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Synthesis And Characterization Of Some New Five Membering Ring Compounds Such As Thiazolidinones and γ -Lactams

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Abstract:

This study concerned with the synthesis and characterization of thiazolidinones & γ- lactams **,** the thiazolidinones compounds are prepared from A mixture of Schiff base (Imine) and thioglycolic acid, γ- lactams compounds are prepared from A mixture of Schiff base (Imine) with phenylsuccinic anhydride in moderate yields (52-71 %). The structures of these thiazolidinones and γ-lactams were established on the basis of the spectral data namely IR, ^{1}H-NMR,^{13}C-NMR, ^{13}C-NMR DEPT , Mass spectra .

Keywords: thiazolidinones , γ- lactams , Imine, NMR

تخليق وتشخيص لبعض المركبات خماسية الحلقه الجديدة مثل الثايازوليدينون و الكاما لاكتام

الخلاصه

تضمنت هذه الدراسه تحضير وتشخيص مركبات الثايازوليدينون و الكاما لاكتام , مركبات الثايازوليدينون حضرت من تفاعل قواعد شف (ايمين) مع حامض الثايا كلايكولك , مركبات الكاما لاكتام حضرت من تفاعل قواعد شف (الايمين) مع انهدريد الفنيل سكسنيك مع حصيله تفاعل متوسطه (52-71%) تراكيب هذه المركبات تم اثباتها بواسطه البيانات الطيفيه لطيف الاشعه تحت الحمراء وطيف الرنين المغناطيسي النووي البروتوني ,طيف الرنين النووي المغناطيسي الكاربوني ,طيف الDEPT وطيف الكتله .

Introduction

Thiazolidinones **(figure 1)** are classified as doubly unsaturated five membered heterocyclic compounds contain one nitrogen, one sulphur and three carbon atoms including a carbonyl group.

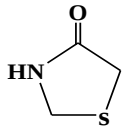


figure 1:**Thiazolidinone ring**

Thiazolidinones and their derivatives presentation a large variety of activities such as antibiotic, diuretic, tuberculostatic, organoleptic, antileukaemic and antiparasitical [1,2]. As far as literature is concerned, little is known about thiazolidinones and their bioactivity. The chemistry of thiazolidin-4-one ring system is a considerable interest because it is the core structure in various synthetic pharmaceuticals, whose display a broad spectrum of biological activities. These heterocyclic compounds are having an atom of sulfur at position 1, an atom of nitrogen at position 3, and a carbonyl group at position 4 [3]. The substitution can be done at positions 2, 3, and 5, the greatest difference in structure and properties is exerted by the group that will be attached with the carbon atom in position 2 **(Figure 2)** The carbonyl group present in the moiety is highly unreactive.

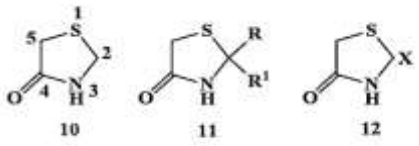


Figure 2: Various Thiazolidinone rings and their substituents

γ-lactam is a Five-membered ring lactams, also known as γ-butyrolactam , pyrrolidin-2- one , azolidin-2-one or 2-oxopyrrolidine **(figure 3)** .It is part of the core structure of a large number of natural and non-natural compounds covering a broad spectrum of biological activities. Accordingly, γ-lactams

are of primary interest in medicinal chemistry and many synthetic strategies have been disclosed to access this structural moiety. [4]

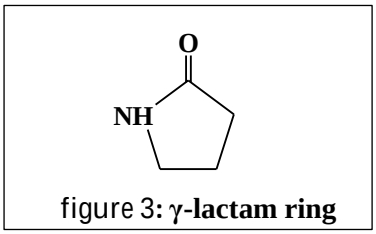


figure 3: **γ-lactam ring**

Experimental part

All solvents were distilled/dried prior to use, whenever this seemed necessary, by standard methods. All solvent extracts were dried over anhydrous sodium sulphate unless otherwise specified.

FT-IR spectrophotometer: was recorded, using shimadzu FT-IR affinity spectrophotometer as KBr disks also Bruker in the department of chemistry, college of Science, Thi-Qar University, Iraq. Only principal absorption bands of interest are reported and expressed in cm^{-1}.

^{1}H-NMR spectra.Were recorded, using BRUKER spectrophotometer (500 MHz) in Tahran university, Institute of Biology Medicinal Chemistry and Biotechnology. The chemical shift values are expressed in δ(ppm), and using tetramethylsilane (TMS) as internal standard and using d_6-DMSO as solvent.

^{13}C-NMR spectra and ^{13}C-NMR DEPT spectra

Were recorded, using BRUKER spectrophotometer (75 MHz) in Tehran university, Institute of Biology Medicinal Chemistry and Biotechnology. The chemical shift values are expressed in δ(ppm), using tetramethylsilane (TMS) as internal standard and using d-$CDCl_3$ as solvent.

