Egypt.J.Chem. **Vol. 63** , No.8. pp.2901-2910 (2020)

Egyptian Journal of Chemistry
http://ejchem.journals.ekb.eg/

Design and Synthesis of Heterocyclic Compounds from 1,4-Diacetylbenzene with Expected Antimicrobial Activity

Amira A. Ghoneim*[a,b] , Rehab M. Elbargisy [c,d] and Afaf Manoer[a]

[a] *Chemistry Department, College of Science, Jouf University, P. O. Box 2014, Sakaka, Aljouf, Kingdom of Saudi Arabia. Tel.: 00966541609390.*

[b]*Chemistry Department, Faculty of Science, Zagazig University, Zagazig, Egypt.*

[c] *Department of Pharmaceutics, College of Pharmacy, Jouf University, Sakaka, AlJouf, Saudi Arabia.*

[d]*Department of Microbiology and Immunology, Faculty of Pharmacy, Mansoura University, Mansoura 35516, Egypt.*

IN this present work, synthesized a novel derivatives of bis-chalcones via condensation of 1,4-diacetylbenzene with different aldehydes in basic media. The reaction of chalcone derivatives **3a,b** with thioglycolic acid gave compounds **4a,b**. That was reacted with ethyl cyanoacetate in presence of ammonium acetate to give the corresponding cyanopyridine derivatives **5a,b**. Furthermore, bis-chalcone **3a,b** was cyclization to pyrazole analogs by using 2,4-dinitrophenylhydrazine to give compounds **7a,b** in good yields. All products were characterized by IR spectrum, ^{1}HNMR, ^{13}CNMR, and elemental analysis. The new compounds have been screened as anti-bacterial activity

Keywords: Synthesis; bis Chalcones; ethylcyanoacetate; cyanopyridine and antimicrobial Activity .

Introduction

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], anti-oxidant [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 thio chromeno pyridines [20].

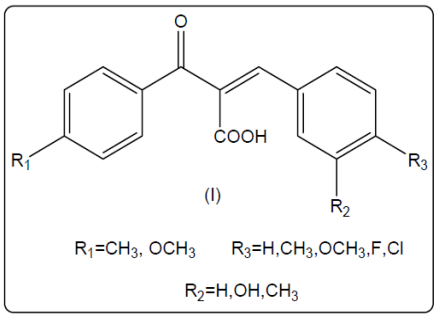


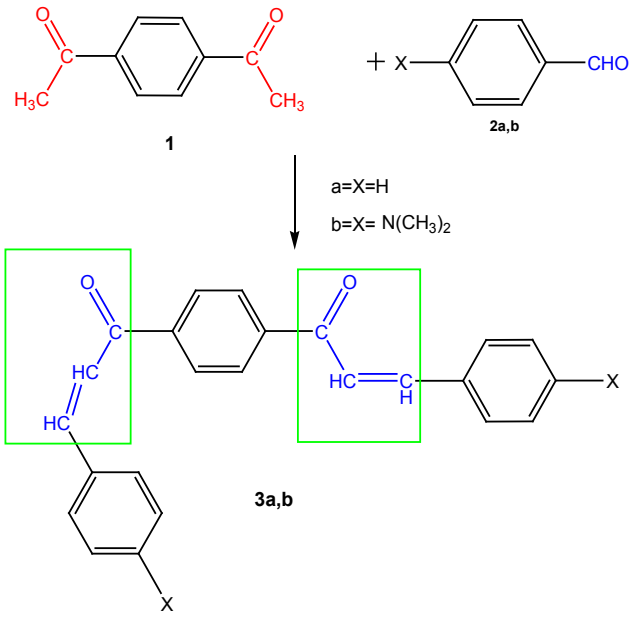
Fig .1. Chalcones, α, β-unsaturated ketones containing of two aromatic rings.

Results and Dicussion

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 (1).

Email*:aa_amiraatef@yahoo.com
Received 29/12/2019; Accepted 12/2/2020
DOI: 10.21608/ejchem.2020.21641.2289

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}.

