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Synthesis of bis chalcones and transformation into bis heterocyclic compounds with expected antimicrobial activity

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One-pot synthesis of novel derivatives of bis-chalcones has been achieved by condensation of 1,4-diacetylbenzene with different aldehydes in basic media. The reaction of chalcone derivatives **3a,b** with thioglycolic acid gives compounds **4a,b**. This, when reacted with ethyl cyanoacetate in presence of ammonium acetate gives the corresponding cyanopyridine derivatives **5a,b**. Furthermore, bis-chalcone **3a,b** has been cyclized to pyrazole analogs by using 2,4-dinitrophenylhydrazine to give compounds **7a,b** in good yields. All products have been characterized by IR, ^{1}H and ^{13}C NMR, and elemental analysis. The newly synthesised compounds have been screened for anti-bacterial activity

Keywords: Synthesis, bis chalcones, heterocyclic, ethylcyanoacetate, cyanopyridine

Chalcones, α, β-unsaturated ketones containing of two aromatic rings (ring A and B) (Figure 1), are abundant in edible plants[1]. Chalcones have many biological activities inclusive of antiviral[2-4], antibacterial[5,6], anti-inflammatory[7,8] antifungal[9,10], anticancer[11], antioxidant[12], analgesic[13], antiulcer[14], antimalarial[15] and antihelmintic[16] and thus include a class with important therapeutic potential. The Michael addition is a very important reaction in organic chemistry because it enables the formation of C-C , C-N , C-S , C-O and C-P[17] bonds. The conjugate addition of thiols to α, β-unsaturated carbonyl compounds are recognized thia-Michael addition, which is a key reaction for the synthesis of β-mercapto carbonyl compounds[18,19]. Those compounds are beneficial intermediates in the synthesized of bioactive organosulfur derivatives which include thiochromenopyridines[20].

Results and Dissection

Chalcone derivatives **3a,b**[21] were synthesized by Claisen-Schmidt Condensation. 1,4-diacetyl benzene was reacted with substituted benzaldehyade **2a,b** in presence of 30% sodium hydroxide as catalyst stirring at room temperature about 8 hrs to yield bis-chalcone derivatives **3a,b** in high yields (Scheme I). Furthermore, compounds of bis-chalcones **3a,b** were confirmed by spectral analysis such as IR spectrum of compound **3a** showed absorption peak at 1654 cm^{-1} for (C=O), 3055 cm^{-1} for an aromatic group and **3b** appearance peak at 1680 cm^{-1} for (C=O) and another peak at for C=C 1570 cm^{-1}. The IR frequency of C=O group is below than the standard value (ca. 1700 cm^{-1}) as a result of the conjugation effect along with the C=C-C=O moiety. UV spectra appearance peak at λ max =460 cm^{-1}.

Mechanism for synthesized bis-chalcones derivatives **3a,b** proceed by two steps as shown in Figure 2.

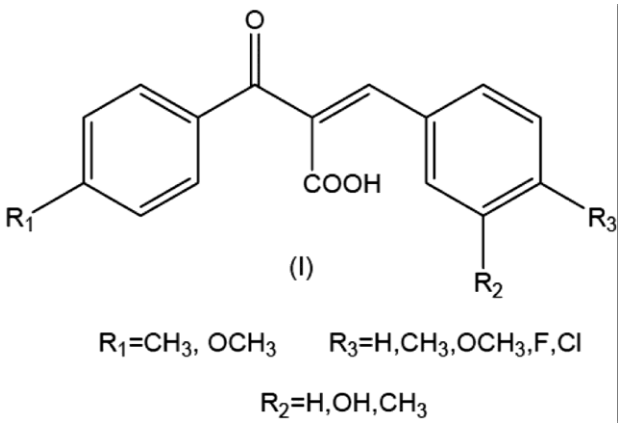

Figure 1

Enolate ions are formed when molecules with hydrogens alpha to a carbonyl group are treated with a base like sodium hydroxide.

