

Synthesis and Characterization of New Schiff Bases Derivative from 2, 5-Dimercaptothiadiazole

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Abstract

This research includes synthesis of new heterocyclic containing Schiff bases derivatives of 2, 5-dimercapto thiadiazole. The preparation process started by the reaction of 2,5-dimercapto-1,3,4-thiadiazole (1) with ethyl chloroacetate to give diethyl 2,2'-(1,3,4-thiadiazole-2,5-diyl)bis(sulfanediyl)diacetate (2). Compound (1) reacted with hydrazine hydrate to give 2, 5-bis (mercapto-acetichydrazide) 1, 3, 4-thiadiazole (3). The reacted with various substituted benzaldehydes in the presence of glacial acetic acid as catalyst in absolute ethanol to obtain new Schiff bases derivatives (4-13).

Keywords: 2, 5-dimercapto-1, 3, 4-thiadiazole, Schiff bases.

Introduction

The development of simple synthetic routes to widely used organic compounds using readily available reagents is one of the main objectives of organic synthesis. Nitrogen heterocycles are of a special interest because they constitute an important class of natural and nonnatural products, many of which exhibit useful biological activities. One-pot efficient synthesis of heterocyclic derivatives may permit the development of novel therapies for the treatment of epilepsy, pain and other neurodegenerative disorders [1]. Heterocyclic chemistry is one of the largest branches of organic chemistry. It is particularly important in nature because of the wide variety of the industrial value and physiological activities [2]. A cyclic organic compound contains all carbon an atom in ring formation is referred to as a carbocyclic compound. If at least one other than carbon forms a part of the ring system designated as heterocyclic compound [3] contain one or more atoms of different elements besides carbon.

The non-carbon atoms in such rings are known as hetero atoms. The most common hetero atoms are (N, O, S). Heterocyclic compounds with three to six carbons in a single ring are numerous. However, so far, only those with five or six atoms in a single

ring are important, the best known of the simple Heterocyclic compounds are pyridine, pyrrole, furan and thiophene [4]. Heterocyclic bearing nitrogen, sulphur and thiadiazole moieties constitute the core structure of a number of biological interesting compounds. Literature survey revealed that 1, 3, 4 thiadiazole derivatives are associated with various biological activities such as anti-inflammatory [5-8], anticonvulsant [9-10], antibacterial [11-12] and antifungal [13-14]. The incorporation of azetidinone moiety in different heterocyclic nuclei markedly modulates the anti-inflammatory activity. Therefore, it was thought worthwhile to synthesized some new azetidinone derivatives [15] of thiadiazole by incorporating it at 2 and 5-position of 1, 3, 4-thiadiazoles nucleus with the hope to get better anti-inflammatory molecule with improved anti-inflammatory activities. All the compounds have been screened for their anti-inflammatory and analgesic activities. The structures of all compounds have been evaluated by elemental and spectral analysis (IR, and ¹HNMR spectrometry).

The first Schiff base compounds were reported by Hugo Schiff in 1864. In recent years, the chemistry of Schiff bases contains N-donor

atom which has been extensively studied and has acquired a great interest because of the azomethine C=N linkage essential for biological activity [16].

Some Schiff bases bearing aryl groups or heterocyclic residues possess excellent biological activities, which has attracted many researchers' attention in recent year [17]. They have been reported to be used as analgesic, anthelmintic, anti-tubercular, and plant growth regulator, antiviral.

General Procedures

Synthesis of 2, 5-dimercapto-1, 3, 4-thiadiazole (1)

A mixture of (99%) hydrazine hydrates (5 mL, 0.02 mol) and carbon disulfide (15 mL, 0.02 mol) with dry pyridine (50 mL) was refluxed for (5 h). Then the excess solvent was then distilled off, and the resulting solid was separated out by adding (25 mL) of water and (5 mL) of hydrochloric acid. The mixture was then filtered and the solid was recrystallized from ethanol.

