Synthesis and characterization of some new novel pyrazoline and thiazepine derivatives from chalcones.

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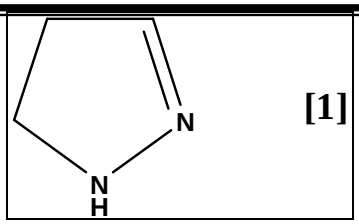
Abstract:

A bis-chalcones(1,2)in scheme 1 were prepared by the reaction of terephthaldehyde with acetophenone to give compound(1) or P-bromo acetophenone to give compound(2) in alkaline medium. treatment of this chalcones with hydrazine hydrate /phenylhydrazine/ semicarbazide hydrochloride / thiosemicarbazide afforded bis-pyrazoline derivatives but treatment chalcones (1,2) with cysteine(amino acid) gave (4E,4'E)-7,7'-(1,4-phenylene)bis(5-phenyl-2,3,6,7-tetrahydro-1,4-thiazepine-3-carboxylic acid) (11,12) in good yields. All new compounds have been characterized by their melting points, FT.IR, H,NMR, ^{13}C-NMR spectra and checked by TLC.

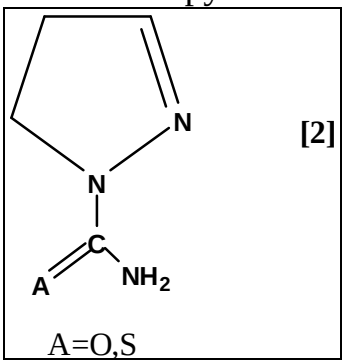
Introduction

Heterocyclic compounds have been synthesized mainly because of their wide range of biological activities. these compounds play an important role in medicinal chemistry. Chalcones are well known intermediates for synthesizing various Heterocyclic compounds. the compounds with the backbone of chalcones have been reported to possess various biological activities such as antimicrobial[1,2] ,anti-inflammatory[3], antimalarial[4,5], antioxidant[6], anticancer[7]. the presence of a reactive α,β-unsaturated keto function in chalcones was found to be responsible for their antimicrobial activity. Pyrazolines[1] are important class of five-member Heterocyclic compounds containing two nitrogen and three carbon atoms, pyrazoline derivatives have been found to possess a broad spectrum of biological activity such as muscle relaxant ,anticonvulsant ,antihypertensive and antidepressant activities[8,9].among various pyrazoline derivatives ,2- Pyrazolines seem to be the most frequently studied pyrazoline type compounds.



[1]

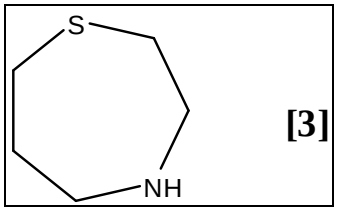
There are many methods for preparing of this compound but one of the most important method is prepared from α,β-unsaturated ketone (chalcone compound) with hydrazine give pyrazoline but with semicarbazide or thiosemicarbazide give N-substituted pyrazoline derivatives[2].



[2]

A=O,S

Thiazepine is one of hetrocyclic compounds which have pharmacological interest. Thiazepine is one of drugs which has biological interest due to their activity on the central nervous system , as enzyme inhibitors , anti-cancer , anxiolytic activity ,anticonvulsant, muscle relaxant[10] and other uses . Thiazepine contains two hetroatoms (nitrogen and sulphur) in seven membered ring[3].



[3]

Many synthetic procedures where existed for the preparation of 1,4 – thiazepine but in this studied was prepared fromα,β-unsaturated ketone (chalcone compound) with cysteine as amino acid to give thiazepine derivatives.

Experimental:

Instruments

1. Melting points were recorded using hot stage Gallenkamp melting point apparatus and were uncorrected.
2. Thin layer chromatography (TLC) was carried out using fertigfollen precoated sheets type polygram silica-gel as stationary phase ethyl acetate as eluent, and the plates were developed with iodine vapor.

3. Infrared spectra were recorded using Fourier transform infrared SHIMADZU (8300) (FT.IR) infrared spectrophtometer, KBr disc .
4. ^{1}H NMR, and ^{13}C– NMR were recorded on Foruier Transform Varian spectrometer, operating at 300 MHz with tetramethylsilane as internal standared in DMSO, Measurments were made at Chemistry Department, Al– Al-Bayt University, Jordan.

