Synthesis of New Bis-1,3,4-Thiadiazoles Substituted from benzidine Containing Oxazepine or benzoxazepine Moieties

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ABSTRACT:

Benzidine was converted to the corresponding bis-diazonium salt which was introduced in coupling reaction with alkaline solution of 2-hydroxybenzaldehyde as coupling reagent to give bis-azo derivative **(1)** containing two aldehyde groups. The resulting bis-aldehyde **(1)** was then introduced in condensation reaction with 2-amino-5-mercapto-1,3,4-thiadiazole to produce the bis-imine **(2).**Then compound **(2)** was reacted with maleic anhydride and phthalic anhydride to give **(3a and 3b)** respectively .All compounds were spectral identification by FTIR and ^{1}H-NMR.

Key word:

Benzedine, azo compounds, thaiadiazol, 2-amino-5-mercapto-1,3,4-thiadiazole ,oxazepine, benzoxazepine.

Introduction

Benzidine (4,4′diaminobiphenyl)H_2N-C_6H_4- C_6H_4-NH_2 or $C_{12}H_{12}N_2$,aromatic amine,is a Known human carcinogenic. It is greyish-yellow, white, or reddish-grey crystalline powder, soluble in hot water, alcohol, ether and slightly soluble in cold water. m.p 127℃;b.p 400℃(1-4). The azo dyes derived from benzidine are important because they are unlike simpler classes of azo dyes, they become strongly fixed to cotton without a mordant(5,6). Benzidine and its analogues can be produced as unwanted by-products via the reduction of azo dyes by intestinal and environmental microorganisms (7,8).

Azo compounds are important and widely used substances ,they used as coloring agent in paper, textile, cosmetics in emerging technologies include liquid crystal, photoconductors and even non linear optics (9).

Because of their specific physic-chemical properties and biological activities they have broad application in pharmaceutical, biological activity of azo colorants mostly results from the specific pathway of their metabolism. In most cases , particularly benzidine-based derivatives demonstrate an increased toxicity, for example the azo dye direct Black 38 is metabolized to the mutagen benzidine by human intestinal micro flora (10-15). The bis-aldehyde was then introduced in condensation reaction with 2-amino-5-mercapto-1,3,4-thiadiazole to produce the bis-imine .Then bis-imine was reacted with maleic anhydride and phthalic anhydride to give oxazepine and benzoxazepine respectively(16-21).

Experimental.

Synthesis of 5,5'-([1,1'-biphenyl]-4,4'-diylbis(diazene-2,1-diyl))bis(2-hydroxy- benzaldehyde (1):

was prepared by the method which described by Q.Acton (22): IR (cm^{-1}): 3365 and 3184 (νO-H), 3039 (νC-H, benzene), 2858 and 2756 (νC-H, aldehyde), (1662 (νC=O, aldehyde), 1583 and 1481 (νC=C, benzene), 831 (δo.o.p. C-H, benzene) **(Fig. 1)** ; ^{1}H NMR: (ppm) =7.20–8.18 (m, 14H, Ar–H), 10.36 (s, 2H, 2×O=CH, aldehyde), 11.6 (s, 2H, 2×O-H). The singlet signals around 2.48 ppm and 3.47 ppm attributed to DMSO and absorbed H_2O in DMSO, respectively **(Fig. 5).**

Synthesis of 4,4'-((1E,1'E)-[1,1'-biphenyl]-4,4'-diylbis(diazene-2,1-diyl))bis(2-((E)-((5-mercapto-1,3,4-thiadiazol-2-yl)imino)methyl)phenol(2):

Bis-azoaldehyde derivative (**1**) (0.9 g, 2 mmol) was dissolved in (30 mL) of absolute ethanol, then 2-amino-5-mercapto-1,3,4-thiadiazole (0.532 g , 4 mmol) was added. The reaction mixture was refluxed with stirring on a water bath at 65^{o}C for 12 h and monitored by TLC. The mixture was then allowed to cool down to room temperature , the colored precipitate was filtered and recrystallized from ethanol: IR (cm-1): 3390 and 3275 (νO-H), 3090 (νN-H, thione form and νC-H, benzene, vib. coupling), 2922 and 2777 (νN-H, intramolecularly hydrogen bonded, thione form), 1602 (νC=N, imine), 1533 and 1489 (νC=C, benzene and νC=N, thiadiazole, vib. coupling), 1060 (νC=S, thione form), 831 (δo.o.p. C-H, benzene) (**Fig. 2**); ^{1}H NMR: (ppm) =7.13–8.19 (m, 14H, Ar–H), 10.2 (s, 2H, 2×HC=N, imine), 10.35 and 11.6 (ss, 2H, 2×O-H),

13.17 (s, 2H, 2×S–H). The singlet signals around 2.47 ppm and 3.49 ppm attributed to DMSO and absorbed H_2O in DMSO, respectively **(Fig. 6)** .

General procedure for the synthesis of oxazepine and benzoxazepine derivatives (3a, 3b):

A mixture of bis-azoimine derivative (**2)** (0.34 g, 0.5 mmol) and maleic or phthalic anhydride (1 mmol) in dry benzene (20 mL) was refluxed on a water bath at 70 ºC for 24 h and monitored by TLC. The mixtures were then allowed to cool down to room temperature, the colored precipitates were filtered, dried and recrystallized from ethanol.

