Preparation of Chalcones and Their Applications in Heterocycles Synthesis

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Abstract: -

Some new heterocyclic compounds containing, cyclohexenone, indazole, isoxazoline, pyrmidine and pyrazoline ring system were prepared from chalcones (1a,b). The starting chalcones (1a,b) were obtained by a base catalyzed condensation of appropriately substituted benzaldehydes and 2-acetylbenzofuran. The reaction of the prepared chalcones with ethylacetoacetate/hydrazine hydrate, hydroxylamine hydrochloride, urea, thiourea, hydrazine hydrate, phenyl hydrazine or hydrazide derivatives gave the mentioned heterocycles. All synthesized compounds have been characterized by physical and spectral methods.

Key words: - chalcones, cyclohexenone, indazole. Isoxazoline, pyrimidine, pyrazoline.

Introduction:-

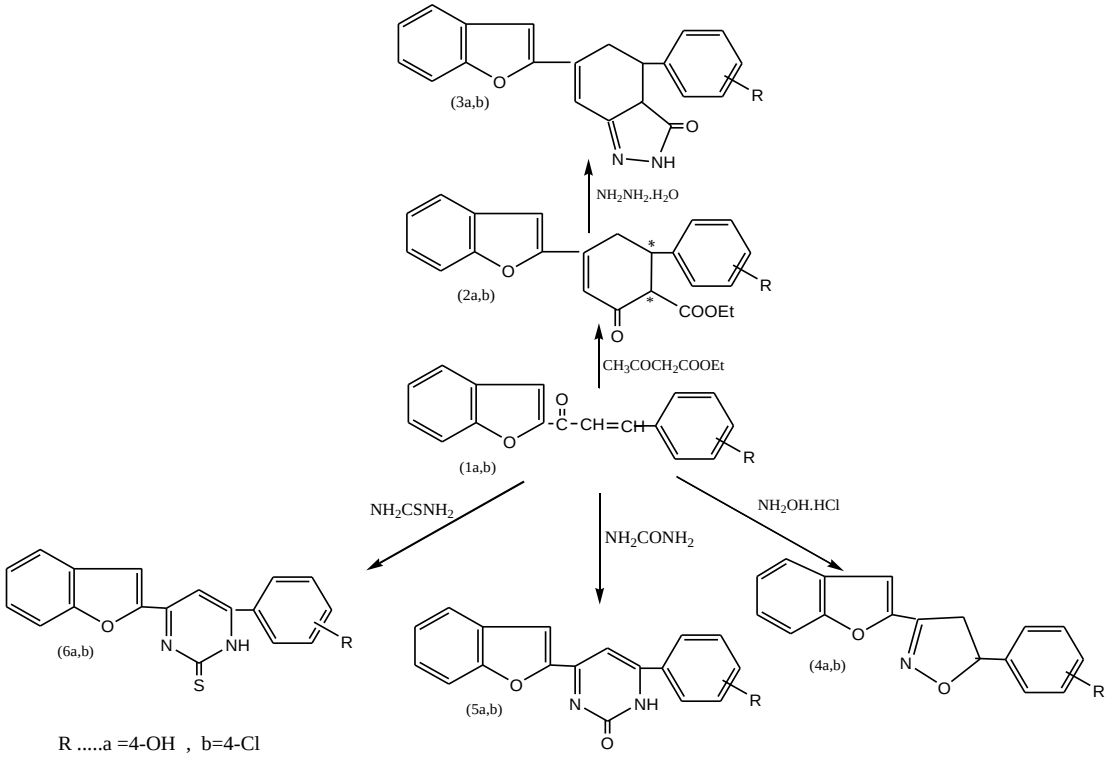
Chalcones, one of the major classes of natural products and belongs to flavonoid family, have been reported to possess several biological activities [1,2]. Chalcones are suitable for the synthesis of an important heterocycles like indazole, cyclohexenone, isoxazoline , pyrmidine and pyrazoline derivatives. Pyrazolines, for example, have attracted increasing attention due to their pharmaceutical applications such as: anti-bacterial [3], anti-fungal [4], enzymatic inhibitors [5] and the treatment of Parkinson's disease or head injuries [6]. Pyrazolines also used in the synthesis of fluorescent dyes due to their optical properties [7], on the other hand isoxazoline known to display impressive therapeutic specifications in treatment of: bacterial infections in humans [8] and animals [9], immunological problems [10] and instance tumor growth [11] in addition to their use as insecticides, nematicides and molluscicides agents [12]. Pyrimidine derivatives play an essential role in the medical field due to their anti-inflammatory, anti-ulcerogenic [13], anti-AIDS [14], anti-depressant [15], HIF prolyl hydroxylase inhibition [16] activities. The importance of chalcones is their flexibility as synthons for the production of fused ring systems such 2H-indazoles via di-arylcyclohexenone derivatives as

intermediates. Indazoles known to have medical uses in treating obesity and related diseases [17,18]. Based on these considerations, we aimed to obtain the titled compounds.