General procedure for the preparation of 3,3-(1,4-phenylene)bis(1-phenylprop-2-en-1-one) (1,2)

A mixture of acetophenone or bromo acetophenone (0.02mol) and terephthaldehyde(0.02mol) in an ethanolic solution of KOH (30%)was stirred over night at room temperature .The solution kept in refrigerator for 2hrs and poured into ice cold water and, acidified with diluted hydrochloric acid. The precipitate separated and dissolved in dichloromethane ,washed with saturated sodiumbicarbonate. recrystallized from ethanol, m.p=171^{0}**C** for compound(1) **yield (89%)**, m.p=256^{0}**C** for compound(2)**, yield (85%).**

Synthesis of 1,4- bis (3- phenyl- 4,5 - dihydro- 1H- pyrazol-5 - yl)benzene (3,4).

Bis-Chalcone (1,2) (0.01mol) was dissolved in ethyl alcohol 95% (20ml) and refluxed with excess of hydrazine hydrate for 12hrs ,the reaction mixture was diluted with cold water 50ml and the white precipitate formed was filtered off and recrystallized with ethyl alcohol m.p=230-232^{0}C for compound(1) yield (90%), m.p=199-200^{0}C for compound(2), yield (82%).

Synthesis of 1,4-bis (3-(alkyl)-1-phenyl-4,5-dihydro-1-H-pyrazol-5-yl)benzene(5,6).

Bis- chalcone (1,2) (0.01mol) was refluxed with phenyl hydrazine (0.02mol) in ethanol absolute (25)ml and a catalytic amount of glacial acetic at 90C for 11 hrs. the progress of the reaction was monitored by TLC .After completion of the reaction , the solvent was removed under reduced pressure and the residue washed with petroleum spirit the product was crystallized from ethanol absolute m.p=214-216^{0}C for compound(1) yield (77%), m.p=135-138^{0}C for compound(2), yield (71%).

Synthesis of 5,5-(1,4-phenylene)bis(3-(alkyl)-4,5-dihydro-1H-pyrazole-1-carboxamide)(7,8).

A mixture of semicarbazide hydrochlide (0.02mol)and potassium hydroxide (0.03mol) in dry ethanol (40ml) with bis chalcone(1,2)(0.01mol) was refluxed At 95C for 15hrs.the progress of the reaction was monitored by TLC., After the completion of reaction, The reaction mixture was poured into acidic ice water .the solid precipitate was filtered off and crystalized from propanol m.p=227^{0}**C**dec for compound(1) yield (76%), m.p=192-194^{0}C for compound(2),

yield (78%).

Synthesis of 5,5(1,4-phenylene)bis(3-(alkyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide)(9,10).

A mixture of bis- chalcone(1,2) (0.01mol) , thiosemicarbazide (0.02mol)and (0.02mol) of potassium hydroxide in ethanol (40ml) was refluxed for 14hrs. the progress of reaction was monitored by TLC. After the completion of the reaction , the mixture was poured onto acidic ice water and the solid was filtered off .The obtained precipitate was crystallized from isopropanol m.p=123-124^{0}C for compound(1) **yield (66%),** m.p=227-229^{0}C for compound(2)**, yield (70%).**

Synthesis of (4,E,4E)-7,7-(1,4-phenylene)bis(5-phenyl-2,3,6,7-tetrahydro-1,4-thiazepine-3-carboxylic acid(11,12).

A mixture of bis chalcone(1,2) (0.01mol)and cysteine (0.02mol) in (35ml) of ethanol absolute was stirring for 2hrs then (5ml) of pyridine was added to the mixture and kept onto cold water then stirring for 30min the precipitate was filtered and dried recrystallized from benzene-petrolum spirit(60-40) m.p=188-189^{0}C for compound(1) **yield (79%)**, m.p=159-162^{0}C for compound(2)**, yield (76%).**

Results and Discussion

Compounds (1,2) containing carbon-carbon double bond (C=C) and carbonyl group (C=O) in conjugation are known as α,β-unsaturated carbonyl compounds. A large number of α,β-unsaturated carbonyl compounds (1,3-disubstituted-2-propene-1-one) were prepared and were considered the principle nucleus for the synthesis of many important heterocyclic organic compounds through their reaction with different compounds. The prepared chalcones(1,2) were identified on basis of elucidation of the compounds by analysis of their spectral data IR, melting point and some simple test with bromine and. This reaction give a ppositive reaction because founding of (C=C) in compound (10a,b).and with tollin and fehling reagent give negative reaction this test were proved not found of any aldehyde in compound (1,2) converted to keto form. The FT-IR spectra of the chalcones(1,2) gives a strong absorption at about (1654 cm^{-1}) which belongs to conjugated carbonyl group. Another strong absorption belonging to carbon-carbon double bond appears at (1606-1604 cm^{-1}) [11]. It is worth mentioning that the intensity of C=C band is generally more than C=O band for most of the chalcones. All characteristic bands of compounds (1,2) are listed in table (1).

