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ORGINAL ARTICLE

Use of Microwave in the Preparation of New Thiazolidines-4-one Rings and Evaluation of Biological Activity and Cancer

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KEYWORDS

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ABSTRACT: The study involved the preparation of novel thiazolidine derivatives by reacting prepared Schiff bases with thioglycolic acid in the presence of pyridine as a solvent. The reaction was carried out using the microwave, a benign, environmentally friendly, and time-saving method. The reaction progress was monitored and described by measuring the melting point and purity. The Rf values were determined by thin-layer chromatography (TLC), fourier-transform infrared spectroscopy (FT-IR), proton and carbon nuclear magnetic resonance (^{1}H and ^{13}C-NMR), and quantitative elemental analysis (C.H.N). The impact of the produced chemicals on the development of tow antibiotic-resistant bacterial isolates—both Gram-positive (*Staphylococcus epidermidis*) and Gram-negative (*Klebsiella pneumoniae*) bacteria—was used to assess their biological activity. The control sample was *ampicillin*, an antibiotic. When tested against the indicated microorganisms, the produced compounds showed good inhibitory efficacy. The capacity of a few of the produced compounds (M6, M9) to stop the development of breast cancer cells in vitro was examined.

INTRODUCTION

Heterocyclic compounds are an essential part of chemistry and life sciences. Heterocyclic compounds play vital roles in our biological systems. Heterocyclic compounds are also found in a variety of drug candidates, such as antibiotics, antitumor, anti-inflammatory, antiviral, antibacterial, antifungal, and antidiabetic agents. Thiazolidines are an essential class of heterocyclic compounds [1, 2].

Many biologically active compounds contain different heteroatoms, including oxygen, sulfur, and nitrogen [3]. On the other hand, 1,3-thiazolidin-4-one has a five-membered isomer core where position 2 is the carbonyl group, position 1 is sulfur, and position 3 is nitrogen. Thiazolidin-4-one compounds offer significant advantages. It is of great importance in pharmaceuticals and medicinal chemistry.

These chemicals have a wide range of biological activities, such as anti-HIV[4, 5], anti-tumour[6], anti-hypertensive[7], antibacterial[8], antioxidant[9], antihyperglycemic[10], antidiabetic[11], antibacterial [12]and antifungal[13], antiviral [14]and antituberculosis [15] activities.

In the field of synthetic organic chemistry, this method truly constitutes a revolution. It creates comparatively clean products and accelerates chemical processes. The Bolognese group discovered that good heterocycles of

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thiazolidine-4-one were generated by microwave heating thioglycolic acid and benzylidene aniline in benzene at 33 °C for under 10 minutes [16]. The majority of hospital-acquired infections are brought on by germs, which endanger patients' health and put a significant strain on the healthcare system. Methicillin-resistant Staphylococcus aureus (MRSA) and Escherichia coli have surfaced [17]. In conclusion, a benign and environmentally safe method, microwave, which is considered safer and less time-consuming, was used to synthesize heterocyclic compounds derived from thiazolidine by reacting the azomethene group in Schiff bases with thioglycolic acid and testing their bacterial sensitivity against two types of bacteria and their anticancer activity against breast cancer.

MATERIALS AND METHODS

Chemicals and instruments

High-purity raw materials and solvents were purchased from Sigma-Aldrich, BDH, Fluka, and Merck. The reactions were tracked by silica TLC plates with aluminum support (0.2 mm, 60 F254). A Cole Paramer MP-200D-120Stuart digital melting point spectrometer was used to measure the melting points. FT-IR spectra were measured on a SHIMADZU FTIR-8400S infrared spectrometer. The spectral data of ^{1}H-NMR and ^{13}C-NMR (300 &75 MHz) were measured on a Varian-INOVAUSA 500 MHz NMR spectrometer using DMSO-d^{6} as solvent and TMS as internal standard at the University of Tehran, Iran.

