Syntheses and Characterizations of some New Pyrazolines Derived from Chalcone Compounds

Abbas F. Abbas

Department of Chemistry, College of Science, University of Basrah

abass_faires@yahoo.com

Abstract

An efficient and practical synthesis of six compounds of pyrazoline derivatives structures was achieved through cyclization of hydrazine hydrate with α,β--unsaturated ketones (chalcones) 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.

Introduction

Chalcones constitute an important class of naturally occurring flavonoid compounds that exhibit a wide spectrum of biological activities and are well-known intermediates for the synthesis of various heterocycles. Chalcones are useful synthons in the synthesis of a large number of bioactive molecules, such as pyrazolines and isoxazoles that are well-known nitrogen-containing heterocyclic compounds (Wattenberg *et al.*, 1968; Shah and Desi, 2007; Mostahar *et al.*, 2007; Patange *et al.*, 2008 and Yar *et al.*, 2007).

The discovery of this class of compounds provides an outstaynding case history of modern drug development and also emphasizes the unpredictability of biological activity from structural modific-ation of a prototype drug molecule. Considerable interest has been focused on the pyrazoline structure, which is known to possess a broad spectrum of biological activities, such as antitumor (Taylor *et al.*, 1992), immunosuppressive (Karthikeyan *et al.*, 2007), antibacterial (Holla *et al.*, 2000), anti-inflammatory (Bansal *et al.*, 2001), anticancer (Manna *et al.*, 2005), antidiabetic (Ahn *et al.*, 2004) and antidepressant activities (Prasad *et al.*, 2005). Thus, the synthesis of the 1,3,5-trisubstituted 2-pyrazolines moietyis always a great challenge.

Among various pyrazolines derivatives, 2-pyrazolines seem to be the most frequently studied pyrazoline type of compounds. Various procedures have been developed for the synthesis of pyrazolines (Elguero *et al.*, 1984; Elguero *et al.*, 1996 and Dabholkar and Gavande, 2003). After the pioneering work of Fischer and Knoevenagel in the

19th century, the reaction of *α,β*-unsaturated aldehydes and ketones with phenylhydrazine in acetic acid under reflux became one of the most popular methods for the preparation of 2-pyrazolines (Levai, 2005; Li *et al.*, 2007 and Kamble *et al.*, 2008).

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 pyrazoline derivatives (2a-f)

General procedure. To a stirred solution of chalcone (**1a**–**f**) which was prepared as mentioned in the literature) (Karamana et al., 2010) (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-(furan-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazole (2a)

It was prepared from the reaction of 3-(furan-2-yl)-1-phenylprop-2-en-1-one (1a) with hydrazine hydrate and gave a 73% yield with a m.p. (202-204)^{o}c. The

CHN analysis for $C_{13}H_{12}N_2O$; C 73.56; H 5.70; N 13.20 Found C 73.52; H 5.68; N 13.13, FT-IR spectra (KBr pellet) $\upsilon(cm^{-1})$ 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), $\delta_H(CDCl_3)$ (7.912-7.921) ppm (1H,d,1); (7.518-7.581) ppm (5H,m,8,9,10,11,12); 7.065 ppm (1H,s,5); (6.211-6.481) ppm (2H,m,2,3); (4.625-4.725) ppm (1H,t,4); (3.927-3.937) ppm (2H,d,7,7\)

5-(furan-2-yl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole (2b)

It was prepared from the reaction of 3-(furan-2-yl)-1-(4-methoxyphenyl) prop-2-en-1-one (1b) with hydrazine hydrate and gave a 75% yield with a m.p. (200-202) ^oC. The CHN analysis for $C_{14}H_{14}N_2O_2$; C 69.41; H 5.82; N 11.56 Found C 69.31; H 5.80; N 11.55, FT-IR spectra (KBr pellet) $\upsilon(cm^{-1})$ 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), $\delta_H(CDCl_3)$ (7.912-7.921) ppm (1H,d,1); (7.455-7.465) ppm (2H,d,8,12); (7.259-7.269) ppm (2H,d,9,11); 7.065 ppm (1H,s,5) ; (6.211-6.481) ppm (2H,m,2,3); (4.625-4.725) ppm (1H,t,4); 4.111 ppm (3H,s,10); (3.350-3.360) ppm (2H,d,7,7\)