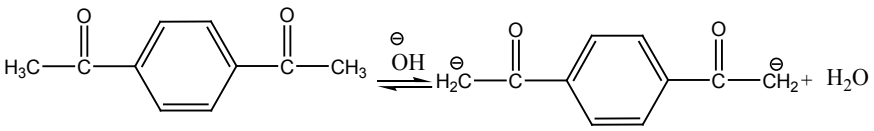


Scheme (1). Synthesized of bis-chalcones derivatives 3a,b.

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

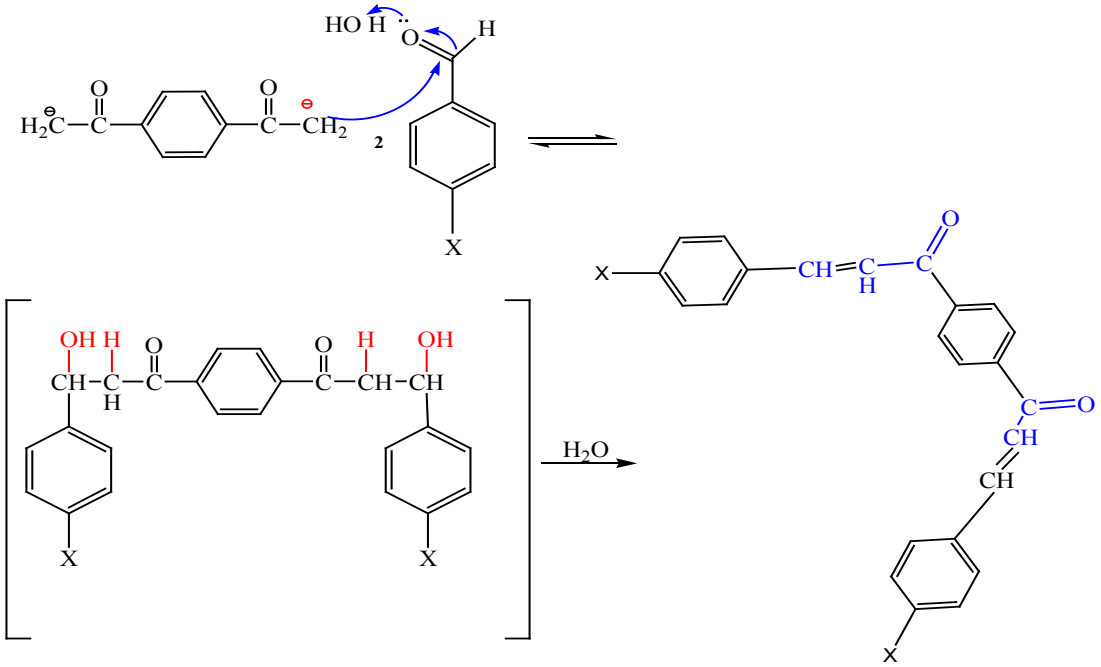
1-Enolate ions are formed when molecules with hydrogens alpha to a carbonyl group are treated with a base like sodium hydroxide.

