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# Cytotoxic Anti-Cancer Activity of Certain Thermotropic Liquid Crystalline Poly (Ester-Amides) Containing 2, 6-Bis (Benzylidene)Cyclohexanone Moiety in the Main Chain

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## ABSTRACT

Five thermotropic liquid crystalline poly(ester-amides) were synthesized by polycondensation method. The poly(ester-amides) were synthesized from varying dicarboxylic acids with a common diamine namely 4,4'-diaminobenzene and a common diol namely 2,6-bis(4-hydroxybenzylidene))cyclohexanone. For qualitative characterization, viscosity measurements and solubility data were used for these synthesized poly(ester-amides). The spectroscopic techniques such as FT-IR, $^{1}H$ NMR, $^{13}C$ NMR were performed to investigate the microstructural features of these synthesized poly(ester-amides). The thermal phase transition behavior of these poly(ester-amides) were studied by Differential Scanning Calorimetry (DSC) and Hot-stage Optical Polarized Microscopy (HOPM). The degree of crystallinity was assessed by X-ray diffraction (XRD) patterns. Scanning Electron Microscopic (SEM) technique was used to illustrate the morphology of these poly(ester-amides). The copolymer synthesized was subjected into *in vitro* anti-cancer activity studies against human breast cancer (MCF-7) cell line.

**Keywords:** Bisbenzylidenecyclohexanone; poly(ester-amides); polycondensation; thermotropic liquid crystalline properties; cytotoxicity, anticancer.

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## 1. INTRODUCTION

The thermotropic liquid crystalline poly(ester-amides) (TLCPs) incorporating flexible methylene groups, aromatic groups, and arylidene-keto moiety were reported.[1-3] The bisbenzylidene cyclohexanone has both mesogenic and photo-active properties. They were found to be a potential mesogen that imparted thermotropic liquid crystalline property to the polymeric materials.[4] Phase transitions of liquid crystals were reported by Marin et al. [5] by using Hot-stage Optical Polarized Microscopy (HOPM), Differential Scanning Calorimetry (DSC), and X-ray Diffraction (XRD) studies. The poly(ester-amides) containing 2,5-bis(benzylidene) cyclopentanone moiety were reported by Kannappan et al.[6] Suhas Thatte and co workers,[7] discussed the new and improved drug delivery methodology in the several polymer-drug systems. The first drug delivery application is reported using hydrogel in 1960.[8] They found that these compounds were cytotoxic to a number of human tumours *in vitro*, particularly towards colon cancer and leukemic cells.

Keeping in mind all these facts, we thought it is interesting to synthesize a series of five thermotropic liquid crystalline poly(ester-amides) containing bisbenzylidenecyclohexanone moiety in the polymer backbone. In the current work, poly(ester-amides) are a category of polymeric materials which contains both ester and amide linkages and are synthesized by the copolymerization of a diacid with that of a diamine and a diol.

## 2. EXPERIMENTAL

### 2.1 *Chemicals*

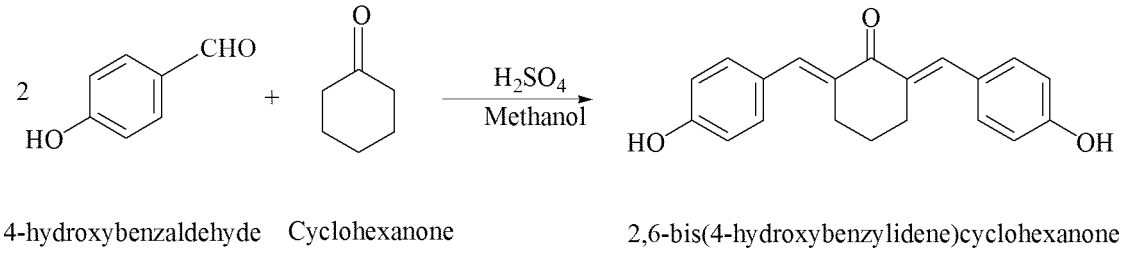
Aldrich samples of diphenyl chlorophosphate, terephthalic acid, isophthalic acid, phthalic acid, adipic acid, azelaic acid, and 4,4'-diaminobenzene were used as received. Lithium chloride (SD Fine), vanillin (CDH), and cyclohexanone (Fluka) were used as received. Merck sample of pyridine, Merck LR sample of methanol, SD-Fine AR samples of N,N-

dimethyl acetamide (DMAc ) and N,N-dimethyl formamide (DMF), and Aldrich spectral grade DMSO-d6 were used.

2.2 *Preparation of monomer*

2.2.1 *Synthesis of arylidene-keto diol*: The arylidene-keto diol namely 2,6-bis(4-hydroxybenzylidene)cyclohexanone (CHBB) was synthesized by the method reported in literature.[7]

***Preparation of 2,6-bis(4-hydroxybenzylidene) cyclohexanone (CHBB)***: In a 250 mL conical flask, a solution containing p-hydroxy benzaldehyde (0.2 mol) in 100 mL of dry methanol was taken. To this solution, cyclohexanone (0.1 mol) was added drop wise and the mixture was shaken well. Then with external cooling in an ice bath, fuming sulphuric acid (5 mL) was added drop wise so that an exothermic reaction took place. The reaction mixture turned bright yellow initially, then dark green and finally pink. The precipitated diol was filtered and washed with aqueous methanol. It was filtered and recrystallised from aqueous methanol. Yield: 95% (m.p.: 195 °C). It is represented in Scheme 1.

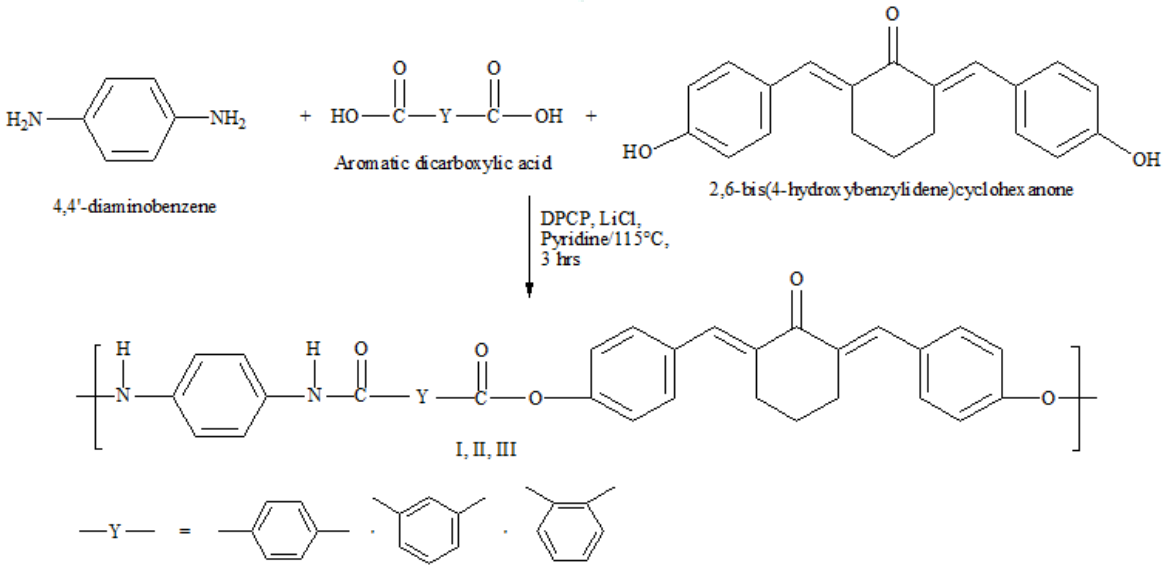



**Scheme 1.** Synthesis of 2,6-bis(4-hydroxybenzylidene))cyclohexanone (CHBB).

2.2.2 *Synthesis of poly(ester-amides)*: Two methods were employed to synthesize the poly(ester-amides) which depends upon the type of dicarboxylic acid monomer (aromatic or aliphatic).