5-(furan-2-yl)-3-(4-bromoxyphenyl)-4,5-dihydro-1H-pyrazole (2c)

This was prepared from the reaction of 3-(furan-2-yl)-1-(4-bromophenyl) prop-2-en-1-one (1c) with hydrazine hydrate and gave a 79% yield with m.p. (206-208) ^oC. The CHN analysis for

$C_{13}H_{11}N_2OBr$; C 53.63; H 3.81; N 9.62 Found C 53.60; H 3.80; N 9.61, FT-IR spectra (KBr pellet) υ(cm^{-1}) 3334 (NH stretching of pyrazoline ring), 3023 (C–H stretching of aromatic ring), 2884 (C–H stretching of aliphatic), 1622 (C=N stretching of pyrazoline ring), 1596 (C=C stretching of aromatic ring), 1217 (C–N stretching of pyrazoline ring), $\delta_H(CDCl_3)$ (7.912-7.921) ppm (1H,d,1); (7.709-7.719) ppm (2H,d,8,12); (7.402-7.412) ppm (2H,d,9,11); 7.065 ppm (1H,s,5) ; (6.211-6.481) ppm (2H,m,2,3); (4.625-4.725) ppm (1H,t,4); (3.927-3.937) ppm (2H,d,7,7\)

5-(furan-2-yl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazole (2d)

It was prepared from the reaction of 3-(furan-2-yl)-1-(4-nitrophenyl)prop-2-en-1-one (1d) with hydrazine hydrate and gave a 85% yield with a m.p. (205-207)^{o}c. The CHN analysis for $C_{13}H_{11}N_3O_3$; C 60.70; H 4.31; N 16.33 Found C 60.60; H 4.30; N 16.27, FT-IR spectra (KBr pellet) υ(cm^{-1}) 3338 (NH stretching of pyrazoline ring), 3021 (C–H stretching of aromatic ring), 2881 (C–H stretching of aliphatic), 1625 (C=N stretching of pyrazoline ring), 1597 (C=C) stretching of aromatic ring), 1212 (C–N stretching of pyrazoline ring), $\delta_H(CDCl_3)$ (8.321-8.331) ppm (2H,d,9,11); (8.111-8.121) ppm (2H,d,8,12); (7.912-7.921) ppm (1H,d,1); 7.065 ppm (1H,s,5) ; (6.211-6.481) ppm (2H,m,2,3); (4.625-4.725) ppm (1H,t,4); (3.927-3.937) ppm (2H,d,7,7\)

5-(furan-2-yl)-3-(3-aminophenyl)-4,5-dihydro-1H-pyrazole (2e)

It was prepared from the reaction of 3-(furan-2-yl)-1-(3-aminophenyl) prop-2-en-1-one (1e) with hydrazine hydrate and

gave a 71% yield with a m.p. (198-200) ^{o}C. The CHN analysis for $C_{13}H_{13}N_3O$; C 68.70; H 5.77; N 18.49 Found C 68.65; H 5.71; N 18.45, 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), $\delta_H(CDCl_3)$ (7.912-7.921) ppm (1H,d,1); (7.218-7.281) ppm (6H,m,2,3,8,10,11,12); 7.065 ppm (1H,s,5); 5.500 ppm (2H,s,9); (4.625-4.725) ppm (1H,t,4); (3.927-3.937) ppm (2H,d,7,7\)

5-(furan-2-yl)-3-(3-nitrophenyl)-4,5-dihydro-1H-pyrazole (2f)

It was as prepared from the reaction of 3-(furan-2-yl)-1-(3-nitrophenyl)prop-2-en-1-one (1f) with hydrazine hydrate and gave a 87% yield with a m.p. (201-203)^{o}c. The CHN analysis for $C_{13}H_{11}N_3O_3$; C 60.70; H 4.31; N 16.33 Found C 60.65; H 4.28; N 16.30, 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), $\delta_H(CDCl_3)$ 8.711 ppm (1H,s,8), (8.318-8.381) ppm (3H,m,10,11,12); (7.900-7.910) ppm (1H,d,1); 7.065 ppm (1H,s,5); (6.211-6.481) ppm (2H,m,2,3); (4.625-4.725) ppm (1H,t,4); (3.927-3.937) ppm (2H,d,7,7\)

Results and discussion

Treatment of chalcones derivatives **(1a-f)** with hydrazine hydrate in boiling ethanol gave pyrazoline derivatives compounds , after purification by recrystallization from ethanol, pure pyrazoline derivatives compounds as shown in (scheme 1) in (71-87)% yield were obtained. 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 pyrazoline 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}.

