A Small Molecule Screen Identifies a Novel Compound that Induces a Homeotic Transformation in *Hydra*

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Supplementary Material

Based on the results of the first round of screening, a series of additional pyridone analogues was prepared via a published one-step reaction of a substituted acrylic (enoic) acid and a substituted benzonitrile, as described below. Unless otherwise noted, the requisite precursors for each analogue were commercially available.

I. General Experimental Details

^{1}H NMR spectra were recorded at ambient temperature at 400, and 500MHz using a Bruker DRX 400, and Bruker 500 spectrometer, respectively. ^{13}C NMR spectra were recorded at ambient temperature at 100, and 125 MHz using a Bruker DRX 400, and Bruker 500spectrometer, respectively. For ^{1}H NMR spectra acquired in $CDCl_3$, chemical shifts are reported as δ values in ppm and are calibrated according to internal $CHCl_3$ (7.26 ppm). For ^{13}C NMR spectra, chemical shifts are reported as δ values in ppm relative to chloroform. The data are reported as follows: chemical shift in ppm on the δ scale, multiplicity (app = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sxt = sextet, m = multiplet), coupling constants (Hz), and integration. Infrared spectra (IR) were obtained on a Mattson Galaxy 5000 series FTIR spectrophotometer and are reported in wavenumbers (cm^{-1}). Melting points (mp) were obtained from a Laboratory Devices Mel-Temp melting point apparatus and are

reported uncorrected. High resolution mass spectra were acquired on a Waters Micromass Analytical 7070E (CI) spectrometer, a Thermo-Finnigan TraceMS (EI) spectrometer, or a Waters Micromass LCT (ESI) spectrometer and were obtained by peak matching.

Analytical thin layer chromatography (TLC) was performed using 0.25 mm Merck precoated silica gel plates (60 F-254). Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on EM Reagents silica gel (SiO_2) 60 (200-400) mesh.

All reactions were carried out using flame-dried or oven-dried glassware and inert atmosphere operations were conducted under N_2 (g) or Ar (g) passed through a Drierite drying tube. Anhydrous tetrahydrofuran (THF), triethylamine (Et_3N), toluene, diethyl ether (Et_2O), dichloromethane (CH_2Cl_2) and *N,N'*-dimethyl formamide (DMF) were filtered through two columns of activated basic alumina and transferred under Ar (g). Triflic anhydride was distilled from P_2O_5 under nitrogen prior to use (· 2). Diisopropylethyl amine (DIPEA) was dried by distillation from CaH_2 under nitrogen.

The concentration of organolithium reagents was established by titration in THF at 0 °C against 3,5-di-*tert*-butyl-4-hydroxytoluene/1,10-phenanthroline. Concentrations of Grignard reagents were established by titration in THF at 0 °C against *sec*-BuOH/1,10-phenanthroline. *N*-Bromosuccinimide (NBS) was recrystallized from water prior to use. All other commercial reagents were used as received and purchased from Aldrich, Lancaster, Acros, Alfa Aesar, or TCI America unless noted otherwise.

II. Procedures for Synthesizing Pyridone Analogues and Precursors

A. General Procedure for preparing substituted pyridones. The pyridones were all prepared by minor modification of the published procedure discussed in the main article. Typically, a solution of *n*BuLi (2.31 M in hexane, 11.1 mmol) was syringed into Et_2NH (2.22 mmol) in THF (16 mL) at -78 °C , the temperature was raised to 0 °C, and after 20 min the solution was cooled back to -78 °C. A solution of the appropriate substituted acrylic acid (5 mmol) dissolved in THF (2 mL) was added dropwise to the resultant diethylamide base, and the reaction mixture was stirred for 30 min at 0 °C and then cooled to -78 °C. A solution of the desired nitrile (5.0 mmol) in THF (2 mL) was added dropwise, after which the temperature of the reaction mixture was allowed to warm to r.t. followed by stirring for 16 h. The reaction was quenched with H_2O (20 mL), and the aqueous layer was extracted with Et_2O (3 · 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was then suspended in EtOAc (10 mL) and allowed to stand at -20 °C for 2 h. The resultant precipitate was collected by filtration to afford the pyridone analog, generally as an off-white or light yellow solid in yields ranging from 20-80%.

Note that the more conventional base, lithium diisopropylamide (LDA) generally gives inferior results. The known pyridones prepared by this General Procedure gave spectra that were consistent with the published values. The remaining analogues, were also prepared by this procedure and gave spectra data consistent with their structures, as given below in **Section III**. Since the structure of the starting acid is unambiguously implicit in the substitution pattern of the respective pyridone products, the starting specifically substituted enoic acids generally are simply designated as “the enoic acid.”

Analogues containing basic nitrogen groups were generally first isolated as the free base, as described above, that were often soluble in aqueous the aqueous medium. Free bases that proved to be very insoluble in initial assays were converted into the corresponding hydrochoride salt by dissolving in methanol containing one equivalent of HCl (prepared as stock solutions by adding thionyl chloride to dry methanol) and evaporating to dryness. Generally, as specified below, the initial products were converted directly into the HCl salts without isolation of the free base.

B. General procedure and analysis data for non-commercial benzonitriles: 4-propoxybenzonitrile. A suspension of cyanophenol (0.6 g, 5 mmol), 1-bromopropane (0.545 mL, 6 mmol), and K_2CO_3 (2.76g, 20 mmol) in acetone (20 mL) was heated to reflux for 12 h. The mixture was concentrated *in vacuo*, then the resulting residue was partitioned between H_2O (20 mL) and CH_2Cl_2 (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 · 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (10:90 EtOAc/Hexane) to give the benzonitrile as a white solid (0.542 g, 80%). Spectral data matched published data.[1]

4-*iso*propoxybenzonitrile. General Procedure B was followed with cyanophenol (3.57 g, 30 mmol), 2-bromopropane (3.38 mL, 36 mmol), and K_2CO_3 (18.65g, 135 mmol) in acetone (120 mL) to afford the benzonitrile as a white solid (3.14 g, 65%). Spectral data matched published data.[1]

4-(benzyloxy)benzonitrile. General Procedure B was followed with cyanophenol (2.38 g, 20 mmol), benzyl bromide (2.85 mL, 24 mmol), and K_2CO_3 (2.85g, 80 mmol) in

acetone (100 mL) to afford the benzonitrile as a white solid (3.76 g, 90%). Spectral data matched published data.[1]

4-(ethyl(methyl)amino)benzonitrile. To a solution of 4-(methylamino)-benzonitrile (2.3 g, 17.5 mmol) and acetaldehyde (1.17 mL, 20.88 mmol) in 1,2-dichloroethane (87 mL) at r.t. was added $NaBH(OAc)_3$ (5.53 g, 26.1 mmol). The reaction mixture was stirred for 5 h, additional $NaBH(OAc)_3$ (2.76 g, 13 mmol) was add. The reaction mixture was stirred for 12 h and the reaction was quenched with sat. aq. $NaHCO_3$ solution (80 mL), then the product was extracted with CH_2Cl_2 (2 · 25 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (10:90 EtOAc/Hexane) to give the benzonitrile as a light yellow solid (2.317 g, 83%): mp = 44 - 45 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 - 7.41 (m, 2 H), 6.62 (d, J = 9.2 Hz, 2 H), 3.43 (q, J = 7.1 Hz, 2 H), 2.97 (s, 3 H), 1.15 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4, 133.6, 120.9, 111.3, 96.9, 46.6, 37.5, 11.5; IR (KBr) 3155, 3060, 3031, 2977, 2906, 2213, 1606, 1525, 1471, 1384, 1349, 1276, 1216, 1180, 1160, 1085 cm^{-1}; HRMS (ESI/methanol) m / z calcd for $C_{10}H_{12}N_2$ $(M + Na)^+$ 183.0898, found 183.0905.

C. Procedure (C.1) and analysis data for non-commerical enoic acids: 2,3-dimethylbut-2-enoic acid. To a cooled (0 °C) suspension of NaH (0.9g, 22 mmol, 60% in mineral oil) in DME (30 mL) was added triethyl 2-phosphonopropionate (4.3 mL, 20 mmol) dropwise and the reaction mixture was stirred at 0 °C for 40 min. To the reaction mixture was added acetone (1.5 mL, 20 mmol) and then it was allowed to warm to r.t. The reaction mixture was refluxed for 12 h, then cool to r.t. The reaction was subsequently quenched with H_2O (20 mL) followed by

extraction of the product with Et_2O (3 ·20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was dissolved in a 1:1 mixture of EtOH/H_2O (14 mL) and KOH (1.84 g, 32.76 mmol) was added in one portion. The reaction mixture was heated to 60 °C and stirred for 10 h. The volatile components were evaporated *in vacuo*, the residue was diluted with H_2O, acidified with 6 M HCl to pH = 2, and extracted the product with EtOAc (3 ·10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (5:95 to 15:85 EtOAc/Hexane) to afford the enoic acid as a yellow oil (1.14 g, 50%). Spectral data matched published data.[2]

2-ethyl-3-methylbut-2-enoic acid. Prepared by following Procedure C.1 with triethyl 2-phosphonobutyrate (2.5 mL, 10.5 mmol) and acetone (0.77 mL, 10.5 mmol) to afford the acid as a yellow oil (0.875 g, 65%). Spectral data matched published data.[2]

2-(propan-2-ylidene)pentanoic acid. Prepared by following Procedure C.1 with triethyl 2-phosphonopentanoate (8.61 mL, 32.3 mmol) and acetone (4.74 mL, 64.6 mmol) to afford the acid as an inseparable mixtures of isomers a/b = 2:1, a yellow oil (2.89 g, 63%): **a:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.54 (br s, 1 H), 4.94 (s, 2 H), 3.08 (t, *J* = 7.6 Hz, 1 H), 1.85 - 1.75 (m, 4 H), 1.65 - 1.53 (m, 1 H), 1.33 (sxt, *J* = 7.4 Hz, 2 H), 0.94 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.6, 142.5, 114.41, 52.9, 32.1, 22.5, 20.7, 14.0; **b:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.54 (br s, 1 H), 2.08 (s, 3 H), 1.87 (s, 3 H), 1.44 (sxt, *J* = 7.7 Hz, 2 H), 0.92 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 147.4, 127.1, 31.9, 23.6, 23.0, 20.2, 14.1IR (thin film) 3155, 3081, 2962, 2873,

1702, 1465, 1380, 1292, 1236, 1101 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_8H_{14}O_2$ $(M + Na)^+$ 142.0994, found 142.0990.

