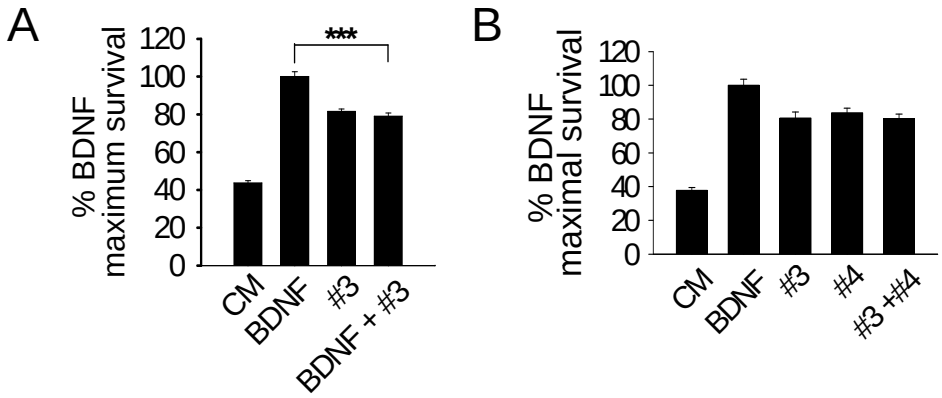

Fig S1. LM22A-3, LM22A-4, BDNF additivity analyses. (A) survival analysis of E16 hippocampal neurons treated with BDNF alone (0.7 nM), LM22A-3 alone (each at 500 nM) or with BDNF + LM22A-3. 59-114 wells (n) for each condition derived from 4 experiments were analyzed. **(B)** survival analysis of E16 hippocampal neurons treated with BDNF alone (0.7 nM), LM22A-3 (500 nM), LM22A-4 (500 nM), or LM22A-3 plus LM22A-4 each at 500 nM. Results from three independent experiments and 30 fields. Statistical analysis performed using ANOVA with post-hoc Tukey-Kramer Multiple Comparisons Test.

In Vitro Pharmacology LM22A-4 Binding Assays

Assay Cerep Compound I.D.	Client Compound I.D.	Test Concentration (M)	% Inhibition of Control Specific Binding
A_1 *(h)* (antagonist radioligand)			
17303-2	LM22A-4	1.0E-05	7
A_{2A} *(h)* (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	8
A_3 *(h)* (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	1
α_1 (non-selective) (antagonist radioligand)			
17303-2	LM22A-4	1.0E-05	14
α_2 (non-selective) (antagonist radioligand)			
17303-2	LM22A-4	1.0E-05	-10
β_1 *(h)* (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	1
β_2 *(h)* (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	4
AT_1 *(h)* (antagonist radioligand)			
17303-2	LM22A-4	1.0E-05	8
BZD (central) (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	10
B_2 *(h)* (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	7
CB_1 *(h)* (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	1
CCK_1 (CCK_A) *(h)* (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	-27
D_1 *(h)* (antagonist radioligand)			
17303-2	LM22A-4	1.0E-05	4
D_{2S} *(h)* (antagonist radioligand)			
17303-2	LM22A-4	1.0E-05	-3
ET_A *(h)* (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	-18
GABA (non-selective) (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	1
GAL_2 *(h)* (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	-13
CXCR2 (IL-8B) *(h)* (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	-25
CCR1 *(h)* (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	-4
H_1 *(h)* (antagonist radioligand)			
17303-2	LM22A-4	1.0E-05	-13
H_2 *(h)* (antagonist radioligand)			
17303-2	LM22A-4	1.0E-05	-14
MC_4 *(h)* (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	-19
MT_1 (ML_{1A}) *(h)* (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	-4
M_1 *(h)* (antagonist radioligand)			
17303-2	LM22A-4	1.0E-05	-2
M_2 *(h)* (antagonist radioligand)			
17303-2	LM22A-4	1.0E-05	-7
M_3 *(h)* (antagonist radioligand)			
17303-2	LM22A-4	1.0E-05	0
NK_2 *(h)* (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	-6
NK_3 *(h)* (antagonist radioligand)			
17303-2	LM22A-4	1.0E-05	1
Y_1 *(h)* (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	-3
Y_2 *(h)* (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	-17

