Supporting Information

2-Aminothiazoles as Therapeutic Leads for Prion Diseases

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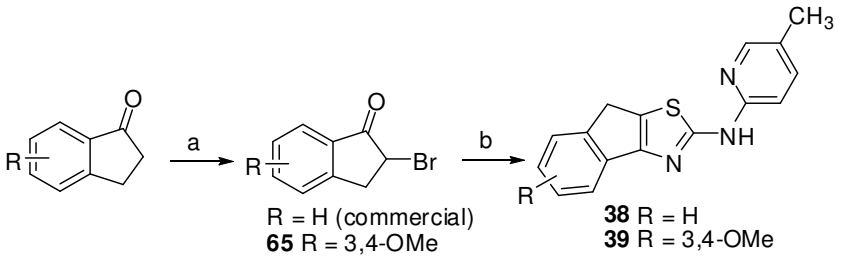
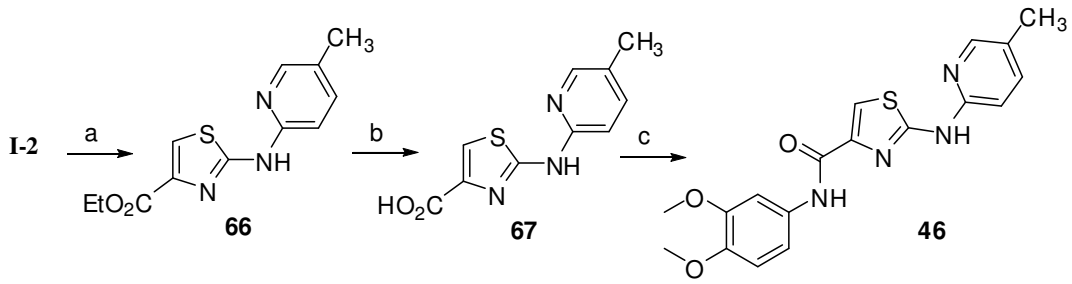
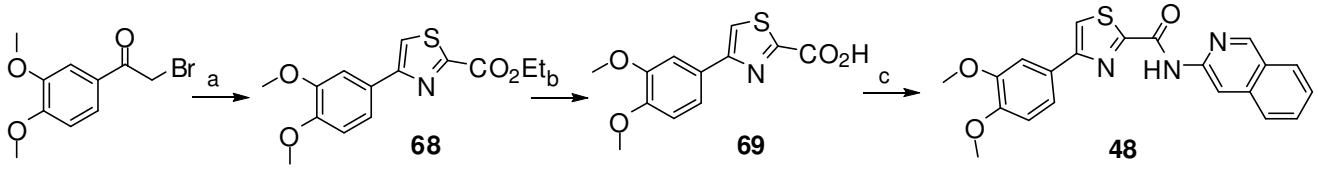
Supplementary Schemes



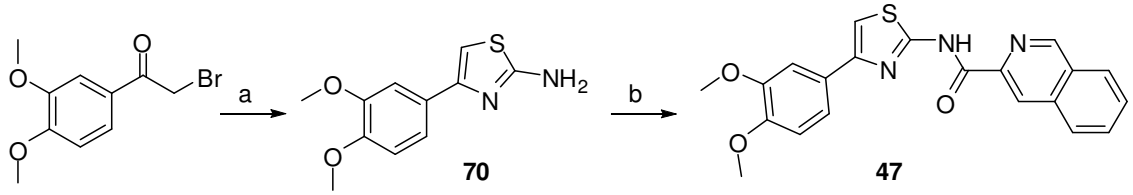
Supplementary Scheme 1. Synthesis of aminothiazole analogs **38** and **39** bearing a fused A-B ring system. Reagents and conditions: a) Br_2, Et_2O (for **65**); b) **52**, EtOH, 60 ^oC



