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Review

Organotin Polymers for the Control of Pancreatic Cancer

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Abstract

Pancreatic cancer is the fourth leading cause of death in the USA. Treatment is seldom successful. A wide variety of organotin polymers exhibit good inhibition of human pancreatic cancer cell lines AsPC-1 and PANC-1. The AsPC-1 is an adenocarcinoma pancreatic cell line and PANC-1 which is an epithelioid carcinoma pancreatic cell line. Synthesis is rapid employing commercially available reactants and the interfacial polymerization that is employed in the commercial synthesis of aramids and polycarbonates.

Keywords

Pancreatic cancer; AsPC-1 cells; PANC-1 cancer cell line; interfacial polycondensation, organotin polymers; tin-containing polymers; anticancer drugs

1. Introduction

Organotin compounds have been used for a variety of applications [1]. For instance, organotin polyethers made by Carraher and coworkers are employed in the commercial production of poly(vinyl chloride) as thermal stabilizers allowing the construction of tubes and other PVC products [2, 3]. More organotin compounds are available commercially than any other metal-containing organometallic [1]. They have been known for over 80 years to inhibit cancer cell growth [4-11] and more organotin compounds have undergone testing as potential anticancer agents than any other single group of compounds [1].

Cancer is the leading cause of death globally [12, 13]. In the USA pancreatic cancer is the fourth leading cause of death with about 32,000 new incidents yearly and about 170,000 globally. The treatment of pancreatic cancer is rarely successful as this disease typically metastasizes throughout the body prior to detection. Current therapies include surgery, radiation and chemotherapy. Standard chemotherapy for patients with locally contained cancer includes gemcitabine. Gemcitabine is employed to improve the quality of life through better pain control, shrinkage of tumor, and prolonged survival. The latest addition is the use of Abraxane, a protein-bound paclitaxel previously used with breast and lung cancer, with Gemcitabine offering a limited additional life expectancy to advanced pancreatic cancer patients [15-19].

2. Particulars

The mechanism of action of organotin compounds towards cancer is not well understood but is believed to involve several biological sites including DNA [20-22]. This variety of biological activity, while more difficult to understand, may be positive since it allows for potential curtailment of cancer growth at several sites.

For our organotin polymers, activity is believed to occur by the entire chain rather through segments of the chain [20-22]. The ability to inhibit pancreatic cancer cell growth by dissolved organotin polymer chains remains for weeks and for some for over a month. The polymers are cytotoxic and cell death is by necrosis [21].

3. Synthesis

Synthesis occurs employing the interfacial polycondensation process developed by Morgan and co-workers at DuPont [23] and later by Carraher and co-workers [24-26]. Briefly, reaction occurs at room temperature using rapid stirring, about 18,000 rpm, about double the speed of a model airplane propeller. A commercial Waring blender is used with reaction occurring in a one-quart Kimax emulsifying jar fitted on top of the blender. The Lewis base is dissolved in water and this phase is added to the emulsifying jar. Stirring is begun and the second phase composed of a water-immiscible liquid such as heptane, containing the dissolved Lewis acid is rapidly added. Stirring is continued for 5 to 15 seconds. The polymer precipitates and is recovered, washed with water and the organic solvent to remove unreacted materials and byproducts.

The Lewis acid/base pair react with an activation energy of 10-20 kcal allowing for the rapid reaction. The other feature promoting rapid reaction is the rapid stirring in the emulsifying jar. The emulsifying jar promotes turbine mixing and the rapid stirring encourages interfacial surface formation since formed polymer is readily removed from the interface resulting in new interface

formation. Compared with a static or slowly stirred system, for the system employed by us the interfacial surface area is increased about 10,000 times. For our reactions only reactants that are commercially available are employed.

The interfacial polycondensation system is used commercially to produce aramids (aromatic nylons) and polycarbonates. This combination of rapid reactions and using only commercially available reactants allows ready scale-up as well as easy reproducibility.

The overall reaction is referred to as a Lewis acid/base reaction with the Lewis acid being the organotin dichloride and the Lewis base being organic bases as amines, hydroxyls, and neutralized organic acids.

