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Synthesis of New -1,3,4-Thiadiazoles Substituted with Oxazepine and Benzoxazepine Moieties

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ABSTRACT

2-amino-5-mercapto-1,3,4-thiadiazole 1 was introduced in condensation reaction with terephthaldehyde to yield bis-imine derivative 2. Compound 1 was also converted to the corresponding diazonium salt which was introduced in coupling reactions with alkaline solution of 2-hydroxybenzaldehyde and 4-hydroxybenzaldehyde as coupling reagents to give azo derivatives 4a and 4b containing aldehyde group, respectively. The resulting aldehydes 4a and 4b were then introduced in condensation reactions with 2-amino-5-mercapto-1,3,4-thiadiazole 1 to obtain the imines 5a and 5b respectively. The resulting imines 2, 5a and 5b were treated with both maleic and phthalic anhydrides, respectively, under (2+5) cycloaddition conditions afforded eight new bis-1,3,4-thiadiazoles substituted with 1,3-oxazepine and 1,3-benzoxazepine moieties (3a, 3b) and (6a-d)respectively. The new synthesized thiadiazoles have some biological, pharmaceutical and medicinal applications.

Keywords: 1,3,4-thiadiazoles, 2-amino-5-mercapto-1,3,4-thiadiazole, imines, 1,3-oxazepines, 1,3-benzoxazepines , heterocyclic, bis-diazonium, terephthaldehyde.

INTRODUCTION

Thiadiazoles are clear to yellowish liquids which are soluble in alcohol, ether and slightly soluble in water; they are starting material for numerous chemical compounds including sulphur drugs[1]. Thiadiazoles are easily metabolized by biochemical reactions and they are non-carcinogenic in nature[2]. Thiadiazoles and their derivatives exhibit wide range of pharmacological activities such as antimicrobial activity[3], antidepressant, cardiotonic[4], antibacterial activity against *Klebsiella pneumonia*[5], antitubercular[6,7], anticonvulsant[8], antileshmanial , analgesic[9], antiinflammtory[10], anticancer[11], phosphodiesterase inhibitors[12] and effect on Tyrosinase enzyme[13]. This diversity of biological activity may be due to the presence of -N=C-S moity[14,15]. There are four isomers of thiadiazole , among these four isomers 1,3,4-thiadiazole is the most thermally stable; which is only isomer doesn´t contain any sulphur- nitrogen bond[16]. 1,3,4-thiadiazole relatively stable in aqueous acid solutions but the nucleus can undergo ring cleavage by aqueous base solutions[17].

Heterocyclic seven-membered ring constitutes the core or a key fragment of a number of bioactive compounds including isolated from natural products, oxazepine derivatives were found to exhibit a vast variety of biological activities[18] and found to be a vital moiety in many psychoactive pharmaceuticals[19]. Thus, in this article, we reported here the synthesis of 1,3,4-thiadiazole derivatives containing biologically active oxazepine and benzoxazepine moieties, which might have some biological activity.

EXPERIMENTAL

General

The chemicals used were purchased from Merck & Co., BDH, Sigma Aldrich and CDH and were used without further purification.Silica TLC plates were used with an aluminum backing (0.2 mm, 60 F_{254}). The progress of reactions were monitored by TLC and visualized by development of the TLC plates with iodine vapor. Melting points were determined on an Electro thermal Stuart SMP 30 capillary melting point apparatus. Infrared spectra were recorded on SHIMADZU FTIR-8400S Infrared Spectrophotometer as potassium bromide discs. ^{1}H NMR spectra were collected on NMR spectrometer, Broker 2009 spectrometer at 400 MHz in DMSO-*d6* as solvent and TMS as an internal standard at Kashan University, Iran. Elemental Analysis (CHNS) was carried out with Perkin Elmer 300A Elemental Analyzer at Kashan University, Iran.Azoaldehyde derivatives 4a and 4b were prepared following the method described by Acton[20].

Chemical methods

Synthesis of 5,5'-(((1E,1'E)-1,4-phenylenebis (methanylidene))bis(azanylylidene))bis(1,3,4-thiadiazole-2-thiol) 2:

Terephthaldehyde(0.67 g, 5 mmol) was dissolved in (35 ml) of absolute ethanol, then 2-amino-5-mercapto-1,3,4-thiadiazole 1 (1.33 g , 10 mmol) was added. The reaction mixture was refluxed with stirring on a water bath at 65°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}): 3194_{br} ($\nu_{N-H,\ thione\ form\ and\ hydrogen\ bonded,\ thione\ form}$ $\nu_{C-H,\ benzene,\ vib.\ coupling}$), 2972 and 2885 ($\nu_{N-H,\ intramolecularly\ hydrogen\ bonded,\ thione\ form}$), 1691($\nu_{C=N,\ imine}$), 1562 and 1508($\nu_{C=C,\ benzene\ and}$ $\nu_{C=N,\ thiadiazole,\ vib.\ coupling}$), 1051 ($\nu_{C=S,\ thione\ form}$), 750 ($\delta_{o.o.p.\ C-H,\ benzene}$); ^{1}H NMR: δ =2.5 (DMSO solvent), 3.4 (H_2O in DMSO), 7.09–8.17 (m, 4H, Ar-H), 8.8 (s, 2H, 2×CH=N, imine), 10.09 (s, 2H, 2×N-H, thione forms), 13.17 (s, 2H, 2×S-H, thiol forms)[21]

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

A mixture of bisimine derivative 2 (0.364 g, 1 mmol)and maleic or phthalic anhydride (2 mmol) in dry benzene (20 ml) was refluxed on a water bath at 70°C for 20 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'-(1,4-phenylene)bis(3-(5-mercapto-1,3,4-thadiazol-2-yl)-2,3-dihydro-1,3-oxazepine-4,7-dione) 3a:

IR (cm^{-1}): 3134 (ν N-H, thione form), 3007 (νC-H, benzene), 1699 (νC=O, O=C-O and O=C-N, oxazepine, vib. coupling), 1564 and 1510 (νC=C, benzene and νC=N, thiadiazole, vib. coupling), 1053 (νC=S, thione form), 752 (δo.o.p. C-H, benzene); ^{1}H NMR: d (ppm) = 6.2 and 6.6 (ss, 4H, 4×olefinic =CH, oxazepine), 7.10–8.16 (m, 6H, Ar–H and C–H, oxazepine), 10.1 (s, 2H, 2×N–H, thione forms, 13.2 (s, 2H, 2×S–H, thiol forms[21]. The singlet signals around 2.5 ppm and 3.3 ppm attributed to DMSO and absorbed H_2O in DMSO, respectively.Anal.Calcd.for $C_{20}H_{12}N_6O_6S_4$: C, 42.85; H, 2.16; N, 14.99; S, 22.88 Found C, 42.52; H, 2.19; N, 15.22; S, 22.51.