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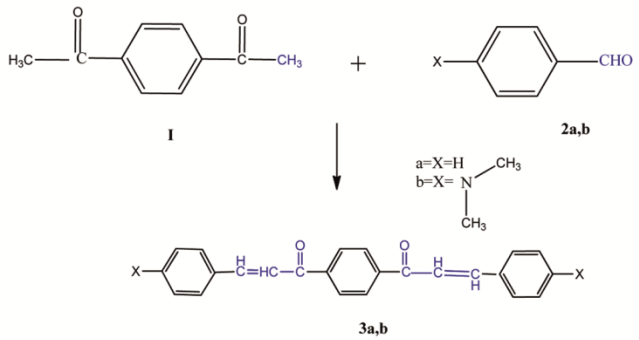
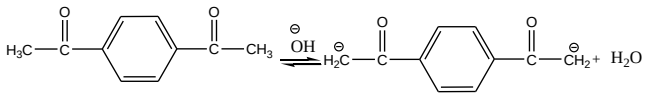


Scheme I — Synthesized of bis-chalcones derivatives **3a,b**

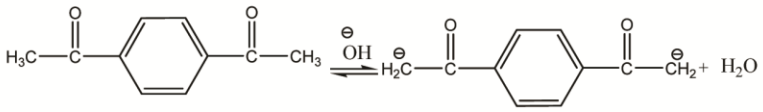


The enolate will normally react with unreached aldehyde to undergo the "aldol addition" or "aldol condensation"

In otherwise, the addition of thioglycolic acid to bis-chalcones derivatives **3a,b** with stirring at room temperature in presence of 10% iodine dissolved in methylene dichloride selectively to afford compounds **4a,b** (Figure 3, Figure 4, Scheme II). Compounds **4a,b** were characterized by IR spectrum showed absorption bands at 1720 $cm^{-1}$for (C=O) of acid,1680 cm^{-1}(C=O) and (C-S) at 1267 cm^{-1}.

Thus, the reaction of bis-chalcone derivatives **3a,b** with ethyl acetoacetate in presence of 10% sodium hydroxides under reflux for 2 hrs to give

Enolate ions are formed when molecules with hydrogens alpha to a carbonyl group are treated with a base like sodium hydroxide.



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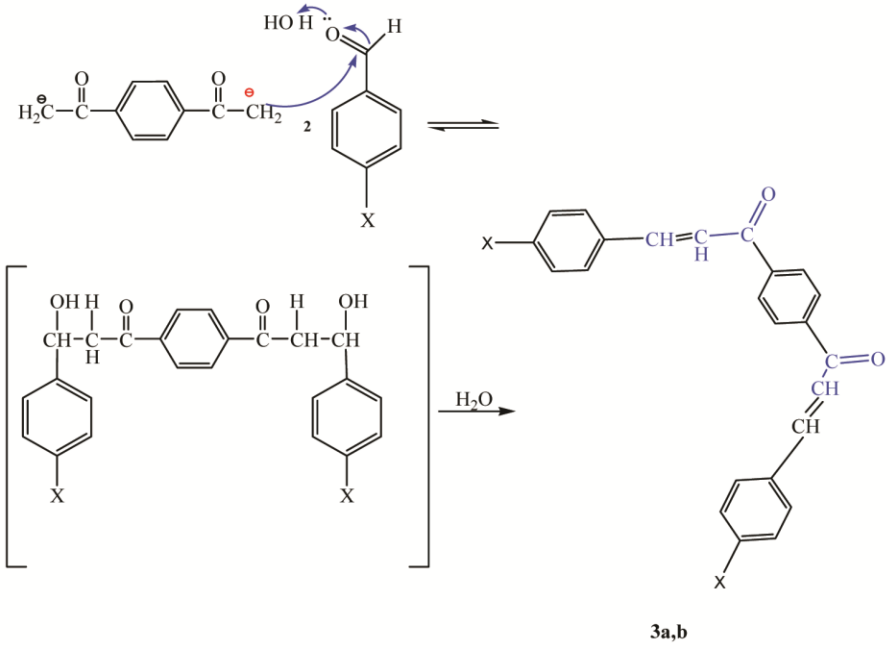


