Peroxynitrite Generators, Compositions Comprising Same, and Methods for Treating Biological Disorders Using Same

Published date: Feb. 1, 2012

Technology description

Summary

Diazeniumdiolates are a class of compounds which release nitric oxide (NO) under physiological conditions. Nitric oxide performs a number of regulatory functions in vivo such as controlling vascular tone and platelet function, but it can also combine with superoxide ion to produce peroxynitrite ion, an especially reactive species. Peroxynitrite-mediated cellular toxicity may have several therapeutic applications. Because of the relatively low amounts of superoxide ion present in some cells, the peroxynitrite mechanism of diazeniumdiolate toxicity is not uniformly available. In order to generate peroxynitrite ions in tissues or other media lacking adequate levels of superoxide ion, this invention provides a new class of compounds which release NO and superoxide ion simultaneously to generate peroxynitrite ions.
Molecules of this invention can be designed to generate peroxynitrite ion at specific biochemical targets. For one type of targeting, the release of NO is designed to be triggered by nucleophilic attack on the diazeniumdiolate drug while superoxide generation is simultaneously occurring at a quinone moiety elsewhere in the molecule. If the required nucleophilic attack is designed to be specifically catalyzed in the active site of glutathione S-transferase-pi, a cytoprotective enzyme overexpressed by certain tumors to render them drug-resistant, compounds of this invention could restore the susceptibility of tumor cells to chemotherapy by knocking out the excess enzyme, thereby preventing the tumor cells from inactivating the chemotherapeutic agents. Attachment of the compounds to polymeric compositions would physically localize the peroxynitrite activity. Physical localization in vivo may have utility against the recently recognized chronic infections caused by biofilms, and generation of peroxynitrite ions in vitro may have utility against infectious biofilms on medical devices.

Institution

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