Synthesis of Diethyl 2, 2`-(1, 3, 4-thiadiazole-2, 5-diyl)bis(sulfanediyl) diacetate (2):[18]

To a solution of 2, 5-dimercapto-1, 3, 4-thiadiazole (0.1 mol, 15 g) in 20 ml of DMF, (0.2 mol, 12g) of potassium hydroxide was added. The solution was stirred for 30 min, then ethyl chloroacetate (0.2mol, 25ml) was added drop wise to the solution. The reaction mixture was refluxed for 4-5 hrs. Then cooled to room temperature poured in 100 ml of ice water. The precipitated was filtered off, washed with water and recrystallized from ethanol.

Synthesis of 2, 5-bis (mercapto-acetichydrazide)-1, 3, 4-thiadiazole (3)

A Suspension of compound [2] (0.02 mol ,6.4 g) in 20 ml of absolute ethanol was stirred for 15 min at 40 °C until the ester was dissolved , (0.04 mol, 2.2ml , 2 g) of hydrazine hydrate (80 %) was added and the solution was stirred for 30 min , cooled , filtrated ,washed and recrystallized from ethanol.

Table 1: some of the Physical properties and percentage of the synthesized compounds [1-3]

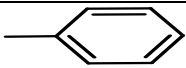
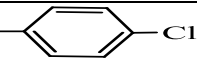
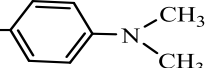
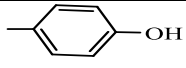
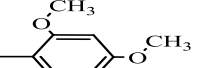
Comp. No.	Molecular formula	M.wt	Yield%	m.p.°C	Colour
1	C ₂ H ₂ N ₂ S ₃	150	77	146-148	Yellow
2	C ₁₀ H ₁₄ N ₂ O ₄ S ₃	322	79	47-48	Off white
3	C ₆ H ₁₀ N ₆ O ₂ S ₃	294	74	140-142	white

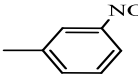
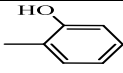
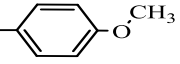
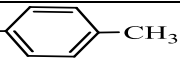
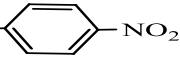
Synthesis of New Schiff bases from 2, 5-bis (mercapto-acetichydrazide)-1, 3, 4 -thiadiazole (4-13)

A mixture of compound [3] (2.14 g., 0.01 mol), aromatic aldehydes (0.01mol) in absolute ethanol (25) ml and (3-5) drops of glacial

acetic acid was refluxed in water bath for about (5-6 h.) The excess solvent was evaporating under reduced pressure. The crude product was dried, recrystallized from chloroform and ethanol. Some of the physical properties and yield of compounds [4-13] are listed in Table (2).

Table 2: Some of the physical properties and percentage of the synthesized compounds [4-13]

