Synthesis and anticonvulsant activity of phenoxyacetyl derivatives of amines, including aminoalkanols and amino acids

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Table 1

Physicochemical parameters calculated for compounds **1-17** by means of molinspiration online toolkit (http://www.molinspiration.com/cgi-bin/properties)

Compd	MW	logP	nON	nOHNH	nrotb	TPSA (Å^2)
1	277.36	2.19	4	2	4	58.56
2	283.37	3.71	3	1	6	38.33
3	299.37	2.71	4	2	6	58.56
4	237.30	1.63	4	2	5	58.56
5	237.30	1.60	4	2	5	58.56
6	237.30	1.60	4	2	5	58.56
7	237.30	1.60	4	2	5	58.56
8	251.28	0.02	5	2	5	75.63
9	251.28	0.02	5	2	5	75.63
10	250.30	1.52	5	3	5	81.43
11	264.32	1.34	5	2	5	67.43
12	251.33	2.13	4	2	6	58.56
13	251.33	2.13	4	2	6	58.56
14	439.55	5.17	6	1	9	73.87
15	265.35	2.54	4	2	6	58.56
16	313.40	3.12	4	2	6	58.56

17	278.35	2.46	5	3	6	81.43

Table 2

Anticonvulsant activity in 6 Hz and neurotoxicity in rotarod of compounds **6** and **8** (mice, *i.p.*).

Compd	Dose [mg/kg]	Time [h]				
		0.25	0.5	1.0	2.0	4.0
6	120	2/4	0/4	0/4	0/4	0/4
8	100	0/4	0/4	1/4	0/4	1/4

Number of animals protected / number of animals tested

Table 3

Results of preliminary hippocampal kindling screen for compound **6** in rats, *i.p.*

Compd	Dose [mg/kg]	Time [h]		Seizure Score		Afterdischarge duration [s]	
6	100	0.25	Rat #1	5	5[a]	58-69	54
			Rat #2	5	1[a]	51-70	22

Seizures are scored according to the following criteria (Racine's scale): stage 1—mouth and facial clonus; stage 2—stage 1 plus head nodding; stage 3—stage 2 plus forelimb clonus; stage 4—stage 3 plus rearing; stage 5—stage 4 plus repeated rearing and falling

[a] significantly different from control

Table 4

Mutagenic activity tested with the Ames test on TA100 and TA1535 strains in the absence and in the presence of metabolic activation.

Compd	Concentration (μg/plate)	Number of revertants			
		S. typhimurium			
		TA100		TA1535	
		-S9	+S9	-S9	+S9
		Mean ± S.D. (MI)	Mean ± S.D. (MI)	Mean ± S.D. (MI)	Mean ± S.D. (MI)
Negative control	-	114 ± 18	130 ± 12	6 ± 2	18 ± 5
Positive control	5	1366 ± 51	858 ± 29	306 ± 17	371 ± 33
3	500	154 ± 4 (1.4)	148 ± 8 (1.1)	9 ± 0 (1.5)	21 ± 6 (1.2)
	250	150 ± 7 (1.3)	147 ± 8 (1.1)	8 ± 6 (1.3)	22 ± 8 (1.2)
	100	83 ± 21 (0.7)	148 ± 4 (1.1)	9 ± 2 (1.5)	18 ± 7 (1.0)