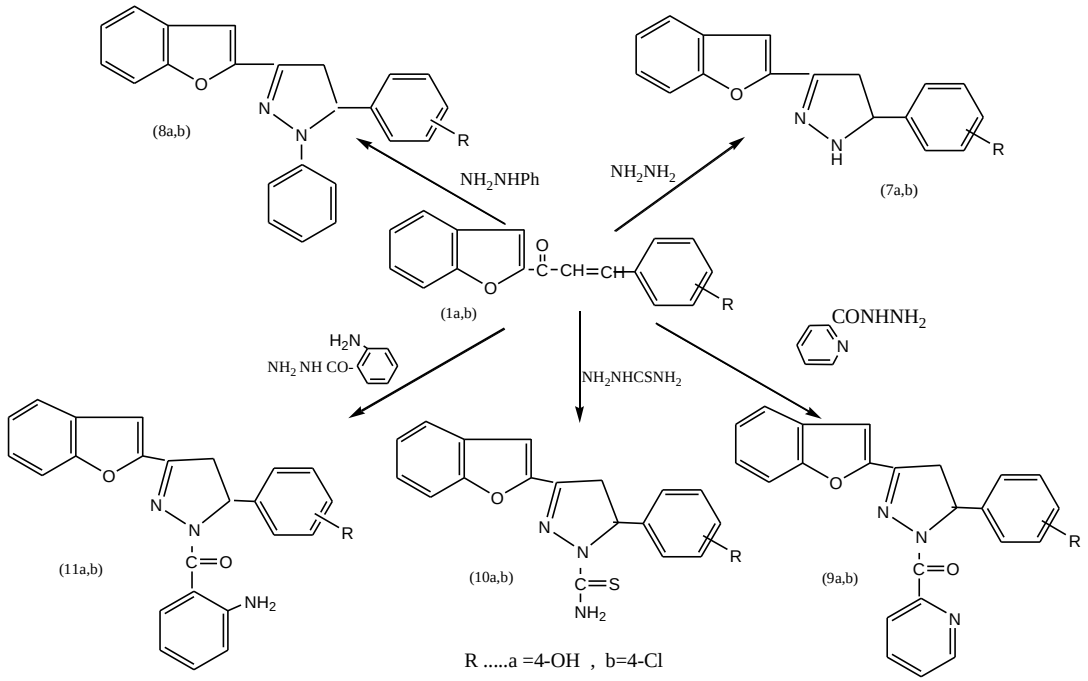
Experimental:-

A- Materials: - All chemicals were supplied by Merck (Germany), Fluka (Germany) and Sigma Aldrich (UK) Chemicals Co. and used as received.

B- Instrumentation: - Melting points were determined in open capillary tubes on an electro thermal digital melting point apparatus (USA) and were uncorrected. IR spectra were recorded on a SHIMADZU -FTIR-8400spectrophotometer in KBR discs. ^{1}H NMR spectra were measured with Bruker Ultra Shield AMX-300 MH2 Spectrometer (Germany) in DMSO and chemical shifts were recorded in a ppm relative to TMS as internal standard solvent. Elemental analyses were carried out using an EuroEA Elemental Analyzer at (The Central Service Laboratory-College of Education For Pure Sciences Ibn Al- Haitham).



Scheme (1)



Scheme (2)

Synthesis procedures:-

All the prepared compounds were synthesized according to literature [19]

Preparation of chalcones 1-(benzofuran-2-yl)-3-(substituted phenyl) prop-2-ene-1-one (1a,b):

A mixture of aromatic benzaldehyde (0.01 mol) (4-hydroxy benzaldehyde or 4-chlorobenzaldehyde) and 2-acetyl bezofuran (0.01 mol, 1.60 g) was dissolved in (15 mL) of ethanol, an aqueous sodium hydroxide solution (10 mL, 25%) was added. The mixture was stirred for 3-4h at room temperature. Then it was diluted with ice-cold distilled water (30 mL), filtered, washed well with cold water, dried in air and recrystallized from ethanol to give the required product (75-82%).

Preparation of cyclohexenone derivatives (2a,b):

A mixture of chalcones (1a,b) (0.01 mol) and ethyl acetoacetate (1.30 mL, 0.01mol) in absolute ethanol (10mL) containing aqueous potassium hydroxide solution (1 mL, 10%) was refluxed for 5h and then left overnight at room temperature. The solid formed was filtered off, air dried and recrystallized form absolute ethanol. The physical data of these compounds are listed in Table (1). Anal. Calcd. for (2a) $C_{2۳}H_{19}O_5$: C, 7۳.60; H, 5.06. Found: C, 72.78; H, 5.85.

