RESEARCH ARTICLE

Synthesis and Characterization of Some 4- Substituted Thiazolidinone Derivatives

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ABSTRACT

This study is concerned with the synthesis and characterization of 4-thiazolidinone derivatives (3a-3e). These compounds were prepared by reacting mercaptoacetic acid with the appropriate Schiff bases (imines) by heating at 50-60 °C in chloroform with moderate yields (51–75 %). The structures of these 4-thiazolidinone derivatives were established on the basis of spectral studies using IR, 1H-NMR, 13C-NMR, and13C-NMR DEPT .

Keywords: Imines, NMR spectroscopy, Synthesis, Thiazolidinones.

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INTRODUCTION

Thiazolidinones are ketone derivatives and are of the saturated form of thiazol (called thiazolidin). 1,3-thiazidolidin-4-one can be described as a heterogeneous pentagonal ring consisting of five members including one nitrogen atom and one sulfur, as shown in Figure 1.

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.

EXPERIMENTAL PART

The 1H-NMR spectra were recorded using VARIAN spectrophotometer (500 MHz), the 13C-NMR spectra were recorded using a VARIAN spectrophotometer (75 MHz). The chemical shift values are expressed in δ (ppm), using tetramethylsilane (TMS) as internal standard and d6-DMSO as the solvent.

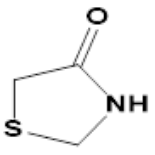


Figure 1. Thiazolidinone ring

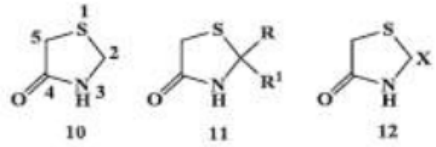
General procedure for the preparation of imines (2a-2e)[4,6]

Preparation of mono-imines (2a-2c).

In general, the mono-imines (2a-2c) were prepared by the reaction of the mixture of 0.01 mol amine with 0.01 mol aldehyde in 20 ml of methanol or ethanol and 4-6 drops of glacial acetic acid. The reaction mixture was refluxed for 0.5-9 hours, and the progress of the reaction was followed by TLC using hexane:ethyl acetate 7:3 as eluent. After completion the reaction, the solvent was evaporated, and the residue was recrystallized from a suitable solvent.

(Z)-3-((4-methoxyphenyl)imino)indolin-2-one (2a)

The compound was prepared by reacting of 4-methoxyaniline (0.0068, 0.8 g) with indoline-2,3-dione(Isatin) (0.0068 mol, 1 g). Rf=1.1 , yield = 79.6%, m.p. = 177-179 °C. IR (KBr disk): 1604 cm-1 (C=N).



X= [=O, =S, NR, NN, CRR^1]
R,R^1 = Cl, F, C_5H_5Cl

Figure 2: Various Thiazolidinone rings and their substituents

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(Z)-3-(p-tolylimino)indolin-2-one (2b)

The compound was prepared by reacting of p-toluidine (0.0068 mol, 0.73 g) with indoline-2,3-dione (0.0068 mol, 1 g). Rf=1, yield = 90%, m.p. = 144-146 **°C**. IR (KBr disk): 1651 cm-1 (C=N).

(Z)-4-(((4-fluorophenyl)imino)methyl)benzaldehyde (2c):

It is prepared by reacting of 4-fluoroaniline (0.0074 mol, 0.82 g) with terephthalaldehyde (0.0074 mol, 1 g). Rf=1.2, yield = 86.12%, m.p. = 178-181 **°C**. IR (KBr disk): 1620 cm-1 (C=N).

