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METALLOCENE POLYMERS AS ANTIVIRIAL ZIKA VIRUS AGENTS FROM THE LEWIS BASES LAMIVUDINE AND CAMPHORIC ACID

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ABSTRACT

The total inhibit of the zika virus is described. Because of the zika virus's structural closeness it is considered a target virus for the inhibition of the current covid-19 virus. Two groups of polymers exhibited ability to totally inhibit the zika virus. These polymers are derived from group 4 metallocene dihalides and camphoric acid and lamivudine. This is the second report of complete inhibition of the zika virus and it is done using commercially available simple drugs. All the drugs described in these studies are rapidly (less than 30 seconds) synthesized at room temperature employing the interfacial reaction system that is employed industrially so that scale up to kilograms is relatively straight forward.

KEYWORDS: Zika virus, group 4 metallocene polymers, lamivudine, camphoric acid, titanocene dichloride, zirconocene dichloride, hafnocene dichloride, organotin polymers.

INTRODUCTION

Recently, we focused on the ability of various metal-containing polymers to inhibit different cancers including those responsible for human breast, prostate, lung, pancreatic, glioblastoma and colon. These efforts have been reviewed for organotin polymers[1-4] and metallocene polymers.[5-10] During this time we have also begun to focus on the ability of these polymers to inhibit various viruses (Table 1).[5,7,9] Initially, we describe some general properties of the

polymers used in the current study. In this paper the inhibition of various viruses and anticancer drugs by metallocene polymers is described. Table 1 contains viruses that are inhibited by some of our metallocene polymers.

Table 01: Viruses inhibited by metallocene polymers.

Virus	Disease in humans	Viral genome	Virus replication in cytoplasm or nucleus	Current antiviral drugs (CDC recommendations)
Zika virus 502	Microcephaly, Guillain-Barré syndrome (GBS)	Single-stranded RNA	Cytoplasm	None
Vaccinia virus (WR) (Vaccine strain for smallpox)	Vaccine strain for smallpox	Double-stranded DNA	Cytoplasm	Vaccine, Tecovirimat, Cidofovir, Brincidofovir
HSV-1 (Herpes simplex-1)	Herpes	Double-stranded DNA	Nucleus	Acyclovir, Valacyclovir, Famciclovir
HSV-2 (Herpes simplex-2)	Herpes	Double-stranded DNA	Nucleus	Acyclovir, Valacyclovir, Famciclovir
VZV (Varicella Zoster)	Chickenpox/shingles	Double-stranded DNA	Nucleus	Vaccine, Acyclovir
Reovirus	Respiratory enteric orphan virus	Double-stranded RNA	Cytoplasm	None

We recently described the syntheses of organotin derived polymers that inhibit the zika virus.[11] Until this paper, the Center for Disease Control and Prevention, CDC, listed no compounds that inhibited the zika virus. The current paper is the second description of compounds that inhibit the zika virus. Because of the structural similarity of the zika virus to the COVID 19 (coronavirus 19) some have suggested that these polymers may effectively inhibit these viruses.

Metallocenes

In this work, three metallocenes are employed as the metal-containing compounds. They are titanocene, zirconocene and hafnocene. Of the elemental families, these are the closest to one another in physical properties. Structurally, they are referred to as having the cyclopentadiene groups in a distorted tetrahedral arrangement facing the metal atom as shown below.

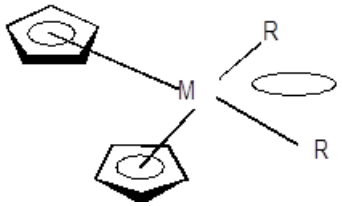

Figure 01: Structure of Group 4 metallocenes.

Cotton and Wilkinson[12] describe Group 4 metallocene compounds as containing 9-coordinate bonding with the hybrid orbitals being derived from one-s, three-p and five-d orbitals. Each pi-Cp ring involves three hybrid orbitals. The remaining three orbitals consist of two equivalent $spd_{x^2-y^2}$, d_{z^2} orbitals (overlapping the halides, oxygen, nitrogen, etc.) and one sp vacant orbital as shown above, 1. This vacant orbital is responsible for many of the physical, chemical, and biological behaviors of the metallocene compounds and polymers that contain units derived from these metallocene units.

