

SUPPORTING INFORMATION

***O*-Phenyl Carbamate and Phenyl Urea Thiiranes as Selective MMP-2 Inhibitors that Cross the Blood-Brain Barrier**

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Table S1: Kinetic Parameters for the Slow-binding Inhibition of MMPs

Inhibitor	Structure	Enzyme	$10^{-3} k_{\text{on}} (\text{M}^{-1}\text{s}^{-1})$	$10^4 k_{\text{off}} (\text{s}^{-1})$	$K_i (\mu\text{M})$
4a		MMP-2	3.1 ± 0.3	4.9 ± 0.2	0.16 ± 0.02
		MMP-9 _{cat}	4.8 ± 0.4	11 ± 3	0.23 ± 0.06
		MMP-14 _{cat}	0.47 ± 0.02	11 ± 1	2.4 ± 0.2
4b		MMP-2	3.4 ± 0.4	7.8 ± 2.1	0.23 ± 0.07
		MMP-9 _{cat}	1.5 ± 0.1	14 ± 1	0.93 ± 0.02
		MMP-14 _{cat}	0.70 ± 0.06	19 ± 2	2.7 ± 0.3
4c		MMP-2	1.8 ± 0.1	8.7 ± 3.1	0.31 ± 0.08
		MMP-9 _{cat}	1.2 ± 0.2	12 ± 1	1.0 ± 0.2
		MMP-14 _{cat}	0.54 ± 0.05	16 ± 1	2.8 ± 0.2
4d		MMP-2	3.2 ± 0.8	9.9 ± 0.4	0.48 ± 0.02
		MMP-9 _{cat}	1.1 ± 0.1	14 ± 2	1.3 ± 0.3
		MMP-14 _{cat}	0.18 ± 0.01	5.0 ± 0.2	3.0 ± 0.3
5a		MMP-2	1.7 ± 0.1	6.4 ± 0.3	0.39 ± 0.03
		MMP-9 _{cat}	0.082 ± 0.007	8.6 ± 0.5	10 ± 1
		MMP-14 _{cat}	0.048 ± 0.005	6.0 ± 0.5	12 ± 2
5b		MMP-2	0.69 ± 0.05	3.8 ± 0.4	0.55 ± 0.08
		MMP-9 _{cat}	0.068 ± 0.006	8.5 ± 0.7	12 ± 2
		MMP-14 _{cat}	0.050 ± 0.002	8.5 ± 0.3	17 ± 1
5c		MMP-2	0.46 ± 0.03	3.5 ± 0.3	0.76 ± 0.09
		MMP-9 _{cat}	0.021 ± 0.003	11 ± 1	52 ± 8
		MMP-14 _{cat}	0.054 ± 0.005	14 ± 1	27 ± 2
5d		MMP-2	0.21 ± 0.05	1.5 ± 0.6	0.69 ± 0.32
6a		MMP-2	3.1 ± 0.4	7.5 ± 1.4	0.24 ± 0.05
		MMP-9 _{cat}	0.12 ± 0.01	12 ± 1	9.9 ± 0.6
		MMP-14 _{cat}	0.024 ± 0.003	10 ± 1	19 ± 2
6b		MMP-2	1.5 ± 0.1	6.8 ± 0.7	0.44 ± 0.06
		MMP-8 _{cat}	0.14 ± 0.01	24 ± 2	17 ± 2
6c		MMP-2	1.5 ± 0.2	8.1 ± 0.8	0.56 ± 0.09
6d		MMP-2	2.2 ± 0.1	8.7 ± 0.5	0.42 ± 0.03

Inhibitor	Structure	Enzyme	$10^{-3} k_{\text{on}} (\text{M}^{-1} \text{s}^{-1})$	$10^4 k_{\text{off}} (\text{s}^{-1})$	$K_i (\mu\text{M})$
7a		MMP-2	5.6 ± 0.3	2.8 ± 1.1	0.050 ± 0.020
		MMP-9 _{cat}	4.7 ± 0.5	8.5 ± 1.2	0.18 ± 0.03
		MMP-14 _{cat}	0.29 ± 0.04	7.5 ± 0.7	2.6 ± 0.4
		MMP-8 _{cat}	0.059 ± 0.005	7.7 ± 0.6	13 ± 2
7b		MMP-2	2.5 ± 0.3	7.2 ± 1.3	0.29 ± 0.06
		MMP-9 _{cat}	0.76 ± 0.05	6.5 ± 0.7	0.86 ± 0.11
		MMP-14 _{cat}	0.43 ± 0.02	8.2 ± 0.6	1.9 ± 0.2
		MMP-8 _{cat}	0.24 ± 0.01	35 ± 6	15 ± 3
7c		MMP-2	0.91 ± 0.13	4.4 ± 0.3	0.49 ± 0.08
		MMP-9 _{cat}	0.57 ± 0.06	6.2 ± 0.6	1.1 ± 0.1
		MMP-14 _{cat}	0.30 ± 0.02	6.4 ± 0.4	2.1 ± 0.2
7d		MMP-2	1.3 ± 0.2	9.1 ± 1.0	0.68 ± 0.13
		MMP-9 _{cat}	0.30 ± 0.05	8.0 ± 0.1	2.7 ± 0.6
		MMP-14 _{cat}	0.25 ± 0.04	6.2 ± 0.9	2.5 ± 0.4

Table S2. Concentrations of Compound **2** after a Single SC Dose of Compound **5b** to Mice at 25 mg/kg

Time (min)	Compound 2 in Brain ^a	Compound 2 in Plasma ^b
10	0.405 ± 0.101	1.24 ± 0.676
20	1.35 ± 1.10	1.05 ± 0.318
30	0.726 ± 0.0997	0.574 ± 0.345
45	0.383 ± 0.0630	0.493 ± 0.0967
60	0.471 ± 0.0676	0.302 ± 0.0343
90	0.275 ± 0.0159	0.185 ± 0.0224
120	0.331 ± 0.0712	0.183 ± 0.0565
180	0.252 ± 0.0400	0.0949 ± 0.0186
240	0.255 ± 0.0154	0.114 ± 0.0147

^a Concentration in pmol/mg tissue

^b Concentration in μM

Table S3. Concentrations of Compound **6b** after a Single SC Dose of Compound **6b** to Mice at 25 mg/kg

Time (min)	Compound 6b in Brain ^a	Compound 6b in Plasma ^b
10	0.114 ± 0.0193	4.39 ± 0.303
20	0.0779 ± 0.012	1.92 ± 0.472
40	0.0627 ± 0.0246	1.10 ± 0.475
90	0.0351 ± 0.00751	0.530 ± 0.285
180	0.0200 ± 0.00490	0.270 ± 0.0252
300	0.0133 ± 0.00337	0.0704 ± 0.0506

^a Concentration in pmol/mg tissue

^b Concentration in μM