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Anticancer Mechanism of Novel Metal Drugs with Different Metal Centers

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ABSTRACT

This study aims to explore new metal drugs with different metal center-[Pt (4'-(2-quin)-terpy) Cl] (SO3CF3), [Au' (4-(2-quin)-terpy) Cl] 2 • CH3CN (PF6), [Cu (4'-(2-quin)-terpy) Cl] (PF6) in anticancer therapy and its mechanism of action. The three metal complexes were synthesized by chemical synthesis, and their structures were identified by means of NMR, mass spectrometry and single crystal X-ray diffraction. In vitro anticancer activity evaluation showed that these metal drugs showed different degrees of inhibitory effects on selected cancer cell lines, and the anticancer activity of [Pt (4'-(2-quin)-Terpy)Cl] (SO3CF3) was the most significant. Further mechanism studies revealed that these metal drugs exert anti-cancer effects mainly through the interaction with DNA and inducing apoptosis of cancer cells. In addition, this study evaluated the toxicity of these drugs to normal cells, providing important safety information for their subsequent clinical use. The research in this paper not only enriches the understanding of anticancer mechanism of metal drugs, but also provides a valuable reference for the development of new, efficient and low-toxicity metal anticancer drugs.

KEYWORDS

[Pt (4-(2-quin)-terpy) Cl] (SO3CF3); [Au' (4-(2-quin)-terpy) Cl] 2 • CH3CN (PF6); [Cu (4'-(2-quin)-terpy) Cl] [PF6); Metal drug; Anticancer mechanism

1. INTRODUCTION

1.1. Research Background

The application of metal drugs in the field of anticancer has a long history. Since the discovery of platinum drugs, its wide application in clinic marks a milestone in the treatment of cancer by metal compounds [1]. However, the toxic side effects and drug resistance of platinum drugs have inspired in-depth research on new metal drugs, especially those containing platinum, gold, copper and other metal centers, to seek safer and more effective anti-cancer treatment schemes.

1.2. Aims at Research

The purpose of this study is to deeply explore the anticancer effect and the mechanism of action of new metal drugs with different metal centers such as platinum, gold and copper, hoping to reveal the principle of their action on cancer cells through the study of these metal drugs with potential clinical application value, and provide theoretical and experimental basis for the design and development of the next generation of anticancer drugs.

1.3. Research Significance

The research of new metal drugs is of great significance for expanding the means of anticancer treatment. Through their unique mechanisms of action, such as interacting with DNA and affecting cell signaling, these drugs provide the possibility to overcome the resistance of traditional platinum drugs and reduce the toxic side effects [2]. Therefore, the in-depth study of these metal drugs can not only promote the enrichment and perfection of the anti-cancer drug library, but also provide new ideas and strategies for the realization of individualized and precise cancer treatment.

1.4. Research Content

The research content of this paper mainly includes the following aspects: firstly, the chemical synthesis of new metal drugs, secondly, the structure identification of drugs through various analysis techniques, and then the in vitro anti-cancer activity test, and finally the anti-cancer mechanism is deeply discussed. The purpose of this research is to comprehensively evaluate the anticancer potential of new metal drugs and its principle of action, and lay the foundation for its clinical application.

1.5. Research Ideas

This research adopts the systematic research idea, starting from the drug molecular design, through the precise chemical synthesis process, the preparation of new metal drugs. Then, the correctness of the synthesized compound was ensured by structural analysis, and its inhibitory effect on cancer cells was evaluated by in vitro experiments. Finally, the anticancer action principle of the drug was elucidated through mechanism discussion, forming a complete research chain from molecular design to functional verification.

1.6. Research Methods

In order to achieve the goal of this paper, this research adopts a variety of research methods. In terms of chemical synthesis, the target metal drug is synthesized by selecting the appropriate precursor and reaction conditions. Nuclear magnetic resonance (NMR), mass spectrometry (MS) and X-ray single crystal diffraction are used to identify the structure of the drug. Biological methods such as MTT and CCK-8 were used to test the anticancer activity in vitro [3]. Finally, the mechanism of action of the drug was discussed through a variety of biochemical experiments to ensure the accuracy and scientific results of the study.

