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Synthesis and Characterization of some 5, 5^{-}-Ethyl Bis- (4-Amino-4*H*-1, 2, 4-Triazole-3-Thiol) Derivatives

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Abstract A new series of heterocyclic compounds including five, six and seven membered rings have been synthesized. These compounds including essential parent compound bis-(4-amino-1,2,4-triazol-3-thiole) were synthesized by the condensation reaction of thiocarbohydrazide with succinic acid by the direct fusion for 10-15 minutes. New Schiff bases (3-5) were also synthesized by dry condensation reaction of bis trizole [2] derivatives with substituted aldehydes and ketone using MW method. The cycloaddition reaction of the Schiff bases (3-5) with (maleic, succinic, phathalic)anhydrides,anthranilic acid, and sodium azide gave a new bis- (1,3-oxazepine, quinazoline, tetrazol) derivatives respectively [6-17]. All of the prepared compounds were characterized by FT-IR and ^{1}H-NMR spectra.

Keywords Schiff bases, Fused Triazole, Tetrazol, Oxazepine, Quinozoline

Introduction

Heterocyclic systems occur widely in nature, distinctly in natural products such as nucleic acids, plant alkaloids and chlorophyll [1] and are considered one of important types of organic compounds due to their application in drugs and industrial studies. A variety of atoms, such as N, O, S, P, Si and As can be embodied into the ring structures [2]. The derivatives of oxazepine (benzodiazepine), which is a non-homologous seven membered ring that contains a couple of hetero atoms (oxygen and nitrogen)[3] were submitted in 1965 to be used in remedy of the psychoneuroses characterized by anxiety and tension. In the last few decades, the chemistry of 1,2,4-triazoles and their fused heterocyclic derivatives has acquired significant attention due to their synthetic and impressive biological importance[4,5].

1,2,4-triazole-containing ring system were incorporated into a wide variety of therapeutically interesting drug candidates including anti-inflammatory, antianxiety, antimicrobial agents[6,7] and antimitotic activity such as fluconazole, intraconazole, voriconazole [8,9] Furthermore, there are well-known drugs containing the 1,2,4-triazole group e.g. Triazolam[10], Alprazolam[11], Etizolam[12], and Furacylin[13].

Besides, sulphur comprising heterocycles stand for prominent group of sulphur compounds that are encouraging to be used in practical applications. Among these heterocycles, the mercapto- and thione-substituted of 1,2,4-triazole ring systems A-C (Fig.1) were well investigated and a lot of biological activities have been recorded for a considerable number of their derivatives, like antibacterial[14,15], antifungal [16,17] ,antitubercular[18], antimycobacterial[19], anticancer[20], diuretic [21],and hypoglycemic[22] properties.

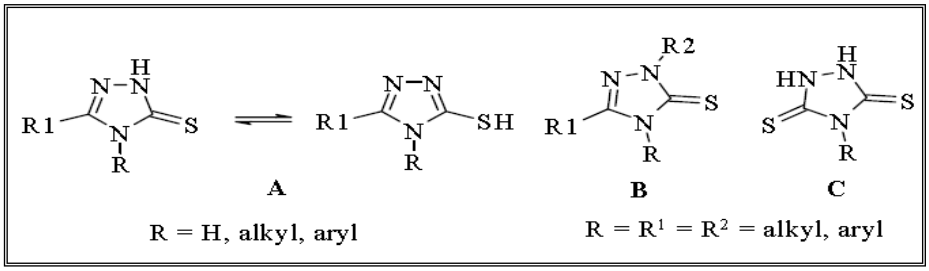


Figure 1: The mercapto- and thione-substituted of 1,2,4-triazole ring systems A-C

Mercapto-1,2,4-triazoles are also of great advantage in synthetic organic chemistry, for instance, in the presence of several reagents, undergo different types of reactions to get other heterocyclic compounds.

Experimental

General

(1) Melting points were recorded using uncorrected Stuart Melting point apparatus.
(2) Infra-red spectra (FT-IR) were recorded on Shimadzu FT-IR-8300 spectrophotometer in College of Education four pure Science –Ibn Al-Haitham, IRAQ.
(3) Thin layer chromatography (TLC) was carried out using Fertigfollen percolated sheets type Polygram Silica gel, and the plates were developed with iodine vapor.
(4) ^{1}H-NMR spectra were recorded on a BRUKER-400 MHz operating at 300 MHz at Chemistry Department, AL-Bayt University-Jordon using TMS as internal standard in DMSO-d^{6} as a solvent.

