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Synthesis, Characterization and Anticancer Activity of polyether Derived from Polyvinyl Alcohol with New benzothiazole Derivatives in Treatment of Liver Cancer Cell line hepG2

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Abstract

A novel benzothiazole derivative compound, [M1], was synthesized by reacting 4-aminoacetophenone with 2-aminobenzothiazole in the presence of glacial acetic acid as a catalyst, enabling the efficient formation of the target compound. Amic acid compounds [M2-M4] were synthesized from the reaction of compound [M1] with various cyclic anhydrides in dry acetone. Cyclic imides derivatives were synthesized by a dehydrated reaction of the prepared amic acid [M2-M4] with acetic anhydride and sodium acetate to produce the corresponding cyclic imides [M5-M7]. The synthesized compounds [M5-M7] reacted with Acetyl chloride to produce the corresponding acetamide derivatives compounds [M8-M10]. The polyether derivatives [M11-M13] were synthesized from the reaction of polyvinyl alcohol with compounds [M8-M10]. All prepared compounds were characterized using infrared spectroscopy FTIR and nuclear magnetic resonance NMR spectroscopy for some of them. The in vitro anticancer efficacy of compound M12 was assessed against the liver cancer cell line hepG2, providing valuable insights into its potential as a therapeutic agent against liver cancer.

Keywords: Liver anticancer, benzothiazole, polyether, Polyvinyl alcohol.

تحضير ,تشخيص والفعالية المضادة للسرطان للبولي ايثر المشتق من البولي فينيل الكحولي مع مشتقات البنزوثيازول الجديدة في معالجة الخط السرطاني للكبد

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الخلاصة

مشتق جديد للبنزوثيازول[M1] تم تحضيره من تفاعل 4-أمينو أسيتوفينون مع 2- امينو بنزوثيازول بوجود حامض الخليك الثلجي كمحفز للتمكن من التحضير الفعال للمركب المطلوب. تم تحضير مركبات حامض الأميك [M2-M4] من تفاعل المركب [M1] مع الانهدريات الحلقية المختلفة في وجود الاسيتون الجاف.

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تم تحضيرمشتقات الايميدات الحلقية بواسطة تفاعل لمركبات حامض الآميك [M2–M4] مع انهدريد الخليك وخلات الصوديوم لتحضير الايميدات الحلقية [M5–M7]. تم مفاعلة المركبات المحضرة [M5–M7]مع كلوريد الاسيتيل لانتاج مشتقات الاستامايد [M8–M10] . تم تحضير مشتقات البولي ايثر [M11–M13]من تفاعل البولي فاينيل الكحولي مع المركبات [M8–M10].
شخصت المركبات المحضرة باستخدام مطيافية الاشعة تحت الحمراء ومطيافية الرنين المغناطيسي النووي لبعض منها. تم قياس الفعالية المضادة للسرطان داخل المختبر لمركب M12 ضد الخط السرطاني للكبد موفرة رؤية ذات قيمة لتأثيرها وامكانية استخدامها كمركب علاجي مضاد لسرطان الكبد.

1. Introduction

The heterocyclic compound 1,3-thiazole contains separated sulfur and nitrogen by one carbon. Heterocycles containing nitrogen and sulfur heteroatoms exhibit substantial biological activities. One of the most important compounds in heterocyclic chemistry, as well as in drug design and detection, is 1,3-thiazole, which exhibits antimicrobial, antitumor, and antiangiogenic, analgesic, antioxidant activity such as anthelmintic, antileshmanial, anticonvulsant, anti-inflammatory, antihumane rhinovirus (HRV) activities, antibiotic, antifungal, anticancer, antiparkinson, anti-HIV, trypanocidal agent, hypoglycemic, antidiabetic, antituberculosis, anti-urease and inhibitor of α-glucosidase properties [1,2]. It is obvious that one of the important compounds are cyclic imides with wide range of biological activities such as anti-inflammatory, anticancer, antibacterial, antibacterial, analgesic, hypoglycemic and antifungal activities [3]. Additionally, these compounds can serve as useful intermediates in the synthesis of numerous drug molecules and pharmaceutical agents [4]. Furthermore, cyclic imides are intrinsic building blocks for the preparation of pharmaceuticals, natural products, polymers, and drugs [5-7]. Polyvinyl alcohol (PVA) is a synthetic polymer that has become popular due to its biodegradable, biocompatible, non-toxic, and water-soluble properties resulting from the presence of hydroxyl groups [8,9]. The modification of polymers is an important area of research, as it allows the creation of modified polymers with increased activity. PVA is a well-known polymer have many applications in nutraceutical, pharmaceutical and medicinal fields due to its smooth film forming, easy processing ability and chemical resistance properties [10,11]. The aim of this study was to synthesize and to examine the effect of the synthesized polyether on the Liver cancer Cell line hepG2.