Over 2 million entries are given when entering the terms “hafnocene” and “polymers” in SciFinder Scholar. Almost all entries for titanocene, zirconocene, and hafnocene connected with polymers are associated with their use as stereoregulating catalysts. These metallocenes are very important Ziegler-Natta catalysts and are also important catalysts in the current generation of so-called soluble catalysts.[12,13]

While the amount of interest in these metallocenes is great, the amount of work involving their incorporation in polymers is small with much of it involving metallocenes being present as part of a supported catalysis system. This may be due to the impression that the mechanism of catalytic activity involves having at least one unoccupied orbital available about the metal atom. For instance, Grubbs and co-workers in 1977 suggested, based on work done with olefin hydrogenations, that the two chlorides in titanocene dichloride are absent in the active catalyst.[14-16]

Halides are more electronegative than the metallocene Cp_2M portion so that they can undergo condensation reactions where the metallocene dihalide acts as a Lewis acid. When the Lewis base is difunctional, as in the current study, a chain is formed.

$$Cp_2MCl_2 + HBABH \longrightarrow \begin{matrix} Cp \\ | \\ -(M\text{-}BAB\text{-})- \\ | \\ Cp \end{matrix} + 2HCl \qquad \textbf{Equation 01.}$$

These reactions are condensation reactions, yet, because of the use of high energy reactants, the metallocene dihalides, and the interfacial polycondensation process, the kinetics are chain and not stepwise. This allows for rapid reactions to occur under non-equilibrium conditions where the need for high purity reactants and equal molar reactant amounts is less than that required for stepwise processes.[12,13]

Naming

A variety of metallocene polymers have been synthesized from various Lewis base connective groups. These are named from the connective group where the metallocene unit is named, compared to organic structures, as methylene groups.

Thus, the products of a metallocene and organotin dichlorides from a diol such as lamivudine is called a polyether as shown and from a diacid camphoric acid called polyesters. Table 1 contains examples of other common connective group names.

Table 02: Repeat units for Group 4 metallocene polymers.

Repeating Unit	Lewis Base	General Polymer Name
-MCp_2-O-R-O-	Diol	Polyether
-MCp_2-NH-R-NH-	Diamine	Polyamine
-MCp_2-O-(O)C-R-C(O)-O-	Diacid	Polyester
-MCp_2-S-R-S-	Dithiol	Polythiol
-MCp_2-NH-R-O-	Amine-acid	Polyamine ether
-MCp_2-O(O)C-R-O-	Acid-alcohol	Polyester ether
-MCp_2-NH-R-C(O)O-	Amine-acid	Polyamine ester

Solubility

Polymer solubility, compared to the solubility of smaller molecules, is more difficult in terms of breath, amount and time.[12,13] Metallocene polymers have even a greater problem with respect to solubility. This has discouraged advancement in some important areas. Biologically, two metal-containing polymers have undergone human testing as anticancer agents. One is the platinum-containing small molecules including one of the most widely employed cisplatin group. The other is titanocene dichloride that underwent testing. Researchers noted solubility difficulty that discouraged researchers in the area. Essentially all of the metallocene-containing polymers made by us are soluble to the extent that allows molecular weight and biological determination. In general, for the metallocene polymers

solubility is the most difficult for the titanocene polymers. Recently, we reported the synthesis of water-soluble polymers based on the reaction of various polyethylene oxides with the metallocene dichlorides. We are currently involved in the synthesis of copolymers that incorporate the Lewis bases that offer outstanding biological activities and polyethylene oxide as the second Lewis base. This has been recently reviewed.[5]

Polymer General Properties

We have studied about 250 different metallocene polymers and over double that of organotin polymers with respect to their ability to inhibit cancer growth. The polymer drugs are cytotoxic and cell death is by necrosis.[17-19] Anticancer activity occurs with the intact polymer without polymer degradation .[17,19,20] This is consistent with the observation that the polymers do not degrade in DMSO with half-chain lives, the time for the polymer chain length to halve, greater than 30 weeks.[17-20] The tested compounds are initially dissolved in dimethyl sulfoxide, DMSO, and then water added such that the DMSO content is generally 1% or less. Most organometallic compounds associate with polar solvents such as DMSO. This association can influence the observed biological results. We find that this is generally not the case.[17-19] for polymers with similar structure to those reported here with the influence less than 20%.[17,20] We assume that the antiviral activity is similar.

