Supporting Information:

Design, Synthesis, and Biological Activity of Novel Polycyclic Aza-amide FKBP12 Ligands

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Experimental details for 7a-7e and combustion analysis for final compounds is attached.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxothiophen-2-yl-acetate]-5,6,9,10,11,12,13,13a-octahydro-1,3-dimethoxy (7a). 0.074 g (64%). MS (APCI) *m/z* 441.1 (M^+ + 1). Anal. ($C_{23}H_{24}N_2O_5S$,$0.12H_2O$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxopyridin-3-yl-acetate]-5,6,9,10,11,12,13,13a-octahydro-1,3-dimethoxy (7b). 0.019 g (24%). MS (APCI) *m/z* 436.2 (M^+ + 1). Anal. ($C_{24}H_{25}N_3O_5$,$0.7H_2O$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxopyridin-4-yl-acetate]-5,6,9,10,11,12,13,13a-octahydro-1,3-dimethoxy (7c). (i) A solution of 2-bromo-1-pyridin-4-yl-ethanone hydrobromide, prepared from 4-acetylpyridine according to literatureprecedent,[23] (1.6 g, 5.8 mmol) in EtOH (50 mL) was added dropwise to a suspension of selenium dioxide (0.7 g, 6.3 mmol) in EtOH (10 mL) at 80 °C and stirred for 5 h. The sample was reduced to 30 °C and stirred for another 60 h. The mixture was filtered through Celite, reduced to ~5 mL, and partitioned between $NaHCO_3$ (sat'd aq.) and EtOAc. The combined organics were washed with brine, dried, and concentrated. The residual oil was purified by flash chromatography on silica using EtOAc/$CHCl_3$ (1:1) as eluent. A second purification was performed by radial chromatography using a gradient of (0:100) to (5:95) EtOAc/$CHCl_3$ as eluent. The desired fractions were combined and concentrated to give oxo-pyridin-4-yl-acetic acid ethyl ester (0.5 g, 50%) as an oil, which solidified upon standing. (ii) To a solution of oxo-pyridin-4-yl-acetic acid ethyl ester (0.10 g, 0.56 mmol) in THF (10 mL) was added NaOH (0.6 mL, 1 N aq) at RT. After the sample was stirred at for 2.5 h, the resulting suspension was reduced to minimum volume, and the residue was suspended in toluene (10 mL) and concentrated to dryness. The residue was dissolved in dry DMF (5 mL) and **4a** (0.17 g, 0.56 mmol) and HATU (0.213 g, 0.56 mmol) were added. After the sample was stirred for 20 h, the mixture was partitioned between NaHCO3 (sat'd aq.) and EtOAc. The combined organics were washed with water and then brine, dried, and concentrated. The residue was purified by flash chromatography on silica using EtOAc/CHCl3 (1:1) as eluent. The desired fractions were combined and concentrated to give a solid residue that was triturated with methyl *tert*-butyl ether and collected by filtration to give **7c** (0.14g, 57%). MS (APCI) *m/z* 436.2 (M^+ + 1). Anal. ($C_{24}H_{25}N_3O_5$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxofuran-2-yl-acetate]-5,6,9,10,11,12,13,13a-octahydro-1,3-dimethoxy (7d). 0.060 g (53%). MS (APCI) *m/z* 425.1 (M^+ + 1). Anal. ($C_{23}H_{24}N_2O_6$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(1*H*-indol-2-yl) -acetate]-5,6,9,10,11,12,13,13a-octahydro-1,3-dimethoxy (7e). 0.061 g (48%). MS (APCI) *m/z* 474.1 (M^+ + 1). Anal. ($C_{27}H_{27}N_3O_5$,$0.76H_2O$) C, H, N.

Table 1: Analytical data for compounds that were evaluated.