3,3'-(1,4-phenylene)bis(4-(5-mercapto-1,3,4-thadiazol-2-yl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione) 3b:

IR (cm^{-1}): 3144 (νN-H, thione form), 3076 and 3016 (νC-H, benzene), 2989 and 2895 ($\nu_{N-H,\ intramolecularly\ hydrogen\ bonded,\ thione\ form}$), 2740 (ν C-H, oxazepine), 2654 and 2526 (νS-H, thiol form), 1695 (ν C=O, O=C-O and O=C-N, oxazepine, vib. coupling), 1564 and 1498 (ν C=C, benzene and ν C=N, thiadiazole, vib. coupling), 1062 (ν C=S, thione form), 798 and 742 (δo.o.p. C-H, benzene); ^{1}H NMR: d (ppm) = 7.08–8.14 (m, 14H, Ar–H and C–H, oxazepine), 10.1 (s, 2H, 2× N–H, thione forms), 13.16 (s, 2H, 2×S–H, thiol forms). The singlet signals around 2.5 ppm and 3.3 ppm attributed to DMSO and absorbed H_2O in DMSO, respectively.

Anal.Calcd. for $C_{28}H_{16}N_6O_6S_4$: C, 50.90 ; H, 2.44; N, 12.72; S, 19.41 Found C, 51.23; H, 2.62; N, 12.43; S, 19.55.

Synthesis of azo-aldehyde derivatives (4a, 4b):

were prepared following the method described by Acton[20].

2-hydroxy-5-((5-mercapto-1,3,4-thiadiazol-yl)diazenyl)benzaldehyde 4a:

IR (cm^{-1}): 3281_{br} (ν_{O-H}), 3093 ($\nu_{N-H, thione form}$ and $\nu_{C-H, benzene, vib. coupling}$), 2953 ($\nu_{N-H, intramolecularly hydrogen bonded, thione form}$), 1629 ($\nu_{C=O, aldehyde}$), 1556 and 1498($\nu_{C=C, benzene}$ and $\nu_{C=N, thiadiazole, vib. coupling}$), 1037($\nu_{C=S, thione form}$), 833 ($\delta_{o.o.p. C-H, benzene}$)); ^{1}H NMR: d (ppm) = 6.93–7.81 (m, 3H, Ar–H), 10.2 (s, 1H, O=CH, aldehyde), 10.7 (s, 1H, O-H), 13.1 (s, 1H, S–H)[20]. The singlet signals around 2.48 ppm and 3.85 ppm attributed to DMSO and absorbed H_2O in DMSO, respectively.

4-hydroxy-5-((5-mercapto-1,3,4-thiadiazol-yl)diazenyl)benzaldehyde 4b:

IR (cm^{-1}): 3284_{br} (ν_{O-H}), 3095_{br} ($\nu_{N-H, thione form}$ and $\nu_{C-H, benzene, vib. coupling}$), 2962 and 2899 ($\nu_{N-H, intramolecularly hydrogen bonded, thione form}$), 2829 and 2700 ($\nu_{C-H, aldehyde}$), 1627 ($\nu_{C=O, aldehyde}$), 1552 and 1498($\nu_{C=C, benzene}$ and $\nu_{C=N, thiadiazole, vib. coupling}$), 1039($\nu_{C=S, thione form}$), 837 ($\delta_{o.o.p. C-H, benzene}$); ^{1}H NMR: d (ppm) = 6.90–7.74 (m, 3H, Ar–H), 8.8 (s, 1H, O-H), 9.7 (s, 1H, O=CH, aldehyde), 12.34 (s, 1H, S–H)

General procedure for the synthesis of azoimine derivatives (5a, 5b):

Azoaldehyde derivatives 4a or 4b(0.665 g, 2.5 mmol) was dissolved in (30 ml) of absolute ethanol, then 2-amino-5-mercapto-1,3,4-thiadiazole 1 (0.3325 g , 2.5 mmol) was added. The reaction mixtures were refluxed with stirring on a water bath at 65 °C for 10 h and monitored by TLC. The mixtures were then allowed to cool down to room temperature , the colored precipitates were filtered and recrystallized from ethanol.

4-((E)-(5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl-2-((E)-((5-mercapto-1,3,4-thiadiazole-2-yl)imino)methyl)phenol 5a:

IR (cm^{-1}): 3269_{br} (ν_{O-H}), 3109 ($\nu_{N-H, thione form}$ and νC-H, benzene, vib. coupling), 2943 ($\nu_{N-H, intramolecularly hydrogen bonded, thione form}$), 1620 ($\nu_{C=N, imine}$), 1554 and 1498($\nu_{C=C, benzene}$ and ν C=N, thiadiazole, vib. coupling), 1051 ($\nu_{C=S, thione form}$), 752 ($\delta_{o.o.p. C-H, benzene}$); ^{1}H NMR: d (ppm) = 7.00–7.77 (m, 4H, Ar–H and HC=N, imine), 10.2 (s, 1H, O-H), 13.16 (s, 2H, 2×S–H)[20].

2-((E)-(5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl-4-((E)-((5-mercapto-1,3,4-thiadiazole-2-yl)imino)methyl)phenol 5b:

IR (cm^{-1}): 3267_{br} (ν_{O-H}), 3099_{br} ($\nu_{N-H, thione form}$ and $\nu_{C-H, benzene, vib. coupling}$), 2949 and 2802 ($\nu_{N-H, intramolecularly hydrogen bonded, thione form}$), 2584 ($\nu_{S-H}$), 1610 ($\nu_{C=N, imine}$), 1554 and 1502($\nu_{C=C, benzene}$ and $\nu_{C=N, thiadiazole,vib. coupling}$), 1051($\nu_{C=S, thione form}$), 752 and 715 ($\delta_{o.o.p. C-H, benzene}$); ^{1}H NMR: d (ppm) = ^{1}H NMR: d (ppm) = 6.9–7.7 (m, 3H, Ar–H), 8.8 (s, 1H, N=CH, imine), 9.6 and 9.7 (ss, 2H, 2×N-H, thione forms), 10.5 (s, 1H, O-H), 13.4 (s, 2H, 2×S–H, thiol forms).

