Supporting Information

6,7-Dihydroxy-1-oxoisoindoline-4-sulfonamide-containing HIV-1 Integrase Inhibitors

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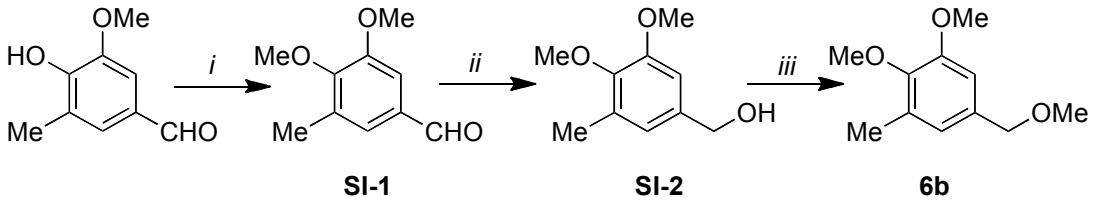
General Synthetic. ^{1}H and ^{13}C NMR data were obtained on a Varian 400 MHz spectrometer and are reported in ppm relative to TMS and referenced to the solvent in which the spectra were collected. Solvent was removed by rotary evaporation under reduced pressure and anhydrous solvents were obtained commercially and used without further drying. Purification by silica gel chromatography was performed using EtOAc–hexanes solvent systems. Preparative high pressure liquid chromatography (HPLC) was conducted using a Waters Prep LC4000 system having photodiode array detection and Phenomenex C_{18} columns (250 mm ×21.2 mm 10 μm particle size, 110 Å pore) at a flow rate of 10 mL/min. Binary solvent systems consisting of A = 0.1% aqueous TFA and B = 0.1% TFA in acetonitrile were employed with gradients as indicated. Products were obtained as amorphous solids following lyophilization. Electrospray ionization-mass spectrometric (ESI-MS) and atmospheric pressure chemical ionization-mass spectrometric (APCI-MS) were acquired with an Agilent LC/MSD system equipped with a multimode ion source. Matrix-assisted laser desorption/ionization (MALDI) mass spectra were acquired with a Shimadzu Biotech Axima-CFR time-of-flight instrument using α–cyano-4-hydroxycinnamic acid as matrix.



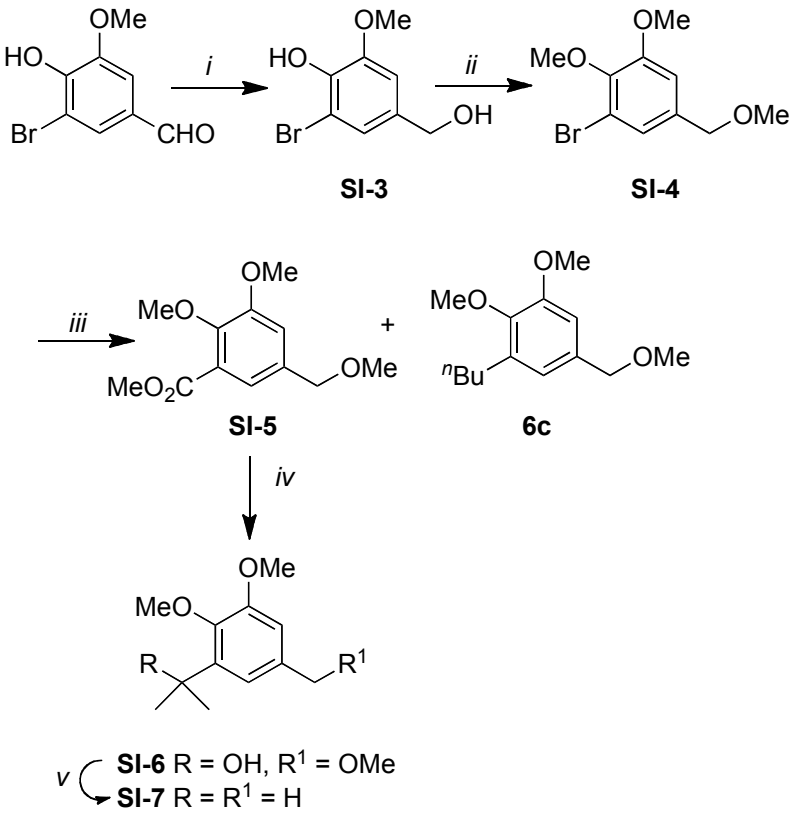
Scheme SI1. Reagents and conditions*: i*) MeI, K_2CO_3, acetone; *ii*) $NaBH_4$, MeOH; *iii*) MeI, NaH.

3,4-Dimethoxy-5-methylbenzaldehyde (SI-1). To 4-hydroxy-3-methoxy-5-methylbenzaldehyde[1] (2.04 g, 12.28 mmol) in acetone (20 mL) was added iodomethane (0.92 mL, 14.73 mmol) and potassium carbonate (2.54 g, 18.41 mmol). The mixture was stirred at reflux (8 h) and then the reaction was quenched by pouring into water and extracting with ether. The organic phase was washed with dilute aqueous NaOH, dried (Na_2SO_4), filtered and evaporated to yield a residue, which was purified by silica gel column chromatography to provide **SI-1** (1.88 g, 85% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.29 (s, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.34, 153.14, 152.83, 132.33, 132.07, 127.21, 108.76, 60.23, 55.81, 15.90. ESI-MS *m/z*: 181.1 (MH^+).

(3,4-Dimethoxy-5-methylphenyl)methanol (SI-2). To the solution of 3,4-dimethoxy-5-methylbenzaldehyde (**SI-1**) (1.88 g, 10.43 mmol) in MeOH (20 mL), at 0 °C was added sodium borohydride (0.47 g, 12.51 mmol) and the mixture was stirred (30 minutes). It was then extracted (EtOAc) and the organic phase was washed with brine, dried (Na_2SO_4), filtered and evaporated to yield a residue, which was purified by silica gel column chromatography to provide **SI-2** (1.75 g, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (d, *J* = 1.5 Hz, 1H), 6.73 (m, 1H), 4.57 (d, *J* = 4.6 Hz, 2H), 3.84 (s, 3H), 3.78 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ

152.69, 146.60, 136.53, 131.82, 121.30, 108.79, 65.16, 60.11, 55.68, 15.79. ESI-MS *m/z*: 205.1 (MNa^+).

1,2-Dimethoxy-5-(methoxymethyl)-3-methylbenzene (6b). To a solution of (3,4-dimethoxy-5-methylphenyl)methanol (**SI-2**) (1.71 g, 9.38 mmol) in THF (100 mL) at 0 °C was added sodium hydride (0.47 g, 18.77 mmol) and the mixture was stirred (20 minutes). Iodomethane (1.17 mL, 18.77 mmol) was added at 0 °C and the mixture was allowed to come to room temperature with stirring (1 h). The reaction was quenched by the addition of ice and then extracted (ether), dried (Na_2SO_4), filtered and evaporated to yield a residue, which was purified by silica gel column chromatography to provide **6b** (1.75 g, 95% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 6.77 (d, *J* = 1.9 Hz, 1H), 6.74 (m, 1H), 4.36 (s, 2H), 3.86 (s, 3H), 3.79 (s, 3H), 3.39 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.68, 146.81, 133.66, 131.66, 122.24, 109.47, 74.69, 60.05, 58.07, 55.68, 15.78. ESI-MS *m/z*: 219.1 (MNa^+).



Scheme SI2. Reagents and conditions: *i*) $NaBH_4$, MeOH; *ii*) (a) MeI, NaH, THF, (b) MeI, K_2CO_3, acetone; *iii*) BuLi, $ClCO_2Me$; *iv*) MeMgBr; *v*) H_2, Pd/C.

1-Bromo-2,3-dimethoxy-5-(methoxymethyl)benzene (SI-4). To a suspension of 5-bromovanillin (12.07 g, 52.2 mmol) in MeOH (100 mL) at 0 °C was added sodium borohydride (2.17 g, 57.5 mmol) and the resulting solution was stirred at 0 °C (1 h). Solvent was evaporated and the residue was extracted (EtOAc), washed with brine, dried (Na_2SO_4), filtered and concentrated and the residue was purified by silica gel column chromatography to provide 2-bromo-4-(hydroxymethyl)-6-methoxyphenol (**SI-3**) (6.3 g, 53%), which was sufficiently pure for further use. To the suspension of sodium hydride (0.859 g, 34.0 mmol) in THF (80 mL) at 0 °C was added **SI-3** (2.59 g) portion-wise. Iodomethane (2.12 mL, 34.0

mmol) was then introduced drop-wise and the resulting mixture was allowed to come to room temperature with stirring (30 minutes) and then stirred at reflux (overnight). Analysis by TLC indicated that only the phenolic hydroxyl had been methylated. Therefore, the reaction mixture was cooled to room temperature and acetone (100 mL), potassium carbonate (11.09 g) and iodomethane (6 mL) were added and the mixture was stirred at reflux (5 h). The reaction was quenched by the addition of ice and then extracted (ether), dried (Na_2SO_4), filtered and evaporated to yied a residue, which was purified by silica gel column chromatography to provide **SI-4** (2.42 g, 82% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 – 7.05 (m, 1H), 6.82 (m, 1H), 4.33 (s, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.69, 145.80, 135.37, 123.70, 117.39, 110.83, 73.77, 60.50, 58.17, 56.02.

