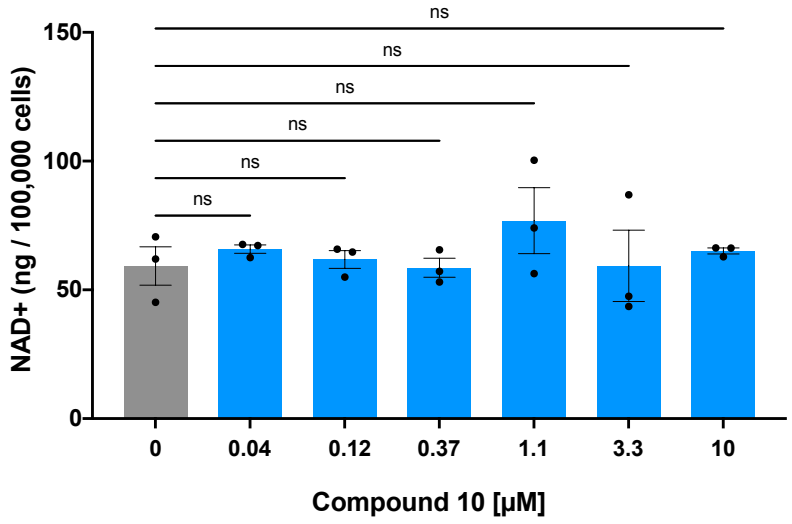
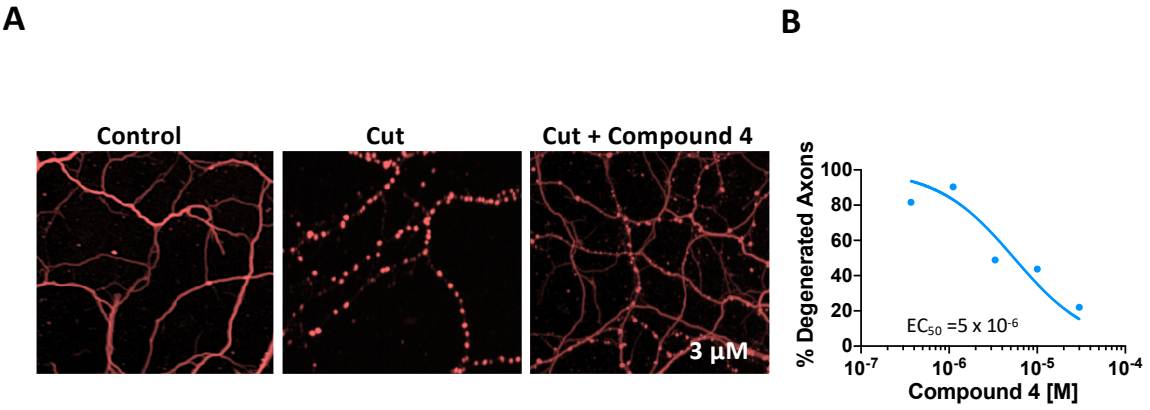
%inhibition @ 10uM	Compound 4	Compound 9	Compound 10
SARM1	100	100	100
PARP1	41	8	3
PARP2	25	4	0
TNKS1	20	2	5
TNKS2	31	5	1
CD38	0	1	0
SIRT1	13	10	7
NAMPT	3	1	2
NMNAT1	54	39	67

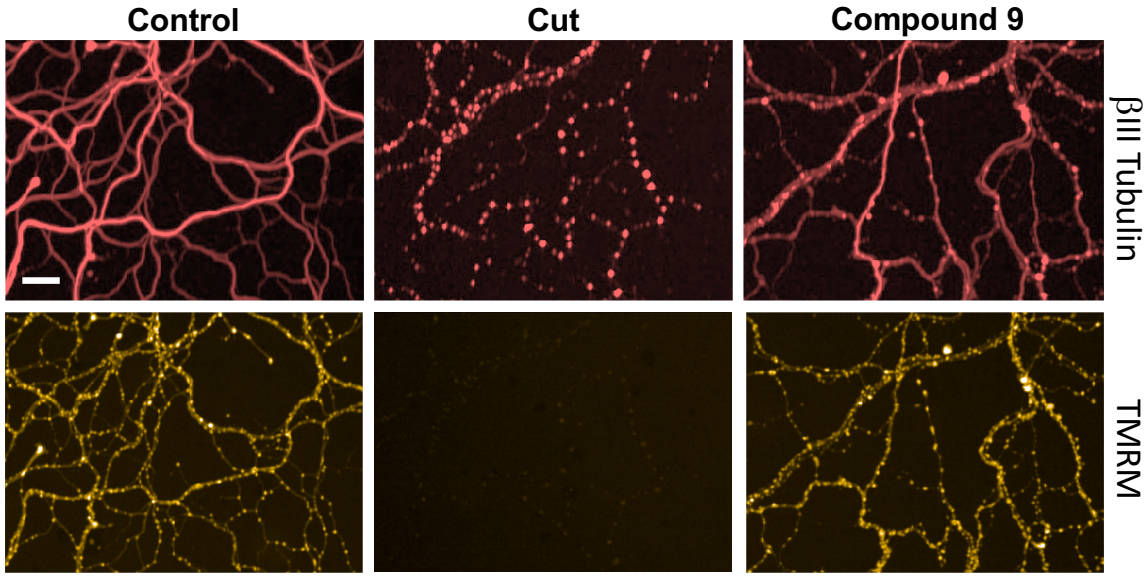