4. Evaluative Measures

The two basic measures, EMs, typically used to evaluate the effectiveness and ability of drugs to inhibit cell growth inhibition are used in our studies. Briefly, one is simply the amount or effective concentration, EC, of test compound necessary to effect inhibition to some amount, typically 50%, EC_{50}. The lower the EC_{50} the better, lower concentrations of the drug demonstrating antitumor activity and likely reduced damage to normal tissues versus higher drug concentrations. The second measure is the amount of drug needed to inhibit a standard cell line, generally the human healthy normal embryonic lung fibroblast given the NCI designation WI-38 and strain ATCC CCL-75 compared to the amount of drug needed to inhibit the studied cell line, here a pancreatic cancer cell line. This is simply the ratio of EC_{50} for the standard cell line divided by the EC_{50} for the pancreatic cancer test cell line. High CI values are preferred since they indicate a possible difference in toxicity between the healthy test cell line and the target cell line. Typically, CI_{50} values of 2 and greater are desired. A CI values of two signifies that the drug is twice as likely to kill the tumor cell as it is the normal cell at the indicated concentration. In our cases, while the measured CI values are for 50% inhibition, in fact inhibition occurs to 100% with a steep concentration verses cell death to 100% death occurring.

5. Cell Lines Employed

The two of the most widely used pancreatic cell lines are employed in our studies. These cell lines are AsPC-1 which is an adenocarcinoma pancreatic cell line and PANC-1 which is an epithelioid carcinoma pancreatic cell line [27, 28]. About 95% of pancreatic cancers are exocrine pancreatic cancers (ductal adenocarcinoma). The AsPC-1 cell line is the usual cell line employed to mimic test drug behavior for this type of cancer.

The PANC-1 human pancreatic carcinoma is the second cell lines used by us. It is an epithelial-like cell line nuclear lysate employed as an in vitro model of non-endocrine pancreatic cancer for tumorigenicity studies. The PANC-1 cell line is estrogen receptor negative. The PANC-1 cells have a type B phenotype for glucose-6-phosphate dehydrogenase G6PD. It overexpresses the heregulin/human epidermal growth-factor receptor 2 (HER2/neu) oncogene present in 60%-70% of human pancreatic carcinomas.

6. Pancreatic Cancer Results

Following presents selective results of our studies that illustrate important points. We have looked at about 500 organotin compounds for their ability to inhibit pancreatic cancer cell lines. Following briefly describes some generalizations of our results with respect to pancreatic cancer.

Of the various organotin compounds employed, those derived from the dibutyltin dichloride are most effective at inhibiting pancreatic cancer. Butyltin-containing monomers have been commercially used for over eighty years, and while they are quite toxic to bacteria, they are the least toxic organotin moiety to humans [1]. It is widely used as a paint additive and in the treatment of materials subjected to both fresh and salt water [1]. Thus, of the organotin moieties used in cancer studies, it is the best-most is known about it, most available, lowest cost, and lowest toxicity to us.

The following generalizations have been found.

First, the nature of the Lewis base is important in determining the EM. For instance, Table 1 contains results from structually similar bases, in this case the hormones diethylstilbestrol, DES, and dienestrol, DE. While structurally similar, the pancreatic evaluative values are very different.

Table 1 Evaluative values for selected products from DES, DE, and organotin dichlorides [29-31].

Sample	EC_{50} WI-38	EC_{50}AsPC-1	EC_{50}PANC-1	EC_{50}WI-38/ EC_{50}AsPC-1	EC_{50}WI-38/ EC_{50} PAN-1
Bu_2Sn/DE	0.06(.01)	0.07(.01)	0.07(0.01)	0.86	0.86
Bu_2Sn/DES	2.5(.5)	0.05(.01)	0.08(.01)	50	31
Cy_2Sn/DES	0.22(.2)	0.30(.05)	0.30(.05)	0.7	0.7

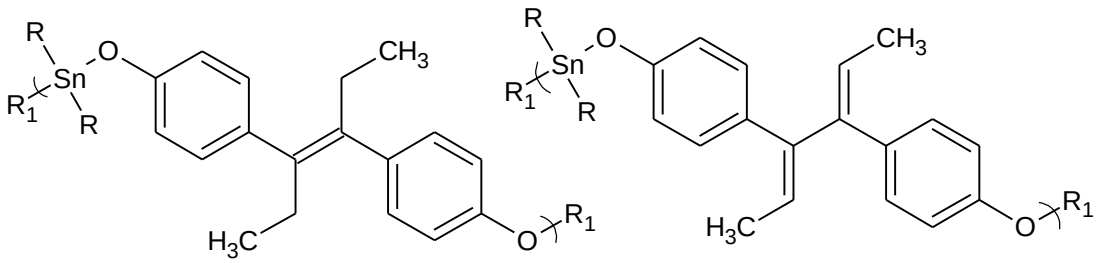

Figure 1 Polymer repeat unit from DES (left) and dienestrol (right) where R_1 represents simple chain extension.

