SUPPORTING INFORMATION FOR

Synthesis of novel imidazo[1,2-a]pyridines with potent activity against herpesviruses.

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Material and Methods. ^1H spectra were obtained on Varian Unity Plus NMR spectrometers at 300 or 400 MHz, and 75 or 100 MHz respectively. ^{19}F NMR spectra were recorded at 282 MHz. LCMS were obtained using a C_{12} column (Phenomenex MAX-RP, 50 x 2.00 mm) and a linear 5 minute gradient from 85:15 H_2O : MeOH (with 0.1 % formic acid) to 100 % MeOH (with 0.1 % formic acid), all compounds described were >97 % pure by this method. The mass spectra (LCMS) were obtained on Micromass Platform, or ZMD mass spectrometers from Micromass Ltd. Altrincham, UK, using either Atmospheric Chemical Ionization (APCI) or Electrospray Ionization (ESI). HRMS were obtained on a Micromass LCT time-of-flight spectrometer via flow injection analysis by electrospray ionization. Solvents were purchased as anhydrous grade and used without further purification. Unless otherwise stated, column chromatography for the purification of some compounds, used Merck Silica gel 60 (230-400 mesh), and the stated solvent system under pressure. Combustion analyses were performed by Atlantic Microlabs, Inc. Norcross, Ga.

2-(4-Fluorophenyl)-8-nitroimidazo[1,2-a]pyridine (5): To a solution of 2-amino-3-nitropyridine **3** (1.3 g, 9.3 mmol) in DMF (20 mL) was added 2-bromo-4'-fluoroacetophenone **4** (2 g, 9.3 mmol) and the reaction mixture was heated at reflux for 6

h. The resulting mixture was concentrated to a solid *in vacuo*. This residue was dissolved in CH_2Cl_2 and the organic phase was washed with aqueous NaHCO_3 and aqueous NaCl solutions. The organic phase was dried (magnesium sulfate), filtered through a silica gel pad and concentrated to give a solid. This solid was recrystallized from methanol to give 870 mg (36%) of **5** as a brown solid. R_f 0.37 (1:1 EtOAc:hexane); ^1H NMR (d_6 -DMSO): δ 8.98 (d, 1H), 8.69 (s, 1H), 8.32 (d, 1H), 8.10 (dd, 2H), 7.36 (t, 2H), 7.15 (t, 1H); ^{19}F NMR (DMSO-d_6) δ -113.7; LCMS m/z 258 ($\text{M}+1$). HRMS calcd for $\text{C}_{13}\text{H}_9\text{FN}_3\text{O}_2$ [$\text{M}+\text{H}$] $^+$ 258.0679, found 258.0680. Anal. calcd for $\text{C}_{13}\text{H}_8\text{FN}_3\text{O}_2$: C, 60.70; H, 3.13; N, 16.34. Found C, 60.77; H, 2.89; N, 16.55.

1-[2-(4-Fluorophenyl)-8-nitroimidazo[1,2-*a*]pyridin-3-yl]ethanone (6): 2-(4-Fluorophenyl)-8-nitroimidazo[1,2-*a*]pyridine **5** (2 g, 7.8 mmol) was added to acetic anhydride (15 mL). To this mixture was added a catalytic amount of conc H_2SO_4 and the reaction mixture was heated to reflux for 1 h. The resulting mixture was concentrated to a slurry, neutralized by addition of saturated aqueous NaHCO_3 and extracted with EtOAc. The organic phase was dried (MgSO_4), filtered and concentrated to a solid. This solid was purified by silica gel chromatography (1:1 EtOAc: hexane) to give 1.3 g (55%) of **6** as a brown solid. R_f 0.53 (1:1 EtOAc:hexane); ^1H NMR (DMSO-d_6): δ 9.93 (d, 1H), 8.62 (d, 1H), 7.78 (dd, 2H), 7.46 (m, 3H), 2.20 (s, 3H); LCMS m/z 300 ($\text{M}+1$). HRMS calcd for $\text{C}_{15}\text{H}_{11}\text{FN}_3\text{O}_3$ [$\text{M}+\text{H}$] $^+$ 300.0784, found 300.0780.

