Fluorescent Nucleoside Analogues

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Technology description

Technical Summary

The technology described here comprises fluorescently labeled nucleoside analogs (fNAs) incorporating labeled nucleobases, their generation, and their use in research and drug discovery. With worldwide epidemics of HIV, Hepatitis B and Hepatitis C as well as the continued threat of viral bio-weapons, interest in the research and development of novel antiviral drugs and compounds continues to grow. Currently, the most dominant group of antiviral drugs is the nucleoside analogs (NAs). These drugs function as competitive substrates for viral reverse transcriptase or polymerase enzymes.
In infected cells the nucleoside analog is converted to a nucleotide analog via multiple phosphorylation steps and then incorporated into the replicating DNA. These analogs however only possess a single site for bonding to other nucleotides, essentially forming a dead-end during polynucleotide generation, and stopping viral DNA production without harming mammalian DNA replication. A key step in the activity of NAs as antiviral drugs, involves their sequential phosphorylation into triphosphate nucleosides by multiple kinases including deoxynucleoside kinases (dNKs).
Once phosphorylated by dNKs, these fNAs become sequestered in the cell; a buildup of fluorescent signal within the cell indicates the nucleoside has been phosphorylated. These fNAs thus can be used to identify to screen for NA drug candidates or as a tool for screening for dNKs exhibiting increased nucleoside phosphorylation activity. Beyond drug discovery applications, these nucleosides could also be used as fluorescent probes to image infected or highly proliferating cells, as well as for general research into the cellular uptake and metabolism of nucleosides or nucleoside-protein interactions.

Application area

High-throughput screening of nucleoside analogs and enzymes for drug discovery,in vitroandin vivoinvestigation of cellular uptake and metabolism of nucleosidic drugs, and study of nucleoside analog-protein interaction.

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