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RESEARCH ARTICLE

NEW SCHIFF BASES DERIVED from 3,4-DIAMINO-1*H*-1,2,4-TRIAZOLE-5(*4H)*-THIONE: SYNTHESIS and CHARACTERIZATION

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ABSTRACT

A new synthetic approach has been applied to obtain a compound 3,4-diamino-1*H*-1,2,4-triazole-5(*4H)*-thione (**2**) by using 5-amino-1,3,4-thiadiazole-2-sulfonamide (**1**) and hydrazine hydrate as starting materials. New Schiff bases (**3a-d**) are obtained by the reaction of the compound 3,4-diamino-1*H*-1,2,4-triazole-5(4*H*)-thione (**2**) and varied aldehydes. The structures of the new compounds were characterized by spectral (IR, ^{1}H and ^{13}C NMR) and elemental analysis.

Keywords: *Thione, Schiff base, Sulfonamide, Triazole, Hydrazine hydrate.*

1. INTRODUCTION

Due to the development of resistance to existing antibiotics, there is increasing interest in the synthesis of new and effective antibacterial agents [1-3]. 1,2,4-Triazoles have interested of the medicinal chemists because of their strong biological activity in a wide range of areas such as antimicrobial [4,5], antibacterial [6,7], antifungal [8], anticancer [9-11], antitubercular [12], antioxidant [13], anticonvulsant [14], antiviral [15, 16], antitubulin [17,18] and inflammatory [19]. 1,2,4-triazole and derivatives have biological properties as well as environmental, [20] industrial [21, 22] and agricultural [23] activities. In order to increase the therapeutic effect of the 1,2,4-Triazole compound, its derivatives were obtained by incorporating it into different compounds [24-26]. Nitrogen-containing heterocyclic molecules, which are a part of many natural products and drugs that are vital for improving the quality of life, constitute a very large part of chemical substances [24]. Schiff bases containing imine groups are formed as a result of condensation of primary amines with aldehydes or ketones [27, 28]. Schiff bases formed from aromatic aldehydes are more stable than those of aliphatic aldehydes [29]. Schiff bases of 1,2,4-triazoles have been found to have extensive biological properties and a variety of applications [30]. Derivatives of 4-amino-4*H*-1,2,4-triazole-3-thiones have been synthesized in different synthetic ways [31-38].

To our knowledge, no example of 1,2,4-triazole yielded from 5-amino-1,3,4-thiadiazole-2-sulfonamide (**1**) was reported. In this study, we synthesized the known 3,4-diamino-1*H*-1,2,4-triazole-

5(4*H*)-thione (**2**) compound from **1** and hydrazine hydrate with a different approach from the literature [39, 40]. In addition, the new Schiff bases **3a-d** were obtained from the condensation of compound **2** with benzaldehyde and substituted benzaldehyde. The structures of the **2** and new Schiff bases **3a-d** were characterized by IR and NMR (^{1}H and ^{13}C) spectra and elemental analysis.

2. EXPERIMENTAL

2.1. General Methods and Materials

The chemicals used in the reactions were used without further purification. The compound **1** was synthesized as in the literature [41]. A Leco CHNS-932 instrument was used for elemental analysis Bruker Avance DPX-400 MHz spectroscopic instrument for ^{1}H and ^{13}C NMR spectra, and Bruker Optics vertex 70 device for IR spectra taken with ATR.

2.2. Synthesis of 3,4-diamino-1H-1,2,4-triazole-5(4H)-thione (2)

To a solution of **1** (554 mmol) in ethanol/xylene (10/5 ml) hydrazine hydrate (554 mmol) was added. The resulting solution was refluxed for 3 days. The volatile component was vaporized using vacuum and then the crude product was crystallized from water to give colorless crystals of **2**. Suggested mechanism for this synthetic approach is given in Figure 1.

Crystals (85 %.), melting point 231-233˚C. ^{1}H-NMR (d$_6$-DMSO) δ/ppm: 12.42 (s, 1H, NH), 5.23 (s, 2H, H$_2$N-C), 5.95 (s, 2H, H$_2$N-N). ^{13}C-NMR (d$_6$-DMSO) δ/ppm: 163.87 (C=S), 152.75 (C=N). IR (cm^{-1}): 3385, 3297/3182 (NH$_2$/NH), 1651 $\nu(C{=}N)_{triazole}$, 1269 (C=S). Anal. Calcd. %, for $C_2H_5N_5S$ (M_r = 131.16): C 18.31, H 3.84, N 53.40, S 24.45; found: C 18.47, H, 3.88, N 53.90, S 24.50.