Synthetic Procedures

Preparation of thiocarbohydrazide(1)[23]

5 ml of carbon disulfide was added gradually to 20 mL of aqueous hydrazine 80%, the reaction mixture refluxed for 30 min., then cooled in ice bath for half an hour. The yellow precipitate formed washed several times with distilled water, ethanol and diethyl ether until the color of the product turned white, then recrystallized from ethanol, the percentage yield 84%, melting point 170 -172 °C.

Synthesis of 5, 5-(ethane-1,2-diyl)bis-(4-amino-4H-1,2,4-triazole-3-thiol)(2) [24]

A mixture of thiocarbohydrazide (0.02 mol) with succinic acid (0.01mole) was heated on a hotplate with continuous stirring by the aid of a glass rod for 10-15 min. till fusion. The product was collected, washed with (10%) aqueous solution of sodium carbonate then with distilled water and recrystallized from dimethyl formamide. Table 1, shows the physical properties.

Synthesis 3,3-(ethane-1,2-diyl) bis-(5-mercapto-4H-1,2,4-triazole 3,4-diyl) bis-(4-substitutedbenzylidene)(3-5)[25]

A mixture of (0.006 mol) compound (2) with (0.012 mol) of appropriate aldehyde and isatien, was milled well using a porcelain mortar, then placed in a glass beaker, and heated in a microwave device (160-260 watt) for different periods of time controlled by TLC results. Then yield was recrystallized from absolute ethanol.

Synthesis of Bis-Oxazepine derivatives (6-14)[26]

A mixture of (0.0046 mol) of the compounds (3-5) with (0.0092 mol) of (maleic, succinic and phthalic) anhydride have been grinded well in a porcelain mortar, then placed in a beaker and heated to fusion for a period of 10-15 min. with stirring using a glass rod until the color and nature of the molten reactant was changed. The yield has been recrystallized from absolute ethanol.

Synthesis of Bis-2,3dihydroquinazolin-4(1H)-one) derivatives(15-17) [26]

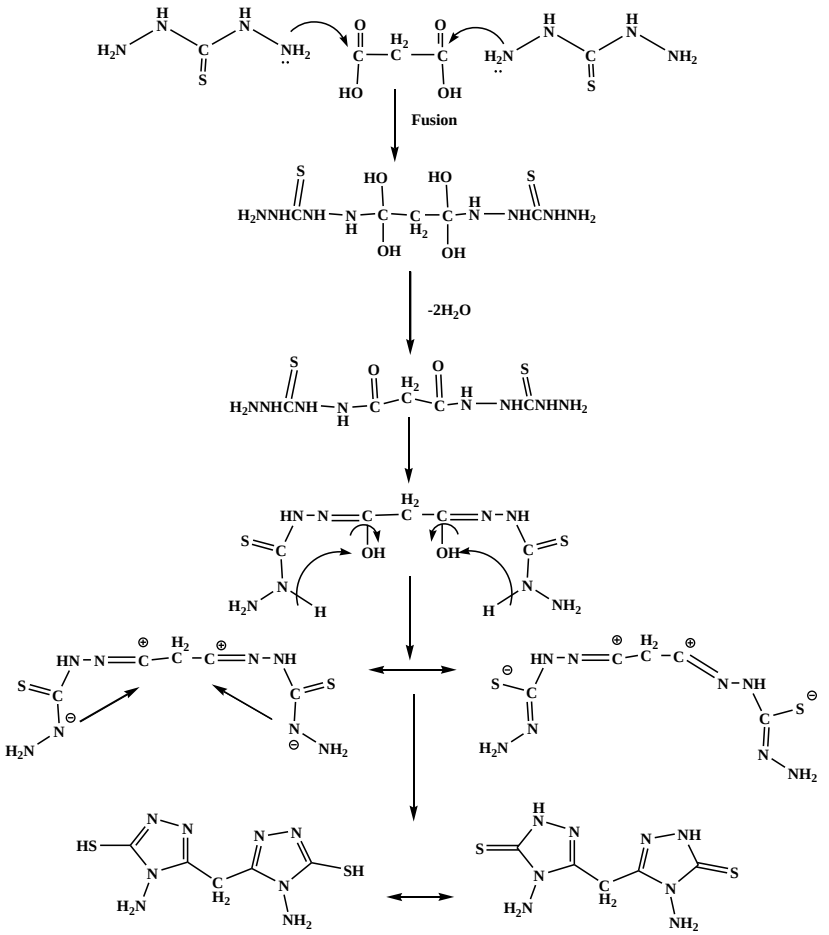
A mixture of (0.004 mol) of the previously prepared compounds (3-5) with (0.119 g, 0.0008 mol) of 2-amino benzoic acid (anthranilic acid) by mole ratio of 1:2 was heated in a beaker with stirring using a glass rod for 10-15 min. till fusion. The completion of the reaction was identified by change in the nature and color of the reactants and confirmed by TLC results. The product was collected and recrystallized from THF solvent.

