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Brief description of the synthesis of new nitrogen oxides

Yingjie Hou[1], Ping Li[1], Jianing Li[2]

[1]Pharmacy, North China University of Science and Technology, Tangshan, China
[2]Pharmaceutical Preparation, North China University of Science and Technology, Tangshan, China

Abstract: *Cancer is one of the major diseases that endanger human life and health. Common anticancer drugs have high side effects and are prone to drug resistance, leading to treatment failure. Due to their special structures and lipophilicity, cage compounds have more pharmacological activities in their derivatives, such as antiviral, immune enhancing, and antitumor activities. Scientists have used cage compounds with good lipophilicity as structural units to develop new drugs with good selectivity, high efficiency and low toxicity. nIT-like nitroxide radicals have excellent antitumor activity, and this paper reviews the investigation of introducing cage structures into NIT-like nitroxide radicals to design and synthesize novel nitrogen oxides.*

Keywords: *cancer, caged compounds, nitrogen-oxygen radicals, novel nitrogen oxides*

1. Introduction

Cancer is a fatal disease with abnormal cell proliferation and metastasis, with an estimated 26 million new cancer cases and 17 million deaths per year worldwide by 2030, and the distribution and dominant types of cancer are constantly changing globally, especially in developing countries[1]. At present, the most important means to treat cancer are: (1) surgical resection; (2) radiation therapy; (3) chemical drug therapy. Cancer mostly has the characteristics of infiltration and metastasis, make the first two treatments in clinical application, and chemical therapy can solve the problem of tumor metastasis is difficult to treat, but the general anticancer drug side effects are bigger, after repeated medication, tumor cells easy to resistance to chemotherapy drugs, lead to the failure of chemotherapy [2]. Finding an anticancer drug with good efficacy, small side effects and anti-resistance activity is still the research focus in this field.

2. Overview

Caged compounds are a class of three-dimensional polyhedral structural compounds formed by the top angle of polyhedra, such as adamantane, cube, four ane, etc. The tension energy of a series of cage compounds was calculated by designing reasonable equal-bond reactions, and the influence of different substituents on the tension of cage compounds was studied. For compounds with the same cage structure and different substituents, the electron-absorbing groups connected to nitrogen atoms on the ring would increase the molecular tension, while the electron-supplying groups would reduce the molecular tension. Density functional theory was used to study the dissociation energy of each potentially broken bond in cage compounds. It was found that in addition to the C(N)-NO2 bond, the C-C or C-N bond on the cage skeleton may also be pyrolytically triggered bonds, and the cage compounds have high thermal stability.

The carbon skeleton structure of adamantane can be regarded as the cell in the diamond lattice network. Adamantane is a kind of circular tetrahedral alkane containing 10 carbon atoms and 16 hydrogen atoms. Its basic structure is a chair shaped cyclohexane, which is a highly symmetrical and extremely stable compound, mainly used in the synthesis of anti-cancer, anti-tumor and other special drugs. The hydrogens on the bridgehead carbons (i.e., 1,3,5,7) of amantadane are prone to substitution reactions, so derivatives of amantadane can be developed for drugs, such as 1-amino-amantadane hydrochloride and 1-amantadine ethylamine hydrochloride, to prevent influenza caused by A2 viruses.

Cuboxane is considered to be a bioelectronic isoform of benzene ring and is often used in drug development. The length of cuboxane vertex line is 2.72, which is close to the diagonal length of benzene ring (2.79). Compared with benzene ring, cuboxane has the advantage of higher biological stability without intrinsic toxicity; Substituents can be introduced into its eight vertices to improve the diversity

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of the three-dimensional structure of the molecule. In addition to the above advantages, cuboane also has a high degree of stability to light, air and humidity, its melting point is 130-131°C, its non-planar structure can increase the solubility of drugs, and the stable sp3 hybrid C-H bond cuboane can make drugs have better stability in metabolism. These properties make cuboxane stable in combination with most reagents, allowing it to maintain its intact structure during synthesis. Today, the synthesis of cuboxanes is well established, and the frequency of cuboxanes is increasing in the development of new active molecules. Cuboxane has been used in active molecules such as morphine derivatives and histone deacetylase (HDAC) inhibitors.

