

Use of metal-containing polymers as potential anticancer agents

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Abstract

Metal containing polymers have been synthesized from a variety of metals that exhibit good inhibition of a variety of human cancer cell lines including pancreatic and breast human cancer cell lines. The products are rapidly synthesized using commercially available reactants and a system that is employed industrially allowing for ready expansion of the amounts of products synthesized. Recently, water soluble polymers have been synthesized using poly(ethylene glycol).

Introduction

We have been involved with including metals into polymers for various reasons. Much of this has been reviewed in a ten volume series [1] and various reviews for platinum [2-5], organotin [5-9], Group 5 [10,11] Group 15 [12-14], uranium [15], ruthenium [16] and vanadocene-containing [17] polymers. This brief review concentrates on the synthesis and characterization of metal-containing polymers for cancer treatment though they also offer good antibacterial, antifungal, and antiviral activity.

Why polymers

Potential advantages of using polymers as drugs has been reviewed by many [2,6,9,18-22]. The following briefly describes several of these potential advantages. A. Polymers limit movement of drugs because of their size. They are not as apt to move through membranes in the body. This may discourage build-up of in the kidneys and other organs decreasing renal and other organ damage. B. They may enhance activity through an increased opportunity for multiple bonding interactions between the target and the polymer. C. They can bypass the cell's defense system, specifically by being different (large size) the cells do not recognize them and/or are not prepared to deal with them. D. Large molecular weight molecules accumulate in solid tumors more than in normal tissues because of the enhanced permeability and retention effect, resulting in high amounts of polymers in the interstitial space due to a leaky vasculature and limited lymphatic drainage typical of tumors. This effect is referred to as the enhanced permeability and retention effect, EPR effect.

Metal-containing drugs in the treatment of cancer

A number of metal-containing drugs are known to be inhibit cancer cell growth. Two metal-containing drugs have been clinically tested. The platinum-containing drugs form the basis for many of the current drug treatments including cisplatinum II diamine, also known as cisplatin. We have synthesized a variety of platinum-containing polymers based on cisplatin that exhibit good ability to inhibit cancer cell growth [2-5]. Our polymers have lowered toxicity compared to cisplatin itself. As researchers know, while the cisplatin-drug types exhibit a broad range of anticancer activity, they also offer high toxicities.

The first non-platinum metal to undergo clinical trial was titanocene dichloride [23]. While the activity of cisplatin involves interaction with DNA, the activity of titanocene dichloride is related to its ability to react with transferrin [23-25]. Titanocene dichloride underwent Phase I clinical trials. The trials indicated a dose-limiting side effect associated with nephrotoxicity and a number of unwanted physical side effects including nausea, reversible metallic taste, pain during infusion, hypoglycemia, with these features undesirable. Counter, the absence of an effect on proliferative activity of the bone marrow, generally a dose-limiting side effect, was positive. Some phase II clinical trials were undertaken with patients with breast metastatic carcinoma and advanced renal cell carcinoma [23]. Unfortunately low activity discouraged further clinical study.

Metal-containing polymers as anticancer agents

Here we focus on the use of organotin, metallocene (mainly Group 4), and Group 15 metal-containing polymers as anticancer agents.

The overall reaction to form these polymers is based on the simple Lewis acid-base concept, illustrated in figure 1 for the reaction of camphoric acid, the Lewis base, and dimethyltin dichloride, the Lewis acid. Some of the philosophy in selecting the reactants is the focus on Lewis acids and bases that both exhibit some biological activity themselves with the hope that a synergetic effect occurs enhancing the ability to curtail cancer cell growth. In almost all cases the polymer exhibits a better ability to inhibit cancer cell growth than either of the reactants. We also find that the active agent is the polymer and not the degradation products [26]. This is consistent with studies that show that the polymers are stable in DMSO with half-chain lives, the time for the chain length to halve, generally in excess of 30 weeks [6-9]. In

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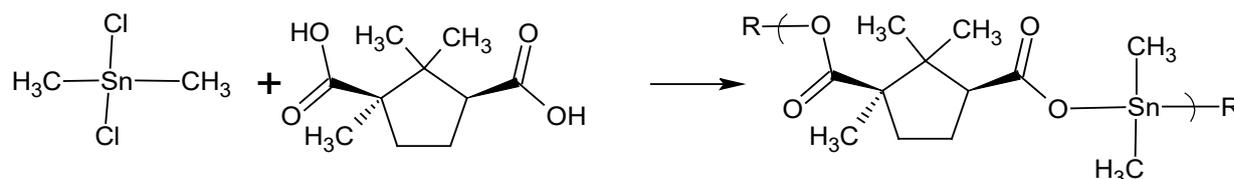


Figure 1. Repeat unit for the product of camphoric acid and dimethyltin dichloride where R represents simple chain extension.

other studies the polymers are found to be cytotoxic and cell death is by necrosis [6-8]. Most organometallic compounds associate with polar solvents such as DMSO and the biological results may be influenced by the presence of the DMSO [27-29]. For organometallic polymers covered here, the influence of DMSO on the tumor results is found to be minimal [30-32].