Alternative procedure (C.2) and analysis data for 2-substituted enoic acids: 2-(but-1-en-2-yl)pent-4-enoic acid. To a cooled (-78 °C) solution of methyl 3-methylbut-2-enoate (1.14 g, 10 mmol) in THF (50 mL) was added freshly prepared LDA (11 mL, 11 mmol, 1.0 M in THF) dropwise, then, the reaction mixture was allowed to warm to r.t. and stirred for 1 h. The reaction mixture was cooled to -78 °C and allyl iodide (1 mL, 11 mmol) was added. The reaction mixture was warmed to r.t. over 2 h, then the reaction was quenched with sat. aq. NH_4Cl solution (30 mL) and the product was extracted with Et_2O (3 ·20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was dissolved in MeOH (50 mL) and treated with 5M NaOH (10 mL, 50 mmol), then stirred at 60 °C for 2h. The reaction mixture was allowed to cool to r.t., acidified with 1 M HCl to pH = 2, and the product was extracted with Et_2O (4 ·20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (5:95 to 10:90 EtOAc/Hexane) to afford the acid as a yellow oil (0.95 g, 67%). Spectral data matched published data.[3]

2-(prop-1-en-2-yl)pent-4-ynoic acid. Prepared by following the Procedure C.2 with methyl 3-methylbut-2-enoate (2.16 g, 18.9 mmol) and propargyl bromide (3.15 mL, 28.35 mmol) to afford the acid as a yellow oil (1.33 g, 50 %): ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (br. s, 1 H), 5.04 - 5.01 (m, 1 H), 5.00 (s, 1 H), 3.31 (t, *J* = 7.6 Hz, 1 H), 2.70 (ddd, *J* = 2.6, 7.6, 16.9 Hz, 1 H), 2.54 - 2.45 (m, 1 H), 2.01 (t, *J* = 2.6 Hz, 1 H), 1.81

(s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 140.5, 122.8, 115.5, 81.3, 70.1, 52.0, 20.3, 19.97; IR (thin film) 3309, 3155, 3085, 2981, 2932, 1710, 1429, 1380, 1286, 1249, 1213, 1095 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_8H_{10}O_2$ $(M - H)^-$ 137.0603, found 137.0609.

Alternative procedure (C.3) and analysis data for the 2,3,3-trisubstituted enoic acid (*E*)-3-methylhept-2-enoic acid:

Step 1. (*E*)-methyl 3-methylhept-2-enoate. To a cooled (-45 °C) stirring suspension of CuI (1.1 g, 5.7 mmol) in THF (15 mL) was added *n*BuLi (4.7 mL, 11.3 mmol, 2.4 M in hexane), followed by stirring for 30 min. The reaction mixture was cooled to -78 °C and methyl 2-butynoate (0.89 mL, 9.1 mmol) in THF (1 mL) was added dropwise over 10 min. After 30 min, the reaction was quenched by dropwise addition of MeOH (1 mL) followed by addition of sat. aq. NH_4Cl solution (10 mL). The mixture was allowed to warm to r.t., then the product was extracted with Et_2O (3 ·10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (5:95 Et_2O/pentane) to give methyl ester **2.53** (in mixtures of *E*/*Z* isomers 7:1) as a colorless oil (0.253 g, 48%). Spectral data matched published data.[4]

Step 2. (*E*)-3-methylhept-2-enoic acid. To a solution of methyl ester of the title compound (1.4 g, 9 mmol) in MeOH (40 mL) was added 5 M NaOH (9 mL, 45 mmol) and stirred at 60 °C for 3 h. The reaction mixture was allowed to cool to r.t., acidified with 1 M HCl to pH = 2, and the product was extracted with Et_2O (4 ·20 mL). The

combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (5:95 to 15:85 EtOAc/Hexane) to afford acid **2.54** (in mixtures of *E*/*Z* isomers 7:1) as a yellow oil (0.96 g, 75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (d, *J* = 1.2 Hz, 1 H), 2.21 (s, 3 H), 1.52 (quin, *J* = 7.2 Hz, 2 H), 1.38 (spt, *J* = 7.4 Hz, 2 H), 0.96 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 163.7, 115.2, 41.07, 29.6, 22.4, 19.2, 14.0; IR (thin film) 3153, 2960, 2935, 2863, 1689, 1641, 1436, 1378, 1294, 1257, 1172, 1105 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_8H_{14}O_2$ $(M - H)^-$ 141.0916, found 141.0910.

III. New Pyridone Analogues Prepared by General Procedure A

6-(4-fluorophenyl)-4-methylpyridin-2(*1H*)-one (SKP-III-6.1). Prepared by following the General Procedure A with the enoic acid (0.5 g, 5 mmol) in THF (2 mL) and 4-fluorobenzonitrile (0.605 g, 5 mmol) in THF (2 mL) to afford the title 2-pyridone analog as a light yellow solid (0.296 g, 30%): mp = 170 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.51 (br s, 1 H), 7.71 (dd, *J* = 8.56, 5.26 Hz, 2 H), 7.17 (t, *J* = 8.56 Hz, 2 H), 6.33 (s, 1 H), 6.28 (s, 1 H), 2.25 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 153.3, 145.1, 129.9, 128.9, 117.3, 116.4, 116.2 107.7, 21.9; IR (KBr) 3155, 3060, 3031, 2985, 2921, 2902, 1650, 1618, 1465, 1380, 1240, 1162, 1097 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{12}H_{10}FNO$ $(M + Na)^+$ 226.0644, found 226.0651.

6-(4-bromophenyl)-4-methylpyridin-2(*1H*)-one (SKP-III-8.1). Prepared by following the General Procedure A with the enoic acid (0.5 g, 5 mmol) and 4-bromobenzonitrile (0.910 g, 5 mmol) to afford the title 2-pyridone analog as a light yellow solid (0.235 g, 18%): mp = 237 -

239 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.52 (br s, 1 H) 7.56 - 7.63 (m, 4 H) 6.36 (s, 1 H) 6.31 (s, 1 H) 2.25 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 153.2, 145.0, 132.6, 132.4, 128.5, 124.5, 117.7, 107.8, 21.9; IR (KBr) 3155, 3060, 3031, 2983, 2923, 2902, 1646, 1614, 1488, 1384 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{12}H_{10}BrNO$ $(M + Na)^+$ 285.9843, found 285.9852.

6-(3-bromophenyl)-4-methylpyridin-2(*1H*)-one (SKP-III-9.1). Prepared by following the General Procedure A with the enoic acid (0.5 g, 5 mmol) and 3-bromobenzonitrile (0.91 g, 5 mmol) to afford the title 2-pyridone analog as a yellow solid (0.425 g, 32%): mp = 198 - 200 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.77 (br. s, 1 H), 7.84 (t, *J* = 1.7 Hz, 1 H), 7.67 (dd, *J* = 0.6, 7.8 Hz, 1 H), 7.54 (dd, *J* = 0.8, 8.0 Hz, 1 H), 7.37 - 7.31 (m, 1 H), 6.38 (s, 1 H), 6.33 (d, *J* = 1.0 Hz, 1 H), 2.26 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 153.2, 144.5, 135.6, 132.8, 130.6, 130.0, 125.5, 123.1, 117.0, 108.2, 21.8; IR (KBr) 3388, 3155, 3060, 3031, 2981, 2923, 1646, 1618, 1479, 1380, 1255, 1164, 1097 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{12}H_{10}BrNO$ $(M + Na)^+$ 285.9843, found 285.9844.

6-(2-fluorophenyl)-4-methylpyridin-2(*1H*)-one (SKP-III-11.1). Prepared by following the General Procedure A with the enoic acid (0.5 g, 5 mmol) and 2-fluorobenzonitrile (0.54 mL, 5 mmol) to afford the title 2-pyridone analog as an off white solid (0.425 g, 42%): mp = 182 - 185 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.31 (br s, 1 H), 7.65 (t, *J* = 7.6 Hz, 1 H), 7.45 (dd, *J* = 6.7, 12.7 Hz, 2 H), 7.33 - 7.28 (m, 2 H), 7.24 - 7.17 (m, 2 H), 6.39 (br s., 2 H), 2.29 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 152.8, 140.5, 131.5, 129.9, 124.8, 122.7, 117.9, 116.7, 116.5, 110.3, 21.8; IR (KBr) 3369, 3155, 3060, 3031, 2983, 2932, 1648, 1615, 1498, 1454, 1380, 1253, 1220, 1166, 1095 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{12}H_{10}FNO$ $(M + Na)^+$ 226.0644,

found 226.0644.

6-(2-bromophenyl)-4-methylpyridin-2(*1H*)-one (SKP-III-13.1). Prepared by following the General Procedure A with the enoic acid (0.5 g, 5 mmol) and 2-bromobenzonitrile (0.91 g, 5 mmol) to afford the title 2-pyridone analog as an off white solid (0.554 g, 42%): mp = 216 - 218 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.73 (br. s, 1 H), 7.66 (d, *J* = 8.1 Hz, 1 H), 7.39 (d, *J* = 4.2 Hz, 2 H), 7.32 - 7.27 (m, 1 H), 6.30 (s, 1 H), 6.13 (s, 1 H), 2.22 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 152.6, 144.76, 135.2, 133.7, 131.1, 127.8, 122.1, 118.1, 110.4, 21.8; IR (KBr) 3386, 3155, 3060, 3031, 2983, 2921, 1648, 1619, 1471, 1380, 1164, 1097 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{12}H_{10}BrNO$ $(M + Na)^+$ 285.9843, found 285.9843.

4-methyl-6-m-tolylpyridin-2(*1H*)-one (SKP-III-14.1). Prepared by following the General Procedure A with 3,3-dimethylacrylic acid (0.5 g, 5 mmol) and m-tolylbenzonitrile (0.6 mL, 5 mmol) to afford 2-pyridone analog as a yellow solid (0.274 g, 28%): mp = 154 - 156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.41 (br. s, 1 H), 7.60 - 7.53 (m, 2 H), 7.40 (t, *J* = 7.6 Hz, 1 H), 7.29 (d, *J* = 7.6 Hz, 1 H), 6.37 (s, 2 H), 2.47 (s, 3 H), 2.29 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 152.9, 146.1, 138.7, 133.5, 130.6, 128.9, 127.5, 123.8, 117.2, 107.3, 21.8, 21.5; IR (KBr) 3388, 3037, 2921, 1648, 1602, 1432, 1276 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{13}H_{13}NO$ $(M + Na)^+$ 222.0895, found 222.0900.

6-(4-methoxyphenyl)-4-methylpyridin-2(*1H*)-one (SKP-III-21.1). Prepared by following the General Procedure A with the enoic acid (0.5 g, 5 mmol) and 4-methoxybenzonitrile (0.67 g, 5 mmol) to afford the title 2-pyridone analog as a white solid (0.67 g, 62%): mp = 195 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.20 (br. s., 1 H), 7.66 (d, *J* = 8.80 Hz, 2 H), 6.99 (d, *J* = 8.93 Hz, 2

H), 6.29 (s, 1 H), 6.26 (d, J = 1.22 Hz, 1 H), 3.85 (s, 3 H), 2.23 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 161.0, 153.1, 145.8, 128.2, 126.1, 116.5, 114.6, 106.7, 55.5, 21.8; IR (KBr) 3392, 3153, 3060, 3031, 2937, 2915, 2840, 1648, 1612, 1513, 1295, 1251, 1182, 1095, 1035 cm^{-1}; HRMS (ESI/methanol) m / z calcd for $C_{13}H_{13}NO_2$ $(M + Na)^+$ 238.0844, found 238.0852.

6-(4-diethylamino)phenyl)-4-methylpyridin-2(1*H*)-one (SKP-III-25.1). Prepared by following the General Procedure A with 3-methylbut-2-enoic acid (0.45 g, 4.5 mmol) in THF (2 mL), 4-(diethylamino)benzonitrile (0.784 g, 4.5 mmol) in THF (2 mL), n-butyllithium (4.11 mL, 9.5 mmol) in hexane (2.31 mL), and diethylamine (0.2 mL, 2.0 mmol) to afford the title 2-pyridone . ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.09 (s, 1H), 7.47 (d, J = 8.7 Hz, 2H), 6.71 (d, J = 8.9 Hz, 2H), 6.22 (s, 2H), 3.40 (q, J = 7.0 Hz, 4H), 2.22 (s, 3H), 1.19 (t, J = 7.1 Hz, 6H).