2. Experimental Part

2.1 Material and Instrumentation

The chemicals and solvents used in this study were sourced from Merck, Sigma Aldrich, and CDH. The Merk company provided thin layer chromatography (TLC) and iodine fumes which was used to identify the spots. The melting point was determined by using the thermal melting point apparatus. A Shimadzu FT-IR Spectrophotometer (FTIR-8400S) was employed to record FT-IR spectral data at the University of Baghdad / College of Sciences. The ^{1}H NMR and ^{13}C NMR data were recording using a Nuclear magnetic resonance spectroscopy (400 MHz) using DMSO-*d*6 as a solvent. Chemical shifts were measured in parts per million (ppm) relative to the internal reference tetramethylsilane (TMS) in Iran.

2.1.1 Synthesis of 4-(1-(benzothiazol-2-ylimino)ethyl) M1. [12-14]

A mixture of 4-aminoacetophenone (0.5 g, 0.0036 mol) and 2-aminobenzothiazol (0.55 g, 0.0036 mol) in absolute ethanol (25 mL) with a few drops of glacial acetic acid was heated and refluxed for 8 hrs. Upon completion of the reflux period, the precipitate was filtered,

washed with water, and recrystallized using acetone to obtain the final product. The physical properties of synthesized compounds are listed in Table 1.

2.1.2 Synthesis of amic acid derivative M2-M4. [12]

In a round bottom flask, various anhydrides [phthalic anhydride, 3-nitrophthalic anhydride, and succinic anhydride] (0.0018 mol) separately were dissolved in dry acetone. Compound M1 (0.5 g, 0.0018mol) was added to the reaction mixture and stirred for 4 hours at room temperature. The solvent was evaporated and the resultant solid was purified by recrystallization from ethanol and collected as crystals. Physical properties are shown in Table 1.

2.1.3 Synthesis of imide compounds M5-M7. [12][6]

The imide compounds M5-M7 were synthesized by refluxing amic acid derivatives M2-M4 (0.01 mol) in acetic anhydride (25 mL) with anhydrous sodium acetate for 5 hours. Specifically, amic acid derivatives M2-M4 were individually dissolved in acetic anhydride in the presence of anhydrous sodium acetate and heated under reflux for 5 hrs. under continuous stirring producing the corresponding cyclic imides in a round flask before pouring into excess of iced water. The precipitated compound was filtered, and washed with cold water and diethyl ether and recrystallized by ethanol to produce brown crystals.

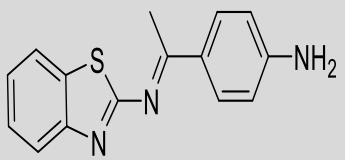
2.1.3 Synthesis of compounds M8-M10. [12-15]

