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A one-pot Synthesis of Some New Heterocyclic Compounds Derived from Chalcones and Study of their Antitumor and Antimicrobial Activities

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Abstract

The aim of the present work is to efficiently synthesize promising novel antitumor and antimicrobial active heterocyclic compounds from chalcones **1a** and **1b** as a precursor which contain naphthalene moiety and indole or piperonal moiety, respectively, using conventional, ultrasonic and microwave irradiation techniques. The best yields and purity were afforded with the microwave irradiation technique. Reaction of **1a** and **1b** with the appropriate reagent gave the corresponding pyrazolines **2a**, **2b**, pyrimidine-2-thiones **3a**, **3b**, oxazepines **4a**, **4b**, diazepines **5a**, **5b**, triazolo-pyrimidines **6a**, **6b**, and pyrimidine-2-thiols **7a**, **7b** derivatives. Compounds **7a**, **7b** were used to produce **8a**, **8b**. Moreover, pyrimidine-2-thione **3a** was used to synthesize pyrimidin-2-ylthioacetic acid **9a**, and 2-hydrazinylpyrido[2,3-d]pyrimidine derivative **10a** which has been used as a functionalizing agent to produce compounds **11a-14a**. The structural formulas of the synthesized compounds were confirmed by their spectral data; FT-IR, ¹H NMR, ¹³C NMR and MS. Compounds **3a**, **5a**, **7a**, **13a** showed a very high activity as antitumor, whereas compounds **4a**, **6a**, and **13a** showed high activity as antibacterial and antifungal agents.

Keywords: A One-pot Synthesis, Antitumor; Chalcone; Diazepines; 2-Hydrazinylpyrido[2,3-d]pyrimidine; Pyrimidine-2-thiones; Microwave and ultrasonic irradiation.

1. Introduction

Pyrimidine-containing compounds have a great interest due to their high biological activities, such as anticancer [1- 3] antiviral,[4] antitumor,[5] anti-inflammatory [6, 7] and antimicrobial activities. [8-10] Also, Schiff bases are considered of high interest from synthetic and biological points of view. [11-13] The literature survey revealed that Schiff bases with various heterocyclic moieties also possess cytotoxic, [14] anticonvulsant, [15, 16] antiproliferative,[12, 17] antimicrobial, [18, 19] anticancer,[20] and antifungal

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activities.[8, 21] Moreover, pyrazole derivatives have been reported to act as antitumor agents against various types of lung, breast, and leukemia carcinomas.[22-25]

The most important requirements in developing new synthetic techniques are to minimize or eliminate the hazardous use of solvents. [26] Therefore, in order to synthesize the desired compounds, the microwave irradiation technique was employed. The most noticeable advancement in microwave-assisted technique in organic synthesis is the spectacular decrease of reaction times, typically from days or hours into minutes or even seconds. [27] Furthermore, the comparison with the conventional methods showed that the microwave-assisted reactions are characterized by saving energy with the improvement of the yield and purity of the reaction products. [28]

Also, heterocycles containing pyrimidinethione nucleus are reported to have a wide spectrum of potent pharmacological activities, [29] since pyrimidinethione derivatives are belonging to the active compounds having a wide range of biological activities such as antitumor, [30-32] anti-fungal, anti-inflammatory and anti-bacterial compounds. [29]

Due to all the previously mentioned benefits, herein, a series of novel compounds containing heterocyclic moieties conjugated with pyrimidine derivatives have been synthesized using microwave-assisted technique.

The aim of this work, is to synthesize a novel series of fused pyrimidine derivatives with a potential to act as antitumor and antibacterial agents.

Considering the above aspects, herein, a series of novel compounds containing heterocyclic moieties conjugated with pyrimidine derivatives (**3a**, **6a-14a** and **3b**, **6b-8b**), have been synthesized using microwave-assisted technique. Moreover, we synthesized pyrazoles (**2a**, **2b**), oxazepines (**4a**, **4b** and **5a**, **5b**) derivatives. Biological assessments for some of the newly synthesized compounds were evaluated as (anticancer potent agents against two cell lines;MCF-7 breast carcinoma and HCT-116 colon carcinoma, and antimicrobial). Chalcones (**1a** and **1b**) are used as precursors to synthesize pyrimidine derivatives.

2. Experimental

General Remarks

All the reagents and solvents used were purified and dried before their use by the usual

procedures. [33] All the chemicals were purchased from Sigma–Aldrich. Melting points were determined with a Gallenkamp melting point apparatus and were uncorrected. TLC was done using aluminum sheets with detection of spots by UV irradiation. Microwave irradiation was carried by a Galanz Microwave Oven, WP 1000AP30-2, IR spectra were measured by Fourier Transformed Infrared spectrometer (FTIR, Nicolet iS 10, Thermo Fisher Scientific), in the Central Lab of Ain Shams University, Cairo, Egypt. ^1H NMR spectra were measured using Bruker, 400 MHz, and the ^{13}C NMR spectra were measured at 125 MHz, in the Development and Research for Drug Discovery Center, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt. MS Spectra were carried out at Micro Analytical Center, Al-Azhar University, using GCMS QP 1000 EX Shimaedzy. Antimicrobial and Antitumor Screening were carried out at the Regional Center for Mycology and Biotechnology (RCMB), Al-Azhar University, Cairo, Egypt.

2.1. Synthesis of Chalcone (1a)

2.1.1 Method A: Conventional Thermal Technique [34]

To a solution of 2-acetylnaphthalene (10 mmol) in ethanol (20 mL), 10% aqueous NaOH solution (40 mmol) and indole-3-carboxaldehyde in ethanol (10 mmol) were added with stirring at room temperature for 24 hrs. The reaction was monitored by TLC. When completed, the reaction mixture was poured on crushed ice to quench the reaction and then neutralized with HCl (10%). The precipitate formed was filtered, washed with distilled water, dried and recrystallized from EtOH to give chalcone (1a).

2.1.2. Method B: Ultrasonic Irradiation Technique

To a stirred equimolar mixture of 2-acetylnaphthalene (0.01 mol) and 1*H*-indole-3-carbaldehyde (0.01 mol) in ethanol (30 mL), 10% NaOH (10 mL) solution was added and the reaction mixture was then exposed to ultrasonic irradiation for 30 min to give chalcone (1a), (yield 90%).

2.1.3. Method C: Microwave Irradiation Technique

To an equimolar mixture of 2-acetylnaphthalene and 1*H*-indole-3-carbaldehyde in ethanol (10 mL), 40% aqueous NaOH (2 mL) was added. The reaction mixture was irradiated with microwave irradiation 160-320 watt for 2 minutes, to give chalcone (1a), (yield 90.9%).

3-(1H-indol-3-yl)-1-(naphthalen-2-yl)prop-2-en-1-one (1a). Yellow crystals from ETOH, m.p. 216–218 °C, 85.8%, yield, in conventional technique, 90% yield in ultrasonic and 90.9% yield in microwave irradiation technique. FTIR (KBr): ν (cm^{-1}) = 3405 (NH), 3063 (CH-Ar), 1674 (C=O), 1631 (C=C). MS: m/z = 297 (M^+ , 18.37%, $\text{C}_{21}\text{H}_{15}\text{NO}$). ^1H NMR (DMSO): δ (ppm) = 6.10-6.13 (2H, s, CH_2 of dioxole), 6.75-8.88(10H, m, Ar-H), 8.93 (1H, s, pyridineH), 12.31 & 12.98 (2H, s, NH's of uracil). ^{13}C NMR (DMSO): δ at 138.89 and 185.43), characteristic for (C=C) and (C=O), respectively.

2.2. Synthesis of Chalcone (1b)

2.2.1 Method A: Conventional Thermal Technique [35]

To a solution of benzo[d][1,3]dioxole-5-carbaldehyde (piperonal) (10 mmol) and 2-acetylnaphthalene (10 mmol), in absolute ethanol (50 mL), sodium hydroxide solution (5 mL, 20%) was added portion wise. The mixture reaction was stirred for 4hrs. The solid product was collected by filtration, washed with water, dried and recrystallized from ethanol to give chalcone (**1b**).

2.2.2. Method B: Ultrasonic Irradiation Technique

To a stirred equimolar mixture of 2-acetylnaphthalene (0.01 mol) and piperonal (0.01 mol) in ethanol (30 mL), 10% NaOH (10 mL) solution was added and the reaction mixture was then exposed to ultrasonic irradiation for 30 min to give chalcone (**1b**), (yield 92%).

2.2.3. Method C: Microwave Irradiation Technique

To an equimolar mixture of 2-acetylnaphthalene and piperonal, in ethanol (10 mL), 40% aqueous NaOH (2 mL) was added. The reaction mixture was irradiated with microwave irradiation 160-320 watt for 2 minutes, to give chalcone (**1b**), (yield 93%).

