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Review

Applications of five-membered ring products of cyclometalation reactions as anticancer agents

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Contents

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ABSTRACT

The use of metal compounds as anticancer agents is one of the applications of the five-membered ring products of cyclometalation reactions, including those with Pt, Pd, Rh, Ir, Ru, Os and Au. The coordinating atoms in these anticancer agents are mainly N and, in very few cases, P, S and O. The substrates used for these cyclometalation reactions are mainly pyridine ring compounds, such as 2-phenylpyridines, benzo[*h*]quinolines, 2,6-diphenylpyridines and so on. The ancillary ligands used are bipyridines, 1,10-phenathrolines, 2,6-bispyridylpyridine, *N*-heterocyclic carbenes and so on.

The platinum compounds of 2,6-phenylpyridylpyridine CNN pincer *N*-heterocyclic carbene, the gold compounds of 2,6-diphenylpyridine CNC pincer alkylphosphine or *N*-heterocarbene, and the osmium compounds of 2-phenylpyridine, phenyloxazole, *m*-bispyridylbenzenes cyclometalated 1,10-phenanthrolines or 2,6-bispyridylpyridines show very high cytotoxicity values compared to those of cisplatin.

1. Introduction

Pharmaceuticals are usually manufactured in a process involving many reaction steps. Both high yields and high selectivity are required in all of these because there is a strong possibility that side effects may be caused by the presence of byproducts.

Cyclometalation reactions are applied for the preparation of pharmaceuticals because many different substrates [1–4] and metal compounds containing almost any of the metal elements [1–3] can be used in these reactions. The preparation of five-membered ring products proceeds especially easily with high regioselectivity because five-membered ring compounds are more stable than other ring products, such as the corresponding four- and six-membered ring products. Their preparations generally proceed with high yields and high selectivities due to the five-membered ring chelate effect [1].

The fact that cyclometalation reactions producing five-membered ring products proceed very easily is apparent from the fact that the number of articles published on these reactions is more than six times that of those concerning any of the three recent Nobel prize-winning synthetic reaction methods: chiral reactions (2001), metathesis (2005) and cross-coupling reactions (2010). It

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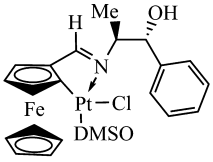
is also apparent from the fact that many reactions proceed at room temperature with a variety of substrates, such as amines, imines, 2-phenylpyridines, benzo[*h*]quinones, other nitrogen compounds, oxygen-containing compounds, phosphorus compounds, sulfur compounds and so on.

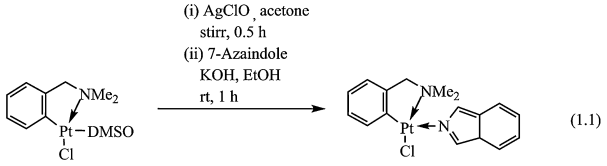
There are five types of applications for both cyclometalation reactions and cyclometalation reaction products [1]. The first are cyclometalation reactions that produce five-membered ring products by themselves. Many examples of the cyclometalation reaction producing the five-membered ring products utilized for producing pharmaceuticals such as antitumor, antibacterial, antifungal agents, *etc.* [1]. For example, in 2014, the ferrocene cyclometalated compound **1.1** was found to induce apoptosis and synergize with cisplatin for inhibiting lung cancer cell proliferation, and moreover, it reveals remarkable activity against large NCE-H460 lung cell lines and its low toxicity against non-tumor cells [5(a)].



1.1

The second type of application includes synthetic reactions of derivatives of five-membered ring products of cyclometalation reactions, such as carbonylations, alkenylations, alkynylations, acylations, isocyanations, Diels-Alder reactions, transmetalations, Ullmann-type coupling reactions, C—C coupling reactions, halogenations, oxidations, resolutions, ring expansions, silylations, hydrogenations, and hydrophosphinations [1].