Table 1: Physical properties of the prepared compounds (1-17)

Comp. No	M.P °C	Yield %	M.F	M .Wt	color	Solvent Rec.
1	170-172	84	CH_6N_4S	106.15	White	EtOH
2	223 – 225	89	$C_6H_{10}N_8S_2$	258.30	Yellow	DFA+EtOH
3	220-223	82	$C_{22}H_{16}N_{10}O_2S_2$	502.53	Deep Maroni	EtOH
4	141 – 143	89	$C_{16}H_{14}N_8S_4$	446.56	Yellow	EtOH
5	116 – 118	90	$C_{18}H_{16}N_{10}S_2$	436.49	Deep Red	EtOH
6	213-215	81	$C_{38}H_{24}N_{10}O_8S_2$	798.77	Auburn	EtOH
7	245-247	88	$C_{30}H_{20}N_{10}O_8S_2$	712.69	Charcoal	EtOH
8	180-182	74	$C_{30}H_{24}N_{10}O_8S_2$	716.69	Maroni	EtOH
9	166-168	85	$C_{32}H_{22}N_8O_6S_4$	742.79	Yellow	EtOH
10	152-154	78	$C_{34}H_{24}N_{10}O_6S_2$	732.72	Brown	EtOH
11	142-144	92	$C_{24}H_{18}N_8O_6S_4$	642.67	Copper	EtOH
12	191-193	88	$C_{26}H_{20}N_{10}O_6S_2$	632.60	Brown	EtOH
13	162-164	93	$C_{24}H_{22}N_8O_6S_2$	644.67	Orange	EtOH
14	152-154	88	$C_{26}H_{24}N_5O_6S_4$	634.60	Yellow	EtOH
15	160-162	83	$C_{36}H_{26}N_{12}O_4S_2$	754.78	Maroni	THF
16	108-110	80	$C_{31}H_{26}N_{10}O_2S_4$	684.80	Light Green	THF
17	68-70	82	$C_{32}H_{26}N_{12}O_2S_2$	674.74	Deep Red	THF

EtOH:Ethanol, THF: Tetrahydrofurane

3. Results and Discussion



Scheme 1: Suggested mechanism of preparation of compound (2)

Synthesis and characterization 5, 5-(ethane-1,2-diyl) bis (4-amino-4H-1,2,4-triazole-3-thiol) (2)

The essential parent compound [2], which was used as a key intermediate for furthersynthesis of compounds , this compound was synthesized through the condensation reaction of thiocarbohydrazide with succinic acid by direct fusion for 10-15 min. The equations and the suggested mechanism for the route of reaction are shown in scheme 1.

The IR spectrum of this compound showed six main bands attributed to the stretching vibrations of the NH_2 asymmetric and symmetric stretching at (3479,3365) cm^{-1}, and an absorption band at (3204) cm^{-1} due to the (-NH) stretching vibration (tautomer form)[27]. The stretching vibrations for (C-H aromatic, CH_2, C-H, C=N) appeared at frequencies located at (3089, 2960, 2820, 1654,) cm^{-1} respectively, the band due to C-N vibration frequency at (1234) cm^{-1} was identical to what is known in the literature [28].

The(S-H) stretching band found as a very weak shoulder at (2530) cm^{-1}. Whereas the absorption bands at, (1514) cm^{-1}, and (1415) cm^{-1} ascribed to the stretching vibrations of the two different types of imine group inside triazole rings due to the tautomerism. Also, the absorption bands at (1311, 1290) cm^{-1} due to the presence of (=N-N-C-) cyclic grouping were observed[29].Moreover, the absorption band at (1166) cm^{-1} for the (C=S) group stretching vibration confirmed the evidence that compound [2] could exist in two tautomeric forms; thiol form I and thione form II (Fig. 2)[30]. The strong absorption band at 1047 cm^{-1} is due to the υ(N-N) inside triazole ring while, the strong absorption band at756 cm^{-1} attributed to the υ(C-S).