Preparation of bis-imines (2d-2e)

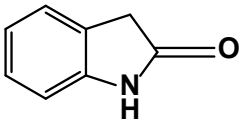
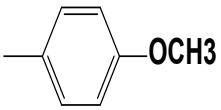
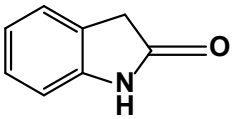
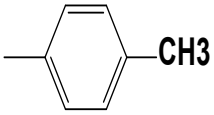
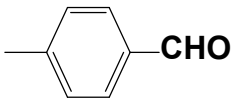
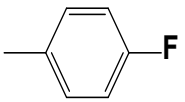
In general, the bis-imines (2d-2e) were prepared by the reaction of 0.01 mol diamine with 0.02 mol of aldehyde (20 ml) of methanol or ethanol and 4-6 drops of glacial acetic acid. The reaction mixture was refluxed for 1-9 h, with monitoring the progress of the reaction by TLC using hexane ethyl acetate 6:4 as eluent. After completion of the reaction, the solvent was evaporated, and the product was recrystallized from a suitable solvent

(1E,1'E)-1,1'-(1,4-phenylene)bis(N-p-tolylmethanimine)(2d):

The compound was prepared by reacting of p-toluidine (0.0148 mol, 1.59g) with terephthalaldehyde (0.0074 mol, 1 g). Rf=2, yield =88%, m.p. = 141 –143°C. IR (KBr disk): 1612 cm-1 (C=N).

(3Z,3'E)3,3'(ethane1,2diylbis(4,1phenylene) bis(azanylylidene))bis(indolin-2-one (2e):

It is prepared by reacting of 4,4'-(ethane-1,2-diyl)dianiline (0.0066 mol, 1.41g) with indoline-2,3-dione (0.0136 mol, 2 g).

Symbol	*R1*	*R2*	*R3*
2a			
2b			
2c		H	

Rf=0.5, yield =90%, m.p. = 127-129**°C**. IR (KBr disk): 1651 cm-1 (C=N).

GENERAL PROCEDURES OF MONO AND BIS THIAZOLIDINONES(3A-3E)[7]

Preparation of mono thiazolidinones (3a-3c)

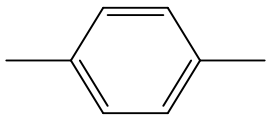
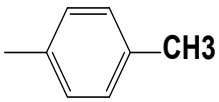
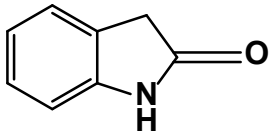
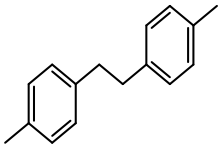
A mixture of appropriate Schiff bases (0.01 mol) (2a-2c) and thioglycolic acid (0.01 mol, 0.20 ml) in a suitable solvent (50) ml was refluxed for 10–30 hours. Water formed during the reaction was removed azeotropically by a Dean-Stark apparatus. The progress of the reaction was monitored by TLC using hexane:ethyl acetate 6:4 as eluent. This mixture of reaction are treated with sodium bicarbonate solution to remove unreacted acid. The obtained solids were filtered, washed and purified by recrystallization from dichloromethane to give color powders.

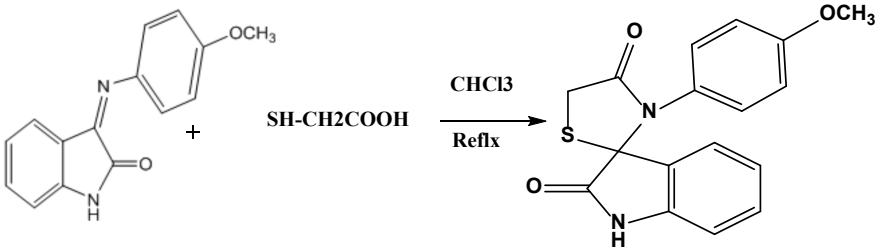
3'-(4-methoxyphenyl)spiro[indoline-3,2'-thiazolidine]-2,4 dione(3a):

