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Synthesis, Characterization and Antibacterial Activity of Some New 5,5'-diphenyl-4,4',5,5'-tetrahydro-1H,1'H-3,3'-bipyrazole Derivatives

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Abstract
An efficient and practical synthesis of five compounds of pyrazoline derivatives structures was achieved through cyclization of hydrazine hydrate with 1,6-diphenylhexa-1,5-diene-3,4-dione using glacial acetic acid as catalyst under thermal conditions. These compounds have been characterized by FT-IR, elemental analysis (C.H.N.) and ^{1}H NMR spectroscopy.
Keywords:pyrazoline, chalcone, heterocyclic

Introduction

The chemistry of chalcones has generated intensive scientific studies throughout the world. Especially interest has been focused on the synthesis and biodynamic activities of chalcones.The name "chalcones"was given by kostanecki and tambor [1]. The most convenient methods are the claisen-schimdt condensation of equimolar quantities of a arylmethylketones with aryl aldehyde in the presence of alcoholic alkali [2]. Chalcone are used to synthesize several derivatives like cyanopyridines, pyrazolines isoxazoles, pyrimidines, having different heterocyclic ring systems [3-6].

It was more than a hundred years ago that Fischer and Knovenagel described the synthesis of a pyrazoline by the reaction of phenyl hydrazine and acrolein [7]. This report is probably the first example of pyrazoline formation by the reaction of a a,ß-unsaturated carbonyl compound with a hydrazine derivative. Formation of 1-phenyl-2-pyrazoline in this way was corroborated by Auwers et al. [8,9].

Synthesis of pyrazolines has been also stimulated by the fact that some of their derivatives were found to possess important bioactivities. Especially their antimicrobial [10], immunosuppressive [11] and central nervous system activity [12] should be emphasized. Although pyrazolines are useful substances in drug research and are well-known fivemembered nitrogen-containing heterocyclic compounds, a comprehensive review on their synthesis was published thirty years ago [13].

Experimental

General. Melting points were uncorrected. FT.IR-8400,SHIMADZU. NMR spectra were acquired with a Bruker Ultra Shield (^{1}H : 300 MHz) (University of AL-al-Bayt,Jordan). The chemical shifts were referenced to tetra methyl silane (TMS) as an internal standard. The elemental analysis were performed by using Euro Vector EA3000A (University of AL-al-Bayt,Jordan).

Synthesis of pyrazoine derivatives (2a-e)

General procedure. To a stirred solution of chalcone (**1a–e**) (which was prepared as mentioned in the literature) [14] (1.0 mmol) in 10 ml EtOH (96 %) was added hydrazine hydrate (2.0 mmol) and glacialaceticacid (2.5 ml) at room temperature. The reaction mixture was heated to reflux overnight. The progress of the reaction was monitored by TLC (ethyl acetate/hexane, 8:2). The EtOH was removed under reduced pressure and the residue was recrystalized from EtOH to afford the pure products (**2a–f**).

5,5'-diphenyl-4,4',5,5'-tetrahydro-1H,1'H-3,3'-bipyrazole (2a)

Was prepared from the reaction of 1,6-diphenylhexa-1,5-diene-3,4-dione (1a) with hydrazine hydrate and gave a 73% yield with a m.p. (202-204)^{o}c. The CHN analysis for $C_{18}H_{18}N_4$; C, 74.46; H, 6.25; N, 19.30 Found C 74.42; H 6.24; N 19.27, FT-IR spectra (KBr pellet) υ(cm^{-1}) 3330 (NH stretching of pyrazoline ring), 3020 (C–H stretching of aromatic ring), 2880 (C–H stretching of aliphatic), 1614 (C=N stretching of pyrazoline ring), 1595 (C=C stretching of aromatic ring), 1219 (C–N stretching of pyrazoline ring), δ_H($CDCl_3$) (7.271-7.417) ppm (10H,m,1,2,3); 7.025 ppm (1H,s,5) ; (3.927-3.937) ppm (2H,t,4) ; (2.625-2.725) ppm (4H,d,6,6/)

5,5'-dip-tolyl-4,4',5,5'-tetrahydro-1H,1'H-3,3'-bipyrazole (2b)

Was prepared from the reaction of 1,6-dip-tolylhexa-1,5-diene-3,4-dione (1b) with hydrazine hydrate and gave a 75% yield with a m.p. (200-202)^{o}c. The CHN analysis for $C_{20}H_{22}N_4$; C, 75.44; H, 6.96; N, 17.60 Found C 75.41; H 6.95; N 17.58, FT-IR spectra (KBr pellet) υ(cm^{-1}) 3332 (NH stretching of pyrazoline ring), 3022 (C–H stretching of aromatic ring), 2883 (C–H stretching of aliphatic), 1619 (C=N stretching of pyrazoline ring), 1594