3-(benzo[d][1,3]dioxol-5-yl)-1-(naphthalen-2-yl)prop-2-en-1-one (1b). Yellow crystals from ETOH m.p. 148-150°C (87% yield in conventional technique, 92% yield in ultrasonic, 93% yield in microwave irradiation technique). FTIR (KBr): ν (cm^{-1}) = 1655 (C=C) and 1690 (C=O). MS: m/z = 302.24 (M^+ , 18.37%, $\text{C}_{20}\text{H}_{14}\text{O}_3$). ^1H NMR (DMSO- d_6) δ ppm: 6.13 (s, 2H, CH_2 of dioxole), 7.01-7.03 (d, 1H, J = 8 Hz, H-6 of benzodioxole), 7.37- 7.38 (d, 1H, J = 4 Hz, H-7 of benzodioxole), 7.62-7.65 (t, 2H, J = 12 Hz, H-6 and H-7 of naphthalene), 7.67-7.69 (dd, 2H, J = 8 Hz, olefinic hydrogens), 7.78 (s, 1H, H-4 of dioxole), 8.01-8.07(m, 3H, olefinic hydrogens, H-3 & H-4), 8.13-

8.17 (m, 2H, H-5 & H-8). ^{13}C NMR (DMSO): δ at 148.61 and 189.23), characteristic for (C=C) and (C=O), respectively.

2.3. Synthesis of Pyrimidine-2-thiones (3a)

2.3.1. Method A: An equimolar mixture of chalcone (**1a**) (10 mmol) and 6-amino-2-thiouracil (1.43 g, 10 mmol) dissolved in (30 mL) glacial acetic acid was refluxed for 5 hours, the reaction mixture was cooled and the precipitate was filtered, dried and crystallized from DMF/EtOH to give compound (**3a**) (yield 45%).

2.3.2. Method B: The above procedure was repeated using ultrasonic irradiation for 60 minutes to give compound (**3a**) (yield 89%).

2.3.3. Method C: An equimolar mixture from chalcone (**1a**) and 6-amino-2-thiouracil was grinded together and dissolved in a minimum amount of DMF. The reaction mixture was irradiated with microwave for 3 minutes to give compound (**3a**) (yield 95%).

The results obtained showed that methods (B and C) are more beneficiary procedures and gave better yields and purity than method (A).

5-(1*H*-Indol-3-yl)-7-(naphthalen-2-yl)-2-thioxo-2,3-dihydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one (3a). Orange crystals from DMF/EtOH, m.p. $>300^\circ\text{C}$, 95% yield in microwave, 89% yield in ultrasonic and 45% yield in thermal. FTIR (KBr): ν (cm^{-1}) = 3443, 3363 (NH 's), 3057 (CH-Ar), 1663 (C=O attached to NH), 1610 (C=C), 1554 (C=N), 1230 (C=S). MS: $m/z = 420$ (M^+ , 26.67%, $\text{C}_{25}\text{H}_{16}\text{N}_4\text{OS}$). ^1H NMR (DMSO): δ (ppm) = 6.79-8.38 (11H, m, Ar-H), 8.65 (1H, s, pyridine H), 9.9 (1H, s, indole H), 11.8 (1H, s, NH of indole), 12.67 & 13.20 (2H, s, NH's of uracil).

2.4 Synthesis of Pyrimidine-2-thiones (3b):

2.4.1. Method A: An equimolar mixture of chalcone (**1b**) (10 mmol) and 6-amino-2-thiouracil (1.43 g, 10 mmol) was dissolved in DMF (30 mL). The reaction mixture was refluxed for 15 hours, cooled and the precipitate formed was filtered, dried and crystallized from DMF/EtOH to give compound (**3b**) (yield 40%).

2.4.2. Method B: the above procedure was repeated using ultrasonic irradiation for 60 minutes to give compound (**3b**) (yield 86%).

2.4. 3. Method C: An equimolar mixture of (**1b**) and 6-amino-2-thiouracil were grinded together then dissolved in a minimum amount of (DMF), the reaction mixture was exposed to microwave irradiation for 3 minutes where compound (**3b**) was obtained (yield 90.5%).

5-(Benzo[d][1,3]dioxol-5-yl)-7-(naphthalen-2-yl)-2-thioxo-2,3-dihydropyrido[2,3-d]pyrimidin-4(1H)-one (3b**).** Yellow crystals from DMF/EtOH, m.p. 230°C, 90.5% yield in microwave, 86% yield in ultrasonic and 40% yield in thermal. FTIR (KBr): ν (cm⁻¹) = 3337, 3243 (NH's), 3055 (CH-Ar), 1703 (C=O attached to NH), 1594 (C=N), 1235 (C=S). MS: m/z = 425 (M⁺, 0%, C₂₄H₁₅N₃O₃S, M⁺-1 = 424, 52.39%, C₂₄H₁₄N₃O₃S). ¹H NMR (DMSO): δ (ppm) = 6.10-6.13(2H, s, CH₂ of dioxole), 6.75-8.88(10H, m, Ar-H), 8.93 (1H, s, pyridineH), 12.31 & 12.98 (2H, s, NH's of uracil).

2.5. Synthesis of Compounds (**2a**, **4a-6a**, and **2b**, **4b-6b**)

2.5.1. General Procedure:

An equimolar mixture of chalcone (**1a**, or **1b**) (10 mmol) and (10 mmol) from the appropriate reagent; hydrazine hydrate, 2-aminophenol, 2,3-diaminomaleonitrile, or 3-amino-1,2,4-triazole was added in the appropriate solvent and refluxed for 5-15 hours, in the presence of a catalyst (cf. scheme 1). The products obtained were crystallized from the appropriate solvents to give the corresponding compounds (**2a**, **4a-6a**, and **2b**, **4b-6b**), respectively.

3-(3-(Naphthalen-2-yl)-1H-pyrazol-5-yl)-1H-indole (2a**).** Shiny yellow crystals from ethyl alcohol, m.p. >300°C, 80% yield. FTIR (KBr): ν (cm⁻¹) = 3375, 3225 (NH), 3059.24 (CH-Ar), 1621 (C=C), 1580 (C=N). MS: m/z = 309 (M⁺, 38.51%, C₂₁H₁₅N₃). ¹H NMR (DMSO): δ (ppm) = 7.17-8.38 (11H, m, Ar-H), 7.92-7.98 (1H, s, pyrazole H), 8.41 (1H, s, NH pyrazole), 8.9 (1H, s, indole H), 11.69 (1H, s, NH of indole).

2-(1H-Indol-3-yl)-4-(naphthalen-2-yl)benzo[b][1,4] oxazepine (4a**).** Dark green crystals from ethanol, m.p. 182 °C, 86% yield. FTIR (KBr): ν (cm⁻¹) = 3375 (NH), 3165 (=CH), 3041 (CH-Ar), 1632 (C=C), 1575 (C=N), 1124 (C-O-C). MS: m/z = 386 (M⁺, 60.93%, C₂₇H₁₈N₂O). ¹H NMR (DMSO): δ (ppm) = 7.2-8.29 (15H, m, Ar-H), 8.29 (1H, s, oxazepine-H), 9.94 (1H, s, indole H), 12.13 (1H, s, NH of indole). ¹³C NMR (DMSO): δ (ppm) = 112.88, 118.63(4C), 121.28 (4C), 122.59(4C), 123.92(4C), 124.59(4C), 137.52(3C), 138.91(2C), 185.43(C=N).

7-(1*H*-Indol-3-yl)-5-(naphthalen-2-yl)-4,5-dihydro-1*H*-1,4-diazepine-2,3-dicarbonitrile

(5a). Orange crystals from ethanol, m.p. 200 °C, 80% yield. FTIR (KBr): ν (cm⁻¹) = 3458, 3381, 3306 (NH 's), 3122 (CH-Ar), 2230 (C≡N), 2202 (C≡N). MS: m/z = 387 (M⁺, 0%, C₂₅H₁₇N₅, M⁺-1 = 386, 32.41%, C₂₅H₁₆N₅). ¹H NMR (DMSO): δ (ppm) = 7.19-8.15 (1H, m, Ar-H), 7.44-7.47 (1H, d, *J*=8.7 Hz, diazepine-H), 8.44-8.47 (1H, d, *J*=8.7Hz, =CH diazepine), 8.51 (1H, s, NH of diazepine), 8.67 (1H, s, NH of diazepine), 9.9 (1H, s, indole H), 11.93 (1H, s, NH of indole). ¹³C NMR (DMSO): δ (ppm)=106.40, 112.42, 114.76, 115.11, 115.75, 121.93(C≡N), 123.26(C≡N), 123.42, 123.67, 124.01, 124.74, 127.39(2C), 128.13, 128.71, 129.09(2C), 130.04, 130.82, 132.68, 134.62, 135.51, 135.81, 137.84, 152.87.

7-(1*H*-Indol-3-yl)-5-(naphthalen-2-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidine (6a). Yellow crystals from ethanol, m.p. 185°C, 58% yield. FTIR (KBr): ν (cm⁻¹) = 3417 (NH), 1630 (C=C), 1530 (C=N). MS: m/z = 361 (M⁺, 0%, C₂₃H₁₅N₅, M⁺-1 = 360, 15.80%, C₂₃H₁₄N₅). ¹H NMR (DMSO): δ (ppm) = 7.20-8.11(1H, m, Ar-H), 8.13 (1H, s, triazole H), 8.29 (1H, s, Pyrimidine H), 9.95 (1H, s, indole H), 12.16 (1H, s, NH of indole).

