EFFICACY OF A SERIES OF ORGANOTIN POLYMERS AS ANTICANCER AND ANTIVIRAL DRUGS

by

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ABSTRACT

EFFICACY OF A SERIES OF ORGANOTIN POLYMERS AS ANTICANCER AND ANTIVIRAL DRUGS

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Anticancer drugs have been shown to have antiviral abilities as well. The two types of diseases are similar in that they hold the cell in a continued growth phase. Therefore, if a drug has anticancer activity, it could have antiviral activity as well. I was interested in drugs that could inhibit DNA replication, since both cancer cells and cells infected with a DNA virus have increased DNA replication. Organotins are known to have anticancer activity and are thought to inhibit DNA replication. In this study, four cancer cell lines (from the NCI 60) and two DNA viruses, HSV-1 and vaccinia, were used to study the anticancer and antiviral activity of several series of organotin polymers. The cancer types and HSV-1 used in this study were chosen due to their prevalence in the human population. Cancer causes 550,000 deaths a year. Also, about

eighty-five percent of the population is infected with HSV-1. Vaccinia is the strain used for vaccination against the small-pox virus, which is a concern due to the threat of bioterrorism, so it was included in the study as well. Several concentrations were used to determine the amount of polymeric drug that inhibits growth of the cancer and normal cell lines by fifty percent. The concentration of the polymeric drugs that inhibited fifty percent of the HSV-1 and vaccinia viruses was also determined. I found that the most effective sets of polymeric drugs for anticancer activity were determined to be the hydroquinone and diethylstilbestrol series. The most effective set of polymeric drugs for antiviral activity was also the hydroquinone series. My study was done to determine if the polymeric drugs would be more effective than cisplatin, a widely used anticancer drug that has platinum as its active moiety, as well as dibutyltin dichloride, an organotin monomer.

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CHAPTER 1

INTRODUCTION

Cisplatin, *cis*-diamminedichloroplatinum, is a widely used chemotherapeutic drug, consisting of a platinum subunit, which has been identified as the site of anticancer activity.[28] Since platinum has been demonstrated to exhibit anticancer abilities, many researchers are testing other metal compounds to see if they can be used as anticancer drugs as well. Organotins, any compound that contains at least one Sn-C bond, are a highly studied group for their cancer-fighting abilities.

The goal of this study was to identify new polymeric organotin drugs that have enhanced anticancer and antiviral activities versus their bioactive moiety alone, dibutyltin dichloride, and to gain an understanding of how the molecular weight, the chemical structure of the linking component and the biological activity of the monomeric component all interact to produce the overall activity of the compound. Polymeric drugs that are used as treatments of disease today are more effective than their monomers, as well as less toxic to normal cells, which in turn results in less side effects. The increase in activity of polymeric drugs is due to their size. Polymeric drugs are larger than monomers, which allow the active centers to be shielded from the cell's defense system. This allows the drug more time to be effective. The shielding of the active site also makes it less toxic to the body, allowing the bioactive moiety to be

slowly released. Polymeric drugs can also have multiple sites of activity, which increases their effectiveness.

It is estimated that there will be about 1.5 million new cases of cancer and more than 550,000 cancer deaths this year alone in the United States. About 300,000 of the new cases and 55000 of the deaths will be due to breast cancer. Another 220,000 of the new cases and 27000 of the deaths will be due to prostate cancer. Also, another 112,000 of the new cases and 52000 of the deaths will be due to colon cancer. [27] The cancer cell lines used in this study originated from these major cancer types.

There is no definitive cure for cancer, and in general, treatments are very harsh. Like cancer, there is no known cure for the viruses used in this study. It is estimated that about 85% of the world's population are infected with Human herpes virus 1 (herpes simplex virus), a member of the family Herpesviridae. Infections with Vaccinia orthopoxvirus, a member of the family Poxviridae, are not as much of a human health threat. Vaccinia is the vaccine strain used for the prevention of smallpox. Treatments for vaccinia are sought because of the threat of bioterrorists using smallpox. Treatment options are limited for the viruses used in this study. New ways to treat these diseases are constantly being sought. The goal of any new treatment is to make them less toxic to the patient by minimizing damage to normal cells. Polymeric drugs have the potential to meet this goal.

Six types of compounds were chosen to make the polymeric drugs because historical evidence suggests that they have properties that would make them effective

polymeric drugs. They include diols, ethylene glycols, kinetin, hydroquinones, diethylstilbestrol, and dienestrol.

CHAPTER 2

BACKGROUND

2.1 Advantages of Polymeric Drugs

Polymeric drugs are advantageous for many reasons. Since they are large, they cannot easily pass through biological membranes, which prevent a build-up of the drugs within the kidneys and other organs. This is particularly true for polymers with chain lengths of 100 units or more. Also, polymers slowly release their active moiety, making it less toxic to the body. Polymers may also increase the activity of the drug by allowing multiple binding at a particular site. Additionally, the structure of polymers protects the bioactive moiety from water and increases the probability of the polymeric drug being able to by-pass the cell's defense system.[10]

2.1.1 Polymeric Drugs Used in this Study

In this study, five types of polymeric drugs will be tested for both anticancer and antiviral activities. All of the polymers have an organotin subunit. Type I polymeric drugs have a dibutyltin base with varying polyethers (derived from either ethylene glycol, polyethylene glycol, or 2-butyne-1,4 diol) attached. Type II polymeric drugs are organotin polyamines made from derivatives of kinetin. Type III polymeric drugs also have a dibutyltin base with different hydroquinones attached. Type IV polymeric drugs have a diethylstilbestrol base with varying organotin moieties attached. Type V

polymeric drugs have a dienestrol base with varying organotin moieties. The activity of these polymeric drugs will be compared to the activity of dibutyltin dichloride (an organotin) and a common anticancer drug that contains platinum, cisplatin. Cisplatin is not highly active against the cell lines chosen, but it was included for comparison because it is a commonly used chemotherapeutic drug, and it has a metal as its bioactive moiety. The activity of the type V polymeric drugs will also be compared to the activity of dienestrol and diethylstilbestrol. The polymeric drugs used in this study were developed by Dr. Charles Carraher's lab at Florida Atlantic University. The following figures show example structures of each polymeric drug type. For a list of the polymeric drugs used in this study, see appendix A.

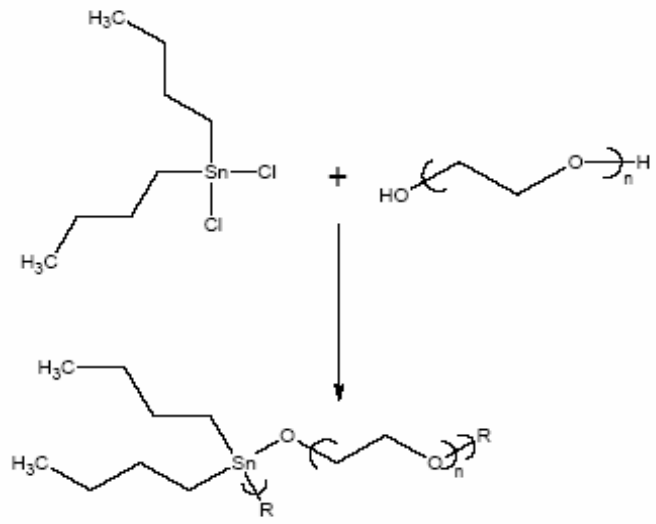

Figure 2.1 Synthesis of dibutyltin polyethylene glycol ethers (Type I polymeric drugs)

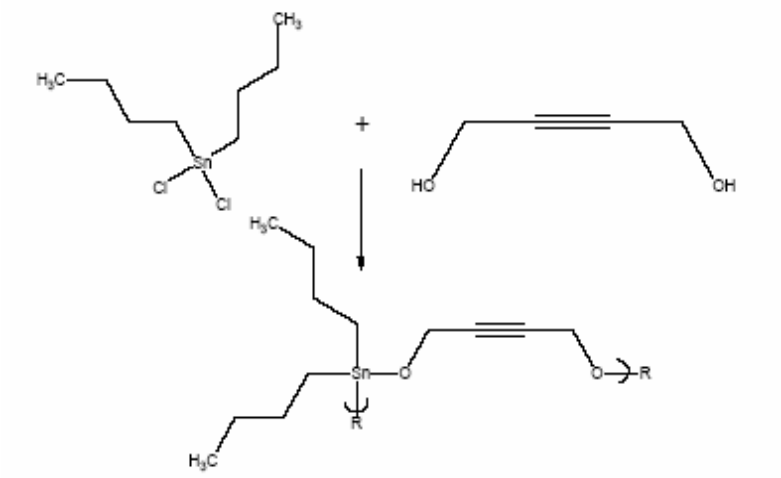

Figure 2.2 Synthesis of dibutyltin 2-butyne-1,4-diol (Type I polymeric drugs)

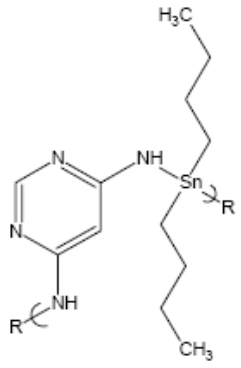

Figure 2.3 Kinetin derived polymeric drug structure (Type II polymeric drugs)

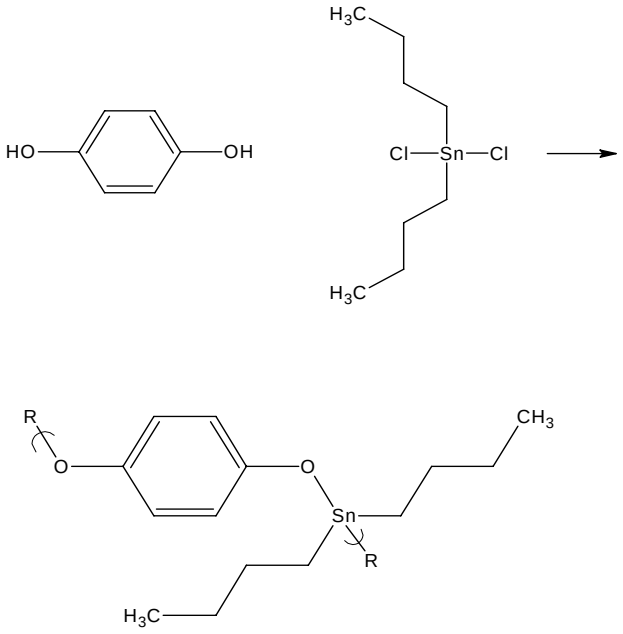

Figure 2.4 Synthesis of Organotin-hydroquinone polymers (Type III polymeric drugs)

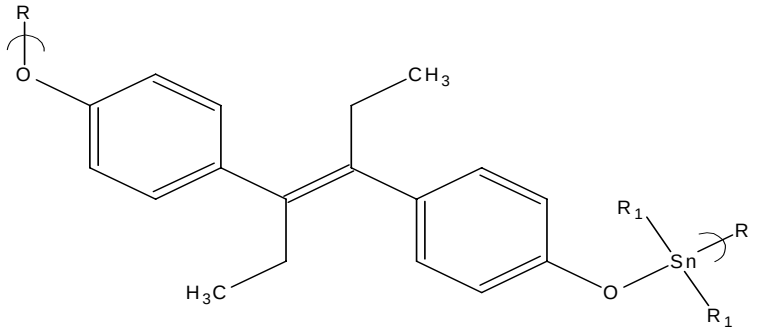

Figure 2.5 Diethylstilbestrol organotin structure (Type IV polymeric drugs)

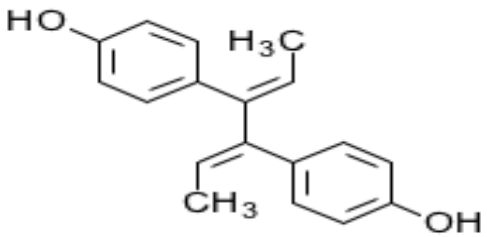

Figure 2.6 Dienestrol structure (Type V polymeric drug monomer)

2.2 Organotins as Anticancer Drugs

An organotin is a compound that contains at least one Sn-C bond.[52] Recently, the use of organotin macromolecules as anticancer drugs has been reviewed.[10,25] Organotin compounds have been tested for antitumor activities as early as 1929.[44] In his 1963 book on the subject, Furst found that chelation plays a role in both the cause and cure of malignancy. Since this discovery, molecules containing metal sites as chelating agents have been employed in the fight against cancer.[20] In 1973, tin was found to have a high affinity for tumors by Atsushi and co-workers.[2]

Organotin halides have been studied for their cancer fighting abilities. One of the first reports on the anticancer activity of organotins was published by Crowe et al in 1980. Their research involved a series of diorganotin dihalides and complexed products. They believed that a stable organotin complex was needed for good activity. Additionally, they found that the diethyltin dichloride compounds had the most anticancer activity, and strongly complexing nitrogen ligands also showed positive activity.[13]

Carderelli and his lab studied the effect of soluble organotins on tumors in mice. They found that the compounds were concentrated in the thymus gland. They thought that the anticancer properties came from the organotins being processed in the thymus into compounds that are anticarcenogens. With further experiments, they were able to isolate organotins that contained steroids.[9] They then patented several steroid-organotin compounds that showed anticancer activity.

In 1989, Saxena and Huber reviewed several studies involving organotin compounds. It was found that the use of chloride as the halide showed the best anticancer ability as compared to other halides. Their opinion is that this may be due to the formation of hydrochloric acid in the cell. However, other organotin halides have shown some activity against tumors, so organotin halides could be active antitumor agents. Saxena and Hubar also discovered that the most active organotin species were the dialkyltin compounds.[44] It should be noted that other studies have found that the dialkyltin compounds may not be the most active, and that anticancer activity varies with the cell lines used and the nature of the organotin compounds.[10]

Gielen and Willem found that tetraorganotin compounds are inactive. However, organotin halides, including those complexed with amines, exhibited some activity against P388 and L1210 leukemias. They also found that the di-*n*-butyltin compounds are the most active. They felt that this discovery was highly beneficial because di-*n*-butyltin oxides are good starting materials and are inexpensive.[24] Borenfreund and Babich's research on the cytotoxicity of organotins on neural cells and fibroblasts agreed with previous results. They used Balb-3T3 and mouse neuroblastoma cells (N_2a) in their study. They used a series of diorganotins and found that the most cytotoxic of the series were the dibutyltin compound.[6]

The structure of the organotin is important to its activity. Triorganotin compounds, which mean the compounds have three Sn-C bonds, have the highest cytotoxicity. [4,14,38,52] As previously stated, dibutyltin compounds have the highest anticancer activity. Also, compounds that contain aryl groups are less active than those

with alkyl groups.[17,33,52] The X group attached to the triorganotin has only minor effects on the activity of the compound. The X group can increase activity if it is biologically active or can assist in the transportation of the compound to the site of activity. However, the X group can decrease activity, if it is chelated to the tin atom.[4,30,52] The most active structures studied are those that contain a polyoxaalkyl moiety linked to the tin either by a carbon-tin or carbon-oxygen bond.[24,29] The structure of the polyoxaalkyl moiety structure is not as important. It can be linear, cyclical, or a crown ether.[24] Compounds with a Sn-O linkage have been shown to have better activity than compounds that have tin connected to sulfur.[7,10] The polymeric drugs used in this study have been designed to try to maximize the activity based on the structure of the compounds.

2.2.1 Effect of Organotins on Mammals

In 2001, Hoch reviewed the effects of organotins in the environment. His study set the butyltin moiety as the toxicity threshold for mammals. Chains longer than butyltin are nontoxic, and shorter chains are somewhat toxic. It was found that 24 hours after exposure in vitro to 500ng of dibutyltin, thymocyte viability was decreased by about 50%.[26] The mono-, di-, and tributyltin at a concentration of 200nM affected natural killer lymphocytes 24 hours after exposure.[58] When tissues of marine mammals were studied, it was found that the butyltin species concentrate in the liver, blubber, and muscles.[54] Lipid soluble triorganotins and diorganotins have been found to be neurotoxicants, causing neuronal changes.[6,12,33,56] Other research has shown that dibutyltin dichloride and tributyltinchloride reduce the thymus weight in rats.[21,45,46]

Further research showed that the tributyltin chloride was dealkylated to dibutyltin dichloride, which is the active compound.[51] Both in vitro and in vivo tests indicate that organotins induce apoptosis in rat thymocytes.[3,22,40]

2.2.2 Molecular Mechanism of Organotin Activity

There have been several studies to elucidate the mechanism behind the cytotoxicity of organotins. Several possible mechanisms have been described. Willem and his coworkers experimented on the interaction of two cytotoxic organotins, bis(di-*n*-butyl 3,6-dioxaheptanoato)tin and tri-*n*-butyltin 3,6,9-trioxodecanoate, with calf thymus DNA. They found that the organotins interacted with DNA, but that the interaction was not sequence or base specific. They believed that the interaction was with the external phosphate groups of the DNA.[11]

It was also found that organotins interfere with macromolecular synthesis. Dibutyltins and tributyltins suppress the synthesis of DNA and proteins, while increasing the synthesis of RNA.[21,32,50] Dibutyltin dichloride was found to inhibit oxidative phosphorylation in mitochondria.[37] The organotins interact directly with the ATP synthase complex.[8] Dialkyltins also inhibit the TCA cycle, leading to a build-up of pyruvic acid and glutarate.[37] It is thought that the mechanism behind this interference comes from the high affinity of dialkyltins for dithiols.[1] Possibly, the dialkyltins bind to the coenzyme lipoic acid or the enzyme lipoyl dehydrogenase.[37]

2.3 Description of the Subunits of the Polymeric Drugs

Polyethylene glycol (PEG) is one of the most popular materials used to make polymeric drugs.[59] It is useful for many reasons. PEG is relatively nontoxic.[36] PEG is

also readily soluble in aqueous solutions.[39] Also, PEG has low immunogenicity and antigenicity.[18] PEG also does not build-up in organs and is easily excreted by living systems.[59]

Kinetin, or 6-furfurylaminopurine, is a plant growth hormone. Kinetin is a substituted aminopurine and interacts with plant nucleic acid.[16] The effect of kinetin-derived organotin polymers on Balb3T3 cells was compared to the effect of cisplatin. Balb3T3 cells are contact-inhibited and non-tumorigenic. It was found that the kinetin-containing compounds inhibited cell growth. Kinetin by itself did not inhibit growth of the cells, leading to the conclusion that the organotin moiety is also needed for activity.[48]

Hydroquinones are commonly used in skin creams that cause depigmentation. Hydorquinones are also found naturally in fruits and vegetables. Hydroquinones are not highly cytotoxic, but they have been implicated in causing cancer. The mechanism is unknown, but it could be due to interaction with DNA. If hydroquinones are capable of interacting with DNA, then they are good candidates for having anticancer and antiviral capabilities. They are also water-soluble, which makes them good candidates for use in polymeric drugs.[15]

Dienestrol and diethylstilbestrol (DES) are synthetic estrogens used commonly as a vaginal cream to replace estrogen lost by menopause. Diethylstilbestrol has also been used in the treatment of prostate cancer. A review of DES used in prostate cancer treatment was written by Malkowicz in 2001. Diethylstilbestrol was originally used to reduce the amounts of testosterone in the body, which plays a role in the growth of

prostate cancer.[31] Further research has shown that DES can also inhibit prostate cancer cell lines. It is believed that the effect of DES on the prostate cancer cell line is through cell cycle control and apoptosis mechanisms.[41]

2.4 Cell Lines Used to Evaluate the Anticancer Activity of the Polymeric Drugs

Four cancer cell lines and two normal cell lines were used to study the anticancer abilities of the polymeric drugs. The cancer cell lines were chosen as they are part of the NCI-60 cell lines, from the National Cancer Institute, that all potential cancer drug therapies must be tested against. The four cancer cell lines were MCF-7, MDA-MB-231, HT29, and PC3. MCF-7 is a human breast adenocarcinoma cell line and is positive for estrogen receptors. MDA-MB-231 is also a human breast adenocarcinoma cell line, but MDA-MB-231 lacks estrogen receptors and is more invasive than MCF-7. HT-29 is a human colon adenocarcinoma. PC-3 is a human prostate adenocarcinoma. The two normal cell lines used were WI-38 and BALB3T3 cells. WI38 cells are human embryonic lung. 3T3 cells are immortal mouse embryo cells with high contact inhibition. WI-38 cells more closely mimic the cells of the body, as they more closely follow a normal cell cycle ending in cell death. The 3T3 cell line was included because the National Cancer Institute uses it as their normal cell line for toxicity studies.

2.5 The Link between Anticancer and Antiviral Activity

It is reasonable to assume that compounds that have anticancer activity might have antiviral activity as well. Both diseases hold the cell in a continued growth phase. The cancer causes the cell to continue growing without arrest, and the virus causes the cell to continuously replicate the virus. In both cases, there is an increased amount of

nucleic acid replication and protein synthesis occurring. Therefore, both types of diseases could have similar targets for drug activity. Several common cancer drugs have been shown to have antiviral activity. Some antiviral drugs have anticancer activity as well.

Previous research in Dr. Roner's lab has shown that cisplatin has antiviral activity, in addition to its previously known anticancer activity.[42] 5-Flurouracil is a common anticancer drug, and it was found to inhibit the replication of rinderpest virus, pseudorabies virus, and SV40 virus.[23] Hydroxyurea, another common anticancer drug, was found to inhibit polyoma virus.[35] Mercaptopurine is used in the treatment of leukemia, but was also found to have activity against human immunodeficiency virus.[43] Mitoxantron, an anthraquinone, has been show to possess both anticancer and antiviral abilities.[47,49] Conversely, Nelfinavir, which is a common protease inhibitor of HIV, has been found to decrease the viability of breast cancer cell lines.[25]

2.6 Viruses Used in this Study

Two DNA viruses were used to evaluate antiviral activity of the polymers. The two viruses are human herpes virus 1 (herpes simplex virus), Herpesviridae (HSV-1) and Vaccinia orthopoxvirus, Poxviridae (vaccinia). HSV-I and vaccinia are both enveloped, linear double-stranded DNA viruses. Vaccinia is more complex and can transcribe its genome with limited host cell machinery, and it is the strain used for the smallpox vaccine.[19] Each virus requires a different cell line for growth. HSV-1 will be grown in vero cells. Vaccinia will be grown in 143 cells.

2.6.1 Overview of HSV-1 Replication

The virion binds to the cell and releases the capsid into the cell. The capsid is then transported to the nucleus, and the viral DNA is released into the nucleus. The viral DNA is transcribed by the host RNA polymerase II. The viral proteins assemble the capsids in the nucleus, where they bud through the nuclear envelope to form an enveloped virus. The viruses are then transported out of the cell by vesicular transport by the Golgi apparatus.[19]

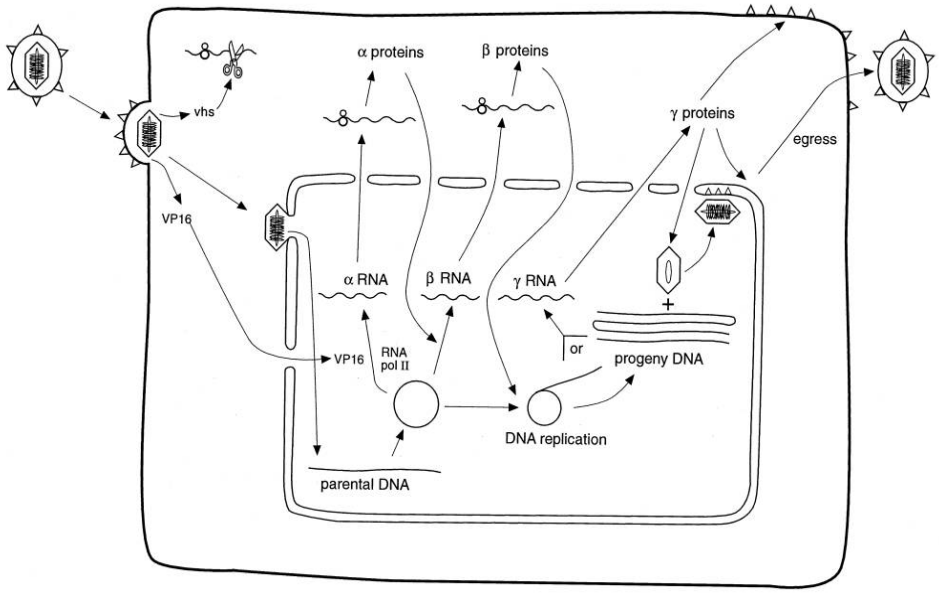

Figure 2.7 Replication scheme of HSV-1[19]

2.6.2 Overview of Vaccinia Replication

The virions attach to the cell, releasing the virion cores into the cytoplasm. The core produces early mRNAs, which are translated into the protein machinery for DNA replication and intermediate mRNA production. The virion matures in the cytoplasm. They are wrapped by modified Golgi apparatus membranes and are transported to the plasma membrane. The virions fuse with the plasma membrane and are released to produce enveloped viruses.[19]

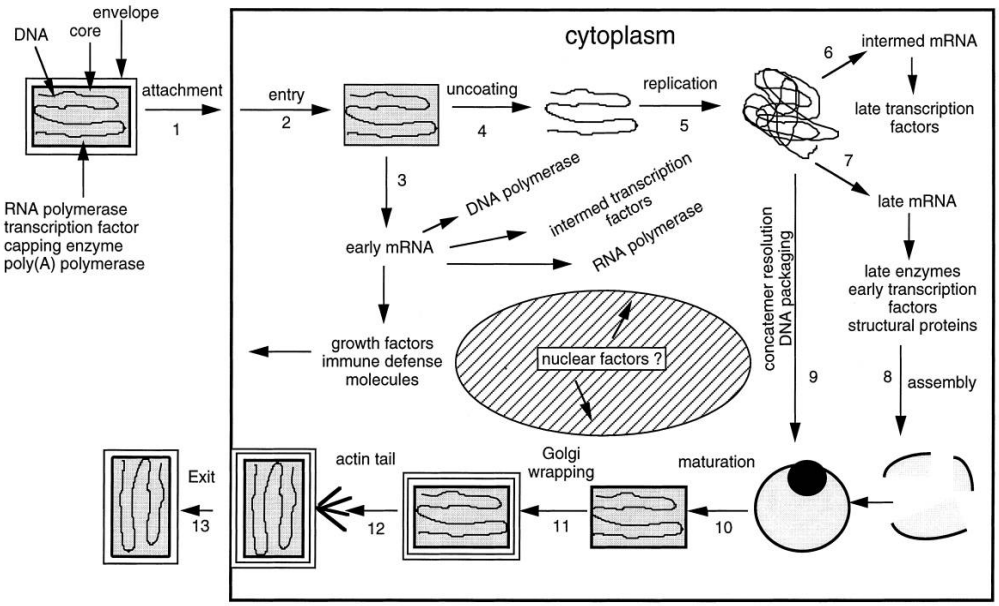

Figure 2.8 Replication scheme of Vaccinia[19]

CHAPTER 3

MATERIALS AND METHODS

3.1 Cell Maintenance and Enumeration

3.1.1 Cell Maintenance

The cell lines used were WI-38, BALB-3T3 (3T3), PC3, MDA-MB-231, HT-29, MCF-7, Vero, and 143, which were cultured in cell culture flasks so that the cells could adhere to the bottom of the flask. Two types of cells lines were used, transformed cells PC3, MDA-MB-231, HT-29, MCF-7, Vero, and 143 cells, and normal or normal-like cells, WI-38 and 3T3. The cancer cells used were PC3, MDA-MB-231, HT-29, and MCF-7. The WI-38, 3T3, PC3, MDA-MB-231, HT-29, and MCF-7 cell lines were maintained in Dulbecco's Modification of Eagles's Medium (MEM), obtained from cellgro®, supplemented with fetal bovine serum (FBS), at a final concentration of 10%, and the antibiotics penicillin [100 units/ml] and streptomycin [100 µg/ml] (APS), at a final concentration of 1X. The Vero, 143, and L929 cell lines were maintained in MEM supplemented with bovine calf serum (BCS), at a final concentration of 5%, and 1X APS. All cells are incubated at 37°C and 5% CO_2.

When the cell lines reached confluency, they were split to propagate the cells for maintenance and to seed plates for experimentation. All of the adherent cell lines were split in the same manner. The media was removed, and the cells were washed with a

1X solution of saline sodium citrate (SSC). After removal of the 1X SSC, trypsin was added to remove the cells from the bottom of the flask. After the cells were released, the appropriate media was added, and the cells were pipetted up and down to evenly mix the cells and media. The dilution ratio of the cells varied depending on need.

3.1.2 Enumeration of Cells

For the cytotoxicity assays and viral infections, $1x10^6$ cells were needed. The cells were enumerated using an hemocytometer. After the cells were trypsinized and mixed, a 1 ml pipette was inserted to remove a small amount of solution. The solution was placed into the grooves of the hemocytometer. The number of cells in five of the large squares of the hemocytometer were counted. The amount obtained was then multiplied by 2000 to calculate the number of cells per milliliter of solution. To calculate the amount of solution needed for an experiment, the number of cells needed was divided by the number of cells per milliliter.

3.2 Determining the Chemotherapeutic Index

3.2.1 Preparation of Polymeric Drug Stock

The polymeric drugs were received from Dr. Charles Carraher's laboratory at Florida Atlantic University in powder form. For all of the drugs tested, the powder form is stable at room temperature for several years, according to Dr. Carraher, based on mass spectrometric analysis. To prepare stock solutions to dilute, 1 milligram was weighed out and resuspended in DMSO. For those that are water soluble two stocks were created, one in DMSO and one in water. The stock solutions were sonicated prior to diluting to ensure a uniform solution. The stock solutions were kept in -20^oC for less

than 6 months. Dilutions were made using MEM with 10% FBS and the antibiotics penicillin [100 units/ml] and streptomycin [100 µg/ml], at a final concentration of 1X. Stock solutions were used within two months to ensure no loss of activity.

3.2.2 Cytotoxicity Assay

Cells were plated in 96 well plates at a concentration of 10,000 cells per well. The final volume of the media was 100µl. After an overnight incubation, 100µl of the polymeric drug at the appropriate dilution was added to the wells. The polymeric drug concentrations used were 0.6 µg/ml and 0.3 µg/ml, bringing the final concentration in the wells to 0.3 µg/ml and 0.15 µg/ml. The plates were then incubated for 72 hours. After 72 hours, the CellTiter 96® AQ_{ueous} One Solution Cell Proliferation Assay from Promega was used to determine cell viability. The solution contained a novel MTS tetrazolium compound that is bioreduced by cells to form a colored formazan product. Twenty µl of the solution was added to the wells. The plate was then incubated for 1-4 hours. After incubation, a UV-visible spectrophotometer, set at 490 nm, was used to measure the amount of formazan product produced by the cells in each well.

3.2.3 Calculating GI_{50} values for the polymeric drugs

There is a direct relationship between the amount of formazan product produced and the number of viable cells present. The higher the spectrophotometer absorption, the more viable cells there were in the well. Experiments were performed in triplicate. The average of the absorbances of each concentration of each polymeric drug was calculated. The average absorbance of the media only controls was subtracted from each polymeric drug and no drug control average. The % viability was then calculated

by dividing the average of the polymeric drugs by the average of the no drug control. The % viability was then graphed in Microsoft EXCEL®. The equation of the line was generated so that the concentration of each polymeric drug that lyses 50% of the cells could be calculated. This value was the 50% growth inhibition (GI_{50}). If none of the cells survived the original concentrations, then 1:10 dilutions were tested. If all of the cells survived the original concentrations, then 10 fold higher dilutions were tested.

3.2.4 Calculating the Chemotherapeutic Index for the polymeric drugs

The chemotherapeutic index is commonly used to compare the toxicity of a drug on normal cell lines to its toxicity on cancer cell lines. The chemotherapeutic index is the 50% lysis polymer drug concentration of the cancer cell divided by the 50% lysis polymer concentration of the normal cells. Chemotherapeutic indexes greater than two were considered to be significant. A chemotherapeutic index of two indicates that the polymeric drug were two times more toxic to the cancer cell than the normal cell. Since the normal cells survived at twice the concentration of the toxicity level of the cancer cells, the polymeric drug were considered to be of interest for further study. The value of two is arbitrary. It was just used as a cut-off point to determine if the drugs merited further study.

3.3 Antiviral Activity Evaluation

3.3.1 Preliminary Vaccinia and HSV-1 Antiviral Activity Evaluation

Initially, the drugs were evaluated with HSV-1 and vaccinia viruses (two DNA viruses). The activity of the drugs was tested to see if they inhibit the lysis of the WI-38 cells by the viruses. The WI-38 cells were infected with each virus at a multiplicity of

infection (MOI) of less than 1 in MEM without serum and with the highest concentration of the polymeric drug tested that was not toxic to the WI-38 cells. An MOI of less than one meant that there was less then one virus per cell in the media.

WI-38 cells were seeded in a 96 well plate at a concentration of 10,000 cells per well. After an overnight incubation, the media was removed and 50 µl of the media containing the polymeric drug and virus was added. The plate was incubated for one hour, and the plate was rocked every 15 minutes for the duration of the hour. After the one hour incubation, 150 µl of media containing the appropriate concentration of the polymeric drugs was added. The vaccinia infections were incubated for 12 hours. The HSV-1 infections were incubated for 96 hours because they take longer to replicate than the vaccinia virus. After the incubation period, the CellTiter 96® AQ_{ueous} One Solution Cell Proliferation Assay was used to determine the amount of lysis of each well. The % viability of the polymeric drugs were compared to a no drug viral infection and a no drug, no virus control. All experiments were done in triplicate. The polymeric drugs that protect at least 30% of the cells when compared to a no drug viral infection were tested further. Vaccinia and HSV-1 plaque assays were performed on the qualified drugs to determine the amount of viral inhibition.

3.3.2 Vaccinia and HSV-1 Plaque Assays

WI-38 cells were plated at 80% confluency in 24 well plates. After an overnight incubation, the media was removed and 100 µl of the media without serum containing the polymeric drug and virus (MOI<1) was added. After one hour of incubation, rocking every 15 minutes, 500µl of MEM with 10% FBS and 1X APS were

added to the wells. The vaccinia infections were incubated for 10 hours. The HSV-1 infections were incubated for 96 hours. The plates were sonicated to release all of the virus in the cells. The samples were stored at -20^{o}C until the plaque assays were performed. The infections were done in duplicate.