Mass spectra. Were recorded,using 5973 Work mass selective Detector, in Sana'at sharifie Research Foundation .

General Procedure for preparation of Imines

In general, the imines **2(a-c)** were prepared by reaction the amine with aldehyde or keton in 40 mL of methanol and 4-6 drops of glacial acetic acid then heated the mixture by hot blate, The reaction mixture is refluxed for (1-5) h with stirring . The progress of the reaction is followed by TLC. After completion , the solvent evaporated and then recrystallized from a suitable solvent .

the physical data of imines **2(a-c)** are gathering in the following table **.**

3-Bromo-2-(pyridine-2-yliminomethyl)-phenol 2a

It was prepared by reacting of 2-amino pyridine (0.01 mol, 1 g) with 5-Bromo-2-hydroxy benzaldehyde (0.01 mol, 2.4 g). Rf=1.2 , yield = 79.6%, m.p. = 138-139 ºC. IR (KBr disk): 1610 cm^{-1} (C=N).

(4-chloro-benzylidene)-pyridin-3-yl-amine 2b:

It was prepared by reacting of 3-amino pyridin (0.006 mol, 1 g) with Para chloro benzaldehyde (0.006 mol, 2.54 g). Rf=2 , yield = 97%, m.p = 73-74 ºC. IR (KBr disk): 1623 cm^{-1} (C=N).

4-(5-Amino-naphthalen-ylimino)-pentan-2-one 2c:

It was prepared by reacting of 1,5-di Amino naphthalene (0.006 mol, 1 g) with Acetylaceton (0.006 mol, 0.63 g ,0.65ml). RF=0.5 , Yield = 52.6%, m.p = 200 ºC. IR (KBr disk): 1612 cm^{-1} (C=N).

Table (2-1) prepared Imines

Imines	m.p°C	Yield %	Colour	Rf In cm
2a	138-139	79.6	orange	1.2
2b	73-74	97	violet	2
2c	200-201	52.6	Grey	0.5

General Procedure of Thiazoledinones 3(a,c):[5]

A mixture of compound **2(a,c)** and thioglycolic acid in Chloroform (15) **ml**, The content is allowed to react in a teflon beaker in microwave oven 100 **w** for (6-12) minutes giving solid product . (Progress of the reaction is checked by TLC using hexane-ethyl acetate as eluent. After the completion of reaction, Chloroform is removed by distillation to give solid state. The solid were washed successively with 1N HCL **20mL**, water **(2×20 mL*)***, 5% $NaHCO_3$ **(20 mL**) and brine **20 mL**. The organic layer was dried Na_2SO_4 The solvent was evaporator by Buckner funnel.

The following methods of thiazoledinones preparations are**:**

2-(2-Bromo-6-hydroxy-phenyl)-3-pyridin-2-yl-thiazolidin-4-one 3a:

It was prepared by reacting **(2a)** (0.003 mole, 1 g) and (0.003 mole, 0.33 gm, 0.25 mL) of thioglycolic acid. Rf=0.7 , yield =63 %, m.p. = 88-89 ºC. IR

(KBr disk): 1673 cm^{-1} (–N–C=O).^{1}H-NMR(500MHz,d_6-DMSO, δ,ppm) 3.81(d,1H), 4.19(d,1H), 5.68(s,1H), 6.15-7.51(m,3H),6.09-8.12(m,4H)and 10.21 (s,1H). ^{13}C-NMR(75MHz ,d - $CDCl_3$, δ , ppm) 38.65, 48.02, (122.03-151.02) and177.86

3-(5-Amino-naphthalen-1-yl)-2-methyl-2-(2-oxo -propyl)-thiazolidin-4-one 3c:

It was prepared by reacting **(2c)** (0.001 mole, 0.41 g) and (0.001 mole, 0.157 gm, 0.12 mL) of thioglycolic acid. 0.6 , Yield =69 %, m.p. = 139-140 ^{o}C. IR (KBr disk): 1676 cm^{-1} (–N–C=O). ^{1}H-NMR(500MHz,d_6-DMSO, δ,ppm) 3.88(d,1H), 4.07(d,1H), 1.90(s,3H), 2.79(s,3H), 4.29(s,2H), 4.60(s,2H) and 7.30-8.02(m,6H). ^{13}C-NMR(75 MHz,d-$CDCl_3$, δ,ppm) 40.80, 61.85, 18.28,26.78, 36.95, (124.44-156.76) ,179.17 and177.86.