	50	98 ± 8 (0.9)	121 ± 16 (0.9)	10 ± 6 (1.7)	19 ± 4 (1.1)
6	500	130 ± 2 (1.1)	162 ± 14 (1.3)	6 ± 2 (1.0)	23 ± 3 (1.3)
	250	112 ± 10 (1.0)	140 ± 3 (1.1)	7 ± 1 (1.2)	24 ± 6 (1.3)
	100	112 ± 2 (1.0)	133 ± 12 (1.0)	5 ± 1 (0.8)	21 ± 3 (1.2)
	50	100 ± 3 (0.9)	123 ± 18 (1.0)	8 ± 2 (1.3)	19 ± 1 (1.1)
12	500	109 ± 14 (1.0)	176 ± 20 (1.4)	5 ± 1 (0.8)	25 ± 9 (1.4)
	250	77 ± 7 (0.7)	163 ± 39 (1.3)	7 ± 2 (1.2)	22 ± 2 (1.2)
	100	134 ± 13 (1.2)	157 ± 10 (1.2)	7 ± 2 (1.2)	26 ± 4 (1.4)
	50	160 ± 4 (1.4)	117 ± 6 (0.9)	6 ± 0 (1.0)	23 ± 4 (1.3)
13	500	147 ± 17 (1.3)	128 ± 11 (1.0)	8 ± 2 (1.3)	25 ± 2 (1.4)
	250	110 ± 11 (1.0)	112 ± 14 (0.9)	8 ± 5 (1.3)	21 ± 8 (1.2)
	100	156 ± 8 (1.4)	154 ± 12 (1.2)	9 ± 10 (1.5)	20 ± 4 (1.1)
	50	110 ± 9 (1.0)	136 ± 8 (1.1)	5 ± 2 (0.8)	21 ± 6 (1.2)

* Mean ± S.D. - mean value ± standard deviation; mutagenicity index (MI, in brackets); Negative control – dimethylsulfoxide (DMSO); Positive control - sodium azide (NaN_3, 5 µg/plate) in the absence of S9; 2-aminoanthracene (2AA, 5 µg/plate) in the presence of S9.

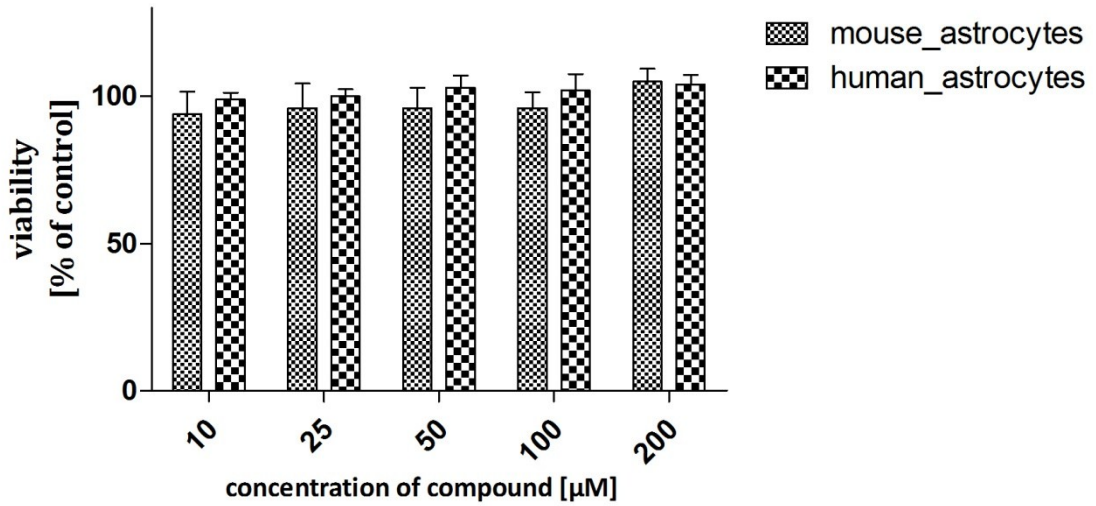

Figure 1. Effect of compound **6** on viability of human astrocytes and mouse actrocytes. Cells were cultured in medium supplemented with 10% FBS and antibiotics in the presence or absence (control) of compound (10, 25, 50, 100 or 200 µM). After 24 hour incubation MTT assay were performed. Results

from MTT assay are presented as percent of living cells compared to control. Values represent means ± SEM of three independent experiments.