Figure 2 — Mechanism for synthesized bis-chalcones derivatives **3a,b**

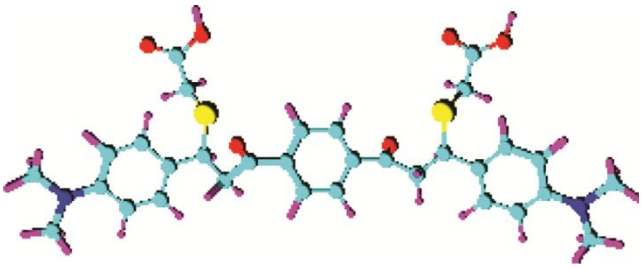


Figure 3 — Compound **4b** Optimized structure with 3D viewer

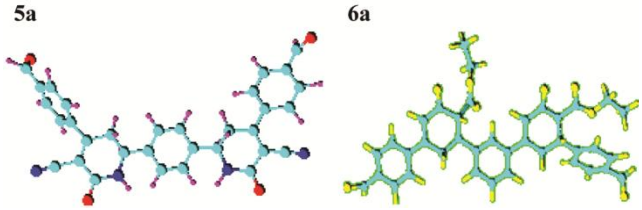
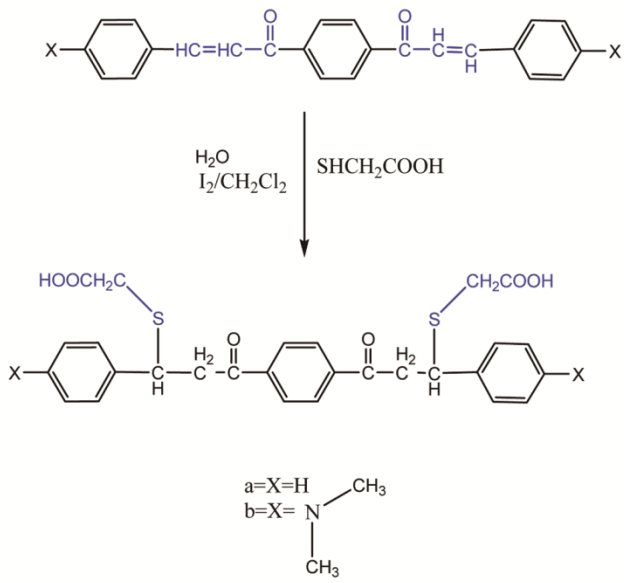


Figure 4 — Compounds **5a** and **6a** Optimized structure with 3D viewer



Scheme II — Synthesis of compounds **4a,b**

cyclohexanone derivatives **5a,b** (by Robinson annulations methods). IR spectrum of compound **5a,b** showed absorption peak at 2218 and 2122 cm^{-1} for (CN) respectively, and another band at 3126 $cm^{-1}$for (NH). The reaction of Chalcone **3a,b** with ethyl cyano acetate in the presence of ammonium acetate and ethanol gave cyanopyridine derivatives **6a,b** (Scheme III).

Probable mechanism of formation for synthesized compound **6a,b** is shown in Figure 5

Chalcone derivatives **3a,b** reacted with 2,4-dinitrophenylhydrazine in presen ce of a drop of glacial acetic acid under reflux for 13 hours yielded pyrazolo derivatives **7a,b** (Scheme IV). IR spectrum of compound **7a**,**b** showed absorption peak at 1352-1556 cm^{-1} for (NO_2) and absent the absorption peak at 1680 cm^{-1} for (C=O).

Results of the antibacterial activity of synthesized compounds

All the tested compounds were active against *E. coli* with variable degrees where NE showed the largest inhibition zone (18 mm) while minimum activity was recorded against *Ps. Aeruginosa* (inhibition zones 12-13 mm).The compounds had no activity against tested gram positive bacterial species *S. aureus* and *B .subtilis* (Table I, Figure 6).

Experimental Section

Melting points have been recorded by Electro Thermal IA 9 100 series digital melting point apparatus contains in capillaries and are not corrected. ir spectrum were recorded in the solid state as KBr discs using a Perkin-Elmer model 1430 spectrometer. ^{1}H NMR spectra have been determined on a Varian /Gemini 400 MHz spectrometer in DMSO-d_6 used AS solvent and TMS used as an internal standard. Chemical shifts are given in δ (ppm). Mass spectra were measured on an instrument VG-7035 at 70 or 15 eV. Elemental analyses were determined at the Micro Analytical Centre, Cairo University and Giza, Egypt.