For the plaque assays, the viral samples were serially diluted from 10^{-1} to 10^{-4} in MEM without serum on the day of the infection. 143 (vaccinia) and vero (HSV-1) cells were plated at 80% confluency in 12 well plates. After an overnight incubation, the media was removed and 125 µl of the serial dilutions viral samples from the WI-38 infections were added. After one hour of incubation, rocking every 15 minutes, one milliliter of MEM with 5% BCS and the antibiotics penicillin [100 units/ml] and streptomycin [100 µg/ml], at a final concentration of 1X, were added to each well. After a 48 hour incubation, the media was removed, and crystal violet was added to the cells. The viable cells were stained with the crystal violet, allowing the plaques to be counted. The wells that contained between 30 and 300 plaques were counted so that the viral titer can be calculated. The GI_{50} of the drugs on the WI-38 cells and the concentration of the drug that inhibits 50% of the virus were compared. If the polymeric drugs inhibit greater than 50% of the virus, then 1:2 dilutions of that drug were tested in order to calculate the concentration of the drug that causes 50% inhibition. Also, the polymeric drugs that inhibit one virus by at least 50% were tested with the other virus. The plaque assays were done in duplicate.

CHAPTER 4

RESULTS

4.1 Anticancer Activity of the Type I Polymeric Drugs

4.1.1 Type I Polymeric Drug GI_{50} values for the cancer and control cell lines

Table 4.1 GI_{50} values, in µg/mL, of the Type I Polymeric Drugs (plus and minus one standard deviation from the mean)

Compound	WI38	3T3	PC-3	MDA-MB-231	HT-29	MCF-7
Bu_2SnCl_2	0.2 +/- .05	0.2 +/- .05	1.4 +/- 0.11	1.4 +/- 0.12	1.2 +/- 0.11	0.7 +/- .06
Cisplatin	0.05 +/-0.04	3 +/- 0.29	1 +/- 0.10	1 +/- 0.10	2 +/- 0.21	3 +/- 0.28
GB1	3 +/- 0.28	1.45 +/-0.15	1.3 +/- 0.10	1.4 +/- 0.12	1.1 +/- 0.10	1.3 +/- 0.10
GB2	1.2 +/- 0.10	0.9 +/- 0.10	0.9 +/- 0.10	1.2 +/- 0.10	1 +/- 0.10	1.2 +/- 0.10
GB3	1.1 +/- 0.10	1 +/- 0.10	1 +/- 0.10	1.2 +/- 0.10	1.6 +/- 0.15	1.2 +/- 0.11
GB5 DMSO	3.5 +/- 0.29	2.4 +/- 0.21	4.3 +/- 0.38	1.9 +/- 0.16	5 +/- 0.41	2.8 +/- 0.22
GB5 Water	0.28 +/-0.03	1.2 +/- 0.10	2.1 +/- 0.19	2.4 +/- 0.22	1.2 +/- 0.10	1.4 +/- 0.10
GB6 DMSO	0.11 +/-0.01	2.3 +/- 0.19	2.2 +/- 0.16	3.2 +/- 0.29	3.5 +/- 0.31	3.2 +/- 0.30
GB6 Water	1 +/- 0.10	10 +/- 0.92	0.25 +/- 0.01	10 +/- .93	9.2 +/- 0.88	10 +/- 0.96
GB7 DMSO	4.2 +/- 0.33	4.5 +/- 0.40	8.1 +/- 0.78	10 +/- 0.89	3 +/- 0.28	5.8 +/- 0.47
GB7 Water	1 +/- 0.10	10 +/- 1.00	10 +/- 1.00	10+/- 0.97	5 +/- 0.45	10 +/- 1.00
GB8	0.9 +/- 0.10	0.75 +/- 0.06	1.4 +/- 0.10	0.3 +/- 0.023	1 +/- 0.10	0.6 +/- 0.05
GB9	0.05 +/-0.01	0.6 +/- 0.05	0.85 +/- 0.10	0.9 +/- 0.10	0.11 +/- 0.01	1.2 +/- 0.10
GB10	0.05 +/-0.01	1 +/- 0.10	0.44 +/- 0.04	0.9 +/- 0.10	0.3 +/- 0.03	1.1 +/- 0.10
GB20	0.05 +/-0.01	0.22 +/- 0.03	0.3 +/- 0.02	0.09 +/- 0.04	0.11 +/- 0.01	0.2 +/- 0.01
GB21	0.04 +/-0.01	0.55 +/- 0.04	0.25 +/- 0.02	0.1 +/- 0.01	0.25 +/- 0.02	0.2 +/- 0.01
GB22	0.02 +/-0.01	0.12 +/- 0.02	0.21 +/-0.02	0.09 +/- 0.01	0.3 +/- 0.04	0.22 +/-0.03
GB23	0.06 +/-0.01	0.28 +/- 0.02	0.12 +/-0.01	0.22 +/- 0.02	0.1 +/- 0.01	0.15 +/-0.02
GB24	0.05 +/-0.01	0.14 +/- 0.01	1 +/- 0.15	0.35 +/- 0.04	0.1 +/- 0.01	0.22 +/-0.02
GB25	1.80 +/- 0.4	0.04 +/- 0.01	1.84 +/- 0.1	0.07 +/- 0.01	2.45 +/- 0.2	0.46 +/- 0.1
GB26	0.21 +/- 0.1	0.02 +/- 0.01	0.32 +/- 0.1	0.22 +/- 0.1	2.22 +/- 0.2	0.40 +/- 0.1
GB27	1.1 +/- 0.3	0.03 +/- 0.01	0.29 +/- 0.1	0.29 +/- 0.08	2.35 +/- 0.2	0.42 +/- 0.1
GB28	1.9 +/- 0.4	0.03 +/- 0.01	0.21 +/- 0.1	0.41 +/- 0.09	2.15 +/- 0.2	1.56 +/- 0.3
GB29	0.15 +/- 0.1	0.02 +/- 0.01	0.18 +/-0.08	0.11 +/- 0.01	2.08 +/- 0.2	0.51 +/- 0.1

The table shows the GI_{50} values of the type I polymeric drugs and the two control drugs, dibutyltin dichloride and cisplatin. The GI_{50} values are the concentration of the polymeric drugs that inhibited the growth of the cell line by 50%. The GI_{50} values were generated using the graphs in appendix B. The values in table 1 highlighted in blue are GI_{50} values of the polymeric drugs for the two control cell lines (WI38 and 3T3) that were higher than the GI_{50} values for dibutyltin dichloride. The values highlighted in red are polymeric drug values that are lower for the cancer cell lines than dibutyltin dichloride.

Many of the polymeric drugs were less toxic to the normal cells, the WI-38s and 3T3s, than the dibutyltin dichloride. GB1, GB2, GB3, GB5 (both in water and DMSO), GB6 (in water only), GB7 (both in water and DMSO), GB8, GB25, GB26, GB27, and GB28 polymeric drugs were less toxic to the WI38 cell line than dibutyltin dichloride. GB1, GB2, GB3, GB5 (both in water and DMSO), GB6 (both in water and DMSO), GB7 (both in water and DMSO), GB8, GB9, GB10, GB20, GB21, and GB23 polymeric drugs were less toxic to the 3T3 cell line than dibutyltin dichloride.

Many of the polymeric drugs showed more activity against the cancer cell lines than the WI38s. The GB1 polymeric drug had more activity against all four of the cancer cell lines than the WI38 cell line. GB2 showed higher activity against the prostate cancer (PC-3) and the colon cancer (HT-29) cell lines than the WI38 cell line. GB3 showed slightly higher activity against the PC-3 cell line than the WI38 cell line. GB5 dissolved in DMSO showed higher activity against the two breast cancer cell lines (MDA-MB-231 and MCF-7) than the WI-38s. GB6 dissolved in water showed higher

activity against the PC-3 cell line than the WI-38 cell line. GB7 dissolved in DMSO showed higher activity against the HT-29 cell line than the WI-38 cell line. GB8 showed higher activity against the MDA-MB-213 and MCF-7 cell lines than the WI-38s. GB25 also showed higher activity against the MDA-MB-213 and MCF-7 cell lines than the WI38s. GB27 and GB28 showed higher activity against all of the cancer cell lines, except HT-29, than the WI38s. GB29 showed slightly higher activity against MDA-MB-231 than the WI38 cell line. The 3T3 values were closer to the values for the cancer cell lines than the values for the WI38 cell line.

In order to study the effects of molecular weight on polymeric drug activity, a series of drugs based on GB5, GB9, GB10, and GB20 were synthesized and tested. The original polymeric drugs had a molarity of 3.0 mM. The polymeric drugs used to evaluate the effects of the molecular weight of the originals were 2.9 mM, 2.5 mM, and 2.0 mM. GB34 (2.9 mM), GB41 (2.5 mM), and GB42 (2.0 mM) were based on GB5. GB35 (2.9 mM), GB36 (2.5 mM), and GB37 (2.0 mM) were based on GB9. GB38 (2.9 mM), GB39 (2.5 mM), and GB40 (2.0 mM) were based on GB10. GB33 (2.9 mM), GB42 (2.5 mM), and GB43 (2.0 mM) were based on GB20. All of the polymeric drugs used in the molecular weight study were dissolved in DMSO.

Table 4.2 GI_{50} values, in µg/mL, of the molecular weight study of GB5, GB9, GB10, and GB20 (plus and minus one standard deviation from the mean)

Compound	WI38	3T3	PC-3	MDA-MB-231	HT-29	MCF-7
GB5	**3.5 +/- 0.29**	**2.4 +/- 0.21**	**4.3 +/- 0.38**	**1.9 +/- 0.16**	**5 +/- 0.41**	**2.8 +/- 0.22**
GB34	0.040 +/- 0.01	0.56 +/- 0.04	0.92 +/- 0.08	0.54 +/- 0.04	1.58 +/- 0.3	0.30 +/- 0.03
GB41	0.041 +/- 0.01	0.71 +/- 0.06	0.84 +/- 0.07	0.50 +/- 0.04	2.24 +/- 0.5	0.36 +/- 0.03
GB42	0.040 +/- 0.01	0.69 +/- 0.06	0.75 +/- 0.07	0.55 +/- 0.04	1.46+/- 0.3	0.34 +/- 0.03
GB9	**0.05 +/- 0.01**	**0.6 +/- 0.05**	**0.85 +/- 0.10**	**0.9 +/- 0.10**	**0.11 +/- 0.01**	**1.2 +/- 0.10**
GB35	1.71 +/- 0.21	0.85 +/- 0.06	2.74 +/- 0.4	0.51 +/- 0.04	0.58 +/- 0.03	0.34 +/- 0.03
GB36	0.26 +/- 0.05	0.84 +/- 0.07	0.90 +/- 0.07	0.50 +/- 0.04	2.20 +/- 0.2	0.35 +/- 0.03
GB37	2.05 +/- 0.03	0.84 +/- 0.08	2.16 +/- 0.3	0.54 +/- 0.04	2.41 +/- 0.2	0.62 +/- 0.04
GB10	**0.05 +/- 0.01**	**1 +/- 0.10**	**0.44 +/- 0.04**	**0.9 +/- 0.10**	**0.3 +/- 0.03**	**1.1 +/- 0.10**
GB38	0.165 +/- 0.03	0.87 +/- 0.07	0.78 +/- 0.06	0.49 +/- 0.04	0.61 +/- 0.05	0.35 +/- 0.03
GB39	0.046 +/- 0.01	0.83 +/- 0.07	0.77 +/- 0.06	0.49 +/- 0.04	0.61 +/- 0.05	0.82 +/- 0.05
GB40	0.045 +/- 0.01	0.84 +/- 0.08	0.73 +/- 0.06	0.48 +/- 0.04	0.74 +/- 0.06	0.11 +/- 0.01
GB20	**0.05 +/- 0.01**	**0.22 +/- 0.03**	**0.3 +/- 0.02**	**0.09 +/- 0.04**	**0.11 +/- 0.01**	**0.2 +/- 0.01**
GB33	0.08 +/- 0.01	0.37 +/- 0.03	2.16 +/- 0.2	2.06 +/- 0.1	0.22 +/- 0.03	0.29 +/- 0.03
GB43	0.087 +/- 0.02	.41 +/- 0.15	2.15 +/- 0.2	0.33 +/- 0.03	2.67 +/- 0.3	0.32 +/- 0.03
GB44	0.23 +/- 0.03	1.87 +/- 0.15	2.66 +/- 0.3	1.94 +/- 0.1	2.19 +/- 0.2	0.61 +/- 0.03

The values in blue are the polymeric drugs used for the molecular weight study that are higher than the values for the polymeric drug they are based on. The polymeric drugs and values in bold are the polymeric drugs the ones below are based on.

The GI_{50} values in blue are higher than the values for the polymeric drugs the compounds are based on. The lower molarities of GB5 were more toxic to the cells than the original. The lower molarities of GB9 were less toxic to the cells, except for the two breast cancer cell lines (MDA-MB-231 and MCF-7. The lower molarities of GB10 were consistently less toxic to the PC-3 and HT-29 cell lines. Only GB38 (2.9 mM) showed higher toxicity to the WI38 cell line. The lower molarities of GB10 were more toxic to the two breast cancer cell lines than the original GB10 polymeric drug.

The lower molarities of GB20 were less toxic to all of the tested cell lines than the GB20 polymeric drug.

4.1.2 Type I Polymeric Drug CI_{50} values for the cancer and control cell lines

Table 4.3 CI_{50} values of the Type I Polymeric Drugs: Comparison of cancer cell lines with WI38 cell line

Compound	WI38/PC-3	WI38/MDA-MB-231	WI38/HT-29	WI38/MCF-7
Bu_2SnCl_2	0.14	0.14	0.17	0.29
Cisplatin	0.05	0.05	0.03	0.02
GB1	**2.31**	**2.14**	**2.73**	**2.31**
GB2	1.33	1.00	1.20	1.00
GB3	1.10	0.92	0.69	0.92
GB5 DMSO	0.81	1.84	0.70	1.25
GB5 Water	0.13	0.12	0.23	0.20
GB6 DMSO	0.05	0.03	0.03	0.03
GB6 Water	**4.00**	0.10	0.11	0.10
GB7 DMSO	0.52	0.42	1.40	0.72
GB7 Water	0.10	0.10	0.20	0.10
GB8	0.64	**3.00**	0.90	1.50
GB9	0.06	0.06	0.45	0.04
GB10	0.11	0.6	0.17	0.05
GB20	0.17	0.56	0.25	0.25
GB21	0.16	0.40	0.16	0.20
GB22	0.10	0.22	0.07	0.09
GB23	0.50	0.27	0.60	0.40
GB24	0.05	0.14	0.50	0.23
GB25	0.98	**25.71**	0.7	**3.91**
GB26	0.7	0.5	0.1	0.52
GB27	**3.8**	**4.8**	0.47	**2.62**
GB28	**9.0**	**9.5**	0.88	1.22
GB29	0.8	3	0.07	0.29

The values in blue are higher than the values for dibutyltin dichloride. The ones in bold are also above two, meaning they are significant.

Table 3 shows the chemotherapeutic index for the cancer cell lines versus the WI38 cell line. The index is the GI_{50} value of the WI38 cell line divided by the GI_{50} value of the cancer cell line. A value of two was considered to be significant because

that indicates that it takes twice the concentration of the drug to kill the WI-38 cell line than the concentration required to kill the cancer cell line. The values in blue are the polymeric drugs that have a CI_{50} value greater than the CI_{50} value of the dibutyltin dichloride monomer for the cell line. The bold values are those that are higher than two. The majority of the polymeric drugs showed greater values than the dibutyltin dichloride monomer. All of the polymeric drugs and dibutyltin dichloride had higher values than cisplatin, the platinum-based anticancer drug. However, only a few of the polymeric drugs showed values higher than two.

GB1, 2-Butyne-1,4-diol dibutyltin, had CI_{50} values greater than two for all of the cancer cell lines tested. The polymeric drug with the highest activity against the prostate cancer cell line was GB28, 3-chloro-1,2-propanediol dibutyltin, with a CI_{50} value of 9.00. GB6, polyethylene glycol (molecular weight of 8,000) dibutyltin, dissolved in water, and GB27, 2,5-butanediol dibutyltin, also had high CI_{50} values for the prostate cancer cell line. GB25, 3-hexane-,5-diol dibutyltin, had the highest activity against the breast cancer cell line MDA-MB-231, with a CI_{50} value of 25.71. This value was the highest of all of the type I polymeric drug values. GB8, ethylene glycol dibutyltin, GB27, and GB28 also showed good activity against MDA-MB-231. The only polymeric drug that had a CI_{50} value greater than two for the colon cancer cell line was GB1. GB25 had the highest activity against the breast cancer cell line MCF-7, with a CI_{50} value of 3.91. GB25 had high activity against both cancer cell lines, but it was more effective against MDA-MB-231, which lacks estrogen receptors. GB27 also had

good activity against both cancer cell lines, but again, it was more effective against MDA-MB-231 than MCF-7.

Table 4.4 CI_{50} values of the Type I Polymeric Drugs: Comparison of cancer cell lines with 3T3 cell line

Compound	3T3/PC-3	3T3/MDA-MB-231	3T3/HT-29	3T3/MCF-7
Bu_2SnCl_2	0.14	0.14	0.17	0.29
Cisplatin	3.00	3.00	1.50	1.00
GB1	1.12	1.04	1.32	1.12
GB2	1.00	0.75	0.90	0.75
GB3	1.00	0.83	0.63	0.83
GB5 DMSO	0.56	1.26	0.48	0.86
GB5 Water	0.57	0.50	1.00	0.86
GB6 DMSO	1.05	0.72	0.66	0.72
GB6 Water	**40.00**	1.00	1.09	1.00
GB7 DMSO	0.56	0.45	1.50	0.78
GB7 Water	1.00	1.00	**2.00**	1.00
GB8	0.54	2.50	0.75	1.25
GB9	0.71	0.67	**5.45**	0.50
GB10	**2.27**	1.11	**3.33**	0.91
GB20	0.73	**2.44**	**2.00**	1.10
GB21	**2.20**	**5.50**	**2.20**	**2.75**
GB22	0.57	1.33	0.40	0.55
GB23	**2.33**	1.27	**2.80**	1.87
GB24	0.14	0.40	1.40	0.64
GB25	0.02	0.57	0.02	0.09
GB26	0.06	0.09	0.01	0.05
GB27	0.10	0.10	0.01	0.07
GB28	0.14	0.07	0.01	0.02
GB29	0.11	0.18	0.01	0.04

The values in blue are higher than the values for dibutyltin dichloride. The ones in bold are also above two, meaning they are significant.

Table 3 shows the chemotherapeutic index for the cancer cell lines versus the 3T3 cell line. The index is the GI_{50} value of the 3T3 cell line divided by the GI_{50} value of the cancer cell line. The values in blue are the polymeric drugs that have a CI_{50} value

greater than the CI_{50} value of the dibutyltin dichloride monomer for the cell line. The majority of the CI_{50} values for the polymeric drugs are higher than the values for the dibutyltin dichloride values, but the majority of the values are also below the values for cisplatin.

The polymeric drug with the best activity against the prostate cancer cell line compared to the 3T3 cell line is the GB6 dissolved in water, with a value of 40.00. This value was much higher than the value for cisplatin, and it was the only polymeric drug to have a higher value than cisplatin. GB21 had the highest activity against MDA-MB-231, and it was the only polymeric drug that had an activity higher than cisplatin for this breast cancer cell line. Several of the polymeric drugs had higher CI_{50} values for the HT-29 cell line than the cisplatin value, with GB9 having the highest activity, with a value of 5.45. GB21 had the highest activity against the MCF-7 cell line, with a value of 2.75. It was the only polymeric drug that had a value greater than two for MCF-7.

Table 4.5 CI_{50} values of the molecular weight study of GB5, GB9, GB10, and GB20: Comparison of cancer cell lines with WI38 cell line

Compound	WI38/PC-3	WI38/MDA-MB-231	WI38/HT-29	WI38/MCF-7
GB5	**0.81**	**1.84**	**0.70**	**1.25**
GB34	0.043	0.074	0.025	0.13
GB41	0.049	0.075	0.018	0.11
GB42	0.053	0.073	0.027	0.12
GB9	**0.06**	**0.06**	**0.45**	**0.04**
GB35	0.62	**3.35**	**2.95**	**5.03**
GB36	0.29	0.52	0.12	0.74
GB37	0.95	**3.80**	0.85	**3.31**
GB10	**0.11**	**0.6**	**0.17**	**0.05**
GB38	0.21	0.34	0.27	0.47
GB39	0.060	0.094	0.075	0.056
GB40	0.062	0.094	0.061	0.41
GB20	**0.17**	**0.56**	**0.25**	**0.25**
GB33	0.037	0.039	0.36	0.28
GB43	0.040	0.26	0.033	0.27
GB44	0.086	0.12	0.10	0.38

The values highlighted in blue are higher than the compound the polymeric drugs are based on, and the blue bolded values are values that are also over 2. The lower molarities of GB5 were less effective than the original GB5. The lower molarities of GB9 were more effective than the original GB9. The 2.5mM concentration of GB10 was the most effective. As the molarity was lowered, the activity decreased. The lower molarities of GB20 were more effective for against the colon cancer cell line and the MCF-7 breast cancer cell line, but they were less effective against the prostate cancer cell line and the MDA-MB-231 breast cancer cell line.

Table 4.6 CI_{50} values of the molecular weight study of GB5, GB9, GB10, and GB20: Comparison of cancer cell lines with 3T3 cell line

Compound	3T3/PC-3	3T3/MDA-MB-231	3T3/HT-29	3T3/MCF-7
GB5	**0.56**	**1.26**	**0.48**	**0.86**
GB34	0.61	1.04	0.35	1.87
GB41	0.85	1.42	0.32	1.97
GB42	0.92	1.25	0.47	2.03
GB9	**0.71**	**0.67**	**5.45**	**0.50**
GB35	0.31	1.67	1.47	2.50
GB36	0.93	1.68	0.38	2.40
GB37	0.39	1.56	0.35	1.35
GB10	**2.27**	**1.11**	**3.33**	**0.91**
GB38	1.12	1.78	1.43	2.49
GB39	1.08	1.69	1.36	1.01
GB40	1.15	1.75	1.14	7.64
GB20	**0.73**	**2.44**	**2.00**	**1.10**
GB33	0.17	0.18	1.68	1.28
GB43	0.66	4.27	0.53	4.41
GB44	0.70	0.96	0.85	3.07

The values in blue are higher than the values for polymeric drugs that the molecular weight studies are based on. The ones in bold are also above two, meaning they are significant.

The values highlighted in blue are higher than the compound the polymeric drugs are based on. The lower molarities of GB5 were more effective than the original GB5, except for the colon cancer cell line. The lower molarities of GB9 were more effective than the original GB9, except for the colon cancer cell line. The lower

molarities of GB10 were more effective in the two breast cancer cell lines. The lower molarities of GB20 were more effective for against the colon cancer cell line and the MCF-7 breast cancer cell line, but they were less effective against the prostate cancer cell line and the MDA-MB-231 breast cancer cell line.

4.2 Anticancer Activity of the Type II Polymeric Drugs

4.2.1 Type II Polymeric Drug GI_{50} values for the cancer and control cell lines

Table 4.7 GI_{50} values, in µg/mL, of the Type II Polymeric Drugs (plus and minus one standard deviation from the mean)

Compound	WI38	3T3	PC-3	MDA-MB-231	HT-29	MCF-7
Bu_2SnCl_2	0.2 +/- .05	0.2 +/- .05	1.4 +/- 0.11	1.4 +/- 0.12	1.2 +/- 0.11	0.7 +/- .06
Cisplatin	0.05 +/-0.04	3 +/- 0.29	1 +/- 0.10	1 +/- 0.10	2 +/- 0.21	3 +/- 0.28
AB1	1.1 +/- 0.10	0.32 +/- 0.03	1.3 +/- 0.10	1.3 +/- 0.10	2.2 +/- 0.20	1.1 +/- 0.10
AB2	1.1 +/- 0.10	0.9 +/- 0.10	1.1 +/- 0.10	1.3 +/- 0.10	0.8 +/- 0.07	1.1 +/- 0.10
AB3	1.4 +/- 0.12	0.9 +/- 0.10	1.1 +/- 0.10	1.4 +/- 0.12	0.6 +/- 0.05	1 +/- 0.10
AB4	1.4 +/- 0.10	0.9 +/- 0..08	0.9 +/- 0.08	1.5 +/- 0.13	0.7 +/- 0.05	1 +/- 0.10
AB5	0.21 +/- 0.01	0.33 +/- 0.03	0.4 +/- 0.04	0.11+/- 0.02	1 +/- 0.11	0.3 +/- 0.02
AB6	0.04 +/- 0.03	0.11 +/- 0.01	0.4 +/- 0.03	0.09 +/- 0.09	1.1 +/- 0.14	0.3 +/- 0.04
AB7	0.05 +/- 0.01	0.31 +/- 0.02	0.41 +/- 0.04	0.35 +/- 0.04	2.5 +/- 0.22	0.9 +/- 0.14
AB8	0.08 +/- 0.01	0.31 +/- 0.02	0.45 +/- 0.04	0.1 +/- 0.01	1.8 +/- 0.12	0.75 +/- 0.08
AB9	0.25 +/- 0.03	0.34 +/- 0.03	0.75 +/- 0.04	0.1 +/- 0.01	1.2 +/- 0.11	0.6 +/- 0.04

The values in blue are polymeric drug values for the normal cell lines that are above the values for the dibutyltin dichloride. The values in red are values for the cancer cell lines that are below the values for the dibutyltin dichloride.

The graphs used to generate the GI_{50} values of the type II polymeric drugs are in appendix D. Many of the type II polymeric drugs were less toxic to the normal cell lines than dibutyltin dichloride. Their GI_{50} values are highlighted in blue in the chart. The values in red indicate polymeric drugs that had more anticancer activity than dibutyltin dichloride. All of the type II polymeric drugs had more activity against the prostate cancer cell line (PC-3) than dibutyltin dichloride. All of the type II polymeric drugs, except AB3 and AB4, had more activity against the breast cancer cell line MDA-

MB-231 than dibutyltin dichloride. Only AB2, AB3, AB4, AB5, and AB6 had more activity against the colon cancer cell line (HT-29) than dibutyltin dichloride. Only AB5, AB6, and AB9 had more activity against the breast cancer cell line MCF-7 than dibutyltin dichloride.

4.2.2 Type II Polymeric Drug CI_{50} values for the cancer and control cell lines

Table 4.8 CI_{50} values of the Type II Polymeric Drugs: Comparison of the cancer cell lines and WI38

Compound	WI38/PC-3	WI38/MDA-MB-231	WI38/HT-29	WI38/MCF-7
Bu_2SnCl_2	0.14	0.14	0.17	0.29
Cisplatin	0.05	0.05	0.03	0.02
AB1	0.85	0.85	0.50	1.00
AB2	1.00	0.85	1.38	1.00
AB3	1.27	1.00	**2.33**	1.40
AB4	1.56	0.93	**2.00**	1.40
AB5	0.53	1.91	0.21	0.70
AB6	0.10	0.44	0.04	0.13
AB7	0.12	0.14	0.02	0.06
AB8	0.18	0.80	0.04	0.11
AB9	0.33	**2.50**	0.21	0.42

The values in blue are higher than the values for dibutyltin dichloride. The ones in bold are also above two, meaning they are significant.

The CI_{50} values highlighted in blue are the polymeric drugs that had higher anticancer activity than dibutyltin dichloride. Only a few of the type II polymeric drugs had significant anticancer activity compared to their toxicity to the WI38 cell line. Three of the drugs had a CI_{50} value of two or more. AB9 had significant activity against the MDA-MB-231 breast cancer cell line. AB3 and AB4 had significant activity against the colon cancer cell line (HT-29).

Table 4.9 CI_{50} values of the Type II Polymeric Drugs: Comparison of the cancer cell lines and 3T3

Compound	3T3/PC-3	3T3/MDA-MB-231	3T3/HT-29	3T3/MCF-7
Bu_2SnCl_2	0.14	0.14	0.17	0.29
Cisplatin	3.00	3.00	1.50	1.00
AB1	0.25	0.25	0.15	0.29
AB2	0.82	0.69	1.13	0.82
AB3	0.82	0.64	1.50	0.90
AB4	1.00	0.60	1.29	0.90
AB5	0.83	**3.00**	0.33	1.10
AB6	1.10	1.22	0.10	0.37
AB7	0.76	0.89	0.12	0.34
AB8	0.69	**3.10**	0.17	0.41
AB9	0.45	**3.40**	0.28	0.57

The values in blue are higher than the values for dibutyltin dichloride. The ones in bold are also above two, meaning they are significant.

Only three of the type II polymeric drugs had significant anticancer activity when compared to their toxicity to the 3T3 cell line. AB5, AB8, and AB9 showed significant activity against the MDA-MB-231 breast cancer cell line. None of the type II polymeric drugs showed significant activity against the PC-3, HT-29, or MCF-7 cancer cell lines.

4.3 Anticancer Activity of the Type III Polymeric Drugs

4.3.1 Type III Polymeric Drug GI_{50} values for the cancer and control cell lines

Table 4.10 GI_{50} values, in µg/mL, of the Type III Polymeric Drugs (plus and minus one standard deviation from the mean)

Compounds	WI38	3T3	PC-3	MDA-MB 231	HT-29	MCF-7
Bu_2SnCl_2	0.2 +/- .05	0.2 +/- .05	1.4 +/- 0.11	1.4 +/- 0.12	1.2 +/- 0.11	0.7 +/- .06
Cisplatin	0.05 +/-0.04	3 +/- 0.29	1 +/- 0.10	1 +/- 0.10	2 +/- 0.21	3 +/- 0.28
GB11	0.25 +/- 0.1	0.15 +/-0.01	2.45 +/- 0.2	0.085 +/- 0.01	0.45 +/- 0.1	2.65 +/- 0.4
GB12	2.35 +/- 0.5	0.16 +/- 0.01	2.60 +/- 0.2	0.22 +/- 0.09	0.51 +/- 0.1	1.90 +/- 0.5
GB13	1.95 +/- 0.5	0.18 +/- 0.01	0.44 +/- 0.1	0.045 +/- 0.01	0.50 +/- 0.1	1.71 +/- 0.5
GB14	2.56 +/- 0.5	0.22 +/- 0.02	0.30 +/- 0.1	0.036 +/- 0.01	0.48 +/- 0.1	1.70 +/- 0.4
GB15	1.75 +/- 0.5	0.28 +/- 0.03	2.45 +/- 0.2	0.23 +/- 0.1	0.46 +/- 0.1	2.44 +/- 0.5
GB16	2.15 +/- 0.5	0.39 +/- 0.03	2.55 +/- 0.2	0.22 +/- 0.1	0.52 +/- 0.1	1.80 +/- 0.5
GB17	0.21 +/- 0.03	0.06 +/- 0.01	0.28 +/- 0.1	0.11+/- 0.01	0.55 +/- 0.1	1.70 +/- 0.4
GB18	1.95 +/- 0.3	0.28 +/- 0.03	0.28 +/- 0.1	0.091+/- 0.01	0.63 +/- 0.1	1.69 +/- 0.4
GB19	2.00 +/- 0.5	0.24 +/- 0.02	3.45 +/- 0.2	0.13 +/- 0.01	0.41 +/- 0.1	2.37 +/- 0.5
GB30	2.22 +/- 0.5	0.44 +/- 0.04	6.45 +/- 0.2	0.12 +/- 0.01	0.66 +/- 0.1	3.90 +/- 0.5
GB31	1.85 +/- 0.3	0.38 +/- 0.04	2.75 +/- 0.2	0.38 +/- 0.09	0.56 +/- 0.1	2.56 +/- 0.5
GB32	1.80 +/- 0.3	0.11 +/- 0.01	2.2 +/- 0.1	0.086 +/- 0.01	0.57 +/- 0.1	1.72 +/- 0.4

The values in blue are polymeric drug values for the normal cell lines that are above the values for the dibutyltin dichloride. The values in red are values for the cancer cell lines that are below the values for the dibutyltin dichloride.

The graphs used to generate the GI_{50} values of the type III polymeric drugs are in appendix E. Many of the type III polymeric drugs were less toxic to the normal cell lines than dibutyltin dichloride. Their GI_{50} values are highlighted in blue in the chart. The values in red indicate polymeric drugs that had more anticancer activity than dibutyltin dichloride. GB13, GB14, GB17, and GB18 had higher activity against the prostate cancer cell line than dibutyltin dichloride. All of the type III polymeric drugs had more anticancer activity against the MDA-MB-231 breast cancer cell line and the HT-29 colon cancer cell line than dibutyltin dichloride. None of the type III polymeric drugs had more anticancer activity against the MCF-7 breast cancer cell line than dibutyltin dichloride.

4.3.2 Type III Polymeric Drug CI_{50} values for the cancer and control cell lines

Table 4.11 CI_{50} values of the Type III Polymeric Drugs: Comparison of cancer cell lines and WI38

Compounds	WI38/PC-3	WI38/MDA-MB-231	WI38/HT-29	WI38/MCF-7
Bu_2SnCl_2	0.14	0.14	0.17	0.29
Cisplatin	0.05	0.05	0.03	0.02
GB11	0.10	**2.94**	0.56	0.09
GB12	0.90	**10.68**	**4.61**	1.24
GB13	**4.43**	**43.33**	**3.90**	1.14
GB14	**8.53**	**71.11**	**5.33**	1.51
GB15	0.71	**7.61**	**3.80**	0.72
GB16	0.84	**9.77**	**4.13**	1.19
GB17	0.75	1.89	0.38	0.12
GB18	**6.96**	**21.43**	**3.10**	1.15
GB19	0.58	**15.38**	**4.88**	0.84
GB30	0.34	**18.50**	**3.36**	0.57
GB31	0.67	**4.87**	**3.30**	0.72
GB32	**4.62**	**20.93**	**3.16**	1.05

The values in blue are higher than the values for dibutyltin dichloride. The ones in bold are also above two, meaning they are significant.

The CI_{50} values highlighted in blue are the polymeric drugs that had higher anticancer activity than dibutyltin dichloride. Several of the type III polymeric drugs had significant anticancer activity compared to their toxicity to the WI38 cell line. GB13, GB14, GB18, and GB32 had significant activity against the prostate cancer cell line. The GB14 polymeric drug had the highest activity against the PC-3 cell line, with a value of 8.53. All of the type III polymeric drugs had significant activity against the MDA-MB-231 breast cancer cell line, except for GB17. GB14 had the highest activity against the MDA-MB-231 cell line, with a CI_{50} value of 71.11. All of the type III polymeric drugs had significant activity against the HT-29 colon cancer cell line, except for GB11 and GB17. GB14 had the highest activity against the HT-29 cell line, with a

value of 5.33. None of the type III polymeric drugs had significant activity against the MCF-7 breast cancer cell line.