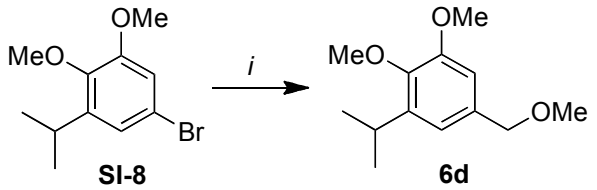
1-Butyl-2,3-dimethoxy-5-(methoxymethyl)benzene (6c). To a solution of 1-bromo-2,3-dimethoxy-5-(methoxymethyl)benzene (**SI-4**) (1.86 g, 7.12 mmol) in THF (40 mL) at -78 °C was added *n*-butyllithium (4.90 mL, 7.84 mmol, 1.6 M in hexanes) and the resulting orange-colored mixture was stirred at -78 °C (1 h). Methyl chloroformate (0.82 mL, 10.7 mmol) was added and the mixture was stirred at -78 °C (1 h) and then the reaction was quenched by pouring into ice. EtOAc (150 mL) was added and the organic phase was washed with aqueous NH_4Cl, then brine (50 mL), dried (Na_2SO_4), filtered and concentrated and the crude residue was purified by silica gel column chromatography to provide methyl 2,3-dimethoxy-5-(methoxymethyl)benzoate (**SI-5**) (820.4 mg, 47.9 % yield) [^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.08 (d, *J* = 1.1 Hz, 1H), 4.42 (s, 2H), 3.91-3.90 (m, 9H), 3.40 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.61, 153.65, 148.63, 134.05,

125.60, 121.24, 114.94, 74.08, 61.52, 58.20, 56.09, 52.18. ESI-MS *m/z*: 241.1 (MH^+).] and the by-product **6c** as a colorless oil (74.1 mg, 4% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, *J* = 1.9 Hz, 1H), 6.70 (d, *J* = 1.9 Hz, 1H), 4.34 (s, 2H), 3.83 (s, 3H), 3.77 (s, 3H), 3.36 (s, 3H), 2.60 – 2.56 (m, 2H), 1.56 – 1.51 (m, 2H), 1.37-1.31 (m, 2H), 0.90 (t, *J* = 8.4, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.63, 146.51, 136.37, 133.51, 121.26, 109.33, 74.76, 60.54, 58.04, 55.61, 32.93, 29.49, 22.63, 13.93. ESI-MS *m/z*: 263.2 (MNa^+).

2-(2,3-Dimethoxy-5-(methoxymethyl)phenyl)propan-2-ol (SI-6). To a solution of methyl 2,3-dimethoxy-5-(methoxymethyl)benzoate (**SI-5**) (774 mg, 3.22 mmol) in THF (10 mL) at 0 °C was added methylmagnesium bromide (3.22 mL, 3.0 M in THF, 9.66 mmol) and then the mixture was stirred at reflux (4 h). The mixture was cooled to 0 °C and quenched by adding aqueous HCl, extracted (EtOAc), washed with brine, dried (Na_2SO_4), filtered and concentrated and the residue was purified by silica gel column chromatography to provide **SI-6** as a colorless oil (630 mg, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (d, *J* = 2.0 Hz, 1H), 6.83 (d, *J* = 1.9 Hz, 1H), 4.35 (s, 2H), 4.14 (brs, 1H), 3.92 (s, 3H), 3.84 (s, 3H), 3.36 (s, 3H), 1.56 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.66, 146.10, 140.85, 133.47, 117.28, 110.92, 74.74, 72.73, 60.91, 58.16, 55.78, 30.69 (2C). ESI-MS *m/z*: 263.1 (MNa^+).

1-Isopropyl-2,3-dimethoxy-5-methylbenzene (**SI-7**). A mixture of 2-(2,3-dimethoxy-5-(methoxymethyl)phenyl)propan-2-ol (**SI-6**) (463 mg, 1.927 mmol) in EtOAc (10 mL) with 3 drops of sulfuric acid and 10% palladium on charcoal (40 mg, 1.927 mmol) was stirred under a hydrogen atmosphere (24 h). Filtration and removal of solvent provided **SI-7** as a colorless oil (341.7 mg, 91% yield). ^{1}H NMR

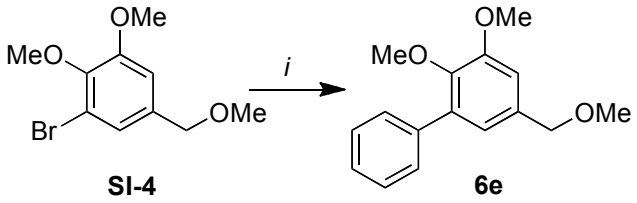
(400 MHz, $CDCl_3$) δ 6.68 (d, *J* = 1.5 Hz, 1H), 6.60 (d, *J* = 1.9 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.38-3.33 (m, 1H), 2.34 (s, 3H), 1.24 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.27, 144.02, 142.01, 133.52, 118.60, 110.58, 60.87, 55.56, 26.66, 23.57 (2C), 21.52. ESI-MS *m/z*: 195.1 (MH^+).



SI-8 **6d**

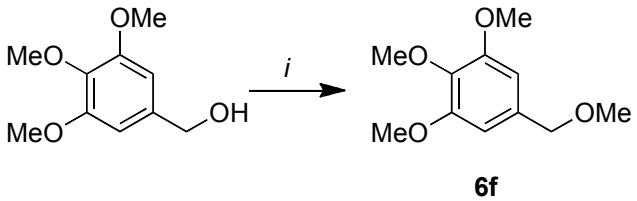
Scheme SI3. Reagents and conditions*: i*) $^{n}BuLi$, $ClCH_2OCH_3$.

1-Isopropyl-2,3-dimethoxy-5-(methoxymethyl)benzene (**6d).** To a solution of 5-bromo-1-isopropyl-2,3-dimethoxybenzene (**SI-8**) (prepared in four steps from 2,3-dimethoxylbenzoicacid methyl ester[2]) (3.48 g, 13.4 mmol) in THF (100 mL) at -78 °C was added *n*-butyllithium (6.55 mL, 16.4 mmol, 2.5 M in hexanes) and the mixture was stirred at -78 °C (1 h). To this was added at -78 ° C chloro(methoxy)methane (1.56 mL, 20.5 mmol) and the mixture was allowed to come to room temperature with stirring (overnight). The reaction was quenched by pouring into ice, extracted (EtOAc), washed with brine, dried (Na_2SO_4), filtered and concentrated and the resulting residue was purified by silica gel column chromatography to provide **6d** as a colorless oil (2.1 g, 68% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 6.76 (d, *J* = 2.0 Hz, 1H), 6.73 (d, *J* = 2.0 Hz, 1H), 4.36 (m, 1H), 7.21 (s, 2H), 3.83 (s, 3H), 3.77 (s, 3H), 3.37 (s, 3H), 3.35 - 3.28 (m, 1H), 1.18 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.58, 145.74, 142.16, 133.82, 117.68, 109.12, 74.96, 60.81, 58.11, 55.62, 26.74, 23.45 (2C).



Scheme SI4. Reagents and conditions: *i*) $PhB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, EtOH, toluene.

2,3-Dimethoxy-5-(methoxymethyl)-1,1'-biphenyl (6e). To 1-bromo-2,3-dimethoxy-5-(methoxymethyl)benzene (**SI-4**) (513 mg, 1.97 mmol) in toluene (8 mL) was added tetrakis(triphenylphosphine)palladium(0) (2.27 g, 1.96 mmol) and phenylboronic acid (359 mg, 2.95 mmol), followed by a saturated solution of potassium carbonate (8 mL) and EtOH (2 mL) and the resulting yellow mixture was stirred at 70 °C (3 days) to provide **6e** following an extractive workup and silica gel chromatographic purification (498 mg, 1.92 mmol, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.52 (m, 2H), 7.41 – 7.37 (m, 2H), 7.33 – 7.31 (m, 1H), 6.91 (dd, *J* = 10.7, 2.0 Hz, 2H), 4.43 (s, 2H), 3.89 (s, 3H), 3.55 (s, 3H), 3.40 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.10, 145.97, 133.92, 129.52, 129.19 (2C), 128.04 (2C), 127.10, 122.02, 115.27, 110.85, 74.62, 60.57, 58.14, 55.91. ESI-MS *m/z*: 281.1 (MNa^+).



Scheme SI5. Reagents and conditions: *i*) MeI, NaH, THF.

1,2,3-Trimethoxy-5-(methoxymethyl)benzene (6f). To a solution of commercially available (3,4,5-trimethoxyphenyl)methanol (25 g, 126 mmol) in THF (150 mL) was added sodium hydride (3.93 g, 164 mmol) portion-wise at 0 °C and the reaction mixture was stirred at 0 °C (10 minutes). Iodomethane (10.2 mL, 164 mmol) was then added drop-wise and the resulting mixture was allowed to come to room temperature with stirring (3 h). The reaction was quenched by pouring into ice, extracted (EtOAc), washed with brine, dried (Na_2SO_4), filtered and concentrated and the resulting residue was purified by silica gel column chromatography to provide **6f** as a colorless oil (26.44 g, 125 mmol, 99 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (s, 2H), 4.35 (s, 2H), 3.82 (s, 6H), 3.79 (s, 3H), 3.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.22 (2C), 137.36, 133.82, 104.53 (2C), 74.83, 60.76, 58.11, 56.02 (2C). ESI-MS *m/z*: 235.0 (MNa^+).