6-(4-(ethyl(methyl)amino)phenyl)-4-methylpyridin-2(*1H*)-one (SKP-III-46.1). Prepared by following the General Procedure A with the enoic acid (0.45 g, 4.5 mmol) and substituted benzonitrile (0,721 g, 4.5 mmol) to afford the title 2-pyridone analog as a orange solid (0.338 g, 31%): mp = 216 - 218 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.15 (br s, 1 H), 7.56 (d, J = 8.8 Hz, 2 H), 6.74 (d, J = 8.9 Hz, 2 H), 6.23 (s, 2 H), 3.44 (q, J = 7.1 Hz, 3 H), 2.97 (s, 3 H), 2.21 (s, 3 H), 1.15 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 153.1, 150.2, 146.1, 127.5, 120.2, 115.4, 112.1, 105.2, 46.7, 37.5, 21.9, 11.5; IR (KBr) 3390, 3155, 3035, 2983, 2917, 2904, 1648, 1612, 1511, 1467, 1380, 1292, 1247, 1182, 1095 cm^{-1}; HRMS (ESI/methanol) m / z calcd for $C_{15}H_{18}N_2O$ $(M + Na)^+$ 265.1317, found 265.1319.

6-(4-propoxyphenyl)-4-methylpyridin-2(*1H*)-one (SKP-III-52.1). Prepared by following the General Procedure A with the enoic acid (0.4 g, 4 mmol) and 4-propoxybenzonitrile (0.642 g, 4

mmol) to afford the title 2-pyridone analog as a white solid (0.487 g, 50%): mp = 153 - 155 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.8 Hz, 2 H), 6.97 (d, *J* = 8.7 Hz, 2 H), 6.28 (s, 1 H), 6.26 (d, *J* = 1.1 Hz, 1 H), 3.96 (t, *J* = 6.6 Hz, 2 H), 2.23 (s, 3 H), 1.83 (sxt, *J* = 7.1 Hz, 2 H), 1.05 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 160.7, 153.2, 145.7, 128.1, 125.8, 116.5, 125.1, 106.6, 69.7, 22.7, 21.9, 10.6; IR (KBr) 3390, 3155, 3060, 3031, 2967, 2939, 1648, 1612, 1513, 1473, 1380, 1292, 1251, 1184, 1095 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{15}H_{17}NO_2$ $(M + Na)^+$ 266.1157, found 266.1155.

6-(4-isopropoxyphenyl)-4-methylpyridin-2(*1H*)-one (SKP-III-53.1). Prepared by following the General Procedure A with the enoic acid (0.5 g, 5 mmol) and 4-*iso*propoxybenzonitrile (0.806 g, 5 mmol) to afford the title 2-pyridone analog as a white solid (0.506 g, 52%): mp = 182 °C (decomp.); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.47 (br s, 1 H), 7.61 (d, *J* = 8.9 Hz, 2 H), 6.96 (d, *J* = 8.8 Hz, 2 H), 6.28 (s, 1 H), 6.25 (d, *J* = 1.2 Hz, 1 H), 4.61 (spt, *J* = 6.0 Hz, 1 H), 2.23 (s, 3 H), 1.37 (d, *J* = 6.1 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 159.6, 153.2, 145.6, 128.0, 125.7, 116.5, 116.2, 106.5, 70.1, 22.1, 21.9; IR (KBr) 3392, 3155, 3060, 3031, 2981, 2921, 2904, 1648, 1610, 1510, 1467, 1384, 1249, 1187, 1108 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{15}H_{17}NO_2$ $(M + Na)^+$ 266.1157, found 266.1151.

6-(4-ethoxyphenyl)-4-methylpyridin-2(*1H*)-one (SKP-III-76.1). Prepared by following the General Procedure A with the enoic acid (0.5 g, 5 mmol) and 2-fluorobenzonitrile (0.736 g, 5 mmol) to afford the title 2-pyridone analog as a white solid (0.657 g, 57%): mp = 174 - 175 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.18 (br s, 1 H), 7.65 (d, *J* = 8.8 Hz, 2 H), 6.97 (d, *J* = 8.7 Hz, 2 H), 6.29 (s, 1 H), 6.25 (d, *J* = 1.1 Hz, 1 H), 4.07 (q, *J* = 7.0 Hz, 3 H), 2.22 (s, 3 H), 1.43 (t, *J* =

7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 160.5, 153.1, 145.8, 128.2, 125.9, 116.5, 115.0, 106.6, 63.9, 21.9, 14.9; IR (KBr) 3390, 3153, 3060, 3031, 2985, 2929, 1648, 1612, 1513, 1394, 1249, 1184, 1112, 1093, 1047 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{14}H_{15}NO_2$ $(M + Na)^+$ 252.1001, found 252.0999.

6-(4-(benzyloxy)phenyl)-4-methylpyridin-2(*1H*)-one (SKP-III-77.1). Prepared by following the General Procedure A with the enoic acid (0.5 g, 5 mmol) and 4-(benzyloxy)-benzonitrile (1.04 g, 5 mmol) to afford the title 2-pyridone analog as a light yellow solid (0.678 g, 46%): mp = 218 - 219 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.98 (br s, 1 H), 7.65 (d, *J* = 8.8 Hz, 2 H), 7.47 - 7.33 (m, 5 H), 7.07 (d, *J* = 8.8 Hz, 2 H), 6.30 (s, 1 H), 6.26 (s, 1 H), 5.11 (s, 2 H), 2.23 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 160.3, 153.1, 145.7, 136.7, 128.8, 128.3, 128.2, 127.6, 126.4, 116.6, 115.5, 106.7, 70.2, 21.9; IR (KBr) 3394, 3155, 3060, 3031, 2977, 2919, 1646, 1604, 1523, 1469, 1380, 1268, 1207, 1159, 1085 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{19}H_{17}NO_2$ $(M + Na)^+$ 314.1157, found 314.1154.

6-(4-(methylthio)phenyl)-4-methylpyridin-2(*1H*)-one (SKP-III-79.1). Prepared by following the General Procedure A with the enoic acid (0.5 g, 5 mmol) and 4-(methylthio)-benzonitrile (0.746 g, 5 mmol) to afford the title 2-pyridone analog as a yellow solid (0.462 g, 40%): mp = 218 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.62 (br s, 1 H), 7.61 (d, *J* = 8.4 Hz, 2 H), 7.32 (d, *J* = 8.6 Hz, 2 H), 6.32 (d, *J* = 1.0 Hz, 1 H), 6.30 (d, *J* = 1.6 Hz, 1 H), 2.52 (s, 3 H), 2.25 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 153.2, 145.3, 141.6, 129.9, 126.9, 126.5, 117.2, 107.09, 21.9, 15.3; IR (KBr) 3290, 3155, 3060, 3031, 2983, 2925, 2902, 1645, 1612, 1494, 1469, 1382, 1166, 1093 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{13}H_{13}NOS$ $(M + Na)^+$ 254.0616, found 254.0619.

6-(4-chlorophenyl)-4-methylpyridin-2(*1H*)-one (SKP-III-80.1). Prepared by following the General Procedure A with the enoic acid (0.5 g, 5 mmol) and 4-chlorobenzonitrile (0.688 g, 5 mmol) to afford the title 2-pyridone analog as a light yellow solid (0.527 g, 48%): mp = 225 - 229 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.67 (br s, 1 H), 7.67 (d, *J* = 8.8 Hz, 2 H), 7.45 (d, *J* = 8.6 Hz, 2 H), 6.35 (s, 1 H), 6.31 (s, 1 H), 2.26 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 153.2, 145.0, 136.1, 132.1, 129.4, 128.3, 117.59, 107.9, 21.8 ; IR (KBr) 3260, 3070, 2900, 1645, 1615, 1384, 1094, 846, 818, 712 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{12}H_{10}ClNO$ $(M + Na)^+$ 242.0349, found 242.0341.

6-(4-tert-butylphenyl)-4-methylpyridin-2(*1H*)-one (SKP-III-114.1). Prepared by following the General Procedure A with the enoic acid (0.5 g, 5 mmol) and 4-*tert*-butylbenzonitrile (0.86 mL, 5 mmol) to afford the title 2-pyridone analog as an off white solid (0.518 g, 43%): mp = 223 °C (decomp.); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.41 (br s, 1 H), 7.62 (d, *J* = 8.4 Hz, 2 H), 7.50 (d, *J* = 8.6 Hz, 2 H), 6.33 (s, 1 H), 6.32 (s, 1 H), 2.25 (s, 3 H), 1.35 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 153.4, 153.2, 145.5, 130.7, 126.3, 126.2, 117.1, 107.1, 34.9, 31.3, 21.9; IR (KBr) 3390, 3155, 3060, 3031, 2967, 2904, 2869, 1648, 1614, 1467, 1382, 1095 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{16}H_{19}NO$ $(M + Na)^+$ 264.1364, found 264.1359.

6-(4-*n*-butylphenyl)-4-methylpyridin-2(*1H*)-one (SKP-III-118.1). Prepared by following the General Procedure A with the enoic acid (0.5 g, 5 mmol) and 4-butylbenzonitrile (0.86 mL, 5 mmol) to afford the title 2-pyridone analog as an off white solid (0.422 g, 35%): mp = 110 - 112

°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.11 (br. s., 1 H), 7.67 (d, *J* = 8.1 Hz, 2 H), 7.33 (d, *J* = 8.1 Hz, 2 H), 6.37 (s, 1 H), 6.35 (s, 1 H), 2.70 (t, *J* = 7.7 Hz, 2 H), 2.29 (s, 3 H), 1.68 (quin, *J* = 7.6 Hz, 2 H), 1.43 (qd, *J* = 7.3, 14.8 Hz, 2 H), 1.00 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 152.9, 145.9, 145.1, 131.0, 129.2, 126.6, 117.0, 107.0, 35.54, 33.4, 22.51, 21.8, 14.0; IR (KBr) 3388, 3031, 2958, 2933, 2859, 1648, 1612, 1513, 1427, 1267 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{16}H_{19}NO$ $(M + Na)^+$ 264.1364, found 264.1362.

1-(2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)ethyl)-6-(4-methoxyphenyl)-4-methylpyridin-2(1*H*)-one (SKP-III-128.1). Prepared by following the General Procedure A to give 1-(2-(2-(2-(2-*tert*-butyldimethylsilyloxy)ethoxy)ethoxy)ethoxy)ethyl)-6-(4-methoxyphenyl)-4-methylpyridin-2(1*H*)-one (0.129 g, 0.26 mmol) in THF (2 mL), which was then deprotected with tetra-*n*-butylammonium fluoride (1.04 mL, 1.04 mmol) and acetic acid (30 mL, 0.52 mmol) to afford the title 2-pyridone analog (0.148 g). ^{1}H NMR (400 MHz, CDCl3) δ 7.95 (d, *J* = 8.8 Hz,2H), 7.10 (s, 1H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.49 (s, 1H), 4.63 – 4.56 (m, 2H), 3.92 – 3.87 (m, 2H), 3.86 (s, 3H), 3.77 – 3.68 (m,6H), 3.67 (s, 4H), 3.63 – 3.56,(m, 2H), 2.55 (s, 1H), 2.33 (s,3H).