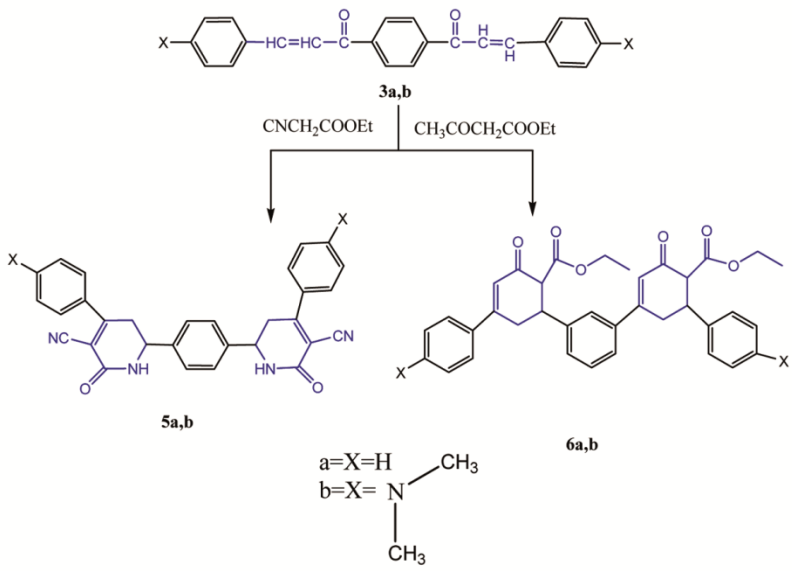
1,4-Diacetylbenzene chalcone (3a); N,N-dimethyl1,4-diacetylbenzene chalcone (3b)

To a mixture of (0.02 mole) of 1,4-acetyl benzene dissolved in solution of (5 ml) 30% sodium hydroxide and (15 ml) ethanol. (0.04 mole) of benzaldehyde derivatives was added with stirring at room temperature for 8 hr. a white-yellowish precipitate was obtained, washed with water, and then recrystallized from ethylacetate, diethylether.

3a: Color yellowish; yield 92% % m.p. 193–195^{o}C; IR (KOH; cm^{-1}): 3055, 1654, 1573, 1207. Anal. Calcd for ($C_{24}H_{18}O_2$; 338.4): C, 85.18; H, 5.36. Found: C, 85.16; H, 5.38.

3b: Color orange; yield 86 % m.p. 267-269^{o}C; IR (KOH; cm^{-1}): 3026, 2887, 1680. Anal. Calcd for ($C_{28}H_{28}N_2O_2$; 424.53): C, 79.22; H, 6.65; N, 6.60. Found: C, 79.25; H, 6.61; N, 6.63.

1, 4-Bis [2-(1-(4-*N*,*N*-dimethylphenyl)-3-oxo-3-propylthio)acetic acid]benzene (4a);1, 4-Bis [2-(1-