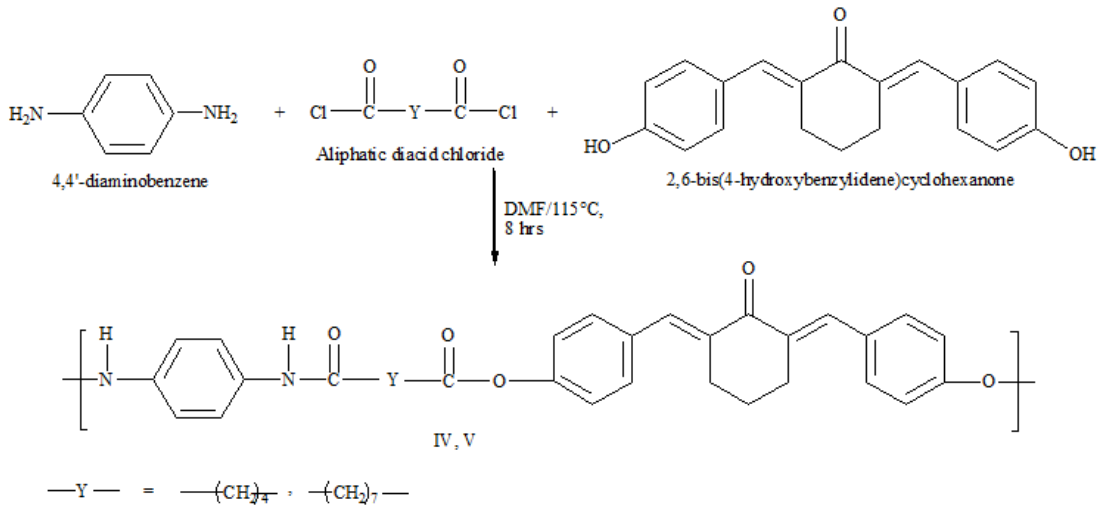
***Method 1***: The procedure for the synthesis of a typical poly(ester amide) derived from aromatic dicarboxylic acid is represented here.[9] Three poly(ester-amides) were prepared by the direct polycondensation method using diphenyl chlorophosphate (DPCP) as the condensation agent in the mole ratio 1:1:2 of a diamine, a diol and a diacid in pyridine solution. This method avoids the tedious preparation of acid chloride and hence, yield of the polymer is high.

In a 100 mL round-bottomed flask, a solution containing aromatic dicarboxylic acid (5 mmol), DPCP (12 mmol), and LiCl (10 mmol) in pyridine was continuously stirred at room temperature for 30 minutes. Then the temperature was raised to 115°C and 4,4'-diaminodiphenyl (2.5 mmol) and the diol (2.5 mmol) were added and the stirring was continued for 3 hours. The reaction mixture was cooled and poured into methanol. The poly(ester-amide) was precipitated, filtered and washed with methanol and dried in vacuum. It is represented in Scheme 2.




**Scheme 2.** Synthesis of poly(ester-amides) PBBT (I), PBBI (II) and PBBP (III) derived from aromatic dicarboxylic acid.

***Method 2:*** The procedure for the synthesis of a typical aliphatic diacid-based polymer is given here. Two aliphatic diacid-based poly(ester-amides) were prepared by the polycondensation method in the mole ratio 1:1:2 of a diamine, a diol and a diacid in DMF solution.[10] It is represented in Scheme 3.




**Scheme 3.** Synthesis of poly(ester-amides) PBBA (IV) and PBBAz (V) derived from aliphatic diacid chloride

In a 100 mL round-bottomed flask, a solution containing 4,4'-diaminodiphenyl (2.5 mmol), diol (2.5 mmol) and DMF (30 ml) were taken. Then, diacid chloride (5 mmol) was added dropwise at 100°C. At nitrogen atmosphere, the reaction mixture was heated at 115°C for 8 hours with constant stirring. The contents were cooled and poured into methanol for precipitation and kept in a refrigerator overnight and then filtered. The poly(ester-amide) was dissolved in acetone, filtered and poured into water for precipitation and was dried in vacuum over phosphorus pentoxide. It is represented in Scheme 3.

In Table 1, the various poly(ester-amides) prepared by these methods were listed along with the polymer code, percentage of yield and inherent viscosities.

**Table 1.** List of monomers used, polymer code of poly(ester-amides) with percentage of yield and inherent viscosities ($\eta_{inh}$)

| S. No. | Common diamine: 4,4'-diamino benzene | | Polymer Code | Yield (%) | $\eta_{inh}$ (dL/g) |
|---|---|---|---|---|---|
| | Diol | Diacid / Diacid chloride | | | |
| 1. | CHBB | Terephthalic acid | PBBT - I | 73 | 1.05 |
| 2. | CHBB | Isophthalic acid | PBBI - II | 70 | 0.98 |
| 3. | CHBB | Phthalic acid | PBBP - III | 69 | 0.95 |
| 4. | CHBB | Adipoyl dichoride | PBBA - IV | 55 | 0.45 |
| 5. | CHBB | Azelaoyl dichloride | PBBAz - V | 58 | 0.53 |

CHBB: 2,6-(bis(4-hydroxybenzylidene))cyclohexanone

2.3 *Characterization methods*

2.3.1 *Solubility*: In a small stoppered test tube, about 50 mg of the polymer containing 1 mL of the solvent was taken and kept for 24 hours with occasional shaking. In various solvents, the solubility was tested qualitatively.

2.3.2 *Viscosity*: The inherent viscosity ($\eta_{inh}$) was determined in DMAc solution by using Ubbelohde viscometer in which the pure solvent had a flow rate of 470 seconds at 30°C. In each case, dry poly(ester-amide) sample (25 mg) was dissolved in 25 mL of DMAc and kept aside for 12 hours with occasional shaking. From the flow time measurement at 30°C, the $\eta_{inh}$ was calculated.

2.3.3 *Fourier Transform Infrared (FT-IR) spectroscopy*: Shimadzu FT-IR instrument was used to record the FT-IR spectra. The sample was taken in the form of potassium bromide pellet.

2.3.4 *$^{1}H$ and $^{13}C$ NMR Spectra*: Bruker AVANCE III 500 MHz instrument was used to record the $^{1}H$ and $^{13}C$ NMR spectra. DMSO-d6 was used as solvent with TMS as internal reference.

2.3.5 *Differential Scanning Calorimetry (DSC)*: NETZSCH DSC 200F3 differential scanning calorimeter using 5mg samples under nitrogen atmosphere was used for thermal analysis of these poly(ester-amides) at a heating rate of 10°C/min.

2.3.6 *Hot-stage Optical Polarized Microscopy (HOPM)*: The polarized optical microscopic technique was used to identify the mesophases using Olympus BX51P model with a source of 100W halogen lamp housing by using Linksys 32 software for Hot Stage temperature controller.

2.3.7 *X-Ray Diffraction (XRD)*: GE-Inspection Technology Diffractometer System XRD 3003 TT model made in Germany with a source of copper target operating voltage 40 Kv 300 mA° current rate was used to record X-ray diffraction

measurements. They were taken to assess the degree of crystallinity of these powdered poly(ester-amides).