General procedure for the synthesis of oxazepine and benzoxazepine derivatives 6a-d:

A mixture of azoimine derivatives 5a or 5b (0.381 g, 1 mmol)and maleic or phthalic anhydride (1 mmol) in dry benzene (20 ml) was refluxed on a water bath at 70°C 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-hydroxy-5-((5-mercapto-1,3,4-thiadiazole-2-yl)diazenyl)phenyl)-3-(5-mercapto-1,3,4-thiadiazole-2-yl)-2,3-dihydro-1,3-oxazepine-4,7-dione 6a:

IR (cm^{-1}): 3280_{br} (νO-H), 3105_{br} (νN-H, thione form and νC-H, benzene, vib. coupling), 2949 and 2791 ($\nu_{N-H, intramolecularly hydrogen bonded, thione form}$), 2708 ($\nu$C-H, oxazepine), 2536 ($\nu_{S-H}$), 1640 ($\nu$C=O, O=C-O and O=C-N, oxazepine, vib. coupling), 1552 and 1498 (νC=C, benzene and νC=N, thiadiazole, vib. coupling), 1055 (νC=S, thione form), 756 (δo.o.p. C-H, benzene); ^{1}H NMR: d (ppm) = 6.2 and 6.6 (ss, 2H, 2×olefinic =CH, oxazepine), 7.13–8.19 (m, 4H, Ar–H and C–H, oxazepine), 10.35 (s, 1H, O-H), 13.16 (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. Anal.Calcd.for $C_{15}H_9N_7O_4S_4$: C, 37.57; H, 1.89; N, 20.45; S, 26.75 Found C, 37.28; H, 2.09; N, 20.22; S, 26.47.

(E)-3-(2-hydroxy-3-((5-mercapto-1,3,4-thiadiazole-2-yl) diazenyl) phenyl)-4-(5-mercapto-1,3,4-thiadiazole-2-yl)-3,4-dihydrobenzo [e] [1,3] oxazepine-1,5-dione 6b:

IR (cm^{-1}): 3267br (νO-H), 3086_{br} (νN-H, thione form and νC-H, benzene, vib. coupling), 2955 and 2806 ($\nu_{N-H,\ intramolecularly\ hydrogen\ bonded,\ thione\ form}$), 2700 (νC-H, oxazepine), 2525 (ν_{S-H}), 1691 (νC=O, O=C-O, oxazepine), 1631 (O=C-N, oxazepine), 1554 and 1500 (νC=C, benzene and νC=N, thiadiazole, vib. coupling), 1062 (νC=S, thione form), 798 (δ o.o.p. C-H, benzene); ^{1}H NMR: d (ppm) = 7.34–7.64 (m, 8H, Ar–H and C–H, oxazepine), 7.79 (s, 1H, O-H), 13.16 (s, 2H, 2×S–H)..Anal.Calcd.for $C_{19}H_{11}N_7O_4S_4$: C, 43.09; H, 2.09; N, 18.51; S, 24.22 Found C, 43.36; H, 2.22; N, 18.21; S, 24.54.

2-(4-hydroxy-3-((5-mercapto-1,3,4-thiadiazole-2-yl)diazenyl)phenyl)-3-(5-mercapto-1,3,4-thiadiazole-2-yl)-2,3-dihydro-1,3-oxazepine-4,7-dione 6c:

IR (cm^{-1}): 3281_{br} (νO-H), 3078 (νN-H, thione form and νC-H, benzene, vib. coupling), 2962 and 2891 ($\nu_{N-H,\ intramolecularly\ hydrogen\ bonded,\ thione\ form}$), 2829 (νC-H, oxazepine), 1705 (νC=O, O=C-O, oxazepine), 1631 (O=C-N, oxazepine), 1550 and 1500 (νC=C, benzene and νC=N, thiadiazole, vib. coupling), 1039 (νC=S, thione form), 866 (δo.o.p. C-H, benzene); ^{1}H NMR: d (ppm) = 6.24 and 6.59 (ss, 2H, 2×olefinic =CH, oxazepine), 7.13–7.32 (m, 4H, Ar–H and C–H, oxazepine), 8.78 (s, 1H, O-H), 9.5 (s, 2H, 2×S–H).Anal.Calcd. For $C_{15}H_9N_7O_4S_4$: C, 37. 57 ; H, 1.89; N, 20. 45 ; S, 26.75 Found C, 37.32; H, 2.06; N, 20.14; S, 27.07.

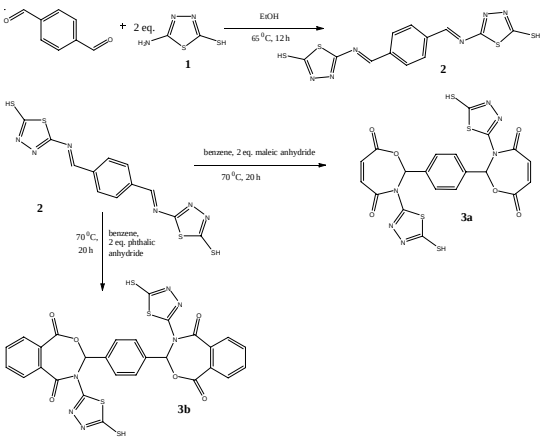
(E)-3-(4-hydroxy-3-((5-mercapto-1,3,4-thiadiazole-2-yl)diazenyl)phenyl)-4-(5-mercapto-1,3,4-thiadiazole-2-yl)-3,4-dihydrobenzo [e] [1,3]oxazepine-1,5-dione 6d:

IR (cm^{-1}): 3277_{br} (νO-H), 3091 (νN-H, thione form and íC-H, benzene, vib. coupling), 2954 ($\nu_{N-H,\ intramolecularly\ hydrogen\ bonded,\ thione\ form}$), 2655 (νC-H, oxazepine), 2530 (νS-H), 1691 (νC=O, O=C-O, oxazepine), 1629 (O=C-N, oxazepine), 1552 and 1500 (νC=C, benzene and νC=N, thiadiazole, vib. coupling), 1070 and 1055 (νC=S, thione forms), 802 and 740 (δo.o.p. C-H, benzene); ^{1}H NMR: d (ppm) = 7.34–7.65 (m, 8H, Ar–H and C–H, oxazepine), 7.80 (s, 1H, O-H), 13.16 (s, 2H, 2×S–H).Anal.Calcd. For $C_{19}H_{11}N_7O_4S_4$: C, 43.09; H, 2.09; N, 18.51; S, 24.22 Found C, 42.88; H, 2.15; N, 18.77; S, 24.48.

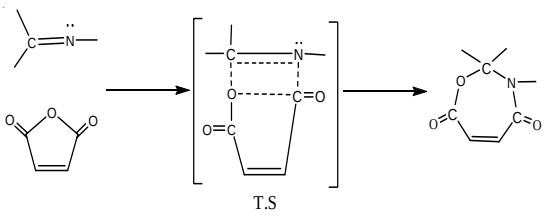
RESULTS AND DISCUSSION

Chemistry

The precursor bisimine2 was synthesized by reacting terephthaldehyde with 2-amino-5-mercapto-1,3,4-thiadiazole 1 in absolute ethanol. Compound 2 was reacted with maleic and phthalic anhydrides to give the bis-1,3-oxazepine and bis-1,3-benzoxazepine derivatives of 1,3,4-thiadiazole 3a and 3b respectively in Scheme (1). The proposed mechanism for the addition of cyclic anhydride to imine was shown in Scheme (2).