Second, the nature of the Lewis acid is important in determining the evaluative values. Again, using the same Lewis base to illustrate that the nature of the Lewis acid is important, Table 1, the evaluative values are very different for the dibutyltin DES product compared to the dicyclohexyltin DES product.

A third generality is that the structural window for creating compounds with good evaluative values for pancreatic cancer is more limited compared with other cancers we have looked at including colon, breast and prostate cancers.

The fourth generalization is that the evaluative values are generally similar for the AsPC-1 and PAN-1 pancreatic cancer cell lines. This is consistent with the possibility that results from these cell lines will be decent indicators for other pancreatic cancers.

Finally, in general, the products containing the dibutyltin moiety compared to those containing other organotin moieties generally have better evaluative values.

For most of our efforts, we have tried to match the organotin dihalide with a Lewis base that exhibits biological activity itself hoping for a synergetic effect. Thus, we have tried a wide variety of Lewis bases such as known antibiotics as ampicillin [32] creating polymers that inhibit pancreatic cancer cell lines. Additional biologically active Lewis bases that inhibit pancreatic cancer include thiamine (vitamin B1) [33], dipicolinic [34], dicumarol [35], camphoric acid [36], 2-ketoglutaric acid [37], histamine [38], and salicylic acid [39]. Recently we have included Lewis bases such as gabapentin [40] that themselves are able to bypass the brain blood barrier in hopes that the resulting organotin polymers can arrest the growth of tumors in the brain. The resulting polymers inhibit the pancreatic cancer test cell lines.

We have studied several polymers from Lewis bases that themselves do not show biological activity. These include a wide variety of diols including ethylene glycol, 1,6-hexanediol and triethylene glycol (Table 2). Many of these showed outstanding evaluative tumor measures. We do not know why they show such good tumor measures and are currently investigating them further. Further, we do not know why some compounds exhibit better activity than others. The variety of potential compounds is almost endless and we are continuing to try to understand more fully structure/property relationships so better potential drugs that exhibit good inhibition pancreatic cancer can be forthcoming.

Included in this group are a series of polymers derived from poly (ethylene glycol) (PEG; also called poly (ethylene oxide)). These formed the foundation for our efforts to create water soluble drugs. Some of these showed good inhibition of the tested pancreatic cancer test cell lines (Table 2). The EMs are similar for the water soluble and non-water soluble tested samples.

PEG, is non-toxic and currently employed in a number of medical-related treatments including as pill coatings and in many laxatives [46, 47]. It is attached to materials to create water soluble materials. When attached to certain protein-medications they allow the drug a longer-activity with reduced toxicity [48]

We also found that organotin polyamines derived from the reaction of organotin dihalides with diamines exhibited good inhibition to the tested pancreatic cancer cell lines [49].

Table 2 Cell growth for dibutyltin polyethers [41-45].

Lewis Base	EC_{50} WI-38	EC_{50} PANC-1	CI_{50} PANC-1	EC_{50} AsPC-1	CI_{50} AsPC-1
Ethylene Glycol	1700(200)	270(20)	6.3	330(20)	5.2
1,3-Propanediol	1000(100)	170(20)	5.9	210(10)	4.8
1,4-Butanediol	110(9)	43(10)	2.6	27(20)	4.1
1,5-Pentandeiol	200(90)	12(1)	17	19(1)	11
1,6-Hexanediol	3500(1000)	1100(700)	3.2	890(220)	3.9
1,7-Heptanediol	950(100)	37(20)	26	550(100)	1.7
1,8-Octanediol	480(200)	23(10)	21	77(20)	6.2
Diethylene Glycol	1500(100)	330(10)	4.5	260(60)	5.8
Triethylene Glycol	1500(100)	300(30)	5	220(80)	6.8
PEG-400	1340(110)	220(20)	6.1	130(30)	10
PEG-8,000	1800(140)	460(40)	3.9	330(20)	5.5
PEH-10,000	1000(200)	50(10)	20	60(10)	17