Scheme III — Synthesis of compounds **5a,b** and **6a,b**

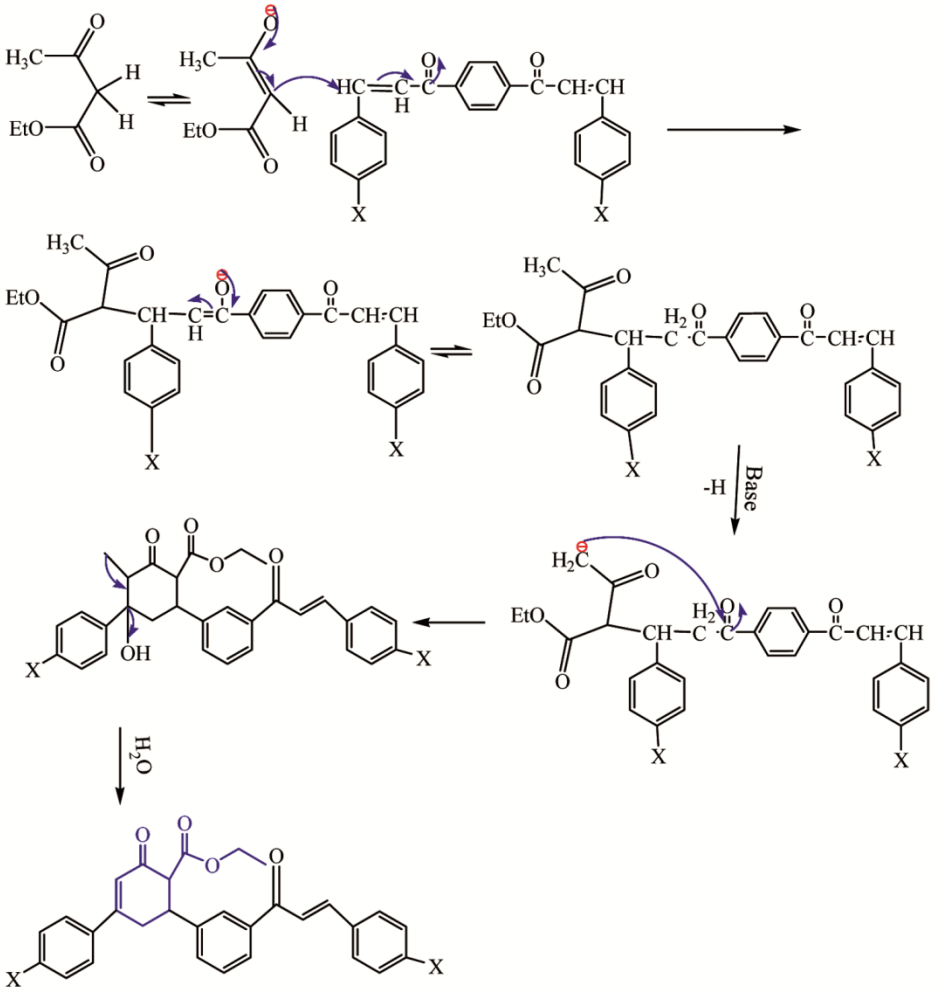
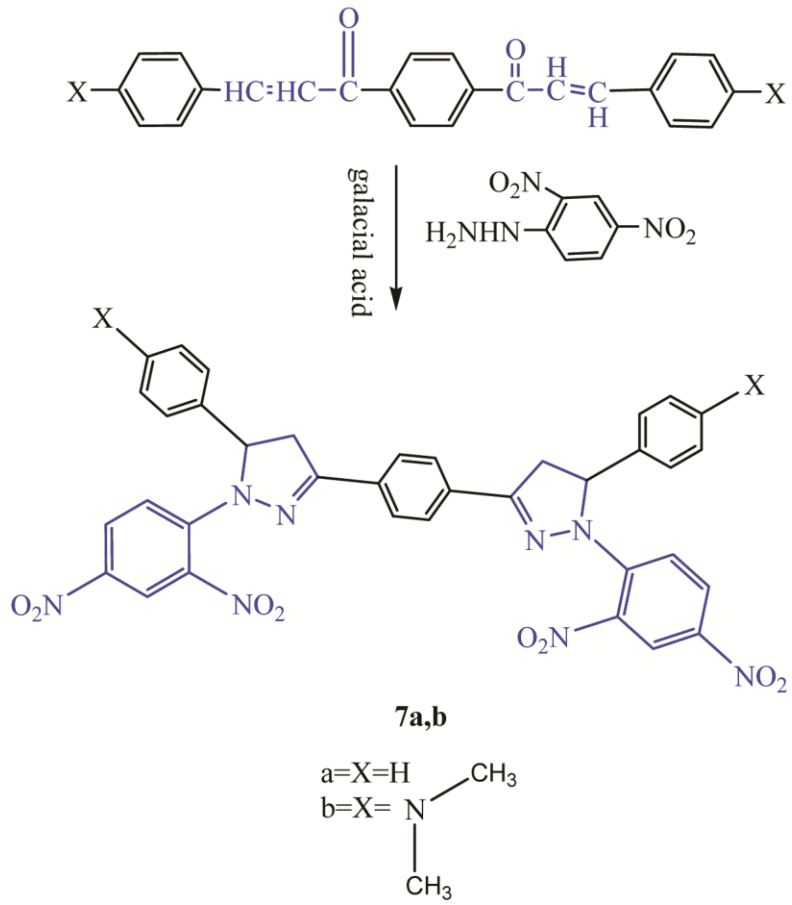


