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A Brief Introduction to New NIT Nitroxoids

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Abstract: Before 2021, it is estimated that there may be 9.96 million new cancer deaths and new metastasis cases per year globally. It is generally believed that chemotherapy drugs used for anticancer drugs have large toxic side effects, easy to cause tissue resistance, low selectivity, and not significant therapeutic effect. Because of the special stereoscopic structure and lipophilicity of caged compounds, some of their derivatives often have some more biological pharmacological activities, such as antiviral, enhancing cellular immunity, and anti-tumor activity. Researchers have found that a cage compound with good lipophilicity can be used as a structural unit to develop new drugs with good selectivity, high efficiency and low toxicity. NIT nitroxide radicals have excellent antitumor activity. This article reviews the design and synthesis of novel nitroxide compounds by introducing cage structure into NIT nitroxide radicals.

1. Introduction

The World Health Organization's International Agency for Research on Cancer (IARC) has released global population and updated human cancer disease data for the period to 2021.The estimated results cover the actual incidence and mortality of the latest malignancies per year in the average human population, including patients in nearly 185 countries with known cancer and more than 36 common cancer types, as well as projected future trends in the global cancer disease. The latest data reports from the three projected studies on the latest global cancer deaths also show that the global population is expected to receive a total of more than 19.29 million new cases of major cancers worldwide during 2021, including more than 10.06 million deaths in men and 9.23 million deaths in women. The estimated global average of new cancer deaths per year prior to 2021 is also approximately 9.96 million new cancer cases, including approximately 5.53 million deaths in men and 4.43 million in women. [1]

At present, the main means of cancer treatment are: ① surgical resection; ② Radiation therapy; ③ Chemical therapy.Most cancer patients with advanced malignant tumor will highly early cancer cells infiltration, fertile, malignant tumor recurrence and metastasis of multiple systemic three common physiological characteristics, make the above two kinds of surgery and radiation therapy as well as the main auxiliary cure early malignant tumor and clinical treatment in early cancer drug research applications is on the basis of clinical application Into the has certain aspects and the time limit, and the modern study of cancer tumor drug clinical individualized treatment guidelines although has basically can do very good solve the terminal cancer patients with tumor recurrence

and metastasis of multiple systemic symptom and is difficult to achieve comprehensive drug treatment in patients with systemic problems of a practical problem, but at the same time, the current general hospital with chemotherapy the dose of cancer drugs is single and the side effects of anticancer drugs are often large. After repeatedly changing the dose range of chemotherapy or drugs, tumor cells may be likely to reoccur and become resistant to or other chemotherapy or drug substrates, leading to the failure of chemotherapy. To find an anticancer drug with good efficacy, few side effects and anti-drug resistance activity is still the focus of research in this field.

1.1. The overview

Stability of organic nitrogen oxygen free radical with electron spin, and its good biocompatibility and cellular biology half better biodegradability, etc., in many cell life scientific or medical research experiment technology in the process, at first it was widely used as a describs distinguishes the invention of cell membrane structure properties and biological features of spin tracer.

A class of three dimensional polyhedral compounds, such as adamantane, cubotane, testachane, are cage compounds formed by the methylene or methylene group occupying the top corner of the polyhedron. Because of the special structure and stable lipophilicity of caged compounds, the introduction of nitroxide radicals into caged compounds has shown a variety of special pharmacological activities on many clinical grounds, such as antiviral, cellular immunity enhancing and anti-tumor effects.

Cage compounds, such as adamantane, cubotane and tetrapstachane, are a class of three-dimensional polyhedral compounds formed by the presence of a methylene or methylene group occupying the top corner of the polyhedron. Cage compound in cell membrane structure model because it has its particularity of many other important structure form and has its own good and stable biological lipotropy sex, the ring derivatives have been gradually on the basis of the experimental animal and clinical experiments on material has been preliminary studies show it has a variety of biochemical and pharmacological activities, natural in some international frontier in life science research In this review, nitroxyl radicals have been initially proposed as a spin tracer that can elucidate the structural type characteristics and main biological functions of the inner and outer membrane of cells.

In recent years, the research work is further evidence that there are some new nitrogen oxygen free radical single molecule compounds had significant widely and the potential for significant medical biological activity, including enzyme activity to remove free radicals, resisting acute toxicity of oxyhydrogen ischemic brain injury, radiation protection, antitumor, resistance to anoxia acute cardiac ischemia protection and myocardial again whole blood perfusion after anesthesia, myocardial injury Vascular nutrition protection, nerve information conduction and protection, anti-inflammatory antipyretic and analgesic drugs in the treatment of injury, etc. [2-3]

1.2. Pharmacological activity of cage-like compounds

Kaufmann et al., for the first time, used adamantane skeleton as a liphilic group to replace the methyl group existing in the molecular structure of tyrosine kinase and its inhibitor AG957, and obtained a novel adamantane skeleton compound (NSC680410), which can highly selectively and effectively directly inhibit the production of epidermal collagen production factor receptor (EGFR) in tumor cells However, NSC680410 played a significant role as an antitumor drug, and its pharmacological activity was 3 times higher than that of its lead compound AG957, and its bioavailability was also significantly higher than that of AG957. The plasma clearance rate was decreased, and the toxic side effects were reduced.