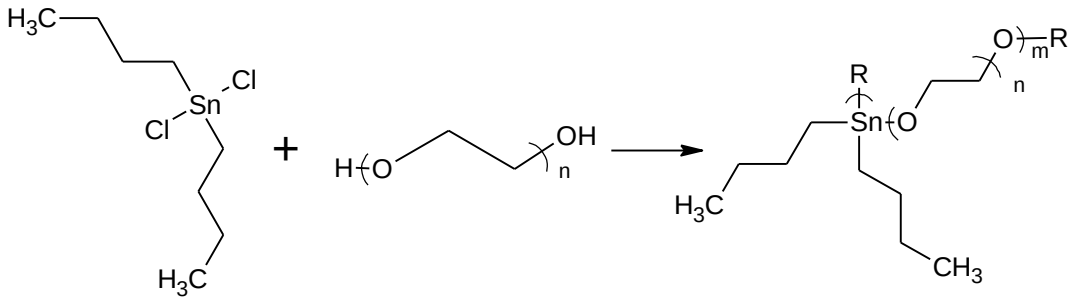

Figure 2 Synthesis of water-soluble organotin polymers from the reaction of PEG with dibutyltin dichloride.

7. Summary

Organotin polymers act as potentially important agents in the effort to successfully treat pancreatic cancer. A wide variety of organotin polymers show moderate to good inhibition of the tested human pancreatic cancer cell lines. Cell line testing has begun. Further studies continue that will solidify/modify/change many of the preliminary results cited here. Most of all, live animal testing must be carried out to validate the invitro cell line results with inhibiting cancer growth within living subjects. This is being planned.

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Author Contributions

All of the coauthors contributed to the proofing, literature review of the paper. They also contributed to the original studies.

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Competing Interests

The authors declare no competing interest exists.

References

1. Carraher Jr. C. Introduction to polymer chemistry. NY: CRC Press; Taylor and Francis; 2017.
2. Hoch M. Organotin compounds in the environment-an overview. Appl Geochem. 2001; 16: 719-743.
3. Carraher Jr. C. Carraher's polymer chemistry. 10th ed. FL: CRC Press ; Boca Raton; 2018.
4. Yamabe Y, Hoshino A, Imura N, Suzuki T, Himeno S. Enhancement of androgen-dependent transcription and cell proliferation by tributyltin and triphenyltin in human prostate cancer cells. Toxicol Appl Pharmacol. 2000; 169: 177-184.
5. Person RJ, Whalen MM. Effects of butyltin exposures on MAP kinase-dependent transcription regulators in human natural killer cells. Toxicol Mech Methods. 2010; 20: 227-233.
6. Koch B, Baul TS, Chatterjee A. Cell proliferation inhibition and antitumor activity of novel alkyl series of diorganotin(IV) compounds. J Appl Toxicol. 2008; 28: 430-438.
7. Hoti N, Ma J, Tabassum S, Wang Y, Wu M. Triphenyl tin benzimidazolethiol, a novel antitumor agent, induces mitochondrial-mediated apoptosis in human cervical cancer cells via suppression of HPV-18 encoded E6. J Biochem. 2003; 134: 521-528.
8. Hoti N, Zhu DE, Song Z, Wu Z, Tabassum S, Wu M. P53-dependent apoptotic mechanism of a new designer bimetallic compound tri-phenyl tin benzimidazolethiol copper chloride (TPT-CuCl2): In vivo studies in Wistar rats as well as in vitro studies in human cervical cancer cells. J Pharmacol Exp Ther. 2004; 311: 22-33.