Preparation of indazole derivatives (3a,b):

A mixture of compounds (2a,b) (0.01 mol) and hydrazine hydrate 99% (5mL, 0.01 mol) in absolute ethanol (10 mL) containing glacial acetic acid (0.5 mL) was refluxed for 2h. After cooling, the solid formed was filtered off, air dried and recrystallized form chloroform. The physical data of these compounds are listed in Table (1).

Preparation of 3-(benzofuran-2-yl)isoxazoline derivatives (4a,b):

To a mixture of chalcones (1a,b) (0.01 mol, 2.91 g) and hydroxyl amine hydrochloride (0.01 mol , 0.69 g) in absolute ethanol (30 mL), aqueous sodium hydroxide (10%, 6 mL) was added then the reaction mixture was heated under reflux for 8h and poured slowly into ice cold water and the product obtained was washed with water and recrystallized from absolute ethanol. The physical data of these compounds are listed in Table (1).

Preparation of pyrimidinone derivatives (5a,b):

To a solution of (0.01 mol, 2.91 g) of chalcones(1a,b) in absolute ethanol (10 mL), urea (0.01 mol, 0.6 g) of aqueous sodium hydroxide (10mL, 10 %) was added. The reaction mixture was heated under reflux for 5h and poured in ice-cold water. The product obtained was filtered washed with water and recrystallized from ethanol (95%). The physical data of these compounds are listed in Table (1).

Preparation of pyrimidinethion derivatives (6a,b):

To a solution of chalcones(1a,b) (0.01 mol) in absolute ethanol (10 mL), thiourea (0.01 mol, 0.6 g) and aqueous sodium hydroxide (10 mL, 20.0 mmol) were added. The reaction mixture was heated under reflux for 7h and poured into iced cold water the product obtained was filtered, washed with water and recrystallized from absolute ethanol. The physical data of these compounds are listed in Table (1).

Preparation of 3-(benzofuran-2-yl) pyrazoline derivatives (7-11a,b): A mixture of chalcone 1(a,b) (0.01 mol, 2.91g) and hydrazine hydrate 99% (5mL, 0.01 mol) or substituted hydrazine hydrate (0.01 mol) in absolute ethanol (10 mL) containing glacial acetic acid (0.5 mL) was refluxed for 2h. After cooling, the solid formed was filtered off , air dried and recrystallized form absolute ethanol. The physical data of these compounds are listed in Table(1).

Results and discussion

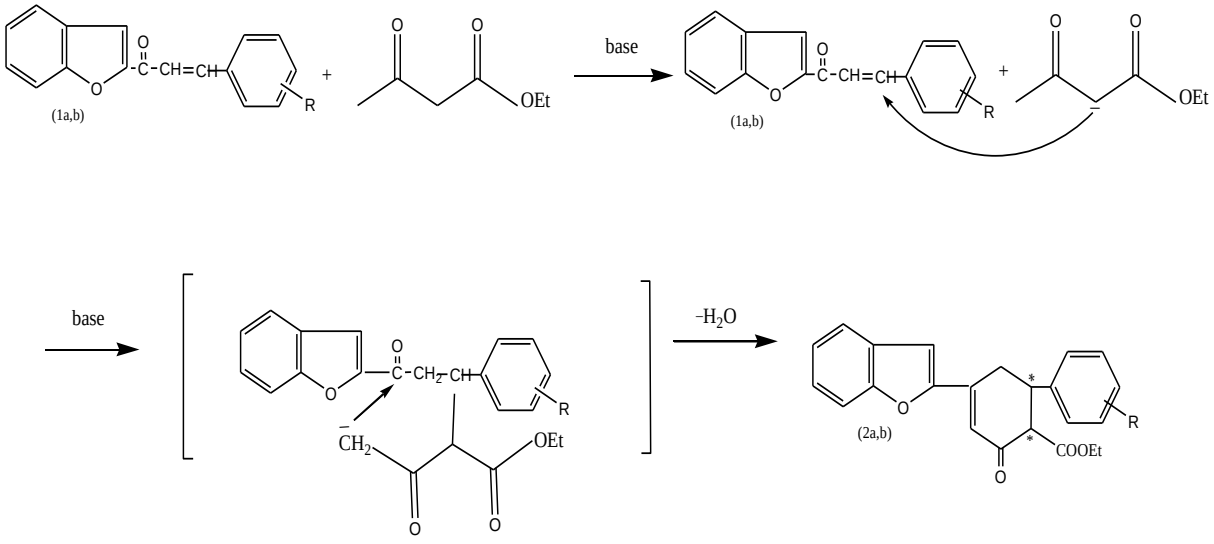
The synthesis of chalcones and heterocyclic derivatives were performed as shown in schemes (1) and (2).

