# Synthesis of Bis-heterocyclic phenyl containing -4 – oxo – 1,3 – thiazolidine, 2,3 – dihydrothiazole, 1, 2,4 – triazolo [3, 4b ] – 1,3,4 – thiadiazine and pyrazol derivatives

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**Abstract**

This research describes the synthesis of some new different substituted bicyclic phenyl derivatives. To obtain the target compounds, the reaction steps shown in scheme (I) and (II) were of a feasible strategy. The synthon terphthalic acid hydrazide [2] which was prepared from methyl terphthalate [1] with hydrazine hydrate, was used for the preparation of six types of new heterocyclic derivatives.

Acid hydrazide [2] reacts with carbon disulfide in the presence of potassium hydroxide and p–hydroxy benzaldehyde to give the corresponding potassium carbodithioate salt [3] and shiff's base [5] derivatives respectively. Treatment of the latter salt with p- bromophenacyl bromide afforded thiazolidine -2- thione[4], cyclization of shiff's base [5] using mercapto acetic acid resulted in the formation of -4- oxo-1,3 - thiazolidne [6].

1,2,4 – triazolo [3, 4b] - 1,3,4 – thiadiazine [9] was synthesized from basic cyclization of the intermediate product [8] which was obtained from the reaction between 2 – mercapto – 1,3,4 – oxadiazole [7] and p-bromo phenacyl bromide.

Furthermore, the hydrazino – 1,3,4 – oxadiazole [10], which was obtained from the reaction between of compound [7] with hydrazine hydrate, was then reacted with $CS_2$ / pyridine and acetyl aceton to give the corresponding 1,3,4 – triazolo [5,1b] oxadiazole [11] and pyrazole [12] derivatives respectively, scheme (II).

All synthesized compounds structures were characterized by measurements some of its physical proprieties and some specific reactions and spectral methods FTIR, $^1$H NMR for compound [6] and [8].

Keyword: oxadiazole,1,3-thiazolidine,fused heterocyclic ring,pyrazol.

## Introduction

The development of simple synthetic routes to widely used organic compounds using readily available reagents is one of the main objectives of organic synthesis 1,3,4-oxadiazole [1,2],1,2,4 – triazol, 4 –oxo – thiazolidine [3] and pyrazol [4] are reported to posses broad spectrum biological activities one-pot efficient synthesis of heterocyclic derivatives. These hetcrocyclic derivatives may permit the development of novel therapies for the treatment of epilepsy, pain and other neurodegenerative disorders.

1,2,4- triazole and its derivatives are found to be associated with various biological activities [5], for example, Fluconazole is used as antimicrobial drug, Anastrozole is nonsteroidal used for treatment of cancer and Loreclezole is used as an anticonvulsant [6].

In addition, it was reported that synthesis of triazoles fused to another heterocyclic ring has attracted wide spread attention due to their divers applications as antidepant, antiviral [7], antitumorial and antiflammatory agents.

Moreover the therapeutic effects of 1,2,4 – triazolo [3,4b]-1,3,4-thiadiazine derivatives has been well documented[8]. Pyrazoles have attracted much attention recently as their synthesis is more accessible and their diverse properities are appreciated. One of the most important pyrazole activities are the effective antirheumatoidal (SC – 58635 Celecoxib) and antiviral agent (Pyrazomycin) and selective Human Cls inhibitors. [4]

Some schiff's bases. bearing arylgroup or heterocyclic residues have excellent biological activities which has attracted many researchers' attention in recent year. [6]

Promoted by these observations, we aimed to obtain new derivatives of these above mentioned heterocyclic rings.

## Experimental

### Instrumental:

Melting points were measured with a Gallen Kamp melting point apparatus and were uncorrected. The IR spectra of the compounds were recorded on a Shimadzu FTIR-8300 spectrophotometer as KBr disc; results are given in $cm^{-1}$. $^1$HNMR spectra were determind on a *Brüker ACF 300* Spectrometer operating at 300 MHz in DMSO-$d_6$. The chemical shifts are reported in (ppm) dowmfield internal tetramethylsilane (TMS) (chemical shift in δ values).