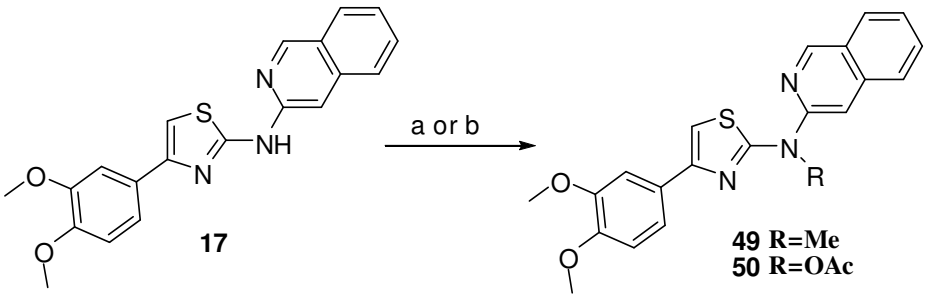
Supplementary Scheme 2. Synthesis of aminothiazole analog **46**. Reagents and conditions: a) Ethyl bromopyruvate, EtOH; b) 5N HCl, MW, 10min, 130 ^oC; c) 3,4-dimethoxyphenylamine, HATU, THF.



Supplementary Scheme 3. Synthesis of aminothiazole analog **48**. Reagents and conditions: a) $NH_2C(=S)CO_2Et$, EtOH; b) 5N NaOH, MeOH; c) isoquinolin-3-ylamine, HATU, THF



Supplementary Scheme 4. Synthesis of aminothiazole analog **47**. Reagents and conditions: a) $NH_2C(=S)NH_2$, EtOH; (ii) 5N NaOH, MeOH; b) isoquinoline-3-carboxylic acid, HATU, Et_3N, THF.