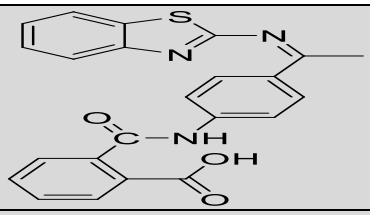
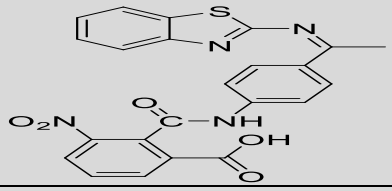
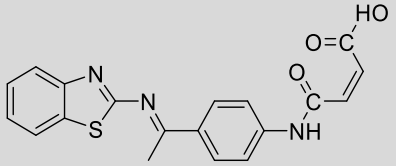
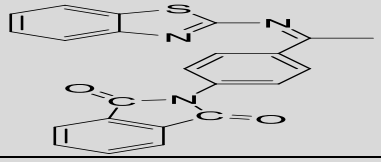
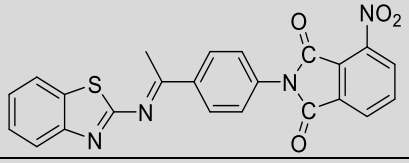
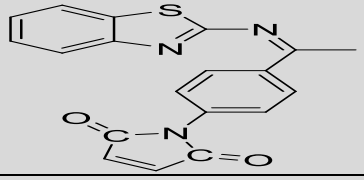
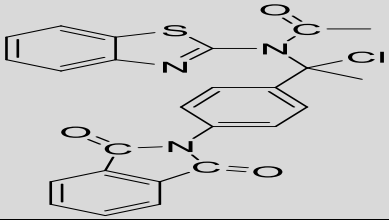
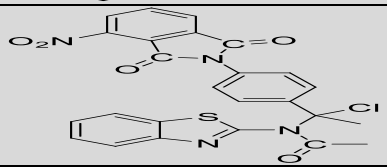
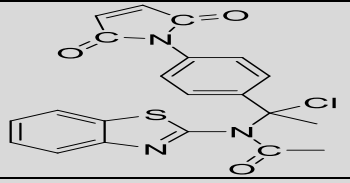
Schiff bases compounds (M5-M7) (0.01 mol) were dissolved in dry benzene (15 mL), then equimolar amounts of acetyl chloride were added dropwise to the solution in an ice water bath and the reaction mixture was allowed to stir at room temperature for a period of one hour, after the solution was refluxed for 5 hours. The solvent was evaporated, and the residue was washed with water multiple times before being washed from petroleum ether. The physical properties are listed in the table 1.

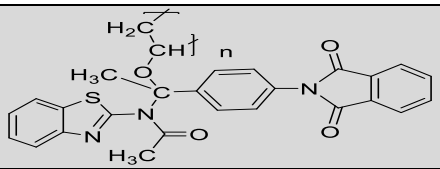
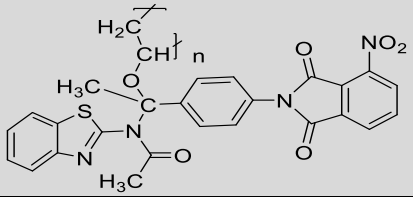
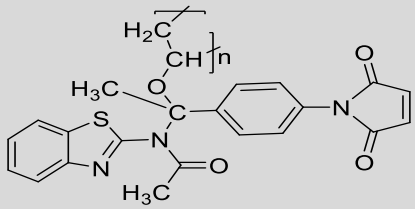
2.1.3 Synthesis of compounds M11-M13. [15]

PVA derivatives M11-M13 were synthesized by dissolving PVA (0.01 mmol) in (25 mL) DMSO. A few drops of triethyl amine were added to the solution and stirred for (10 min) before adding the compounds (M8-M10) (0.01 mmol) and reflux for 18 hours. The solvent was then evaporated and washed with acetone.

Table 1: Some of the physical properties of the synthesized compounds **M1- M13**

No.	Compound structure	Molecular formula and Molecular weight (g\mol)	m.p.(°C)	Colour	Yield (%)
M1		$C_{15}H_{13}N_3S$, 267.35	142-144	off white	93
M2		$C_{23}H_{17}N_3O_3S$ 415.47	173-175	light brown	85

					
M3		$C_{23}H_{16}N_4O_5S$ 460.46	106-108	light brown	87
M4		$C_{19}H_{15}N_3O_3S$ 365.08	157-159	reddish brown	81
M5		$C_{23}H_{15}N_3O_2S$ 397.45	250 dec	gray	83
M6		$C_{23}H_{14}N_4O_4S$ 442.45	300 dec	gray	85
M7		$C_{19}H_{13}N_3O_2S$ 347.39	218-220	gray	78
M8		$C_{25}H_{18}ClN_3O_3S$ 475.95	200-202	brown	68
M9		$C_{25}H_{17}ClN_4O_5S$ 520.94	157-159	brown	70
M10		$C_{21}H_{16}ClN_3O_3S$ 425.89	183-185	brown	64

