# Synthesis and evaluation of heterocyclic catechol mimics as inhibitors of catechol-O-methyltransferase (COMT)

## SUPPORTING INFORMATION

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**X-ray crystallography**

A bacterial expression construct for human COMT was generated in pET29b(+) consisting of the coding region for residues 47-271 of the protein, an M51A point mutation to eliminate a secondary start codon, and a C-terminal enterokinase cleavage site followed by a hexhistidine affinity purification tag. The protein was overexpressed in BL21-Gold(DE3) cells by induction with 1mM IPTG, and purified from bacterial lysates using standard nickel affinity and ion exchange techniques. The protein was complexed with ligand at low concentration and then gradually concentrated to 7-12 mg/ml for use in crystallization trials. Crystallization conditions were found to be ligand-dependent, and required co-crystallization broad screening in each case. Compound 18 was crystallized in 0.1M MES pH 6.5, 0.1M sodium acetate, and 30% PEG 2000MME using 100uM ligand and 11mg/ml protein. Compound 27b crystallized at 100uM ligand and 7.5mg/ml protein from 0.1M Tris, pH 8.5, 0.2M Lithium Sulfate, and 20% PEG 4000. Compound 32 was found to yield optimal crystals from 0.1M HEPES, pH 7.0, and 30% PEG 6000 with 100uM ligand and 12mg/ml protein. All crystals were grown in standard sitting and hanging drop vapor diffusion crystallization plates at 20 ºC.

Diffraction data were collected from single crystals at 100 K using an in-house Rigaku FR-E rotating anode generator on a Saturn 944+ CCD area detector. Data were integrated and scaled using HKL2000 and structures determined by molecular replacement using the structure of rat COMT (RCSB code 1VID) as a search model. All structures were built in Coot and refined using the CCP4 suite of programs to final resolutions of 1.9 Ang. (Cmpd 18), 2.3 Ang. (Cmpd 27b), and 2.4 Ang. (Cmpd 32). Structures and all associated data files have been deposited with the Protein Data Bank under accession codes 4XUC, 4XUE, and 4XUD, respectively.

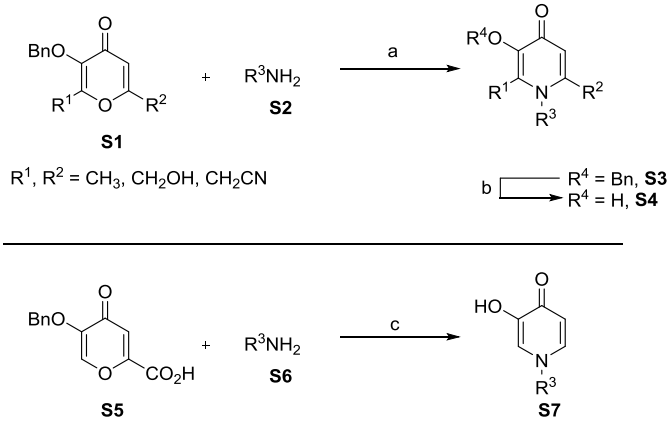
**General**

Normal phase column chromatography was carried out in the indicated solvent system (in the percentage of volume) using pre-packed silica gel cartridges for use on the Isco CombiFlash® or Biotage SP1®. Analytical thin layer chromatography (TLC) visualization was performed using 254 nm wavelength ultraviolet light. The LC/MS analyses were performed using a MICROMASS ZMD mass spectrometer coupled to an AGILENT 1100 Series HPLC utilizing a YMC ODS-A 4.6 x 50 mm column eluting at 4.5 mL/min with a solvent gradient of 10 to 95% B