The compound was prepared by reacting **(2a)** (0.0013 mole, 0.33 g) and (0.0013 mole, 0.1gm, 0.09 mL) of thioglycolic acid. Rf=0.7 , yield =63 %, m.p. = 117–119 **°C**. colour: white. IR (KBr disk): 1681 cm-1 (–N–C=O of thiazolidinone ring), 3024cm-1 (Ar-H), 2924 cm-1 (C-H aliphatic), 1296 cm-1 (C-N),756 cm-1 (C-S). 1H-NMR (500 MHz, DMSO-d6) δ=3.7 (s, 3H, methoxy group); δ=4.14 (d, 2H, C5H); 7.3-8.01 (m, 8H, ArH); 10.6(s, 1H, N-H). 13C NMR (75 MHz, DMSO-d6) δ=55 (s, methoxy group); δ=70(s, -CH2-), 111.5(s, -C-), 118-140.5(m, Ar-C); 172(s, CH2-C=O); 178(s, N-H-C=O).as shown in Table (1-1),(1-2).

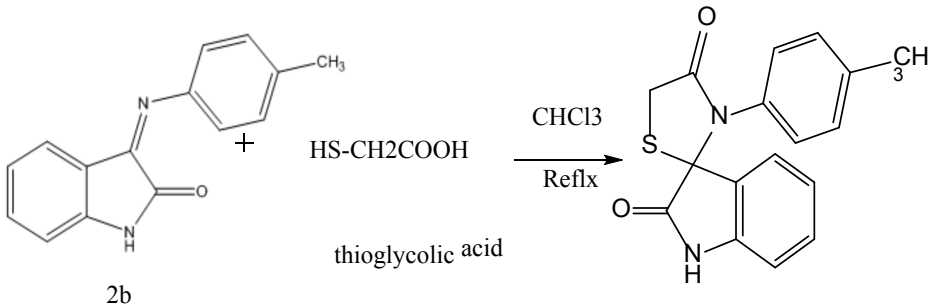
3'-(p-tolyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (3b):

The compound was prepared by reacting (2b) (0.0021 mole, 0.5 g) and (0.0021 mole, 0.19 gm, 0.15 mL) of thioglycolic acid. Rf=0.5 , yield =67%, m.p. = 102 104 °C. colour: white. IR (KBr disk): 1681 cm-1 (–N–C=O of thiazolidinone ring), 3132cm-1

Symbol	*R1*	*R2*	*R3*
2d		H	
2e			



2a **2-mercaptoacetic acid** **3'-(4-methoxyphenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione**



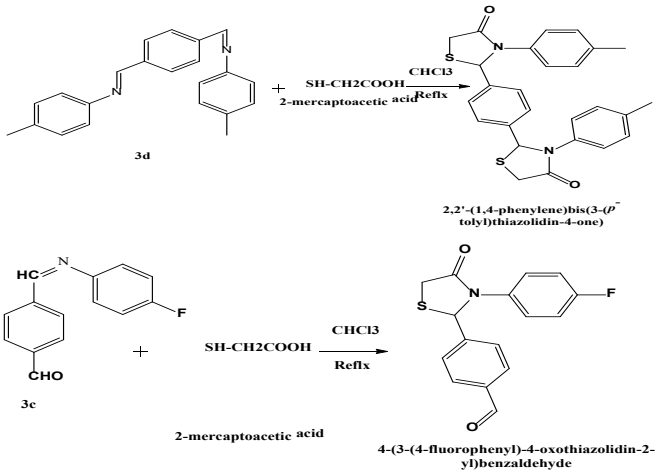
(Ar-H), 2924 cm-1 (C-H aliphatic), 1219 cm-1 (C-N),763 cm-1 (C-S). 1H-NMR (500 MHz, DMSO-d6) δ=2.2 (s, 3H, methyl group); δ=4.2 (d, 2H, C5H); 6.81-7.88 (m, 8H, ArH); 10.8(s, 1H, N-H). 13C NMR (75 MHz, DMSO-d6) δ=32 (s, methyl group); δ=70(s, -CH2-), 110.5(s, -C-), 118-142.5(m, Ar-C); 172(s, CH2-C=O); 178(s, N-H-C=O). as shown in table (1-1),(1-2).