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



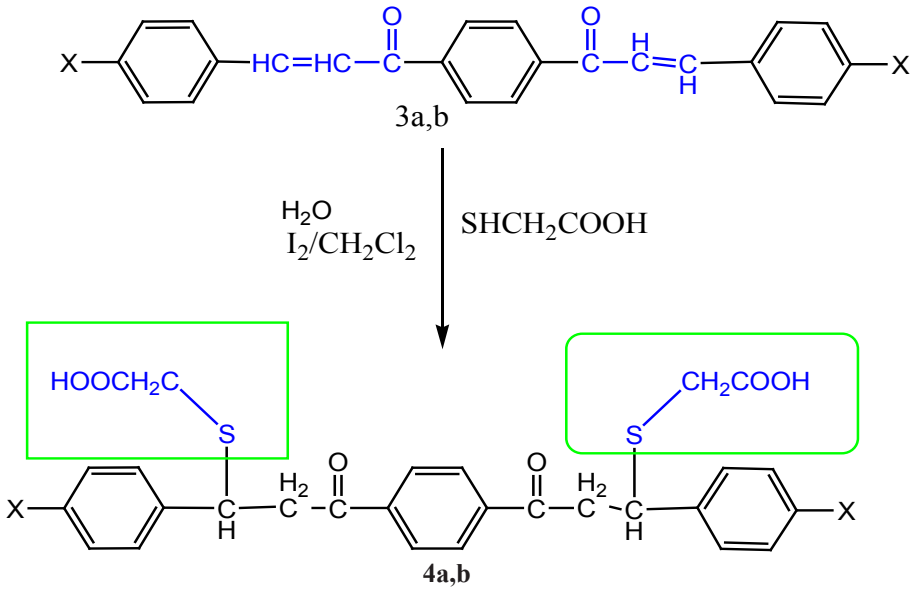
In otherwise, the addition of thioglycolic acid to bis-chalcones derivatives **3a,b** with stirring at room temperature in presence of 10% iodine dissolved in methylene dichloride selectively to afford compounds **4a,b** scheme 2**.** Compounds **4a,b** were characterized by IR spectrum showed absorption 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 cyclohexanone derivatives **5a,b** by (robins on 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 cyeno acetate in the present of ammonium acetate and ethanol gave cyanopyridine derivatives **6a,b** scheme 3**.**



3a,b

Fig.2. Mechanism for synthesized bis-chalcones derivatives 3a,b.



4a,b

Scheme 2. Synthesized of compounds 4a,b.

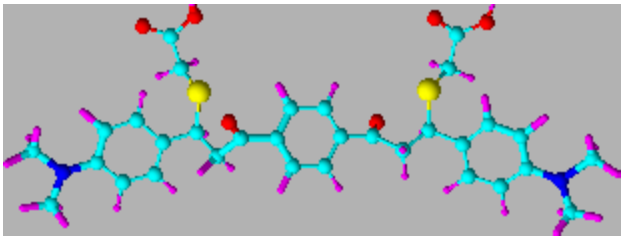
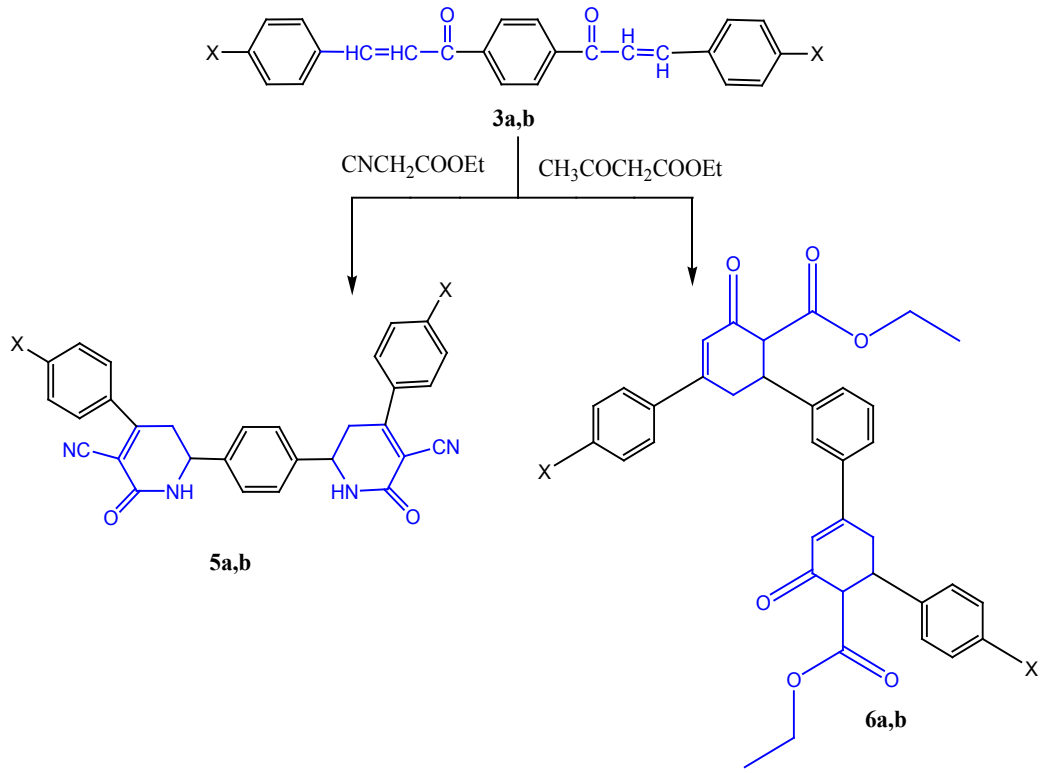