Supplementary Table 1. Selectivity profile of isothiazoles.



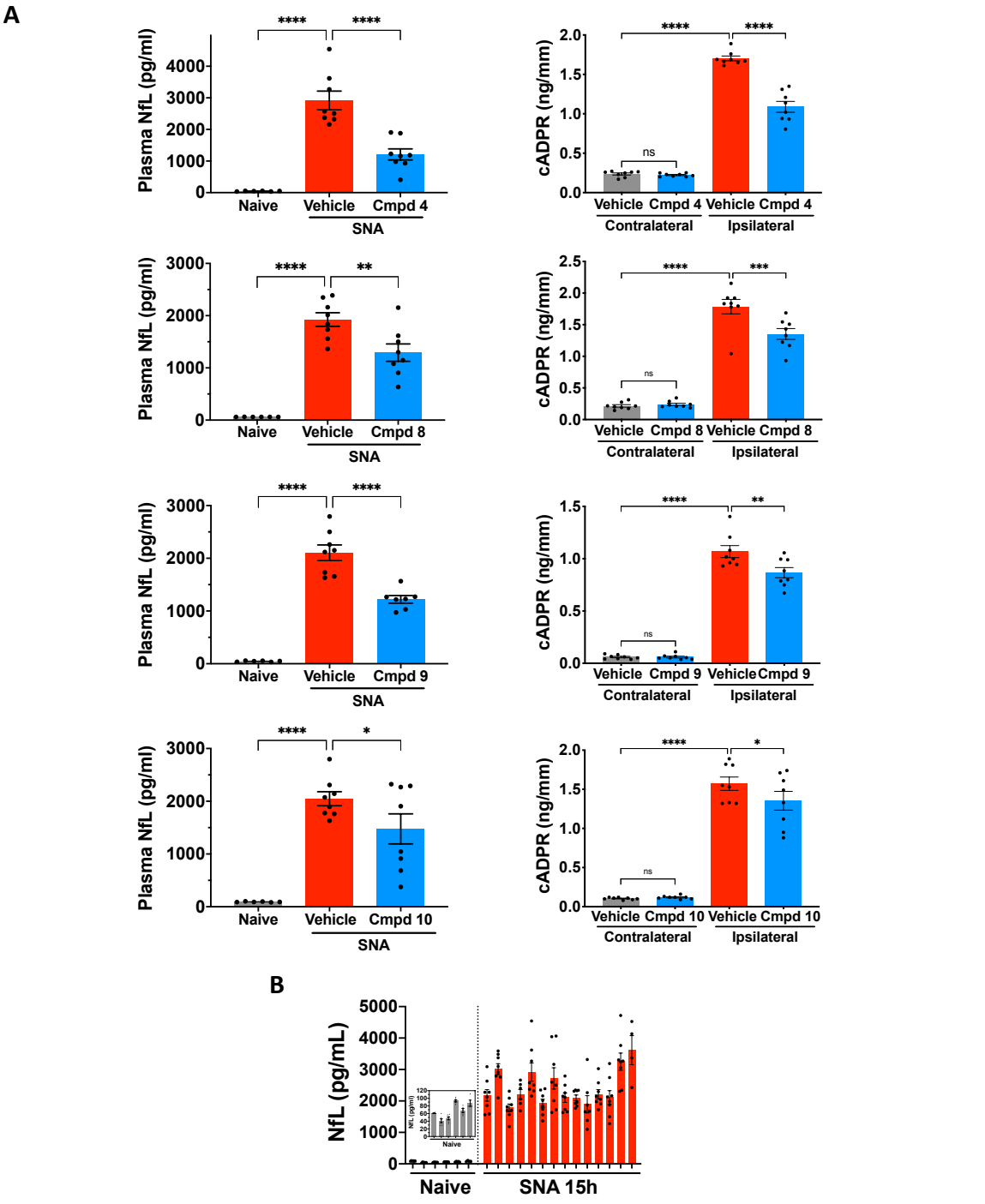
Supplementary Figure 1. Isothiazole SARM1 inhibitors do not prevent NAD⁺ synthesis.
Intact mouse DRG neurons were exposed to isothiazole compound **(10)** and NAD+ levels were measured after 