Table (1): Show FT-IR spectral data of compounds (10a,b)

Comp. No.	υ(C-H) Aliphatic cm^{-1}	υ(C-H) aromatic cm^{-1}	υ(C=O) cm^{-1}	υ(C=C) olefin cm^{-1}	υ(C=C) aromatic cm^{-1}	Others bands cm^{-1}

1	2922	3055	1654	1604	1577	-
2	2926	3035	1654	1606	1566	υ **(C-Br) 669**

Synthesis of 1,4-bis(3-phenyl-4,5-dihydro-1H-pyrazol-5-yl)benzene (11a,b).

The condensation reactions of chalcones (1,2) with hydrazine hydrate ($NH_2NH_2.H_2O$) in ethanol absolute gave compounds (3,4) as final products.

The IR spectra data for compound (3,4) as a representative model show the disappearance of the characteristic absorption at about 1604cm^{-1} of the olefinic C=C which is present in the IR spectra of starting material. The strong absorption at 1654cm^{-1} is attributed to the carbonyl group in the chalcone compound. C-N is identified as a medium band at 1284-1294 cm^{-1}, and absorption at 3354-3352cm^{-1} is due to the N-H stretching.

All characteristic bands of compounds (3,4) are listed in table (2).

Table (2): Show FT-IR spectral data of compounds (3,4)

Comp. No.	υ(C-H) Aliphatic cm^{-1}	υ(C-H) aromatic cm^{-1}	υ(N-H)	υ(C=N)	υ(C=C) aromatic cm^{-1}	υ(C-N)
3	2939	3026	3354	1633	1585	1294
4	2950	3032	3352	1637	1585	1284

^{1}H-NMR spectrum of compounds (3,4), shows the following characteristic chemical shift, (DMSO-d_6) ppm.Four protons of aromatic ring appear signal at the (δ 7.3). Furthermore, the signal at (δ 7.5-7.6) due to proton in an aromatic ring .the doublet at(3.1and 3.2)ppm for the methylene group in pyrazoline and triplet (3.53-3.58)ppm for the(-CH)moiety in the same ring. (-NH) group appeared the signal at(4.8ppm).

^{13}CNMR show singlate at (148.9-142.2) for C=N , (-CH) of the aromatic carbon appear at 121 - 133 ppm.and the carbon in methylene group at 63.8-83.0 ppm ,(-CH) in pyrazoline group at 40.8ppm

Synthesis of 1,4-bis (3-(alkyl)-1-phenyl-4,5-dihydro-1-H-pyrazol-5-yl)benzene(5,6)

The condensation reactions of phenyl hydrazine and few drops of glacial acetic acid with chalcone derivatives(1,2) The reactions afforded the corresponding compounds (5,6). These products were synthesized by_classical method under reflux**,** The IR spectral data for compounds (5,6) exhibit the absence of any absorption in the expected region of absorption (N-H) group (stretching) All characteristic bands of compounds (5,6) are listed in table (3).

Table (3): Show FT-IR spectral data of compounds (5,6)

Comp. No.	**υ(C-H) Aliphatic cm^{-1}**	**υ(C-H) aromatic cm^{-1}**	**υ(C=N) cm^{-1}**	**υ(C-N) olefin cm^{-1}**	**υ(C=C) aromatic cm^{-1}**	**Others bands cm^{-1}**
5	2895	3026	1643	1267	1595	

6	2926	3051	1641	1261	1597	υ **(C-Br)** **692**

the ^{1}HNMR spectrum of compound(5) shows a doublet at δ(3.6) ppm which is attributed to methine proton in pyrazoline ring. A triplet signal at δ(5.6-5.3) ppm for the (-CH)proton in pyrazoline ring. the signal (6.7-8.1)ppm due to of aromatic proton.