over 2.5 min, followed by 0.5 min at 95% B: solvent A = 0.06% TFA in water; solvent B =0.05% TFA in acetonitrile. HRMS measurements were acquired by use of a Bruker Daltonics 7T Fourier transform ion cyclotron resonance (FTICR) mass spectrometer. Samples were dissolved in acetonitrile:water:acetic acid [50:50:0.1%(v/v)], and ionized by use of electrospray ionization (ESI). External calibration was accomplished with oligomers of polypropylene glycol (PPG, average molecular weight 1000 Da). $^{1}$H-NMR data were collected on a Varian 500 MHz instrument equipped with a Protasis flow NMR probe. Mass-guided purifications were accomplished on Agilent 1100 hardware utilizing Penomenex Luna 5 micron C18 columns (2 cm x 5 cm), eluting at 25 mL / min with a custom 8 minute focused gradient containing acetonitrile and water with 0.1% TFA. Final compound purity exceeded 95% by this method.

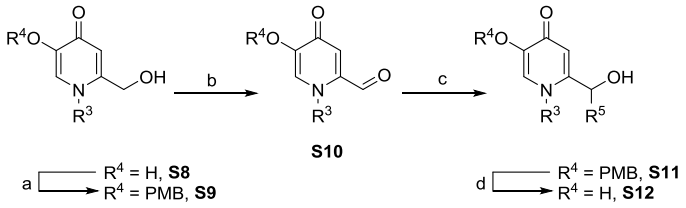
In vitro COMT inhibition assays were performed as described (Characterization of Non-Nitrocatechol Pan and Isoform Specific Catechol-O-methyltransferase Inhibitors and Substrates. *ACS Chemical Neuroscience* **2012,** 3, (2), 129-140), are reported as the average of ≥2 independent replicates, and the assay exhibits interassay variability of approximately ±30%.

**Scheme S1. Synthesis of hydroxy-4-pyridinones**[a]



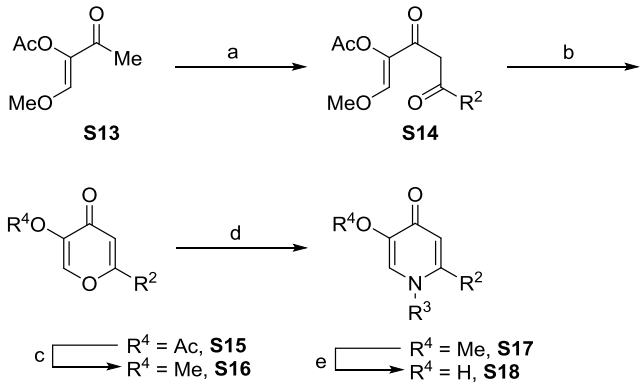

[a]Reagents and conditions: (a) AcOH, $H_2O$, 100-140 °C; (b) $H_2$, Pd/C or 4 M aq HCl, 100 °C; (c) AcOH, $H_2O$, 200 °C.

**Scheme S2. Synthesis of 2-hydroxymethyl-5-hydroxy-4-pyridinones**[a]



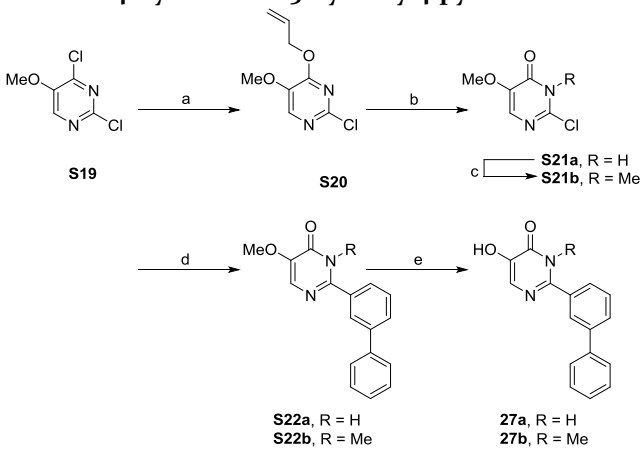

[a]Reagents and conditions: (a) PMB-Cl; (b) $MnO_2$; (c) $R^5MgX$; (d) TFA.