Figure 5 — Mechanism for synthesised compounds **6a,b**



Scheme IV — Synthesis of compounds **7a,b**

Table I — The antibacterial activity of the synthesized compounds against tested isolates

Compd	Diameter of inhibition zone (mm)			
	S. aureus	*B. subtilis*	*E. coli*	*P .aeruginosa*
4b	–	–	14	13
5b	–	–	18	12
6b	–	–	15	13
7a	–	–	16	13
7b	–	–	16	12

(4-*N*,*N*-dimethylphenyl)-3-oxo-3-propylthio)acetic acid]benzene (4b)

To a solution of bis-chalcone derivative **3a,b** (1 1mmol) and thioglycollic acid (2mmol) in dichloromethane (20ml) was added the solution of iodine (10% mole) in dichloromethane (1 mL) and the mixture was stirred at room temperature for 5 hours. Then, iodine removed with diluted $Na_2S_2O_3$ solution and washed with H_2O. The organic layer was dried over Na_2SO_4 and the solvent removed under vacuum. The crude product was purified on by crystallized in CCl_4/*n*-hexane (1:3).

4a: IR (KOH; cm^{-1}). 3348, 3028, 2943, 2360, 1720, 1680, 1594, 1337, 1267, 1227, 1451. ^{1}HNMR(400MHz, DMSO, δ, ppm): 10.23 (s, 2H, 2OH); 7.42-7.21(m, 10H, 2Ph); 7.05-7.02 (m, 4H, Ph); 4.32(t, J=6.1Hz, 2H); 2.81(d, 4H, $2CH_2$); 2.53(d, 4H, $2CH_2$). ^{13}C NMR (DMSO-d_6) δ: 196.3, 137.4, 134.2, 128.5, 127.0, 128.9, 127.4, 45.4, 33.1. Anal. Calcd for ($C_{28}H_{26}O_6S_2$; 522.63). C, 64.35; H, 5.01; S, 12.27.Found: C, 64.38; H, 5.04; S, 12.25.

4b: IR (KOH; cm^{-1}): 3421, 3324, 2971, 2885, 2679, 1712, 1675, 1608, 1573, 1259, 1307, 1239. ^{1}HNMR (400MHz, DMSO, δ, ppm): 12.51 (s, 2H, 2OH); 7.92-7.71(m, 8H, 2Ph); 7.45-7.34 (m, 4H, Ph); 4.52(t, *J*=6. 9Hz, 2H); 3.61(d, *J*=15.2, 4H, $2CH_2$); 3.12 (d, *J*=17.1, 4H, $2CH_2$), 2.86 (s, 12H, $4CH_3$). Anal. Calcd for ($C_{32}H_{36}N_2O_6S_2$, 608.77): C, 63.13; H, 5.96; N, 4.60; S, 10.53.Found: C, 63.10; H, 5.92; N, 4.63; S, 10.56.

1, 4-Bis (1,2,5,6-tetrahydro-2-oxo-4,6-pyridine-3-carbonitrile) benzene (5a); 1, 4-Bis (4-(4-(dimethylamino)phenyl)-1,2,5,6-tetrahydro-2-oxo-pyridine-3-carbonitrile) benzene (5b)