The starting chalcones, namely 1-(benzofuran-2-yl)-3-(4-hydroxyphenyl) prop-2-ene-1-one (1a) and 1-(benzofuran-2-yl)-3-(4-

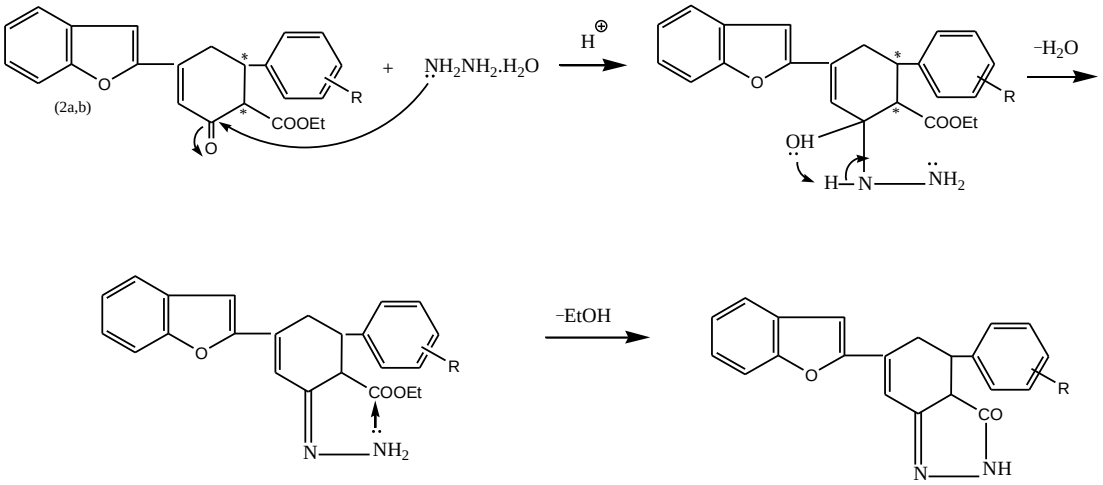
chlorophenyl) prop-2-ene-1-one (1b), were synthesized via the Claisen-Schmidt reaction of 2-acetyl benzofuran with 4- hydroxybenzaldehyde and 4-chlorobenzaldehyde, respectively, in ethanol in the presence of aqueous sodium hydroxide at room temperature. The glow red and pale brown solids obtained were filtered, washed and recrystallized from chloroform, (65% and 78%), m.p = 105-107 ^{0}C and 88-90 ^{0}C, respectively. The structural assignments of the chalcones (1a,b) based on melting points and FTIR spectroscopy. The FTIR spectra of chalcones indicated the appearance of two peaks around 1655-1666 cm^{-1} and 1573-1612cm^{-1} due to C=O and C=C stretching vibrations, respectively.

The chalcones (1a,b) were allowed to react with ethyl acetoacetate (1:1) in the presence of an aqueous potassium hydroxide 10 % to give new cyclohexenone derivatives (2a,b) which were identified by their melting points, C.H.N analysis and FTIR spectroscopy. The FTIR spectral data of these compounds are shown in Table (2).

The formation of cyclohexenones can be explained by based-catalyzed Michael addition conversion of the intermediates into cyclohexenones [20].



Cyclocondensation of (2a,b) with hydrazine hydrate in the presence of glacial acetic acid afforded the corresponding indazoles. The reaction may have proceeded through condensation between C=O of cyclohexenone and NH_2 of hydrazine hydrate, followed by cyclization with the loss of an ethanol molecule [19].



The new indazole derivatives (3a,b) were identified by their melting points, FTIR and ^{1}H NMR spectroscopy. The FTIR spectra of these compounds showed the disappearance of C=O and C-O-C absorption bands of esters and appearance of new absorption bands of NH and C=N group at 3228 cm^{-1} and 1610 cm^{-1}, respectively. Functional groups which are characteristic of these compounds are given in Table (2). The ^{1}H NMR spectrum of compound (3b) (in DMSO) shows the following signals: eight aromatic protons appeared in the region δ 7.20-8.73 ppm, a singlet signal at δ 6.80 ppm for furan ring conjugate with benzene ring, a signal at δ 3.12 ppm that are attributed to cyclohexene protons and a singlet signal at δ 2.93 ppm which was assigned to NH proton.

Isoxazoline compounds (4a,b) were synthesized from the reaction of chalcones (1a,b) with hydroxylamine hydrochloride in alkaline medium. These compounds (4a,b) were identified by their melting points, FTIR and ^{1}H NMR spectroscopy. The FTIR spectra of isoxazoline (4a, b) showed the disappearance of two absorption bands of CH=CH and C=O groups of the starting materials with the appearance of new absorption bands for C=N group around 1630 cm^{-1} and C-O (cyclic ether) group around 1091 cm^{-1}. The FTIR spectral data for isoxazoline (4a, b) are listed in Table (2).