4-(3-(4-fluorophenyl)-4-oxothiazolidin-2-yl)benzaldehyde (3c)

The compound was prepared by reacting (2c) (0.0028 mole, 0.64 g) and (0.0028 mole, 0.32 gm, 0.19 mL) of thioglycolic acid. Rf=1 , yield =62%, m.p. = 125-127°C. colour: white. IR (KBr disk): 1674 cm-1 (–N–C=O of thiazolidinone ring), 3047cm-1 (Ar-H), 2962 cm-1 (C-H aliphatic), 1313 cm-1 (C-N),846 cm-1 (C-S). 1H-NMR (500 MHz, DMSO-d6) δ=4.0 (d, 2H, C5H); δ=6.4 (s, 1H, C2H); δ= 6.99-7.55 (m, 8H, ArH); δ 9.9(s, 1H, C=O ald). 13C NMR (75 MHz, DMSO-d6) δ=32(s, -CH2-), δ 63(s, -CH-), 118-159(m, Ar-C); 161(s,C=O Ald); 170.5(s CH2-C=O). as shown in table (1-1),(1-2).

Preparation of bis thiazolidinones (3d-3e)

A mixture of appropriate Schiff bases (0.02 mol) (2d-2e) and thioglycolic acid (0.02 mole, 0.40 mL) in a suitable solvent (50 ml) was refluxed for 10-30 h, water formed during the reaction was removed azeotropically by a Dean-Stark apparatus. The progress of the reaction was checked by TLC using hexane : ethyl acetate 6:4 as eluent . This mixture of reaction was treated with sodium bicarbonate solution to remove unreacted acid. The obtained solid was filtered, washed and purified by recrystallization from dichloromethane to give color powder.

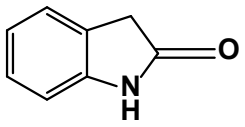
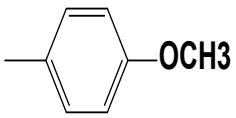
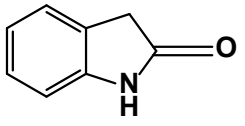
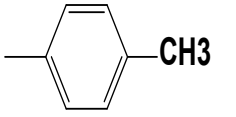
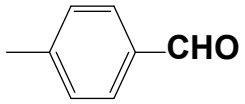
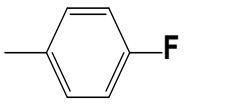


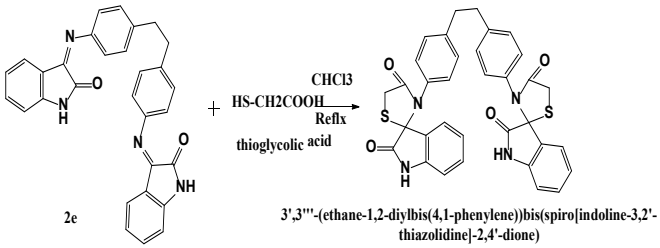
3 2,2'-(1,4-phenylene)bis(3-(p-tolyl)thiazolidin-4-one)(3d):

The compound was prepared by reacting (2d) (0.0025mole, 0.8 g) and (0.005 mole, 0.46 gm, 0.35 mL) of thioglycolic acid. Rf=0.8 , yield =66%, m.p. =134-136°C. colour: white. IR (KBr disk): 1674 cm-1 (–N–C=O of thiazolidinone ring), 3039cm-1 (Ar-H), 2962 cm-1 (C-H aliphatic), 1381cm-1 (C-N),817 cm-1 (C-S). 1H-NMR (500 MHz, DMSO-d6) δ=2.3 (s, 6H, methyl group) (equivalent carbon) ; δ=4.2 (d, 4H, C5H); δ=6.4 (s, 2H, C2H) (equivalent carbon); 7.10-7.98 (m, 8H, ArH); 13C NMR (75 MHz, DMSO-d6) δ=21 (s, methyl group) (equivalent carbon), δ=33(s, -CH2-) (equivalent carbon), δ 63(s, -CH-) (equivalent carbon), δ 121-141(m, Ar-C); 170.5(s CH2-C=O of thiazolidinone ring), (equivalent carbon). as shown in table (1-1),(1-2).