**Scheme S3. Synthesis of 2-substituted-5-hydroxy-4-pyridinones**[a]



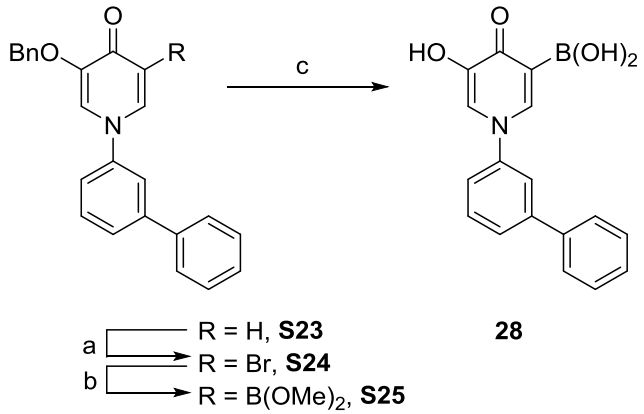

[a]Reagents and conditions: (a) 1. LHMDS; 2. $R^2COCl$; (b) PPTS, 110 °C; (c) 1. $K_2CO_3$; 2. MeI; (d) $R^3NH_2$, AcOH, $H_2O$, 160 °C; (e) $BBr_3$.

**Scheme S4. Synthesis of 5-hydroxy-4-pyrimidinones**[a]



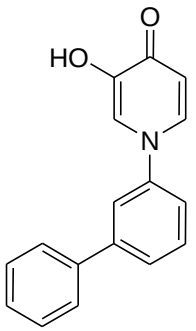

[a]Reagents and conditions: (a) allyl alcohol, $K_2CO_3$; (b) $Pd(PPh_3)_4$, morpholine; (c) MeI; (d) 3-biphenyl boronic acid, $Cl_2Pd(dppf)$; (e) $BBr_3$.

**Scheme S5. Synthesis of boronic acid inhibitor 28**[a]

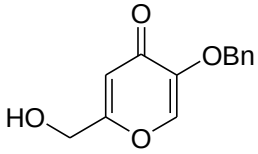



[a]Reagents and conditions: (a) NBS; (b) 1. *i*-PrMgCl, 2. $B(OMe)_3$; (c) 1. $H_2$, Pd/C; 2. aq. HCl.

**1-(Biphenyl-3-yl)-5-hydroxy-2-(methylamino)pyridin-4(1H)-one (18)**



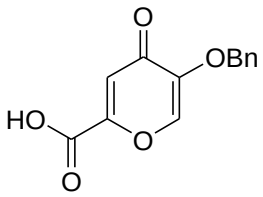

**5-(Benzyloxy)-2-(hydroxymethyl)-4*H*-pyran-4-one**




To a stirred solution of kojic acid (71.05 g, 0.5 mmol) and sodium hydroxide (22 g, 0.55 mol) in 750 mL of MeOH and 75 mL of water was added benzylchloride (73 g, 0.575 mmol) drop-wise. The resulting mixture was heated at reflux for 4.5 h with stirring. The mixture was then allowed to cool and concentrated to half of the starting volume. The mixture was poured into water, the resultant solid was collected, washed with water, and dried to give 110 g crude compound. The crude compound was re-crystallized from EtOAc to give 5-(benzyloxy)-2-

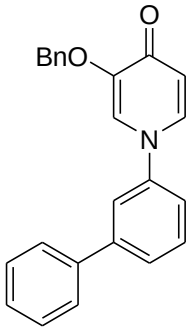
(hydroxymethyl)-4H-pyran-4-one (93.4 g, 80.1%). $^1$H NMR δ (400 MHz, $d_6$-DMSO): 8.14 (s, 1H), 7.40-7.30 (m, 5H), 6.29(s, 1H), 5.68 (t, J= 6.0 Hz, 1H), 4.91 (s, 2H), 4.26 (d, J= 6.0 Hz,1H).

