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REVIEW ARTICLE

Phosphoroorganic Metal Complexes in Therapeutics

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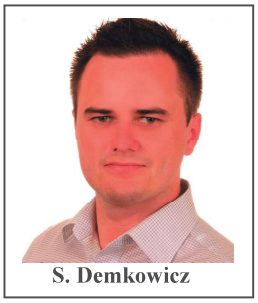
Abstract: The present mini-review highlights recent developments on antitumor activity of metal-based therapeutics which have been a subject of researches for the last few decades. In 1965, Rosenberg found that during an electrolysis on platinum electrodes a complex of Pt is generated which inhibited to a great extent a binary fission in *Escherichia coli* bacteria. This discovery started a new chapter in medicinal chemistry and the interesting properties of cisplatin were soon applied in cancer therapy especially in curing genitourinary tumors. However, various side effects limited its use in medical treatment. Since then a great number of other metal-organic complexes based on platinum, palladium, ruthenium, gold, copper, silver, rhodium, osmium, rhenium, iridium and others have been synthesized. Among them, NAMI-A and KP1019 have recently undergone clinical trials. In this review paper we report a detailed account of metal complexes with phosphorus-based ligands which are of particular interest in therapeutics.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1. INTRODUCTION

Research about the applications of metal complexes in medicine is one of the most integrated areas of science, combining data regarding structure, properties of metal complexes, and conduct or control of the body's vital processes. The design of new drugs based on metal complexes is an important contribution for the development of more efficient chemotherapy methods. These metal complexes are used in the treatment of many diseases. However, it was not until the early 1960's that the biological effect of cisplatin was discovered [1]. Primary research by Rosenberg indicated that metal ions were capable of binding to nucleic acids, thereby altering their conformation and biological function [2]. Metal complexes play an important role in many biological processes [3] including cell division and gene expression, as well as processes such as carcinogenicity or toxicity [4]. Among the synthesized compounds, many very important complexes are based on organophosphorus compounds. Their activity against many types of cancer is currently the subject of intensive research. In general metal complexes include platinum, ruthenium, palladium, gold, copper, silver, rhodium, rhenium, osmium or iridium metal centers. When it comes to metal complexes with phosphorus-based ligands, the ones that are of great interest are platinum, ruthenium, palladium, gold and copper.

Many metal complexes with triphenylphosphine and other tertiary phosphines have been reported to be catalysts for various processes, such as polymerization of alkenes and acetylenes, Wilkinson catalyst [5], oxo hydroformylation of alkenes with hydrogen and CO [6], asymmetric Pauson-Khand [7] and Morita-Baylis-Hillman [8] reactions, synthesis of enantiomerically enriched cyclohexadiene by reaction of terminal dieneyne using a chiral iridium complex [9] and asymmetric allylation and propargylation of ketones [10]. Many phosphines and diphosphines are optically active due to an asymmetric phosphorus or a carbon atom and have been used for asymmetric hydrogenations [11].

2. PLATINUM COMPLEXES

Despite clinical disadvantages, cisplatin is widely used against various types of cancer. It affects DNA in both sick and healthy cells to a great extent causing its strands to crosslink which eventually leads to the cell apoptosis. Aforementioned fact generates harsh side effects such as hepatotoxicity, ototoxicity, nephrotoxicity or neurotoxicity [12, 13]. Since the success of cisplatin much research attention has been paid to platinum complexes as potential antitumoral drugs.

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