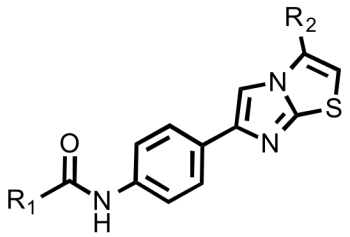
SUPPLEMENTAL INFORMATION

Optimizing aryl amides that extend survival in prion-infected mice

Kurt Giles, David B. Berry, Carlo Condello, Brittany N. Dugger, Zhe Li, Abby Oehler, Sumita Bhardwaj, Manuel Elepano, Shenheng Guan, B. Michael Silber, Steven H. Olson, and Stanley B. Prusiner

Journal of Pharmacology and Experimental Therapeutics

Supplemental Table 1. Efficacy of imidazothiazoles in prion cell assay. Mean EC_{50} values and number of replicates (*n*) for compounds with the N-linked aryl imidazothiazole scaffold.



	R_1	R_2	EC_{50} (μM)	*n*
25	cPr	Me	> 10	2
26	cPr	$CONMe_2$	> 10	2
27	CH_2OMe	Me	> 10	2

Supplemental Table 2. Quantitation of spongiform degeneration in brains of treated mice. Vacuolation scored by a skilled observer on a semiquantitative scale of 0–3 for each brain region.

Mouse line	Inoculum	Compound	*n*	Median vacuolation score (range) by brain region					
				Cortex	Hippocampus	Thalamus	Hypothalamus	Cerebellum	Brainstem
FVB	none	none	2	0	0	0	0	0	0
FVB	RML	none	4	1 (0.5–1.5)	1	1.5 (1–2)	0.5 (0–1)	3 (2–3)	2.5 (2–2.5)
FVB	RML	**1**	4	2 (1–3)	1.75 (1.5–2)	2 (1–2)	1 (0.5–1)	0 (0–2)	2 (1–2)
Tg4053	RML	none	7	1 (1–2)	1.5 (1–2)	1 (1–2)	1	2 (0–3)	2 (1–3)
Tg4053	RML	**14**	8	0 (0–3)	0.5 (0.5–3)	0.5 (0–1)	1 (0–2)	0	1.5 (1–3)
Tg4053	RML	**37**	8	1 (0–2)	0.5 (0.5–3)	1 (0.5–2)	1.5 (1–2)	0 (0–1)	2 (1–3)
Tg4053	RML	**41**	8	2 (0.5–3)	1 (0.5–3)	2 (1–3)	1.5 (0–3)	0	2 (1–3)

Supplemental Table 3. Sensitivity of CAD5-RML[IND24] prions to aryl amides. CAD5 cells infected with the RML[IND24] strain were incubated with aryl amides at concentrations up to 10 μM for 5 days, then the level of PK-resistant PrP was determined. No reduction in PK-resistant PrP was observed with any compound.

Compound	EC_{50} (μM)
IND24	> 20[a]
1	> 10
14	> 10
37	> 3.2[b]
41	> 10

[a]Data previously reported (Berry et al., 2013).

[b]Highest concentration tested was 3.2 μM

SUPPLEMENTAL REFERENCE

Berry DB, Lu D, Geva M, Watts JC, Bhardwaj S, Oehler A, Renslo AR, DeArmond SJ, Prusiner SB and Giles K (2013) Drug resistance confounding prion therapeutics. *Proc Natl Acad Sci USA* **110**:E4160–E4169.