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



Scheme. 2. Proposedmechani sm for the formation of oxazepinering.

The chemical structures of these newly oxazepines were confirmed by IR, ^{1}H NMR spectral measurements and (CHNS) elemental analysis and were in good agreement with the proposed structures.

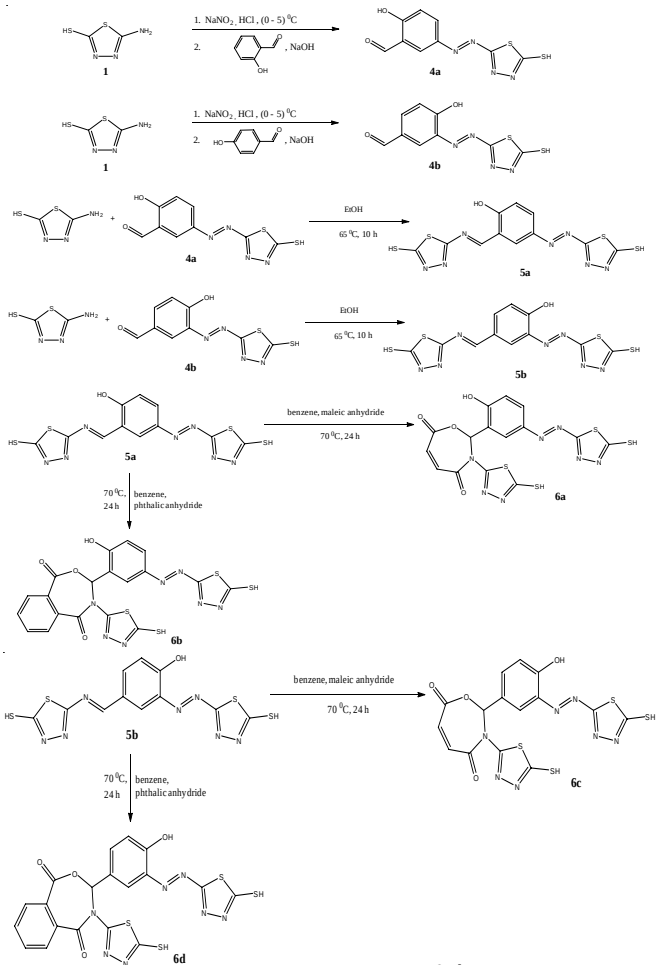
The IR spectrum of bis-imine 2 showed the stretching absorption band of the (C=N) function at 1691 cm^{-1}, while the absorption bands due to (NH_2) group at 3336 and 3267 cm^{-1} have disappeared.The broad absorption band at 3194 attributed to the (N-H)str. in thione form. The stretching band of (C=S) function in thione form

appeared as strong band at 1051 cm^{-1}. The IR spectra of compounds 3a and 3b indicated the absence of (C=N) absorption band and the appearance of (C=O)str. for oxazepine ring at 1699 and 1695 cm^{-1}, respectively.

The ^1H NMR spectrum of bisimine 2 showed the (HC=N) protons as a singlet at δ 8.8 ppm, the (N-H) protons of thione forms appeared as a singlet at 10.09 ppm, the (Ar-H) protons at δ 7.09 — 8.17 ppm. Moreover, the spectrum showed the (SH) protons asa singlet at 13.17 ppm.[21].

The ^1H NMR spectra of oxazepine compounds 3a and 3b showed the disappearance of the (CH=N) protons at 8.8 ppm, the thioic (S-H) protons appeared as a singlet at δ 13.2 and 13.16 ppm, respectively. The (N-H) protons for thione forms as a singlet at 10.1. The signals of aromatic protons (Ar–H) and (C–H) protons of oxazepine rings appeared at δ 7.08-8.16 ppm. Moreover, the olefinic (=CH) protons of the oxazepine rings in compound 3a appeared as singlet at 6.2 and 6.6 ppm.

The initiators azoaldehydes4a and 4b were synthesized by reacting the diazonium salt of 2-amino-5-mercapto-1,3,4-thiadiazole 1 with alkaline solutions of 2-hydroxybenzaldehyde and 4-hydroxybenzaldehyde respectively using the method described by acton[20]. The resulting aldehydes 4a and 4b werecondensed with 2-amino-5-mercapto-1, 3, 4-thiadiazole 1 in absolute ethanol to give the azoimine derivatives 5a and 5b respectively. The resulting imines 5a and 5b were allowed to react with maleic and phthalic anhydrides leading to the formation of oxazepine-1,3,4-thiadiazole derivatives 6a-d respectively (Scheme 4).



Scheme. 3. Synthesis of oxazepines 6a-d.

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

The IR spectra of azoaldehde derivatives 4a and 4b indicated the absence of the doublet band at 3336 and 3267 cm^{-1} for (-NH_2)str. and appearance of broad band at 3281 and 3284 cm^{-1} assigned to (O-H)str., the absorption band at 1629 and 1627 cm^{-1} belong to the aldehydic (C=O)str., respectively. The IR spectra of imine derivatives 5a and 5b showed the disappearance of the absorption bands at 1629 and 1627 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 bands attributed to (C=N)str.appeared at 1620 and 1610 cm^{-1}, respectively. In the IR spectra of oxazepine compounds 6a-d, the stretching absorption band due to the stretching of (C=O, oxazepine) was found at 1640, (1691 and 1631), (1705 and 1631), (1691 and 1629) cm^{-1}, respectively, while the absorption bands due to (C=N)str. at 1620 and 1610 cm^{-1} have disappeared.

The ^{1}H NMR spectra of azoaldehyde compounds 4a and 4b showed the (S-H) proton as a singlet at δ 13.1 and 12.34 ppm[20] .the (O-H) proton appeared as a singlet at 10.7 and 8.8 ppm, the (HC=O) proton as a singlet at δ10.2 and 9.7 ppm, , the (Ar-H) protons at δ 6.90—7.81 ppm.

The ^{1}H NMR spectra of imine compounds 5a and 5b showed the (S-H) proton as a singlet at δ 13.6 and 13.4 ppm, the (O-H) proton appeared as a singlet at 10.2 and 10.5 ppm, the (HC=N) proton as a singlet at δ 7.77 and 8.8 ppm, , the (Ar-H) protons at δ 6.90 —7.77 ppm.

Table. 1: Physical Properties Of The Synthesized Compounds.