1.7. Paper Structure and Framework

This paper is divided into seven chapters, the first chapter is the introduction, introducing the research background, purpose, significance, content, ideas, methods and paper structure. The second chapter is a literature review, sorting out the research progress in related fields. The third chapter describes the experimental materials and methods. The fourth chapter reports the results of synthesis and structure identification. In chapter 5, evaluation of anticancer activity in vitro is presented. Chapter 6 discusses the anticancer mechanism. Chapter 7 summarizes the research conclusions and puts forward the direction of future research.

1.8. Innovation of the Thesis

The innovation of this research lies in the introduction of new metal drugs with different metal centers, and the systematic study of their anticancer properties and mechanisms. In particular, the anticancer mechanism of gold-based drugs such as [Au(4′-(2-quin) -Terpy)Cl] (PF6)2 CH3CN was deeply explored, which filled the research gap in this field. At the same time, a variety of modern analytical

techniques and biological methods were used in this study to provide a new theoretical basis for the mechanism of metal-based drugs.

2. LITERATURE REVIEW

2.1. Development of Metal Drugs

The development of metal drugs can be traced back to 1965, when Barnett Rosenberg discovered that electric currents can inhibit bacterial growth, and thus discovered the anti-cancer activity of cisplatin. Since then, platinum drugs have become the mainstay of chemotherapy, but problems with toxicity and drug resistance have spurred research into drugs for other metals such as gold and copper [4]. These new metal drugs show a variety of anti-cancer mechanisms and lower toxic side effects, opening up a new way for cancer treatment.

2.2. Research Progress of New Metal Drugs

In recent years, remarkable progress has been made in the research of novel metal drugs, especially gold and copper-based drugs, which have attracted attention due to their unique anti-cancer mechanisms. These drugs exhibit anticancer activity by binding to DNA, affecting signaling pathways, and inducing cell apoptosis in a variety of ways [5]. For example, certain gold-based drugs have been shown to be able to inhibit enzyme activity, while copper-based drugs have been found to kill cancer cells by affecting their internal REDOX state. These findings not only enrich the variety of metal drugs, but also provide new strategies for cancer treatment [6].

2.3. Metal Drug Mechanism of Action

The anti-cancer mechanism of metal drugs mainly includes forming cross-linking with DNA, affecting protein function and inducing apoptosis. Platinum drugs can inhibit the proliferation of cancer cells by cross-linking with DNA intracellular, blocking the replication and transcription of DNA. While gold, copper and other non-platinum drugs work through different mechanisms, such as gold drugs may inhibit the activity of specific enzymes, copper drugs may induce oxidative stress by producing reactive oxygen species (ROS), leading to cancer cell death [7]. The diversity of these mechanisms provides a vast scope for the development of metal drugs.

3. EXPERIMENTAL MATERIALS AND METHODS

3.1. Methods of Drug Synthesis

Ligand exchange reaction is used for drug synthesis. Ligand 4′-(2-quin)-terpy is first synthesized and then reacted with corresponding metal salts [PtCl2], [AuCl3] and [CuCl2] in appropriate solvent. The reaction conditions include temperature control from room temperature to reflux, and the time is adjusted according to the progress of the reaction. After the reaction is completed, the product is purified by evaporating solvent, recrystallization and other steps, and the target metal drug is finally obtained. During the whole synthesis process, attention is paid to controlling the reaction conditions and purification steps to ensure the purity and yield of the product.

3.2. Structural Identification of Drugs

Nuclear magnetic resonance (NMR), mass spectrometry (MS) and single crystal X-ray diffraction were used to identify the structure of drugs. NMR is used to determine the skeleton structure and functional group environment of drug molecules, MS provides verification of molecular mass and molecular formula, and X-ray single crystal diffraction is used to accurately determine the three-

dimensional structure of the molecule and the coordination environment of the metal center. The integrated application of these techniques ensures a comprehensive and accurate identification of the structure of new synthetic drugs.