22h. No significant changes in NAD+ were observed. Values represent Mean ± SEM. One-way ANOVA with Holm-Sidak post-hoc $F(6,14) = 0.6588$; n=3/group; ns: not significant.



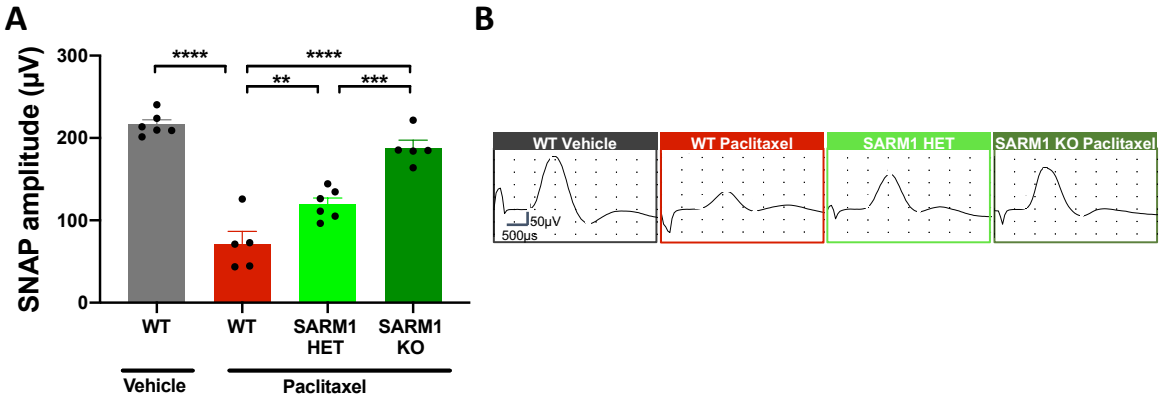
Supplementary Figure 2. Isothiazole SARM1 inhibitors protect human axons in vitro.