(C=C stretching of aromatic ring), 1216 (C–N stretching of pyrazoline ring), $\delta_H(CDCl_3)$ (7.000-7.012) ppm (4H,t,2); (7.100-7.180) ppm (4H,d,3); 7.035 ppm (1H,s,5) ; (3.920-3.930) ppm (2H,t,4) ; (2.630-2.740) ppm (4H,d,6,6/) ; 2.340 ppm (6H,s,1)

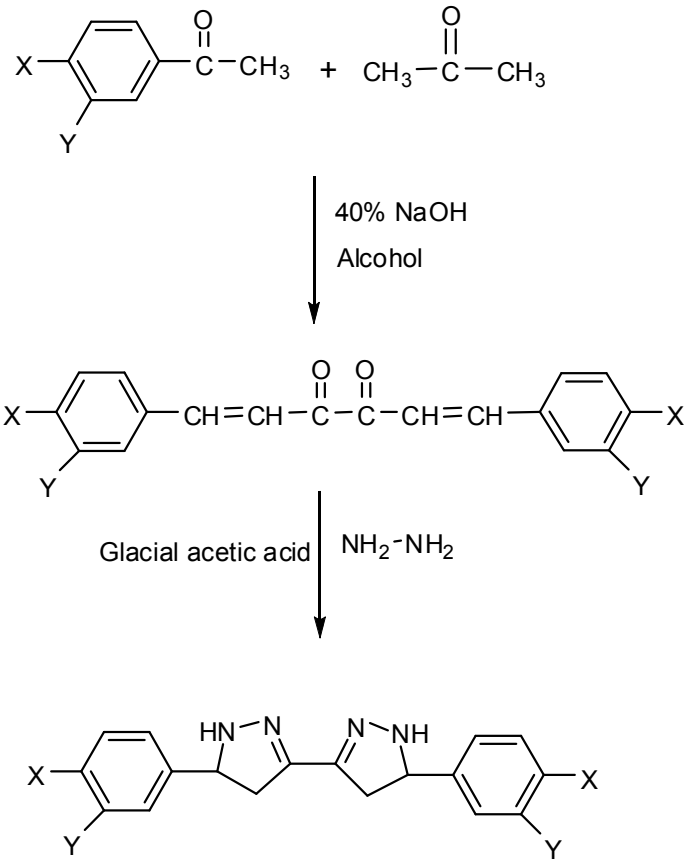
5,5/- bis(4-methoxyphenyl)-4,4',5,5'-tetrahydro-1H,1'H-3,3'-bipyrazole (2C)
Was prepared from the reaction of 1,6-bis(4-methoxyphenyl)hexa-1,5-diene-3,4-dione (1c) with hydrazine hydrate and gave a 71% yield with a m.p. (198-200)^{o}c. The CHN analysis for $C_{20}H_{22}N_4O_2$; C, 68.55; H, 6.33; N, 15.99 Found C 68.55; H 6.31; N 15.98, FT-IR spectra (KBr pellet) υ(cm^{-1}) 3336 (NH stretching of pyrazoline ring), 3020 (C–H stretching of aromatic ring), 2880 (C–H stretching of aliphatic), 1620 (C=N stretching of pyrazoline ring), 1590 (C=C stretching of aromatic ring), 1210 (C–N stretching of pyrazoline ring), $\delta_H(CDCl_3)$ (6.940-6.950) ppm (4H,t,2); (7.180-7.190) ppm (4H,d,3); 7.030 ppm (1H,s,5) ; (3.910-3.920) ppm (2H,t,4) ; (2.626-2.726) ppm (4H,d,6,6/) ; 3.700 ppm (6H,s,1)

5,5 /-bis(4-chlorophenyl)-4,4',5,5'-tetrahydro-1H,1'H-3,3'-bipyrazole (2d)
Was prepared from the reaction of 1,6-bis(4-chlorophenyl)hexa-1,5-diene-3,4-dione (1d) with hydrazine hydrate and gave a 87% yield with a m.p. (201-203)^{o}c. The CHN analysis for $C_{18}H_{16}Cl_2N_4$; C, 60.18; H, 4.49; N, 15.60 Found C 60.15; H 4.93; N 15.60, FT-IR spectra (KBr pellet) υ(cm^{-1}) 3333 (NH stretching of pyrazoline ring), 3024 (C–H stretching of aromatic ring), 2885 (C–H stretching of aliphatic), 1622 (C=N stretching of pyrazoline ring), 1595 (C=C stretching of aromatic ring), 1214(C–N stretching of pyrazoline ring), $\delta_H(CDCl_3)$ (7.440-7.480) ppm (8H,m,2,3); 7.010 ppm (1H,s,5) ; (3.940-3.950) ppm (2H,t,4) ; (2.629-2.739) ppm (4H,d,6,6/) .