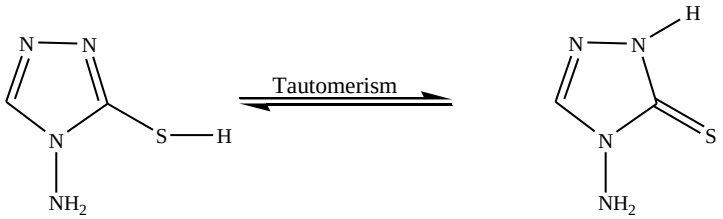
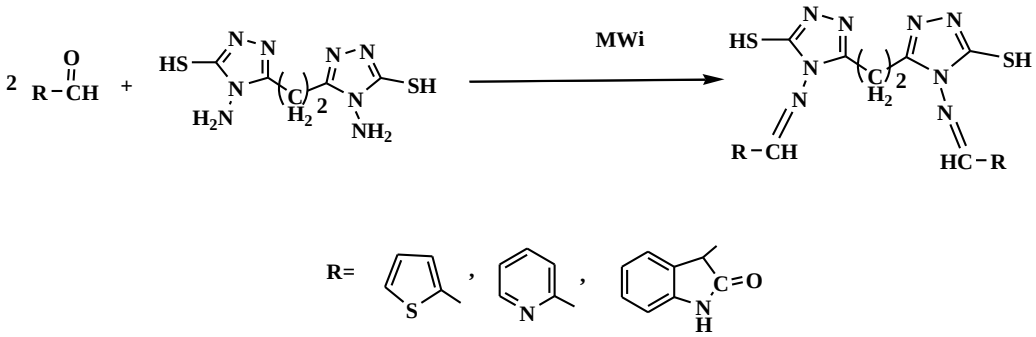


Figure 2: Tautomer forms of compound (2)

Synthesis and characterization of 3,3-((ethane-1,2-diyl) bis(5-mercapto-4H-1,2,4-triazole 3,4-diyl) bis-(4-substituted benzylidene) (3-5)

Schiff bases (3-5)were prepared from direct fusion reaction of the triazole diamine (2) with appropriate aromatic aldehyde and ketones (without use any solvents) according to the equation shown in scheme 2.