1-[8-Amino-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl]ethanone (8): A solution of 1-[2-(4-fluorophenyl)-8-nitroimidazo[1,2-*a*]pyridin-3-yl]ethanone **6** (100 mg, 0.33 mmol) in MeOH (3 mL) was added to a suspension of iron (93 mg, 1.7 mmol) and NH_4Cl (149 mg, 2.8 mmol) in aqueous MeOH. This reaction mixture was heated to reflux for 10 h. The reaction mixture was filtered and the filtrate concentrated under reduced pressure to a solid. This solid was purified by silica gel chromatography (5% MeOH in CH_2Cl_2) to give 72 mg (80%) of **8** as a foam. R_f 0.27 (1:1 EtOAc:hexane); ^1H NMR (CDCl_3): δ 9.21 (d, 1H), 7.61 (m, 2H), 7.25 (m, 2H), 6.94 (t, 1H) 6.72 (d, 1H), 4.63 (broad s, 2H), 2.19 (s, 3H); LCMS m/z 270 ($\text{M}+1$). HRMS calcd for $\text{C}_{15}\text{H}_{13}\text{FN}_3\text{O}$ [$\text{M}+\text{H}$] $^+$ 270.1043, found 270.1040. Anal. calcd for $\text{C}_{15}\text{H}_{12}\text{FN}_3\text{O} \cdot \text{xH}_2\text{O}$: C, 62.71; H, 4.91; N, 14.63. Found C, 62.75; H, 5.02; N, 14.31.

***N'*-[3-[(2*E*)-3-(Dimethylamino)-2-propenoyl]-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridin-8-yl]-*N,N*-dimethylimidoforamide (9):** A solution of 1-[8-amino-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl]ethanone **8** (150 mg, 0.56 mmol) in *N,N*-dimethylformamide dimethyl acetal (DMF-DMA, 5 mL) was heated at reflux for 6 days. The mixture was cooled to room temperature, EtOAc and water were added. The phases were separated and the organic layer was washed with brine. The aqueous layer was extracted with EtOAc and the combined organics were dried over magnesium sulfate. Filtration and concentration followed by silica gel chromatography (1:1 acetone:EtOAc) gave 130 mg (62%) of **9** as a foam. *R*_f 0.48 (1:1 EtOAc:acetone); ¹H NMR (CDCl₃): δ 9.28 (d, 1H), 8.53 (s, 1H), 7.76 (dd, 2H), 7.62 (d, 1H), 7.13 (t, 2H), 6.87 (m, 2H), 5.12 (d, 1H), 2.4-3.3 (m, 12 H); LCMS *m/z* 380 (M+1). HRMS calcd for C₂₁H₂₃FN₅O [M+H]⁺ 380.1886, found 380.1884.

***N*-Cyclopentylguanidine hydrochloride (10):** To a solution of 2-methyl-2-thiopseudourea sulfate (13.9 g, 50.0 mmol) in water (40 mL) was added cyclopentylamine (14.8 mL, 150 mmol). The resultant mixture was heated to 55 °C for 20 minutes and then to reflux for 2.5 hours. The mixture was cooled to room temperature and concentrated *in vacuo* and azeotroped with MeOH. Water was added (~100 mL) and Amberlite IRA 400 (Cl⁻) resin was added. The mixture was stirred for 1 h and then the resin was removed by filtration. The solution was concentrated *in vacuo* and azeotroped with MeOH. The residue was recrystallized from MeOH-acetone to yield **10** (7.0 g, 86%) as a fine white solid. ¹H NMR (D₂O): δ 3.62 (m, 1 H), 1.75 (m, 2 H), 1.52-1.32 (m, 6 H); ¹³C NMR (D₂O) δ 156.23, 53.11, 32.15, 23.13; LCMS *m/z* 128 (M+1).