6-(4-(2-(2-(2-(2-(allyloxy)ethoxy)ethoxy)ethoxy)ethoxy)phenyl)-4-methylpyridin-2(1*H*)-one (SKP-III-133.1). Prepared by following the General Procedure A with 3-methylbut-2-enoic acid (0.263 g, 2.63 mmol), 4-(2-(2-(2-(2-(allyloxy)ethoxy)ethoxy)ethoxy)ethoxy)benzonitrile (0.883 g, 2.63 mmol) in THF (2 mL), n-butyllithium (2.12 mL, 5.26 mmol) in hexane (2.31 mL), and diethylamine (0.11 mL, 1.052 mmol) to afford the title 2-pyridone analog. ^{1}H NMR (400 MHz, CDCl3) δ 11.33 (s, 1H), 7.60 (d, *J* = 8.7 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.27 (d, *J* = 12.3 Hz,

2H), 5.96 – 5.85 (m, 1H), 5.26 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.17 (d, *J* = 10.4 Hz, 1H), 4.23 – 4.14 (m, 2H), 4.01 (d, *J* = 5.7 Hz, 2H), 3.92 – 3.85 (m, 2H), 3.77 – 3.55 (m, 13H), 2.23 (s, 3H).

6-(4-(dimethylamino)phenyl)-4-ethyl-5-methylpyridin-2(1*H*)-one (SKP-IV-1.1). Prepared by following the General Procedure C with pentan-3-one (1.06 mL, 10 mmol) in THF (2 mL), methyl 2-(dimethoxyphosphoryl)acetate (2.0 mL, 11 mmol), and sodium hydride (0.44 g, 11 mmol) to afford the title 2-pyridone analog. This product (0.25 g, 0.097 mmol) was treated with thionyl chloride (0.28 μL, 0.39 mmol) in methanol to afford the corresponding hydrochoride salt.

6-(4-(dimethylamino)phenyl)-3,4-dimethylpyridin-2(*1H*)-one (SKP-IV-9.1). Prepared by following the General Procedure A with the enoic acid (0.39 g, 3.9 mmol) and 4-(dimethylamino)-benzonitrile (0.57 g, 3.9 mmol) to afford the title 2-pyridone analog as a yellow solid (0.302 g, 32%): mp = 273 - 275 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.26 (br s, 1 H), 7.53 (d, *J* = 8.9 Hz, 2 H), 6.74 (d, *J* = 8.9 Hz, 2 H), 6.24 (s, 1 H), 3.01 (s, 6 H), 2.21 (s, 3 H), 2.12 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4, 151.3, 148.1, 126.8, 122.6, 121.0, 112.4, 106.1, 40.4, 20.4, 12.0; IR (KBr) 3394, 3155, 3060, 3031, 2985, 2902, 2813, 1633, 1608, 1525, 1469, 1367, 1205, 1168, 1095 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{15}H_{18}N_2O$ $(M + Na)^+$ 265.1317, found 265.1318.

6-(3-chloro-4-(dimethylamino)phenyl)-4-methylpyridin-2(1H)-one hydrochoride (SKP-IV-24.1). Prepared by following the General Procedure A to give the title compound (0.20 g, 0.78 mmol), which was treated directly with thionyl chloride (0.28 μL, 0.38 mmol) in methanol to afford the 2-pyridone analog (0.240 g) as the hydrochloride salt: ^{1}H NMR (400 MHz, DMSO) δ

12.03 (s, 3H), 7.91 (d, J = 2.1 Hz, 1H), 7.75 (dd, J = 8.5, 2.1 Hz, 1H), 7.29 (d, J = 8.5 Hz, 1H), 7.12 (s, 1H), 6.79 (s, 1H), 2.84 (s, 6H), 2.47 (s, 2H), 2.33 (s, 3H).

6-(2-chloro-4-(dimethylamino)phenyl)-4-methylpyridin-2(1H)-one (SKP-IV-27.1). Prepared by following the General Procedure A to give to give 0.157 g, 0.6 mmol of the title 2-pyridone analog: ^{1}H NMR (400 MHz, DMSO) δ 7.33 (d, J = 8.7 Hz, 1H), 6.89 – 6.83 (m, 2H), 6.83 – 6.76 (m, 2H), 2.97 (s, 6H), 2.50 – 2.45 (m, 2H), 2.35 (s, 3H).

6-(4-(ethyl(methyl)amino)phenyl)-3,4-dimethylpyridin-2(1H)-one hydrochloride (SKP-IV.86.1). Prepared by following the General Procedure A to give the free base of 6-(4-(ethyl(methyl)amino)-phenyl-3,4-dimethylpyridin-2(1H)-one (0.224 g, 0.87 mmol), which was treated with thionyl chloride (0.13 mL, 1.174 mmol) in methanol to afford the hydrochoride salt of the title 2-pyridone analog.

6-(4-(ethyl(methyl)amino)phenyl)-3-ethyl-4-methylpyridin-2(*1H*)-one (SKP-IV-112.1). Prepared by following the General Procedure A with the enoic acid (0.476 g, 3.73 mmol) and the benzonitrile (0.597 g, 3.73 mmol) to afford the title 2-pyridone analog as a yellow solid (0.363 g, 36%): mp = 147 - 148 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.18 (br s, 1 H), 7.50 (d, J = 8.9 Hz, 2 H), 6.72 (d, J = 8.9 Hz, 2 H), 6.21 (s, 1 H), 3.44 (q, J = 7.1 Hz, 2 H), 2.97 (s, 3 H), 2.62 (q, J = 7.5 Hz, 2 H), 2.23 (s, 3 H), 1.14 (td, J = 7.3, 10.9 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 149.9, 147.8, 142.3, 128.5, 127.0, 120.6, 112.2, 106.1, 46.8, 37.6, 19.8, 19.6, 13.0, 11.5; IR (KBr) 3392, 3155, 3060, 3031, 2975, 2933, 2902, 1629, 1608, 1523, 1469, 1380, 1272, 1214, 1160, 1095 cm^{-1}; HRMS (ESI/methanol) m / z calcd for $C_{17}H_{22}N_2O$ $(M + Na)^+$ 293.1630, found

293.1638.

6-(4-(ethyl(methyl)amino)phenyl)-4-methyl-3-propylpyridin-2(*1H*)-one (SKP-IV-113.1). Prepared by following the General Procedure A with the enoic acid (0.755 g, 5.3 mmol) and the benzonitrile (0.849 g, 5.3 mmol) to afford the title 2-pyridone analog as a light yellow solid (0.6 g, 40%): mp = 198 - 200 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.33 (br s, 1 H), 7.61 (d, *J* = 9.0 Hz, 2 H), 6.72 (d, *J* = 9.0 Hz, 2 H), 6.23 (s, 1 H), 3.44 (q, *J* = 7.1 Hz, 3 H), 2.96 (s, 3 H), 2.60 - 2.53 (m, 2 H), 2.23 (s, 3 H), 1.58 (sxt, *J* = 7.5 Hz 2 H), 1.15 (t, *J* = 7.2 Hz, 3 H), 1.02 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 149.8, 148.0, 142.6, 127.3, 126.9, 120.7, 112.0, 106.0, 46.7, 37.5, 28.8, 21.8, 19.8, 14.7, 11.4; IR (KBr) 3394, 3155, 3060, 3031, 2962, 2931, 2871, 1608, 1523, 1469, 1378, 1349, 1213, 1160, 1085 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{17}H_{22}N_2O$ $(M + Na)^+$ 307.1786, found 307.1784.

6-(4-(dimethylamino)phenyl)-4-methyl-3-propylpyridin-2(*1H*)-one (SKP-IV-114.1). Prepared by following the General Procedure A with the enoic acid (0.99 g, 7 mmol) and 4-(dimethylamino)-benzonitrile (1.02 g, 7 mmol) to afford the title 2-pyridone analog as a light yellow solid (0.857 g, 45%):mp = 198 - 200 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.20 (br s, 1 H), 7.61 (d, *J* = 8.9 Hz, 2 H), 6.74 (d, *J* = 8.8 Hz, 2 H), 6.24 (s, 1 H), 3.01 (s, 6 H), 2.59 - 2.54 (m, 2 H), 2.23 (s, 3 H), 1.57 (sxt, *J* = 7.5 Hz, 2 H), 1.02 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 151.2, 148.0, 142.5, 127.1, 121.1, 112.3, 106.1, 40.4, 28.8, 21.9, 19.9, 14.7; IR (KBr) 3394, 3155, 3060, 3031,2960, 2929, 2871, 2813, 1608, 1525, 1465, 1365, 1205, 1170, 1091 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{17}H_{22}N_2O$ $(M + Na)^+$ 293.1630, found 293.1631.

6-(4-(dimethylamino)phenyl)-3-ethyl-4-methylpyridin-2(*1H*)-one (SKP-IV-115.1). Prepared by following the General Procedure A with the enoic acid (0.918 g, 7.16 mmol) and 4-(dimethylamino)-benzonitrile (1.05 g, 7.16 mmol) to afford the title 2-pyridone analog as a yellow solid (0.789 g, 43%): mp = 203 - 205 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.94 (br s, 1 H), 7.58 (d, *J* = 9.0 Hz, 2 H), 6.74 (d, *J* = 8.9 Hz, 2 H), 6.23 (s, 1 H), 3.00 (d, *J* = 1.1 Hz, 6 H), 2.62 (q, *J* = 7.4 Hz, 2 H), 2.23 (s, 3 H), 1.13 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 151.2, 147.7, 142.5, 128.5, 127.0, 121.1, 112.3, 106.2, 40.4, 19.8, 19.6, 13.0; IR (KBr) 3394, 3155, 3060, 3031,2966, 2931, 2900, 2871, 1627, 1608, 1525, 1466, 1365, 1205, 1168, 1093, 1062 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{16}H_{20}N_2O$ $(M + Na)^+$ 279.1493, found 279.1477.

6-(4-(dimethylamino)phenyl)-4-methyl-3-(prop-2-ynyl)pyridin-2(*1H*)-one (SKP-IV-180.1). Prepared by following the General Procedure A with the enoic acid (0.552 g, 4 mmol) and 4-(dimethylamino)-benzonitrile (0.585 g, 4 mmol) to afford the title 2-pyridone analog as a yellow solid (0.238 g, 22%): mp = 235 - 237 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.34 (br s, 1 H), 7.62 (d, *J* = 8.8 Hz, 2 H), 6.77 (d, *J* = 8.8 Hz, 2 H), 6.29 (s, 1 H), 3.57 (d, *J* = 2.0 Hz, 2 H), 3.02 (s, 6 H), 2.35 (s, 3 H), 1.95 (d, *J* = 0.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 151.5, 150.0, 144.2, 127.4, 120.8, 120.6, 112.3, 106.2, 82.2, 67.4, 40.4, 20.0, 15.5; IR (KBr) 3394, 3307, 3155, 3060, 3031, 2987, 2902, 2125, 1629, 1606, 1525, 1367, 1205, 1168, 1097 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{17}H_{18}N_2O$ $(M + Na)^+$ 298.1317, found 298.1324.

