Supporting Information

Anticonvulsant Activity of 2,4(5)-Diarylimidazoles in Mice and Rats Acute Seizure Models

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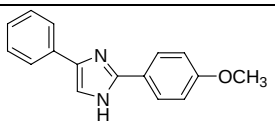
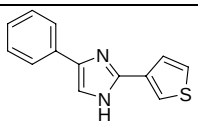
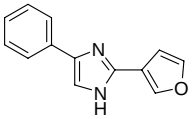
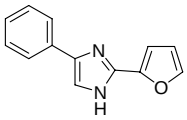
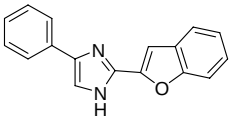
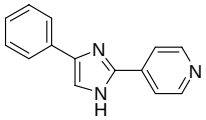
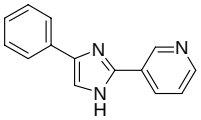
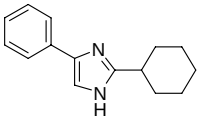
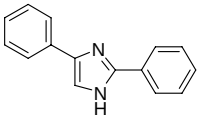
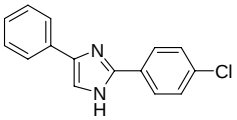
Table 1. Anticonvulsant Activity and Toxicity of Compounds **3-29** Administered Intraperitoneally to Mice

13		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	3/3	2/3	0/1	0/1	0/8	0/4
		300	1/1	1/1	1/1	0/1	4/4	2/2

Compd	**Structure**	**Dose**	**MES**[a]		**scMet**[b]		**Tox**[c]	
		mg/kg	**0.5h**[d]	**4h**[d]	**0.5h**[d]	**4h**[d]	**0.5h**[d]	**4h**[d]
3		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	3/3	0/3	0/1	0/1	5/8	0/4
		300	1/1	1/1	0/1	0/1	4/4	1/2
4		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	1/3	0/3	0/1	0/1	1/8	0/4
		300	1/1	0/0	1/1	0/0	4/4	1/1
5		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	1/3	0/3	0/1	0/1	0/8	0/4
		300	1/1	1/1	0/1	0/1	4/4	2/2
6		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	0/3	0/3	0/1	0/1	0/8	0/4
		300	0/1	0/1	0/1	0/1	0/4	0/4
7		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	2/3	1/3	0/1	0/1	5/8	0/4
		300	1/1	1/1	0/1	1/1	4/4	2/2
8		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	3/3	0/3	1/1	0/1	1/8	0/4
		300	1/1	1/1	1/1	0/1	3/4	1/2
9		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	0/2	0/2	0/0	0/1	4/8	0/3
		300	0/0	0/1	0/0	0/0	3/4	0/1
10		30	1/1	0/1	0/1	0/1	0/4	0/2
		100	3/3	0/3	0/1	0/1	1/8	0/4
		300	1/1	1/1	0/1	0/1	4/4	1/2
11		30	0/1	0/1	0/1	0/1	0/4	0/2
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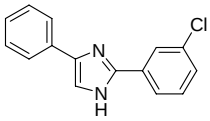
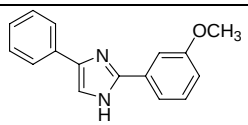
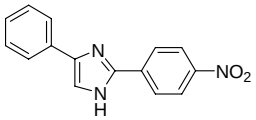
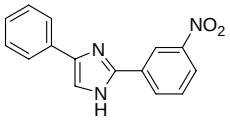
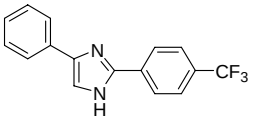
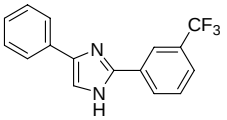
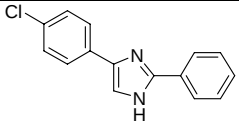
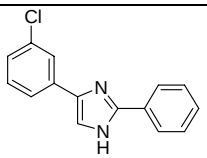
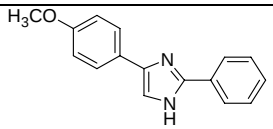
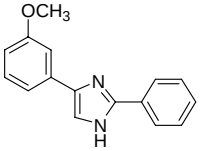
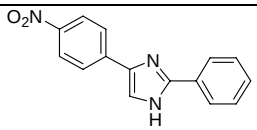
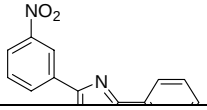
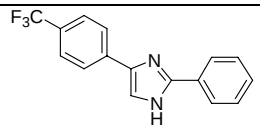
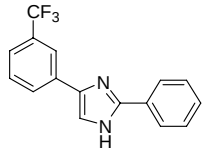
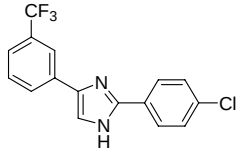
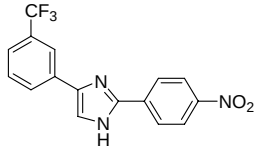
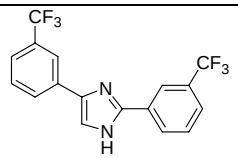
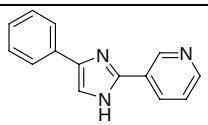
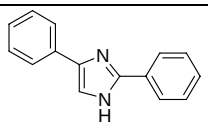
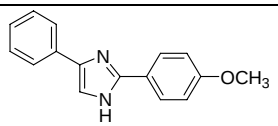
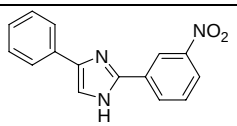
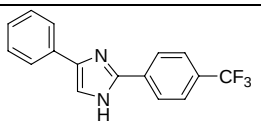
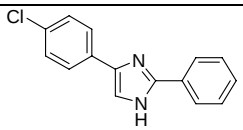
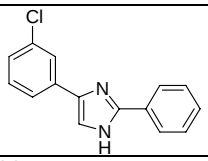
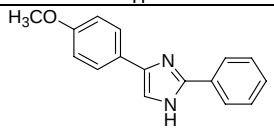
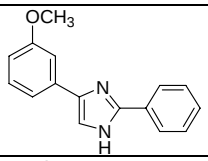
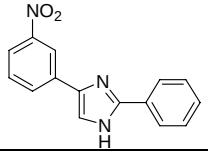
		300	0/1	0/1	0/1	0/1	0/4	0/2
12		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	1/3	0/3	0/1	0/1	0/8	0/4
		300	1/1	1/1	1/1	0/1	2/4	0/2