^{1}H NMR spectrum of compound (4b), Figure (1), (in DMSO as a solvent), showed many signals of aromatic protons appeared in the region δ 7.04-7.88 ppm and a signal in the region δ 6.68 ppm for furan ring conjugate with benzene ring. Furthermore, the triplet signal at δ 2.97 ppm and a doublet signal at δ 3.64 ppm due to one proton C-5 and two protons C-4 in the isoxazoline ring, respectively. In addition to a signal at δ 8.25 ppm which was assigned to the proton of OH.

The pyrimidinone derivatives (5a, b) were synthesized from the reaction of chalcones (1a,b) with urea in basic medium. The structures of

the pyrimidinones (5a,b) are characterized by FTIR spectra which are showing the disappearance of two absorption bands and appearance of new absorption bands for NH and C=O groups around 3338cm^{-1} and 1665cm^{-1}, respectively. The other data of functional groups which are characteristic of these compounds are given in Table (2).

^{1}H NMR spectrum of pyrimidinone (6a), Figure (2), exhibited eight aromatic protons appeared at δ 7.11-7.88 ppm, a singlet signal at δ 6.78 ppm for furan ring conjugate with benzene ring, a singlet doublet at δ 3.04 ppm for proton at C-5 of pyrimidinone ring, a singlet at δ 2.51ppm that could be attributed to one proton of NH group.In addition to a signal at 9.66 ppm which was assigned to the proton of OH.

Pyrimidinethion derivatives (6a,b) were synthesized from the reaction of chalcones (1a,b) with thiourea in basic medium. The structures of compounds (6a,b) are characterized by FTIR and ^{1}H NMR spectroscopy. The characteristic FTIR adsorption band of pyrimidinethion showed the disappearance of two absorption bands of the CH=CH and C=O groups in the chalcones and appearance of new absorption bands for NH and C=S groups around 3283cm^{-1} and 1280cm^{-1}, respectively. The FTIR spectral data of these compounds are shown in Table (2).

The reaction of chalcones (1a,b) with hydrazine hydrate, phenyl hydrazine, 2-pyridinecarboxylic acid hydrazide, thiosemicarbazide and 2-aminobenzohydrazide under reflux in the presence of glacial acetic acid yielded the corresponding pyrazoline derivatives (7-11a,b), respectively.

The structure of the pyrazoline derivatives (7-11a,b) were identified by their melting points, FTIR and ^{1}H NMR spectroscopy. The FTIR spectra of these compounds showed the disappearance of two absorption bands of the CH=CH and C=O groups in the chalcones (1a,b) and appearance of new absorption stretching bands of NH and C=N groups Table (2). ^{1}H NMR spectrum of compound (7b), (Figure 3), (in DMSO as a solvent), shows the following signals: a sharp singlet signal at δ 2.49 ppm due to a proton of the N-H group, sharp signals at δ 1.78 ppm could be attributed to two protons of CH_2 pyrazoline, signal in the region δ 7.35 ppm for furan ring conjugate with benzene ring and many signals (aromatic protons) appeared in the region δ 7.80-7.95 ppm.

Table 1: Physical properties of synthesized compounds (2-11a,b)