Recently, an example of a cyclometalation reaction producing a five-membered ring product used in an anticancer agent involving 7-azaindole platinum compound **1.3** was reported. This cyclometalation reaction product is very easily prepared by simple ligand exchange reactions with the most conventional cycloplatinated benzylamine product **1.2** as shown in Eq. (1.1). At 48 h incubation time the new product **1.3** shows sub-micromolar activities both in A2780 and T45D [IC_{50} (μM) = 0.34 and 0.53, respectively (cisplatin: 0.87 and 37, respectively)] [5(b)]

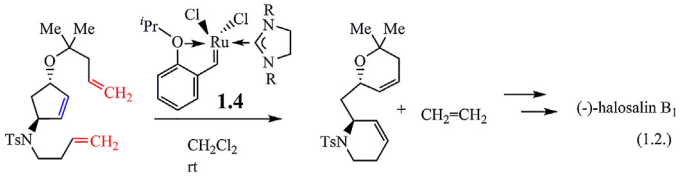


(1.1)

1.2 **1.3** 73 %

The third type of application includes synthetic reactions utilizing the intermediates of five-membered ring products of cyclometalation reactions, such as carbonylations, cross-coupling reactions, hydroacylations, ring expansion reactions, carbocyclization reactions, decarbonylative cleavage reactions, asymmetric hydrogenations, reductive eliminations, one-pot preparations of chiral homoallylic alcohol or amine derivatives, CO/olefin copolymerizations, lactone formations, hydrolysis of methyl parathion, and acetoxylations. Recently, an enormous number of articles with titles such as "C—H Activation", "C—X Activation", "C—H Functionalization" and "Chelation-assisted Reactions" have claimed to report new types of synthetic reactions. However, these various reactions proceed *via* the intermediates of cyclometalation reactions to produce five-membered ring products. In other words, these various reactions proceed *via* the third type of application [1].

The fourth type is the application of five-membered ring products of cyclometalation reactions as catalysts for reactions such as chiral reactions, metathesis, cross-coupling reactions, reductions, dehydrogenations, Diels–Alder reactions, aldol-type condensations, cyclopropanations, allylations, reductive eliminations, transfer hydrogenations, hydroaminations, and polymerizations [1–3]. Many catalysts applied in the three recent Nobel prize-winning synthetic organic reactions employed five-membered ring products of cyclometalation reactions [1]. Thus, these reactions proceed *via* the fourth type of reaction [1–3]. For example, piperidine alkaloid (−)-holsalin B_1 is prepared *via* metathesis with the Grubbs 2nd-generation catalyst **1.4**, which is the five-membered ring product of a cyclometalation reaction, as shown in Eq. (1.2) [6].



(1.2.)

The fifth type includes other applications of five-membered ring products of cyclometalation reactions in industrial fields such as pharmaceuticals, organic electric devices, dye-sensitized solar cells, carbon dioxide utilization, and sensors.

The author previously reported a summary of pharmaceuticals as one of the five types of applications as well as other applications in a recent monograph [1].

This article therefore reports only on pharmaceutical anticancer agents produced through the application of five-membered ring products of cyclometalation reactions.

2. Applications of five-membered ring products of cyclometalation reactions as anticancer agents

2.1. Introduction

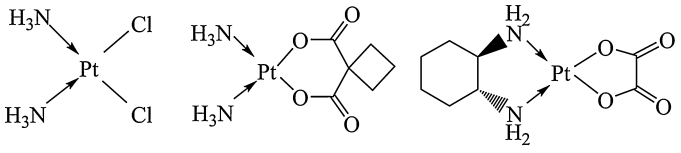
The author has previously reported a summary of the activities of five-membered ring products of cyclometalation reactions, including their antitumor, antimicrobial, antiparasitic, and antifungal activities and their applications in pharmaceuticals [1].

This article focuses on the medical applications of five-membered ring products of cyclometalation reactions as anticancer agents.

2.2. Applications of five-membered ring products of cyclometalation reactions as anticancer agents

2.2.1. Introduction

Recently, in a review of the cyclometalated compounds of platinum group metals and gold with anticancer activities [7], the breakthrough synthesis of cisplatin in 1965 revolutionizing cancer chemotherapy was described, however, while many cisplatin analogs have been biologically evaluated, only three platinum-based anticancer drugs (cisplatin **2.1**, carboplatin **2.2**, and oxaliplatin **2.3**) have been approved worldwide as shown in Fig. 1, and these agents are still used in greater than 50% of treatment regimens for cancer patients. The global market for platinum-based



Cisplatin **2.1.** Carboplatin **2.2.** Oxaliplatin **2.3.**

Fig. 1. Platinum-based anticancer drugs currently in use globally [7].