Conventional and Microwave Irradiation Methods, Synthesis and Antibacterial Evaluation of Thiophene Chalcones Derivatives

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Abstract

Chalcones (3a-3d) were synthesized by two routes conventional and microwave assisted synthesis methods. Claisen-Schmidt reaction (route A) entails base catalyzed cross-aldol condensation of appropriate aldehydes. Microwave aided synthesis (Route B) resulted in a significant increase in reaction rate, as well as higher yields. This method provides a simple, clean, quick, efficient, and cost-effective way to synthesize a large number of organic compounds. The compounds have been screened for they possess a broad spectrum of antibacterial activities.

Keywords: *Microwave irradiation, Chalcone, Antibacterial, Claisen-Schmidt condensation.*

تخليق مشتقات الجالكون ثايوفين وتقييمها كمضادات للبكتيريا باستخدام الطرق التقليدية والتشعيع بالميكروويف

ريتا سالم ادم [1] ، وصفي عبود المسعودي[2] وَ هناء كاظم ابراهيم[3]

الخلاصة

تم تحضير عدد من الجالكونات (3a-3d) من خلال طريقين طريقة تقليدية والاخرى بمساعدة الميكروويف. تفاعل كليزين شميدت (الطريق A) هو تكثيف القاعدة عبر الألدول المحفز للألدهيدات المناسبة. أما التحضير بمساعدة الميكروويف (الطريق B) يؤدي إلى زيادة كبيرة في معدل التفاعل ، فضلاً عن زيادة الحصيلة .

توفر هذه الطريقة طريقة بسيطة ونظيفة وسريعة وفعالة من حيث التكلفة لتحضير عدد كبير من المركبات العضوية. تم فحص المركبات بيولوجيا ووجد انها تمتلك مجموعة واسعة من الأنشطة المضادة للبكتيريا.

الكلمات المفتاحية: *التشعيع بالمايكروويف، جالكون، مضادات للبكتريا، تكاثف كليزين شميدت .*

Introduction

Microwave-assisted organic synthesis is a common method of heating in organic synthesis reactions, is also known as green chemistry. High-frequency electric fields, such as microwaves, anything with mobile electric charges, such polar molecules in a fluid or conducting ions in a solid, can be heated. Chalcones with derivatives are key intermediates in the production of physiologically relevant heterocyclic compounds.

The investigation of chemical processes influenced by microwave radiation is known as microwave chemistry. Microwaves have been promoted as a way to speed up chemical reactions in laboratories [1].

When compared to traditional heating methods, microwave heating has been demonstrated to dramatically reducing the reaction times, boost product yields, and improve product purity by minimizing undesired side reactions. In the last year, microwaves have been used to aid in the synthesis of chalcones [2]. Chalcones are widely used as intermediates in the synthesis of heterocyclic compounds with a wide range of pharmacological effects [3]. In a base media, the Claisen-Schmidt condensation of equimolar of simple or substituted aromatic aldehyde with simple or substituted acetophenone is the easiest method for synthesis of chalcones [4]. In recent years, researchers have become increasingly interested in preparing many of the chalcone derivatives due to their biological properties.

The biological activity depends mostly on the chalcone substitution group. Chalcones are known as the precursors of isoflavonoids and Flavonoids [5].

Chalcone derivative are extremely flexible as physiologically active substances and substrates for the assessment of different organic matter physical synthesis. Studies of

these chemicals with various biological functions, such as anti-cancer, have been reported [6], antimalarial [7] anti-inflammatory [8], anti-HIV [9,10] and antifungal [11] have been reported. Pharmacological tests of some chalcones showed high antioxidant activity [12]. Curcumin was also found to have antioxidant and anti-inflammatory properties in it. Because of those properties, curcumin may be used in the pharmacological and food industries [13]. A little has been published concerning the application of thiophene moiety to isoxazole ring. Asiri and Khan were prepared chalcone by the reaction of Tetraphthalaldehyde with 3-acetyl-2,5-dimethylthiophene [14]. Chemical synthesis, structural quantitative alterations, and a wide spectrum of chalcone biological activity were all documented in this study.

