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SPECIAL ISSUE ARTICLE

Synthesis and Characterization of Novel Derivatives of Imides 1,2,4-triazole Polymers via Microwave and Study Biological Activities

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ABSTRACT

New derivatives of imides 1,2,4-triazole polymers as pharmaceutical compounds were prepared from the synthesis of amic acid compounds (1A-E) by reacted of benzocaine with different cyclic anhydrides. Then cyclic imide compounds (2A-E), which prepared from converted amic acid compounds by using acetic anhydrate $(CH_3CO)_2O$ and anhydrous sodium acetate CH_3COONa as a water drawer agent. Compounds (2A-E) were react with nucleophilic addition of hydrazine hydrate to ester cyclic imide compound to produce acid hydrazide cyclic imide compounds. Thereafter, cyclization of compounds (4A-E) and (5A-E) were prepared from react of acid hydrazide cyclic imide compounds with poly acryl amide via microwave to give imides 1,2,4-triazole polymers (4A-E) and in other path acid hydrazide cyclic imide react with poly acrylonitrile via microwave to give imides 1,2,4-triazole polymers (5A-E). All prepared compounds were characterization by physical properties such as melting point, softening point and analytic technique like FT-IR, ^{1}H-NMR for some of them, the compounds were tested anticancer and antibacterial applications were studied.

Keywords: Microwave, Triazole, Polymers, Anticancer, Antibacterial

1. Introduction

Triazoles are the major type of non-exogenous Caritas that are found in a wide range of patients. Carbocyclic triazoles, also known as pyridazoles, are a type of non-expanding organic cyclic compounds, which consist of a bi-unsaturated ring structure composed of 2 nickel atoms and 3 nickel atoms in non-adjacent positions. 1H-1,2,4-triazole and 1H-1,2,3-triazole are two isomers of triazoles [1, 2].

1,2,4-triazole derivatives are known to possess a wide range of biological activities including antifungal [3], anti-inflammatory [4] antiviral [5], antitumor [6], antimicrobial [7] and insecticidal [8] properties. A few 1,2,4-triazole derivatives have also been widely used in medicine and agriculture. For example, fluconazole and bromoconazole have been used as commercial antifungals for several years [9], while anastrozole has recently been improved as anticancer drugs and furozole has also been used for the same disease [10]. Therefore, as part of our research work on the development of novel biologically active nitrogen atoms including heterocyclic rings, we are very interested in the synthesis and efficient design of 1,2,4-triazole moiety with imide rings, which are probable to offer several interesting features due to the coexistence of two types of drugs [11].

1,2,4-Triazole compounds are pharmaceutical compounds used in medical applications over the past few decades, and the pharmaceutical and biological properties of 1,2,4-triazole compounds have been determined due to the great interest in their synthesis and characterization [12]. 1,2,4-triazole derivatives and 1,2,4-triazole compounds have many pharmaceutical and biological activities on a wide range, as shown in Fig. 1.

Imides, especially maleimides, are very good substrates in chemical, biological and pharmaceutical

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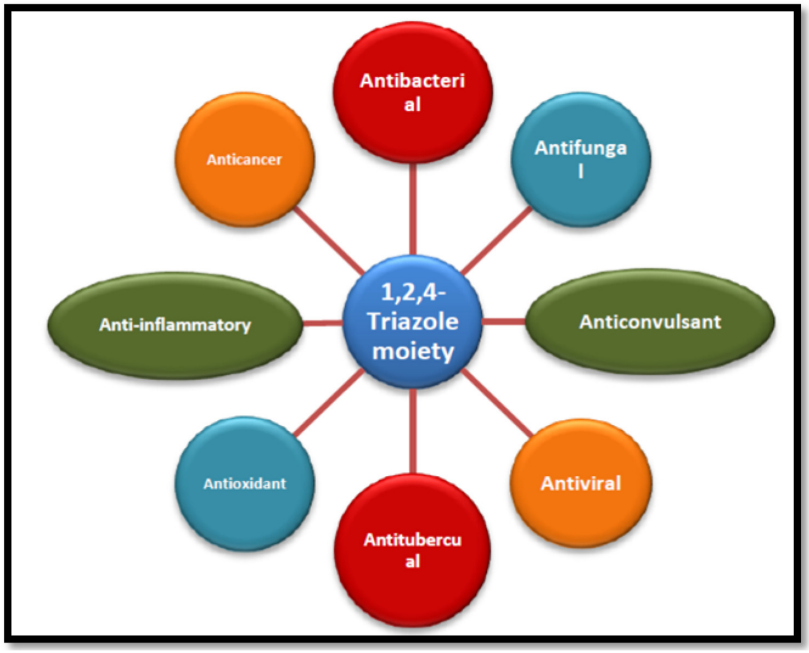