General procedure of γ-lactams [6]

In general the γ-lactam were prepared by reaction the mixture of imines with of Phenylsuccinic anhydride in **20 mL** of
chloroform then heated the mixture by hot blate , The reaction mixture was refluxed for (1-12) h with stirring .The progress of the reaction was followed by TLC. After completion , the solvent evaporated and then recrystallized from ethanol. The following methods of γ-lactam preparations are**:**

2-(2-Bromo-6-hydroxy-phenyl)-5-oxo-3-phenyl-1-pyridin-2-yl-pyrrolidine-3-carboxylicacid 4a:

It was prepared by reacting (**2a**) (0.003 mole, 1 g) and (0.003 mole, 0.64g) of phenylsuccinic anhydride. Rf=0.7 , yield =55 %, m.p. = 121-122 ^{o}C. IR (KBr disk): 1638 cm^{-1} (–N–C=O), 1727 cm^{-1} (HO–C=O).
^{1}H-NMR(500MHz,d_6-DMSO, δ,ppm) 3.28(d,1H), 3.52(d,1H), 4.12 (s,1H), 6.15-6.70 (m,5H),7.63-8.35(m,7H), 10.31 (s,1H)and 11.42 (s,1H).^{13}C-NMR(75 MHz,d-$CDCl_3$, δ,ppm)42.88,53.02, 59.79 ,121.23-158.52,125.95-135.95,127.89-138.11 ,172.13 and185.88.

2-(4-Chloro-phenyl)-5-oxo-3-phenyl-1-pyridin-3 -yl-pyrrolidine-3-carboxylic acid 4b:

It was prepared by reacting (**2b**) (0.0046 mole, 1 g) and (0.0046 mole, 0.8g) of phenylsuccinic anhydride. Rf=0.1 yield =55 %, m.p. = 159-160 ^{o}C. IR (KBr disk): 1602 cm^{-1} (–N–C=O), 1695 cm^{-1} (HO–C=O). ^{1}H-NMR(500MHz,d_6-DMSO, δ,ppm) 3.32(d,1H), 3.56(d,1H),4.53(s,1H),6.21-6.64(m,5H),7.30-8.20 (m,7H), and11.40(s,1H).^{13}C-NMR (75MHz, d-$CDCl_3$,

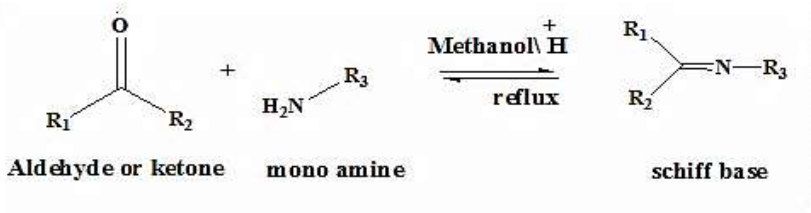
δ,ppm)40.13,51.28,58.54, (121.67-151.66) (124.56-138.54),169.18 and 183.05.

Prepared thiazoledinones & γ-lactam

Results and discussion

Schiff base

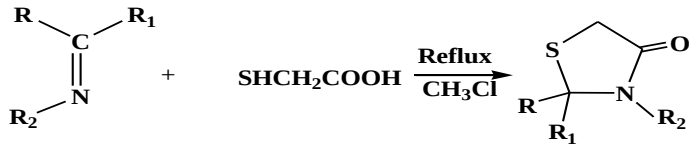
Schiff bases are formed by the condensation of a primary amine and an aldehyde or keton



comps	Yield (%)	m.p. (°C)	Rf In cm	Colour
3a	63	88-89	0.7	Yellowish
3c	69	139-140	0.6	Brown
4a	55	121-122	0.7	orange
4b	55	159-160	0.1	violet

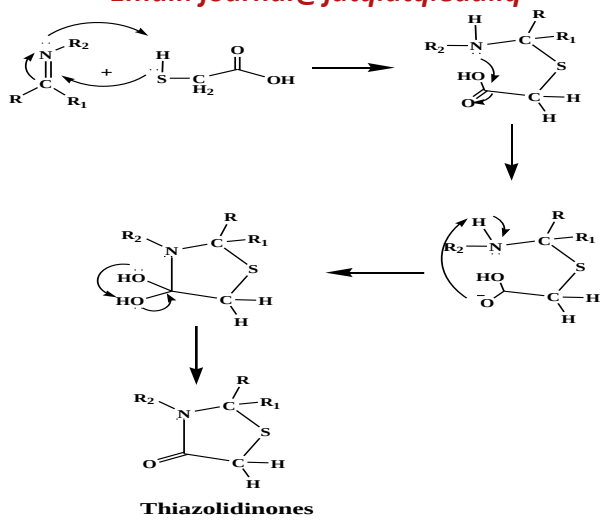
Thiazolidinones

Thiazolidinones are an important group of heterocyclic compounds, which have several biological activities in the areas of agriculture and medicine [7,8], they are obtained from reaction of imines with thioglycolic acid to give thiazolidinones .



imines thioglycolic acid thiazolidinones

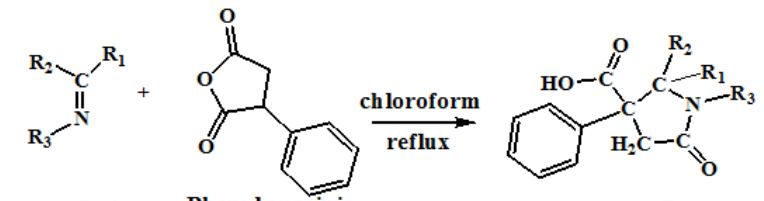
The suggested mechanism of preparation of thiazolidinones as the following scheme.