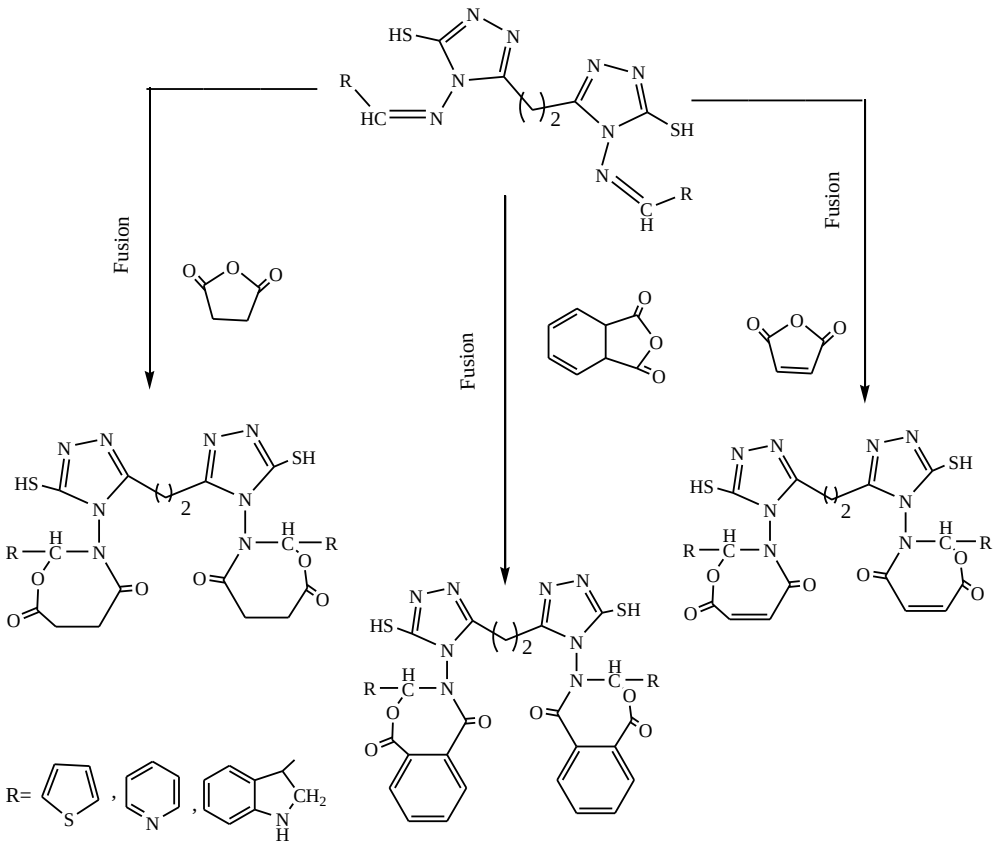


Scheme 2: Preparation of compounds (3-5)

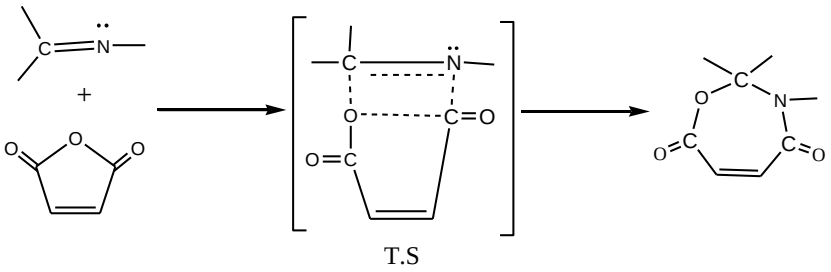
The FT-IR spectra, showed the disappearance of the two stretching absorption bands due to (NH_2) groups [31] of amino triazole(2). All the prepared compounds (Schiff bases) exhibited stretching bands near the region (1219-1250) cm^{-1} due to (=N-N=C-) cyclic group. The whole spectral data for prepared compounds are listed in table 2.

Synthesis and characterization of Oxazepine compounds (6-14)

Precyclic reactions were held between the imine groups of Schiff bases derivatives (3-5), as three-membered components, and cyclic anhydrides (maleic, phathalic and succinic). Our cycloaddition reaction is classified as a 5+2→7, implying 5-atom component plus 2-atom component leading to 7-membered cyclic ring by fusion for 10-15 min. The outline of precyclic reaction leading to the synthesis 1, 3-oxazepine rings is shown in schemes 3-4[32].



Scheme 3: Synthesis 1, 3-Oxazepine compounds (6-14)



Scheme 4: Approximate transition state geometry for maleic anhydride addition to imine group

The validity of the prepared compounds (6-14) confirmed by the FT-IR spectra throughout the appearance of absorption stretching bands due to lactones and lactam carbonyl groups; (1710-1750) cm^{-1} for the lactone as well as (1640-1685) cm^{-1} for lactam in addition to (C-H) aliphatic band at (2865-2880) cm^{-1}, (C-H) aromatic band at (3089-3022) cm^{-1} and also bands at (1265 and1091) cm^{-1} belonging to asymmetric and symmetric (C-O-C) bond . The detailed information of FT-IR spectral data for the prepared compounds is listed in table 3.