Advantages to use of Polymers as Drugs

The use of polymeric drugs is widespread including their use to inhibit cancer growth.[21-32] Some advantages in comparison to small, monomeric drugs are briefly described as follows.

First, because of their large size, they can be designed with particular components incorporated to impart desired characteristics including drug release or retention and if released, how fast it is to be released; polymer solubility, preferred location for activity, etc. This fine-tuning includes chain length, polarity, monomer characteristics, crosslinking, and preferred duration of activity. Second, the polymer chain can be designed to deliver the "drug" as part of the entire chain that enters the cell by pinocytosis[33,34] being active in the polymer form or sufficiently unstable as to release the drug in some sustained release mode.[35-37] As noted before, our polymers act against the cancer cells intact rather than through some decomposition product. Third, when characteristics of solid cancers are listed, one that is often omitted, but that is important, is the difference in characteristic between healthy and cancer cell walls. Cell walls of cancer cells, compared to normal cells, are more ragged allowing polymer chains to become "hooked" resulting in a longer contact time and

enhanced activity against these cancer cells in comparison to smoother healthy cells. Fourth, polymers are filtered out by the kidneys more slowly than small compounds[38] decreasing kidney damage and allowing for prolonged retention. Fifth, because of its large size the polymer can be designed to provide more bonding sites to cellular targets increasing their effectiveness. Sixth, polymers can be designed to contain several different anti-cancer agents. Thus, cisplatin and other platinum-containing compounds which are among the most widely employed cancer agent, can be incorporated in the same polymer chain with metallocene agents, as described in the present paper, offering different mechanisms for cancer inhibition. Seventh, polymers may be active against cancer cells that have developed resistance. This resistance is believed to be partially due to the cell being alerted through the prior exposure of small molecule chemo agents. Special "housekeeping" proteins are alerted to the invasion of the original anticancer agents and are then prepared to do "warfare" when other invaders arrive.[39] Some of our polymers have been effective at inhibition of cell lines that have become resistant[40] possibility because of their polymeric nature compared to the smaller size of the typical anticancer agents.

Finally, as noted before, cancer cells are both irregular and leaky compared to normal cells with the potential of polymers occupying the interstitial space due to the leaky vasculature and limited lymphatic drainage typical of cancer cells.[41] This effect is called the enhanced permeability and retention, EPR, effect.[30-32,41] This listing is not exhaustive but highlights the advantages of polymers in the fight against cancer.

EXPERIMENTAL

Cell Culture Maintenance

The cell lines used in this study were Vero cells and 143 cells. All the cell lines that were used are transformed cell lines with the ability to replicate indefinitely in cell culture. Vero cells are African green monkey kidney cells and support the growth of Zika virus. 143 cells, which allow for the growth of vaccinia virus, are derived from a human osteosarcoma cancer. All cells lines were maintained in 75 cm^2 flasks in Dulbecco's Modified Eagle's Media (1X MEM) with 5% fetal bovine serum (or 10% bovine growth serum) and the antibiotics streptomycin/penicillin at a final concentration of 100U/mL. All cells were kept in a 5% CO2 incubator. The cells were subcultured as often as needed to seed new flasks or plates for experiments. Briefly, confluent cells were washed in the culture flask with 1x sodium saline citrate (SSC), or MEM without serum. Trypsin (0.05%) was then added to the cells to detach

them from their flask. The trypsinized cells were placed in the 5% CO2 incubator for 5 minutes. Following detachment, 5 mL of fresh media was added to the cells to wash them from the side of the flask. New media (up to 5 mL total for a 25 cm^2 flask and 10 mL total for a 75 cm^2 flask) was added to the flasks, usually in a 1:4 dilution (2 mL of cell suspension in 8 mL of fresh media). The cells were seeded at varying dilutions, depending on when they were next needed.