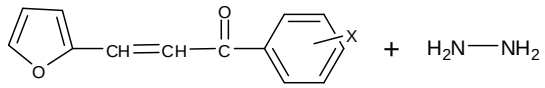
Table (1): Data of the FT-IR spectra of pyrazoline compounds

Sym.	C=N Str. (w)	C-N Str. (m)	C=C Ar.Str. (w)	C-H Ar.Str. (m)	C-H, alip. Str. (w)	NH.Str.(m)
2a	1614	1219	1595	3020	2880	3330
2b	1619	1216	1594	3022	2883	3332
2c	1622	1217	1596	3023	2884	3334
2d	1625	1212	1597	3021	2881	3338
2e	1620	1210	1590	3020	2880	3336
2f	1614	1219	1595	3020	2880	3333

Str. = stretching, w= weak, m = medium, Ar.=aromatic, alip.= aliphatic

The ^{1}H NMR spectra of pyrazoline compounds are shown in figures **(1-6)**. ^{1}H NMR data of these compounds are summarized in table (2). All the ^{1}H NMR spectra of pyrazoline ring were characterized (Silverstien *et al.*, 2005; Cooper, 1980 and Shriner and Hermann, 2004) by the presence protons (5) of pyrazoline ring showed singlet signals within the range 7.065 ppm and showed triplet signals within the range (4.625-4.725) ppm which appeared to proton in (4) position because interaction with two protons in (7 and 7$^{\backslash}$) position , while the two protons in (7 and 7$^{\backslash}$) position showed doublet signals within the range (3.350-3.937) ppm because interaction with protons in (4) position. These peaks confirmed the correct expected chemical structure of pyrazoline compounds. The proton in

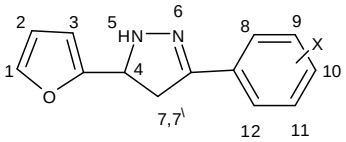
position (1) of furan ring showed doublet signals at (7.900-7.921) ppm, while the other two protons in positions (2 and 3) of furan ring showed multiplet signals within the range (6.211-7.281) ppm. The protons of aromatic rings in compound (2a) showed multiplet signals within the range (7.518-7.581) ppm which appeared to five protons in (8,9,10,11 and 12). While the compounds (2b,2c and 2d) including AB system in ^{1}H NMR spectra therefore showed doublet signals within the range (7.455-8.121) ppm which appeared to the two protons in (8 and 12) positions. The other two protons in positions (9 and 11) showed doublet signals within the range (7.259-8.331) ppm. The four protons in compound (2e) appeared multiplet signals for aromatic ring in (7.218-7.281) ppm, while compound (2f) showed singlet signal at the range 8.711 ppm which related to proton in position (8) and showed multiplet signals within the range(8.318-8.381) ppm which appeared to the three protons in positions (10,11 and 12). The OCH_3 protons showed singlet signal for three protons at 4.111 ppm. The NH_2 protons showed singlet signal for two protons in the region δ=5.500 ppm.