3.3. In Vitro Anticancer Activity Test

In vitro anticancer activity test mainly used MTT and CCK-8 two methods. First, different concentrations of metal drugs are co-cultured with specific cancer cell lines for a certain period of time, and then MTT or CCK-8 reagents are added to evaluate the anticancer effect of the drugs by measuring the changes in cell activity. These methods are based on the principle that living cells can restore MTT or CCK-8 to produce color change, and reflect the survival rate of cells by measuring absorbance, thus assessing the inhibitory effect of drugs[8]. In addition, the drug-induced apoptosis of cells will be further analyzed by techniques such as flow cytometry.

4. DRUG SYNTHESIS AND STRUCTURE IDENTIFICATION

4.1. Results of Drug Synthesis

Through a carefully designed synthesis route, The successful synthesis of [Pt (4′-(2-quin)-terpy) Cl] (SO3CF3), [Au′(4-(2-quin)-terpy) Cl] (PF6) 2 ·CH3CN and [Cu (4′-(2-quin)-terpy) Cl] (PF6) three kind of new metal drugs. In the synthesis process, the reaction conditions of each step were optimized to improve the yield and purity. In the end, high purity target products were obtained through steps such as recrystallization and washing, with yields of 78%, 85% and 82%, respectively. These results show that the synthesis strategy used is effective and reliable, which lays a solid foundation for the subsequent structural identification and activity evaluation.

4.2. Results of Structural Identification

The results of structural identification show that the spectra obtained by nuclear magnetic resonance (NMR) agree with the expected structure, the mass of the molecule is confirmed by mass spectrometry (MS), and the precise three-dimensional structure of the molecule is revealed by X-ray single crystal diffraction analysis. In particular, the coordination environment of the metal center and the spatial orientation of the ligands were clearly resolved. These structural information verified the structural integrity of the synthetic drug and provided the necessary structural basis for further activity testing and mechanism study.

4.3. Physicochemical Properties of Drugs

The results of physicochemical properties of the drug show that the synthesized metal drug has good solubility and chemical stability under physiological pH conditions. Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) tests showed that the drug had appropriate thermal stability and could withstand conventional storage and handling conditions. The results of ultraviolet-visible spectroscopy (UV-Vis) analysis showed that the drug was stable under light and did not degrade significantly, which provided the possibility for further in vivo and in vitro studies. The evaluation of these physicochemical properties laid the foundation for subsequent biological activity testing and pharmacokinetic studies of the drug.

5. IN VITRO ANTICANCER ACTIVITY EVALUATION

5.1. Test Method of Anticancer Activity

In order to evaluate the anticancer activity of new metal drugs, two classical methods of MTT and CCK-8 were used in this study. These methods are based on the detection of cell metabolic activity, and indirectly reflect the survival rate of cells by measuring the reduction capacity of cells to MTT and CCK-8 [9]. In the experiment, different concentrations of metal drugs were co-cultured with multiple cancer cell lines respectively, and compared with the corresponding blank control group and positive drug control group, so as to accurately evaluate the anticancer potential of the drugs. In addition, flow cytometry was used to analyze the effects of the drugs on the cell cycle and their ability to induce apoptosis.

5.2. Results of Anticancer Activity

The results of in vitro anticancer activity test showed that the new metal drug showed obvious inhibitory effect on a variety of cancer cell lines. Among them, [Pt (4′-(2-quin)-Terpy) Cl] (SO3CF3) had the most significant inhibitory effect on human breast cancer cell line (MCF-7), and its semi-inhibitory concentration (IC50) was much lower than that of cisplatin. [Au (4′-(2-quin)-Terpy) Cl] (PF6) 2 ĊH3CN and [Cu (4′-(2-quin)-Terpy) Cl] (PF6) also showed good activity, especially against human hepatoma cell line (HepG2). These results suggest that highly effective anticancer drugs with selectivity for specific cancer cell lines can be obtained by adjusting the metal center.

5.3. Evaluation of Drug Toxicity

The drug toxicity evaluation was conducted using normal human fibroblasts (WI-38) and human hepatocytes (LO2), and the results showed that the novel metal drug was less toxic to these normal cells. By comparing the selectivity index (SI) of the drug against cancer cells and normal cells, it was found that [Pt (4′-(2-quin)-Terpy) Cl] (SO3CF3) and [Au (4′-(2-quin)-Terpy) Cl] (PF6) 2 CH3CN had high selectivity. While the SI value of [Cu (4′-(2-quin)-Terpy) Cl] (PF6) was relatively low, but still within the acceptable range. These data suggest that novel metal drugs have potential as anticancer treatment options with a low risk of toxicity and are suitable for further pharmacological and clinical studies.

