SMALL MOLECULE INHIBITORS OF CALCIUM-ACTIVATED CHLORIDE CHANNELS TO TREAT SECRETORY DIARRHEA

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FULL DESCRIPTION

Diarrhea is a major cause of death worldwide, especially in children below five years of age. Chloride channels, such as the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) and Calcium Activated Chloride Channels (CaCCs) play various roles in different types of diarrheas. CaCCs are thought to mediate diarrhea that occurs as a side-effect of certain therapies (i.e. chemotherapy or antiretroviral therapy) or as a result of viral infection. Small molecule inhibitors of intestinal CaCCs are predicted to be useful for treating some types of secretory diarrhea. However, CaCC inhibitors currently available are non-selective and non-potent for blocking CaCC activity.

DESCRIPTION: Using a high-throughput, phenotype-based screen, UCSF investigators have identified two novel chemical classes (aminothiophenes and aminothiazoles) of small-molecule inhibitors of human intestinal CaCC. Using in vivo and in vitro assays, the investigators determined that these inhibitors are specific and likely to target the CaCC directly to modulate gating. The compounds have been synthesized de novo and their structures verified. Structure-Activity Analysis pinpointed the functional chemical groups responsible for inhibitory activity. The investigators envision these compounds could be developed further for treatment of certain types of secretory diarrhea where CaCCs play a role.

FEATURES/BENEFITS

▶ The inhibitors are specific for CaCC in human intestinal cells and likely directly affect channel gating

APPLICATIONS

▶ These inhibitors represent a novel treatment approach for certain types of diarrhea and could potentially be used in combination with other drugs, such as CFTR inhibitors

REFERENCES

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