14		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	3/3	1/3	0/1	0/1	8/8	0/4
		300	1/1	1/1	0/1	0/1	3/4	0/2
15		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	1/3	1/3	0/1	0/1	0/8	0/4
		300	1/1	1/1	0/1	2/5	0/4	0/2
16		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	2/3	0/3	0/1	0/1	0/8	0/4
		300	1/1	1/1	0/1	0/1	0/4	0/2
17		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	0/3[e]	0/3[e]	0/1	0/1	0/8[f]	0/4[f]
		300	1/1	1/1	0/1	0/1	0/4	0/2
18		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	0/3[g]	0/3[g]	0/1	0/1	0/8[h]	0/4[h]
		300	0/1	1/1	0/1	0/1	2/4	0/2
19		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	3/3	0/3	0/1	0/1	0/8	0/4
		300	1/1	1/1	0/1	0/1	2/4	0/2
20		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	3/3	0/3	0/1	0/1	0/8	0/4
		300	1/1	1/1	0/1	0/1	2/4	0/2
21		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	3/3	1/3	0/1	0/1	0/8	0/4
		300	1/1	1/1	1/1	0/1	4/4	2/2
22		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	3/3	1/7	0/1	0/1	1/8	0/4
		300	1/1	0/5	0/1	0/1	1/4	0/2
23		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	1/3	0/3	0/1	0/1	0/8	0/4
		300	1/1	1/1	0/1	0/1	0/4	0/2
24		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	2/3	0/3	0/1	0/1	0/8	0/4

		300	1/1	1/1	0/1	0/1	0/4	0/2
25		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	1/3	0/3	0/1	0/1	1/8	0/4
		300	1/1	0/0	0/1	1/1	3/4	1/1
26		30	1/1[i]	0/1	0/1	0/1	0/4[l]	0/2
		100	1/2[i]	1/3	0/1	0/1	1/8[l]	0/4
		300	1/1[i]	1/1	0/1	0/1	2/4[l]	1/2
27		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	0/3	0/3	0/1	0/1	0/8	0/4
		300	0/1	0/1	0/1	0/1	0/4	0/2
28		30	0/1	0/1	0/1	0/1	0/4	0/2
		100	0/3	0/3	0/1	0/1	0/8	0/4
		300	0/1	1/1	0/1	0/1	0/4	0/2
29		30	1/5	0/1	0/1	0/1	0/4	0/2
		100	0/3	1/3	0/1	0/1	0/8	0/4
		300	0/1	1/1	0/1	0/1	0/4	0/2

[a]Maximal electroshock test (number of animals protected/number of animals tested at the given time point). [b]Subcutaneous metrazol test (number of animals protected/number of animals tested). [c]Neurotoxicity (number of animals protected/number of animals tested). [d]Time of test after drug administration. [e]Also tested at 0.25h (2/3), 1h (1/3) and 2h (0/3). [f]Also tested at 0.25h (0/3), 1h (0/3) and 2h (0/3). [g]Also tested at 2h (1/3). [h]Also tested at 2h (0/3). [i]Also tested at 3 mg/kg (0/4) and 10 mg/kg (0/4). [l]Also tested at 3 mg/kg (0/4) and 10 mg/kg (0/4).