		Calculated			Found		
Cpd. #	**Anal. Calcd.**	**C**	**H**	**N**	**C**	**H**	**N**
5a	$C_{28}H_{32}N_2O_8$	64.11	6.15	5.34	63.94	6.30	5.18
5b	$C_{27}H_{30}N_2O_6$	67.77	6.32	5.85	67.76	6.60	5.47
5d	$C_{26}H_{27}ClN_2O_6 \cdot 0.36CH_3OH$	62.59	5.45	5.61	61.62	5.61	5.12
5e	$C_{27}H_{30}N_2O_7 \cdot 0.2H_2O$	65.10	6.15	5.62	65.06	6.06	5.64
5f	$C_{26}H_{27}ClN_2O_6 \cdot 0.15C_6H_{14} \cdot 0.25CH_2Cl_2$	62.59	5.45	5.61	61.50	5.73	4.89
5g	$C_{26}H_{27}ClN_2O_6 \cdot 0.07CH_2Cl_2$	62.59	5.45	5.61	61.65	5.69	5.79
5h	$C_{26}H_{27}FN_2O_6 \cdot 0.15CH_2Cl_2 \cdot 0.3C_4H_8O$	64.72	5.64	5.81	62.49	5.71	5.68
5i	$C_{26}H_{28}N_2O_6 \cdot 0.2H_2O$	66.71	6.12	5.98	66.61	6.30	5.80
5j	$C_{26}H_{27}FN_2O_6 \cdot 0.8H_2O$	64.72	5.64	5.81	62.51	5.52	6.11
6a	$C_{25}H_{24}Cl_2N_2O_5$	59.65	4.81	5.56	59.82	4.81	5.34
6b	$C_{27}H_{30}N_2O_7$	65.58	6.11	5.66	5.41	6.09	5.43
6c	$C_{25}H_{25}Cl_1N_2O_5 \cdot 0.05C_6H_{14}$	64.21	5.47	5.92	63.99	5.50	5.52
6d	$C_{27}H_{30}N_2O_7 \cdot 0.50CH_2Cl_2$	61.51	5.82	5.22	61.12	5.84	4.92
6e	$C_{25}H_{25}BrN_2O_5 \cdot 0.15CH_2Cl_2$	57.41	4.85	5.32	57.44	4.86	4.94
6f	$C_{25}H_{25}ClN_2O_5 \cdot 0.75H_2O$	62.24	5.54	5.81	62.26	5.36	5.43
6g	$C_{25}H_{26}N_2O_5$	69.11	6.03	6.45	68.95	6.09	6.44
6h	$C_{25}H_{25}FN_2O_5 \cdot 1.20H_2O \cdot 0.15C_6H_{14}$	63.87	6.11	5.75	63.73	5.78	5.6
6i	$C_{27}H_{30}N_2O_5 \cdot 0.05H_2O$	69.97	6.55	6.04	69.59	6.61	5.84
6j	$C_{26}H_{28}N_2O_6 \cdot 0.15C_4H_8O_2$	66.88	6.16	5.86	66.59	5.99	5.64
6k	$C_{25}H_{24}Cl_2N_2O_5 \cdot 0.05C_6H_{14}$	59.85	4.90	5.52	60.20	5.22	5.18
6l	$C_{25}H_{26}N_2O_6 \cdot 0.30H_2O$	65.86	5.88	6.14	65.58	5.93	5.81
6m	$C_{25}H_{24}Cl_2N_2O_5 \cdot 0.45C_6H_{14}$	61.37	5.63	5.17	61.68	5.61	4.92
6n	$C_{25}H_{25}Cl_1N_2O_5 \cdot 0.05C_6H_{14} \cdot 0.15H_2O$	63.85	5.51	5.89	63.54	5.41	5.50
6o	$C_{25}H_{24}Cl_2N_2O_5 \cdot 0.6C_6H_{14} \cdot 0.15H_2O \cdot 0.30CH_2Cl_2$	59.51	5.75	4.80	59.43	5.46	4.41
6p	$C_{29}H_{35}N_3O_5 \cdot 0.15C_6H_{14} \cdot 0.30H_2O$	68.54	7.25	8.02	68.27	7.47	7.78

6q	$C_{25}H_{24}Cl_2N_2O_5 \cdot 0.45C_6H_{14}$	61.37	5.63	5.17	61.44	5.54	5.41
6r	$C_{33}H_{42}N_2O_6 \cdot 0.07H_2O$	70.28	7.53	4.97	69.89	7.66	4.79
7a	$C_{23}H_{24}N_2O_5S \cdot 0.12H_2O$	62.40	5.52	6.33	62.01	5.47	6.05
7b	$C_{24}H_{25}N_3O_5 \cdot 0.7H_2O$	64.33	5.94	9.38	64.67	5.87	8.98
7c	$C_{24}H_{25}N_3O_5 \cdot 0.9H_2O$	63.82	5.98	9.30	63.71	5.75	9.18
7d	$C_{23}H_{24}N_2O_6$	65.08	5.70	6.60	64.78	5.74	6.43
7e	$C_{27}H_{27}N_3O_5 \cdot 0.76H_2O$	66.56	5.90	8.62	66.55	6.30	8.39