General Procedure A: Synthesis of Benzoic Acid Methyl Esters (7). To benzyl methyl ether **6** (5.0 mmol) in anhydrous ether (15 mL) was added *n*-butyl lithium (1.6 M in hexanes, 6.0 mmol) drop-wise with stirring at 0 °C (1 h). The resulting suspension was cooled to -78 °C, methyl chloroformate (24.0 mmol) was added, and the reaction mixture was allowed to come to room temperature. The mixture was partitioned between H_2O and ether, and the organic phase was dried (Na_2SO_4) and concentrated to provide a residue, which was purified by silica gel column chromatography to yield **7**.

Methyl 2,3-dimethoxy-6-(methoxymethyl)-4-methylbenzoate (7b). Treatment of 1,2-dimethoxy-5-(methoxymethyl)-3-methylbenzene (**6b**) as indicated in General Procedure A provided product **7b** in 39% yield. ^{1}H NMR (500 MHz,

$CDCl_3$) δ 6.93 (s, 1H), 4.38 (s, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 3.82 (s, 3H), 3.33 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.77, 150.77, 150.37, 134.08, 131.41, 125.96, 125.85, 72.12, 61.36, 60.07, 58.30, 52.14, 15.89. ESI-MS *m/z*: 277.1 ($M+Na^+$).

Methyl 4-butyl-2,3-dimethoxy-6-(methoxymethyl)benzoate (7c). Treatment of 1-butyl-2,3-dimethoxy-5-(methoxymethyl)benzene (**6c**) as indicated in General Procedure A provided product **7c** in 42% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 1H), 6.89 (s, 2H), 4.36 (s, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.31 (s, 3H), 2.59 – 2.55 (m, 2H), 1.55 – 1.48 (m, 2H), 1.34 (dq, *J* = 14.5, 7.3 Hz, 2H), 0.90 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.83, 150.49, 150.31, 138.78, 131.26, 125.84, 124.95, 72.21, 61.22, 60.45, 58.31, 52.12, 32.77, 29.59, 22.60, 13.89.

Methyl 4-isopropyl-2,3-dimethoxy-6-(methoxymethyl)benzoate (7d). Treatment of 1-isopropyl-2,3-dimethoxy-5-(methoxymethyl)benzene (**6d**) as indicated in General Procedure A afforded product **7d** in 60% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 1H), 4.37 (s, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.31 (s, 3H), 3.33 – 3.24 (m, 1H), 1.17 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.81, 150.25, 149.79, 144.46, 131.51, 125.69, 121.56, 72.40, 61.18, 60.64, 58.33, 52.08, 26.90, 23.24 (2C).

Methyl 2,3-dimethoxy-5-(methoxymethyl)-[1,1'-biphenyl]-4-carboxylate (7e). Treatment of methyl 2,3-dimethoxy-5-(methoxymethyl)-1,1'-biphenyl (**6e**) as indicated in General Procedure A afforded product **7e** in 43% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.46 (m, 2H), 7.41 – 7.37 (m, 2H), 7.35 – 7.33 (m, 1H), 7.08 (s, 1H), 4.43 (s, 2H), 3.93 (s, 3H), 3.91 (s, 3H), 3.60 (s, 3H), 3.33 (s,

3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.55, 150.86, 150.01, 137.58, 137.27, 131.67, 129.05 (2C), 128.17 (2C), 127.55, 127.32, 125.62, 72.13, 61.63, 60.55, 58.40, 52.24.

Methyl 2,3,4-trimethoxy-6-(methoxymethyl)benzoate (7f). Treatment of 1,2,3-trimethoxy-5-(methoxymethyl)benzene (**6f**) as indicated in General Procedure A afforded product **7f** in 54% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (s, 1H), 4.40 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.47, 154.57, 151.48, 141.29, 132.41, 119.96, 107.00, 72.07, 61.70, 60.75, 58.30, 55.98, 52.02.

General Procedure B: Synthesis of Benzyl Chlorides (8). Acetyl chloride (5.0 mmol) was added drop-wise with stirring to a solution of methyl ether **7** (1.5 mmol) and anhydrous zinc chloride (0.05 mmol) in anhydrous ether (3 mL) at 0 °C and the solution was stirred at 0 °C (30 minutes). Aluminum oxide (350 mg) was added and the mixture was filtered through a short pad of aluminum oxide. The eluent taken to dryness and the residue was purified by silica gel column chromatography to yield **8**.

Methyl 6-(chloromethyl)-2,3-dimethoxy-4-methylbenzoate (8b). Treatment of methyl 2,3-dimethoxy-6-(methoxymethyl)-4-methylbenzoate **7b** as described in General Procedure B afforded **8b** in 89% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (s, 1H), 4.58 (s, 2H), 3.96 (s, 3H), 3.90 (s, 3H), 3.84 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.20, 151.62, 150.76, 134.80, 130.49, 127.47, 126.54, 61.40, 60.10, 52.48, 43.51, 15.94.

Methyl 4-butyl-6-(chloromethyl)-2,3-dimethoxybenzoate (8c). Treatment of methyl 4-butyl-2,3-dimethoxy-6-(methoxymethyl)benzoate (**7c**) as

described in General Procedure B afforded **8c** in 48% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 1H), 4.54 (s, 2H), 3.91 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 2.56 (t, *J* = 7.8 Hz, 2H), 1.55-1.47 (m, 2H), 1.36-1.31 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.17, 151.31, 150.67, 139.40, 130.35, 126.54, 126.41, 61.20, 60.41, 52.39, 43.56, 32.62, 29.57, 22.57, 13.85. ESI-MS *m/z*: 301.10 ($M+H^+$), 323.1 ($M+Na^+$).

Methyl 6-(chloromethyl)-4-isopropyl-2,3-dimethoxybenzoate (8d). Treatment of methyl 4-isopropyl-2,3-dimethoxy-6-(methoxymethyl)benzoate (**7d**) as described in General Procedure B afforded **8d** in 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 1H), 4.60 (s, 2H), 3.95 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 3.34 – 3.30 (m, 1H), 1.22 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.20, 150.65, 145.10, 130.62, 127.78, 126.26, 123.24, 61.22, 60.65, 52.42, 43.77, 27.00, 23.15 (2C).

Methyl 5-(chloromethyl)-2,3-dimethoxy-[1,1'-biphenyl]-4-carboxylate (8e). Treatment of methyl 2,3-dimethoxy-5-(methoxymethyl)-[1,1'-biphenyl]-4-carboxylate (**7e**) as described in General Procedure B afforded **8e** in 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.46 (m, 2H), 7.43 – 7.38 (m, 2H), 7.37 – 7.35 (m, 1H), 7.13 (s, 1H), 4.60 (s, 2H), 3.96 (s, 3H), 3.94 (s, 3H), 3.60 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.95, 151.26, 150.82, 138.12, 136.79, 130.71, 129.00 (2C), 128.27 (2C), 127.80 (2C), 127.21, 61.66, 60.56, 52.55, 43.39.

General Procedure C: Synthesis of Amides (9). Triethylamine (2.0 mmol) was added to a solution of methyl benzoate **8** (1.0 mmol), and appropriate amine (1.0 mmol) in anhydrous acetonitrile (3.0 mL) was then added. The mixture was stirred at reflux until the starting material was consumed as indicated by TLC. The

solvent was evaporated and the residue was partitioned between $CHCl_3$ and brine. The combined organic phase was dried (Na_2SO_4) and evaporated, and the residue was purified by silica gel column chromatography to provide amides **9**.

2-(3-Chloro-4-fluorobenzyl)-6,7-dimethoxy-5-methylisoindolin-1-one (9b). Treatment of methyl 6-(chloromethyl)-2,3-dimethoxy-4-methylbenzoate **8b** as indicated General Procedure C provided **9b** in 49%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 6.9, 1.8 Hz, 1H), 7.21 – 7.16 (m, 1H), 7.09 (t, *J* = 8.6 Hz, 1H), 6.91 (s, 1H), 4.69 (s, 2H), 4.15 (s, 2H), 4.13 (s, 3H), 3.88 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.91, 155.56 (d, *J* = 247.1 Hz, 1C), 150.95, 150.87, 137.31 (d, *J* = 9.5 Hz, 1C), 134.43 (d, *J* = 3.8 Hz, 1C), 130.21, 127.87 (d, *J* = 6.8 Hz, 1C), 127.85, 122.64, 121.27 (d, *J* = 18.1 Hz, 1C), 119.52, 116.84 (d, *J* = 21.0 Hz, 1C), 62.45, 60.79, 48.63, 45.23, 16.77. ESI-MS *m/z*: 366.0 (MH^+).