Table 4.12 CI_{50} values of the Type III Polymeric Drugs: Comparison of cancer cell lines and 3T3

Compounds	3T3/PC-3	3T3/MDA-MB-231	3T3/HT-29	3T3/MCF-7
Bu_2SnCl_2	0.14	0.14	0.17	0.29
Cisplatin	3.00	3.00	1.50	1.00
GB11	0.06	1.76	0.33	0.06
GB12	0.06	0.73	0.31	0.08
GB13	0.41	**4.00**	0.36	0.11
GB14	0.73	**6.11**	0.46	0.13
GB15	0.11	1.22	0.61	0.11
GB16	0.15	1.77	0.75	0.22
GB17	0.21	0.55	0.11	0.04
GB18	1.00	**3.08**	0.44	0.17
GB19	0.07	1.85	0.59	0.10
GB30	0.07	**3.67**	0.67	0.11
GB31	0.14	1.00	0.68	0.15
GB32	0.05	1.28	0.19	0.06

The values in blue are higher than the values for dibutyltin dichloride. The ones in bold are also above two, meaning they are significant.

Only four of the type III polymeric drugs had significant anticancer activity compared to their toxicity to the 3T3 cell line, and they only had significant activity against the MDA-MB-231 breast cancer cell line. GB13, GB14, GB18, and GB30 had significant activity against the MDA-MB-231 cell line. GB14 had the highest activity, with a value of 6.11.

4.4 Anticancer Activity of the Type IV Polymeric Drugs

4.4.1 Type IV Polymeric Drug GI_{50} values for the cancer and control cell lines

Table 4.13 GI_{50} values, in µg/mL, of the Type IV Polymeric Drugs (plus and minus one standard deviation from the mean)

Compound	WI38	3T3	PC-3	MDA-MB-231	HT-29	MCF-7
Bu_2SnCl_2	0.2 +/- .05	0.2 +/- .05	1.4 +/- 0.11	1.4 +/- 0.12	1.2 +/- 0.11	0.7 +/- .06
Cisplatin	0.05 +/-0.04	3 +/- 0.29	1 +/- 0.10	1 +/- 0.10	2 +/- 0.21	3 +/- 0.28
Diethylstilbestrol	0.25 +/- 0.2	0.11 +/- 0.05	0.67 +/- 0.05	0.05 +/- 0.01	0.22 +/- 0.02	0.64 +/- 0.05
Zirconium	18.5 +/- 1.2	39.6 +/- 3.2	38.8 +/- 3.6	38.0 +/- 3.2	53.0 +/- 4.6	122.0 +/- 9.0
Hafnocene	18.0 +/- 1.2	41.2 +/- 3.7	35.6 +/- 3.8	44.5 +/- 3.2	52.5 +/- 4.6	94.0 +/- 8.0
Titanocene	19.0 +/- 1.2	81.0 +/- 5.1	29.4 +/- 3.0	46.0 +/- 3.2	35.0 +/- 4.6	112.0 +/- 8.5
YA1	2.5 +/- 0.5	0.08 +/- 0.01	0.74 +/- 0.05	0.05 +/- 0.01	0.45 +/- 0.04	0.62 +/- 0.05
YA2	1.6 +/- 0.5	0.09 +/- 0.01	0.53 +/- 0.05	0.47 +/- 0.04	0.42 +/- 0.03	0.65 +/- 0.05
YA3	0.05 +/- 0.01	0.33 +/- 0.09	0.09 +/- 0.01	0.16 +/- 0.01	0.26 +/- 0.01	0.55 +/- 0.05
YA4	2.3 +/- 0.5	0.10 +/- 0.03	0.81 +/- 0.05	0.09 +/- 0.01	0.49 +/- 0.04	0.66 +/- 0.05
YA5	0.22 +/- 0.2	0.17 +/- 0.02	0.10 +/- 0.01	0.21 +/- 0.02	0.22 +/- 0.01	0.50 +/- 0.05
YA6	2.3 +/- 0.5	0.08 +/- 0.01	0.85 +/- 0.05	0.11 +/- 0.02	0.12 +/- 0.01	0.65 +/- 0.05
YA7	3.1 +/- 0.5	0.08 +/- 0.01	0.76 +/- 0.05	0.04 +/- 0.01	0.51 +/- 0.04	0.80 +/- 0.05
YA8	0.25 +/- 0.2	0.05 +/- 0.05	0.77 +/- 0.05	0.17 +/- 0.02	0.23 +/- 0.02	0.81 +/- 0.05
YA9	0.20 +/- 0.2	0.37 +/- 0.05	0.20 +/- 0.02	0.32 +/- 0.03	0.36 +/- 0.05	0.80 +/- 0.05

The values in blue are polymeric drug values for the normal cell lines that are above the values for the dibutyltin dichloride. The values in red are values for the cancer cell lines that are below the values for the dibutyltin dichloride.

The graphs used to generate the GI_{50} values of the type IV polymeric drugs are in appendix F. Titanocene was included for comparison because YA7 contains this compound. Hafnocene was included for comparison because YA9 contains this compound. Zirconium was included for comparison because YA8 contains this compound. Many of the type IV polymeric drugs were less toxic to the normal cell

lines than dibutyltin dichloride or diethylstilbestrol. Their GI_{50} values are highlighted in blue in the chart. The values in red indicate polymeric drugs that had more anticancer activity than dibutyltin dichloride. YA2, YA3, YA5, and YA9 had higher activity than dibutyltin dichloride against the prostate cancer cell line. Only YA7 had higher activity than dibutyltin dichloride against the MDA-MB-231 breast cancer cell line. Only YA6 had higher activity than dibutyltin dichloride against the colon cancer cell line. YA1, YA3. and YA5 had higher activity than dibutyltin dichloride against the MCF-7 cancer cell line.

4.4.2 Type IV Polymeric Drug CI_{50} values for the cancer and control cell lines

Table 4.14 CI_{50} values of the Type IV Polymeric Drugs: Comparison of cancer cell lines and WI38

Compounds	WI38/PC-3	WI38/MDA-MB-231	WI38/HT-29	WI38/MCF-7
Bu_2SnCl_2	0.14	0.14	0.17	0.29
Cisplatin	0.05	0.05	0.03	0.02
Diethylstilbestrol	0.4	5	1.1	0.4
Zirconium	0.48	0.49	0.35	0.15
Hafnocene	0.51	0.40	0.34	0.19
Titanocene	0.65	0.41	0.54	0.17
YA1	**3.4**	**50.0**	**5.6**	**4**
YA2	**3.0**	3.4	**3.8**	**2.5**
YA3	1.8	0.3	0.2	0.1
YA4	**2.8**	**25.6**	**4.7**	**3.5**
YA5	**2.2**	1.0	1.0	0.4
YA6	**2.7**	**20.9**	**19.2**	**3.5**
YA7	**4.1**	**77.5**	**6.1**	**3.9**
YA8	0.3	1.5	1.1	0.3
YA9	1.0	0.6	0.6	0.3

The values in blue are higher than the values for dibutyltin dichloride. The ones in bold are also above two, meaning they are significant.

Many of the type IV polymeric drugs had significant anticancer activity compared to their toxicity to the WI38 cell line. All of the type IV polymeric drugs had significant activity against the prostate cancer cell line, except YA3 and YA8. YA7 had

the highest activity against the PC-3 cell line, with a value of 4.1. YA1, YA4, YA6, and YA7 had significant activity against the MDA-MB-231 breast cancer cell line. YA7 had the highest activity against the MDA-MB-231 cell line, with a value of 77.5. YA1, YA2, YA4, YA6, and YA7 had significant activity against the HT-29 colon cancer cell line. YA6 had the highest activity against the HT-29 cell line, with a CI_{50} value of 19.2. YA1, YA2, YA4, YA6, and YA7 had significant activity against the MCF-7 breast cancer cell line. YA1 had the highest activity against the MCF-7 cell line, with a CI_{50} value of 4. YA7 had significant activity against all of the cancer cell lines, and its activity was higher than dibutyltin dichloride, cisplatin, diethylstilbestrol, and titanocene.

Table 4.15 CI_{50} values of the Type IV Polymeric Drugs: Comparison of cancer cell lines and 3T3

Compounds	3T3/PC-3	3T3/MDA-MB-231	3T3/HT-29	3T3/MCF-7
Bu_2SnCl_2	0.14	0.14	0.17	0.29
Cisplatin	3.00	3.00	1.50	1.00
Diethylstilbestrol	0.16	2.20	0.50	0.17
Zirconium	1.02	1.04	0.75	0.32
Hafnocene	1.16	0.93	0.78	0.44
Titanocene	2.76	1.76	2.31	0.72
YA1	0.11	1.60	0.18	0.13
YA2	0.17	0.19	0.21	0.14
YA3	**3.67**	2.06	0.01	0.60
YA4	0.12	1.11	0.20	0.15
YA5	1.70	0.81	0.77	0.34
YA6	0.09	0.73	0.67	0.12
YA7	0.11	2.00	0.16	0.10
YA8	0.06	0.29	0.22	0.06
YA9	1.85	1.16	1.03	0.46

The values in blue are higher than the values for dibutyltin dichloride. The ones in bold are also above two, meaning they are significant.

Only one type IV polymeric drug had significant anticancer activity when compared to its toxicity to the 3T3 cell line. YA3 had significant activity against the PC-3 prostate cancer cell line, with a value of 3.67.

4.5 Anticancer Activity of the Type V Polymeric Drugs

4.5.1 Type V Polymeric Drug GI_{50} values for the cancer and control cell lines

Table 4.16 GI_{50} values, in µg/mL, of the Type V Polymeric Drugs (plus and minus one standard deviation from the mean)

Compound	WI38	3T3	PC-3	MDA-MB-231	HT-29	MCF-7
Bu_2SnCl_2	0.2 +/- .05	0.2 +/- .05	1.4 +/- 0.11	1.4 +/- 0.12	1.2 +/- 0.11	0.7 +/- .06
Cisplatin	0.05 +/-0.04	3 +/- 0.29	1 +/- 0.10	1 +/- 0.10	2 +/- 0.21	3 +/- 0.28
Dienestrol	0.25 +/- 0.2	0.05 +/- 0.01	0.66 +/- 0.05	0.11 +/- 0.02	0.31 +/- 0.02	0.44 +/- 0.05
Zirconium	18.5+/- 1.2	39.6+/- 3.2	38.8+/- 3.6	38.0+/- 3.2	53.0+/- 4.6	122.0 +/- 9.0
Hafnocene	18.0+/- 1.2	41.2+/- 3.7	35.6+/- 3.8	44.5+/- 3.2	52.5+/- 4.6	94.0 +/- 8.0
Titanocene	19.0+/- 1.2	81.0 +/- 5.1	29.4+/- 3.0	46.0+/- 3.2	35.0+/- 4.6	112.0 +/- 8.5
YA12	0.06 +/- 0.01	0.11 +/- 0.05	0.77 +/- 0.05	0.03 +/- 0.01	0.33 +/- 0.02	0.76 +/- 0.05
YA13	1.5 +/- 0.5	0.08 +/- 0.02	0.81 +/- 0.06	0.13 +/- 0.02	0.36 +/- 0.03	0.76 +/- 0.06
YA14	1.4 +/- 0.5	0.09 +/- 0.02	0.68 +/- 0.05	0.04 +/- 0.01	0.46 +/- 0.04	0.81 +/- 0.06
YA15	0.31 +/- 0.2	0.08 +/- 0.01	0.68 +/- 0.06	0.21 +/- 0.02	0.28 +/- 0.02	0.69 +/- 0.05
YA16	0.26 +/- 0.2	0.15 +/- 0.01	0.31 +/- 0.04	0.24 +/- 0.02	0.21 +/- 0.01	0.70 +/- 0.05
YA17	0.19 +/- 0.2	0.16 +/- 0.01	0.28 +/- 0.04	0.31 +/- 0.04	0.40 +/- 0.04	0.70 +/- 0.05
YA18	0.91 +/- 0.3	0.07 +/- 0.01	0.59 +/- 0.05	0.08 +/- 0.01	0.09 +/- 0.01	0.72 +/- 0.05
YA22	2.5 +/- 0.5	0.07 +/- 0.01	0.61 +/- 0.05	0.16 +/- 0.02	0.24 +/- 0.02	0.55 +/- 0.05

The values in blue are polymeric drug values for the normal cell lines that are above the values for the dibutyltin dichloride. The values in red are values for the cancer cell lines that are below the values for the dibutyltin dichloride.

The graphs used to generate the GI_{50} values of the type V polymeric drugs are in appendix G. Titanocene was included for comparison to YA18, which contains the compound. Hafnocene was included for comparison to YA22, which contains the compound. Many of the type V polymeric drugs were less toxic to the WI38 cell line than dibutyltin dichloride. None of the type V polymeric drugs were less toxic to the 3T3 cell line than dibutyltin dichloride. Their GI_{50} values are highlighted in blue in the chart. The values in red indicate polymeric drugs that had more anticancer activity than

dibutyltin dichloride. YA18, YA17, YA18, and YA22 had more anticancer activity than dibutyltin dichloride against the prostate cancer cell line. YA12, YA14, and YA18 had more anticancer activity than dibutyltin dichloride against the MDA-MB-231 breast cancer cell line. YA15, YA16, YA17, YA18, and YA22 had more anticancer activity than dibutyltin dichloride against the MCF-7 breast cancer cell line.

4.5.2 Type V Polymeric Drug CI_{50} values for the cancer and control cell lines

Table 4.17 CI_{50} values of the Type V Polymeric Drugs: Comparison of cancer cell lines and WI38

Compounds	WI38/PC-3	WI38/MDA-MB-231	WI38/HT-29	WI38/MCF-7
Bu_2SnCl_2	0.14	0.14	0.17	0.29
Cisplatin	0.05	0.05	0.03	0.02
Dienestrol	0.4	2.2	0.8	0.6
Hafnocene	0.51	0.40	0.34	0.19
Titanocene	0.65	0.41	0.54	0.17
YA12	0.08	2.0	0.18	0.08
YA13	1.9	**11.54**	**4.2**	1.97
YA14	**2.1**	**35.0**	**3.04**	1.7
YA15	0.46	1.48	1.1	0.45
YA16	0.8	1.1	1.2	0.4
YA17	0.7	0.6	0.5	0.3
YA18	1.5	**11.4**	**10.1**	1.3
YA22	**4.1**	**15.6**	**10.4**	**4.5**

The values in blue are higher than the values for dibutyltin dichloride. The ones in bold are also above two, meaning they are significant.

Several of the type V polymeric drugs had significant anticancer activity compared to their toxicity to the WI38 cell line. YA14 and YA22 had significant activity against the prostate cancer cell line. YA22 had the highest activity, with a CI_{50} value of 4.1. YA13, YA14, YA18, and YA22 had significant activity against the MDA-MB-231 breast cancer cell line. YA14 had the highest activity, with a CI_{50} value of 35. YA13, YA14, YA18, and YA22 had significant activity against the colon cancer cell line. YA22 had the highest activity, with a CI_{50} value of 10.4. YA22 had

significant activity against the MCF-7 breast cancer cell line, with a CI_{50} value of 4.5. All of the type V polymeric drugs with significant anticancer activity had much higher activities than dibutyltin dichloride, dienestrol, titanocene, and hafnocene.

Table 4.18 CI_{50} values of the Type V Polymeric Drugs: Comparison of cancer cell lines and 3T3

Compounds	3T3/PC-3	3T3/MDA-MB-231	3T3/HT-29	3T3/MCF-7
Bu_2SnCl_2	0.14	0.14	0.17	0.29
Cisplatin	3.00	3.00	1.50	1.00
Dienestrol	0.08	0.45	0.16	0.11
Hafnocene	1.16	0.93	0.78	0.44
Titanocene	2.76	1.76	2.31	0.72
YA12	0.14	**3.67**	0.33	0.14
YA13	0.10	0.62	0.22	0.11
YA14	0.13	**2.25**	0.20	0.11
YA15	0.12	0.38	0.29	0.12
YA16	0.48	0.63	0.71	0.21
YA17	0.57	0.52	0.40	0.23
YA18	0.12	0.88	0.78	0.10
YA22	0.11	0.44	0.29	0.13

The values in blue are higher than the values for dibutyltin dichloride. The ones in bold are also above two, meaning they are significant.

Two of the type V polymeric drugs had significant anticancer activity compared to their toxicity to the 3T3 cell line. YA12 and YA14 had significant activity against the MDA-MB-231 breast cancer cell line. YA12 had the highest activity, with a CI_{50} value of 3.67.

4.6 Antiviral Activity of the Polymeric Drugs

4.6.1 Preliminary Antiviral Activity of the Type I Polymeric Drugs

Table 4.19 Screen for the percentage of WI38 cells protected (with standard deviations) by the type I polymeric drugs from HSV-1 and Vaccinia.

Compound	Concentration (in micrograms/mL)	Average % of cells protected from HSV-1	Standard Deviation HSV-1	Average % of cells protected from Vaccinia	Standard Deviation Vaccinia
Bu_2SnCl_2	0.15	16.58	21.53	20.95	11.63
Cisplatin	0.015	12.88	2.28	0	23.97
GB1	0.3	0	9.26	0	20.74
GB2	0.3	3.43	5.49	0	13.58
GB3	0.3	0.03	11.02	0	17.83
GB5 DMSO	0.015	0	2.42	0	14.51
GB5 Water	0.015	0	19.45	29.63	8.69
GB6 DMSO	0.015	7.15	11.79	0	18.81
GB6 Water	0.015	7.65	15.24	0	9.43
GB7 DMSO	3	0	12.72	13.77	24.60
GB7 Water	0.3	0	13.84	0	27.51
GB8	0.15	8.32	8.55	6.53	5.17
GB9	0.015	11.59	6.12	3.89	1.80
GB10	0.015	5.19	6.54	0	26.36
GB20	0.015	0	10.53	0	15.46
GB21	0.015	0	11.92	13.07	11.62
GB22	0.015	0	3.41	5.38	38.37
GB23	0.015	0	4.88	0	24.91
GB24	0.015	22.36	22.39	1.57	36.49
GB25	1	0	0.23	0	21.68
GB26	0.15	46.08	14.43	1.23	11.42
GB27	0.15	16.88	24.90	0.12	12.54
GB28	1	0	1.58	0	17.37
GB29	0.015	10.18	4.52	21.83	0.24

The percentages in blue were considered to be high enough to merit further viral testing. The polymeric drugs that gave those values were tested by plaque assays.

Most of the type I polymeric drugs did not have antiviral activity. Only GB26 was chosen for further testing with the HSV-1 virus. GB5 in water, GB7 in DMSO, GB9, GB21, GB22, and GB24 were chosen for further testing with the vaccinia virus. Some of those chosen protected less than thirty percent of the WI38 cells, but the viral-infected control used for comparison with those polymeric drugs only lysed five percent

of the cells. Dibutyltin dichloride will be further tested with both viruses for comparison.

4.6.2 Preliminary Antiviral Activity of the molecular weight study of GB5, GB9, GB10, and GB20

Table 4.20 Screen for the percentage of WI38 cells protected (with standard deviations) by GB5, GB9, GB10, and GB20 with varying molecular weights from HSV-1 and Vaccinia.

Compound	Concentration (in micrograms/mL)	Average % of cells protected from HSV-1	Standard Deviation HSV-1	Average % of cells protected from Vaccinia	Standard Deviation Vaccinia
GB5	0.015	0	2.42	0	14.51
GB34	0.015	32.33	15.26	0	7.26
GB41	0.015	0	1.61	4.75	10.59
GB42	0.015	0	3.81	0	24.94
GB9	0.015	11.59	6.12	3.89	1.80
GB35	0.3	0	14.11	0	8.05
GB36	0.15	0	10.88	0	18.80
GB37	0.3	3.00	5.58	1.98	9.61
GB10	0.015	5.19	6.54	0	26.36
GB38	0.03	0	3.75	0	27.01
GB39	0.03	0	18.01	6.81	39.55
GB40	0.03	0	4.26	0	14.61
GB20	0.015	0	10.53	0	15.46
GB33	0.03	14.77	22.92	4.01	26.21
GB43	0.03	0	11.14	0	1.49
GB44	0.03	0.30	2.48	4.99	1.68

The percentages in blue were considered to be high enough to merit further viral testing. The polymeric drugs that gave those values were tested by plaque assays.

GB34, which has a lower molecular weight, had higher activity against the HSV-1 virus than GB5, the polymeric drug it is based on. GB34 was the only polymeric drug chosen for further testing with HSV-1 from this group. GB33, which has a lower molecular weight, had higher activity against the vaccinia virus than GB20, the polymeric drug it is based on. GB33 was the only polymeric drug from this group chosen for further testing with vaccinia.

4.6.3 Preliminary Antiviral Activity of the Type II Polymeric Drugs

Table 4.21 Screen for the percentage of WI38 cells protected (with standard deviations) by the type II polymeric drugs from HSV-1 and Vaccinia.

Compound	Concentration (in micrograms/mL)	Average % of cells protected from HSV-1	Standard Deviation HSV-1	Average % of cells protected from Vaccinia	Standard Deviation Vaccinia
AB1	0.3	30.90	8.61	0	8.65
AB2	0.3	16.44	14.55	0	19.19
AB3	0.3	19.15	12.73	0	9.63
AB4	0.3	21.11	16.96	0	26.61
AB5	0.03	19.01	5.86	18.69	17.17
AB6	0.015	0	6.08	0	24.94
AB7	0.015	17.28	16.98	0	16.76
AB8	0.015	7.65	21.21	0	6.06
AB9	0.015	19.01	5.86	19.60	16.36

The percentages in blue were considered to be high enough to merit further viral testing. The polymeric drugs that gave those values were tested by plaque assays.

AB1 was the only type II polymeric drug chosen for further study with HSV-1. AB5 and AB9 were the only type II polymeric drugs chosen for further study with vaccinia. Both gave a value of less than thirty percent, but the viral-infected WI38 cells used for comparison only lysed five percent of the cells.

4.6.4 Preliminary Antiviral Activity of the Type III Polymeric Drugs

Table 4.22 Screen for the percentage of WI38 cells protected (with standard deviations) by the type III polymeric drugs from HSV-1 and Vaccinia.

Compound	Concentration (in micrograms/mL)	Average % of cells protected from HSV-1	Standard Deviation HSV-1	Average % of cells protected from Vaccinia	Standard Deviation Vaccinia
GB11	0.15	0	21.77	0	14.43
GB12	0.3	35.19	10.62	1.43	5.35
GB13	0.03	21.36	8.65	20.33	6.57
GB14	0.3	10.18	4.52	26.75	8.53
GB15	0.3	69.69	9.63	26.81	5.90
GB16	0.3	77.80	19.95	0	8.50
GB17	0.15	33.18	13.73	9.79	0.61
GB18	0.3	0	0.34	5.50	3.37
GB19	0.3	0	0.34	0	3.95
GB30	0.3	0	2.25	0	16.05
GB31	0.3	19.97	2.02	3.94	12.63
GB32	0.3	0	1.01	22.98	14.96

The percentages in blue were considered to be high enough to merit further viral testing. The polymeric drugs that gave those values were tested by plaque assays.

The type V polymeric drugs showed the most antiviral activity, but they only had major activity against the HSV-1 virus. GB12, GB15, GB16, and GB17 were chosen for further testing with HSV-1.

4.6.5 Preliminary Antiviral Activity of the Type IV Polymeric Drugs

Table 4.23 Screen for the percentage of WI38 cells protected (with standard deviations) by the type IV polymeric drugs from HSV-1 and Vaccinia.

Compound	Concentration (in micrograms/mL)	Average % of cells protected from HSV-1	Standard Deviation HSV-1	Average % of cells protected from Vaccinia	Standard Deviation Vaccinia
Diethylstilbestrol	0.15	0	6.67	19.34	19.95
Zirconium	5	0	3.75	2.72	4.28
Hafnocene	5	1.50	27.63	0	1.80
Titanocene	5	0	8.33	0	0.34
YA1	0.3	1.80	4.65	0.72	10.25
YA2	0.3	0	5.78	1.12	5.62
YA3	0.015	0	1.18	3.08	4.49
YA4	0.15	0	3.04	31.90	45.90
YA5	0.15	3.23	25.92	8.38	3.79
YA6	0.3	24.37	11.51	5.30	6.12
YA7	0.3	21.43	13.74	0	17.29
YA8	0.15	12.83	12.21	35.73	28.45
YA9	0.15	0	9.41	15.87	0.98

The percentages in blue were considered to be high enough to merit further viral testing. The polymeric drugs that gave those values were tested by plaque assays.

Only two of the type IV polymeric drugs were chosen for further study. YA4 and YA8 were chosen for further study with the vaccinia virus.

4.6.6 Preliminary Antiviral Activity of the Type V Polymeric Drugs

Table 4.24 Screen for the percentage of WI38 cells protected (with standard deviations) by the type V polymeric drugs from HSV-1 and Vaccinia.

Compound	Concentration (in micrograms/mL)	Average % of cells protected from HSV-1	Standard Deviation HSV-1	Average % of cells protected from Vaccinia	Standard Deviation Vaccinia
Dienestrol	0.015	0	7.81	6.41	6.42
YA12	0.3	23.85	4.28	26.20	7.15
YA13	0.3	5.06	9.01	23.78	12.21
YA14	0.3	6.90	16.34	10.34	10.64
YA15	0.015	0	5.33	9.62	13.85
YA16	0.015	0.69	4.23	25.63	12.25
YA17	0.15	2.52	4.38	10.71	7.73
YA18	0.015	0	8.60	4.32	13.47
YA22	0.3	0	10.78	16.30	7.73

None of the type V polymeric drugs had significant antiviral activity, so none of them were chosen for further study with either virus.

4.6.7 Plaque Assay Results of HSV-1 with the Polymeric Drugs Tested

Table 4.25 Percentage of inhibition of HSV-1 (with standard deviations) by the tested polymeric drugs

Drug name	Plaque Assay Results: % of Virus Produced				Average % of Virus Produced	Average % Inhibition	SD
	1	2	3	4			
GB8	67.81	60.83	113.59	105.88	87.03	12.97	26.56
AB1	6.91	7.23	61.47	42.15	29.44	70.56	27.01
AB1 1:2	100.85	77.50	74.76	71.76	81.22	18.78	13.30
GB34	80.43	90.14	75.00	65.97	77.89	22.11	10.12
GB26	83.91	83.57	31.18	31.68	57.58	42.42	30.20
GB12	32.61	30.05	21.76	33.51	29.48	70.52	5.35
GB12 1:2	111.68	70.83	33.98	40.00	64.12	35.88	35.58
GB15	23.04	32.86	3.18	2.91	15.50	84.50	14.93
GB15 1:2	92.59	88.33	58.25	42.35	70.38	29.62	24.14
GB16	53.48	52.58	27.35	31.94	41.34	58.66	13.64
GB16 1:2	91.45	80.00	50.49	74.12	74.01	25.99	17.26
GB17	18.26	22.54	22.35	15.71	19.71	80.29	3.32
GB17 1:2	109.40	73.13	30.10	37.65	62.57	37.43	36.42
GB24	86.09	103.76	98.53	93.72	95.52	4.48	7.51
Dibutyltin dichloride	56.09	70.89	30.29	28.01	46.32	53.68	20.75
BuSn 1:2	109.40	62.29	95.15	127.06	98.47	1.53	27.43
No Drug	100.00	100.00	100.00	100.00	100.00	0.00	0.00

The polymeric drugs highlighted in red inhibited the HSV-1 virus by at least fifty percent.

The chart contains the percentage of inhibition caused by the tested polymeric drugs. The values in red indicate that the polymeric drugs inhibited at least fifty percent of the virus. GB8 was tested because it inhibited at least fifty percent of the vaccinia

virus when tested. If the polymeric drug inhibited at least fifty percent of the virus, then a one to two dilution of the polymeric drug was tested. AB1, GB12, GB15, GB16, GB17, and dibutyltin dichloride inhibited HSV-1 production by at least fifty percent. GB15 had the highest activity with 84.50% inhibition. All of the polymeric drugs with over fifty percent inhibition had more inhibition than dibutyltin dichloride.

4.6.8 Concentration of polymeric drugs tested that causes inhibition of 50% of HSV-1 compared with the concentration that kills 50% of the WI38 and 3T3 cell lines

Table 4.26 Concentration that causes inhibition of 50% of HSV-1 compared with the concentration that kills 50% of the WI38 and 3T3 cell lines

Drug name	Calculated concentration that causes 50% inhibition of HSV-1 (in micrograms/mL)	Concentration that causes death of 50% of WI38 cells	Concentration that causes death of 50% of 3T3 cells	HSV-1 compared to WI38	HSV-1 compared to 3T3
AB1	0.23	1.1	0.32	**4.78**	1.39
GB12	0.211	2.35	0.16	**11.14**	0.76
GB15	0.206	1.75	0.28	**8.50**	1.36
GB16	0.26	2.15	0.39	**8.27**	1.5
GB17	0.097	0.21	0.06	**2.16**	0.62
Dibutyltin dichloride	0.145	0.2	0.2	1.38	1.38

The comparison values in red are those that are higher than the comparison value of dibutyltin dichloride. The values in bold are also higher than two and are considered to be significant.

AB1, GB12, GB15, GB16, and GB17 had higher chemotherapeutic indexes than dibutyltin dichloride, and all of the chemotherapeutic indexes were greater than two. The highest activity against HSV-1 was with GB-12. GB12 had a chemotherapeutic index of 11.14.

4.6.9 Plaque Assay Results of Vaccinia with the Polymeric Drugs Tested

Table 4.27 Percentage of inhibition of vaccinia (with standard deviations) by the tested polymeric drugs

Drug name	Plaque Assay Results: % of Virus Produced				Average % of Virus Produced	Average % Inhibition	SD
	1	2	3	4			
YA4	52.78	137.84	50.55	95.52	84.17	15.83	41.33
YA8	52.78	118.92	43.96	123.88	84.88	15.12	42.37
GB5W	72.13	154.55	68.81	116.67	103.04	-3.04	40.68
GB7D	70.49	161.36	53.21	75.56	90.16	9.84	48.43
GB8	29.84	43.18	32.11	43.33	37.12	62.88	7.15
GB8 1:2	52.92	62.79	71.21	86.67	68.40	31.60	14.29
GB9	95.08	111.36	70.64	76.67	88.44	11.56	18.48
GB21	72.13	60.68	71.56	45.56	62.48	37.52	12.45
GB22	96.72	53.18	67.89	46.67	66.11	33.89	22.25
GB24	104.92	54.32	79.82	52.22	72.82	27.18	24.80
AB1	38.96	45.54	60.61	54.00	49.78	50.22	9.49
AB5	157.38	113.64	44.95	50.00	91.49	8.51	53.91
AB9	83.61	102.27	85.32	78.89	87.52	12.48	10.20
GB33	109.84	118.18	56.88	74.44	89.84	10.16	29.02
GB12	44.97	39.15	76.52	61.33	55.49	44.51	16.87
GB15	42.53	36.43	55.30	43.33	44.40	55.60	7.89
GB15 1:2	30.06	56.15	52.02	55.24	48.37	51.63	12.33
GB15 1:4	71.16	93.98	59.48	89.26	78.47	21.53	16.03
GB16	41.40	39.15	59.09	60.67	50.08	49.92	11.38
GB17	48.21	47.67	44.70	22.67	40.81	59.19	12.20
GB17 1:2	68.71	74.62	65.92	63.33	68.14	31.86	4.84
GB17 1:4	78.60	125.30	86.93	84.56	93.85	6.15	21.26
$BuSnCl_2$	22.79	11.36	23.85	23.33	20.33	79.67	6.00
BuSn 1:2	48.21	56.40	49.24	52.00	51.46	48.54	3.66
BuSn 1:4	57.209302	78.9157	123.529	89.9329	87.396816	12.6032	27.6599
No Drug	100.00	100.00	100.00	100.00	100.00	0.00	0.00

The polymeric drugs highlighted in red inhibited the vaccinia virus by at least fifty percent.

The chart contains the percentage of inhibition caused by the tested polymeric drugs. The values in red indicate that the polymeric drugs inhibited at least fifty percent of the virus. AB1, GB12, GB15, GB16, and GB17 were tested because they inhibited at least fifty percent of the vaccinia virus when tested. If the polymeric drug inhibited at least fifty percent of the virus, then a one to two dilution of the polymeric drug was tested. One to four dilutions of some of the polymeric drugs were also tested, because the one to two dilutions did cause a fifty percent reduction of viral production compared to the non-diluted virus. The one to four dilutions did have a fifty percent of more reduction of viral production compared to the one to two dilutions. GB8, AB1, GB12, GB15, GB16, GB17, and dibutyltin dichloride inhibited vaccinia production by at least fifty percent. Dibutyltin dichloride had the highest activity with 79.67% inhibition.

4.6.10 Concentration of polymeric drugs tested that causes inhibition of 50% of Vaccinia compared with the concentration that kills 50% of the WI38 and 3T3 cell lines

Table 4.28 Concentration that causes inhibition of 50% of vaccinia compared with the concentration that kills 50% of the WI38 and 3T3 cell lines

Drug name	Calculated concentration that causes 50% inhibition of vaccinia (in micrograms/mL)	Concentration that causes death of 50% of WI38 cells	Concentration that causes death of 50% of 3T3 cells	Vaccinia compared to WI38	Vaccinia compared to 3T3
GB8	0.119	0.9	0.75	**7.56**	**6.302521**
AB1	0.3	1.1	0.32	**3.67**	1.066667
GB15	0.146	1.75	0.16	**11.99**	1.09589
GB16	0.3	2.15	0.28	**7.17**	0.933333
GB17	0.0998	0.21	0.39	**2.10**	**3.907816**
Dibutyltin dichloride	0.078	0.2	0.06	**2.56**	0.769231

The comparison values in red are those that are higher than the comparison value of dibutyltin dichloride. The values in bold are also higher than two and are considered to be significant.

GB8, AB1, GB15, and GB16 had higher chemotherapeutic indexes than dibutyltin dichloride, and all of the chemotherapeutic indexes were greater than two. The highest activity against vaccinia was with GB15. GB15 had a chemotherapeutic index of 11.99.

CHAPTER 5

DISCUSSION AND CONCLUSION

Three types of cells were used to evaluate the anticancer and antiviral activity of our test compounds. The WI-38 cell line was developed in July 1962 from lung tissue taken from a therapeutically aborted fetus of about 3 months gestational age. Cells released by trypsin digestion of the lung tissue were used for the primary culture. The cell morphology is fibroblast-like. The karyotype is 46,XX; a normal diploid female. A maximum lifespan of 50 population doublings exists for this culture. The 3T3 cell line was developed by transferring the cells every 3 days and plating at 300,000 cells per plate.[55] The 3T3 cells possess a high sensitivity to contact inhibition, and unlike normal cells are immortal. As one would expect, during this research project, the 3T3 cell line behaved more like the cancer cell lines than the WI38 cell line. To evaluate the anticancer and antiviral activity of the polymeric drugs, comparisons to their activity in the WI38 cell line were preferred for these reasons. Most of the drugs that had significant activity only worked against one cancer cell line or one virus, which is to be expected because the cancer cell lines have different characteristics, and the viruses have different mechanisms of replication. Most chemotherapeutic drugs only inhibit one cancer cell type. Antiviral drugs are also specific for one virus, in most cases.