Fig. 1. Pharmacological activities of triazole moiety [13].

application's. It is worked in biological applications as immunoassays, as protein for structure chemical probes [14, 15] for cancer therapy, and also used for synthetic applications for antibody production as solid-supported enzymes [16]. They are used as analogues of photoactivatable fluorescein derivatives [17], or the good antioxidant activity [18], or the cyclic tetrapeptide chlamydocine [19], or as insecticides and herbicides [20] in pharmaceutical applications. The N-(3,5-dichlorophenyl)maleimide to furan ring has fungicidal properties [21].

2. Experimental

2.1. Material

All chemicals with purity and chemical formal were used in this project work were taken from Fluka and Sigma Aldrich and utilized without extra purification unless otherwise stated.

FT-IR spectra were measured on (Shimadzu FT-IR-8400 spectrophotometer) by using KBr disc.

^{1}H-NMR spectra were measured by Bruker, Germany NMR spectrometer (400 MHZ) Avance (400). In this measured using DMSO-d_6 as solvents and tetra methyl silane as internal standard.

Melting points and softening points (S.P.) were measured by Gallen Kamp capillary melting point and slid softening points apparatus.

The biological activates of anticancer activity has been measured and these measurements were carried out at RPMI-1640 and antibacterial at (University of Baghdad college of science).

2.2. Methods

2.2.1. Synthesis of different N-(p-ethyl benzoate) amic acid compounds (1A-E) [22]

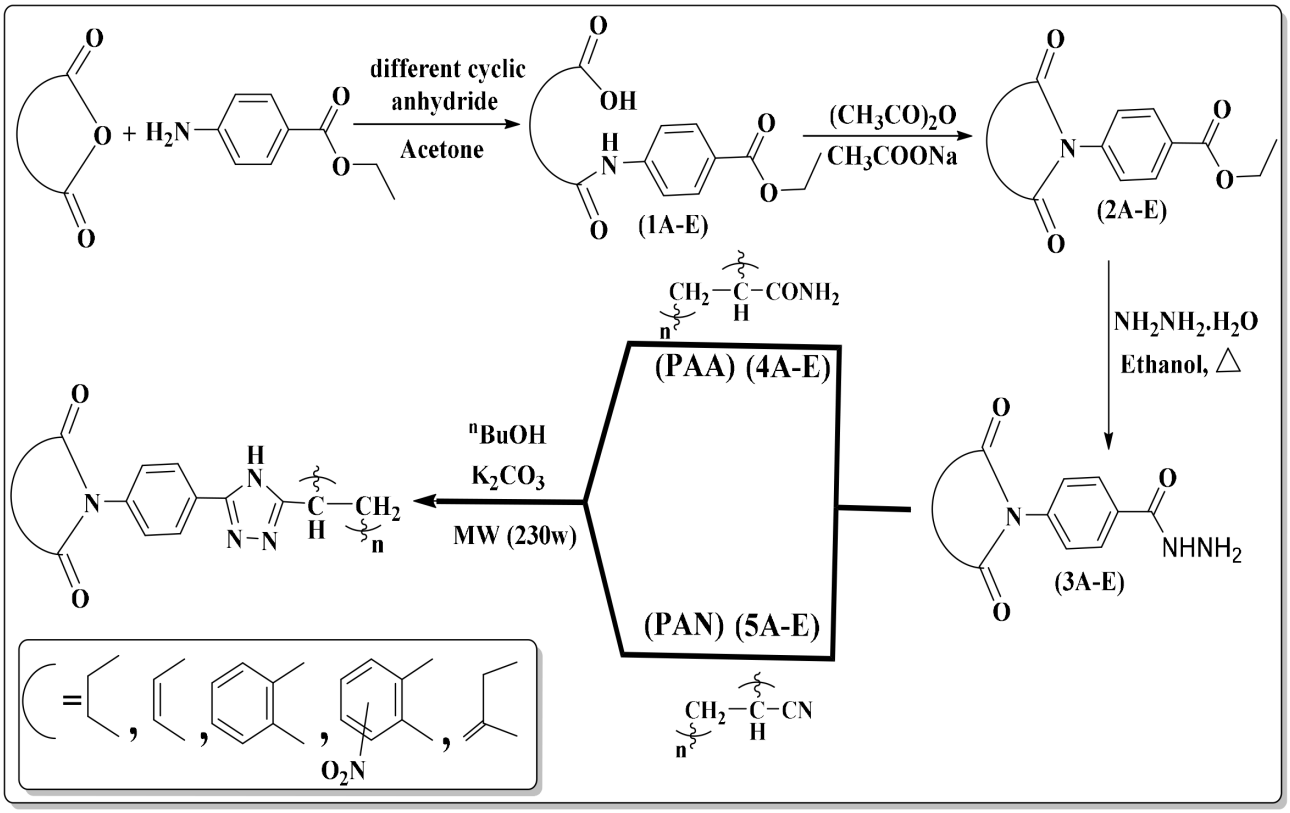
In 100 ml conical flask was placed a mixture of different anhydrides (0.98 gm, 0.01 mole) and ethyl *p*-aminobenzoate (benzocaine) (1.65 gm, 0.01 mole) with stirring and dissolved in (40 ml) of acetone for three-four hrs. the solid result obtained was filtered, used acetone for wishing precipitate, dried and ethanol used for pure it by recrystallization.