Fig.3. Compound 4b Optimized structure with 3D viewer.



Scheme 3. Synthesized of compounds 5a,b and 6a,b .

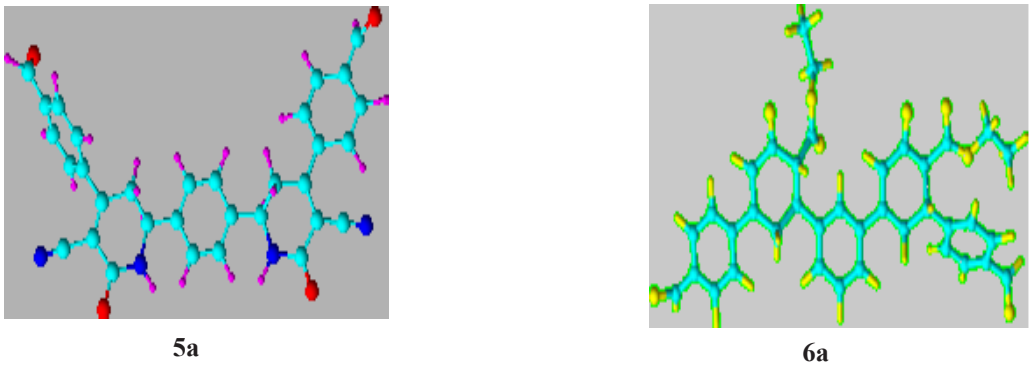


Fig.4. Compounds 5a and 6a Optimized structure with 3D viewer.

Mechanism for synthesized compound **6a,b** in figure (5).

Chalcone derivatives **3a,b** were reacted with 2,4-dinitrophenylhydrazine in the presence of a drop of glacial acetic acid under reflux for 13 hours yielded pyrazolo derivatives **7a,b** scheme 4. 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 **7b** 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*), see table 1and figure 6