Product	Physical state	R_f(developer)	m.p. (°C)	Yield (%)
2	Light yellow solid	0.64 (Toluene/ EtOH, 7:3)	186-188	79
3a	Light yellow solid	0.81 (Toluene/ EtOH, 7:3)	148-150	77
3b	Light yellow solid	0.78 (Toluene/ EtOH, 7:3)	170-172	79
4a	Dark orange solid	0.54 (Toluene/ EtOH, 7:3)	181-183	61
4b	Dark orange solid	0.49 (Toluene/ EtOH, 7:3)	129-131	55
5a	Orange solid	0.57 (Toluene/ EtOH, 7:3)	179-181	70
5b	Orange solid	0.73 (Toluene/ EtOH, 7:3)	178-180	71
6a	Dark yellow solid	0.8 (Toluene/ EtOH, 7:3)	163-165	78
6b	Dark yellow solid	0.75 (Toluene/ EtOH, 7:3)	161-163	80
6c	Orange solid	0.56 (Toluene/ EtOH, 7:3)	123-125	79
6d	Dark yellow solid	0.72 (Toluene/ EtOH, 7:3)	156-158	81

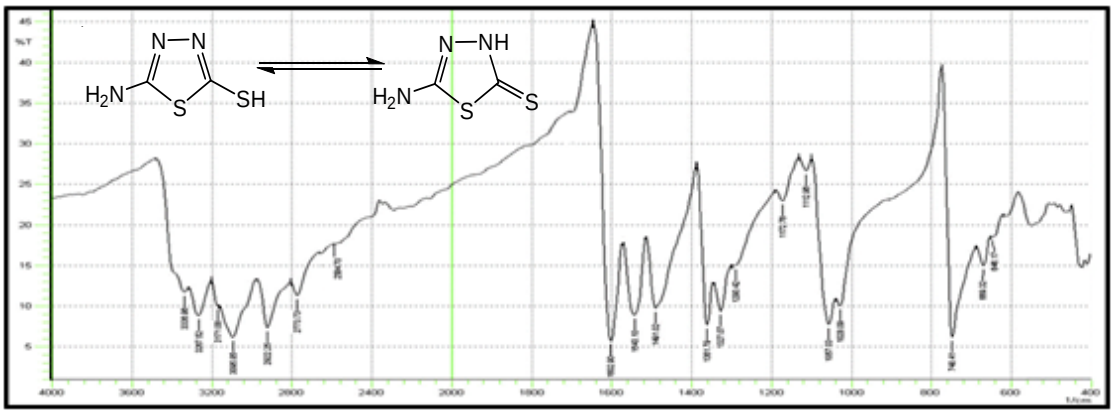
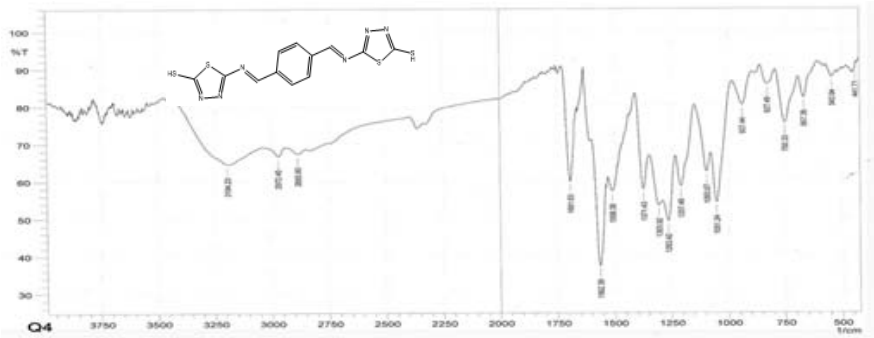


Fig. 1. FTIR spectrum of compound 1



Figu. 2. FTIR spectrum of compound 2

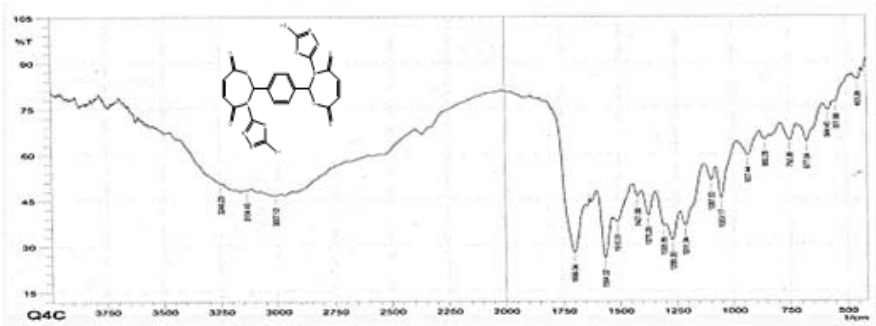


Fig. 3. FTIR spectrum of compound 3a

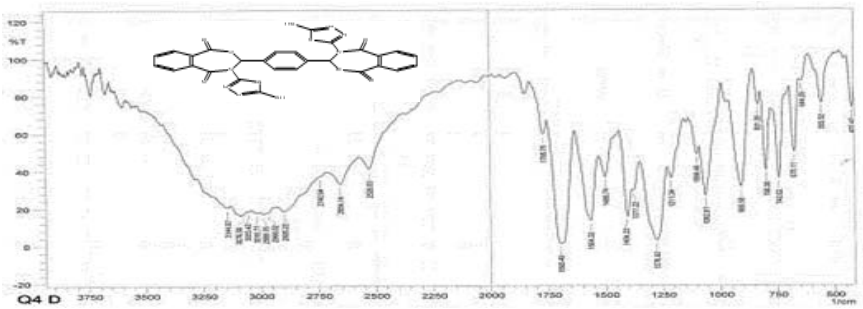


Fig. 4. FTIR spectrum of compound 3b

The ^{1}H NMR spectra of oxazepine compounds 6a-d showed the disappearance of the (CH=N) protons at 7.77 and 8.8 ppm, the (S-H) proton appeared as a singlet at δ 13.6, 13.6, 9.5 and 13.16 ppm, respectively. The (O-H) proton as a singlet at 10.35, 7.79, 8.78 and 7.80 ppm. The signals of aromatic protons (Ar–H) and (C–H) proton of oxazepine rings appeared at δ 7.13-8.19 ppm. Moreover, the olefinic (=CH) protons of the oxazepine ring in compounds 6a and 6c appeared as a singlets at (6.2, 6.6) and (6.24, 6.59) ppm, respectively.

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

The IR spectrum of bis-azoaldehde derivative 7 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 8 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 9a and 9b showedthe 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 biological activity of the synthesized oxazepines of 1,3,4-thiadiazole 3a, 3b and6a-dwill be measured in subsequent study.