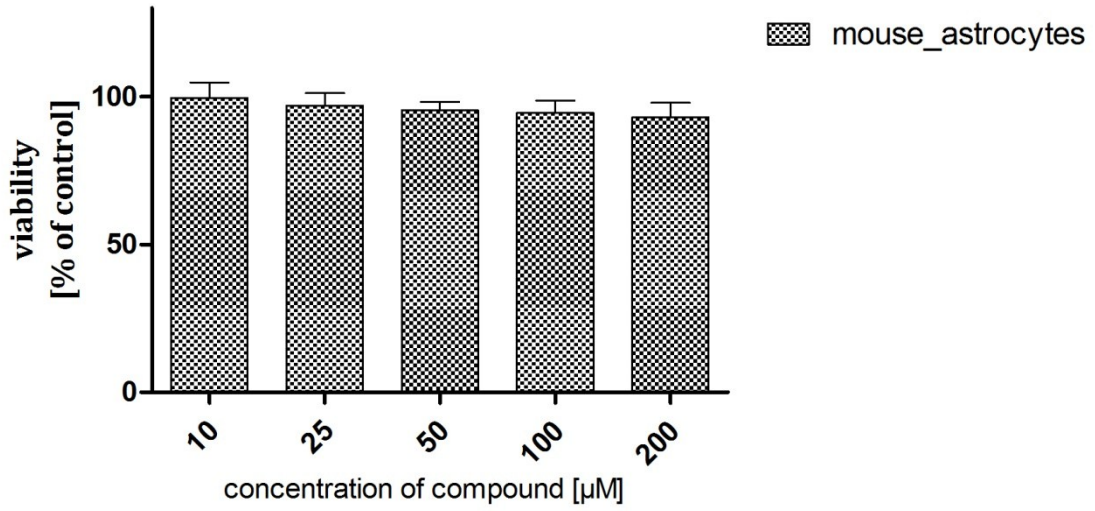

Figure 2. Effect of compound **6** on viability of mouse astrocytes. Cells were cultured in medium supplemented with 10% FBS and antibiotics in the presence or absence (control) of compound (10, 25, 50, 100 or 200 μM). After 24 hour incubation neutral red (NR) assay were performed. Results from NR assay are presented as percent of living cells in compare to control. Values represent means ± SEM of three independent experiments.

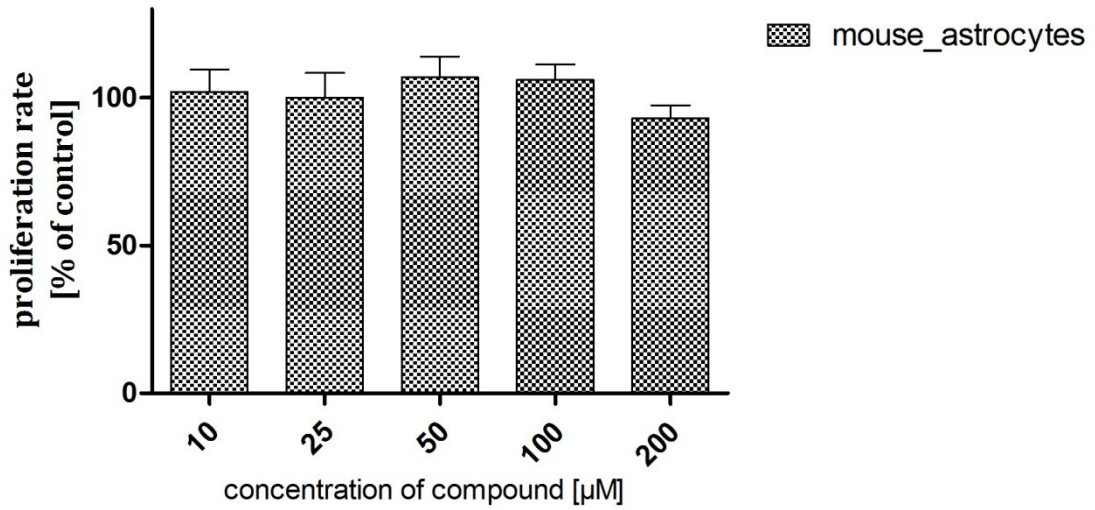

Figure 3. Effect of compound **6** on mouse astrocytes proliferation. Cells were cultured in medium supplemented with 10% FBS and antibiotics in the presence or absence (control) of compound (10, 25,

50, 100 or 200 μM). After 24 hour incubation crystal violet (CV) assay was performed. Results from CV assay are presented as number of proliferating cells in compare to control. Values represent means ± SEM of three independent experiments.