**Supporting Information**

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**Fig. S1.** Effect of 2-PMPA on immune cell populations. Daily administration of 2-PMPA in EAE mice does not affect splenic or CNS lymphocyte populations 28 d postimmunization. (A) Splenocytes isolated from 2-PMPA–treated and control mice on day 28 postimmunization were stained directly ex vivo for CD4 and CD8. Cells were gated on live lymphocytes, and percentages of CD4+ (Left) and CD8+ (Right) T lymphocytes were determined. (B) CD4+ T cells from A were stained for CD44 and CD62L. Percent of each subtype, T effector memory (T_{EM} CD44^{hi}CD62L^{lo}), T central memory (T_{CM} CD44^{hi}CD62L^{hi}), and T naive (CD44^{lo}CD62L^{hi}), are shown in the graph. (C) Mononuclear cells isolated from brains of mice used in A were stained directly ex vivo for CD4 and CD8. Percentages of infiltrating CD4+ (Left) and CD8+ (Right) T lymphocytes were determined. Representative FACS plots are shown. Statistical significance was determined with \( P < 0.05 \). \( n = 4 \) mice per group.
**Fig. S2.** GCPII activity is equivalent in control and EAE mice. Control and EAE mice have similar levels of hippocampal GCPII activity. Daily administration of 2-PMPA for 15 d decreases the level of GCPII activity compared with vehicle-treated counterparts by ∼68 and 75% in control and EAE mice, respectively. Significant difference is shown from control + vehicle or EAE + vehicle at $P < 0.01 (**). $n = 3$ mice per group.

**Fig. S3.** Effect of 2-PMSA on cognition in EAE mice. Daily administration of 2-PMSA, an inactive analog of 2-PMPA, does not affect Barnes maze performance as indicated by total latency delta (A, day 1 total latency – day 4 total latency) and path efficiency delta (day 1 path efficiency – day 4 path efficiency) compared with vehicle-treated controls. Daily administration of 2-PMSA does not affect fear conditioning performance (B) compared with vehicle-treated controls. $n = 10$ mice per group. Statistical significance was determined with $P < 0.05$. $n = 9–10$ mice per group.
Sample spectra of mouse brain NAAG (A) and 2-PMPA (B). Chromatographic separation for NAAG and NAA in brain tissue homogenates was achieved using Waters Atlantis column and mobile phase delivered isocratically (acetonitrile: 2 mM ammonium acetate; 35:65, vol/vol; containing 0.1% formic acid). NAA, NAAG, and the internal standard were monitored by tandem mass spectrometry in electrospray negative ionization mode. Linear calibration curves were generated over the range of 5–5,000 ng/mL and tissue samples quantified as μg/g. For determination of 2-PMPA, separations were achieved on a Waters XTerra MS C18 column, using MeOH and 2 mM N, N-dimethylhexylamine buffer (50:50, vol/vol at pH 8.5) delivered isocratically. 2-PMPA and the internal standard were monitored by tandem mass spectrometry with electrospray negative ionization mode. Linear calibration curves were generated over the 1–100 ng/mL range and converted to μg/g.