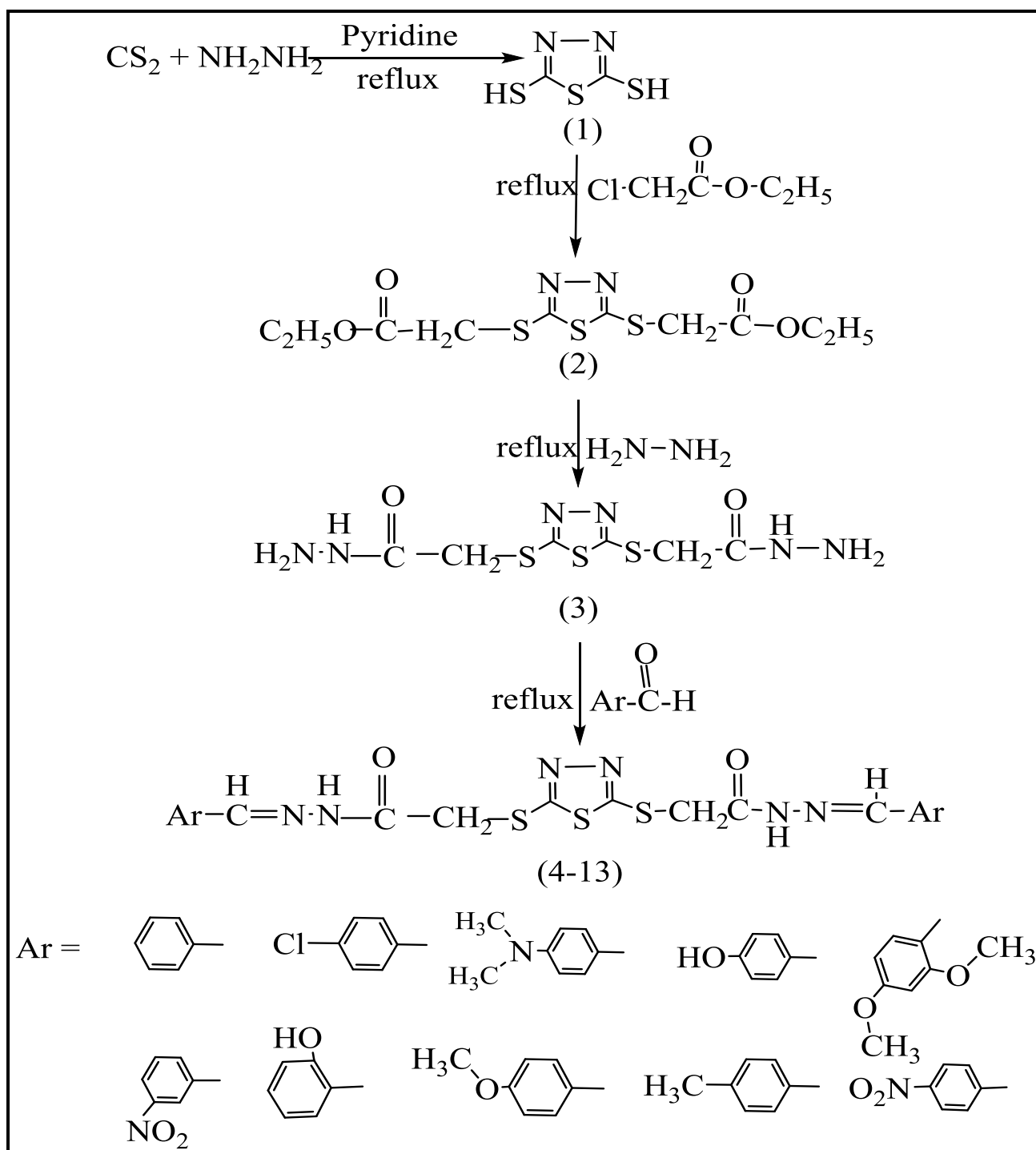
Com. No.	Ar	Molecular formula	M. wt	Yield%	m.p.°C	Colour
4		C ₂₀ H ₁₈ N ₆ O ₂ S ₃	470	90	196-198	white
5		C ₂₀ H ₁₆ ClN ₆ O ₂ S ₃	503.5	90	178-180	Brown
6		C ₂₄ H ₂₈ N ₈ O ₂ S ₃	556	85	198-200	Orange
7		C ₂₀ H ₁₈ N ₆ O ₄ S ₃	502	80	155-157	Off white
8		C ₂₄ H ₂₆ N ₆ O ₆ S ₃	590	90	184-186	Off white

9		C ₂₀ H ₁₆ N ₈ O ₆ S ₃	560	87	210-112	Yellow
10		C ₂₀ H ₁₈ N ₆ O ₄ S ₃	502	85	218-220	Off white
11		C ₂₂ H ₂₂ N ₆ O ₄ S ₃	530	90	176-178	Yellow
12		C ₂₀ H ₁₆ N ₈ O ₆ S ₃	498	70	200-202	Off white
13		C ₂₀ H ₁₈ N ₆ O ₄ S ₃	560	90	251-253	Yellow

Result and Discussion

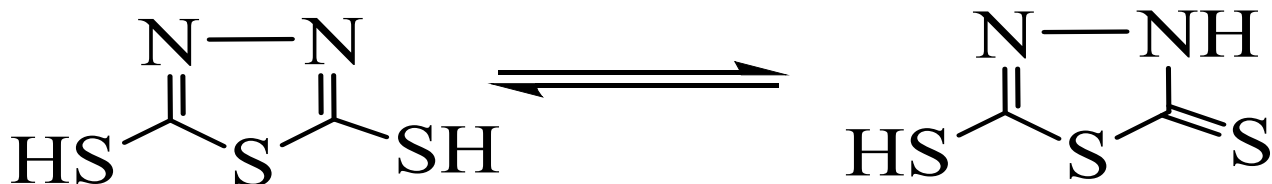
Chemistry

Compounds [1-14] were synthesized as shown in scheme 1. Some physical properties for this compound were listed in Table 1.