2,2'-(((1E,1'E)-[1,1'-biphenyl]-4,4'-diylbis(diazene-2,1-diyl))bis(6-hydroxy-3,1-phenylene))bis(3-(5-mercapto-1,3,4-thiadiazole-2-yl)-2,3-dihydro-1,3-oxazepine-4,7-dione) (3a):

IR (cm^{-1}): 3400 and 3278 (νO-H), 3170 (νN-H, thione form) 3089 (νC-H, benzene), 2924 (νN-H, intramolecularly hydrogen bonded, thione form), 2550 (νS-H), 1714 (νC=O, O=C-O, oxazepine), 1662 (νC=O, O=C-N, oxazepine), 1535 and 1490 (νC=C, benzene and νC=N, thiadiazole, vib. coupling), 1404 (νN=N), 1060 (νC=S, thione forms), 829 (δo.o.p. C-H, benzene**(Fig. 3))** ; ^{1}H NMR: (ppm) =6.26 and 6.61 (ss, 4H, 4×olefinic =CH, oxazepine), 7.1–8.2 (m, 16H, Ar–H and C–H, oxazepine), 10.35 and 11.6 (ss, 2H, 2×O-H), 13.17 (s, 2H, 2×S–H). The singlet signals around 2.49 ppm and 3.4 ppm attributed to DMSO and absorbed H_2O in DMSO, respectively **(Fig. 7)** . Anal. Calcd. for $C_{38}H_{24}N_{10}O_8S_4$: C, 52.05; H, 2.76; N, 15.97; S, 14.63 Found C, 53.27; H, 2.62; N, 16.24; S, 14.49.

3,3'-(((1E,1'E)-[1,1'-biphenyl]-4,4'-diylbis(diazene-2,1-diyl))bis(6-hydroxy-3,1-phenylene))bis(4-(5-mercapto-1,3,4-thiadiazole-2-yl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione) (3b):

IR (cm^{-1}): 3394 and 3275 (νO-H), 3089 (νN-H, thione form), 3032 (νC-H, benzene), 2916 and 2779 (νN-H, intramolecularly hydrogen bonded, thione form), 2652 (νC-H, oxazepine), 2526 (νS-H), 1689 (νC=O, O=C-O and νC=O, O=C-N, oxazepine, vib. coupling), 1597, 1533 and 1492 (νC=C, benzene and νC=N, thiadiazole, vib. coupling), 1404 (νN=N), 1066 (νC=S, thione forms) **(Fig. 4)** ; ^{1}H NMR: (ppm) =7.1–8.2 (m, 24H, Ar–H and C–H, oxazepine), 10.35 and 11.6

(ss, 2H, 2×O-H), 13.17 (s, 2H, 2×S–H). The singlet signals around 2.48 ppm and 3.41 ppm attributed to DMSO and absorbed H_2O in DMSO, respectively **(Fig. 8)** . Anal. Calcd. for $C_{46}H_{28}N_{10}O_8S_4$: C, 56.55; H, 2.89; N, 14.34; S, 13.13 Found C, 56.20; H, 2.81; N, 14.71; S, 12.77.

The initiator bis-imine derivative (**1)** was synthesized by reacting the bis-diazonium salt of benzidine with alkaline solution of 2-hydroxybenzaldehyde using the method described by Q. acton (22). The resulting bis-aldehyde **(1)** was condensed with 2-amino-5-mercapto-1,3,4-thiadiazole in absolute ethanol to give the bis-imine derivative 8. The resulting imine 8 was reacted with maleic and phthalic anhydrides leading to the formation of oxazepine-1,3,4-thiadiazole derivatives **(3a and 3b)** respectively **(Scheme 1).**

Result and Discussion.

The structures of the synthesized compounds were identified by IR, ^{1}H NMR spectral measurements and (C.H.N.S.) elemental analysis and were in good agreement with the proposed structures.