9. Whalen MM, Walker L, Loganathan BG. Interleukins 2 and 12 produce significant recovery of cytotoxic function in dibutyltin-exposed human natural killer cells. Environ Res. 2002; 88: 103-115.
10. Syng-Ai C, Basu Baul TS, Chatterjee A. Inhibition of cell proliferation and antitumor activity of a novel organotin compound. J Environ Pathol Toxicol Oncol. 2001; 20: 333-342.
11. Takahashi M, Furukawa F, Kokubo T, Kurata Y, Hayashi Y. Effect of dibutyltin dichloride on incidence of pancreatic adenocarcinoma induced in hamsters by a single dose of N-nitrosobis(2-oxopropyl)amine. Cancer Lett. 1983; 20: 271-276.
12. Carraher. Macromolecules containing metal and metal-like elements. Hoboken: Wiley; 2005.
13. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: The impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin. 2011; 61: 212-236.
14. Hariharan D, Saied A, Kocher HM. Analysis of mortality rates for pancreatic cancer across the world. HPB (Oxford). 2008; 10: 58-62.
15. Gradishar WJ. Albumin-bound paclitaxel: A next-generation taxane. Expert Opin Pharmacother. 2006; 7: 1041-1053.
16. Green MR, Manikhas GM, Orlov S, Afanasyev B, Makhson AM, Bhar P, et al. Abraxane, a novel Cremophor-free, albumin-bound particle form of paclitaxel for the treatment of advanced non-small-cell lung cancer. Ann Oncol. 2006; 17: 1263-1268.
17. Miele E, Spinelli GP, Miele E, Tomao F, Tomao S. Albumin-bound formulation of paclitaxel (Abraxane ABI-007) in the treatment of breast cancer. Int J Nanomedicine. 2009; 4: 99-105.
18. Stinchcombe TE, Socinski MA, Walko CM, O'Neil BH, Collichio FA, Ivanova A, et al. Phase I and pharmacokinetic trial of carboplatin and albumin-bound paclitaxel, ABI-007 (Abraxane) on three treatment schedules in patients with solid tumors. Cancer Chemother Pharmacol. 2007; 60: 759-766.
19. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013; 369: 1691-1703.
20. Carraher C, Roner M. Organotin polyethers as potential biomaterials. Materials. 2009; 2: 1558-1598.
21. Carraher C, JR., Barot, G., Vetter, V.G., Nayak, G. and Roner, M.R. Degradation of the organotin polyether derived from dibutyltin dichloride and hydroxyl-capped poly(ethylene glycol) in trypsin and evaluation of trypsin activity employing light scattering photometry and gel electrophoresis. JCAMS. 2013;1:1-6.
22. Carraher CE, Roner MR. Organotin polymers as anticancer and antiviral agents. J Organomet Chem. 2014; 751: 67-82.
23. Morgan PW. Condensation polymers: by interfacial and solution methods. NY: Wiley-Interscience; 1965.
24. Millich F, Carraher CE, Preston J. Interfacial synthesis. New York: M. Dekker; 1977. v. <1-3 > p.
25. Millich F, Carraher C. Interfacial Synthesis. Vol. II. NY: Dekker; 1977.
26. Carraher C, Preston J. Interfacial Synthesis Vol. III. NY: Dekker; 1982.
27. Deer EL, Gonzalez-Hernandez J, Coursen JD, Shea JE, Ngatia J, Scaife CL, et al. Phenotype and genotype of pancreatic cancer cell lines. Pancreas. 2010; 39: 425-435.
28. Ulrich AB, Schmied BM, Standop J, Schneider MB, Pour PM. Pancreatic cell lines: A review. Pancreas. 2002; 24: 111-120.