5-(Benzo[d][1,3]dioxol-5-yl)-3-(naphthalen-2-yl)-4,5-dihydro-1*H*-pyrazole (2b). Shiny orange crystals from methyl alcohol, m.p. 120°C, 85% yield. FTIR (KBr): ν (cm⁻¹) = 3344 (NH), 3058 (CH-Ar), 1624 (C=C), 1580 (C=N). MS: m/z = 316 (M⁺, 0%, C₂₀H₁₆N₂O₂, M⁺-2 = 314, 16.81%, C₂₀H₁₄N₂O₂). ¹H NMR (DMSO): δ (ppm) = 2.91-2.99((1H, dd, *J*=11.6Hz, *J*=11.6Hz, Pyrazoline H_a), 3.48-3.55 (1H, dd, *J*=9.6Hz, *J*=7.6Hz, Pyrazoline H_b), 4.79-4.88 (1H, dd, *J*=12.8Hz, *J*=10.4Hz, Pyrazoline H_c), 5.99-5.998 (2H, d, *J*=3.2Hz, CH₂ of dioxole), 6.88 (2H, s, H-6 &H-7 of benzodioxole), 6.96 (1H, s, H-4 of benzodioxole), 7.47-7.53 (2H, m, naphthyl H), 7.65 (1H, s, NH), 7.87-7.97 (5H, s, naphthyl H).

2-(Benzo[d][1,3]dioxol-5-yl)-4-(naphthalen-2-yl)benzo[b][1,4]oxazepine (4b). Reddish brown crystals from ethanol, m.p. 220 °C, 86% yield. FTIR (KBr): ν (cm⁻¹) = 3423 (NH), 3100 (=CH), 3051 (CH-Ar), 1655 (C=C), 1583 (C=N), 1122 (C-O-C). MS: m/z = 391 (M⁺, 26.97%, C₂₆H₁₇NO₃). ¹H NMR (DMSO): δ (ppm) = 6.13 (2H, s, CH₂ of dioxole), 7.02-7.04 (2H, d, *J*=7.6Hz, Ar-H), 7.37-7.39 (2H, d, *J*=8Hz, Ar-H), 7.64-8.17 (10H, m, Ar-H), 8.93 (1H, s, Oxazepine H). ¹³C NMR (DMSO): δ (ppm) = 102.17, 107.45, 109.06, 120.49, 124.61(4C).

126.48(2C), 127.42(2C), 128.18(2C), 128.88, 129.10, 129.74, 130.02, 130.74, 132.81, 135.47, 135.51, 144.43, 148.62, 150.10, 189.21(C=N).

7-(Benzo[d][1,3]dioxol-5-yl)-5-(naphthalen-2-yl)-4,5-dihydro-1H-1,4-diazepine-2,3-dicarbonitrile (5b). Black crystals from ethanol, m.p. 170 °C, 75% yield. FTIR (KBr): ν (cm⁻¹) = 3406, 3319 (NH 's), 3052 (CH-Ar), 2248 (C≡N), 2211 (C≡N). MS: m/z = 392 (M⁺, 26.63%, C₂₄H₁₆N₄O₂). ¹H NMR (DMSO): δ (ppm) = 6.12 (2H, s, CH₂ of dioxole), 6.99-7.01 (1H, d, *J*=8 Hz, diazepine-H), 7.35 -7.37 (1H, d, *J*=8 Hz, =CH diazepine), 7.62–8.15 (10H, m, Ar-H), 8.91 (1H, s, NH of diazepine), 9.15 (1H, s, NH of diazepine). ¹³C NMR (DMSO): δ (ppm) = 89.99, 102.17, 107.44, 109.03, 114.38, 117.35, 120.48(C≡N), 124.61(C≡N), 126.45, 126.91, 127.39, 128.16, 128.85, 129.06, 129.75, 130.01, 130.73, 132.81, 135.46, 135.53, 144.40, 148.61, 150.09, 169.02.

7-(Benzo[d][1,3]dioxol-5-yl)-5-(naphthalen-2-yl)-[1,2,4]triazolo[1,5-a]pyrimidine (6b). Red crystals from ethanol, m.p. 180°C, 50% yield. FTIR (KBr): ν (cm⁻¹) = 3056 (CH-Ar), 1676 (C=C), 1502 (C=N). MS: m/z = 366 (M⁺, 18.13%, C₂₂H₁₄N₄O₂). ¹H NMR (DMSO): δ (ppm) = 6.13(2H, s, CH₂ of dioxole), 6.86-8.13(10H, m, Ar-H), 8.15(1H, s, triazole H), 8.68(1H, s, Pyrimidine H).

2.6. Synthesis of Compounds (7a, and 7b)

To a mixture from chalcone (**1a**, or **1b**) (10 mmol) and thiourea (1.2 g, 12 mmol) dissolved in ethanol (50 mL), sodium hydroxide (1.0 g, 25 mmol) was added. The reaction mixture was refluxed for 6 hours then left to cool overnight. The precipitate was filtered, washed, and crystallized from ethanol to afford (**7a**) and (**7b**), respectively.

4-(1H-Indol-3-yl)-6-(naphthalen-2-yl)pyrimidine-2-thiol (7a). Brown crystals from ethanol, m.p. 178 °C, 65% yield. FTIR (KBr): ν (cm⁻¹) = 3443 (NH), 3250 (SH), 3041 (CH-Ar), 1633 (C=C), 1575 (C=N). MS: m/z = 353 (M⁺, 16.52%, C₂₂H₁₅N₃S). ¹H NMR (DMSO): δ (ppm) = 2.69 (1H, s, SH), 7.2–7.29 (7H, m, Ar-H), 7.51-8.14 (4H, m, Ar-H), 8.29 (1H, s, Pyrimidine H), 9.95 (1H, s, indole H), 12.16 (1H, s, NH of indole).

4-(Benzo[d][1,3]dioxol-5-yl)-6-(naphthalen-2-yl)pyrimidine-2-thiol (7b). Red crystals from ethanol, m.p. 170 °C, 58% yield. FTIR (KBr): ν (cm⁻¹) = 3384 (SH), 3056 (CH-Ar), 1674 (C=C), 1566 (C=N). MS: m/z = 358 (M⁺, 33.40%, C₂₁H₁₄N₂O₂S). ¹H NMR (DMSO): δ (ppm) =

2.71(1H, s, SH), 6.02 (2H, s, CH₂ of dioxole), 6.67-8.6 (10H, m, Ar-H), 8.70 (1H, s, Pyrimidine H).

2.7. Synthesis of Compounds (8a and 8b)

An equimolar mixture of compound (7a) or (7b) (10 mmol) and hydrazine hydrate (10 mmol), dissolved in ethanol acidified with glacial acetic acid (5 drops) was refluxed for 6 hours then left to cool down overnight. The precipitate obtained was filtered, washed, and recrystallized from ethanol to afford (8a), and (8b), respectively.

3-(2-Hydrazinyl-6-(naphthalen-2-yl)pyrimidin-4-yl)-1H-indole (8a). Yellow crystals from ethanol, m.p. 190°C, 74% yield. FTIR (KBr): ν (cm⁻¹) = 3409 (NH), 3214 (NH₂), 3110 (NH), 3055 (CH-Ar), 1618 (C=N), 1574 (C=N). MS: m/z = 351 (M⁺, 3.83%, C₂₂H₁₇N₅). ¹H NMR (DMSO): δ (ppm) = 6.51-8.38 (14H, m, Ar-H, NH, NH₂), 8.42(1H, s, Pyrimidine H), 8.92 (1H, s, indole H), 11.71 (1H, s, NH of indole).

4-(Benzo[d][1,3]dioxol-5-yl)-2-hydrazinyl-6-(naphthalen-2-yl)pyrimidine (8b). Orange crystals from ethanol, m.p. 205 °C, 74% yield. FTIR (KBr): ν (cm⁻¹) = 3383 (NH), 3179 (NH₂), 3055 (CH-Ar), 1600 (C=C), 1566 (C=N). MS: m/z = 356 (M⁺, 59.19%, C₂₁H₁₆N₄O₂). ¹H NMR (DMSO): δ (ppm) = 6.10-6.13 (2H, d, $J=8$ Hz, CH₂ of dioxole), 6.79-8.15 (12H, m, Ar-H, NH₂), 8.5(1H, s, NH), 8.6(1H, s, Pyrimidine H).

2.8. Synthesis of Compound (9a):

An equimolar mixture of compound (3a) (4.78, 10mmol) in glacial acetic acid (40 mL) containing fused sodium acetate (1g) and chloroacetic acid (0.95g, 10 mmol) was heated under reflux for 3 hours. The reaction mixture was then poured onto water and the precipitate formed was filtered, dried and recrystallized from ethanol/ DMF to afford compound (9a).

2-((5-(1H-Indol-3-yl)-7-(naphthalen-2-yl)-4-oxo-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl)thio)acetic acid (9a). Yellow crystals from DMF/EtOH, m.p. >300°C, 80% yield. FTIR (KBr): ν (cm⁻¹) = 2500-3500 (NH, OH), 3213, 3110 (NH 's), 3058 (CH-Ar), 2925 and 2724 (CH₂ aliphatic), 1667 (C=O), 1576 (C=N). MS: m/z = 478 (M⁺, 6.52%, C₂₇H₁₈N₄O₃S). ¹H NMR (DMSO): δ (ppm) = 1.93 (2H, s, CH₂), 6.73-7.48 (11H, m, Ar-H), 8.27 (1H, s, Pyridine H), 8.71 (1H, s, indole H), 9.53 (1H, s, NH of Pyrimidine), 12.67 (1H, s, NH of indole), 13.29 (1H, s, OH).

2.9. Synthesis of 2-Hydrazinylpyrido[2,3-d]pyrimidine (10a)

2.9.1. Method A: A mixture of (3a) (1.91 g, 4 mmol) and hydrazine hydrate (3 mL, 99%, 60 mmol) in absolute ethanol (20 mL) was heated under reflux for 15 hours. The reaction mixture was cooled, and the precipitate formed was filtered, dried and crystallized from DMF to give (10a) (yield 74%).