Table 2. Anticonvulsant Activity and Toxicity of Compounds **8**, **10**, **13**, **16**, **17**, **19-22**, **24** Administered Orally (30 mg/kg) to Rats

Compd	Structure	MES[a]					TOX[b]
		0.25h[c]	0.5h[c]	1h[c]	2h[c]	4h[c]	
8		1/4	0/4	1/4	0/4	0/4	0/4 (-)[d]
10		2/4	2/4	1/4	0/4	0/4	0/4 (-)[d]
13		2/4	0/4	3/4	2/4	0/4	0/4 (-)[d]
16		0/4	0/4	1/4	0/4	1/4	0/4(-)[d]
17		0/4	1/4	2/4	1/4	2/4	0/4(-)[d]
19		0/4	0/4	0/4	0/4	0/4	0/4 (-)[d]
20		0/4	0/4	2/4	0/4	0/4	0/4 (-)[d]
21		0/4	0/4	0/4	0/4	1/4	0/4 (-)[d]
22		1/4	0/4	0/4	0/4	0/4	0/4 (-)[d]
24		0/4	0/4	0/4	0/4	0/4	0/4 (-)[d]

[a]Maximal electroshock test (number of animals protected/number of animals tested). [b]Neurotoxicity (number of animals protected/number of animals tested). [c]Time after drug administration. [d](-) No neurotoxicity at doses tested.

Table 3. Quantitative anticonvulsant activity (MES and scMet), toxicity in mice (i.p.; tested at 0.25h) and IC_{50} values for inhibition of $hNa_V1.2$ Na currents of compounds **10**, **13**, **17** and **20**

Compd	MES[a] ED_{50}[b]	PI[c]	scMet[d] ED_{50}[b]	PI[e]	TD_{50}[f,b]	$hNa_v1.2$ IC_{50} (μM)
10	61.7[g] (51.9-71.4)	2.1	160.9[g] (138.6-187.0)	0.8	126.8[g] (107.6-140.2)	40.6
13	46.8[h] (44.0-52.0)	4.3	142.2[h] (103.6-203.4)	1.4	200.8[h] (163.0-243.6)	21.4
17[i]	129.5[j] (101.5-163.3)	~5.0	>300[j]	/	>500[j]	10.1
20	136.7[k] (112.3-159.9)	~5.0	>250[k]	/	>500[k]	17.9
Phenytoin	9.5 (8.1-10.4)	6.9	/	/	65.5	>100

[a]Maximal electroshock test (number of animals protected/number of animals tested). [b]The interval in parentheses stands for the 95% confidence interval. [c]Protective index (PI = TD_{50}/ED_{50}) in the MES test. [d]Subcutaneous metrazol test (number of animals protected/number of animals tested). [e]Protective index (PI = TD_{50}/ED_{50}) in the scMet test. [f]Neurotoxicity (number of animals protected/number of animals tested). [g]The ratios of protected-to-tested mice were 1/8 (45 mg/Kg), 3/8 (60 mg/Kg), 7/8 (80 mg/Kg) and 8/8 (100 mg/Kg) (MES) and 1/8 (130 mg/Kg), 4/8 (160 mg/Kg) and 7/8 (200 mg/Kg) (scMet). The ratio of neurotoxic-to-tested mice was 0/8 (80 mg/Kg), 2/8 (120 mg/Kg), 6/8 (130 mg/Kg), 7/8 (160 mg/Kg) and 8/8 (200 mg/Kg). [h]The ratios of protected-to-tested mice were 0/8 (35 mg/Kg), 1/8 (41 mg/Kg), 8/16 (46 mg/Kg), 5/8 (50 mg/Kg) and 8/8 (70 mg/Kg) (MES) and 0/8 (70 mg/Kg), 4/8 (125 mg/Kg) and 6/8 (200 mg/Kg) (scMet). The ratio of

neurotoxic-to-tested mice was 0/8 (70 mg/Kg), 1/8 (125 mg/Kg), 4/8 (175 mg/Kg), 8/16 (225 mg/Kg) and 8/8 (350 mg/Kg). [i]Tested at 1h. [j]The ratios of protected-to-tested mice were 0/8 (60 mg/Kg), 2/8 (100 mg/Kg), 5/8 (140 mg/Kg) and 7/8 (200 mg/Kg) (MES) and 0/3 (75 mg/Kg), 0/3 (150 mg/Kg) and 0/3 (300 mg/Kg) (scMet). The ratio of neurotoxic-to-tested mice was 0/8 (140 mg/Kg) and 4/8 (500 mg/Kg). [k]The ratios of protected-to-tested mice were 1/8 (100 mg/Kg), 4/8 (135 mg/Kg), 6/8 (170 mg/Kg) and 8/8 (230 mg/Kg) (MES) and 0/3 (125 mg/Kg) and 0/3 (250 mg/Kg) (scMet). The ratio of neurotoxic-to-tested mice was 0/8 (350 mg/Kg) and 0/8 (500 mg/Kg).