**5-(Benzyloxy)-4-oxo-4*H*-pyran-2-carboxylic acid**




To a solution of 5-(benzyloxy)-2-(hydroxymethyl)-4H-pyran-4-one (93.4 g, 401 mmol) in 2.6 L of acetone was added 400 mL of Jone's reagent (2.45 M) at 0 °C. The reaction was warmed to room temperature, and the mixture was stirred overnight. The solid was removed by filtration, and the filtrate was concentrated. The concentrated residue was poured into water. The resulting white solid was collected and washed with water and dried to obtain 5-(benzyloxy)-4-oxo-4H-pyran-2-carboxylic acid (79.4 g, 80.2 %).$^1$H NMR $\delta$ (400 MHz, $d_6$-DMSO): 8.34 (s, 1H), 7.42-7.33 (m, 5H), 6.91(s, 1H), 4.95 (s, 2H).

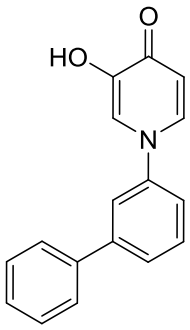
**3-(Benzyloxy)-1-(biphenyl-3-yl)pyridin-4(1*H*)-one**




5-(Benzyloxy)-4-oxo-4H-pyran-2-carboxylic acid (36.9 g, 150 mmol) and 3-aminobiphenyl (25.35 g, 150 mmol) were combined in diphenyl ether (110 ml). The mixture was heated to 250 °C (pre-heated block) in an open flask. After 10 min, the mixture was cooled to room temperature. The residue was purified by silica gel chromatography to provide 3-(benzyloxy)-1-(biphenyl-3-yl)pyridin-4(1H)-one (26.53 g, 50.1%). $^1$H NMR $\delta$ (400 MHz, $d_6$-DMSO): 7.55 (d,

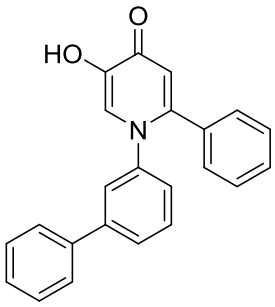
J=7.6 Hz, 1H), 7.46 (m, 4H), 7.44-7.31 (m, 5H), 7.29-7.11 (m, 4H), 6.51 (d, J=7.2 Hz, 1H), 5.17 (s, 2H).MS $(M+H)^+$ 354.

**1-(Biphenyl-3-yl)-5-hydroxy-2-(methylamino)pyridin-4(1*H*)-one (18)**

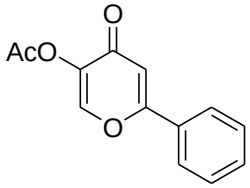



3-(Benzyloxy)-1-(biphenyl-3-yl)pyridin-4(1H)-one (3.53g, 10 mmol) and 10% Pd/C (306 mg) in MeOH (300 mL) was stirred under an $H_2$ balloon for 2 h. After this time, LC/MS indicated that the reaction was complete. After evacuation and purge with $N_2$ (3x), the MeOH solution was filtered and the catalyst was washed with MeOH (4 X 50 mL). The combined MeOH solution was concentrated to give 1-(Biphenyl-3-yl)-5-hydroxy-2-(methylamino)pyridin-4(1*H*)-one as a slightly yellow solid (2.55 g, 97%). $^1$H NMR (500 MHz, DMSO): δ 8.02 (dd, J = 7.3, 2.5 Hz, 1 H); 7.89 (d, J = 2.4 Hz, 1 H); 7.81 (m, 3 H); 7.73 (d, J = 7.7 Hz, 1 H); 7.62 (t, J = 7.8 Hz, 1 H); 7.58-7.47 (m, 3 H); 7.42 (t, J = 7.3 Hz, 1 H); 6.34 (d, J = 7.3 Hz, 1 H); LC/MS $(M+H)^+$ 264; HRMS Calcd for $(C_{17}H_{13}NO_2+H)^+$ 264.1019, found 264.1021.