2.9.2. Method B: The above procedure was repeated using ultrasonic irradiation for 45 minutes to give (10a) (yield 87%).

2.9.3. Method C: The above procedure was repeated in absence of solvent and, the reaction mixture was exposed to microwave irradiation for 2 minutes, to give compound (10a) (yield 95%).

2-Hydrazinyl-5-(1H-indol-3-yl)-7-(naphthalen-2-yl)pyrido[2,3-d]pyrimidin-4(3H)-one (10a). Yellow crystals from DMF, m.p. >300°C, 95% yield in microwave, 87% yield in ultrasonic and 74% yield in thermal. FTIR (KBr): ν (cm⁻¹) = 3435 (NH), 3350, 3272 (NH, NH₂), 3002 (CH-Ar), 1708 (C=O), 1688 (C=C), 1573 (C=N). MS: m/z = 418 (M⁺, 13.04%, C₂₅H₁₈N₆O). ¹H NMR (DMSO): δ (ppm) = 4.93 (2H, s, NH₂), 6.64-7.48 (11H, m, Ar-H), 8.17 (1H, s, NH), 8.23 (1H, s, Pyridine H), 8.6 (1H, s, indole H), 8.64 (1H, s, NH of Pyrimidine), 9.47 (1H, s, NH of indole).

2.10. Synthesis of Compounds (11a-13a)

2.10.1. General Procedure:

2-Hydrazinylpyrido[2,3-d]pyrimidine (10a) (0.418 g, 1 mmol) was reacted with excess of benzaldehyde, maleic anhydride or phenylisothiocyanate, (1 mmol) in the appropriate solvent for 4 hours. The products obtained were recrystallized from the appropriate solvent to give compounds (11a-13a), respectively.

2-(2-Benzylidenehydrazinyl)-5-(1H-indol-3-yl)-7-(naphthalen-2-yl)pyrido[2,3-d]pyrimidin-4(3H)-one (11a). Brown crystals from DMF/Ethanol [1:1], m.p. > 300 °C, 53% yield. FTIR (KBr): ν (cm⁻¹) = 3422, 3263, 3143 (NH 's), 3060 (CH-Ar), 1682 (C=O), 1659 (C=C), 1579 (C=N). MS: m/z = 506 (M⁺, 51.66%, C₃₂H₂₂N₆O). ¹H NMR (DMSO): δ (ppm) = 6.67-7.49 (16H, m, Ar-H), 8.19 (1H, s, CH=N), 8.68 (1H, s, Pyridine H), 9.53 (1H, s, indole H), 11.85 (1H, s, N-NH), 12.71 (1H, s, NH of Pyrimidine), 13.27 (1H, s, NH of indole).

1-((5-(1H-Indol-3-yl)-7-(naphthalen-2-yl)-4-oxo-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl)amino)-1H-pyrrole-2,5-dione (12a). Yellow crystals from DMF/Ethanol, m.p. >300°C, 82%

yield. FTIR (KBr): ν (cm^{-1}) = 3438, 3259 (NH 's), 3058 (CH-Ar), 1681&1660 (C=O), 1621 (C=C), 1579 (C=N). MS: m/z = 498 (M^+ , 27.07%, $C_{29}H_{18}N_6O_3$). 1H NMR (DMSO): δ (ppm) = 1.87 (1H, s, NH), 6.66-6.88 (2H, d, $J=8.8\text{Hz}$, =CH), 7.02-8.70 (11H, m, Ar-H), 8.23(1H, s, Pyridine H), 8.64 (1H, s, indole H), 9.48 (1H, s, NH of Pyrimidine), 12.65 (1H, s, NH of indole).

2-(5-(1H-Indol-3-yl)-7-(naphthalen-2-yl)-4-oxo-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl)-N-phenylhydrazinecarbothioamide (13a). Orange crystals from ethanol, m.p. 298 °C, 82% yield. FTIR (KBr): ν (cm^{-1}) = 3426, 3325, 3258 (NH 's), 3057 (CH-Ar), 1681 (C=O), 1622 (C=C), 1579 (C=N), 1233 (C=S). MS: m/z = 553 (M^+ , 12.39%, $C_{32}H_{23}N_7OS$). 1H NMR (DMSO): δ (ppm) = 6.95-7.56 (16H, m, Ar-H), 8.56-9.02 (3H, s, NH), 9.47-10.13 (3H, s, NH of Pyrimidine, indole H, Pyridine H), 13.66 (1H, s, NH of indole). ^{13}C NMR (DMSO): δ (ppm) = 114.38, 116.17, 117.28, 117.88, 121.50, 122.69, 124.12, 124.66(2C), 124.89, 126.38(2C), 128.43, 128.90, 129.27, 129.44(2C), 129.62(2C), 129.76(2C), 130.36, 139.93, 140.24, 141.68(2C), 156.18(2C), 156.89(2C=N), 180.10(C=O), 181.70(C=S).

2.11. Synthesis of Compound (14a)

An equimolecular mixture of (**10a**) (0.418 g, 1 mmol) and acetyl chloride (1 mmol) in dry pyridine was refluxed for 20 hours. The reaction mixture was cooled and the precipitate formed was filtered, dried and crystallized DMF/ethanol (1:1) to give (**14a**) (yield 79%).

6-(1H-Indol-3-yl)-3-methyl-8-(naphthalen-2-yl)pyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one (14a). Yellow crystals from DMF/Ethanol [1:1], m.p. > 300 °C, 79% yield. FTIR (KBr): ν (cm^{-1}) = 3421, 3348 (NH 's), 3054 (CH-Ar), 1700 (C=O), 1652 (C=C), 1515 (C=N). MS: m/z = 442 (M^+ , 17.46%, $C_{27}H_{18}N_6O$). 1H NMR (DMSO): δ (ppm) = 123(3H, s, CH_3), 6.64-7.13 (13H, m, Ar-H, indole H, Pyridine H), 8.18 (1H, s, NH of triazole), 8.55 (1H, s, NH of indole).

3. Medicinal and Biological Activities

3.1. Evaluation of Cytotoxic (Antitumor) Activity of Some Synthesized Compounds

The antitumor activity of the newly synthesized compounds containing indole moiety (**3a-5a**, **7a**, and **13a**) and compounds containing benzodioxole moiety (**3b-5b** and **7b**) was evaluated against two tumor cell lines (MCF-7 breast carcinoma cell line, HCT-116 colon carcinoma cell line). The results obtained shows that compounds containing indole moiety are

having higher antitumor activity than those which are having benzodioxole moiety. Compound (5a) shows the highest antitumor activity agent against HCT-116 and MCF-7 cell lines, whereas (7a), and (13a) shows high antitumor activity agent against HCT-116 and moderate against MCF-7 cell line. Compound (4a) shows moderate activity against both HCT-116 and MCF-7 cell lines. Whereas (3a) was the lowest activity against both the two cell lines. The tested compounds (3b-5b and 7b) show that compound (4b) is the highest active one against both cell lines.

However, all compounds (3a-5a, 7a, and 13a) and (3b-5b and 7b) are having antitumor activity against the HCT-116 cell higher than against MCF-7 cell line, the results obtained are given in (Table 1) which represents the IC₅₀ values, i.e., the doses that reduces survival to 50%.

Table 1. Antitumor activities of compounds (3a), (4a), (5a), (7a), (13a), (3b), (4b), (5b), (7b) against two tumor cell lines (survival, %, and IC₅₀, µg/mL)

		Cell survival, %								
tumor cell line	Concentration, µg/mL	(3a)	(4a)	(5a)	(7a)	(13a)	(3b)	(4b)	(5b)	(7b)
MCF-7 cell line	500	29.73	5.86	2.31	4.76	6.25	17.46	1.89	5.28	2.85
	250	47.52	12.53	5.68	9.83	11.89	33.97	4.57	11.94	6.34
	125	76.64	19.47	10.94	16.42	22.74	58.06	9.46	24.61	10.29
	62.5	95.01	34.69	17.52	25.34	31.57	81.37	18.73	39.70	23.75
	31.25	99.48	42.83	27.03	32.69	39.02	97.14	30.64	68.23	39.12
	15.6	100	62.67	36.54	43.12	48.19	100	48.75	88.04	76.28
	7.8	100	81.47	45.69	54.95	59.24	100	79.41	98.26	89.43
	3.9	100	93.04	60.34	69.23	78.16	100	88.27	100	96.21
	2	100	99.52	76.92	84.15	92.65	100	94.86	100	99.46
	1	100	100	91.43	93.91	98.73	100	97.35	100	100
	0	100	100	100	100	100	100	100	100	100
IC ₅₀ , µg/mL		239	25.6	6.65	11	14.3	166.8	15.3	51.2	26.6

HCT-116 cell line	500	18.46	3.18	1.04	2.36	2.85	13.81	1.23	4.72	2.48
	250	38.29	7.61	3.19	5.97	6.54	27.45	3.85	9.87	5.71
	125	57.02	14.93	7.41	11.28	12.78	49.21	8.17	21.43	11.87
	62.5	81.43	23.08	12.35	18.65	20.39	78.34	15.94	33.89	20.93
	31.25	97.65	32.87	19.48	24.60	27.83	90.63	26.59	57.41	34.69
	15.6	100	45.23	26.79	33.64	35.20	98.40	37.48	80.67	53.75
	7.8	100	70.91	34.72	42.96	45.85	100	52.61	94.23	78.04
	3.9	100	88.42	47.08	59.21	78.64	100	76.34	99.65	91.75
	2	100	98.27	69.13	80.34	93.21	100	89.06	100	98.69
	1	100	100	85.22	89.62	97.46	100	95.72	100	100
	0	100	100	100	100	100	100	100	100	100
IC ₅₀ , µg/mL		172	14.2	3.74	6.11	7.31	123.3	9.15	41.1	18.7