^{13}CNMR of the compound(5,6) show singlate at (160.4-159.6) for C=N , (-CH) of the aromatic carbon appear at 125 - 130 ppm.and the carbon in methylene group at 65.4-67.6 ppm ,(-CH) in pyrazoline group at 113.5ppm .

Synthesis of 5,5-(1,4-phenylene)bis(3-(alkyl)-4,5-dihydro-1H-pyrazole-1-carboxamide)(7,8)and Synthesis of 5,5(1,4-phenylene)bis(3-(alkyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide)(9,10).

The condensation reactions of a chalcones(1,2)with semicarbazide give compound(7,8)but with thiosemicarbazide give compound(9,10). the suggest mechanism of this reaction may be occurred by 1,4 Michael addition The FT-IR spectral data of these compounds(7-10) indicate the absence of a strong characteristic absorption at about (1604 cm^{-1}) corresponding to olefinic double bond of chalcone(1,2) which confirms the Michael addition, and the disappearance of a strong absorption of carbonyl group in the chalcone(1,2),the carbonyl amide give a strong absorption at(1670-1676 cm^{-1})in compound (7,8)but in compound (9,10)give aband at.(1095-1093 cm^{-1}) for the (C=S) [12], aperance of a band at (3140-3325cm^{-1}) for the symmetric and asymmetric of(-NH_2) group is good evidence for the structure given to these compounds also absorbed in FT-IR spectra of these compounds are listed in table (4)**.**

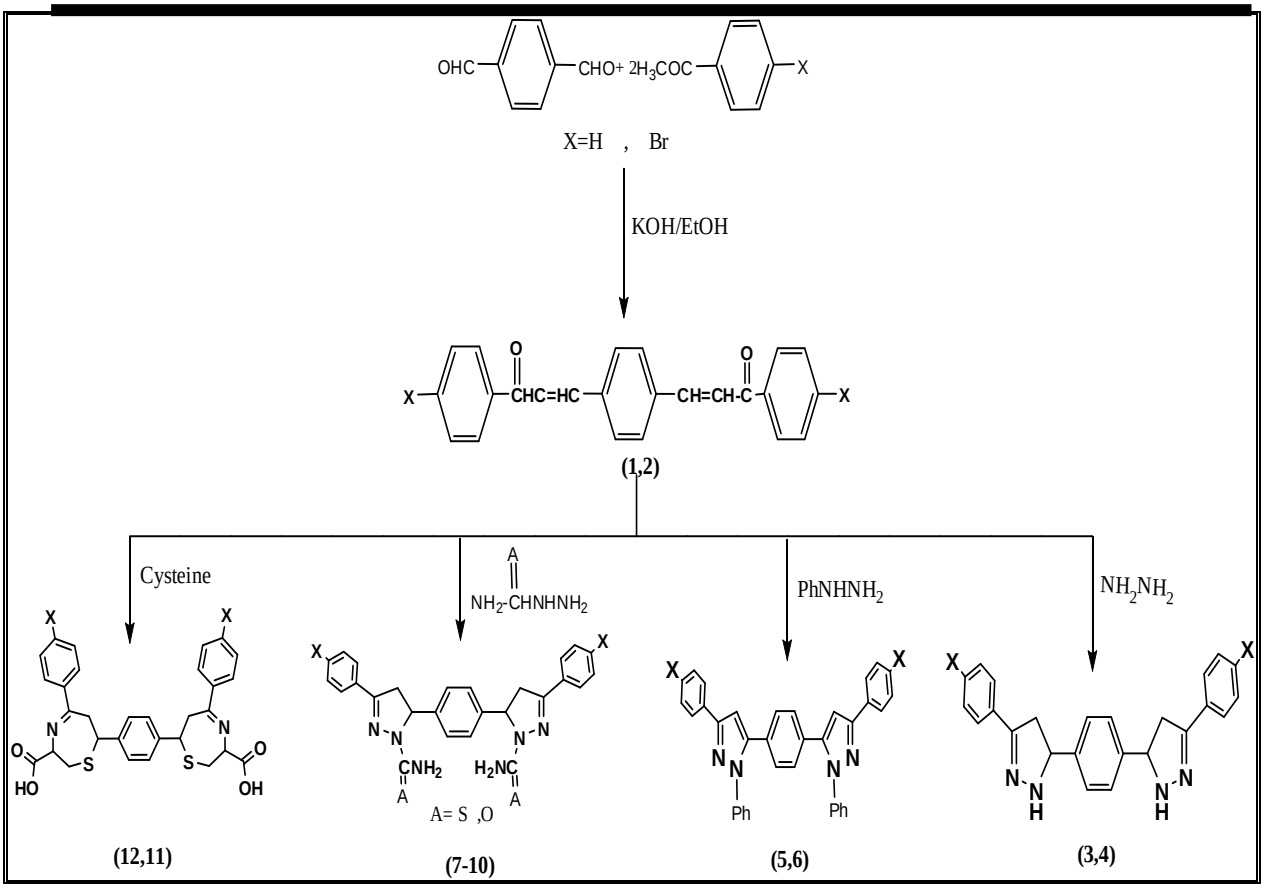
Table (4): FT-IR spectral data of compounds (4).