Experimental

Material and Methods

KBr discs were used to record IR spectra in the range 4000-200 cm-1 on a Pye-Unicam SP3-300 spectrometer at College of Science, University of Basrah, Iraq. On a Bruker, 1H and 13C-NMR spectra were obtained at 300 and 600 MHz, respectively, with TMS as an internal reference at Konstanz University, Germany, and Al-Elbiat University, Gordan. A Philip Harris melting point equipment was used to determine the melting point.

General procedure for synthesis chalcones (3a–3d).

(A) Conventional method: 2-acetylthiophene **1** (0.001 mol) and respective aldehydes **2** (0.001 mol) were mixed in 3 ml of ethanol. (0.003 mol) Potassium hydroxide solution was gently added and mixed occasionally for 24 h, at room temperature. Observation on percolated TLC plates confirmed the reaction's completion. The reaction mixture was put onto crushed ice after it was finished then acidified with dilution HCl. Filtered and dried solids were separated. It was purified using ethyl acetate and hexane as the mobile phase in recrystallization or column chromatography on a silica gel

(100–200 mesh). Scheme1.

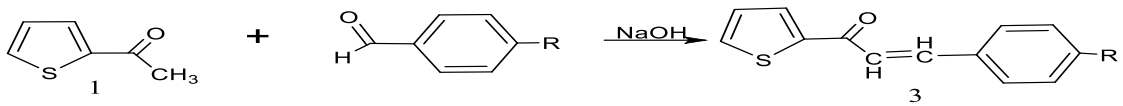

Fig. (1): Preparation of Chalcone derivatives by conventional method

(B) Microwave irradiation method: (5mmol) of 2-acetyl thiophene**1** and (5mmol) of Substituted benzaldehyde **2** were dissolved in 5mL ethanol. This solution was poured over calcium oxide and stirred thoroughly. The solvent was extracted by using a rotator evaporator. The resulting free-flowing powder was placed in a 25mL beaker and microwaved for 15 minutes at 400W. TLC was used to track the reaction's progress. The reaction mixture was chilled after completion, then added to 20mL ice cold water and acidified with Conc. HCl. Solids were precipitated, then filtered using a suction pump, washed, and dried. Recrystallization from methyl alcohol yielded a pure sample. Scheme2.

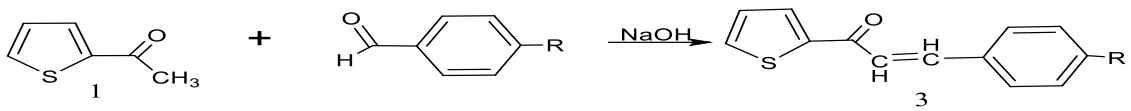

Fig. (2): Preparation of Chalcone derivatives by microwave irradiation method

The spectral data of the all chalcone derivatives is given below 3-(4- -N, N-dimethyl phenyl)-1-(α-thiophene) propene -1-one **(3a)** Mol. formula: $C_{15}H_{15}NOS$, conventional method yields 68%, microwave irradiation yields 74%, as a pale-yellow powder the range of m.p.113–115°C. IR spectrum, film, ν, cm^{-1}: 3045 (C–H aromatic