Comp. No.	Nomenclature	Molecular Formula	M.P ^{0}C	Yield %	Color
2a	Ethyl-4-(1-benzofuran-2-yl)- 6- (4-hydroxyphenyl)-2-oxocyclohexa-3-enecarboxylate	$C_{23}H_{19}O_5$	260-262	70	Gray
2b	Ethyl-4-(1-benzofuran-2-yl)- 6- (4-chlorophenyl)-2-oxocyclohexa-3-enecarboxylate	$C_{23}H_{18}O_4$ Cl	127-129	65	Brown
3a	4,5-dihydro-4-(4-hydroxyphenyl)- 6-(1-benzofuran-2-yl)-2H-indazol-3(H)ones	$C_{21}H_{14}N_2O_3$	75-77	60	Off-white
3b	4,5-dihydro-4-(4-chlorophenyl)- 6-(1-benzofuran-2-yl)-2H-indazol-3(H)ones	$C_{21}H_{13}N_2O_2$ Cl	113-115	50	Yellow Green-
4a	3-(1-benzofuran-2-yl)-5-(4-hydroxy phenyl)-4,5-dihydroisoxazole	$C_{17}H_{13}NO_3$	153-155	70	Yellowish brown
4b	3-(1-benzofuran-2-yl)-5-(4-chloro phenyl) -4,5-dihydroisoxazole	$C_{17}H_{12}NO_2Cl$	157-159	66	Bright Brown
5a	6-(1-benzofuran-2-yl)-4-(4-hydroxy phenyl) pyrimidin -2(1*H*)- one	$C_{18}H_{12}N_2O_3$	60-62	68	Yellowish Brown
5b	6-(1-benzofuran-2-yl)-4-(4-chloro phenyl) pyrimidin -2(1*H*)- one	$C_{18}H_{11}N_2O_2Cl$	97-99	64	Light brown
6a	6-(1-benzofuran-2-yl)-4-(4-hydroxy phenyl) pyrimidine- 2(1*H*)- thione	$C_{18}H_{12}N_2O_2$ S	222-224	76	Pale red
6b	6-(1-benzofuran-2-yl)-4-(4-chloro phenyl) pyrimidine- 2(1*H*)- thione	$C_{18}H_{11}N_2OClS$	120-122	75	Brownish yellow
7a	4,5-dihydro-3-(1-benzofuran-2-yl)-5-(4-hydroxyphenyl) -1H- pyrazole	$C_{17}H_{12}N_2O_2$	75-77	78	Dark brown
7b	4,5-dihydro-3-(1-benzofuran-2-yl)-5-(4-chlorophenyl) - 1H- pyrazole	$C_{17}H_{11}N_2OCl$	139-141	72	Yellow
8a	4,5-dihydro- 3-(1-benzofuran-2-yl)-5-(2-hydroxyphenyl) -1-phenyl-1H- pyrazole	$C_{23}H_{16}N_2O_2$	114-116	68	Brown
8b	4,5-dihydro-3-(1-benzofuran-2-yl)-5-(4-chlorophenyl) -1-phenyl-1H- pyrazole	$C_{23}H_{15}N_2OCl$	171-173	67	Orange
9a	4,5-dihydro- 3-(1-benzofuran-2-yl)-5-(4-hydroxyphenyl) pyrazole-1-carbothioamide	$C_{17}H_{13}N_3O_2S$	200-202	76	Pale Brown
9b	4,5-dihydro- 3-(1-benzofuran-2-yl)-5-(4-chlorophenyl) pyrazole-1-carbothioamide	$C_{17}H_{12}N_3OClS$	157-159	72	White
10a	4,5-dihydro-3-(1-benzofuran-2-yl)-5-(4-hydroxyphenyl) -1 (2-pyridine carboxylic acid) -1H- pyrazole	$C_{23}H_{15}N_3O_3$	108-110	77	Yellowish Brown
10b	4,5-dihydro-3-(1-benzofuran-2-yl)-5-(4-chlorophenyl -1 (2- pyridine carboxylic acid)-1H-pyrazole	$C_{22}H_{14}N_3O_2Cl$	258-260	75	Yellow
11a	4,5-dihydro- 3-(1-benzofuran-2-yl)-5-(4-hydroxyphenyl) -1(2-aminobenzo) - 1H-pyrazole	$C_{23}H_{16}N_3O_3$	98-100	60	Pale yellow
11b	4,5-dihydro-3-(1-benzofuran-2-yl)-5-(4-chlorophenyl) -1(2-aminobenzo -1H-pyrazole	$C_{24}H_{15}N_3O_2Cl$	110-112	68	Brownish Yellow

Table2: Characteristic FTIR absorption bands of synthesized compounds (2-11a,b)

Comp. No.	ν N-H	ν C=O	ν C=N	ν C=C aromatic	ν C=S	Others
2a	-	1731	-	1598	-	OH: 3341
2b	-	1743	-	1592	-	C-Cl:750
3a	3228	1709	1602	1598		OH: 3363
3b	3344	1713	1600	1596		C-Cl:773
4a	-	-	1649	1595	-	C-O-N: 1255
4b	-	-	1647	1558	-	C-O-N: 1342
5a	3356	1662	1654	1559	-	OH: 3462
5b	3344	1660	1650	1555	-	C-Cl:751
6a	3201	-	1618	1549	1280	OH: 3441
6b	3425	-	1620	1545	1257	C-Cl:751
7a	3280	-	1654	1551	-	OH:3379
7b	3310	-	1644	1559	-	C-Cl:750
8a	-	-	1640	1590	-	OH:3410
8b	-	-	١٦٤٦	١٥٩٨	-	C-Cl:751
9a	-	١٦٦٤	1674	1558	-	OH:3456
9b	-	١٦٦٢	1622	1554	-	C-Cl:750
10a	3236	1664	1654	1585	١٢٥٩	OH:3470
10b	3332	1662	1632	1558	١٢٤٩	C-Cl:752
11a	-	1680	1654	1573	-	OH:3420
11b	-	1666	1612	1551	-	C-Cl:750