3.2. Evaluation of Antibacterial Activity of Some Synthesized Compounds

Employing the diffusion method, [36] the compounds were studied in vitro for their antibacterial activity against two gram-positive bacteria, *Staphylococcus aureus* (S. a.) and *Bacillus subtilis* (B. s.), and two gram-negative bacteria, *Escherichia coli* (E. c.) and *Proteus vulgaris* (P. v.), and also for their antifungal activity against fungus strain, namely, *Aspergillus fumigatus*. In this method, screening tests regarding the inhibition zone were carried out, where the compounds were dissolved in (DMSO) as a solvent in different concentrations (10, 5, and 2.5 mg/ml) and the inhibition zone of bacterial and fungi growth around the disc. The results of the antibacterial and antifungal activities showed that compounds containing indole moiety (**2a-14a**) are more biologically active than compounds containing benzodioxole moiety (**2b-8b**) (Table 2). From the first group, compounds (**4a,6a,13a**) were the most potent towards all the Gram-positive and Gram-negative bacteria, as well as studied fungi. However, compounds containing indole moiety showed moderate to high effects toward the studied bacteria and fungi, while the results of compounds containing benzodioxole moiety (**2b-8b**) showed that only compound (**2b**) showed high effects against *proteus vulgaris* bacteria and showed low or no effect against the other species,

the other compounds containing benzodioxole moiety showed low or no effect against the studied bacteria and fungi.

Table 2. Antibacterial and antifungal activities of the synthesized compounds

Comp. (10mg/mL)	Inhibition zone, mm				
	Antibacterial activity				Antifungal activity
	<i>S. aureus</i>	<i>B. subtilis</i>	<i>E. coli</i>	<i>P. vulgaris</i>	<i>A. fumigatus</i>
2a	—	—	15	20	—
3a	—	—	14	18	—
4a	2	17	18	25	17
5a	16	11	13	18	—
6a	15	13	16	17	14
7a	11	9	10	13	15
8a	20	14	15	18	—
9a	—	—	12	15	—
10a	—	—	13	14	—
11a	13	—	8	9	—
12a	—	10	14	13	—
13a	17	18	20	21	20
14a	—	—	12	15	—
2b	—	12	—	24	—
3b	—	—	—	—	—
4b	—	12	—	—	—
5b	—	10	—	—	—
6b	—	13	—	—	—
7b	—	13	—	—	—
8b	—	11	—	—	—
Std. a	24	26	30	25	17

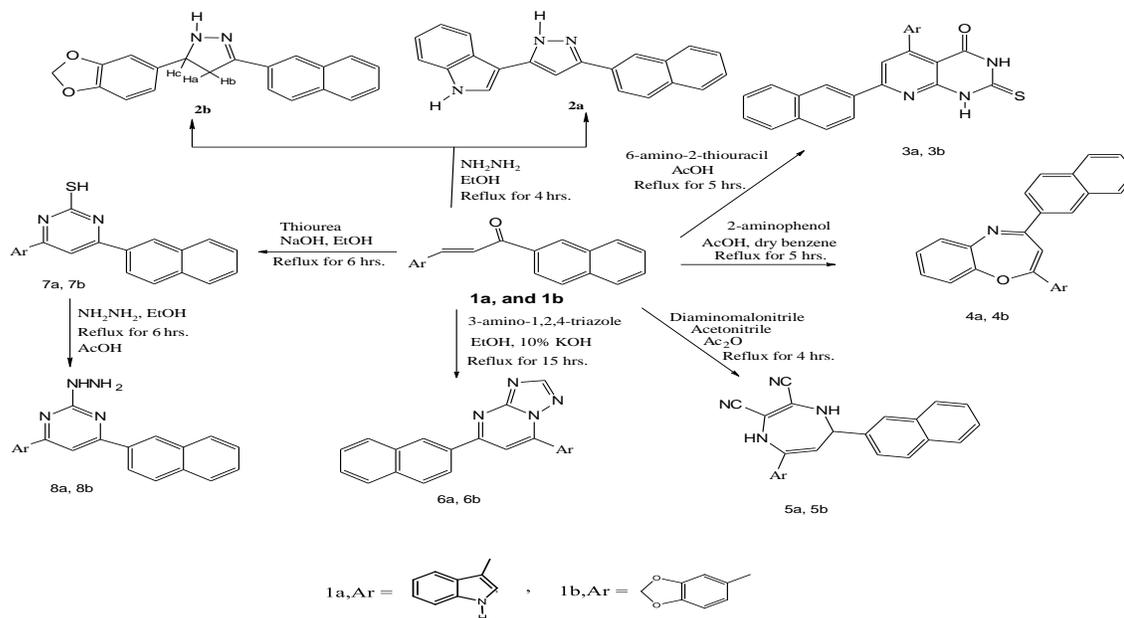
4. Discussion of the Results

Chalcones (**1a** and **1b**) have been prepared the by conventional technique (Method A) [31,32], but due to their importance in medicinal chemistry, we aimed to prepare them using green chemistry tools, such as ultrasonic (Method B) [37] and microwave (Method C) [38] irradiation techniques in order to achieve their synthesis with clean environment in good yield and purity.

Comparison the three techniques (A), (B) and (C), showed that microwave irradiation technique (C) facile more advantages over the conventional technique (A) and ultrasonic irradiation technique (B), since it reduces the reaction time, by-products, use of solvents, and most importantly it enhances yield and purity of products (Green Chemistry).

According to Scheme 1 chalcones **1a** and **1b** were used for building newly synthesized heterocycles pyrazolines (**2a**, and **2b**), pyrimidine-2-thiones (**3a**, **3b**), oxazepines (**4a**, and **4b**),

diazepines (**5a**, and **5b**), triazolo-pyrimidine (**6a**, and **6b**), and pyrimidine-2-thiol derivatives (**7a**, and **7b**), respectively. Moreover, reaction of (**7a**, and **7b**) with hydrazine hydrate afforded the corresponding (**8a**, and **8b**) (Scheme 1).



Scheme 1: Reactions of chalcones (**1a**) and (**1b**)

Moreover, pyrimidine-2-thiones (**3a**) reacted with chloroacetic acid in glacial acetic acid containing fused sodium acetate to yield pyrimidin-2-ylthioacetic acid derivative (**9a**), whereas, its reaction with hydrazine hydrate, gave 2-hydrazinylpyrido[2,3-d]pyrimidine derivative (**10a**). The latter has been used as a functionalizing agent and reacted with benzaldehyde to give (**11a**), with maleic anhydride and phenylisothiocyanate to afford (**12a**), (**13a**), respectively. Also, (**10a**) reacted with acetyl chloride to afford (**14a**) (Scheme 2).

Structural formulas of compounds (**2a-14a**) and (**2b-8b**), have been confirmed through their spectral data; FT-IR, ^1H NMR, ^{13}C NMR and MS. The FT-IR of (**2a**) showed the disappearance of at 1700 cm^{-1} assigned to CO stretching vibration in (**1a**) and appearance of two absorption bands at 3375 , 3225 cm^{-1} assignable for two NH groups. The formation of (**2b**) was confirmed by the disappearance of at 1690 cm^{-1} assigned to CO stretching vibration in chalcone (**1b**) and appearance of an absorption band at 3344 cm^{-1} , assignable for one NH group; both (**2a**) and (**2b**) showed band at 1580 cm^{-1} , assignable for C=N group. ^1H NMR spectrum of compound (**2a**) showed the disappearance of the doublet at δ 7.84 and 8.14 ppm ($J = 15.6$) that was

characterized for HC=CH in chalcone (**1a**) with the appearance of pyrazole NH singlets (D_2O exchangeable) at δ 8.41 ppm, and pyrazole H singlet at (7.92-7.98) ppm. Also (**2b**) showed disappearance of the doublet signal 7.67–7.69 ($J = 8$) characteristic HC=CH in chalcone (**1b**), and appearance of signals at δ 2.91-2.99 (dd; pyrazoline H_a), 3.48-3.55 (dd; pyrazoline H_b) and 4.79-4.88 (dd; pyrazoline H_c) ppm, respectively, also it showed pyrazole NH singlet (D_2O exchangeable) at 7.65 ppm.

The FT-IR spectrum of (**3a**) showed disappearance of carbonyl stretching vibrations of chalcone (**1a**) and appearance of absorption bands at 3443, 3363 1554 and 1230 cm^{-1} assignable for the (NH 's), (C=N) and (C=S) groups, respectively, also (**3b**) showed the disappearance of CO stretching vibrations in chalcone (**1b**) and appearance of absorption bands at 3337, 3243, 1594 and 1235 cm^{-1} characteristic for the (NH 's), (C=N) and (C=S) groups, respectively. Moreover, its 1H NMR spectrum showed the disappearance of the characteristic HC=CH proton peaks of chalcone (**1a**) with the appearance of signals at δ 7.84 and 8.14 ppm (dd; $J = 15.6$), 12.67 (s; NH) and 13.20 (s; NH) ppm assignable for the two protons of the two NH groups in the pyrimidine ring. Also, pyrimidinethione (**3b**) showed signals in the region of 7.67–7.69 (dd; $J = 8$) and two protons assignable for two signals at δ 12.31 (s; NH) and at 12.98 (s; NH) representing the two NH groups in the pyrimidine ring, respectively.