### Chemical:

All chemicals were of reagent grade.Methyl terphthalate [1][(9)], terphthalic acid hydrazide [2][(10)] and 1,4-Bis –[1,3,4-oxadiazole-2-thione-5-yl] phenyl [7][(11)] were prepared following the literature.

### Dipotassium 1,4-Bis –[(dithiocarbazoate) carbonyl] Phenyl [3]

To a stirred ethanolic solution of KOH (1.68 g, 0.03 mole) in abs. ethanol (20 ml) and acid hydrazide [2] (1.94 g, 0.01 mole), was added slowly $CS_2$ (1.80 ml, 0.03 mole). The reaction mixture was refluxed for 8hrs, then concentrated and the yellow precipitate that separated on cooling and filtered off, washed with ether and dried. The salt was obtained in almost quantitative yield and employed in the next step without further purification. Yield 90%, M.P > 350 C°. IR: 3425 (4NH), 1651 (C=O), 1290 (N–N), 1050 (C=S).

### 1,4 –Bis-[carbamido -4-p-bromo phenyl -2,3 –di hydrothiazole -2 –thione] phenyl [4]

A mixture of potassium salt [3] (0.42g, 0.001 mole) and p-bromophenacyl bromide (0.55g, 0.002 mole) was heated under reflux for 7hrs in abs. ethanol (20 ml), then left to cool. The solid was collected by filtration, washed with ethanol, dried and recrystallized from ethanol to afford the corresponding thiazole derivative [4] in 60% yield,M.P.173-175C°.

IR:3400(2NH),3098(ArH),1670(C=O),1072(C=S),818 (out of plane bending of p-disubstituted benzene ring).

### p-hydroxy benzylidine terphthalic hydrazide [5]

A mixture of acid hydrazide [2] (1.94g, 0.01 mole), p-hydroxy benzaldehyde (3.05g, 0.025 mole) and 2drops from glacial acetic acid in abs. ethanol (20 ml) was refluxed for 12hrs. The reaction mixture was left 2hrs at room temperature, the solid produced was filtered, dried and recrystallized from ether to affored the corresponding shiff's base derivative [5] in 85% yield, M.P. 330 C° decomp. IR : 3490 (OH), 3224,3190 (2NH), 3090 (ArH), 1649 (C=N), 1600.8 (C=O).

### 1,4-Bis –[2-p-hydroxy phenyl - 4 – oxo – 1,3 –thiazolidine -3 –yl] terphthalic hydrazide [6]

Mercapto acetic acid (0.34ml, 0.005 mole) was dissolved in DMSO (5ml) and the resulting mixture was added dropwise with stirring to compound [5] (0.92g, 0.0025 mole) in DMSO, the addition was continued about 10 mints, then refluxed for 24hrs. Excess solvent was evaporated under reduced pressure and the remaining mixture was neutralized with 10% $NaHCO_3$ and cooling, the formed precipitate was collected, washed with hot water dried to give compound [6] in 40% yield, M.P. 271C° decomp. IR : 3450 (OH),3244(2NH), 1708.8 (C=O), 1600(C=O amide) ; $^1$HNMR (DMSO – $d_6$, δ ppm) : 5.38 (s, 2H, OH), 7.09 – 7.39 (dd, 4H, ArH), 7.64 – 7.75 (dd, 8H, ArH), 8.64 (s, 4H, Cyclic $CH_2$), 9.24 (s, 2H, NH).

### 1,4-Bis –[2-p-bromo benzoyl methyl thio – 1,3,4 – oxadiazole -5 -yl] phenyl [8]

A mixture of compound [7] (0.27g, 0.001 mole), p-bromo phenacyl bromide (0.55g, 0.002mole) and anhydrous $K_2CO_3$ (0.3g, 0.0022mole) in dry aceton (30 ml) was refluxed for 8h. The filtrate was concentrated till dryness, the residue was treated with water, The solid formed was filtered, washed with water, dried and recrystallized from ethanol to affored compound [8] in 46% yield,M.P. 142 – 145 C°; IR: 3452 (OH), 3100(ArH), 2922-2854 (aliph H),1650(C=O), 1581 (endocyclic C=N),827 (p- disubstituted benzene ring).