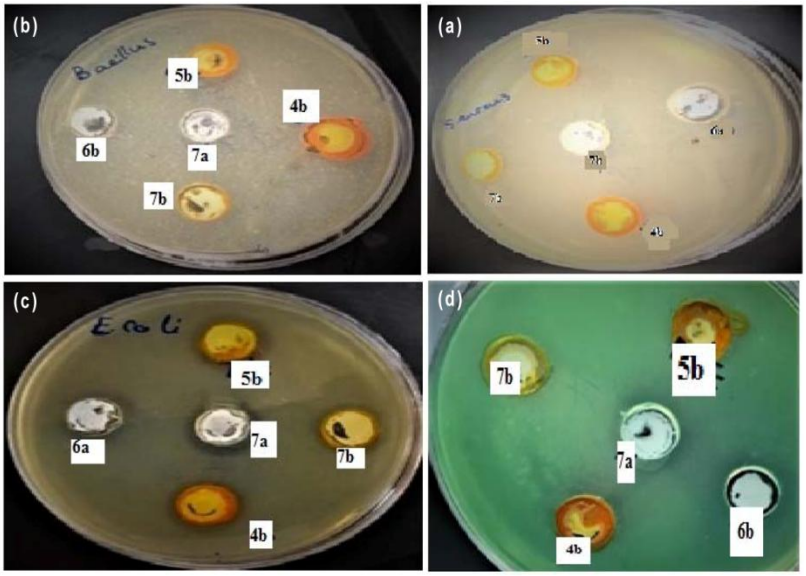


Figure 6 — The antibacterial activity of synthesized compounds against tested bacterial species: *S. aureus* (B) *B. subtilis* (C) *E. coli* (D) *P. aeruginosa*

Chalcone **3a,b** (1mmol), ethylacetoacetate (2 mmol) were dissolved in ethanol (15ml) in presence of 10% NaOH(0.5ml). the mixture was refluxed for 3hr,then cooling at room temperature and the reside filtrated m recrystallization from ethanol.

5a: IR (KOH; cm^{-1}): 3126, 3068, 2953, 1559, 2131 cm^{-1}. ^{1}HNMR (400MHz, DMSO, δ, ppm): 9.63 (1H, NH); 7.36-8.25 (m, 12H, Ar-H); 2.42 (d, *J*=13.4, 4H, $2CH_2$); 3.98 (t, 2H, CH). Anal. Calcd for ($C_{30}H_{22}N_4O_2$; 470.52): C, 76.58; H, 4.71; N, 11.91. Found: C, 76.60; H, 4.77; N, 11.96.

5b: IR (KOH; cm^{-1}): 3326, 3079, 2953, 2122, 1602. ^{1}HNMR (400MHz, DMSO, δ, ppm): 10.12 (s, 1H, NH); 7.36-8.25 (m, 10H, Ar-H); 2.63 (d, *J*=13.4, 4H, $2CH_2$); 4.13 (t, 2H, CH). Anal. Calcd for: ($C_{34}H_{32}N_6O_2$; 556.66): C, 73.36; H, 5.79; N, 15.10. Found: C, 73.42; H, 5.81; N, 15.14.

1, 4-Bis (ethyl 6(phenyl)-2-oxo-4-cyclohex-3-enecarboxylate) benzene (6a); 1, 4-Bis (ethyl 6-(4-N,N-dimethylphenyl)-2-oxo-4-cyclohex-3-enecarboxylate) benzene (6b)

Solution of bis- chalcone **3a,b** (1mmol) and ethylcynao acetate (2mmol) in ethanol (25ml) was added to ammonium acetate (4mmol), the reaction mixture was heated under reflux for 12 hr. the solution cooled and poured into ice water (30 ml). The residue was precipitated and filtration, recrystallization from ethanol.

6a: IR (KOH; cm^{-1}): 3386, 3020, 2953, 2839, 1725, 1652, 1643, 1397, 1248. ^{1}HNMR (DMSO-d_6, 400 MHz) δ: 1.23(t, 3H, $2CH_2$-CH_3), 6.45 (s,2H, 2C=CH), 6.95-7.75 (m, 14H, Ar-H) 3.12 (q, 4H, $2COOCH_2CH_3$), 3.86-3.88 (d, 2H, 2Ha), 3.98 (d, 2H, 2Hb), 3.71-3.72(d, 4H, $2CH_2$). ^{13}C NMR (DMSO-d_6) δ:14.3, 26.8, 36.2, 59.6, 64.8, 127.3, 128.2, 129.5, 138.2, 149.1, 1. 151.6, 172.4, 196.7. Anal. Calcd for ($C_{36}H_{34}O_6$; 562.65): C, 76.85; H, 6.09. Found: C, 76.81; H, 6.13.