M11		$C_{29}H_{27}N_3O_4S$ 513.61	Rubbery	brown	93
M12		$C_{29}H_{26}N_4O_6S$ 558.61	Rubbery	brown	90
M13		$C_{25}H_{25}N_3O_4S$ 463.55	Rubbery	brown	88

2.2 Cytotoxic Effect of Compound M12

The impact of M12 on the HepG2 cell line was evaluated using in vitro experimental methods.

2.2. 1 Cell Line Maintenance [17]

A layer of cells is created in a vessel, following these steps:

1. The medium was removed and wash the cell sheet with PBS.
2. 2-3 ml of Trypsin/versne was added solution to the cells and gently rock the vessel to ensure that the entire cell layer is covered.
3. The vessel was incubated at 37°C for 1 to 2 minutes to help detach the cells from the surface.
4. Fresh complete medium RPMI medium (15-20ml) to disperse the cells into the growth medium using pipetting.
5. Culture cells based on required concentration and incubate in a 5% CO_2 incubator at 37°C.
6. The concentration of cell was determined by counting the cells using a hemocytometer. The formula used for the total cell count per ml is cell count × dilution factor × $10^{\wedge 4}$.

2.2.2 MTT Assay

This study aimed to evaluate the cytotoxic effect of various concentrations (25, 50, 100, 200, and 400 µg/mL) of green synthetic nanoparticles loaded on S. officinalis. For this purpose, MTT kit includes 10 vils of 1ml and 2 bottles of 50ml of solubilization solution was used.

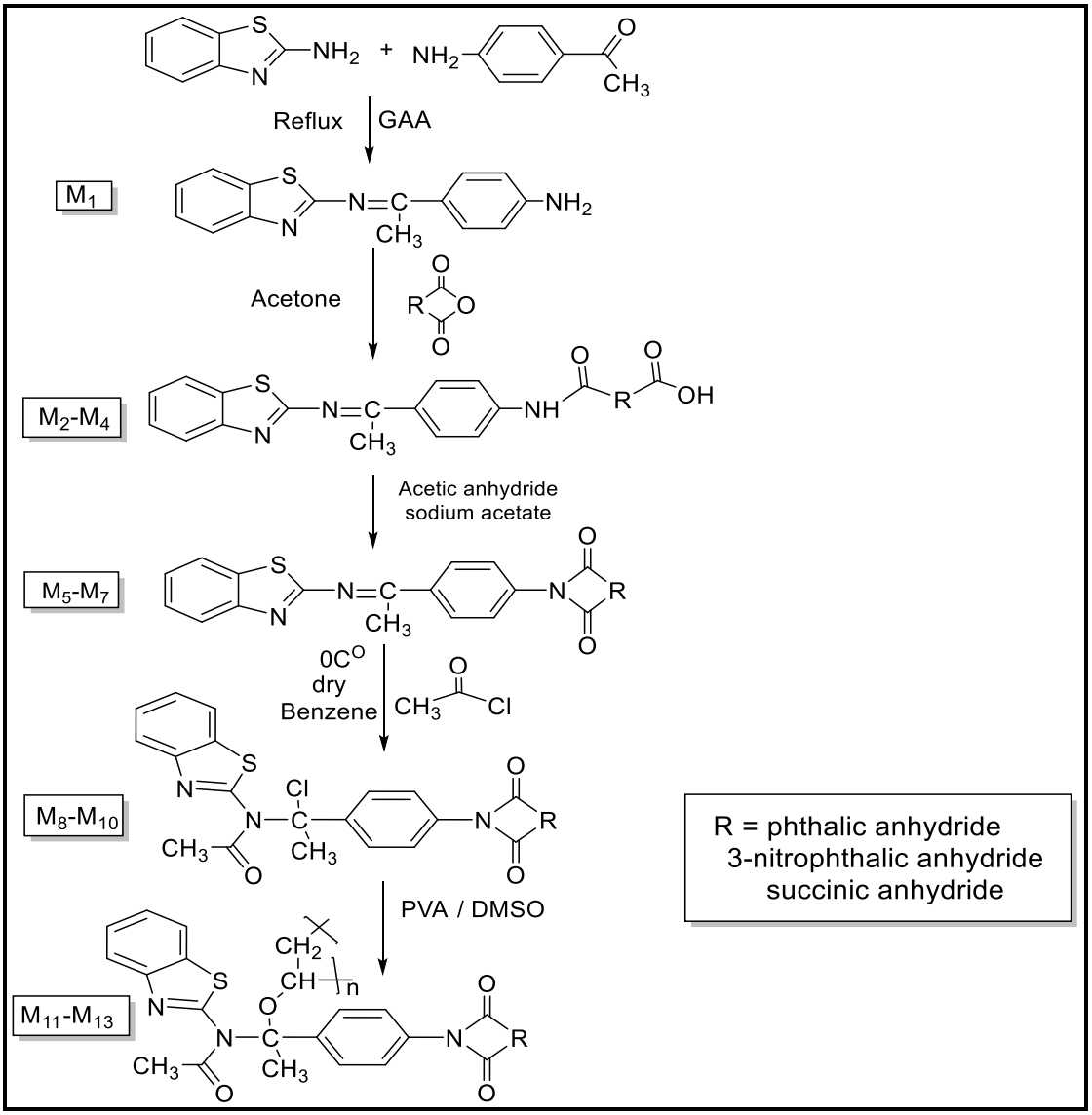
2.2.2.1 Assay [17]