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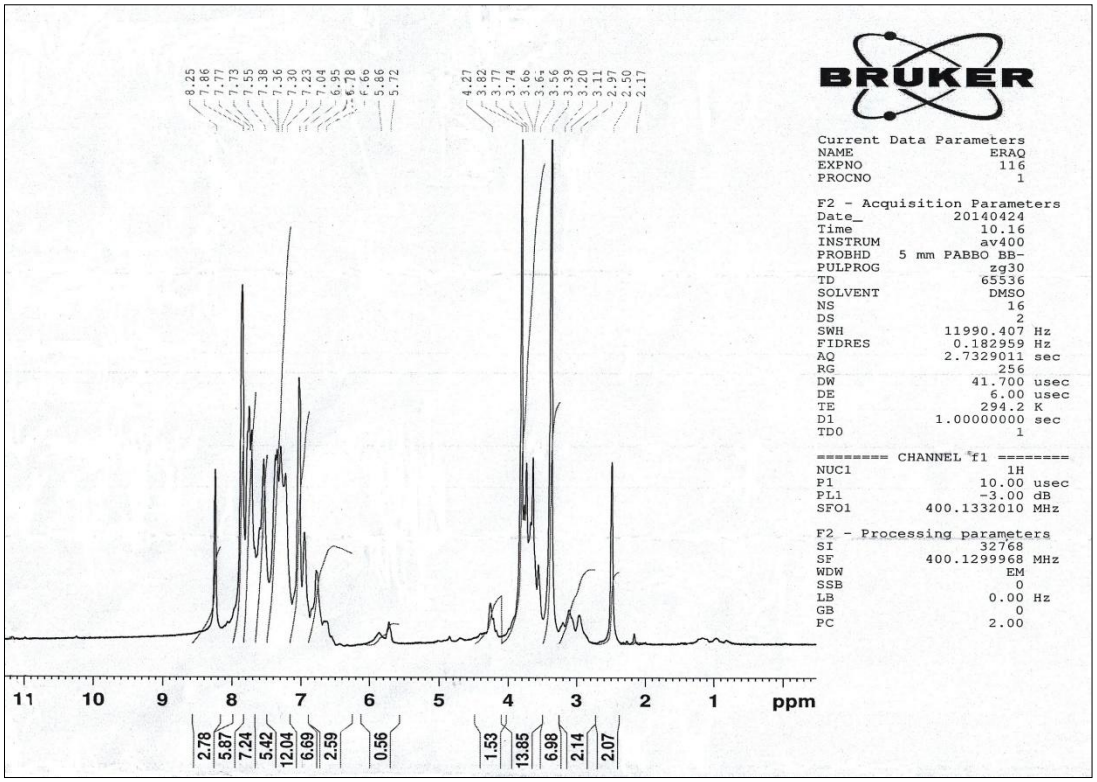

Figure (1):[1]HNMR spectrum of compound (4b)

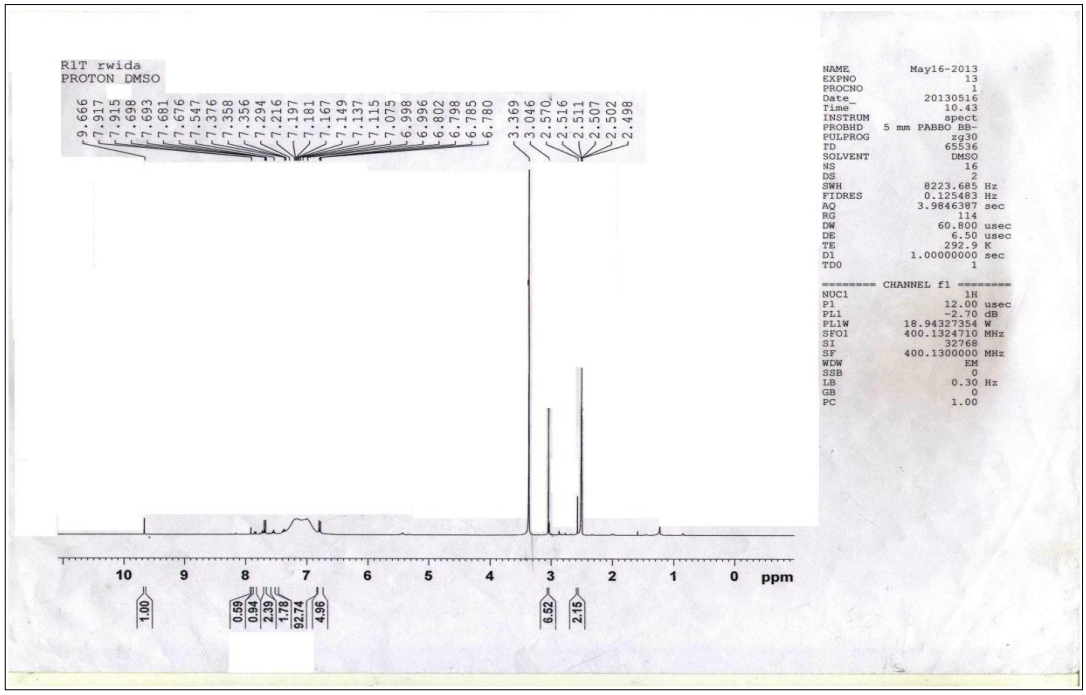

Figure (2):[1]HNMR spectrum of compound (6a)