$^1$HNMR (DMSO – $d_6$, δ ppm) : 4.25 (s, 4H, $CH_2$), 7.07 – 7.40 (dd, 4H, ArH), 7.66 – 7.77 (dd, 8H, ArH).

**1,4-Bis –[6- p- bromo phenyl –[7H] -1,2,4-triazolo[3,4b]-1,3,4-thiadiazine–5-yl] phenyl [9].**

To compound [8] (0.67g, 0.001 mole) in abs. ethanol (20 ml), hydrazine hydrate (1 ml) was added with stirring. The mixture was heated under reflux for 7 hrs, then concentrated, left to cool. The precipitate appeared after added of water was filtered, washed with water and dried. 40% yield, M.P. 183-186 C°. IR: 3142 (ArH), 1609, 1598 (C=N), 817 (p- disubstituted benzene ring).

**1,4 –Bis- [1,3,4 – oxadiazole -2- hydrazino – 5 -yl] phenyl [10]**

Compound [7] (0.27g, 0.001 mole) with hydrazine hydrate (1ml) in abs. ethanol (15ml) was refluxed for 20hrs. The solvent was evaporated, cool the mixture and the formed precipitate was filtered, washed with ethanol and dried to affored compound [10] in 80% yield, M.P. 172-174 C°. IR: 3435, 3350 (ν $NH_2$), 3236 (ν NH), 3078 (ν ArH), 1610 (δ NH), 1523 (C=N), 1305 (C-O-C).

**1,4-Bis-[2-mercapto – 1,3,4- triazolo [5,1b] -1,3,4- oxadiazole -5-yl] phenyl [11]**

To a stirred solution of compound [10] (0.27g, 0.001 mole) in pyridine (2.6 ml) was added slowly $CS_2$ (1ml). The mixture was refluxed for 24hrs, then allowed to cool. The solid product was obtained by filtration, dried and recrystallized from acid to affored compound [11] in 50% yield, M.P. 233-235 C°.

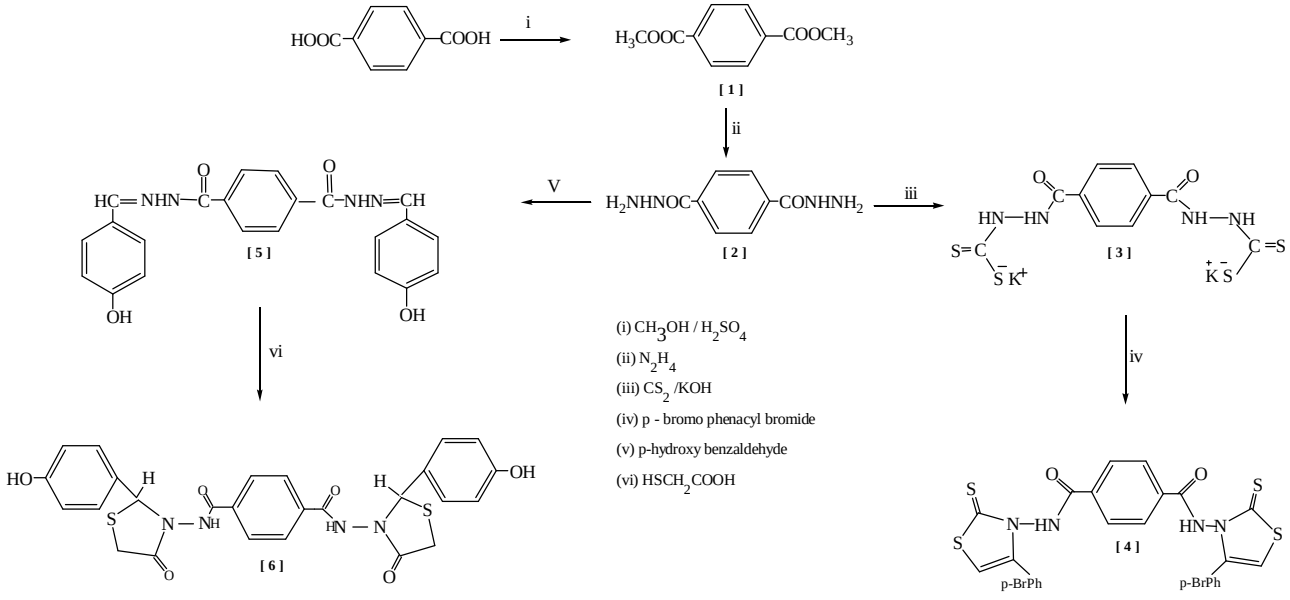
IR: 3300(NH), 2337 (SH), 1620(C=N), 1346 (C=S).