3-[2-(Cyclopentylamino)-4-pyrimidinyl]-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridin-8-amine (11): To a solution of *N'*-[3-[(2*E*)-3-(dimethylamino)-2-propenoyl]-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridin-8-yl]-*N,N*-dimethylimidoforamide **9** (130 mg, 0.34 mmol) in EtOH was added **10** (168 mg, 1.02 mmol), followed by K₂CO₃ (140 mg, 1.02 mmol). The resulting solution was heated at 80°C for 16 h. Upon cooling to room temperature, EtOAc and water were added. The phases were separated and the organics were washed with brine. The aqueous layer was extracted with EtOAc. The combined organics were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc) to give *N'*-[3-[2-

(cyclopentylamino)-4-pyrimidinyl]-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridin-8-yl]-*N,N*-dimethylimidoformamide (86 mg, 57%) as a solid. ¹H NMR (CDCl₃): δ 9.09 (broad s, 1H), 8.60 (s, 1H), 8.04 (d, 1H), 7.63 (dd, 2H), 7.04 (t, 2H), 6.78 (m, 2H), 6.36 (d, 1H), 5.14 (d, 1H), 4.31 (m, 1H), 3.10 (s, 3H), 3.05 (s, 3H), 2.0-2.1 (m, 2H), 1.4-1.9 (m, 6H); LCMS *m/z* 444 (M+1). *N'*-[3-[2-(Cyclopentylamino)-4-pyrimidinyl]-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridin-8-yl]-*N,N*-dimethylimidoformamide (70 mg, 0.16 mmol) was dissolved in MeOH. To this solution was added 1N NaOH and the resulting mixture heated at reflux for 6 h. The resulting mixture was concentrated *in vacuo* followed by addition of EtOAc and water. The phases were separated and the EtOAc phase dried (magnesium sulfate), filtered and concentrated. The resulting solid was purified by silica gel chromatography (EtOAc) to give 55 mg (88%) of **11** as a solid. *R*_f 0.22 (1:1 EtOAc:hexane); ¹H NMR (CDCl₃): δ 8.97 (d, 1H), 8.12 (d, 1H), 7.68 (dd, 2H), 7.15 (t, 2H), 6.78 (t, 1H), 6.54 (d, 1H), 6.41 (d, 1H), 5.24 (d, 1H), 4.60 (s, 2H), 4.40 (m, 1H), 2.0-2.1 (m, 2H), 1.4-1.9 (m, 6H); ¹⁹F NMR (CDCl₃) δ -113.7; LCMS *m/z* 389 (M+1). HRMS calcd for C₂₂H₂₂FN₆ [M+H]⁺ 389.1890, found 389.1889. Anal. calcd for C₂₂H₂₁FN₆: C, 68.03; H, 5.45; N, 21.64. Found C, 68.30; H, 5.30; N, 21.32.

***N*-Cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridin-8-amine (2):** To a solution of 3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridin-8-amine **11** (23 mg, 0.06 mmol) in ClCH₂CH₂Cl (2 mL) was added, cyclopentanone (10 uL, 0.09 mmol), NaBH(OAc)₃ (25 mg, 0.12 mmol) and AcOH (17 uL, 0.3 mmol). The resulting mixture was stirred for 12 hours at which time the reaction was judged complete by thin layer chromatography. Methanol was added to the reaction and the mixture stirred for 30 minutes. EtOAc and water were added. The phases were separated and the organic layer was washed with water and brine. The combined organics were dried (magnesium sulfate), filtered and concentrated to a solid. This solid was purified by silica gel chromatography (1:1 hexanes:EtOAc) to give **2** (22 mg, 80%) as a solid. *R*_f 0.30 (1:1 EtOAc:hexane); ¹H NMR (CDCl₃) δ 8.80 (d, 1H), 8.06 (d, 1H), 7.62 (dd, 2H), 7.10 (t, 2H), 6.76 (t, 1H), 6.34 (d, 1H), 6.27 (d, 1H), 5.22 (d, 2H), 4.34 (m, 1H), 3.93 (m, 1H), 2.0-2.1 (m, 4H), 1.4-1.9 (m, 12H); ¹⁹F NMR (CDCl₃) δ -113.9; LCMS *m/z* 457 (M+1).