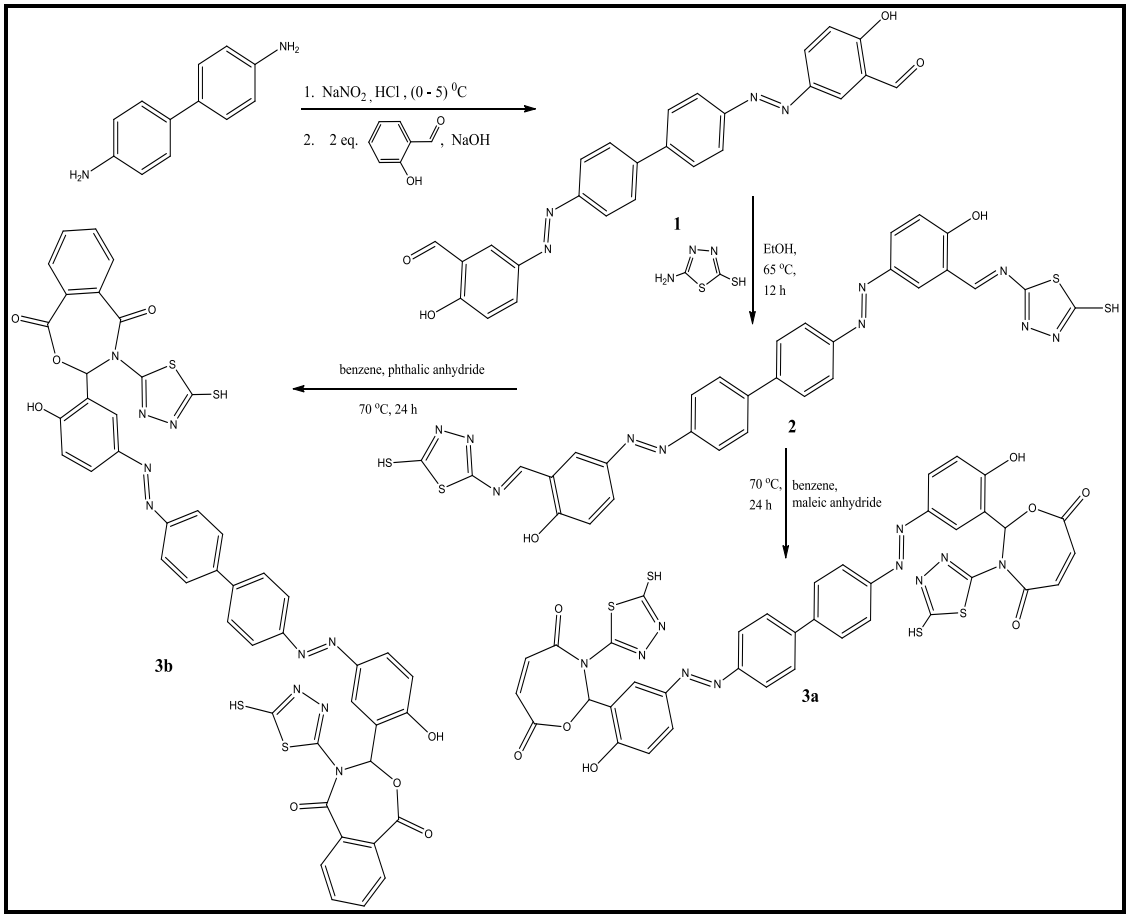
The IR spectrum of bis-imine derivative(**1**) showed disappearance of the sharp doublet band for (-NH_2)str. at the range (3400-3250) cm^{-1} and appearance of band at 3365 cm-1 assigned to (O-H)str., the strong absorption band at 1662 cm^{-1} due to the aldehydic (C=O)str. The IR spectrum of bis-imine derivative (**2**) indicated the disappearance of the absorption band at 1662 cm^{-1} for aldehydic (C=O)str., also disappearing the doublet band for (-NH_2)str. in 2-amino-5-mercapto-1,3,4-thiadiazole at 3336 and 3267 cm^{-1}, while the absorption band attributed to (C=N)str. appeared at 1602 cm^{-1}. The IR spectra of oxazepine compounds (**3a and 3b)** showed the stretching absorption band due to (C=O, oxazepine) at (1714, 1662) cm^{-1} and 1689 cm^{-1} respectively, while the absorption band due to (C=N) at 1602 cm^{-1} has disappeared.

The 1H NMR spectrum of bis-aldehyde derivative (**1)** showed the (O-H) protons as a singlet at δ 11.6 ppm, the (HC=O) protons as a singlet at δ 10.36 ppm, the (Ar-H) protons at δ 7.20 –8.18 ppm.

The 1H NMR spectrum of bis-imine derivative (**2)** showed the (S-H) protons as a singlet at δ 13.17 ppm, the (O-H) protons appeared as a singlets at 10.35 and 11.6 ppm, the (HC=N) protons as a singlet at δ 10.2 ppm, , the (Ar-H) protons at δ 7.13 –8.19 ppm.

The 1H NMR spectra of oxazepine compounds (**3a and 3b)** showed the disappearance of the (HC=N) protons at 10.2 ppm, the (S-H) protons appeared as a singlet at δ 13.17 ppm. The (O-H) protons as a singlets at 10.35 and 11.6 ppm. The signals of aromatic protons (Ar–H) and (C–H) protons of oxazepine rings appeared at δ 7.1-8.2 ppm. Moreover, the olefinic (=CH) protons of the oxazepine rings in compound (**3a**) appeared as a singlet's at 6.26 and 6.61 ppm.

The biological activity of the synthesized oxazepines of 1,3,4-thiadiazole (**3a and 3b**) will be measured in subsequent study.