2.3.8 *Scanning Electron Microscopy (SEM)*: Hitachi S-3000 Hz scanning electron microscopy was used to investigate the morphology of these poly(ester-amides).

2.3.9 . *Cytotoxic anticancer evaluation of synthesized polymer.*

***MTT assay*** (MTT = 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl--tetrazolium bromide =5mg/ml in PBS) The cancer activity of samples on MCF7 cell was determined by the MTT assay.[11] Cells (1 × $10^5$/well) were plated in 0.2 ml of medium/well in 96-well plates. Incubate at 5 % $CO_2$ incubator for 72 hours. Then, added various concentrations of the samples in 0.1% DMSO for 48hrs at 5 % $CO_2$ incubator. View the images under Inverted microscope 40X and take the photos. After removal of the sample solution and 20µl/well MTT reagent was added. Viable cells were determined by the absorbance at 540nm. 50% inhibition of cell viability (IC50 value) was determined graphically. The effect of the samples on the proliferation of MCF7 cells was expressed as the % cell viability, using the following formula:

**Calculation**

% cell viability = A540 of treated cells / A540 of control cells × 100%

## 3. RESULTS AND DISCUSSION

3.1 *Solubility*

These poly(ester-amides) were found to be soluble in highly polar solvents such as DMAc, DMSO, and TFA, partially soluble in moderately polar solvents and insoluble in non-polar solvents such as benzene and hexane. This is because of the inter-molecular interactions of polar solvents with ether linkages of the polymer backbone.[12] In Table 2, the results of the solubility of these poly(ester-amides) are represented.

**Table 2.** Solubility of the poly(ester-amides) in common organic solvents

| S. No. | Polymers | Hexane | $CHCl_3$ | THF | ODCB | EMK | Acetone | MeOH | DMF | $CH_3CN$ | DMAc | TFA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | I | -- | -- | -- | +- | +- | +- | +- | +- | +- | ++ | ++ |
| 2 | II | -- | -- | +- | +- | +- | ++ | +- | ++ | ++ | ++ | ++ |
| 3 | III | -- | -- | +- | +- | +- | ++ | +- | ++ | ++ | ++ | ++ |
| 4 | IV | -- | +- | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ |
| 5 | V | -- | +- | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ |

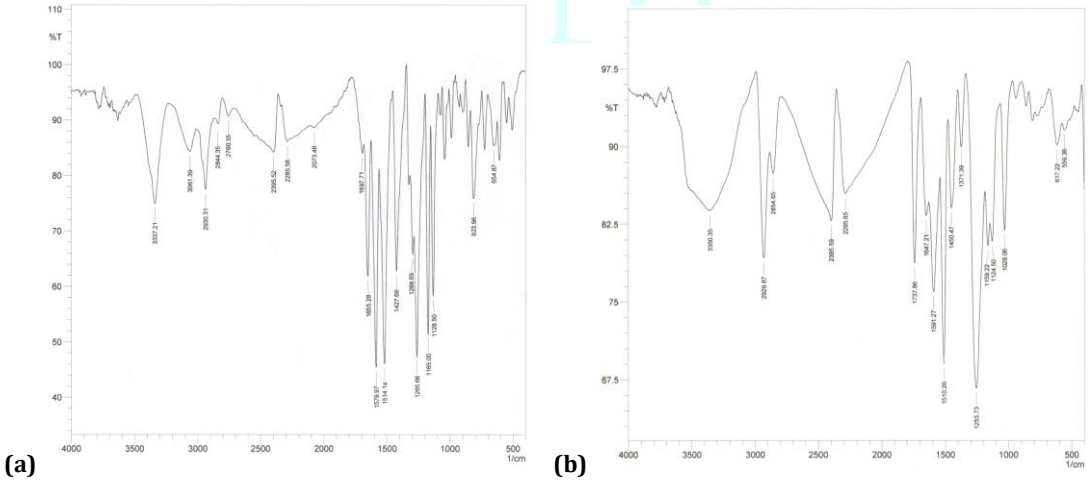
*++ =Freely Soluble; -- = Insoluble; +- = Partially soluble*

3.2 *Viscosity*

In Table 1, the $\eta_{inh}$ values of all these five poly(ester-amides) are represented and were found to be in the range of 0.45–1.05 dL/g. It is noted that the poly(ester-amides) synthesized from aromatic dicarboxylic acids have higher $\eta_{inh}$ values than those prepared from aliphatic diacid chloride. Since the data shows higher viscosity values, they are reasonably of higher molecular weight.

3.3 *Spectral studies*

By FT-IR spectra, the ester and amide functional groups present in the poly(ester-amide) chain were identified. It showed characteristic absorption at $\bar{\upsilon}$ = 1630–1750 $cm^{-1}$ due to ester and amide C=O stretching frequency and an absorption at $\bar{\upsilon}$ = 3240–3380 $cm^{-1}$ due to the amide N-H stretching frequency.[13] They are represented in Figures 1(a) and 1(b) for PBBT and PBBA, respectively.




**(a)** **(b)**

**Figure 1(a,b).** FT-IR spectrum of random poly(ester-amides) (a) PBBT and (b) PBBA.

By $^1H$ and $^{13}C$ NMR spectra, the structural units present in the poly(ester-amide) chain were identified. A singlet was appeared in the range ??9.5–10.15 ppm is due to the presence of secondary amide proton.[6] Due to the presence of aromatic protons, peaks were observed in the range of ??6.5–8.54 ppm. They are represented in Figures 2(a) and 2(b) for PVBT and PVBA, respectively.

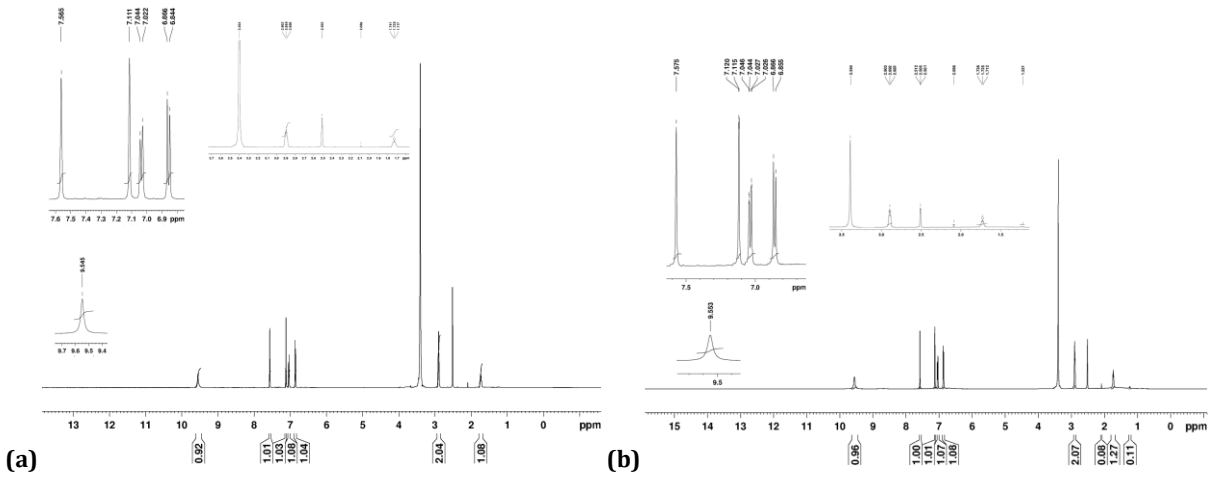



**Figure 2(a,b).** [1]H NMR spectrum of random poly(ester-amides) (a) PBBT and (b) PBBA.

In the [13]C NMR spectra of the poly(ester-amides), the signal in the range of  188–200 ppm is due to the carbonyl carbon of the -unsaturated ketone. Due to the carbonyl carbon of the amide and ester groups, the signals in the range of  171–185 ppm and  160 –170 ppm were appeared which indicates the formation of poly(ester-amide).[6] They are represented in Figures 3(a) and 3(b) for PBDT and PBDA, respectively.