6. DISCUSSES THE ANTICANCER MECHANISM

6.1. The Interaction between Drugs and DNA

The interaction between novel metal drugs and DNA was investigated by electrophoretic mobility experiment and fluorescence competition experiment. The results showed that all three metal drugs could bind DNA closely, and [Pt (4′-(2-quin)-Terpy) Cl] (SO3CF3) showed the strongest DNA-binding ability. Further circular dichroic spectroscopy (CD) analysis revealed that this binding resulted in changes in the secondary structure of DNA. These findings suggest that the drug's interaction with DNA may be one of the important mechanisms of its anticancer activity, inhibiting the proliferation of cancer cells by interfering with the normal function of DNA.

6.2. Drug-Induced Apoptosis

The results of apoptosis detection showed that the new metal drugs could significantly increase the proportion of early and late apoptosis of cancer cells. In particular, [Au (4′-(2-quin)-Terpy) Cl] (PF6) 2 ĊH3CN showed the most significant apoptosis-inducing effect in human breast cancer cell line (MCF-7). Flow cytometry analysis further confirmed the phenomenon of drug-induced apoptosis,

and Western blot analysis showed that the expression of apoptosis-related proteins such as caspase-3 and PARP was changed after drug treatment. These results revealed the potential mechanism of drug-induced apoptosis of cancer cells, and provided important clues for further understanding of its anticancer effects.

6.3. Other Anticancer Mechanisms

In addition to interacting with DNA and inducing apoptosis, this study also found that novel metal drugs may play an anticancer role through other mechanisms. Experiments have shown that [Cu (4′-(2-quin)-Terpy) Cl] (PF6) is able to significantly inhibit a variety of key signaling pathways within cancer cells, such as the PI3K/Akt and MAPK pathways, which play a key role in cell growth and survival. In addition, these drugs were able to activate oxidative stress pathways and increase the level of reactive oxygen species (ROS) within cells, thus leading to the death of cancer cells. These findings provide a more comprehensive understanding of the anti-cancer effects of metal drugs.

7. CONCLUSION AND PROSPECT

7.1. Research Conclusion

In this study, new metal drugs with different metal centers were synthesized successfully, and their molecular structures were confirmed by structural identification. In vitro anticancer activity evaluation showed that these drugs have significant inhibitory effect on specific cancer cell lines, especially [Pt (4′-(2-quin)-Terpy) Cl] (SO3CF3) showed excellent activity. The mechanism studies showed that the main anticancer mechanisms of these drugs were the binding of DNA, the induction of apoptosis and the influence of key signaling pathways. These findings not only provide important information for the research and development of novel metal drugs, but also have guiding significance for the design and mechanism research of future anticancer drugs.

7.2. Research Deficiencies and Limitations

Although this study has made some achievements, there are still some deficiencies and limitations. First of all, the research mainly focuses on in vitro experiments and lacks the evaluation of anticancer activity and pharmacokinetics in vivo, which limits the understanding of the overall mechanism of action of drugs. Second, although several possible anticancer mechanisms have been explored, the detailed mechanisms of action of signaling pathways and molecular targets for drug effects have not been fully defined. In addition, the long-term toxic effects of the drugs on normal cells have not been studied in depth. These limitations suggest that these areas need to be explored in greater depth in future studies.

7.3. Future Research Direction

Future research will focus on addressing the limitations of existing research and further exploring new areas. First, in vivo experiments are planned to evaluate the anticancer effects and pharmacokinetic properties of the novel metal drugs. Secondly, the molecular mechanism of action of the drug will be studied in depth, especially the signaling pathways and molecular targets targeted by the drug will be discussed in more detail. In addition, the long-term effects of the drugs on normal cells will also be evaluated to ensure the safety of the drugs. Through these studies, it is hoped to provide a solid foundation for the development of safe and effective new anticancer drugs.

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