Assay Cerep Compound I.D.	Client Compound I.D.	Test Concentration (M)	% Inhibition of Control Specific Binding
NTS_1 (NT_1) *(h)* (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	1
δ_2 (DOP) *(h)* (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	3
κ (KOP) (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	-4
μ (MOP) *(h)* (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	6
NOP (ORL1) *(h)* (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	4
TP *(h)* (TXA_2/PGH_2) (antagonist radioligand)			
17303-2	LM22A-4	1.0E-05	-6
5-HT_{1A} *(h)* (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	-3
5-HT_{1B} (antagonist radioligand)			
17303-2	LM22A-4	1.0E-05	-4
5-HT_{2A} *(h)* (antagonist radioligand)			
17303-2	LM22A-4	1.0E-05	-2
5-HT_{2B} *(h)* (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	9
5-HT_3 *(h)* (antagonist radioligand)			
17303-2	LM22A-4	1.0E-05	2
5-HT_{5a} *(h)* (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	0
5-HT_6 *(h)* (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	0
5-HT_7 *(h)* (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	-2
sst (non-selective) (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	-11
$VPAC_1$ (VIP_1) *(h)* (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	-6
V_{1a} *(h)* (agonist radioligand)			
17303-2	LM22A-4	1.0E-05	4
Ca^{2+} channel (L, verapamil site) (phenylalkylamine) (antagonist radioligand)			
17303-2	LM22A-4	1.0E-05	-12
K_V channel (antagonist radioligand)			
17303-2	LM22A-4	1.0E-05	-3
SK_{Ca} channel (antagonist radioligand)			
17303-2	LM22A-4	1.0E-05	-1
Na^+ channel (site 2) (antagonist radioligand)			
17303-2	LM22A-4	1.0E-05	9
Cl^- channel (GABA-gated) (antagonist radioligand)			
17303-2	LM22A-4	1.0E-05	1
norepinephrine transporter *(h)* (antagonist radioligand)			
17303-2	LM22A-4	1.0E-05	-7
dopamine transporter *(h)* (antagonist radioligand)			
17303-2	LM22A-4	1.0E-05	14
5-HT transporter *(h)* (antagonist radioligand)			
17303-2	LM22A-4	1.0E-05	4

Fig S2. Cerep ExpresSProfile screen of LM22A-4 binding to pharmacologically relevant receptors.