**1,4 – Bis – [1,3,4 – oxadiazole -2- (3,5 – dimethyl –[2H]-pyrazol -2-yl)-5-yl] phenyl [12]**

A mixture of compound [10] (0.1 g, 0.36 mmole) and acetyl aceton (0.078 ml, 0.72 mmole) in abs. ethanol (15 ml) was refluxed for 10h. The mixture was concentrated, filtered the hot solution, cool in the refrigerator for 24hrs.The formed precipitate was filtered off, dried and recrystallized from ethanol to give the title compound [12] in 45% yield, M.P. 180 – 182 C°. IR: 3041 (ArH), 2916 (aliph H), 1602 (C=N), 1550 (Ar C=C).

**Results and Discussion**

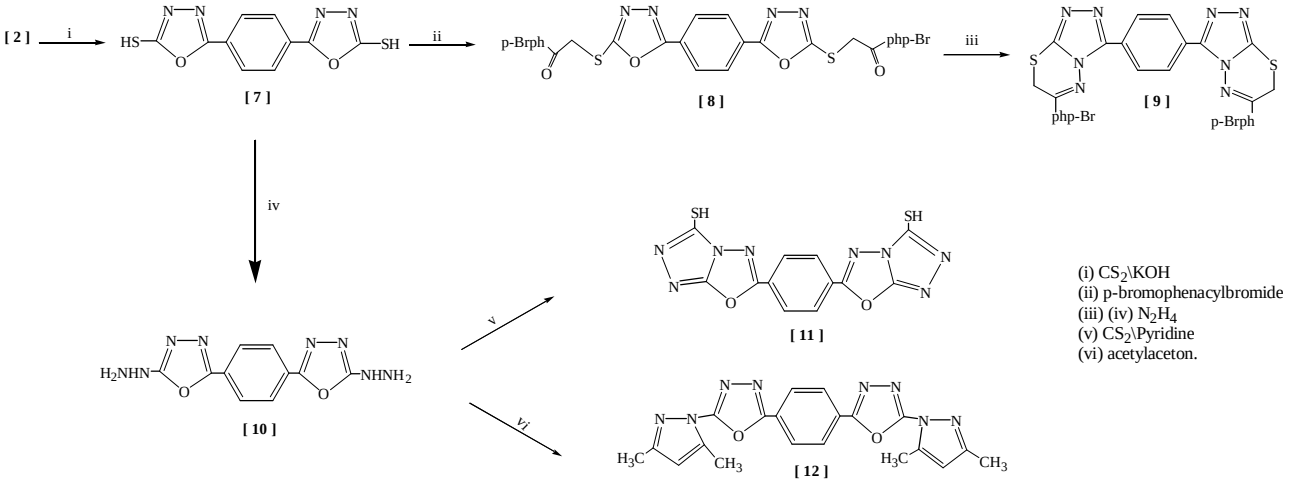
Treatment of acid hydrazide [2] with $CS_2$ / KOH in ethanol resulted in the formation of the potassium salt of dithiocarbazoate [3] scheme (I). The salt was characterized from FTIR spectrum which was appeared intense broad band at 3425.3 $cm^{-1}$, its regarded as combination of bands due to multiple (NH) stretching bands and (OH) band (Keto – enol tautomers). The spectrum also showed absorpitions at 1651, 1290 and 1050 $cm^{-1}$ as weak peak attributed to (C=O), (N-N) and (C=S) stretching vibrations respectively.