A) Human IPSC-derived motor neurons were treated with 3 µM isothiazole SARM1 inhibitor compound **4,** subjected to axotomy, and examined at 16 h (right panel). Scale bar, 25 µM. **B)** Quantification of fragmentation 16 h post-axotomy showed dose-dependent protection by compound **4**, with an EC_{50} = 5 µM. Values represent Mean +/- SEM. n=4; representative of 2 independent experiments with similar results.



Supplementary Figure 3. SARM1 inhibition with isothiazoles preserves mitochondrial viability.
Mouse DRG neurons were exposed to Isothiazole compound **(9)** for 2h and then subject to axotomy. Cultures were examined 16 h later for axonal morphology (βIII-tubulin; top panels) and TMRM fluorescence (bottom panels). Scale bar, 25 μM. Representative images of n=4



Supplementary Figure 4. Isothiazoles inhibit SARM1 in vivo. A) Mice were treated with isothiazole SARM1 inhibitors **4, 8, 9,** and **10** at the doses indicated and subjected to unilateral SNA 30 min after the first dose. Compounds 4, 8, and 9 received a second dose administered 8 hours after the first dose. 15 h after SNA NfL levels were measured in plasma and cADPR levels were measured in cut and uncut contralateral nerves. Compounds **4** (30 mg/kg), **8** (120 mg/kg) and **9** (45 mg/kg) were dosed by intraperitoneal injection and compound **10** (300 mg/kg) was dosed orally. All compounds prevented increases in plasma NfL and cADPR. Values represent Means ± SEM. Compound **4**, NfL, ANOVA with Holm-Sidak post-hoc $F(2,19) = 43.18$, $P < 0.0001$ n=6-8/group; cADPR, ANOVA with Holm-Sidak post-hoc $F(3,28) = 350.8$, $P < 0.0001$, n=8. Compound **8**, NfL, ANOVA with Holm- Sidak post-hoc $F(2,19) = 46.02$, $P < 0.0001$ n=6-8/group; cADPR, ANOVA with Holm-Sidak post-hoc $F(3,28) = 120.1$, $P < 0.0001$, n=8. Compound **9**, NfL, ANOVA with Holm-Sidak post-hoc $F(2,18) = 90.68$, $P < 0.0001$ n=6-8/group; cADPR, ANOVA with Holm-Sidak post-hoc $F(5,42) = 131.5$, $P < 0.0001$, n=7-8/group. Compound **10**, NfL, ANOVA with Holm-Sidak post-hoc $F(2,19) = 23.17$ $P < 0.0001$ n=6- 8/group; cADPR, ANOVA with Holm-Sidak post-hoc $F(3,28) = 113.7$, $P < 0.0001$, n=8. ns not significant; * $p < 0.05$; ** $p < 0.01$; ; *** $p < 0.001$; **** $p < 0.0001$. **B)** Baseline plasma NfL levels from 6 independent naïve cohorts (n=4-6; gray bars), and mean plasma NfL levels 15 hours after SNA in 14 independent cohorts (n=6-8). The inset shows an enlarged view of the naïve cohorts.



Supplementary Figure 5. SARM1 loss of function prevents decreases in SNAP amplitudes induced by paclitaxel. WT, SARM1 heterozygous (HET) and SARM1 null mutant mice were treated with 2 doses of 50 mg/kg paclitaxel of days 1 and 2. 15 Days after the first dose of paclitaxel, SNAP amplitudes of the tail nerves were recorded as described in Methods. **A)** Paclitaxel induced a 67% decrease in SNAP amplitude in WT. SARM1 mutants showed gene-dosage protection of SNAP amplitudes. Values represent Mean +/- SEM, ANOVA with Holm-Sidak post-hoc $F(3,18) = 47.18$, $P < 0.0001$, n=5-6 per group; ** $p < 0.01$;*** $p < 0.001$; **** $p < 0.0001$. **B)** Representative SNAP traces from the groups analyzed in panel (A).