3',3'''-(ethane-1,2-diylbis(4,1-phenylene))bis(spiro[indoline-3,2'-thiazolidine]-2,4'-dione)(3e):

The compound was prepared by reacting (2e) (0.001mole, 0.5 g) and (0.002 mole, 0.18 gm, 0.148 mL) of thioglycolic acid. Rf=0.6 , yield =65%, m.p. =147-149°C. colour: white. IR (KBr disk): 1689 cm-1 (–N–C=O of thiazolidinone ring), 3062cm-1 (Ar-H), 2924 cm-1 (C-H aliphatic), 1373cm-1 (C-N),756 cm-1 (C-S). 1H-NMR (500 MHz, DMSO-d6) δ=2.7 (t, 4H, CH2-CH2 opening chain) (equivalent carbon) ; δ=4.2 (d, 4H, C5H);(equivalent carbon); 6.89-8.25(m, 8H, ArH), δ 10.8(s, 1H, N-H).; 13C NMR (75 MHz, DMSO-d6) δ=31 (s, CH2-CH2 opening chain) (equivalent carbon) δ=70(s, -CH2-

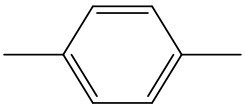
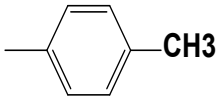
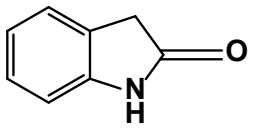
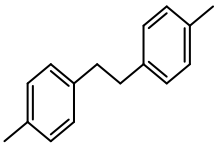
Symbol	*R1*	*R2*	*R3*
3a			
3b			
3c		H	



of thiazolidinone ring), (equivalent carbon), δ 111(s, -C- of thiazolidinone ring),) (equivalent carbon), δ 121-142(m, Ar-C); 171.5(s, CH2-C=O of thiazolidinone ring); 176(s, N-H-C=O). (equivalent carbon). as shown in Table (1 to 1), (1 to 2).

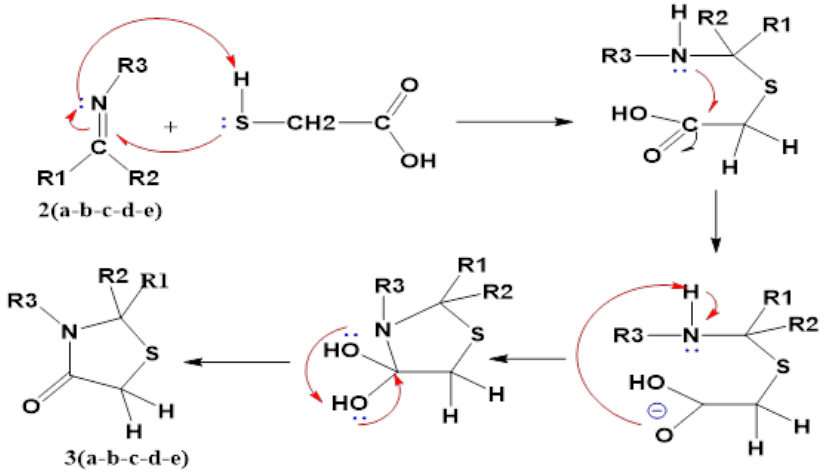
RESULTS AND DISCUSSION

Thiazolidinones 3a-3e have been prepared by reaction of the appropriate Schiff bases (2a to 2e) with thioglycolic acid in a suitable solvent (benzene or chloroform).