Scheme 1: the steps for synthesis of compounds [1-13]

2, 5-dithiol-3, 4-thiadiazole was prepared by the reaction of carbon disulfide with hydrazine hydrate in presence of dry pyridine as showed in Scheme (1). 2, 5-dithiol-3, 4-thiadiazole (1) showed a medium intensity band at 1625 cm^{-1} that could corresponds with (C=N) bond in the vicinity



As indicated in the Scheme (1) synthesis of compound (4) involved three steps the first one was performed by a nucleophilic attack of (SH) group in 2,5-dithiol-3,4-thiadiazole on α -carbon in ethyl chloroacetate because the halo group is good leaving group and sulfur compounds are a good nucleophile thus, the reaction is a typical of the substitution nucleophilic reaction ($\text{S}_{\text{N}}2$) of the thiol group followed by elimination of HCl molecule, where the halo group could be replaced easily in this reaction to get good yield producing compound (2). Reaction of compound (1) with ethyl chloroacetate in presence DMF to give compound (2). Compound 2 was characterized by FTIR and $^1\text{H-NMR}$ spectroscopy, FTIR spectrum shows strong absorption band at 1741 cm^{-1} due to carbonyl group for ester and bands at 2987.84 cm^{-1} and 2939.61 cm^{-1} for aliphatic (CH_2) group.

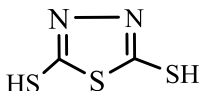
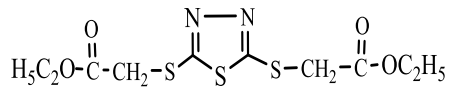
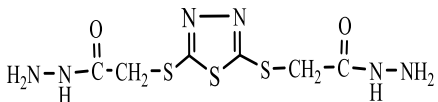
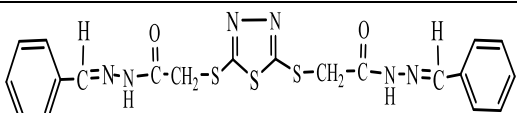
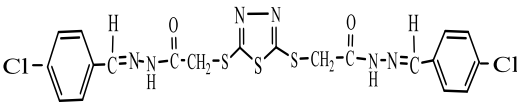
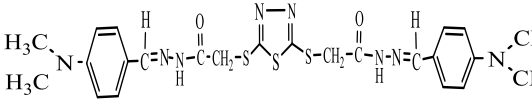
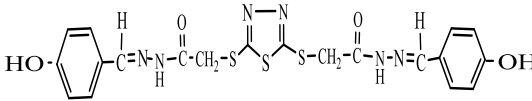
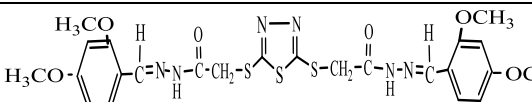
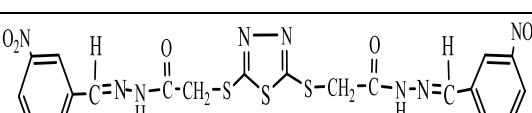
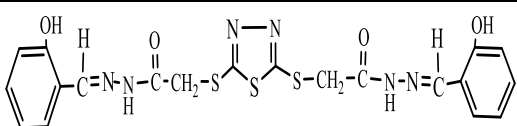
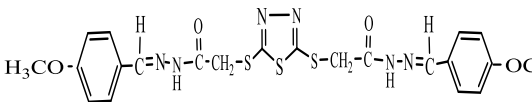
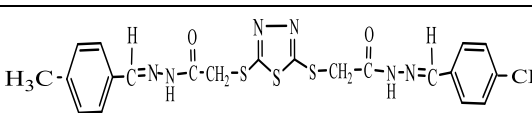
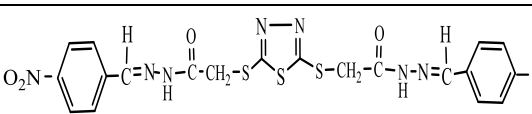
Disappearance of S-H and N-H absorption bands was also detected Fig. (1). $^1\text{H-NMR}$ spectrum of compound [2] showed triplet signal at $\delta = (1.23)$ ppm belong to ($-\text{CH}_2-\text{CH}_3$) protons, singlet signal at $\delta = (4.02)$ ppm belong to ($-\text{S}-\text{CH}_2-$) protons, quartet signal at $\delta = (4.09)$ ppm belongs to ($-\text{O}-\text{CH}_2-$) protons and singlet signal at $\delta = (2.50)$ ppm and 3.39 ppm due to the solvent DMSO- d_6 and water dissolved in DMSO- d_6 respectively. In the second step Compound (2) was introduced in nucleophilic substitution reaction with hydrazine hydrate leading to replace an ethoxy group with hydrazine ($\text{NH}-\text{NH}_2$) group producing the corresponding acetohydrazide (3). FTIR spectrum of compound (3) showed disappearance of (C=O) ester band and appearance of clear absorption bands at 3319 cm^{-1} for N-H and ($3292-3269\text{ cm}^{-1}$) due to the asymmetric and symmetric stretching vibrations of (NH_2)