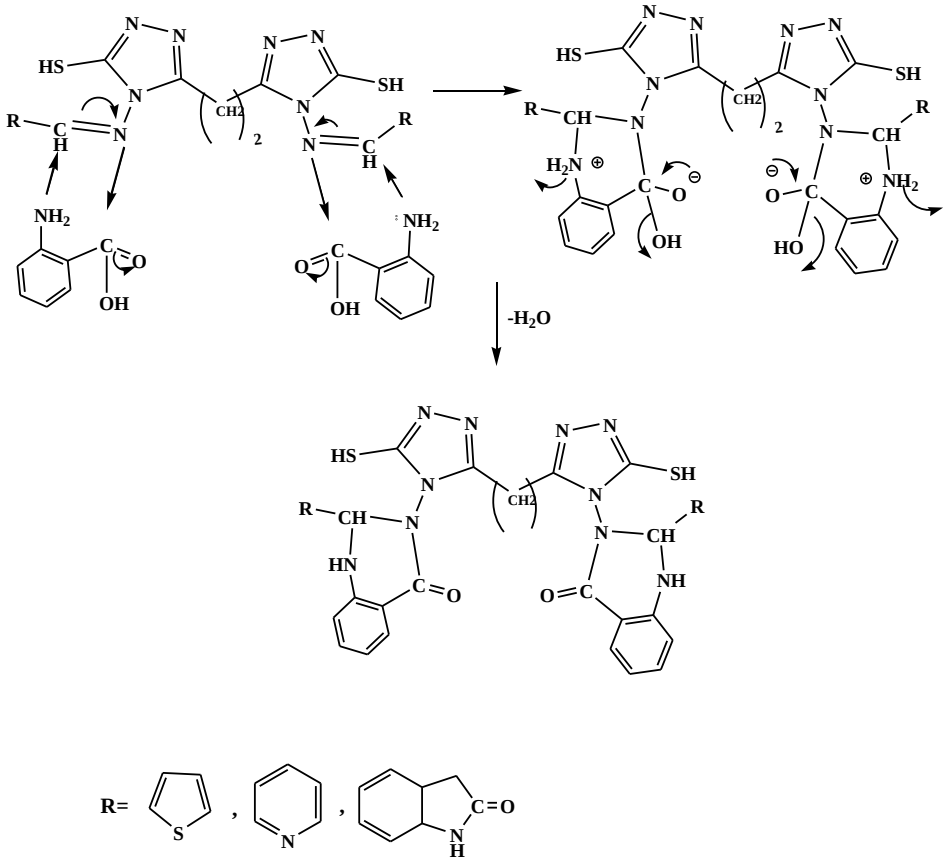
Synthesis and characterizacation of Bis-2,3dihydroquinazolin-4(1H)-one) derivatives (15-17)

Pyrimidine derivatives were synthesized by fusion of Schiff bases derivatives with anthranilic acid (*o*-amino benzoic acid). The products were identified by the FT-IR spectra which showed the appearance of NH vibration in (3361-3373) cm^{-1} and the disappearance of C=N band at (1609-1625) cm^{-1} as well as the appearance of carbonyl amide C=O vibration in (1685-1668) cm^{-1}. Mechanism of the precyclic reaction for this synthesis is shown in scheme 5. Figure 5, exhibits the IR spectrum of compound (17) whereas the detailed FT-IR spectral data for these compounds are listed in table 4.

Discussion of ^{1}H-NMR spectra

The ^{1}H-NMR spectra information of the prepared compounds (6, 9, 15) in DMSO-d^{6} are summarized in table 5,

whereas figures 6 and 7exhibit the spectra of the compounds (6) and (15) respectively. The signal of the methylene group appeared at 1.75, 1.05, 1.70 ppm for the (6, 9, and 15) compounds respectively. While the thiol groups for the (6, 9, and 15)compounds appeared as a singlet at 11.43, 11.85, 10.79 ppm respectively. All signals of the other protons are listed in the table 5.



Scheme 5: Mechanism of the pericyclic reaction for preparation compounds (15-17)

Table 2: FT-IR spectral data of compounds (3-5)

Comp no.	IR ν (cm^{-1})					
	N-H	**C –H aro.**	**C-H ali.**	**C=O lactone**	**C=N**	**υ(C=C)aro.**
3	3266	3106	2955	1712	1618	1461
			2801			1618
4	-----	3047	2907		1609	1586
			2800			1490
5	------	3039	2990		1625	1598
			2851			1423

Table 3: FT-IR spectral data of compounds (6-14)

Comp No.	IR ν (cm^{-1})					
	N-H	**C –H aro.**	**C-H ali.**	**C=O lactonelactam**	**C=C**	**Other**
6	3178	3118	2955	1743	1512	υ (C-O)1119
			2811	1686		
7	3190	3080	2879	1731	1502	υ (C-O) 1122
				1701		
8	3198	3057	2939	1730	1544	υ (C-O) 1217
				1647		

9	------	3052	2922 2809	1749 1695	1580	υ(C-O)1037
10	----	3039	2990 2851	1747 1673	1583	υ(C-O)1133
11	------	3011	2943	1736 1679	1498	υ (C-O) 1146
12	------	3027	2951	1746 1665	1523	υ (C-O) 1222
13	------	3022	2937	1739 1663	1556	υ (C-O) 1139
14	-------	3065	2981	1744 1697	1566	υ (C-O) 1209

Table 4: FT-IR spectral data of compounds (15-17)