In recent years, scientists have used cage compounds with good lipophilicity as building blocks to develop new drugs with good selectivity, high efficiency and low toxicity. For example, cuboxane has a similar size and shape to the benzene ring and can be used as its bioelectron isoplaten. Substituting the benzene ring with cuboxane in some drug structures showed the same or higher pharmacological activity. This is because the non-planar structure of cuboxane makes it have increased solubility and stable C-H bond gives it better stability advantage in metabolism. These advantages make cuboxane appear more frequently in the field of drug development.

Due to their structural specificity and good lipophilicity, cage compounds' derivatives exhibit multiple pharmacological activities clinically, such as antiviral [3] Enhance immunity [4] and anti-tumor[5]. In recent years, scientists have used caged compounds with good lipophilic properties as structural units for the development of new drugs with good selectivity, high efficiency and low toxicity.

3. Pharmacological activity studies on the structure of cage-like compounds

Kaufmann Group[6]The adamantane skeleton as a lipophilic group, replace the methyl in the tyrosine kinase inhibitor AG 957, the adamantane compounds (NSC680410) can selectively inhibit cell epidermal ogenesis factor receptor (EGFR), thus play an anti-tumor effect, its activity than the lead compound AG 9573 times, bioavailability than AG 957 also has significantly improved, plasma clearance, side effects[7]. The structure-activity relationship study shows that adamantane can better meet the spatial geometry requirements of drug binding and EGFR receptors, enhance the hydrophobic interaction and the affinity for the receptor; and the good lipophility of adamantane makes the compounds more likely to pass through the cell membrane and improve the kinetic properties of drug metabolism[8]。

Hilgeroth's group found in the pharmacological activity of 3, 9-diazatestrane that this compound can reduce the expression of cell membrane P-glycoprotein (P-gp) and reverse multidrug resistance in tumors, and its activity is 50 times that of Verapamil.

In addition, the multi-substituted cubic alkyl chloride can react with more than 20 amino acids in the body to produce thousands of new molecules, providing a suitable environment to react with the ADIS virus or cancer cells. Moreover, drugs containing polyhedral alkane molecules are fat-soluble and do not degrade easily in the human body, so they are more durable and reactive than long-chain hydrocarbon molecules (such as peptide-based molecules). The significance of the cuboxane substitution lies in its ability to increase the lipophilicity of other molecules, thus allowing them to pass through cell membranes more easily. What's more, none of the substitutions have been reported to damage healthy cells, meaning that at least some of them are drug-free.

In the study of effective inhibitors of HIV, it has been found that butyl urea can effectively inhibit the activity of HIV-1 in the cell and in the cell, alkyl urea can destroy the two liquid layers of the virus, and cuboane molecules are lipophilic and can be connected to the surface of the virus. These two substances can be successively used or connected together to achieve the synergistic destruction of the virus surface. And the researchers think that by binding cuboxane to monoclonal antibodies and delivering them to pathogens or cancer cells in the human body, the high energy released from cuboxane could destroy these viruses or cancer cells. Therefore, cuboxane derivatives have great potential as therapeutic agents due to their unique structure.

4. Design of new caged alkane NOx

In the study of [2+2] ring reaction, it was found for the first time that when asymmetric 1, 4-dihydropyridine compounds were used as substrates for photoreaction, they could selectively generate cage compounds with different skeleton according to different photoreaction conditions. Compared with traditional tetracarbane, these cage compounds had fewer substituent groups and unique skeleton types.

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It can provide a new choice for the research of antitumor drugs.

Nitrogen and oxygen free radical is a stable free radical with unique antioxidant properties, which can promote the metabolism of various reactive oxygen species and has curative effect on a variety of diseases[9-10], Especially the excellent antitumor activity exhibited by NIT nitrogen-oxygen radicals[11-12]. NIT nitrogen free radicals are a new type of free radical scavenger, whose molecules contain not only nitrogen free radicals against oxidative damage, but also nitrogen and oxygen dipole that can release nitric oxide. Nitric oxide can play the role of inhibiting tumor cells in two ways: on the one hand, NO suppresses mitochondrial respiration by binding with cytochrome C oxidase and enhances the sensitivity of tumor cells to drugs; on the other hand, NO can bind to oxygen free radicals and directly act on DNA, causing tumor cell death[13]. Nits have good inhibitory effects on the proliferation of a variety of tumor cells, especially compounds L-NNP and NIT16, which have particularly obvious efficacy against liver cancer in vitro and in vivo. The results show that NOx radicals have anti-HCC activity and can serve as an anti-HCC pharmacophore. Therefore, the structural modification of nitrogen and oxygen radicals of NIT and the mechanism of action against liver cancer need to be further investigated.

