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Synthesis and Study of Modified Polyvinyl Alcohol Containing Amino Acid Moieties as Anticancer Agent

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ABSTRACT

A series of new phthalimides compounds[3-7]$_{a-i}$ were synthesized from reaction of Malic anhydride, phthalic anhydride, nitro phthalic anhydride, 2-phenyl-4H-benzo[d][1,3]oxazin-4-one, 2-(4-nitrophenyl)-4H-benzo[d][1,3]oxazin-4-one with different amino acids as glycine, alanine, valine, leucine, isoleucine, serine, threonine, tyrosine and Phenyl alanine [1]$_{a-i}$ under fusion conditions. Compounds [3-7]$_{a-i}$ react with $SOCl_2$ in the presence of benzene to produce compounds [8-12]$_{a-i}$. Chemical modification of Poly(vinyl alcohol)were obtained by reaction of PVA with compounds [8-12]$_{a-i}$ using the dimethyl formamide to give compounds [13-17]$_{a-i}$. The structure of the synthesized compounds was characterized by their analytical and spectral data as, IR spectra, ^{1}H, ^{13}C-NMR, Elemental analysis (CHN), UV-Vis Spectroscopy, Scanning electron microscopy (SEM), Antibacterial activity were screened via two kinds of bacteria. Also, anticancer activity were examined for most of the modified polyvinyl alcohol.

Keywords: Phthalimide, Polyvinyl alcohol, antibacterial and anticancer activities.

INTRODUCTION

Cyclic imides and their derivatives brought much attention to chemist and pharmacist in the field of research and development[1], These compounds play an important role in medicinal chemistry in drug development and drug discovery[2]. They Researches used these compounds as antibacterial[3], analgesic[4], nerve conduction blocking[5], hypotensive[6], muscle relaxant[7], antitumor[8] antitubercular agents[9] and antinociceptive agents , Also, these compounds interest as reactants for polymer synthesis[10].

In addition compounds containing phthalimide moiety are distinguished with antimicrobial[11-13], anti-inflammatory, anxiolytic, antiviral, antibacterial and antitumor properties[14,15] .

Polyvinyl alcohol (PVA)is a water-soluble polyhydroxy polymer, non-halogenated aliphatic polymers, that has a two dimensional hydrogen-bonded network sheet structure[16].

PVA is a semi-crystalline polymer containing crystalline and amorphous phase[17] which is used in biomedical and pharmaceutical applications[18] and in industries due to the excellent chemical and physical properties, non-toxicity, good chemical resistance, good film formation capacity.[19]

It has been applied in production of many end products, as lacquers, resins, surgical threads , and food packaging materials[20].

Encouraged by these observation, the present study to synthesize new series of imide compounds containing amino acids with different heterocycles they may be have more activity and less toxicity as anticancer agents.

Aim of the present work is directed toward modification of polyvinyl alcohol containing active moiety with screened of antibacterial and anticancer activities.

EXPERIMENTAL

A-Materials

All the chemical used in the synthesis were supplied from BDH and Sigma-Aldrich.

B – Instrumentation

Melting points were recorded using electro thermal melting point apparatus and are uncorrected.

Infrared spectra were recorded as KBr disc on SHIMADZU-FT-IR-8400 spectrometer. ^{1}H, ^{13}C-NMR spectra was recorded on Bruker 500 MHz instrument using DMSO-d_6 as a solvent and TMS as internal reference, measurement were made at Central lab, Tahran University (Iran). the progress of the reaction was monitored by TLC using aluminum silica gel plates .

Synthesis of compounds $[2]_{a,b}$[21].

Benzoyl chloride or 4-nitrobenzoyl chloride (0.02 mole) was added to a solution of 2-aminobenzoic acid (0.01 mole) in (30 ml.) pyridine. The mixture was shaken for 5 min. and then kept in room temperature with shaking for 25 min. Mixture was reacted with 15 ml. 10% $NaHCO_3$, filtered, washed with water, dried and the crude product was recrystalized from absolute ethanol. The yield of compound$[2]_a$ was 81% , m.p. (126) and $[2]_b$ was 77% , m.p (144).