HRMS calcd for $C_{27}H_{30}FN_6$ $[M+H]^+$ 457.2516, found 457.2517. Anal. calcd for $C_{27}H_{29}FN_6 \cdot x1/4 H_2O$ C, 70.34; H, 6.45; N, 18.23. Found C, 70.14; H, 6.45; N, 18.02.

2-Amino-3-chloropyridine (12): 2,3-Dichloropyridine (20 g, 0.14 moles) was placed in a steel bomb. To this was added concentrated NH_4OH (300 mL), the bomb sealed and heated at 190 °C for 48 hours. The vessel was cooled to room temperature and opened. EtOAc and water were added. The phases were separated and the EtOAc phase washed with water, dried (magnesium sulfate), filtered and concentrated to a solid. This solid was crystallized from a small volume of EtOAc to give 12.6 g (70%) of **12** as a white solid. 1H NMR ($CDCl_3$) δ 7.95 (dd, 1H), 7.46 (dd, 1H), 6.58 (dd, 1H), 5.0 (broad s, 2H); LCMS m/z 129 (M+H).

8-Chloro-2-(4-fluorophenyl)imidazo[1,2-a]pyridine (13): To a solution of 2-amino-3-chloropyridine **12** (6.51 g, 51 mmol) and 2-bromo-4'-fluoroacetophenone **4** (13.0 g, 60 mmol) in *i*-PrOH (100 mL) was added $NaHCO_3$ (4.91 g, 60 mmol) and the reaction mixture was heated at reflux for 6 h. The resulting mixture was concentrated to a solid *in vacuo*. This residue was dissolved in EtOAc and the organic phase was washed with water and an aqueous NaCl solution. The organic phase was dried (magnesium sulfate), filtered through a silica gel pad and concentrated to give a solid. This solid was recrystallized from CH_3CN , to give 10.9 g (87%) **13** as a solid. R_f 0.50 (1:1 EtOAc:hexane); 1H NMR ($CDCl_3$): δ 8.06 (d, 1H), 7.96 (dd, 2H), 7.86 (s, 1H), 7.25 (d, 1H), 7.13 (t, 2H), 6.73 (t, 1H); ^{19}F NMR ($CDCl_3$) δ -114.0; LCMS m/z 247 (M+1). HRMS calcd for $C_{13}H_9ClFN_2$ $[M+H]^+$ 247.0438, found 247.0437. Anal. calcd for $C_{13}H_8ClFN_2$: C, 63.30; H, 3.27; N, 11.35. Found C, 63.53; H, 3.41; N, 11.32.

8-Chloro-2-(4-fluorophenyl)imidazo[1,2-a]pyridine-3-carbaldehyde (20): DMF (10 mL) was cooled to 0°C and treated with $POCl_3$ (1.0 mL, 11 mmol). After the addition was complete, the mixture was warmed to room temperature and stirred for 10 minutes. To this was added 8-chloro-2-(4-fluorophenyl)imidazo[1,2-a]pyridine **13** (1.15 g, 4.7 mmol) and the resulting solution was stirred overnight. Water was added to the reaction. The mixture was neutralized to pH 7 with NH_4OH . The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organics were washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was recrystallized from

CH₃CN to give **20** (1.2 g, 96%) as a white solid. R_f 0.60 (1:1 EtOAc:hexane); ¹H NMR (CDCl₃): δ 10.05 (s, 1 H), 9.60 (d, 1H), 7.86 (dd, 2H), 7.65 (d, 1H), 7.23 (t, 2H), 7.08 (t, 1H); ¹⁹F NMR (CDCl₃) δ -110.8; LCMS *m/z* 275 (M+1). HRMS calcd for C₁₄H₉ClFN₂O [M+H]⁺ 275.0387, found 275.0397. Anal. calcd for C₁₄H₈ClFN₂O: C, 61.22; H, 2.94; N, 10.20. Found C, 61.45; H, 3.02; N, 10.47.