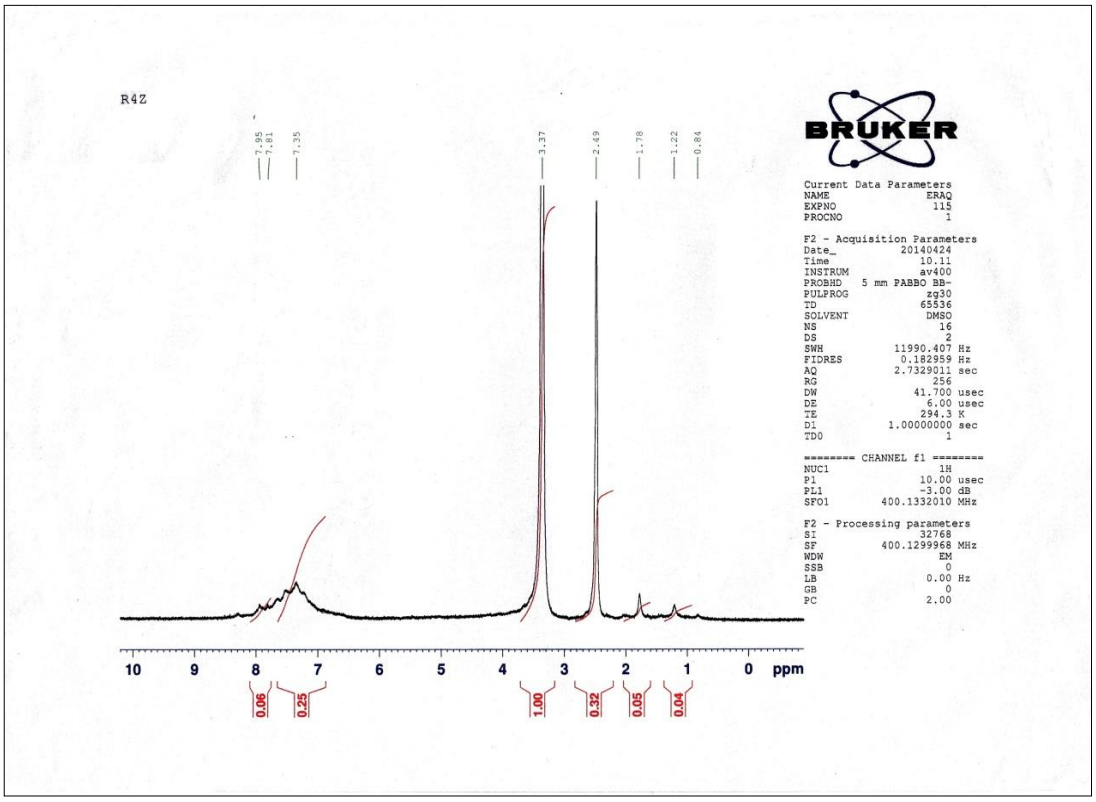

Figure (3):[1]HNMR spectrum of compound (7b)

تحضير جالكونات وتطبيقاتها في تحضير مركبات حلقية غير متجانسة

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الخلاصة

حضرت مركبات حلقية غير متجانسة جديدة تتضمن الحلقات الاتية: السايكلوهكسينون والاندازول والايسواكسازولين والبريمدين والبايرازولين من الجالكونات (1a,b).حضرت الجالكونات من تفاعل تكاثف المحفز بقاعدة لالديهايدات معوضة مع ٢–استيل بنزوفيوران ومن ثم بمفاعلة هذه الجالكونات مع اثيل اسيتو اسيتيت/هيدرازين هيدريت او هيدروكسيل امين هايدروكلورايد او يوريا او ثايويوريا او هايدرازين هايدريت او فنيل هيدرازين او مشتقات الهيدرازايد تكونت المركبات المذكورة. شخصت المركبات المحضرة باستخدام الطرق الفيزيائية والطيفية.

الكلمات المفتاحية: جالكونات ، سايكلوهكسينون ، اندازول ،ايسوكسازولين ،بريميدين ، بايرازولين.