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Research Article

SYNTHESIS AND IN-VITRO EVALUATION OF COPOLYESTER-CHALCONE DERIVATIVES AS POTENTIAL ANTICANCER AGENTS

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ABSTRACT
A new series of copolyester chalcone derivatives were synthesised from 1, 3-bis (4-hydroxy-3-methoxyphenyl) propenone (BHMPP) and 1- (3, 5-dihydroxyphenyl)-3-(4-methoxyphenyl) propenone (DHPMPP) with adipoyl, suberoyl, azeloyl and sebacoyl chlorides by phase transfer catalysed polycondensation method. The microstructure of the repeating unit was confirmed by IR, ^{1}H and ^{13}C NMR. These copolyesters are evaluated for anticancer activity. These chalcone derivatives showed good activity against HepG2 cells with IC_{50} values.

Key Words: *Chalcones, Copolyesters, Polycondensation, Anticancer Agents*

INTRODUCTION
The family of polyesters comprises all polymers with ester functional groups in the polymer back bone. In principle, the synthesis of polyesters or esters in the presence of large amount of water has only been studied by a few research groups. (Saam et al., 1982) studied the polycondensation in suspension of hydrophobic diol and diacid compounds using different sulfonate surfactants (Edlund et al., 2003; Carothers et al., 1929). Copolyesters, obtained from a multiplicity of reactions having the component groups linked in a random or statistical order, are termed random copolyesters. They retain their strength, clarity and other mechanical properties, despite being exposed to a variety of chemicals that typically affect other materials, such as polycarbonates. This includes their versatility and flexibility which enhances their application effectively in the design of high-volume, low cast parts as well as critical, more expensive component parts.

Phase transfer catalysis is a synthetic technique which involves transport of an organic or inorganic salt form a solid or aqueous phase into an organic/liquid phase where reaction with an organic soluble substrate takes place.

Chalcones are 1, 3-diphenyl-2-propene-1-one, in which two aromatic rings are linked by a three carbon α, β-unsaturated carbonyl system. They possess conjugated double bonds and a completely delocalised π-electron system on both benzene rings. Molecules possessing such system have relatively low redox potentials and have a greater probability of undergoing electron transfer reactions. They represent an essential group of natural as well as synthetic products and some of them possess wide range of pharmacological activity such as antibacterial (Ahmed Kamel et al., 2010) antitumour (Siva Kumar et al., 2007) anticancer (Francesco et al., 2007) anti-inflammatory (Won et al., 2005) antioxidant (Calliste et al., 2001) antimalarial (Liu et al., 2001) antiulcerative (Mukarami et al., 1991) antitubercular (Rajendra Prasad et al., 2008) etc. The presence of reactive α, β-unsaturated keto group in chalcones is found to be responsible for their biological activity (Nowakowska et al., 2008). Chalcones are natural or synthetic flavonoids displaying an impressive array of biological properties. Chalcone constitute an important group of natural products and some of them possess a wide range of biological activities such as anticancer and (Jevwon et al., 2005), antitubercular (Shiva kumar et al., 2007).

The anticancer activity of certain chalcones is believed to be a result of binding to tubulin and preventing it from polymerizing into microtubules. Tubulin exists as a heterodimer of two homologous α- and β-subunits. This dimer can couple together to make profilaments consisting of alternating α- and β-subunits. Compounds such as these that target tumour vasculature clearly have significant clinical promise for the

treatment of cancer. Among the currently identified antitumor agents, chalcones represent an important class of molecules that are abundant in edible plants.

MATERIALS AND METHODS

Adipic acid (Ranbaxy), sebacic acid (SDS) and thionyl chloride (SDS) were purchased and used. 4-hydroxy benzaldehyde (Merck), 4-hydroxy-3-methoxy benzaldehyde (Merck) were used as received. Tetra-n-butylammonium bromide (TBABr, Fluka) was purchased and used. Spectral grade DMSO-d6 (Aldrich) containing TMS as internal standard was used as received. The monomers are 1, 3-bis (4-hydroxy-3-methoxyphenyl) propenone and 1-(3, 5-dihydroxyphenyl)-3-(4-methoxyphenyl) propenone were synthesised and used.