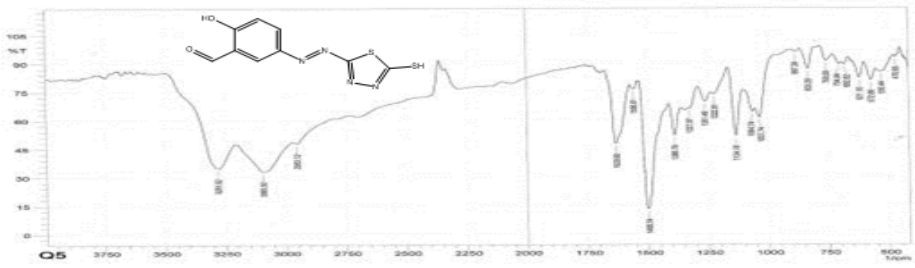


Fig. 5. FTIR spectrum of compound 4a

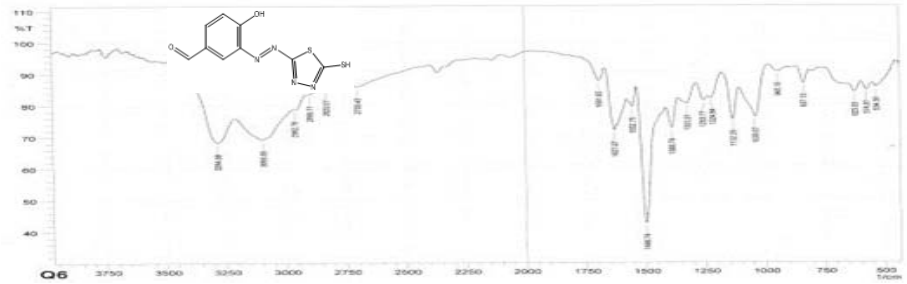


Fig. 6. FTIR spectrum of compound 4b

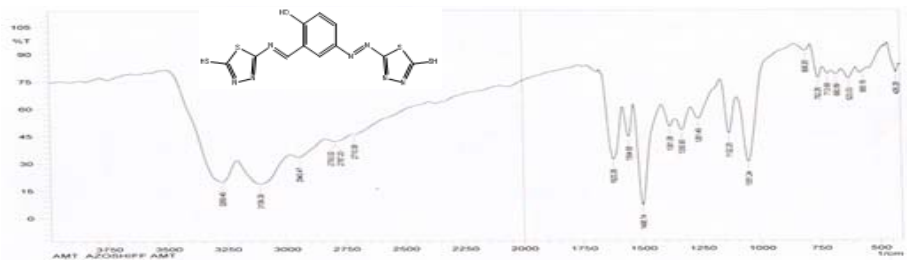


Fig. 7. FTIR spectrum of compound 5a

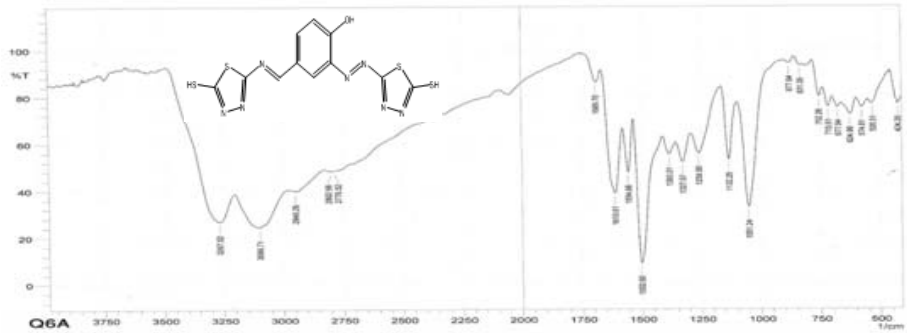


Fig. 8. FTIR spectrum of compound 5b

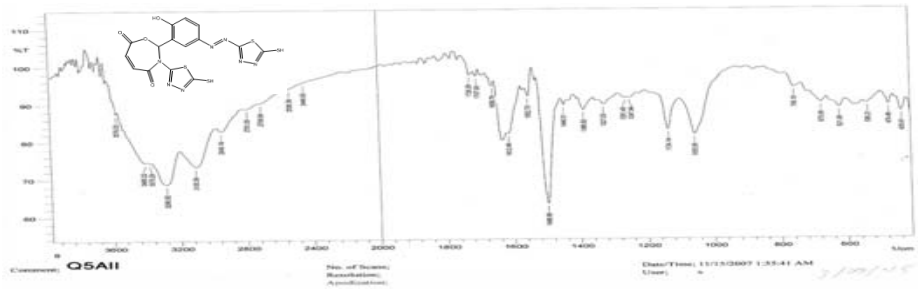


Fig. 9. FTIR spectrum of compound 6a

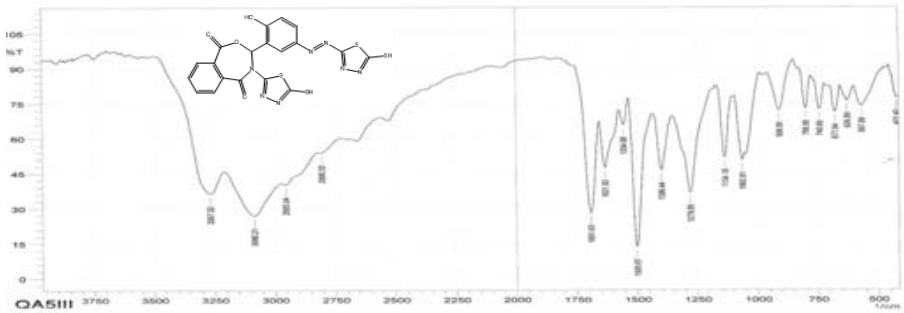


Fig. 10. FTIR spectrum of compound 6b

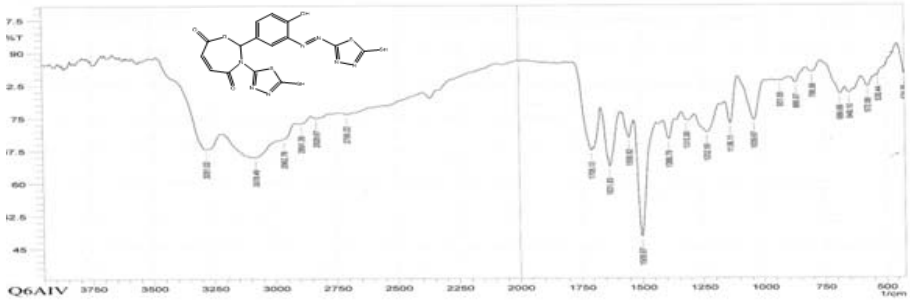


Fig. 11. FTIR spectrum of compound 6c