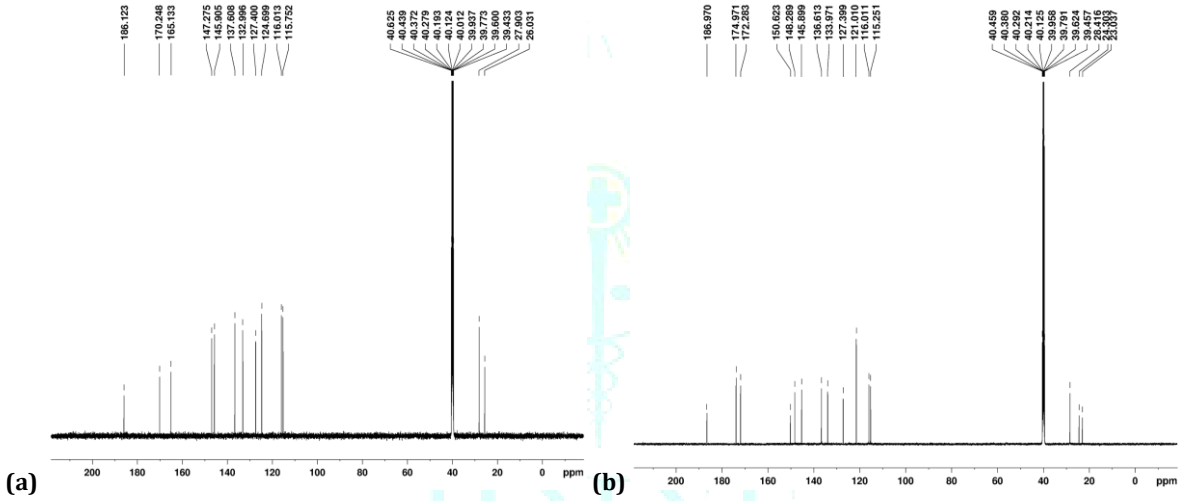



**Figure 3(a,b)**. [1]C NMR spectrum of random poly(ester-amides) (a) PBBT and (b) PBBA.

3.4 *Thermal analysis and phase behavior*

By using Differential Scanning Calorimetry (DSC) and Hot-stage Optical Polarized Microscopy (HOPM), the thermal and phase behaviors of the five poly(ester-amides) were investigated.

3.4.1 *Differential Scanning Calorimetry (DSC)*: In Table 3, the glass transition temperature ($T_g$), crystal to crystal transition ($T_{K1\rightarrow K2}$), melting temperature ($T_m$), isotropization temperature ($T_i$), and liquid crystalline range ($\Delta T$) obtained from DSC are tabulated.

**Table 3.** Differential Scanning Calorimetry (DSC) data of poly(ester-amides)

| S.No. | Polymers | Differential Scanning Calorimetry (DSC) | | | | |
|---|---|---|---|---|---|---|
| | | $T_g$ (ºC) | $T_{K\rightarrow K}$ (ºC) | $T_m$ (ºC) | $T_i$ (ºC) | $\Delta T$ |
| 1 | PBBT | 59.31 | 189.34 | 369.44 | 536 | 166.56 |
| 2 | PBBI | 52.73 | 188.49 | 360.78 | 521 | 160.22 |
| 3 | PBBP | 49.34 | 187.98 | 351 | 509 | 158 |
| 4 | PBBA | 45.45 | 179.87 | 340.21 | 493.21 | 153 |
| 5 | PBBAz | 37.868 | 180.898 | 333.868 | 430.86 | 96.992 |

In Figure 4, the DSC thermograms of all poly(ester-amides) are shown. By analyzing the DSC data, we could interpret that the poly(ester-amides) II and III synthesized from aliphatic dicarboxylic acids have lower glass transition temperature ($T_g$) values than those synthesized from aromatic diacid chloride monomers. In these polymers, an exothermic peak appears before melting transition, which seems to be related to crystal to crystal transition resulted from different crystalline polymorphs.[14] The liquid crystalline range (□□□□of the poly(ester-amide) derived from terephthalic acid monomer is broader than compared to the poly(ester-amide) derived from other monomers. This may be due to effective molecular packing by coplanar geometry. The other monomers molecular packing may be due to the rigidity of o-phenylene or m-phenylene moiety in the polymer chain.

3.4.2 *Hot-stage Optical Polarized Microscopy (HOPM)*: Mesophase identification of poly(ester-amides) have been achieved by Hot-stage Polarized Optical Microscopy (HOPM). From Figures 5 to 9, the different textures of poly(ester-amides) have been identified at different temperatures. The poly(ester-amides) exhibited high birefringence when it analyzed with a HOPM.[15] In Figure 5(a), crystalline phases of the mesogens has been shown. By increasing the temperature, crystal to crystal transition was observed. They are shown in Figure 5(b). This on further heating, a crystalline to nematic transition of the mesogens takes place. They are shown in Figure 5(c). On further heating of these poly(ester-amides), the nematic phase lost its birefringence and transformed to an isotropic phase where there is no texture identification i.e. it appears as black domain.

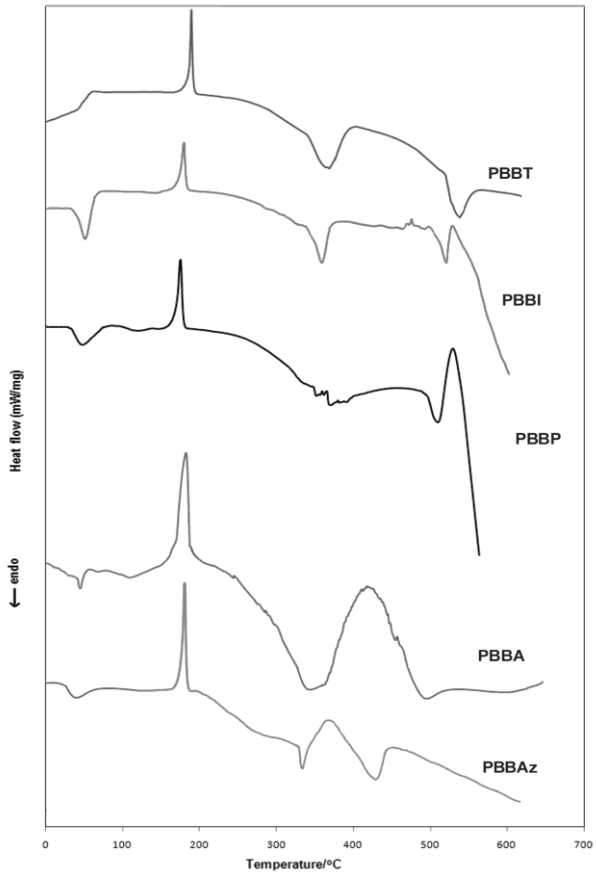



**Figure 4.** DSC thermograms of random poly(ester-amides).

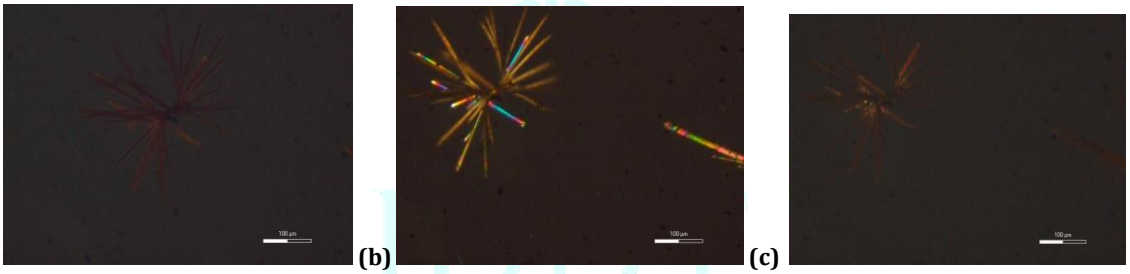



**Figure 5(a-c).** Hot-stage optical polarized micrographs for (a) PBBA at 25ºC, crystalline phase of the mesogens (b) PBBA at 135ºC, crystal to crystal transition, and (c) PBBA at 267ºC, crystalline to nematic transition.