***Scheme (I) Synthetic path ways for preparation of compounds 3-6.***

Reaction of potassium salt [3] with p-bromo phenacyl bromide furnished a compound identified as the thiazolidine derivative [4][(12)] which showed the important spectral data in FTIR , a broad peak for (NH) group at 3400 $cm^{-1}$ which was overlap with obsorpition of (-OH) group, 3098(ArH), 1670 (C=O amide group) and 1072 $cm^{-1}$ for (C=S) group. The treatment of acid hydrazide [2] with p-hydroxy benzaldehyde affored a single product that was identified as compound [5] on the basis of its spectral data. The FTIR spectrum showed the disappearance of ($NH_2$) stretching vibration presence in the spectrum of acid hydrazide [2] at 3323 and 3244 $cm^{-1}$, and showed bands at 3490 (OH), 1649 (C=N) of shiff's base and 1600.8 $cm^{-1}$ for (C=O amide group). Cyclization occure where thiol group in mercapto acetic acid attack as a neucleophile the carbon of C=N bond[(13)] when compound [5] reacted with mercapto acetic acid in DMSO to produce compound [6], which was characterized by its melting point, FTIR and $^1$HNMR spectral data. The FTIR spectrum was conformed from the disappearance of (C=N) vibration and appearance of (C=O) band of oxo – thiazolidine ring at 1708.8 and other bands. While in the 1HMNR spectrum the signal observed at 5.38 ppm integrated for two protons was assigned to (– OH) group of p-hydroxy phenyl, and signal at 9.24 ppm was integrated for two protons of (- NH) as shown in Fig.(1).

When compound [2] was treated with $CS_2$ / KOH[(14)], 1,4 – Bis - [1,3,4-oxadiazole-2-thione-5-yl] phenyl [7] was obtained scheme(II). In the IR spectrum of compound [7], no signal derived from exocyclic carbonyl function was observed. Moreover, $NHNH_2$ stretching vibration was disappeared.




***Scheme (II) Synthetic path ways for preparation of compounds 7-12.***

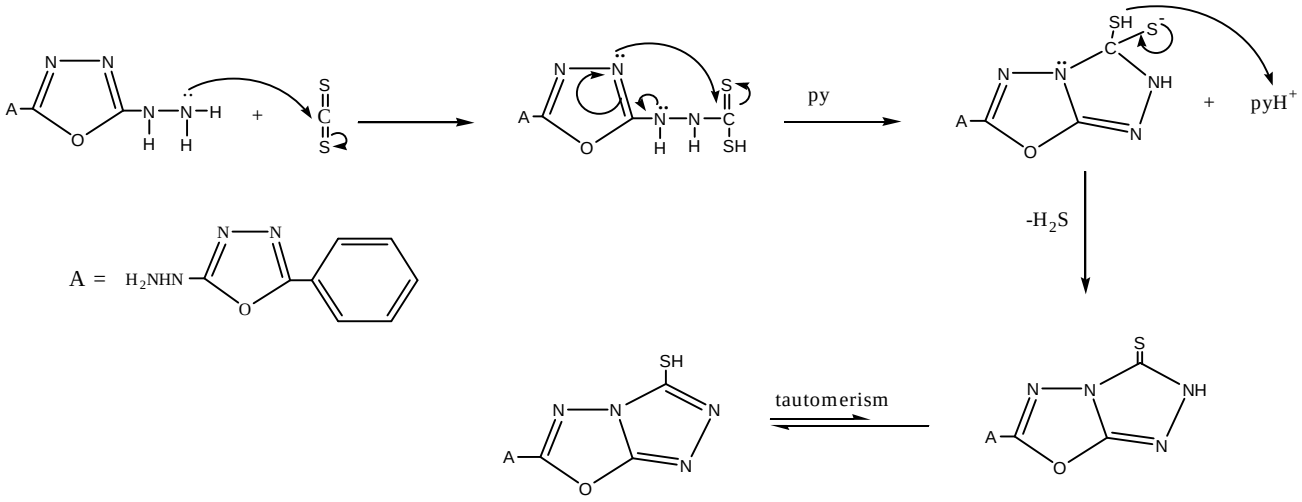
Next, the treatment of compound [7] with p-bromo phenacyl bromide, in the presence of anhydrous potassium carbonate afforded single product that was identified as compound [8] (Scheme II) on the basic of its spectral data. The structure of the latter product was confirmed by the appearance of carbonyl band at 1650 $cm^{-1}$ in its FTIR spectrum and the presence of a characteristic signal was due to methylene protons at δ 4.25 in its $^1$HNMR spectrum and signal doublet of doublet at 7.66 –7.77 ppm integrated for eight protons of p-substituted phenyl group while a signal at 7.07 – 7.40 ppm integrated for four protons