5-Butyl-2-(3-chloro-4-fluorobenzyl)-6,7-dimethoxyisoindolin-1-one (9c). Treatment of methyl 4-butyl-6-(chloromethyl)-2,3-dimethoxybenzoate (**8c**) as indicated in General Procedure C provided **9c** in 40% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.28 (m, 1H), 7.14 – 7.11 (m, 1H), 7.02 (t, *J* = 8.8 Hz, 1H), 6.60 (s, 1H), 4.61 (s, 2H), 4.11 (s, 2H), 4.09 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.85, 157.50 (d, *J* = 248.9 Hz, 1C), 150.86, 150.70, 141.89, 137.20, 134.39 (d, *J* = 3.9 Hz, 1C), 130.17, 127.84 (d, *J* = 7.3 Hz, 1C), 122.47, 121.20 (d, *J* = 17.8 Hz, 1C), 118.56, 116.76 (d, *J* = 21.3 Hz, 1C), 62.36, 61.20, 48.64, 45.18, 32.74, 30.27, 22.60, 13.88. ESI-MS *m/z*: 392.1 (MH^+).

2-(3-Chloro-4-fluorobenzyl)-5-isopropyl-6,7-dimethoxyisoindolin-1-one (9d). Treatment of methyl 6-(chloromethyl)-4-isopropyl-2,3-

dimethoxybenzoate (**8d**) as indicated in General Procedure C afforded **9d** in 52% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 7.0, 2.2 Hz, 1H), 7.19 (ddd, *J* = 8.4, 4.5, 2.2 Hz, 1H), 7.08 (t, *J* = 8.6 Hz, 1H), 6.97 (s, 1H), 4.69 (s, 2H), 4.18 (s, 2H), 4.13 (s, 3H), 3.90 (s, 3H), 3.42 – 3.35 (m, 1H), 1.22 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.82, 157.48 (d, *J* = 248.8 Hz, 1C), 150.84, 150.00, 147.66, 137.48, 134.40 (d, *J* = 3.9 Hz, 1C), 130.17, 127.84 (d, *J* = 7.3 Hz, 1C), 122.18, 121.18 (d, *J* = 18.0 Hz, 1C), 116.75 (d, *J* = 21.2 Hz, 1C), 115.21, 62.36, 61.45, 48.75, 45.16, 27.36, 23.31 (2C).

2-(3-Chloro-4-fluorobenzyl)-6,7-dimethoxy-5-phenylisoindolin-1-one (9e). Treatment of methyl 5-(chloromethyl)-2,3-dimethoxy-[1,1'-biphenyl]-4-carboxylate (**8e**) as described in General Procedure C afforded **9e** in 48% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.45 (m, 2H), 7.42 – 7.38 (m, 2H), 7.36 – 7.32 (m, 2H), 7.17 (ddd, *J* = 8.4, 4.6, 2.2 Hz, 1H), 7.07 (t, *J* = 8.6 Hz, 1H), 7.03 (s, 1H), 4.68 (s, 2H), 4.20 (s, 2H), 4.15 (s, 3H), 3.62 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.61, 157.55 (d, *J* = 248.9 Hz, 1C), 151.50, 150.21, 140.42, 137.50, 137.40, 134.26 (d, *J* = 4.0 Hz, 1C), 130.22, 129.08 (2C), 128.19 (2C), 127.88 (d, *J* = 7.3 Hz, 1C), 127.73, 123.71, 121.27 (d, *J* = 18.0 Hz, 1C), 119.38, 116.83 (d, *J* = 21.2 Hz, 1C), 62.60, 61.20, 48.74, 45.26. ESI-MS *m/z*: 412.0 (MH^+).

2-(3-Chloro-4-fluorobenzyl)-5,6,7-trimethoxyisoindolin-1-one (9f). Treatment of 2,3,4-trimethoxy-6-(methoxymethyl)benzoate (**7f**) in two consecutive steps as described in General Procedures B and C afforded **9f** in 37% combined yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.28 (m, 1H), 7.14 – 7.11 (m, 1H), 7.02 (t, *J* = 8.8 Hz, 1H), 6.60 (s, 1H), 4.61 (s, 2H), 4.11 (s, 2H), 4.09 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.90, 157.45 (d, *J* = 248.8 Hz, 1C), 157.28,

151.56, 141.72, 138.48, 134.45 (d, *J* = 3.9 Hz, 1C), 130.11, 127.80 (d, *J* = 7.3 Hz, 1C), 121.15 (d, *J* = 17.9 Hz, 1C), 116.88, 116.75 (d, *J* = 21.2 Hz, 1C), 101.27, 62.53, 61.39, 56.24, 48.92, 45.08. ESI-MS *m/z*: 366.0 (MH^+).

4-(2-(3-Chloro-4-fluorobenzyl)-6,7-dimethoxy-1-oxoisoindolin-5-yl)-*N,N*-dimethylbenzenesulfonamide (9h). Treatment 2-(3-chloro-4-fluorobenzyl)-6,7-dimethoxy-5-phenylisoindolin-1-one (**9e**) with chlorosulfonic acid at room temperature (2 h) based on General Procedure D and followed by General Procedure E (see below) provided **9h** (44% combined yield for two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81-7.78 (m, 2H), 7.65 – 7.62 (m, 2H), 7.35-7.33 (m, 1H), 7.19 – 7.16 (m, 1H), 7.07 (t, *J* = 8.4 Hz, 1H), 7.03 (s, 1H), 4.69 (s, 2H), 4.21 (s, 2H), 4.16 (s, 3H), 3.66 (s, 3H), 2.73 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.28, 157.60 (d, *J* = 249.2 Hz), 151.62, 150.19, 142.01, 138.25, 137.58, 134.85, 134.07 (d, *J* = 4.0 Hz), 130.23, 129.77 (2C), 127.88 (d, *J* = 7.3 Hz), 127.59 (2C), 124.72, 121.34 (d, *J* = 18.1 Hz), 119.10, 116.87 (d, *J* = 21.2 Hz), 62.74, 61.40, 48.70, 45.31, 37.91 (2C). ESI-MS *m/z*: 519.1 (MH^+).

General Procedure D: Synthesis of Sulfonyl Chlorides (10). A dark mixture of dimethoxylisoindole (**9**) (1 mmol) in chlorosulfonic acid (1 mL) was stirred at room temperature (1 h), then the mixture was diluted with $CHCl_3$ (100 mL) and quenched by pouring into ice. The organic phase was separated, dried (Na_2SO_4), filtered and concentrated to afforded sulfonyl chlorides (**10**) as brown oils, which were used without further purification.

2-(3-Chloro-4-fluorobenzyl)-6,7-dimethoxy-1-oxoisoindoline-4-sulfonyl chloride (**10a).** Treatment of 2-(3-chloro-4-fluorobenzyl)-6,7-dimethoxyisoindolin-

1-one (**9a**)[3] using General Procedure D afforded **10a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.35 (dd, *J* = 6.9, 2.2 Hz, 1H), 7.18 (ddd, *J* = 8.4, 4.5, 2.2 Hz, 1H), 7.08 (t, *J* = 8.6 Hz, 1H), 4.67 (s, 2H), 4.51 (s, 2H), 4.24 (s, 3H), 3.94 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.48, 157.76 (d, *J* = 249.6 Hz), 153.42, 152.61, 133.64, 133.30 (d, *J* = 4.0 Hz), 131.73, 130.41, 128.04 (d, *J* = 7.4 Hz), 125.00, 121.50 (d, *J* = 18.0 Hz), 117.00 (d, *J* = 21.3 Hz), 113.87, 63.19, 57.06, 48.34, 45.52.

General Procedure E: Synthesis of Dimethoxylisoindole Sulfonamides (11). To a solution of sulfonyl chloride (**10**) (0.2 mmol) in CH_2Cl_2 (1 mL) was added amine (0.4 mmol) [or amine (0.2 mmol) along with triethylamine (0.4 mmol)] and the mixture was stirred at room temperature (30 minutes), then solvent was evaporated and the residue was placed under high vacuum. The resulting crude sulfonamides (**11**) were either purified by silica gel column chromatography or used without further purification.

2-(3-Chloro-4-fluorobenzyl)-6,7-dimethoxy-*N,N*,5-trimethyl-1-oxoisoindoline-4-sulfonamide (11b-2). Treatment of 2-(3-chloro-4-fluorobenzyl)-6,7-dimethoxy-5-methylisoindolin-1-one (**9a**)[3] sequentially using General Procedures D and E afforded **11b-2** (72% combined yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 6.9, 2.1 Hz, 1H), 7.20 (ddd, *J* = 8.3, 4.5, 2.2 Hz, 1H), 7.09 (t, *J* = 8.6 Hz, 1H), 4.69 (s, 2H), 4.56 (s, 2H), 4.20 (d, *J* = 0.5 Hz, 3H), 3.87 (d, *J* = 0.4 Hz, 3H), 2.77 (s, 2H), 2.77 (s, 4H), 2.54 (s, 3H). ESI-MS *m/z*: 457.1 (MH^+).