6-(4-(dimethylamino)phenyl)-4-butylpyridin-2(*1H*)-one (SKP-VI-167). Prepared by following the General Procedure A with the enoic acid (0.374 g, 2.63 mmol) and 4-

(dimethylamino)-benzonitrile (0.384 g, 2.63 mmol) to afford the 2-pyridone analog as a light yellow solid (0.201 g, 28%): mp = 202 - 205 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.05 (br. s., 1 H), 7.57 (d, *J* = 8.9 Hz, 2 H), 6.76 (d, *J* = 8.9 Hz, 2 H), 6.25 (s, 1 H), 6.24 (s, 1 H), 3.02 (s, 6 H), 2.47 (t, *J* = 7.7 Hz, 2 H), 1.64 - 1.56 (m, 2 H), 1.38 (sxt, *J* = 7.6 Hz, 2 H), 0.93 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 157.7, 151.5, 146.1, 127.4, 120.9, 114.8, 112.4, 104.7, 40.3, 35.7, 31.7, 22.4, 14.0; IR (KBr) 3155, 3060, 3031, 2958, 2933, 2863, 1643, 1604, 1523, 1459, 1365, 1205, 1172, 1095 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{17}H_{22}N_2O$ $(M + H)^+$ 271.1810, found 271.1813.

Library (DAC) Compounds

4-Methyl-6-phenylpyridin-2(1H)-one (DAC-1-217). Prepared by following the General Procedure A with 3-methylbut-2-enoic acid (0.675 g, 6.75 mmol) in THF (2 mL), benzonitrile (0.690 g, 6.75 mmol) in THF (2 mL), *n*-butyllithium (7 mL, 15 mmol) in hexane (2.31 mL), and diethylamine (0.31 mL, 3.0 mmol) to afford the title 4-methyl-6-phenylpyridin-2(1H)-one. 2.46 g, mp 174-175^{o}C.

4-methyl-[2,2'-bipyridin]-6(1H)-one (DAC-1-283). Prepared by following the General Procedure A with diethylamine (0.2 mL, 2 mmol) added to a solution of *n*-butyllithium (4 mL, 10 mmol) in THF (20 mL), 3-methylbut-2-enoic acid (0.45 g, 4.5 mmol) in THF (4 mL), and picolinonitrile (0.468 g, 4.5 mmol) in THF (4 mL), to afford the title 4-methyl-[2,2'-bipyridin]-6(1H)-one (0.5 g) off-white solid, mp 119-120. 1H NMR (500 MHz, CDCl3) δ 11.43 (s, 1H),

8.67 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.95 (td, *J* = 7.8, 1.8 Hz, 1H), 7.47 (ddd, *J* = 7.5, 4.8, 0.9 Hz, 1H), 7.09 (s, 1H), 6.32 (s, 1H), 1.91 (s, 3H).

6-(4-(dimethylamino)phenyl)-4-methylpyridin-2(1H)-one (DAC-2-25). Prepared by following the General Procedure A with 3-methylbut-2-enoic acid (0.45 g, 4.5 mmol) in THF (2 mL), 4-(dimethylamino)benzonitrile (0.6586g, 4.5 mmol) in THF (2 mL), *n*-butyllithium (6.5 mL, 9.5 mmol) in hexane (2.31 mL), and diethylamine (0.2 mL, 2.0 mmol) to afford the title compound, 280 mg, mp 251-253^{o}C. 1H NMR (500 MHz, DMSO) δ 7.60 (d, *J* = 8.6 Hz, 2H), 6.74 (d, *J* = 8.7 Hz, 2H), 6.32 (s,1H), 6.00 (s,1H), 2.96 (s, 6H), 2.15 (s, 3H).

4-(1-hydroxyethyl)-[2,2'-bipyridin]-6(1H)-one (DAC-2-40). Prepared by following the General Procedure A to give 4-(1-((tert-butyldimethylsilyl) oxy)ethyl)-[2,2'-bipyridin]-6(1H)-one (0.4 g, 1.21 mmol), which was deprotected without further purification with tetra-butyl ammonium fluoride (2.5 mL, 2.50 mmol) in in THF (12 mL), affording the title 4-(1-hydroxyethyl) -[2,2'-bipyridin]-6(1H)-one (0.16 g, brown solid). 1H NMR (500 MHz, CDCl3) δ 10.93 (s, 1H), 8.74 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 8.01 (td, *J* = 7.8, 1.8 Hz, 1H), 7.53 (ddd, *J* = 7.5, 4.8, 0.9 Hz, 1H), 7.26 (s, 1H), 6.51 (s, 1H), 5.44 (d, *J* = 4.5 Hz, 1H), 4.81 – 4.59 (m, 1H), 1.39 (d, *J* = 6.5 Hz, 3H).

6-(2-(Dimethylamino)phenyl)-4-methylpyridin-2(1H)-one (SKP-IV-79.1). Prepared by following the General Procedure A with 3-methylbut-2-enoic acid (0.448 g, 4.48 mmol), 2-(dimethylamino)benzonitrile (0.656 mg, 4.48 mmol) and *n*-butyllithium (3.1 mL, 9 mmol) in THF (20 mL) to afford the title compound. 1H NMR (400 MHz, CDCl3) δ 11.04 (s, 1H), 7.46

(d, *J* = 7.7 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.17 – 7.04 (m, 2H), 6.29 (d, *J* = 12.3 Hz, 2H), 2.68 (s, 6H), 2.25 (s, 3H).

IV. Synthesis of Isoquinolinones

3-phenylisoquinolin-1(*2H*)-one (SKP-V-139). To a cooled (-78 °C) solution of *o*-toluic acid (0.681 g, 5 mmol) in THF (5 mL) was added freshly prepared LDA (11 mL, 11 mmol, 1.0 M in THF) dropwise. The reaction mixture was allowed to warm to r.t. and stirred for 1 hr. The temperature of the reaction mixture was re-cooled to -78 °C, then, benzonitrile (0.605 g, 5 mmol) was added in THF (2 mL) dropwise. The reaction mixture was allowed to warm to r.t. slowly, stirred for 16 h, then the reaction quenched with H_2O (20 mL). The aqueous layer was extracted with Et_2O (3 · 10 mL) and combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was suspended in EtOAc (10 mL) and was allowed to stand at low temperature (-20 °C) for 2 h. The precipitate was collected by filtration to afford the title 2-pyridone analog (as a mixture of 2-isoquinolinone and 2-isoquinolinol tautomers) as an off white solid (0.938 g, 71%): mp = 199 - 200 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.59 (br s, 1 H), 8.41 (d, *J* = 8.1 Hz, 1 H), 7.78 (d, *J* = 7.6 Hz, 2 H), 7.68 (t, *J* = 7.8 Hz, 1 H), 7.60 (d, *J* = 7.8 Hz, 1 H), 7.56 - 7.45 (m, 4 H), 6.80 (s, 1 H), 1.76 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2, 139.8,

138.5, 134.4, 133.0, 130.0, 129.3, 127.6, 127.6, 126.7, 126.4, 125.1, 104.5; IR (KBr) 3689, 3398, 3155, 3062, 2987, 2902, 1648, 1484, 1382, 1348, 1147, 1095 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{15}H_{11}NO$ $(M + H)^+$ 226.0644, found 226.0651.

3-(4-methoxyphenyl)isoquinolin-1(*2H*)-one (SKP-III-122.1). Prepared as in the preceding using *o*-toluic acid (0.681 g, 5 mmol) and 4-methoxybenzonitrile (0.67 g, 5 mmol) to afford the title 2-pyridone analog (as a mixture of 2-isoquinolinone and 2-isoquinolinol tautomers) as an off white solid (0.778 g, 62%): mp = 243 - 244 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.52 (br s, 1 H), 8.39 (d, *J* = 7.8 Hz, 1 H), 7.69 - 7.66 (m, 1 H), 7.64 (d, *J* = 8.7 Hz, 2 H), 7.58 (d, *J* = 7.8 Hz, 1 H), 7.46 (t, *J* = 7.5 Hz, 1 H), 7.04 (d, *J* = 8.7 Hz, 2 H), 6.70 (s, 1 H), 3.89 (s, 3 H), 1.61 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8, 160.9, 139.3, 138.6, 133.0, 127.6, 127.5, 126.9, 126.5, 126.4, 124.8, 114.8, 103.4, 55.6; IR (KBr) 3693, 3398, 3155, 3060, 3031, 2985, 2902, 2840, 1650, 1606, 1517, 1467, 1382, 1290, 1253, 1155, 1095 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{16}H_{13}NO_2$ $(M + H)^+$ 252.1024, found 252.1024.

3-(4-(dimethylamino)phenyl)isoquinolin-1(*2H*)-one (SKP-V-137). Prepared as in the preceding using *o*-toluic acid (0.681 g, 5 mmol) and 4-(dimethylamino)-benzonitrile (0.731 g, 5 mmol) to afford the title 2-pyridone analog (as mixtures of 2-isoquinolinone and 2-isoquinolinol tautomers) as a bright yellow solid (0.938 g, 71%): mp = 244 - 246 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.31 (br s, 1 H), 8.38 (d, *J* = 7.9 Hz, 1 H), 7.66 - 7.59 (m, 1 H), 7.59 - 7.51 (m, 3 H), 7.41 (t, *J* = 7.5 Hz, 1 H), 6.79 (d, *J* = 8.8 Hz, 2 H), 6.67 (s, 1 H), 3.04 (s, 6 H), 1.68 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8, 151.3, 139.8, 139.0, 132.8, 127.6, 126.8, 126.3, 125.9, 124.5, 121.6, 112.5, 102.1, 40.4; IR (KBr) 3691, 3398, 3155, 3060, 3031, 2985, 2902, 1650, 1610, 1527, 1446, 1378, 1168, 1095 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{17}H_{16}NO$ (M +

H)$^+$ 265.1341, found 265.1336.

7-(4-(dimethylamino)phenyl)-1,6-naphthyridin-5(*6H*)-one (SKP-V-140). Prepared as in the preceding using nicotinic acid (0.274 g, 2 mmol) and 4-(dimethylamino)-benzonitrile (0.292 g, 2 mmol) to afford the title 2-pyridone analog (as a mixture of 5-naphthyridone and 5-naphthyridinol tautomers) as an orange solid (0.154 g, 29%): mp = 254 - 256 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (br s, 1 H), 8.88 (dd, *J* = 1.8, 4.5 Hz, 0 H), 8.61 (dd, *J* = 1.1, 8.1 Hz, 0 H), 7.61 (d, *J* = 8.9 Hz, 2 H), 7.31 (dd, *J* = 4.6, 8.0 Hz, 1 H), 6.95 (s, 1 H), 6.79 (d, *J* = 8.9 Hz, 2 H), 3.05 (s, 6 H), 1.75 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9, 155.5, 155.2, 151.7, 143.7, 135.9, 127.1, 120.7, 120.5, 112.4, 103.6, 40.3; IR (KBr) 3398, 3155, 3060, 3031, 2985, 2902, 1658, 1608, 1529, 1467, 1380, 1295, 1218, 1168, 1095 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{16}H_{15}N_3O$ (M + H)$^+$ 266.1293, found 266.1297.