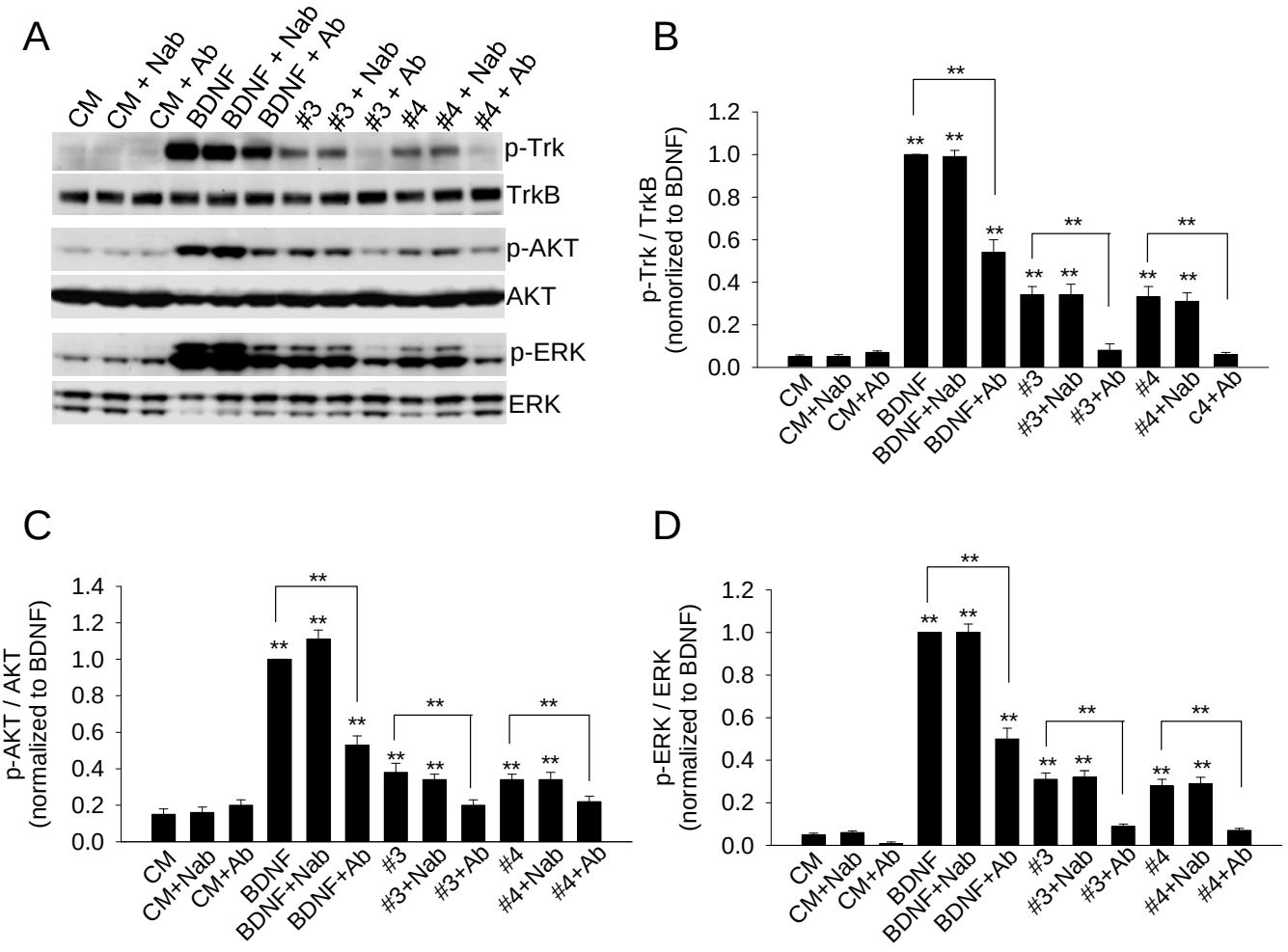

Fig S3. TrkB blocking antibody blocks LM22A-3 and LM22A-4 induced Trk, AKT and ERK activation in cultured hippocampal neurons. Western blot analysis of hippocampal neurons treated with CM, BDNF (0.7 nM), LM22A-3 or LM22A-4 (500 nM) with or without TrkB-extracellular domain monoclonal antibody or control non-immune serum (Nab) at a final dilution of 1:400. Cells were pretreated with TrkB-extracellular domain monoclonal antibody or control non-immune serum for 4 hours, followed by BDNF, LM22A-3 or LM22A-4 for 30 min. Cell lysates were analyzed by immunoblotting. n = 12 western analyses assessing four independent protein preparations. **(A)** representative blot. **(B-D)** densitometric quantification as indicated. Statistical analysis performed using ANOVA with post-hoc Tukey-Kramer Multiple Comparisons Test.