of 1, 3, 4-thiadiazole ring. In this spectrum there are two other characteristic bands at 3200 cm^{-1} and 2550 cm^{-1} due to (N-H, thion form) and (S-H) stretching vibrations, respectively. That means compound 1 can exist in the thiol and thion form.

indicating success of acetohydrazide formation (Fig 2). In the third step the Compound (3) was introduced in reaction with various aromatic aldehydes were condensed in absolute ethanol under reflux conditions. The reaction proceed through nucleophilic attack of amino group in the compound (3) on electron-deficient carbonyl group in aromatic aldehyde in the presence of a few drops of the catalyst glacial acetic acid, and abstraction of water molecule to produce the desired new Schiff-bases derivatives in a good yield (Scheme 1)(4-13). The formation of Schiff bases (4-13) were indicated by the presence in its FTIR-spectra of the azomethine (C=N) stretching band at ($1600-1614\text{ cm}^{-1}$), other absorption bands appeared at ($1635-1677$) and ($696-102\text{ cm}^{-1}$) due to (C=O) amide and (C-S) respectively.

All the spectral data show disappearance the absorption of the (NH_2) stretching band indicating success of formation reaction as shown in table (2). $^1\text{H-NMR}$ spectral data of compound [6] showed the following signals: a singlet signal at $\delta=(3.04)$ ppm due to (N- $(\text{CH}_3)_2$) protons, singlet signal at $\delta=(4.23)$ ppm due to (S- CH_2-) protons, singlet signal at $\delta=(6.8)$ ppm due (N=CH) proton, multi signals at $\delta= (7.59-8.15)$ ppm that could be attributed to aromatic rings protons, Singlet signal at $\delta= (8.62)$ ppm due to (C=O)NH-) proton. $^1\text{H-NMR}$ spectrum of compound [13] showed singlet signal at $\delta = (4.31)$ ppm belong to ($-\text{S}-\text{CH}_2-$) protons, singlet signal at $\delta= (5.56)$ ppm due ($-\text{N}=\text{CH}$) proton, multi signals at $\delta= (7.53-8.43)$ ppm that could be attributed to aromatic rings protons, Singlet signal at $\delta= (10.29)$ ppm due to (C=O) NH-) proton. The Figure (3) belongs to compound (11) of some them.

Table 3: FTIR spectral data cm⁻¹ of compounds [1-13]

Com. No.	Structures	FT-IR(KBr), spectral data vcm ⁻¹				
		v(C-H) Arom.	v(C-H) Aliph.	v(C=O)	v(C=N)	Others
1		-	-	-	1623	v(S-H) 2513
2		-	2947	1741	1631	-
3		3060	2956	1670	1633	v (NH ₂) asym. 3332, Sym. 3292
4		3080	2974	1674	1614	-
5		3024	2921	1635	1604	v(C-Cl) 719
6		3056	2812	1668	1606	v(C-N) 1365
7		3029	2900	1666	1604	v(O-H) 3213
8		3051	2970	1666	1600	vC-O-C (1111, 1207) δ(CH ₃) (1357, 1460)
9		3082	2866	1679	1614	v(NO ₂) asym. 1529, Sym. 1352
10		3009	2975	1670	1618	v(O-H) 3326
11		3056	2927	1670	1608	vC-O-C (1108, 1253)
12		3053	2925	1672	1608	δ(CH ₃) (1363, 1392)
13		3082	2972	1677	1614	v (NO ₂) asym. 1517, Sym. 1340