Virus Stock Preparation

Virus stocks were grown in their appropriate cell lines. Initially, cells were seeded in a 25 cm^2 culture flask to 90-100 percent confluency. The following day, the cells were infected with virus. For the first passage, a multiplicity of infection (MOI) of 1 was used, which means that there was one virus particle per cell. The viral inoculum was made using diluent which consisted of 1X MEM with 100U/mL of penicillin/streptomycin and no growth serum. After one hour of virus adsorption with rocking every 15 minutes, 5 mL of 1X MEM with 5% BCS and 1% P/S was added. When the virus had killed 50% of the infected cells, which was seen microscopically as a cytopathic effect (CPE), the cells were sonicated to release all of the virus particles from the cells. Upon second passage, 1 mL of the passage 1 viral lysate was used to infect a confluent 75 cm^2 flask. The third and final passage involved infecting cells in a 150 cm^2 flask with 2 mL of the second viral passage. The third passage is the viral passage that was titered.

Viral Titration

To determine the titer of each virus stock in PFU/mL, standard plaque assays were used. Initially, the virus was serially passaged three times in a tissue culture of the appropriate cell line (vaccinia: 143; Zika: Vero), first in a 25 cm^2 flask, followed by a 75 cm^2 and then a 150cm^2 flask. The cells in the 150 flask cm^2 were then sonicated to lyse the cells and release the virus. The third passage lysate was then used to infect confluent monolayers of cells for a plaque assay. Vero cells were seeded into 6-well plates for Zika virus and 143 cells were seeded into 12-well plates for vaccinia virus in 1x MEM containing 5% fetal bovine serum (FBS) and penicillin/streptomycin at the concentration seen above. When the cells reached around 80 percent confluency ~24 hours later, the media was aspirated off, and the cells were infected with serial dilutions (10^{-1} to 10^{-7}) of virus at an inoculum size of 250 microliters (6-well plate) or 125 microliters (12-well plate). To obtain serial dilutions, 100 microliters of the third passage viral lysate was suspended in 900 microliters of diluent, which is 1x MEM with

no FBS, and 1% penicillin/streptomycin. This yields a 10^{-1} dilution. This dilution was then vortexed, and 100 microliters of this dilution was then placed into another tube containing 900 microliters of diluent. The process was repeated until all desired dilutions had been created. The control for each plate contained cells and 250 microliters (or 125 uL) of diluent without added virus. Following one hour of incubation with agitation every 15 minutes**,** the cells were washed, and fresh media was added to each well. After the assays were incubated 5 days for Zika, they were stained with 1% crystal violet in 50% ethanol.

Compound Preparation

Compounds began as solid powers. Initially, 0.01 g (10 mg) of compound was dissolved in 1 mL of DMSO, giving a stock concentration of 10 mg/mL. One microliter of the stock solution was then placed into 1 mL of AquaPure sterile water, giving a concentration of 10 microgram/mL. Finally, 1 mL of this solution was placed into 10 mL of AquaPure water, giving a beginning concentration of 1 microgram/mL for compound testing.

Cytotoxicity Assays

To determine the highest concentration of compound that the cell lines could tolerate without showing cytopathic effects, cytotoxicity assays were performed for each compound. For each of the three cell lines, 125,000 cells were seeded in 500 microliters of media in each well of a 24 well plate. When the cells reached confluency around 24 hours later, compounds were added to the wells. The 1 microgram/mL starting concentration for each compound was ten-fold serially diluted in 1x MEM, yielding 10^{-1} to 10^{-4} compound dilutions. The media from each well of the 24 well plates were removed, and 500 microliters of the compound dilutions were added to each well. After 96 hours, 50 microliters of trypan blue were added to each well and allowed to stain the cells for 5 minutes. After 5 minutes, the cells were observed microscopically to determine the highest concentration of drug for each cell line that did not cause cell death.