General procedure for Preparation of compounds $[3\text{-}7]_{a\text{-}i}$[22].

A mixture of equimolar amounts (0.001 mole) of commercially available malic anhydride, phthalic anhydride, nitro phthalic anhydride, 2-phenyl-4H-benzo[d][1,3]oxazin-4-one, 2-(4-nitrophenyl)-4H-benzo[d] [1,3] oxazin-4-one were treated with corresponding amino acids$[1]_{a\text{-}i}$ in glacial acetic acid (15 ml.).

Mixture was refluxed for (5 h) . A liquot of 25 ml. of ice distilled water was added to the reaction. The compounds was filtered, dried and recrystallized from ethanol . The nomenclature and physical properties for prepared compounds

$[3\text{-}7]_{a\text{-}i}$. were shown in Table. (1)

Elemental analysis of compound$[3]_c$

Calcd: C%=54.82	H%= 5.58	N% =7.10
Found: C%= 54.69	H%= 5.42	N% = 6.21

Elemental analysis of compound$[5]_i$

Calcd: C%=60	H%= 3.52	N% =8.23
Found: C%=58.7	H%= 4.62	N% = 7.71

Synthesis of compounds $[8\text{-}12]_{a\text{-}i}$.[23]

A mixture of compound $[3\text{-}7]_{a\text{-}i}$ (0.01mole) and thionyl chloride (0.01mole) placed in dry benzene (10 ml.) and refluxed for 7 hours. The excess of thionyl chloride and benzene were removed under vacuum after cooling .

Synthesis of polymers $[13\text{-}17]_{a\text{-}i}$[24]

(1mole) of PVA and (1mole) of compounds $[8\text{-}12]_{a\text{-}i}$ were placed in 20 ml DMF. The mixture was frequent shaking for 3hr. then refluxed for 2 h product was poured into the water , washed with a little sodium bicarbonate, washed with water , then with ethanol. The product purified by DMSO and reprecipitating from ethanol.

Biological Activity

Antibacterial activity

Some of synthesized compounds have been screend for antibacterial activities against (*Bacillus cereus* and *Esherichia coli*) using cup-plate agar diffusion method[25]. The zone of inhibition measured in mm. Pencilin was (50 µg /ml) were used as a standard drug for antibacterial activity to compare with the activity of the synthesized compounds.

Cytotoxicity Assay

Preparation of Cell Lines for Cytotoxicity Assay[26]

Fifteen modified PVA compound with different sizes and concentrations were screened for their anticancer activity and cytotoxicity by using cultured cells in microtiter plate (96 wells). The assay was applied by the following steps:

A-Seeding: When cells in the incubated falcon became monolayer, the confluent monolayer was trypsinzed to get single cell suspension. A liquot 200 µl/10^4-10^5 cells/well from single cell suspension then were added to all the 96 wells of the microtiter plates, which covered by plate lids and sealed with adhesive parafilm. The plate was shaked gently and returned to the incubator.

B-Incubation: Microtiter Plates were then incubated in humidified chamber at 37 °C, 5% CO_2 until the cells reached confluence (i.e., vary according to the type of cell line). The plate was checked out for contamination , after cells attachment

C- Exposure: When the cells are in full of its activity, they were expose.d to three concentrations of the fifteen modified of PVA µg/ml for cell line . Aliquot of 200 µl of each concentration were pipette into each well, while 200 µl of maintenance medium were added to each well of control group, then plates were sealed with adhesive parrafilm and returned to the incubator. Evaluation of cytotoxicity was carried out after 48hours. The photo picture were taken after 24 hours.