5-Butyl-2-(3-chloro-4-fluorobenzyl)-6,7-dimethoxy-*N,N*-dimethyl-1-oxoisoindoline-4-sulfonamide (11c-2). Treatment of 5-butyl-2-(3-chloro-4-fluorobenzyl)-6,7-dimethoxyisoindolin-1-one (**9c**) sequentially using General

Procedures D and E afforded **11c-2** (56% combined yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 7.1, 2.4 Hz, 1H), 7.13 (ddd, *J* = 8.7, 4.7, 2.3 Hz, 1H), 7.03 (t, *J* = 8.7 Hz, 1H), 4.62 (s, 2H), 4.49 (s, 2H), 4.11 (s, 3H), 3.87 (s, 3H), 2.87 – 2.83 (m, 2H), 2.69 (s, 3H), 2.69-2.66 (m, 2H), 2.66 (s, 3H), 1.43-1.38 (m, 2H), 0.92-0.88 (m, 3H). ESI-MS *m/z*: 499.1 (MH^+).

2-(3-Chloro-4-fluorobenzyl)-5-isopropyl-6,7-dimethoxy-*N,N*-dimethyl-1-oxoisoindoline-4-sulfonamide (11d-2). Treatment of 2-(3-chloro-4-fluorobenzyl)-5-isopropyl-6,7-dimethoxyisoindolin-1-one (**9d**) sequentially using General Procedures D and E afforded **11d-2** (39% combined yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 6.9, 2.2 Hz, 1H), 7.20 (ddd, *J* = 8.4, 4.5, 2.2 Hz, 1H), 7.09 (t, *J* = 8.6 Hz, 1H), 4.69 (s, 2H), 4.56 (s, 2H), 4.16 (s, 3H), 3.97 (s, 3H), 3.83 – 3.76 (m, 1H), 2.77 (s, 6H), 1.34 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.85, 157.57 (d, *J* = 249.0 Hz, 1C), 155.01, 154.18, 147.15, 139.16, 133.94 (d, *J* = 4.0 Hz, 1C), 130.29, 127.93 (d, *J* = 7.3 Hz, 1C), 126.65, 123.66, 121.28 (d, *J* = 17.9 Hz, 1C), 116.78 (d, *J* = 21.3 Hz, 1C), 62.58, 61.23, 51.29, 45.09, 36.11 (2C), 29.31, 20.69 (2C). ESI-MS *m/z*: 485.1 (MH^+).

2-(3-Chloro-4-fluorobenzyl)-5-isopropyl-6,7-dimethoxy-4-morpholinosulfonyl)isoindolin-1-one (11d-10). Treatment of 2-(3-chloro-4-fluorobenzyl)-5-isopropyl-6,7-dimethoxyisoindolin-1-one (**9d**) sequentially using morpholine and General Procedures D and E afforded **11d-10 (**47% combined yield for two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $cdcl_3$) δ 7.38 (dd, *J* = 6.9, 2.0 Hz, 1H), 7.23 – 7.19 (m, 1H), 7.10 (t, *J* = 8.6 Hz, 1H), 4.68 (s, 2H), 4.56 (s, 2H), 4.17 (s, 3H), 3.98 (s, 3H), 3.88-3.81 (m, 1H), 3.72 – 3.70 (m, 4H), 3.17 – 3.15 (m, 4H),

1.38 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.71, 157.62 (d, *J* = 249.2 Hz), 155.37, 154.30, 147.41, 139.47, 133.86 (d, *J* = 4.0 Hz), 130.32, 127.96 (d, *J* = 7.3 Hz), 125.62, 123.74, 121.34 (d, *J* = 18.0 Hz), 116.81 (d, *J* = 21.2 Hz), 66.17, 62.65, 61.26, 51.24, 45.13, 44.52, 29.32, 20.89. ESI-MS *m/z*: 527.1 (MH^+).

2-(3-Chloro-4-fluorobenzyl)-5,6,7-trimethoxy-*N,N*-dimethyl-1-oxoisoindoline-4-sulfonamide (11f-2). Treatment of methyl 6-(chloromethyl)-2,3,4-trimethoxybenzoate (**9f**) sequentially using General Procedures D and E afforded **11f-2** (96% combined yield for two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.37 (m, 1H), 7.22 – 7.19 (m, 1H), 7.10 (t, *J* = 8.6 Hz, 1H), 4.68 (s, 2H), 4.50 (s, 2H), 4.22 (s, 3H), 4.05 (s, 3H), 3.96 (s, 3H), 2.86 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.98, 157.54 (d, *J* = 248.6 Hz, 1C), 155.65, 155.47, 146.58, 138.66, 133.98 (d, *J* = 4.1 Hz, 1C), 130.26, 127.93 (d, *J* = 7.3 Hz, 1C), 122.82, 121.24 (d, *J* = 17.6 Hz, 1C), 120.45, 116.75 (d, *J* = 21.1 Hz, 1C), 62.85, 61.76, 61.45, 50.59, 45.11, 37.42 (2C). ESI-MS *m/z*: 473.0 (MH^+).

2-(3-Chloro-4-fluorobenzyl)-5-(4-(*N,N*-dimethylsulfamoyl)phenyl)-6,7-dimethoxy-*N,N*-dimethyl-1-oxoisoindoline-4-sulfonamide (11h-2). Treatment of 2-(3-chloro-4-fluorobenzyl)-6,7-dimethoxy-5-phenylisoindolin-1-one (**9e**) with chlorosulfonic acid at room temperature (overnight) based on General Procedure D and followed by General Procedure E provided **11h-2** (89% combined yield for two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.83 (m, 2H), 7.43 – 7.41 (m, 2H), 7.38 (dd, *J* = 6.9, 2.1 Hz, 1H), 7.21 – 7.18 (m, 1H), 7.09 (t, *J* = 8.6 Hz, 1H), 4.69 (s, 2H), 4.60 (s, 2H), 4.21 (s, 3H), 3.52 (s, 3H), 2.72 (s, 6H), 2.22 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.54, 157.68 (d, *J* = 249.2 Hz, 1C), 154.92, 151.42, 139.33, 138.93, 138.30, 135.28,

133.88, 133.68 (d, *J* = 4.1 Hz, 1C), 130.37, 130.28, 128.02 (d, *J* = 7.2 Hz, 1C), 127.95, 126.77, 125.54, 121.42 (d, *J* = 17.8 Hz, 1C), 116.89 (d, *J* = 21.2 Hz, 1C), 63.04, 61.29, 50.87, 45.29, 37.91 (2C), 35.33 (2C), 34.85. ESI-MS *m/z*: 626.1 (MH^+).

General Procedure F: Demethylation of Methyl Phenyl Ethers 9 & 11. Boron tribromide (1.0 M in CH_2Cl_2, 8.5 mmol) was carefully added to a solution of appropriate methyl ether **9** or **11** (1.0 mmol in 1.0 mL anhydrous CH_2Cl_2) and the mixture was stirred at room temperature (overnight). The reaction was quenched by the addition of ice–water (1.0 mL) and the resulting suspension was filtered and the collected solid was purified by preparative HPLC to provide dihydroxylisoindoles **4** or **5**.

2-(3-Chloro-4-fluorobenzyl)-6,7-dihydroxy-5-methylisoindolin-1-one (4b). Treatment of **9b** according to General Procedure F and purification by preparative HPLC (as indicated in the General Synthetic Procedures using a 00G-4436-P0-AX column with a linear gradient of 40% B to 60% B over 30 minutes; retention time = 27.4 minutes) provided **4b** as a fluffy white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (brs, 1H), 8.62 (brs, 1H), 7.44 (dd, *J* = 7.2, 2.2 Hz, 1H), 7.37 – 7.32 (m, 1H), 7.25 – 7.21 (m, 1H), 6.67 (s, 1H), 4.58 (s, 2H), 4.16 (s, 2H), 2.13 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.63, 156.86 (d, *J* = 245.9 Hz, 1C), 142.83, 142.71, 136.11 (d, *J* = 3.7 Hz, 1C), 132.38, 130.50, 130.14, 128.78 (d, *J* = 7.5 Hz, 1C), 119.89 (d, *J* = 17.7 Hz, 1C), 117.51 (d, *J* = 20.9 Hz, 1C), 116.09, 116.00, 49.19, 44.40, 17.26.

5-Butyl-2-(3-chloro-4-fluorobenzyl)-6,7-dihydroxyisoindolin-1-one (4c). Treatment of **9c** according to General Procedure F and purification by preparative HPLC (as indicated in the General Synthetic Procedures using a 00G-

4436-P0-AX column with a linear gradient of 50% B to 90% B over 30 minutes; retention time = 24.0 minutes) provided **4c** as a fluffy white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (s, 1H), 8.57 (s, 1H), 7.44 (dd, *J* = 7.3, 2.2 Hz, 1H), 7.34 (t, *J* = 9.0 Hz, 1H), 7.25-7.21 (m, 1H), 6.67 (s, 1H), 4.58 (s, 2H), 4.17 (s, 2H), 2.54 – 2.50 (m, 2H), 1.47-1.41 (m, 2H), 1.28-1.22 (m, 2H), 0.83 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.67, 156.86 (d, *J* = 245.7 Hz), 142.68, 142.61, 136.10 (d, *J* = 3.9 Hz), 135.08, 132.30, 130.15, 128.78 (d, *J* = 7.5 Hz), 119.89 (d, *J* = 17.5 Hz), 117.50 (d, *J* = 21.0 Hz), 116.00, 115.25, 49.28, 44.41, 31.91, 30.37, 22.46, 14.26. ESI-MS m/z: 364.1 (MH^+).