Six series of cage alkane nitrogen oxides were synthesized according to the bioelectron isoarrangement by means of splice, local modification or bioelectron isoarrangement. The novel cage structure with potential antitumor activity was introduced into the NIT-like oxyazide radical, and cubic alkane was used as the skeleton structure to design and synthesize NIT series derivatives. The effects of bridge chain length, spatial volume of different substituents (methoxy, halogen, ester group, etc.) at the four sites, electrical properties, hydrophilic lipophilic properties and so on on anti-tumor activity were investigated. Using 1, 4-dicarboxylic acid cuboane as the skeleton, the antitumor activity difference between diazoxylic radical and mono-azoxylic radical was investigated by introducing nitrogen oxide radical into both carboxylic acid. 3, 9-diazatestrane can reduce the expression of cell membrane P-glycoprotein (P-gp), reverse multidrug resistance, and produce strong antagonism against EGFR receptor. A series of 3, 9-diazotetraxane nitrogen oxides can be designed and synthesized by using azotetraxane as framework and introducing azooxide free radical pharmacophore (NIT). 3, 6-diazatetrane is a novel cage skeleton structure discovered for the first time. Due to its structural similarity with 3, 9-diazatetrane, a series of 3, 6-diazatetrane nitrogen oxides can be designed and synthesized by introducing nitrogen oxide free radical pharmacophore (NIT) to its skeleton.

Asymmetric azatetrachrocuboxane, diazatetrachrododecadiene, and ditetrachrododecane are novel cage compounds discovered for the first time. Using this structure as the framework, a series of azatetrachrocuboxane nitrogen oxides, diazatetrachrododecadiene nitrogen oxides, and ditetrachrododecadodecane nitrogen oxides can be designed and synthesized by introducing nitrous oxide free radical pharmacophore (NIT). The effect of the position, electricity, hydrophilic and lipophilic properties on the activity of benzene ring was further investigated.

In the preparation of canales, the synthesis of new canales is the key step of the whole route. How to synthesize the canales with smaller steric hindrance and fewer substituents, it is proposed to remove benzyl groups in the canales by palladium-catalyzed hydrogen reduction method, so as to reduce the volume of the canales.

In conclusion, the cage compound structure is introduced into the antitumor compound by means of combination, local modification or bioelectronic arrangement: on the one hand, the hydrophobic interaction between the compound and the active pocket around the surface recognition area of the receptor can be enhanced to improve the affinity for the receptor; on the other hand, the good lipophilicity of the cage compound makes the compound easier to pass through the cell membrane, thus exerting stronger antitumor activity.

5. Summary and Outlook

Caged compounds, are a class of compounds with special spatial structure and good lipophilicity, whose derivatives exhibit diverse pharmacological activities in clinical practice. Innovative synthesis of novel caged compounds can provide a theoretical basis and basis for their potential pharmacological research. A large number of existing research data show that the introduction of cage compounds into anti-tumor compounds can effectively improve the affinity of the compounds to the active pocket around the surface recognition area of the receptor, and enhance the anti-tumor activity of the compounds[14]. The NIT nitrogen radical is a stable free radical against oxidative damage and is found to be radito radiation[15], ganglion protection[16]And myocardial protection[17]And so on. In particular, it was found that NIT nitrogen and oxygen radicals showed significant antiHCC activity in in vitro and in vivo

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experiments[18].

The cage compound is regarded as a stereoscopic hydrophobic skeleton, which can improve the interaction with the receptor surface. Nitrogen oxide free radical has anti-liver cancer activity and can be used as anti-liver cancer pharmacophore. The future research direction is to introduce the cage structure into the anti-liver cancer activity by means of combination, local modification or bioelectron emission, design and synthesize a series of new caged ane nitrogen oxides, and explore the anti-action mechanism of anti-liver cancer and structure-activity relationship of active compounds.

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