Non-Polyamine-Based Polyamine Transport Inhibitors to Treat Cancer and Infectious Diseases

Published date: March 6, 2019

Technology description

Novel PTIs help block escape pathways of cancers treated with polyamine biosynthesis inhibitors like alpha-difluoromethylornithine (DFMO).

Researchers at UCF and Sanford Burnham Prebys Medical Discovery Institute (SBPMDI) have identified novel non-polyamine-based polyamine transport inhibitor (PTI) compounds to treat cancers with high polyamine requirements. Since the compounds are not based on polyamine scaffolds, they can provide multiple therapeutic advantages over traditional polyamine-based transport inhibitors, including the ability to inhibit specific modes of polyamine transport, improve half-life, and limit toxicity and off-target effects, such as binding to biological anions like DNA, RNA and proteoglycans. When used in combination with polyamine biosynthesis inhibitors, they can starve the cancer cells of polyamines, limiting their growth. These new PTI agents may also provide new medicines for treating parasitic infections such as Chagas (by blocking the ability of the parasite to import polyamines) and bacterial infections.

Technical Details

The invention comprises compositions for non-polyamine-based PTIs and methods for administering the PTIs. The small molecules represent a first-in-class design of compounds that inhibit specific modes of polyamine import. UCF and SBPMDI researchers developed two orthogonal screens which monitored changes in cell viability as an indirect measure of polyamine import. The assays were tailored for high throughput screening (HTS) and facilitated the survey of large molecular libraries to identify scaffolds of interest. As a result of these screening efforts, substituted benzoic acid derivatives were found to be active PTI compounds. The synthesis of these new compounds occurs in four synthetic steps from commercially available starting materials. They can be administered alone or in combination with other agents, drugs or hormones. For example, the new PTI compounds can be used in combination with an existing FDA-approved drug, difluoromethylornithine (DFMO), which blocks the import of ornithine decarboxylase (ODC), a polyamine biosynthetic enzyme. The new compound blocks the escape pathway that cancers use to overcome the effects of the DFMO drug. Melanoma, colorectal cancers, breast cancers and pancreatic cancers may be especially sensitive to the DFMO+PTI approach due to their addiction to polyamine growth factors.

Application area

Small molecule anticancer therapies
Anti-infective or antiviral medications
Immuno-oncology therapy

Advantages

Limits off-target effects and toxicity.
Ability to work in combination with a polyamine biosynthetic inhibitor to limit the growth of proliferative cells.

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