In 96-well flat-bottom microtiter plates, cancer cells were cultured in complete culture medium (200µL per well) at concentrations ranging from 1x10^4 to 1x10^6 cells/mL. The microplate was then sealed with sterilized parafilm and gently agitated. After the plates were incubated for 24 hrs at 37°C and 5% CO_2. After diluted concentrations ranging from 25 to 400µg/mL were added to the wells including compound M12. Each concentration, including cells treated with serum-free medium (controls) were Triplicated. Then cells were incubated for 24hrs at 37°C and 5% CO_2. Further incubation for 4hrs at 37°C and 5% CO_2 after adding solution to each well of 10µL of MTT.

After the incubation, the media was removed, and 100 µL of dissolution solution was added to each well. The plates were then left for 5 min. Finally, an ELISA reader was used to measure the optical density at a wavelength of 575nm. The cell viability reduction concentration for each cell line was determined by analyzing the data statistically to determine the concentration of compound required for a 50% reduction.

3. Results and discussion

3.1 Synthesis of compounds M1-M13



Scheme 1: Synthesis of compounds **M1- M13**

Compound [M1], a thiazol derivative, was synthesized by reacting 2 aminobenzothiazole with 4-amino acetophenone in glacial acetic acid as catalysts. In the next step, compound [M1] was reacted with various cyclic anhydrides to produce amic acid compounds [M2-M4]. The FTIR spectroscopy data for compound M1 showed peaks at 3396 and 3334 cm^{-1} belonging to the NH_2 group and extending to the imine group of Schiff base (C=N) located at 1645 cm^{-1}. After the reaction of M1 with different anhydrides, the NH_2 band disappeared and new peaks appeared attributed to the C=O of the carboxyl group in the region 1714-1720 cm^{-}

[1] and the amide group in the region 1640-1660 cm^{-1} for amic acid compounds [M2-M4]. The hydroxyl group OH for amic acid derivatives appeared in the region 2400-3400 cm^{-1}.
The ^{1}H NMR spectrum analysis of [M1] showed individual signals at (1.89) ppm for (s, 3H, CH_3-C=N) of Schiff bases, (5.98) ppm for (s, 2H, Ar-NH_2), and 6.53-7.66 ppm for (m, 8H, Ar-H). The ^{13}C NMR spectrum showed signals at 154.08 ppm for the imine bond (C=N) of Schiff bases.
Analysis of the ^{1}H NMR spectrum of [M2, M3] showed distinct signals at 10.68, 12.20 ppm due to (s, 1H, -COOH-) and 10.28, 10.33 ppm belonging to (-CO-NH-) of amic acid, respectively. The ^{13}C NMR for compounds M2 and M3 of amic acid spectra showed signals at 191.9, 195.4 ppm due to (-COOH-) and 183.7, 174.1 ppm due to (N-C=O) as shown in Table 6.