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stretching), 2958 (C–H methyl stretching), 1740 (C=O),1687 (HC=CH), ^{1}H NMR spectrum $CDCl_3$, δ, ppm: 7.86-6.69 (m, 7H, H arom), 3.28, 3.05 (s, 2H, CH=CH), 1.55 (s, 6H, $2CH_3$). Elemental Analysis Found, %: C: 69.94; H: 5.82; N: 5.44, Calculated, C: 70.03; H: 5.83; N: 5.44 3-(4- -methyl phenyl)-1-(α-thiophene) propene -1-one **(3b)** Mol. formula: $C_{14}H_{12}OS$, conventional method yields 72%, microwave irradiation yields 92 %, as a pale-yellow powder the range of m.p.106–108°C. IR spectrum, film, ν, cm^{-1}: 3041(C–H aromatic stretching),2961 (C–H methyl stretching),1755 (C=O),1672 (HC=CH), 1 H NMR spectrum $CDCl_3$, δ, ppm: 7.75-6.91 (m, 7H, H arom), 3.41, 3.26 (s, 2H, CH=CH), 1.73 (s, 3H, CH_3). Elemental Analysis Found, %: C: 73.94; H: 5.28, Calculated, %: C 73.68; H 5.26. 3-(4- -nitro phenyl)-1-(α-thiophene) propene -1-one **(3c)** Mol. formula: $C_{13}H_9NO_3S$, conventional method yields 80%, microwave irradiation yields 91 %, as a pale-yellow powder the range of m.p.146–148°C. IR spectrum, film, ν, cm^{-1}: 3063(C–H aromatic stretching),1750 (C=O),1665 (HC=CH), 1 H NMR spectrum $DMSO_{6d}$, δ, ppm: 8.77 (t, 1H, H-5 thiophen), 8.44-7.33 (m, 6H, H arom) 3.31, 3.34 (s, 2H, CH=CH), ^{13}C NMR spectrum $DMSO_{6d}$, δ, ppm: 181.4(C=O), 148.3(C-NO_2), 145.1(C=C)b, 140.5(C-Ar), 136.3(C2 thiophen) ,135.0-124.5(C-Ar), 122.9 (C=C)a. Elemental Analysis Found, %: C: 60.24; H: 3.42, ; N 5.39.Calculated, %: C 60.23.58; H 3.47; N 5.40. 3-(4- - chloro phenyl)-1-(α-thiophene) propene -1-one **(3d)** Mol. formula: $C_{13}H_9ClOS$, conventional method yields 85%, microwave irradiation yields 96 %, as a pale-yellow powder the range of m.p.130–132°C. IR spectrum, film, ν, cm^{-1}: 3038(C–H aromatic stretching),1746 (C=O),1670 (HC=CH), 1 H NMR spectrum CDCl3, δ, ppm: 7.92-6.82 (m, 7H, H-arom), 3.31, 3.01 (s, 2H, CH=CH). Elemental Analysis Found, %: C: 62.72; H: 3.59. Calculated, C: 62.65; H: 3.61.

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Result and Discussion

Chemistry

The chalcones (3a-3d) were prepared by reacting equimolar 2-acetyl thiophene**1** and substituted benzaldehyde **2** in the presence of a base by conventional Claisen-Schmidt condensation [15] as well as microwave-assisted synthesis. Microwave aided synthesis has resulted in a significant increase in reaction rate, as well as higher yields. CHN analysis and spectral data (IR, ^{1}H NMR, and [13] C NMR) were used to confirm the structures of the synthesized compounds, which were in line with the proposed structures.

Biological activity

Using the paper disc-agar diffusion technique, three bacterial types were assigned to this activity (*Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumonia*) [16]. In the incubator, overnight cultures of selected bacteria were incubated at 37°C for 24 hours. Values of the compound's inhibition zone for all microorganisms tested. Three serial dilutions (dimethyl sulfoxide DMSO) with doses (50,100,200g/ml) of the produced chemical, on the other hand. Each of the dilutions was impregnated into 7 mm filter paper discs (Whatman, no. 3) with 20 ml of each.

The discs were left at room temperature until all of the diluents had been added. Discs with natural and synthetic materials were placed on the agar's surface. After a 24-hour incubation period. The antibacterial activity was assessed based on its inhibition zone (mm).

Antibacterial activity

The screening results show that as the concentration of the solution rises, so does the activity of the synthesized compounds. The synthesized compound **3b** show high activity against *Klebsiella pneumonia* and *E.colli*. whereas the compound **3c** show relatively a good activity *E. coli* and *Staphylococcus aureus*,

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the compound **3b** show a good activity for all bacteria, while Bacillus *subtillus* show a good biological activity against all concentration of compound **3b**.