Comp	IR ν (cm^{-1})					
No.	**ν NH**	**ν C-H aro.**	**ν C-H ali.**	**ν S-H**	**ν C=O**	**ν C=C**
15	3201	3058	2964 2799	2360	1685	1504
16	3352	3004	2955 2869	2440	1668	1600
17	3101	3047	2927 2790	2525	1681	1585

Table 5: ^{1}H- NMR chemical shifts for the prepared compounds (6, 9, 15)

Comp. no.	δH (δ in ppm)
6	1.75(t, 2H, CH_2), 6.83-7.90(m, 16H, Ph), 9.04(S, 2H, NH), 11.43(S, 2H, SH).
9	1.05(t, 2H, CH_2), 8.85(S, 2H, N-C<u>H</u>), 6.92-8.11(m, 14H, Ph and thiophene), 11.85(S, 2H, SH).
15	1.70(s, 4H, CH_2), 5.52(s, 2H, NH^{a}), 9.03(S, 2H, NH^{b}), 6.47-7.96(m, 14H, Ph), 10.79(S, 2H, SH).

S: singlet; b: broad singlet; m: multipletes

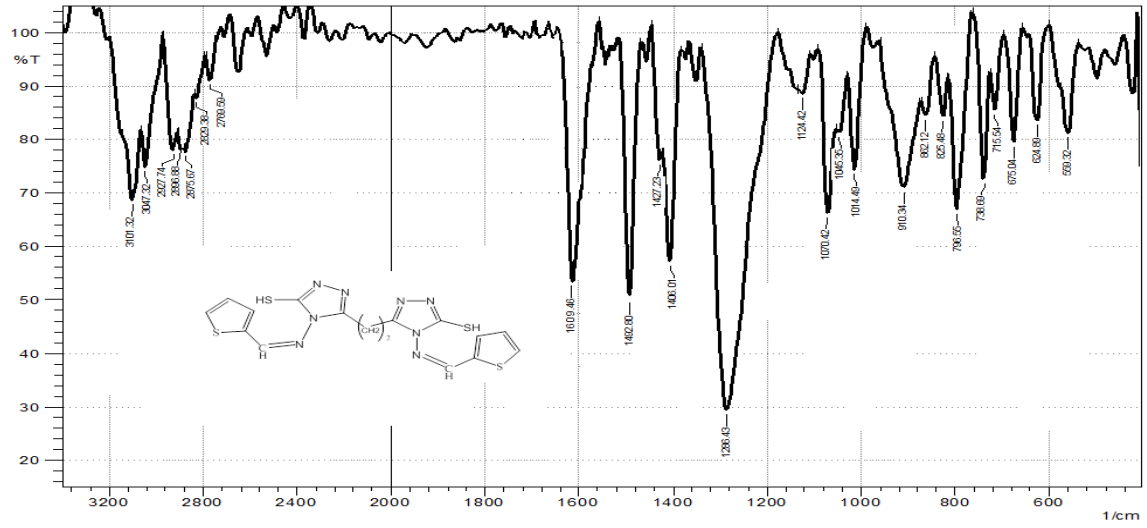


Figure 3: FT-IR spectrum of compound (4)

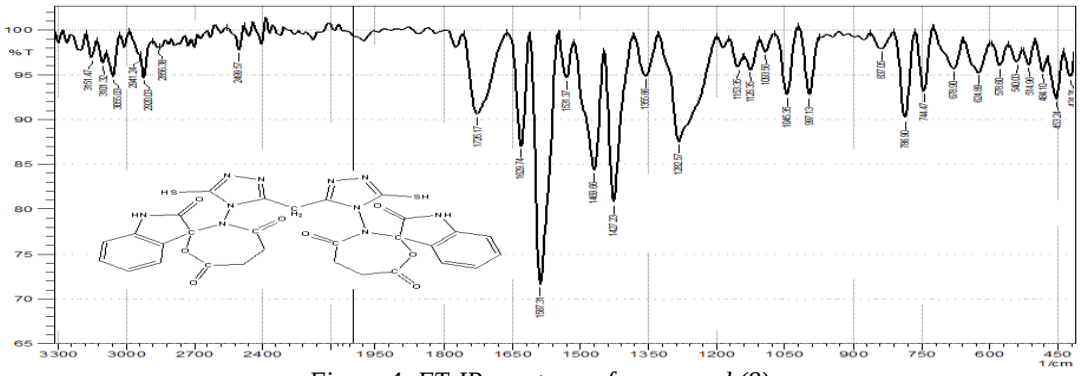


Figure 4: FT-IR spectrum of compound (8)