2.2.2. Synthesis of different N-(4-ethyl benzoate) imide compounds (2A-E) [23]

A mixture of different *N*-(4-ethyl benzoate) amic acid compounds (1A-E) (0.01 mole) dissolved in acetic anhydride (10 ml) and sodium acetate (0.2 g) was refluxed for 3 hrs. When the reaction was completed, the solution was put on ice water with vigorously stirred. The solid yield product was filtered, washed with bicarbonate solution then by cold water many times, dried and recrystallized from ethanol solvent.

2.2.3. Synthesis of different derivate imide compounds (3A-E) [24]

In 100 ml round bottom flask was placed a mixture of compound (2A-E) (0.02 mole), hydrazine hydrate



Scheme 1. The chemical steps for synthesis polymers (4A-E) and (5A-E).

(80%) (30 ml, 0.06 mole) and ethanol (10 ml), was refluxed for 6–8 hrs. after that the product mixture solute was concentrated by evaporation of ethanol, keep it for cooled and put into grindery ice. The solid was filtered, washed the precipitate with ice water, recrystallization from ethanol: dioxane (1:1).

2.2.4. Synthesis of new imides 1,2,4-triazole polymers (4A-E) [25]

In a round-bottomed flask (100 ml) replaced the polyacrylamide (0.03 mol) with K_2CO_3 (0.5 mmol) and different hydrazide compounds 3A-E (1 mmol) in nBuOH (2 mL) under M.W irradiation at temperature controlled at 150 °C and normal absorption. When the reaction mixture was colded, added methanol and the precipitate was obtained. After that the yield purified by dissolving in DMF and re-precipitating by H_2O.

2.2.5. Synthesis of new imides 1,2,4-triazole polymers (5A-E) [25]

In a round-bottomed flask (100 ml) put the poly acrylonitrile (0.03 mol) with K_2CO_3 (0.5 mmol) and different hydrazide compounds 3A-E (1 mmol) in nBuOH (2 mL) under M.W irradiation at temperature controlled at 150 °C and normal absorption. When the reaction was colded, added methanol and the precipitate was obtained, added methanol and the precipitate was obtained. After that the yield was purified by dissolving in DMF and re-precipitating by H_2O.

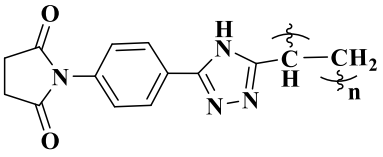
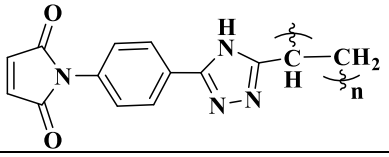
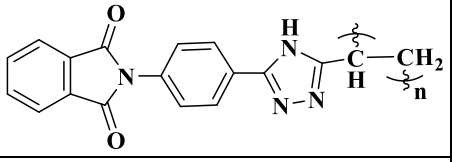
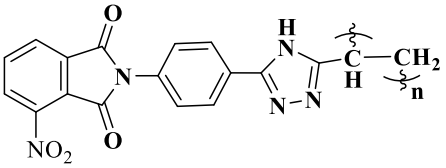
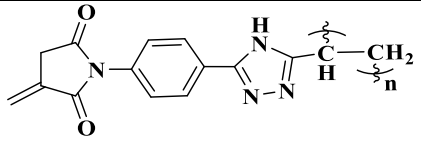
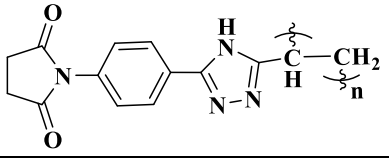
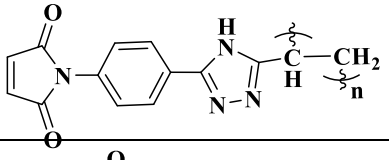
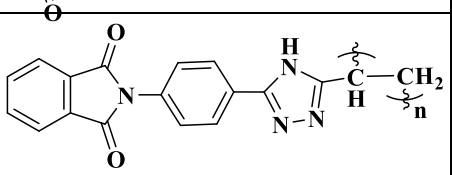
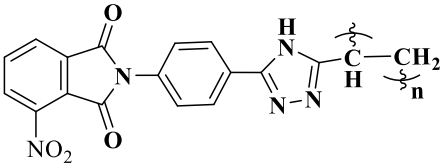
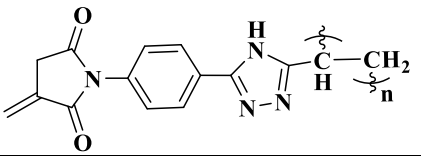
2.2.6. Antibacterial activity study