1-[8-Chloro-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-2-propyn-1-one (21): To a cold (-78°C) suspension of 8-chloro-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde **20** (0.94 g, 3.42 mmol) in THF (20 mL) was added ethynylmagnesium bromide (15 mL, 0.5 M in THF, 7.5 mmol) dropwise. The reaction mixture was stirred at -78°C for 1 hour, then at 0°C for 2 hours. The resulting solution was poured into water and extracted with EtOAc. The organic layer was washed with water and brine and the combined organics were dried over magnesium sulfate. Filtration and concentration gave a white solid. This solid was dissolved in CH₂Cl₂ (60 mL) and to this solution was added MnO₂ (10 g, 115 mmol). The reaction mixture was stirred at room temperature for 1 h. The suspension was filtered through a pad of Celite® and the filtrate was concentrated and purified by silica gel chromatography (1:1 hexanes:EtOAc) to give **21** (0.81 g, 80%) as a white solid. R_f 0.61 (1:2 EtOAc:hexane); ¹H NMR (CDCl₃) δ 9.67 (d, 1H), 7.68 (m, 3H), 7.12 (m, 3H), 2.89 (s, 1H); ¹⁹F NMR (CDCl₃) δ -111.6; LCMS *m/z* 299 (M+1). HRMS calcd for C₁₆H₉ClFN₂O [M+H]⁺ 299.0387, found 299.0391. Anal. calcd for C₁₆H₈ClFN₂O: C, 64.34; H, 2.70; N, 9.38. Found C, 64.51; H, 2.97; N, 9.69.

4-[8-Chloro-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-*N*-cyclopentyl-2-pyrimidinamine (16): To a solution of 1-[8-chloro-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-2-propyn-1-one **21** (740 mg, 2.5 mmol) in ethanol (20 mL) was added cyclopentyl guanidine hydrochloride (**10**, 600 mg, 3.7 mmol), followed by solid K₂CO₃ (510 mg, 3.7 mmol). The resulting solution was heated at 80°C for 12 hours. The reaction mixture was concentrated to a solid. Water and CH₂Cl₂ were added. The phases were separated and the organics were washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting solid was crystallized from CH₃CN, to give **16** (946 mg, 93%) as a white solid. R_f 0.52 (1:2 EtOAc:hexane); ¹H NMR (CDCl₃) δ 9.48 (d, 1H), 8.11 (d, 1H), 7.68 (dd, 2H), 7.42 (d, 1H), 7.11 (t, 2H), 6.86 (t, 1H), 6.40 (d, 1H), 5.28 (d, 1H), 4.35 (m, 1H), 2.0-2.1 (m, 2H), 1.4-1.9 (m, 6H); ¹⁹F NMR (CDCl₃)

δ -113.0; LCMS m/z 408 (M+1). HRMS calcd for C₂₂H₂₀ClFN₅ [M+H]⁺ 408.1391, found 408.1389. Anal. calcd for C₂₂H₁₉ClFN₅: C, 64.78; H, 4.70; N, 17.17. Found C, 64.58; H, 4.69; N, 16.93.

***N*-Cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridin-8-amine (2):** To a solution of 4-[8-chloro-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-*N*-cyclopentyl-2-pyrimidinamine **16** (200 mg, 0.49 mmol) in cyclopentylamine (neat, 10 mL) was added, successively, *o*-(biphenyl)P(*t*-Bu)₂ (20 mg, 0.07 mmol), NaO(*t*-Bu) (67 mg, 0.7 mmol) and Pd(OAc)₂ (10 mg, 0.04 mmol). The resulting mixture was heated at 100°C for 12 hours at which time the reaction was judged complete by thin layer chromatography. The solution was cooled to room temperature and EtOAc and water were added. The phases were separated and the organic layer was washed with water and brine. The combined organics were dried (magnesium sulfate), filtered and concentrated to a solid. This solid was purified by silica gel chromatography (1:1 hexanes:EtOAc) to give **2** (206 mg, 92%) as a solid. For analytical data see above.