Preparation of Thiazolidines -4-one derivatives (M6-M10) [18,19]

Equal moles (0.001 mol) of the previously prepared Schiff bases were mixed with thioglycolic acid (20 ml) of pyridine. The mixture was placed in a microwave oven and heated for (3-7) minutes at a temperature of (78 C˚) and a power of (400 W). The completion of the reaction was confirmed using the TLC technique, and it was recrystallized with ethanol. As in Figure 1

2,2'-(1,4-phenylene)bis(3-(5-chloropyrimidin-2-yl)thiazolidin-4-one)

M6: red; yield: 86%; Rf: 0.65; mp = 187-189˚C; Elemental analysis $C_{20}H_{14}Cl_2N_6O_2S_2$; Calcd: C, 47.53; H, 2.79; N, 16.63; S, 12.69. Found: C, 47.41; H, 2.70; N, 16.56; S, 12.45; IR (KBr) v(cm^{-1})= 3020(Ar-CH), 2958,2931 ($CH_{ALiphatic}$), 1672 (C=O), 1614 ($C=N_{thiadiazole}$), 1512,1454 (C=C), 1244 (C-N), 740 (C-S), 649 (C-Cl) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d^{6}) δ(ppm):8.14 (s, 4H, C-H $_{Pyrmidine}$), 7.93 (s, 4H, C-H_{arom}), 6.55 (s, 2H, C-H $_{thiazolidin-4-one}$), 3.98 (s,4H,CH_2 $_{thiazolidin-4-one}$). ^{13}C-NMR (75 MHz, DMSO-d^{6}) δ(ppm):167.95($C=O_{thiazolidin-4-one}$),153.42-125.55(ArC=C),78.87($CH_{thiazolidin-4-one}$) and 22.67 (CH_2 $_{thiazolidin-4-one}$).

2,2'-(1,4-phenylene)bis(3-(5-nitropyrimidin-2-yl)thiazolidin-4-one)

M7: Brown; yield: 84%; Rf: 0.72; mp = 196-198 ˚C; Elemental analysis $C_{20}H_{14}N_8O_6S_2$; Calcd: C, 45.63; H, 2.68; N, 21.28; S, 12.18. Found: C, 45.53; H, 2.60; N, 21.19; S, 12.10; IR (KBr) v(cm^{-1})= 3035(Ar-CH), 2945,2921 ($CH_{ALiphatic}$), 1664 (C=O), 1608 ($C=N_{thiadiazole}$), 1542,1461 (C=C), 1220 (C-N), 752 (C-S), 1510,1330 (NO_2) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d^{6}) δ(ppm):8.70 (s, 4H, C-H $_{Pyrmidine}$), 7.58 (s, 4H, C-H_{arom}), 5.75 (s, 2H, C-H $_{thiazolidin-4-one}$), 3.34 (s,4H,CH_2 $_{thiazolidin-4-one}$). ^{13}C-NMR (75 MHz, DMSO-d^{6})δ(ppm):170.50($C=O_{thiazolidin-4-one}$),161.15-129.57(ArC=C),71.60($CH_{thiazolidin-4-one}$) and 32.88 (CH_2 $_{thiazolidin-4-one}$).

2,2'-(1,4-phenylene)bis(3-(5-methylpyrimidin-2-yl)thiazolidin-4-one)

M8: Yellow; yield: 90%; Rf: 0.57; mp = 204-206 ˚C; Elemental analysis $C_{22}H_{20}N_6O_2S_2$; Calcd: C, 56.88; H, 4.34; N, 18.09; S, 13.80. Found: C, 56.80; H, 4.26; N, 18.01; S, 13.67; IR (KBr) v(cm^{-1})= 3091(Ar-CH), 2923,2887 ($CH_{ALiphatic}$), 1662 (C=O), 1593 ($C=N_{thiadiazole}$), 1517,1485 (C=C), 1251 (C-N), 779 (C-S) cm^{-1} ;^{1}H NMR (300 MHz, DMSO-d^{6}) δ(ppm):8.34 (s, 4H, C-H $_{Pyrmidine}$), 7.74 (s, 4H, C-H_{arom}), 5.89 (s, 2H, C-H $_{thiazolidin-4-one}$), 3.62 (s,4H,CH_2 $_{thiazolidin-4-one}$),2.18 (s,6H,CH_3).^{13}C-NMR (75 MHz,DMSO-

d^6)δ(ppm):176.19(C=$O_{thiazolidin-4-one}$),153.20-124.54(ArC=C),79.83($CH_{thiazolidin-4-one}$), 28.42(CH_2 thiazolidin-4-one) and 22.28(CH_3).