Formation of (**4a**) was confirmed through its FT-IR spectrum where it showed the appearance of bands at 1575 and 1124 cm^{-1} , characteristic for C=N and C-O-C groups, respectively, and also (**4b**) showed the appearance of bands at 1690 and 1583 cm^{-1} , assignable for C=N, and 1122 cm^{-1} , characteristic for C-O-C. The 1H NMR spectrum of (**4a**) represented signals at 7.84 and 8.14 (d; $J = 15.6$), and 8.29 ppm (s; oxazepine H). Also, the 1H NMR spectrum of (**4b**) represented signals in the region 7.67–7.69 (d; $J = 8$), and 8.93 ppm (s; oxazepine H). Moreover, The ^{13}C NMR spectra showed the disappearance of the peak's characteristic for (C=C) carbon of chalcones (**1a**) and (**1b**) at 147 and 149, respectively with the appearance of the resulted (C=N) carbon at 185.43 and 189.21, for (**4a**) and (**4b**), respectively.

The FT-IR spectrum of (**5a**) showed the disappearance of CO stretching vibration and appearance of the two absorption bands at 2230 and 2202 cm^{-1} assignable for $C\equiv N$ group, and two absorption bands ranging from 3458 to 3381 cm^{-1} representing two NH groups. Also, the FT-IR

spectrum of (**5b**) showed the disappearance of CO stretching vibrations characteristic for chalcone (**1b**) with the appearance of two absorption bands at 2248 and 2211 cm^{-1} assignable for two $\text{C}\equiv\text{N}$ groups, and two absorption bands at 3406 and 3319 cm^{-1} representing two NH groups.

In addition to the IR, the ^1H NMR spectrum of (**5a**) showed the disappearance of the characteristic $\text{HC}=\text{CH}$ proton peaks of chalcone (**1a**) and appearance of signals at 7.84 and 8.14 (d; $J = 15.6$) and two singlets (D_2O exchangeable) at 8.51 and 8.67 ppm (2s; NH). Moreover, ^{13}C NMR spectrum of (**5b**) showed the disappearance of the characteristic ($\text{C}=\text{C}$) carbon peaks of chalcone (**1b**) appeared at 147 and appearance of the resulted two ($\text{C}\equiv\text{N}$) carbon at 120.48 and 124.61. Also, the ^1H NMR spectrum of (**5b**) showed the disappearance of the characteristic $\text{HC}=\text{CH}$ proton peaks of chalcone (**1b**) and appearance of signals in the region 7.67–7.69 (d; $J = 8$) and two singlets (D_2O exchangeable) at 8.91 and 9.15 ppm (2s; NH).

Formation of (**6a**) and (**6b**) has been established by carrying out their FT-IR spectrum where they showed the appearance of absorption bands at 1530 and 1502 cm^{-1} , confirming the presence of the $\text{C}=\text{N}$ group in (**6a**) and (**6b**), respectively. The ^1H NMR spectrum of (**6a**) showed the appearance of doublet at δ 7.84 and 8.14 ($J = 15.6$), the triazole proton singlet at 8.13 ppm, and pyrimidine proton singlet at 8.29 ppm. Compound (**6b**) showed the appearance of doublet signals in the region of 7.67–7.69 ppm ($J = 8$), the triazole proton singlet at 8.15 ppm, and pyrimidine proton singlet at 8.68 ppm.

IR spectrum of (**7a**) represented the appearance of absorption bands at 3250 and 1575 cm^{-1} assignable for (SH) and ($\text{C}=\text{N}$), respectively, (**7b**) showed absorption bands at 3384 and 1566 cm^{-1} assigned for (SH) and ($\text{C}=\text{N}$), respectively. Moreover, the formation of (**8a**) and (**8b**) was confirmed by their FT-IR, where disappearance of sulfur (SH) absorption bands takes place with the appearance of (NH) bands at 3110 and 3383 cm^{-1} , and (NH_2) absorption band at 3214 and 3179 cm^{-1} corresponding to (**8a**) and (**8b**), respectively. Also, the ^1H NMR spectrum for (**7a**) showed appearance of a doublet at 7.84 and 8.14 ($J = 15.6$) singlets at 2.69 ppm assignable for SH groups, for (**7b**) it showed the appearance of a doublet signals in the region of 7.67–7.69 ppm ($J = 8$) and a singlet at 2.71 ppm assignable for SH proton. However, the ^1H NMR spectra showed the protons assignable for (NH), (NH_2) groups at the region of 6.51-8.38 ppm for (**8a**) and for (**8b**) (NH)

appears singlet at 8.5 ppm, and (NH₂) groups at the region of 6.79-8.15. Moreover, the elemental analysis showed no sulfur in products **(8a)** and **(8b)**.

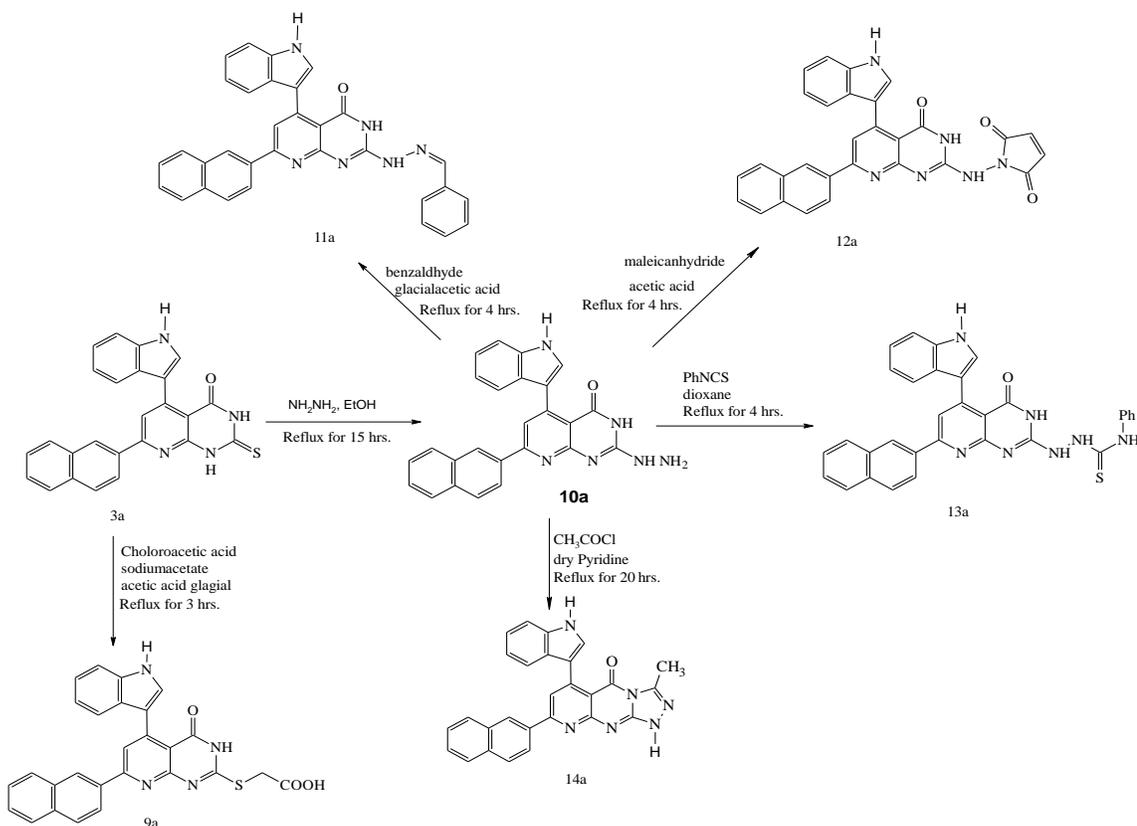
The FT-IR spectrum of **(9a)** showed the disappearance of (C=S) absorption bands at 1235 Cm⁻¹ and appearance of absorption bands at 2500-3500 cm⁻¹, assignable for (NH, OH) group, and at 2925 and 2724 cm⁻¹ assignable for aliphatic CH₂ group. Moreover, it showed a band at 1622 Cm⁻¹ ascribed to C=O group attached to NH group. Its ¹H NMR spectrum showed the disappearance of NH proton of uracil singlet at 13.20 ppm and appearance of the carboxyl proton singlet at 13.29 ppm.

The formation of **(10a)** was confirmed by its FT-IR spectrum where it showed the disappearance of (C=S) absorption bands at 1235 Cm⁻¹ and appearance of absorption bands at 3435 and 3272 cm⁻¹, assignable for NH and NH₂ groups, respectively. Its ¹H NMR spectrum showed the disappearance of the singlets at 12.67 ppm assigned to NH proton of pyrimidine ring **(3a)** and shift of the other NH singlet proton of pyrimidine ring from δ 13.20 to 8.64, also a new singlet appeared at δ 8.17 ppm assigned to the NH (D₂O exchangeable), and another singlet appeared at δ 4.93 ppm which has been assigned to NH₂ protons. However, formation of compound **(11a)** was attributed to its FT-IR and ¹H NMR spectra where the IR showed an absorption band at 1579 cm⁻¹ assignable for C=N group. Its ¹H NMR spectrum also displayed the N-NH proton singlet at 11.85 ppm with the disappearance of the singlet at 4.93 ppm assigned for NH₂ protons in **(10a)**, with the appearance of (CH=N) singlet proton at 8.19 ppm.