2.2.6.1. Antibacterial activity study. The antibacterial activity of the synthesized polymers were studied by (beaker plate technique) against two types of microorganisms (*E. coli* and *S. aureus*) [26]. Using DMSO solvent to dissolve the polymers and using a nutrient agar medium. Sample volume and sample solution for all the studied polymers were re-labeled (0.1 ml). The Petri dishes were incubated in a sterile beaker on an incubator. The research was completed in the beakers, (0.1 ml) of the polymer solution was added into small bores in the agar, then the Petri dishes were incubated for testing at (37 °C) for (24 h). Inhibition zones of the polymers solution were measured in mm, the diameter of the solvent (DMSO) was determined in the same way [16].

2.2.7. Anticancer activity study

2.2.7.1. Preparation of cell cultures. For the purpose of conducting tests for anti-cancer activaty, it was provided with cells from the Iraqi Cell Bank Unit for maintained and Biotechnology with (100 units/ml

Table 1. Physical properties of the synthesis polymers (4A-E) and (5A-E).

Comp No.	Compound Structure	Chemical Formula	s. p. °C	Color	Yield %
4a		$C_{14}H_{12}N_4O_2$	91-101	Pale yellow	88
4b		$C_{14}H_{10}N_4O_2$	120-130	Yellow	93
4c		$C_{18}H_{12}N_4O_2$	155-165	Yellow	92
4d		$C_{18}H_{11}N_5O_4$	105-115	Orange	90
4e		$C_{15}H_{12}N_4O_2$	85-95	Yellow	91
5a		$C_{14}H_{12}N_4O_2$	91-101	Pale yellow	71
5b		$C_{14}H_{10}N_4O_2$	120-130	Yellow	76
5c		$C_{18}H_{12}N_4O_2$	155-165	Yellow	73
5d		$C_{18}H_{11}N_5O_4$	105-115	Orange	75
5e		$C_{15}H_{12}N_4O_2$	85-95	Yellow	80