Results had been shown that the all bacteria resistance to Ampicillin broad-spectrum 100% in all compounds these results agreed with Vivek *et al.* [17]. Cell walls of Gram positive and Gram-negative bacteria are made up of strongly cross-linked peptidoglycan layers that are catalyzed by cell-wall trans peptidases (also known as penicillin binding proteins) (PBP). Peptide bond formation is disrupted by -lactam antibiotics, which operate as competitive inhibitors of these PBPs. As a result, penicilloyl-enzyme complexes with weak cross-linked peptidoglycans generate irreversibly covalently bonded penicilloyl-enzyme complexes.

Thus, ease bacteria lyses and death [18]. As a result, it is obvious that these bacteria are resistant to antibiotics, such as broad-spectrum penicillins, as described by Soubhi and Mahmood [19]. Previous studies have shown that bacteria have methods of resistance to many of the most significant enzymes - Lactamaes, bacteria have numerous kinds of these enzymes that operate to break down a wide spectrum of antibiotic beta-lactamase, according to studies [20].

Table (1): Antibacterial activity of synthesized compounds (3a-3b)

Microorganism	Compound 3a			Compound 3b			Compound 3c			Standard
	200 µg/ml	100 µg/ml	50 µg/ml	200 µg/ml	100 µg/ml	50 µg/ml	200 µg/ml	100 µg/ml	50 µg/ml	Ampicillin
Staphylococcus aureus	20	15	10	22	16	8	15	10	0	25
Bacillus subtillus	14	12	7	28	25	18	25	20	15	30
Escherichia coli	22	19	12	25	23	18	20	18	13	28
Klebsiella pneumonia	12	10	0	20	15	0	18	13	10	22

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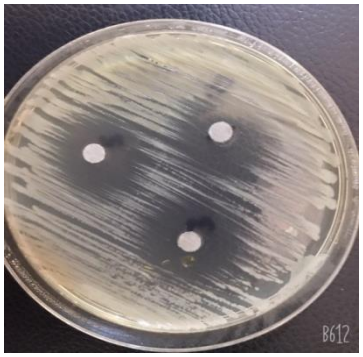
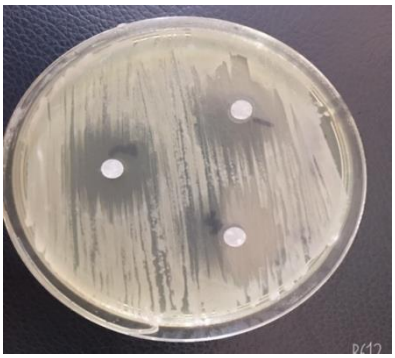
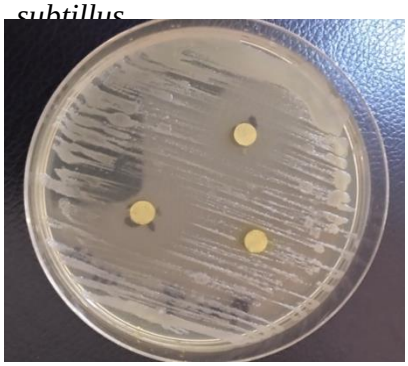
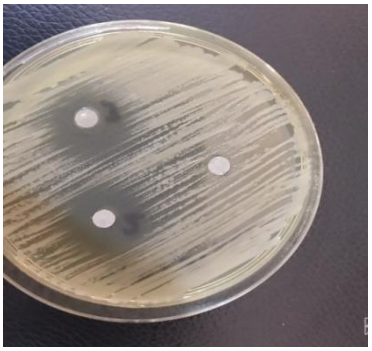
Compound 2





Staphylococcus aureus *Escherichia Coli* *Bacillus subtillus*





Staphylococcusaureus *Klebsiella pneumonia*

Compound 3 **Compound1**

(A) concentration 50µg/ml, (B) concentration 100µg/ml,(C) concentration 200µg/ml

Conclusions

Microwave represents an alternative method and source of energy for chemical reactions and processes. From dielectric heating the reaction mixtures are heated homogeneously without touching the walls. Drop Significantly significant reaction time compared to conventionally heated (heat) systems while keeping the product percentile and selectivity accepted. The simple negative is the fact that the chemical reaction and the processes in the microwave field is more dependent on the tools and materials used for this more than the case heating with heat.

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