29. Carraher CE, Roner MR, Shahi K, Ashida Y, Barot G. Synthesis, structural characterization, and anti-cancer evaluation of group IVB-metallocene polyethers containing the synthetic estrogen diethylstilbestrol. J Polym Mater. 2007; 24: 357-369.
30. Carraher C, Roner MR, Shahi K, Ashida Y, Barot G. Synthesis and initial cell line results of organotin polyethers containing diethylstilbestrol. JIOPM. 2008; 18: 180-188.
31. Carraher C, Ashida Y, Barot G. Synthesis of organotin polyethers containing the sex hormone dienestrol. PMSE. 2009; 101: 1405-1407.
32. Carraher Jr. C, Roner M, Dorestant J, Moric-Johnson A, Al-Huniti M. Group VA Poly(amine Esters) Containing the Antibacterial Ampicillin. JIOPM. 2015;25:400-410
33. Carraher CE, Roner MR, Lambert RE, Arroyo L, Miller LC. synthesis of organotin polyamine ethers containing thiamine (Vitamin B1) and preliminary ability to inhibit select cancer cell lines. J Inorg Organomet P. 2015; 25: 1414-1424.
34. Carraher CE, Slawek PP, Roner MR, Moric-Johnson A, Miller LC, Einkauf JD, et al. Synthesis and structural and initial cancer cell line characterization of organotin polyesters from dipicolinic acid. J Inorg Organomet P. 2016; 26: 1338-1350.
35. Charles E. Carraher J, Roner MR, Sookedo N, Moric-Johnson A, Miller L, Johnson JD. Synthesis and initial cancer cell results of organotin polyethers derived from the anticoagulant dicumarol. IJAPBR. 2017; 2: 1-9.
36. Carraher CE, Roner MR, Campbell AG, Moric-Johnson A, Miller L, Slawek P, et al. Synthesis of organotin polyesters from reaction of the salt of d-camphoric acid and organotin dihalides and initial anticancer activity. J Inorg Organomet P. 2018; 28: 481-491.
37. Carraher Jr. C, Roner M, Patel D, Miller L, Moric-Johnon A, Slawek P, et al. Synthesis of organotin polymers from 2-ketoglutaric acid and their ability to inhibit the growth of human cancer cell lines. HMO. 2018; 3: 1-9.
38. Carraher C, Roner M, Islam Z, Moric-Johnson A. Group 15 organotin containing polyamines from histamine and their ability to inhibit cancer cell lines from pancreatic, breast and other cancers. J Pharmacy & Pharmacetical Res. 2018; 2: 1-10.
39. Carraher C, Roner M, Lynch M, Moric-Johnson A, Miller L, PSlawek F, et al. Organotin poly(ester ethers) from salicylic acid and their ability to inhibit human cancer cell lines. JCRO. 2018;1:1-11.
40. Carrher CE, Roner MR, Frank J, Mosca F, Slawek P, Miller L. Inhibiiton of huma glioblastomas brain cancer cell lines by methyl-containing polymers. WJPR, in press.
41. Carraher CE, Barot, G., Shahi, K. and Roner, M.R. Influence of DMSO on the inhibition of various cancer cells by water-soluble organotin poly(ethers). JCAMS. 2013; 1: 294-304.
42. Carraher Jr. C, MR. R, Shahi K, Battin A, Barot A, Arnold T. Organotin polymers as chemotherapeutic agents: Breast and pancreatic cancers. J Polym Mater. 2014; 31: 1-14.
43. Carraher CE, Barot G, Roner MR, Shahi K, Pellerito C, Fiore T, et al. Synthesis, structural analysis, fiber formation and preliminary anticancer characterization of the organotin polyether from dibutyltin dichloride and 2,5-dimethyl-3-hexyne-2,5-diol. J Polym Mater. 2012; 29: 371-386.
44. Barot G, Shahi K, Roner M, Carraher C. Synthesis, anomalous fiber formation, and preliminary anticancer study of the organotin polyether derived from 2-butyne-1,4-diol. J Polym Mater 2006; 23: 423-436.

45. Barot G, Shahi K, Roner M, Carraher C. Synthesis, structural characterization, and ability to inhibit cancer growth of a series of organotin poly (ethylene glycols). JIOPM. 2007; 17: 595-603.
46. Dipalma JA, Cleveland MV, McGowan J, Herrera JL. A randomized, multicenter, placebo-controlled trial of polyethylene glycol laxative for chronic treatment of chronic constipation. Am J Gastroenterol. 2007; 102: 1436-1441.
47. Sheftel V. Indirect food additives and polymers: Migration and toxicology. 2000: 1114-1116.
48. Delgado C, Francis GE, Fisher D. The uses and properties of PEG-linked proteins. Crit Rev Ther Drug Carrier Syst. 1992; 9: 249-304.
49. Carraher CE, Battin A, Shahi K, Roner MR. Synthesis, structural characterization, and initial evaluation as anticancer drugs of dibutyltin polyamines derived from various 4,6-diaminopyrimidines. synthesis, structural characterization, and initial evaluation as anticancer drugs of dibutyltim polyamines derived from various 4,6-diaminopyrimidines. J Inorganic & Organ Poly and Mat. 2007; 17: 631-639.