Also, synthesis of **(12a)** was proved by its FT-IR spectrum where it represented two absorption bands at 1681 and 1660 cm⁻¹ assignable for (2C=O) groups, and at 1621 cm⁻¹ characteristic for (C=C). The ¹H NMR spectrum did not show the singlet at 4.93 ppm that was assigned to NH₂ protons in **(10a)**. It showed singlet at 1.87 ppm representing an NH proton, doublet at the region of 6.66-6.88 ppm assigned to two (=CH) protons.

Confirmation of compound **(13a)** structure was arrived at by its FT-IR, ¹H NMR and ¹³C NMR spectra, where its IR spectrum showed absorption bands at 1622 cm⁻¹ and 1233 cm⁻¹ assignable for C=C and (C=S) groups. Its ¹H NMR spectrum confirmed its formation where it showed three singlets at the region of δ 8.56-9.02 ppm, assigned to NH protons, with the disappearance of the singlet at 4.93 ppm that was assigned to the NH₂ protons in **(10a)**, and its

^{13}C NMR also showed the (C=S) carbon at 181.70. The formation of compound (**14a**) was arrived at by its FT-IR spectrum where it showed absorption band at 1515 cm^{-1} indicating the presence of (C=N) group. Its ^1H NMR spectrum, also displayed singlet signal at 1.23 ppm, for the methyl protons and singlet at 8.18 ppm for triazole NH proton. The MS data of all the compounds prepared were in accordance with their structural formulas.



Scheme 2: Reactions of pyrimidine-2-thiones (**3a**), and hydrazinylpyrido[2,3-d]pyrimidine derivative (**10a**).

5. Conclusion

In the present work, we successfully in one-pot synthesized and evaluated a new interesting heterocyclic compound (**2a-14a**) and (**2b-8b**) such as pyrazolines, pyrimidine-2-thioness, diazepines, oxazepines, triazolo-pyrimidines, pyrimidine-2-thiols and hydrazinyl-pyrimidine compounds based on chalcone compound. [39-41] [42] Moreover, pyrimidine-2-thiones (**3a**) was used to synthesize pyrimidin-2-ylthioacetic acid (**9a**), and 2-hydrazinylpyrido[2,3-d]pyrimidine derivative (**10a**) which has been used as a functionalizing agent to produce compounds (**11a-14a**).

Interesting compounds that are having pyrimidine-2-thiones and hydrazinylpyrido[2,3-d]pyrimidine moiety were synthesized using conventional, microwave, and ultrasound assisted synthesis technique in order to compare between them. Comparison between the three methods of preparation showed that both ultrasonic (B) and) microwave (C) irradiation techniques are more beneficiary than conventional (A) technique, where they gave better yields and purity, reduce the reaction time, by-products, amounts of solvents. Method (C) has more advantages than (B) where it eliminates the use of solvents, hazardous and most importantly formed the best yield and purity in shorter time (Green Chemistry). The structural formulas of the synthesized compounds were confirmed by their spectral data; FT-IR, ¹H NMR, ¹³C NMR and MS. The results of the antibacterial and antitumor activity showed that compounds containing indole moiety are highly biologically active than compounds containing benzodioxole moiety. [42]

Declaration of Competing Interest

Authors have declared no conflict of interest for publication of this work.

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References

- [1] M. M. Kandeel, S. M. Ali, E. K. A. Abed El Ali, M. A. Abdelgawad, P. F. Lamie, Synthesis and Characterisation of novel Schiff bases containing pyrimidine unit, *Org. Chem. Indian J*, 9: (2013) 81-91.
- [2] C. R. Petrie, H. B. Cottam, P. A. Mckernan, R. K. Robins, G. R. Revankar, Synthesis and biological activity of 6-azacadeguomycin and certain 3, 4, 6-trisubstituted pyrazolo [3, 4-d] pyrimidine ribonucleosides, *Journal of medicinal chemistry*, 28: (1985) 1010-1016.
- [3] Elham Zarenezhad, Mojtaba Farjam, Aida Iraj, Synthesis and biological activity of pyrimidines-containing hybrids: Focusing on pharmacological application, *Journal of Molecular Structure*, 1230: (2021) 129833.
- [4] M. N. Nasr, M. Gineinah, Pyrido [2, 3-d] pyrimidines and Pyrimido [5', 4': 5, 6] pyrido [2, 3-d] pyrimidines as New Antiviral Agents: Synthesis and Biological Activity, *Archiv der Pharmazie: An International Journal Pharmaceutical and Medicinal Chemistry*, 335: (2002) 289-295.
- [5] P. G. Baraldi, M. G. Pavani, M. Nunez, P. Brigidi, B. Vitali, R. Gambari, R. I. Romagnoli, Antimicrobial and antitumor activity of N-heteroimine-1, 2, 3-dithiazoles and their transformation in triazolo-, imidazo-, and pyrazolopyrimidines, *Bioorganic & medicinal chemistry*, 10: (2002) 449-456, [https://doi.org/10.1016/S0968-0896\(01\)00294-2](https://doi.org/10.1016/S0968-0896(01)00294-2).
- [6] R. V. Antre, A. Cendilkumar, D. Goli, G. S. Andhale, R. J. Oswal, Microwave assisted synthesis of novel pyrazolone derivatives attached to a pyrimidine moiety and evaluation of their anti-inflammatory,

analgesic and antipyretic activities, Saudi pharmaceutical journal, 19: (2011) 233-243, <https://doi.org/10.1016/j.jsps.2011.05.006>.

[7] S. M. Sondhi, M. Johar, S. Rajvanshi, S. G. Dastidar, R. Shukla, R. Raghubir, J. W. Lown, Anticancer, anti-inflammatory and analgesic activity evaluation of heterocyclic compounds synthesized by the reaction of 4-isothiocyanato-4-methylpentan-2-one with substituted o-phenylenediamines, o-diaminopyridine and (un) substituted o, Australian Journal of Chemistry 54: (2001) 69-74, <https://doi.org/10.1071/CH00141>.

[8] A. Z. Chowdhury, M. M. Matin, M. N. Anwar, Chittagong Univ. Stud Part II Sci, (1997) 21-79; ref. Chem Abstr 1999;130:237530.

[9] K. S. Parikh, S. P. Vyas, Synthesis and Microbial Studies of Some Novel Schiff Base Containing Pyrimidine, International Journal of Pharmaceutical Sciences and Research, 3: (2012) 3425.

[10] N. P. Singh, A. N. Srivastava, Synthesis, Characterization and Antimicrobial Studies of Novel Binuclear Transition Metal Complexes of Schiff Base Derived from 1-Amino-5-methyl-2,6-pyrimidinedione and 2,3-Butanedione, Asian Journal of Chemistry, 25: (2013) 533-537, <http://dx.doi.org/10.14233/ajchem.2013.13484>.

[11] S. Maddila, A. S. Kumar, S. Gorle, M. Singh, P. Lavanya, S. B. Jonnalagadda, Synthesis and antioxidant activity of 1, 2, 4-triazole linked thieno [2, 3-d] pyrimidine derivatives, Letters in Drug Design & Discovery, 10: 186-193 (2013) 186-193, <https://doi.org/10.2174/157018013804725152>.

[12] P. Vicini, A. Geronikaki, M. Incerti, B. Busonera, G. Ooni, C. A. Kabras, P. L. Colla, Synthesis and biological evaluation of benzo [d] isothiazole, benzothiazole and thiazole Schiff bases, Bioorganic & medicinal chemistry 11: (2003) 4785-4789, [https://doi.org/10.1016/S0968-0896\(03\)00493-0](https://doi.org/10.1016/S0968-0896(03)00493-0).

[13] R. Yerra, K. Naresh, K. N. Jayaveera, Int. J. PharmTech Res. 4: (2012) 648-654.

[14] K. S. Parikh, S. P. Vyas, Design, Spectral & Therapeutic Studies of Some New Schiff Base, Asian Journal of Biochemical and Pharmaceutical Research, 2: (2012) 1-7.

[15] H. M. Hassanin, S. M. El-Edfawy, Novel heterocyclic derivatives of 2-quinolinone associated with antibacterial and antitumor potencies, Heterocycles: an international journal for reviews and communications in heterocyclic chemistry, 85: (2012) 2421-2436.

[16] M. R. Shiradkar, M. Ghodake, K. G. Bothara, S. V. Bhandari, A. Nikalje, K. C. Akula, P. J. Burange, Synthesis and anticonvulsant activity of clubbed thiazolidinone-barbituric acid and thiazolidinone-triazole derivatives, ARKIVOC, 14: (2007) 58-74.

[17] S. Sharma, R. Jain, V. Sharma, C. Chawla, Synthesis and biological evaluation of some new 4-aryl-1-(4,6-diaryl pyrimidine)-2-azetidinone by conventional and microwave methods and their biological activities, J. Indian Chem. Soc., 90: (2013) 221-229.

[18] M. Gulcan, M. Sonmez, I. Berber, Synthesis, characterization, and antimicrobial activity of a new pyrimidine Schiff base and its Cu (II), Ni (II), Co (II), Pt (II), and Pd (II) complexes, Turkish Journal of Chemistry, 36: (2012) 189-200.