3.5 *X-Ray Diffraction studies*

In Figures 10(a) and 10(b), the X-Ray diffraction pattern of poly(ester-amides) PBDT and PBDA has been shown that indicates the semi-crystallinity of these polymers with an amorphous background which may be due to the presence of carbonyl and C=C groups. In the region 2θ = 10 – 50°, these poly(ester-amides) showed few reflection peaks that confirms the presence of semi-crystallinity.[9,10]

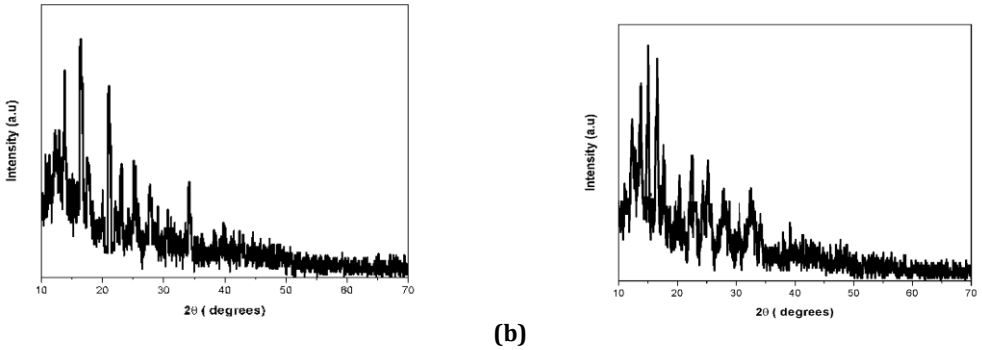



**Figure 10(a,b).** X-ray diffraction pattern of random poly(ester-amides) (a) PBDT and (b) PBDA.

3.6. *Morphological study by SEM*

In Figure 11, the SEM images of the poly(ester-amides) have been shown that illustrates the morphology of these poly(ester-amides).

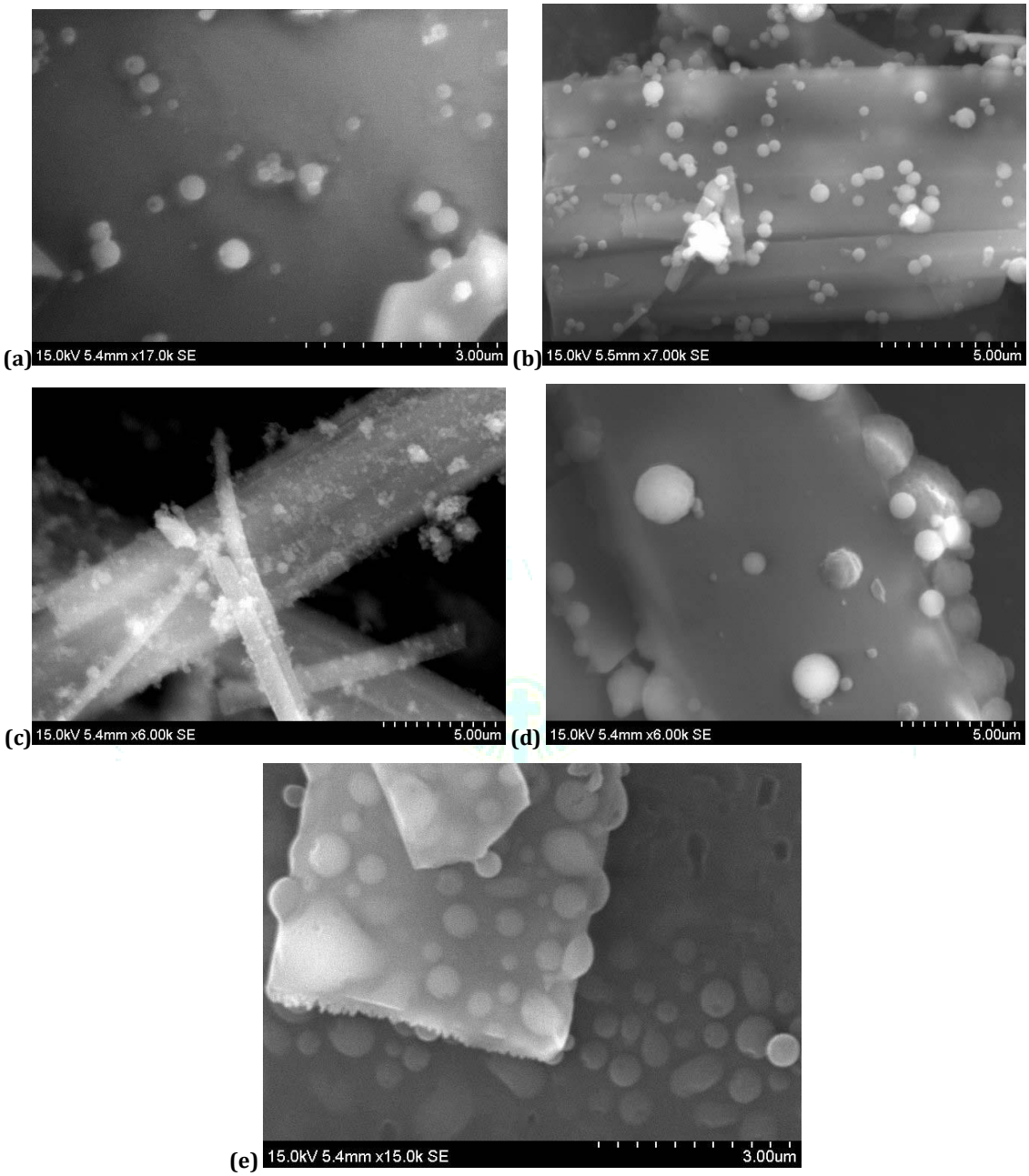



**Figure 11(a-e)**. Scanning electron micrographs of random poly(ester-amides) (a) PBBT, (b) PBBI, (c) PBBP, (d) PBBA, and (e) PBBAz.