Scheme 1. Synthesis of oxazepines (3a and 3b)

TABLE-1:Physical Properties of The Synthesized Compoundes (1-3b)

Product	Physical state	Rf (developer)	m.p. (°C)	Yield (%)
1	Brown solid	0.69 (Toluene/ EtOH, 7:3)	191-193	52
2	Brown solid	0.78 (Toluene/ EtOH, 7:3)	228-230	69
3a	Light brown solid	0.64 (Toluene/ EtOH, 7:3)	164-166	73
3b	Light brown solid	0.77 (Toluene/ EtOH, 7:3)	189-191	77

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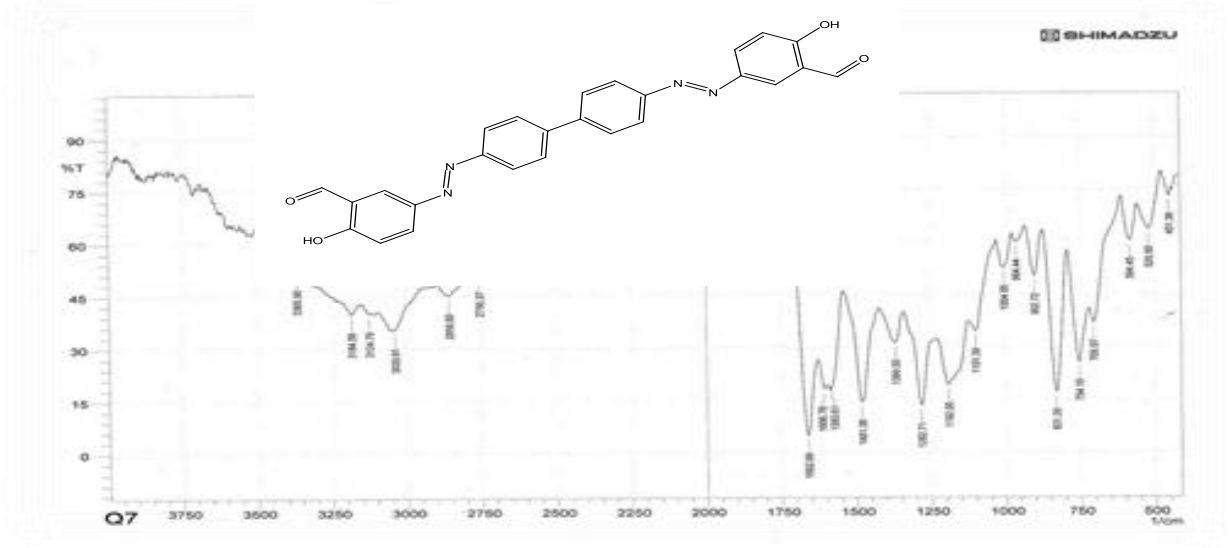