X= H , 4-OCH_3,4-Br ,4- NO_2, 3-NH_2, 3-NO_2

1a, 1b, ,1c , 1d , 1e , 1f

glacial acetic acid
ethanol



X= H , 4-OCH_3,4-Br ,4- NO_2, 3-NH_2, 3-NO_2

2a, 2b, ,2c , 2d ,2e , 2f

Scheme (1)

Table (2): Chemical shift (ppm) of the synthesized pyrazoline compounds

Symb.	**δ (ppm) of Proton (1)**	**δ (ppm) of Protons (2 and 3)**	**δ (ppm) of Proton (4)**	**δ (ppm) of Proton (5)**	**δ (ppm) of Protons (7 and 7\')**	**δ (ppm) of Protons NH_2**	**δ (ppm) of Protons OCH_3**	**δ (ppm) of Aromatic Protons**
2a	(7.912-7.921) d	(6.211-6.481) m	(4.625-4.725) t	7.065 s	(3.927-3.937) d	---	---	(7.518-7.581) m (8,9,10,11 and 12)
2b	(7.912-7.921) d	(6.211-6.481) m	(4.625-4.725) t	7.065 s	(3.350-3.360) d	---	4.111 s	(7.455-7.465) d (8 and 12) (7.259-7.269) d (9 and 11)

2c	(7.912-7.921) d	(6.211-6.481) m	(4.625-4.725) t	7.065 s	(3.927-3.937) d	---	---	(7.709-7.719) d (8 and 12) (7.402-7.412) d (9 and 11)
2d	(7.912-7.921) d	(6.211-6.481) m	(4.625-4.725) t	7.065 s	(3.927-3.937) d	---	---	(8.111-8.121) d (8 and 12) (8.321-8.331) d (9 and 11)
2e	(7.912-7.921) d	(7.218-7.281) m Me.wi. arom.	(4.625-4.725) t	7.065 s	(3.927-3.937) d	5.500 s	---	(7.218-7.281) m (8,10,11 and 12) Me.wi. (2 and 3)
2f	(7.900-7.910) d	(6.211-6.481) m	(4.625-4.725) t	7.065 s	(3.927-3.937) d	---	---	8.711 s (8) (8.318-8.381) m (10,11 and 12)

Symb. = symbol, s = singlet, d = doublet, t = triplet, m=multiplet, Me.wi.= merge with