*3.7 Cytotoxic Anticancer Evaluation of Synthesized Polymer*

Viable cells were determined by the absorbance. Measurements were performed and the concentration required for a 50% inhibition of viability ($IC_{50}$) was determined graphically. The anti cancer activity and anti bacterial activity have been studied by Chitra and Roop Singh.[16] The absorbance was measured with a UV-Spectrophotometer using wells without sample containing cells as blanks. The effect of the polymer on the proliferation of MCF-7 was expressed as the % cell viability. In Figure 12, a graphical representation of the polymer effect on cancer cells by % cell viability is shown.The affected MCF-7[17] cell line at different concentration was shown in Figure 13. IC of the polymer was determined and was shown in Table 4. The study on anti-cancer activity containing arylidene ketone moiety was studied by Rajam and Roop Singh.[18-20]

**Table 4.** MCF7 Cell line for PBBP

| S.No | Concentration µg/ml | Absorbance 540nm | % cell Viability |
|---|---|---|---|
| 1 | 100 | 0.00 | 0.0 |
| 2 | 50 | 0.00 | 0.0 |
| 3 | 25 | 0.00 | 0.0 |
| 4 | 12.5 | 0.17 | 15.0 |
| 5 | 6.25 | 0.30 | 26.5 |
| 6 | 3.12 | 0.57 | 50.4 |
| 7 | 1.56 | 0.81 | 71.6 |
| 8 | Control Cells | 1.13 | 100 |

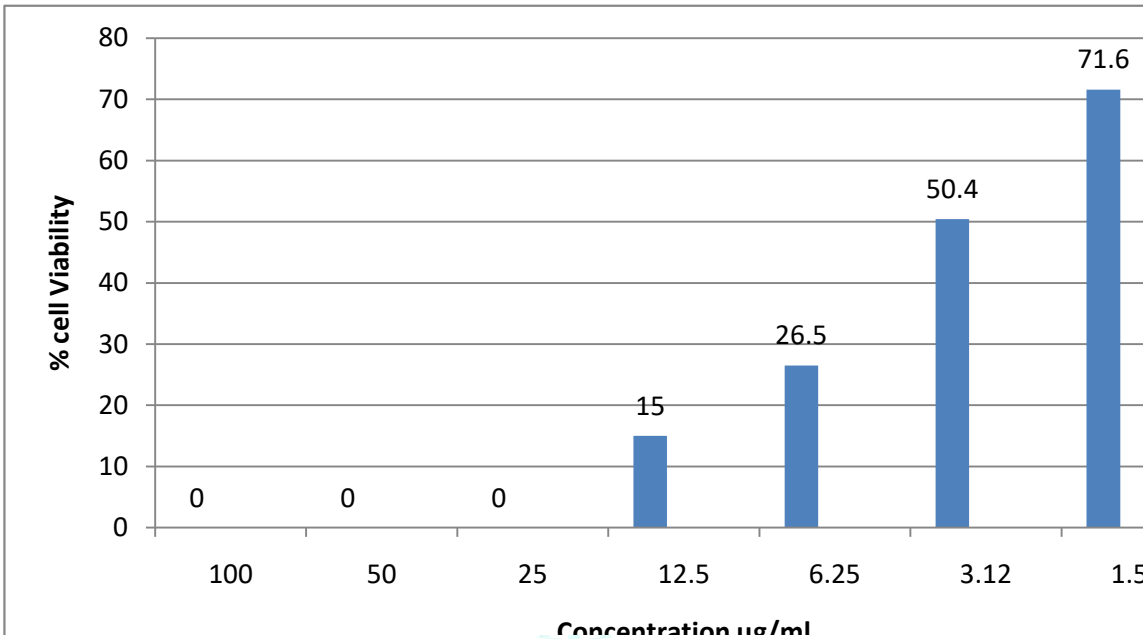



**Figure 12**. A graphical representation of PBBP polymer effect on cancer cells by % cell viability

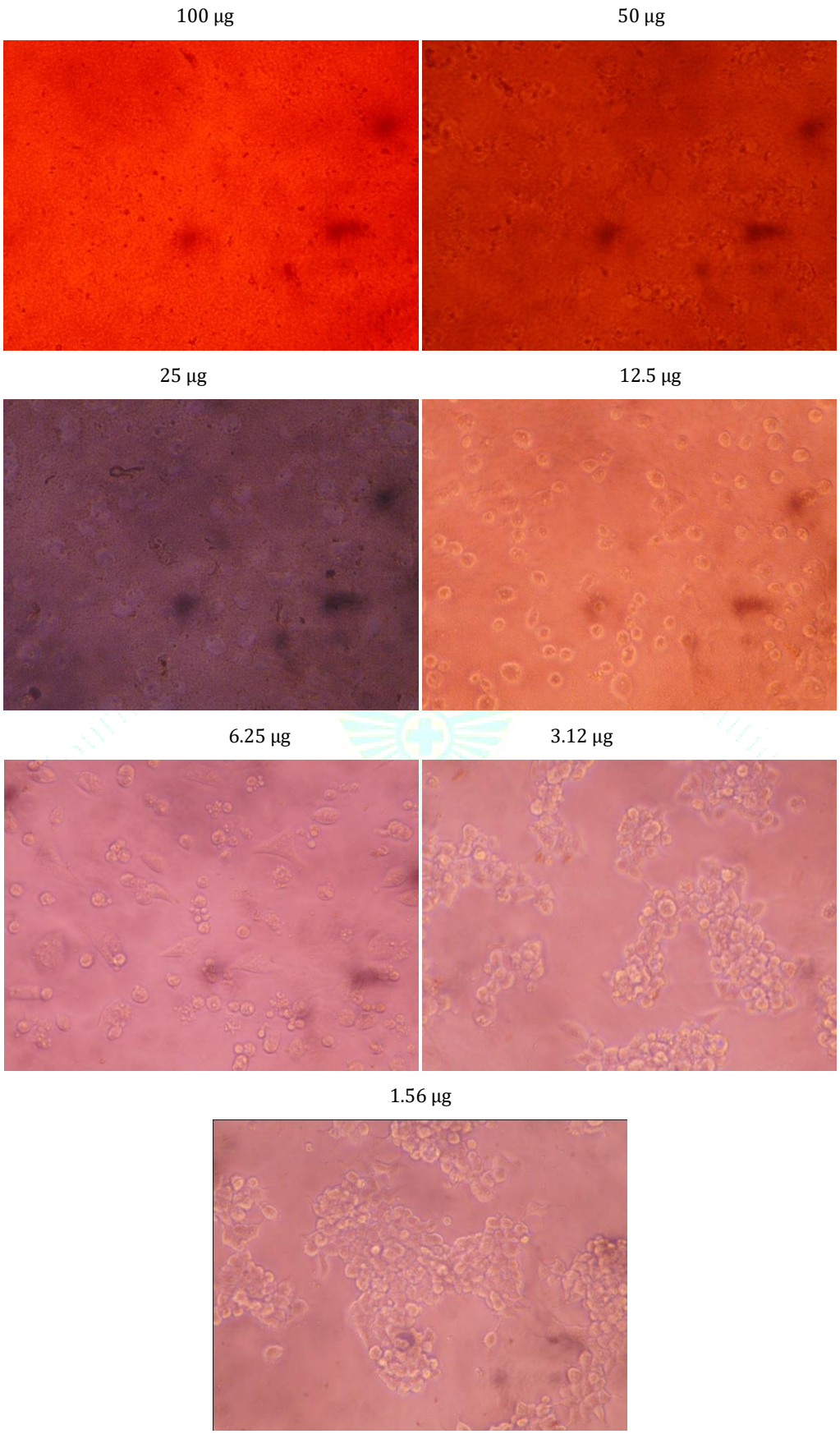



**Figure 13.** The affected MCF-7 cell line PBBP at different concentration

**Table 5.** MCF7 Cell line for PBBA

| S.No | Concentration µg/ml | Absorbance 540nm | % cell Viability |
|---|---|---|---|
| 1 | 100 | 0.00 | 0.0 |
| 2 | 50 | 0.00 | 0.0 |
| 3 | 25 | 0.00 | 0.0 |
| 4 | 12.5 | 0.09 | 7.9 |
| 5 | 6.25 | 0.20 | 17.6 |
| 6 | 3.12 | 0.43 | 38.0 |
| 7 | 1.56 | 0.79 | 69.9 |
| 8 | Control Cells | 1.13 | 100 |