We employ the interfacial reaction system dissolving the Lewis base in water and the organotin, or other metal-containing reactant, in a suitable organic liquid such as heptane. The two reactants are mixed in a Waring blender and product is formed generally within 15 seconds. The product is polymeric with repeat units varying from 20 to 2,000 depending on the particular reaction conditions and reactants. Typically commercially available reactants are employed and the interfacial reaction system is used industrially to produce aromatic polyamides, aramids, and polycarbonates [33-35]. Thus, a straightforward path exists to form gram to ton quantities of the products.

The ability to inhibit cancer cell growth is determined employing the two most widely used measures. The initial measure describes the concentration of the drug that inhibits 50% cell inhibition after a specified exposure time. This term will be described as the effective concentration EC_{50} . The EC_{50} values for our polymers range from milligrams/mL to nanograms/mL for EC_{50} values. The second measure of the potential effectiveness is the concentration of compound necessary to inhibit the standard cells compared to the concentration of drug necessary to inhibit the growth of the test cell line. A variety of symbols are employed to describe similar calculations. The term chemotherapeutic index, CI_{50} , is employed by us. Thus, the CI_{50} is the ratio of the EC_{50} for the standard cell line divided by the EC_{50} for the particular test cell. Values greater than two are considered significant with some of our polymers having values greater than one thousand. Values for cisplatin are included for comparison.

In general, the nature of the metal has a marked effect on the overall ability to inhibit cancer cell growth. Thus, the most active based on the two biological markers, CI_{50} and EC_{50} , are the metallocene polymers, followed by the organotin, and lastly those derived from the Group 15 metals (arsenic, antimony, and bismuth). Within the metallocenes, the hafnocene and zirconocene are the most active, highest CI_{50} and lowest EC_{50} values. Thus, had the researchers chosen these products to test rather than the titanocene product, we might have a new anticancer family of drugs in the market. For clarity, the inhibition curve is sigmoid and the EC_{50} determined at the midpoint of the curve. Once inhibition begins the concentration difference between the initial inhibition and final total inhibition is small with the region between initial inhibitions to final total inhibition essentially linear.

These metal-containing polymers show good inhibition of a variety of human cancer cell lines [9,10,36-42]. One focus is on pancreatic cancer since there is no good treatment once it has spread. Two pancreatic cancer cell lines are employed in the typical studies. These are the AsPC-1 cell line which is an adenocarcinoma pancreatic cell line

and the PANC-1 cell line which is an epithelioid carcinoma pancreatic cell line. The two tested pancreatic cancer cells are human cell lines widely employed in testing for inhibition of pancreatic cancer. The AsPC-1 cell line represents about 80% of the human cancers found. The PANC-1 represents about 10% of the human cancers detected. We also employ a pair of breast cancer cell lines. They represent a matched pair of cell lines. The MDA-MB-231 (strain number 7233) cells are estrogen-independent, estrogen receptor negative while the MCF-7 (strain line 7259) cells are estrogen receptor (ER) positive. Also typically included are the following: PC-3 (strain 3465) prostate cell line, HT-29 (1507) human recto-sigmoid colon; and for control cells a WI-38 (ATCC CL-75) normal embryonic cell line and NIH/3T3 mouse line cell line. And less usual we study resistant cell lines and other specialty cell lines.

Water soluble polymers

Polymer solutions employed in most industrial testing involve initially dissolving the test compound in dimethyl sulfoxide, DMSO, followed by addition of water. This is precisely the procedure employed by us. The greatest amount of water in our solutions is generally less than 0.1%. Even so, the effect of the presence of water can have an effect on the biological activity. As noted before, this effect is not large for our polymers [29-31].