D- Staining: Cell viability was measured after 48 h of exposure by removing the medium, adding 20 µl/well solution of MTT and incubating for 4 h at 37 °C. The crystals remaining in the wells were solubilized by the addition of 200 µl/well of (DMSO) followed by incubation in 37 °C for 15 min. with shaking. The absorbance was measured on a microplate reader at 620 nm . The rate of inhibition of cell growth was calculated according to[27] follow equation.

$$\text{Inhibition rate} = \frac{\text{mean of control-mean of treatment}}{\text{mean of control}} \times 100 \quad (1.1)$$

RESULTS AND DISCUSSION

Scheme (1) summarized the performed reactions in this work. The structure of compounds $[2]_{a,b}$ were confirmed from its correct analytical and spectral data . FT-IR spectrum of compound $[2]_b$, Fig. (3.1), showed[21] appearance band at (1766) cm^{-1} due to the carbonyl group of cyclic ester, (1666, 1614) cm^{-1} due to the C=N group and (1585) cm^{-1} due to the C=C group. The ^{1}H-NMR spectrum of compound $[2]_b$, Fig. (3.2) display the following characteristic chemical shifts , (DMSO) ppm : the aromatic ring protons of compound $[2]_b$ appeared as multiple at δ (6.41-8.64) ppm .

N-phthaloyl amino acid derivative $[3\text{-}7]_{a-i}$ using economical experimental conditions via reaction Malic anhydride , phthalic anhydride , nitro phthalic anhydride, 2-phenyl-4H-benzo[d] [1,3] oxazin-4-one, 2-(4-nitrophenyl)-4H-benzo[d] [1,3] oxazin-4-one and different amino acids namely$[1]_{a-i}$, glycine, alanine, valine , leucine , isoleucine, serine, threonine, tyrosine and Phenyl alanine in (15 ml.) of glacial acetic acid , then mixture was refluxed for (5 h) . The mechanism[28]. involves nucleophilic addition reaction, as follows scheme (3.1).

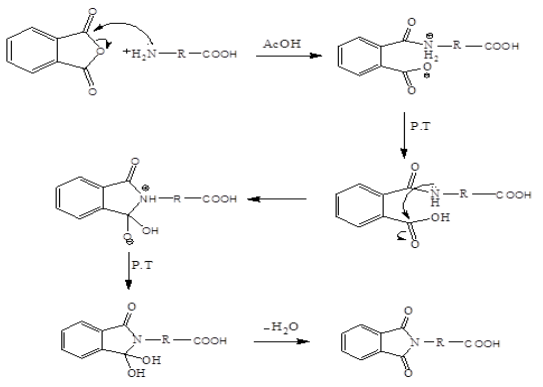

Fig. 1. The mechanism of preparing compound $(3\text{-}7)_{a-i}$

The structure of compounds $[3\text{-}7]_{a\text{-}i}$ was confirmed from its correct analytical and spectral data, FT-IR spectra of compounds $[5]_{a,i}$, Fig. [(3.3),(3.4)], showed[22] bands at (3300-2400) cm^{-1} for (OH) of carboxylic acids, (1780,1735) cm^{-1} due to two (N-C=O), (1699) cm^{-1} for (C=O) of carboxylic acid .While ^{1}H-NMR spectrum of compound $[5]_a$, Fig. (3.5) , showed characteristic chemical shifts (DMSO-d_6) ppm as follow: the aromatic ring protons appeared as multiple at δ (7.69-8.32) ppm and appearance singlet at δ (4.31) ppm due to CH_2 proton and singlet in the region of δ 10.50 due to COOH proton.

The ^{1}H-NMR spectrum of compound $[5]_i$, Fig. (3.6) , display characteristic chemical shifts (DMSO-d_6) ppm as follow: the aromatic ring protons appeared as multiple at δ (7.14-7.97) ppm and appearance doublet signal at δ (3.14) ppm related to CH_2 proton and triplate signal at δ (3.99) due to CH proton.