6b: IR (KOH; cm^{-1}): 3386, 3020, 2953, 2839, 1725, 1652, 1643, 1397, 1248.

^{1}HNMR (DMSO-d_6, 400 MHz) δ: ^{13}C NMR (DMSO-d_6) δ: 14.2, 26.6, 35. 6, 42.3, 60.6, 63.8, 128.3, 129.2, 130.1, 139.2, 149.13, 152.6, 173.1, 193.7. Anal. Calcd for ($C_{40}H_{44}N_2O_6$; 648.79): C, 74.05; H, 6.84; N, 4.32. Found: C, 74.12; H, 6.89; N, 4.35.

1, 4-Bis [(4-(4,5-dihydro-1-(2,4-dinitrophenyl) -5-phenyl-1H-pyrazol-5-yl]) benzene (7a) 1, 4-Bis [(4-(4,5-dihydro-1-(2,4-dinitrophenyl)-5-N,N-dimeth ylbenzenamine -1H-pyrazol-5-yl]) benzene (7b)

A mixture of **3a,b** (1 mmol) in ethanol (15 ml) and 2,4-dinitrophenylhydrazine (2mmol) was added with (2 drops) glacial acetic acid and the solution was refluxed on water bath at 80°C gently for 13 hours. After the reaction completed, the solution was concentrated and allowed to cool, the product was filtered and washed with distilled water, dried and recrystallised from ethanol (15 ml).

7a: IR (KOH; cm^{-1}): 3016, 1559, 1552-1332. ^{1}HNMR (400MHz, DMSO, δ, ppm): 6.94-7.76(m, 20H, Ar-H); 3.65 (d, *J*=15.3, 4H, $2CH_2$); 3.91 (t, 2H,

CH). Calcd for ($C_{36}H_{26}N_8O_8$; 698.64): C, 61.89; H, 3.75; N, 16.04. Found: C, 61.92; H, 3.79; N, 16.12.

7b: IR (KOH; cm^{-1}): 3026, 2981, 1445, 1602, 1352-1556. ^{1}HNMR (400MHz, DMSO, δ, ppm): 6.89-7.92 (m, 18H, Ar-H); 3.46 (d, *J*=14.32, 4H, $2CH_2$); 3.86 (t, 2H, CH); 1.29 (s, 12H, $4CH_3$). ^{13}C NMR (DMSO-d_6) δ: 152.8, 145.5, 138.2, 134.2, 128.5, 127.0, 128.9, 127.4, 53.5, 40.4. Anal. Calcd for ($C_{40}H_{36}N_{10}O_8$; 784.78): C, 61.22; H, 4.62; N, 17.85. Found: C, 61.39; H, 4.68; N, 17.80.

Screening of the antibacterial activity of synthesized compounds

(i) Test microorganisms

The bacterial isolates used in this test were supplied by Microbiology and Immunology lab, Faculty of pharmacy, Mansoura university. The selected species were *S. aureus*, *B. subtilis*, *E. coli* and *Ps. aeruginosa*.The isolates were grown overnight in a rotary shaker at 37°C then adjusted to a concentration of 10^8 cells/ml using 0.5 McFarland standard.

(ii) Screening of the antibacterial activity

Agar well diffusion method[22] was used to evaluate the antibacterial activity of the synthesized compounds. Thirty micro liters of each readjusted bacterial culture was inoculated into 15 ml of Muller Hinton agar, mixed well and poured into 10 mm Petri dish. Using a sterile Wassermann tube, wells were made in the seeded agar plates and 50 µl of each compound (500 mg) were added to the corresponding wells. Then, plates were incubated at 37°C for 18 h. Cloxacillin and tobramycin were used as reference antimicrobials. Dimethyl formamide (solvent) was used as negative control. Results were recorded by measuring the diameter of growth inhibition zone (in mm).

Conclusions

Some new of heterocyclic compounds derivatives have been synthesized from 1,4-diacetylbenzene derivatives. Chemical properties of these compounds were studied, and some of these compounds showed potential antimicrobial activity.

Acknowledgements

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