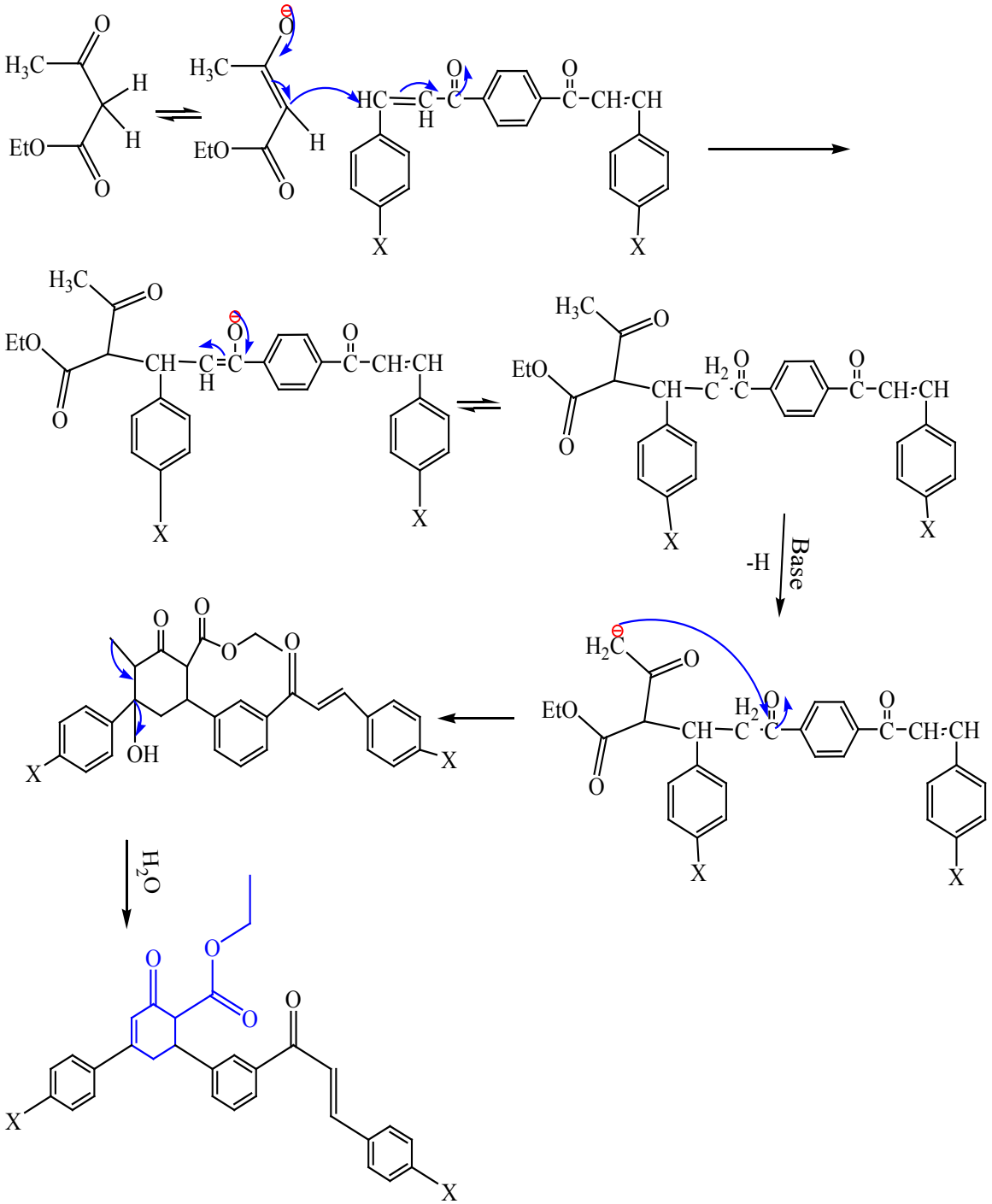
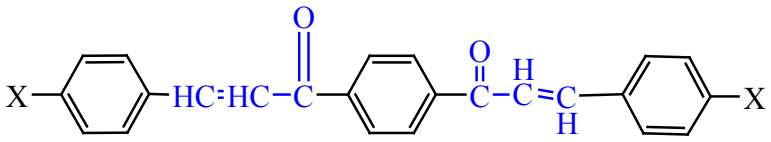
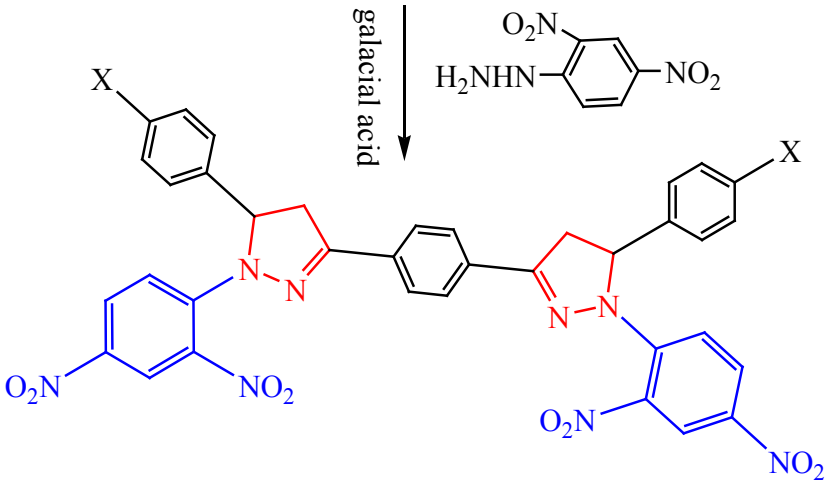


Fig.5. Mechanism for synthesized compound 6a,b.