Figure (1) FT-IR spectrum of compound 1

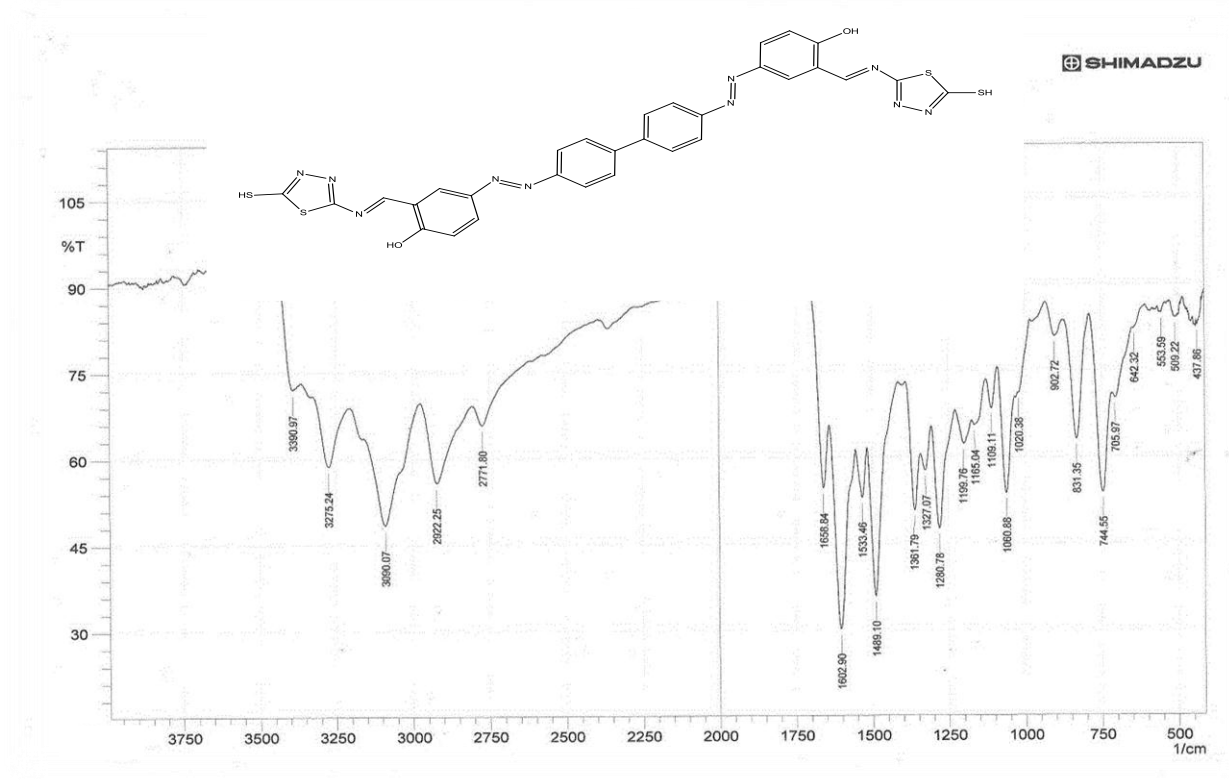

Figure (2) FT-IR spectrum of compound 2

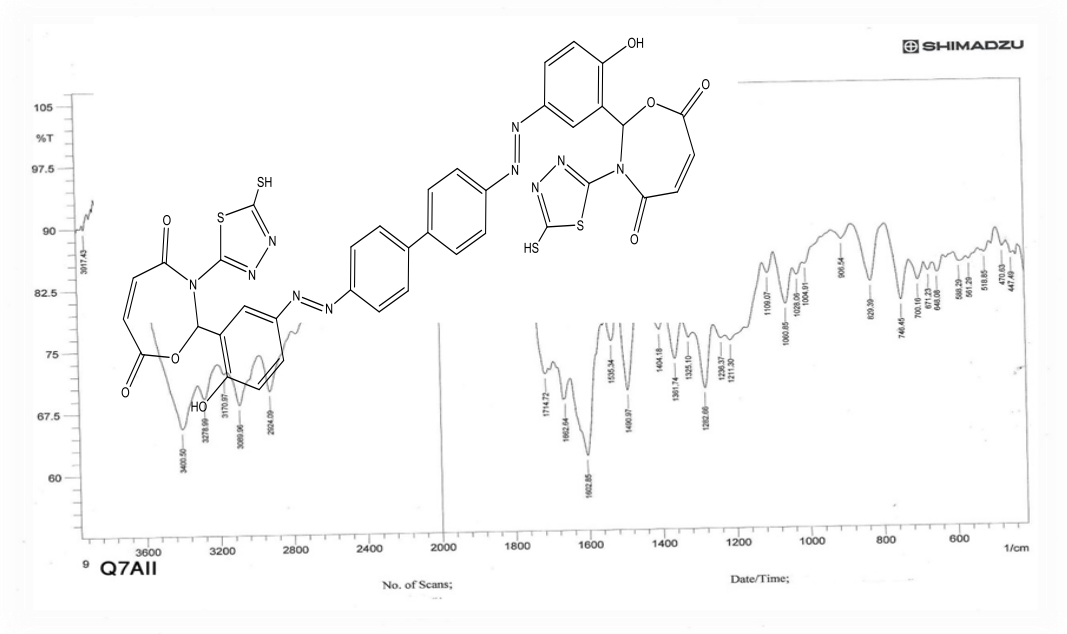