V. Synthesis of Benzophenone-containing Pyridones

6-(4-(4-benzoylbenzyloxy)phenyl)-4-methylpyridin-2(*1H*)-one (SKP-VI-86). To a solution of the 2-pyridone ketal described immediately below (0.2 g, 0.45 mmol) in CH_2Cl_2 (4 mL) was added TFA (2 mL). The reaction mixture was strirred at r.t. for 12 h. Then, the reaction mixture was neutralized with sat. aq. $NaHCO_3$ solution and the product was extracted with CH_2Cl_2 (3 · 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was suspended in EtOAc (10 mL) and was allowed to stand at low temperature (-20 °C) for 2 h. The precipitate was collected by filtration to afford 2-pyridone analog **2.74** as a yellow solid (0.134 g, 75%): mp = 188 - 190 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.45 (br s, 1 H), 7.85

(dt, *J* = 8.2, 2.0 Hz, 2 H), 7.81 (dd, *J* = 1.3, 8.2 Hz, 2 H), 7.64 (dt, *J* = 8.9, 2.1 Hz, 2 H), 7.60 (tt, *J* = 1.3, 7.5 Hz, 2 H), 7.56 (d, *J* = 8.3 Hz, 2 H), 7.49 (t, *J* = 7.5 Hz, 3 H), 7.08 (dt, *J* = 8.9, 2.4 Hz, 2 H), 6.30 (s, 1 H), 6.28 (d, *J* = 1.3 Hz, 1 H), 5.22 (s, 2 H), 2.24 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.4, 165.1, 160.0, 153.3, 145.4, 141.3, 137.6, 137.4, 132.6, 130.6, 130.2, 128.5, 128.1, 127.1, 126.7, 116.7, 115.6, 106.8, 69.6, 21.9; IR (KBr) 3386, 3155, 3060, 3031, 2985, 2902, 1650, 1612, 1511, 1469, 1380, 1278, 1247, 1180, 1095 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{26}H_{21}NO_3$ $(M + Na)^+$ 418.1419, found 418.1415.

Precursors of SKP-VI-86, in reverse order of synthesis:

6-(4-(4-(2-phenyl-1,3-dioxolan-2-yl)benzyloxy)phenyl)-4-methylpyridin-2(*1H*)-one. Prepared by following the General Procedure A with 3,3-dimethylacrylic acid (0.4 g, 4 mmol) and the benzonitrile ketal described immediately below (1.43 g, 4 mmol) to afford the title 2-pyridone ketal as an off white solid (0.557 g, 66%): mp = 225 °C (decomp.); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.23 (br. s, 1 H), 7.60 (d, *J* = 8.6 Hz, 2 H), 7.56 (d, *J* = 8.1 Hz, 2 H), 7.54 - 7.50 (m, 2 H), 7.40 (d, *J* = 8.1 Hz, 2 H), 7.36 - 7.27 (m, 3 H), 7.04 (d, *J* = 8.8 Hz, 2 H), 6.29 (s, 1 H), 6.25 (d, *J* = 1.0 Hz, 1 H), 5.08 (s, 2 H), 4.07 (s, 4 H), 2.23 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 160.3, 153.2, 145.4, 142.3, 142.1, 128.3, 128.3, 128.0, 127.5, 126.6, 126.4, 126.2, 116.7, 115.5, 109.4, 106.6, 69.9, 65.1 (· 2), 21.9 ; IR (KBr) 3394, 3155, 3060, 3031, 2985, 2900, 1648, 1612, 1510, 1469, 1380, 1247, 1180, 1089 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{28}H_{25}NO_4$ $(M + Na)^+$ 462.1681, found 462.1668.

4-(4-(2-phenyl-1,3-dioxolan-2-yl)benzyloxy)benzonitrile. A suspension of cyanophenol (0.119 g, 1 mmol), the bromide **IV** described in the following section (0.319 g, 1 mmol),

K_2CO_3 (0.7 g, 5 mmol), and nBu$_4$NI (0.037 g, 0.1 mmol) in DMF (3 mL) was stirred at 100 °C for 2 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (4 ·10 mL). The combined organic layer was washed with 1 M NaOH, H_2O, brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (15:85 EtOAc/Hexane) to give the title benzonitrile as a pale yellow solid (0.26 g, 72%): mp = 92 - 94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 - 7.55 (m, 4 H), 7.55 - 7.52 (m, 2 H), 7.38 (d, *J* = 8.3 Hz, 2 H), 7.36 - 7.29 (m, 2 H), 7.00 (d, *J* = 9.0 Hz, 2 H), 5.09 (s, 2 H), 4.08 (s, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 142.6, 142.0, 135.6, 134.1, 128.3, 127.4, 126.7, 126.2, 119.3, 115.7, 109.3, 104.4, 70.0, 65.0 (· 2); IR (KBr) 3155, 3060, 3031, 2985, 2952, 2894, 2215, 1731, 1606, 1523, 1475, 1450, 1384, 1346, 1253, 1213, 1180, 1085 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{23}H_{19}NO_3$ $(M + Na)^+$ 380.1263, found 380.1265.

6-(4-((4-benzoylbenzyl)(methyl)amino)phenyl)-4-methylpyridin-2(*1H*)-one (SKP-VI-156). To a solution of 2-pyridone ketal described immediately below (0.169 g, 0.39 mmol) in CH_2Cl_2 (4 mL) was added TFA (2 mL). The reaction mixture was strirred at r.t. for 12 h. Then, the reaction mixture was neutralized with sat. aq. $NaHCO_3$ solution and the product was extracted with CH_2Cl_2 (3 · 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was suspended in EtOAc (10 mL) and was allowed to stand at low temperature (-20 °C) for 2 h. The precipitate was collected by filtration to afford the title 2-pyridone analog as a yellow solid (0.127 g, 80%): mp = 165 - 167 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.75 (br s, 1 H), 7.81 - 7.77 (m, 4 H), 7.58 (tt, *J* = 1.5, 7.3 Hz, 1 H), 7.53 (d, *J* = 8.9 Hz, 2 H), 7.47 (t, *J* = 7.7 Hz, 2 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 6.78 (d, *J* = 8.8 Hz, 2 H), 6.24 (s, 1

H), 6.21 (br s, 1 H), 4.68 (s, 2 H), 3.15 (s, 3 H), 2.20 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.4, 164.8, 150.6, 145.7, 143.3, 137.7, 136.7, 132.6, 130.8 (· 2), 130.1, 128.4, 127.5 (· 2), 126.5, 121.3, 115.7, 112.4, 56.26, 39.1, 22.0; IR (KBr) 3394, 3155, 3060, 3031, 2985, 2902, 1650, 1604, 1521, 1471, 1380, 1380, 1205, 1095 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{27}H_{24}N_2O_2$ $(M + H)^+$ 409.1916, found 409.1924.

Precursors of SKP-VI-156, in reverse order of synthesis:

6-(4-(methyl(4-(2-phenyl-1,3-dioxolan-2-yl)benzyl)amino)phenyl)-4-methylpyridin-2(*1H*)-one. Prepared by following the General Procedure A with 3,3-dimethylacrylic acid (0.43 g, 4.3 mmol) and the benzonitrile described in the following procedure (1.6 g, 4.32 mmol) to afford 2-pyridone analog as a yellow solid (0.564 g, 29%): mp = 238 - 240 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.29 (br s, 1 H), 7.53 - 7.49 (m, 2 H), 7.49 - 7.44 (m, 4 H), 7.35 - 7.30 (m, 2 H), 7.30 - 7.27 (m, 1 H), 7.15 (d, *J* = 8.4 Hz, 2 H), 6.75 (d, *J* = 9.3 Hz, 2 H), 6.22 (s, 1 H), 6.21 (d, *J* = 1.3 Hz, 1 H), 4.57 (s, 3 H), 4.10 - 4.00 (m, 4 H), 3.10 - 3.03 (m, 3 H), 2.21 (d, *J* = 0.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 153.3, 150.8, 145.6, 142.2, 141.3, 138.1, 128.3, 128.2, 127.3, 126.7, 126.4, 126.2, 120.9, 115.7, 112.4, 109.4, 105.3, 65.1 (· 2), 56.0, 38.8, 22.0; IR (KBr) 3392, 3155, 3060, 3031, 2985, 2900, 1648, 1604, 1521, 1380, 1207, 1091 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{29}H_{28}N_2O_3$ $(M + Na)^+$ 475.1998, found 475.1988.

4-(methyl(4-(2-phenyl-1,3-dioxolan-2-yl)benzyl)amino)benzonitrile. To a cooled (0 °C) solution of secondary amine described in the following procedure in DMF (20 mL) was added NaH (0.568 g, 14.2 mmol, 60 % in mineral oil) in one portion. Once the bubbling ceased (c.a. 20 min), MeI (2.2 mL, 35.5 mmol) was added dropwise. The

reaction mixture was allowed to warm to r.t. and stirred for 1 h. The reaction was quenched with H_2O (20 mL), then the product was extracted with EtOAc (3 ·10 mL). The combined organic layers were washed with sat. aq. $Na_2S_2O_4$ solution, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (20:80 EtOAc/Hexane) to give the title benzonitrile as a pale yellow oil (2.47 g, 94%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 - 7.51 (m, 2 H), 7.49 (d, *J* = 8.2 Hz, 2 H), 7.46 - 7.42 (m, 2 H), 7.37 - 7.29 (m, 3 H), 7.12 (d, *J* = 8.1 Hz, 2 H), 6.67 (d, *J* = 9.1 Hz, 2 H), 4.58 (s, 2 H), 4.12 - 4.01 (m, 4 H), 3.10 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 142.1, 141.6, 137.2, 133.6, 128.3, 128.2, 126.8, 126.2, 120.6, 111.7, 109.3, 98.0, 65.0 (· 2), 55.7, 38.9; IR (thin film) 3428, 3153, 3062, 3031, 2983, 2894, 2215, 1708, 1608, 1523, 1471, 1448, 1415, 1332, 1270, 1209, 1174, 1085 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{24}H_{22}N_2O_2$ $(M + Na)^+$ 393.1579, found 393.1584.

4-(4-(2-phenyl-1,3-dioxolan-2-yl)benzylamino)benzonitrile. To a solution of 4-amino benzonitrile (1.36 g, 11.5 mmol) and aldehyde **II** (3.2 g, 12.6 mmol) in 1,2-dichloroethane (57 mL) at r.t. was added $NaBH(OAc)_3$ (3.67 g, 17.3 mmol) followed by addition of acetic acid (0.66 mL, 11.5 mmol). The reaction mixture was stirred for 16 h until the reaction was quenched with sat. aq. $NaHCO_3$ solution (30 mL), then the product was extracted with CH_2Cl_2 (3 ·15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by recrystallization from hexane/EtOAc to afford the title amine as a white solid (3.26 g, 79%): mp = 128 - 130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 - 7.49 (m, 4 H), 7.41 (d, *J* = 8.8 Hz, 2 H), 7.38 - 7.27 (m, 5 H), 6.57 (d, *J* = 8.8 Hz, 2 H), 4.59 (app t, *J* = 5.2 Hz, 1 H), 4.34 (d, *J* = 5.5 Hz, 2 H), 4.12 - 4.02 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1,

142.1, 141.9, 137.8, 133.8, 128.3, 128.2, 127.5, 126.8, 126.2, 120.5, 112.5, 109.3, 99.3, 65.1 (· 2), 47.3; IR (KBr) 3428, 3155, 3062, 2031, 2983, 2894, 2215, 1608, 1523, 1471, 1272, 1209, 1174, 1085 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{23}H_{20}N_2O_2$ $(M + Na)^+$ 379.1422, found 379.1428.