3a,b



7a,b

Scheme 4. Synthesized of compounds 7a,b.

TABLE 1.The antibacterial activity of the synthesized compounds against tested isolates .

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

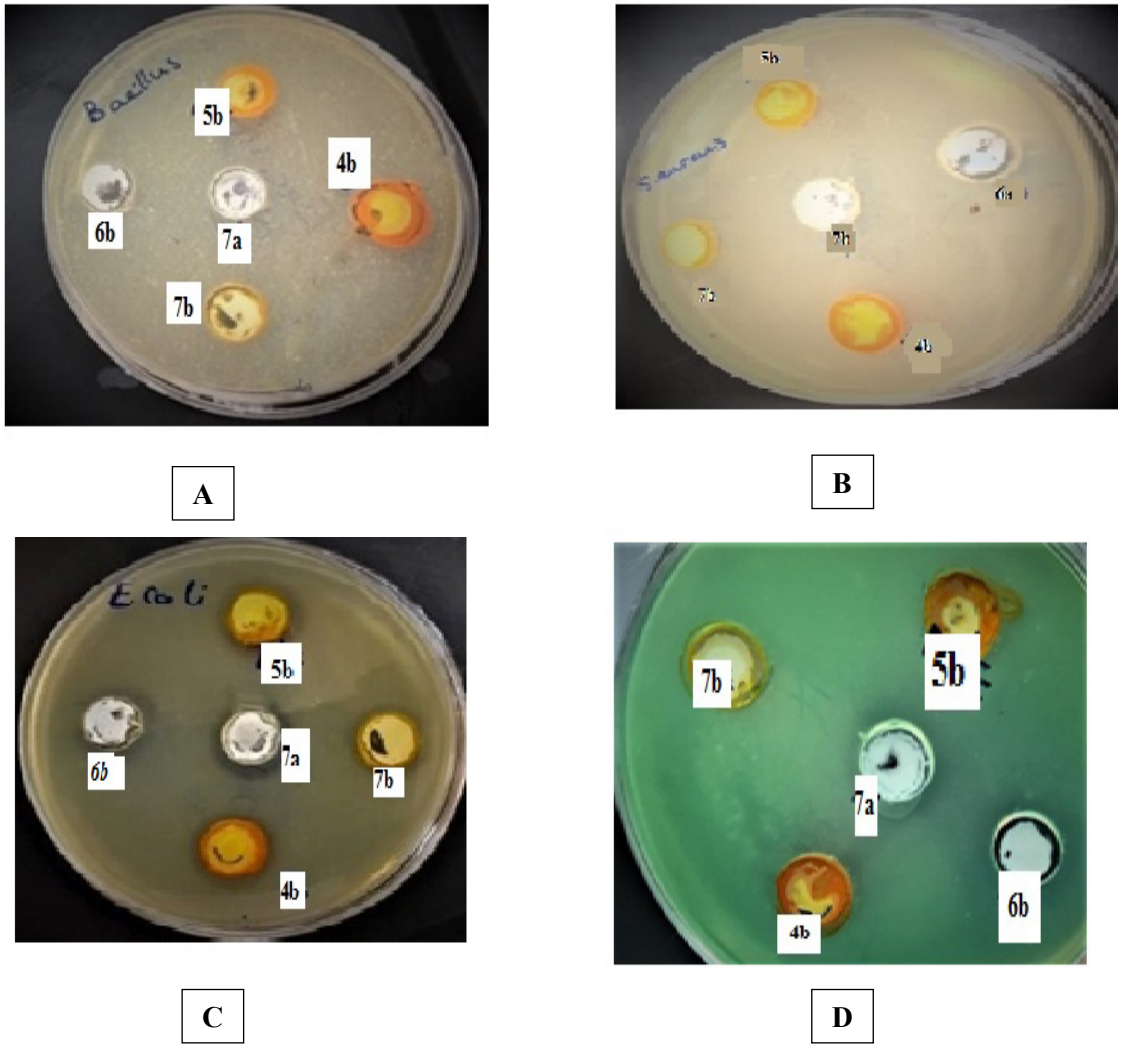


Fig .6. The antibacterial activity of synthesized compounds against tested bacterial species;

(A) . S.aureus (B) *B.subtilis* (C) *E.coli* (D) *Ps.aeruginosa*

Experimental

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 took in the solid state as potassium bromide discs using a Perkin Elmer model 1430 spectrometer . ^{1}HNMR spectra have been *determined* on a varian / gemini 400 MHz spectrometer in DMSO-d_6 used as a solvent *a*nd TMS used as an internal standard chemical shifts in 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, and 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°C; IR (KOH; cm^{-1}): 3026, 2887, and 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-(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 dried over Na_2SO_4 and the solvent removed under vacuum. The crude product purified and recrystallized from CCl4/*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, and 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)

Chalcone **3a,b** (1mmol), ethyl cyanoacetate (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 residue filtrated and 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 ethyl acetoacetate (2mmol) was added to ammonium acetate (4 mmol) were dissolved in ethanol (15ml), 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 (400MHz, DMSO, δ, ppm): 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.^{13}CNMR (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, and 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-dimethylbenzenamine -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 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:

Test microorganisms

The bacterial isolates used in this test had 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.