-4,4 /-(4,4 /,5,5 /-tetrahydro-1H,1'H-3,3'-bipyrazole-5,5'-diyl)bis(2-methoxyphenol) (2e)
Was prepared from the reaction of 1,6-bis(4-hydroxy-3-methoxyphenyl)hexa-1,5-diene-3,4-dione (1e) with hydrazine hydrate and gave a 70% yield with a m.p. (201-203)^{o}c. The CHN analysis for $C_{20}H_{22}N_4O_4$; C, 62.82; H, 5.80; N, 14.65 Found C 62.80; H 5.79; N 14.64, FT-IR spectra (KBr pellet) υ(cm^{-1}) 3250 (OH stretching of phenol ring), 3333 (NH stretching of pyrazoline ring), 3024 (C–H stretching of aromatic ring), 2885 (C–H stretching of aliphatic), 1622 (C=N stretching of pyrazoline ring), 1595 (C=C stretching of aromatic ring), 1214(C–N stretching of pyrazoline ring), $\delta_H(CDCl_3)$ 9.711 ppm (1H,s,1 (OH)), (6.680-6.900) ppm (5H,m,2,3); 7.065 ppm (1H,s,5) ; (3.900-3.910) ppm (2H,t,4) ; (2.620-2.730) ppm (4H,d,6,6/) ; 3.800 ppm (6H,s,2/)

Results and discussion
Treatment of chalcones derivatives **(1a-e)** with hydrazine hydrate in boiling ethanol gave pyrazine derivatives compounds, after purification by recrystallization from ethanol, pure pyrazine derivatives compounds as shown in (scheme 1) in (70-87)% yield. The structures of these products were established from their elemental analysis, FT-IR,C.H.N and ^{1}H NMR spectra. The FT-IR spectra of pyrazoline compounds were characterized by the disappearance of the absorption band that was attributed to the (C=O) stretching which appeared at (1672-1710) cm^{-1}. These fact confirmed the correct expected chemical structure of these compounds. The representative absorption bands are shown in table (1). All the IR spectra of pyrazine derivatives showed a peak at (1614-1625) cm^{-1} which related to (C=N) stretching of pyrazoline ring , a peak at (1210-1219) cm^{-1} which appeared due to (C-N) stretching of pyrazoline ring and a peak at (1590-1597) cm^{-1} which appeared due to (C=C stretching of aromatic ring). While, the C-H stretching aromatic rings showed a peak within the range (3020-3024) cm^{-1} and the C-H stretching aliphatic showed a peak within the range (2880-2885) cm^{-1}. The N-H stretching showed a peak within the range (3330-3338) cm^{-1}.The OH stretching of phenolic ring showed a peak within the range 3250 cm^{-1}.

All the ^{1}H NMR spectra of pyrazoline ring were characterized [15-18] by the presence protons (5) of pyrazoline ring showed singlet signals within the range (7.010-7.065) ppm and showed triplet signals within the range (3.900-3.950) ppm which appeared to proton in (4) position because interaction with two protons in (6 and 6\) position , while the two protons in (6 and 6\) position showed doublet signals within the range (2.620-2.740) ppm because interaction with protons in (4) position. The protons of aromatic rings in compound (2a) and (2d) showed multiplet signals within the range (6.680-7.480) ppm which appeared to protons in (1,2 and 3). While the compounds (2b,2c) showed doublet signals within the range (6.940-7.012) ppm which appeared to the two protons in (2 and 3) positions.. The OCH_3 protons showed singlet signal for six protons at (3.700-3.800) ppm. The OH protons showed singlet signal for two protons in the region δ= 9.711 ppm.While the CH_3 protons showed singlet signal for six protons at 2.340 ppm.



Scheme (1)

X	Y	Compound Chalcone	Compound Pyrazoline
H	H	1a	2a
CH_3	H	1b	2b
OCH_3	H	1c	2c
Cl	H	1d	2d
OH	OCH_3	1e	2e

The biological activity

The antibacterial activities of the synthesized pyrazoline compounds against the tested organisms; *Staphylococcus aureus* and *Escherichia coli* using Hahn method[35], were summarized in table (1) and figures (1-5). This method was based on the disc diffusion for testing chemical agents and antimicrobial effectiveness by measuring and determining the agents zones of inhibitions which sizes are proportional to how sensitive the organism is to the particular antibiotic in the disc [36].