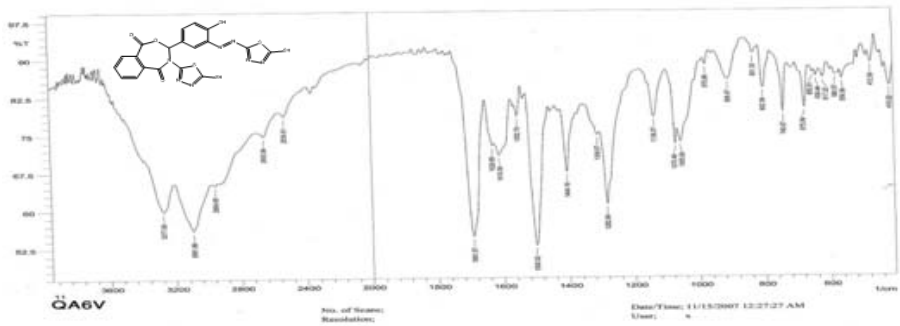


Fig. 12. FTIR spectrum of compound 6d

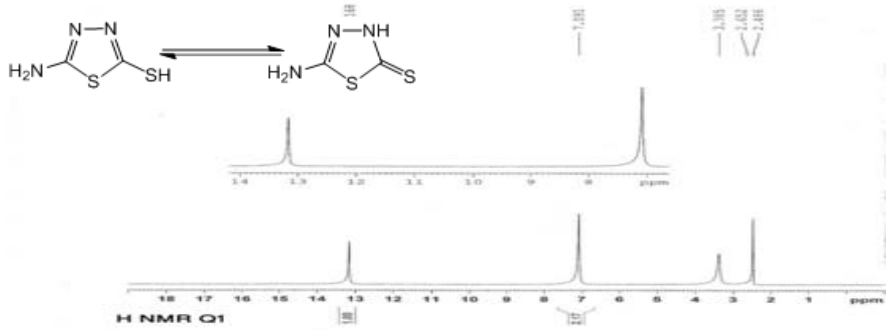


Fig. 13. [1]HNMR spectrum of compound 1

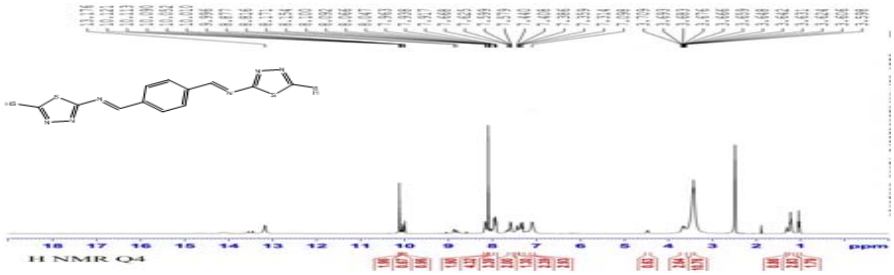


Fig. 14. [1]HNMR spectrum of compound 2

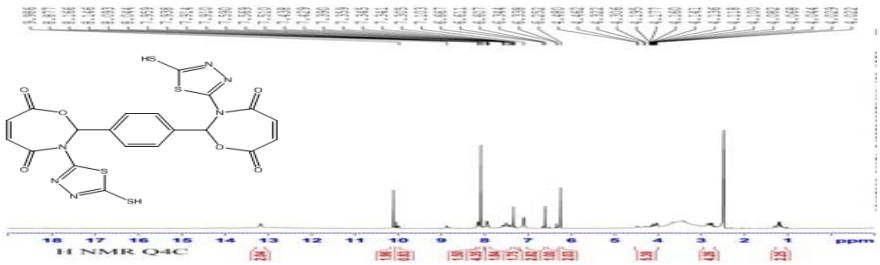


Fig. 15. [1]HNMR spectrum of compound 3a

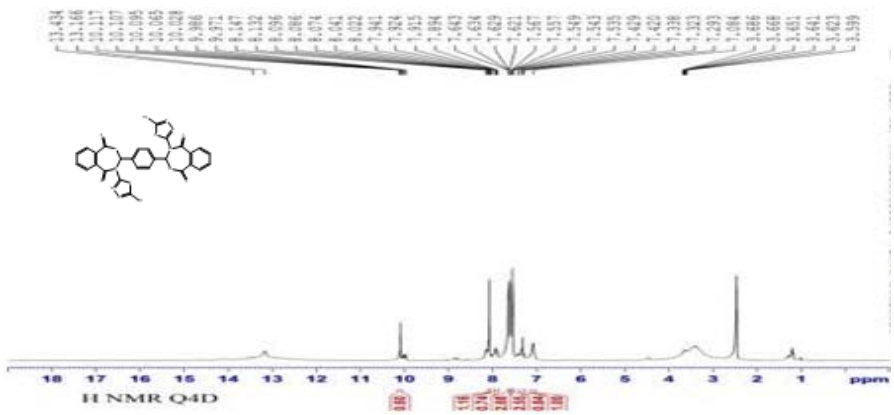


Fig. 16. [1]HNMR spectrum of compound 3b

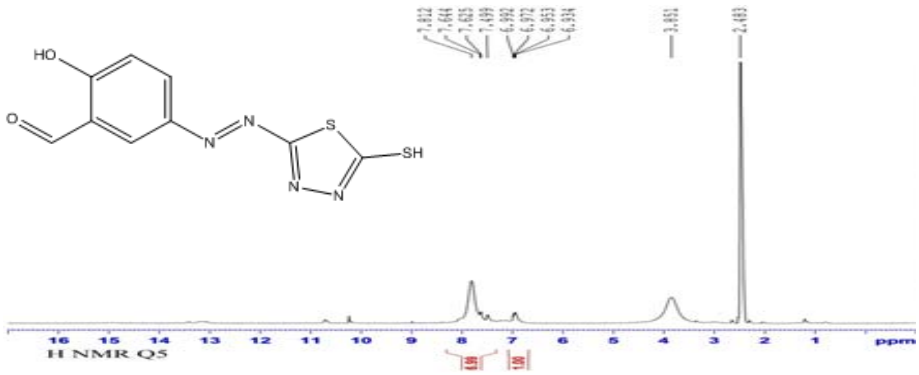


Fig. 17. [1]HNMR spectrum of compound 4a

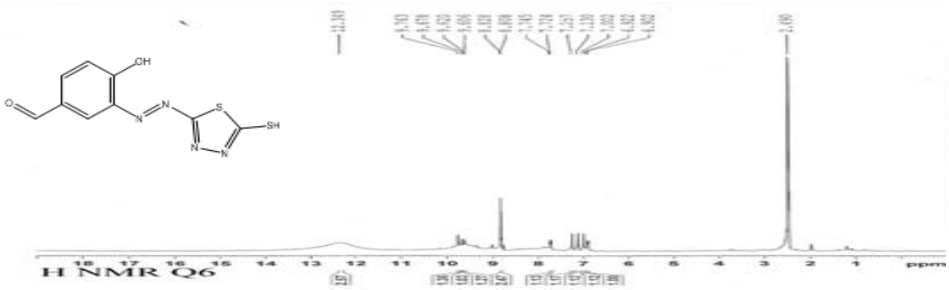


Fig. 18. [1]HNMR spectrum of compound 4b