Table 2: Shows the FTIR spectral data (ν, cm^{-1}) for **(M1-M4).**

Comp. No.	O-H amic acid	C-H arom.	C-H aliph.	C=O acid	C=O amide	C=N imine	C=N thiazol	C=C arom.	Other bands
M1		3078	2999, 2912			1645	1589	1564, 1442	3396,3334 NH_2
M2	3400-2400	3051	2980	1714	1660	1660 Overlap	1583	1554, 1465	3226 NH amide
M3	3200-2500	3076	2987, 2977	1720	1635 Overlap	1635	1598	1585 1465	3172 NH amide 1529,1348 NO_2asym, sym
M4	3438-2400	3062	2968, 2939	1714	1641	1641 Overlap	1589	1529, 1454	3328 NH amide

Cyclic imides derivatives were synthesized by a dehydrated reaction of the prepared amic acid [M2-M4] with acetic anhydride and sodium acetate to produce the corresponding cyclic imides [M5-M7]. FT-IR results confirm the formation of the desired compounds through the band appearance of the two carbonyl groups C=O in the range (1677-1743) cm^{-1} for the imide compounds, and the disappearance of the peaks of the carbonyl bond for the carboxylic acid (C=O) and the peak of the hydroxyl group OH for the amic acid compounds.
Analysis of the ^{1}HNMR spectrum of [M7] showed distinct signal at 4.11 ppm due to (t, 4H, CO-CH_2-CH_2-CO). The 1H NMR spectrum revealed the presence of several signals in the range of 6.95-8.95 ppm, corresponding to the aromatic protons of the HC=CH group. The ^{13}CNMR for imid compound of [M7] spectra showed signals at149.07 ppm for the imine bond (C=N) of Schiff bases, and 154.04 ppm due to carbonyl band (CO-CH_2-CH_2-CO) as shown in Table 6.

Table 3: Shows the FTIR spectral data (ν, cm^{-1}) for **(M5-M7).**

Comp. No.	C-H Arom.	C-H Aliph.	C=O Imide	C=N Imine	C=N thiazol	C=C Arom.	Other bands
M5	3124, 3055	2966, 2925	1695, 1677	1639	1598	1548, 1442	
M6	3107, 3058	2958, 2937	1743, 1697	1630 Overlap	1593	1544, 1454	1504,1348 NO_2asym, sym
M7	3143, 3062	2966, 2933	1697 Overlap	1637	1598	1550, 1448	

The compounds [M6-M7] were reacted with acetyl chloride to produce the corresponding acetamide derivatives compounds [M8-M10]. The FTIR results showed the presence of an acetamide group band in the region 1724-1727cm^{-1} with the disappearance of the imine group of Schiff base (C=N). The ^{1}HNMR spectra of compound M8 displayed a signal at 3.32 ppm, attributable to the CH_3 group in (-N-CO-CH_3) acetamide compound. Acetamide derivatives [M8-M10] were introduced by reacting with polyvinyl alcohol to produce modified polyvinyl alcohol [M11-M13]. The FTIR spectroscopic data for these compounds showed new bands at 1037-1076 cm^{-1} for the new ether group formed. The ^{1}HNMR spectra of compound M11 displayed a signal at 2.10 ppm, attributable to the (CH_2-) group and a signal at 2.24 ppm, corresponding to the (CH-) group in PVA.