Thiazolidinones

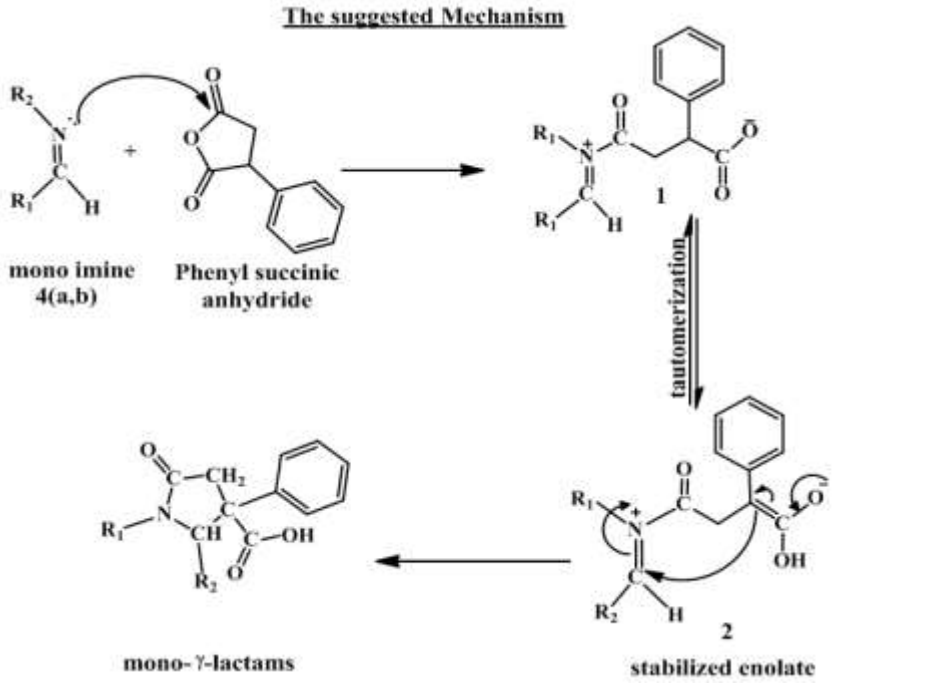
γ-lactams

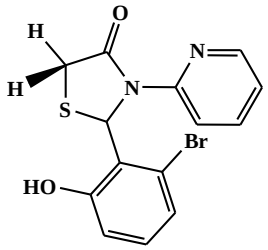
γ-Lactams represent important substructures for the synthesis of natural products [9,10] and biologically important compounds in drug discovery[11]. The prevalence of these structures [12,13] has resulted in the development of many efficient syntheses[14] ,which have led to the production of diverse libraries of small molecules for biological evaluation.[15,16] taking a lead from earlier studies, it is considered to utilize imine phenyl succinic anhydride cyclization in the presence of chloroform formation γ-lactams as shown in the following equation .



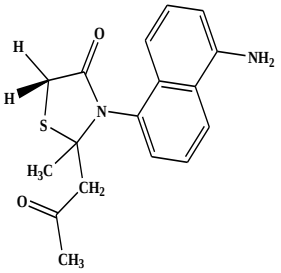
mono Imines Phenyl succinic anhydride mono γ-Lactams

The suggested mechanism of preparation of thiazolidinones as the following scheme.

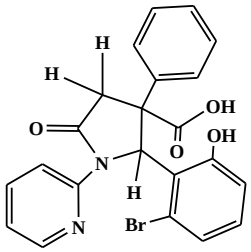




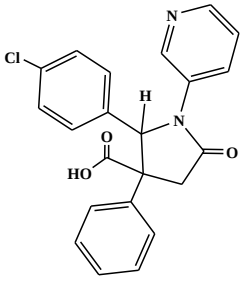
3a



3c



4a



4b

Figure 4 : prepared compounds

IR Spectrum

The **IR** spectra of imines **2(a-c)** as KBr disc are characterized by four bands corresponding to the stretching vibrations of the aromatic (C-H) , aliphatic (C-H) , azomethine band (C=N), and aromatic (C=C). and substituted ring which occurs within the ranges 3224-3020, 3007-2777, 1638-1610, 1586-1475 and 925-617 cm^{-} respectively**.**

The **IR** spectrum of Thiazolidinones **3(a,c)**as KBr disk and representative spectra are characterized by six bands corresponding to the stretching vibration of the aromatic C-H, aliphatic C-H, carbonyl amide group N-C=O, aromatic C=C, C-N band, and bending vibration of S-C band , and substituted ring which occurs within the ranges (3042,3369), (2946,2925), (1694,1686), (1631,1546), (1276,1282), (626,778), and (925,617) cm^{-1} respectively .