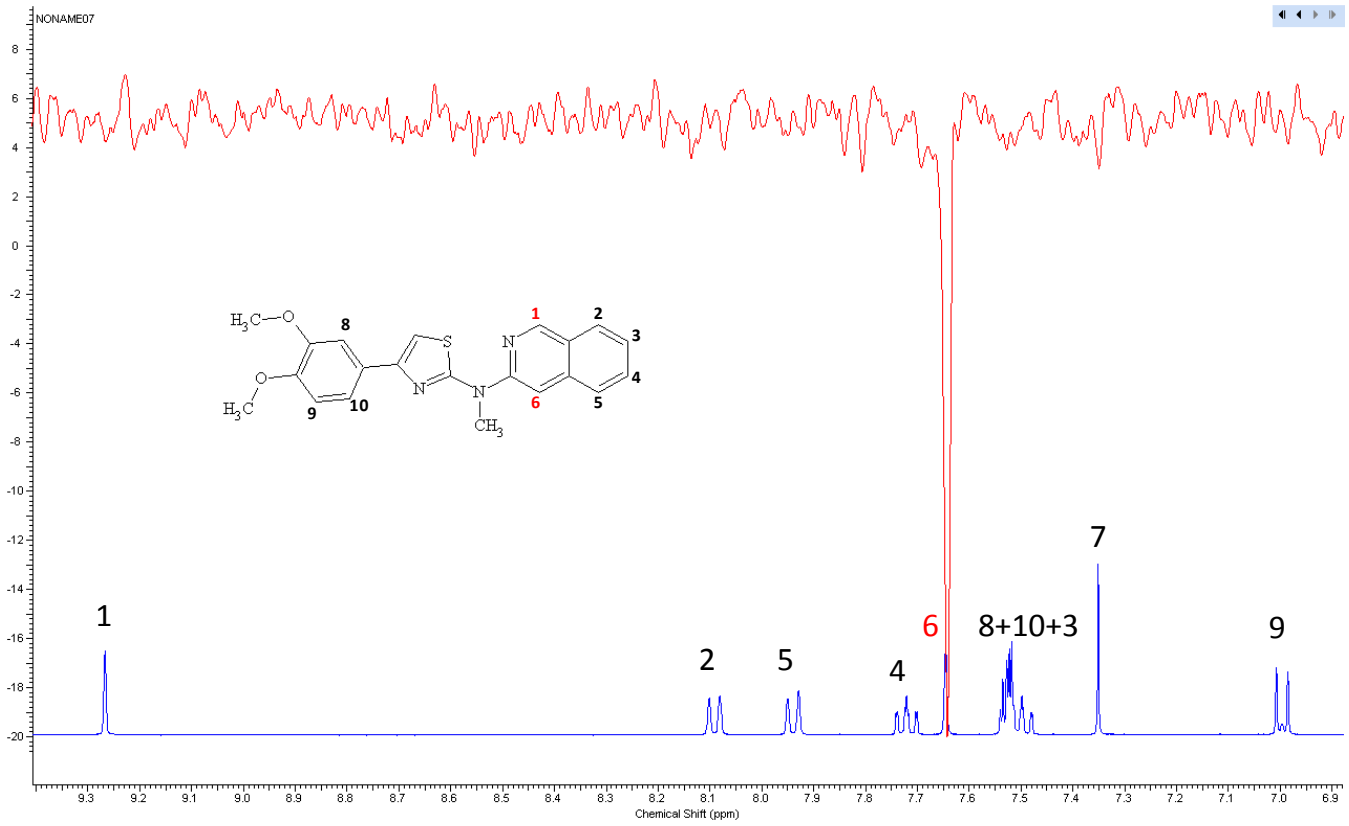


Supplementary Scheme 5. Synthesis of aminothiazole analogs **49**-**50**. Reagents and conditions: a) NaH, MeI, THF (for **49**); b) acetic anhydride, 100 ^{o}C (for **50**)