Synthesis of monomer

1, 3-bis (4-hydroxy-3-methoxyphenyl) prop-2-en-1-one (BHMPP)

A mixture of 4-hydroxy3-methoxy benzaldehyde and 4-hydroxy-3-methoxy acetophenone kept dissolved in methanol. The reaction was allowed to proceed for an hour and then poured into ice cold water the yellow precipitate of BHMPP was filtered, dried and further recrystallised from methanol.Yield:90%, m.p:200^{o}C. FT IR (KBr): 3400 cm^{-1}(ν_{OH}); 1591 cm^{-1}($\nu_{C=C}$); 1641 cm^{-1}($\nu_{C=O}$). ^{1}H NMR (DMSO-d6):7.1-8.2δ (aromatic), 9.7 δ (S, 2H,-OH), 3.6 δ (S, 3H,-OCH_3). ^{13}C NMR (DMSO-d_6): 188.51 δ (>C=O), 158.24 δ (C-OH), 55.63 δ (-OCH_3). Molecular formula: $C_{17}H_{16}O_5$, MS (El) m/z 300[M^+].

1-(3, 5-dihydroxyphenyl)-3-(4-methoxyphenyl) propenone (DHPMPP)

A similar procedure followed for the synthesis of DHPMPP was adopted for the preparation of 3, 5-dihydroxy acetophenone and 4-methoxy benzaldehyde.

Synthesis of polymer

Equimolar quantities of BHMPP (1 mmole) and DHPMPP (1mmole) were dissolved in 25 mL of aqueous sodium hydroxide (0.1 N) solution and taken in a round- bottomed flask (100 mL). After 15 minutes a solution of 2 mL of 2% TBABr was added and stirred. The mixture was stirred continuously at room temperature for 30 minutes in inert atmosphere. About 25 mL solution of adipoyl chloride (2 mmole) in dichloromethane (DCM) was added. The mixture was maintained at room temperature with continuous stirring for seven hours. The reaction mixture was poured into 100 mL of n-hexane when the solid copolyester was obtained. It was then filtered in vaccum. The crude sample was purified and used. Copolyester PBHR2, PBHR3 and PBHR4 were prepared by a similar method using azeloyl, suberoyl and sebacoyl chlorides (Muthusamy et al., 2006).

RESULTS AND DISCUSSION

The copolyesters synthesised in the present work were characterised by solubility studies, viscosity

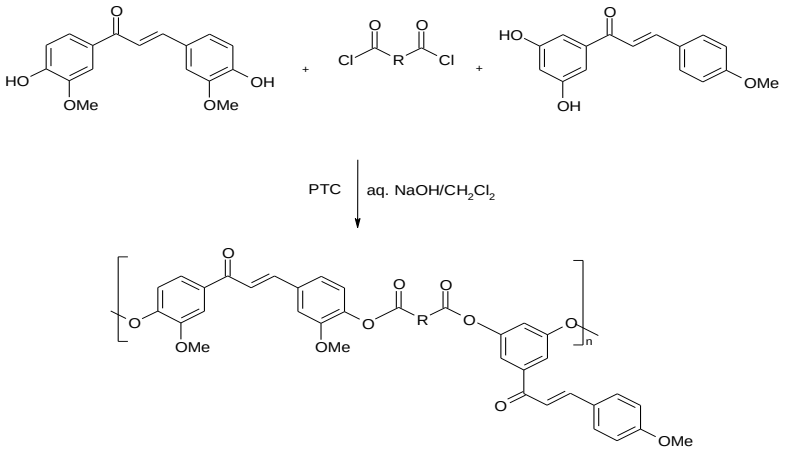

Figure 1. Synthesis of polyester by using tetra-n-butyl ammonium bromide as PTC catalyst.

measurements and spectral data. The copolyesters were also evaluated for anticancer activity against HepG2 cells.

Table 1. Aliphatic acid chlorides used and the copolyester code of the four polyesters.

