Supplementary Methods

Inhibition studies of TGH using a substrate assay. Inhibition of TGH activity was assayed using COS-7-expressed TGH and the chromogenic substrate, *p*-nitrophenyl laurate at 37°C as described previously (ref. 18). Mock-transfected COS-7 cells expressed negligible hydrolysis activity. IC_{50} values were determined from the inhibition observed at 7 different inhibitor concentrations (three trials each) by using the formula $IC_{50} = [I]/[(\upsilon_0/\upsilon_i)-1]$, where υ_0 is the control reaction rate without inhibitor and υ_i is the rate with inhibitor at concentration [I]. K_i values were determined by the Dixon plot {x-intercepts of weighted linear fits of [I] vs 1/rate plots at a constant substrate concentration ([S] = 100μM), which were converted to K_i values by using the formula $K_i = -x_{int}/[1+[S]/K_m]$}.

Cluster analysis of inhibitor sensitivity profiles. For the comparison of IC_{50} and K_i values for FAAH inhibition (Fig. 3A), the reciprocal IC_{50} (or K_i) value for the most potent inhibitor was normalized to 1 and the reciprocal IC_{50} (or K_i) values of other inhibitors expressed as a fraction of this value. These data were multiplied by 100,000, log-transformed, and, for the purpose of visualization, shifted by -2.5 to create a range of values from –2.5 to 2.5. For the potency cluster analysis (Fig. 3B), reciprocal IC_{50} values (in nM) were divided by 0.00001, log-transformed, and, for the purpose of visualization, shifted by -2.7 to create a range of values from –2.7 to +2.7, with the most potent inhibitor being +2.7 (IC_{50} value = 0.4 nM). For the selectivity cluster analysis (Fig. 3C), the reciprocal IC_{50} value for the most potently inhibited target of each inhibitor was normalized to 1 and the degree of inhibition of the other targets expressed as a fraction of this value. All data were analyzed with a hierarchical clustering algorithm using the Pearson correlation coefficient as the measure of similarity (Gene Cluster computer package; ref. 19).