Water soluble drugs offer greater ease of treatment and delivery and they avoid possible side-effects due to the presence of DMSO. Poly(ethylene glycol), PEG, was employed to achieve this. PEG is known to assist biologically important molecules to become water soluble. PEG is relatively inexpensive and considered nontoxic. Further, there are a number of PEG chains available with differing end-groups and chain lengths so that tailoring the PEG is possible. In the future we plan to employ this variability to design systems that allow a focus on Lewis bases that offer good ability to inhibit unwanted pathogens and infectious agents but where the polymer is not water soluble. We are at the initial juncture of this study [43].

The synthesis of water soluble polymer organotin-containing polymers was initially achieved employing organotin polyethers as described in Figure 2 [44-46].

More recently we described the synthesis of analogous metallocene-containing polyethers [47-49].

Lack of solubility is a major problem limiting efforts to employ Group 5 metallocenes as anticancer agents [50-56]. The present effort involving PEG offers an avenue allowing metallocene-containing small and large molecules to be soluble.

Water-soluble polymers future

A number of polymers that exhibit good ability to inhibit a range of cancer cell lines, viruses and bacterial agents have been synthesized. For instance, polymers from organotin (Figure 1) and metallocene (Figure 3,4) exhibit good ability to inhibit cancer cell lines. In fact, the hafnocene and zirconocene products show EC_{50} values in the

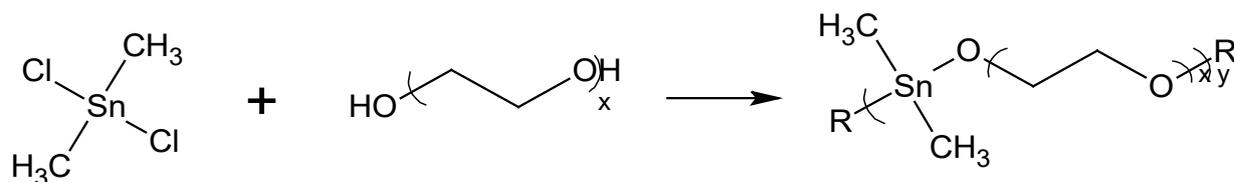


Figure 2. Synthesis of organotin polyethers from reaction of dimethyltin dichloride with PEG where x is the chain length for the PEG and y is the chain length for the polymer; R is simple chain extension.

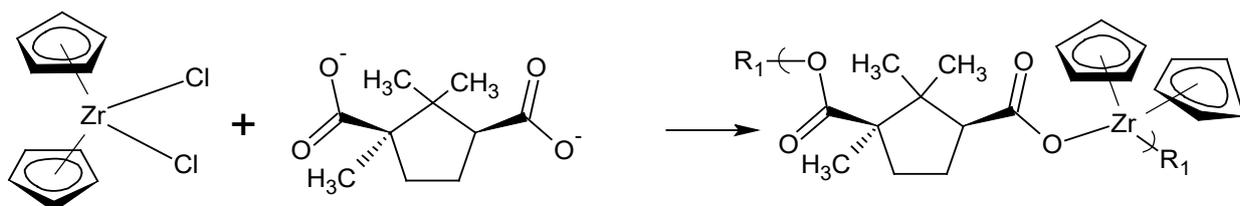


Figure 3. Reaction scheme for the reaction between D-camphoric acid and zirconocene dichloride where R₁ represents simple chain extension.

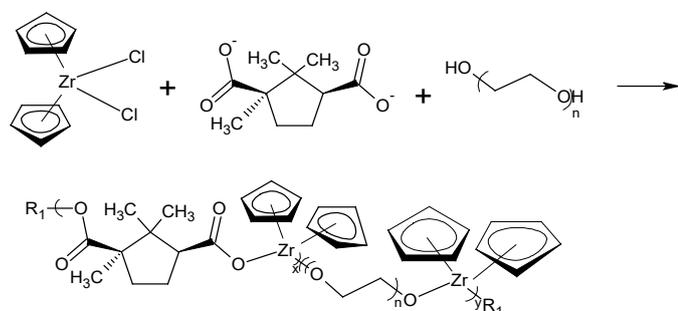


Figure 4. Reaction scheme for inclusion of PEG into the Cp₂Zr/camphoric acid product.

nanogram/mL range and CI₅₀ values in the thousands but they are not water soluble. We are currently working at creating water soluble derivatives through formation of co-polymers from reaction of the metallocene dihalides in the presence of camphoric acid and PEG.

The synthesis and study of water-soluble metal-containing polymers has begun. The results are promising allowing the synthesis of water-soluble products that exhibit good inhibition of a host of cancer cell lines. This is the beginning of a long journey.

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