2,2'-(1,4-phenylene)bis(3-(5-bromopyrimidin-2-yl)thiazolidin-4-one)

M9: Orange; yield: 78%; Rf: 0.62; mp = 170-172 ˚C; Elemental analysis $C_{20}H_{14}Br_2N_6O_2S_2$; Calcd: C, 40.42; H, 2.37; N, 14.14; S, 10.79. Found: C, 40.31; H, 2.34; N, 14.02; S, 10.67; IR (KBr) ν(cm^{-1})= 3056 (Ar-CH), 2975,2918 ($CH_{ALiphatic}$), 1666 (C=O), 1596 ($C=N_{thiadiazole}$), 1575,1525 (C=C), 1245 (C-N), 748 (C-S), 582 (C-Br) cm^{-1}1H NMR (300 MHz, DMSO-d^6) δ(ppm):8.57 (s, 4H, C-H $_{Pyrmidine}$), 7.30 (s, 4H, C-H_{arom}), 6.30 (s, 2H, C-H $_{thiazolidin-4-one}$), 3.08 (s,4H,CH_2 thiazolidin-4-one); ^{13}C-NMR (75 MHz,DMSO-d^6) δ(ppm):171.21(C=$O_{thiazolidin-4-one}$),152.99-125.60(ArC=C),64.83($CH_{thiazolidin-4-one}$), and 45.78(CH_2 thiazolidin-4-one).

2,2'-(1,4-phenylene)bis(3-(pyrimidin-2-yl)thiazolidin-4-one)

M10: White; yield: 82%; Rf: 0.68; mp = 173-175 ˚C; Elemental analysis $C_{20}H_{16}N_6O_2S_2$; Calcd: C, 55.03; H, 3.69; N, 19.25; S, 14.69. Found: C, 54.87; H, 3.53; N, 19.13; S, 14.58; IR (KBr) ν(cm^{-1})= 3082 (Ar-CH), 2891,2827 ($CH_{ALiphatic}$), 1652 (C=O), 1589 ($C=N_{thiadiazole}$), 1531,1485 (C=C), 1269(C-N), 730 (C-S) cm^{-1} ; ^{1}H NMR (300 MHz, DMSO-d^6) δ(ppm):8.99-8.42 (m, 6H, C-H $_{Pyrmidine}$), 7.56 (s, 4H, C-H_{arom}), 5.58 (s, 2H, C-H $_{thiazolidin-4-one}$), 4.20 (s,4H,CH_2 thiazolidin-4-one);^{13}C-NMR(75MHz,DMSO-d^6) δ(ppm):173.06(C=$O_{thiazolidin-4-one}$),159.22-133.55(ArC=C),70.51($CH_{thiazolidin-4-one}$), and 45.77(CH_2 thiazolidin-4-one).

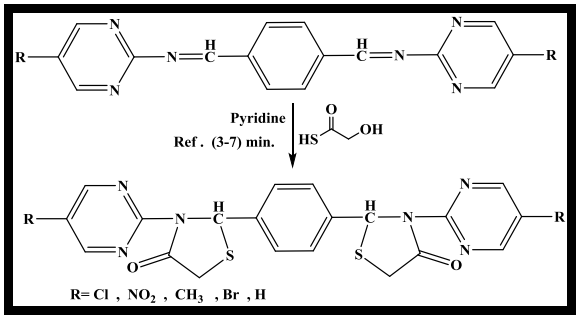

Figure 1. Prepared compounds (M6-M10)

Biological activity study

Thirty-nine grams of Mueller Hinton agar medium were dissolved in one litre of distilled water. The four bacterial isolates evaluated were a Gram-negative *Klebsiella pneumoniae* strain and a Gram-positive *Staphylococcus epidermidis* strain. Dimethyl sulfoxide was then used as a solvent to create chemical solutions of the produced compounds, with each solid derivative having a concentration of (0.01, 0.001, 0.0001) m m^{-1} [20, 21]. Mueller Hinton agar (MHA) was injected using a sterile cotton swab soaked in a test tube containing a diluted bacterial culture. To ensure uniform sample dispersion, the medium was streaked in three directions. The plates were soaked and dried for five to fifteen minutes [22]. We used the agar diffusion technique to assess the resultant chemicals. Using a cylindrical measuring tube and a cork punch, holes were created after the bacterial isolate was injected into the agar medium (per USP 35).Each subject received 40 µl of the prepared compound divided into three doses. The plates were incubated at 37°C for 24 h [23]. The sensitivity of the compound was determined by measuring the diameter of the inhibition zone around the well, and the results were analyzed twice after 24 and 48 h. The expansion of the inhibition zone corresponds to an increase in the biological activity of the compound these results were compared with the inhibition zones of common antibiotics. The samples were designed to be similar to those used in the laboratories of the Ministry of Health. They were based on samples of common antibiotics (such as ampicillin) recommended by the World Health Organization [24].