**1-(Biphenyl-3-yl)-5-hydroxy-2-phenylpyridin-4(1*H*)-one (20)**



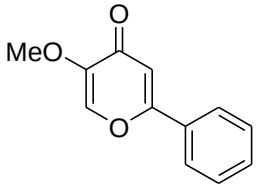
**4-Oxo-6-phenyl-4*H*-pyran-3-yl acetate**




To a solution of 545 mg (3.5 mmol) of 1-methoxy-3-oxobut-1-en-2-yl acetate in THF (14.2 mL) at –78 °C was added LHMDS (3.45 mL of a 1 M solution in toluene) dropwise. After stirring for 20 min at –78 °C, the reaction mixture was treated with 0.4 mL (3.5 mmol) of benzoyl chloride dropwise, then removed from the cold bath and allowed to warm to room temperature and continue stirring for 18 h. The reaction was quenched with 10 mL 10% aq HCl and extracted with diethyl ether (3 x 10 mL). The organic fractions were combined, washed with sat. aq. NaCl, dried ($Na_2SO_4$), and concentrated under reduced pressure to provide 1-methoxy-3,5-dioxo-5-phenylpent-1-en-2-yl acetate which was used the subsequent step without further purification.

To a solution of crude 1-methoxy-3,5-dioxo-5-phenylpent-1-en-2-yl acetate (3.5 mmol) in toluene (35 mL) was added pyridinium *p*-toluenesulfonate (130 mg, 0.5 mmol). The reaction mixture was heated at reflux under a nitrogen atmosphere for 1 h before being cooled and concentrated under reduced pressure and purified by flash chromatography (80 g $SiO_2$, 0–100% ethyl acetate/hexanes gradient elution) to provide 250 mg (32%) of 4-oxo-6-phenyl-4*H*-pyran-3-yl acetate. LC/MS $(M+H)^+$ 231.

**5-Methoxy-2-phenyl-4*H*-pyran-4-one**

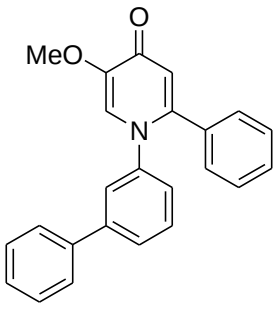



To a solution of 4-oxo-6-phenyl-4*H*-pyran-3-yl acetate (100 mg, 0.4 mmol) in MeOH (10.9 mL) is added $K_2CO_3$ (180 mg, 1.3 mmol) and the reaction was stirred for 15 min at room temperature.

The reaction mixture was concentrated under reduced pressure to provide 5-hydroxy-2-phenyl-4*H*-pyran-4-one which was used in the subsequent step without further purification.

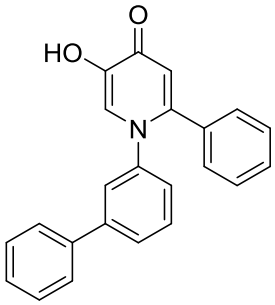
To a solution of crude 5-hydroxy-2-phenyl-4*H*-pyran-4-one (0.4 mmol) in acetone (10.9 mL) is added iodomethane (0.7 mL, 11.3 mmol) and the reaction mixture was heated at 60 °C for 2 h. After being cooled to room temperature, the reaction was concentrated under reduced pressure and diluted with $CHCl_3$ (10 mL) and water (10 mL). The layers were separated and the organic fraction washed with sat. aq. NaCl, dried ($Na_2SO_4$), and concentrated under reduced pressure to provide 82 mg (93%) of 5-methoxy-2-phenyl-4*H*-pyran-4-one as tan crystals which were used in the subsequent step without further purification. LC/MS $(M+H)^+$ 203.