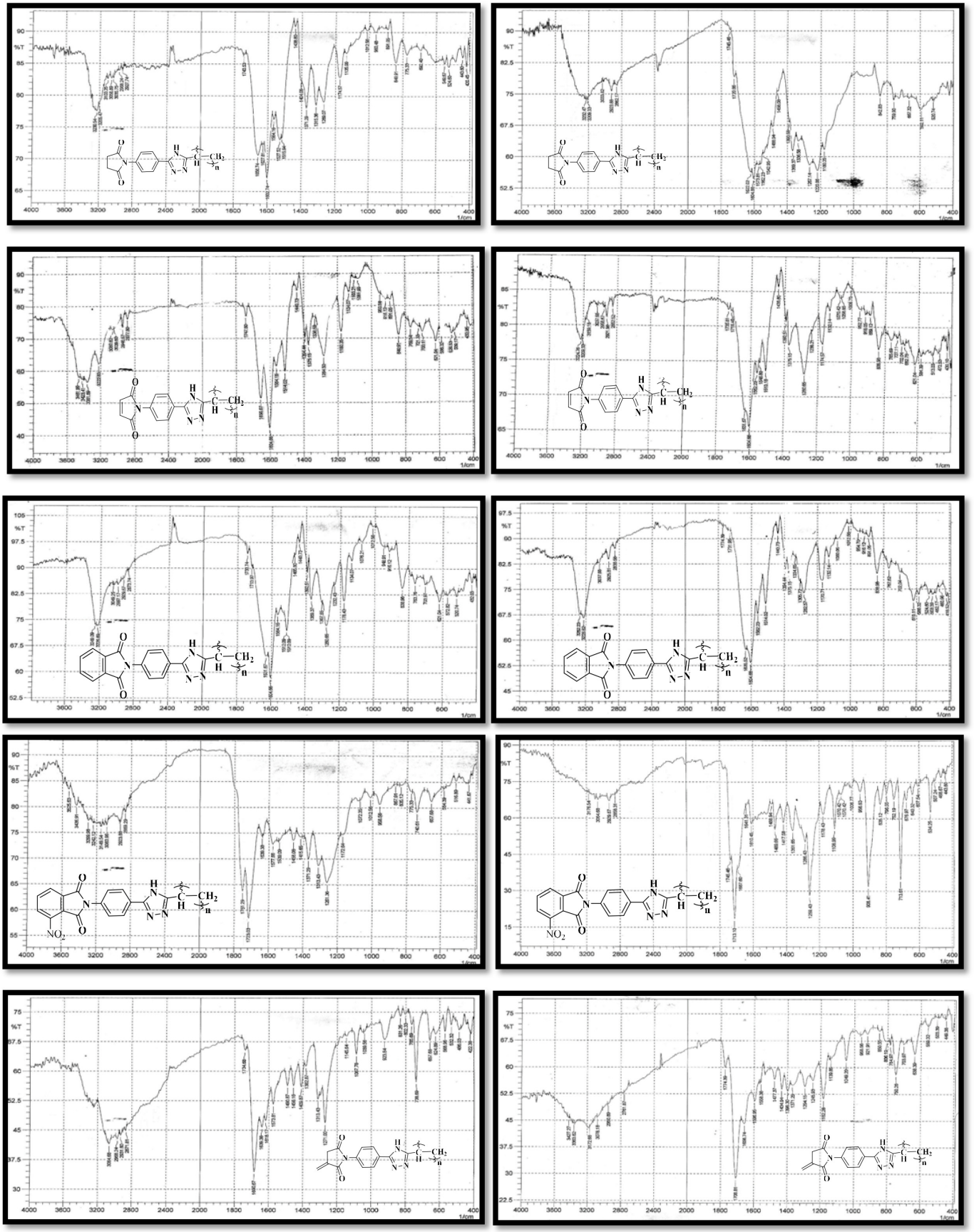


Fig. 2. FT-IR spectrum of compounds [4A, 4B, 4C, 4D, 4E, 5A, 5B, 5C, 5D and 5E].

penicillin), (100 μg/ml streptomycin) and (10% Fetal bovine) in RPMI-1640 supplemented. After that the Cells were passaged within (50% Trypsin-EDTA) reconstituted two time a week and incubated at 37°C [27].

The toxic effect to determine of the prepared compounds (x-), Using 96-well plates, cell viability assay was performed. Cell lines were cultivated at 1 × 104 cells/well. After that waiting for 24 h at 37 °C, the polymers stock solutions of (4B, 4C, 5B, and 5C) were diluted and prepared to the required concentrations (100 μM, 50 μM, 25 μM, 12.5 μM and 6.125 μM) in culture medium or a flowing monolayer was obtained. At different concentrations the prepared polymers stock solutions were treated with the prepared cultured cells and tested. After 72 h of treatment cell viability was measured by removing the medium, then 28 μL of 2 mg/mL MTT solution was added and incubating the cells for 2 h and 30 min at 37 °C. After that the MTT solution was removed, and then the crystals were remaining in the wells were dissolved by adding 130 μl of dimethyl sulfoxide (DMSO) followed by incubation at 37 °C for 15 min with shaking [28]. The absorbency was determined on a microplate reader at 492 nm, the assay was performed in triplicate. The absorbance was determined on a microplate reader at 492 nm, and the assay was achieved in triplicate. The cell growth inhibition rate (cytotoxicity ratio) was calculated as follows: -

$$\text{Cytotoxicity} = A - B/A * 100$$

Where (A) the optical density of control, and (B) the optical density of samples.

2.3. Statistical analysis

The data gotten were statistically analyzed using unpaired t-test with GraphPad Prism 6. Values are offered as mean ± SEM of triplicate measurements [29].

3. Result and discussion

Number of polymers were prepared in this work, that contain the important 1,2,4-triazole ring, which gives distinctive properties to the polymer, as this type of heterogeneous rings enters into many and varied applications. The preparation of these polymers was carried out through simple reactions starting with the use of benzocaine, which contains an amino group and an ester group, and its reaction with different cyclic anhydrides to obtain the corresponding amic acids, which in turn were introduced into a ring-closure reaction to produce the corresponding imides. Then the ester group was converted to hydrazide by reacting the compounds with hydrazine. In the final reaction, the triazole ring was prepared and linked to the polymer by using two polymers, the first being acrylamide and the second being polyacrylonitrile. In the preparation step of the triazole compound, the microwave was used in the preparation process, and it was a successful step with a good yield of product.

