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Inhibitors of Cyclic Mononucleotide and Cyclic Dinucleotide Phosphodiesterases

A highly specific and non-toxic inhibitor targeting a bacterial enzyme has been identified for development as a next-generation antibiotic or antivirulence drug.

Purdue University researchers have identified a cyclic dinucleotide phosphodiesterase inhibitor for future development as an agent to combat Mycobacterium tuberculosis (MTB). Bacterial and viral phosphodiesterases contribute to infection by preventing the host from mounting a full immune response. The Purdue researchers employed a high throughput screening assay to identify inhibitors of MTB c-di-AMP phosphodiesterase (CdnP). The researchers selected compounds that displayed greater than 40 percent inhibition in a fluorescence-based assay of MTB CdnP activity. They then identified the most potent of the MTB CdnP inhibitors in enzymatic assays monitored by HPLC and comparative radioisotope thin layer chromatography. The researchers used MTB CdnP intrinsic fluorescence to further confirm that the identified compound binds directly to MTB CdnP. The researchers also confirmed that the inhibitor is specific to MTB CdnP; it did not inhibit any other enzymes in a panel of bacterial, mammalian, and viral phosphodiesterases. The compound further shows promise as an antibiotic because it does not affect mammalian cell viability at concentrations up to 100 micromolar.

Advantages:

-Effective

-Specific

-Nontoxic

Potential Applications:

-Antivirulence drugs

-Antibiotics

Technology ID

2021-SINT-69252

Category

Pharmaceuticals/Pharmaceutical Packaging & Delivery Systems
Pharmaceuticals/Computational Drug Delivery & Nanomedicine
Chemicals & Advanced Materials/Materials Processing & Manufacturing Technologies
Pharmaceuticals/Small Molecule Therapeutics
Pharmaceuticals/Research Tools & Assays

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View online

-Anti-inflammatory drugs

-Cancer immunotherapy

Technology Validation:

The researchers tested over 90,000 compounds for cyclic dinucleotide phosphodiesterase (CdnP) inhibition capability using high-throughput screening (HTS) with the group's Coralyne assay; over 40% of the drugs had inhibitory capability. They then confirmed the inhibitory effects of these compounds using chromatography. The researchers used the HTS and chromatography data to identify the most effective CdnP inhibitor. They were then able to determine the mechanism by which this compounds inhibits CdnP.

Related Publication:

Identification of a Mycobacterium tuberculosis Cyclic Dinucleotide Phosphodiesterase Inhibitor

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