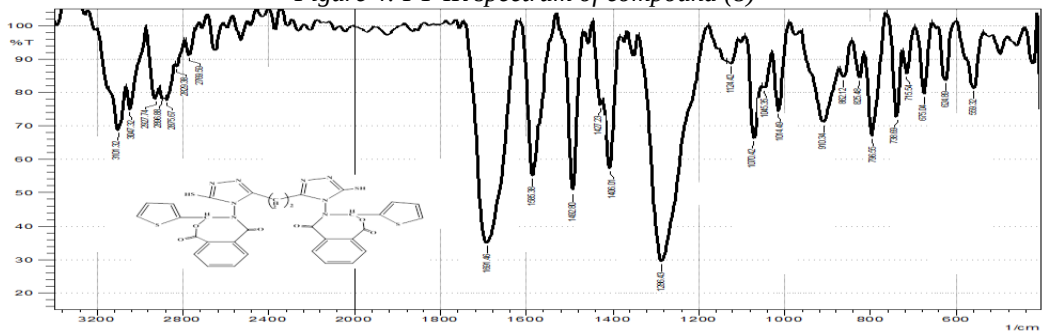


Figure 5: FT-IR spectrum of compound (17)

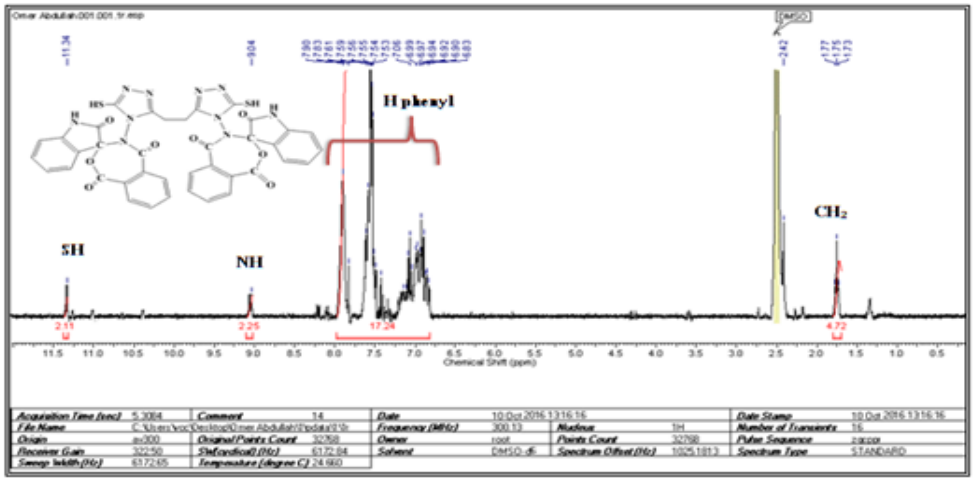


Figure 6: The ^{1}H NMR spectrum of compound (6)

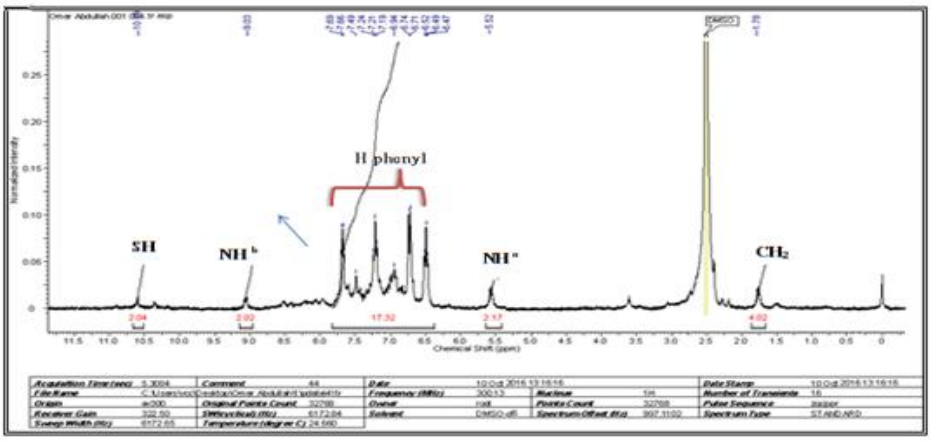


Figure 7: The ^{1}H N.M.R. spectrum of compound (15)

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