2-(3-Chloro-4-fluorobenzyl)-6,7-dihydroxy-5-isopropylisoindolin-1-one (4d). Treatment of **9d** according to General Procedure F and purification by preparative HPLC (as indicated in the General Synthetic Procedures using a 00G-4436-P0-AX column with a linear gradient of 50% B to 80% B over 30 minutes; retention time = 23.1 minutes) provided **4d** as a fluffy white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.89 (s, 1H), 8.57 (s, 1H), 7.44 (dd, J = 7.2, 2.1 Hz, 1H), 7.36 – 7.32 (m, 1H), 7.25 – 7.21 (m, 1H), 6.75 (s, 1H), 4.59 (s, 2H), 4.19 (s, 2H), 3.28 - 3.21 (m, 1H), 1.09 (d, J = 6.9 Hz, 6H).^{13}C NMR (101 MHz, DMSO-d_6) δ 168.65, 156.84 (d, *J* = 245.7 Hz, 1C), 142.60, 141.90, 140.81, 136.11 (d, *J* = 3.8 Hz, 1C), 132.53, 130.08, 128.71 (d, *J* = 7.5 Hz, 1C), 119.89 (d, *J* = 17.8 Hz, 1C), 117.49 (d, *J* = 21.0 Hz), 115.75, 111.58, 49.44, 44.39, 27.31, 22.86 (2C). ESI-MS m/z: 350.1 (MH^+).

2-(3-Chloro-4-fluorobenzyl)-6,7-dihydroxy-5-phenylisoindolin-1-one (4e). Treatment of **9e** according to General Procedure F and purification by preparative HPLC (as indicated in the General Synthetic Procedures using a 00G-

4436-P0-AX column with a linear gradient of 50% B to 90% B over 30 minutes; retention time = 21.2 minutes) provided **4e** as a fluffy white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (brs, 1H), 8.77 (brs, 1H), 7.48 -7.46 (m, 3H), 7.38-7.36 (m, 2H), 7.35 – 7.34 (m, 1H), 7.30-7.24 (m, 1H), 7.27 – 7.24 (m, 1H), 6.84 (s, 1H), 4.63 (s, 2H), 4.25 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.33, 156.89 (d, *J* = 245.9 Hz, 1C), 143.44, 142.37, 138.71, 136.02 (d, *J* = 3.8 Hz), 133.30, 132.61, 130.18, 129.57 (2C), 128.81 (d, *J* = 7.5 Hz, 1C), 128.37 (2C), 127.49, 119.93 (d, *J* = 17.8 Hz, 1C), 117.53 (d, *J* = 21.0 Hz, 1C), 117.15, 115.89, 49.37, 44.47. ESI-MS m/z: 384.0 (MH^+).

2-(3-Chloro-4-fluorobenzyl)-5,6,7-trihydroxyisoindolin-1-one (4g). Treatment of **9f** according to General Procedure F and purification by preparative HPLC (as indicated in the General Synthetic Procedures using a 00G-4436-P0-AX column with a linear gradient of 30% B to 70% B over 30 minutes; retention time = 20.0 minutes) provided **4g** as a fluffy white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 – 7.36 (m, 1H), 7.32 (t, *J* = 8.9 Hz, 1H), 7.26 – 7.15 (m, 1H), 6.37 (s, 1H), 4.53 (s, 2H), 4.09 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.81, 156.81 (d, *J* = 245.7 Hz), 151.12, 144.16, 136.30 (d, *J* = 3.8 Hz), 133.63, 132.45, 130.07, 128.73 (d, *J* = 7.5 Hz), 119.86 (d, *J* = 17.9 Hz), 117.45 (d, *J* = 21.1 Hz), 109.92, 102.21, 49.26, 44.30.

4-(2-(3-Chloro-4-fluorobenzyl)-6,7-dihydroxy-1-oxoisoindolin-5-yl)-*N,N*-dimethylbenzenesulfonamide (4h). Treatment of **9h** according to General Procedure F and purification by preparative HPLC (as indicated in the General Synthetic Procedures using a 00G-4436-P0-AX column with a linear gradient of 50% B to 65% B over 30 minutes; retention time = 25.2 minutes) provided **4h** as a fluffy white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.34 (brs, 1H), 9.07 (brs, 1H), 7.74 (s,

4H), 7.48 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.36 (t, *J* = 8.9 Hz, 1H), 7.28 – 7.25 (m, 1H), 6.92 (s, 1H), 4.64 (s, 2H), 4.27 (s, 2H), 2.60 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.11, 156.90 (d, *J* = 246.0 Hz, 1C), 143.49, 143.30, 142.76, 135.96 (d, *J* = 3.7 Hz, 1C), 133.66, 132.72, 131.20, 130.39(2C), 130.22, 128.84 (d, *J* = 7.5 Hz, 1C), 127.71(2C), 119.94 (d, *J* = 17.8 Hz, 1C), 117.98, 117.54 (d, *J* = 21.0 Hz, 1C), 115.87, 49.37, 44.51, 38.02(2C). ESI-MS m/z: 391.0 (MH^+).

2-(3-Chloro-4-fluorobenzyl)-6,7-dihydroxy-*N*-methyl-1-oxoisoindoline-4-sulfonamide (5a-1). Treatment of **10a** with methylamine based on General Procedures E and F followed by preparative HPLC purification (as indicated in the General Synthetic Procedures using a 00G-4436-P0-AX column with a linear gradient of 30% B to 70% B over 30 minutes; retention time = 22.7 minutes) provided **5a-1** as a fluffy white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (bs, 1H), 9.83 (bs, 1H), 7.50 - 7.48 (m, 1H), 7.38 - 7.34 (m, 1H), 7.30 - 7.29 (m, 1H), 7.23 (s, 1H), 4.62 (s, 2H), 4.38 (s, 2H), 2.33 (d, *J* = 5.1 Hz, 2H). MALDI-MS *m/z*: 400.92 ($M+H^+$). HRMS calcd for $C_{16}H_{15}N_2O_5FSCl$ [MH^+]:401.0369. Found:401.0375.

2-(3-Chloro-4-fluorobenzyl)-*N,N*-diethyl-6,7-dihydroxy-1-oxoisoindoline-4-sulfonamide (5a-2). Treatment of **10a** with diethylamine and further reaction based on General Procedures E and F followed by preparative HPLC purification (as indicated in the General Synthetic Procedures using a 00G-4436-P0-AX column with a linear gradient of 30% B to 70% B over 30 minutes; retention time = 20.2 minutes) provided **5a-2** as a fluffy white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14 (bs, 1H), 9.87 (bs, 1H), 7.46 (dd, *J* = 7.2, 2.1 Hz, 1H), 7.37 – 7.31 (m, 1H), 7.25 (ddd, *J* = 8.5, 4.8, 2.2 Hz, 1H), 7.20 (s, 1H), 4.62 (s, 2H), 4.35 (s, 2H),

3.10 (q, *J* = 7.1 Hz, 4H), 0.94 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.76, 156.90 (d, *J* = 246.0 Hz), 147.79, 145.82, 135.71 (d, *J* = 3.8 Hz), 131.71, 130.22, 128.84 (d, *J* = 7.4 Hz), 124.80, 119.93 (d, *J* = 17.8 Hz), 118.79, 117.53 (d, *J* = 21.0 Hz), 117.35, 49.64, 44.40, 41.58 (2C), 14.16 (2C). ESI-MS *m/z*: 443.0 ($M+H^+$).

***N*-(3-Bromopropyl)-2-(3-chloro-4-fluorobenzyl)-6,7-dihydroxy-1-oxoisoindoline-4-sulfonamide (5a-3).** Treatment of **10a** with 3,3'-((oxybis(ethane-2,1-diyl))bis(oxy))bis(propan-1-amine) and further reaction based on General Procedures E and F followed by preparative HPLC purification (as indicated in the General Synthetic Procedures using a 00G-4436-P0-AX column with a linear gradient of 30% B to 70% B over 30 minutes; retention time = 27.8 minutes) provided **5a-3** as a fluffy white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.57 (t, *J* = 5.8 Hz, 1H), 7.47 (dd, *J* = 7.1, 1.9 Hz, 1H), 7.35 (t, *J* = 8.9 Hz, 1H), 7.25 (s, 1H), 4.62 (s, 2H), 4.39 (s, 2H), 3.39 (t, *J* = 6.4 Hz, 2H), 2.78 (dd, *J* = 12.7, 6.6 Hz, 2H), 1.83 – 1.73 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.77, 156.96 (d, *J* = 246.1 Hz), 147.64, 145.59, 135.78 (d, *J* = 3.7 Hz), 131.56, 130.30, 128.93 (d, *J* = 7.6 Hz), 124.78, 119.98 (d, *J* = 17.8 Hz), 118.77, 117.67, 117.57 (d, *J* = 21.0 Hz), 49.26, 44.44, 41.03, 32.44, 32.19. ESI-MS *m/z*: 508.9 ($M+H^+$).