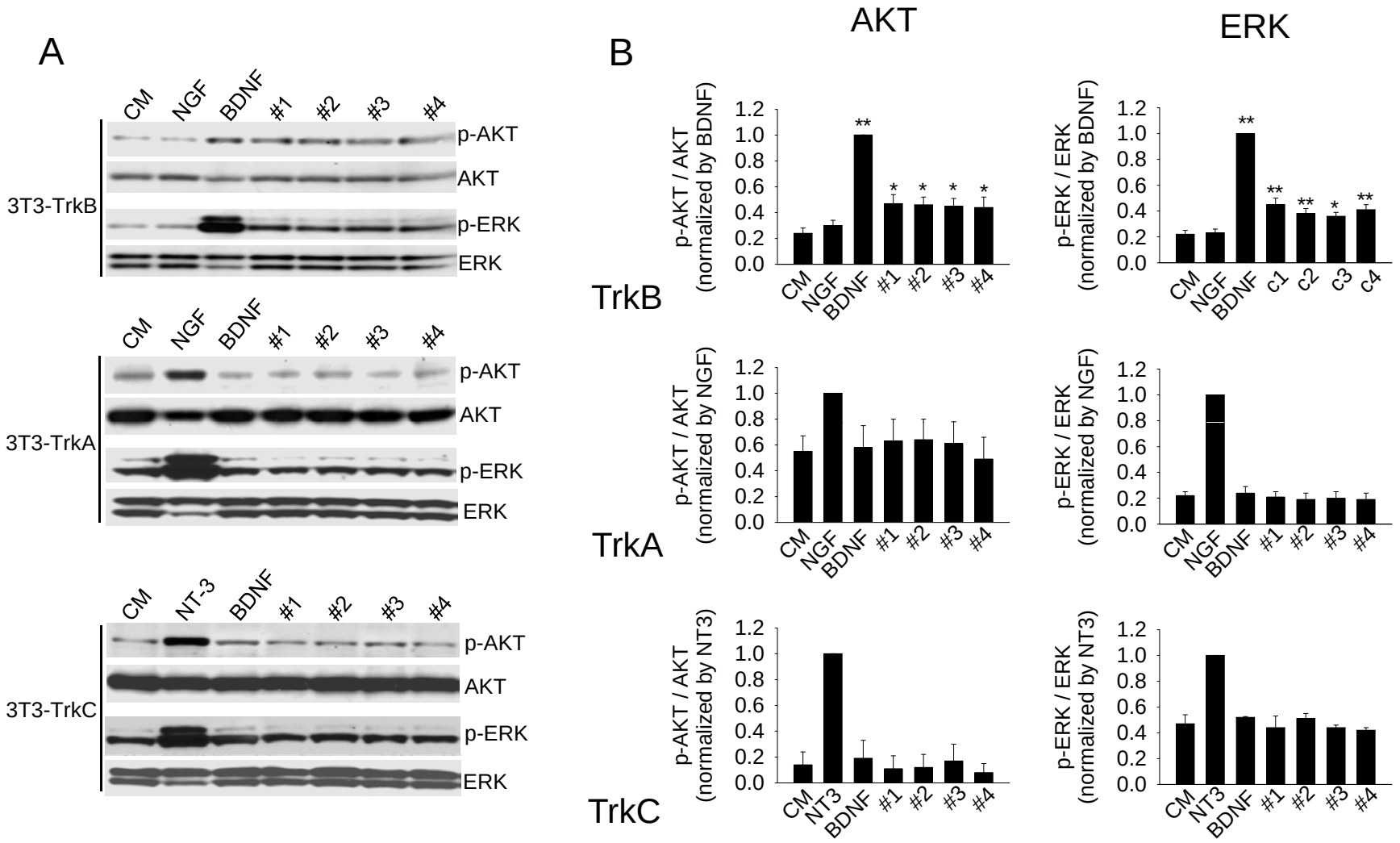

Fig S4. LM22A compounds induce AKT and ERK activation in 3T3-TrkB cells, but not in 3T3-TrkA or 3T3-TrkC cells. 3T3-TrkB, 3T3-TrkA or 3T3-TrkC cells were grown in DMEM supplemented with 10% fetal bovine serum to 90% confluence, then switched to serum free DMEM for 24 hours; cells were treated with BDNF (0.7 nM), NGF (0.6 nM), NT3 (0.76 nM), LM22A-1-4 (500 nM) for 60 min. Cell lysates were analyzed by immunoblotting. n = 12 western analyses assessing four independent protein preparations. Statistical analysis performed using ANOVA with post-hoc Dunnett's Multiple Comparisons Test. **(A)** representative blots. **(B)** densitometric quantification as indicated.