Cytotoxicity test for breast cancer (MCF-7)

The cancer cells were sourced from the University of Kashan, Iran. The Fleshney technique was used to culture the cancer cells. Separate cytotoxicity experiments were performed. In this test, the harmful effects of the produced compounds (M6, M9) on breast cancer cells and the normal cell line WRL68 were compared. Breast cancer cells were produced, and cell suspensions were cultured in a 96-well plate at concentrations ranging from (0, 7.81, 15.62, 31.25, 62.5, 125, 250, and 500) $m\ m^{-1}$, until each well contained 200 µl of complete culture medium. After gently stirring and covering the well with sterile parafilm, the plate was incubated for 24 hours at 37°C in an incubator containing 5% carbon dioxide. After exposure to the compounds under study (M6, M9), 10 µL of MTT solution was added to each well, and the two plates were then incubated in an incubator containing 5% carbon dioxide for 4 hours at 37°C. Each well was filled with 100 µL of DMSO solution and left to stand for five minutes. ELISA was then used to read the absorbance at 570 nm [25].

RESULTS AND DISCUSSION

The prepared compounds (M6-M10) were confirmed by FT-IR analysis, showing the disappearance of the azomethine (C=N) band belonging to the Schiff base with the formation of new bands indicating ring closure and the formation of thiazolidine-4-one derivatives. A band attributed to the carbonyl group (C=O) at (1672-1652) cm^{-1} and another band indicative of the breaking of the azomethine group (C-N) at (1220-1269) cm^{-1}. The spectrum also showed a new band indicative of ring formation in the thiazolidine-4-one ring, namely the (C-S) band at (730-779) cm^{-1}[26,27].

The prepared compounds were also characterised using ^{1}H-NMR by the disappearance of the protonation of the azomethine group (HC=N) in the Schiff bases with a signal indicative of (CH) ring bonding in the range (6.55-5.58 ppm) and another signal indicative of (CH_2) protons in the range (4.20-3.08) ppm, As the rest of the groups maintained their ranges, signals attributed to the aromatic ring protons were observed in the range (8.70-7.30) ppm[28].

In the ^{13}C-NMR spectrum of the compounds, the disappearance of azomethine carbon (C=N) in the Schiff bases was observed, and a signal attributed to carbon (C=O) appeared at (176.19 -167.95) ppm, a signal indicative of carbon (CH) at (79.83-64.83) ppm, and a typical signal for carbon (CH_2) at (45.77-22.67) ppm. And the spectrum showed signals belonging to the aromatic ring carbon atoms at (161.15-124.54) ppm [29].

To ensure the correct synthesis and structure of the compounds, a careful examination of their components (C.H.N.S.) was carried out, and the resulting ratios were identical or nearly identical to the estimated ratios, confirming the accuracy of the synthesised compound [30].

By comparing these results with the study of (Taha, S. T) through which thiazolidinone rings derived from chalcones were formed, in both studies it was reported that (C=N) disappeared in all spectra, whether FT-IR or (^{1}H&^{13}C-NMR), with the appearance of a (C=O) band in the FT-IR spectra in the range of (1650-1675) cm^{-1}, with the presence of other bands such as (C-S) indicating ring closure and the formation of a five-membered ring derived from thiazolidine. As for the ^{1}H-NMR spectrum, it showed signals attributed to (CH_2) in the range of (3.45) ppm, which is consistent with our current study, which showed the presence of these signals at (4.20-3.08) ppm. This structural compatibility in the two studies positively reflects the reliability of the synthetic approach adopted in the synthesis of the thiazolidine ring, as the slight difference in the appearance of the spectrum bands FT-IR and ^{1}H-NMR spectral signals can be attributed to the effect of substituted groups on the aromatic ring [31].

Evaluation of the biological activity of prepared compounds

The bioactivity of these compounds was tested in vitro against Gram-negative bacteria, ***Klebsiella pneumonia*** and ***Staphylococcus epidermidis***. Agar diffusion test shows Gram-positive skin [32]; dip a sterile cotton swab in the prepared suspension and wipe its surface evenly on a Mueller-Hinton agar plate. Make 3 wells of 7 mm diameter at 20 mm intervals on the agar gel and add 100

µl of the prepared dilution concentrations (0.01, 0.001, 0.0001) m m^{-1} to each well [33]. Dimethyl sulfoxide was used as the solvent. One well was filled with dimethyl sulfoxide or ethanol to observe the effect of the solvent. The plates were incubated at 37 °C for 24 h, growth was observed, and growth inhibition was measured in mm [34], with compound M8 showing the highest inhibition against Klebsiella pneumoniae with a diameter of 15 mm. In contrast, compound M9 showed the highest inhibitory effect against Staphylococcus aureus. The skin inhibitory diameter is 33 mm[35]. As shown in Table 1, and Figure 2-4.