2-(3-Chloro-4-fluorobenzyl)-*N*-(3-(dimethylamino)propyl)-7-hydroxy-6-methoxy-1-oxoisoindoline-4-sulfonamide (5a-4). Treatment of **10a** with N1,N1-dimethylpropane-1,3-diamine and further reaction based on General Procedures E and F followed by preparative HPLC purification (as indicated in the General Synthetic Procedures using a 00G-4436-P0-AX column with a linear gradient of 20% B to 50% B over 30 minutes; retention time = 21.3 minutes)

provided **5a-4** as a fluffy white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 9.88 (s, 1H), 7.60 (t, *J* = 6.0 Hz, 1H), 7.49 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.37 (t, *J* = 8.8 Hz, 1H), 7.29 – 7.25 (m, 1H), 7.24 (s, 1H), 4.63 (s, 2H), 4.39 (s, 2H), 2.95 (m, 2H), 2.72 – 2.70 (m, 2H), 2.67 (s, 6H), 1.69 – 1.62 (m, 2H). MALDI-MS *m/z*: 472.13 ($M+H^+$). ESI-MS *m/z*: 472.0 ($M+H^+$), 494.0 ($M+Na^+$).

2-(3-Chloro-4-fluorobenzyl)-6,7-dihydroxy-*N*-(2-morpholinoethyl)-1-oxoisoindoline-4-sulfonamide (5a-5). Treatment of **10a** with 2-morpholinoethanamine and further reaction based on General Procedures E and F followed by preparative HPLC purification (as indicated in the General Synthetic Procedures using a 00G-4436-P0-AX column with a linear gradient of 20% B to 45% B over 30 minutes; retention time = 23.2 minutes) provided **5a-5** as a fluffy white solid. MALDI-MS *m/z*: 500.48 ($M+H^+$). ESI-MS *m/z*: 500.0 ($M+H^+$).

2-(3-Chloro-4-fluorobenzyl)-6,7-dihydroxy-1-oxo-*N*-(2-(piperazin-1-yl)ethyl)isoindoline-4-sulfonamide (5a-6). Treatment of **10a** with 2-(piperazin-1-yl)ethanamine and further reaction based on General Procedures E and F followed by preparative HPLC purification (as indicated in the General Synthetic Procedures using a 00G-4436-P0-AX column with a linear gradient of 20% B to 35% B over 30 minutes; retention time = 25.6 minutes) provided **5a-6** as a fluffy white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.31 (bs, 1H), 10.04 (bs, 1H), 7.52 – 7.47 (m, 1H), 7.37 – 7.33 (m, 1H), 7.28 – 7.24 (m, 1H), 7.16 (s, 1H), 4.61 (s, 2H), 4.39 (s, 2H), 2.91 – 2.84 (m, 6H), 2.54 – 2.45 (m, 6H). MALDI-MS *m/z*: 499.13 ($M+H^+$).

2-(3-Chloro-4-fluorobenzyl)-6,7-dihydroxy-1-oxo-N-(pyridin-2-ylmethyl)isoindoline-4-sulfonamide (5a-7). Treatment of **10a** with pyridin-2-

ylmethanamine and further reaction based on General Procedures E and F followed by preparative HPLC purification (as indicated in the General Synthetic using a 00G-4436-P0-AX column with a linear gradient of 30% B to 70% B over 30 minutes; retention time = 13.1 minutes) provided **5a-7** as a fluffy white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.06 (bs, 1H), 9.80 (bs, 1H), 8.32 (d, *J* = 4.2 Hz, 1H), 8.23 (t, *J* = 6.4 Hz, 1H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.48 (dd, *J* = 7.2, 2.2 Hz, 1H), 7.37 (t, *J* = 9.0 Hz, 1H), 7.29 – 7.23 (m, 3H), 7.21 (s, 1H), 4.61 (s, 2H), 4.37 (s, 2H), 4.07 (d, *J* = 6.2 Hz, 2H). MALDI-MS *m/z*: 478.13 ($M+H^+$).

2-(3-Chloro-4-fluorobenzyl)-6,7-dihydroxy-4-((4-methylpiperazin-1-yl)sulfonyl)isoindolin-1-one (5a-8). Treatment of **10a** with 1-methylpiperazine and further reaction based on General Procedures E and F followed by preparative HPLC purification (as indicated in the General Synthetic Procedures using a 00G-4436-P0-AX column with a linear gradient of 30% B to 45% B over 30 minutes; retention time = 16.3 minutes) provided **5a-8** as a fluffy white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.35 (bs, 1H), 10.18 (bs, 1H), 7.48 (dd, *J* = 7.2, 2.1 Hz, 1H), 7.38 – 7.30 (m, 1H), 7.27 (dd, *J* = 4.8, 2.0 Hz, 1H), 7.17 (s, 1H), 4.62 (s, 2H), 4.40 (s, 2H), 3.67 (bs, 2H), 3.38 (bs, 2H), 3.08 (bs, 2H), 2.74 (s, 3H), 2.62 (bs, 2H). ESI-MS *m/z*: 470.0 ($M+H^+$). HRMS calcd for $C_{20}H_{22}N_3O_5FSCl$ [MH^+]: 470.0947. Found: 470.0948.

4-((4-(2-Aminoethyl)piperazin-1-yl)sulfonyl)-2-(3-chloro-4-fluorobenzyl)-6,7-dihydroxyisoindolin-1-one (5a-9). Treatment of **10a** with 2-(piperazin-1-yl)ethanamine and further reaction based on General Procedures E and F followed by preparative HPLC purification (as indicated in the General Synthetic Procedures using a 00G-4436-P0-AX column with a linear gradient of 20%

B to 35% B over 30 minutes; retention time = 20.8 minutes) provided **5a-9** as a fluffy white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (bs, 1H), 9.86 (bs, 1H), 8.51 (bs, 2H), 7.53 – 7.47 (m, 2H), 7.39 – 7.34 (m, 1H), 7.28 – 7.26 (m, 1H), 4.63 (s, 2H), 4.39 (s, 2H), 2.99 (bs, 4H), 2.84 – 2.82 (m, 4H), 2.54 (bs, 4H). MALDI-MS *m/z*: 499.13 ($M+H^+$).

2-(3-Chloro-4-fluorobenzyl)-6,7-dihydroxy-4-(morpholinosulfonyl)isoindolin-1-one (5a-10). Treatment of **10a** with morpholine and further reaction based on General Procedures E and F followed by preparative HPLC purification (as indicated in the General Synthetic Procedures using a 00G-4436-P0-AX column with a linear gradient of 30% B to 70% B over 30 minutes; retention time = 25.2 minutes) provided **5a-10** as a fluffy white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.22 (bs, 1H), 10.00 (bs, 1H), 7.48 (dd, *J* = 7.2, 2.1 Hz, 1H), 7.34 (dd, *J* = 14.5, 5.2 Hz, 1H), 7.29 – 7.18 (m, 1H), 7.15 (s, 1H), 4.61 (s, 2H), 4.38 (s, 2H), 3.57 – 3.55 (m, 2H), 3.48 – 3.45 (m, 1H), 3.40 (t, *J* = 6.0 Hz, 1H), 3.15 (t, *J* = 5.9 Hz, 1H), 2.87 – 2.85 (m, 3H). ESI-MS *m/z*: 457.0 ($M+H^+$). HRMS calcd for $C_{19}H_{19}N_2O_6FSCl$ [MH^+]:457.0631. Found:457.0641.

2-(2-(3-Chloro-4-fluorobenzyl)-6,7-dihydroxy-1-oxoisoindoline-4-sulfonamido)acetic acid (5a-11). Treatment of **10a** with glycine methyl ester hydrochloride and further reaction based on General Procedures E and F followed by preparative HPLC purification (as indicated in the General Synthetic Procedures using a 00G-4436-P0-AX column with a linear gradient of 30% B to 70% B over 30 minutes; retention time = 19.5 minutes) provided **5a-11** as a fluffy white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.60 (bs, 1H), 10.04 (bs, 1H), 9.81 (bs, 1H), 7.97 (bs, 1H), 7.48 (dd, *J* = 7.2, 2.2 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.27 – 7.25 (m, 1H), 7.24 (s, 1H), 4.62 (s, 2H),

4.42 (s, 2H), 3.50 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.59, 166.90, 156.94 (d, *J* = 244.8 Hz), 147.60, 145.31, 135.86 (d, *J* = 3.8 Hz), 131.86, 130.26, 128.85 (d, *J* = 6.9 Hz), 124.99, 119.96 (d, *J* = 18.3 Hz), 118.71, 117.83, 117.55 (d, *J* = 21.4 Hz), 49.28, 44.46, 44.01. ESI-MS *m/z*: 443.0 (M-H). 887.0 (M_2-H). HRMS calcd for $C_{17}H_{15}N_2O_7FSCl$ [MH^+]:445.0267. Found:445.0259.