due to the center phenyl ring as shown in Fig.(2).

Bicyclic fuced ring derivative [9] which was synthesized from the reaction of compound [8] with hydrazine hydrate showed absence of absorpition band due to (C=O) stretching frequencies of compound [8] clearly indicated the fusing between compound [8] and hydrazine hydrate.

Compound [10] was synthesized from refluxing of compound [7] with hydrazine hydrate in absolute ethanol. The FTIR spectrum showed the appearance of ($NH_2$) asymmetric and symmetric stretching bands at 3435 $cm^{-1}$, 3350 $cm^{-1}$, respectively. And (NH) absorpition at 3236 and other important bands at 3078,1610, 1523 and 1305 $cm^{-1}$ due to (ArH), (C=N) and (C–O–C) absorpition, respectively.

Compound [10] was converted to compound [11] by the reaction with $CS_2$ / Pyridine. The FTIR spectrum showed that there is an equilibrium between thiole and thione form (SH) band and (C=S) bands at 2337 and 1346 $cm^{-1}$ respectively, as well as (NH) vibration at 3350 $cm^{-1}$. The latter compound prepared according to the following mechanism[13]:




***Scheme (III).***

When compound [10] refluxing with acetylaceton for 10 hrs the result product was compound [12] [15] which was showed the disappearance of ($NH_2$) and (NH) vibrations of the starting material [10] at 3435 (asymm.), 3350 (symm.) and 3236 $cm^{-1}$ respectively. Also the compound showed very clear bands of aromatic and aliphatic (CH) at 3041 and 2916 $cm^{-1}$, (C=N) band appeared at 1602 $cm^{-1}$ and (C=C) aromatic at 1550 $cm^{-1}$.