FTIR spectrum of the amic acids of compounds (1A-E) were showed the main absorption bands at 3485–3415 cm^{-1} due to (OH), 3373–3331 cm^{-1} belong to (NH), the aromatic (C-H) groups appear at 3015–3031 cm^{-1}, ester, carboxylic acid and amide (C=O) were appear at 1722–1721, 1688–1671 and 1622–1615 cm^{-1} respectively.

The preparation of imide compounds (2A-E) were showed the disappearance of number of bands, also appearance of new bands. Among the bands that disappeared were the carboxylic acid band, the amine band, as well as the (C=O) bands. New imide bands appeared at 1787, 1716 cm^{-1}, In addition to the presence of the ester band at 1723–1722 cm^{-1}.

Hydrazide compounds were appearing a new band for amide groups at 1625–1620 cm^{-1} and (NH) groups at 3469–3412, 3329 cm^{-1}, and disappear of ester groups.

In final step for the synthesis new polymers were showed the disappearance some bands and appearance of new bands among the bands that disappeared were the amine band, C≡N band of poly acrylonitrile, C=O band of polyacrylamide as well as the (C=O) bands of hydrazide.

^{1}H-NMR spectrum data of polymers (4A&5A) were gave the same signals ^{1}H-NMR spectrum, δ ppm in (DMSO) showed presence of methyl protons of CH_2 and CH at 1.77–1.9 and 2.78–42.88 signals respectively, proton of CH_2 in imide ring give signals at 2.95. aromatic rings protons appear at 7.31–8.11, furthermore, the important signal at 11.11 belong to proton of triazole ring.

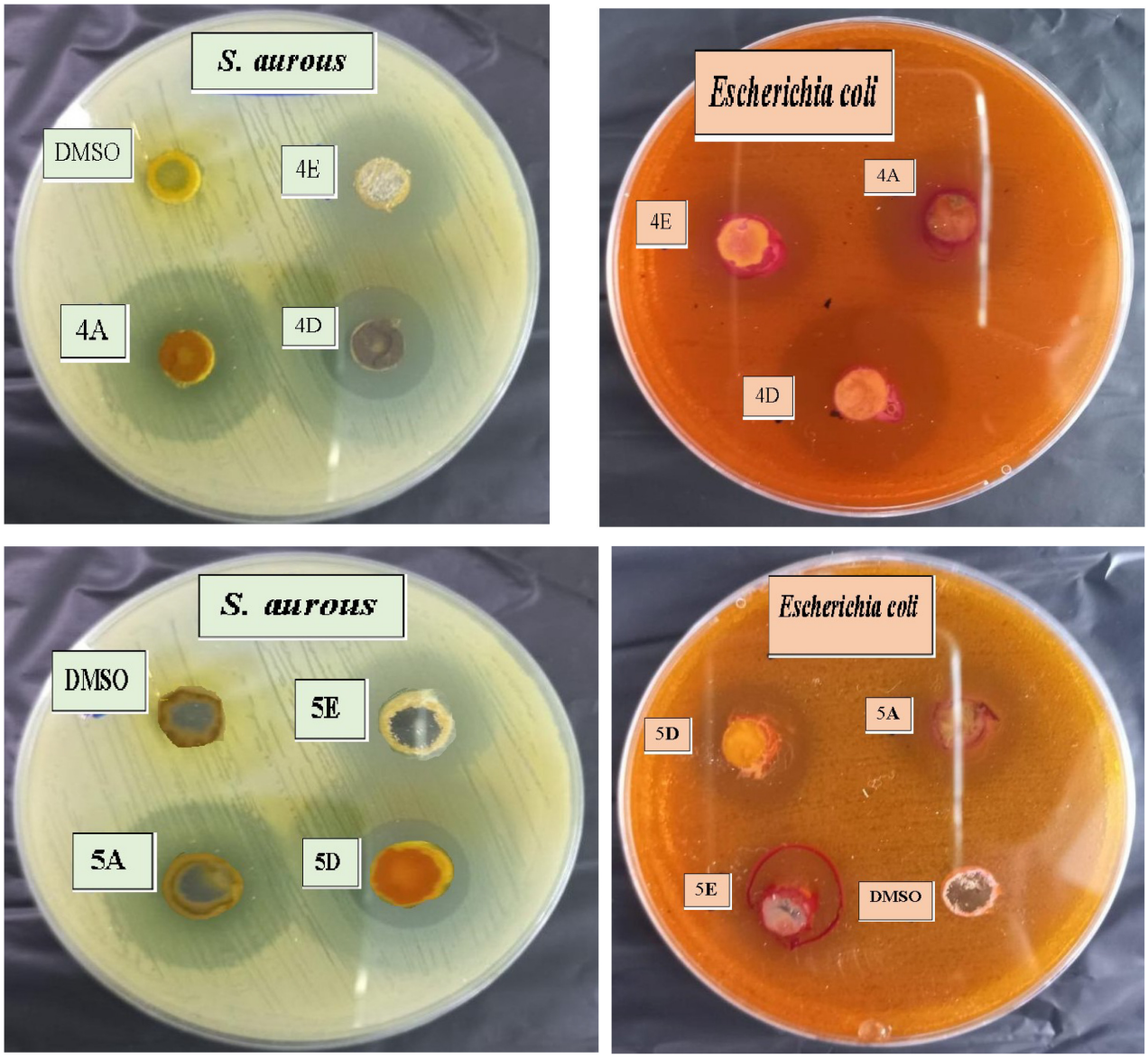
The other synthesized polymers give the same position of signals of (4A&5A) polymers, but the different in the signals in imide moieties were in (4B&5B) polymers give signals at 6.5 for the protons of maleimide rings, while in polymers (4C&5C) give other aromatic ring protons for phthaleimide, (4D&5D) polymers have also signals of protons ring at 8.86 ppm for proton belong the nitro group. The (4E&5E) polymers have new groups of protons are CH_2 citraconimide appear at 5.59 ppm.