Figure (3) FT-IR spectrum of compound 3a

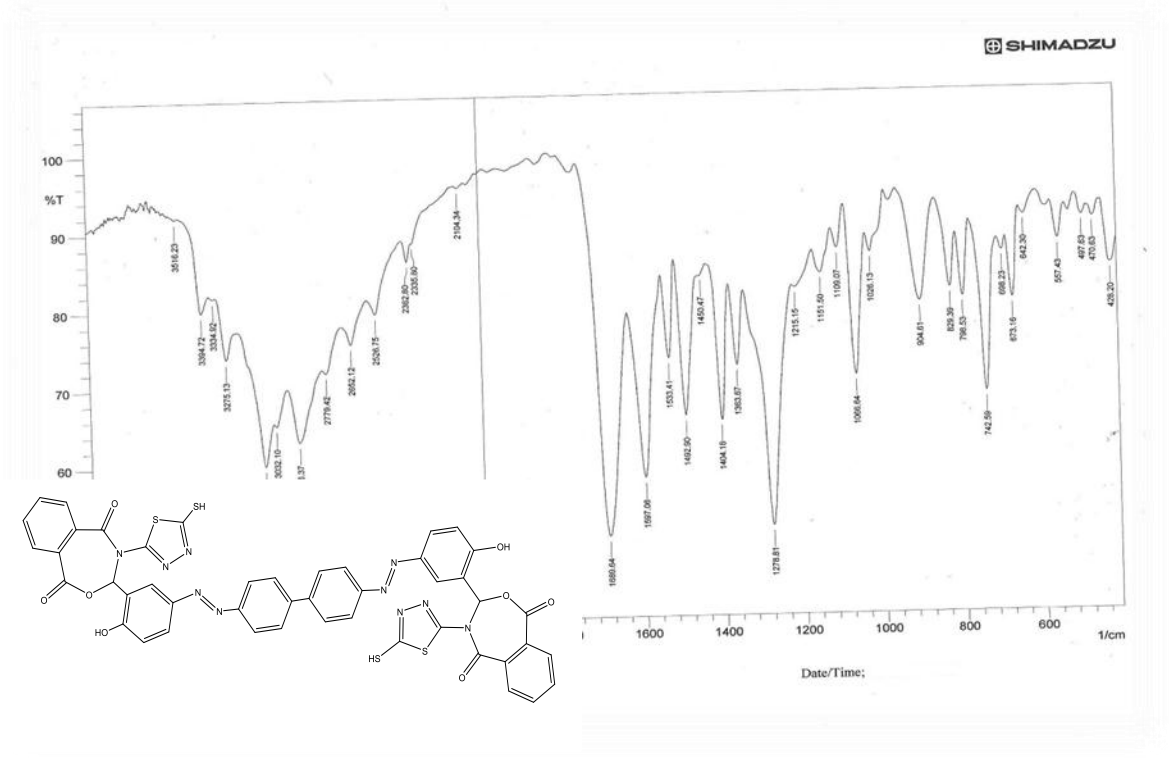

Figure (4) FT-IR spectrum of compound 3b

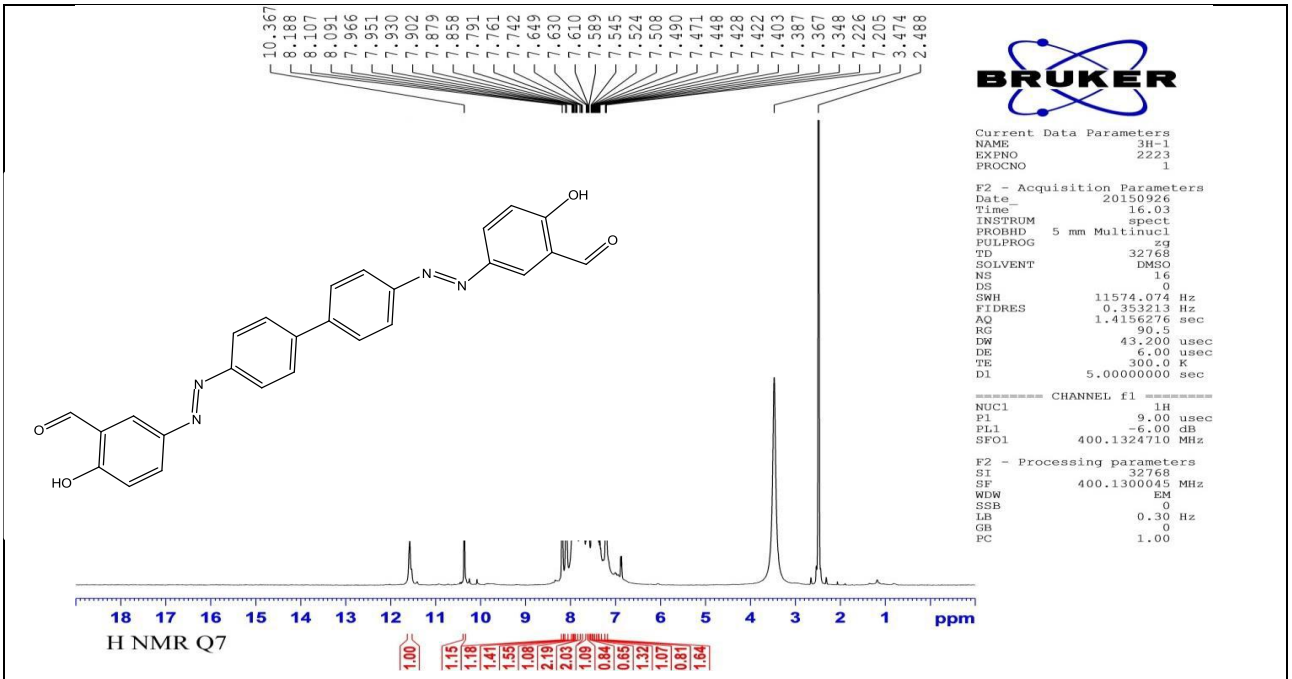

Figure (5) : ^{1}H NMR spectrum of compound 1