The **IR** spectra of γ-lactam **4(a,b)** are characterized by bands corresponding to the stretching vibration of the -OH carboxylic, aromatic C-H,aliphatic C-H, carbonyl amide group, carbonyl carboxylic group, aromatic C=C and substituted ring which occur within the ranges (3026,3134) , (2991,3064) , (1727,1695) , (1586,1651), (1555,1587) and (817-839) cm^{-1} respectively **.**

^{1}H-NMR spectral analysis of Thiazolidinones

The **^{1}H-NMR** spectra of 2-(2-Bromo-6-hydroxy-phenyl)-3-pyridin-2-yl-thiazolidin-4-one **(3a)** , show triplet signal at chemical shift δ (2.50-2.51 ppm) for **d_6-DMSO** solvent. Also it showed doublet signal at chemical shift δ (3.81 ppm , J=3Hz) ,and doublet signal at chemical shift δ (4.19 ppm, J=3Hz) for methylene thiazolidin-4-one ring for two protons , and showed proton carbon No2,this carbon atom is a chiral carbon gives racemic mixture (**R** , **S**) configration [17,18] show a singlet signal at δ (5.68 ppm) , and a multiplet signal for three proton for phenol ring at δ (6.15-7.51) as shown in **figure 5** . and also the spectrum data showed a multiplet signal at δ (6.02), (7.80-8.12ppm) for four protons of pyridine ring , and finally showed singlet signal at δ (10.21ppm) for one proton of phenol hydroxyl . as shown in tne following **figure 6** .

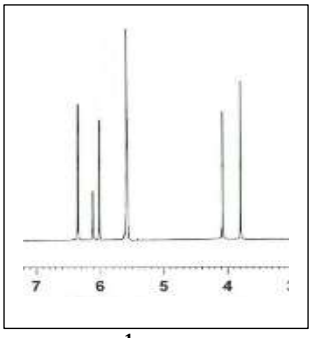


Figure 5:The **^{1}H-NMR** spectra of aliphatic proton of **3a**

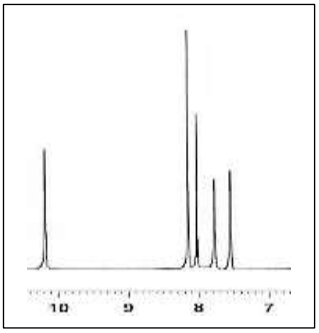


Figure 6:The **^{1}H-NMR** spectra of aromatic proton of **3a**

The **^{1}H-NMR** spectra of 2-(2-Bromo-6-hydroxy-phenyl)-5-oxo-3-phenyl-1-pyridin-2-yl-pyrrolidine-3-carboxylic acid **4a**, showed triplet signal at chemical shift δ (2.57-2.58 ppm) for **d_6-DMSO** solvent. Also showed douplet signal at chemical shift δ (3.28 ppm,J=4Hz) and douplet signal at chemical shift δ (3.52 ppm, J=4Hz) for methylene of pyrrolidine ring for two protons, and showed proton carbon No2,this carbon is a chiral carbon gives racemic mixture(R,S) configration show a singlet signal at δ (4.12 ppm) , and a multiplet signal for five protons for benzene ring at δ (6.15-6.70) as shown in **figure 7.**

and show a multiplet signal at δ (7.63-8.35) for seven aromatic protons of phenol and pyridine rings , and singlet signal at chemical shift δ (10.31 ppm) for proton of phenol hydroxyl group , and singlet signal at chemical shift δ (11.42 ppm) for proton of hydroxyl group as shown in **figure 8**.