Hilgeroth's group recently reported in an in vitro pharmacological study of 3, 9-

methyldiazotestanol, and found that the active compound also reduced the expression of P-glycoprotein receptor (P-gp) protein on the cell membrane surface of mice, and reversed the multi-enzyme drug cross-resistance of cell tumor drugs, 50 with the activity of Verapamil Times.

1.3. Design novel caged alkane nitrogen oxides

Nitroxide is a stable free radical with unique antioxidant properties discovered in recent years, which can promote the metabolism of a variety of reactive oxygen species and has therapeutic effects on a variety of diseases [4-5]. NIT nitroxide radicals exhibit excellent anti-tumor activity, and their molecules contain not only nitroxide radicals that can resist oxidative damage, but also nitroxide dipoles that can release nitric oxide.NO can inhibit tumor cells through two ways: on the one hand, it can inhibit mitochondrial respiration by binding with cytochrome C oxidase and enhance the sensitivity of tumor cells to drugs; On the other hand, NO can bind to oxygen free radicals and directly act on DNA to cause tumor cell death [6]. Both NIT nitroxide radicals have good inhibitory effects on the proliferation of tumor cells. L-NNP and NIT16 have obvious anti-hepatocellular carcinoma activity in vitro and in vivo. The results showed that NIT free radicals had anti-hepatocellular carcinoma activity and could be used as anti-hepatocellular carcinoma pharmacophore. Therefore, the structural modification of NIT nitroxide radicals and the mechanism of anti-hepatocellular carcinoma need to be further studied.

1.4. Advantages of new caged alkane nitrogen oxides

In the process of human life activities, a large number of ROS can be produced by the mitochondria, most of which are oxygen free radicals, such as $O_2^{\cdot-}$ and $^{\cdot}OH$. Excess ROS can lead to changes in cell structure and destruction of function, stimulate the production and growth of cancer cells, and cancer cells can produce ROS.

The growth and proliferation of cancer cells can be inhibited by inhibiting the level of reactive oxygen free radicals in cancer cells. Therefore, through the in-depth study of nitroxide radicals, it is possible to find innovative anticancer drugs that are completely different from the existing anticancer drugs. Fan et al. first studied the protective effect of NIT nitroxide free radical 4' -hydroxy-2-phenyl nitroxide free radical (HPN) on mice with acute altitude hypoxia.

The results showed that HPN could significantly prolong the survival time of mice in atmospheric pressure closed hypoxia model, and was significantly better than acetazolamide positive drug. At the same time, HPN could reduce the contents of H2O2 and malondialdehyde in the heart and brain tissue of mice in low pressure hypoxia model, and maintain the activities of superoxide dismutase, glutathione peroxidase and hydroperoxide. Therefore, HPN is an effective free-base scavenger and a potential protective agent for acute mountain sickness. The chemical definition of free radicals refers to the 1435 chemical reagents with unpaired electrons December 2020, atoms, radicals, ions and groups. In the process of normal life activities of human body, the metabolism of cells (such as intracellular mitochondria, endoplasmic reticulum, nucleus, plasma membrane and cell fluid, etc.) can produce a variety of free radicals. Under normal conditions, the production and elimination of free radicals are in a dynamic equilibrium.

For example, coenzyme Q10 is an important antioxidant and free radical scavenger that is indispensable for human body to maintain normal physiological function. It is an important component involved in electron transport in mitochondrial inner membrane respiratory chain and plays an important role in reducing free radical damage, improving myocardial fine cells and preventing cardiovascular diseases.

However, when the body injury and inflammation, damage to, or affected by external factors such as radiation cause human body free radical balance is destroyed, the excess of highly reactive

free radicals randomly with the body, such as protein, enzyme, lipid and nucleic acid molecules, gain the latter's electronic and oxidative damage of injury and cause catastrophic results - damage chromosomes, the enzyme residual disease, Damage to the structure and function of cell membranes, thereby triggering the generation of diseases .

Because stable nitroxyl radicals can continuously decompose reactive oxygen species such as O ·-2 in a "catalytic" way, the rate constant of the catalytic reaction is as high as 108 M-1 s-1, which is incomparable to stoichiometric free radical scavenger. Therefore, stable nitrogen-oxygen free radical compounds have become the focus of research in the field of organic synthesis and bioactivity in recent years. Although some potential innovative drugs have been discovered in the fields of anti-tumor and anti-radiation, there is still a lack of drugs that can be applied in clinical practice. With the development of nitrogen-oxygen free radical compounds

2. Summary and prospect

Cage compounds are a class of compounds with special spatial structure and good lipophilicity, and their derivatives show a variety of pharmacological activities in clinical practice. The innovative synthesis of cage compounds can provide theoretical basis and basis for their potential pharmacological studies. A large number of studies have shown that the introduction of cage compounds into antitumor compounds can effectively improve the affinity of the compounds with the active pocket around the recognition region of the receptor surface, and enhance the antitumor activity of the compounds.

The NIT nitroxoid free radical is a stable free radical against oxidative damage. It has been found that it has radiation resistance, ganglion protection and myocardial protection. NIT nitroxoid radicals showed significant anti-hepatocellular carcinoma activity in vitro and in vivo. It is a future research direction to design and synthesize a series of novel caged alkane nitrogen oxides by introducing caged structures into NIT nitroxoids with anti-hepatocellular carcinoma activity by means of combination, local modification or bioelectron arrangement. The mechanism and structure-activity relationship of active compounds against hepatocellular carcinoma are discussed.

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