**1-(Biphenyl-3-yl)-5-methoxy-2-phenylpyridin-4(1*H*)-one**



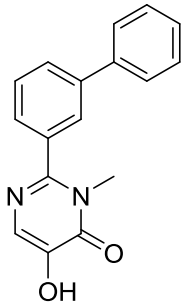

To a solution of 5-methoxy-2-phenyl-4*H*-pyran-4-one (35 mg, 0.17 mmol) in a 1:1 mixture of AcOH:water (0.6 mL) was added 3-aminobiphenyl (59 mg, 0.35 mmol). The reaction vessel was sealed and heated at 130 °C for 3 h before being cooled to room temperature and purified by reversed phase HPLC (2 cm x 5 cm C18, acetonitrile-water gradient, 0.05% TFA added) to provide 27 mg (44%) 1-(biphenyl-3-yl)-5-methoxy-2-phenylpyridin-4(1*H*)-one. LC/MS $(M+H)^+$ 354.

**1-(Biphenyl-3-yl)-5-hydroxy-2-phenylpyridin-4(1*H*)-one (20)**

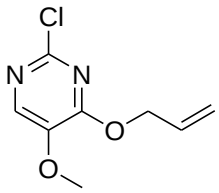


1-(Biphenyl-3-yl)-5-methoxy-2-phenylpyridin-4(1*H*)-one (20 mg, 0.056 mmol) was treated with $BBr_3$ (0.5 mL of a 1 M solution in $CH_2Cl_2$) and stirred at room temperature. After 1 h, the reaction mixture was cooled to 0 °C and quenched with dropwise addition of MeOH (0.1 mL), before being concentrated under a stream of $N_2$, diluted with MeOH (0.8 mL) and purified by reversed phase HPLC (2 cm x 5 cm C18, acetonitrile-water gradient, 0.05% TFA added) to provide 19 mg (99%) of 1-(biphenyl-3-yl)-5-hydroxy-2-phenylpyridin-4(1*H*)-one. $^1$H NMR (499 MHz, DMSO): δ 7.88 (s, 1 H); 7.64-7.60 (m, 2 H); 7.53 (d, J = 7.7 Hz, 2 H); 7.46-7.40 (m, 3 H); 7.40-7.36 (m, 1 H); 7.30-7.26 (m, 6 H); 6.58 (s, 1 H). HRMS (ES) calc $(M+H)^+$ 340.1332, found 340.1326.

**2-biphenyl-3-yl-5-hydroxy-3-methylpyrimidin-4(3*H*)-one (27b)**

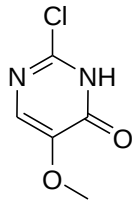


**2-chloro-5-methoxy-4-(prop-2-en-1-yloxy)pyrimidine**



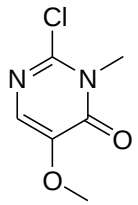
A mixture of 2,4-dichloro-5-methoxypyrimidine (85 g, 475 mmol), and $K_2CO_3$ (78.8 g, 570 mmol) in allyl alcohol (320 mL, 4.75 mol) was heated to 70 °C for 5 h before being cooled to r.t. and diluted with DCM, filtered through Celite (DCM wash) and concentrated to give 95.0 g (99.7%) of 2-chloro-5-methoxy-4-(prop-2-en-1-yloxy)pyrimidine. $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 7.85 (s, 1H), 6.09–5.99 (m, 1H), 5.43–5.38 (m, 1H), 5.31–5.27 (m, 1H), 4.91 (m, 2H), 3.87(s, 3H). MS (ESI) m/z $(M+H)^+$ 201.0.

**2-chloro-5-methoxypyrimidin-4(3*H*)-one**




To a solution of 2-chloro-5-methoxy-4-(prop-2-en-1-yloxy)pyrimidine (95.0 g, 475 mmol) in anhydrous DCM (2 L) under nitrogen atmosphere was added morpholine (124 mL, 1.425 moL) and then $Pd(Ph_3P)_4$ (13.7 g, 11.9 mmol) and the reaction mixture was stirred at room temperature for 15 min. The reaction mixture was concentrated until thick, then poured into EtOAc. The precipitate was collected and dried to give 52 g of a mixture of 2-chloro-5-methoxypyrimidin-4(3*H*)-one and morpholine (1:1). $^1$H-NMR ($CDCl_3$, 400MHz) $\delta$ 7.45 (s, 1H), 3.67 (s, 3H). MS (ESI) m/z $(M+H)^+$ 161.0.