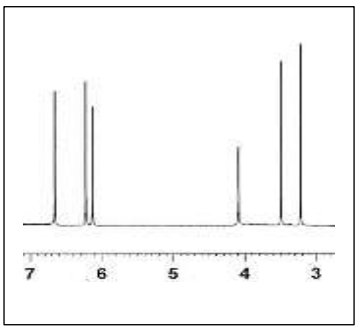


Figure 7:The **^{1}H-NMR** spectra of aliphatic proton of **4a**

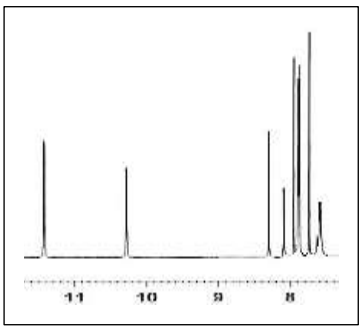


Figure 8:The **^{1}H-NMR** spectra of aromatic proton of **4a**

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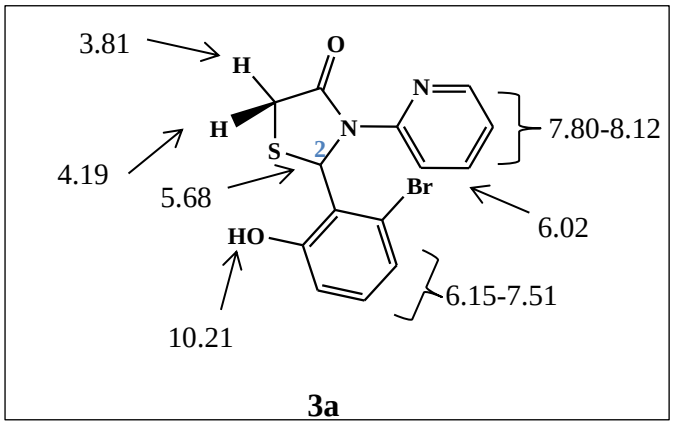

Figure 9:The ^{1}**H-NMR** spectrum of **3a**

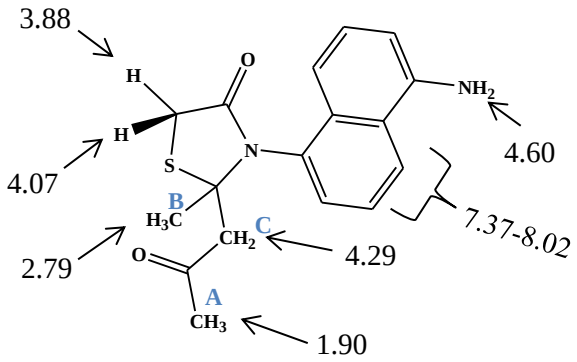

Figure 10 : The ^{1}**H-NMR** spectrum of **3c**

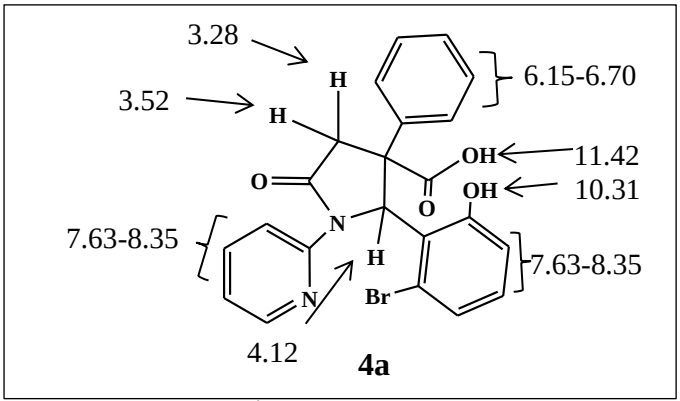

Figure 11:The ^{1}**H-NMR** spectrum of **4a**

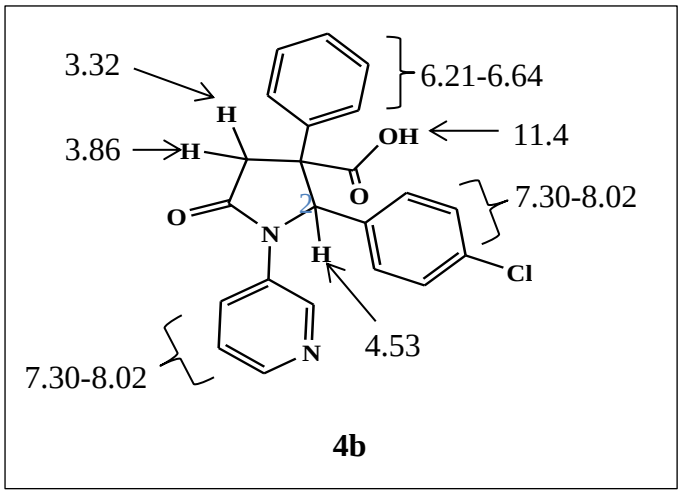

Figure 12:The **^{1}H-NMR** spectrum of **4b**

The ^{13}C-NMR spectrum

The **^{13}C-NMR** spectrum of 2-(2-Bromo-6-hydroxy-phenyl)-3-pyridin-2-yl-thiazolidin-4-one **3a** give triplet signal at δ (76.02-78.15 ppm) for d-$CDCl_3$ solvent , and also show two signals, one singlet signal at δ (38.65 ppm) for carbon methylene group and another singlet signal at δ (48.02 ppm) for carbon No.2 in pyrrolidine ring. The **^{13}C-NMR** spectrum of **3a** also show multiplet signals at δ (122.03-151.02 ppm) for aromatic carbon atoms (pyridine ring+ phenol), and finally show singlet signal at δ (177.86 ppm) for one carbon of amide carbonyl .