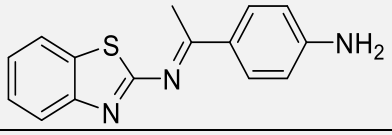
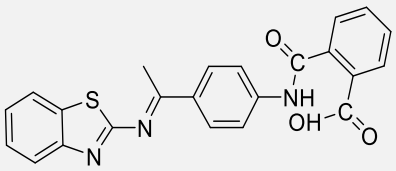
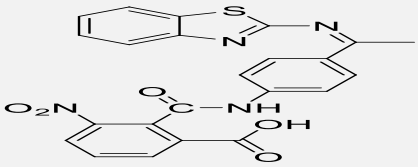
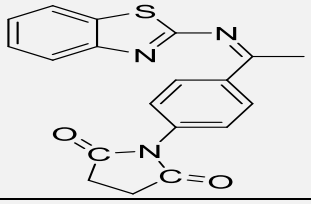
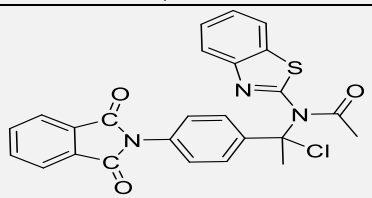
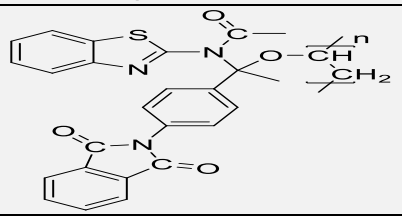
Table 4: Shows the FTIR spectral data (ν, cm^{-1}) for **(M8-M10).**

Comp. No.	C-H Arom.	C-H Aliph.	C=O Amide	C=O Imide	C=N thiazol	C=C Arom.	Other bands
M8	3120 3050	2964, 2933	1724	1693, 1676	1598 Overlap	1546, 1463	
M9	3178, 3062	2958, 2925	1727 Overlap	1697 1704	1602	1546, 1450	1530,1367 NO_2asym, sym
M10	3176, 3022	2975, 2889	1724	1693 Overlap	1589	1560, 1469	

Table 5: Shows the FTIR spectral data (ν, cm^{-1}) for **(M11-M13).**

Comp. No.	C-H Arom.	C-H Aliph.	C=O Amide	C=O Imide	C=N thiazol	C=C Arom.	C-O-C Ether	Other bands
M11	3118, 3085	2966, 2860	1720	1695	1602	1544, 1450	1076	
M12	3191, 3055	2952, 2925	1718	1697	Overlap	1542, 1452	1037	1530, 1382 NO_2asym, sym
M13	3191, 3074	2977, 2854	1722	1697	604	1546, 1444	1049	

Table 6: shows NMR spectral data (δ, ppm)

Comp. No.	Structure	^{1}H NMR spectral data (δ ppm)	^{13}C NMR spectral data (δ ppm)
M1		1.89 (s, 3H, CH_3-C=N), 5.98 (s, 2H, Ar-NH_2), 6.53-7.66 (m, 8H, Ar-H)	26.3 (CH_3-C=N), 131.32-112.09 (13C, Ar-C), 154.08(C=N_{imin}), 166.9 (C=$N_{thiazol}$).
M2		2.03 (s, 3H, CH_3-C=N), 6.94-7.95 (m, 12H, Ar-H), 10.28 (s, 1H, -CO-NH-), 10.68 (s, 1H, -COOH-)	26.3 (CH_3-C=N), 156-112.1(19C, Ar-C), 166.9 (C=N_{imin}), 169.14(C=$N_{thiazol}$), 183.7(N-C=O), 191.9 (-COOH)
M3		2.35 (s, 3H, CH_3-C=N), 6.02-7.65 (m, 11H, Ar-H), 10.33 (s, 1H, -CO-NH-) , 12.20 (s, 1H, -COOH-)	28.9 (CH_3-C=N), 154.07 - 112.9 (19C, Ar-C), 166.9 (C=N_{imin}), 174.1 (N-C=O), 195.4 (-COOH).
M7		2.13 (s, 3H, CH_3-C=N), 4.11 (t, 4H, CO-C$\underline{H}_2$-C$\underline{H}_2$-CO), 6.95-8.95(m, 8H, Ar-H).	30.08 (CH_3 C=N), 56.25, 60.57 (CO-$\underline{C}H_2\underline{C}H_2$-CO), 114.38- 139.93(13C, Ar-C),140.25(C=$N_{thiazol}$), 149.07 (C=N_{imin}), 154.04 ($\underline{C}$O-CH_2-CH_2-$\underline{C}$O),
M8		2.45 (s, 3H, CH_3-C-Cl), 3.32 (s, 3H, -N-CO-CH_3), 6.76-8.08(m, 12H, Ar-H).	
M11		1.23 (s, 3H, CH_3-C-N), 2.10 (s, 2H, C$\underline{H}_2$-CH_{poly}), 2.24 (s, 1H, CH_2-C$\underline{H}_{poly}$), 3.32 (s, 3H, CH3-C=O), 6.53-8.35 (m, 12H, Ar-H).	