The majority of the type I polymeric drugs had very little anticancer or antiviral activity. One parameter that was explored was the potential benefit of altering the molecular weight of GB5, GB9, GB10, and GB20. GB35, which has a smaller molecular weight of the polymer than GB9, was the only one to have significant anticancer activity. For the remaining compounds, the lower molecular weights slightly increased the anticancer activity, but none of them had significant anticancer activity. Future studies should concentrate on investigating the effect of molecular weight of those that had significant anticancer or antiviral activity such as GB1, GB8, GB25 and GB28. Based on the results obtained with GB9 it is reasonable to predict that the activity would be increased by varying the molecular weight of these polymers.

GB25, 3-hexane-5-diol dibutyltin, had the highest anticancer activity of any of the type I polymeric drugs. GB28, 3-chloro-1,2-propanediol dibutyltin, also had high anticancer activity. GB1, GB6 dissolved in water, GB8, and GB27 also had anticancer activity, but their activities were less than the activity of GB25 and GB28. All of the drugs had the highest activity against the MDA-MB-231 breast cancer cell line. MDA-MB-231 does not have estrogen receptors.

GB8, ethylene glycol dibutyltin, was the only type I polymeric drugs to have significant antiviral activity. GB8 had high activity against the vaccinia virus, but not against the HSV-1 virus. None of the type I polymeric drugs had high activity against the HSV-1 virus.

The polymeric drugs that were based on diols had better anticancer activity than the polymers based on the ethylene glycols overall. Both GB25 and GB1, 2-butyne-1,4-

diol, have multiple bonds. GB25, 3-hexene-5-diol dibutyltin, has a double bond, while GB1 has a triple bond between adjacent carbons. The multiple bonds could make the molecule more reactive, which could increase the activity of the polymeric drug. GB28, 3-chloro-1,2-propanediol dibutyltin, has a halide attached. The two hydroxyl groups of GB28 are also located on adjacent carbons, as opposed to being located on both ends of the molecule. GB27, 2,3-butanediol dibutyltin, which is the only polymer, besides GB28, to have the two hydroxyl groups located on adjacent carbons, instead of with spaces between them, also had significant anticancer activity. The proximity of the hydroxyl groups on the molecule seems to affect the activity of the polymeric drug. GB28 has higher anticancer activity than GB27, but it could be due to halide located on the polymer. Previous research with organotins showed that halides, especially chloride, could increase anticancer activity.[10,44]

The only two ethylene glycols that had significant anticancer activity were GB6 and GB8. GB6 is the polymeric drug with the highest molecular weight of polyethylene glycol tested. GB6 would be the hardest of the polyethylene glycols to break down, due to its size. GB8, ethylene glycol dibutyltin, was the only type I polymeric drug to have antiviral abilities. The smaller size of the GB8 would indicate that it is easier to break down than the other polymeric drugs. Perhaps the smaller size makes it easier for the polymeric drugs to enter the cell. Also, that would be the reason why it could inhibit vaccinia viral production, but not HSV-1 viral production. Vaccinia replicates inside the cytoplasm, but HSV-1 replicates inside the nucleus. GB8 could be able to enter the cytoplasm, but then be degraded by the cell.

The type II polymeric drugs, which are based on kinetin, had very little anticancer activity. AB9, pyrimethamine dibutyltin, had the highest anticancer activity in this group, and the activity was against the MDA-MB-231 breast cancer cell line. Pyrimethamine is a folic acid antagonist that is used in the treatment of malaria. It is possible that the activity of AB9 comes from the fact that the cells use this compound instead of folic acid.

The only type II polymeric drug that showed antiviral activity was AB1, 4,6-diamino pyrimidine dibutyltin. AB1 was able to inhibit both HSV-1 and vaccinia. It was the only type I polymeric drug to have antiviral activity. The antiviral activity is most likely due to AB1 being used as a nucleoside analog. The virus incorporates the AB1 into its nucleic acid instead of a pyrimidine.

Most of the type III polymeric drugs had significant anticancer activity. The two that showed the highest anticancer activity had simple structures compared to the others. GB14, methylhydroquinone dibutyltin, and GB13, hydroquinone dibutyltin, had the highest activity. GB17, phenylhydroquinone dibutyltin, was the only type III polymeric drug that did not have any significant anticancer activity. Perhaps the two ring structure is too big to interact with cellular targets.

The type III polymeric drug group had the highest antiviral activity of the polymeric drugs tested. GB12, GB15, GB16, and GB17 had activity against HSV-1. GB12 is 2,3-dicyanohydroquinone dibutyltin. GB15 is tert-butylhydroquinone dibutyltin, and GB16 is 2,5-ditertbutylhydroquinone dibutyltin. GB12 inhibited HSV-1 the most of all of the drugs studied, followed by GB15 and GB16, which showed

comparable amounts of inhibition. GB15, GB16, and GB17 also inhibited the vaccinia virus. GB15 had the highest activity against the vaccinia virus of all of the drugs studied. The ring structure of the type III polymeric drugs make them very stable, which allows them more time to have activity inside the cell. The site of activity of the hydroquinone is most likely the hydroxyl groups. The combination of the active sites of the tin and the hydroxyl groups is the reason behind the high activity of the type III polymeric drugs.

GB15, tert-butylhydroquinone dibutyltin, and GB16, 2,5-ditert-butylhydroquinone dibutyltin, have very similar structures. Their anticancer and antiviral abilities were also very similar. They were some of the most active compounds, because they had activity against both viruses and against the MDA-MB-231 breast cancer cell line and HT-29 colon cancer cell line. The highly branched structure of these polymeric drugs gives them more opportunities to interact with the cell. These drugs could also interact with virus outside of the cell, so that they cannot attach to the cell.

Many of the type IV polymeric drugs, which are based on a synthetic estrogen diethylstilbestrol, had significant anticancer activity. The chemotherapeutic indexes of these drugs were some of the highest of all of the drugs. They worked the best against the MDA-MB-231 breast cancer cell line. MDA-MB-231 lacks estrogen receptors, unlike MCF-7. There was very little activity against MCF-7 with the type IV polymeric drugs. Therefore, the estrogen receptors do not help the polymeric drug enter the cell. YA7, titanocene dichloride diethylstilbestrol, had the highest activity of any of the

drugs. Its activity was higher than the activities of diethylstilbestrol and titanocene alone, which are the subunits YA7 is based on. The type IV polymeric drug containing dibutyltin did have higher activity than the polymeric drugs containing dimethyltin, diethyltin, and dipropyltin. This concurs with previous research that found that the dibutyltin moiety has the highest activity.[6,10,24]

Some of the type V polymeric drugs also exhibited high anticancer activity. The highest activity was against the MCA-MB-231 breast cancer cell line, but they also had activity against the HT-29 colon cancer cell line. YA14, diethyltin dienestrol, had the highest activity. YA13, YA18, and YA22 also had significant anticancer activity, but it was much less than the activity from YA14. YA13 is dimethyltin dienestrol. YA18 is titanocene dienestrol, and YA22 is hafnocene dienestrol. YA18 had more activity than titanocene and dienestrol alone, which are its two constituents. YA22 had more activity than hafnocene and dienestrol alone, which are its two constituents. In this case, the dibutyltin polymeric drug had less activity than dimethyltin and diethyltin, which is the opposite of the results of previous research. Diethyltin dienestrol had the highest activity of the three. Perhaps the activity of these compounds is due to the dienestrol moiety more than the organotin moiety. The dienestrol molecule also might be more stable than the diethylstilbestrol because of the double bonds found in the dienestrol. The length of the carbon attached to the organotin might not be as important if it is attached to a more stable molecule. A shorter length may help the tin interact more with cellular targets in this case.

None of the type IV or type V polymeric drugs had significant antiviral activity against either virus. Most likely the anticancer activity was due to the combination of the synthetic estrogens and the organotin moieties. Synthetic estrogens have been used in the treatment of cancer[31], but none have ever been shown to have antiviral activities.

The polymeric drugs had the highest activity against the MDA-MB-231 breast cancer cell line. Of the two breast cancer cell lines tested, the MDA-MB-231 is more invasive, indicating that they bring in more nutrients than the other cells. The higher activity could be due to those cells bringing in more of the drugs than the other cell lines.

The hydroquinone and diethylstilbestrol series of polymeric drugs had the most promise as anticancer and antiviral drugs. Hydroquinones with simple carbon moieties (single or double) attached made the best polymers for dibutyltin, especially for antiviral activity. Diethylstilbestrol organotins also show a great deal of promise as anticancer drugs. The diethylstilbestrol organotin polymers tested have more activity than their monomers, indicating that there are several sites of activity in the polymers. YA1, YA7, GB13, GB14, and GB25 showed the highest anticancer activity. They should be tested against breast cancer *in vivo* to see if they have the same effect. GB15 and GB16 should be tested *in vivo* against both the HSV-1 and vaccinia viruses. Also, GB12 merits further testing with the HSV-1 virus, and GB8 merits further testing against the vaccinia virus.

APPENDIX A

DESIGNATION AND MOLECULES USED TO SYNTHESIZE THE POLYMERIC DRUGS USED IN THIS STUDY

Table A.1 Type I Polymeric Drugs

Polymer Designation	Compounds Used to Synthesize Polymers
GB1	2-Butyne-1,4-diol + dibutyltin
GB2	Diethylene Glycol + dibutyltin
GB3	Triethylene Glycol + dibutyltin
GB5	polyethylene glycol mol wt 400 (3mM) (76,000) + dibutyltin
GB6	Polyethylene glycol mol wt 8,000 + dibutyltin
GB7	Poly(ethylene glycol) + dibutyltin
GB8	Ethylene Glycol + dibutyltin
GB9	Pentaethyleneglycol (3mM) (470,000) + dibutyltin
GB10	l,3 propanediol (3mM) (30,000) + dibutyltin
GB20	1,5-pentanediol (3mM) (18,000) + dibutyltin
GB21	1,7-heptanediol + dibutyltin
GB22	1,8-octanediol + dibutyltin
GB23	1,4-butanediol + dibutyltin
GB24	1,6-hexanediol + dibutyltin
GB25	3-hexene-2,5-diol + dibutyltin
GB26	2,5-dimethyl-3-hexyn-2,5-diol + dibutyltin
GB27	2,3-butanediol + dibutyltin
GB28	3-chloro-1,2-propanediol + dibutyltin
GB29	Neopentanediol + dibutyltin

Table A.2 Polymeric Drugs used to study Molecular Weight based on GB5, GB9, GB10, and GB20

Polymer Designation	Compounds Used to Synthesize Polymers
GB33 (based on 20)	(2.9 mM) 1,5-pentanediol (16,000) + dibutyltin
GB34 (based on 5)	(2.9 mM) PEG(MW400) (66,700) + dibutyltin
GB35 (based on 9)	(2.9 mM) Pentaethyleneglycol (405,000) + dibutyltin
GB36 (based on 9)	(2.5 mM) Pentaethyleneglycol (341,000) + dibutyltin
GB37 (based on 9)	(2.0 mM) Pentaethyleneglycol (297,000) + dibutyltin
GB38 (based on 10)	(2.9 mM) l,3 propanediol (24,500) + dibutyltin
GB39 (based on 10)	(2.5 mM) l,3 propanediol (20,700) + dibutyltin
GB40 (based on 10)	(2.0 mM) l,3 propanediol (17,400) + dibutyltin
GB41 (based on 5)	(2.5 mM) PEG(MW400) (52,500) + dibutyltin
GB42 (based on 5)	(2.0 mM) PEG(MW400) (40,900) + dibutyltin
GB43 (based on 20)	(2.5 mM) 1,5-pentanediol (13,000) + dibutyltin
GB44 (based on 20)	(2.0 mM) 1,5-pentanediol (10,600) + dibutyltin

Table A.3 Type II Polymeric Drugs

Polymer Designation	Compounds Used to Synthesize Polymers
AB1	4,6-diamino pyrimidine + dibutyltin
AB2	4,6-diamino-5-nitropyrimidine + dibutyltin
AB3	4,6-diamino-2-methyl mercaptopyrimidine + dibutyltin
AB4	4,6-diamino-2-methyl-5-nitrosopyrimidine + dibutyltin
AB5	4,6-diamino-2-mercaptopyridine + dibutyltin
AB6	4-chloro-2,6-diaminopyrimidine + dibutyltin
AB7	2,4-diamino-6-hydroxypyrimidine + dibutyltin
AB8	4-diamino-6-hydroxy-5-nitrosopyrimidine + dibutyltin
AB9	pyrimethamine + dibutyltin

Table A.4 Type III Polymeric Drugs

Polymer Designation	Compounds Used to Synthesize Polymers
GB11	Bromohydroquinone + dibutyltin
GB12	2,3-dicyanohydroquinone + dibutyltin
GB13	Hydroquinone + dibutyltin
GB14	Methylhydroquinone + dibutyltin
GB15	Tert-butylhydroquinone + dibutyltin
GB16	2,5-ditert-butylhydroquinone + dibutyltin
GB17	Phenylhydroquinone + dibutyltin
GB18	2-methoxyhydroquinone + dibutyltin
GB19	2,5-dihydroxylbenzaldehyde + dibutyltin
GB30	Tetrachlorohydroquinone + dibutyltin
GB31	2,5-dichlorohydroquinone + dibutyltin
GB32	Chlorohydoquinone + dibutyltin

Table A.5 Type IV Polymeric Drugs

Polymer Designation	Compounds Used to Synthesize Polymers
YA1	Dibutyltin dichloride + Diethylstilbestrol
YA2	Dimethyltin dichloride + Diethylstilbestrol
YA3	Diethyltin dichloride + Diethylstilbestrol
YA4	Dipropyltin dichloride + Diethylstilbestrol
YA5	Dicyclohexyltin dichloride + Diethylstilbestrol
YA6	Diphenyltin dichloride + Diethylstilbestrol
YA7	Titanocene dichloride + Diethylstilbestrol
YA8	Bis(cyclopentadienyl)zirconium dichloride + Diethylstilbestrol
YA9	Hafnocene dichloride + Diethylstilbestrol

Table A.6 Type V Polymeric Drugs

Polymer Designation	**Compounds Used to Synthesize Polymers**
YA12	Dibutyltin dichloride + Dienestrol
YA13	Dimethyltin dichloride + Dienestrol
YA14	Diethyltin dichloride + Dienestrol
YA15	Dipropyltin dichloride + Dienestrol
YA16	Dicyclohexyltin dichloride + Dienestrol
YA17	Diphenyltin dichloride + Dienestrol
YA18	Titanocene dichloride + Dienestrol
YA22	Hafnocene dichloride + Dienestrol

APPENDIX B

GRAPHS USED TO GENERATE THE GI_{50} VALUES OF THE TYPE I POLYMERIC DRUGS, DIBUTYLTIN DICHLORIDE, AND CISPLATIN

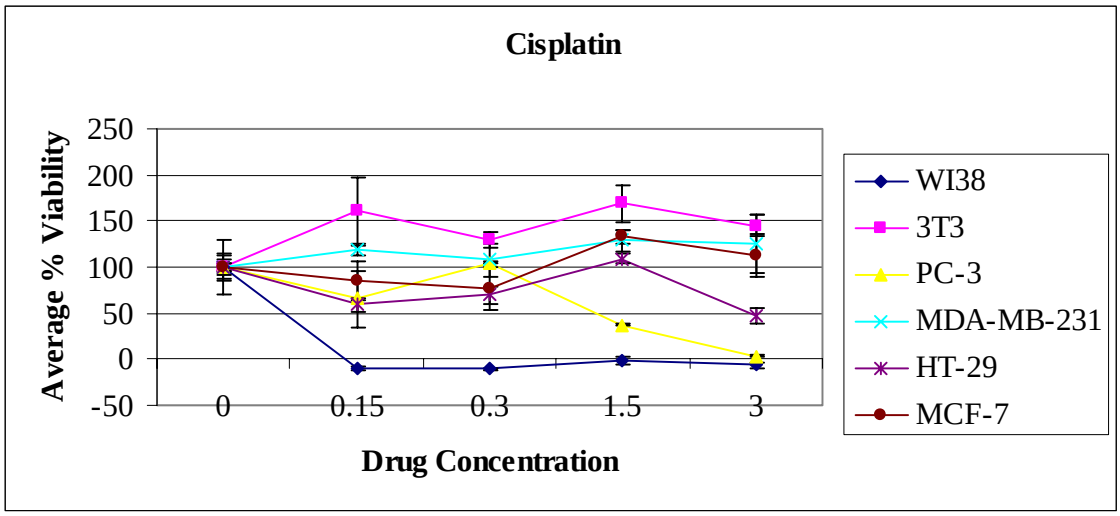

Figure B.1 Anticancer activity of cisplatin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

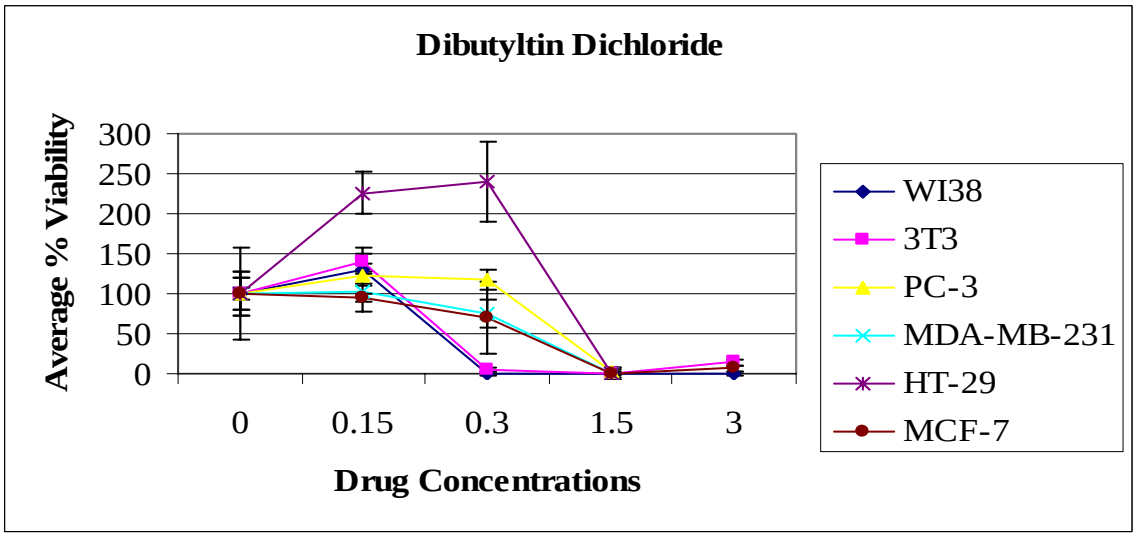

Figure B.2 Anticancer activity of dibutyltin dichloride after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

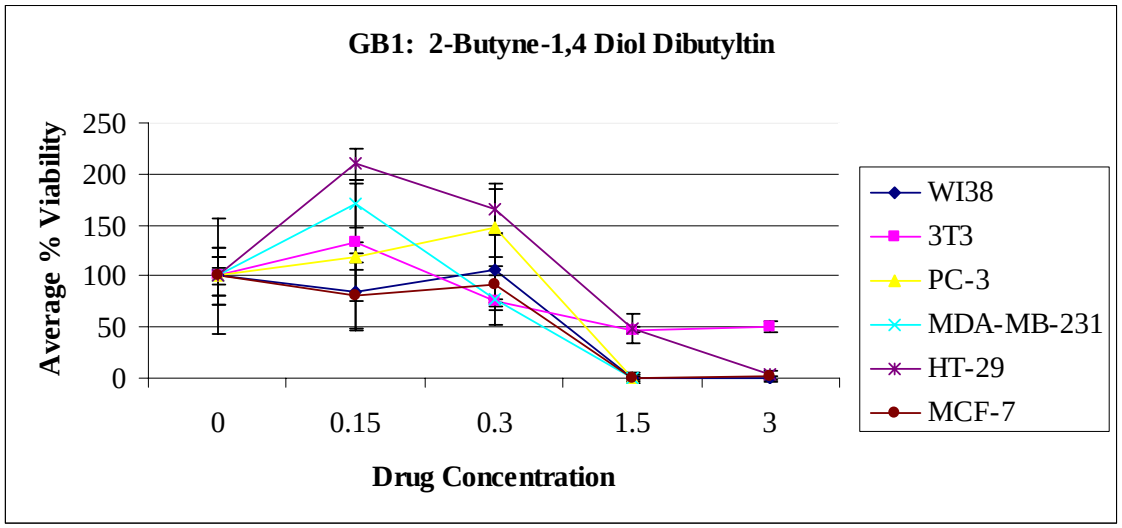

Figure B.3 Anticancer activity of 2-butyne-1,4-diol dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

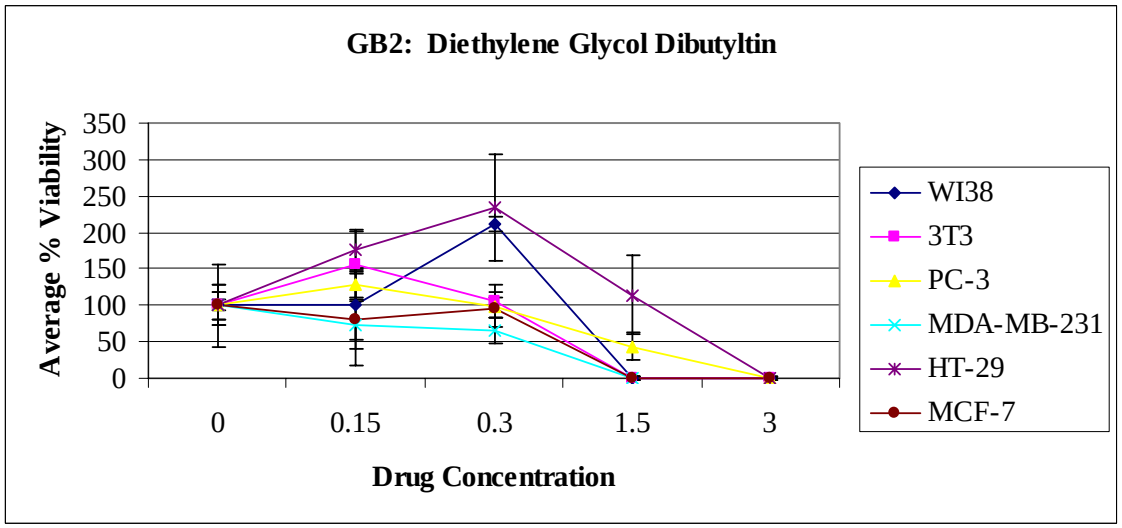

Figure B.4 Anticancer activity of diethylene glycol dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

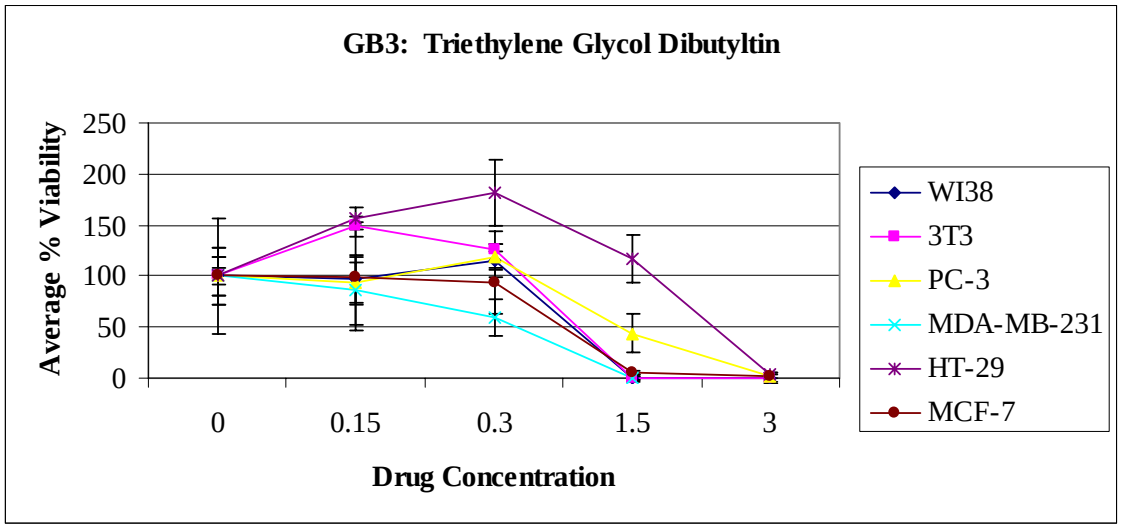

Figure B.5 Anticancer activity of triethylene glycol dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

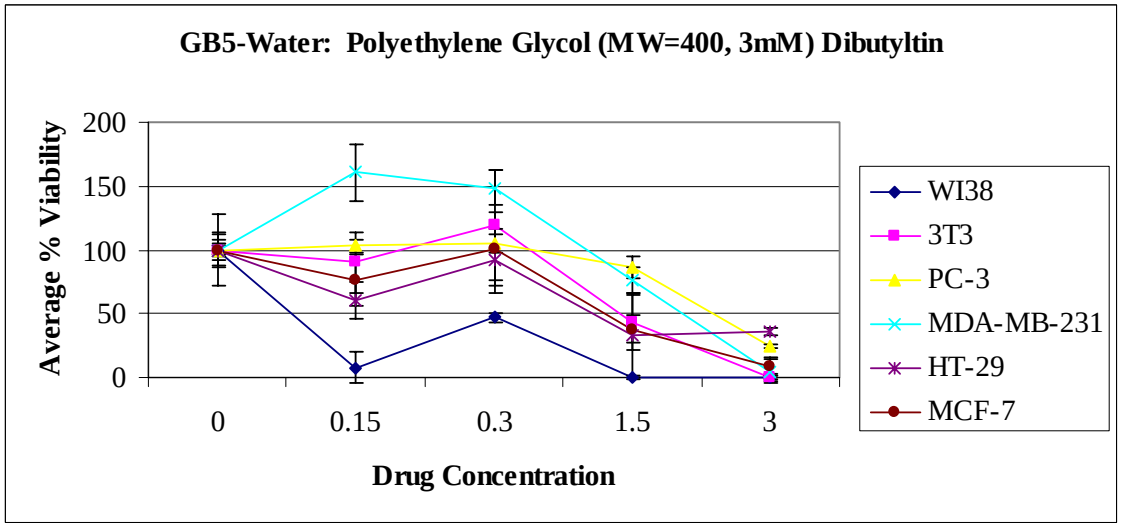

Figure B.6 Anticancer activity of polyethylene glycol dibutyltin, with a molecular weight of 400 and a molarity of 3mM, dissolved in water, after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

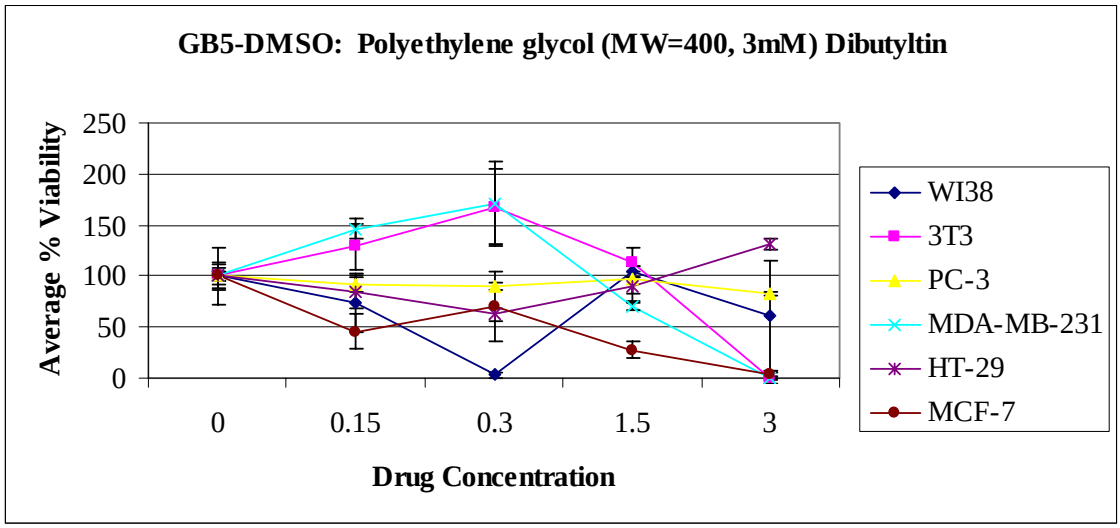

Figure B.7 Anticancer activity of polyethylene glycol dibutyltin, with a molecular weight of 400 and a molarity of 3mM, dissolved in DMSO, after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

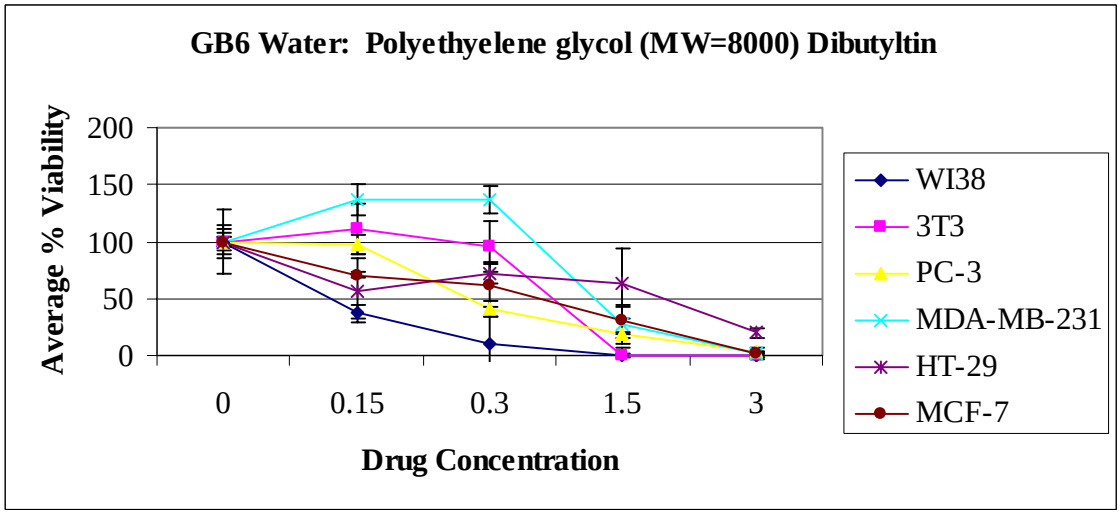

Figure B.8 Anticancer activity of polyethylene glycol dibutyltin, with a molecular weight of 8000, dissolved in water, after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

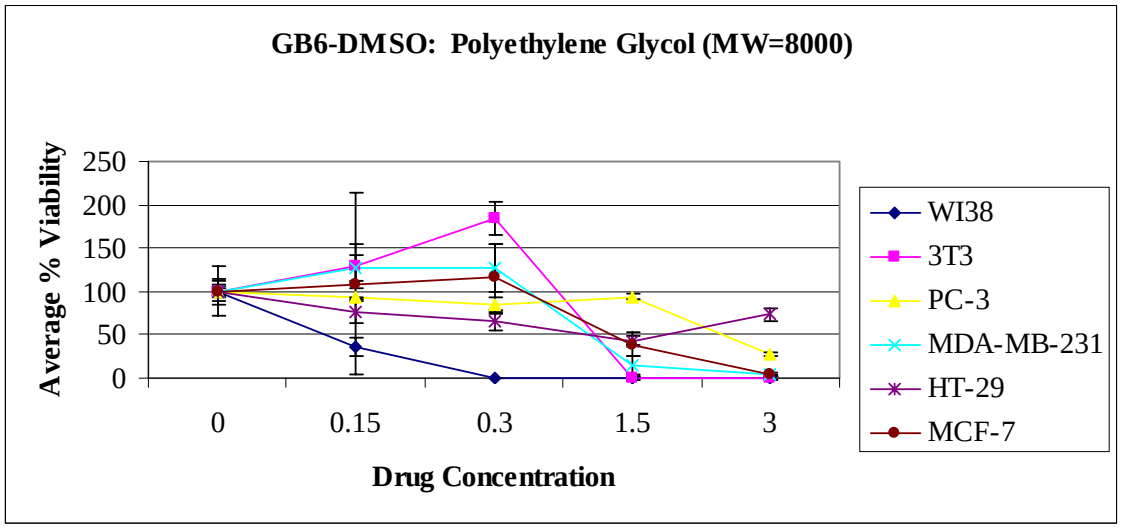

Figure B.9 Anticancer activity of polyethylene glycol dibutyltin, with a molecular weight of 8000, dissolved in DMSO, after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

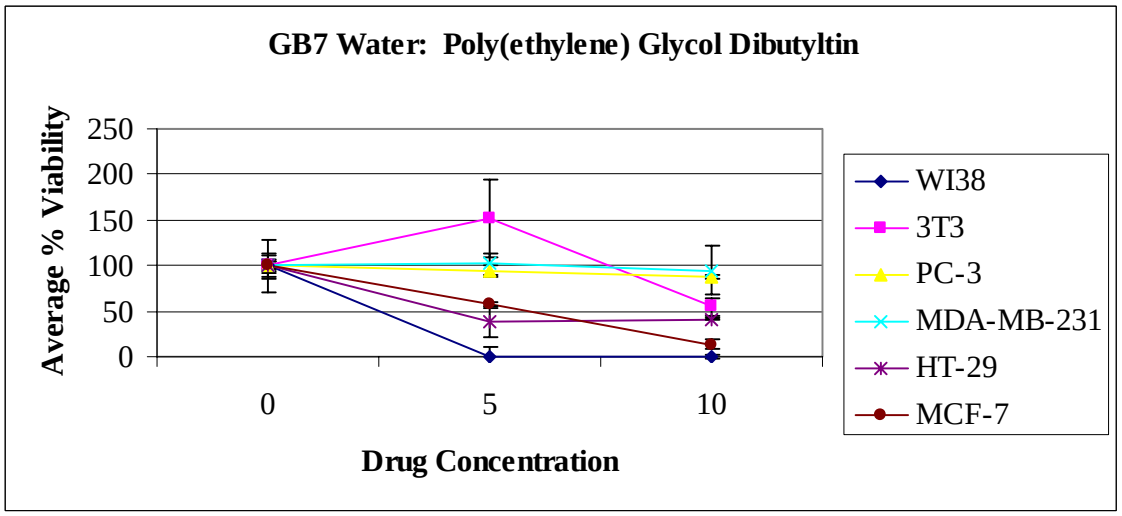

Figure B.10 Anticancer activity of poly(ethylene) glycol dibutyltin, dissolved in water, after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

