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Extracellular vesicles (EVs) are constitutively shed from cells and released in response to various stimuli. Their protein and RNA cargo are modified by the stimulus, and in disease conditions EVs can carry pathological cargo involved in disease progression. Neutral sphingomyelinase2 (nSMase2) is a major regulator of at least one of several independent routes of EV biogenesis and its inhibition is a promising new therapeutic approach for neurological disorders. Unfortunately, known nSMase2 inhibitors exhibit µM potency, poor physicochemical properties, and/or limited brain penetration. The purpose of this work has been to identify a drug-like inhibitor of nSMase2. We conducted a human nSMase2 high throughput screening campaign employing over 365,000 compounds. Selected hits were optimized focusing on potency, selectivity, metabolic stability, pharmacokinetics and ability to inhibit EV release in vitro and in vivo. Optimization of one of the selected hits led to the identification of phenyl(R)-(1-(3-(3,4-dimethoxyphenyl)-2,6-dimethylimidazo[1,2-b] pyridazin-8-yl) pyrrolidin-3-yl)-carbamate (PDDC), a potent (IC50 = 0.30 µM) and selective non-competitive inhibitor of nSMase2. PDDC was metabolically stable, with excellent oral bioavailability (%F=88), and brain penetration (AUCbrain/AUCplasma=0.60). PDDC dose-dependently (EC50 = 0.5 µM) inhibited the release of astrocyte-derived-extracellular-vesicles (ADEV). In an in vivo inflammatory brain injury model, PDDC robustly inhibited ADEV release and the associated peripheral immunological response. A closely related inactive structural analog of PDDC showed no effect. In summary, PDDC is a structurally novel, potent, orally available, and brain penetrant inhibitor of nSMase2. PDDC inhibits the release of ADEVs in tissue culture and in vivo. PDDC is actively being tested in animal models of neurological disease and along with closely related analogs, it is being considered for clinical translation.