

The present invention relates to the administration of a nitroxyl anion donating compound prior to ischemia to attenuate ischemia/reperfusion injury. Accordingly, nitroxyl anion donating compounds such as Angeli's salt would be useful treatment agents to prevent or protect against such adverse conditions especially since the beneficial effect is a surprising result given that nitroxyl anion was previously reported to increase ischemia/reperfusion injury.

Preparation and Medical Uses of Novel Nitric Oxide Releasing Imidates, Amidines Derived Therefrom, and Enamines

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DHHS Reference Nos. E-149-2001
Filed June 13, 2001 and E-276-2002
Filed July 18, 2002.

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Nucleophile/nitric oxide adducts (N_2O_2 -diazoniumdiolates) spontaneously dissociate at physiological pH to release nitric oxide (NO) by stable first order kinetics. The bulk of the known and patented NIH compositions and methods using diazoniumdiolates are derived from amine nucleophiles. The formation of these amine-derived diazoniumdiolates requires exposure of the nucleophile to NO gas with the attendant occurrence of possible unwanted side reactions, or preparation of O_2 alkylated diazoniumdiolates that may release toxic by-products. Also, amine-derived diazoniumdiolates may dissociate into carcinogenic N-nitroso compounds and the primary amines may decompose into unstable diazotates. These inventors thus developed diazoniumdiolates in which the N_2O_2 -functional groups are bonded to carbon atoms. This work has resulted in imidoester-, amidine- and enamine-derived diazoniumdiolates that spontaneously release NO under physiological conditions.

Previous amidine-linked NO releasing compounds were prepared using NO gas after acetamidation of amine groups. This invention provides a simple, robust method of preparing diazoniumdiolated imidates from cyano compounds. As with other imidoesters, these diazoniumdiolated imidoesters react with nucleophiles allowing formation of a wide range of NO releasing derivatives. For example, imidoesters are extensively used as protein crosslinking reagents because they react with primary amines to form amidine bonds. These already diazoniumdiolated and purified imidoesters can thus be

used to directly attach amidine NO-releasing groups onto molecules such as peptides and medicinals without exposing them to NO gas or its potentially toxic by-products. Some of these compounds may also release nitroxyl (HNO , NO) in solution under physiological conditions. *See Arnold et al., Tetrahedron Lett.*, 41, 8421-8424(2000).

Postnatal Stem Cells and Uses Thereof

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DHHS Reference No. E-018-2003/0-PCT-01.

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Many individuals with ongoing and severe dental problems are faced with the prospect of permanent tooth loss. Examples of such dental problems include: dentinal degradation due to chronic dental disease (caries or periodontal); mouth injury; or through surgical removal, such as with tumors associated with the jaw. For many, a technology that offers a possible alternative to artificial dentures by designing and transplanting a set of living teeth fashioned from an individual's own pulp cells would greatly improve their quality of life.

The NIH announces a new technology wherein human postnatal deciduous dental pulp stem cells commonly known as "baby teeth", are used to create dentin and have been shown to differentiate into cells of specialized function such as neural cells, adipocytes, and odontoblasts. It is believed that these cells could be manipulated to repair damaged teeth, induce the regeneration of bone, and treat neural injury or disease.

This research is described, in part, in Miura *et al.*, "SHED: Stem cells from human exfoliated deciduous teeth," *Proc. Natl. Acad. Sci. USA*, vol. 100 (no. 10; May 13, 2003) pp. 5807-5812.

Methanocarba Cycloalkyl Nucleoside Analogues

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Serial No. 10/169,975

Filed July 12, 2002, (and related National Stage patent applications).

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Purines such as adenosine and ATP have been shown to play a wide array of roles in biological systems such as inter alia, modulator of vasodilation and hypotension, muscle relaxant, central depressant, inhibitor of platelet aggregation, regulator of energy supply/demand, responder to oxygen

availability, neurotransmitter and neuromodulator. All P1 and P2 receptor nucleoside ligands suffer from chemical instability that is caused by the labile glycosidic linkage in the sugar moiety of the nucleoside. However, it has been found that relatively few ribose modifications are tolerated by the presently known agonists and antagonists of P1 and P2 receptors.

The NIH announces a new technology wherein a new class of nucleoside and nucleotide analogs has been identified that serve as selective agonists or antagonists for P1 and P2 receptors. The technology relates to a chemical modification of purines and pyrimidines, which provide enhanced therapeutic profile and potentially greater in vivo stability, because of the absence of a glycosidic bond. The P2Y receptor agonists and antagonists could potentially be used in immune modulation, inflammation, cardiovascular diseases, neurodegeneration, diabetes, and cancer. In addition, the A3 receptor agonists and antagonists could be useful in cardioprotection, neuroprotection, and asthma.

This research is described, in part, in *J. Med. Chem.*, 2000, 43:2196-2203 and *J. Med. Chem.*, 2002, 45:208-218.

Orally Active Derivatives of 1,3,5(10)-estratriene

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U.S. Patent 5,554,603

Issued Sep. 10, 1996.

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The utility of estrogenic substances in the practice of medicine is well documented. Estrogens may be used for the replacement of the natural hormone, estradiol, in hypogonadism, and following the removal of the ovaries or cessation of ovarian activity during menopause. They are also widely employed as a component of oral contraceptives. However, the orally active synthetic estrogens are associated with a number of side effects such as enhanced risk of endometrial carcinoma; induction of malignant carcinoma especially in the cervix, breast, vagina and liver; promotion of gallbladder disease, thromboembolic and thrombotic diseases, myocardial infarction, hepatic adenoma, elevated blood pressure, and hypercalcemia; and a worsening of glucose tolerance can occur.

The NIH announces a new family of novel, active estrogens that are esters of estradiol. These esters possess enhanced estrogenic activity following oral administration in the absence of a 17-