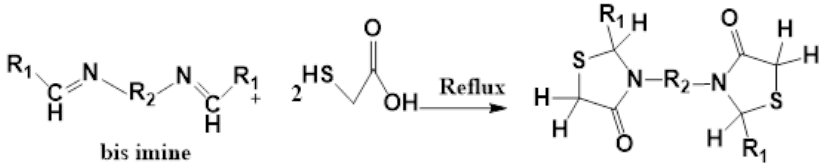
Symbol	*R1*	*R2*	*R3*
2d		H	
2e			

Analysis of infrared spectra

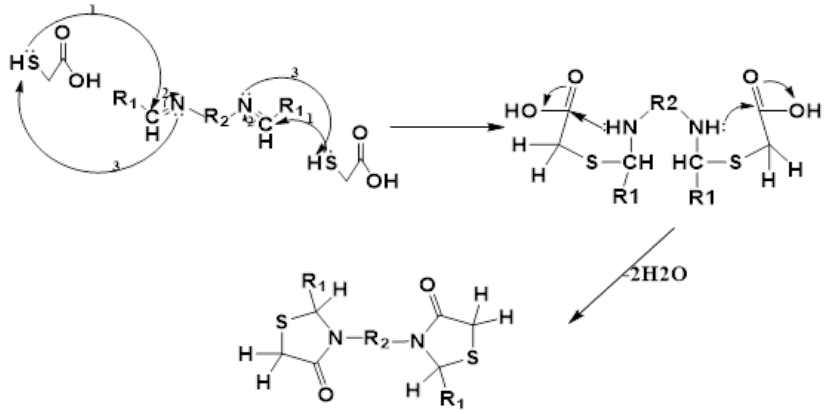
The IR spectra of thiazolidinones 3a to 3e in KBr disk show six band groups correspond to the stretching vibration of the aromatic C-H, aliphatic C-H, carbonyl amide group, aromatic C=C, the C-N and bending vibration of S-C bonds, occur within the ranges 3107–2980, 2975–2887, 1691–1654, 1399–



Scheme 1: Mechanism of formation of mono thiazolidinone



Scheme 2: Synthesis of bis thiazolidinone.



Scheme 3: Probable mechanism of the formation of bis-thiazolidinone

Table (1-1): FT-IR spectra of thiazolidinones

Comps	*Aromatic C-H stretching cm^{-1}*	*Aliphatic C-H stretching cm^{-1}*	*Amide C=O stretching cm^{-1}*	*Aromatic C=C stretching cm^{-1}*	*Aromatic C-N Bending cm^{-1}*	*Aromatic C-S Bending cm^{-1}*
3a	3217	2924	1681	1620	1296	750
3b	3132	2924	1681	1620	1219	763
3c	3047	2962	1674	1597	1313	840
3d	3039	2962	1674	1512	1381	817
3e	3062	2924	1689	1612	1373	756

Table (1-2): Chemical shift data of Thiazolidinones

N0.	*thiazolidin-4-one ring*	*Aromatic proton*	*Aliphatic proton*	*others proton*
3a	δ 3.81ppm d , 1H δ 4.19ppm d ,1H	δ (7.3–8.01)ppm m ,8H	δ 3.7ppm S,3H Methoxy Group	δ 10.6ppm S,1H (N-H)
3b	δ 4.0ppm d , 1H δ 4.19ppm d ,1H	δ (6.81-7.88 ppm) m ,8H	δ 2.2ppm S,3H Methyl Group	δ 10.8ppm S,1H (N-H)
3c	δ 4.0ppm d , 1H δ 4.19ppm d ,1H δ 6.4ppm s ,1H	δ (7.10-7.98 ppm) m ,8H	----------	δ 9.9ppm S,1H (C=OAld)
3d	δ 4.0ppm d , 2H δ 4.2ppm d ,2H δ 6.4ppm s ,2H	δ (7.10-7.98 ppm) m ,8H	δ 2.3ppm S,6H Methyl Group	
3e	δ 4.0ppm d , 2H δ 4.2ppm d ,2H	δ (6.81-8.25 ppm) m ,8H	δ 2.7ppm S,4H CH2-CH2	δ 10.8ppm S,1H (N-H)