	Dividing ELISA EC_{50} (μM)				Dividing ELISA pEC_{50} (μM)					
Compound	**1st Expt.**	**2nd Expt.**	**3rd Expt.**	**Mean**	**1st Expt.**	**2nd Expt.**	**3rd Expt.**	**Mean**	**SD**	**CV (%)**
3	1.4	2.774	9.249	4.474	5.85	5.56	5.03	5.48	0.42	8
4	5.618	1.194	2.218	3.010	5.25	5.92	5.65	5.61	0.34	6
5	> 32	> 32	> 32	> 32	> 4.5	> 4.5	> 4.5			
6	11.8	6.474	6.384	8.219	4.93	5.19	5.19	5.10	0.15	3
7	1.413	1.159	1.097	1.223	5.85	5.94	5.96	5.92	0.06	1
8	> 32	25.2	26.9	>28	> 4.5	4.60	4.57			
9	7.402	7.295	4.445	6.381	5.13	5.14	5.35	5.21	0.13	2
10	3.254	6.706	1.85	3.937	5.49	5.17	5.73	5.46	0.28	5
11	26	9.233	11.7	15.644	4.59	5.03	4.93	4.85	0.24	5
12	2.93	2.048	2.617	2.532	5.53	5.69	5.58	5.60	0.08	1
13	1.073	1.004	0.917	0.998	5.97	6.00	6.04	6.00	0.03	1
14	0.974	0.577	0.815	0.789	6.01	6.24	6.09	6.11	0.12	2
15	13	2.067	6.809	7.292	4.89	5.68	5.17	5.25	0.41	8
16	1.134	0.736	1.131	1.000	5.95	6.13	5.95	6.01	0.11	2
17	0.101	0.117	0.108	0.109	7.00	6.93	6.97	6.96	0.03	0
18	0.486	0.34	0.453	0.426	6.31	6.47	6.34	6.38	0.08	1
19	0.436	0.317	0.413	0.389	6.36	6.50	6.38	6.41	0.07	1
20	> 32	> 32	> 32	> 32	> 4.5	> 4.5	> 4.5			
21	5.016	1.889	2.187	3.031	5.30	5.72	5.66	5.56	0.23	4
22	> 32	26.1	30.2	>29	> 4.5	4.58	4.52			
23	1.119	1.746	1.85	1.572	5.95	5.76	5.73	5.81	0.12	2
24	1.624	0.507	0.449	0.860	5.79	6.29	6.35	6.14	0.31	5
25	13	4.9	5.735	7.878	4.89	5.31	5.24	5.15	0.23	4
26	1.578	0.879	1.22	1.226	5.80	6.06	5.91	5.92	0.13	2
27	1.093	0.747	0.994	0.945	5.96	6.13	6.00	6.03	0.09	1
28	30	15.2	> 32	>26	4.52	4.82	> 4.5			
29	> 32	> 32	> 32	> 32	> 4.5	> 4.5	> 4.5			
30	0.226	0.385	0.414	0.342	6.65	6.41	6.38	6.48	0.14	2
31	> 32	> 32	> 32	> 32	> 4.5	> 4.5	> 4.5			
32	0.261	0.277	0.383	0.307	6.58	6.56	6.42	6.52	0.09	1
33	2.062	2.849	4.315	3.075	5.69	5.55	5.37	5.53	0.16	3
34	2.248	1.609	2.16	2.006	5.65	5.79	5.67	5.70	0.08	1
35	1.162	0.573	0.663	0.799	5.93	6.24	6.18	6.12	0.16	3
36	> 32	> 32	> 32	> 32	> 4.5	> 4.5	> 4.5			
37	8.999	7.257	9.711	8.656	5.05	5.14	5.01	5.07	0.07	1
38	1.989	2.993	2.339	2.440	5.70	5.52	5.63	5.62	0.09	2
39	3.454	5.926	7.382	5.587	5.46	5.23	5.13	5.27	0.17	3
40	0.395	0.11	0.183	0.229	6.40	6.96	6.74	6.70	0.28	4
41	0.369	0.166	0.219	0.251	6.43	6.78	6.66	6.62	0.18	3
42	0.629	0.599	0.585	0.604	6.20	6.22	6.23	6.22	0.02	0
43	1.054	1.1	1.671	1.275	5.98	5.96	5.78	5.90	0.11	2
44	0.926	0.733	0.794	0.818	6.03	6.13	6.10	6.09	0.05	1
45	3.161	3.254	6.833	4.416	5.50	5.49	5.17	5.38	0.19	4
46	3.194	1.927	2.205	2.442	5.50	5.72	5.66	5.62	0.11	2
47	9.812	3.932	10.8	8.181	5.01	5.41	4.97	5.13	0.24	5
48	> 10	> 10	> 10	> 10	> 4.5	> 4.5	> 4.5			
49	0.152	0.196	0.083	0.144	6.82	6.71	7.08	6.87	0.19	3
50	0.091	0.089	0.065	0.082	7.04	7.05	7.19	7.09	0.08	1

Compound	Dividing Calcein EC_{50} (μM) Mean (n = 3)	Non-Dividing ELISA EC_{50} (μM) Mean (n = 3)
3	> 10	> 10
4	> 32	> 32
5	> 32	> 32
6	> 32	> 32
7	> 32	> 32
8	> 32	> 32
9	> 32	> 32
10	> 32	> 32
11	> 32	> 32
12	> 32	> 32
13	> 32	> 32
14	> 32	> 32
15	> 32	> 32
16	> 32	> 32
17	> 32	> 32
18	> 32	> 32
19	> 32	> 32
20	> 32	> 32
21	> 32	> 32
22	> 32	> 32
23	> 32	> 32
24	0.389	> 32
25	> 32	> 32
26	> 32	> 32
27	> 32	> 32
28	> 32	> 32
29	> 32	> 32
30	> 32	> 32
31	> 32	> 32
32	> 32	> 32
33	> 32	> 32
34	> 32	> 32
35	> 32	> 32
36	> 32	> 32
37	> 32	> 32
38	> 32	> 32
39	> 32	> 32
40	> 32	> 32
41	> 32	> 32
42	> 32	> 32
43	> 32	> 32
44	> 32	> 32
45	> 32	> 32
46	> 32	> 32
47	> 10	> 10
48	> 10	> 10
49	> 10	> 10
50	> 10	> 10

1D NOESY Compound 49



1D NOESY Compound 50