6-(4-benzoylphenyl)-4-methylpyridin-2(*1H*)-one (SKP-VI-177). To a solution of the ketal described directly below (0.1 g, 0.3 mmol) in CH_2Cl_2 (4 mL) was added TFA (2 mL) and strirred at r.t. for 12 h. The reaction mixture was neutralized with sat. aq. $NaHCO_3$ solution and the product was extracted with CH_2Cl_2 (3 · 10 mL). The combine organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was suspended in EtOAc (10 mL) and was allowed to stand at low temperature (-20 °C) for 2 h. The precipitate was collected by filtration to afford the title 2-pyridone analog as yellow solid (0.065 g, 73%): mp = 192 - 194 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 12.45 (br s, 1 H), 7.93 (d, *J* = 8.2 Hz, 2 H), 7.88 - 7.81 (m, 4 H), 7.62 (tt, *J* = 1.3, 7.5 Hz, 1 H), 7.51 (t, *J* = 7.9 Hz, 2 H), 6.43 (s, 1 H), 6.40 (s, 1 H), 2.28 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.0, 165.5, 153.1, 144.7, 138.6, 137.4, 137.3, 132.8, 130.9, 130.2, 128.6, 126.8, 118.4, 108.6, 21.9; IR (KBr) 3390, 3060, 3031, 3155, 2985, 2902, 1646, 1602, 1469, 1382, 1317, 1276, 1095 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{19}H_{15}NO_2$ $(M + Na)^+$ 312.1000, found 312.0998.

Precursors of SKP-VI-177, in reverse order of synthesis:

6-(4-(2-phenyl-1,3-dioxolan-2-yl)phenyl)-4-methylpyridin-2(*1H*)-one. Prepared by following the General Procedure A with 3,3-dimethylacrylic acid (0.5 g, 5 mmol) and benzonitrile (directly below, 0.628 g, 2.5 mmol) to afford the title 2-pyridone analog as a

light yellow solid (0.557 g, 66%): mp = 222 - 224 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.54 (br. s, 1 H), 7.67 - 7.61 (m, 4 H), 7.55 - 7.51 (m, 2 H), 7.37 - 7.28 (m, 3 H), 6.33 (s, 1 H), 6.29 (d, *J* = 1.2 Hz, 1 H), 4.09 (s, 4 H), 2.24 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 153.0, 145.2, 144.2, 141.8, 133.4, 128.4, 127.1, 126.4, 126.2, 117.6, 109.2, 107.6, 65.2 (· 2), 21.9; IR (KBr) 3388, 3155, 3060, 3031, 2985, 2898, 1648, 1608, 1471, 1382, 1267, 1210, 1087 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{21}H_{19}NO_3$ $(M + Na)^+$ 356.1263, found 356.1255.

4-(2-phenyl-1,3-dioxolan-2-yl)benzonitrile. To a solution of oxime (directly below, 0.47 g, 1.74 mmol) in CH_3CN (10 mL) was added dimethyl acetylenedicarboxylate (0.42 mL, 3.48 mmol) followed by Et_3N (0.24 mL, 1.74 mmol) and the reaction mixture was stirred at r.t for 12 hrs. The solvent was concentrated *in vacuo*, then the residue was diluted with H_2O (10 mL), and the product was extracted with CH_2Cl_2 (3 ·10 mL). The combined organic layer was washed with H_2O (·2), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (8:92 EtOAc/Hexane) to give the title benzonitrile as a white solid (0.34 g, 77%): mp = 99 - 101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (app q, *J* = 7.7 Hz, 4 H), 7.53 - 7.47 (m, 2 H), 7.39 - 7.28 (m, 3 H), 4.13 - 4.04 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 141.2, 132.2, 128.6, 128.5 127.0, 126.0, 118.8, 112.0, 108.7, 65.2 (· 2); IR (KBr) 3064, 3031, 2983, 2894, 2231, 1608, 1490, 1450, 1265, 1209, 1076, 997, 836, 748, 732, 701 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{16}H_{13}NO_2$ $(M + H)^+$ 252.1024, found 252.1031.

4-(2-phenyl-1,3-dioxolan-2-yl)benzaldehyde oxime. To a cooled (0 °C) suspension of aldehyde **II (**described below, 0.5 g, 1.96 mmol) and hydroxyl amine hydrochloride

(0.163 g, 2.35 mmol) in MeOH/H_2O 1:1 (4 mL) was added NaOH (1 mL, 5 M, 5 mmol) dropwise. The reaction mixture was stirred at r.t. for 12 h, then diluted with H_2O (10 mL) and the product was extracted with EtOAc (3 ·10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the title oxime as a white solid that was carried on to the next step without further purification (0.5 g, 94%): mp = 112 - 114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1 H), 8.07 (br s, 1 H), 7.59 - 7.50 (m, 6 H), 7.38 - 7.29 (m, 3 H), 4.11 - 4.06 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 144.2, 141.8, 131.9, 128.4, 127.0, 126.8, 126.2, 122.8, 109.3, 65.1 (· 2); IR (KBr) 3347, 3060, 3031, 2979, 2892, 1674, 1473, 1448, 1386, 1263, 1211, 1085 cm^{-1}; HRMS (ESI/methanol) *m* / *z* calcd for $C_{16}H_{15}NO_3$ $(M + H)^+$ 270.1130, found 270.1125.

6-(4-((4-benzoylbenzyl)(methyl)amino)phenyl)-4-methyl-3-(prop-2-ynyl)pyridin-2(*1H*)-one (SKP-VI-190). Prepared by following the General Procedure A with the enone (0.177 g, 1.28 mmol) and benzonitrile (0.474 g, 1.28 mmol) to afford the ketal of the title 2-pyridone analog as a light yellow solid. To a stirred solution of this ketal (0.2 g, 0.4 mmol) in CH_2Cl_2 (4 mL) was added TFA (2 mL), followed by additional stirring at r.t. for 12 h. The reaction mixture was neutralized with sat. aq. $NaHCO_3$ solution and the product was extracted with CH_2Cl_2 (3 · 10 mL). The combine organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was suspended in EtOAc (10 mL) and was allowed to stand at low temperature (-20 °C) for 2 h. The precipitate was collected by filtration to afford **SKP-VI-190** (a mixture of 2-pyridone and 2-pyridinol tautomers) as a orange solid (0.296 g, 25%): mp = 92 - 94 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.02 (br s, 1 H), 7.81 - 7.76 (m, 4 H), 7.59 - 7.55 (m, 3 H), 7.47 (t, *J* = 7.8 Hz, 2 H), 7.33 (d, *J* = 7.9 Hz, 2 H), 6.79 (d, *J* = 9.0 Hz, 2 H), 6.27 (s, 1 H), 4.69 (s, 2 H), 3.53 (d,

J = 2.6 Hz, 2 H), 3.15 (s, 3 H), 2.33 (s, 3 H), 1.88 (t, J = 2.7 Hz, 1 H), 1.68 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.4, 163.5, 150.5, 150.0, 143.9, 143.4, 137.7, 136.7, 132.6, 130.8, 130.1, 128.4, 127.5, 126.5, 121.3, 121.1, 112.4, 106.4, 82.0, 67.5, 56.3, 39.1, 20.0, 15.5 ; IR (KBr) 3394, 3307, 3155, 3060, 3031, 2985, 2902, 2125, 1631, 1606, 1523, 1471, 1380, 1205, 1097 cm^{-1}; HRMS (ESI/methanol) m / z calcd for $C_{30}H_{26}N_2O_2$ $(M + Na)^+$ 469.1892, found 469.1877.

Simple Precursors (I-IV) of Benzophenone Pyridones:

2-(4-bromophenyl)-2-phenyl-1,3-dioxolane (I). A solution of 4-bromobenzophenone (10 g, 38.3 mmol), ethylene glycol (2.35 mL, 42.13 mmol), and p-TsOH (0.077 g, 0.415 mmol) in benzene (30 mL) was refluxed for 48 h with a Dean-Stark condenser. The reaction mixture was allowed to cool to r.t. and was washed with sat. aq. $NaHCO_3$ solution (20 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (25:75 CH_2Cl_2/Hexane) to give bromide **2.61** as white solid (11.0 g, 95%). Spectral data matched published data.[6]

4-(2-phenyl-1,3-dioxolan-2-yl)benzaldehyde (II). To a cooled (-78 °C) solution of aryl bromide **I** (1 g, 3.27 mmol) in THF (9 mL) was added *n*BuLi (1.43 mL, 3.6 mmol, 2.52 M in hexane) dropwise, followed by additional stirring at -78 °C for 30 min. To the reaction mixture, DMF (0.28 mL, 3.6 mmol) was added and the reaction was allowed to warm to r.t. The reaction was quenched with sat. aq. NH_4Cl solution (10 mL), the product was extracted with Et_2O (3 ·10 mL), the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. No further purification was needed to afford aldehyde **II** as a white solid (0.741 g, 90%). Spectral data matched published data.[6]

2-phenyl-2-p-tolyl-1,3-dioxolane (III). This compound was prepared following the method described above for the preparation of bromide **I** starting from 4-methyl benzophenone (3.9 g, 20 mmol) to afford acetal **III** as a white solid (4.56 g, 95 %). Spectral data matched published data.[7]

2-(4-(bromomethyl)phenyl)-2-phenyl-1,3-dioxolane (IV). A solution of acetal **III** (3.4 g, 14.1 mmol), *N*-bromosuccinimide (2.56 g, 15.5 mmol), and dibenzoyl peroxide (0.034 g, 0.14 mmol) in CCl_4 (70 mL) was refluxed for 3 h. The reaction mixture was cooled to r.t. and washed with H_2O, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was recrystallized from EtOAc/hexane to afford bromide **IV** as a white solid (3.37 g, 75%). Spectral data matched published data.[7]

