Novel diazeniumdiolate-based aspirin prodrugs for cancer treatment

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Technology description

Treating Disease and Pain using Nitroxyl (HNO) Releasing Compounds

Invention:
A compound has been developed for releasing controlled fluxes of HNO in physiological media or conditions. The compound undergoes a slow hydrolysis at physiological pH, such that it generates a correspondingly lower steady-state concentration of HNO, minimizing its dimerization/dehydration to N2O. As a result the compound can provide increased efficacy against pain, cancer, or cardiovascular disease.The invention is the formulation of a diazeniumdiolate, a NO donor prodrug. The invention expands on this drug prototype by covalently attaching non-steroidal anti-inflammatory drugs (NSAIDs), specifically aspirin, to nitrate esters. NSAIDs are used for treatment of pain and inflammation. The ester linkage of a diazeniumdiolate is designed to reduce NSAID toxicity by increasing stability and absorption rate in the gastrointestinal tract. The linkage also allows localized delivery of NO. An advantage of diazeniumdiolates is the ability to manage the amount of NO donation by manipulating the rate of decomposition. The compound is designed to be a well-tolerated agent able to damage DNA and induce cell death of cancer cells with little toxicity in normal cells.

Background
Nitroxyl (HNO) is an elusive chemical species that has been shown to possess intriguing biological properties. For example, nitroxyl has been implicated in the mechanism of cyanamide's inhibitory effect on aldehyde dehydrogenase in treating alcohol abuse as well as reversing experimental heart failure. Despite HNO having been described in the chemical literature for decades, there are surprising gaps in the literature that complicate the rational exploitation of its pharmacological properties.

Application area

Pain
Anti-inflammatory
Cancer

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