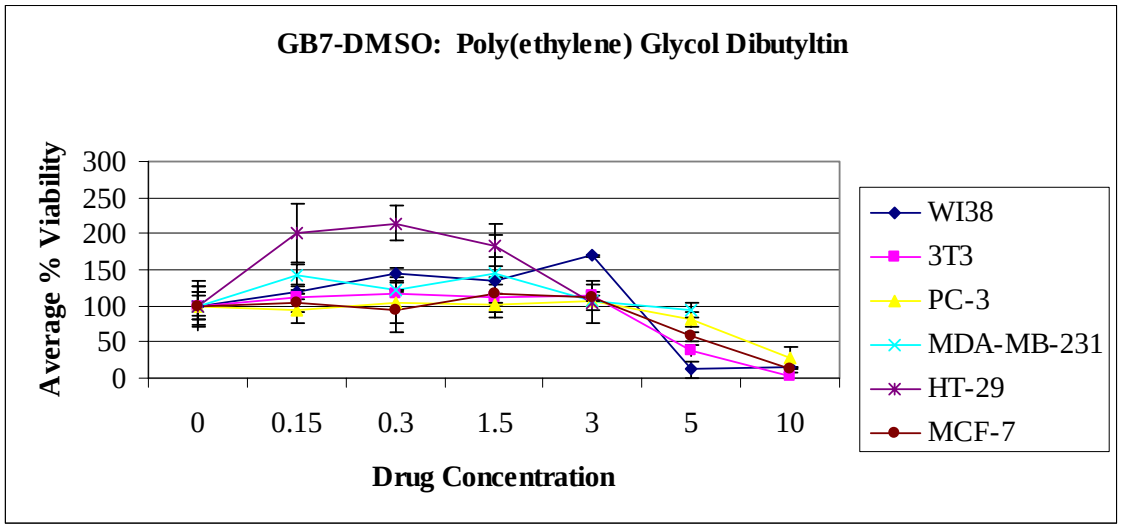

Figure B.11 Anticancer activity of poly(ethylene) glycol dibutyltin, dissolved in DMSO, after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

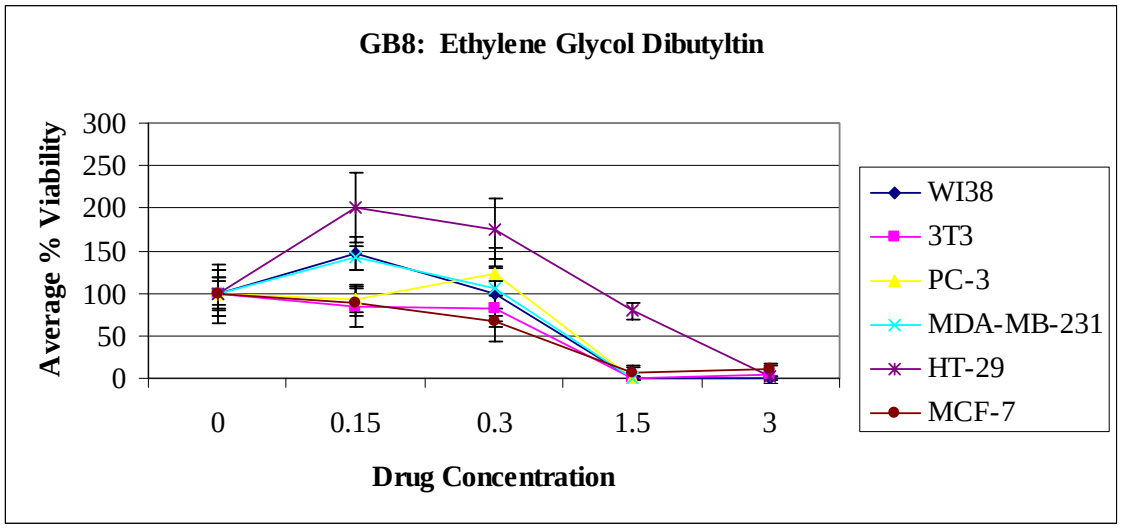

Figure B.12 Anticancer activity of ethylene glycol dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

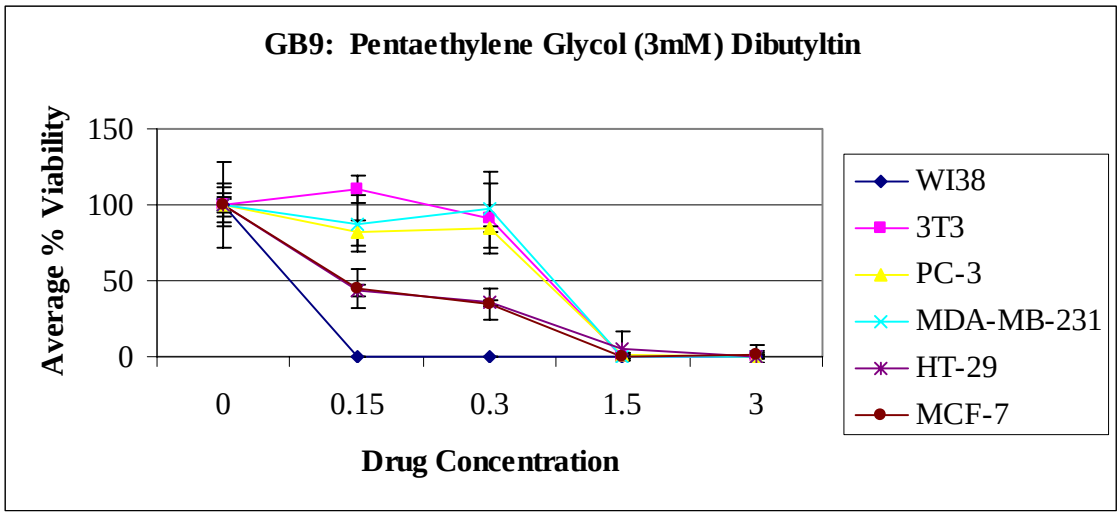

Figure B.13 Anticancer activity of pentaethylene glycol dibutyltin, at a molarity of 3mM, after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

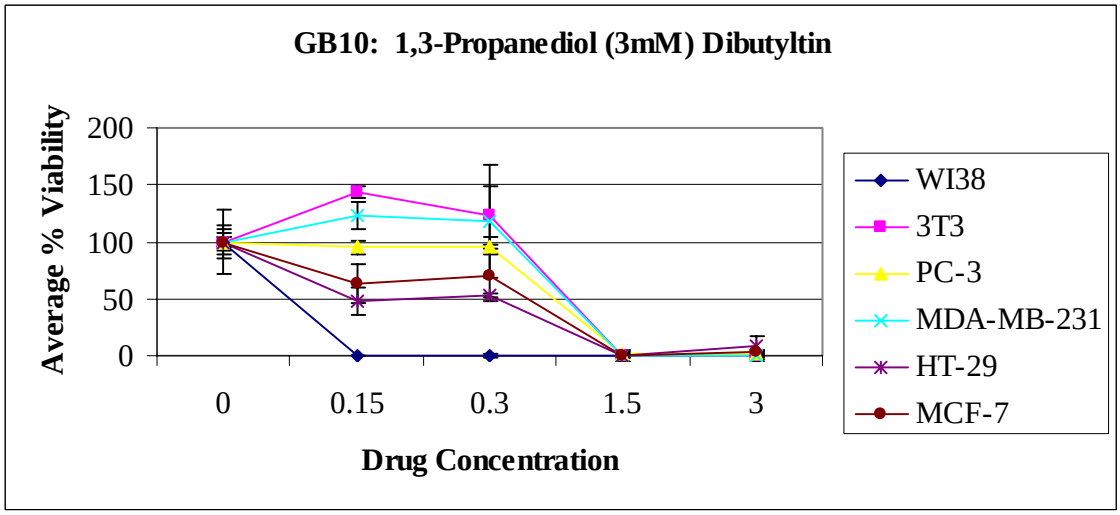

Figure B.14 Anticancer activity of l,3-propanediol dibutyltin, at a molarity of 3mM, after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

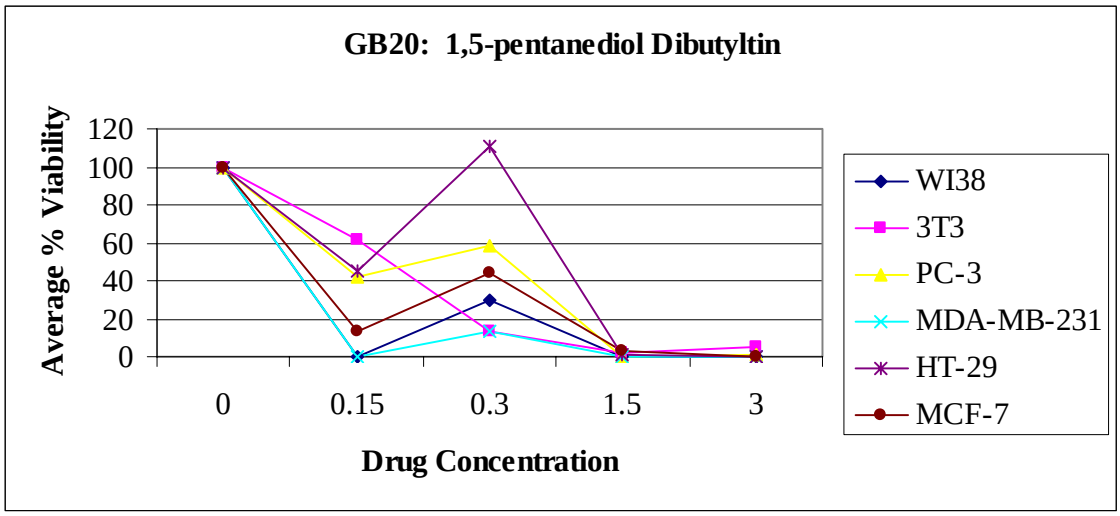

Figure B.15 Anticancer activity of l,5-pentanediol dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

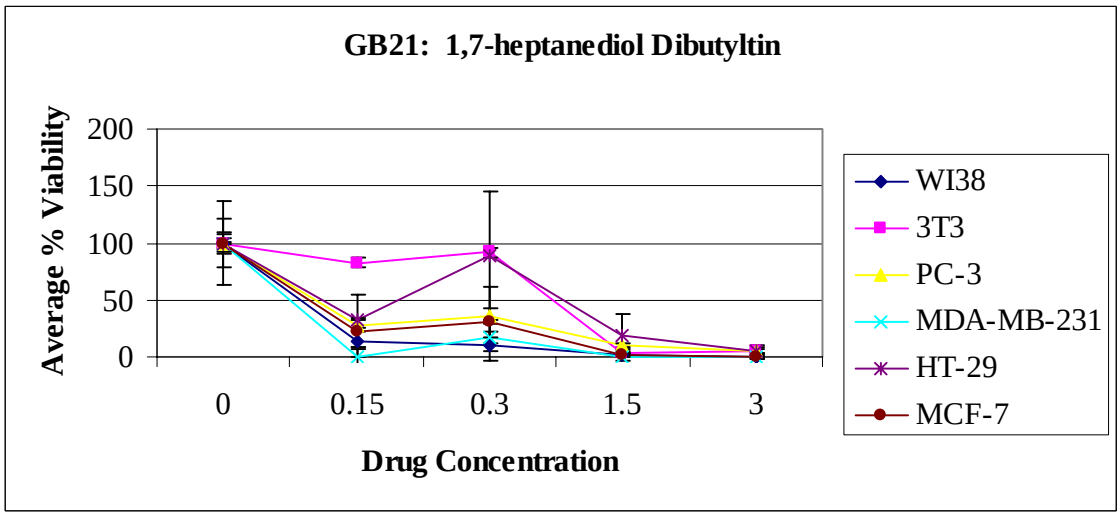

Figure B.16 Anticancer activity of l,7-heptanediol dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

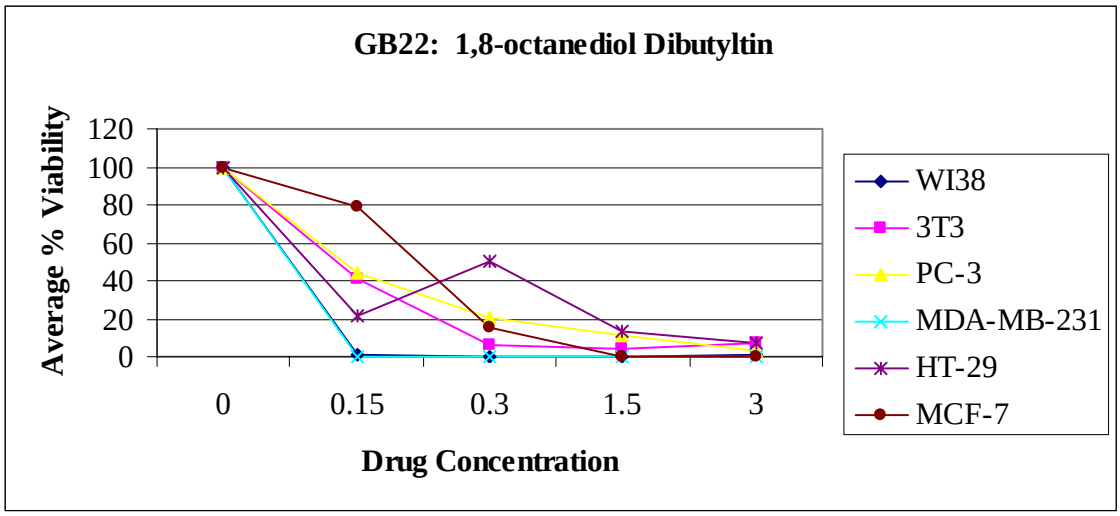

Figure B.17 Anticancer activity of l,8-octanediol dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

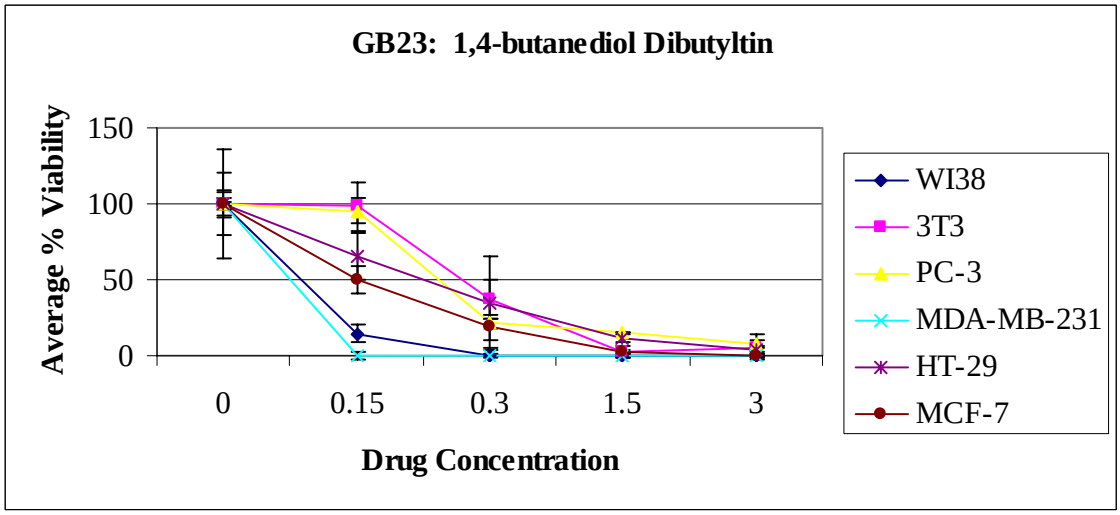

Figure B.18 Anticancer activity of l,4-butanediol dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

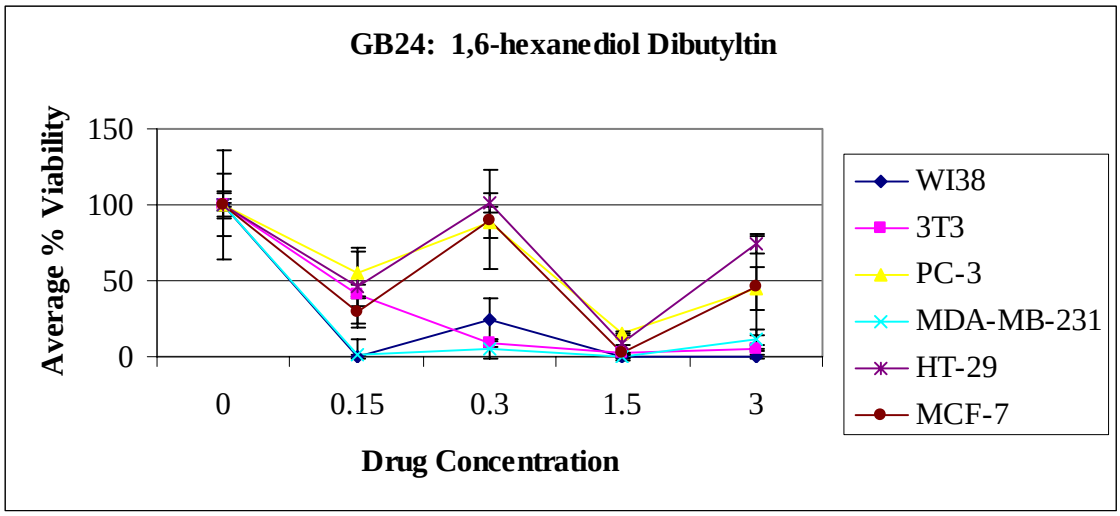

Figure B.19 Anticancer activity of l,6-hexanediol dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

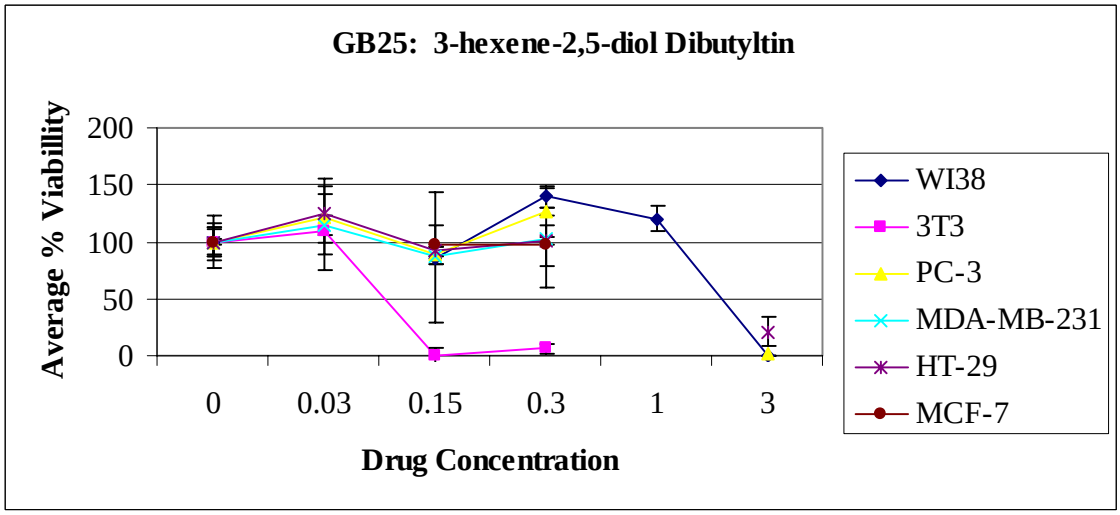

Figure B.20 Anticancer activity of 3-hexane-5-diol dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

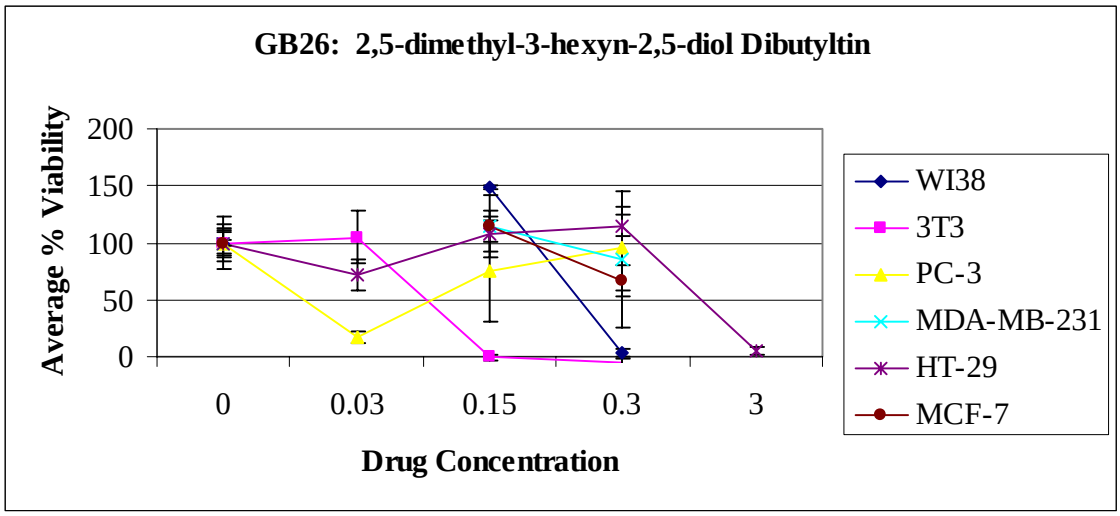

Figure B.21 Anticancer activity of 2,5-dimethyl-3-hexyn-2,5-diol dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

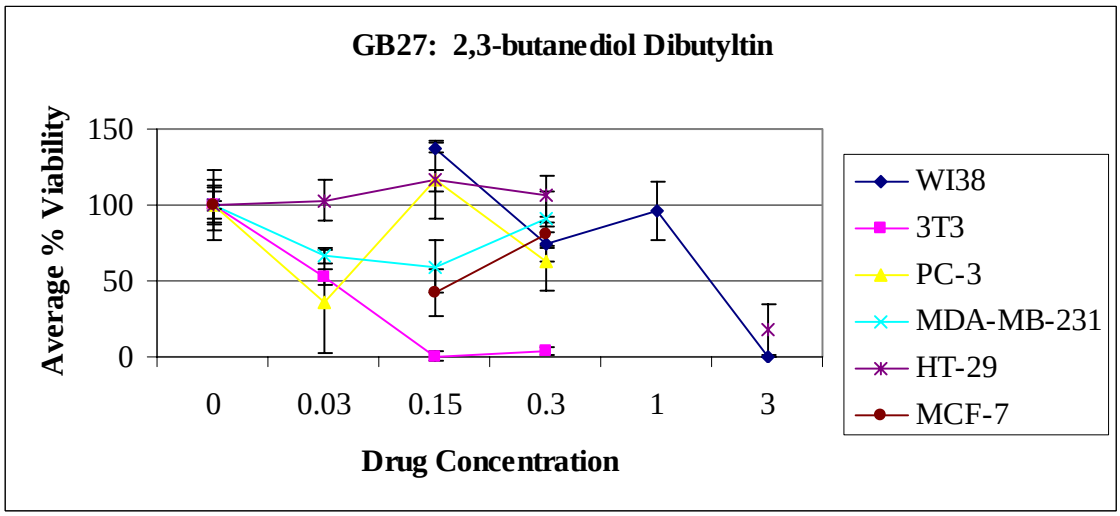

Figure B.22 Anticancer activity of 2,3-butanediol dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

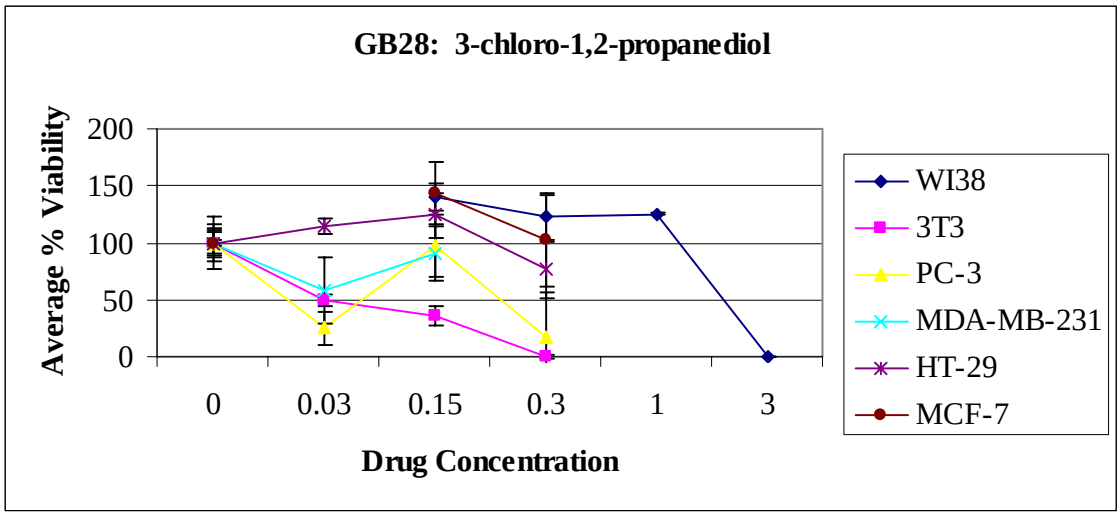

Figure B.23 Anticancer activity of 3-chloro-1,2-propanediol dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

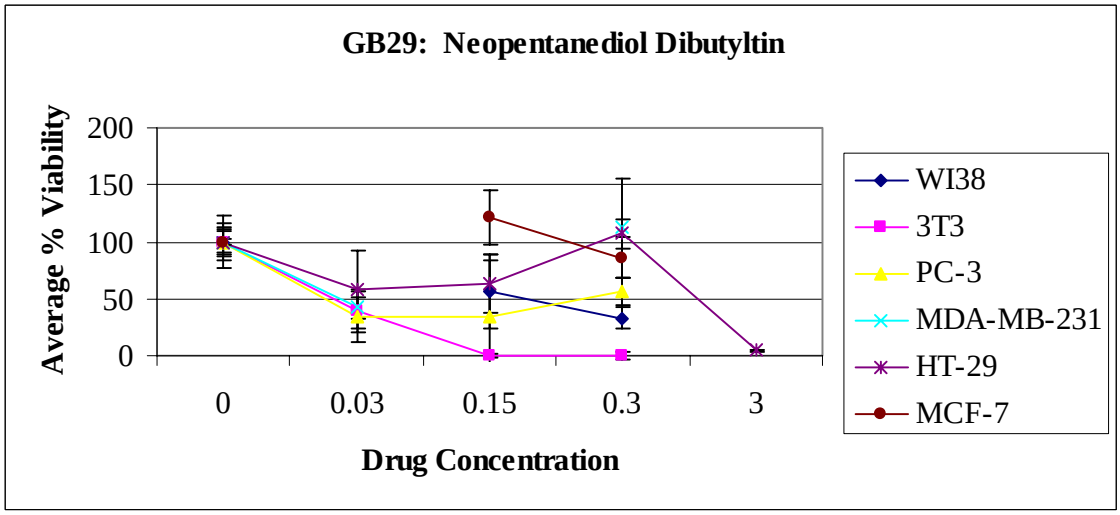

Figure B.24 Anticancer activity of neopentanediol dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

APPENDIX C

GRAPHS USED TO GENERATE THE GI_{50} VALUES OF THE MOLECULAR WEIGHT STUDY OF GB5, GB9, GB10, AND GB20

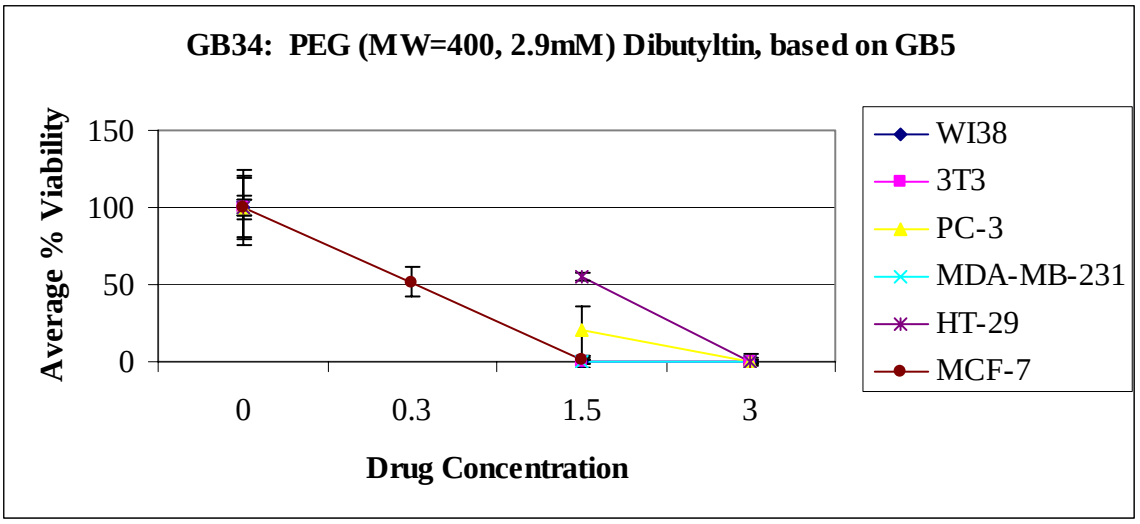

Figure C.1 Anticancer activity of polyethylene glycol dibutyltin, with a molecular weight of 400 and a molarity of 2.9mM, after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

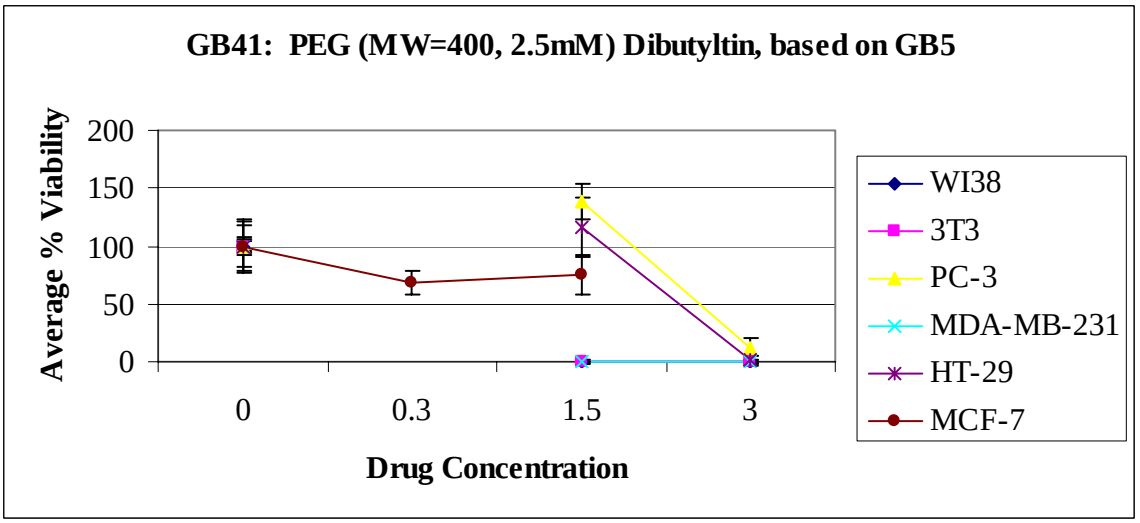

Figure C.2 Anticancer activity of polyethylene glycol dibutyltin, with a molecular weight of 400 and a molarity of 2.5mM, after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

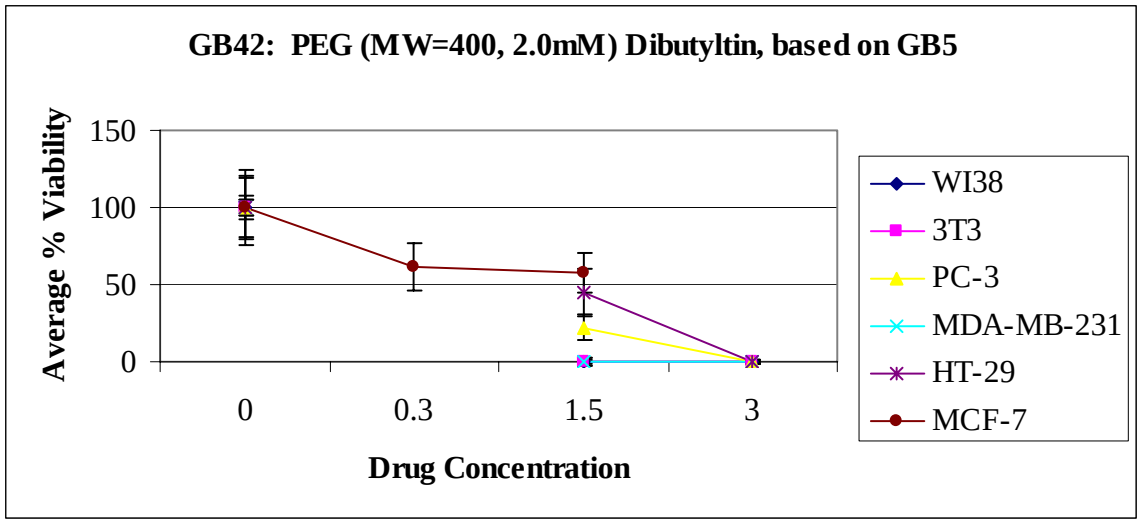

Figure C.3 Anticancer activity of polyethylene glycol dibutyltin, with a molecular weight of 400 and a molarity of 2.0mM, after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

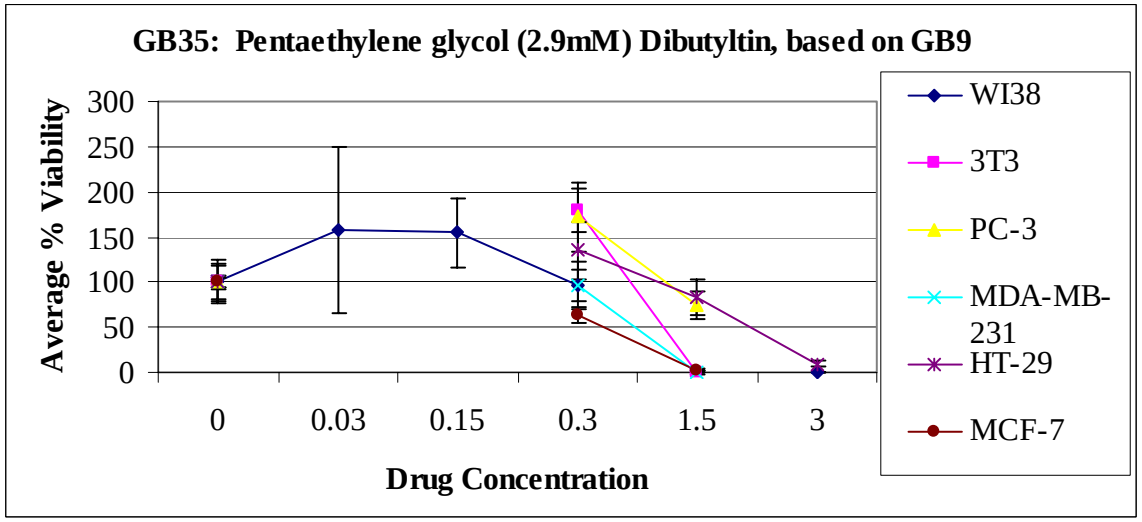

Figure C.4 Anticancer activity of pentaethylene glycol dibutyltin, with a molarity of 2.9mM, after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