Zika Plaque Reduction Assay

For the zika virus assay, 96-well plates were used. After the cells reached confluency in their wells ~24 hours later, the old media was removed from each well and 100 microliters of fresh media was added. For each compound, 200 microliters of drug were added to the first well of each column. After mixing the solution, 100 microliters were taken from the first well and placed into the second well. The compounds were serially two-fold diluted across the 96-well

plates. Following the addition of the compounds, 10 microliters of Zika virus was added to the test wells. The assays were placed in the incubator for 5 days and then viewed microscopically. The lowest concentration of compound that prevented the Zika-infected cells from showing cytopathic effects (CPE) was recorded.

Polymer synthesis and characterization

Synthesis is rapid (generally less than 30 seconds) occurring under mild conditions at room temperature employing the interfacial polymerization process.

An aqueous solution containing the Lewis base (camphoric acid (0.00300 mole) or lamivudine (0.00300 mole) with sodium hydroxide (0.0060 mole) was transferred to a one-quart Kimax emulsifying jar fitted on top of a Waring Blender (model 1120; no load speed of about 18,000 rpm; reactions were carried out at about 25 ^{o}C). Stirring was begun and a chloroform solution containing the metallocene dihalide (0.0030 mole) was rapidly added through a hole in the jar lid using a powder funnel and the resulting solution blended for 15 sec. The precipitate was recovered using vacuum filtration and washed several times with deionized water and chloroform to remove unreacted materials and unwanted by-products. The solid was washed onto a glass petri dish using acetone and dried at room temperature.

Structural characterization includes product yield, infrared spectroscopy, mass spectrometry, molecular weight determination, nuclear magnetic resonance spectroscopy and preliminary ability to inhibit important solid tumor cancer cell lines.[7]

RESULTS AND DISCUSSION

Due to the success of a variety of organometallic polymers as anticancer agents a number of these compounds were tested for their efficacy as antiviral agents. There are a few compounds which show promising activity against the zika virus (+RNA). They are presented here.

Zika virus

Zika virus, an enveloped, plus-stranded RNA virus belonging to the *Flavivirus* genus, was first discovered in Uganda in 1947.[42] Usually, Zika virus causes asymptomatic infection; if symptoms do occur, they include a low-grade fever, itchy rash, and arthralgia.[42] The concern for Zika virus, however, emanates from its potential to cause severe neurological disease, such as microcephaly in newborns, as well as a handful of cases which involved development

of Guillain-Barre syndrome, which causes the immune system to attack the peripheral nervous system.[42] It gained much publicity during the recent Olympics in Brazil because of the fear by the participants, particularly women, and attenders of contracting the zika virus.

Zika virus particles contain an inner nucleocapsid surrounding the genomic RNA, and the nucleocapsid is wrapped in an envelope that contains the viral membrane protein (M) and the viral envelope protein (E).[42] The RNA of Zika virus encodes 3,423 amino acids which are translated as a large polyprotein, which is subsequently cleaved into 10+ individual viral proteins. The viral nonstructural protein NS3 has helicase and nucleoside triphosphatase activities, while NS5 is the viral RNA-dependent RNA polymerase which is required for viral genome replication. Zika virus infects human neural progenitor cells (hNPCs) through clathrin-mediated endocytosis. The acidic environment of the endosome induces conformational changes in the viral envelope (E) glycoprotein leading to fusion between the viral and endosomal membrane and subsequent release of the zika virus RNA into the cellular cytoplasm. The viral RNA-dependent RNA polymerase is responsible for replication and translation of the viral genome, along with currently unidentified cellular factors. Immature virions bud into the endoplasmic reticulum, where they receive their cellular-derived envelope with embedded viral prM (membrane) and envelope proteins. Immature virions complete the process of maturation as they proceed through the trans-Golgi network, and the virions are eventually released from the cell through exocytosis.