The **^{13}C-NMR** spectrum of 2-(2-Bromo-6-hydroxy-phenyl)-5-oxo-3-phenyl -1- pyridin-2-yl-pyrrolidine-3 -carboxylic acid **4a** show triplet signal at δ (77.13-77.59 ppm) for d-$CDCl_3$ solvent , and also show three signals , one singlet signal at δ (42.88 ppm) for one carbon of methylene group and another singlet signal at δ (53.02) for carbon No.2 , and singlet signal at δ (59.79) for carbon No.3 in pyrrolidine rinThe **^{13}C-NMR** spectrum of **4a** also showed a multiplet signals at δ (121.23-158.52 ppm) for the aromatic carbon atoms of pyridine ring, and showed multiplet signals at δ (125.95-138.11 ppm) for the aromatic carbon atoms of two phenyl rings , and showed singlet signal at δ (172.13 ppm) for one carbon atom of the amide carbonyl group ,and finally show singlet signal at δ (185.88 ppm) for one carbon atom of carboxyl group **.**

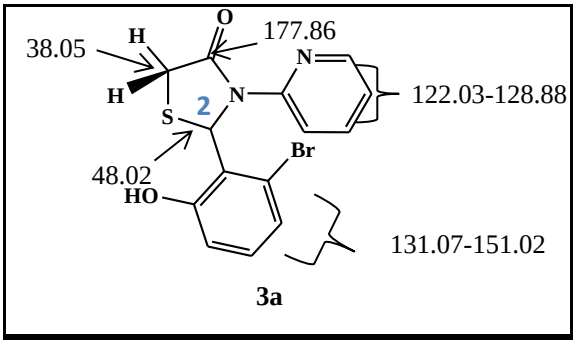

Figure 13 :^{13}**C-NMR** spectrum of **3a**

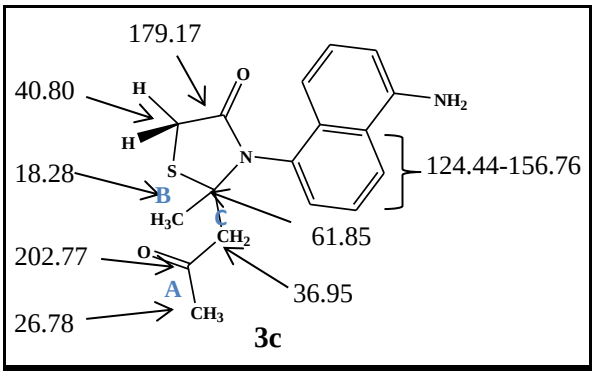

Figure 14 :^{13}**C-NMR** spectrum of **3c**

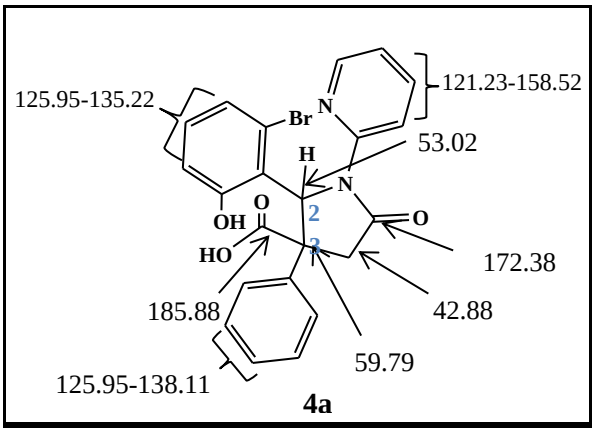

Figure 15: ^{13}**C-NMR** spectrum of **4a**

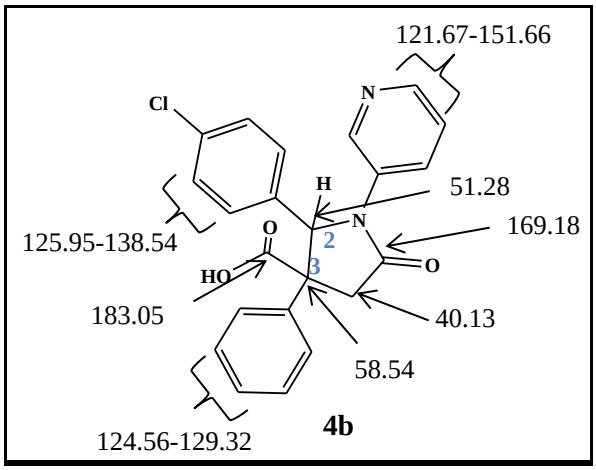

Figure 16: ^{13}**C-NMR** spectrum of **4b**

The ^{13}**C-NMR DEPT** spectrum of 2-(2-Bromo-6-hydroxy-phenyl)-3-pyridin-2-yl-thiazolidin-4-one **3a** is show a signal at δ 48 (-) ppm for (CH2), And signal at δ 38 (+) ppm of one carbon off –CH- of thiazolidin-4-one ring, and The ^{13}**C-NMR DEPT** spectrum of the aromatic region are within the range(125-135)(+)ppm , and show signal at δ (122-148)(+)ppm for the pyridine ring, as shown in figure 17.