S.No.	Codes of polyesters	Acid chlorides (R)
1	PBHR1	- $(CH_2)_4$ -
2	PBHR2	- $(CH_2)_6$ -
3	PBHR3	- $(CH_2)_7$ -
4	PBHR4	- $(CH_2)_8$ -

IR spectra of the four copolyesters were recorded using Nicolet 510 FT-IR instrument. IR spectra of all the four copolyesters showed characteristic absorption in the range of 1742-1764 cm^{-1} due to ester C=O stretching frequency. From the spectra, it could be observed that characteristic absorption frequencies in the range 1585-1598 cm^{-1} and 976-986 cm^{-1} are characteristic of trans olefinic double bonds. The stretching vibration of methylene group show characteristic absorption band in the range-2851-2875 cm^{-1}. The ^{1}H and ^{13}C NMR spectra were recorded with JEOL GSX-400MHz instrument in DMSO-d6 solvent to identify the structural units present in the copolyester chain. The aromatic protons are observed in the range of 7.5-8.0 ppm. The methoxy protons in the chalcone moiety are showed by a signal at 3.4 ppm. The signal in the range of 185-200 ppm and 168-172 ppm in the ^{13}C NMR spectra due to the presence of ketone carbonyl and ester carbonyl carbon (Kannappan et al., 2002).

Anticancer activity of polymers

A random copolyester of PBHR4 was assayed for antitumour activity in vitro human cells. The results of synthesised copolyester was summarised in Table 2. From these results it is clear that, the copolyester PBHR4 containing higher alkyl chain length of sebacoyl moiety (C_8 exhibits higher antitumor activity than other compounds of PBHR1, PBHR2 and PBHR3 containing lower alkyl chain length of adipoyl, azeloyl and suberoyl moiety (C_4, C_6 and C_7) present in the polyester. As in the literature reported, the antitumor activity increases when the alkyl chain length is increased (Cesar Echecerria et al., 2009). The IC_{50} concentration was calculated as the drug concentration resulting in 50% loss of cell viability with reference to untreated cells after 24 hours incubation. IC_{50} was 50 µg/ml, and maximal inhibition of cell

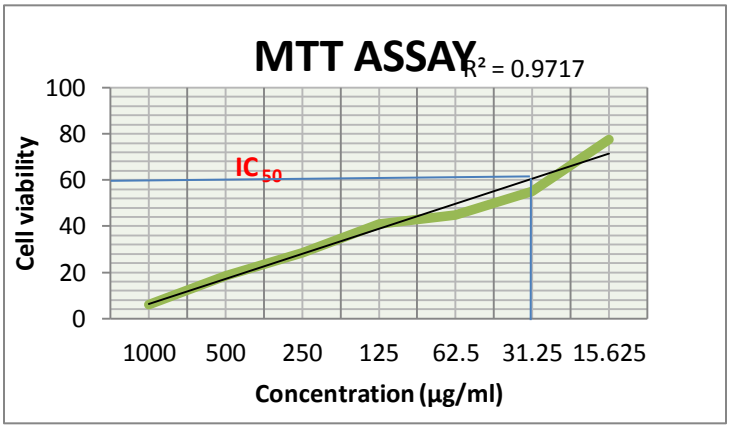

Figure 2. Activities of PBHR4 in the MTT assay.

Table 2. Cytotoxic effect of PBHR4

S.No.	Concentration (µg/ml)	Dilutions	Absorbance at 540nm	Cell viability
1	1000	Neat	0.09	21.42
2	500	1:1	0.15	35.71
3	250	1:2	0.20	47.61
4	125	1:4	0.24	57.14
5	62.5	1:8	0.34	80.95
6	31.25	1:16	0.38	90.47
7	15.625	1:32	0.41	97.61
8	Cell control	-	0.42	100

growth (>50%) was obtained at 125 µg/ml (Srinivas et al., 2003; Ducki et al., 1998; Robinson et al., 2005).This was evident from the relatively high activity of the PBHR4 compound, suggesting that higher lipophilicity lowered the cell permeation and thus reduced dramatically the cell arrest activity of the resulting derivatives. This phenomenon was particularly explained in the basis of ‘‘Enhanced Permeability and Retention’’effect (EPR). (Maeda et al., 1997; Muggia FM 1999; Matsumura et al., 1989). Finally, graph was plotted between concentration of polymers and cell viability.

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