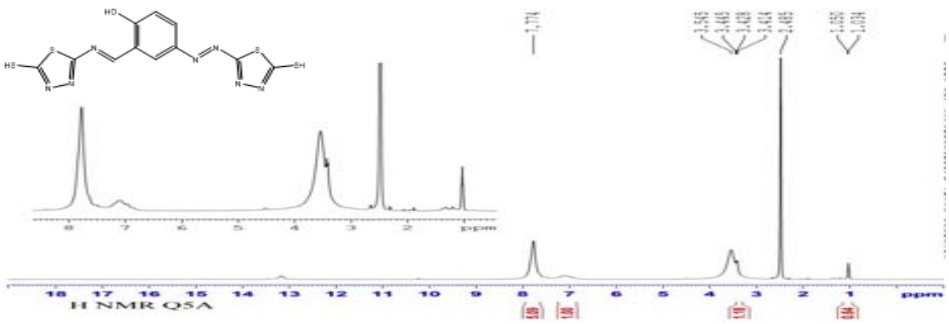


Fig. 19. [1]HNMR spectrum of compound 5a

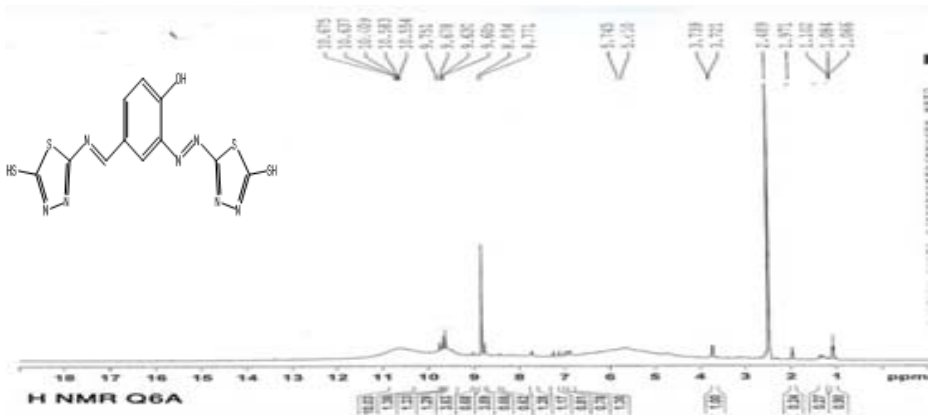


Fig. 20. [1]HNMR spectrum of compound 5b

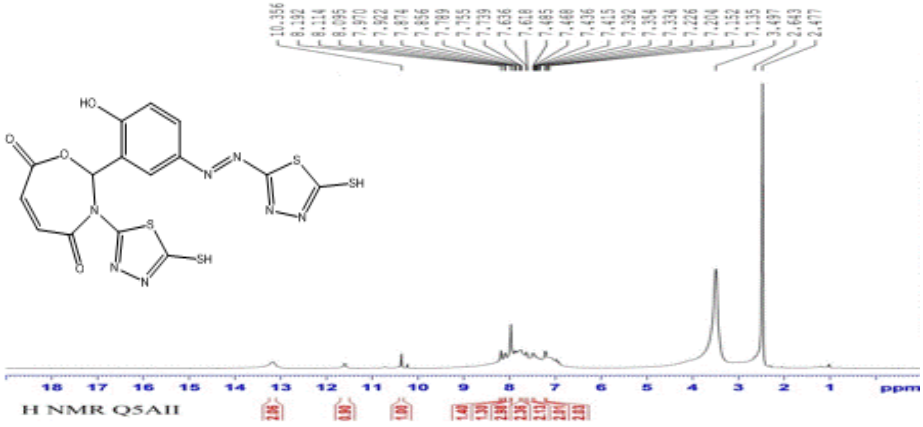


Fig. 21. 1HNMR spectrum of compound 6a

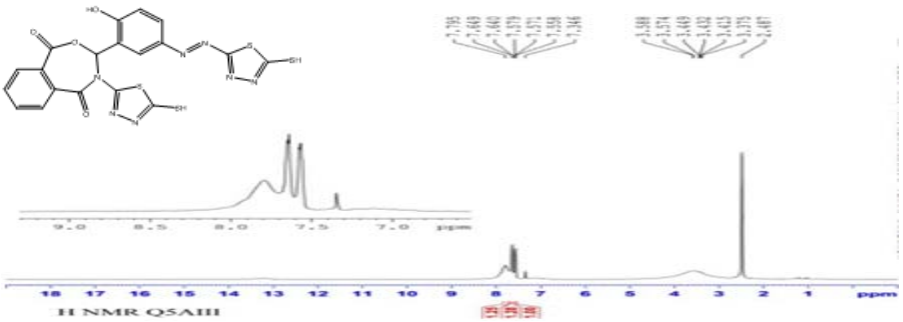


Fig. 22. [1]HNMR spectrum of compound 6b

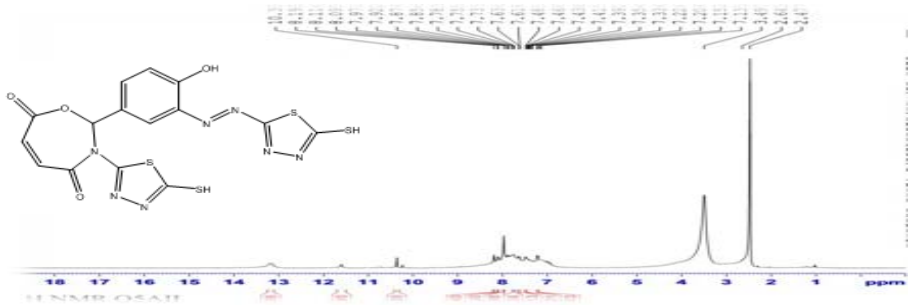


Fig. 23. [1]HNMR spectrum of compound 6c

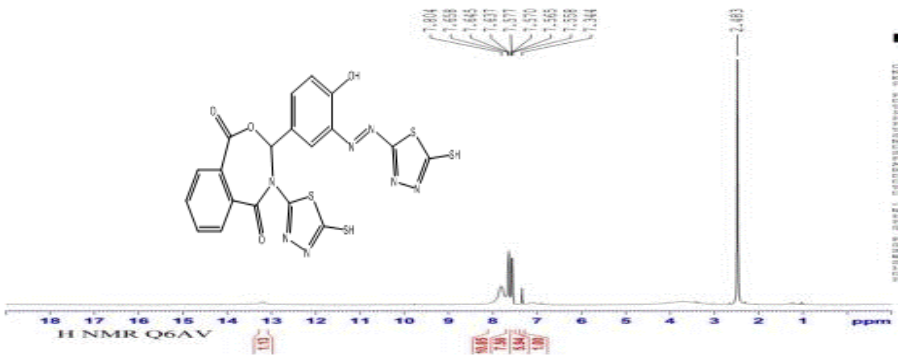


Fig. 24. [1]HNMR spectrum of compound 6d

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