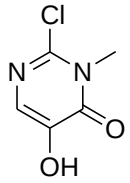
**2-chloro-5-methoxy-3-methylpyrimidin-4(3*H*)-one**




128 g (0.9 mol) of MeI was added dropwise to the suspension of 2-chloro-5-methoxypyrimidin-4(3*H*)-one (74 g, crude, about 0.3 mol) and $Cs_2CO_3$ (195 g, 0.6 mol) in 600 mL of DMF at 0 °C and the reaction mixture was stirred at this temperature for 1 h, then warmed to r.t., and stirred another 1 h. The mixture was poured into water and extracted with EtOAc several times. The extract was washed with water, brine and dried over $Na_2SO_4$ before being filtered and

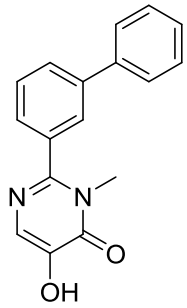
concentrated to give a crude product, which was purified by silica gel chromatography to give 31.2 g (71.2%) of 2-chloro-5-methoxy-3-methylpyrimidin-4(3*H*)-one. $^{1}$H-NMR ($CDCl_3$, 400 MHz) $\delta$ 7.37 (s, 1H), 3.80 (s, 3H), 3.61 (s, 3H). MS (ESI) m/z $(M+H)^+$ 175.0/176.0.

**2-chloro-5-hydroxy-3-methylpyrimidin-4(3*H*)-one**




To a solution of 1.18 g (6.76 mmol) 2-chloro-5-methoxy-3-methylpyrimidin-4(3H)-one in 35 ml $CH_2Cl_2$ was added 47.3 ml (47.3 mmol) of a 1 M solution of $BBr_3$ in $CH_2Cl_2$. The reaction mixture was stirred for 1 h, cooled to 0 °C, quenched with 100 ml MeOH, and concentrated *in vacuo*. The solid was suspended in ether, and collected by filtration to give 1.09 g (100% yield) of 2-chloro-5-hydroxy-3-methylpyrimidin-4(3*H*)-one. LCMS $[M+H]^+$ = 161.0.

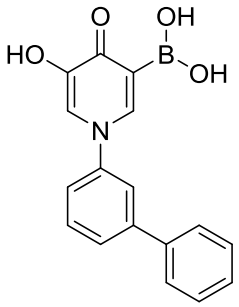
**2-biphenyl-3-yl-5-hydroxy-3-methylpyrimidin-4(3*H*)-one (27b)**



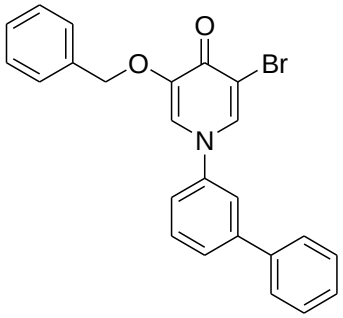

To a solution of 40 mg (0.249 mmol) 2-chloro-5-hydroxy-3-methylpyrimidin-4(3*H*)-one in 1 ml THF was added 20.3 mg (0.025 mmol) 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane adduct, 74 mg (0.374 mmol) biphenyl-3-boronic acid, and 0.747 ml (0.747 mmol) 1 M aq $Cs_2CO_3$. The reaction mixture was heated to 120 °C for 20 min in the microwave, then diluted with 2 ml water, extracted with 10 ml EtOAc, dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. Purification by HPLC gave 10 mg (14% yield) of 2-biphenyl-3-yl-5-hydroxy-3-methylpyrimidin-4(3*H*)-one. $^{1}$H NMR $\delta$ (ppm)($CH_3OH$-$d_4$): 7.83-

7.77 (2 H, m), 7.67 (2 H, d, J = 7.69 Hz), 7.64-7.55 (2 H, m), 7.53-7.42 (3 H, m), 7.37 (1 H, t, J = 7.33 Hz), 3.50 (3 H, s). HRMS (ESI positive) calc $(M+H)^+$ = 279.1128 found 279.1127.