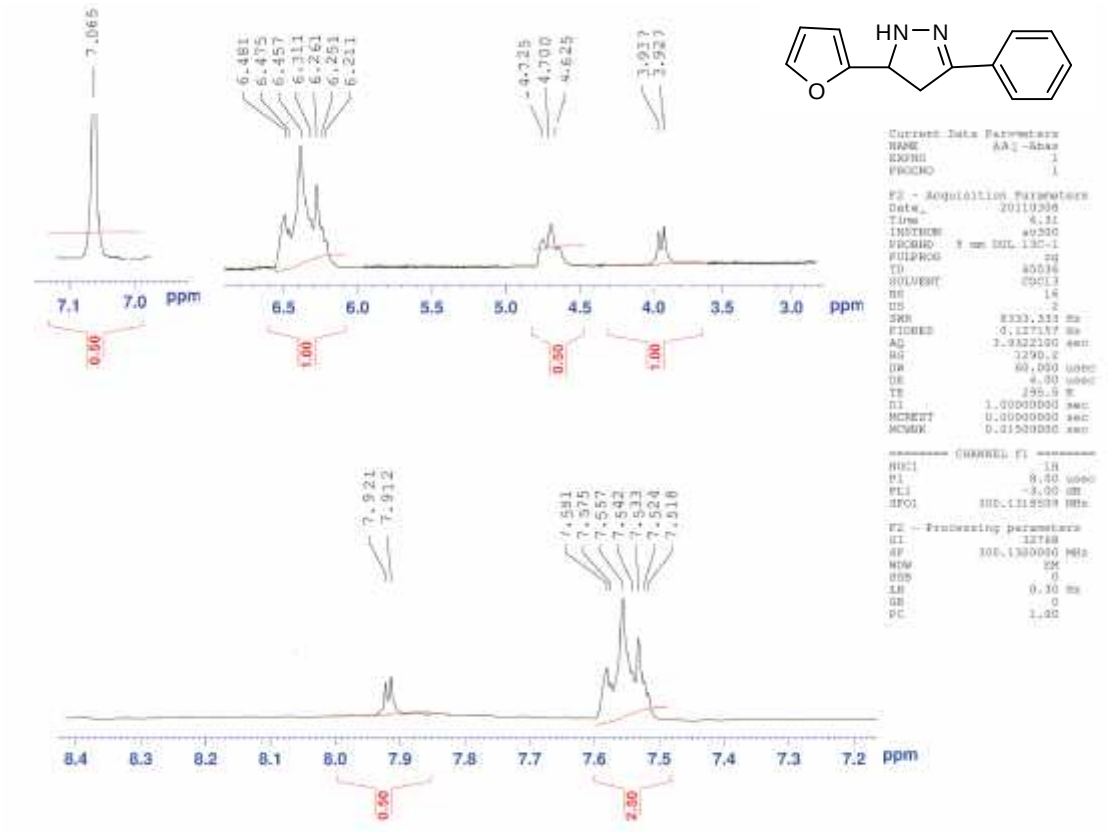


Figure (1): H NMR spectrum of compound (2a)

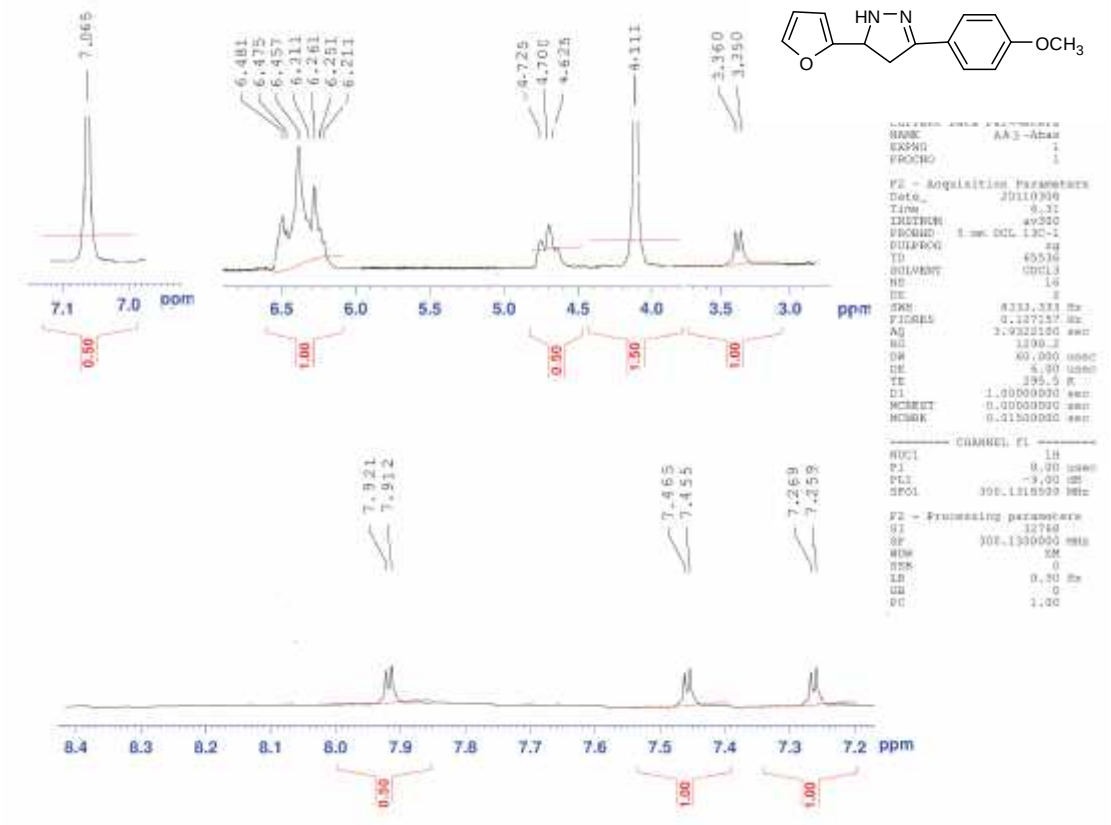


Figure (2): H NMR spectrum of compound (2b)