3.2. Anticancer cell line [18][19]

The aim of this study is to develop a new compound that can effectively treat liver cancer. The study investigated the impact of compound M12 on human hepatocellular carcinoma (HepG2) cells through experimental analysis. After 24 hours of incubation, sample M12 was analyzed for its cytotoxic effects on both hepG2 and normal cells, and the results are presented in Table 7. These findings indicated that compound M12 is more effective against hepG2 liver cancer cells. The evaluated cytotoxic effect of M12 on hepG2 hepatocellular carcinoma cell lines using the MTT assay. An assay was conducted to determine cell viability and cancer cell line inhibition rate using varying compound concentrations (25-400 µg/mL), as shown in Table 7. The results indicated that as the concentration of compound M12 increased, cell viability decreased. The highest viability of hepG2 cells was observed at 25 µg/mL (95.60 ± 0.75), while the maximum decrease in compound M12 in hepG2 cell viability (%) was at 400 µg/mL (41.82 ± 3.30). The synthetic compound exhibited highly cytotoxic activity, with an IC_{50} value of 132.5 µg/mL. on the normal HdFn cell line (Figure 1).

Table 7: displays the cytotoxicity effects of compound M12 on HepG2 and HdFn cells after (24 hrs.) of incubation at 37°C.

Conc. (µg/mL)	HdFn mean ± S.D	hepG2 mean ± S.D
400	66.7 ± 4.05	41.82 ± 3.30
200	72.87 ± 2.60	51.65 ± 2.98
100	86.80 ± 1.47	63.15 ± 4.29
50	95.33 ± 1.98	82.06 ± 8.99
25	95.79 ± 2.68	95.60 ± 0.75

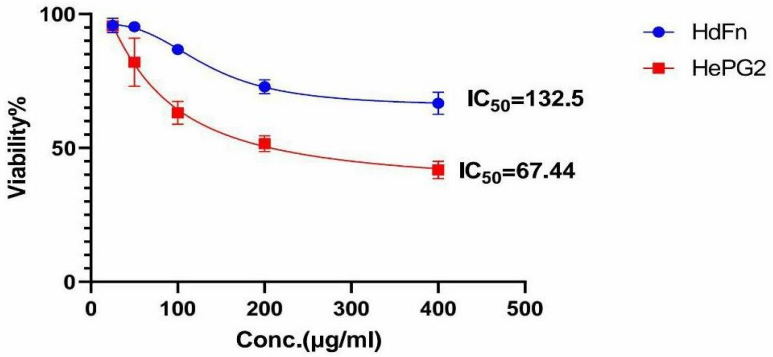


Figure 1: The cytotoxicity effect of compound M12 on HepG2 and HdFn cells measured after a 24-hour incubation at 37°C.

Conclusion

In this study, the alterations in various physical characteristics of the synthesized compounds were thoroughly examined. Additionally, the anticancer potential of the modified polyvinyl alcohol derivative, M12, was systematically evaluated. The obtained compounds were characterized by FT-IR, ^{1}H-NMR, and ^{13}C-NMR spectroscopy for some of them. Polyvinyl alcohol was developed by introducing benzothiazole group and cyclic imide groups into the backbone. The anticancer activities of the modified polyvinyl alcohol M12 was investigated towards Liver cancer Cell line hepG2. The results revealed that Compound M12 has demonstrated good anticancer activity. These promising results may lead to the development of new compounds with good efficacy against Liver cancer Cell line hepG2.

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