Supporting Information

Biaryl Ethers as Novel Non-nucleoside Reverse Transcriptase Inhibitors with Improved Potency against Key Mutant Viruses

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PhenoScreen data of compound **6** (IC50) (Monogram Bioscience)

IC50 and FC Summary

Drug	EFV	compound 6	compound 2	compound 1
Unit	(uM)	(uM)	(uM)	(uM)
Toxicity (# dilns)	0	0	0	0
Virus				
MDRC4	0.0080	0.0064	0.0090	0.0051
CNDO	0.0005	0.0011	0.0014	0.0011
L100I	0.0210	0.0006	0.0013	0.0007
K103N	0.0168	0.0033	0.0026	0.0016
Y181C	0.0011	0.0022	0.0048	0.0031
Y188L	0.1243	0.3261	0.8807	0.6162
G190A	0.0036	0.0020	0.0029	0.0018
G190S	0.1145	0.0373	0.0123	0.0048
L100I/K103N	>0.5000	0.1120	0.0348	0.0165
K103N/Y181C	0.0278	0.1845	0.0777	0.0236
K103N/G190A	0.1407	0.0096	0.0072	0.0024
Y181C/G190A	0.0077	0.0043	0.0116	0.0046
K103N/P225H	0.1531	0.0033	0.0022	0.0036
K101E/G190A	0.0174	0.0034	0.0069	0.0021
K101E/Y181C/G190A	0.1065	0.0192	0.0295	0.0116
K103N/Y181C/G190A	>0.5000	0.0843	0.1105	0.0309
V106A/G190A/F227L	>0.5000	>1.0000	>1.0000	>1.0000

PhenoScreen data of compound **6** (fold change) (Monogram Bioscience)

Drug Unit Toxicity (# dilns)	EFV FC(CNDO) 0	compound 6 FC(CNDO) 0	compound 2 FC(CNDO) 0	compound 1 FC(CNDO) 0
Virus				
MDRC4	16.00	5.82	6.43	4.64
CNDO	1.00	1.00	1.00	1.00
L100I	42.00	0.55	0.93	0.64
K103N	33.60	3.00	1.86	1.45
Y181C	2.20	2.00	3.43	2.82
Y188L	248.60	296.45	629.07	560.18
G190A	7.20	1.82	2.07	1.64
G190S	229.00	33.91	8.79	4.36
L100I/K103N	>454	101.82	24.86	15.00
K103N/Y181C	55.60	167.73	55.50	21.45
K103N/G190A	281.40	8.73	5.14	2.18
Y181C/G190A	15.40	3.91	8.29	4.18
K103N/P225H	306.20	3.00	1.57	3.27
K101E/G190A	34.80	3.09	4.93	1.91
K101E/Y181C/G190A	213.00	17.45	21.07	10.55
K103N/Y181C/G190A	>454	76.64	78.93	28.09
V106A/G190A/F227L	>454	>909	>714	>909

Rat Pharmacokinetics of Selected Compounds (iv administration)[a]

compound #	AUC	CL	Vd	$t_{1/2}$
3[c]	3.5	5.5	1.8	9.4
4[c]	0.7	29.4	2.5	1.9
5[c]	0.9	24.2	11.1	8.1
6[b]	7.4	10.1	3.5	4.6
13[b]	0.8	93.4	44.7	5.8
14[c]	0.4	44.9	5.1	1.9
15[c]	0.8	24.6	2.0	2.0
20[c]	0.7	26.9	2.2	1.7

[a]AUC: μM*h, CL: mL/min/Kg, Vd: L/kg, $t_{1/2}$: hours. Sprague-Dawley rats (n=3), vehicle: DMSO. Interanimal variability was less than 20%. [b]*iv*: singles, 2mg/Kg, [c]*iv.* cassette (co-administration with other analogues): 0.5mg/Kg .