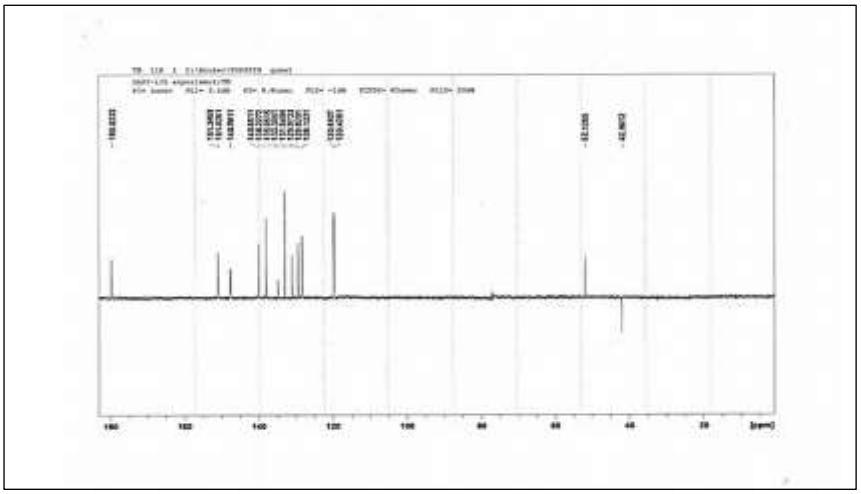

Figure 17 :^{13}**C-NMR DEPT** spectrum of **3a**

Mass spectra

The Mass spectra of 2-(2-Bromo-6-hydroxy-phenyl)-5-oxo-3-phenyl-1-pyridin-2-yl-pyrrolidine-3-carboxylic acid **(4a)** showed the molecular ion peak in453,455m/z,R=27% and important fragmentation peaks in 452,454 **m/z**,R=19**%**,424,426 **m/z**,R=16%,399,401 **m/z**,R=28**%**, 382,384 **m/z**, R=20**%**, 354,356 **m/z**,R=100**%**, 223 **m/z**,R=30**%**, 181 **m/z**,R=10**%**, 103 **m/z**,R=36**%**, 78 **m/z**,R=26**%**, 77 **m/z**,R=51**%**, 65 **m/z**,R=18**%**. As shown in **figure 18.**

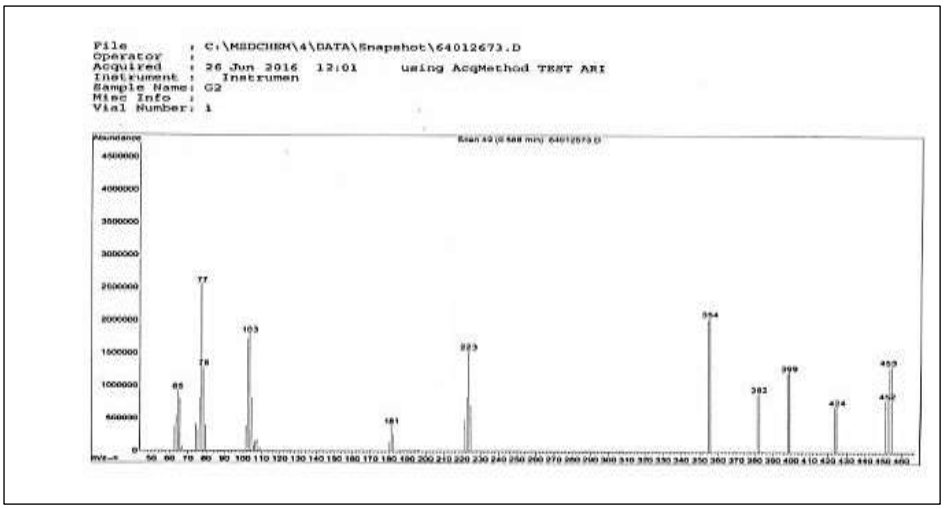

figure 18: **Mass** spectra of 4a

Aknowledgment

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List of Figures

figure 8: ^{1}H-NMR of aromatic protons of 4a.

figure 9: ^{1}H-NMR spectra of 3a.

figure 10: ^{1}H-NMR spectra of 3c.

figure 11: ^{1}H-NMR spectra of 4a.

figure 12: ^{1}H-NMR spectra of 4b.

figure 13: ^{13} C-NMR spectra of 3a.

figure 14: ^{13} C-NMR spectra of 3c.

figure 15: ^{13} C-NMR spectra of 4a.

figure 16: ^{13} C-NMR spectra of 4b.

figure 17: ^{13} C-NMR DEPT spectra of 3a.

figure 18: Mass spectra of 4a.

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