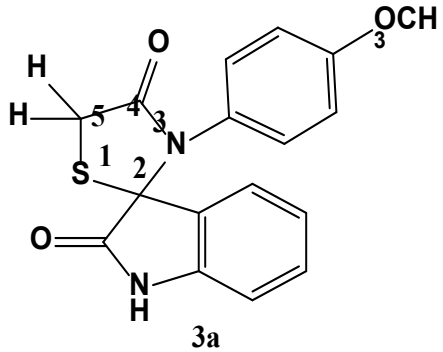
1361, 738–654, and 925–617 cm-1 respectively. The absorption frequencies are affected by substitution of the phenyl ring, and the substitution by electron-donating groups (methyl group decreases) while substitution by electron-withdrawing groups (flouro) increase the vibrational frequencies.

1H-NMR spectral analysis

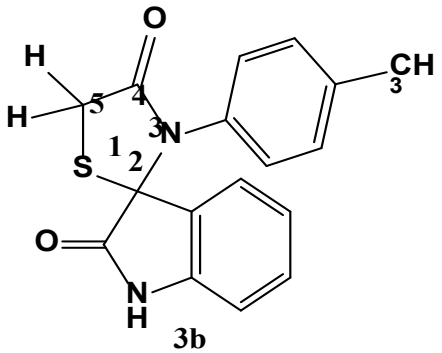
The 1H-NMR spectrum of **3a** shows a singlet signal at δ 4.4ppm for methylene group of thiazolidin-4-one ring, a multiplet signal at δ 7.3-8.01 ppm for aromatic protons (m, 8H, Ar-H), finally a singlet signal at δ 9.2 ppm for amide proton (1H, N-H).

Analysis of 13C-NMR spectra

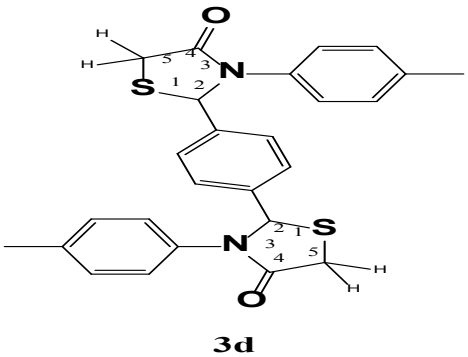
The 13C NMR spectrum of **3a** showed thiazolidin-4-one ring signals at δ 36 ppm for C5 carbon 5) at δ 49.94 ppm for C2 atom. A multiplet for aromatic carbons at δ 107-139 ppm, a singlet of carbonyl group at δ 177.06 ppm and a signal for C4 carbon of the ring were observed at δ 179.78 ppm.



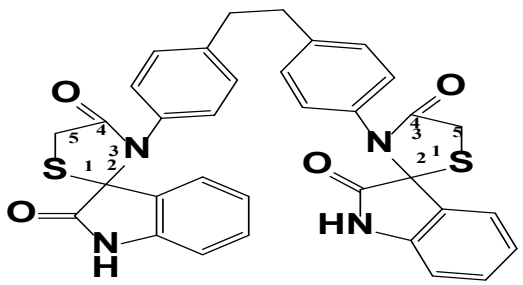
3a



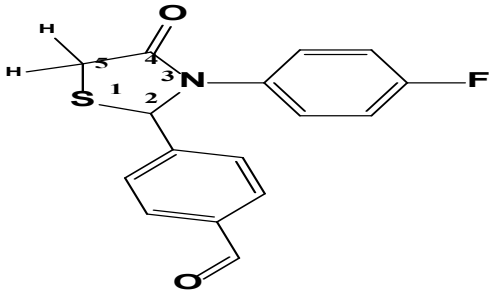
3b



3d



3□e



3c

CONCLUSION

In this study five compounds from Schiff bases with thioglycolic acid in a suitable solvent (chloroform) and refluxe (50-60) °C. this method gave an excellent result with high yield and the duration of the reaction was shorter.

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