2-(2-(3-Chloro-4-fluorobenzyl)-6,7-dihydroxy-N-methyl-1-oxoisoindoline-4-sulfonamido)acetic acid (5a-12). Treatment of **10a** with sarcosine ethyl ester hydrochloride and further reaction based on General Procedures E and F followed by preparative HPLC purification (as indicated in the General Synthetic using a 00G-4436-P0-AX column with a linear gradient of 40% B to 55% B over 30 minutes; retention time = 18.5 minutes) provided **5a-12** as a fluffy white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.78 (bs, 1H), 10.14 (s, 1H), 9.90 (s, 1H), 7.49 – 7.48 (m, 1H), 7.34 (t, *J* = 8.9 Hz, 1H), 7.26 – 7.23 (m, 1H), 7.21 (s, 1H), 4.61 (s, 2H), 4.37 (s, 2H), 3.84 (s, 2H), 2.73 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.25, 166.75, 156.89 (d, *J* = 246.0 Hz), 148.03, 145.67, 135.70 (d, *J* = 3.8 Hz), 132.20, 130.26, 128.77 (d, *J* = 7.6 Hz), 123.01, 119.92 (d, *J* = 17.7 Hz), 118.79, 117.87, 117.50 (d, *J* = 21.0 Hz), 50.73, 49.77, 44.46, 35.72. MALDI-MS *m/z*: 458.98 ($M+H^+$).

2-(3-Chloro-4-fluorobenzyl)-6,7-dihydroxy-*N,N*,5-trimethyl-1-oxoisoindoline-4-sulfonamide (5b-2). Treatment of **11b-2** according to General Procedure F and purification by preparative HPLC (as indicated in the General Synthetic Procedures using a 00G-4436-P0-AX column with a linear gradient of 40% B to 70% B over 30 minutes; retention time = 24.7 minutes) provided **5b-2** as a fluffy white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (brs, 1H), 9.42 (brs, 1H), 7.49

(dd, *J* = 7.2, 2.1 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.28 – 7.25 (m, 1H), 4.63 (s, 2H), 4.44 (s, 2H), 2.60 (s, 6H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.26, 156.93 (d, *J* = 244.8 Hz, 1C), 147.01, 144.44, 135.68 (d, 1C), 134.78, 130.28, 130.15 (d, *J* = 16.0 Hz, 1C), 128.83 (d, *J* = 7.7 Hz, 1C), 121.15, 120.04 (d, 1C), 117.59 (d, *J* = 20.6 Hz, 1C), 115.97, 51.64, 44.30, 36.50 (2C), 13.56. ESI-MS *m/z*: 429.0 ($M+H^+$).

5-Butyl-2-(3-chloro-4-fluorobenzyl)-6,7-dihydroxy-*N,N*-dimethyl-1-oxoisoindoline-4-sulfonamide (5c-2). Treatment of **11c-2** according to General Procedure F and purification by preparative HPLC (as indicated in the General Synthetic Procedures using a 00G-4436-P0-AX column with a linear gradient of 40% B to 70% B over 30 minutes; retention time = 29.1 minutes) provided **5c-2** as a fluffy white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (brs, 1H), 9.37 (brs, 1H), 7.50 (d, *J* = 7.1 Hz, 1H), 7.37 – 7.32 (m, 1H), 7.29 – 7.25 (m, 1H), 4.63 (s, 2H), 4.44 (s, 2H), 2.79 (d, *J* = 8.4 Hz, 2H), 2.58 (s, 6H), 1.35 – 1.32 (m, 4H), 0.86 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.33, 156.91 (d, *J* = 246.1 Hz), 146.96, 144.58, 135.64 (d, *J* = 3.7 Hz), 135.22, 134.73, 130.25, 128.80 (d, *J* = 7.5 Hz), 121.71, 119.96 (d, *J* = 17.7 Hz), 117.50 (d, *J* = 21.0 Hz), 116.07, 51.79, 44.29, 36.36, 34.43, 31.24, 27.68, 23.36, 14.19. MALDI-MS *m/z*: ($M+H^+$).

2-(3-Chloro-4-fluorobenzyl)-6,7-dihydroxy-5-isopropyl-*N,N*-dimethyl-1-oxoisoindoline-4-sulfonamide (5d-2). Treatment of **11d-2** according to General Procedure F and purification by preparative HPLC (as indicated in the General Synthetic Procedures using a 00G-4436-P0-AX column with a linear gradient of 50% B to 70% B over 30 minutes; retention time = 26.2 minutes) provided **5d-2** as a fluffy white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (brs, 1H), 9.27 (brs, 1H), 7.50

(dd, *J* = 7.2, 2.1 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.26 (ddd, *J* = 8.5, 4.8, 2.2 Hz, 1H), 4.64 (s, 2H), 4.45 (s, 2H), 3.72 – 3.65 (m, 1H), 2.61 (s, 6H), 1.25 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.32, 156.91 (d, *J* = 246.0 Hz, 1C), 147.40, 145.99, 138.88, 135.62 (d, *J* = 3.6 Hz, 1C), 134.62, 130.23, 128.77 (d, *J* = 7.5 Hz, 1C), 122.33, 119.96 (d, *J* = 17.8 Hz, 1C), 117.51 (d, *J* = 21.0 Hz, 1C), 115.99, 52.09, 44.26, 36.10 (2C), 28.84, 19.72 (2C). ESI-MS *m/z*: 457.0 ($M+H^+$).

2-(3-Chloro-4-fluorobenzyl)-6,7-dihydroxy-5-isopropyl-4-(morpholinosulfonyl)isoindolin-1-one (5d-10) Treatment of **11d-10** according to General Procedure F and purification by preparative HPLC (as indicated in the General Synthetic Procedures using a 00G-4436-P0-AX column with a linear gradient of 40% B to 80% B over 30 minutes; retention time = 26.3 minutes) provided **5d-10** as a fluffy white solid.^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (brs, 1H), 9.31 (brs, 1H), 7.50 (dd, *J* = 7.2, 2.1 Hz, 1H), 7.37 – 7.32 (m, 1H), 7.29 – 7.25 (m, 1H), 4.63 (s, 2H), 4.46 (s, 2H), 3.76 – 3.69 (m, 1H), 3.53 – 3.51 (m, 4H), 2.97 – 2.95 (m, 4H), 1.29 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.24, 156.92 (d, *J* = 246.0 Hz, 1C), 147.75, 146.11, 139.10, 135.63 (d, *J* = 3.7 Hz, 1C), 135.16, 130.25, 128.80 (d, *J* = 7.5 Hz, 1C), 121.27, 119.95 (d, *J* = 17.8 Hz, 1C), 117.49 (d, *J* = 21.0 Hz), 116.05, 66.06 (2C), 52.05 (2C), 44.57, 44.29, 28.79, 19.85 (2C). ESI-MS *m/z*: 499.1 ($M+H^+$).

2-(3-Chloro-4-fluorobenzyl)-5,6,7-trihydroxy-*N,N*-dimethyl-1-oxoisoindoline-4-sulfonamide (5g-2). Treatment of **11f-2** according to General Procedure F and purification by preparative (as indicated in the General Synthetic Procedures using a 00G-4436-P0-AX column with a linear gradient of 30% B to 70%

B over 30 minutes; retention time = 19.8 minutes) provided **5g-2** as a fluffy white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 9.63 (s, 1H), 9.42 (s, 1H), 7.47 (dd, *J* = 7.2, 2.1 Hz, 1H), 7.39 – 7.29 (m, 1H), 7.28 – 7.21 (m, 1H), 4.59 (s, 2H), 4.35 (s, 2H), 2.66 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.83, 156.89 (d, *J* = 245.7 Hz), 150.56, 147.57, 135.90 (d, *J* = 3.7 Hz), 134.94, 133.10, 130.26, 128.82 (d, *J* = 7.4 Hz), 119.91 (d, *J* = 17.6 Hz), 117.53 (d, *J* = 21.0 Hz), 112.20, 110.19, 51.35, 44.21, 37.7 (2C). MALDI-MS *m/z*: 430.9 ($M+H^+$).

2-(3-Chloro-4-fluorobenzyl)-5-(4-(*N,N*-dimethylsulfamoyl)phenyl)-6,7-dihydroxy-*N,N*-dimethyl-1-oxoisoindoline-4-sulfonamide (5h-2). Treatment of **11h-2** according to General Procedure F and purification by preparative (as indicated in the General Synthetic using a 00G-4436-P0-AX column with a linear gradient of 50% B to 60% B over 30 minutes; retention time = 23.7 minutes) provided **5h-2** as a fluffy white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (brs, 1H), 9.36 (brs, 1H), 7.74 – 7.72 (m, 2H), 7.53 (dd, *J* = 7.2, 2.1 Hz, 1H), 7.39 – 7.35 (m, 3H), 7.32 – 7.28 (m, 1H), 4.68 (s, 2H), 4.51 (s, 2H), 2.58 (s, 6H), 2.14 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.92, 156.95 (d, *J* = 245.9 Hz), 147.46, 144.62, 140.10, 135.65, 135.62 (d, *J* = 3.6 Hz), 134.28, 134.01, 131.64, 131.01, 130.32, 128.88 (d, *J* = 7.6 Hz), 128.53, 126.92, 123.38, 119.98 (d, *J* = 17.9 Hz), 117.70, 117.54 (d, *J* = 20.8 Hz), 51.54, 44.39, 38.05 (2C), 35.28 (2C). ESI-MS *m/z*: 598.0($M+H^+$).

Supporting Information References

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