The source of the zika 502 virus is described following. (Zika Virus 502) NR-50240 Zika Virus strain PRVABC59 was isolated from the blood of a human in Puerto Rico in December 2015.[43] The complete genomic sequence of ZIKV, PRVABC59 has been determined (GenBank: KU501215).[43,44]The complete coding sequence of NR- 50240, Lot No. 64112564 has also been determined (GenBank: KX087101).[45])

Zika Virus Inhibition

Zika virus is a single-stranded, plus-sense RNA virus that has garnered worldwide attention recently due to its connection to neurological birth defects. We recently described the ability of selected organotin polymers to inhibit the zika virus.[11] These compounds are derived from camphoric acid, Figure 2, and lamivudine, Figure 4. The structures of the corresponding organotin polymers are given in Figures 3 and 5.

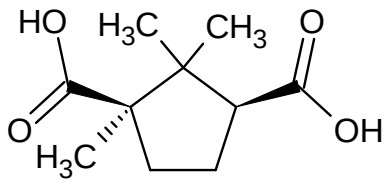

Figure 02: Structure of D-camphoric acid.

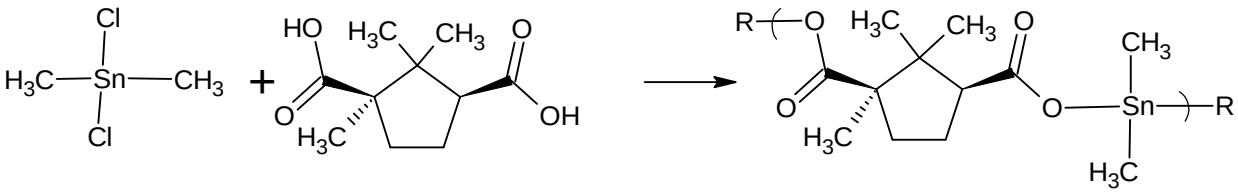

Figure 03: Synthesis of organotin polyesters from reaction of D-camphoric acid and dimethyltin dichloride.

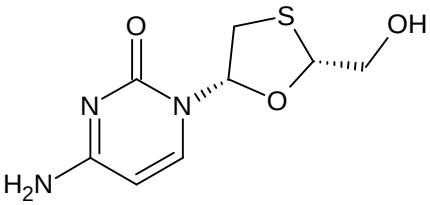

Figure 04: **Structure of lamivudine**.

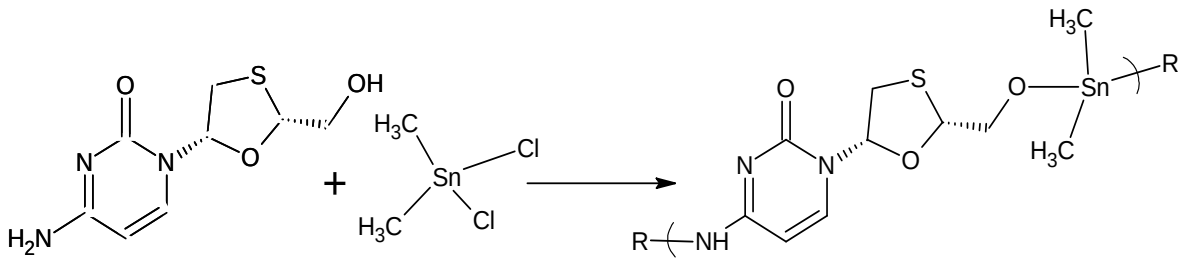

Figure 05: Synthesis of organotin polyamine ethers from the reaction of lamivudine and dimethyltin dichloride.

Lamivudine (Figure 5; also called 3TC) is a potent reverse transcriptase prodrug antiviral molecule employed in the treatment of AIDS.[46-50] Structurally, lamivudine is a nucleoside analogue. It is administered several times daily because of its short half-life of 5-7 hours. It has additional problems including negative effects from the accumulation of the drug, high cost, and lack of patient compliance. Further, there is an increased incidence of co-infection of HIV with such diseases as tuberculosis. Co-treatments are being investigated. For instance, co-loaded polymer microspheres containing lamivudine and an anti-tuberculosis drug such as isoniazid have been described that allow the treatment of both the HIV and tuberculosis.[51]

In this paper we report the zika virus inhibition of the corresponding polymers except derived from Group 4 metallocene dichlorides, Table 3 and Figures 6 and 7.