3.1. Evaluation of antibacterial activity

in *vitro* antibacterial activity was visualized against two selected microorganisms (Gram-positive *Staphylococcus aureus* and Gram-negative *Escherichia*

Table 2. Antibacterial activities for the prepared polymers [4A, 4D, 4E, 5A, 5D and 5E].

	Inhibition zone (mm)	
Poly. No.	*Staphylococcus aurous*	*Escherichia coli*
4A	20	13
4D	24	18
4E	18	13
5A	18	12
5D	23	16
5E	16	11



coli) by titrating the inhibition zone in (mm unit) for the synthesized polymers, the results are listed in Table 2.

The results showed that their antibacterial performance was optimal against Gram-positive bacteria (*S. aureus*), but all the polymers showed moderate to very low activity against Gram-negative bacteria (*E. coli*) compared to tetracycline.

3.2. Evaluation of anticancer activity

3.2.1. Combination chemotherapy and viral cytotoxicity in vitro

To study the potential interaction of polymers [4B, 4C, 5B and 5C] with chemotherapy in vitro, a concentration-dependent method was used [30, 31]. and co-treatment of a range of concentrations of the

Table 3. Cytotoxicity assays of (MCF-7) cells for polymers [4A, 4C, 5B and 5C].

Comp. No.	IR%, (C) μg/Ml	PR%, (C) μg/Ml	Other effect cytotoxicity%, (C) μg/Ml		
4B	66.36(100)	11.13(6.125)	22.62(12.5)	37.40(25)	47.54(50)
4C	70.62(100)	10.17(6.125)	23.85(12.5)	30.23(25)	53.91(50)
5B	66.34(100)	11.14(6.125)	22.61(12.5)	37.42(25)	47.53(50)
5C	70.59(100)	10.19(6.125)	23.77(12.5)	30.21(25)	53.88(50)

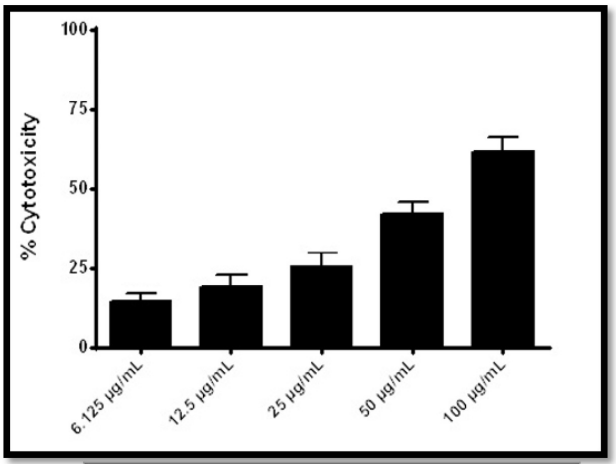


Fig. 3. Cytotoxicity effect of comp. [4C].