Generally, it is clear that Gram possative bacteria (*S. aureus*) are more affected than Gram negative bacteria (*E. coli*). It has been postulated that the cell membrane of *S. aureus* contains many condensed fat layers as compared to *E. coli*. Accordingly, chemicals, antibiotics or antiseptics face difficulty in penetrating these membranes and therefore their effectiveness is diminished [37].

Table (1) shows the values of inhibition zones in (mm) of the pyrazoline compounds against the two tested microorganisms.

Table (1): Inhibition zones (mm) of the synthesized pyrazoline compounds against – standard microorganisms

Compounds	IZ (*E. coli*) mm	IZ (*S. aureus*) mm
2a	11.5	13
2b	12	13.5
2c	12	14
2d	7.5	8
2e	16	18

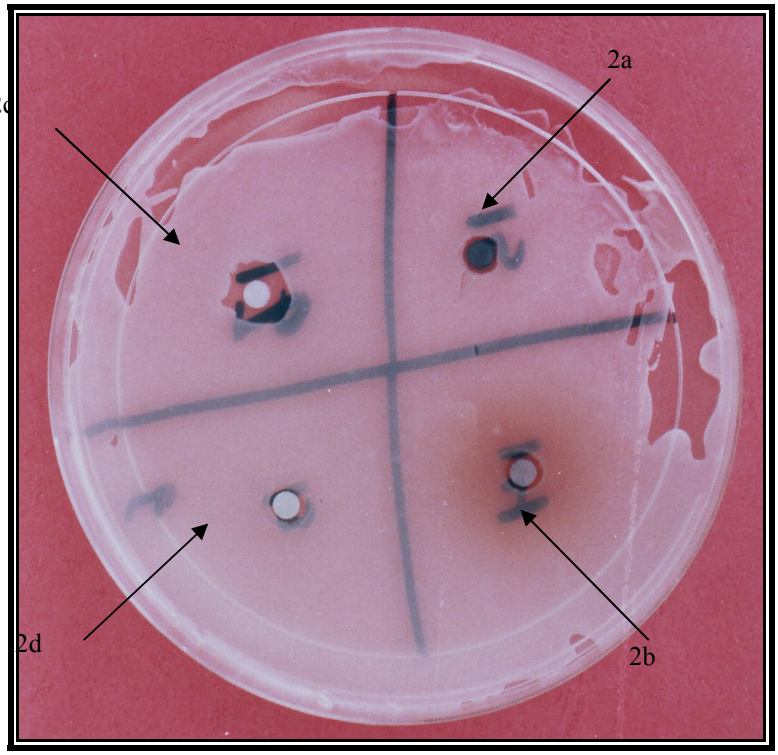


Figure (1) : Inhibition Zones of 2a, 2b, 2c and 2d against *E.coli*

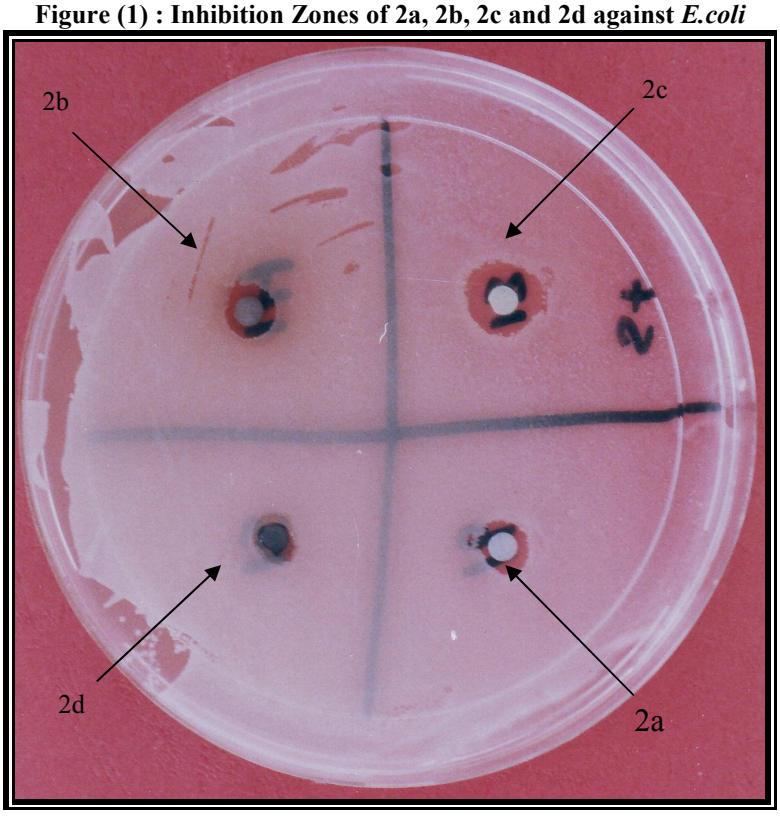


Figure (2) : Inhibition Zones of 2a, 2b, 2c and 2d against *S. aureus*

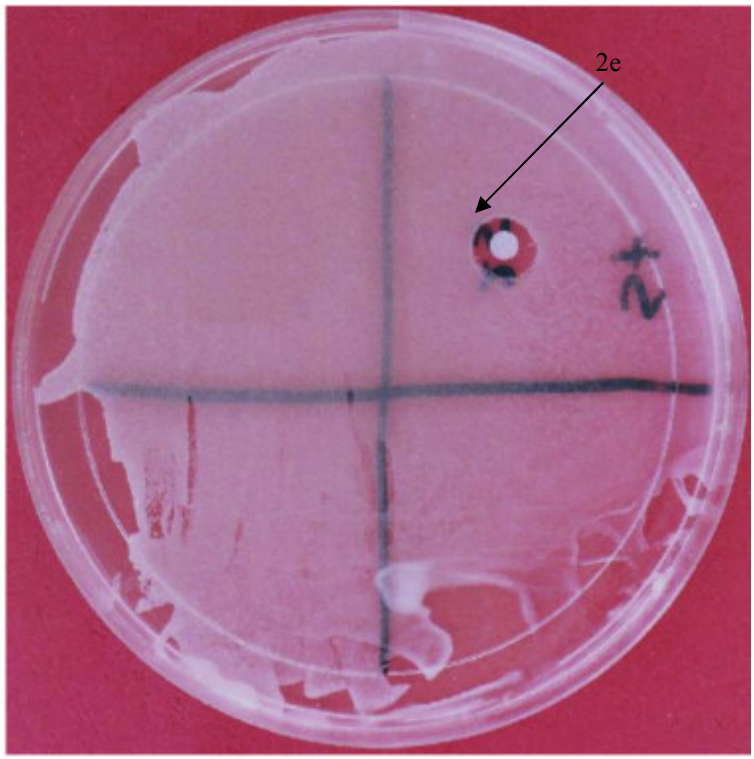


Figure (3) : Inhibition Zones of 2e, against *S. aureus*

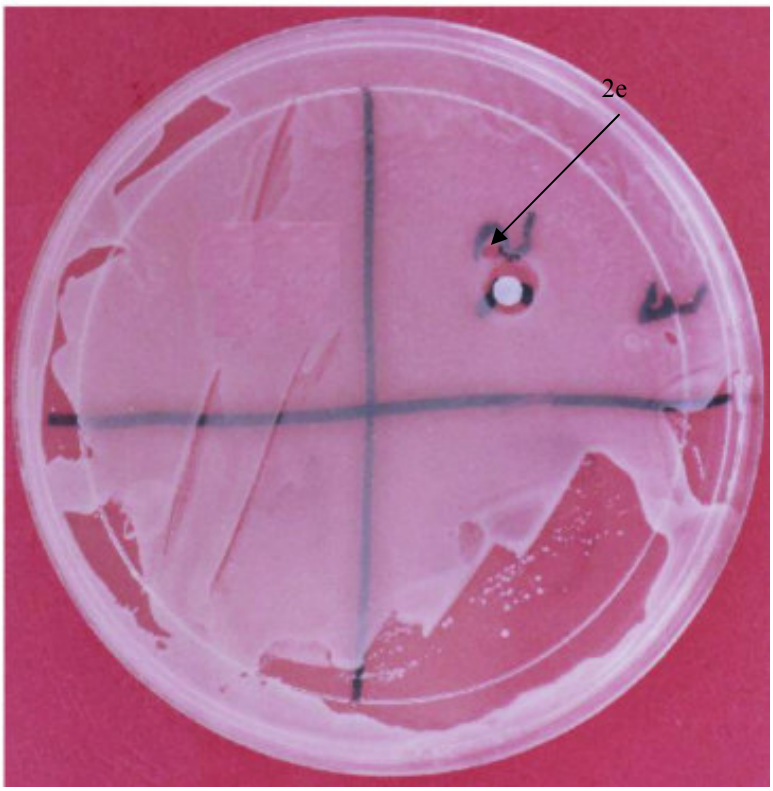


Figure (4) : Inhibition Zones of 2e against *E.coli*

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