3.3 References

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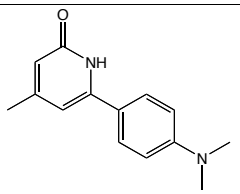
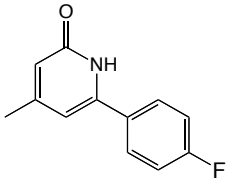
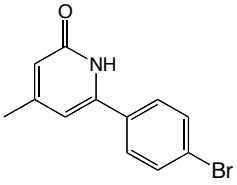
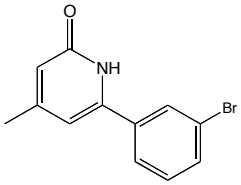
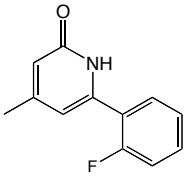
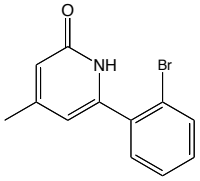
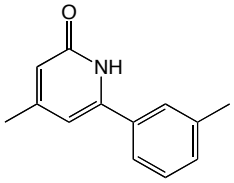
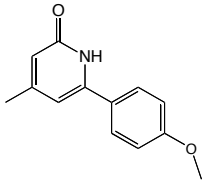
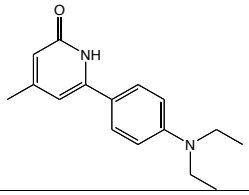
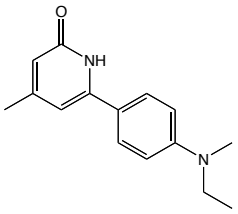
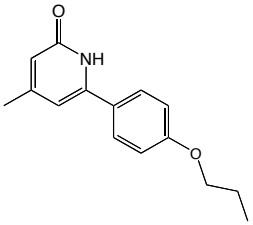
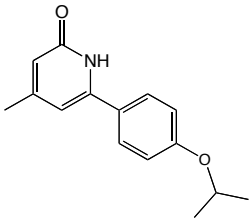
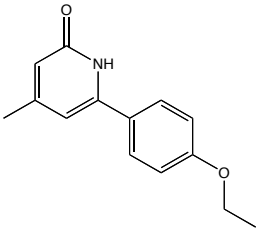
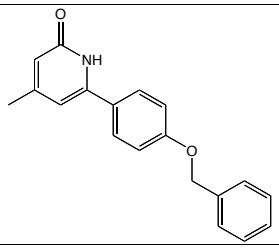
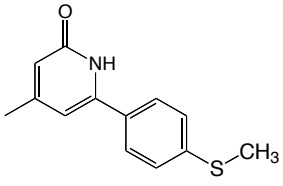
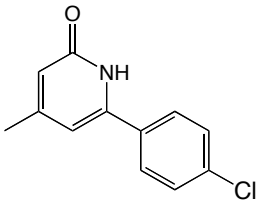
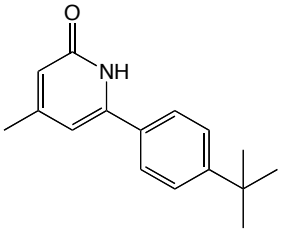
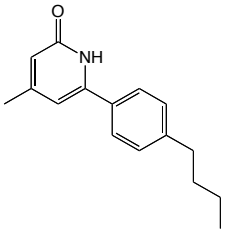
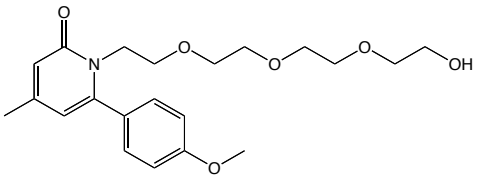
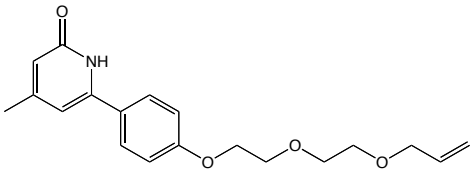
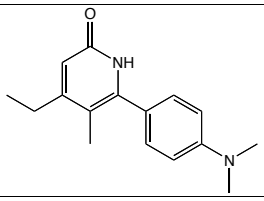
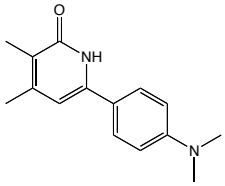
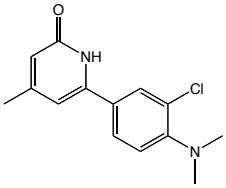
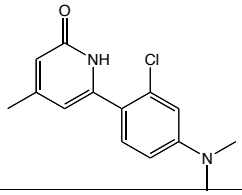
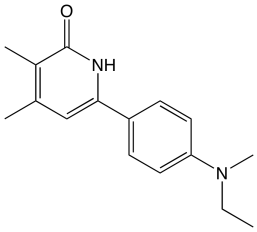
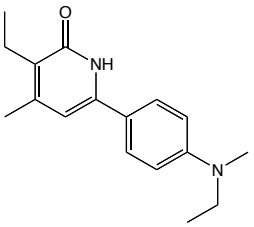
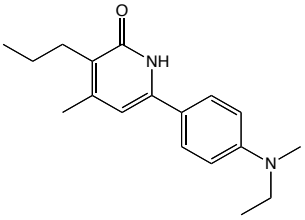
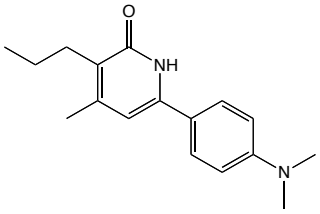
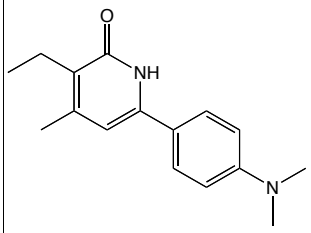
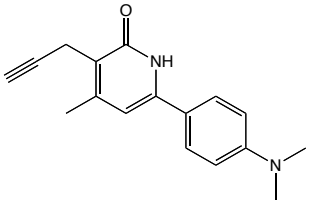
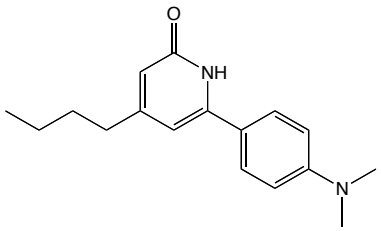
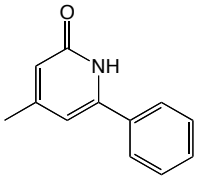
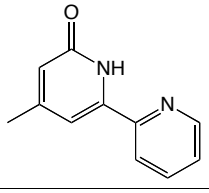
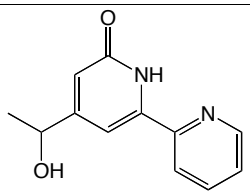
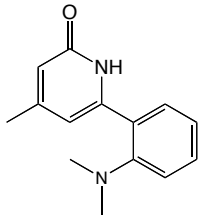
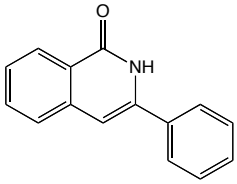
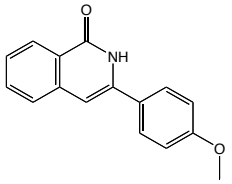
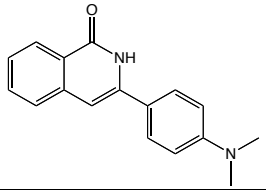
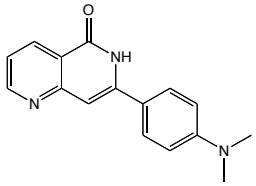
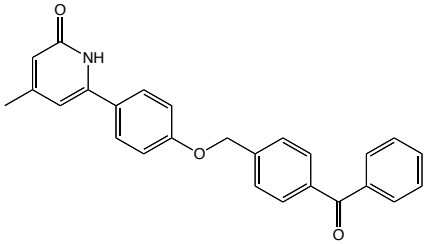
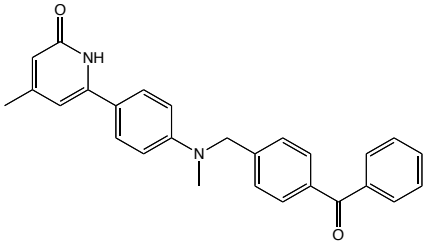
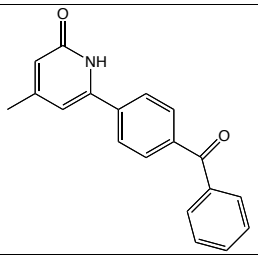
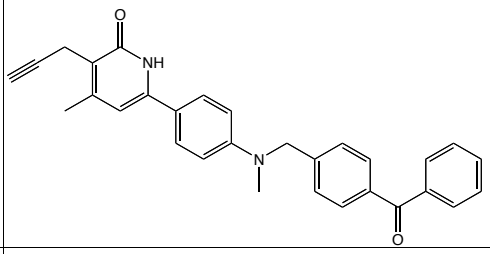
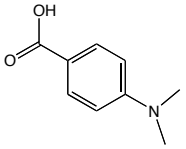
Compound	Structure	Activity	Form tested	Comments
DAC-2-25		Active	free base in DMSO and hydrochloride salt	original hit
SKP-III.6.1		Inactive	free base in DMSO	
SKP-III.8.1		Toxic	free base in DMSO	
SKP-III.9.1		Toxic	free base in DMSO	
SKP-III.11.1		Inactive	free base in DMSO	
SKP-III.13.1		Inactive	free base in DMSO	
SKP-III.14.1		Toxic	free base in DMSO	
SKP-III.21.1		Active	free base in DMSO	Active at 5 μM, 1 μM
SKP-III.25.1		Active	hydrochloride salt	Active at 5 μM, 1 μM

SKP-III.46.1		Active	hydrochloride salt	Active at 5 μM, 1 μM, 500 nM
SKP-III.52.1		Active	free base in DMSO	Active at 5 μM, 1 μM
SKP-III.53.1		Active	free base in DMSO	Active at 5 μM, 1 μM
SKP-III.76.1		Active	free base in DMSO	Active at 5 μM, 1 μM
SKP-III.77.1		Inactive	free base in DMSO	
SKP-III.79.1		Toxic	free base in DMSO	Toxic at 5 μM, 1 μM and 500 nM
SKP-III.80.1		Toxic	free base in DMSO	

SKP-III.114.1		Active	free base in DMSO	Active at 5 μM
SKP-III.118.1		Active	free base in DMSO	Active at 5 μM, 1 μM
SKP-III.128.1		Inactive	free base in DMSO	
SKP-III.133.1		Inactive	free base in DMSO	
SKP-IV.1.1		Active	hydrochloride salt	Active at 20 μM
SKP-IV.9.1		Active	hydrochloride salt	Active at 5 μM, 1 μM, 500 nM, 100 nM
SKP-IV.24.1		Active	hydrochloride salt	weakly Active (Ectopic tentacles on buds, not adults)
SKP-IV.27.1		Active	free base in DMSO	weakly Active (Ectopic tentacles on buds, not adults)
SKP-IV.86.1		Active	free base in DMSO	weakly Active (Ectopic tentacles on buds, not adults)

SKP-IV.112.1		Active	hydrochloride salt	Active at 5 μM
SKP-IV.113.1		Toxic	hydrochloride salt	
SKP-IV.114.1		Active	hydrochloride salt	Active at 5 μM
SKP-IV.115.1		Active	hydrochloride salt	Active at 5 μM
SKP-IV.180.1		Active	free base in DMSO	Active at 5 μM
SKP-VI.167		Toxic/Inactive	free base in DMSO	Toxic at 5 μM/ Inactive at lower concentrations
DAC-1-217		Inactive	free base in DMSO	Significantly slowed morphogenesis of aggregates when compared to 5uM DAC-2-25
DAC-1-283		Inactive		

DAC-2-40		Inactive		
SKP-IV.79.1		Inactive		
SKP-V.139		Toxic	free base in DMSO	Toxic at 5 µM, 500 nM
SKP-III.122.1		Toxic	free base in DMSO	
SKP-V.137		Active	free base in DMSO	Toxic at 5 µM, weakly Active at 500 nM, but still slightly Toxic
SKP-V.140		Active	free base in DMSO	Active at 5 µM, 500 nM
SKP-VI.86		Inactive	free base in DMSO	
SKP-VI.156		Active	free base in DMSO	Active at 5 µM

SKP-VI.177		Toxic/Inactive	free base in DMSO	Toxic at 5 μM/ Inactive at lower concentrations
SKP-VI.190		Inactive	free base in DMSO	
4-(Dimethylamino) benzoic acid		Inactive		