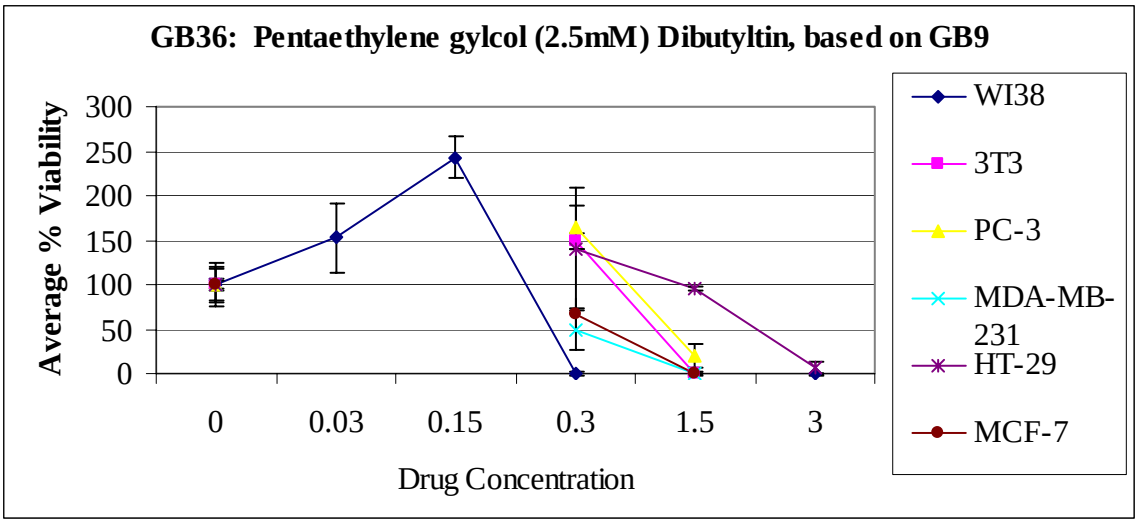

Figure C.5 Anticancer activity of pentaethylene glycol dibutyltin, with a molarity of 2.5mM, after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

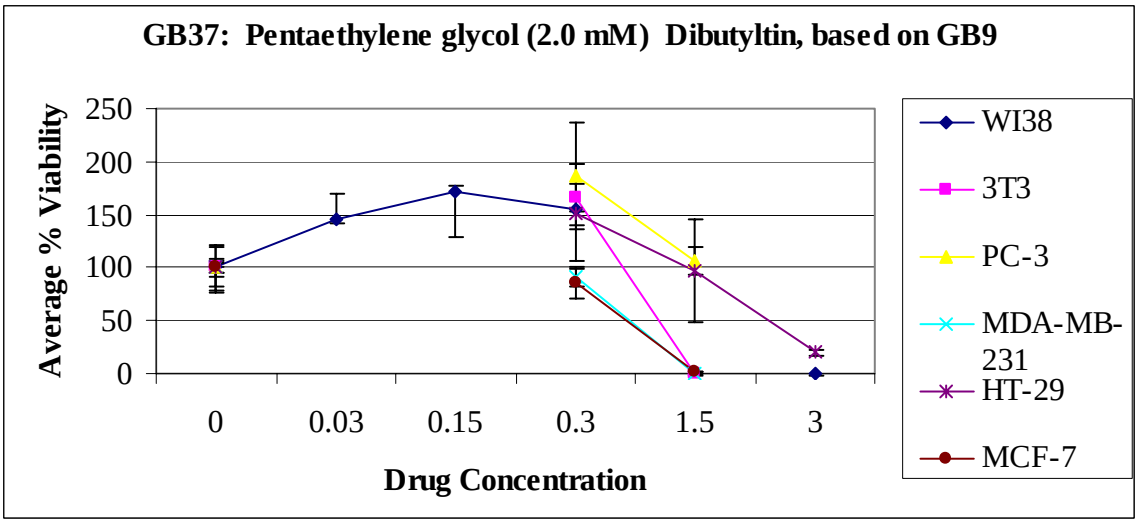

Figure C.6 Anticancer activity of pentaethylene glycol dibutyltin, with a molarity of 2.0mM, after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

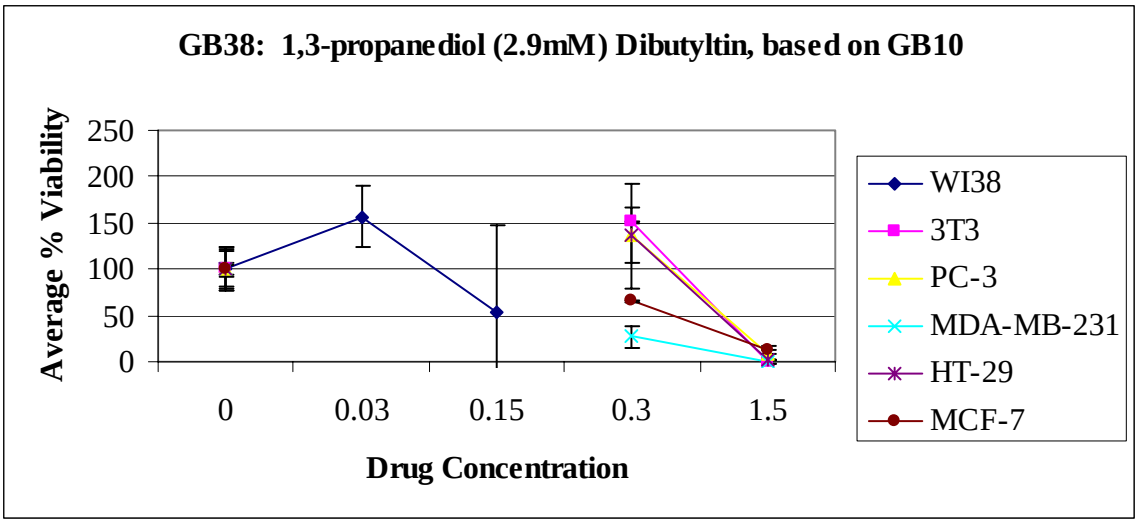

Figure C.7 Anticancer activity of 1,3-propanediol dibutyltin, with a molarity of 2.9mM, after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

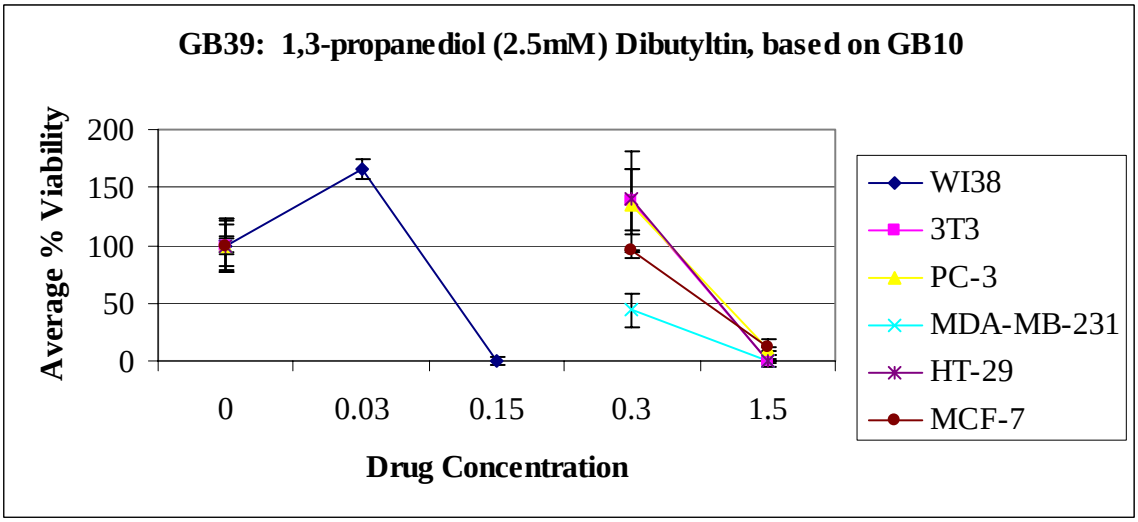

Figure C.8 Anticancer activity of 1,3-propanediol dibutyltin, with a molarity of 2.5mM, after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

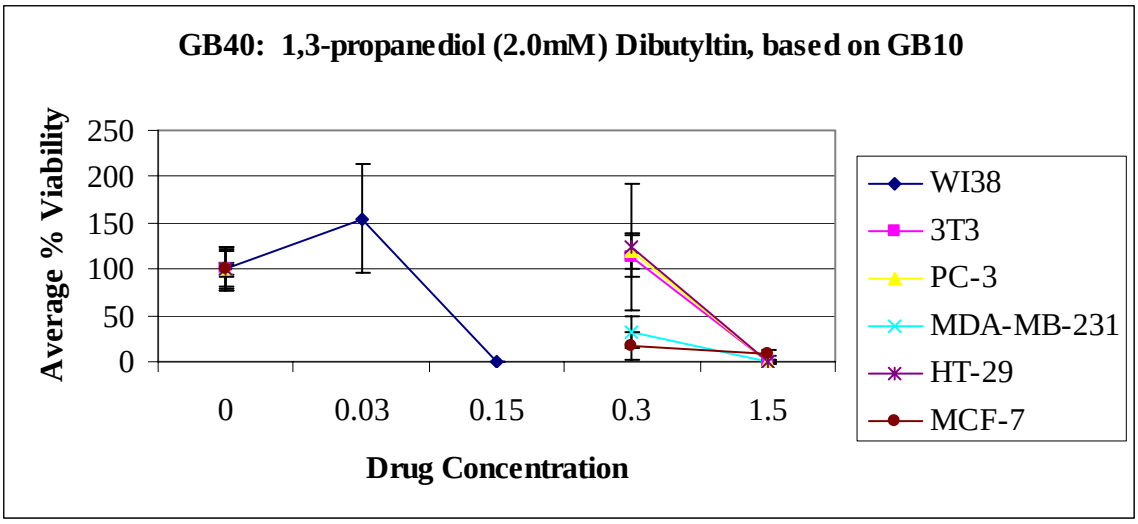

Figure C.9 Anticancer activity of 1,3-propanediol dibutyltin, with a molarity of 2.0mM, after 72 hours. The error bars indicate one standard deviation from the mean.

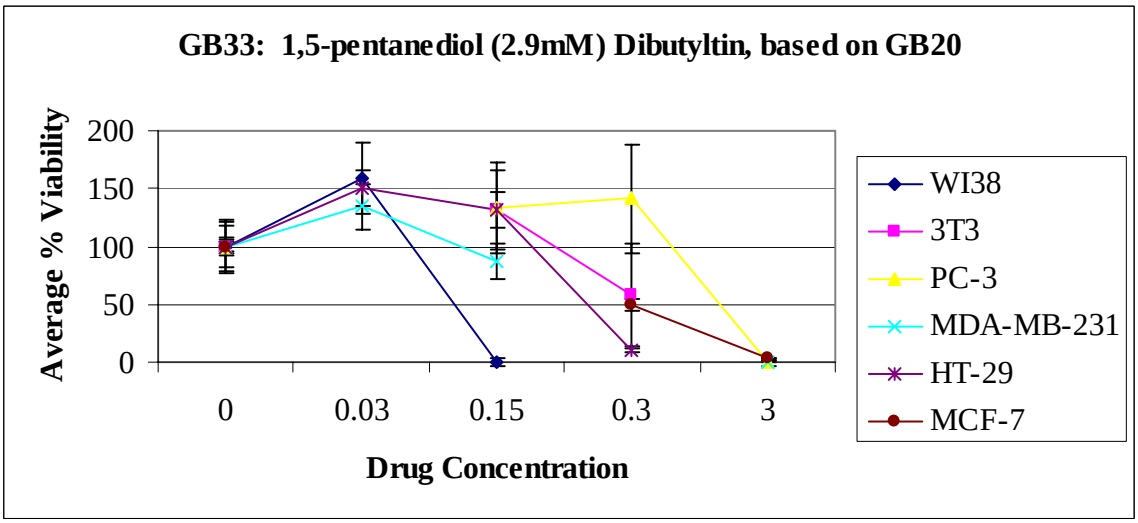

Figure C.10 Anticancer activity of 1,5-pentanediol dibutyltin, with a molarity of 2.9mM, after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

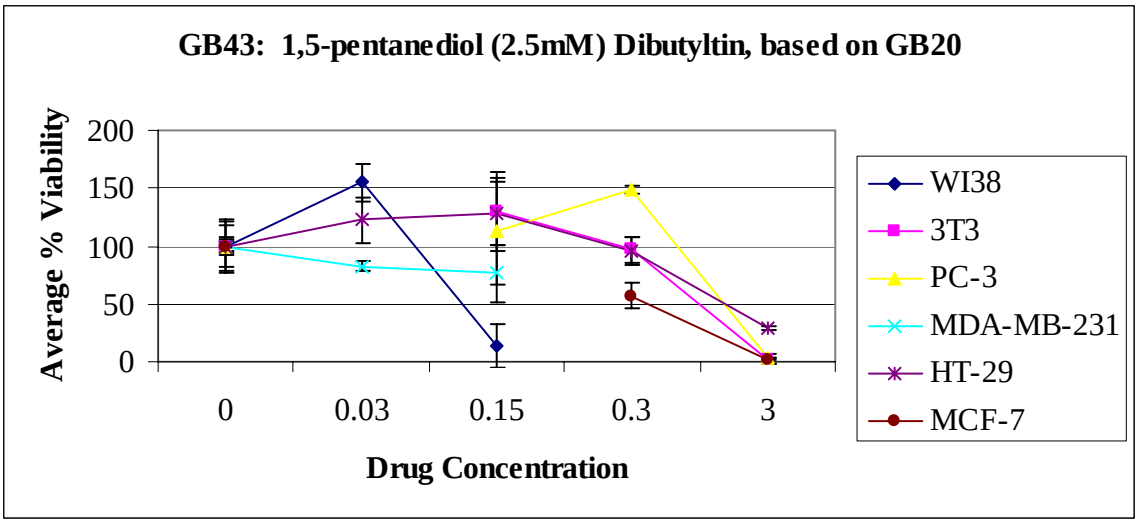

Figure C.11 Anticancer activity of 1,5-pentanediol dibutyltin, with a molarity of 2.5mM, after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

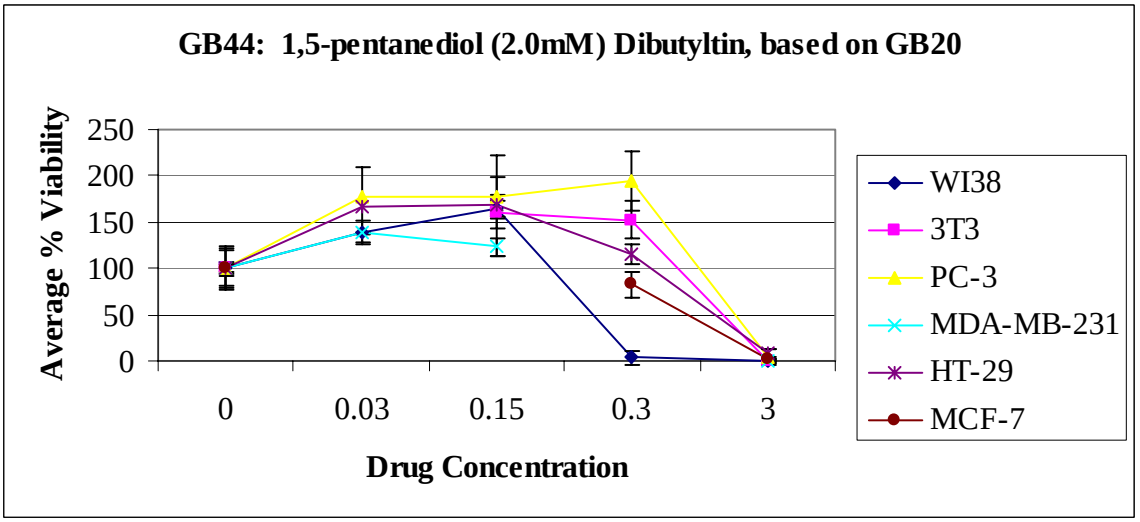

Figure C.12 Anticancer activity of 1,5-pentanediol dibutyltin, with a molarity of 2.0mM, after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

APPENDIX D

GRAPHS USED TO GENERATE THE GI_{50} VALUES OF THE TYPE II POLYMERIC DRUGS

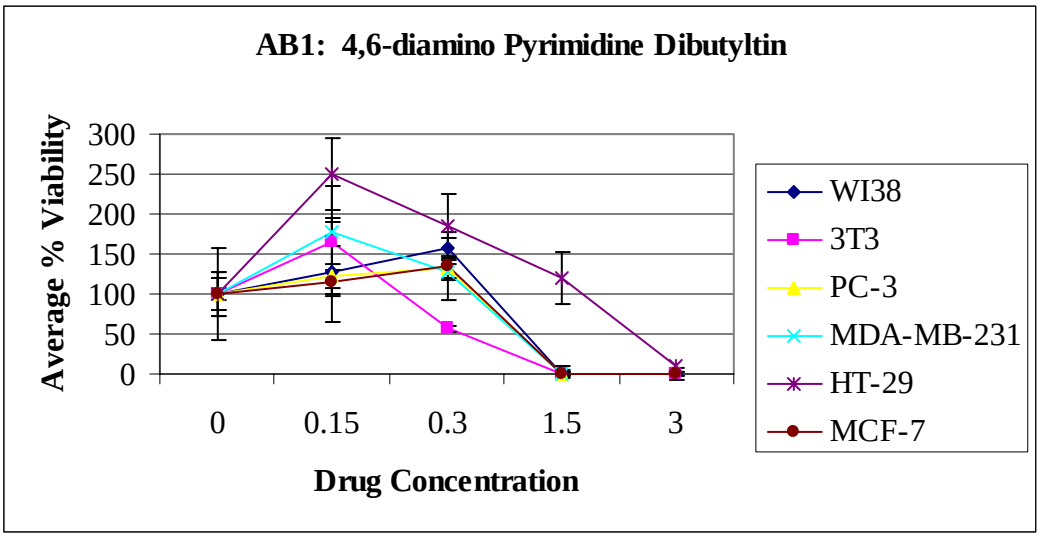

Figure D.1 Anticancer activity of 4,6-diamino pyrimidine dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

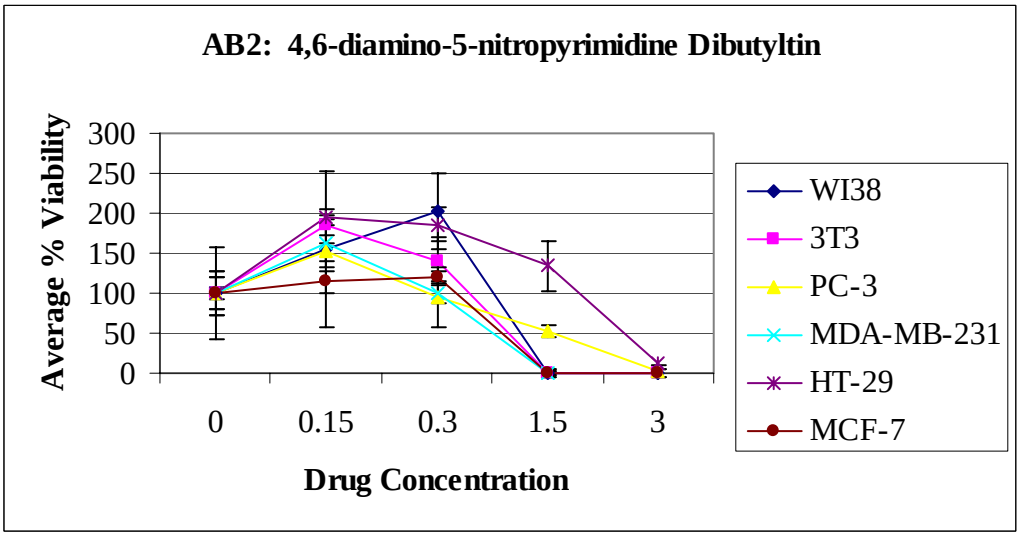

Figure D.2 Anticancer activity of 4,6-diamino-5-nitropyrimidine dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

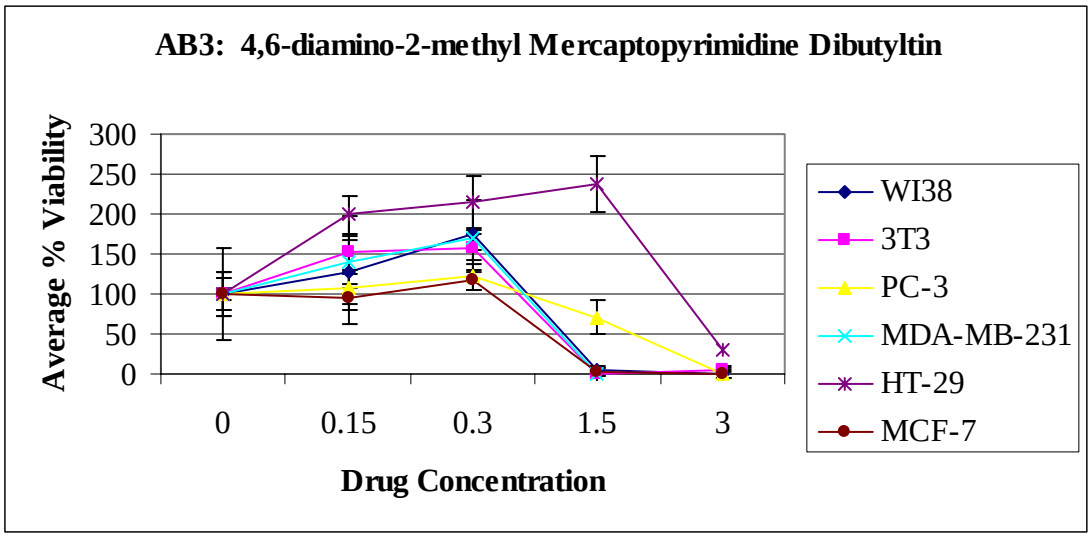

Figure D.3 Anticancer activity of 4,6-diamino-2-methyl mercaptopyrimidine dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

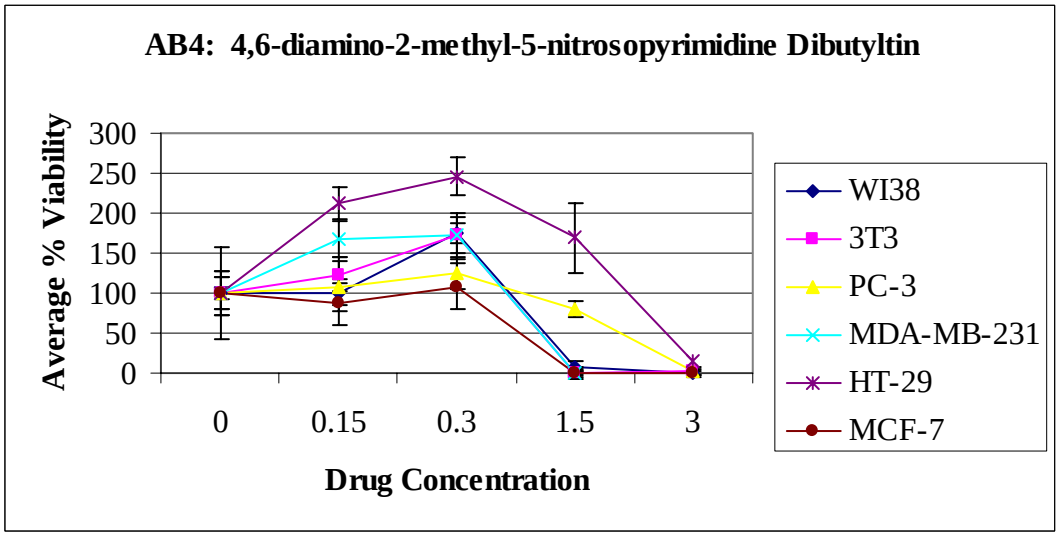

Figure D.4 Anticancer activity of 4,6-diamino-2-methyl-5-nitrosopyrimidine dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

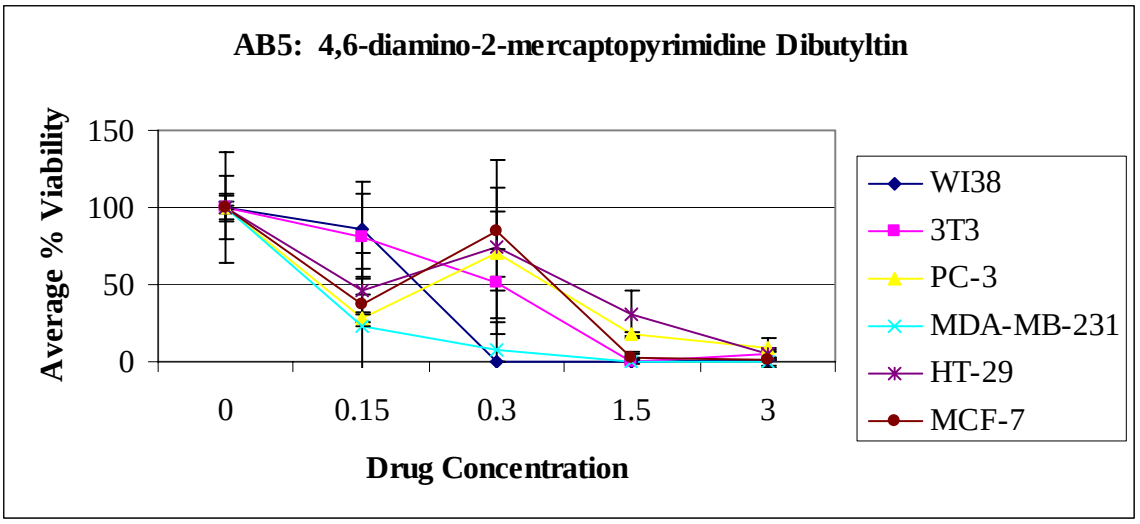

Figure D.5 Anticancer activity of 4,6-diamino-2-mercaptopyrimidine dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

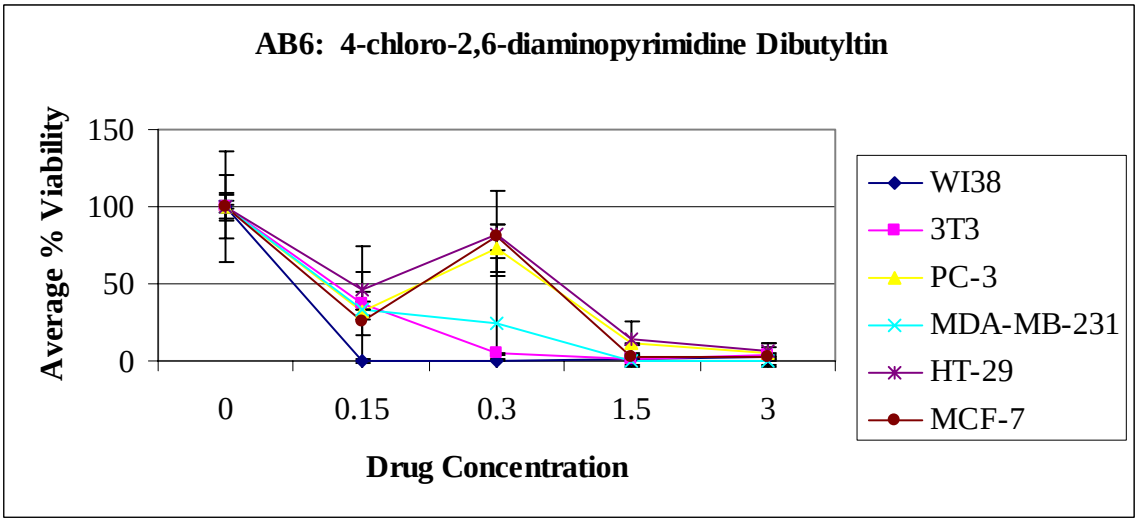

Figure D.6 Anticancer activity of 4-chloro-2,6-diaminopyrimidine dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

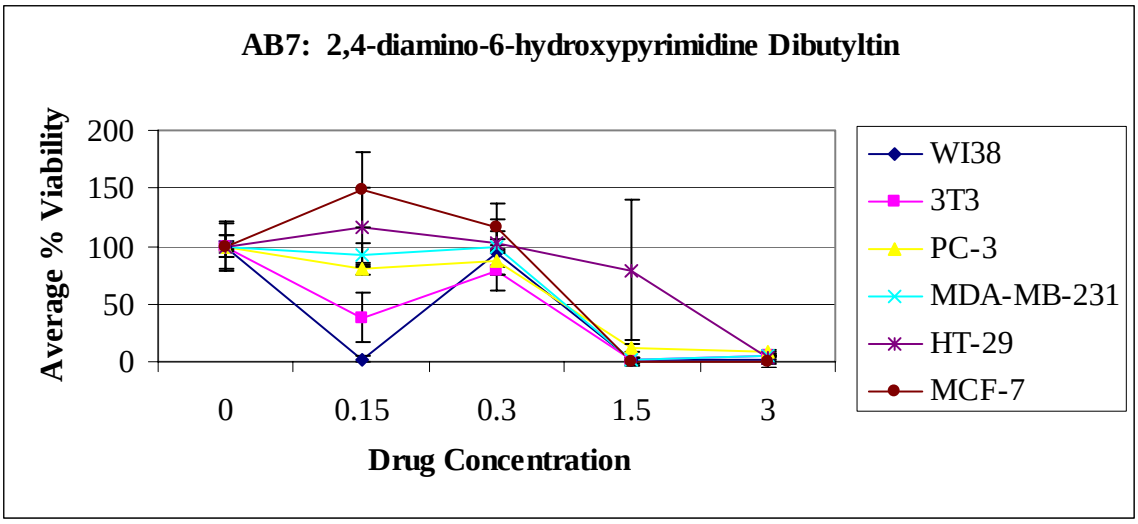

Figure D.7 Anticancer activity of 2,4-diamino-6-hydroxypyrimidine dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

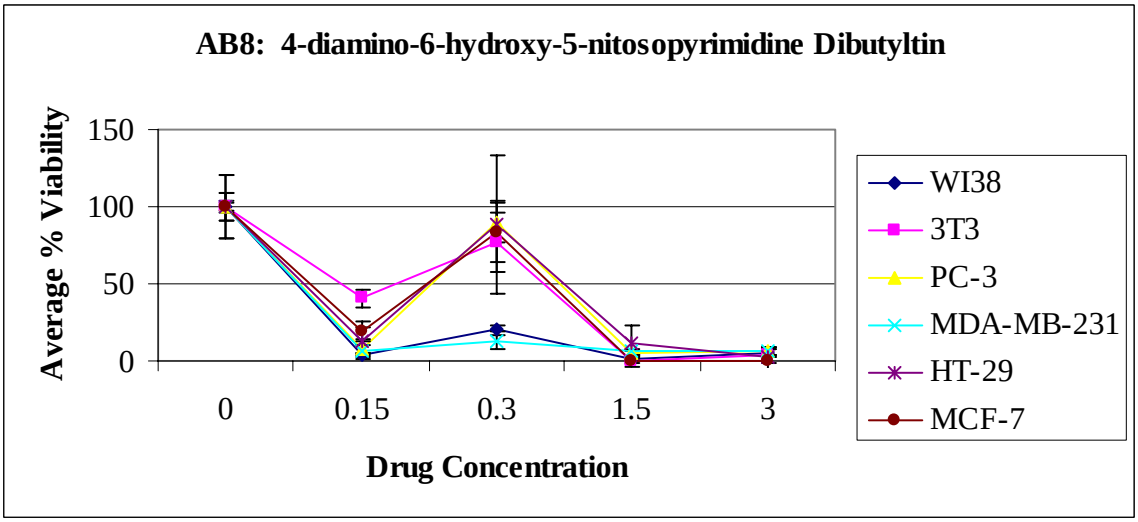

Figure D.8 Anticancer activity of 4-diamino-6-hydroxy-5-nitrosopyrimidine dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

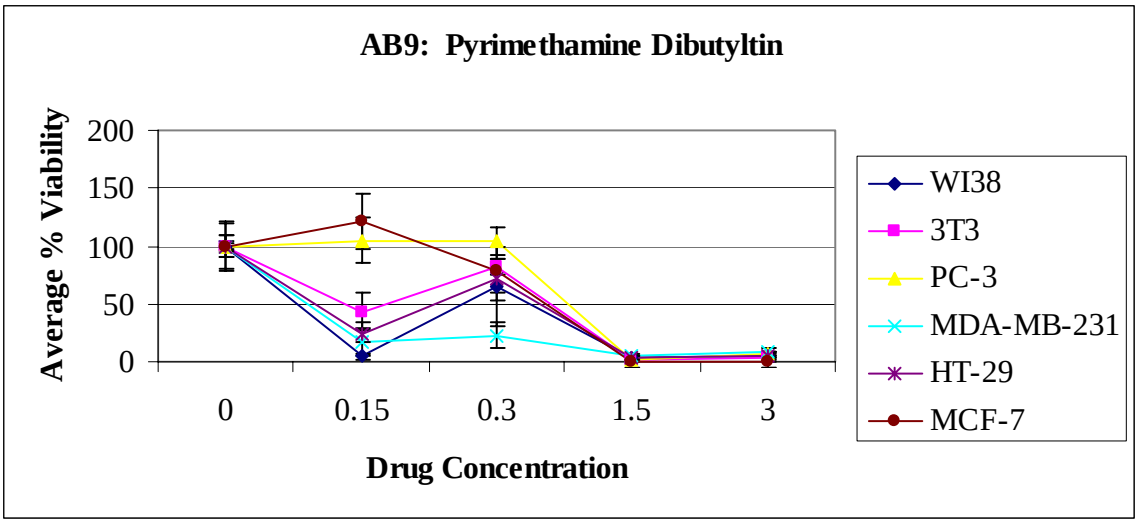

Figure D.9 Anticancer activity of pyrimethamine dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