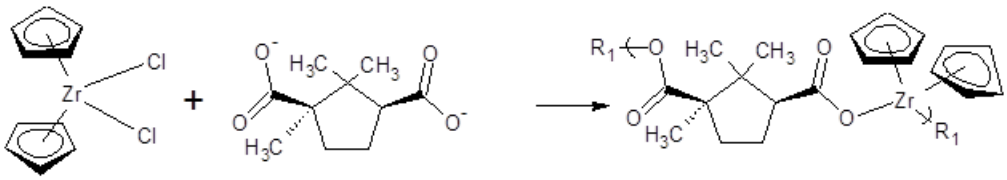

Figure 06: Scheme for the between camphoric acid and zirconocene dichloride.

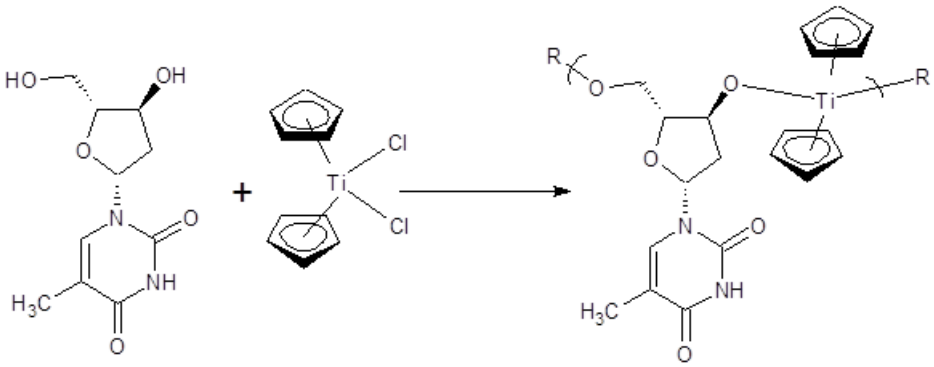

Figure 07: Reaction scheme for polymer formation between lamivudine and titanocene dichloride.

All of these compounds exhibit total inhibition of the zika virus. Against Zika, the products from camphoric acid and lamivudine and the metallocene dichlorides and camphoric acid and lamivudine itself inhibited infection of the zika virus for the lamivudine polymers at concentrations of about 0.030 microgram/mL and for camphoric acid about 0.0003 microgram/mL. Thus, it appears that the metallocene and lamivudine and camphoric acid-derived compounds merit further testing against zika virus as potential novel antiviral agents. These concentrations are in the nano or near nanogram region. For comparison, results from the organotin polymers are added.[7]

Table 03: Inhibition of Zika virus strain from organotin[7] and metallocene polymers and monomers.

Reactants	Concentration in microg/ml that showed 100% inhibition of Zika 502 virus after 5 days
Me_2SnCl_2 /Lamivudine	0.025
Et_2SnCl_2/Lamivudine	0.025
Bu_2SnCl_2 /Lamivudine	0.030
Oc_2SnCl_2/ Lamivudine	0.030
Ph_2SnCl_2 /Lamivudine	0.030
Cp_2TiCl_2/Lamivudine	0.035
Cp_2ZrCl_2/Lamivudine	0.039
Cp_2HfCl_2/Lamivudine	0.032
Me_2SnCl_2 /Camphoric acid	0.0003
Et_2SnCl_2/Camphoric acid	0.0004
Bu_2SnCl_2 /Camphoric acid	0.0003
Oc_2SnCl_2/ Camphoric acid	0.0004
Ph_2SnCl_2 /Camphoric acid	0.0008
Cp_2TiCl_2/Camphoric acid	0.0003
Cp_2ZrCl_2 /Camphoric acid	0.0003
Cp_2HfCl_2/Camphoric acid	0.0003
Monomers	
Camphoric acid	0.005
Lamivudine	0.019
Dibutyltin dichloride, Bu_2SnCl_2	>0.1
Dimethyltin dichloride, Me_2SnCl_2	>0.1
Diethyltin dichloride, Et_2SnCl_2	>0.1
Diphenyltin dichloride, Ph_2SnCl_2	>0.1
Dioctyltin dichloride, Oc_2SnCl_2	>0.1
Cp_2TiCl_2	>.0.1
Cp_2ZrCl_2	>0.1
Cp_2HfCl_2	>0.1