Comp. No.	**υ(C-H) Aliphatic cm^{-1}**	**υ(C-H) aromatic cm^{-1}**	**υ(C=O) cm^{-1}**	**υ(C-N) olefin cm^{-1}**	**υ(C=N) aromatic cm^{-1}**	**Others bands cm^{-1}**
7	2840	3016	1676	1247	1622	-
8	2839	2912	1670	1258	1621	υ (C-Br) 756
9	3169 and3371	3016	1095	1626	1593	-
10	3157 and 3383	3012	1093	1635	1585	υ (C-Br) 763

Synthesis of (4,E,4E)-7,7-(1,4-phenylene)bis(5-phenyl-2,3,6,7-tetrahydro-1,4-thiazepine-3-carboxylic acid(11,12).

Condensation between chalcones(10a,b) with (2moles) of cysteine in absolute ethanol with some quantity of pyridine give the title compounds(11,12). The structural assignment of the product was based on it's melting point and spectral FT-IR, ^{1}H-NMR data. and simple tests. The simple test is the reacted between compounds(11,12) with sodium bicarbonate give appositive reaction this reaction is proved found of carboxyl group in the title compounds. The F.T.IR spectrum of compound (11,12) indicates the disappearance of the carbonyl group band at (1654 cm^{-1}) in the starting materials(1,2)and disappearance of doublet bands of NH_2 group asymmetric and symmetric at (3267, 3211) in cystein and disappearance of bands in the region (1604-1606) cm^{-1} due to olefinic double bond, and appeared bands in the region (1709-1712) cm^{-1} were due to acidic ν(C=O) and appeared bands in the region (3419-3423) cm^{-1} were due to ν(OH).

The ^{1}HNMR spectral data of compounds (11) show a doublet at δ(2.5) ppm for (-CH_2) in thiazepine ring. Another doublet appeared at δ(2.7) ppm (2H) proton of (-CH_2) in the same ring. a triplet at(4.2-4.3) ppm another triplet at(4.4-4.5)ppm for. A signal at δ(10.7) ppm (1H) of (-OH) in carboxyl group.
^{13}CNMR compound(11) show singlate at (189) ppm for the (C=O) in carboxylic group. The signal (165) ppm due to the (C=N) in thiazepine ring. a signal at(122-144) ppm due to the carbon in aromatic ring.



Scheme(1)

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الخلاصة

تم تحضير المركب ثنائي الجالكون(1و2) في الشكل رقم (1) من خلال تفاعل التيرفثالديهايد(1,4ثنائي فورميل بنزين) مع الاسيتوفينون ليعطي مركب(1) ومع (بارا–برومو اسيتوفينون)ليعطي مركب(2) في الوسط القاعدي وتم معاملة هذه الجالكونات(1و2) مع الهيدرازين المائي/الفنيل هدرازين/السمسكاربازايد هيدروكلورايد /الثايوسيميكاربازايد لينتج مشتقات البيرازولين لكن عند تفاعل الجالكونات(1و2) مع السستين (احد الحوامض الامينية) أعطى مشتقات الثايازبين الثنائية بنسبة منتوج عالية . تم تشخيص جميع المركبات المحضرة بواسطة درجات الانصهار وبجهاز الاشعة تحت الحمراء وطيف الرنين النووي المغناطيسي للبروتون وطيف الرنين النووي المغناطيسي للكاربون 13وكذلك بواسطة تقنية كروموتوكرافيا الطبقة الرقيقة.