APPENDIX E

GRAPHS USED TO GENERATE THE GI_{50} VALUES OF THE TYPE III POLYMERIC DRUGS

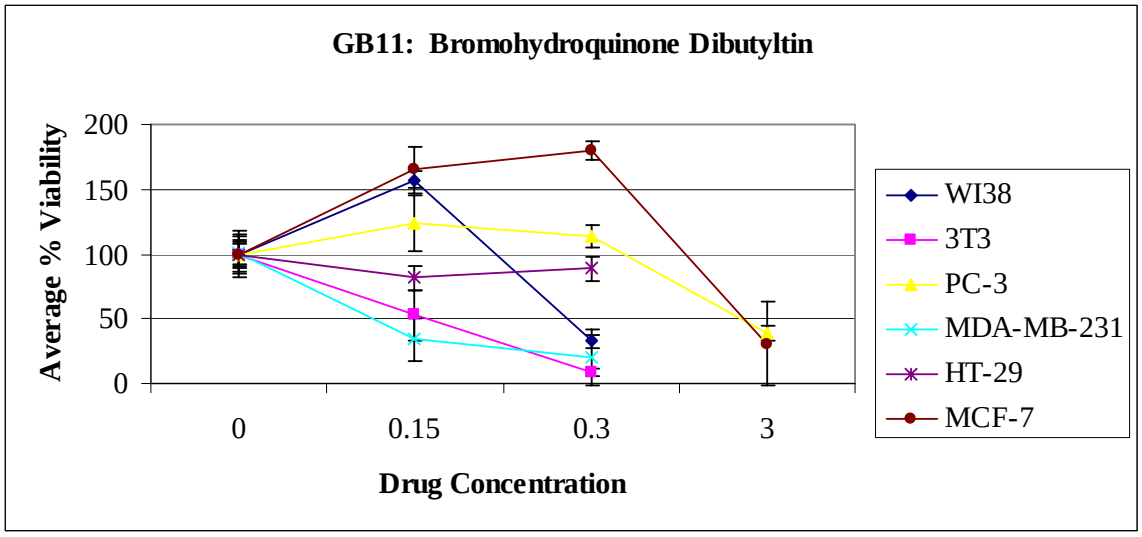

Figure E.1 Anticancer activity of bromohydroquinone dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

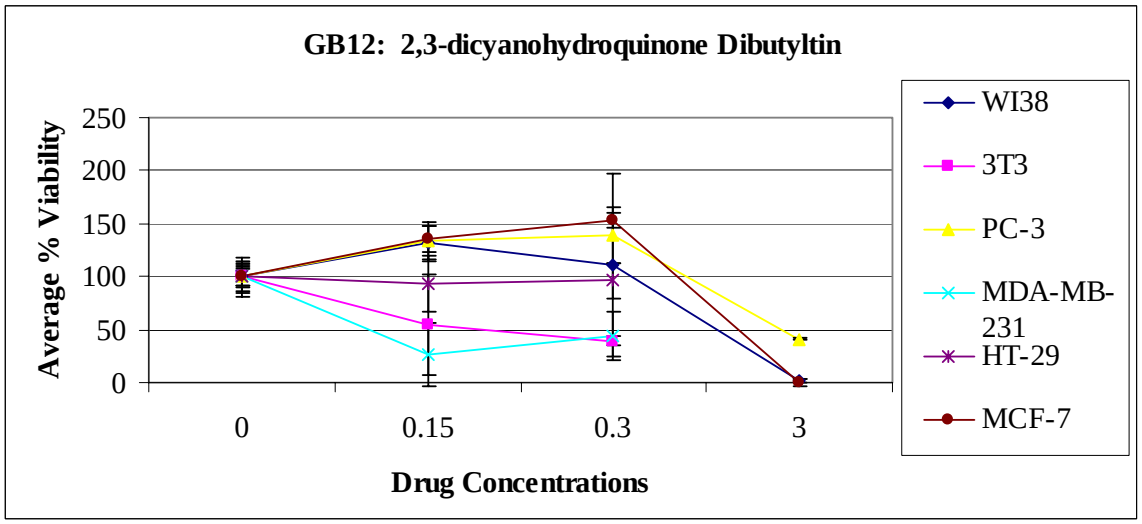

Figure E.2 Anticancer activity of 2,3-dicyanohydroquinone dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

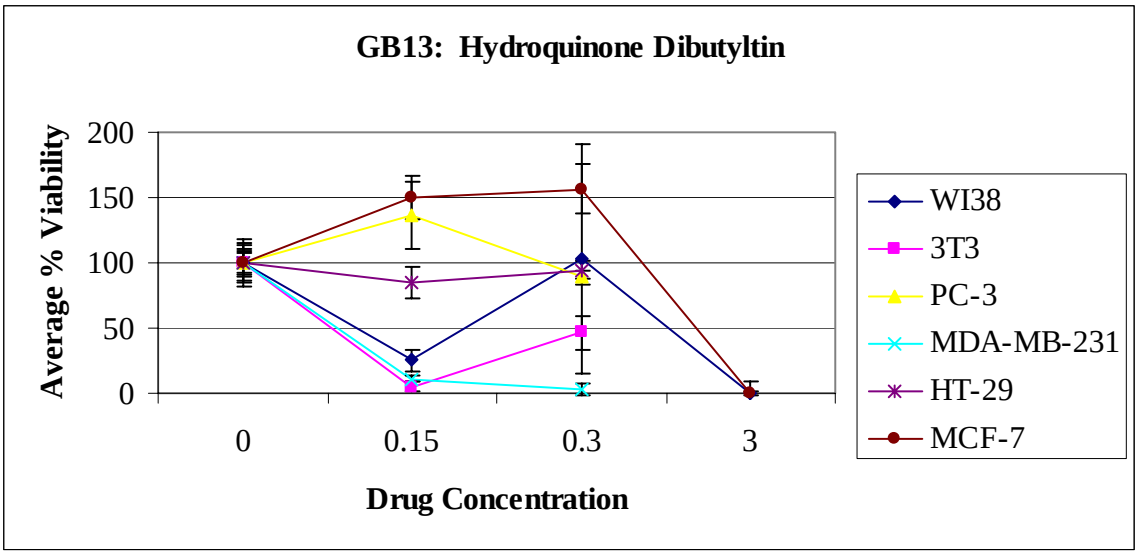

Figure E.3 Anticancer activity of hydroquinone dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

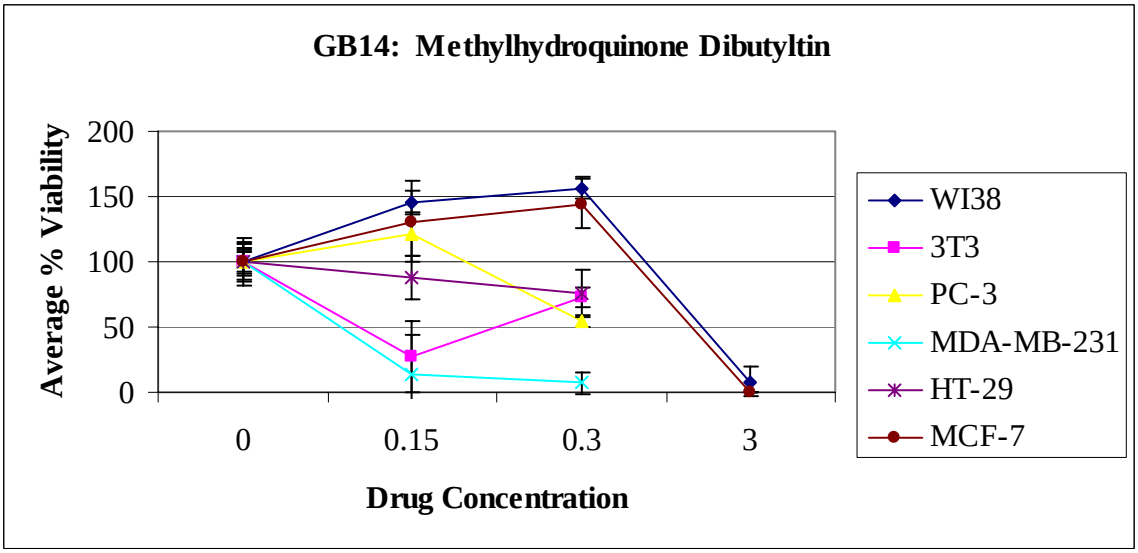

Figure E.4 Anticancer activity of methylhydroquinone dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

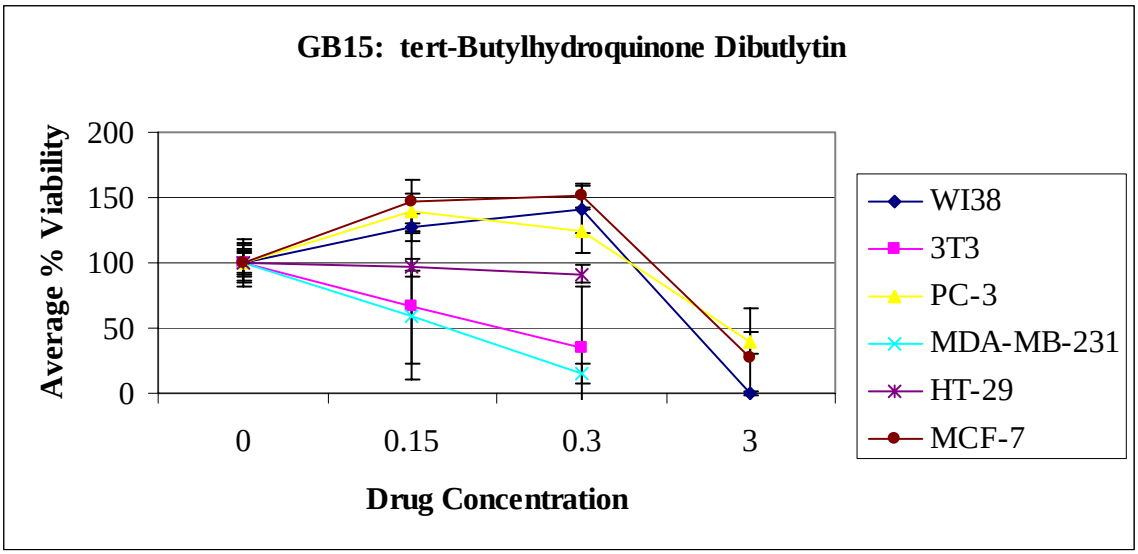

Figure E.5 Anticancer activity of tert-butylhydroquinone dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

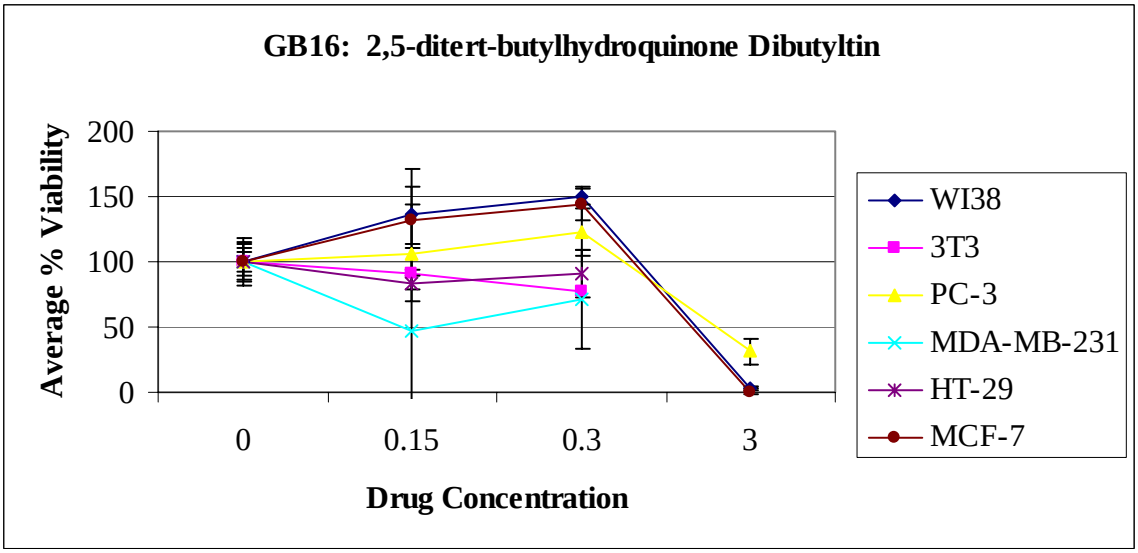

Figure E.6 Anticancer activity of 2,5-ditert-butylhydroquinone dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

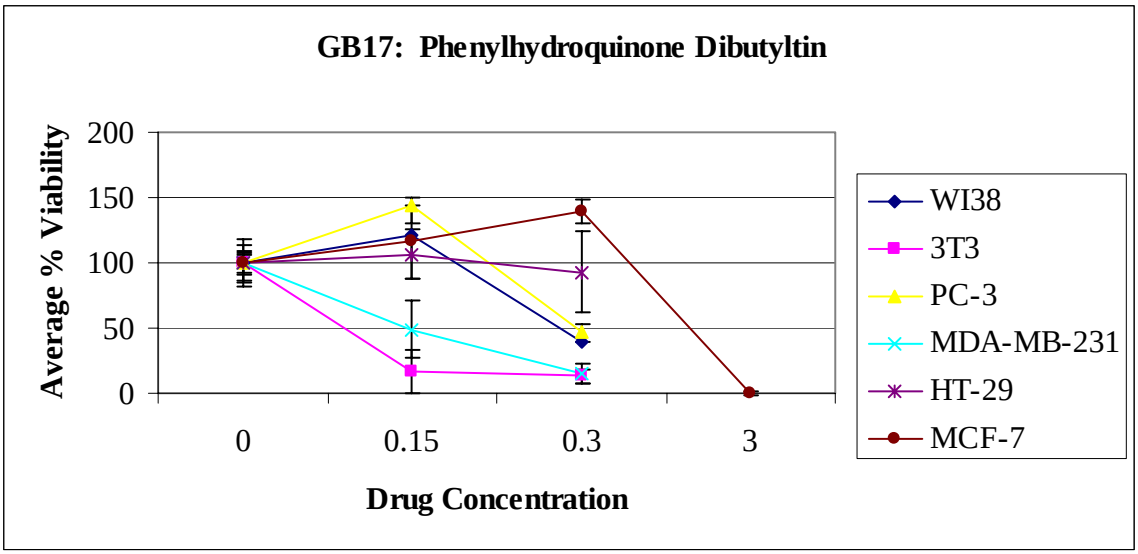

Figure E.7 Anticancer activity of phenylhydroquinone dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

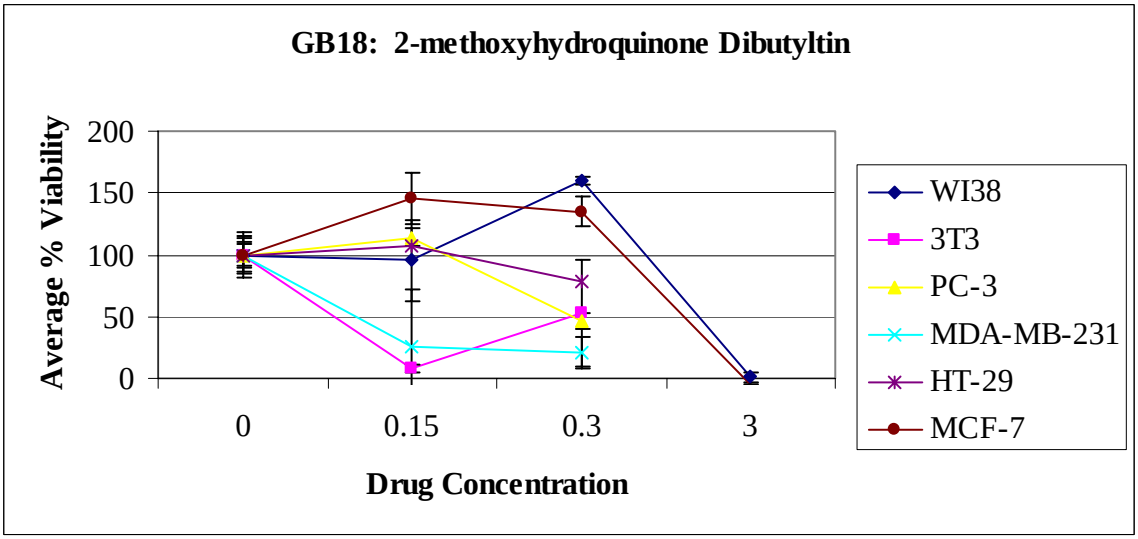

Figure E.8 Anticancer activity of 2-methoxyhydroquinone dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

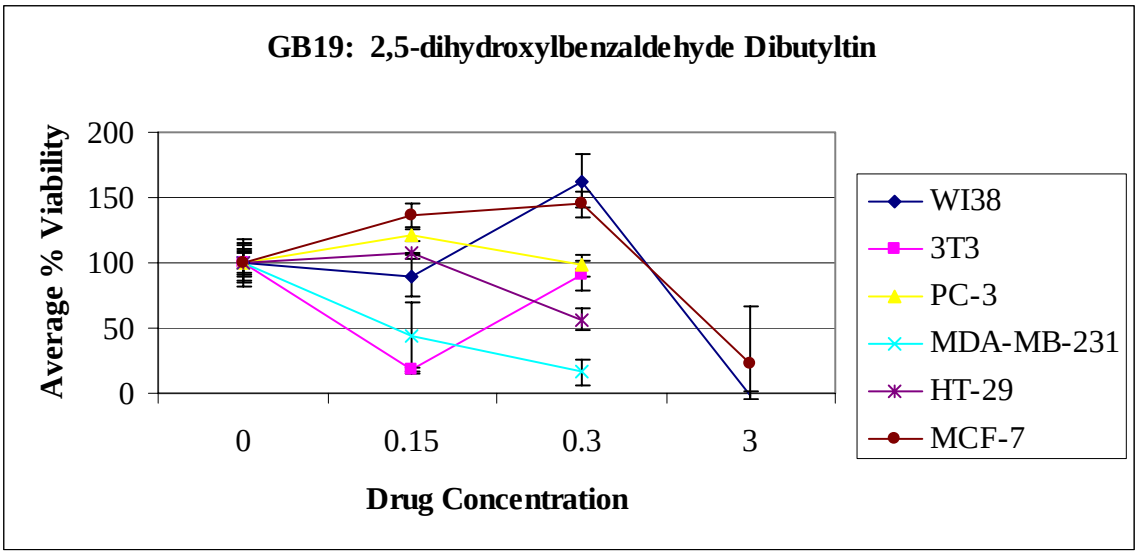

Figure E.9 Anticancer activity of 2,5-dihydroxybenzaldehyde dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

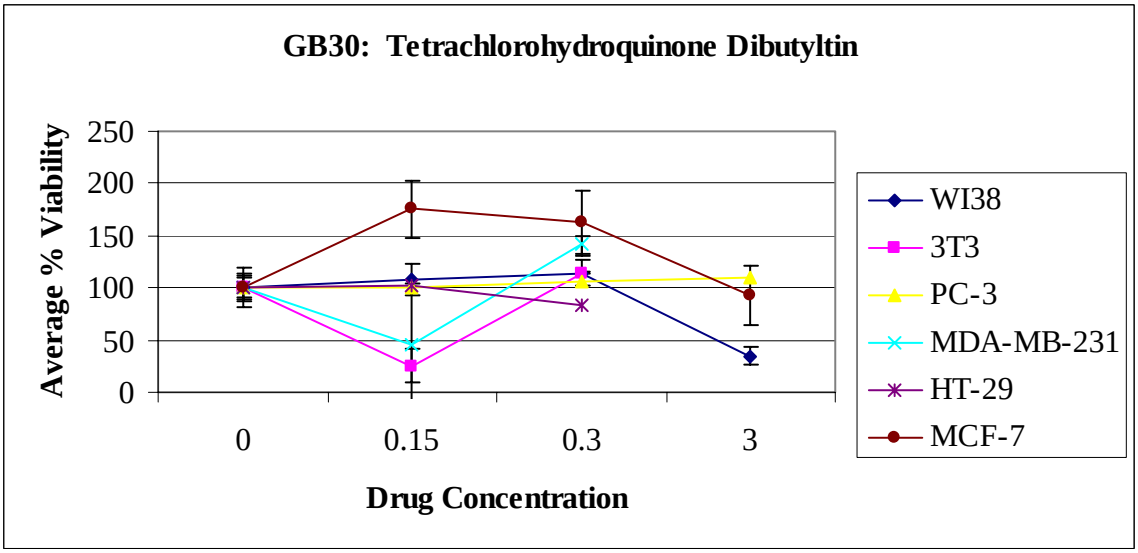

Figure E.10 Anticancer activity of tetrachlorohydroquinone dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

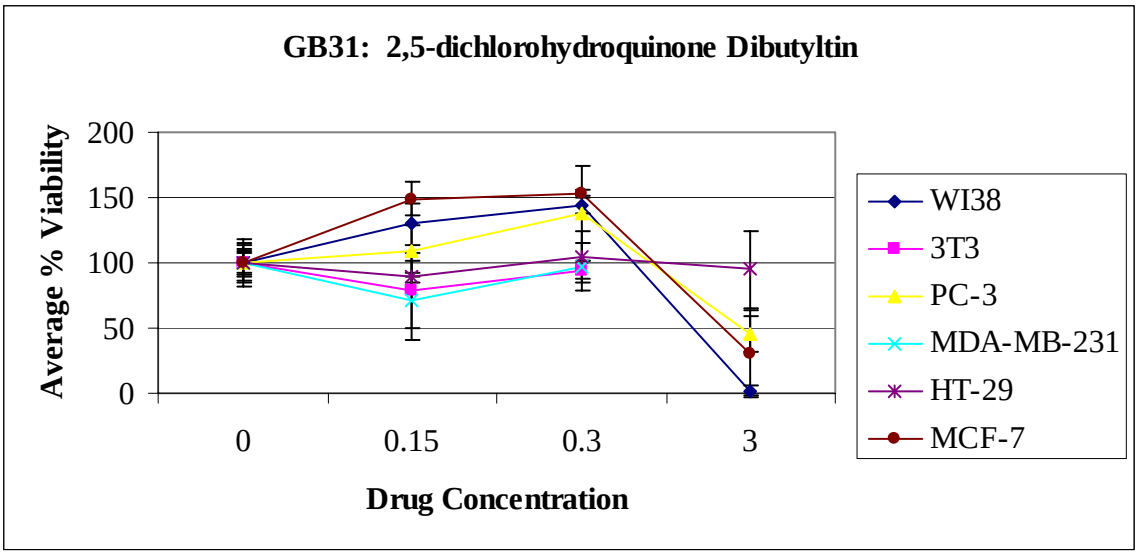

Figure E.11 Anticancer activity of 2,5-dichlorohydroquinone dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

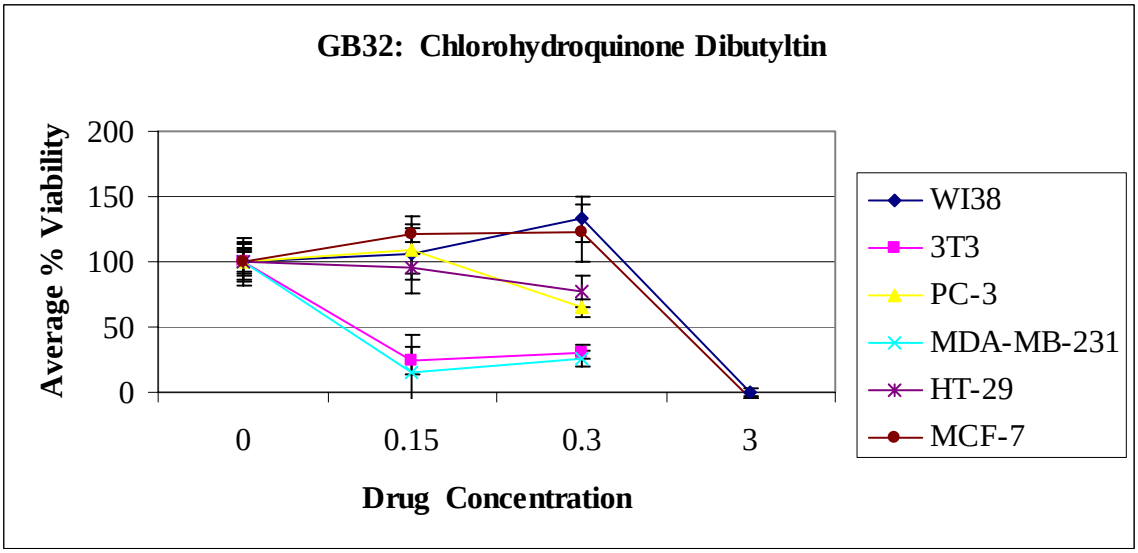

Figure E.12 Anticancer activity of chlorohydroquinone dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

APPENDIX F

GRAPHS USED TO GENERATE THE GI_{50} VALUES OF THE TYPE IV POLYMERIC DRUGS, DIETHYLSTILBESTROL, HAFNOCENE, TITANOCENE. AND ZIRCONIA

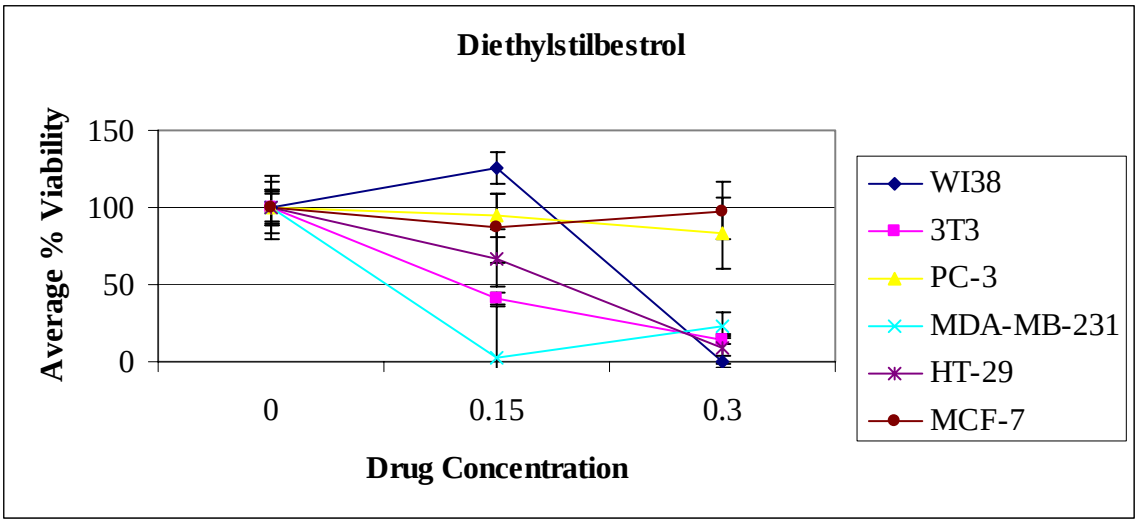

Figure F.1 Anticancer activity of diethylstilbestrol after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

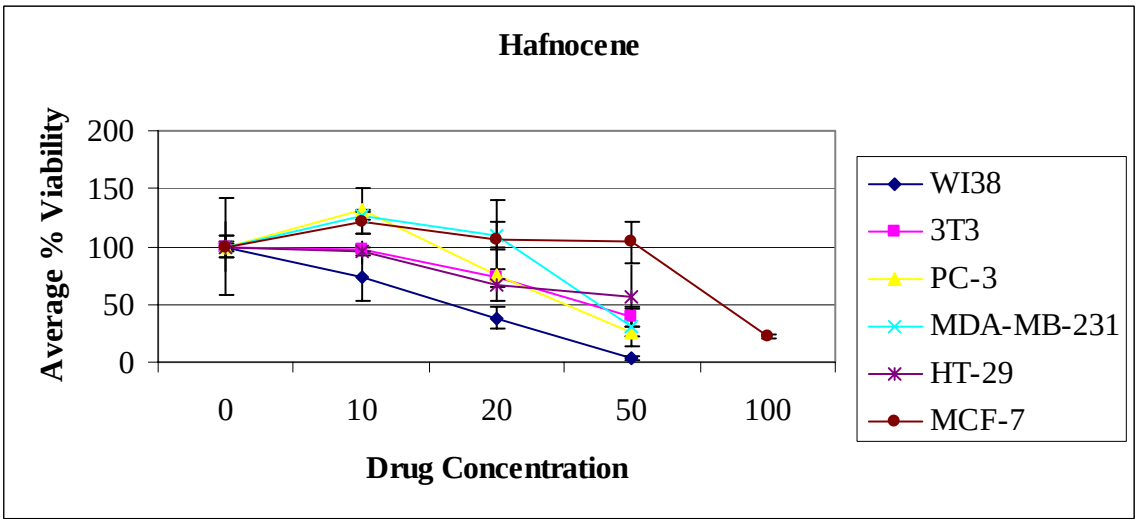

Figure F.2 Anticancer activity of hafnocene after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

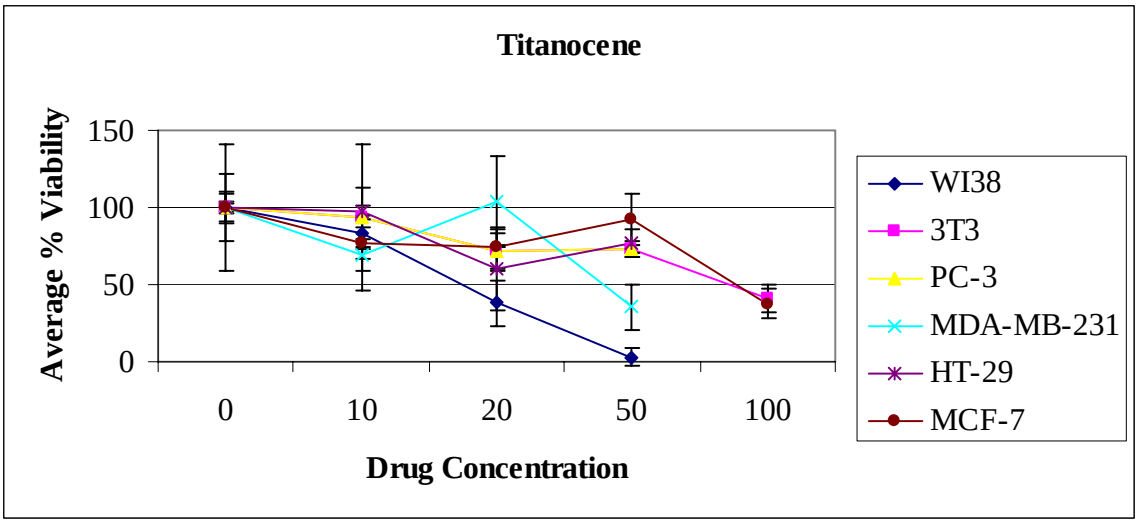

Figure F.3 Anticancer activity of titanocene after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

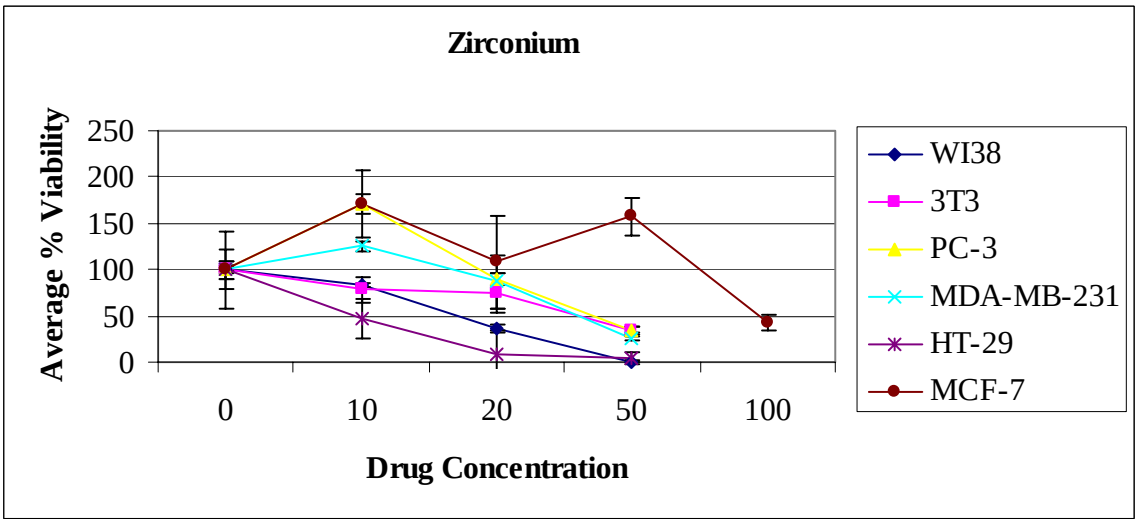

Figure F.4 Anticancer activity of zirconium after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

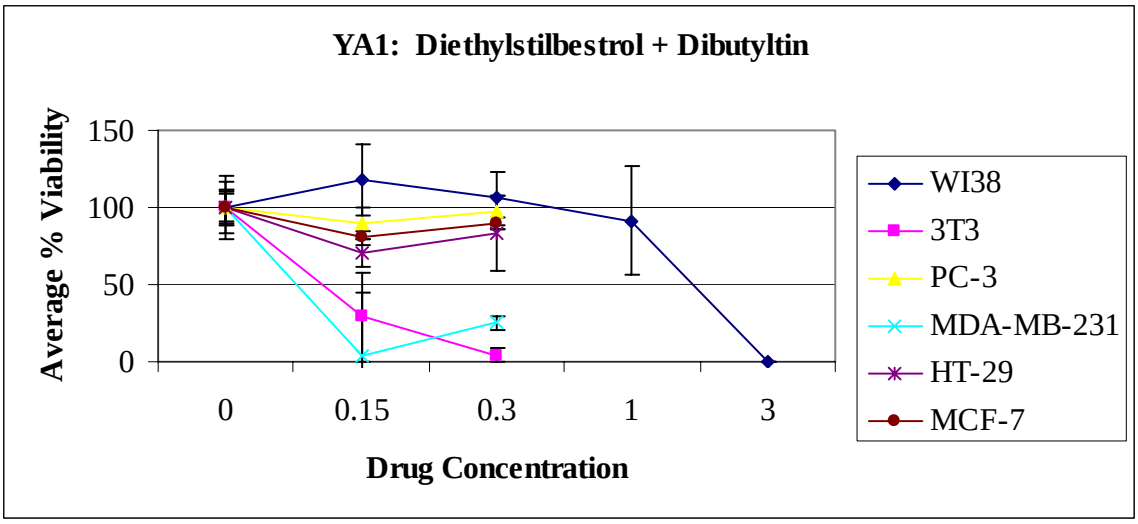

Figure F.5 Anticancer activity of diethylstilbestrol dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

