Numerous loss-of-function mutations in the progranulin (GRN) gene cause frontotemporal lobar degeneration with ubiquitin and TAR-DNA binding protein 43 positive inclusions by reduced production and secretion of GRN. Consistent with the observation that GRN has neurotrophic properties pharmacological stimulation of GRN production is a hopeful approach to rescue GRN haploinsufficiency and prevent disease progression. We therefore searched for compounds capable to selectively increase GRN levels. Here we demonstrate that four independent and highly selective inhibitors of vacuolar ATPase (Bafilomycin A1, concanamycin A, archazolid B and apicularen A) significantly elevate intracellular and secreted GRN. Furthermore, alkalizing reagents including chloroquine, a frequently used anti-malaria drug, similarly stimulate GRN production. Elevation of GRN levels occurs via a translational mechanism independent of lysosomal degradation, autophagocytosis or endocytosis. Importantly, Bafilomycin A1 as well as chloroquine rescue GRN deficiency in organotypic cortical slice cultures of a mouse model for GRN deficiency and in primary cells derived from human patients with GRN loss-of-function mutations. Thus alkalizing reagents, specifically those already used in humans for other applications, and vacuolar ATPase inhibitors may be therapeutically employed to prevent GRN dependent neurodegeneration.