The FT-IR spectrum of compounds$[7]_c$, Fig. (3.7) showed disappearance of due to the carbonyl group of cyclic ester at (1766) cm^{-1} and appearance band at (1685) cm^{-1} due to carbonyl group of carboxylic acid. Also, absorption bands at (1643) cm^{-1}, (1608) cm^{-1} and (1587) cm^{-1} due to (C=O) of amide, (C=N) and (C=C) respectively . The ^{1}H-NMR spectrum of compound $[7]_c$, Fig. (3.8), showed characteristic chemical shifts (DMSO-d_6) ppm as follow: a singlet signal at δ (12.36) ppm for proton COOH group, Many signals in the region δ (7.19-8.73) ppm that could be attributed to aromatic protons. Also appearance doublet signal at δ (4.13) ppm for proton CH-N group and many signals in the region δ (1.88) ppm that could be attributed to proton of CH in $CH(CH_3)_2$ and doublet signal at δ (0.96) ppm is due to $(CH_3)_2$ group. Where as ^{13}C-NMR spectrum of compound $[7]_c$, Fig. (3.9), showed: a signal at δ (172.91) ppm could be attributed to COOH group,while signal at δ (171.72) ppm is due to carbon of C=O amide group. Signal at δ (164.45) due to carbon of ph-C=N group. Many signal a δ (120-140) ppm could be attributed to carbon of benzene ring. Also signal at δ (59.1) ppm related to N-CH group. Signal appeared at δ (58.2) ppm is related to carbon of CH in $CH(CH_3)_2$. Two signal at δ (19.05-29.55)ppm could be attributed to$(CH_3)_2$.

N-phthaloyl amino acid chloride derivatives $[8\text{-}12]_{a\text{-}i}$ through h the reaction of *N*- phthaloyl amino acids $[3\text{-}7]_{a\text{-}i}$ with thionyl chloride in dry benzene was refluxed for (7 h). A mechanism[29] for this reaction may be outlined as followed in scheme (3.2) .

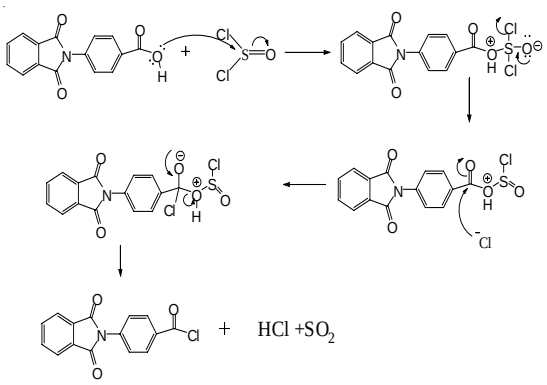

Fig. 2. The mechanism of preparing compound $(8\text{-}12)_{a\text{-}i}$

Compound $[10]_b$ was characterized by melting point and FT-IR spectrum . FT-IR spectrum of compound $[10]_b$, Fig. (3.10) , showed[23] the absence of absorption band at (1695) cm^{-1} and (3392) cm^{-1}due to (carbonyl , hydroxyl) group of carboxylic acid and presence of band at (1761) cm^{-1} related to acyl chloride .

Chemical modification of Poly(vinyl alcohol)$[13\text{-}17\ ]_{a\text{-}i}$ was obtained by reaction of PVA with compounds $[8\text{-}12]_{a\text{-}i}$ using the dimethyl formamide.

The compounds $[13\text{-}17\ ]_{a\text{-}i}$ were identified by FT-IR spectrum . FT-IR spectrum of compound $[15]_a$, Fig. (3.11) illustrated the presence of a large peak at 3390 cm^{-1} this peak is related to the stretching of O–H from the intramolecular and intermolecular hydrogen bonds, which seen at 2908 cm^{-1} and 2943 cm^{-1} respectively due to the symmetric and asymmetric stretching vibrational of C–H from alkyl groups [30], showed the disappearance of absorption band at (1761) cm^{-1} due to acyl chloride and appearance of absorption band at (1724) cm^{-1} due to carbonyl group of ester[31] and appearance of absorption bands at (C=O) of cyclic imide at (1710-1778) cm^{-1}.

The ^{1}H-NMR spectrum of compound $[13]_a$, Fig. (3.12), showed[32,33] the following characteristic chemical shifts (DMSO-d_6) ppm showed the following signals: signal at δ (6.63) ppm for proton (CH=CH) group, singlet peak at δ (4.48) ppm for proton of (N-CH_2)group, triplet peak at δ (4.24) ppm for (CH)group and doublet peak at δ (1.37) ppm for proton (CH_2) group.