We have synthesized many polymers that exhibit good anticancer activity Table 1. We found that none of these showed activity against the zika virus. These included 3-amino-1,2,4-triazole, dicumarol, and cyano-4-hydroxycinnamic acid. In hopes of determining additional products that exhibit good inhibition of the Zika virus we tried several polymers that had structural characteristics like camphoric acid and lamivudine We identified possible structural characteristics that we have begun to explore. Camphoric acid has two acid groups and further a ring system from which the acid groups are attached. Figure 8 contains the structures for some of these. In no case did we find any inhibition of the zika virus. Lamivudine has as functional groups the amine and alcohol. Again, we have made polymers that are polyamine ethers and none of them showed inhibition of the zika virus.

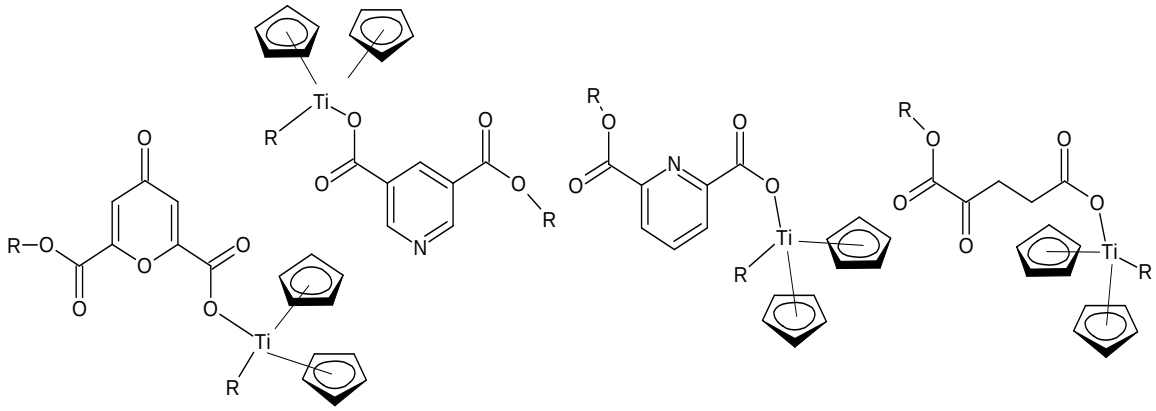

Figure 08: Structures of diacid-containing compounds whose metallocene polymer derivatives were tested for their ability to inhibit the zika virus. From left to right the structures are derived from chelidonic acid, 3,5-pyridinedicarboxylic acid, dipicolinic acid and 2-ketoglutaric acid . While they are drawn as the titanocene derivatives, all three metallocene polymers were tested.

Thus, the structural window for zika inhibition is narrow. All of these tested polymers exhibit good inhibition of a variety of human cancer cell lines including those derived from camphoric acid and lamivudine.

The inhibition levels for the organotins and Group 4 metallocenes and camphoric acid is about one tenth that for the lamivudine.

SUMMARY

The organotin and metallocene derived polymers from lamivudine and camphoric acid all showed good inhibition of the zika virus at the nanogram/mL level. The inhibition levels for the camphoric acid polymers are about one tenth that for the lamivudine polymers. The structural window for inhibition is narrow. The results are consistent with these polymers representing compounds worthy of additional study as antiviral agents. They are currently being studied for their ability to inhibit the Covid-19 virus.

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