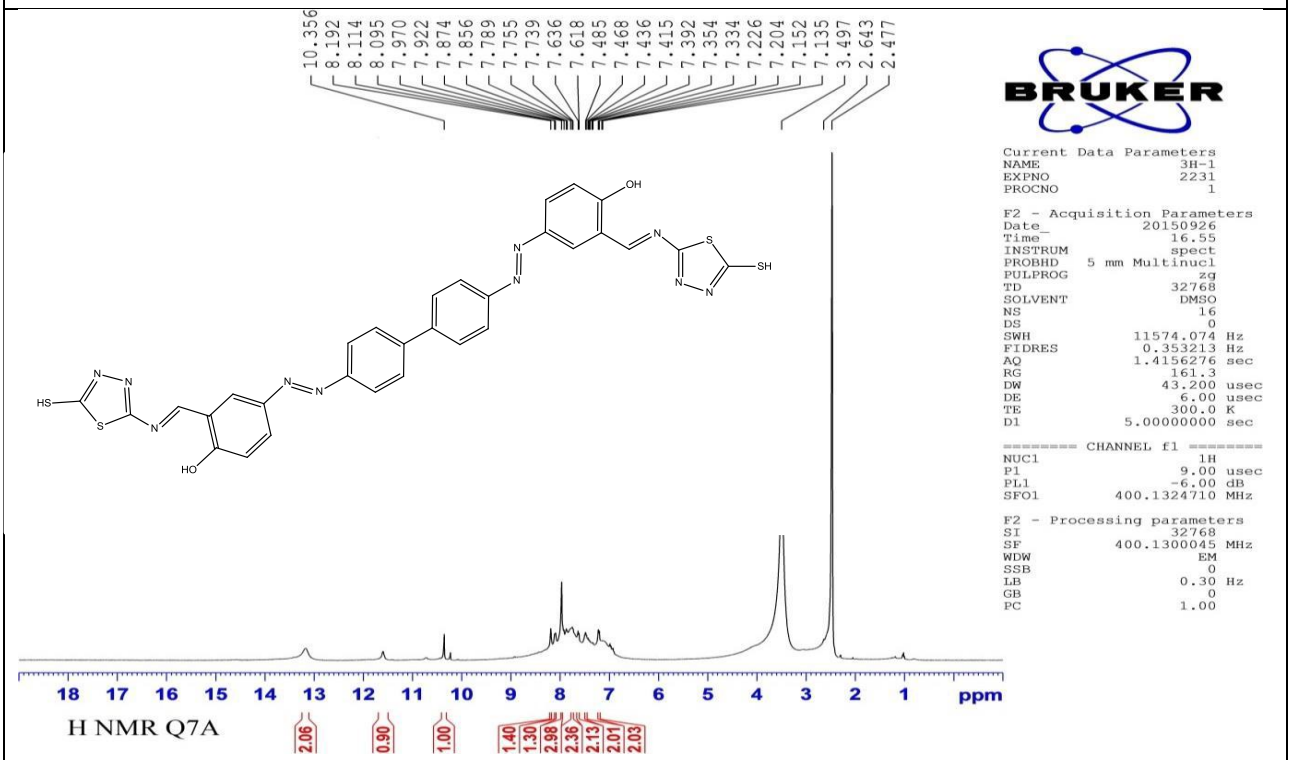

Figure (6) : ^{1}H NMR spectrum of compound 2

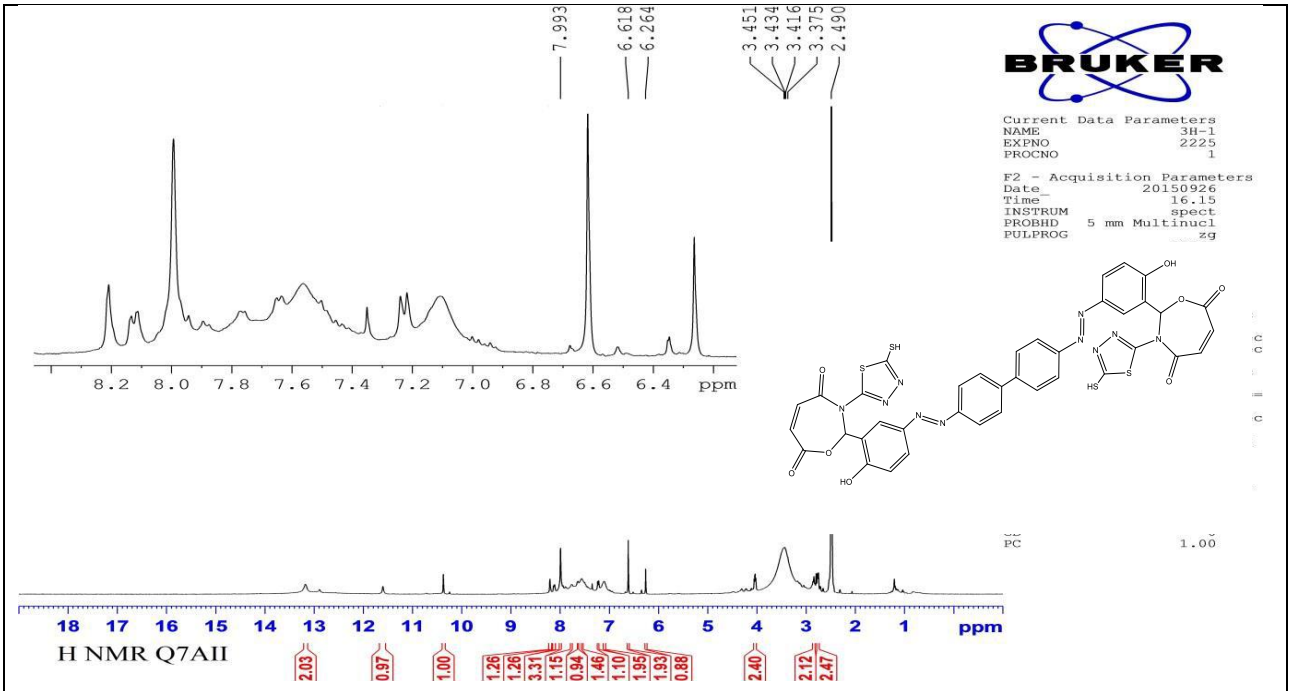

Figure (7) : 1H NMR spectrum of compound 3a