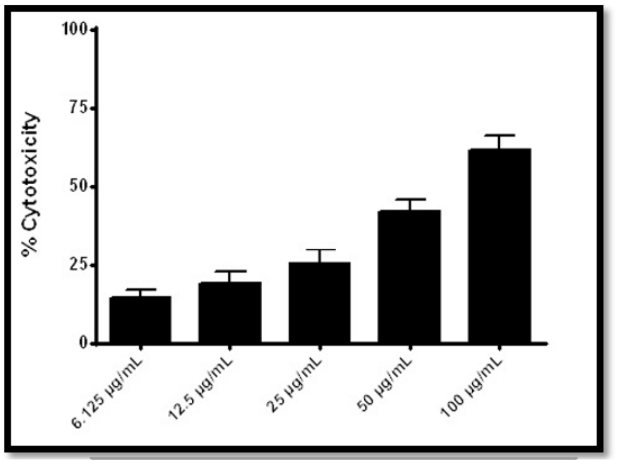


Fig. 4. Cytotoxicity effect of comp. [5C].

prepared polymers with breast cancer cells (MCF-7) was performed and different agglomeration conditions were evaluated.

Laboratory results for most doses showed an increase in cytotoxicity of the combination of cancer cells with polymers [4B, 4C, 5B and 5C]. The percentage of viable cells and their comparison with untreated cells were calculated [32].

3.2.2. Inhibition of proliferation of human breast cancer cells (MCF-7) cells by the polymers [4B, 4C, 5B and 5C]

The effect of polymers [4B, 4C, 5B and 5C] on the growth of cancer cells was compared. Human breast cancer cells (MCF-7) were treated with different polymer concentrations (6.125, 12.5, 25, 50 and 100) μg/ml sequentially of prepared polymers for 72 h. Then, the compound 3-(4, 5-dimethyltriazol2-yl)−2,5diphenyltetrazolium bromide (MTT) was used a colorimetric assay of performed [33]. This was done by treating the cells with DMSO solvent. It was found that the polymers prepared in this article have growth inhibitory activity in a manner that depended on the dose used, the concentrations used and the prepared polymer, as presented in Table 2.

(MCF-7) cells with polymer 4B breast cancer resulted in an inhibition rate (IR) at a conc. of 100 μg/ml gives 66.36% which is statistically significant at a concentration of (C = 6.125) μg/ml gives a proliferation rate (PR = 11.13%), and the cytotoxic effect (22.62%) at a conc. of 12.5 μg/ml, the cytotoxic effect (37.40%) at a concentration of 25 μg/ml and the cytotoxic effect (47.54%) at a concentration of 50 μg/ml.

(MCF-7) cells with polymer 5B breast cancer resulted in an inhibition rate (IR) at a conc. of 100 μg/ml gives 66.34% which is statistically significant at a concentration of (C = 6.125) μg/ml gives a proliferation rate (PR = 11.14%), and the cytotoxic effect (22.61%) at a conc. of 12.5 μg/ml, the cytotoxic effect (37.42%) at a concentration of 25 μg/ml and the cytotoxic effect (47.53%) at a concentration of 50 μg/ml.

The same polymer (4B&5B) were prepared in a different way and gave the same result as shown in Table 2.

(MCF-7) cells with polymer 4C breast cancer resulted in an inhibition rate (IR) at a conc. of 100 μg/ml gives 70.62%, which is statistically significant at a conc. of (C = 6.125) μg/ml gives a proliferation rate (PR = 10.17%), and the cytotoxic effect (23.85%) at a conc. of 12.5 μg/ml, the cytotoxic effect (30.23%) at a concentration of 25 μg/ml and the cytotoxic effect (53.91%) at a concentration of 50 μg/ml.

(MCF-7) cells with polymer 5C breast cancer resulted in an inhibition rate (IR) at a conc. of 100 μg/ml gives 70.59%, which is statistically significant at a conc. of (C = 6.125) μg/ml gives a proliferation rate (PR = 10.19%), and the cytotoxic

effect (23.77%) at a conc. of 12.5 μg/ml, the cytotoxic effect (30.21%) at a concentration of 25 μg/ml and the cytotoxic effect (53.88%) at a concentration of 50 μg/ml.

The same polymer (4C&5C) were prepared in a different way and gave the same result as shown in Table 2.

4. Conclusion

In this article the novel derivatives of imides 1,2,4-triazole polymers via microwave were prepared in different method to give same polymer, also that the prepared polymers give good result of biological activity applications such as anti-cancer and antibacterial to same polymers.

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