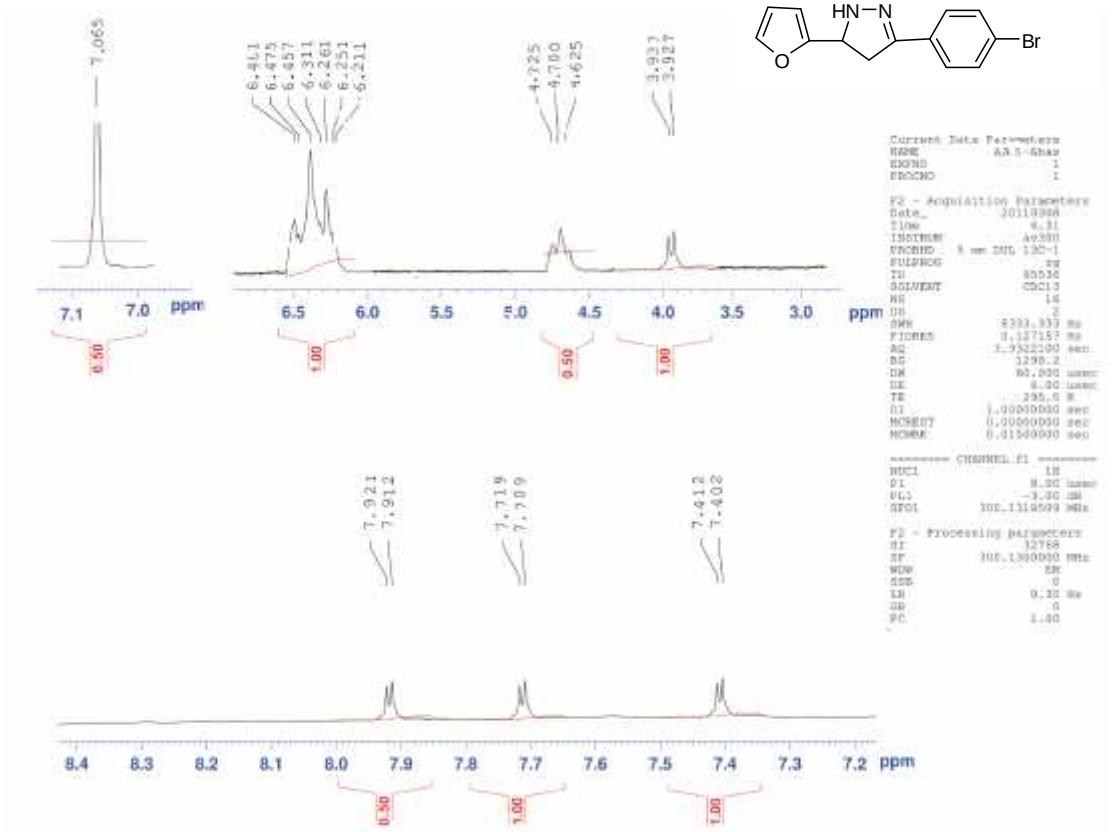


Figure (3): H NMR spectrum of compound (2c)