Screening of the antibacterial activity

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

Acknowledgements

A. A. Ghoneim. Thanks Professor Ahmed Fouad El Farargy, Chemistry Department, Faculty of Science, Zagazig University, Zagazig, Egypt for the facilities offered of his effort and abundant facilities in the science of chemistry during the previous stages. The authors thanks College of Science, Jouf University, Sakaka, Kingdom of Saudi and Chemistry Department and Faculty of Science, Zagazig University, Zagazig, Egypt for the continuous help and support.

References

1. Rahman MA. Chalcone: A valuable insight into the recent advances and potential pharmacological activities. *Chem Sci J* 2011: CSJ-29, 2011.

2. Campos-Buzzi F, Campos JP, Tonini PP, Correa R, Yunes RA, Boeck P, Cechinel-Filho V. Antinociceptive effects of synthetic chalcones obtained from Xanthoxyline. *Arch Pharm Chem Life* Sci 339: 361- 365, 2006.

3. Nowakowska Z. A review of anti-infective and anti-inflammatory chalcones. *Eur J Med Chem* 42 (2): 125-137, 2007.

4. Kozlowski D, Trouillas P, Calliste C, Marsal P, Lazzaroni R, Duroux JL. Density functional theory study of the conformational, electronic and antioxidant properties of natural chalcones. *J Phys Chem A* 111: 1138-1145, 2007.

5. Nielsen SF, Boesen T, Larsen M, Kristian Schonning K, Kromann H. Antibacterial chalcones-bioisosteric replacement of the 4´-hydroxy group. *Bioorg Med Chem* 12: 3047-3054, 2004.

6. Nowakowska, Z. Structural assignment of stilbenethiols and chalconethiols and differentiation of their isomeric derivatives by means of 1H- and 13C-NMR spectroscopy. *Spectrosc Lett* 38: 477-485, 2005.

7. Lopez SN, Castelli MV, Zacchino SA, Domınguez JN, Lobo G, Charris-Charris J, Cortes JCG, Ribas JC, Devia C, Rodrıguez AM, Enriz RD. In vitro antifungal evaluation and structure-activity relationships of a new series of chalcone derivatives and synthetic analogues, with inhibitory properties against polymers of the fungal cell wall. *Bioorg Med Chem* 9: 1999-2013, 2001.