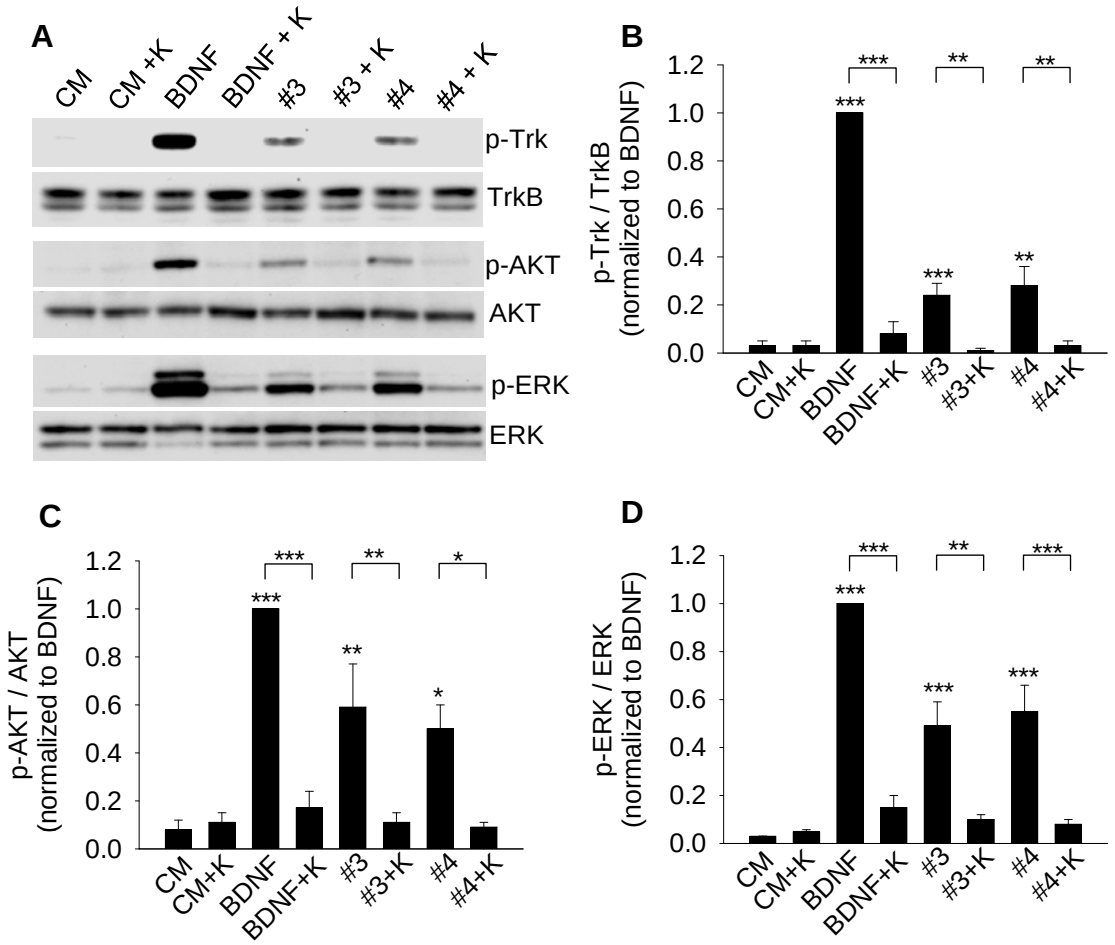

Fig S5. K252a blocks LM22A-3 and LM22A-4-induced TrkB, AKT and ERK activation in cultured 3T3-TrkB cells. 3T3-TrkB cells were grown in DMEM supplemented with 10% fetal bovine serum to 90% confluence then switched into serum free DMEM for 24 hours; cells were pretreated with K252a (200nM) for 30 min, followed by BDNF (0.7 nM), LM22A-3 (500 nM) or LM22A-4 (500 nM) for 60 min. Cell lysates were analyzed by immunoblotting. n = 6, assessing three independent protein preparations. Statistical analysis performed using ANOVA with post-hoc Tukey-Kramer Multiple Comparisons Test. **(A)** representative blot. **(B-D)** densitometric quantification as indicated.

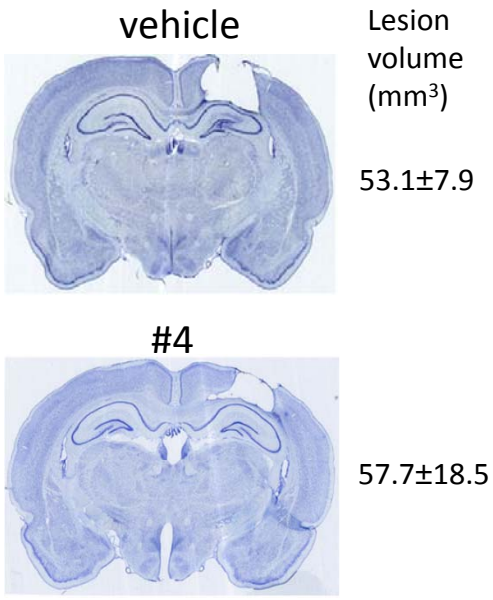

Fig S6. LM22A-4 does not affect lesion volume following TBI. Representative Nissl-stained sections showing cavitary lesions 21 days following impact. Lesion volumes were as indicated (mean±SE, n=6/group, P=0.82, no significant difference by Student t testing).