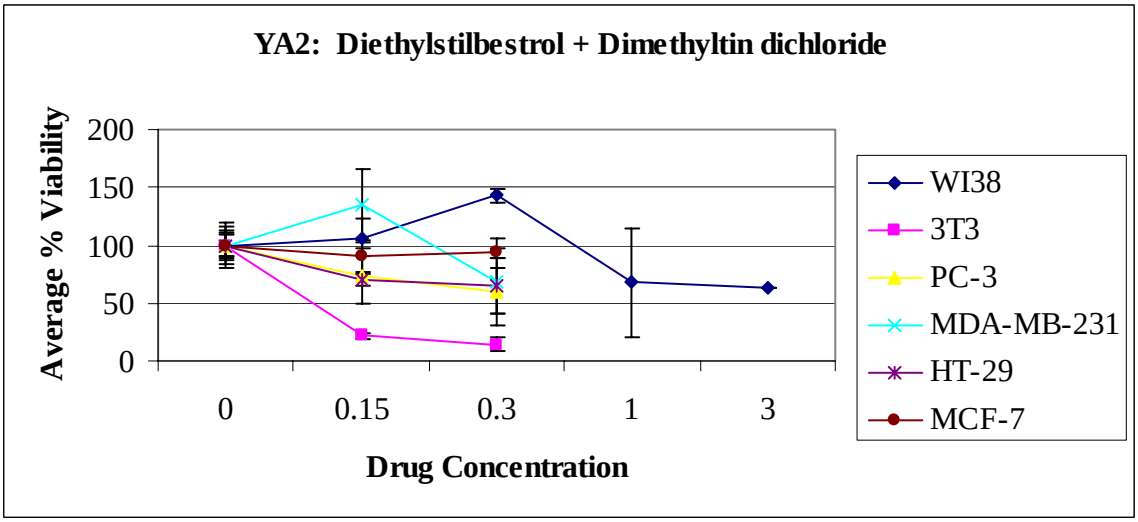

Figure F.6 Anticancer activity of diethylstilbestrol dimethyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

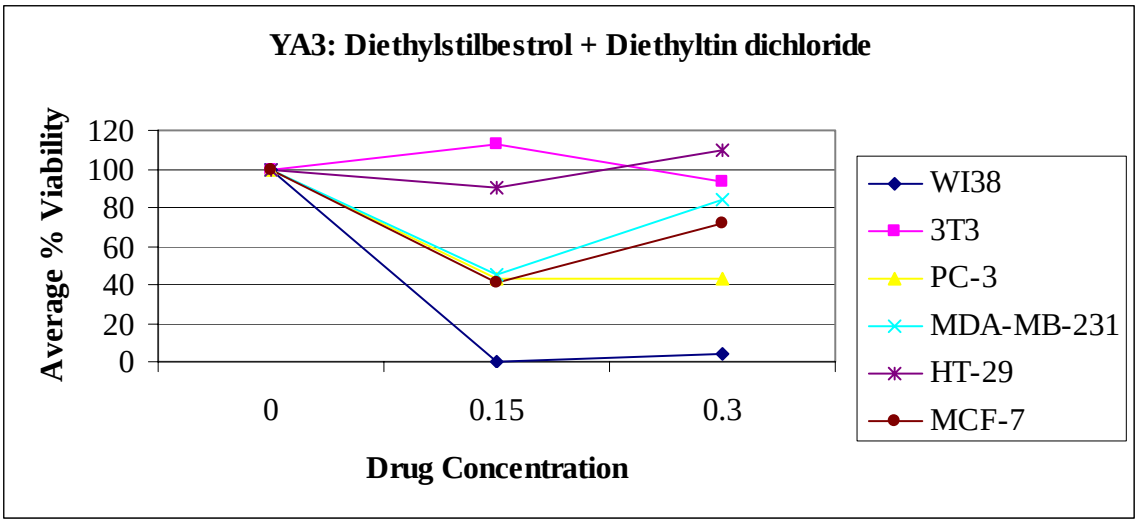

Figure F.7 Anticancer activity of diethylstilbestrol diethyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

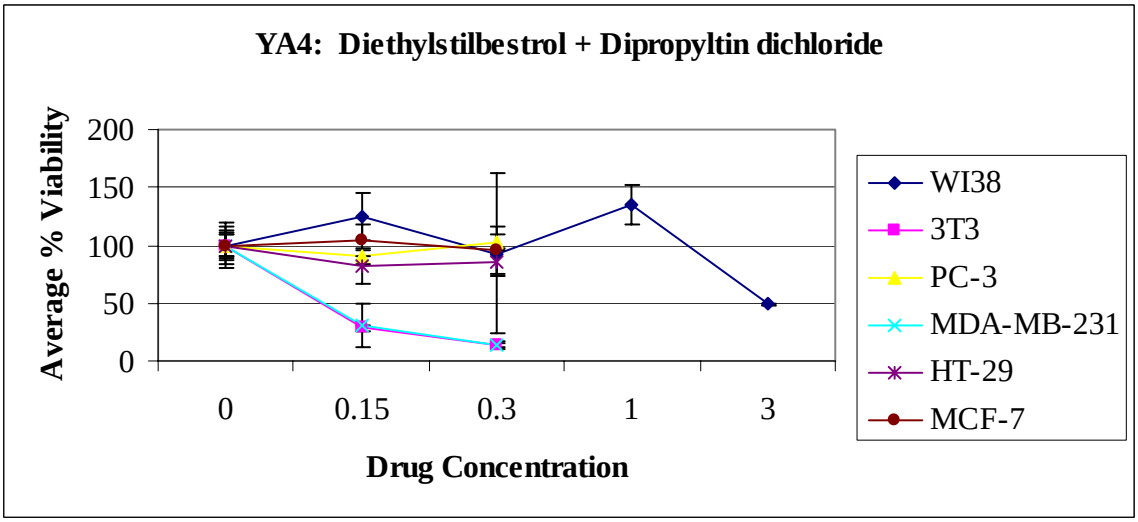

Figure F.8 Anticancer activity of diethylstilbestrol dipropyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

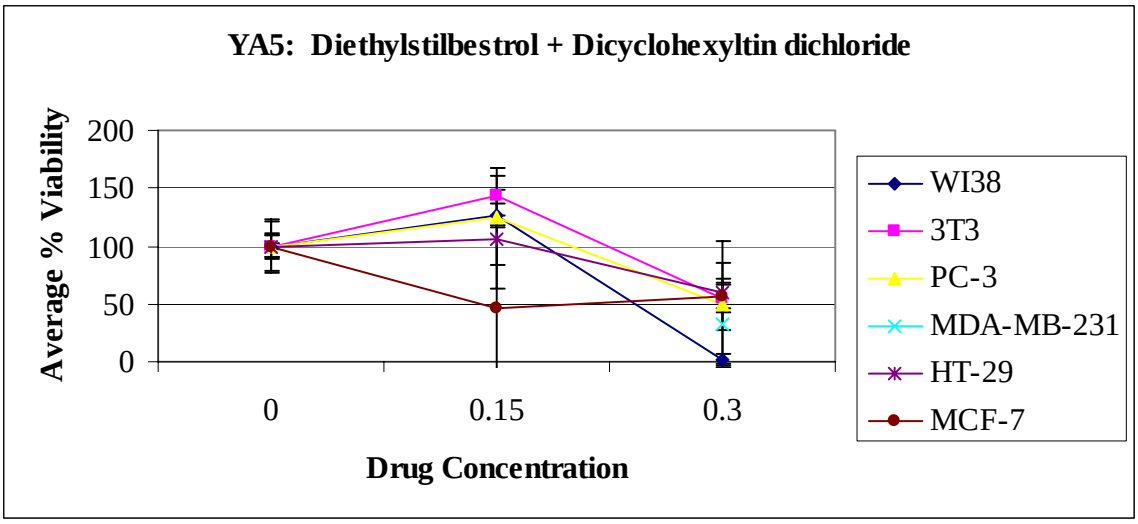

Figure F.9 Anticancer activity of diethylstilbestrol dicyclohexyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

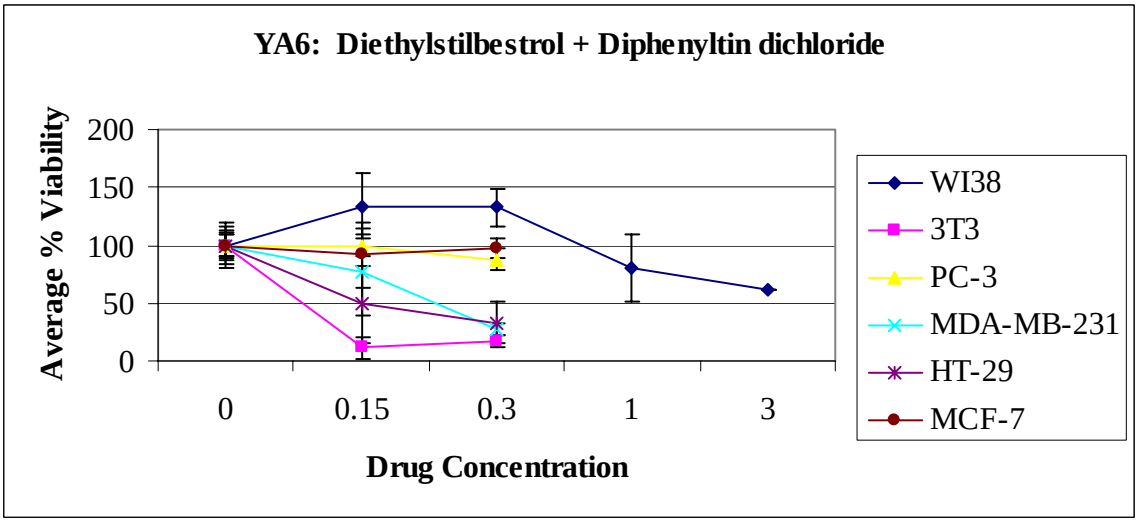

Figure F.10 Anticancer activity of diethylstilbestrol diphenyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

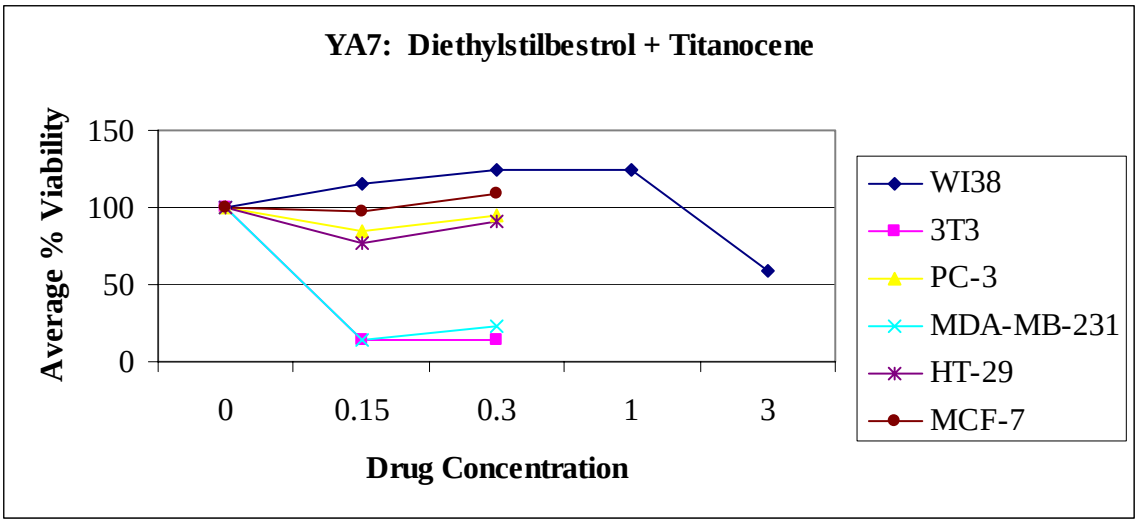

Figure F.11 Anticancer activity of diethylstilbestrol titanocene after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

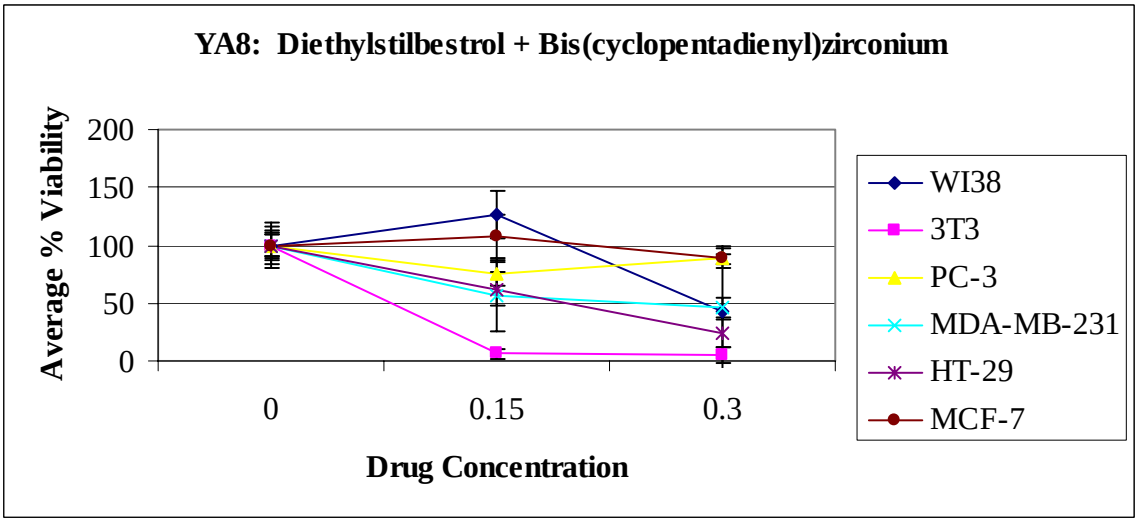

Figure F.12 Anticancer activity of diethylstilbestrol bis(cyclopentadienyl)zirconium after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

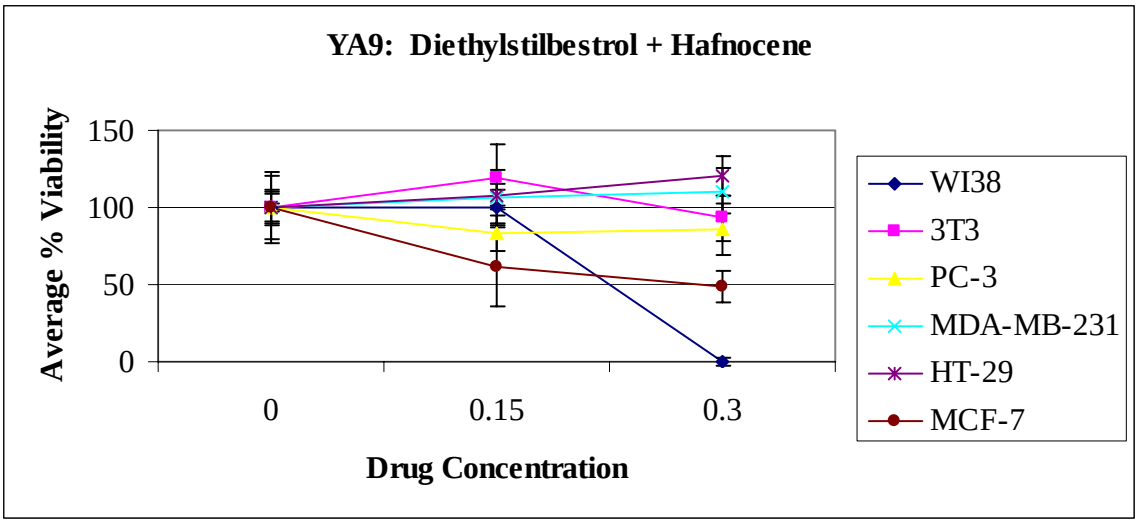

Figure F.13 Anticancer activity of diethylstilbestrol hafnocene after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

APPENDIX G

GRAPHS USED TO GENERATE THE GI_{50} VALUES OF THE TYPE V POLYMERIC DRUGS AND DIENESTROL

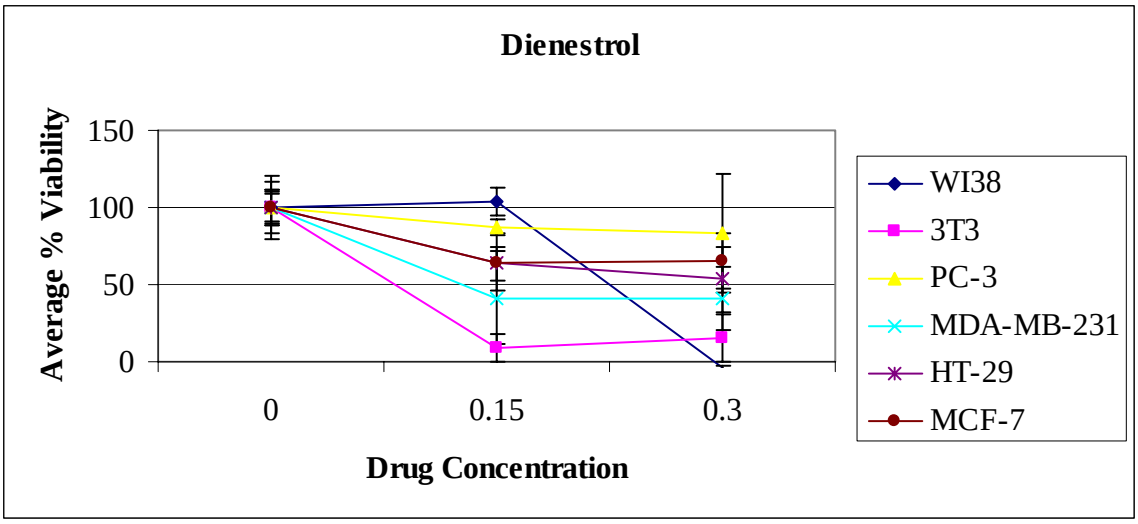

Figure G.1 Anticancer activity of dienestrol after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

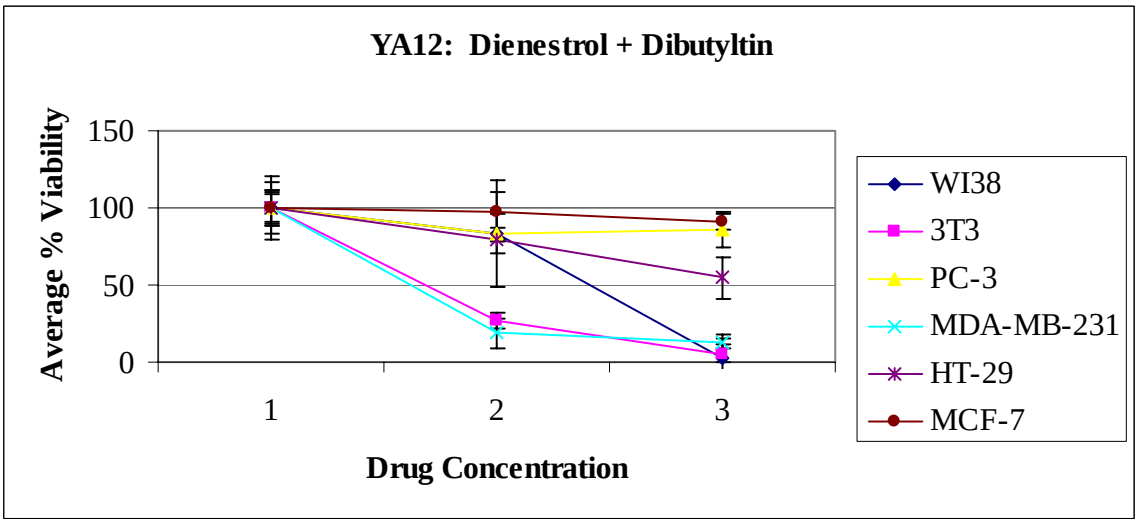

Figure G.2 Anticancer activity of dienestrol dibutyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

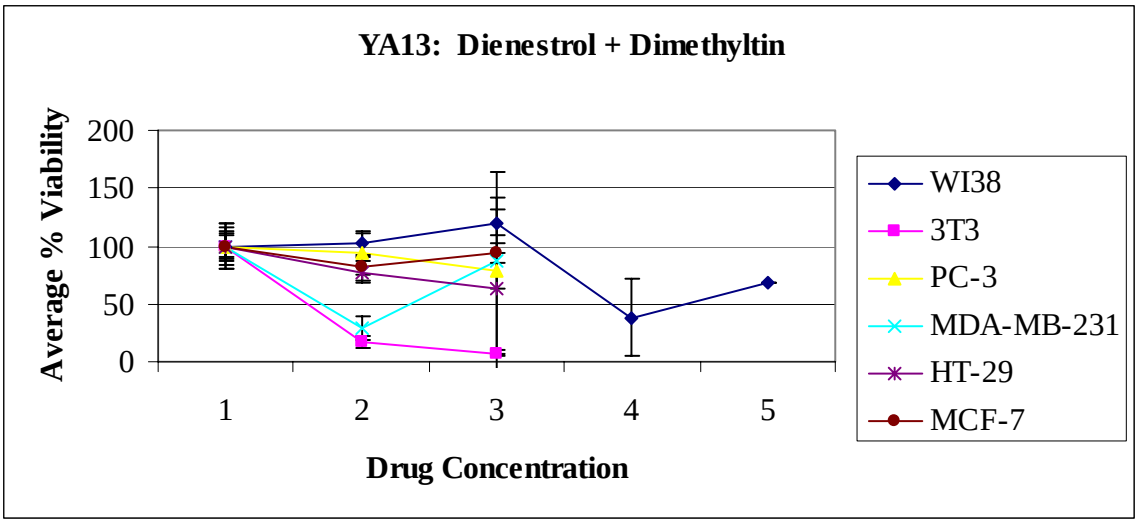

Figure G.3 Anticancer activity of dienestrol dimethyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

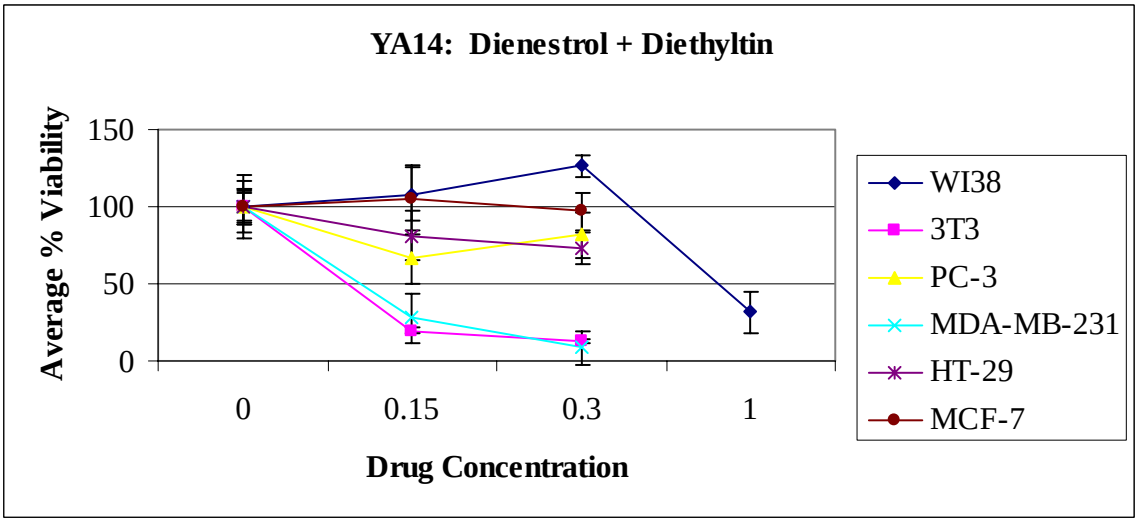

Figure G.4 Anticancer activity of dienestrol diethyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

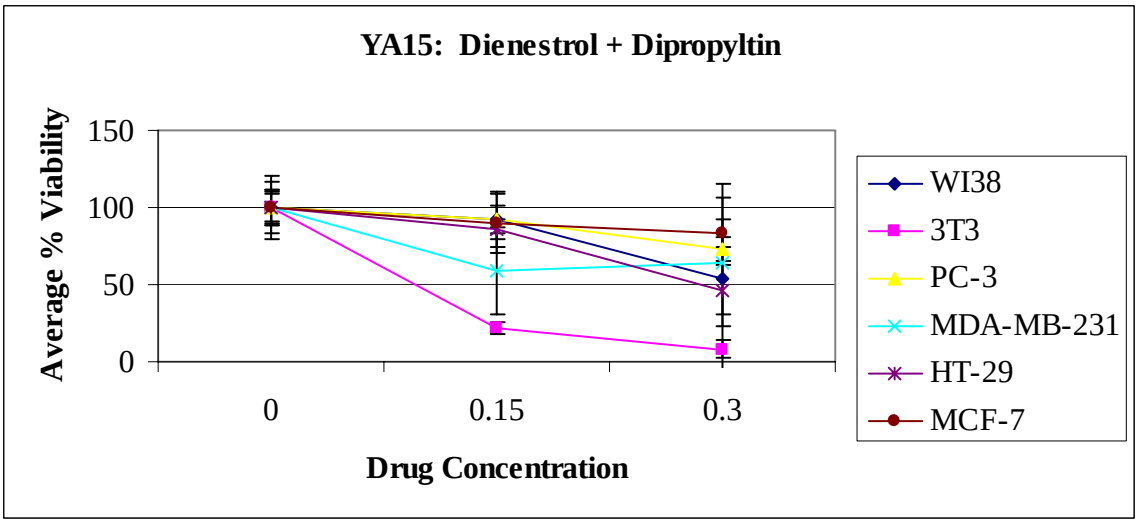

Figure G.5 Anticancer activity of dienestrol dipropyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

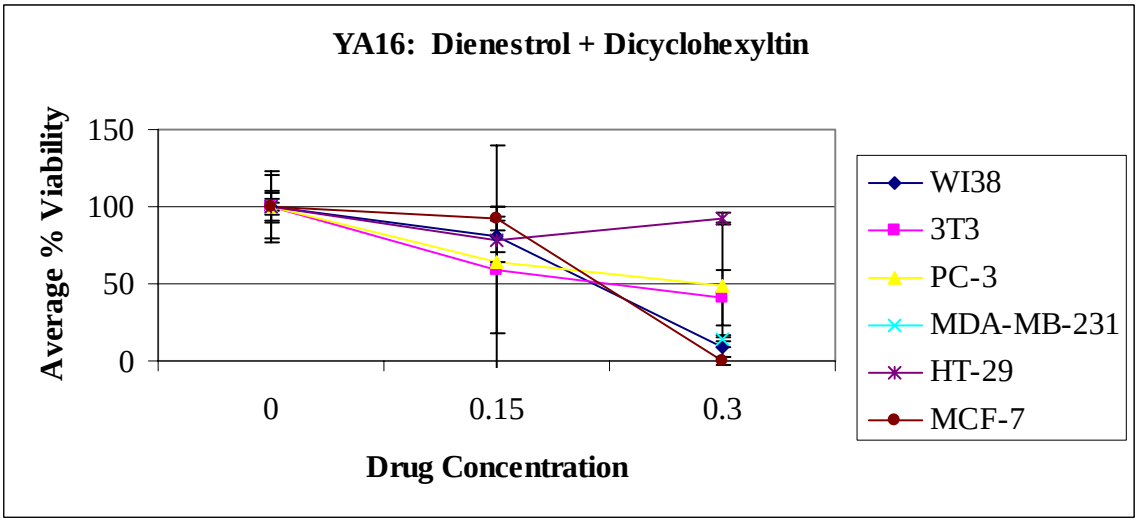

Figure G.6 Anticancer activity of dienestrol dicyclohexyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

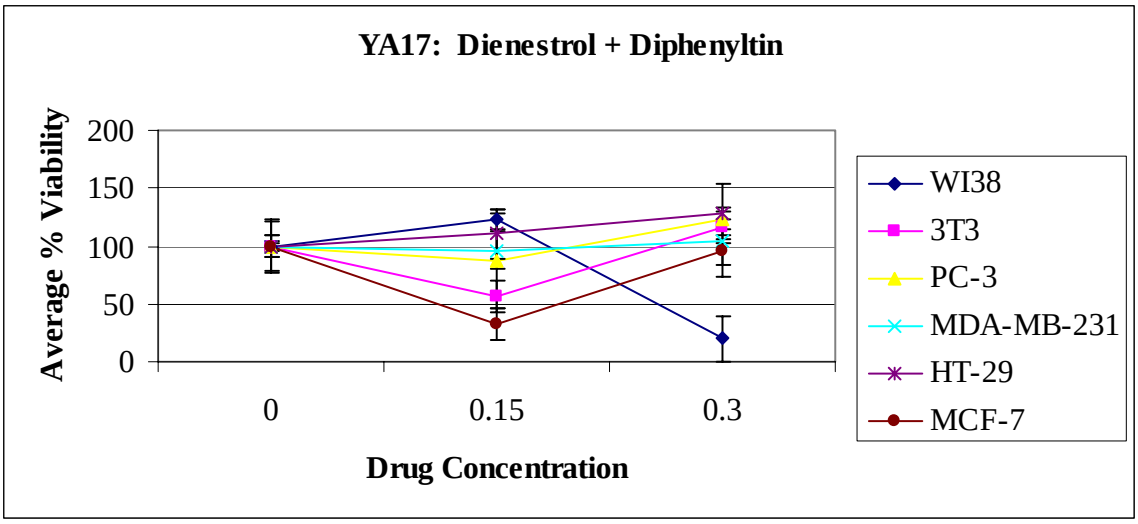

Figure G.7 Anticancer activity of dienestrol diphenyltin after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

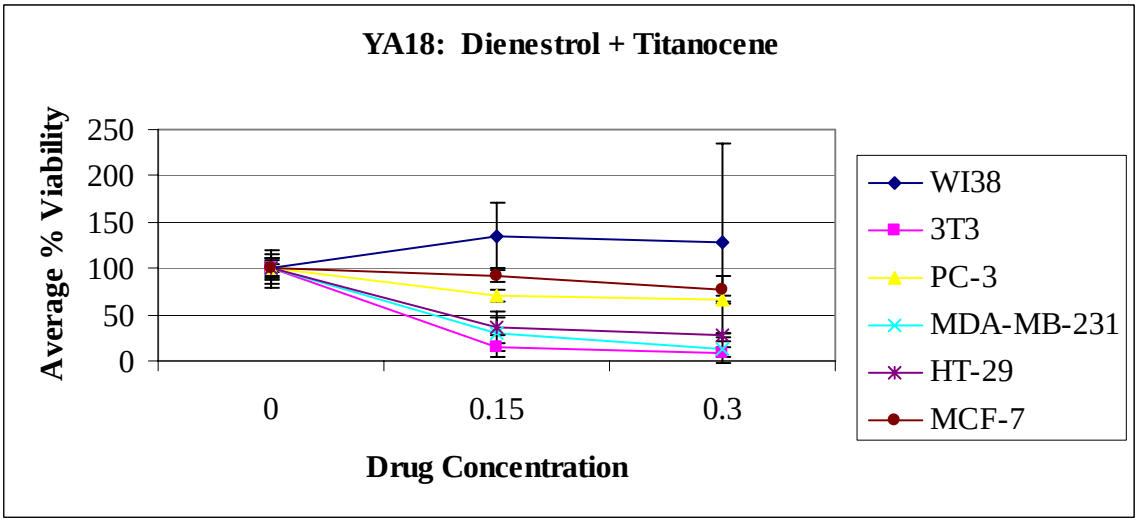

Figure G.8 Anticancer activity of dienestrol titanocene after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

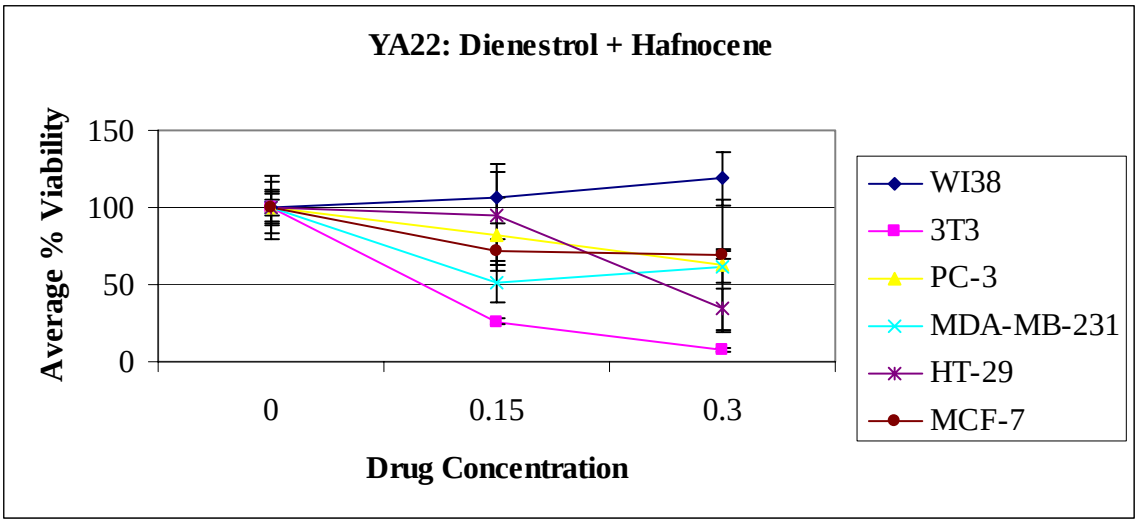

Figure G.9 Anticancer activity of dienestrol hafnocene after 72 hours. Drug concentrations are in µg/mL. The error bars indicate one standard deviation from the mean.

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BIOGRAPHICAL INFORMATION

Kim started college at the University of South Alabama in 1996. She transferred to the University of Central Oklahoma after getting married in 1998. After her husband graduated from UCO in 2000, they moved to Arlington, Texas. Kim graduated from the University of Texas at Arlington in 2002 with a Bachelors of Science degree in Microbiology. She entered the graduate program for biology at UTA the same year. She began working for Dr. van Waasbergen. Her project was to study the regulatory pathway of *hliA* and *nblA* in cyanobacteria using transposon mutagenesis. She joined Dr. Roner's lab in December 2004. Her project was to find polymeric organotin drugs that were more effective anticancer and antiviral drugs than organotin monomers. In December 2007, she received her PhD in Quantitative Biology, under Dr. Roner's tutelage. She would like to work in industry, preferably the pharmaceutical industry. She wants to use molecular biological techniques to study bacteria and viruses to find new ways to fight diseases caused by the two groups.