When comparing the results of the effectiveness of the compounds of this study with a study (Taha, S. T) although the two studies used different bacterial isolates in both cases, the results show the ability of thiazolidine derivatives to show remarkable inhibitory activity against both positive and negative bacteria [31]

Table 1. Antibacterial activity of the synthesized compounds (inhibition zone in mm).

Comp.No.	*K. pneumoniae* m m^{-1}			*Staph. epidermidis* m m^{-1}		
	0.01	**0.001**	**0.0001**	**0.01**	**0.001**	**0.0001**
M 6	10	10	10	26	26	15
M 7	12	8	5	20	10	5
M 8	15	10	10	25	16	10
M 9	11	5	0	33	27	15
M 10	10	5	5	18	12	8
***Ampicillin*.**	23	18	13	35	30	25

Cytotoxicity test for breast cancer (MCF-7)

In the MTT study of compounds (M6 and M9) on cancer cells (MCF-7) at concentrations of (0, 7.81, 15.62, 31.25, 62.5, 125, 250 and 500) m m^{-1} , the percentage of toxic cell survival at zero concentration reached 100%, which shows that there is no inhibition of these cells, and the study showed that the percentage of toxic cell survival is inversely proportional to the increase in concentration, that is, the higher the concentration, the lower the percentage of toxic cell survival, at the low concentration of 7.81 m m^{-1} the percentage of cell survival was 98.42% for compound M6 and 97.29% for compound M9. At a concentration of 250 m m^{-1}, the percentage of cell survival for compound M9 was higher than compound M6, the percentage of survival of toxic cells reached 27.94 m m^{-1} for compound M9 and 26.9 m m^{-1} for compound M6, but this percentage quickly decreased at a concentration of 500 m m^{-1} for compound M9 to reach 12.78%, while the percentage of cell survival for compound M6 reached 15.23%. It can be seen that compound M9 had a higher effect than compound M6, although the results were similar. These results show that the two compounds can have an effect on cancer cells and can be used in the development of therapies or anti-cancer drugs [36, 37]. As shown in Table 1 and Figure 5-7.

Table 2. Effect of the two compounds (M6, M9) on MCF-7 and HdFn cells using the MTT assay.

Dose (m m^{-1})	%Viability-M6	Dose (m m^{-1})	%Viability-M9
0	100	0	100
7.81	98.42	7.81	97.29
15.62	92.41	15.62	88.85
31.25	79.11	31.25	70.16
62.5	64.57	62.5	57.89
125	40.87	125	38.62
250	26.9	250	27.94
500	15.23	500	12.78

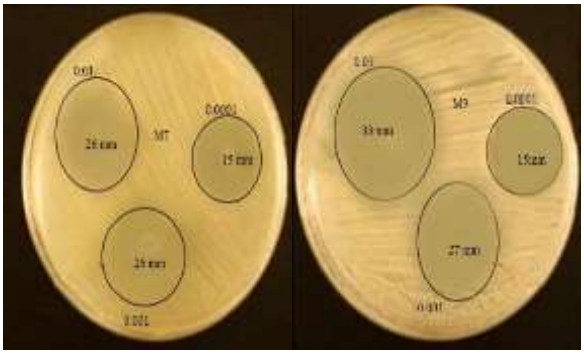

Figure 2. Inhibitory activity of the two compounds (M7,M9) against Staph. epidermidis

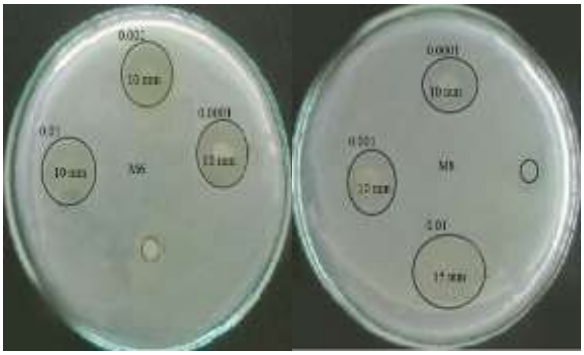

Figure 3. Inhibitory activity of the two compounds (M6,M8) against *K. pneumoniae*