8. Batovska D, Parushev ST, Slavova A, Bankova V, Tsvetkova I, Ninova M, Najdenski H. Study on the substituents' effects of a series of synthetic

chalcones against the yeast Candida albicans. *Eur J Med Chem* 42: 87-92, 2007.

9. Valla A, Valla B, Cartier D, Guillou RL, Labia R, Florent L, Charneau S, Schrevel J, Potier P. New syntheses and potential antimalarial activities of new 'retinoid-like chalcones'. *Eur J Med Chem* 41: 142- 146, 2006.

10. Nielsen SF, Kharazmi A, Christensen SB. Modifications of the a,b-double bond in chalcones only marginally affect the antiprotozoal activities. *Bioorg Med Chem* 6: 937-945, 1998.

11. Ducki S, Forrest R, Hadfield JA, Kendall A, Lawrence NJ, Mcgown AT, Rennison D. Potent antimitotic and cell growth inhibitory properties of substituted chalcones. *Bioorg Med Chem Lett* 8: 1051- 1056, 1998.

12. Jayasinghe L, Rupasinghe GK, Hara N, Fujimoto Y. Geranylated phenolic constituents from the fruits of Artocarpus nobilis. *Phytochemistry* 67: 1353-1358, 2006.

13. Tanaka H, Nakamura S, Onda K, Tazaki T, Hirano T. Sofalcone, an anti-ulcer chalcone derivative, suppresses inflammatory crosstalk between macrophages and adipocytes and adipocyte differentiation: implication of heme-oxygenase-1 induction. *Biochem Biophys Res Commun* 381: 566-571, 2009.

14. Batovska D, Parushev S, Stamboliyska B, Tsvetkova I, Ninova M, Najdenski H. Examination of growth inhibitory properties of synthetic chalcones for which antibacterial activity was predicted. *Eur J Med Chem* 44: 2211-2218, 2009.

15. Ravichandran R, Rajendran M, Devapiriam D. Studies on chalcone derivatives antioxidant and stability constant. *J Chem Bio Phy Sci Sec A* 3 (4): 2446-2458, 2013.

16. Liu M, Wilairat P, Go ML. Antimalarial alkoxylated and hydroxylated chalcones: Structure-activity relationship analysis. *J Med Chem* 44 (25): 4443-4452, 2001.

17. Guo W., Lv G., Chen J., Gao W., Ding J., WuH. Rongalite® and base-promoted cleavage of disulfides and subsequent Michael addition to α,β-unsaturated ketones/esters: an odorless synthesis of β-sulfido carbonyl compounds. Tetrahedron 66, 2297, 2010.

18. Firouzabadi H., Iranpoor N., Abbasi M. A facile generation of C–S bonds via one-pot, odourless and efficient thia-Michael addition reactions using alkyl, aryl or allyl halides, thiourea and electron-deficient. *Tetrahedron* 65, 5293, 2009.

19. Carlone A., Bartoli G., Bosco M., Sambri L., Melchiorre P. Organocatalytic asymmetric hydrophosphination of alpha,beta-unsaturated aldehydes. *Angew. Chem. Int. Ed*. 46, 4504, 2007.

20. Wen L.-R., Ji C., Li M., Xie H.-Y. Solvent-free and efficient synthesis of imidazo[1,2-*a*]pyridine derivatives *via* a one-pot three-component reaction. *Tetrahedron* 65, 1287, 2009.

21. Ghoneim A., El-Farargy A. Synthesis of Some Novel Fused Heterocyclic Compounds Derivatives from Bis-chalcones. *Org. Chem Curr. Res*., 5, 2016.

22. Rath and Padhy, 2013: Monitoring *in vitro* antibacterial efficacy of *Terminalia alata* Heyne ex. Roth, against MDR enteropathogenic bacteria isolated from clinical samples. *Journal of Acute Medicine, 3 (3): 93-102.*