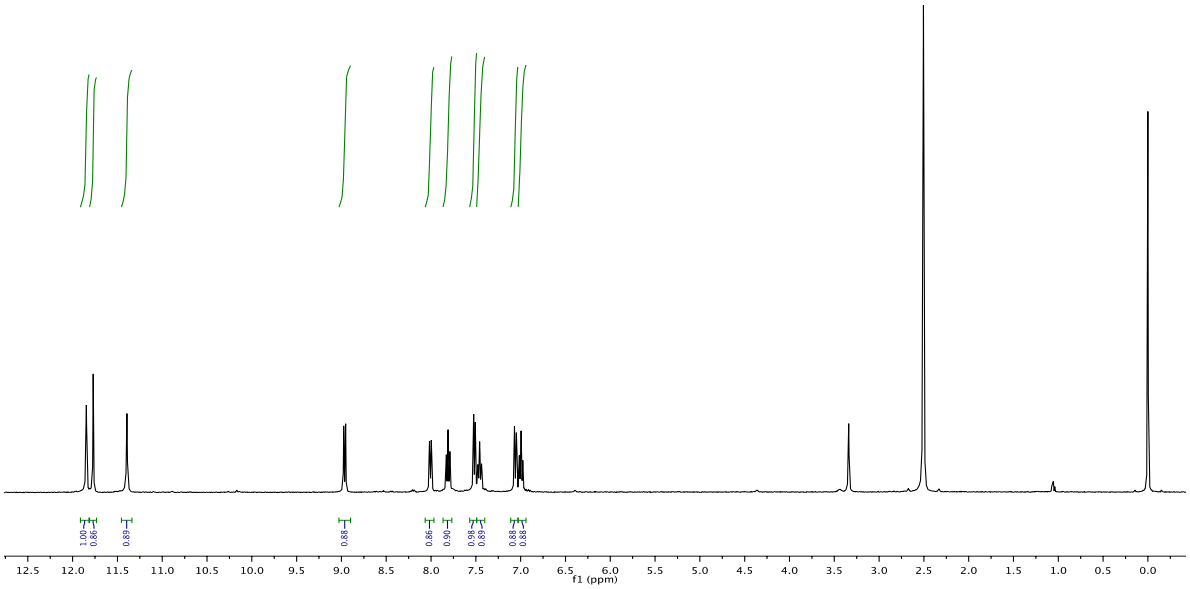


^{13}C NMR:

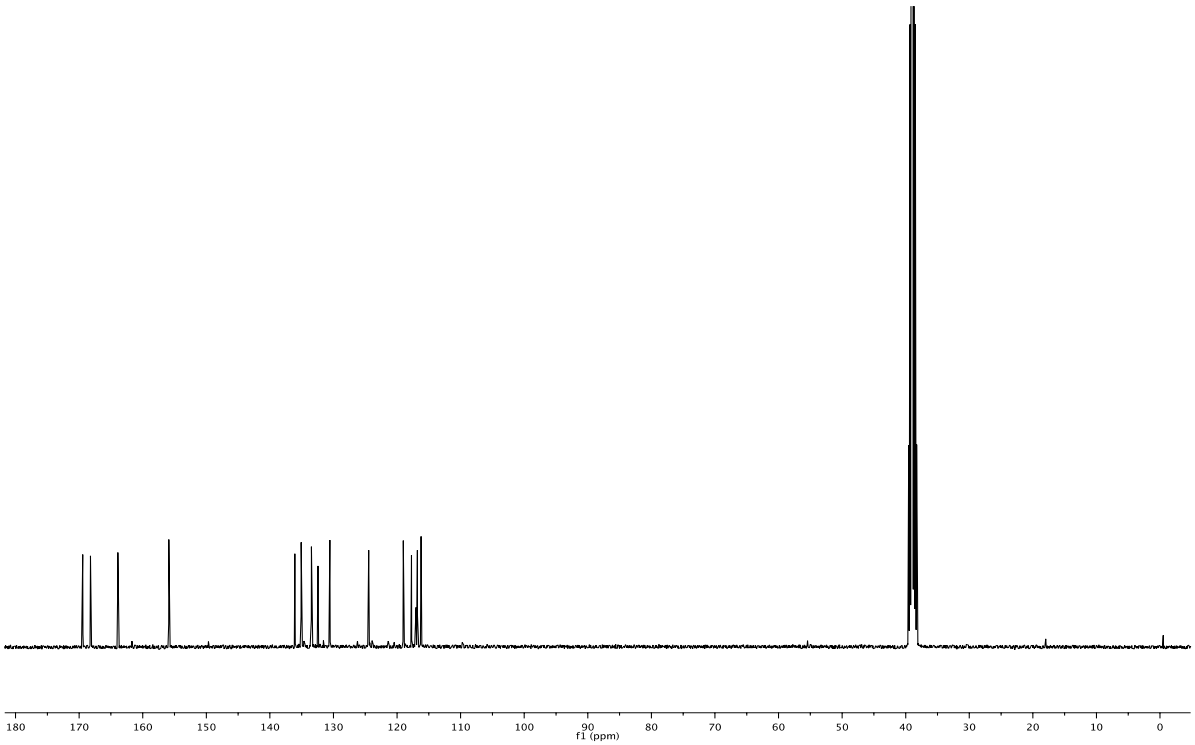


N-(1,3-Dioxoisoindolin-4-yl)-2-hydroxybenzamide: GKK-010-075

^{1}H NMR:

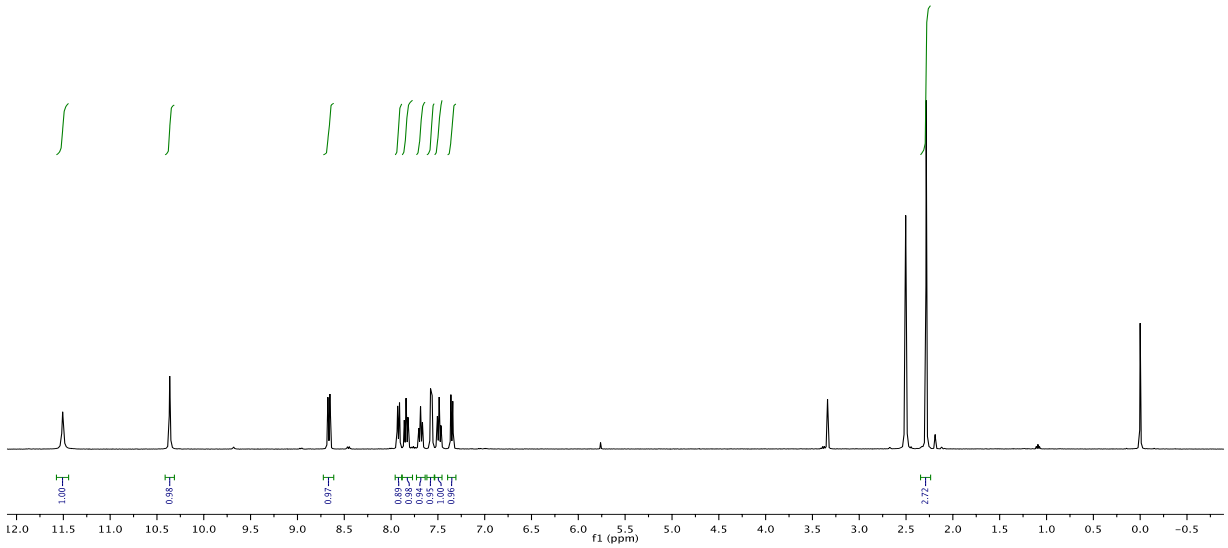


^{13}C NMR:

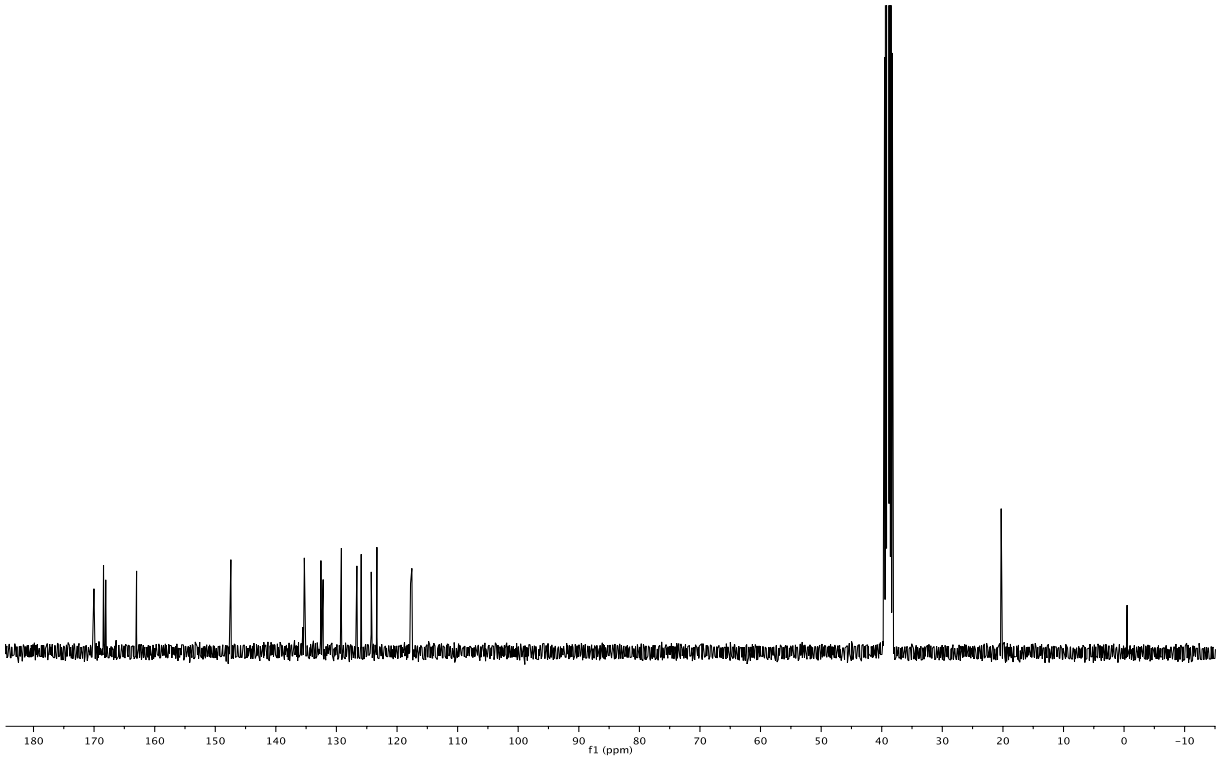


N-(1,3-Dioxoisoindolin-4-yl)carbamoyl)phenyl acetate: GKK-010-070

^{1}H NMR:

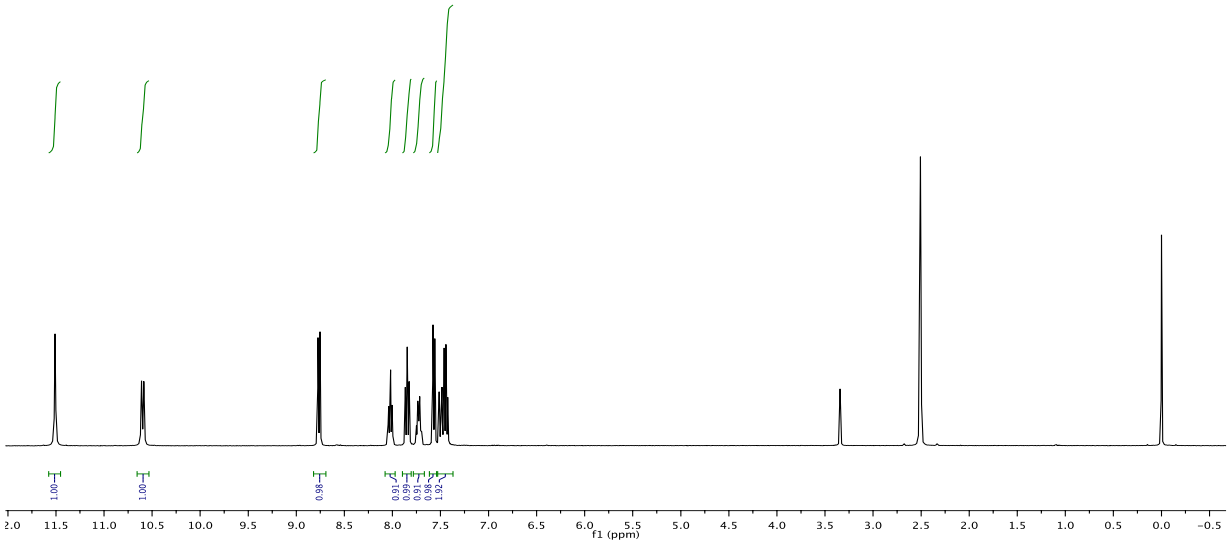


^{13}C NMR:

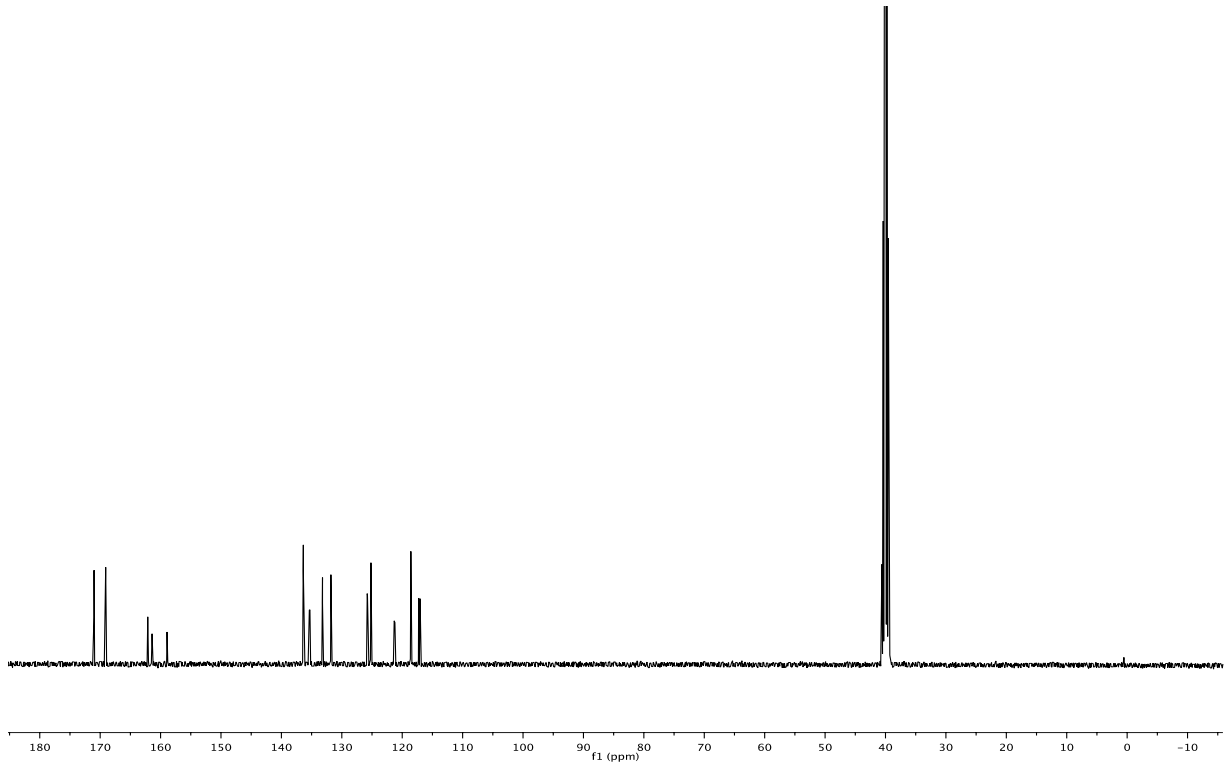


N-(1,3-Dioxoisoindolin-4-yl)-2-fluorobenzamide: GKK-010-069

^{1}H NMR:

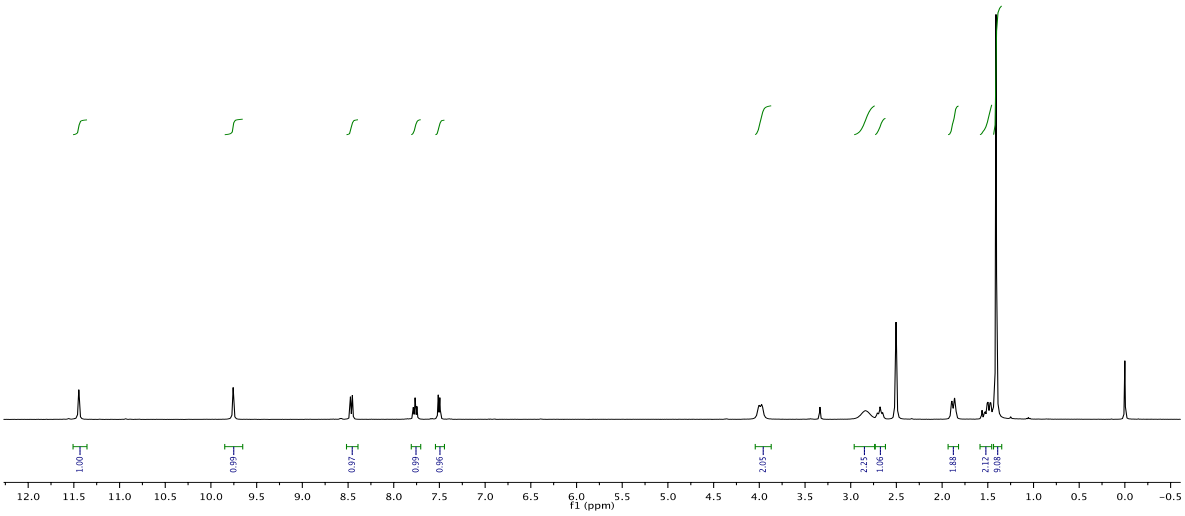


^{13}C NMR:

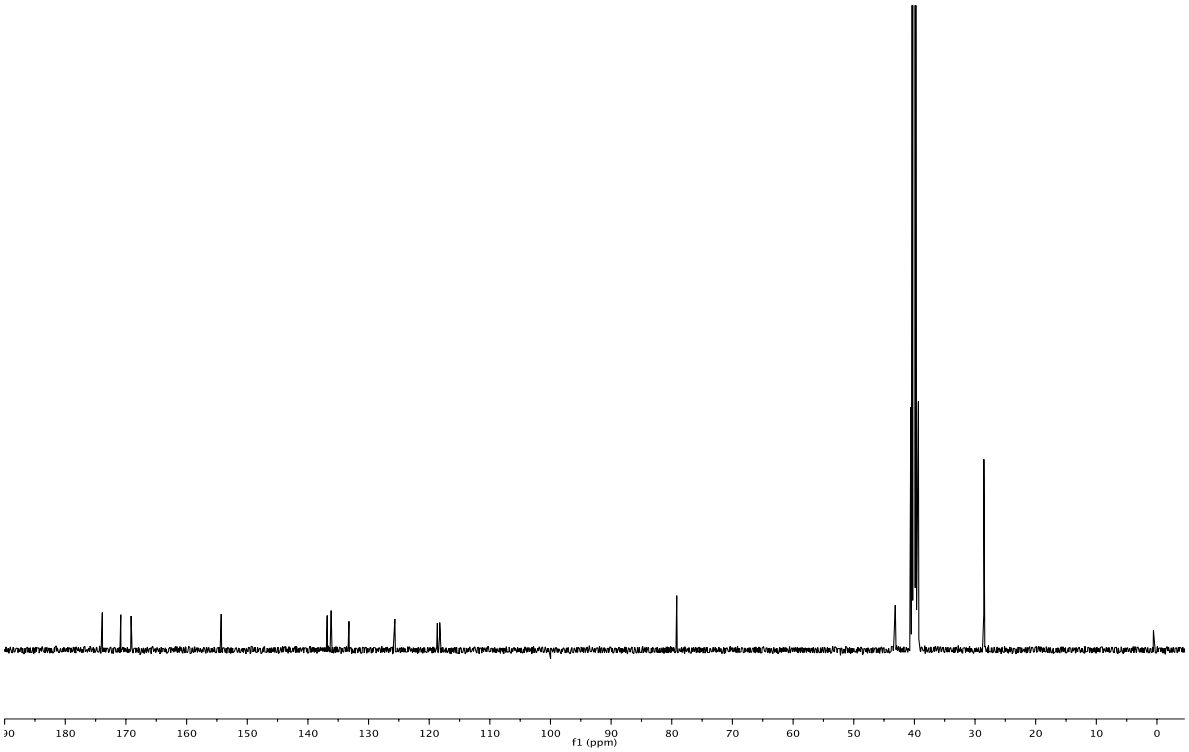


tert-Butyl 4-((1,3-dioxoindolin-4-yl)carbamoyl)piperidine-1-carboxylate: GKK-010-072

^{1}H NMR:

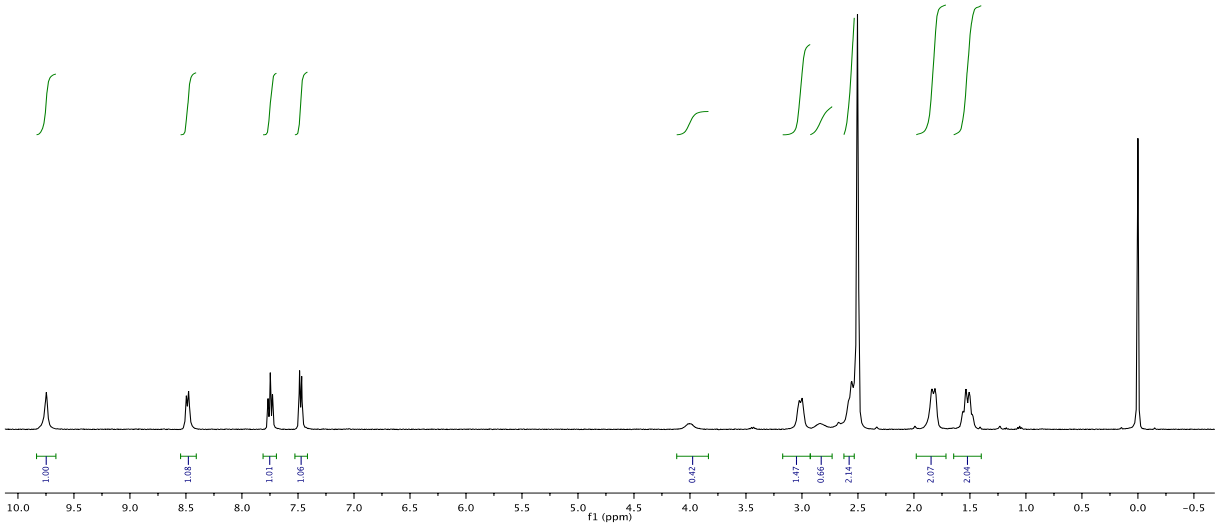


^{13}C NMR:

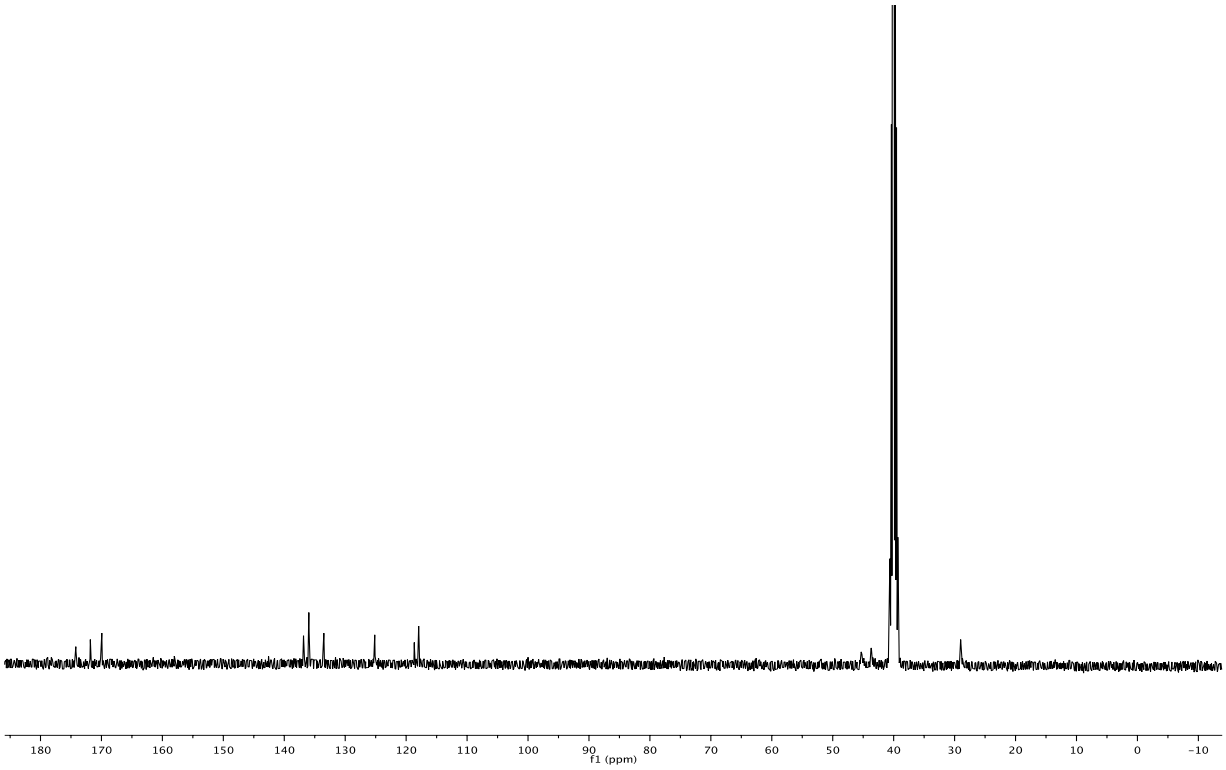


N-(1,3-Dioxoindolin-4-yl)piperidine-4-carboxamide: GKK-010-073

^{1}H NMR:



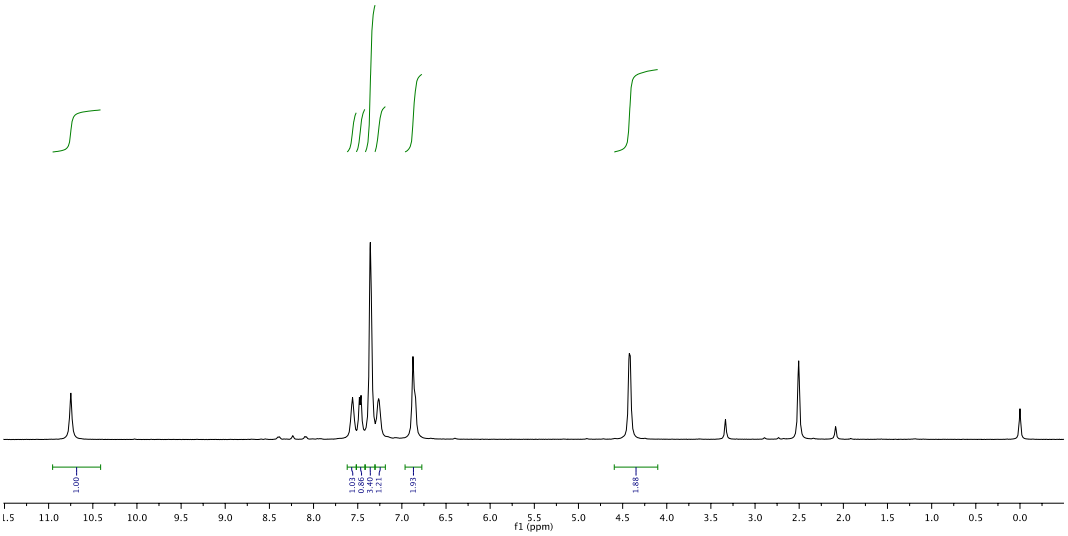
^{13}C NMR:



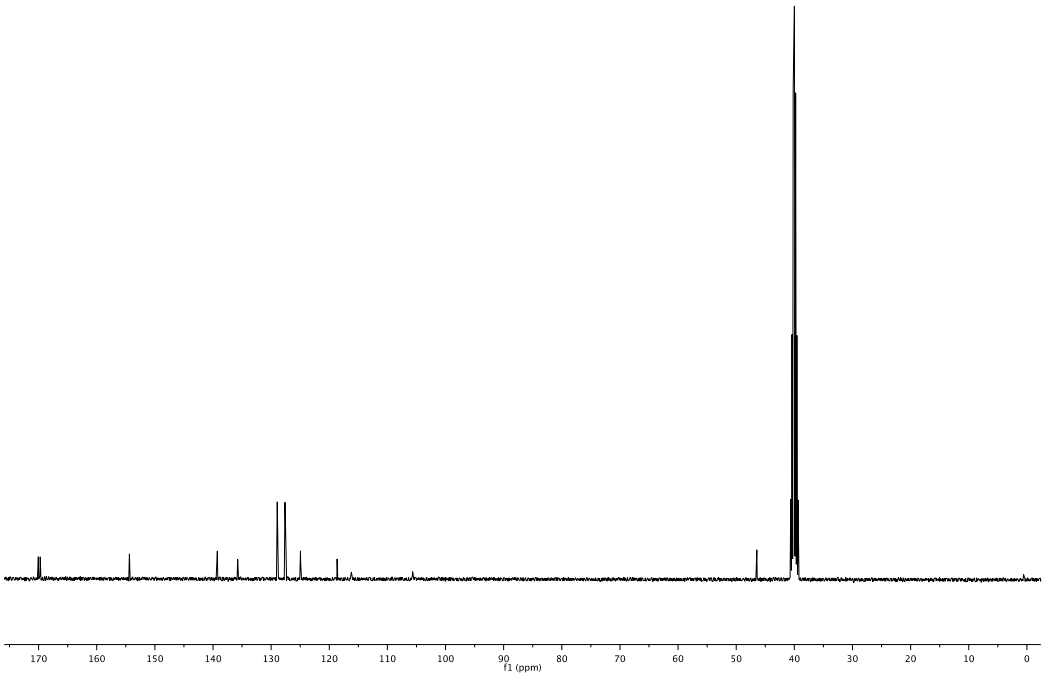
^{1}H and ^{13}C spectra for 5-aminoisoindoline-1,3-dione series

5-(Benzylamino)isoindoline-1,3-dione: BN-XIII-063

^{1}H NMR:

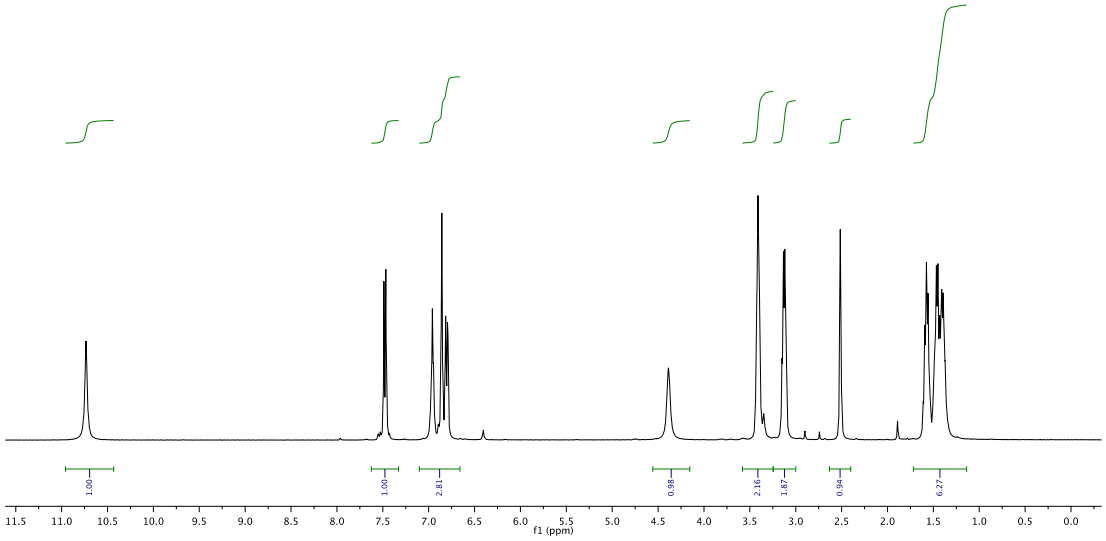


^{13}C NMR:

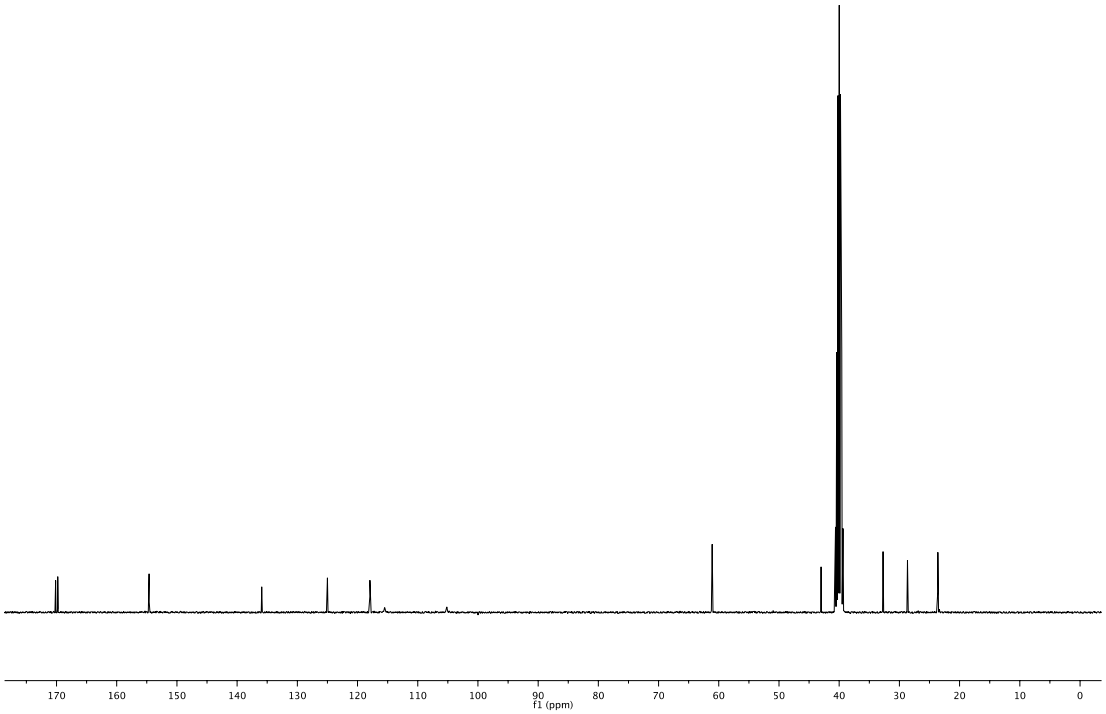


5-((5-Hydroxypentyl)amino)isoindoline-1,3-dione: BN-XIV-035

^{1}H NMR:

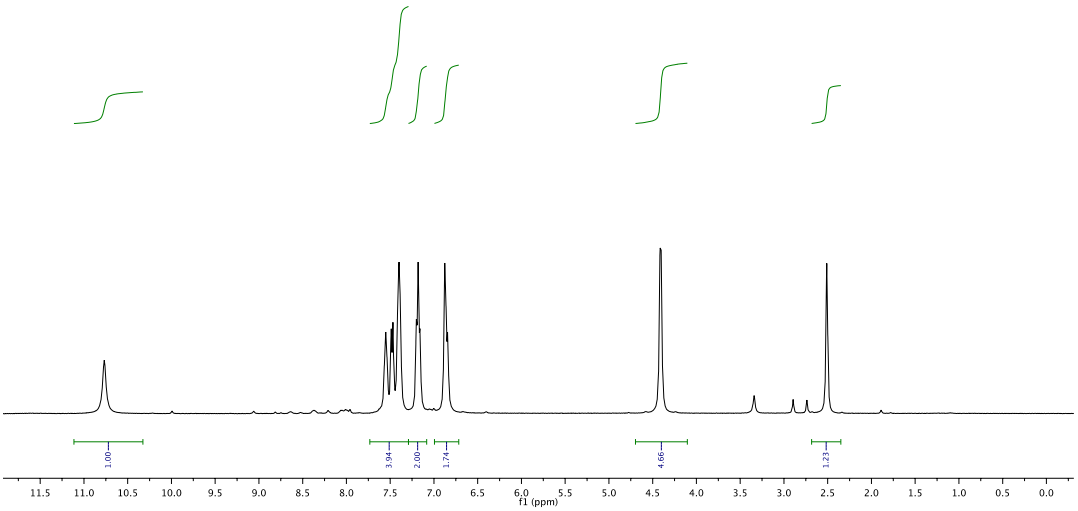


^{13}C NMR:

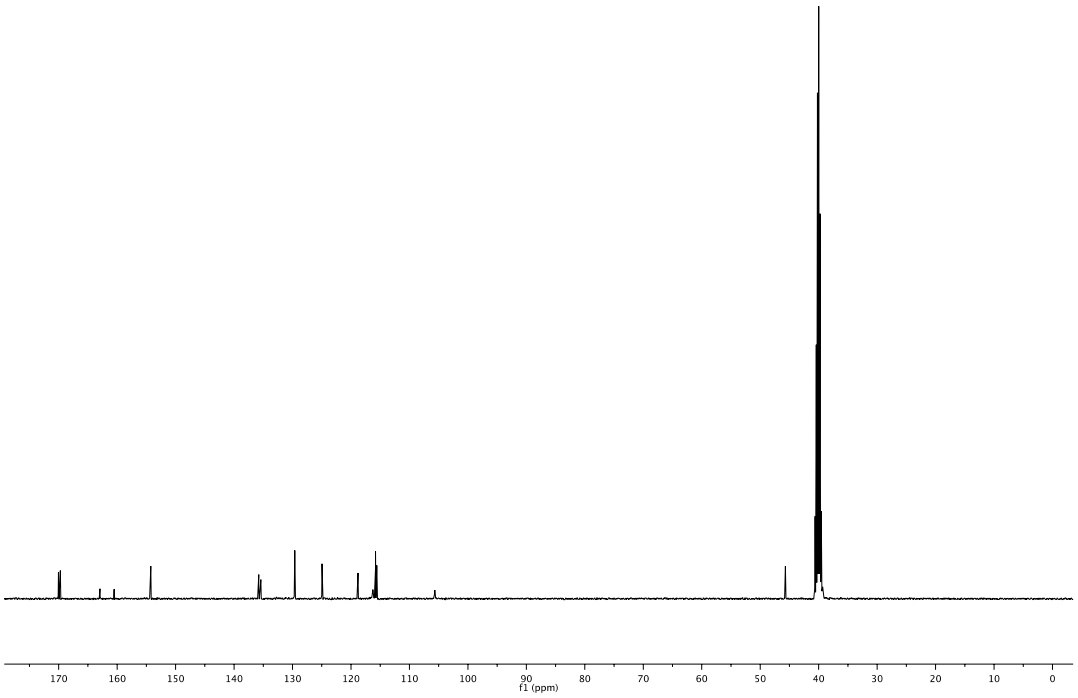


5-((4-Fluorobenzyl)amino)isoindoline-1,3-dione: BN-XIII-069

^{1}H NMR:

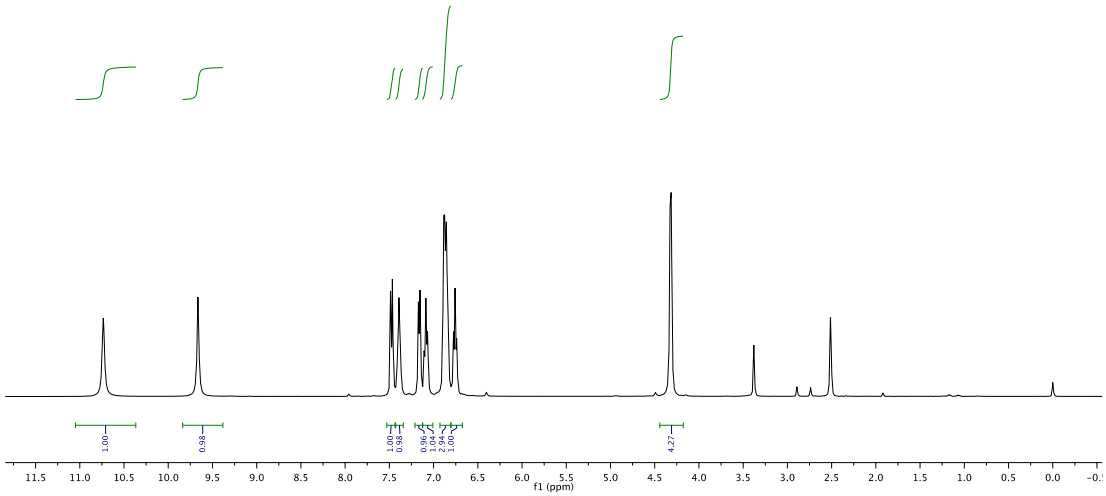


^{13}C NMR:

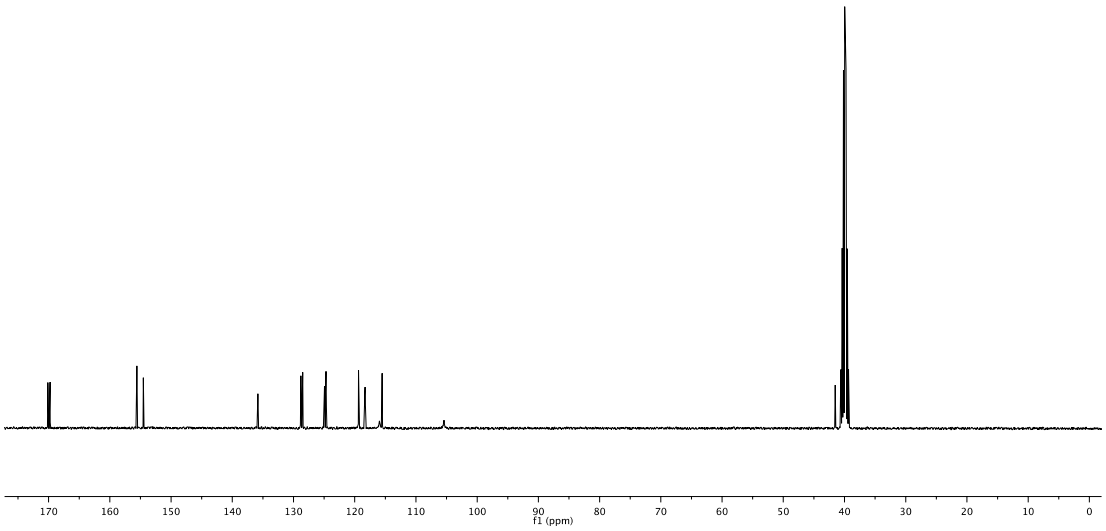


5-((2-Hydroxybenzyl)amino)isoindoline-1,3-dione: BN-XIII-093

^{1}H NMR:

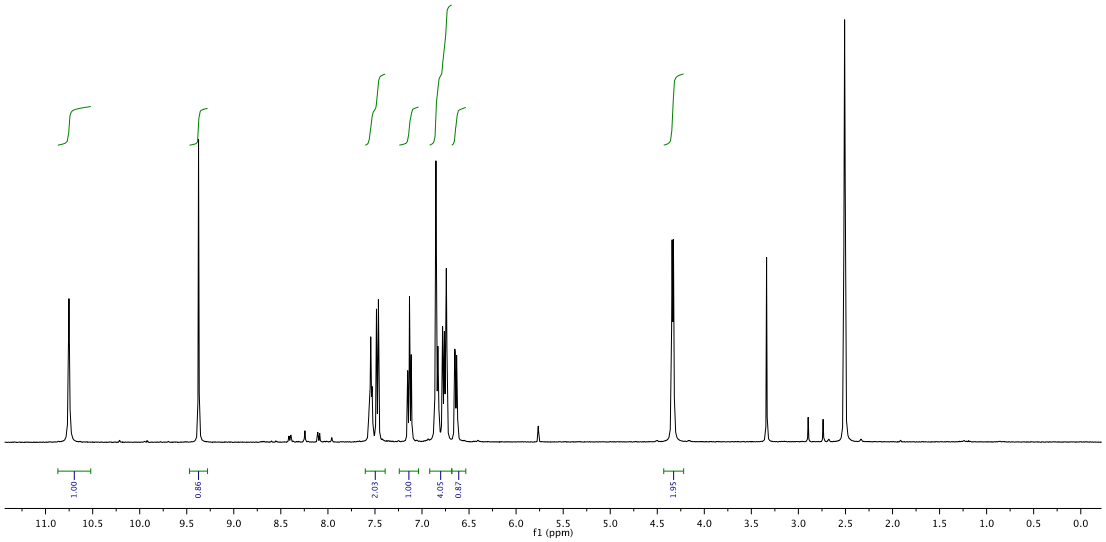


^{13}C NMR:

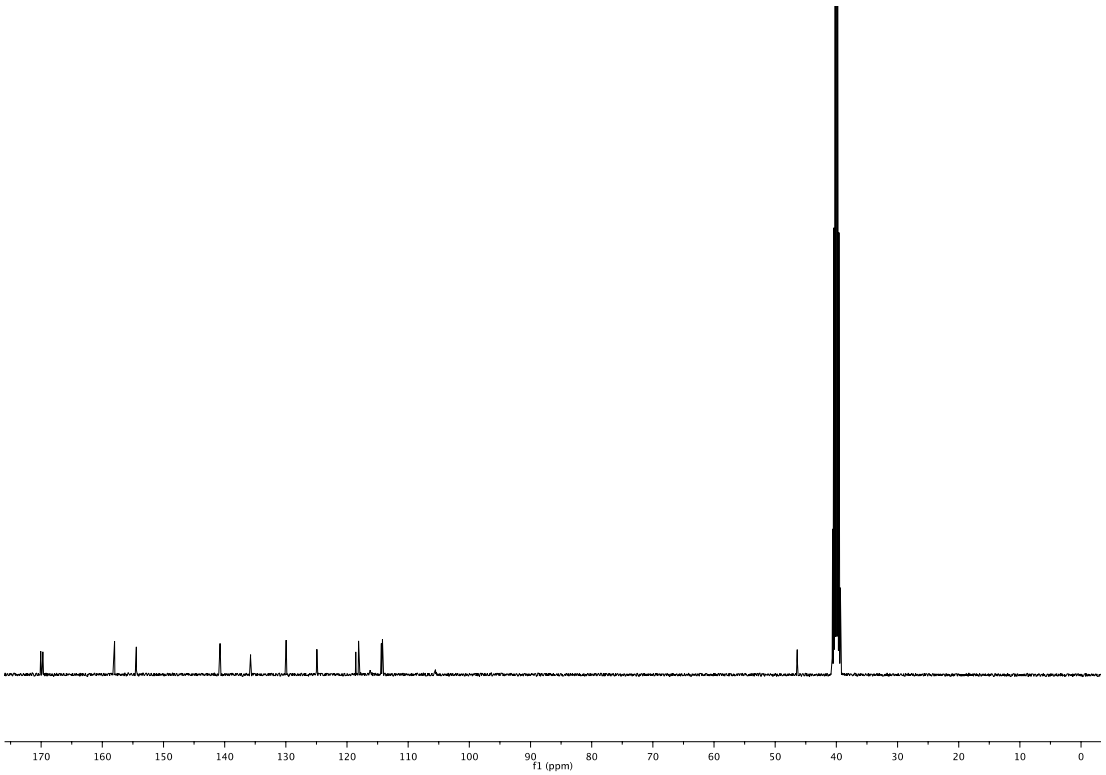


5-((3-Hydroxybenzyl)amino)isoindoline-1,3-dione: BN-XIII-092

^{1}H NMR:

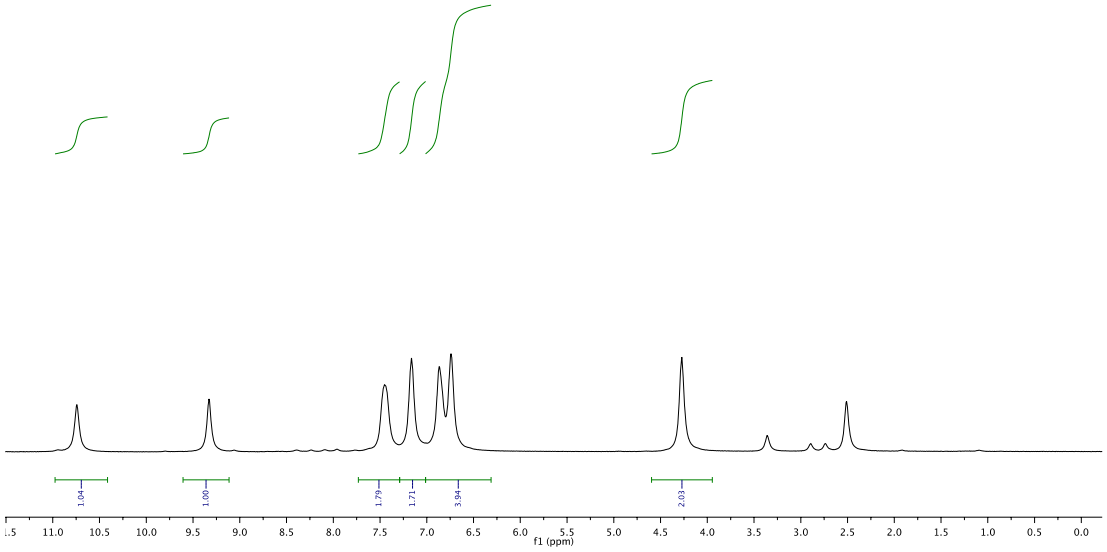


^{13}C NMR:

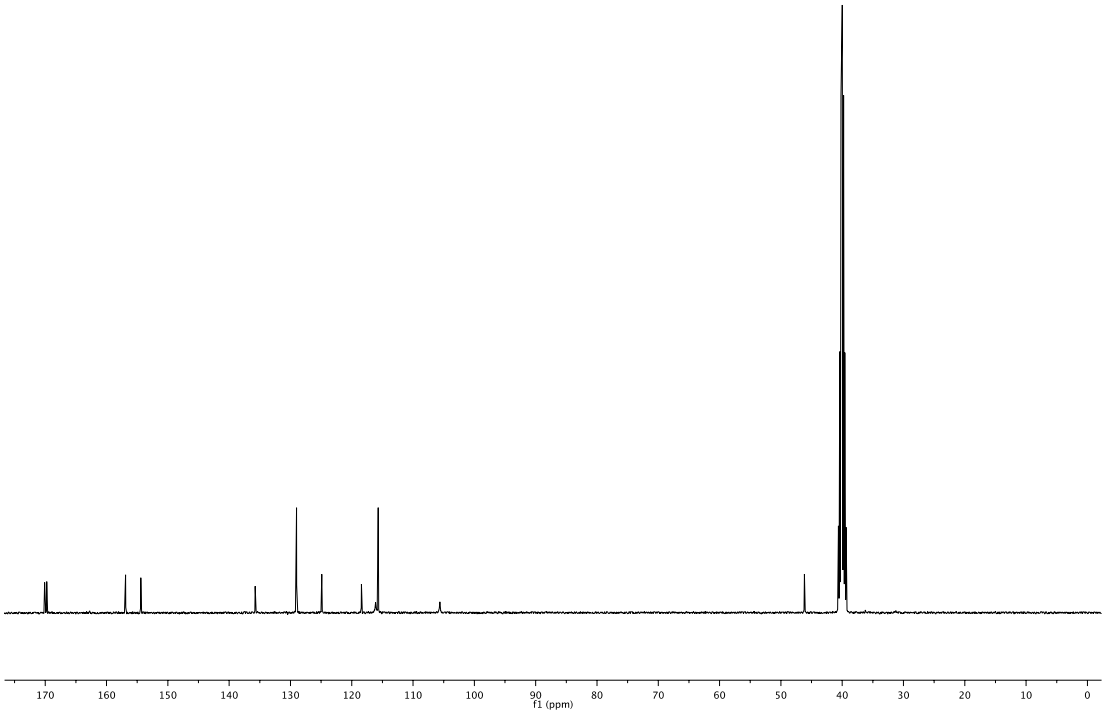


5-((4-Hydroxybenzyl)amino)isoindoline-1,3-dione: BN-XIII-068

^{1}H NMR:

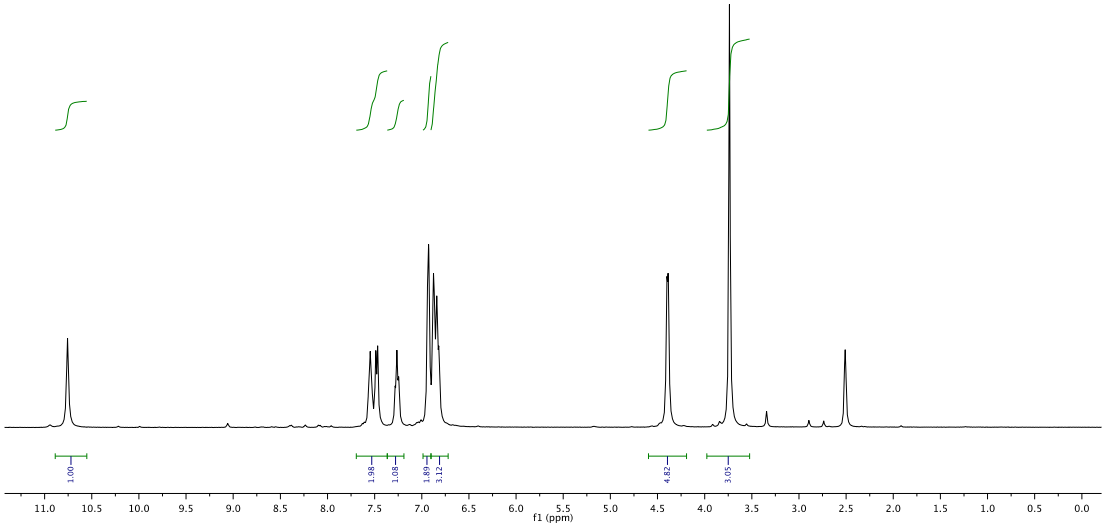


^{13}C NMR:

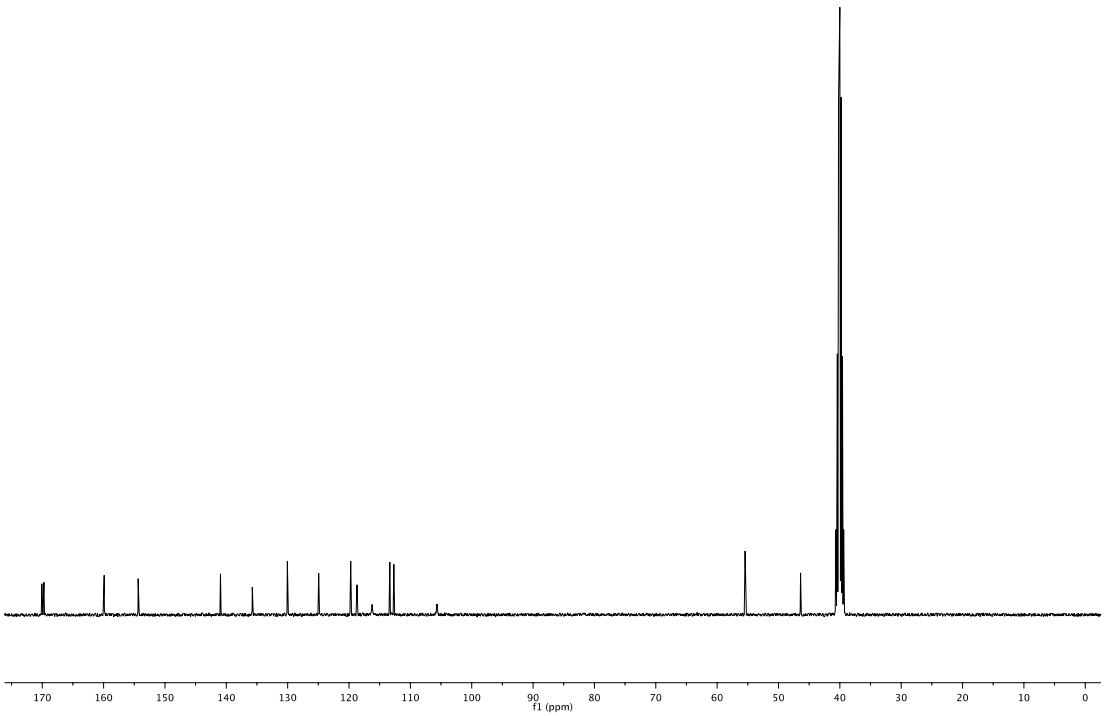


5-((3-Methoxybenzyl)amino)isoindoline-1,3-dione: BN-XIII-070

^{1}H NMR:

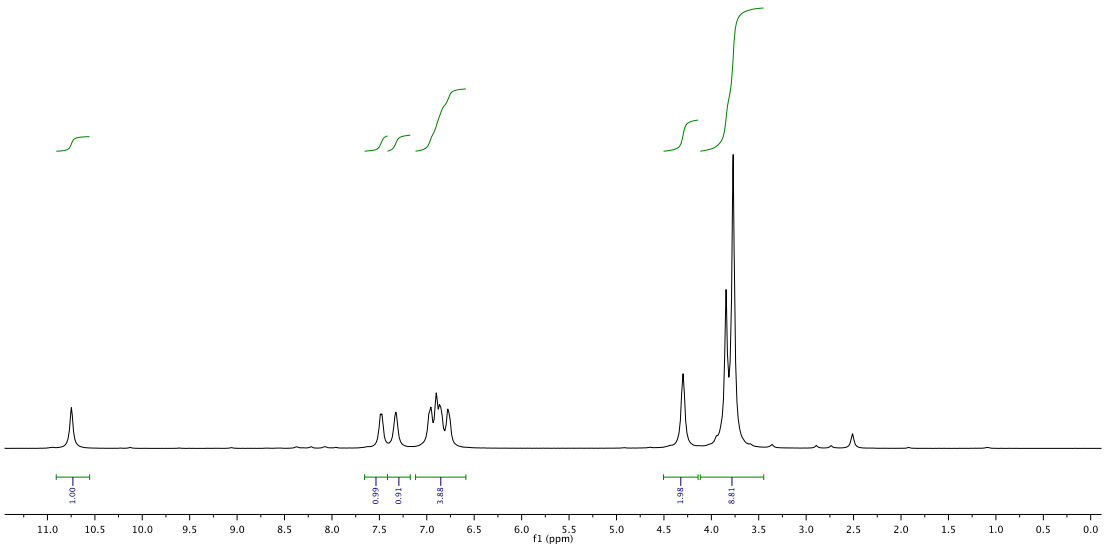


^{13}C NMR:

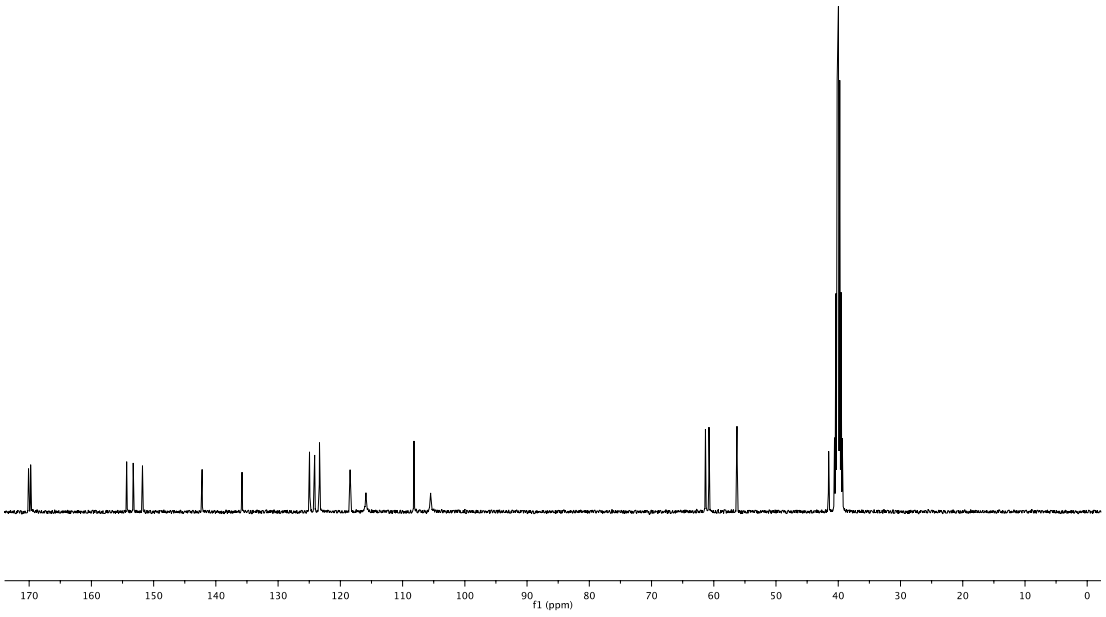


5-((2,3,4-Trimethoxybenzyl)amino)isoindoline-1,3-dione: BN-XIII-067

^{1}H NMR:

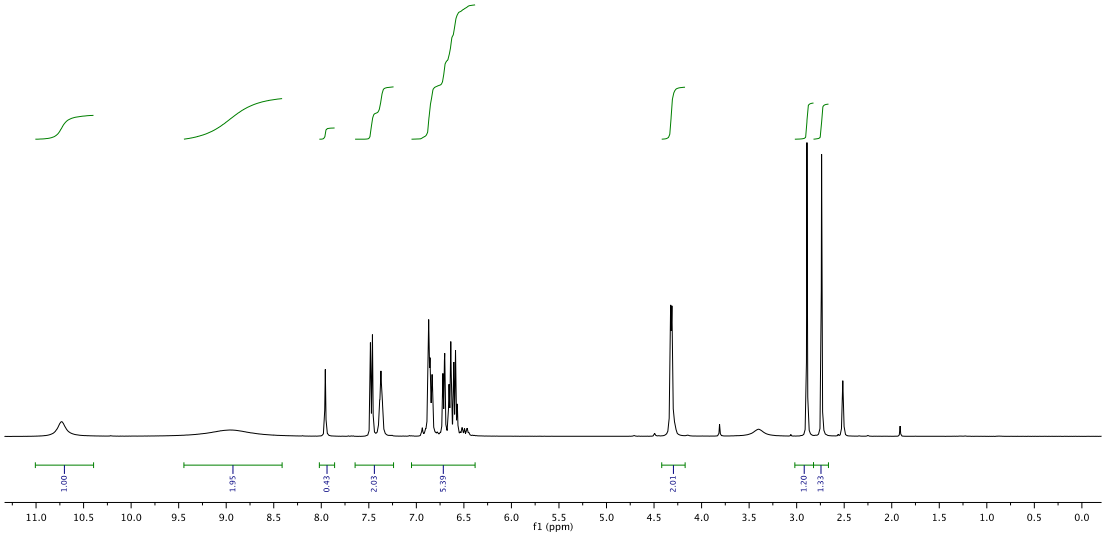


^{13}C NMR:

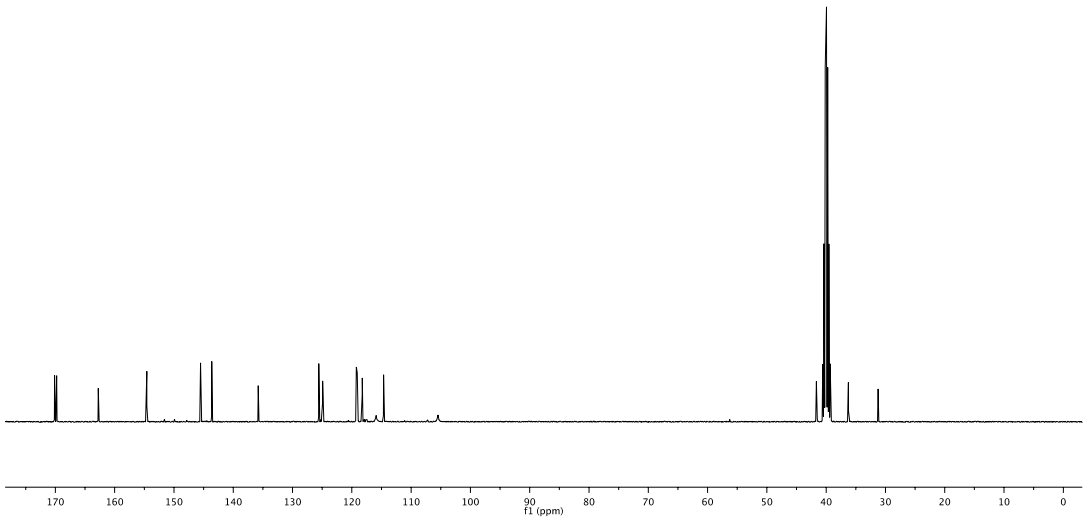


5-((2,3-Dihydroxybenzyl)amino)isoindoline-1,3-dione: BN-XIV-073

^{1}H NMR:

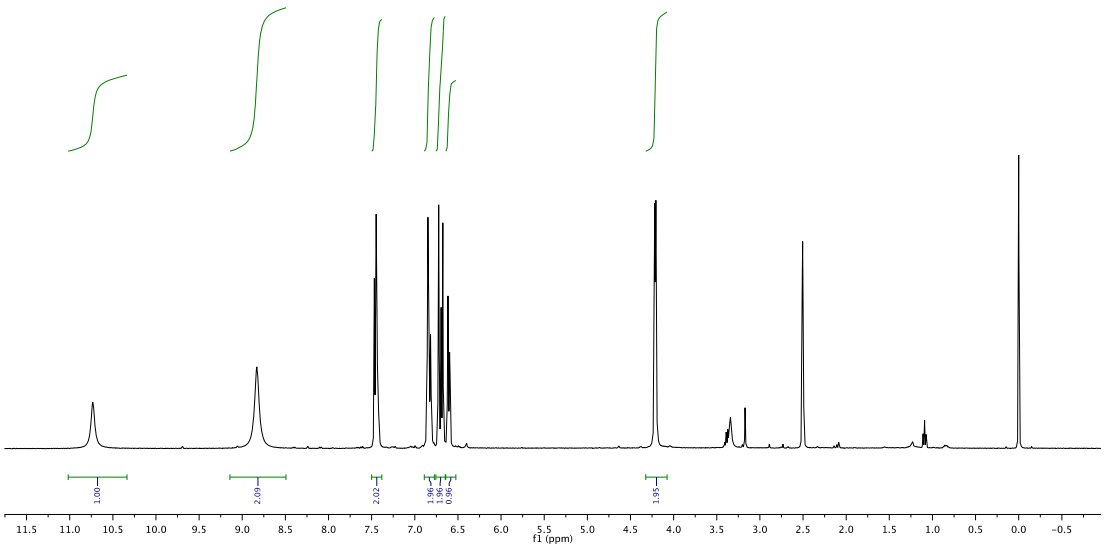


^{13}C NMR:

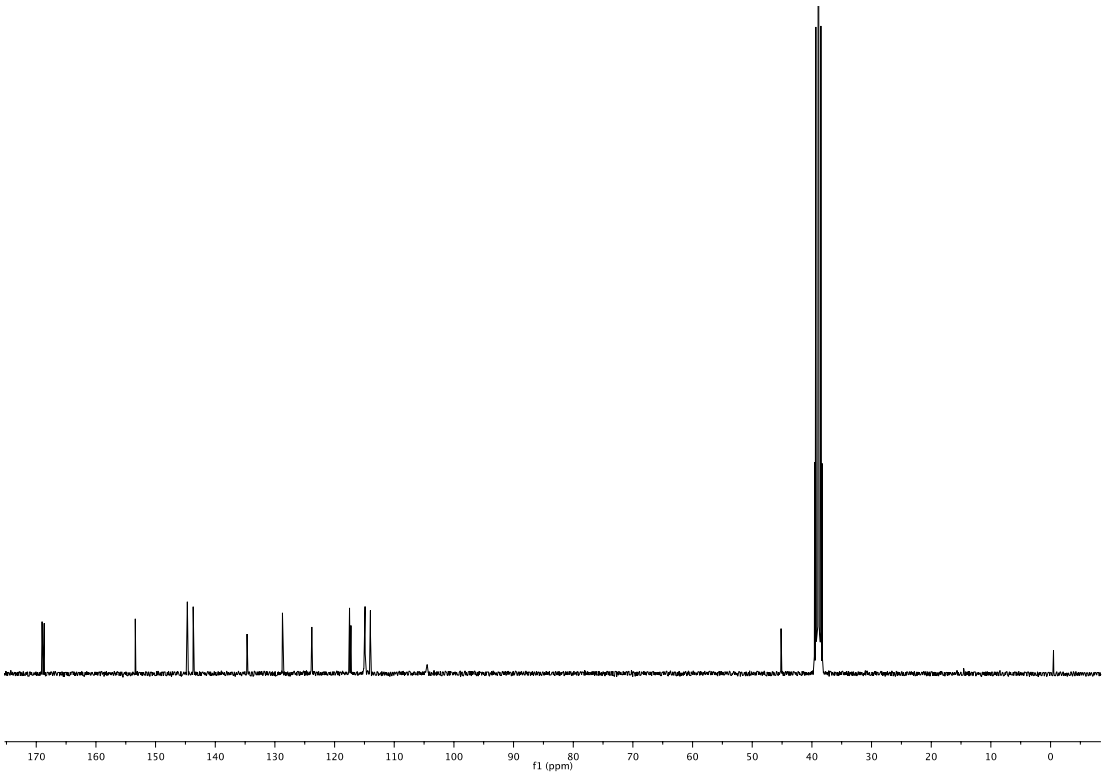


5-((3,4-Dihydroxybenzyl)amino)isoindoline-1,3-dione: BN-XIII-091

^{1}H NMR:

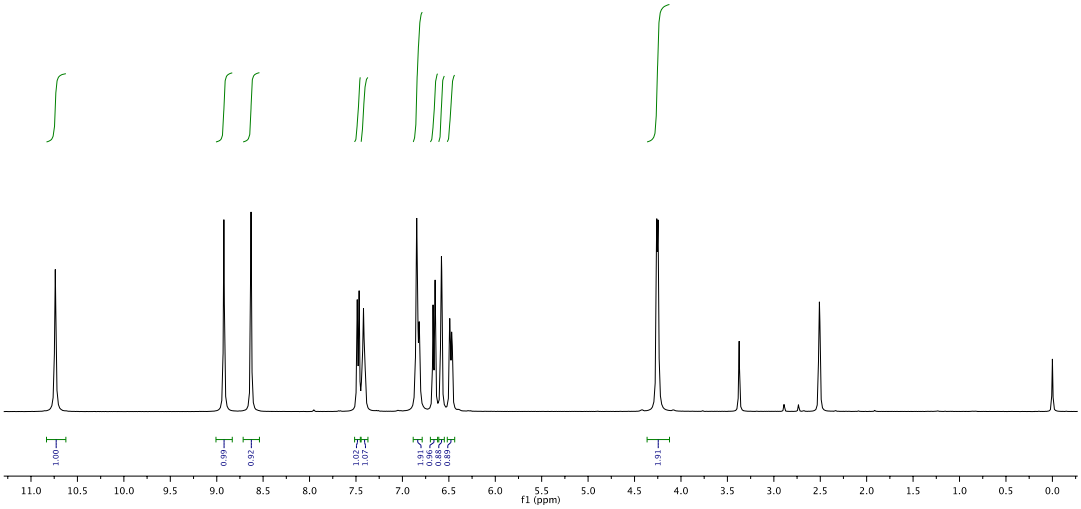


^{13}C NMR:

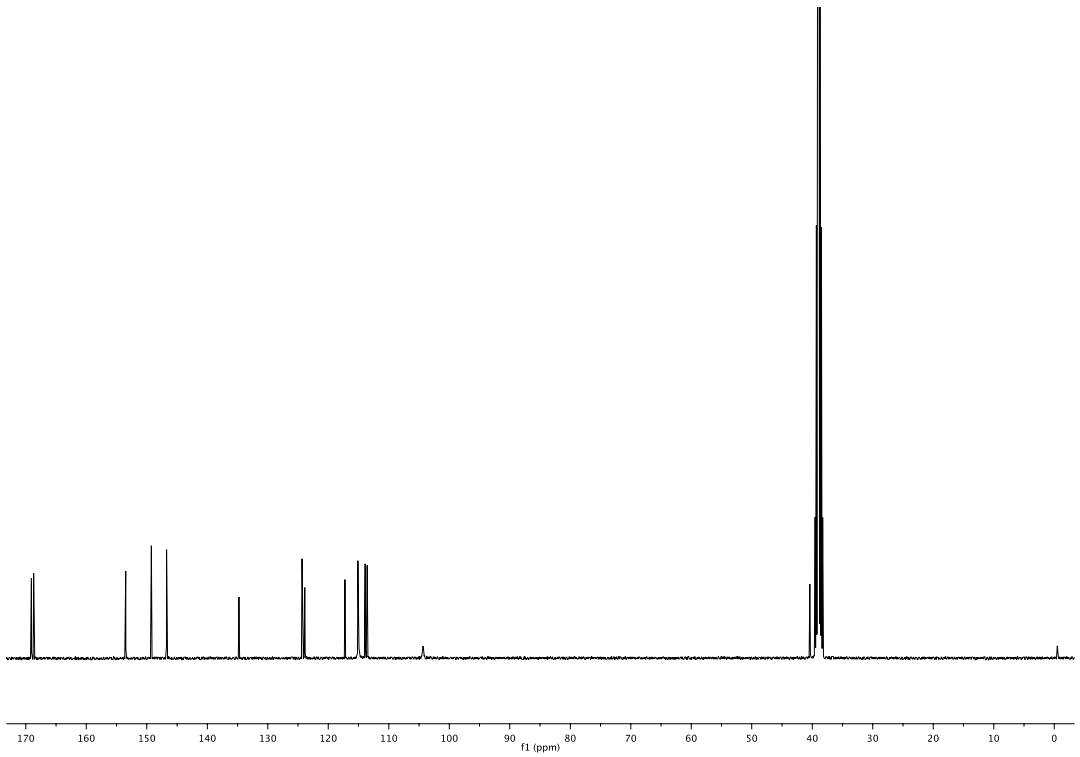


5-((2,5-Dihydroxybenzyl)amino)isoindoline-1,3-dione: BN-XV-062

^{1}H NMR:

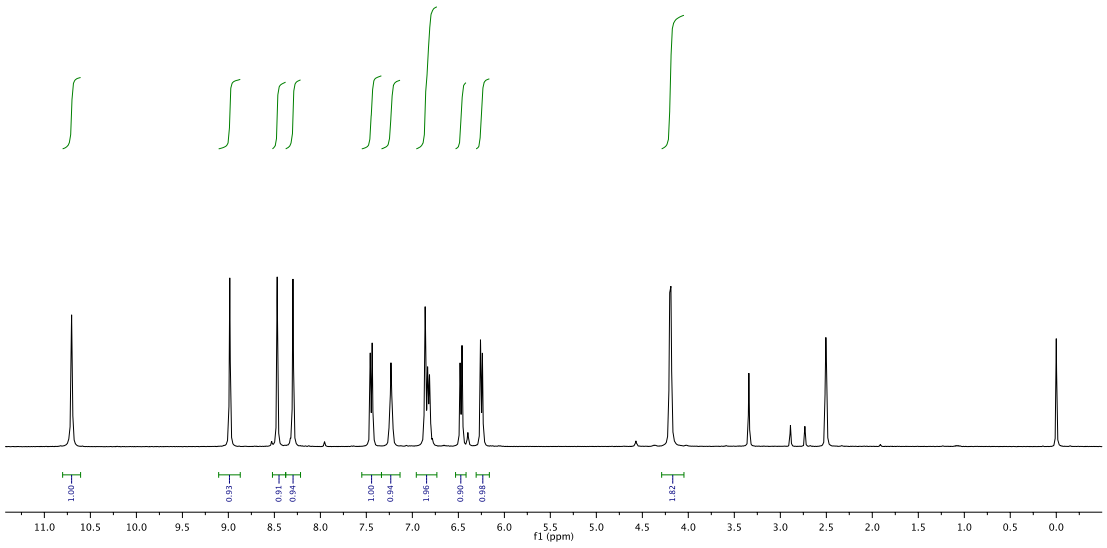


^{13}C NMR:

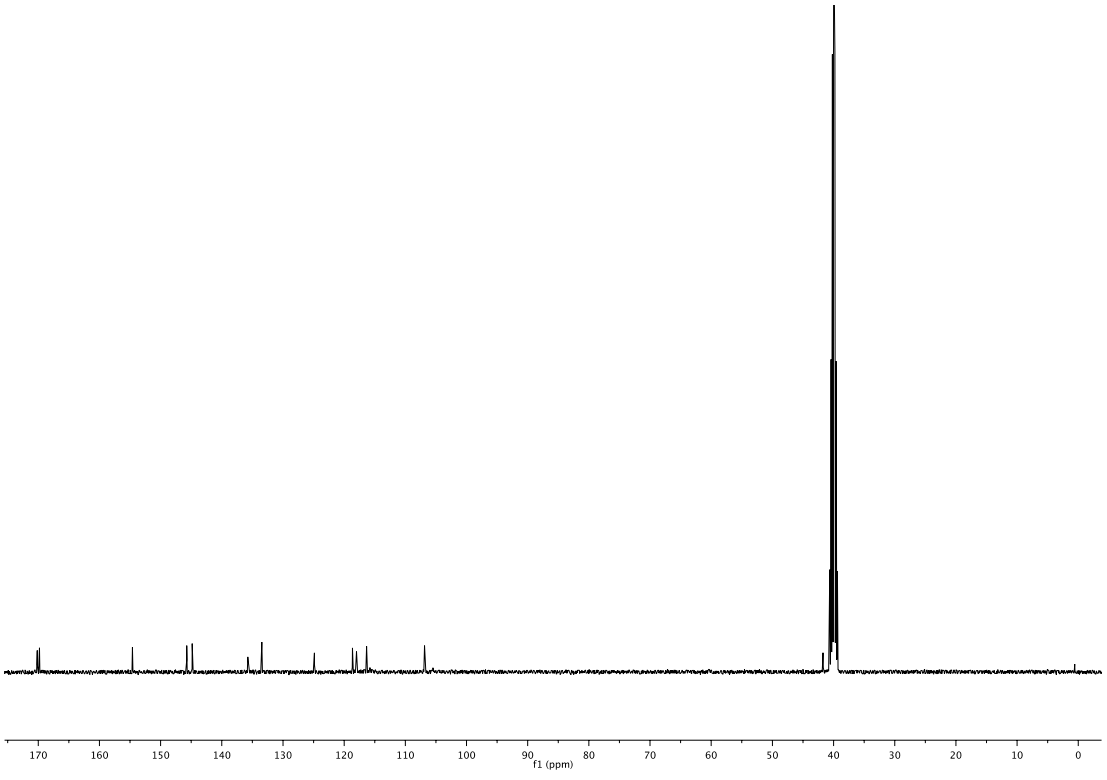


5-((2,3,4-Trihydroxybenzyl)amino)isoindoline-1,3-dione: BN-XVI-031

^{1}H NMR:

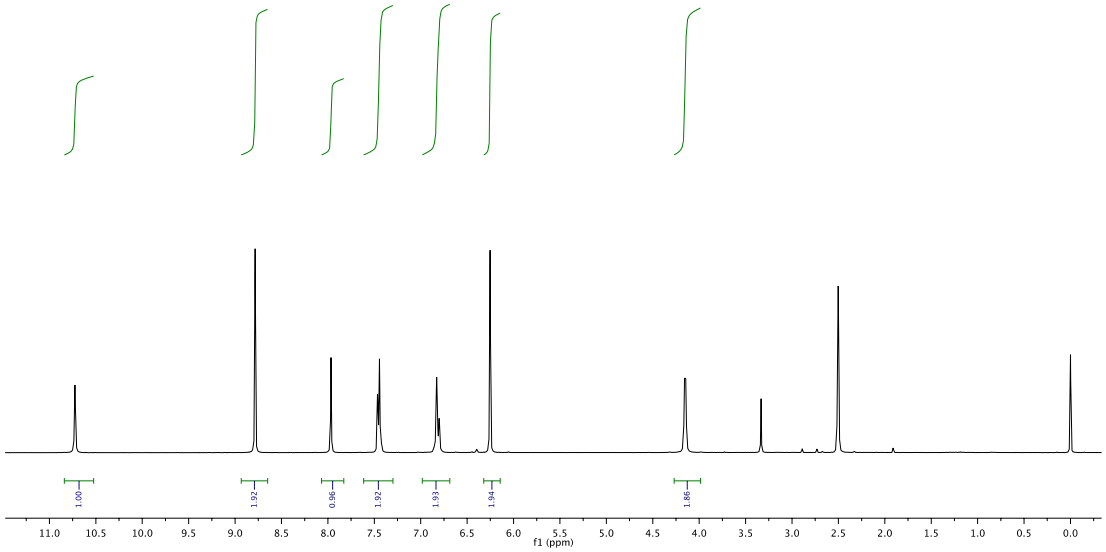


^{13}C NMR:

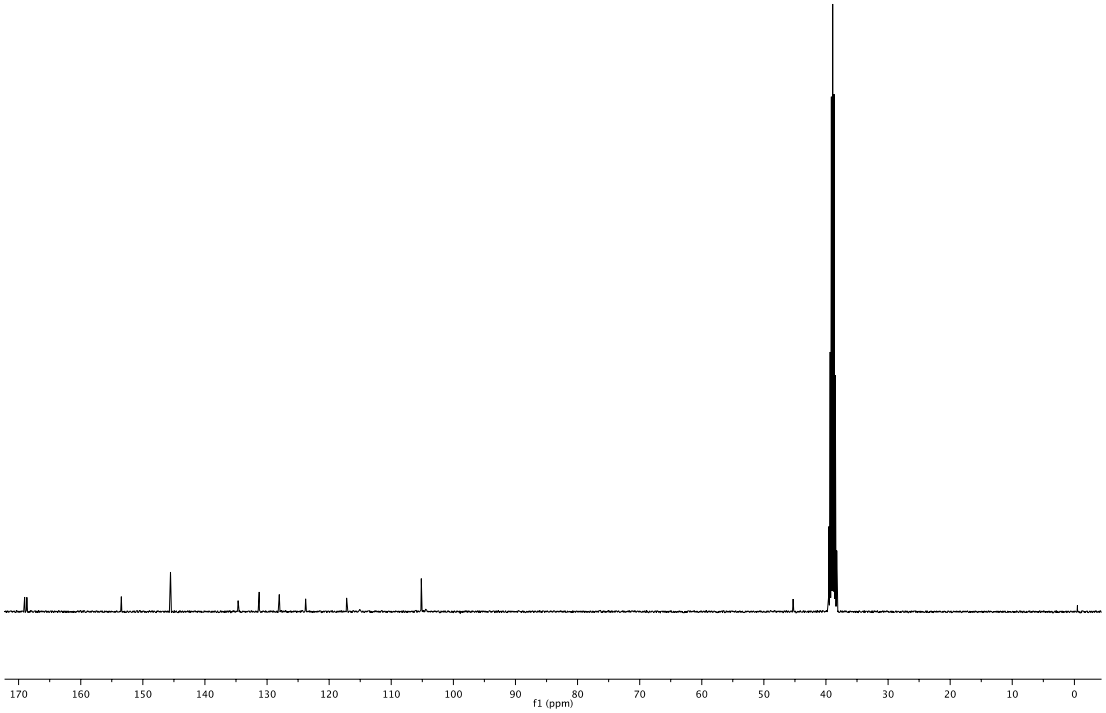


5-((3,4,5-Trihydroxybenzyl)amino)isoindoline-1,3-dione: BN-XVI-037

^{1}H NMR:

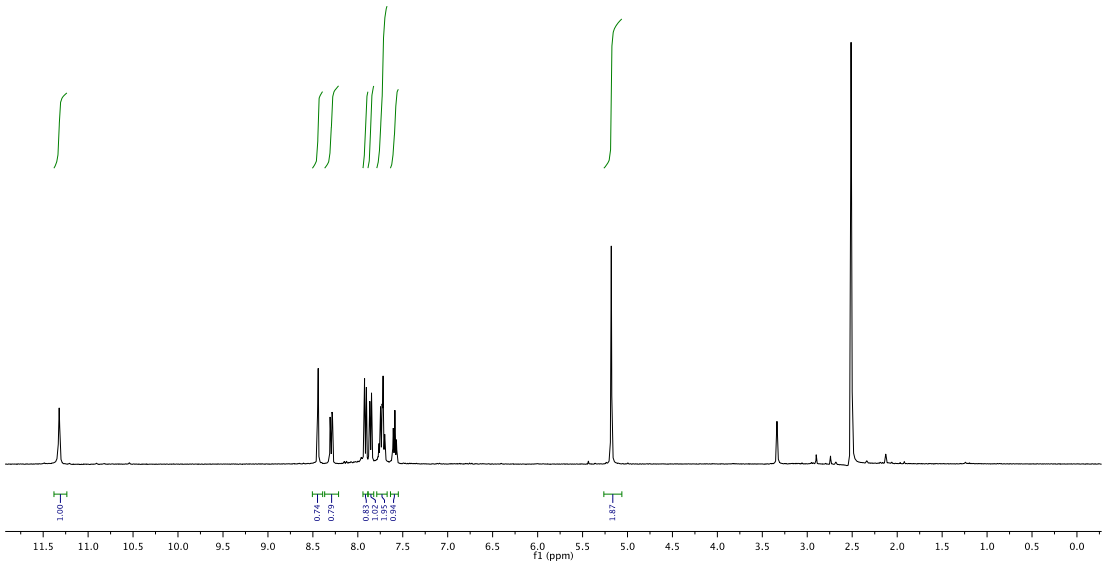


^{13}C NMR:

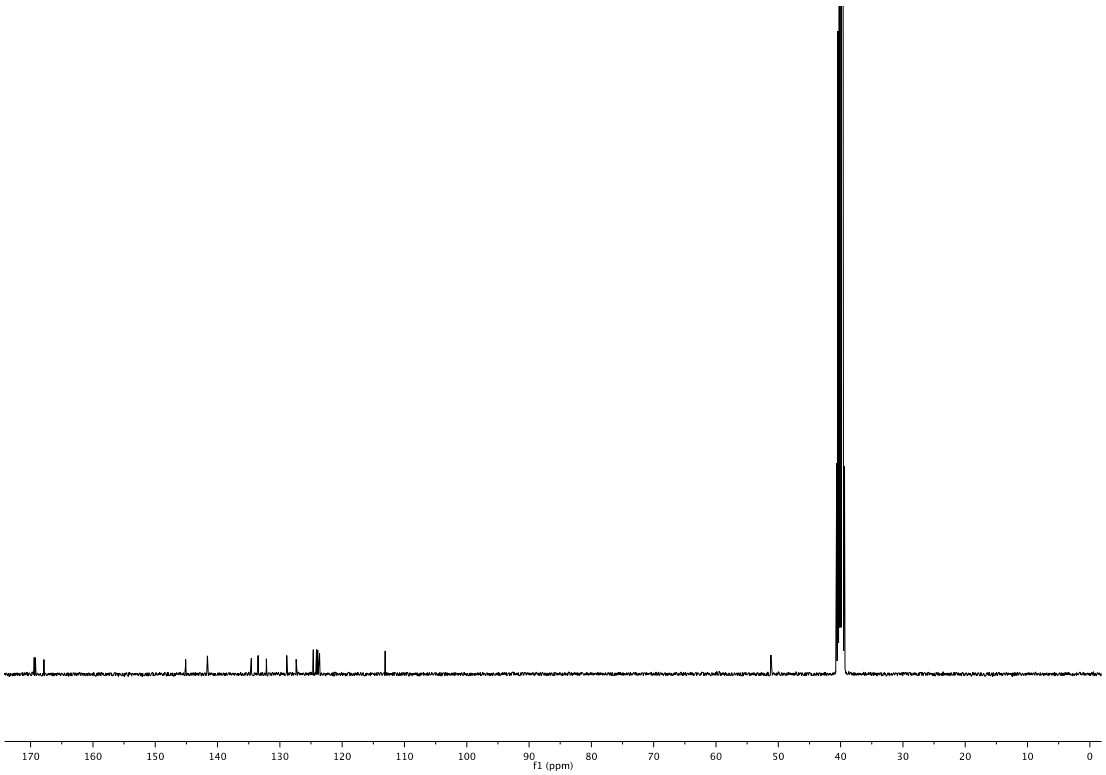


2-(((1,3-Dioxoisoindolin-5-yl)amino)methyl)benzoic acid: BN-XIV-037

^{1}H NMR:

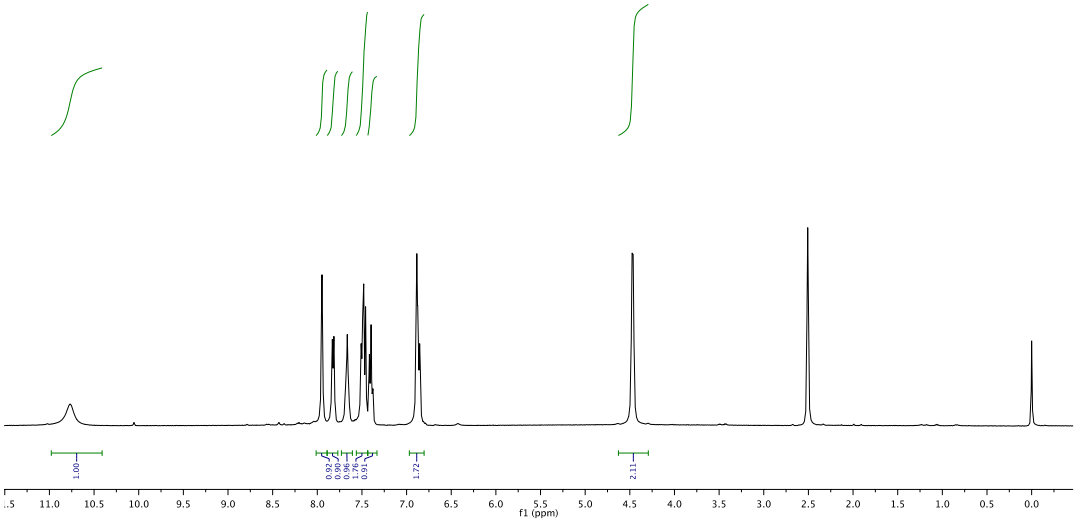


^{13}C NMR:

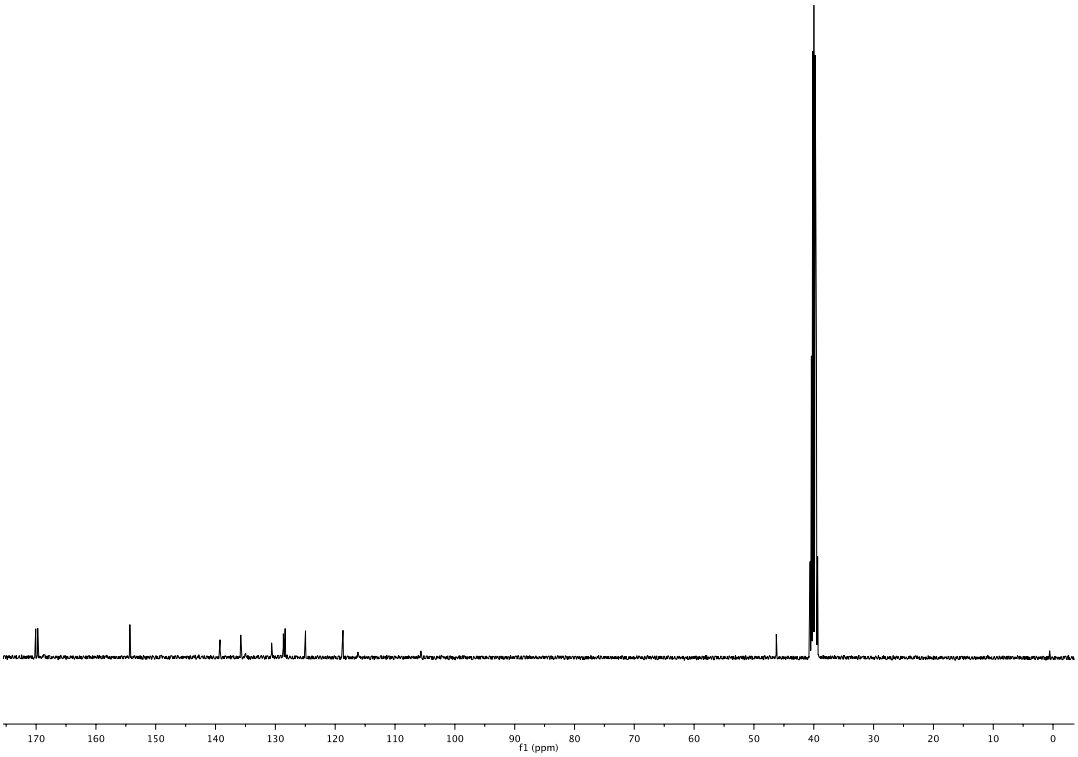


3-(((1,3-Dioxoisoindolin-5-yl)amino)methyl)benzoic acid: BN-XIII-088

^{1}H NMR:

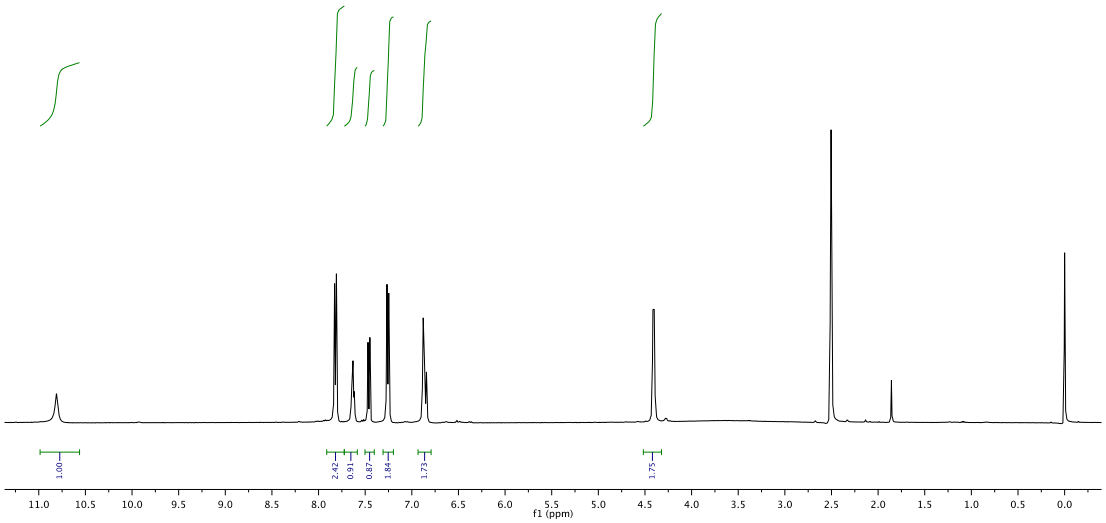


^{13}C NMR:

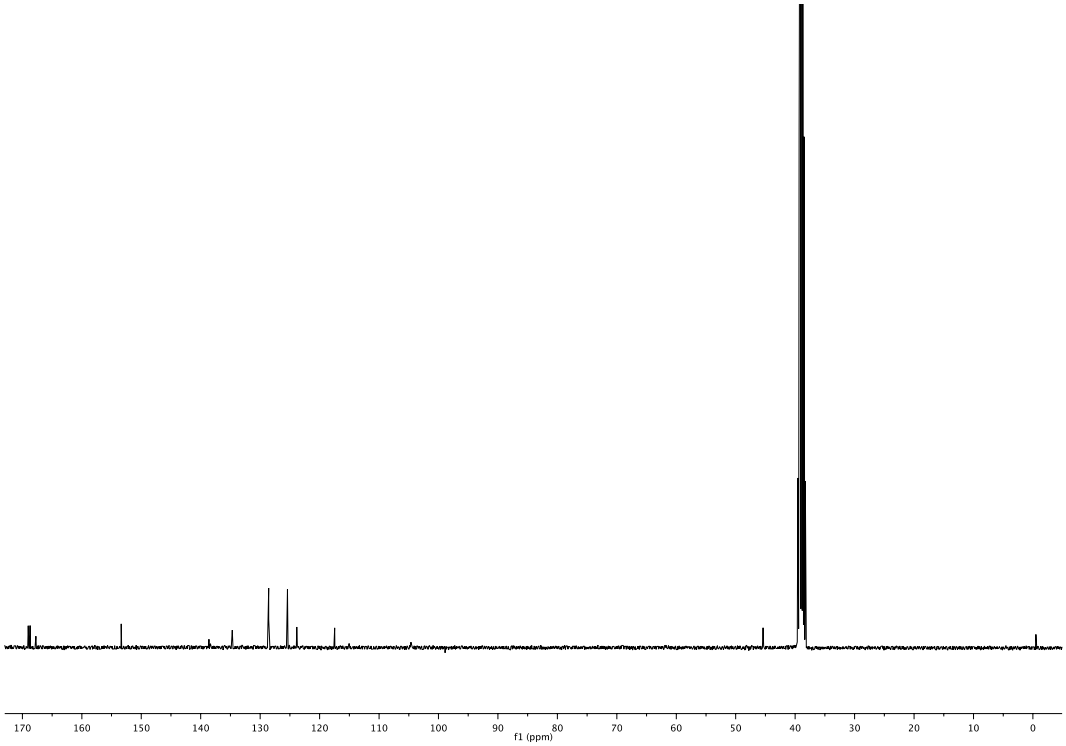


4-(((1,3-Dioxoisoindolin-5-yl)amino)methyl)benzoic acid: BN-XVI-041

^{1}H NMR:

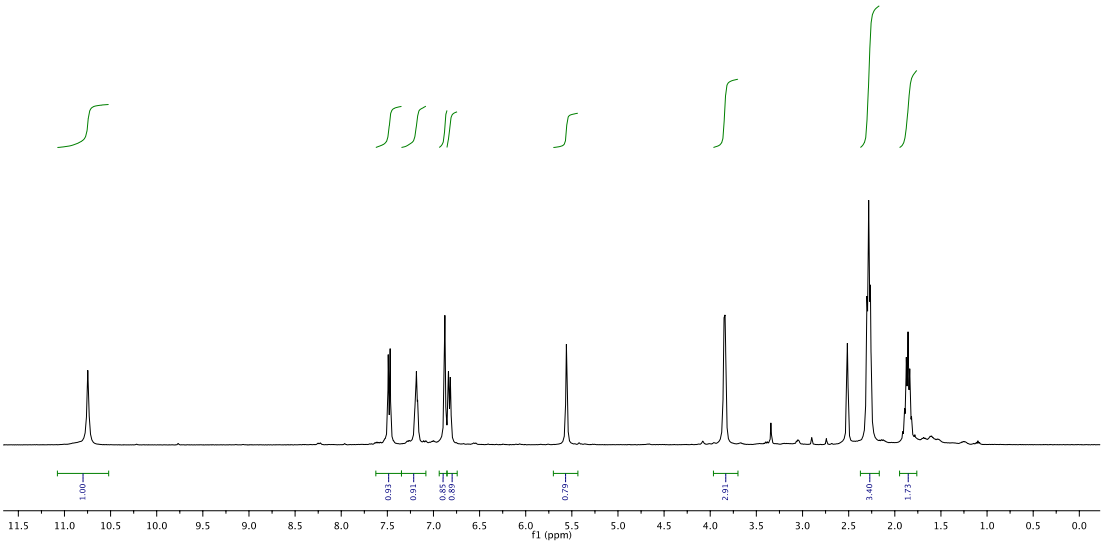


^{13}C NMR:

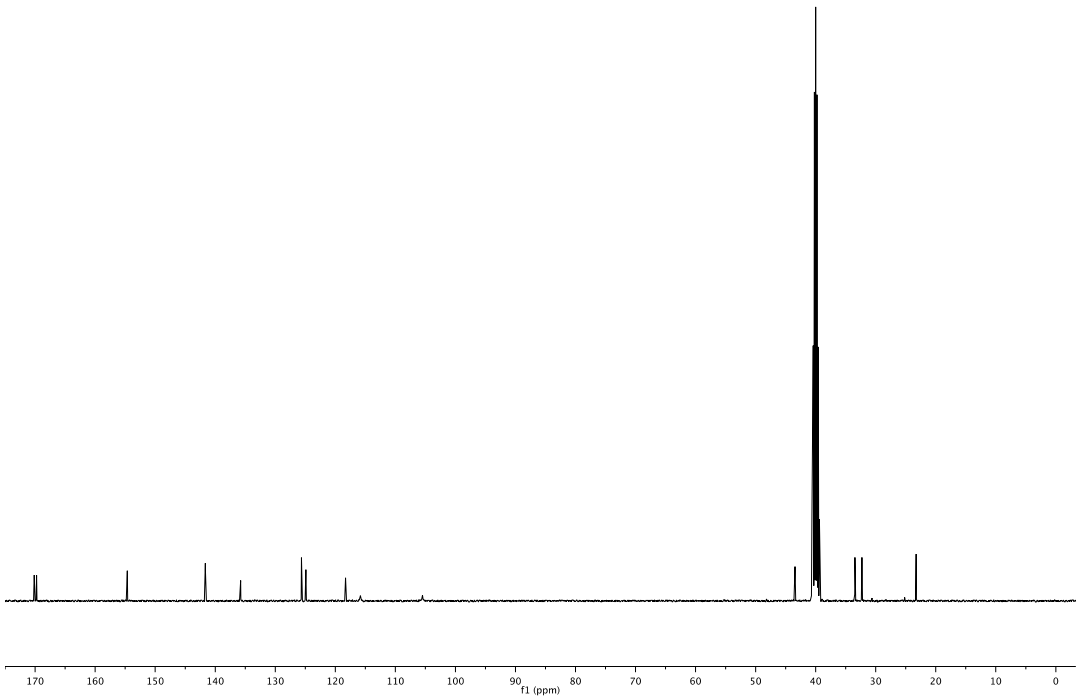


5-((Cyclopent-1-en-1-ylmethyl)amino)isoindoline-1,3-dione: BN-XIV-031

^{1}H NMR:

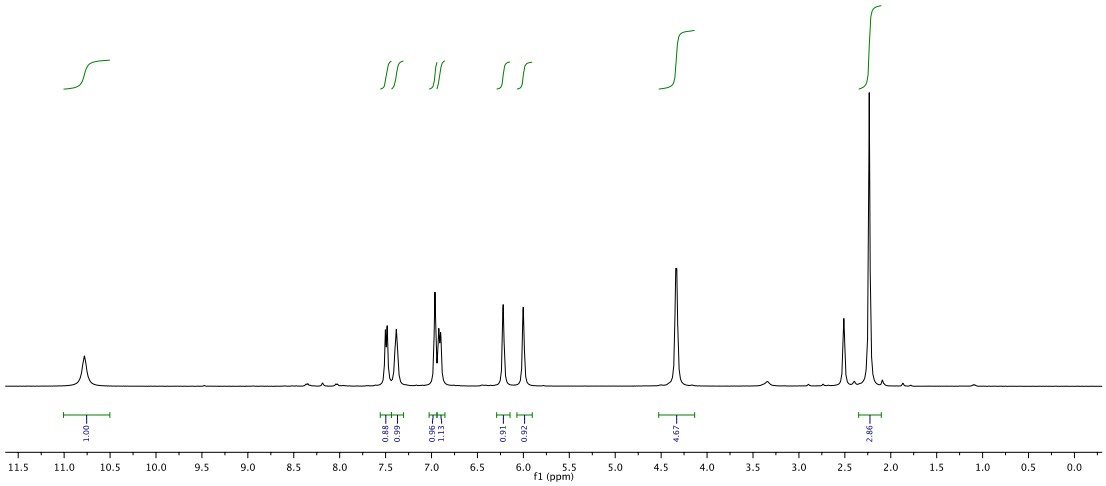


^{13}C NMR:

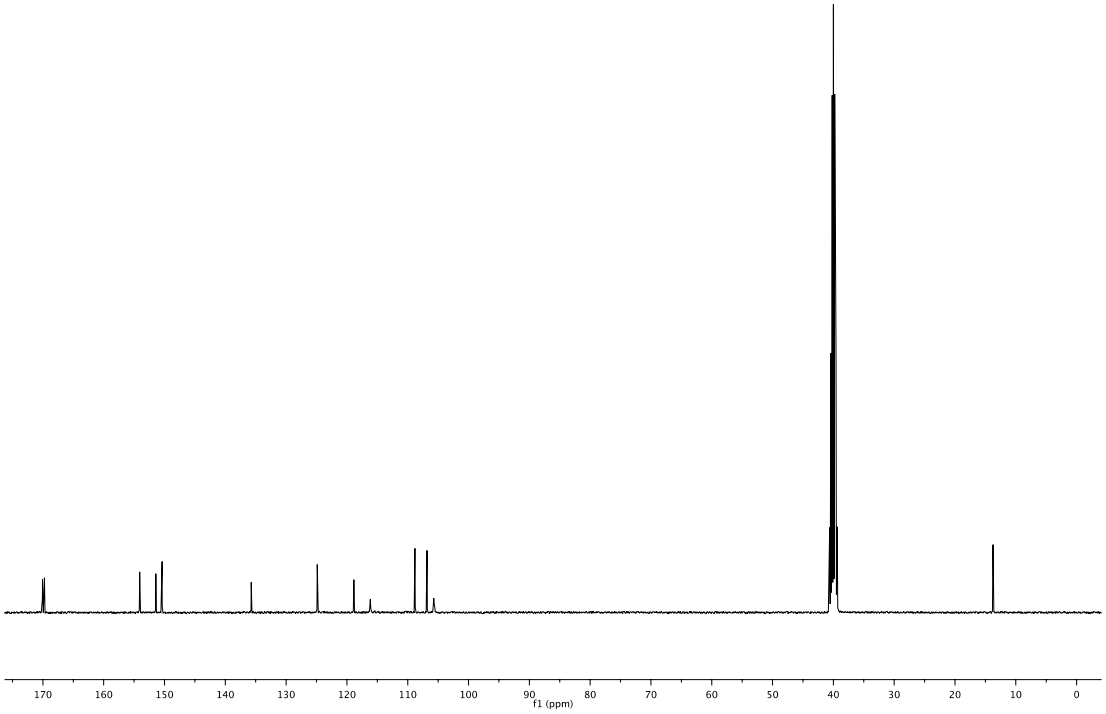


5-(((2-Methylfuran-3-yl)methyl)amino)isoindoline-1,3-dione: BN-XIII-072

^{1}H NMR:

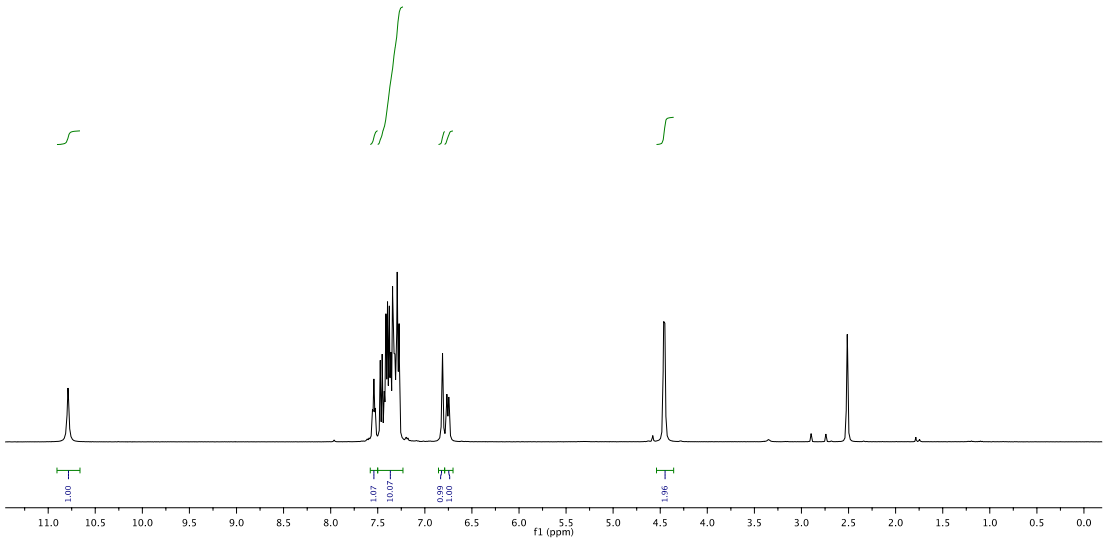


^{13}C NMR:

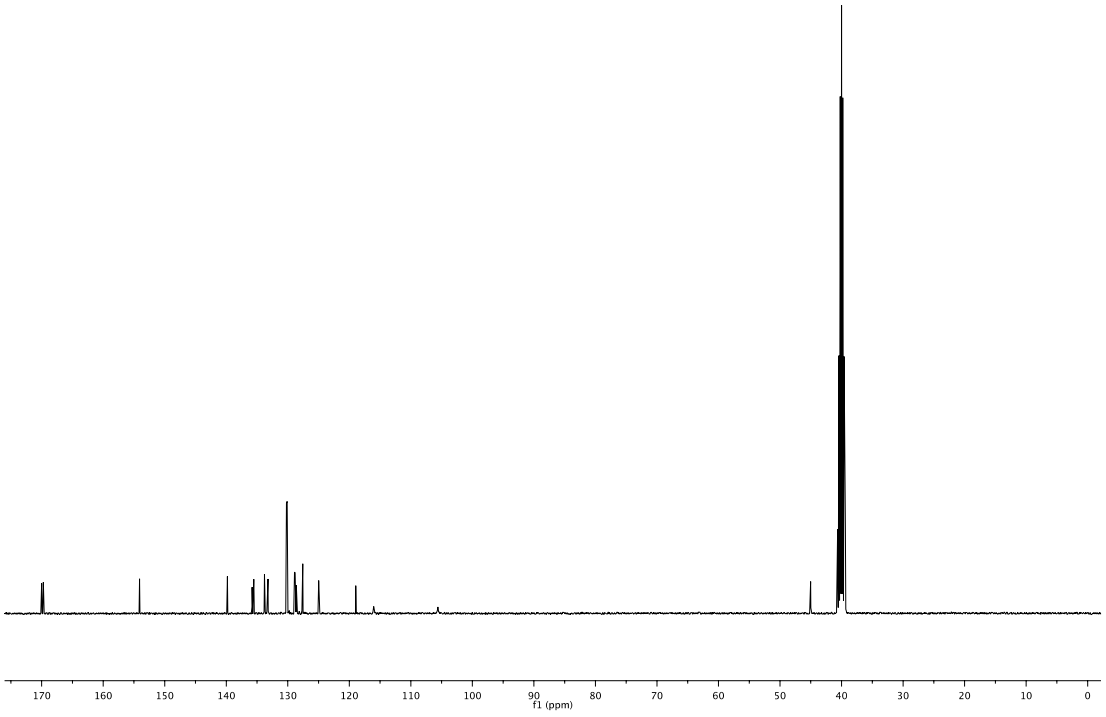


5-((2-(Phenylthio)benzyl)amino)isoindoline-1,3-dione: BN-XIV-036

^{1}H NMR:



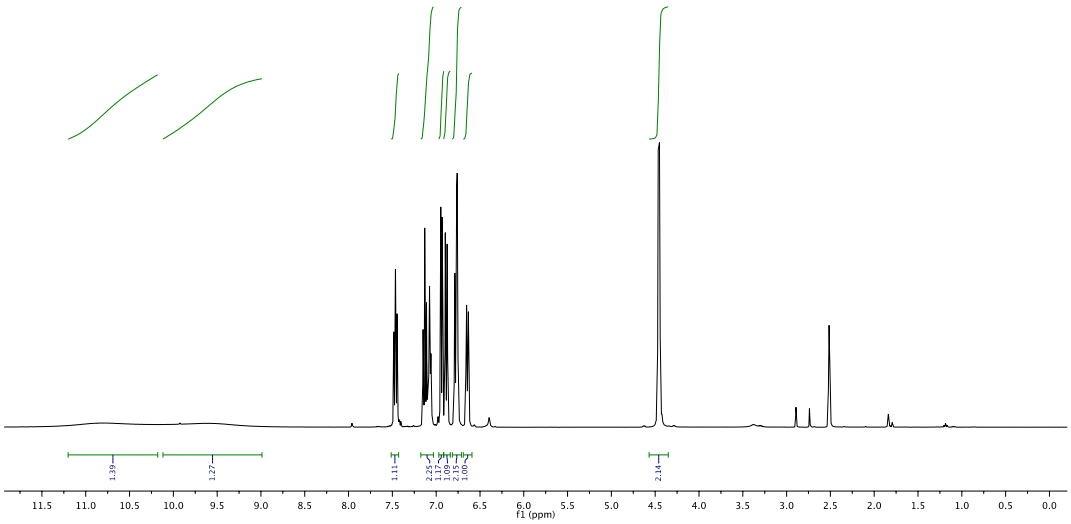
^{13}C NMR:



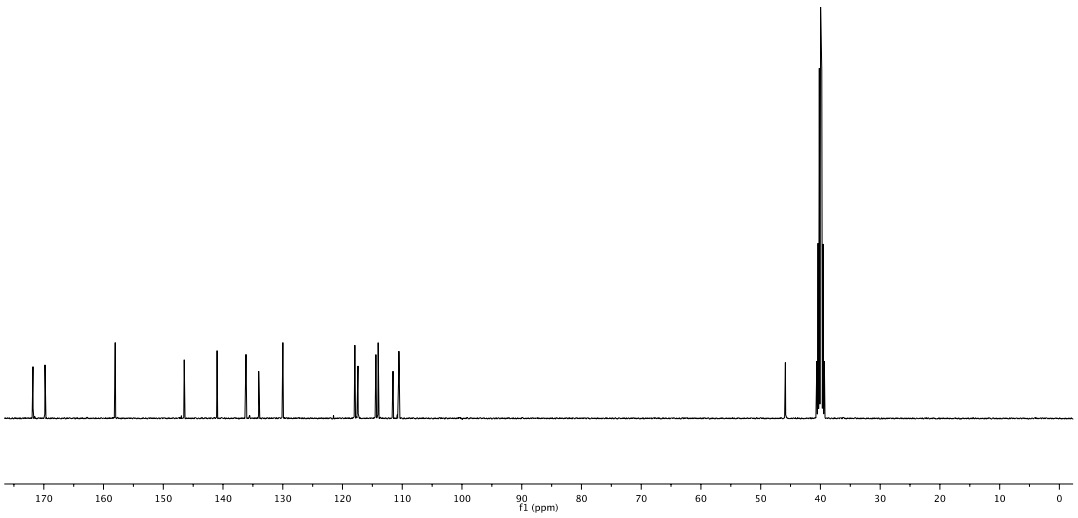
^{1}H and ^{13}C spectra for 4-aminoisoindoline-1,3-dione series

4-((3-Hydroxybenzyl)amino)isoindoline-1,3-dione: BN-XIV-053 (**Analog 12**)

^{1}H NMR:

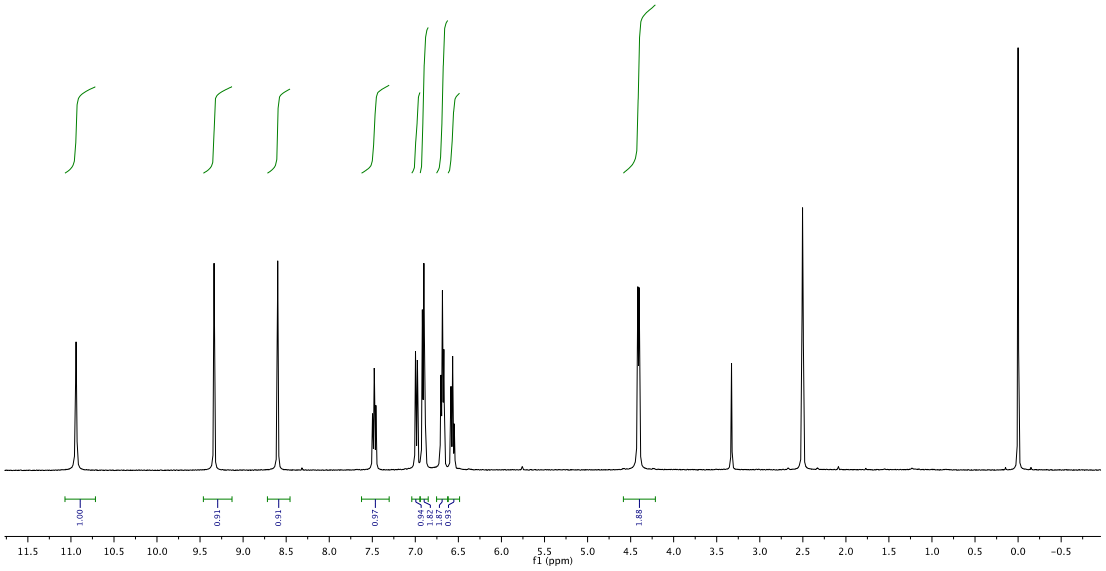


^{13}C NMR:

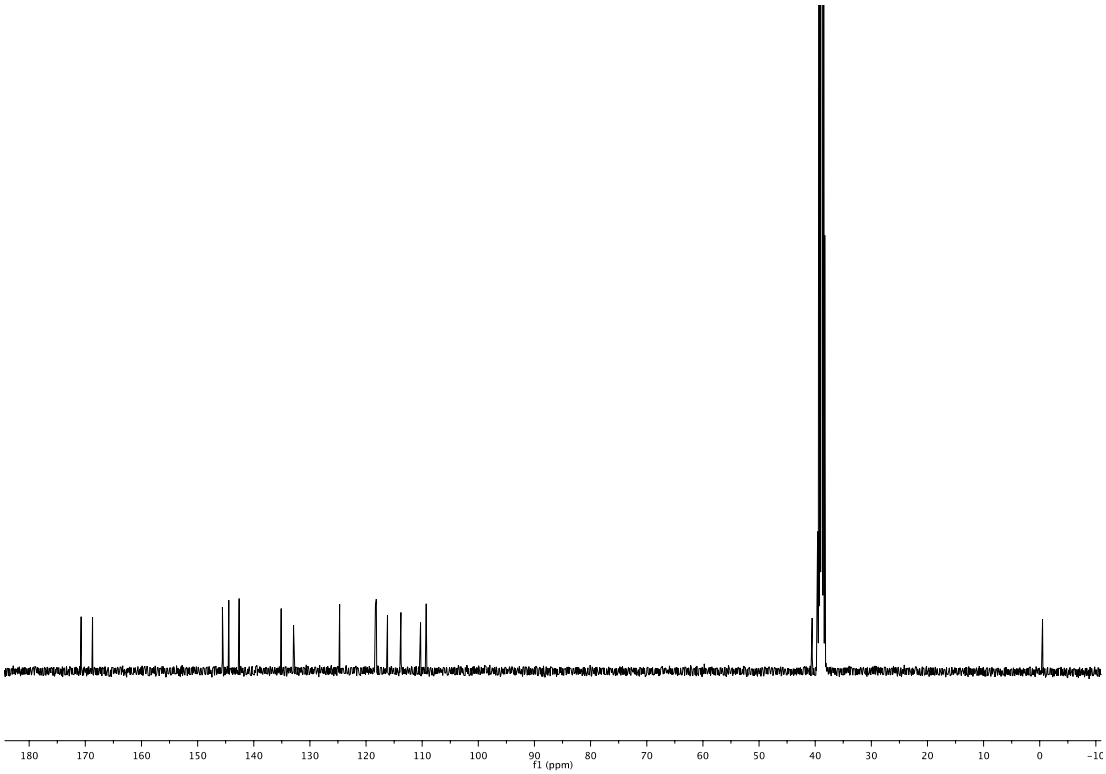


4-((2,3-Dihydroxybenzyl)amino)isoindoline-1,3-dione: BN-XIV-074

^{1}H NMR:

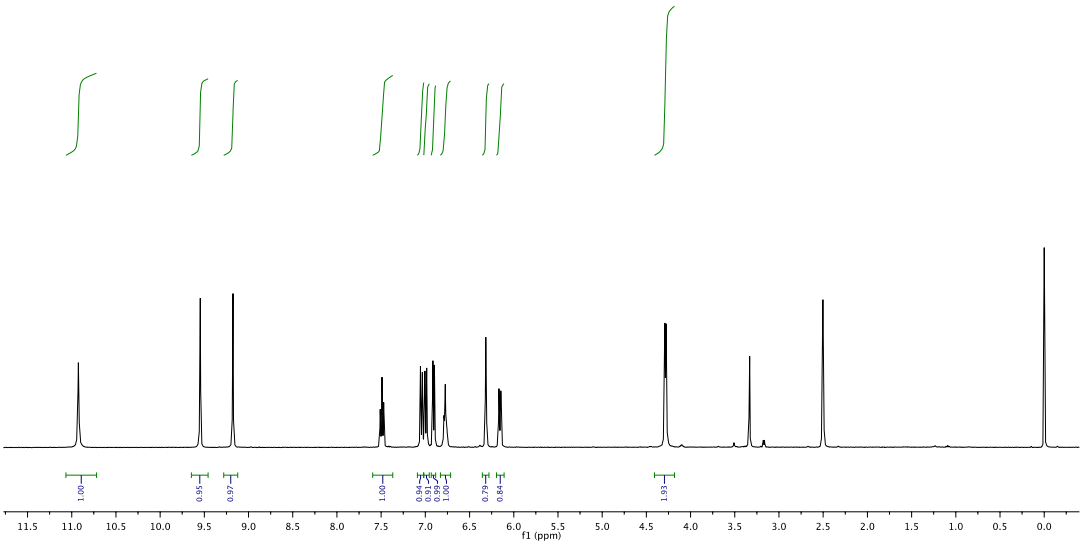


^{13}C NMR:

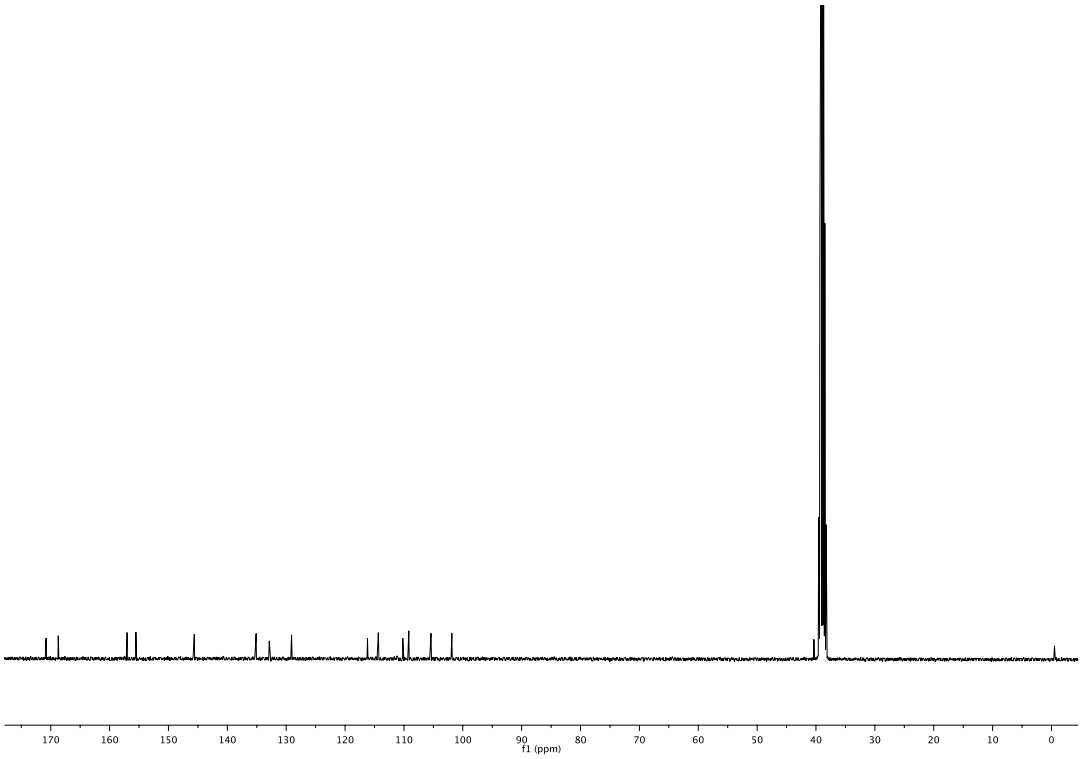


4-((2,5-Dihydroxybenzyl)amino)isoindoline-1,3-dione: BN-XVI-069

^{1}H NMR:

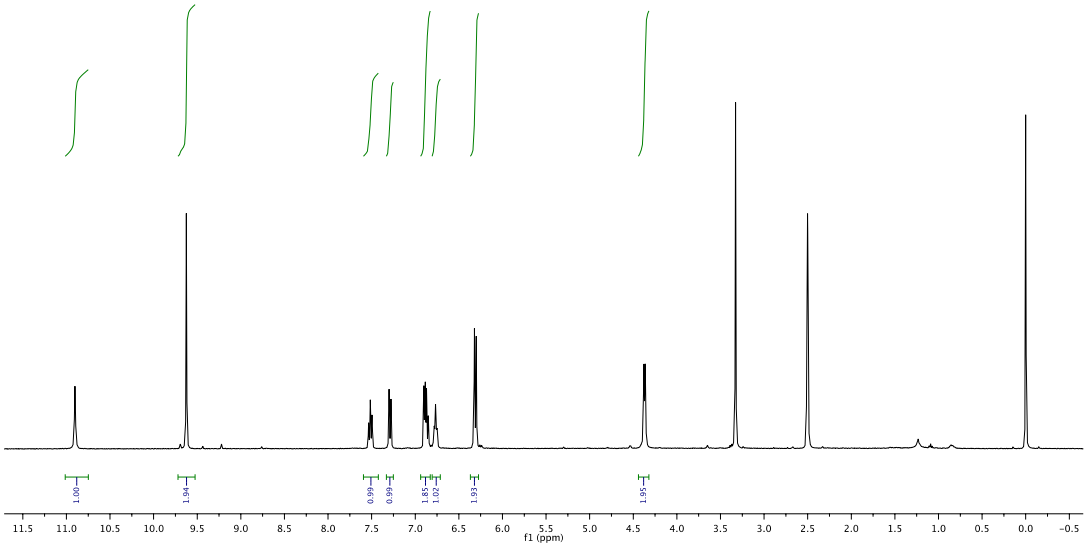


^{13}C NMR:

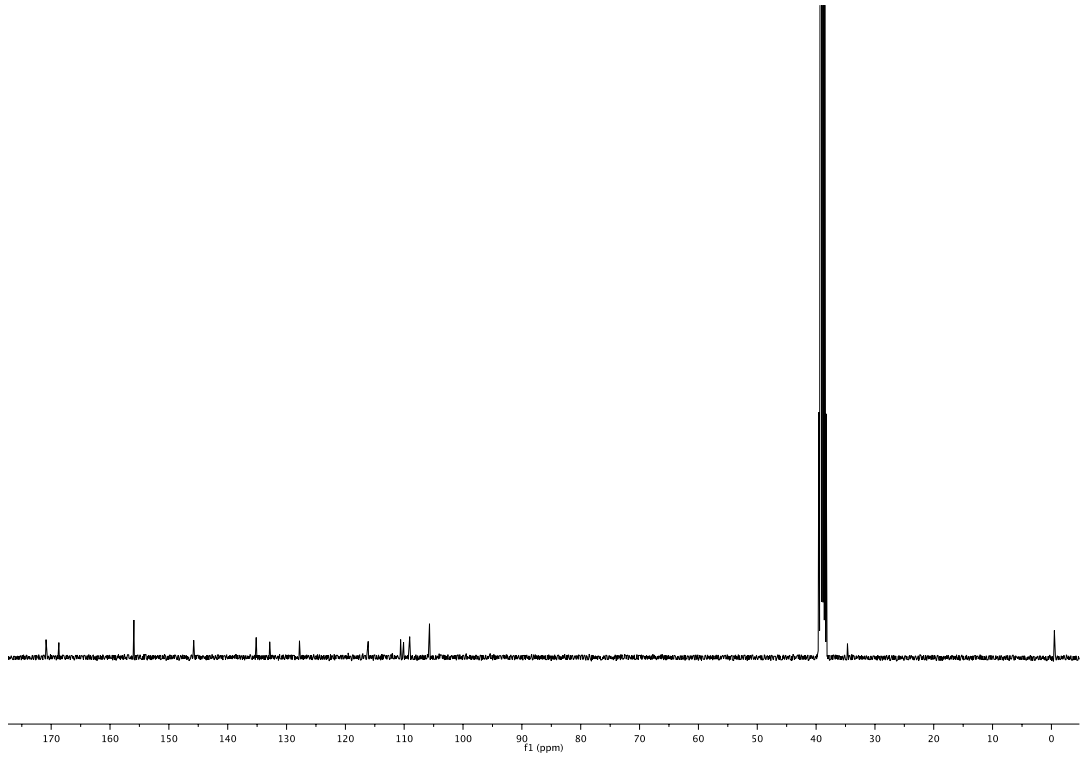


4-((2,6-Dihydroxybenzyl)amino)isoindoline-1,3-dione: BN-XVI-070

^{1}H NMR:

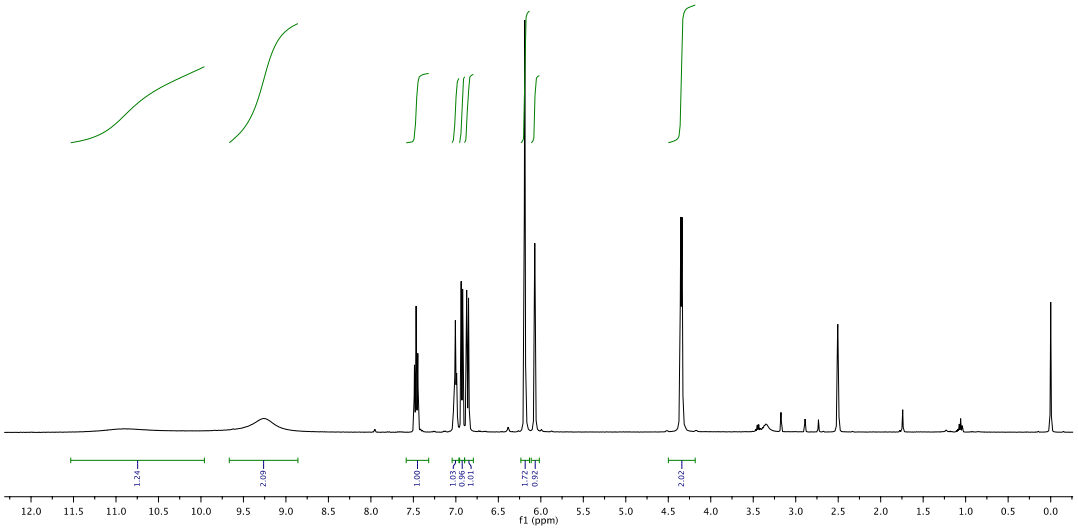


^{13}C NMR:

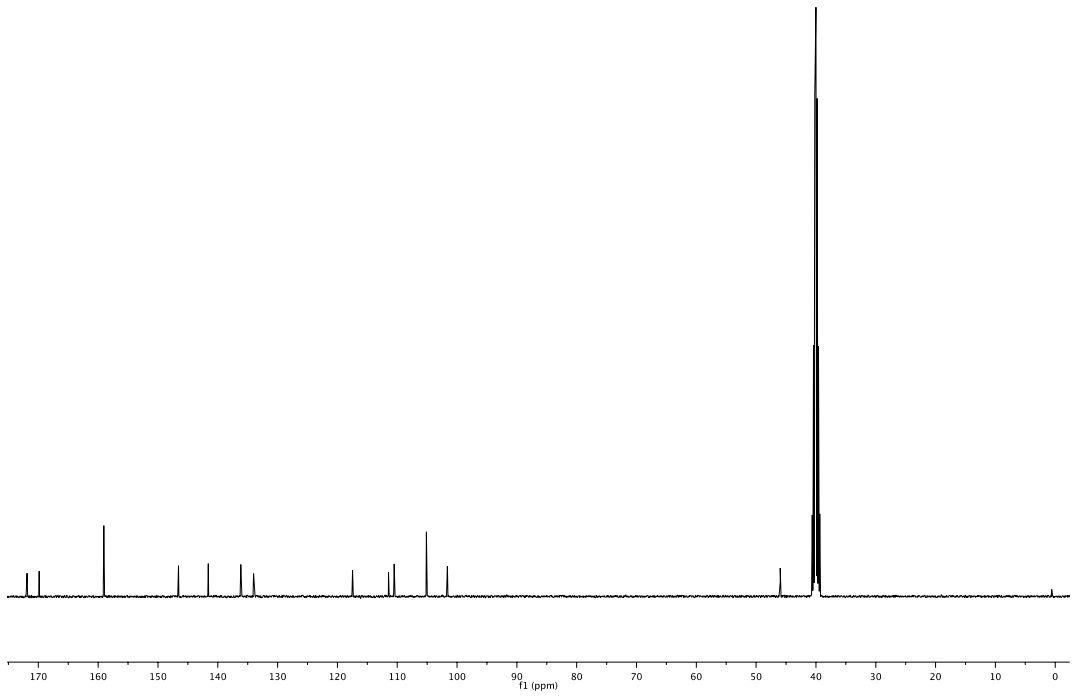


4-((3,5-Dihydroxybenzyl)amino)isoindoline-1,3-dione: BN-XVI-071

^{1}H NMR:

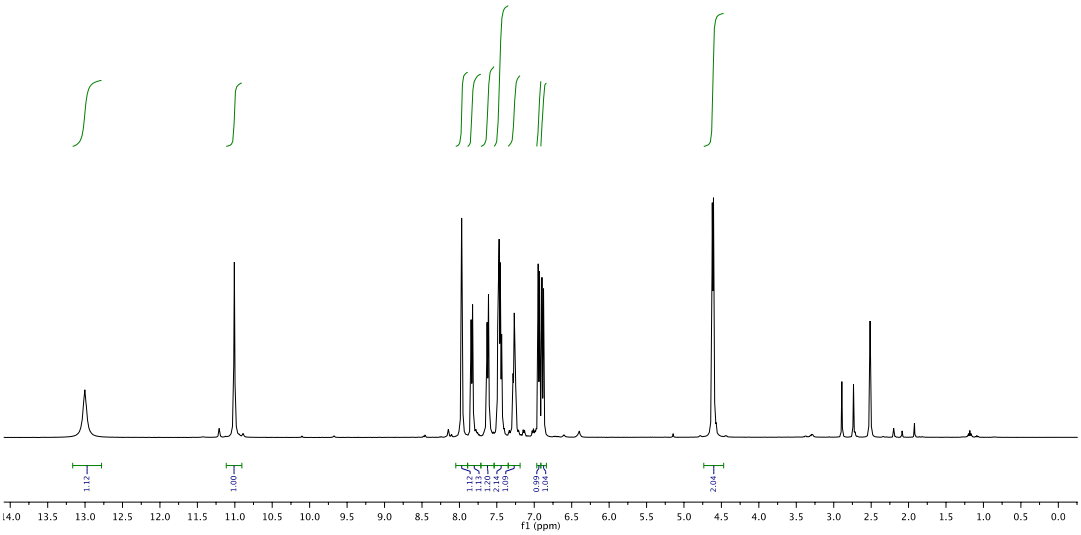


^{13}C NMR:

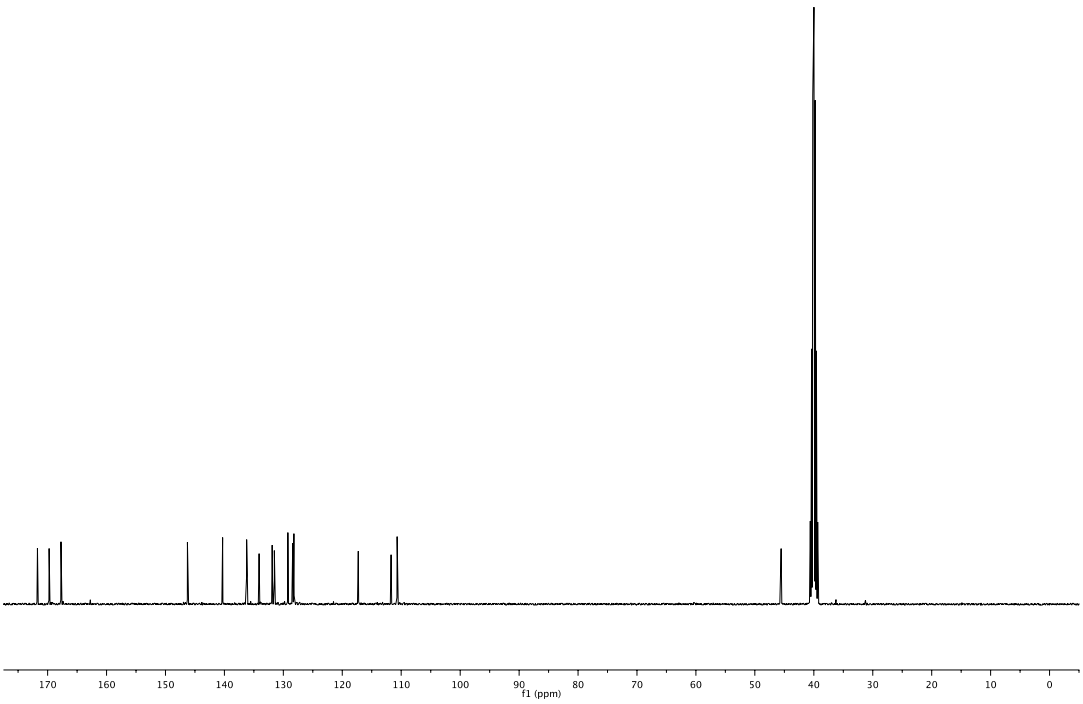


3-(((1,3-Dioxoisoindolin-4-yl)amino)methyl)benzoic acid: BN-XIV-059

^{1}H NMR:

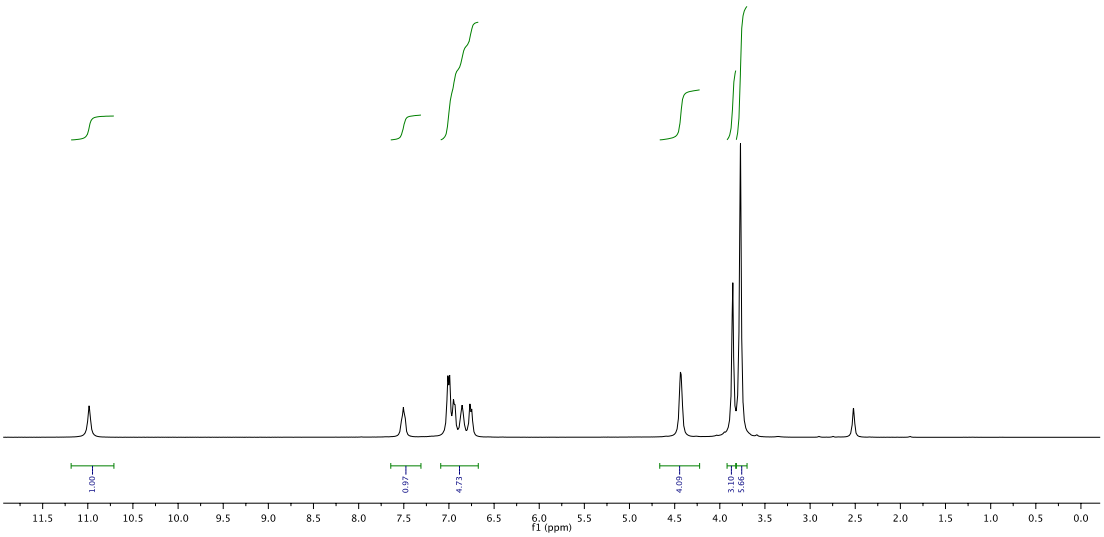


^{13}C NMR:

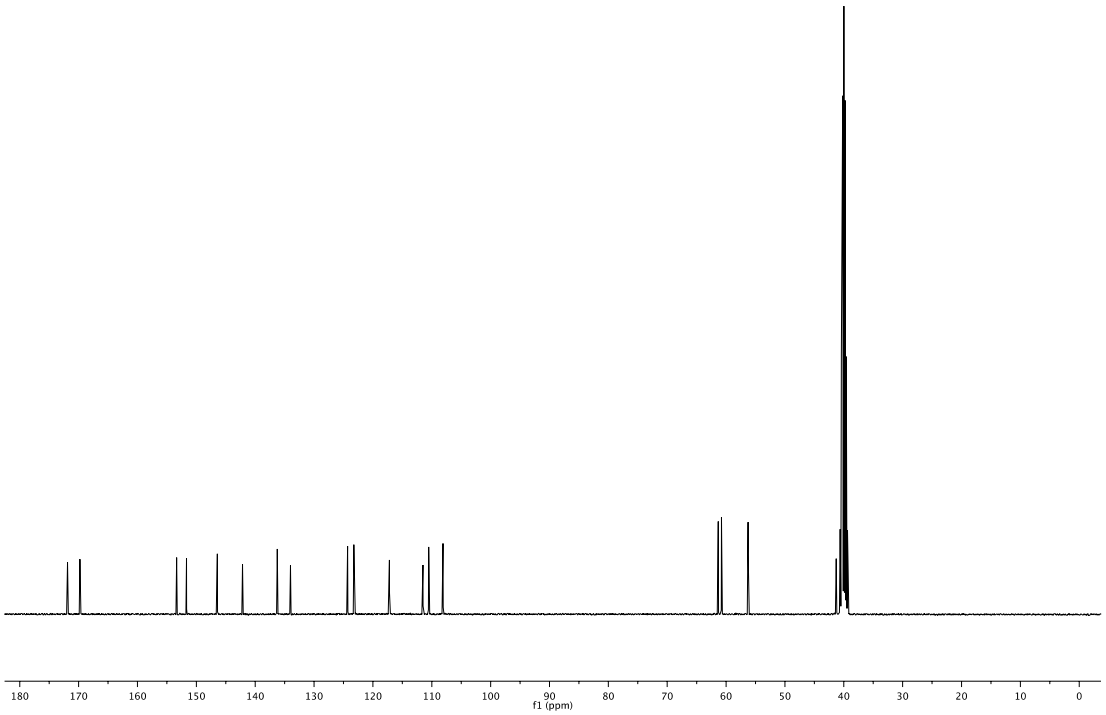


4-((2,3,4-Trimethoxybenzyl)amino)isoindoline-1,3-dione: BN-XIV-060

^{1}H NMR:

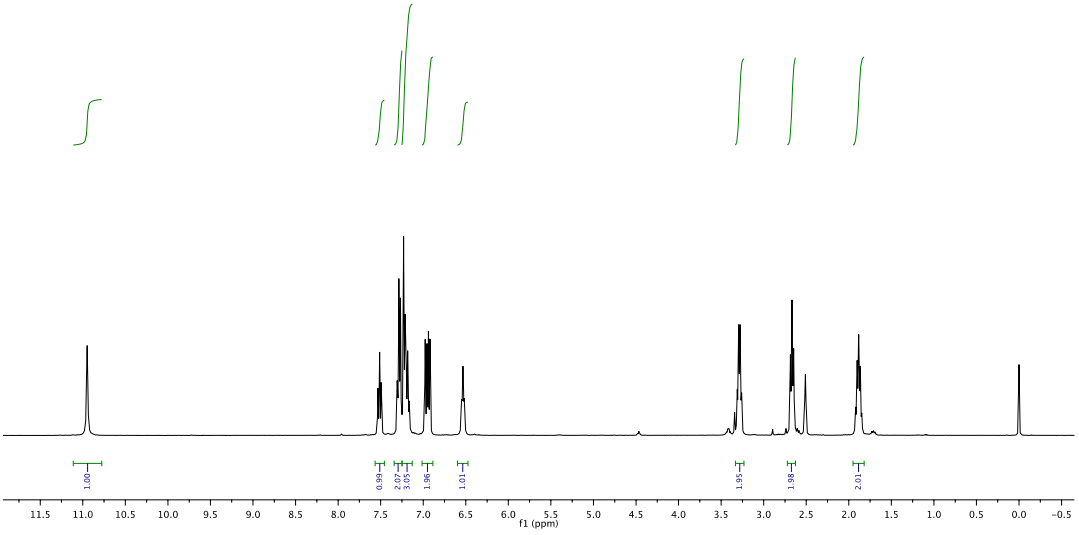


^{13}C NMR:

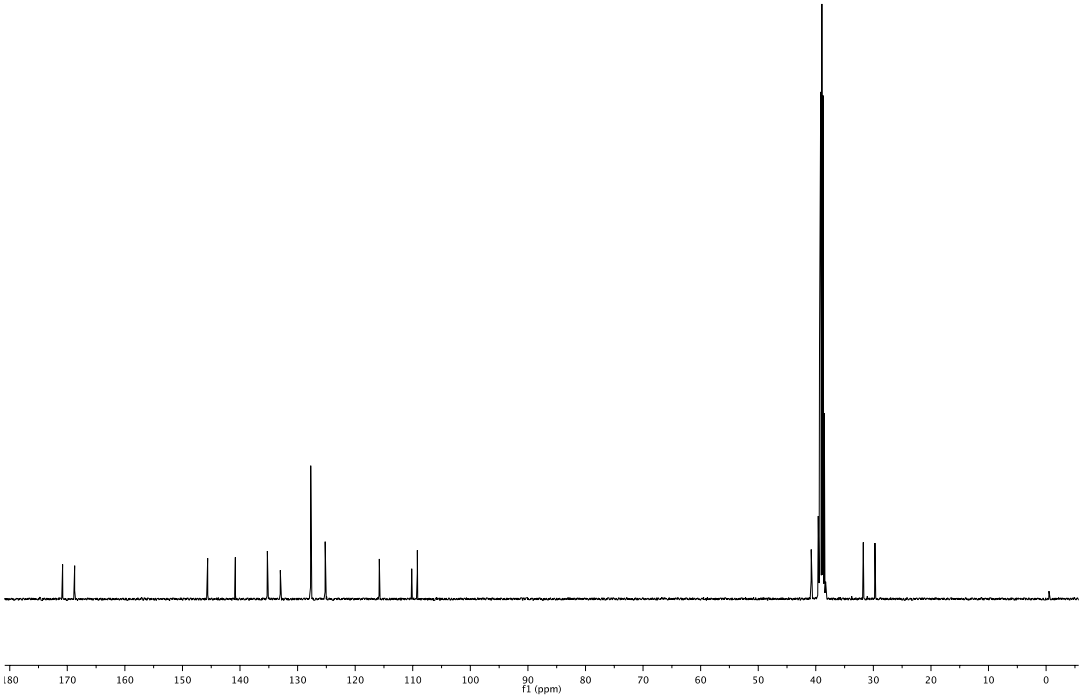


4-(3-Phenylpropylamino)isoindoline-1,3-dione: BN-XVI-067

^{1}H NMR:

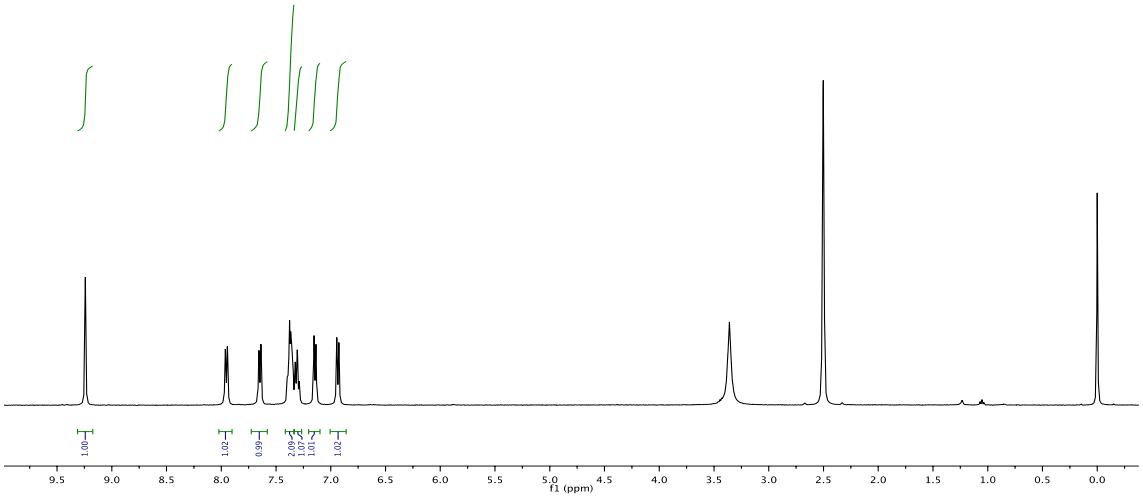


^{13}C NMR:

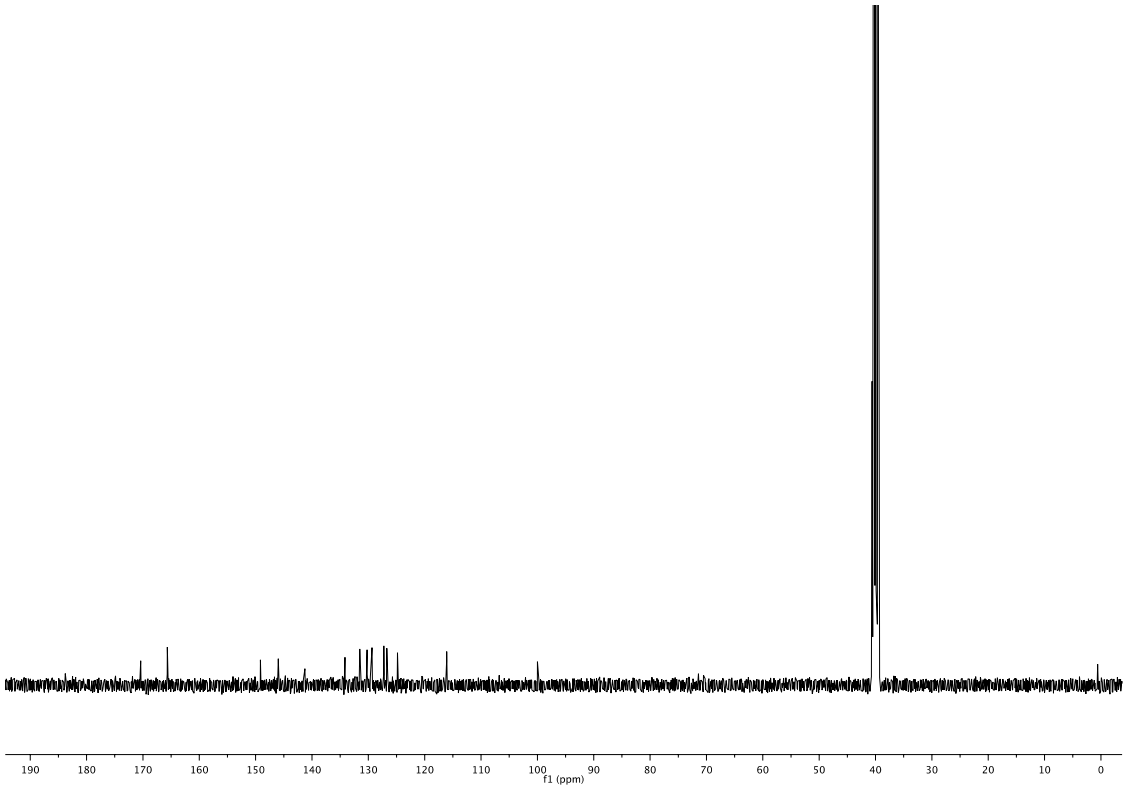


Potassium 2-(((1,3-dioxoisoindolin-4-yl)amino)methyl)benzoate: GKK-011-011

^{1}H NMR:

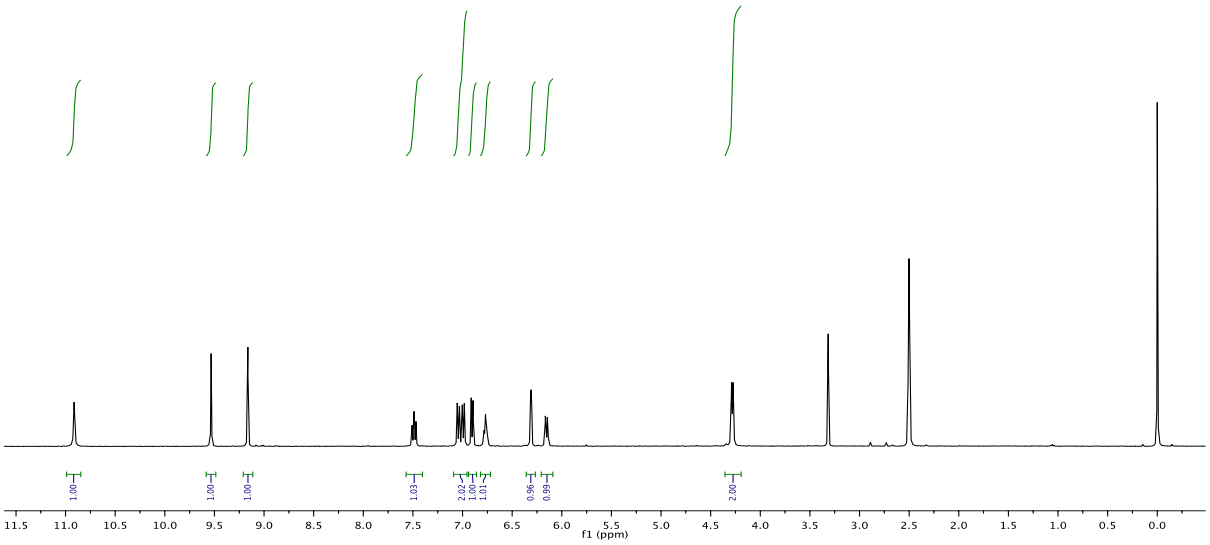


^{13}C NMR:

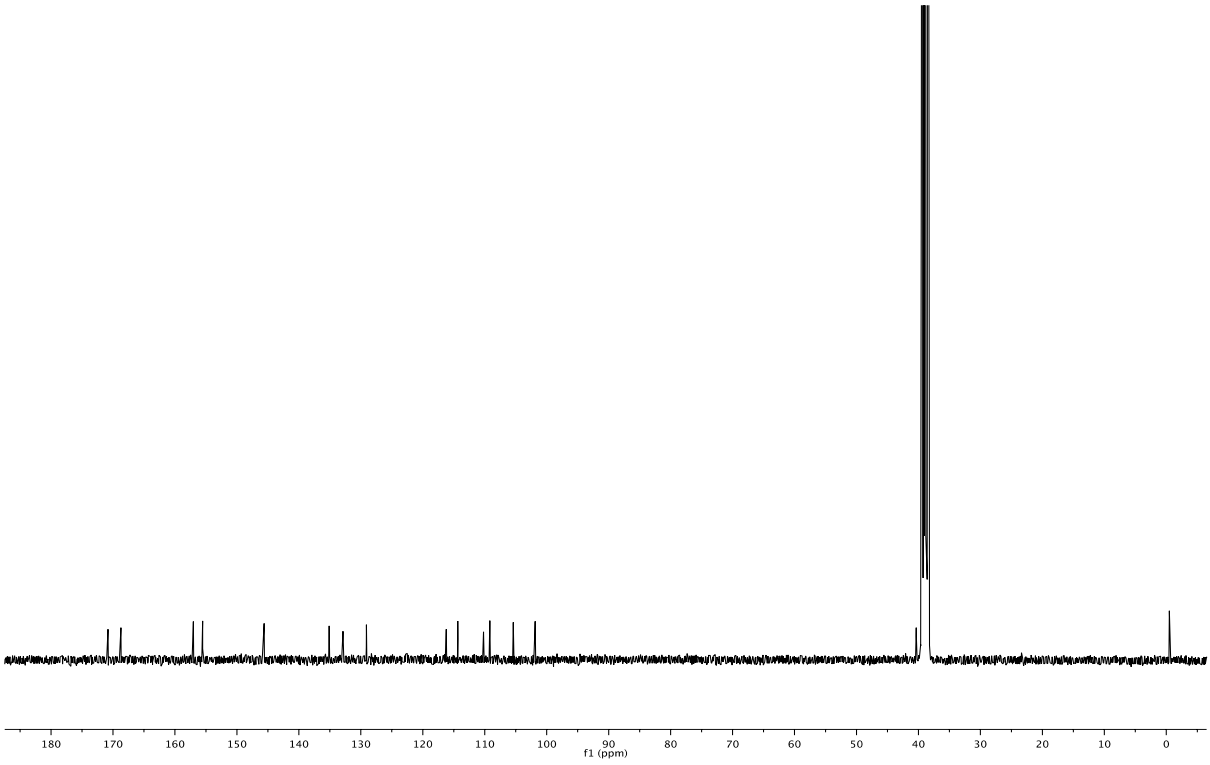


4-((2,4-Dihydroxybenzyl)amino)isoindoline-1,3-dione: GKK-006-092

^{1}H NMR:

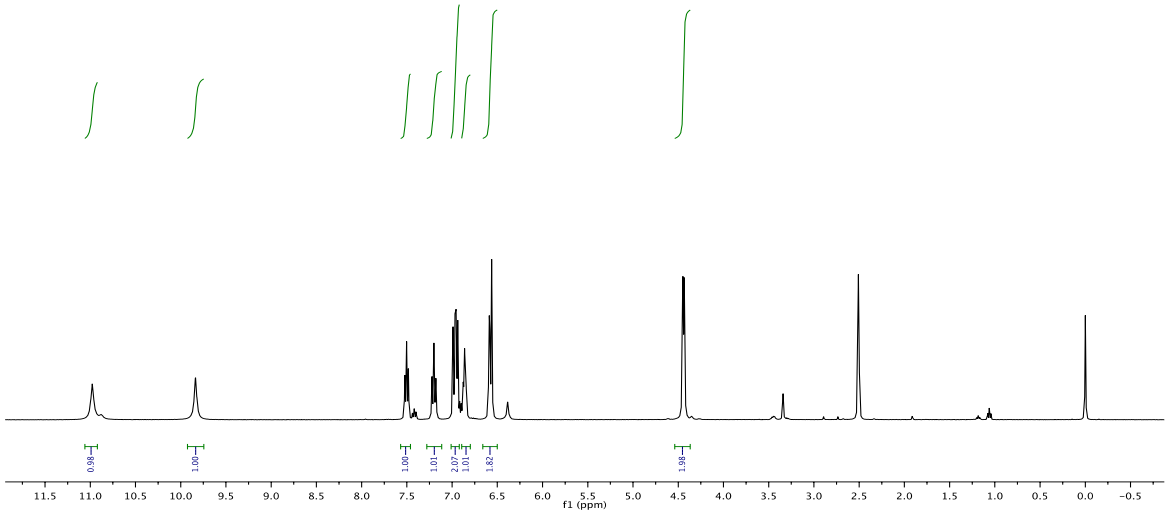


^{13}C NMR:

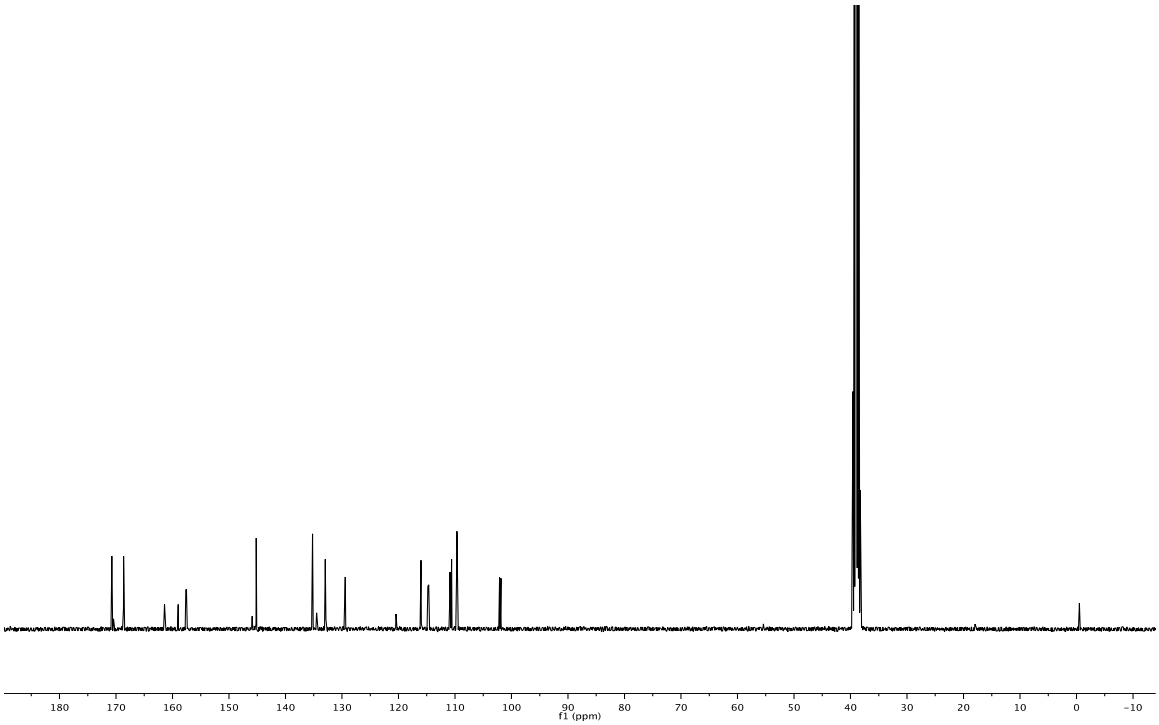


4-((2-Fluoro-4-hydroxybenzyl)amino)isoindoline-1,3-dione: GKK-010-096A

^{1}H NMR:

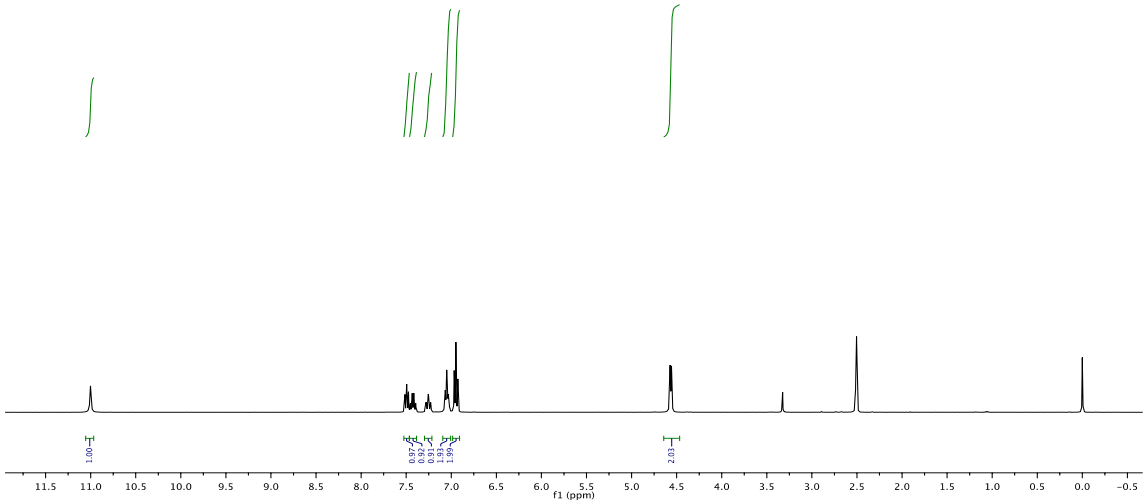


^{13}C NMR:

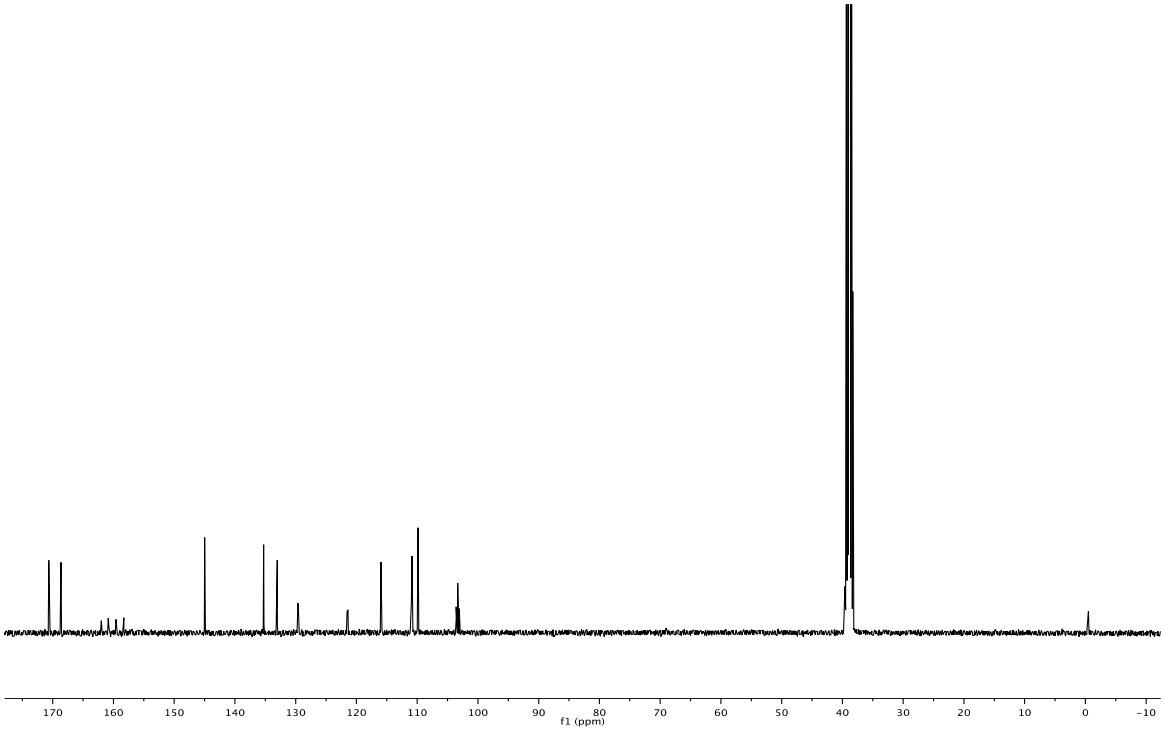


4-((2,4-Difluorobenzyl)amino)isoindoline-1,3-dione: GKK-010-096B

^{1}H NMR:

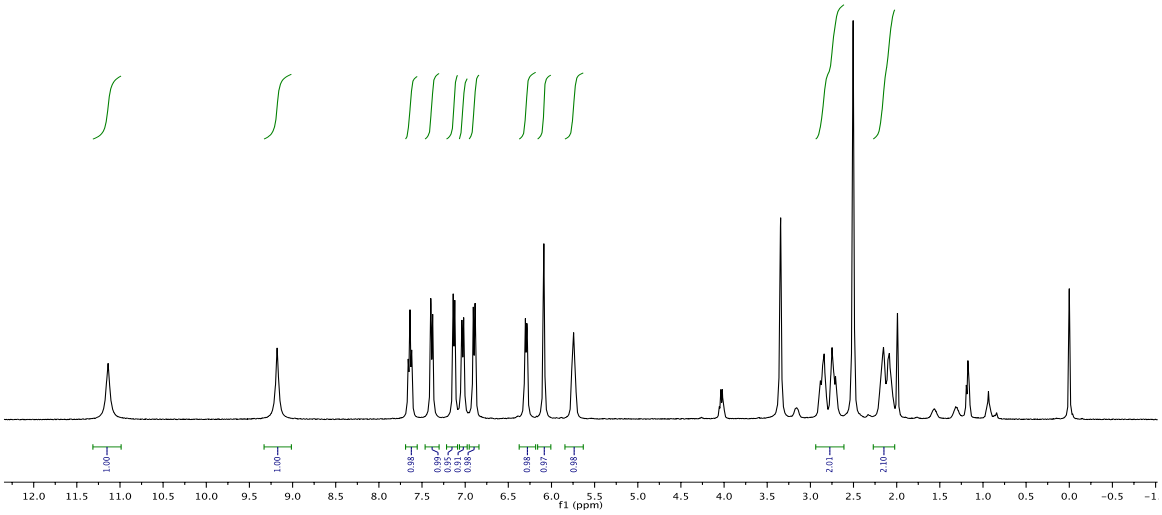


^{13}C NMR:

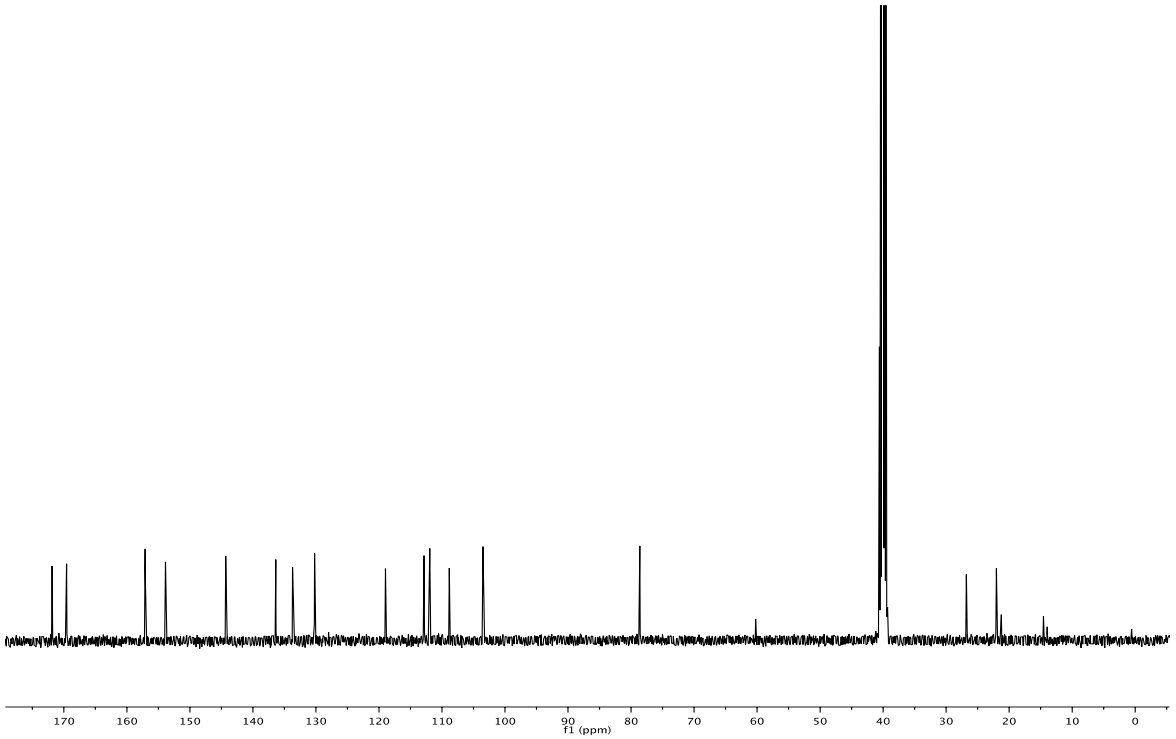


4-((7-Hydroxychroman-2-yl)amino)isoindoline-1,3-dione: GKK-007-019

^{1}H NMR:

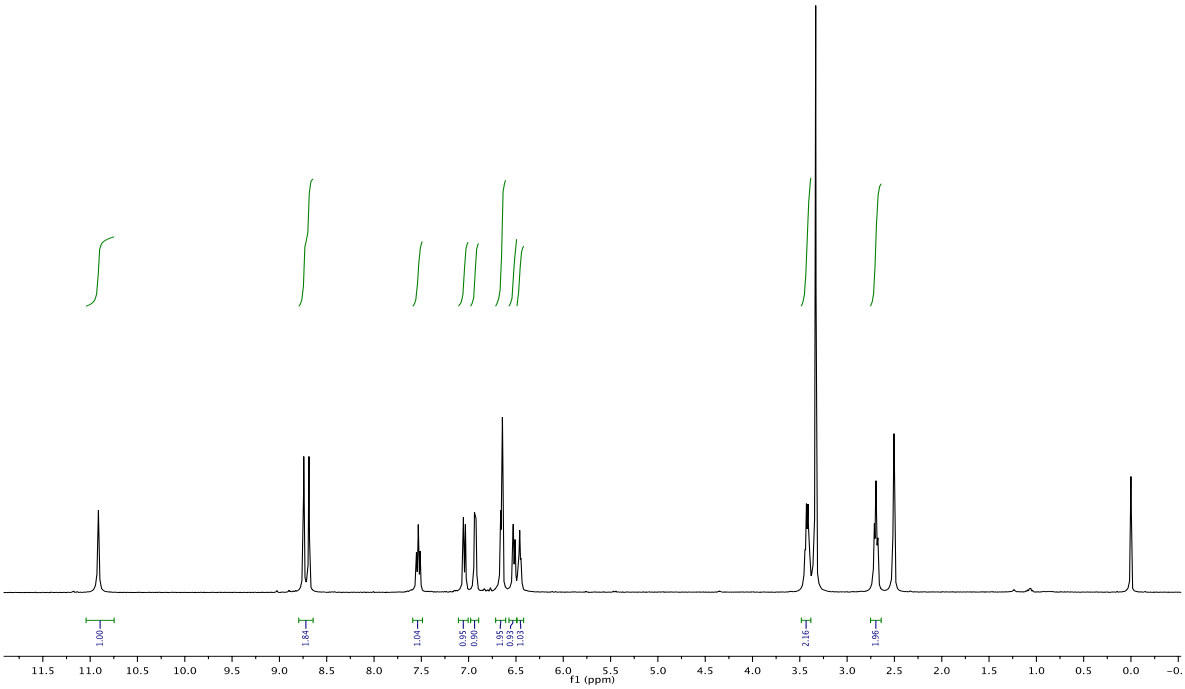


^{13}C NMR:

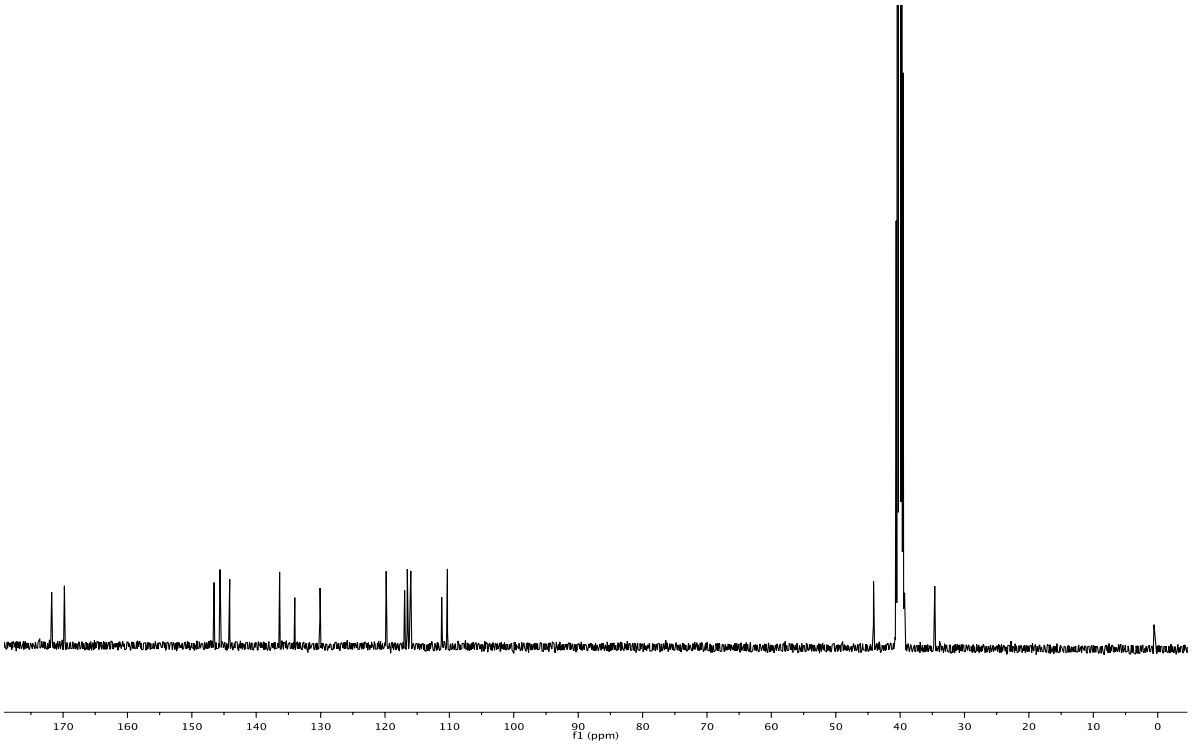


4-((3,4-Dihydroxyphenethyl)amino)isoindoline-1,3-dione: GKK-007-027B

^{1}H NMR:

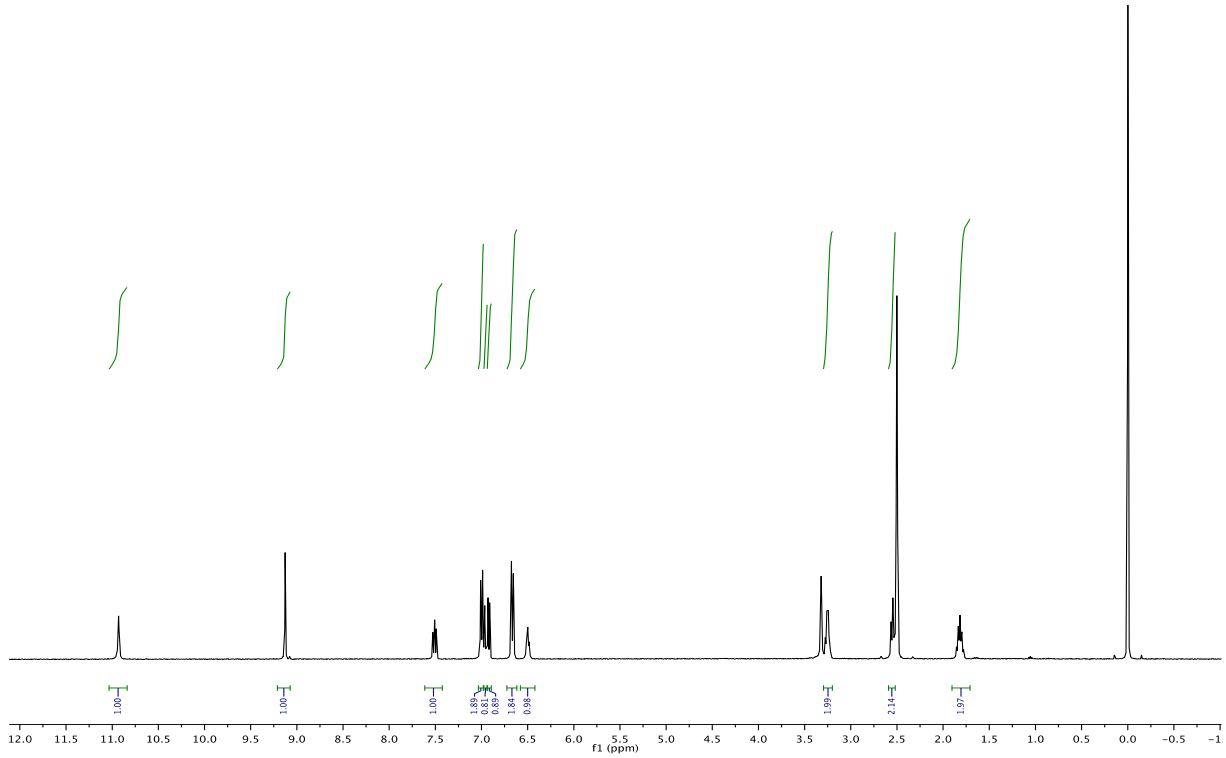


^{13}C NMR:

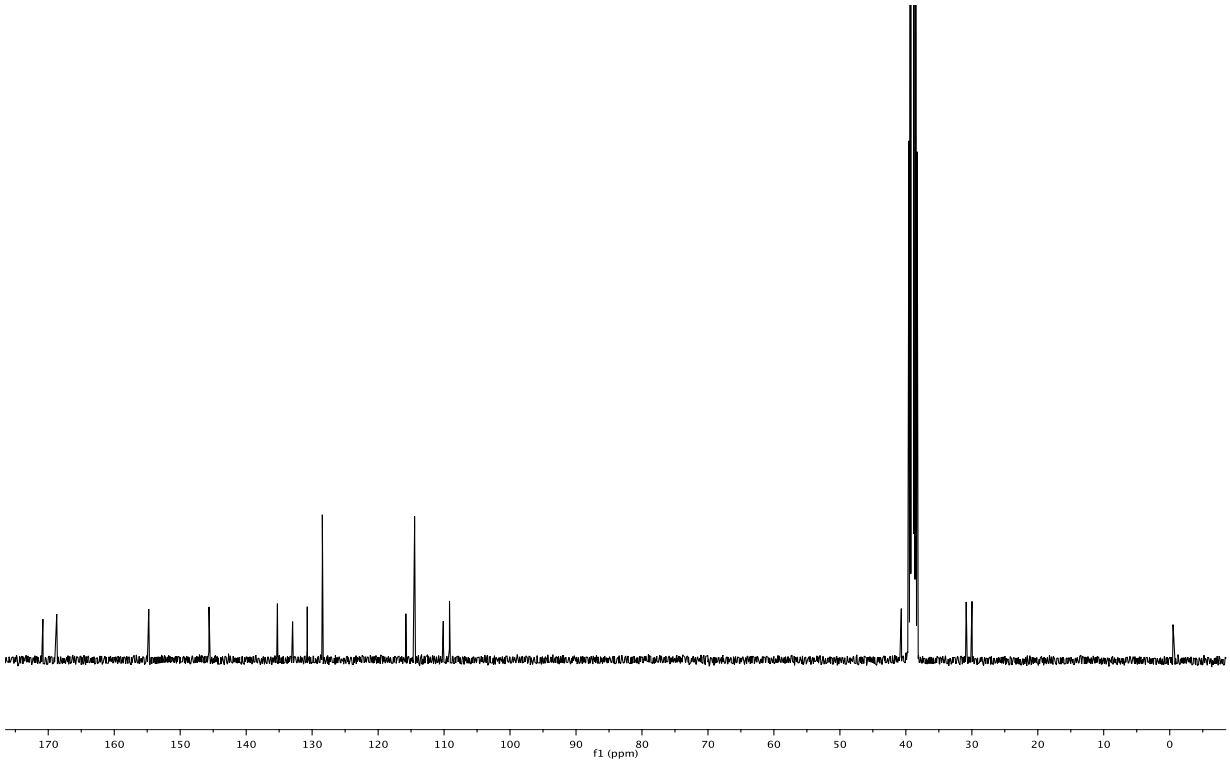


4-((3-(4-Hydroxyphenyl)propyl)amino)isoindoline-1,3-dione: GKK-006-080 (**Analog 13**)

^{1}H NMR:

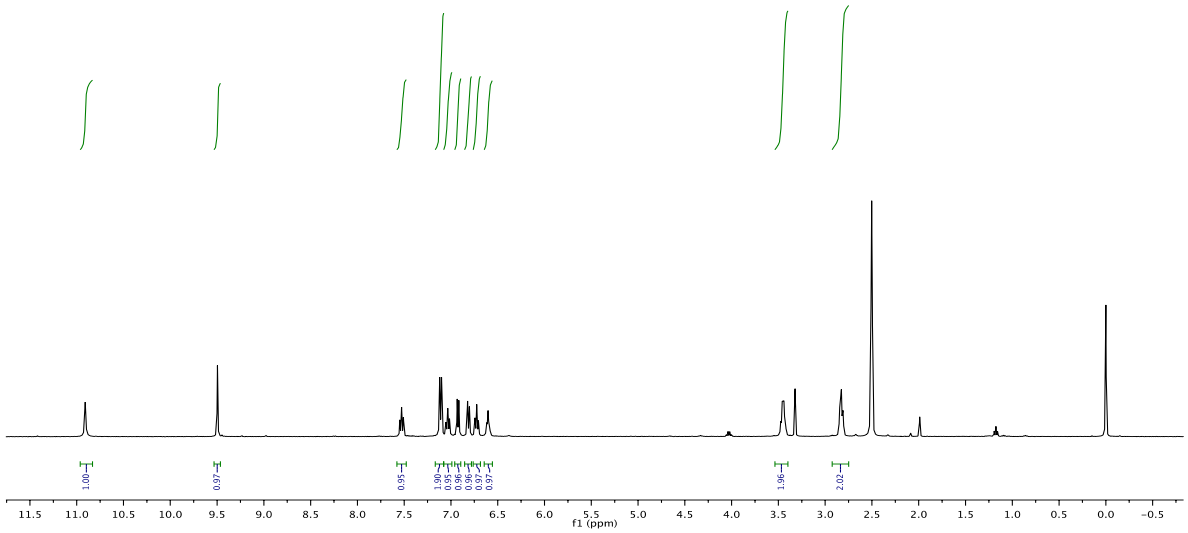


^{13}C NMR:

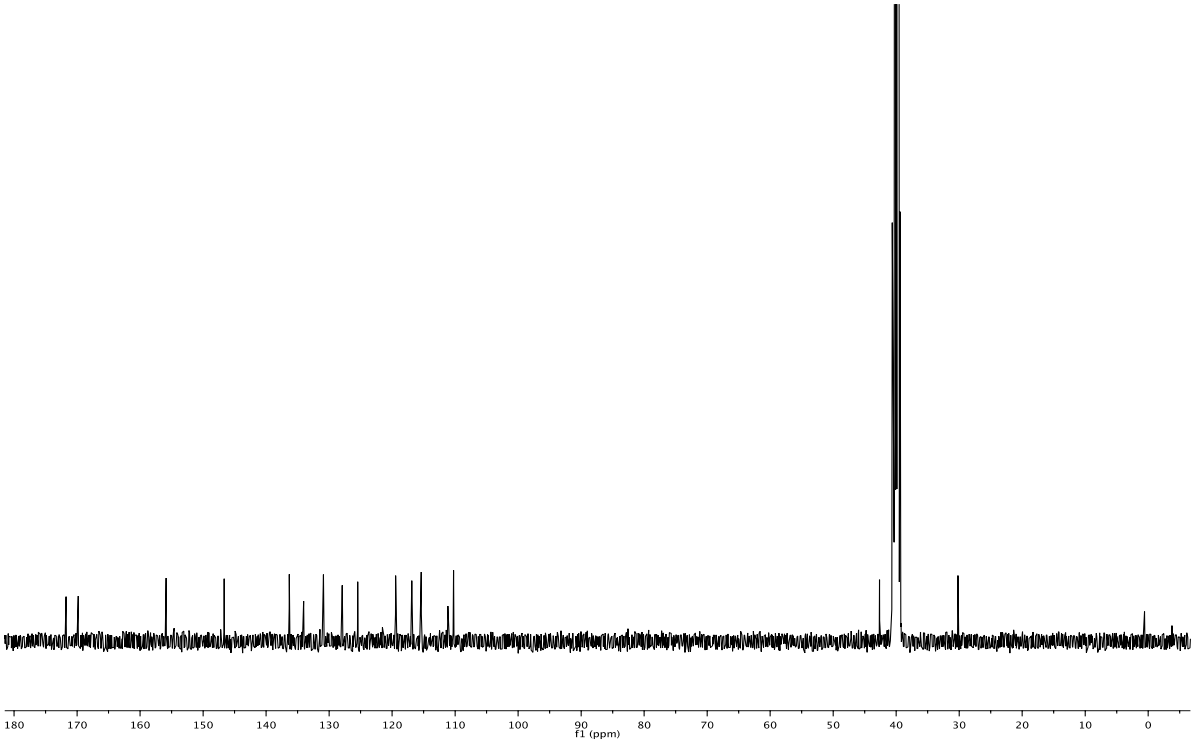


4-((2-Hydroxyphenethyl)amino)isoindoline-1,3-dione: GKK-010-054

^{1}H NMR:

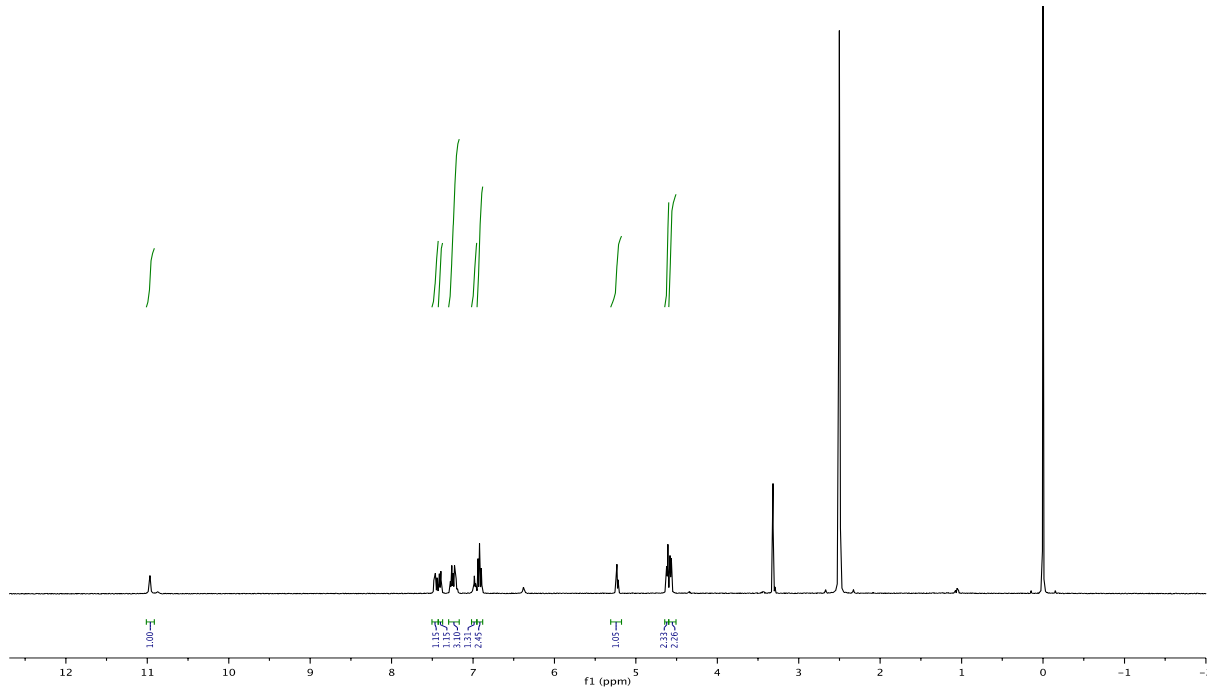


^{13}C NMR:

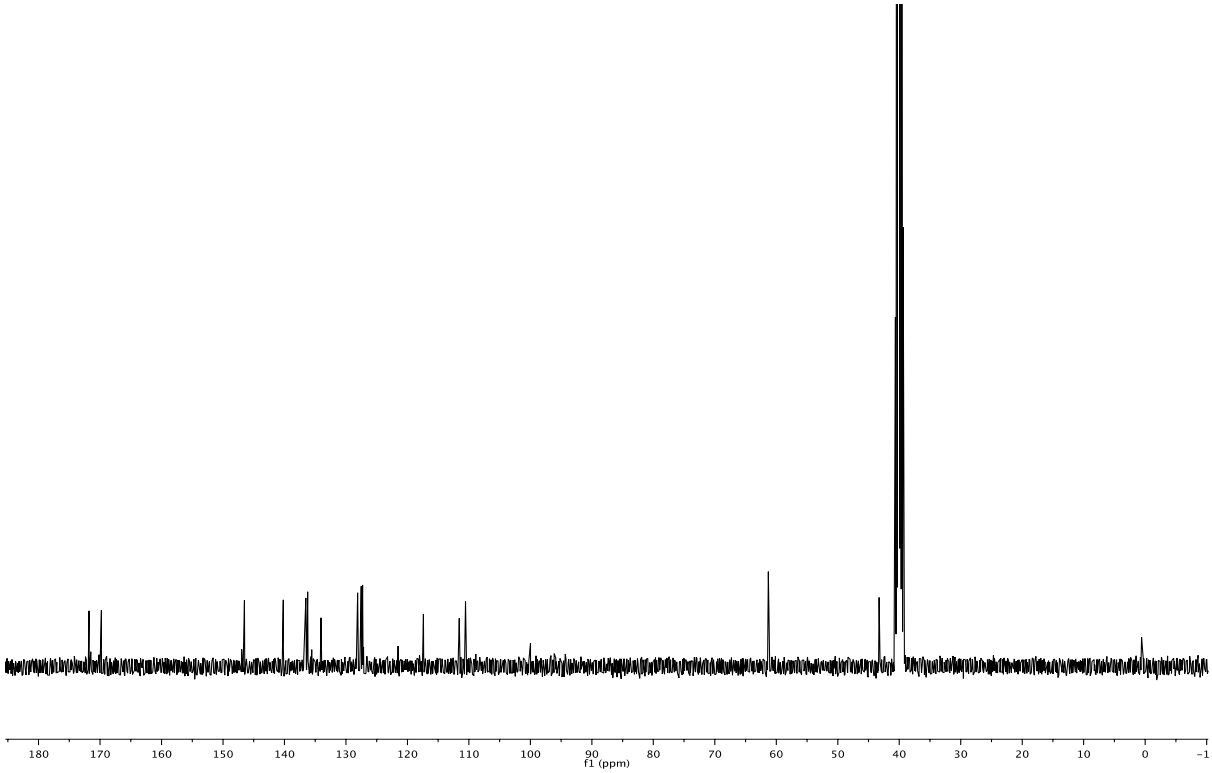


4-((2-(Hydroxymethyl)benzyl)amino)isoindoline-1,3-dione: GKK-010-091

^{1}H NMR:

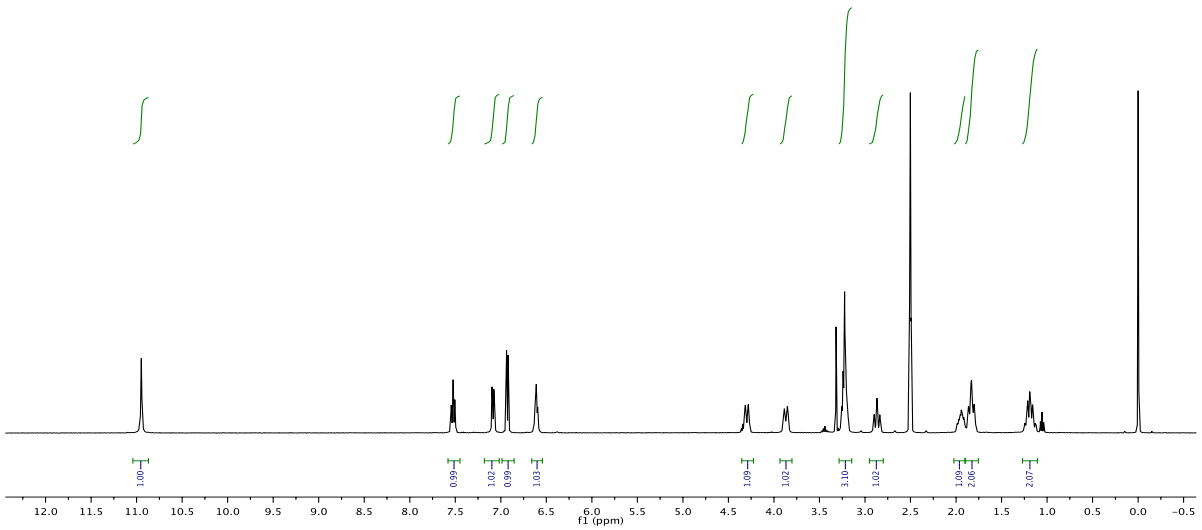


^{13}C NMR:

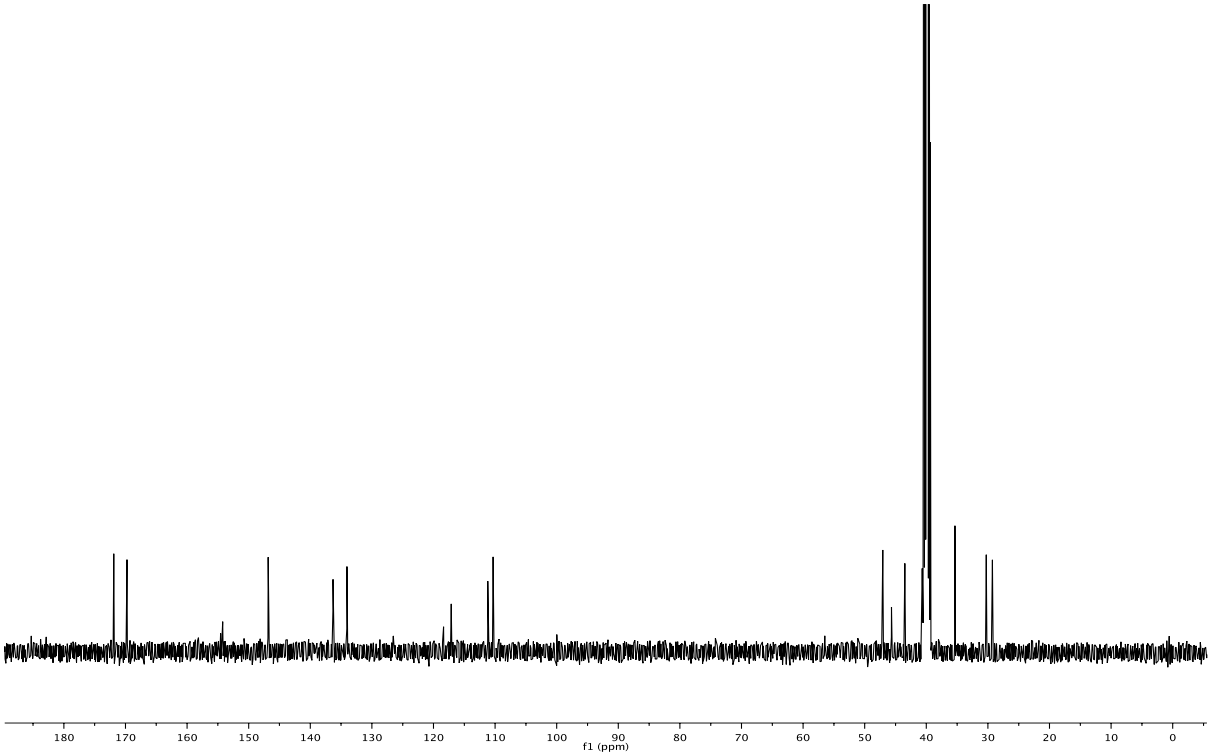


4-(((1-(2,2,2-Trifluoroacetyl)piperidin-4-yl)methyl)amino)isoindoline-1,3-dione: GKK-008-031

^{1}H NMR:

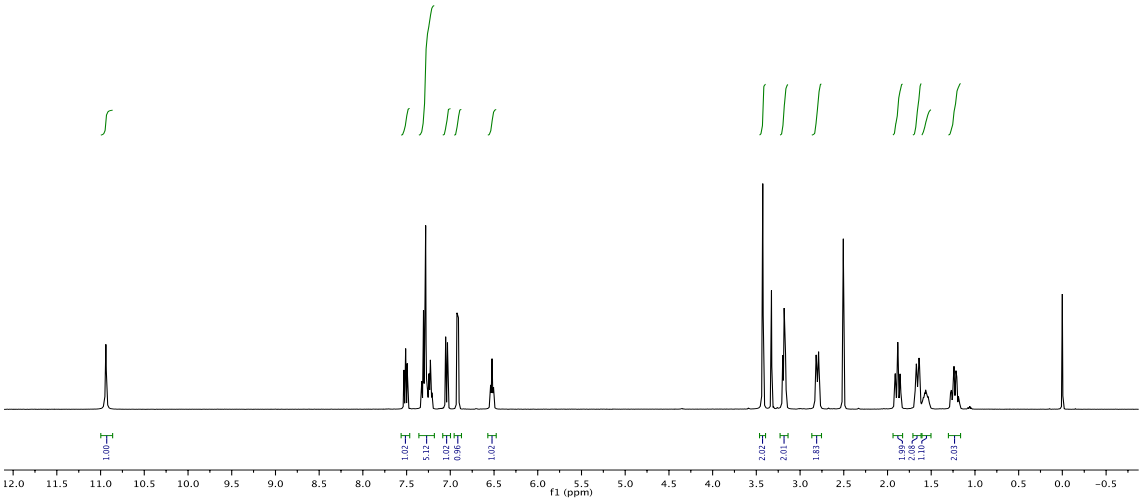


^{13}C NMR:

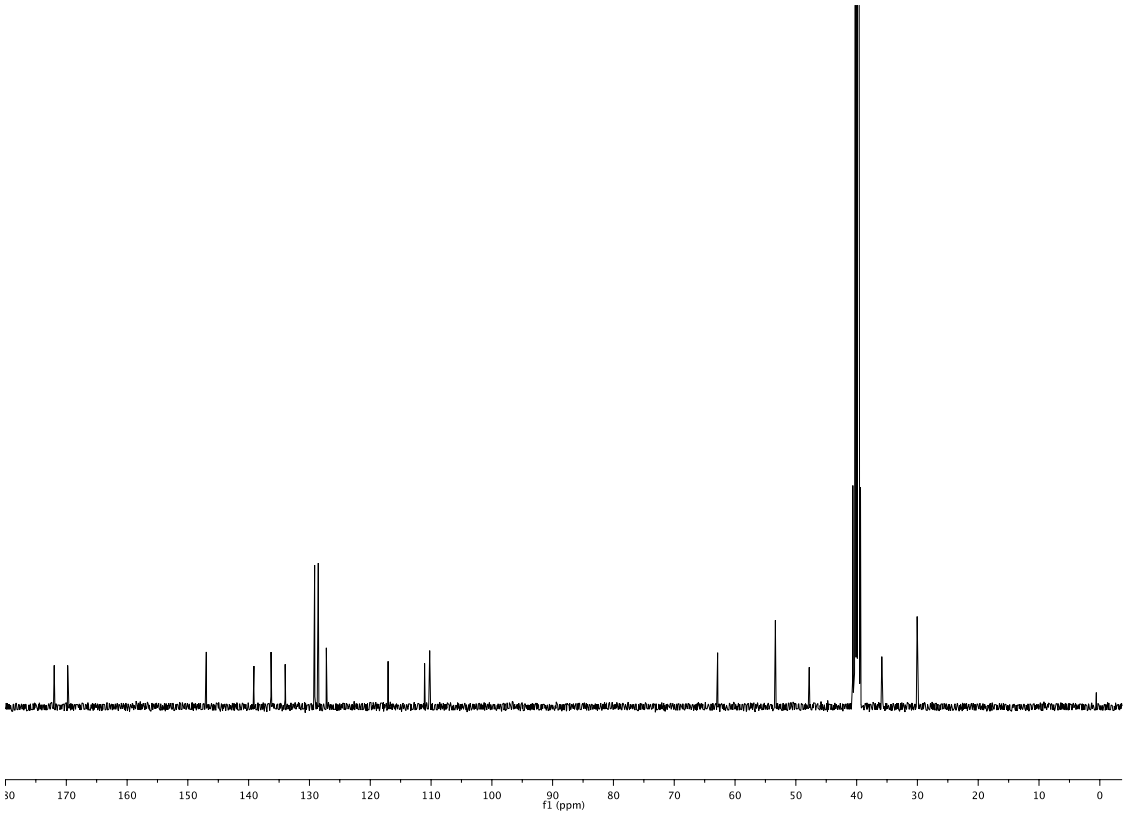


4-(((1-Benzylpiperidin-4-yl)methyl)amino)isoindoline-1,3-dione: GKK-008-025

^{1}H NMR:

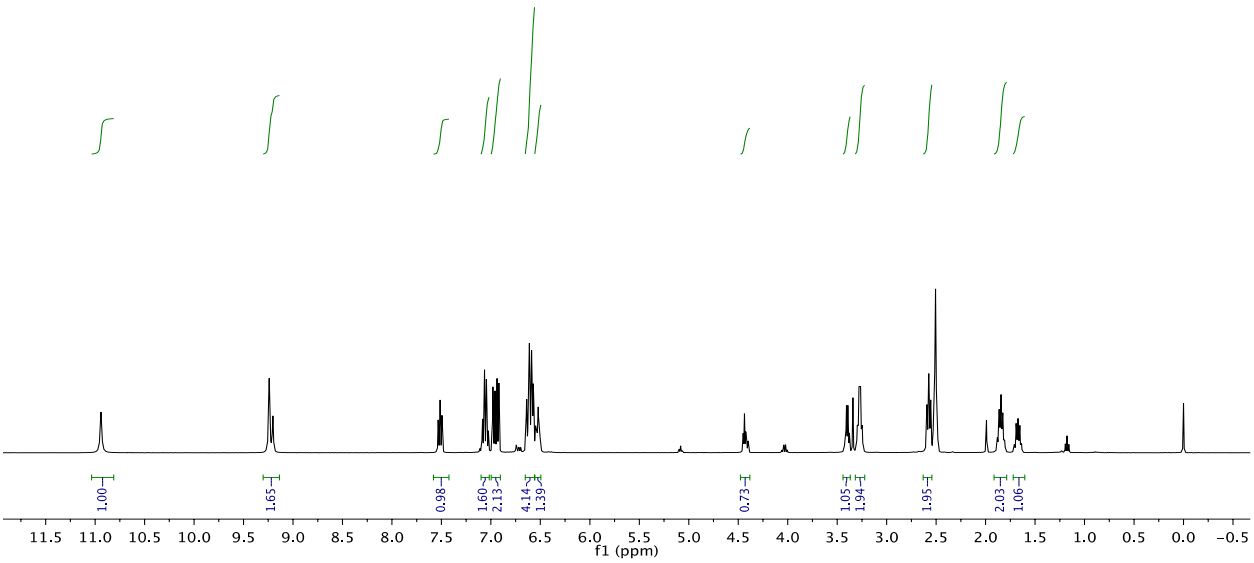


^{13}C NMR:

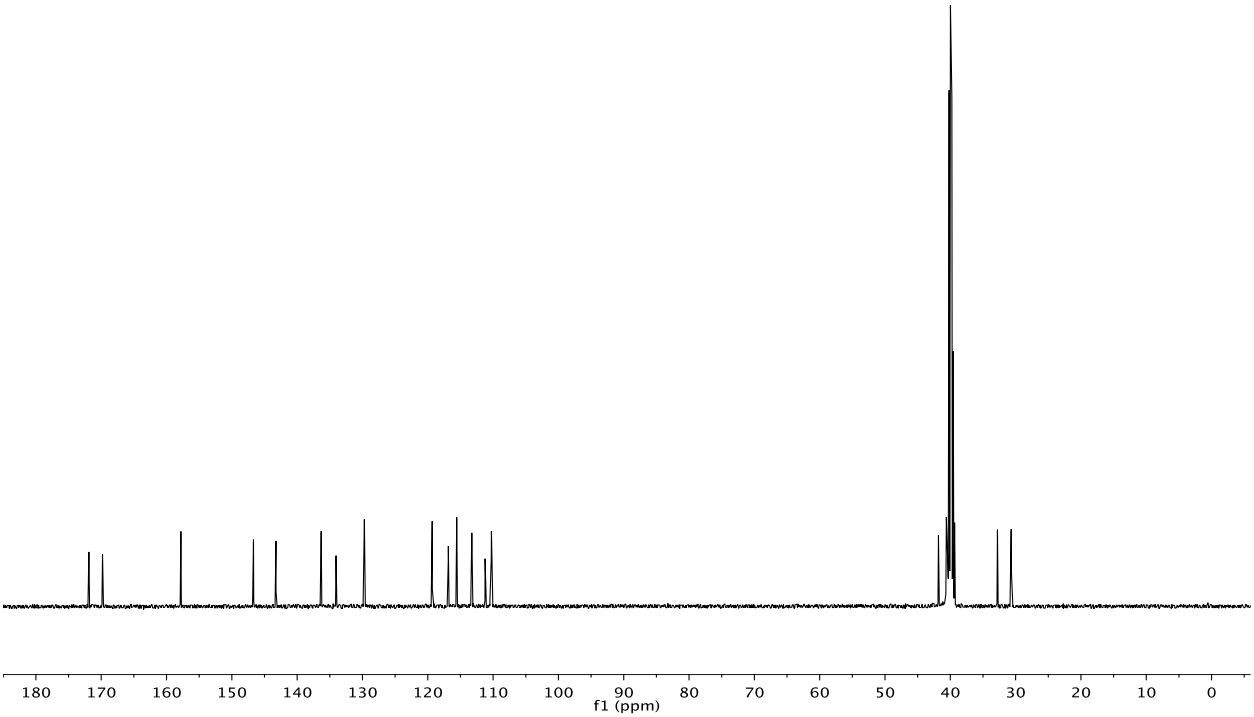


4-((3-(3-Hydroxyphenyl)propyl)amino)isoindoline-1,3-dione: GKK-011-045 (**Analog 16**)

^{1}H NMR:

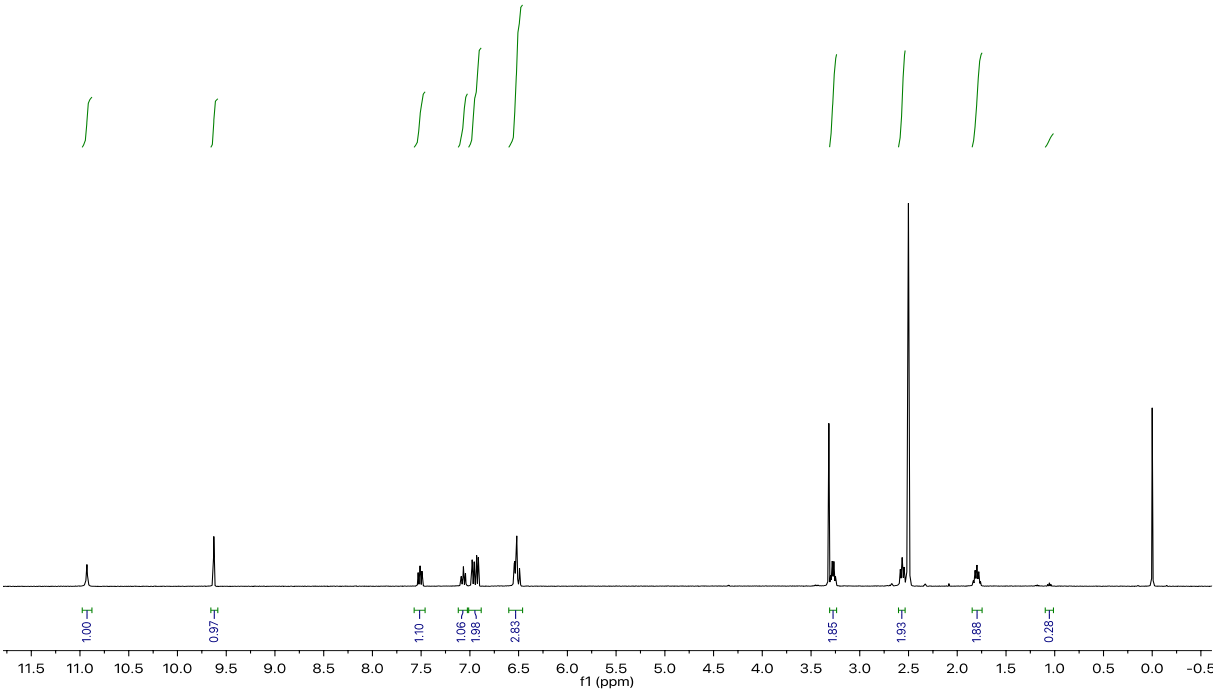


^{13}C NMR:

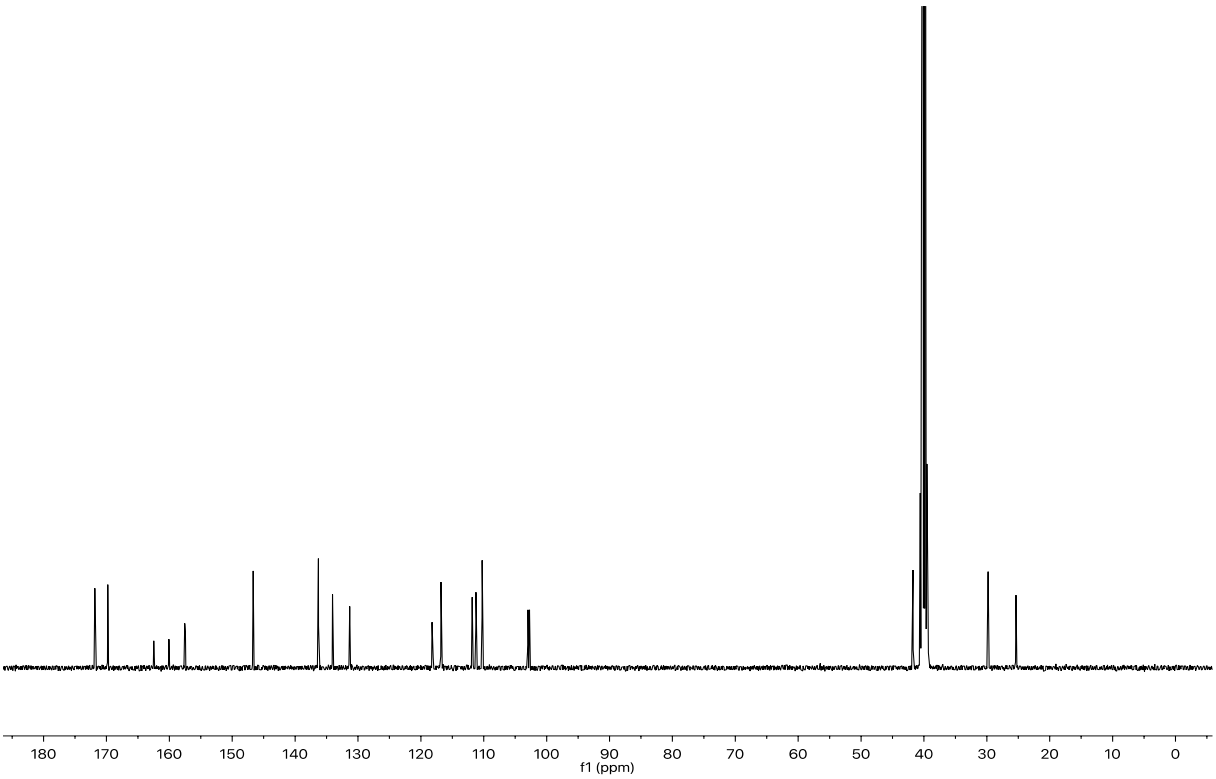


4-((3-(2-Fluoro-4-hydroxyphenyl)propyl)amino)isoindoline-1,3-dione: GKK-011-048

^{1}H NMR:

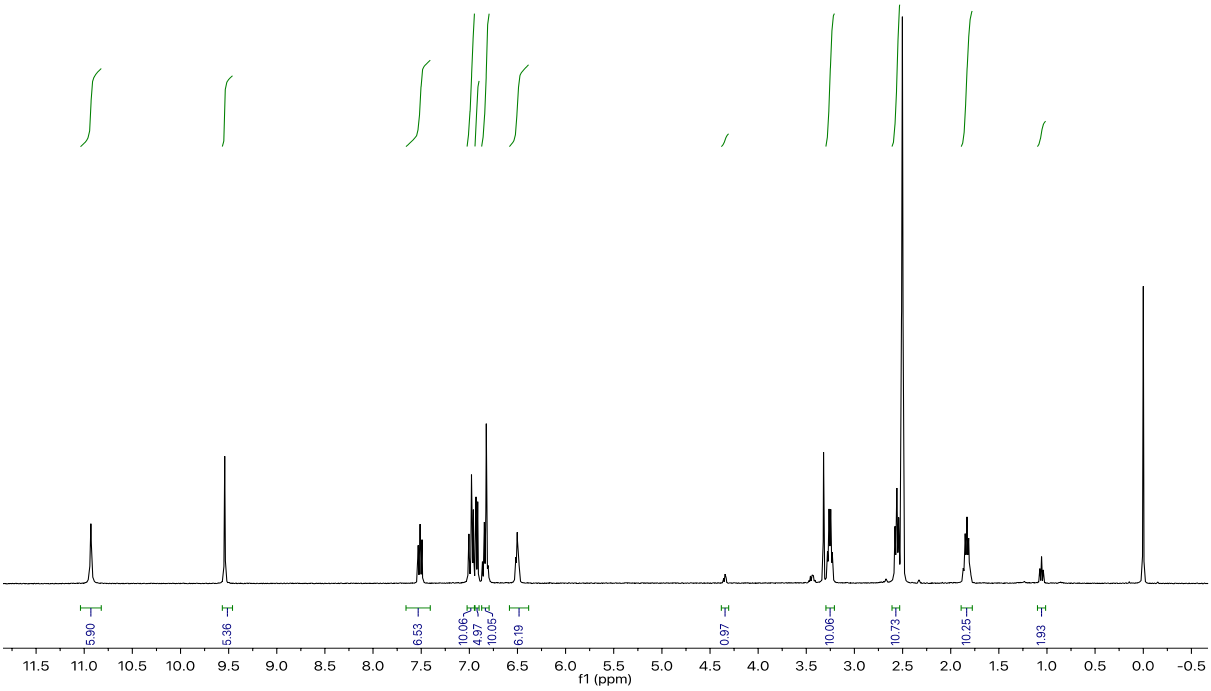


^{13}C NMR:

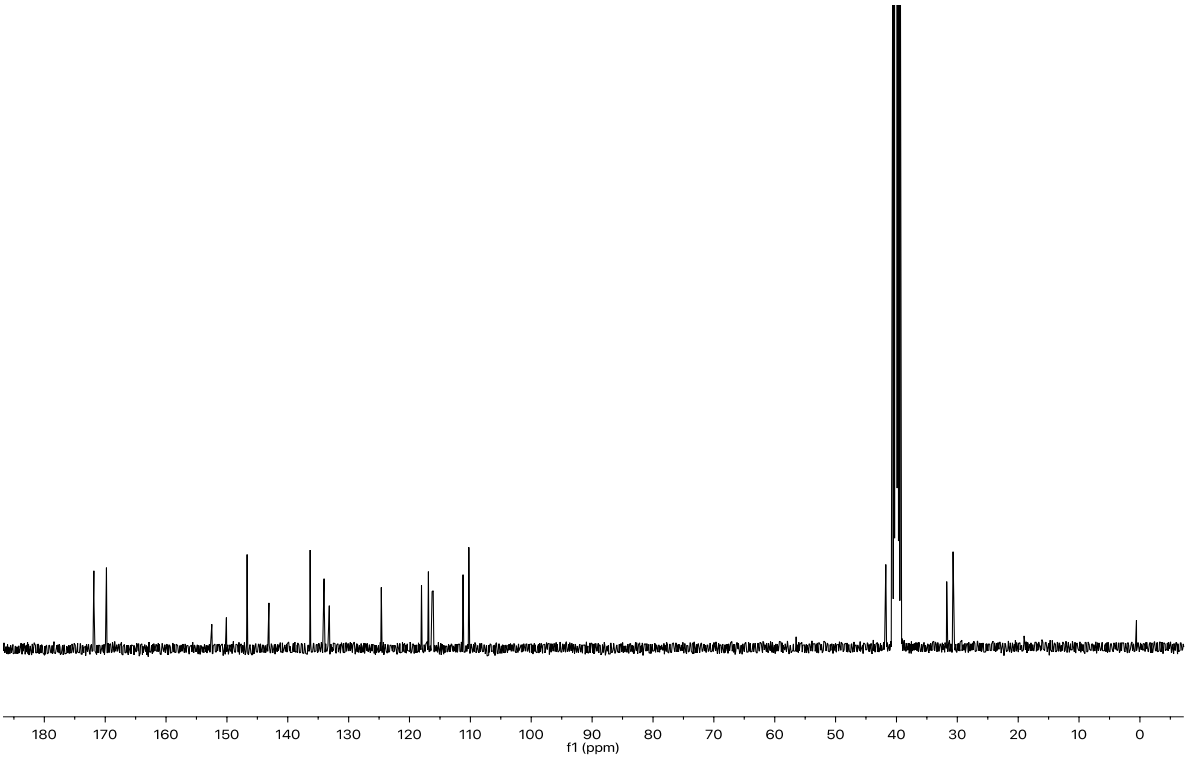


4-((3-(3-Fluoro-4-hydroxyphenyl)propyl)amino)isoindoline-1,3-dione: GKK-011-054

^{1}H NMR:

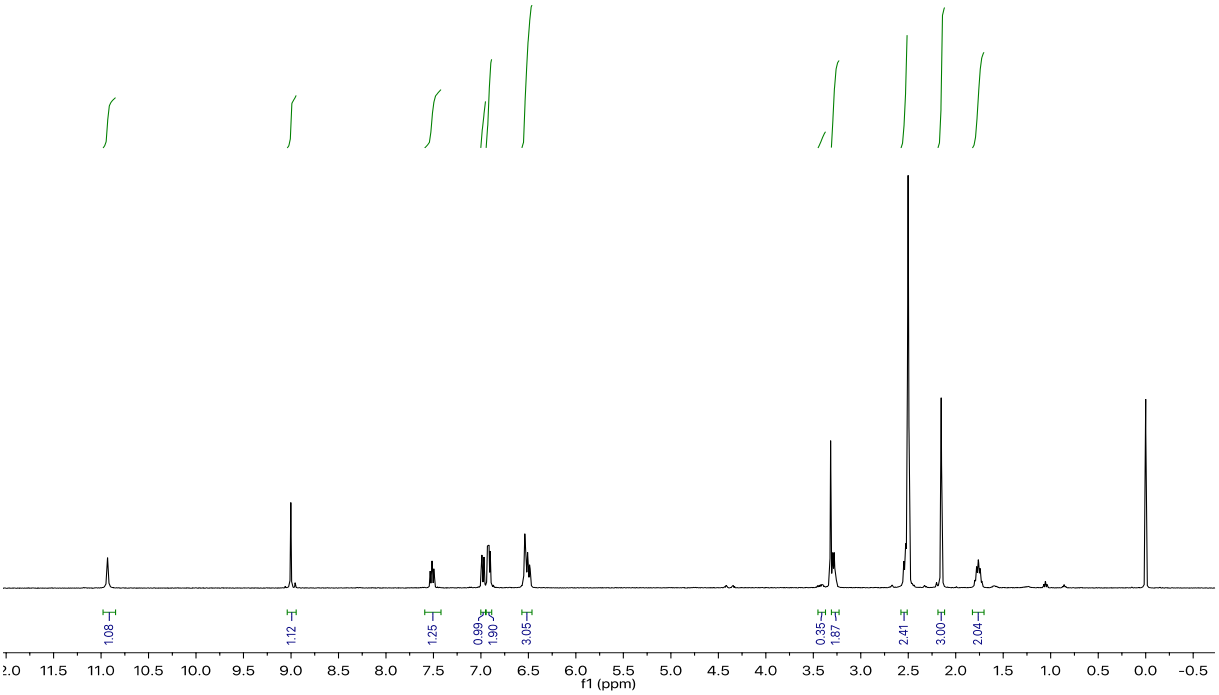


^{13}C NMR:

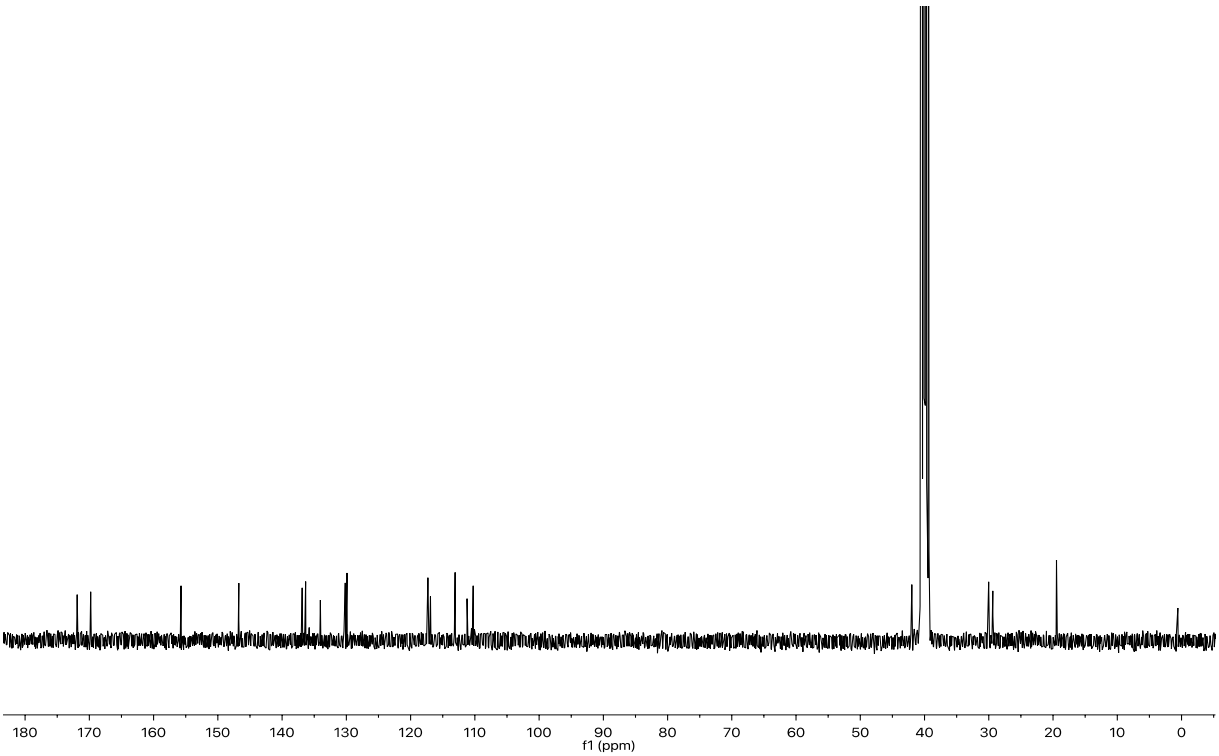


4-((3-(4-Hydroxy-2-methylphenyl)propyl)amino)isoindoline-1,3-dione: GKK-011-059

^{1}H NMR:

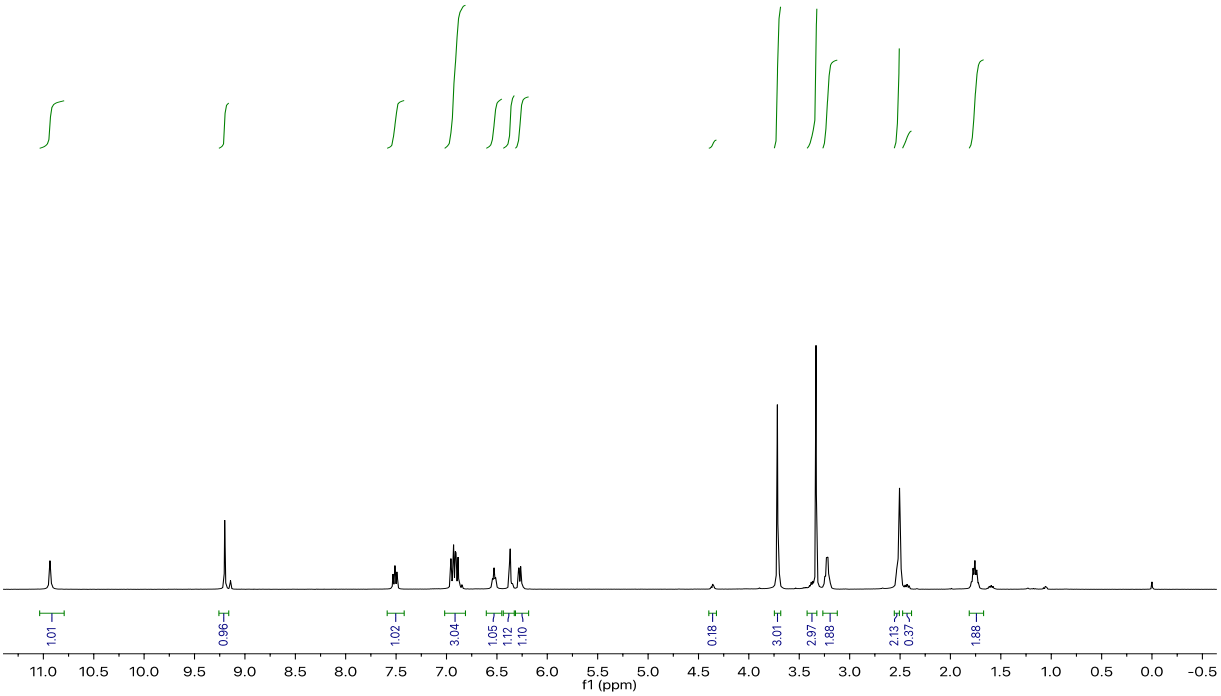


^{13}C NMR:

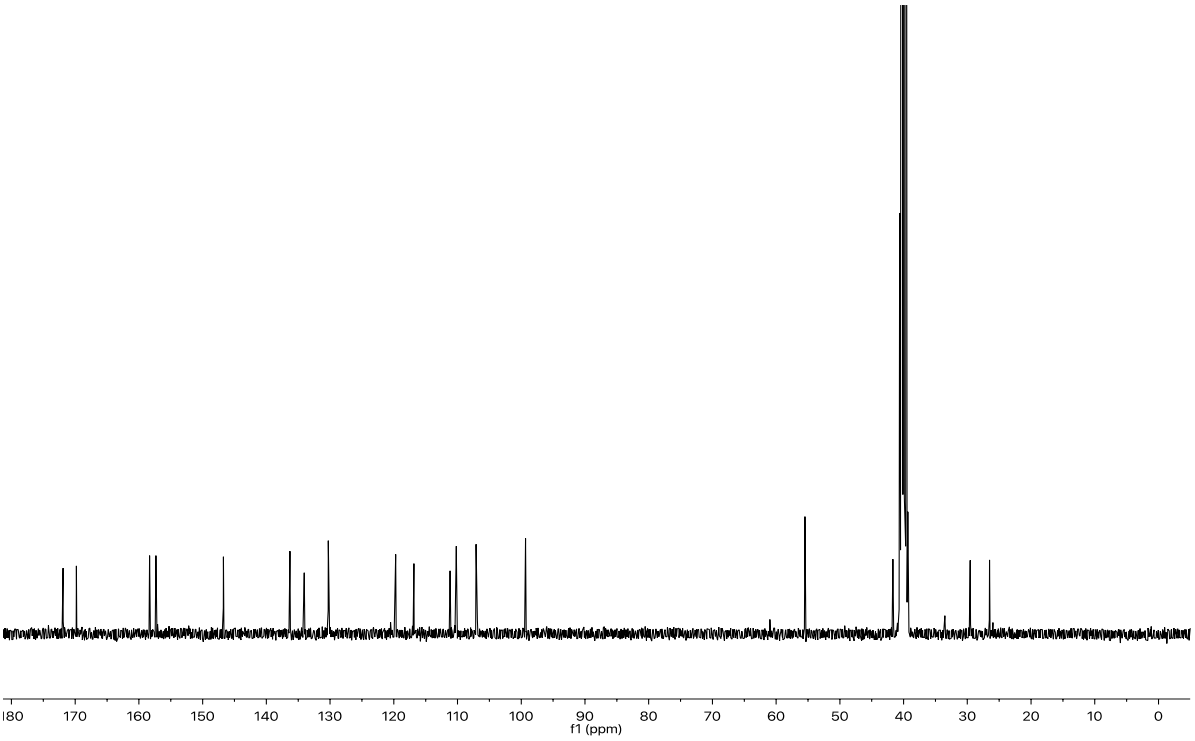


4-((3-(4-Hydroxy-2-methoxyphenyl)propyl)amino)isoindoline-1,3-dione: GKK-011-067 (**Analog 15**)

^{1}H NMR:

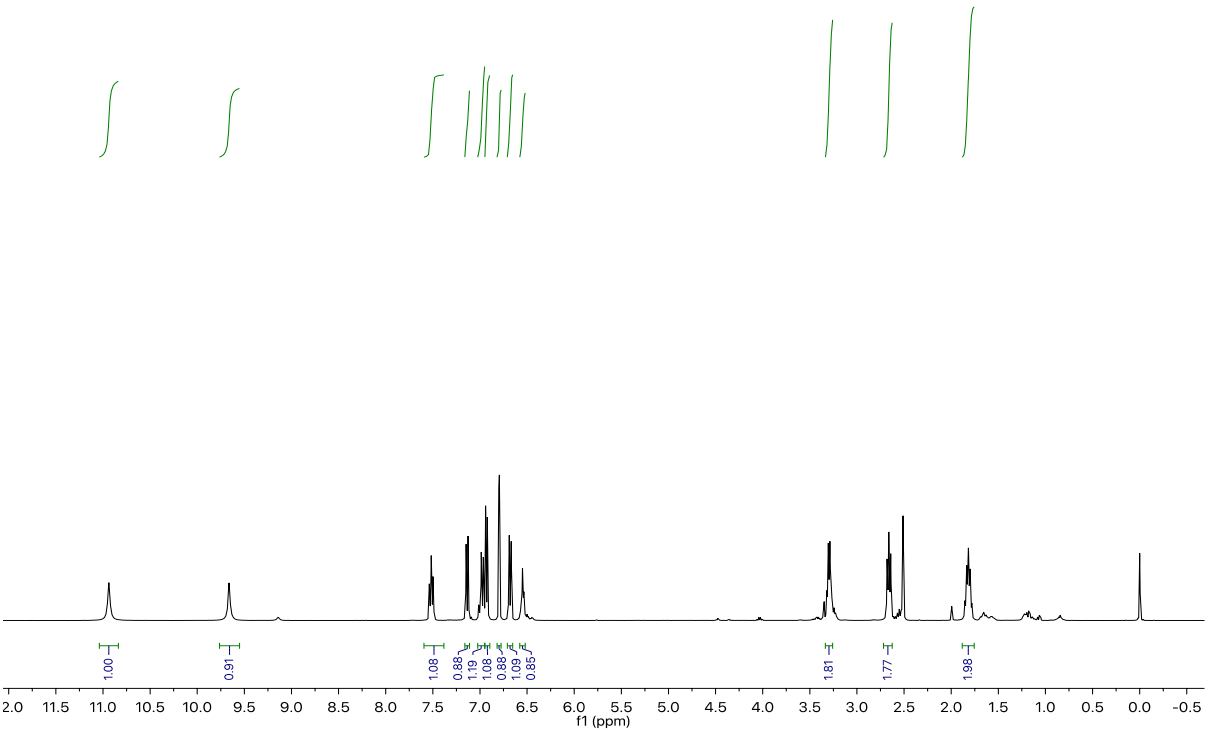


^{13}C NMR:

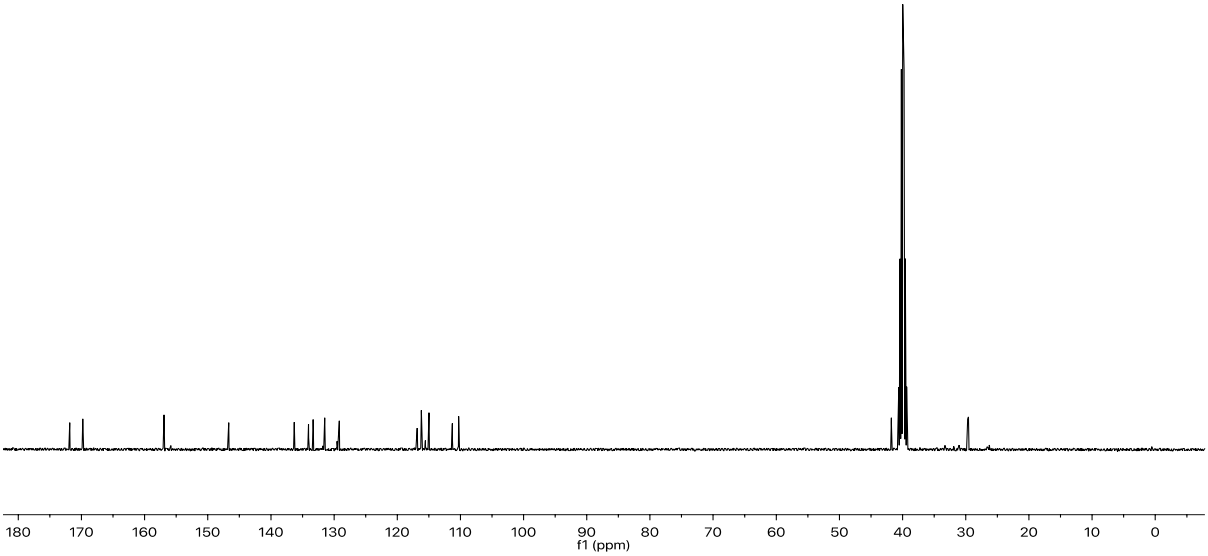


4-((3-(2-Chloro-4-hydroxyphenyl)propyl)amino)isoindoline-1,3-dione: GKK-011-077

^{1}H NMR:

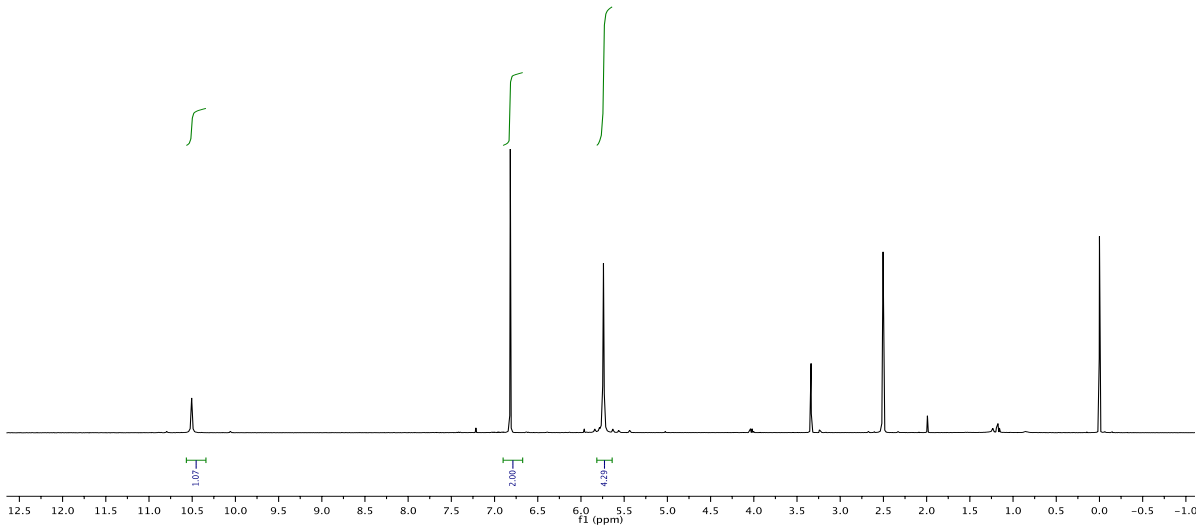


^{13}C NMR:

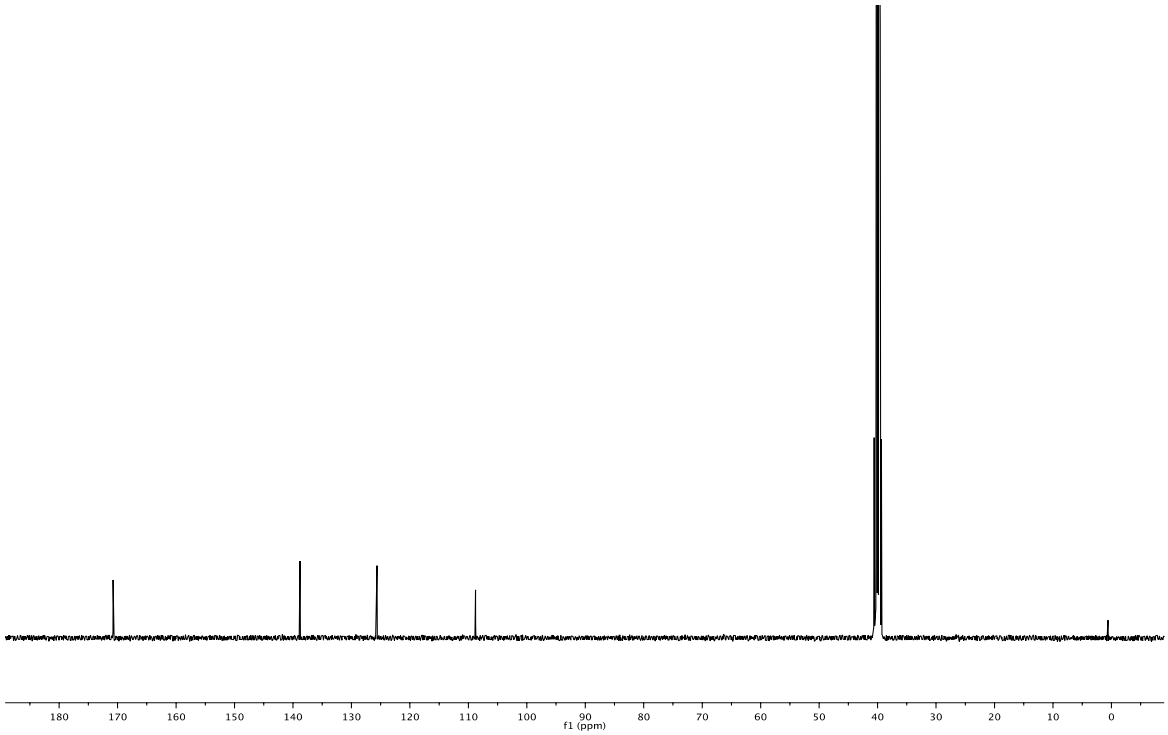


4,7-Diaminoisoindoline-1,3-dione: GKK-011-016

^{1}H NMR:



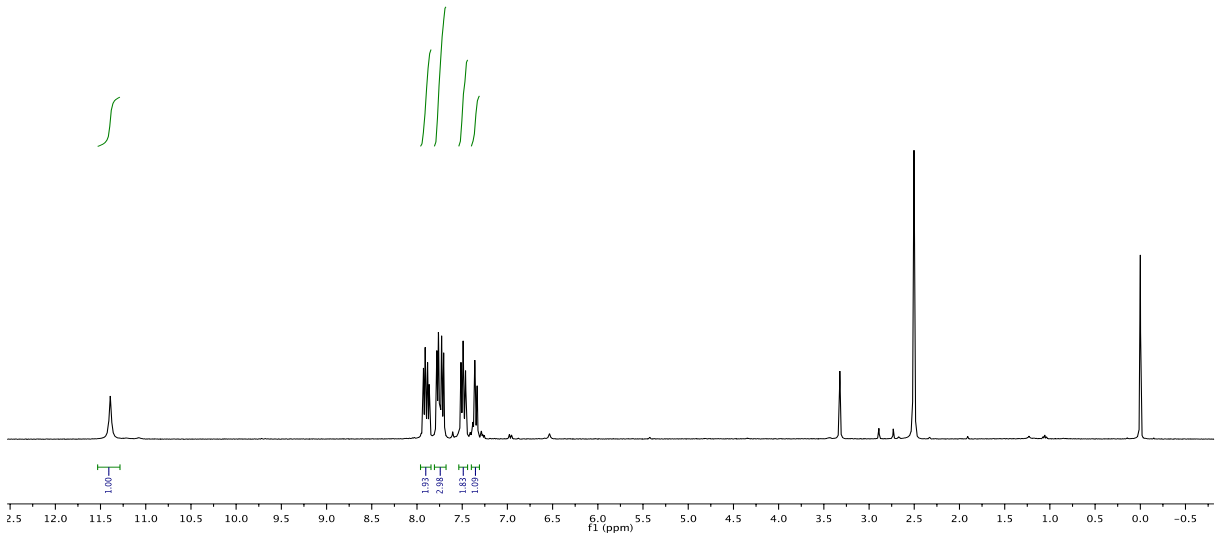
^{13}C NMR:



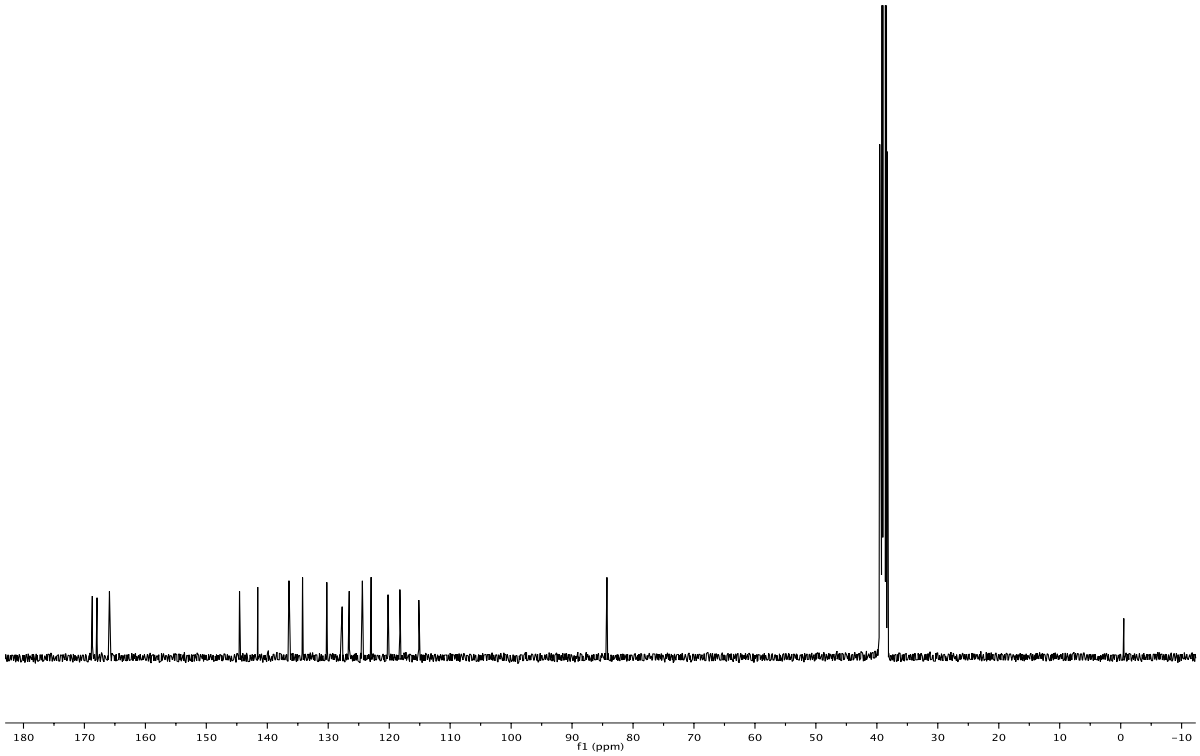
^{1}H and ^{13}C spectra for 4,7-diaminoisoindoline-1,3-dione series

2-(((7-Amino-1,3-dioxoisoindolin-4-yl)amino-methyl)benzoic acid: GKK-008-080

^{1}H NMR:

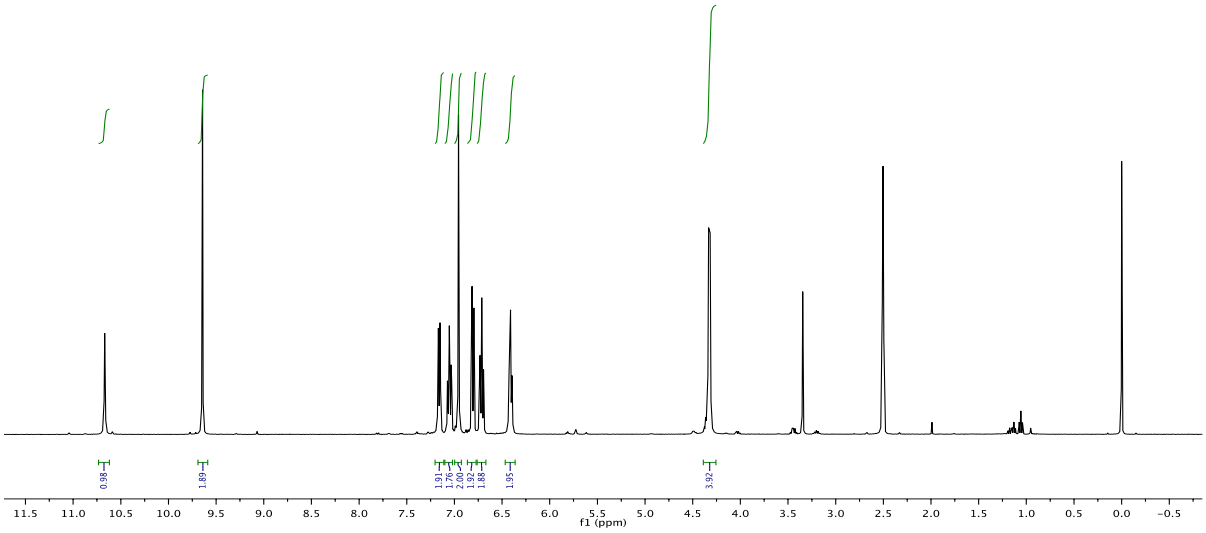


^{13}C NMR:

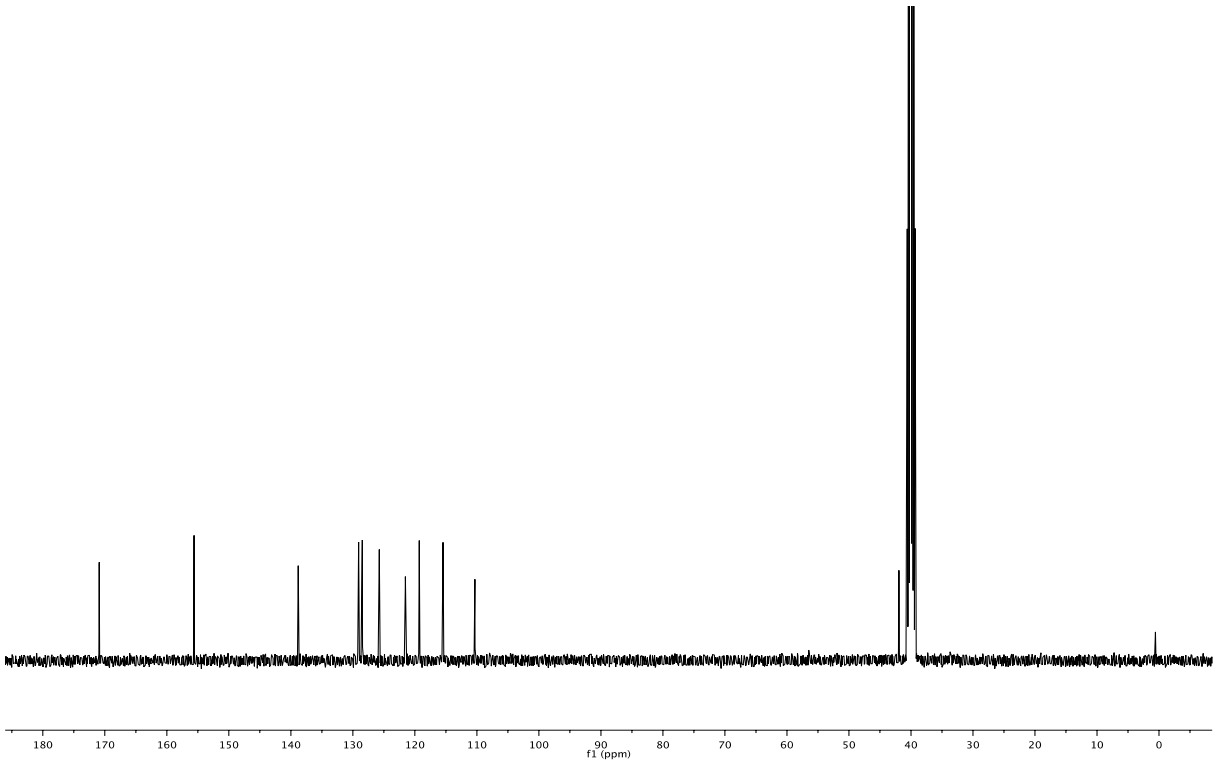


4,7-Bis((2-hydroxybenzyl)amino)isoindoline-1,3-dione: GKK-011-023F1

^{1}H NMR:

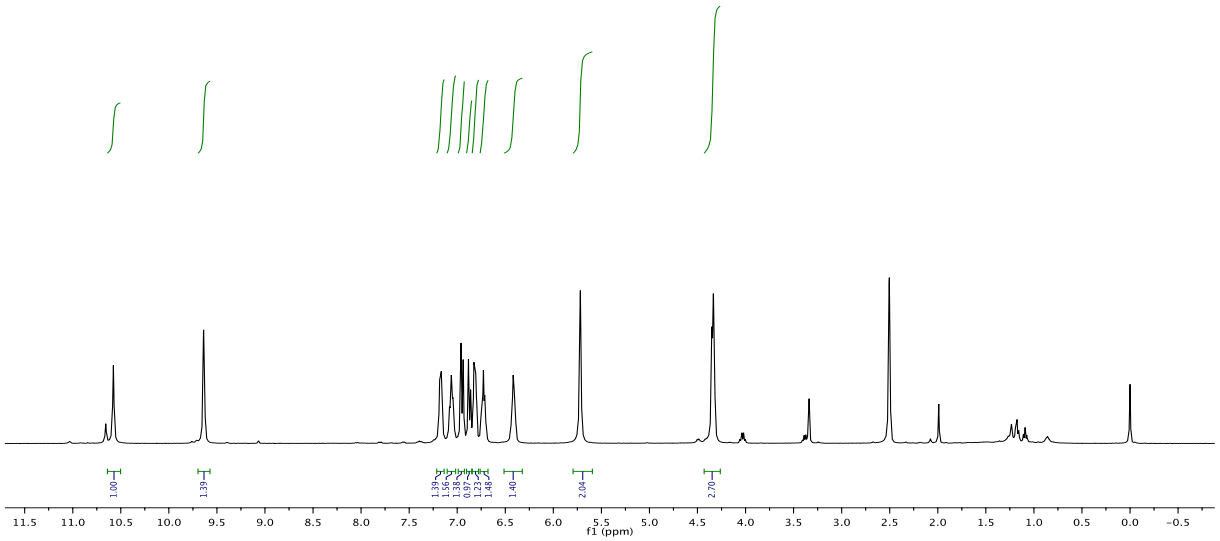


^{13}C NMR:

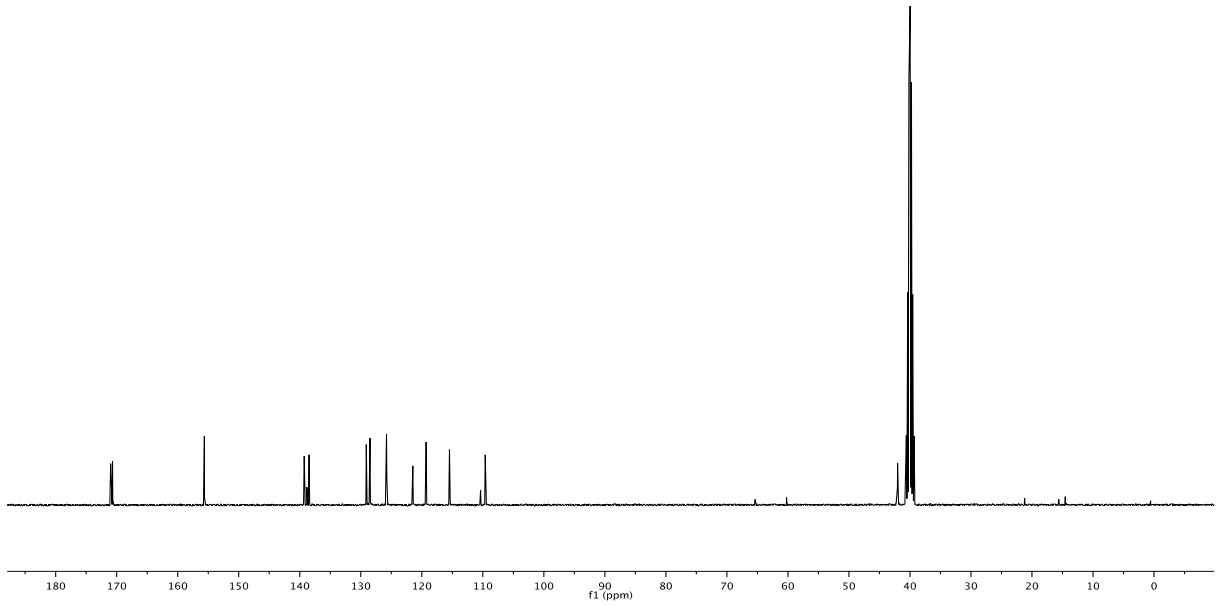


4-Amino-7-((2-hydroxybenzyl)amino)isoindoline-1,3-dione: GKK-011-023F2

^{1}H NMR:

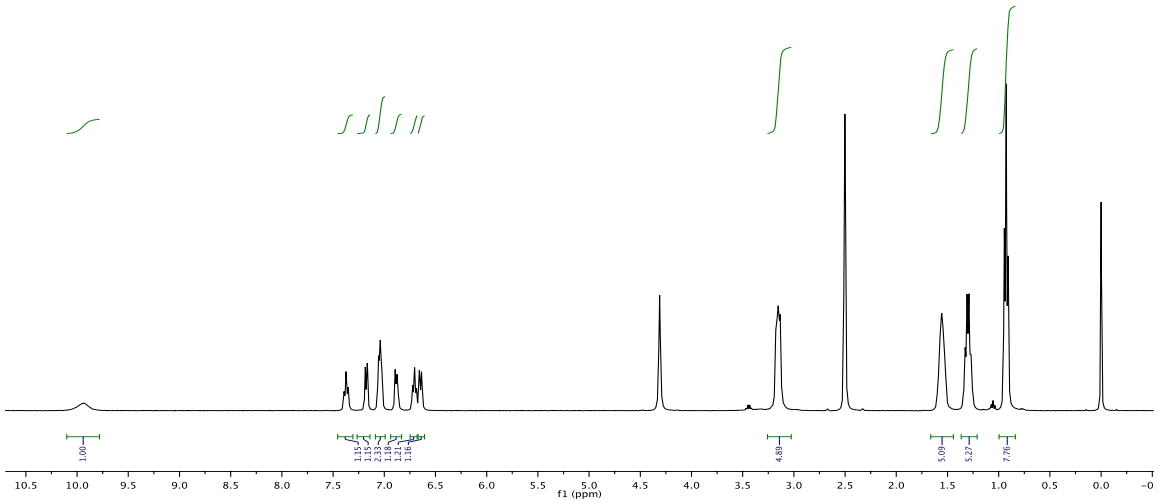


^{13}C NMR:

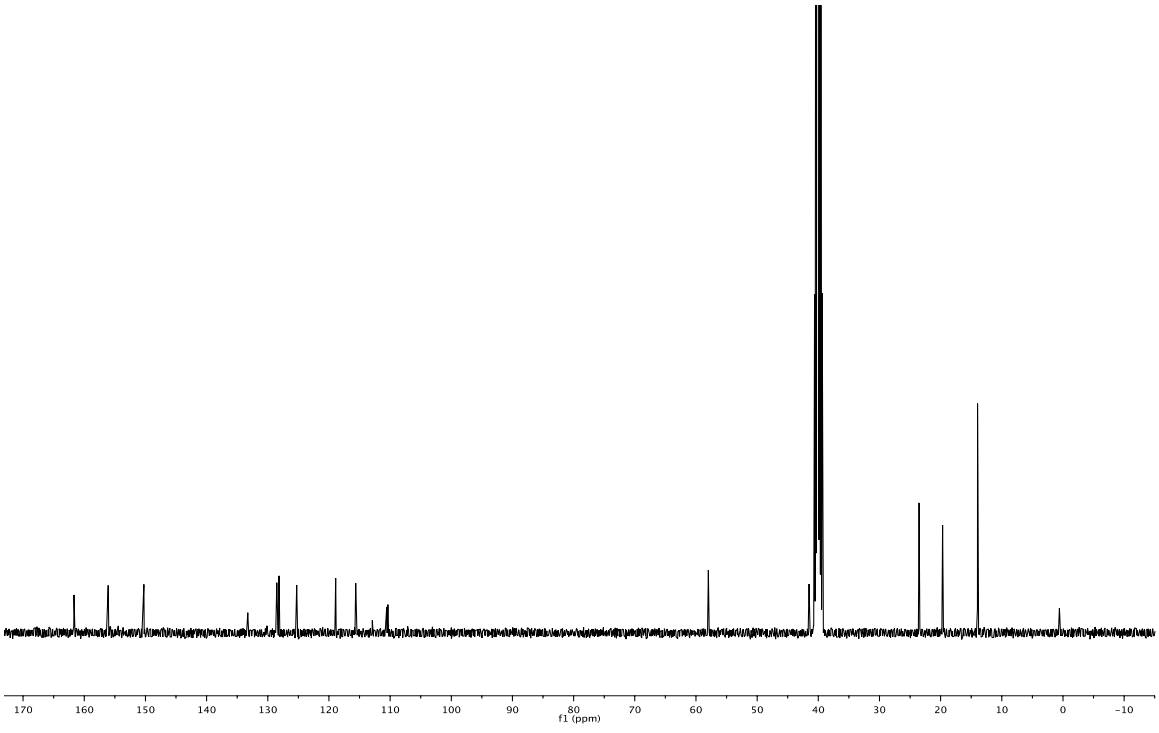


2,3-Dibutyl-5-((2-hydroxybenzyl)amino)-2,3-dihydrophthalazine-1,4-dione: GKK-011-022

^{1}H NMR:

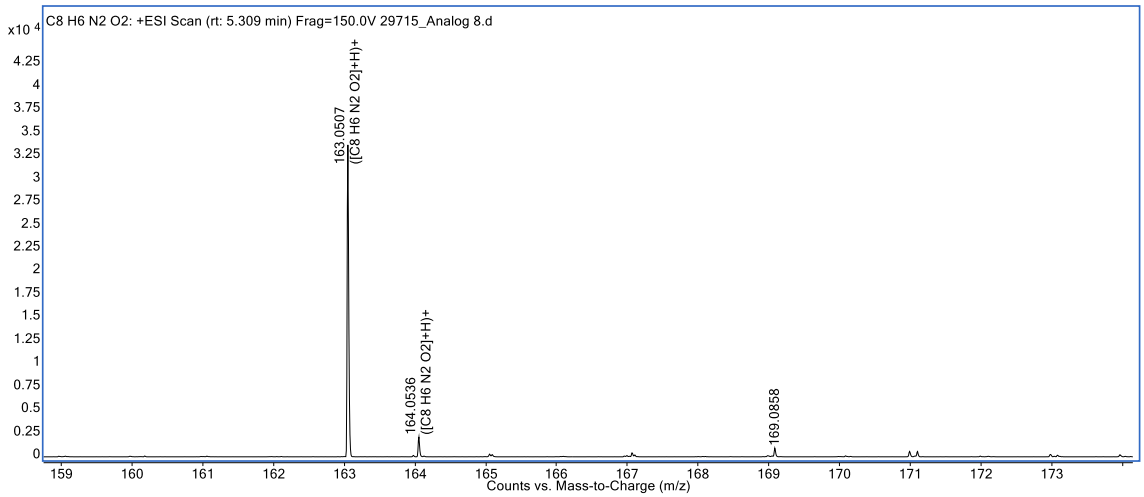


^{13}C NMR:

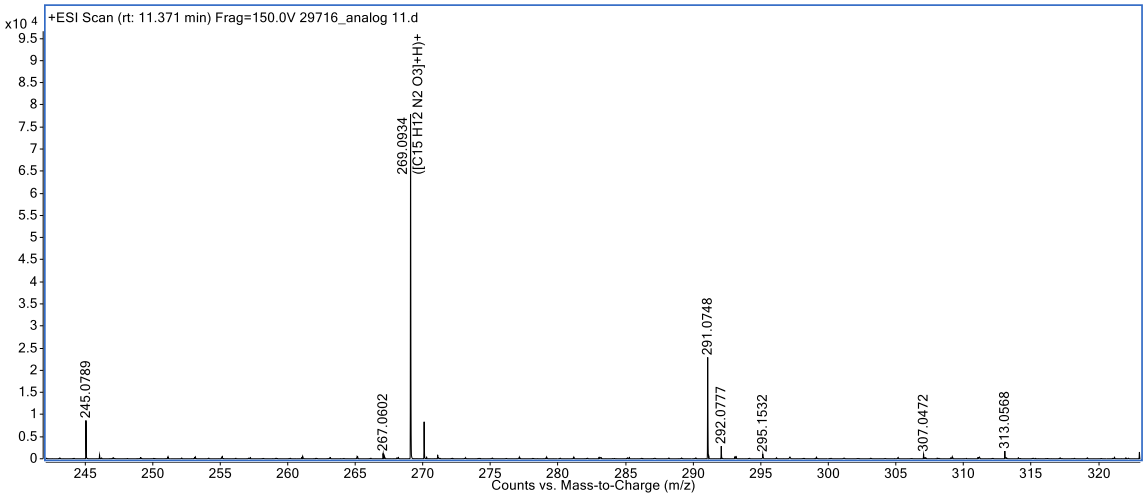


High resolution mass spectra of analogs in Table 1

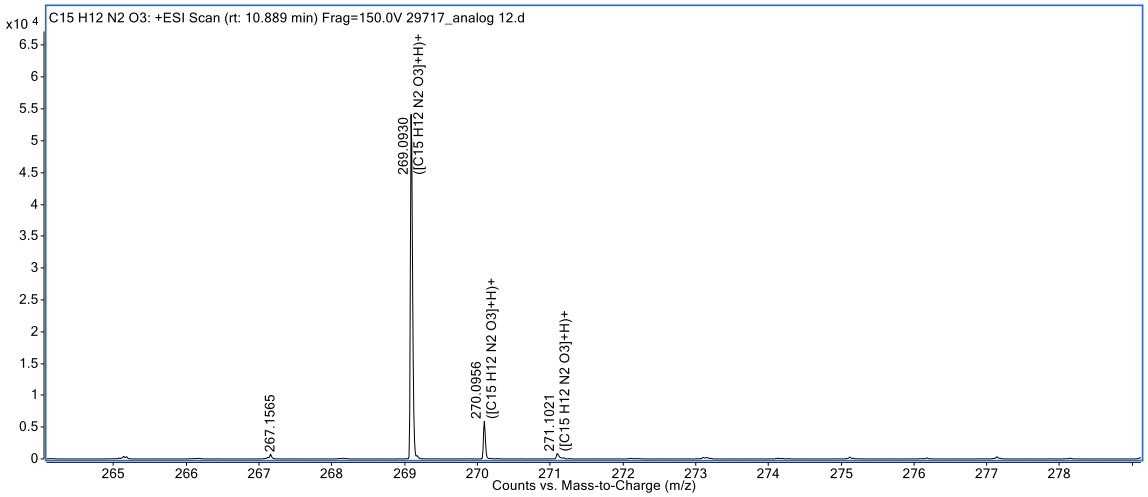
Analog **8**



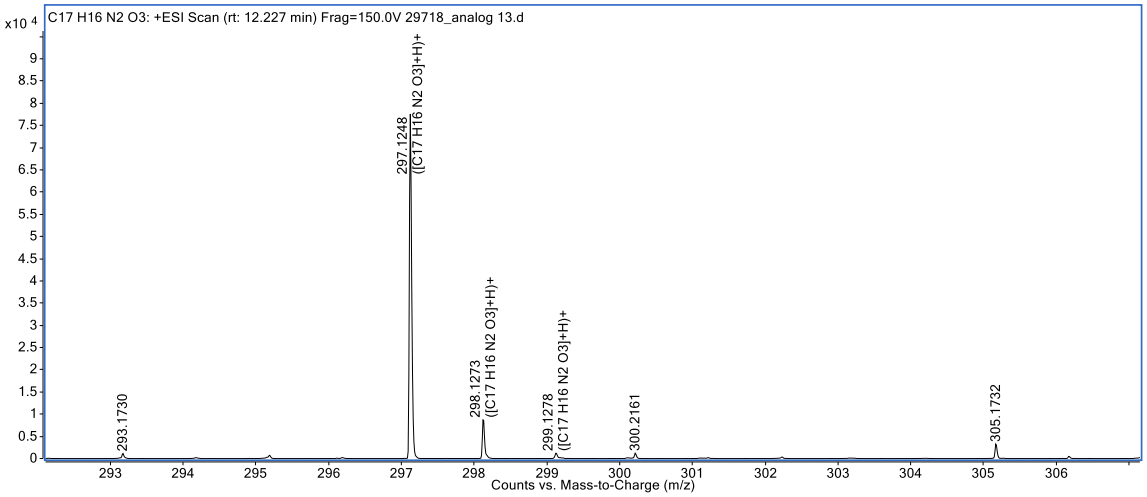
Analog **11**



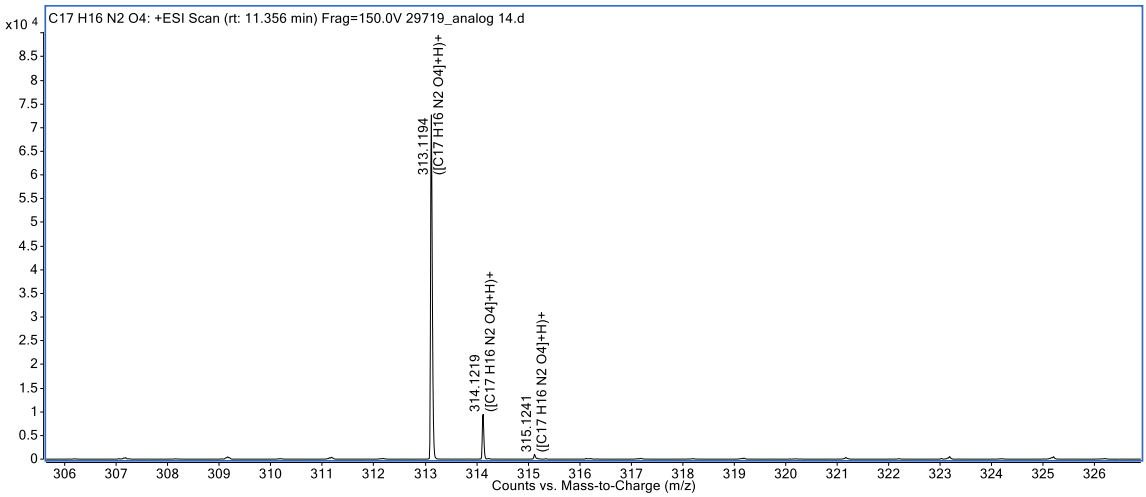
Analog **12**



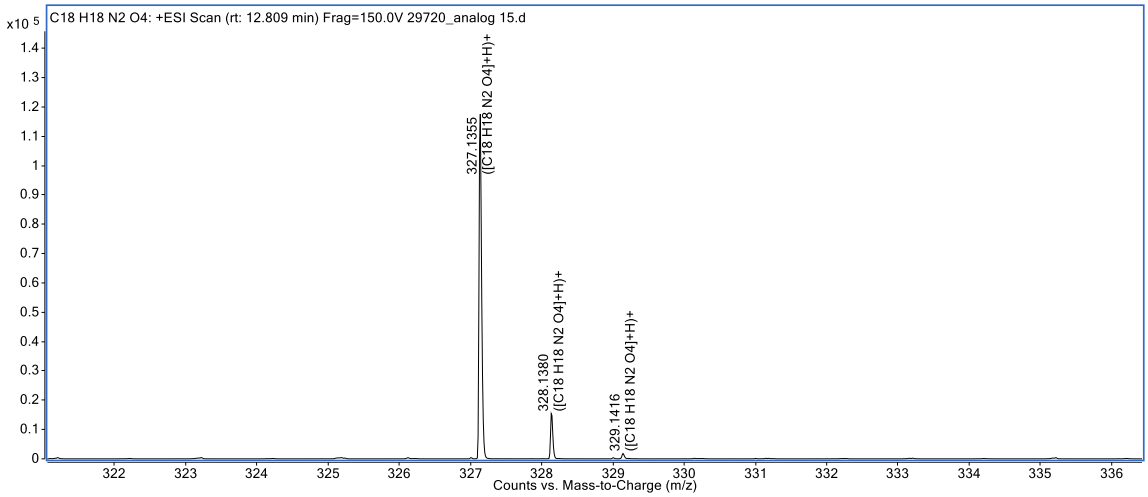
Analog **13**



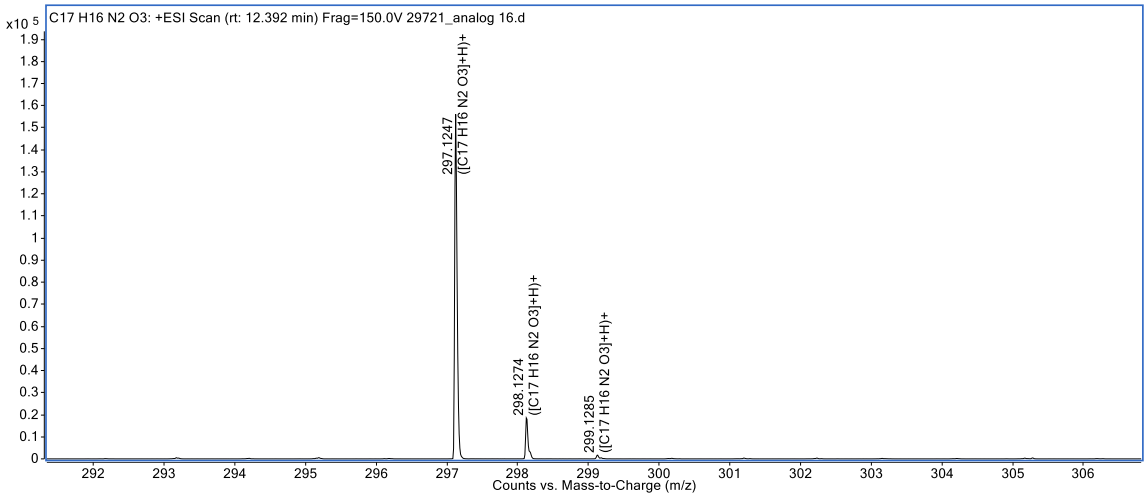
Analog **14**



Analog **15**



Analog **16**


C17 H16 N2 O3: +ESI Scan (rt: 12.392 min) Frag=150.0V 29721_analog 16.d
x10 5
297.1247
([C17 H16 N2 O3]+H)+
298.1274
([C17 H16 N2 O3]+H)+
299.1285
([C17 H16 N2 O3]+H)+
Counts vs. Mass-to-Charge (m/z)