**[1-(biphenyl-3-yl)-5-hydroxy-4-oxo-1,4-dihydropyridin-3-yl]boronic acid (28)**

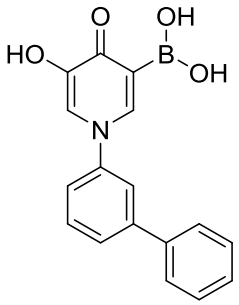



**3-(Benzyloxy)-1-(biphenyl-3-yl)-5-bromopyridin-4(1*H*)-one**




To a solution of 3-(benzyloxy)-1-(biphenyl-3-yl)pyridin-4(1*H*)-one (2.41 g, 6.8 mmol) in AcOH (68 mL) was added *N*-bromosuccinamide (2.67 g, 15 mmol) and the reaction mixture was stirred at room temperature. After 1 h, the mixture was concentrated under reduced pressure and purified by flash chromatography (80 g $SiO_2$, 0–100% ethyl acetate/hexanes) to provide 2.73 g (93%) of 3-(benzyloxy)-1-(biphenyl-3-yl)-5-bromopyridin-4(1*H*)-one. LC/MS $(M+H)^+$ 432/434.

**[1-(biphenyl-3-yl)-5-hydroxy-4-oxo-1,4-dihydropyridin-3-yl]boronic acid (28)**




Lithium chloride (515 mg, 12.1 mmol) in a 25 mL round bottom flask under high vacuum was heated with a heat gun until a free flowing granular solid was obtained (~5 min). The flask was cooled to room temperature, purged with $N_2$, and treated with isopropylmagnesium chloride (6.1 mL of a 2 M solution in THF). After stirring at room temperature for 1 h, the mixture was cooled to –10 °C and treated with 3-(benzyloxy)-1-(biphenyl-3-yl)-5-bromopyridin-4(1*H*)-one (1.05 g, 2.4 mmol) as a suspension in 3.5 mL of THF. After stirring for 0.5 h, trimethylborate (1.35 mL, 12.1 mmol) was added dropwise and the reaction mixture was stirred an additional 3.5 h, before being quenched with the addition of MeOH (12 mL) to provide a solution of crude dimethyl [5-(benzyloxy)-1-(biphenyl-3-yl)-4-oxo-1,4-dihydropyridin-3-yl]boronate which was used directly in the subsequent step. LC/MS $(M+H)^+$ 398.

The solution of crude dimethyl [5-(benzyloxy)-1-(biphenyl-3-yl)-4-oxo-1,4-dihydropyridin-3-yl]boronate (2.4 mmol) in THF/MeOH from the preceeding step and 10% Pd/C (52 mg, 0.49 mmol) was stirred under $H_2$ (1 atm) for 18 h. The reaction mixture was diluted with MeOH (20 mL), filtered through a pad of Celite (MeOH wash), and concentrated under reduced pressure. The residue was diluted with DMF (10 mL) and 0.5 M aq. HCl (0.4 mL) and purified by reversed phase HPLC (2 cm x 5 cm C18, acetonitrile-water gradient, 0.05% TFA added, fractions were lyopholized) to provide 70 mg (9%) of [1-(biphenyl-3-yl)-5-hydroxy-4-oxo-1,4-dihydropyridin-3-yl]boronic acid. $^1$H NMR (599 MHz, DMSO, 75 °C): δ 8.19 (d, J = 2.3 Hz, 1 H); 7.89 (d, J = 2.3 Hz, 1 H); 7.83 (s, 1 H); 7.79-7.74 (m, 3 H); 7.67-7.61 (m, 1 H); 7.56 (d, J = 8.1 Hz, 1 H); 7.49 (t, J = 7.6 Hz, 2 H); 7.46-7.38 (m, 1 H).. HRMS (ES) calc $(M+H)^+$ = 308.1089, found 308.1092.