The ^{1}H-NMR spectrum of compound $[15]_f$, Fig. (3.13), showed[32,33] the following characteristic chemical shifts (DMSO-d_6) ppm showed the following signals: many signals at δ (8.30-8.32) ppm for proton aromatic protons.triplet peak at δ (4.32-4.77) ppm for proton of (N-CH)group, doublet peak at δ (3.99) ppm for protonCH_2 in (CH_2-OH), singelt peak at δ (3.45) ppm for proton (OH) group, triplet peak at δ (3.05) ppm for (CH-CH_2) group and doublet peak at δ (1.54) ppm for proton (CH_2-CH) group .

The UV-Vis spectrum of compound $[14]_f$, Fig. (3.14) shows the absorption peaks at (332-402) may attributed to(π- π*) and (n-π*).

Biological Activity

Antibacterial activity

All the newly synthesized derivatives were screened for their *in vitro* antimicrobial activity against *Escherichia coli* , *Bacillus cereus* by measuring the zone of inhibition in mm . Result showed that compounds$[6]_f$ and $[16]_f$ exhibit some antibacterial activity with penciline against *E .coli* while compounds $[15]_f$ and $[17]_f$ showed antibacterial activity closed to penciline against *Bacillus cereus* . Resalts of all compounds all compounds and their antibacterial activities listed in Table. (3.4).

Table. 1: FT-IR data of compounds$[3\text{-}5]_{a\text{-}i}$

Com. No.	(O-H) cm^{-1}	(C-H) arom. cm^{-1}	(C-H) aliph. cm^{-1}	(C=O) imide. cm^{-1}	(C=O) carboxlic
$[3]_a$	3400-2400	3053	2968-2879	1732-1770	1681
$[3]_b$	3473	3072	2987-2873	1722-1784	1691
$[3]_c$	3392	3066	2970-2890	1743-1782	1680
$[3]_d$	3400-2400	3055	2965-2877	1728-1770	1690
$[3]_e$	3464	3075	2939-2855	1716—1774	1691
$[3]_f$	3462	3084	2939-2872	1749-1772	1697
$[3]_g$	3442	3093	2920-2850	1745-1774	1693
$[3]_h$	3400-2600	3051	2985-2939	1718-1735	1685
$[3]_i$	3400-2400	3086	2972-2926	1722-1780	1680
$[4]_a$	3344	3049	2989-2883	1734-1780	1683
$[4]_b$	3400-2400	3080	2990-2951	1755-1786	1697
$[4]_c$	3300-2400	3049	2966-2890	1712-1761	1691
$[4]_d$	3400-2600	3109	3018-2990	1712-1764	1701
$[4]_e$	3396	3090	2933-2877	1710-1772	1696
$[4]_f$	3394	3089	2947-2885	1735-1776	1697
$[4]_g$	3462	3084	2939-2872	1749-1772	1697
$[4]_h$	3435	3088	2962-2893	1716-1772	1685
$[4]_i$	3392	3045	2980-2943	1710-1770	1662
$[5]_b$	3392	3089	2995-2941	1724-1784	1695
$[5]_c$	3408	3041	2970-2881	1726-1784	1690
$[5]_d$	3400-2400	3115	2960-2860	1732-1782	1683
$[5]_e$	3400-2400	3064	2926-2854	1716-1780	1683
$[5]_f$	3398	3024	2990-2889	1732-1776	1681
$[5]_g$	3408	3097	3039-2926	1716-1780	1690
$[5]_h$	3400-2600	3026	2929-2856	1716-1734	1701