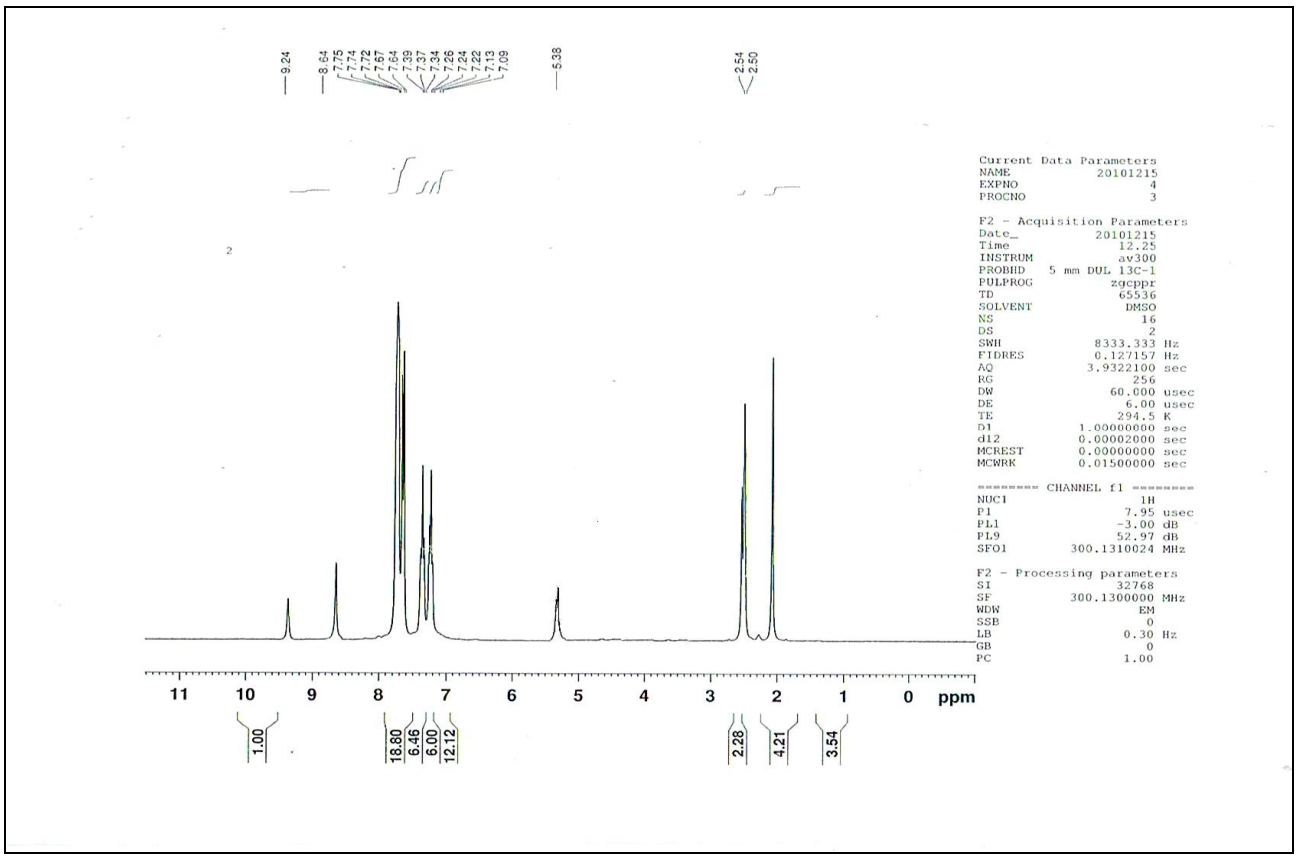



***Fig. (1) $^{1}$HNMR Spectrum of compound [6].***

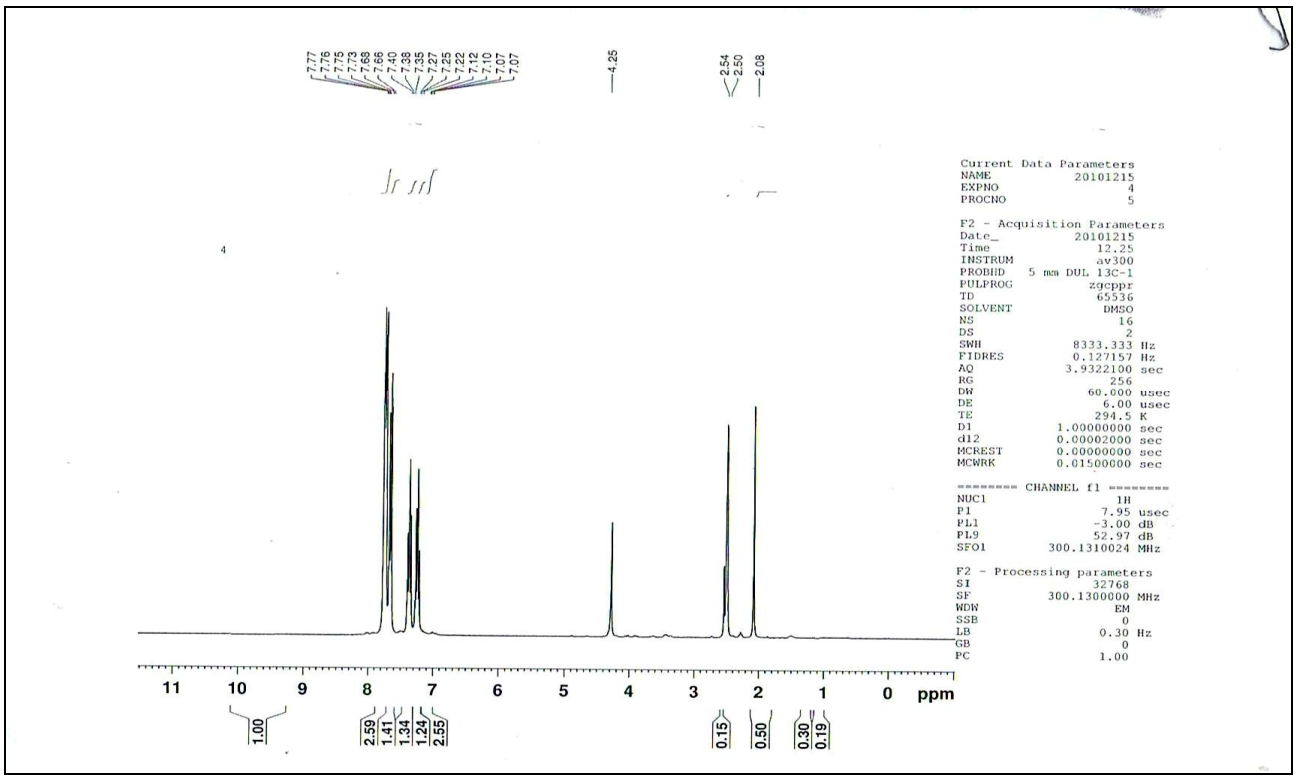



***Fig. (2) $^{1}$HNMR Spectrum of compound [8].***

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**الخلاصة**

تم في هذا البحث تحضير مشتقات لفينل ثنائي الحلقات الغير متجانسة,حضرة المادة الاولية terphthalic acid حيث methyl terphthalate [1] من hydrazide [2] استخدمت لتحضير ستة انواع من المشتقات الحلقية غير المتجانسة. حيث تم تحويل Acid hydrazide [2] الى potassium carbodithioate salt [3] و shiff's base [5] وذلك بتفاعله مع ثنائي كبريتيد الكاربون

و بارا– هايدروكسي بنزالديهايد على التوالي, ليعقبها معاملة الملح الاخير مع بارا–بروموفيناسيل بروميد للحصول على thiazolidine -2- thione [4] و كذلك غلق حلقي للمركب [5] باستخدام مركبتوا اسيتك اسد ليعطي -oxo -4- 1,3 - thiazolidne [6].

لقد تم كذلك تحضير - 1,2,4 – triazolo [3, 4b] [9] 1,3,4 – thiadiazine بواسطة الغلق الحلقي القاعدي للمركب [8] والذي تمة تحضيره من خلال تفاعل بين – 2 mercapto – 1,3,4 – oxadiazole [7] و بارا– بروموفيناسيل بروميد وبالاضافة الى ذلك – hydrazino 1,3,4 – oxadiazole [10] والذي تمة تحضيره بواسطة التفاعل بين المركب [7] مع الهيدرازين المائي, قد استخدم بتفاعله مع ثنائي كبريتيد الكاربون بوجود البريدين و اسيتيل الاسيتون لتحضير 1,3,4 – triazolo [5,1b] oxadiazole [11] and pyrazole [12].

تم تشخيص جميع المركبات المحضرة بواسطة طيف الاشعة تحت الحمراء وبعض منها بواسطة طيف الرنين المغناطيس وتعيين بعض خواصها الفيزيائية.