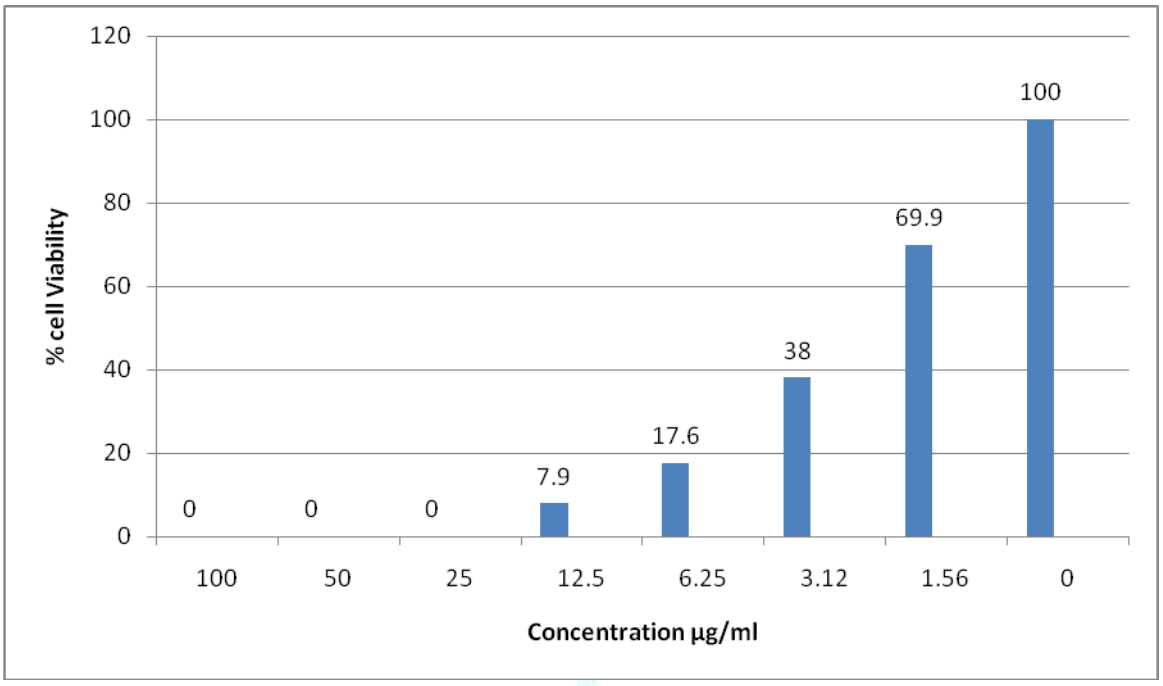



**Figure 14**. A graphical representation of PBBA polymer effect on cancer cells by % cell viability

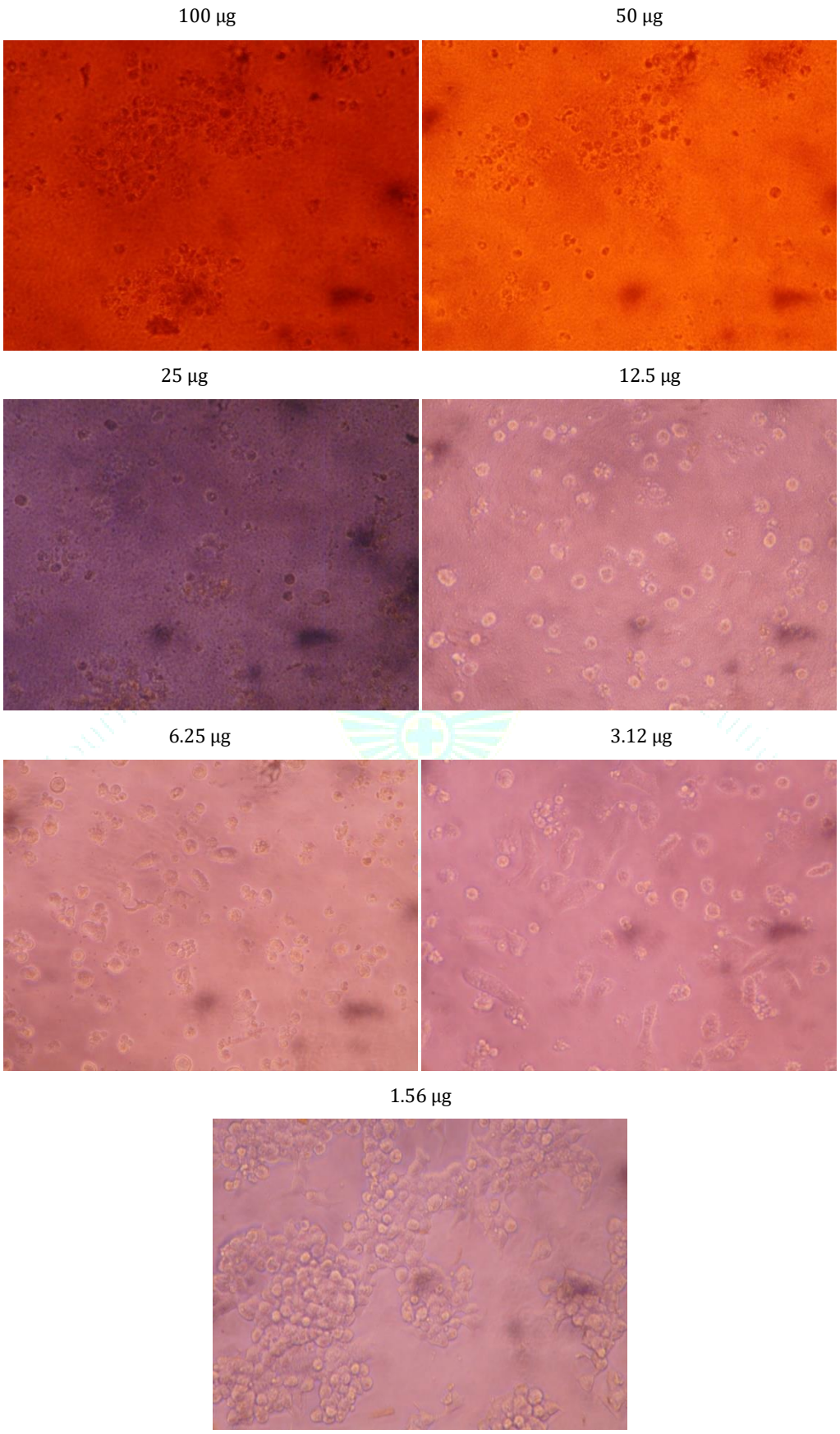



**Figure 15.** The affected MCF-7 cell line at PBBA different concentration

**Table 5.** MCF7 Cell line for PBBI

| S.No | Concentration µg/ml | Absorbance 540nm | % cell Viability |
|---|---|---|---|
| 1 | 100 | 0.00 | 0.0 |
| 2 | 50 | 0.00 | 0.0 |
| 3 | 25 | 0.00 | 0.0 |
| 4 | 12.5 | 0.09 | 7.9 |
| 5 | 6.25 | 0.21 | 18.5 |
| 6 | 3.12 | 0.40 | 35.3 |
| 7 | 1.56 | 0.78 | 69.0 |
| 8 | Control Cells | 1.13 | 100 |