[19] B. Kahveci, O. Bekircan, S. A. Karaoglu, Synthesis and antimicrobial activity of some 3-alkyl-4-(arylmethyleneamino)-4, 5-dihydro-1H-1, 2, 4-triazol-5-ones, Indian Journal of Chemistry, 44B: (2005) 2614-2617.

- [20] O. Bekircan, B. Kahveci, M. Küçük, Synthesis and anticancer evaluation of some new unsymmetrical 3, 5-diaryl-4H-1, 2, 4-triazole derivatives, *Turkish Journal of Chemistry*, 30: (2006) 29-40.
- [21] W. M. Singh, B. C. Dash, Synthesis of some new Schiff bases containing thiazole and oxazole nuclei and their fungicidal activity, *Pesticides*, 22: (1988) 33-37.
- [22] T. Usui, H. S. Ban, J. Kawada, T. Hirokawa, H. Nakamura, Discovery of indenopyrazoles as EGFR and VEGFR-2 tyrosine kinase inhibitors by in silico high-throughput screening, *Bioorganic & medicinal chemistry letters*, 18: (2008) 285–288.
- [23] Y. Xia, C. D. Fan, B. X. Zhao, J. Zhao, D. S. Shin, J. Y. Miao, Synthesis and structure–activity relationships of novel 1-arylmethyl-3-aryl-1H-pyrazole-5-carbohydrazide hydrazone derivatives as potential agents against A549 lung cancer cells, *Eur J Med Chem*, 43: (2008) 2347-2353, <https://doi.org/10.1016/j.ejmech.2008.01.021>.
- [24] Mohamed Ramadan, Ashraf A. Aly, Lamiaa E. Abd El-Haleem, Stefan Bräse, Substituted Pyrazoles and their Heteroannulated Analogs—Recent Syntheses and Biological Activities, *Molecules* 26(16): (2021), 4995
- [25] Oluwakemi Ebenezer, Michael Shapi, Jack A. Tuszynski, A Review of the Recent Development in the Synthesis and Biological Evaluations of Pyrazole Derivatives, *Biomedicines*, 10 (5), (2022), 1124; <https://doi.org/10.3390/biomedicines10051124>
- [26] C. O. Kappe, Microwave dielectric heating in synthetic organic chemistry, *Chemical Society Reviews* 37: (2008) 1127-1139, <https://doi.org/10.1039/b803001b>.
- [27] B. L. Hayes, Recent advances in microwave-assisted synthesis, *Aldrichimica Acta*, 37: (2004) 333-375, <https://doi.org/10.2174/1570179054368518>.
- [28] C. O. Kappe, B. Pieber, D. Dallinger, Microwave effects in organic synthesis: myth or reality, *Angewandte Chemie International Edition*, 52: (2013) 1088–1094.
- [29] V. S. Dinakaran, D. Jacop, J. E Mathew, Synthesis and biological evaluation of novel pyrimidine-2 (1H)-ones/thiones as potent anti-inflammatory and anticancer agents, *Medicinal chemistry research*, 21: (2012) 3598-3606.
- [30] A. M. Asiri, S. A. Khan, Synthesis and anti-bacterial activities of a bis-chalcone derived from thiophene and its bis-cyclized products, *Molecules*, 16: (2011) 523-531.
- [31] D. Kumar, N. M. Kumar, K. Akamatsu, E. Kusaka, H. Harada, T. Ito, Synthesis and biological evaluation of indolyl chalcones as antitumor agents, *Bioorg. Med. Chem. Lett*, 20: (2010) 3916-3919.
- [32] M. R. P. Queiroz, A. S. Abreu, M. S. D. Carvalho, P. M. T. Ferreira, N. Nazareth, M. S. Nascimento, Synthesis of new heteroaryl and heteroannulated indoles from dehydrophenylalanines: Antitumor evaluation, *Bioorganic & medicinal chemistry*, 16: (2008) 5584-5589, <https://doi.org/10.1016/j.bmc.2008.04.004>.
- [33] B. J. Leo, *Organic chemistry, Vol. II: Stereochemistry and the chemistry of natural products* (Finar, IL), ACS Publications, A352: (1957).

- [34] F. Zhao, Q. J. Zhao, J. X. Zhao, D. Z. Zhang, Q. Y. Wu, Y. S. Jin, Synthesis and cdc25B inhibitory activity evaluation of chalcones, *Chemistry of Natural Compounds*, 49: (2013) 206-214.
- [35] E. Mansour, A. Aboelnaga, E. M. Nassar, S. I. Elewa, A new series of thiazolylpyrazoline derivatives linked to benzo [1, 3] dioxole moiety: Synthesis and evaluation of antimicrobial and anti-proliferative activities, *Synthetic Communications* 50: (2020) 368-379.
- [36] J. A. Hindler, B. J. Howard, and J. F. Keiser, Antimicrobial agents and antimicrobial susceptibility testing., Howard BJ(Editor), *Clinical and pathogenic Microbiology*. Mosby- 2nd Ed. (1994), St. Louis.
- [37] N. Z. El-sayed , S. A. El-Abbady, S. M. Agamy, Preparation and Evaluation of some polyaniline/ cycloadductcomposites for their biocidalactivity against some biofouling-causing organisms, *J. Sci. Res. Sci.*, 35: (2018) 466-482.
- [38] E. M. Azmy, B. M. Awad, H. A. Hefni, H. A. Saad, A. M. Eltoukhya, A. F. Mabied, Efficient One-pot Microwave-assisted Synthesis and Spectroscopic Characterization of Novel Antitumor and Antimicrobial Hydroxypyrrolidin2-ones, *J. Sci. Res. Sci.*, 35: (2018) 203-217.
- [39] A. S. Bhatiwala, A. Bendi, A. Tiwari, A study on synthesis of benzodiazepine scaffolds, using biologically active chalcones as precursors, *Journal of Molecular Structure*, 1258: (2022) 132649.
- [40] E. Sanabria, R. Cuenca, M. Estes, M. Maldonado, Benzodiazepines: Their Use either as Essential Medicines or as Toxics Substances, *Toxics, Review*, 9: (2021) 25; <https://doi.org/10.3390/toxics9020025>.
- [41] A. Khalil, N. Jaradat, M. Hawash, L. Issa, In Vitro Biological Evaluation of Benzodioxol Derivatives as Antimicrobial and Antioxidant Agents, *Arabian Journal for Science and Engineering*, 46: (2021) 5447–5453.
- [42] M. M. Aftan, M. Q. Jabbar, A. H. Dalaf, H. K. Salih, Application of biological activity of oxazepine and 2-azetidinone compounds and study of their liquid crystalline behavior, *Materials Today: Proceedings* 43: (2021) 2040-2050.

الملخص العربي

تحضير بعض المركبات الجديدة غير متجانسة الحلقة المشتقة من الشالكونات في وعاء واحد ودراسة أنشطتها المضادة للأورام والميكروبات

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الملخص العربي

الهدف من إجراء البحث الحالي هو تحضير مركبات جديدة حلقة غير متجانسة (2a-14a) و (2b-8b) المتوقع لها نشاط علاجي للأورام وكمضادة للبكتيريا باستخدام الشالكون **1a** و **1b** الذي يحتوي على جزئ النفتالين والإندول أو البيبيرونال، على التوالي، كمادة أولية باستخدام الطريقة المألوفة، أو الموجات فوق الصوتية، أو أشعه الميكروويف. وقد وجد أن استخدام الأشعاع بالميكروويف يعطي أفضل النتائج من حيث السرعة في وقت التفاعل ونقاء ونسبة كمية المركبات الناتجة من التفاعل. وقد تم إثبات التركيب البنائي للمركبات الناتجة

وقد أعطى تفاعل **1a** و **1b** مع الكاشف المناسب مركبات البيرازولين **2a**, **2b** المقابل، بيريميدين-2-ثيون **3a**, **3b**، أوكسازيبينات **4a**, **4b**، ديازيبينات **5a**, **5b**، تريازولو-بيريميدين **6a**, **6b**، مشتقات البيريميدين-2-ثيولز **7a**, **7b**. وقد تم استخدام المركبات **7a**, **7b** لإنتاج **8a**, **8b** على التوالي.

علاوة على ذلك، تم استخدام بيريميدين-2-ثيون **3a** لتحضير حمض بيريميدين-2-إيلثيواسيتيك **9a**، ومركب 2-هيدرازينيل بيريدو[d-3,2] بيريميدين **10a** والذي تم استخدامه كعامل وظيفي لإنتاج المركبات **11a**-**14a**.

تم تأكيد التركيب البنائي للمركبات التي تم تحضيرها (**14a-2a**) و (**8b-2b**) من التحاليل الطيفية؛ الأشعة تحت الحمراء (FT-IR)، (¹H NMR)، (¹³C NMR)، والكتلة الطيفية (MS)

وأظهرت المركبات **4a**, **5a**, **7a**, **13a** نشاطاً عالياً جداً كمضادات للأورام، كما أظهرت المركبات **4a**, **6a**, **13a** نشاطاً عالياً كعوامل مضادة للبكتيريا والفطريات أما المركبات **3b**, **5b**, **7b** فقد أظهرت نشاطاً أقل كمضادات للأورام وكذلك أظهرت المركبات **4b**, **6b** نشاطاً أقل كعوامل مضادة للبكتيريا والفطريات.