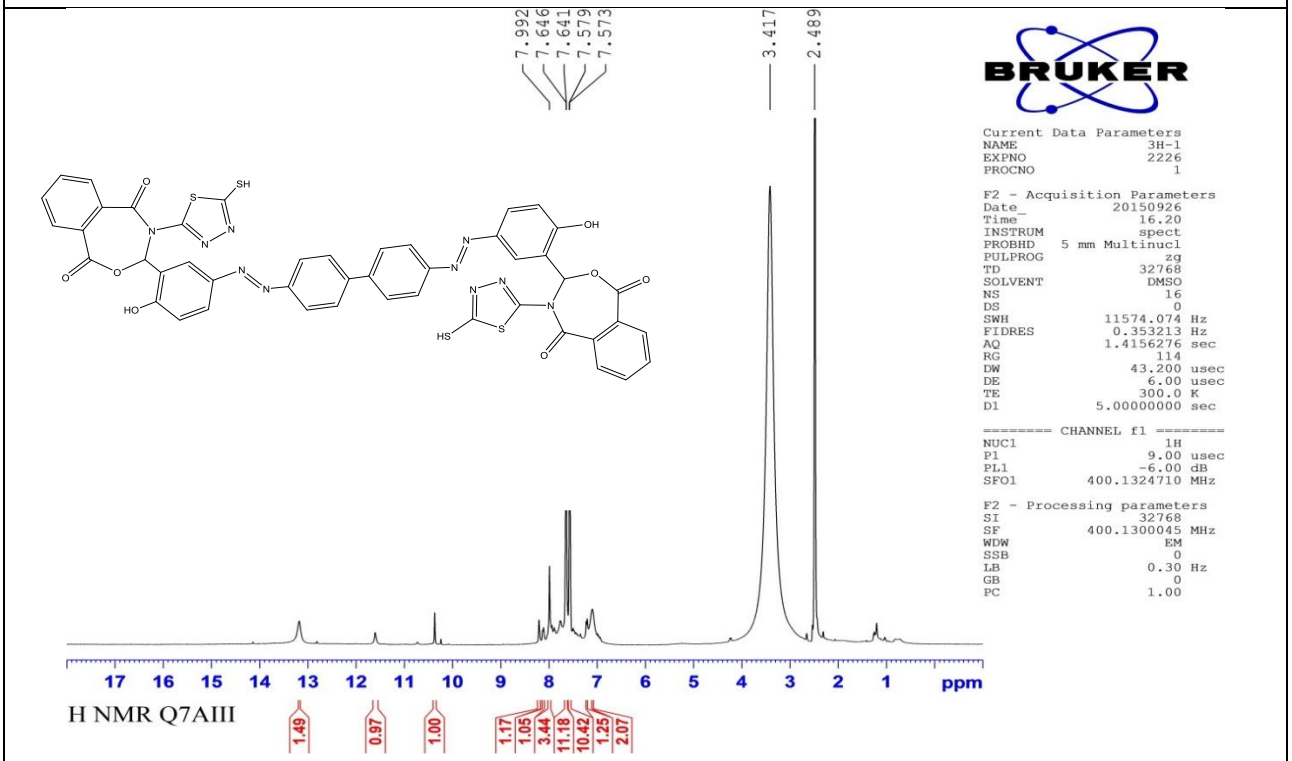

Figure (8) : 1H NMR spectrum of compound 3b

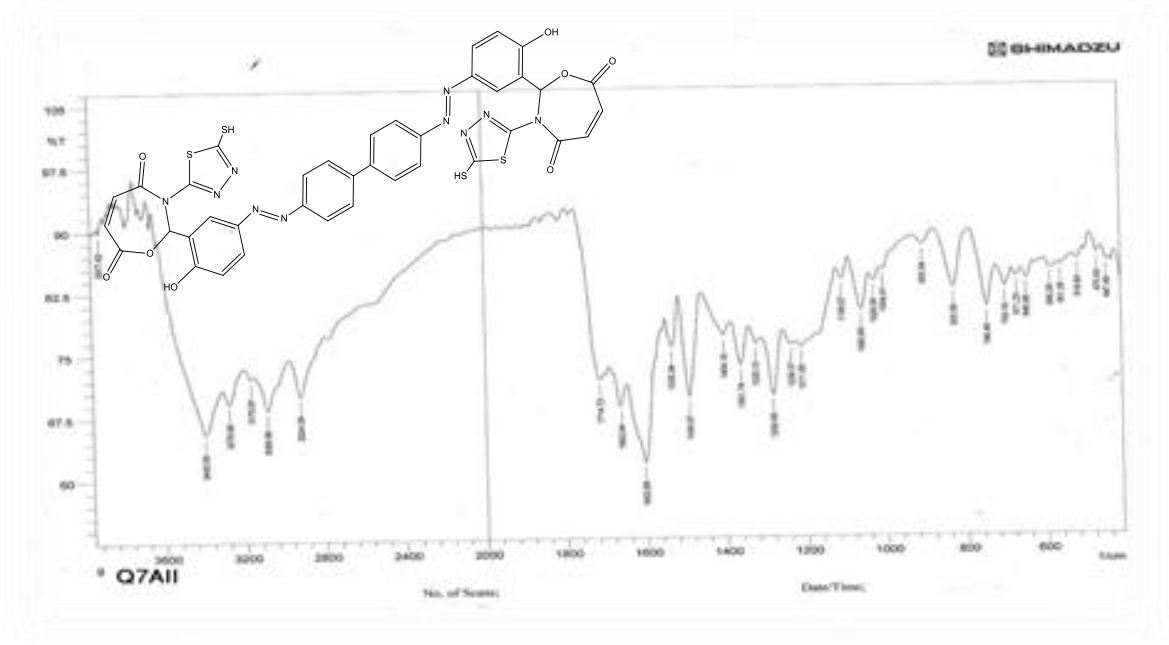

Figure (14) FT-IR spectrum of compound 9a