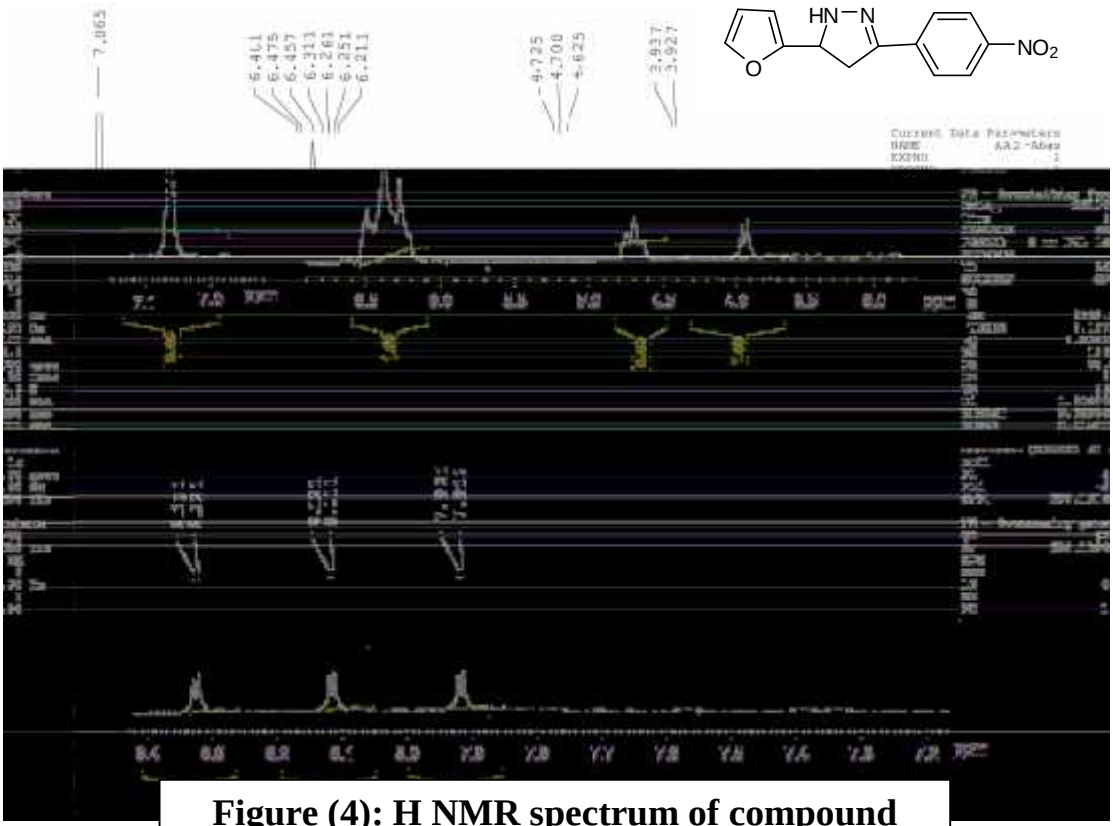


Figure (4): H NMR spectrum of compound

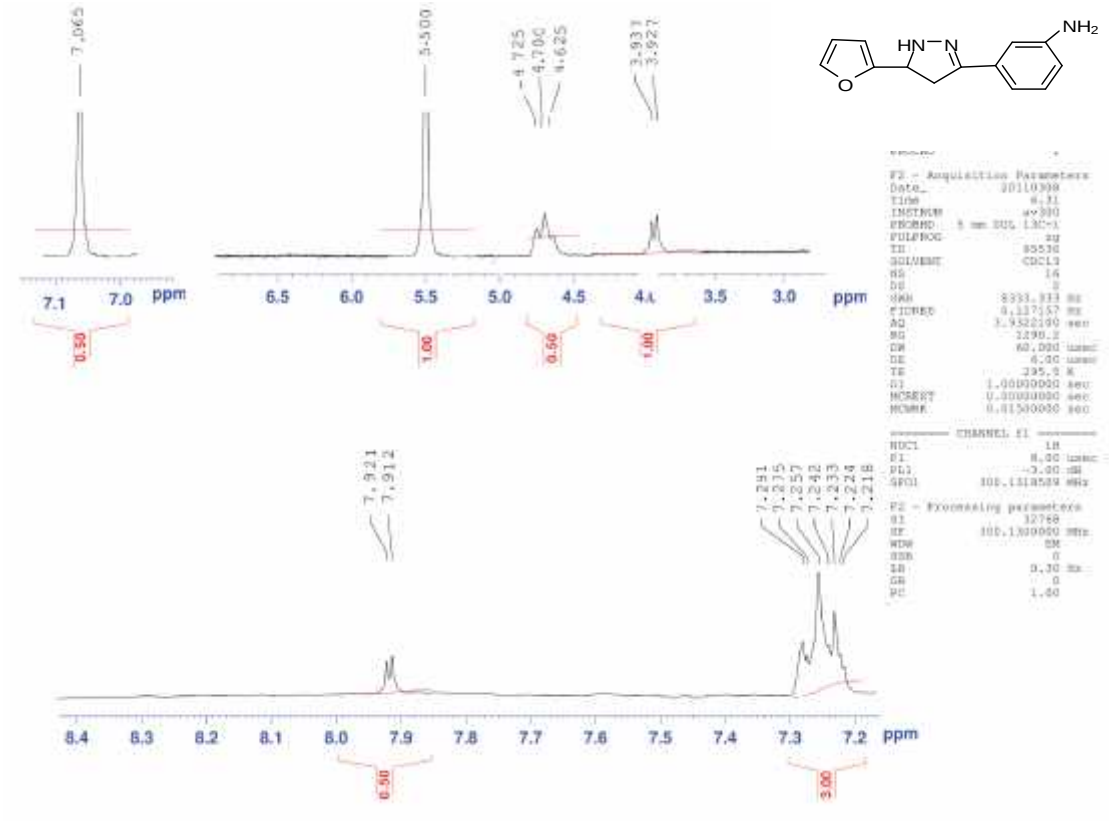


Figure (5): H NMR spectrum of compound (2e)

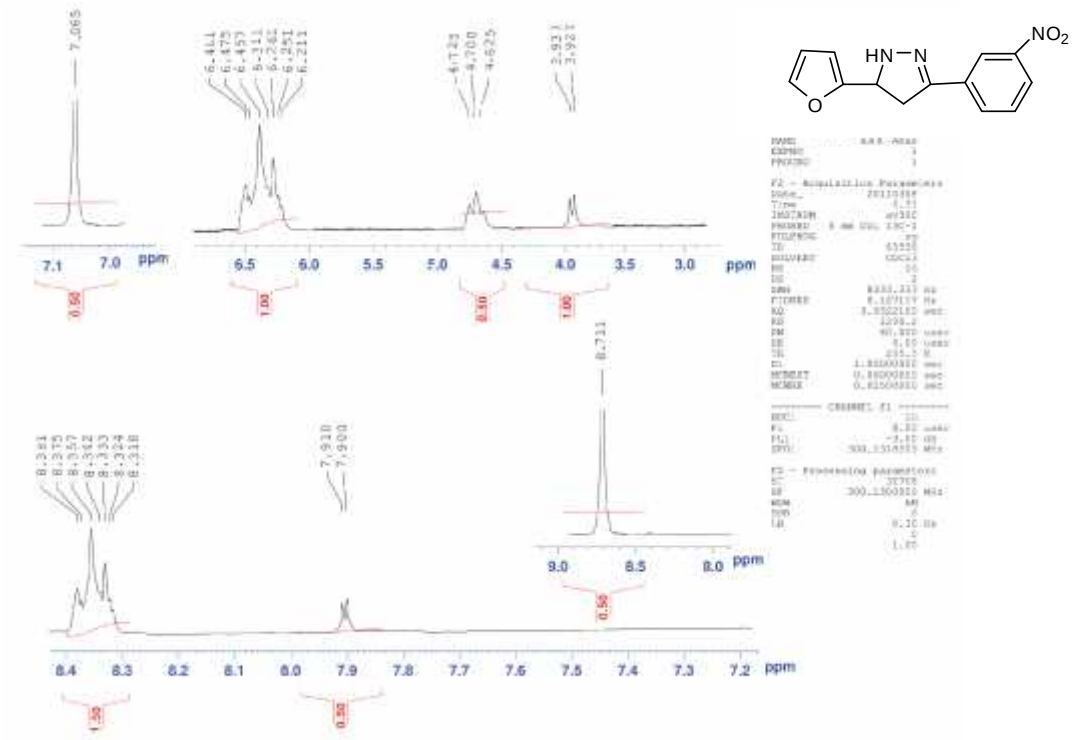


Figure (6): H NMR spectrum of compound (2f)

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تحضير وتشخيص بعض مركبات البايرازولين الجديدة المشتقة من الجالكونات

عباس فاضل عباس

قسم الكيمياء – كلية العلوم – جامعة البصرة

abass_faires@yahoo.com

الخلاصة

حضر في هذا البحث ستة مركبات من مشتقات البايروزولين من خلال تأحلق الهيدرازين المائي مع مشتقات الجالكون(α و β-كيتون غير مشبع) بأستخدام حامض الخليك الثلجي كعامل مساعد تحت ظروف حرارية. وشخصت المركبات الجديدة بأستخدام مطيافية الاشعة تحت الحمراء وتحليل العناصر الدقيق ومطيافية الرنين النووي المغناطيسي للبروتون.