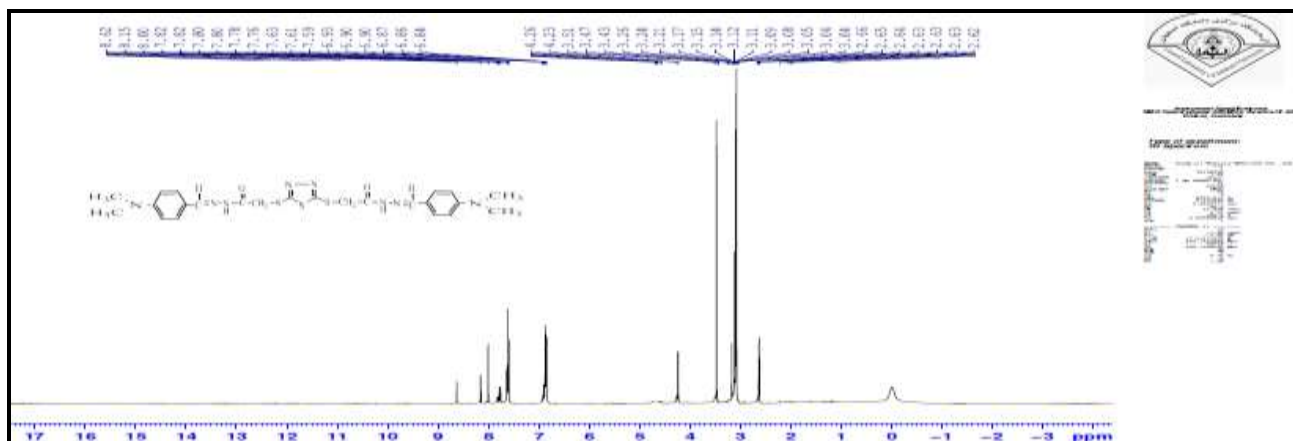


Figure 5: ¹H-NMR spectrum for compound [6]

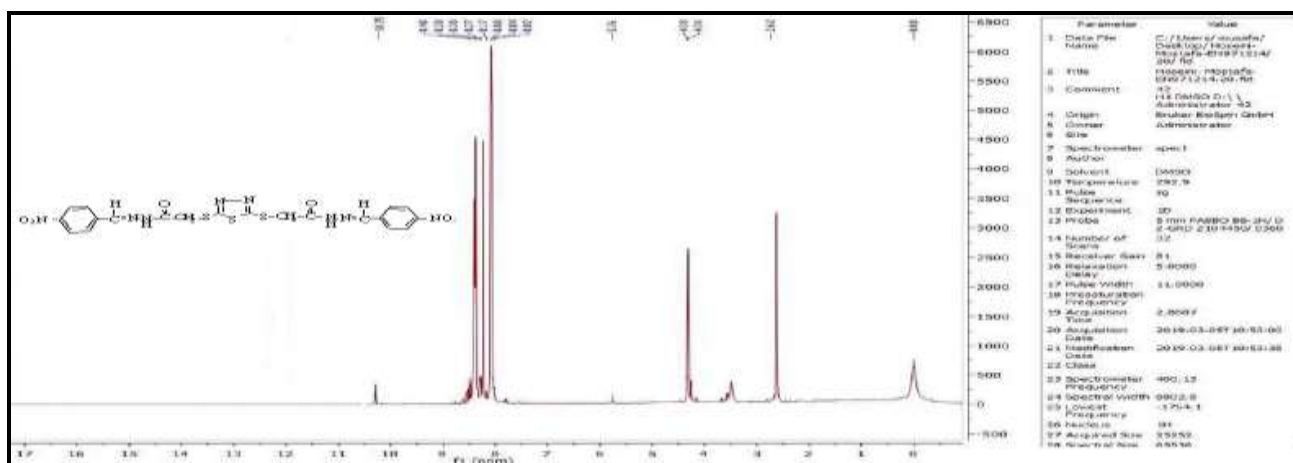


Figure 6: ¹H-NMR spectrum for compound [13]

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