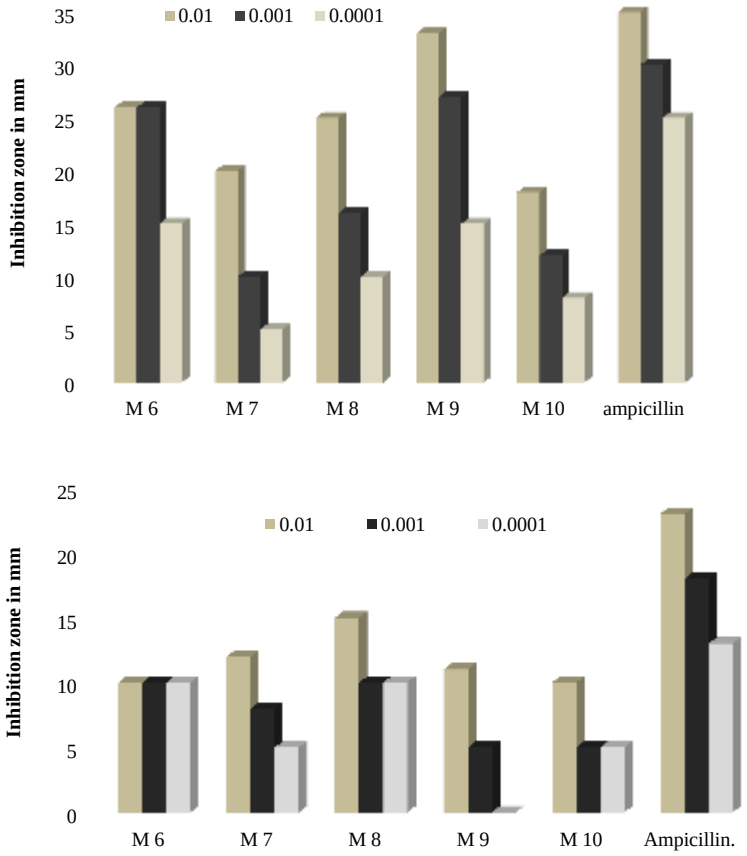

Figure 4. Inhibitory activity of (M6-M10) for Staph. epidermidis & K. pneumoniae

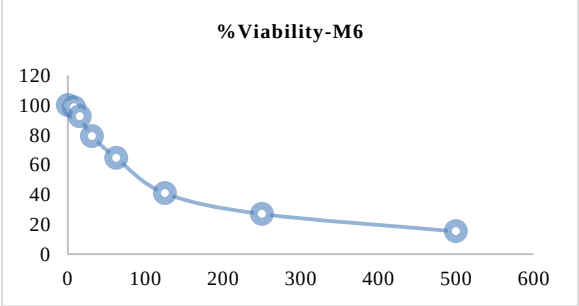

Figure 5. Effect of compound (M6) on MCF-7 cells and HdFn cells using MTT assay

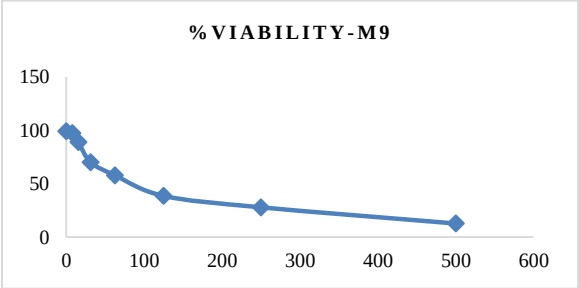

Figure 6. Effect of compound (M9) on MCF-7 cells and HdFn cells using MTT assay.

Figure 7. Effect of compounds (M6, M9) on MCF-7 cells.

CONCLUSIONS

Compared with conventional methods, microwave methods achieve better results in obtaining organic compounds. This technology has proven to be economical because it saves time, effort, solvents and catalysts while providing higher product yield. Therefore, it can be concluded that microwave method is preferred, especially for small reactions, making it an environmentally friendly technology. The reaction of Schiff base derivatives with compounds containing suitable functional groups usually results in five-membered heterocycles. The spectroscopic measurements also proved the validity and accuracy of the results, which showed very high purity. Biological studies have shown that the synthesized compounds have antimicrobial activity and can inhibit the growth of bacteria. These compounds show higher biological activity than the parent material, which is important because the starting material is a drug used in the medical field. The prepared compounds (M6, M9) showed sound inhibitory effects on breast cancer cells.

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Conflict of interests

There are no conflicting interests.

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