Table. 2: FT-IR data of compounds[6,7]$_{a-i}$

Com. No.	(O-H) cm^{-1}	(C-H) arom. cm^{-1}	(C-H) aliph. cm^{-1}	(C=O) carboxlic	(C=O) amid. cm^{-1}
$[6]_a$	3442	3049	2943-2895	1685	1643
$[6]_b$	3400-2400	3043	2989-2933	1683	1643
$[6]_c$	3442	3061	2966-2879	1680	1645
$[6]_d$	3433	3024	2968-2889	1697	1676
$[6]_e$	3305	3064	2966-2877	1683	1645
$[6]_f$	3400-2600	3062	3030-2951	1683	1668
$[6]_g$	3400-2400	3064	2960-2883	1685	1643
$[6]_h$	3300-2600	3051	2960-2887	1685	1643
$[6]_i$	3400-2600	3062	2926-2858	1690	1654
$[7]_a$	3502	3078	2965-2879	1681	1645
$[7]_b$	3400-2400	3082	2985-2858	1693	1655
$[7]_d$	3400-2600	3059	2999-2854	1689	1645
$[7]_e$	3508	3057	2962-2875	1681	1640
$[7]_f$	3498	3080	2924-2850	1689	1655
$[7]_g$	3508	3061	2985-2856	1681	1647
$[7]_h$	3300-2400	3007	2929-2827	1690	1666
$[7]_i$	3508	3061	2929—2856	1681	1668

Table. 3 : The inhibition zone of some synthesized compounds

Compound	*E .coli* (mm)	*Bacillus cereus* mm
Peinciline	16	22
DMSO	Nil	Nil
$[3]_h$	10	10
$[13]_h$	15	16
$[4]_h$	10	10
$[14]_h$	10	21
$[5]_f$	15	16
$[15]_f$	15	23
$[6]_f$	16	13
$[16]_f$	16	21
$[7]_f$	14	18
$[17]_f$	14	25

Table. 4 : The inhibition zone of some synthesized compounds

Compound	*E .coli* mm	*Bacillus cereus* mm
Penciline	16	22
DMSO	Nil	Nil
$[3]_h$	10	10
$[13]_h$	15	16
$[4]_h$	10	10
$[14]_h$	10	21
$[5]_f$	15	16
$[15]_f$	15	23
$[6]_f$	16	13
$[16]_f$	16	21
$[7]_f$	14	18
$[17]_f$	14	25