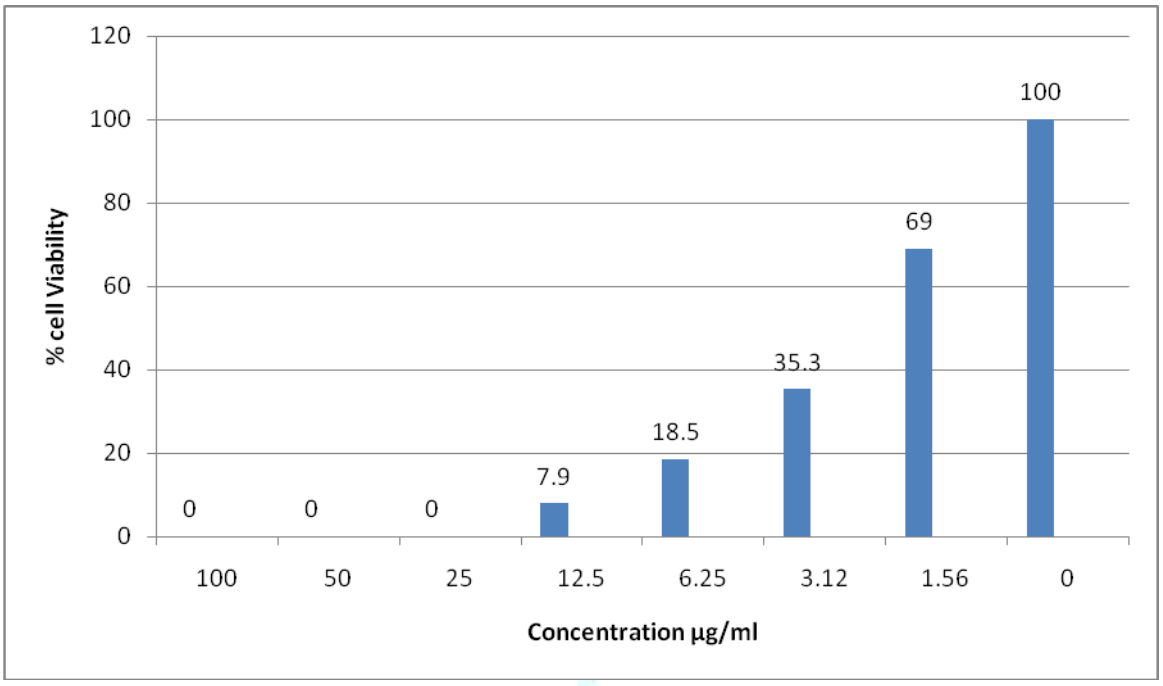



**Figure 16**. A graphical representation of PBBI polymer effect on cancer cells by % cell viability

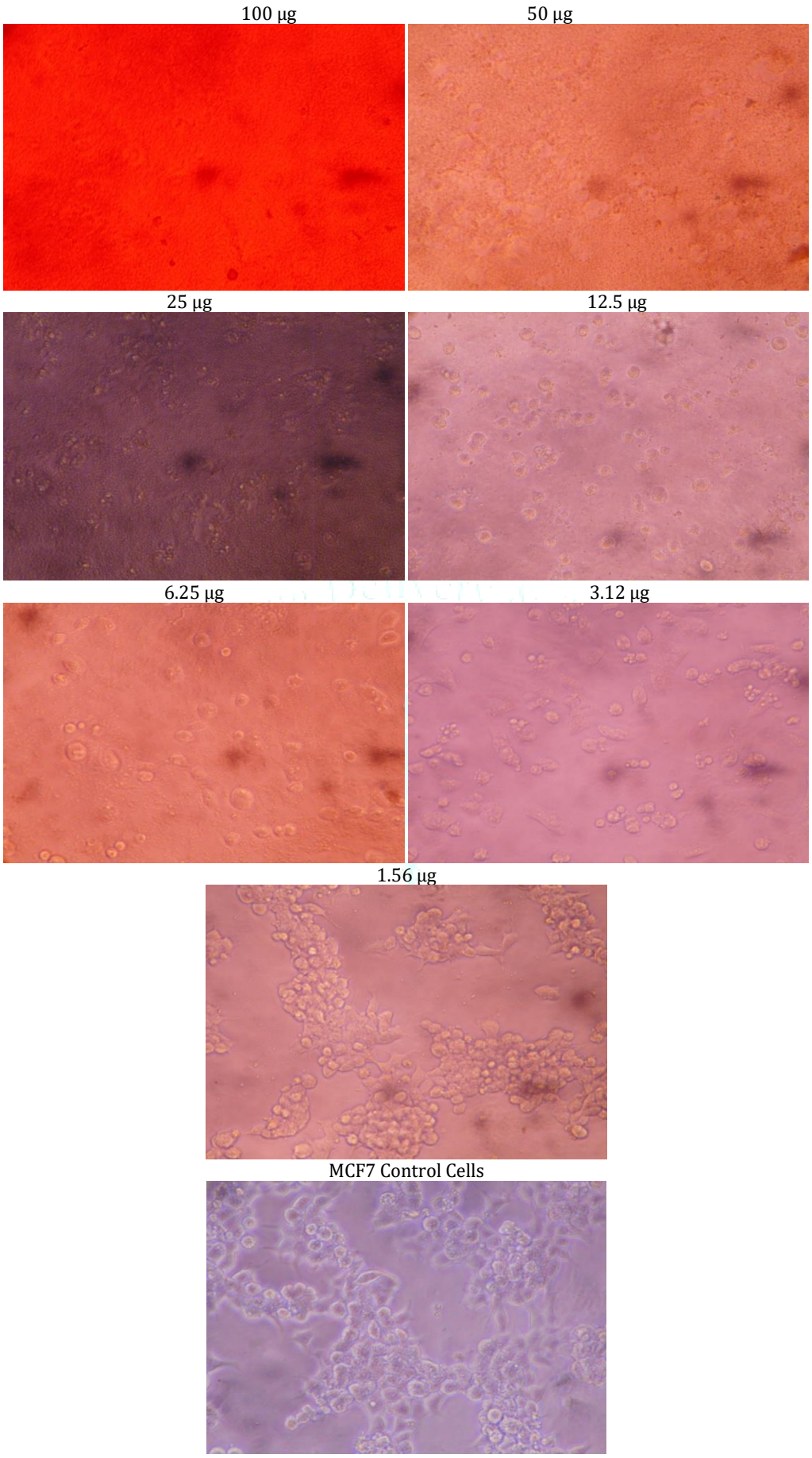



**Figure 17.** The affected MCF-7 cell line at PBBI different concentration
IC50 Value, MCF7
PBBP= 3.12µg; PBBA=2.496 µg; PBBI= 2.496 µg
By comparing MCF7 $IC_{50}$ values, PBBP has the highest MCF7 $IC_{50}$ values

## 4. CONCLUSION

A series of five poly(ester-amides) have been synthesized successfully by direct polycondensation method. Solubility studies reveal that these poly(ester-amides) are highly soluble in polar organic solvents and the viscosity studies reveal that these are of high molecular weight. These are characterized by FT-IR, $^{1}$H-NMR, and $^{13}$C-NMR spectral studies that supports the structural assignments. From the thermal studies such as DSC and HOPM, the phase transition and texture behavior of these poly(ester-amides) were identified. The degree of crystallinity were confirmed by X-ray diffractograms. The morphology of these five poly(ester-amides) are illustrated by SEM. Because of their high thermal stability as thermotropic liquid crystals, they might be utilized for flame retardant applications and optical device technology. Some of the synthesized poly(ester-amides) tested for anti-cancer activity against human breast cancer MTC7 cells using MTT assay showed an excellent anti-cancer activity against human breast cancer cells.

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