Fig. 3. Antibacterial activities of compounds against *E.coli*

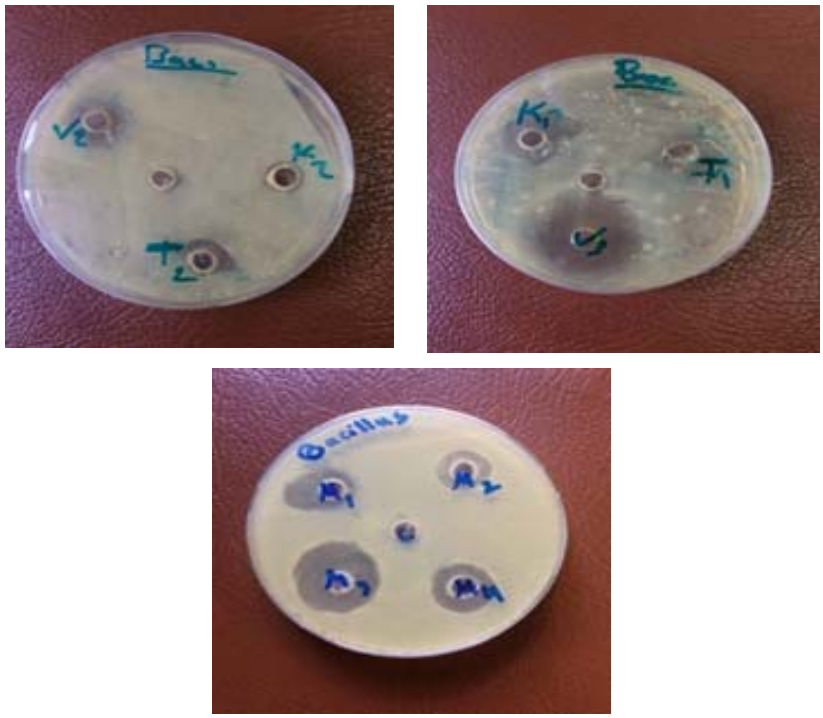

Fig. 4. Antibacterial activities of compounds against *Bacillus cereus*

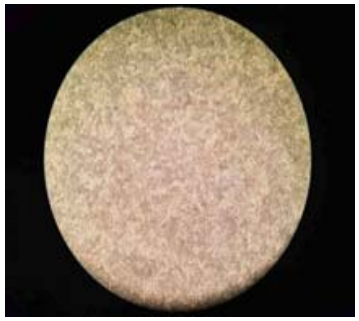

Fig. 5. Image of before well Staining

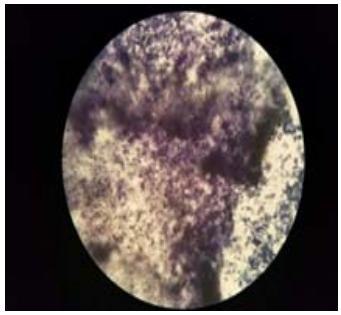

Fig. 6. Image of well after Staining

Fig. 7. Image of plate before Staining

Fig.8. Image of plate after Staining

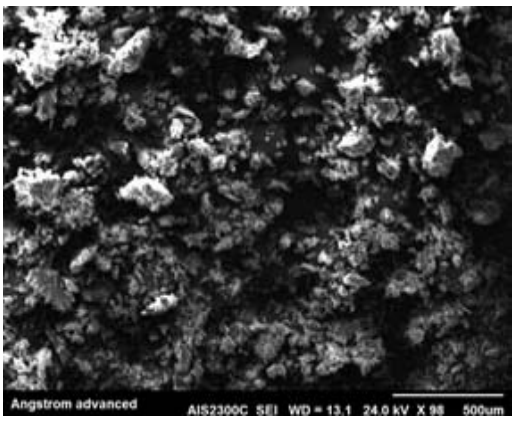

Fig. 9. SEM of compound[9]f

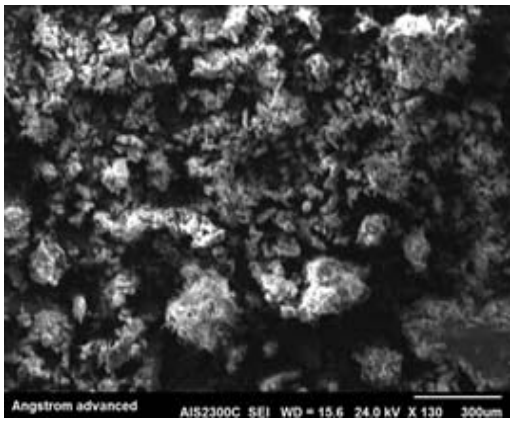

Fig. 10. SEM of compound[9]f

Anticancer activity

Fifteen compounds modified polyvinyl alcohol were selected for examend their anticancer activity in Bio-technology research center, Al-Nahrain University, Baghdad, Iraq. Two cell lines were used (mice intestines carcinoma cell line L20b and human pelvic rhabdomyosarcoma (RD). according to the method described by Freshney[26] Results are expressed in percentage. All compounds except $[17]_b$ and $[17]_d$ showed more than 50% inhibition for mice intestines carcinoma cell line, while these compounds$[17]_b$ and $[17]_d$ exhibit inhibition more than 50% inhibition for human pelvic rhabdomyosarcoma.

CONCLUSION

Compounds react with $SOCl_2$ in the presence of benzene to produce compounds. Chemical modification of Poly(vinyl alcohol) were obtained by reaction of PVA with compounds using the dimethyl formamide to give compounds. The structure of the synthesized compounds was characterized by their analytical and spectral data as, IR spectra, ^1H, ^{13}C-NMR, Elemental analysis (CHN), UV-Vis Spectroscopy, Scanning electron microscopy (SEM), Antibacterial activity were screened via two kinds of bacteria. Also, anticancer activity were examined for most of the modified polyvinyl alcohol.

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