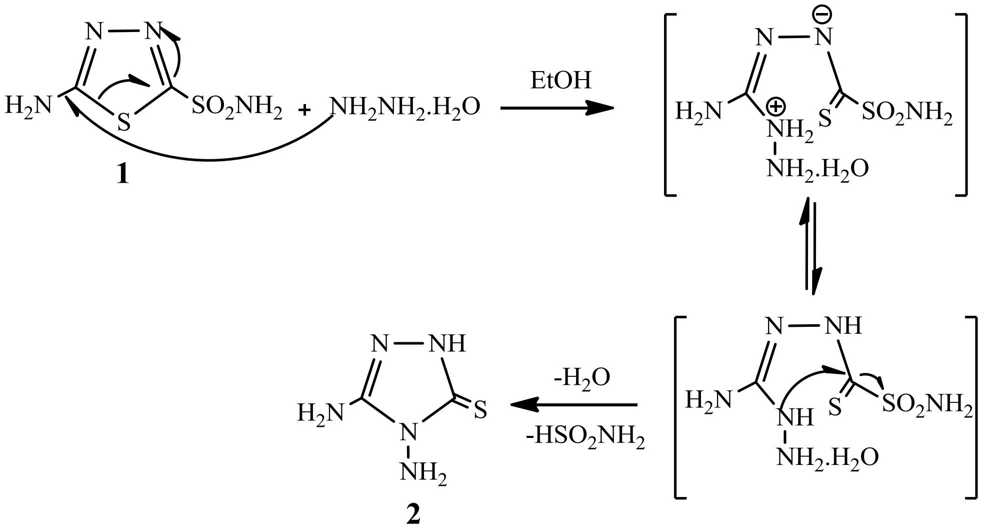
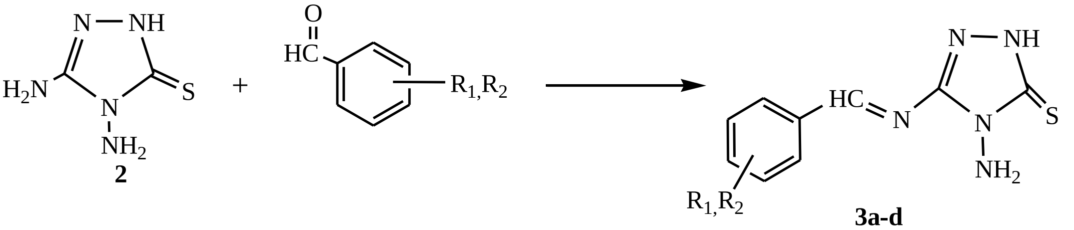


Figure 1. Synthesis of **2**.

2.3. General Procedure for the Preparation of the Schiff Bases (3a-D)

The mixture of **2** (0.40 mmol) in water (10 mL) and benzaldehydes (benzaldehyde, 3,4-dimethoxybenzaldehyde, 4-*N*,*N*'-dimethylbenzaldehyde, 2-hydroxybenzaldehyde) (0.36 mmol) in EtOH (10 mL) with the addition of a few drops of CH_3COOH was stirred for two days. The solid was filtered, washed with water and dried in air. Ethanol was used for the recrystallization of the obtained compounds (**3a-d**) (Figure 2). All prepared compounds are soluble in DMSO solvent and stable in air.



2

3a-d

3a: R_1 = H, R_2 = H
3b: R_1 = 3-OCH_3, R_2 = 4-OCH_3
3c: R_1 = 4-$N(CH_3)_2$, R_2 = H
3d: R_1 = 2-OH, R_2 = H

Figure 2. Syntheses of Schiff bases **3a-d**

2.3.1. (E)-4-amino-3-(benzylideneamino)-1*H*-1,2,4-triazole-5(4*H*)-thione (3a)

Light green crystals (68 %), melting point 212-214˚C. ^{1}H-NMR (d_6-DMSO) δ/ppm: 13.73 (s, 1H, NH), 8.05 (s, 1H, $CH=N)_{imine}$, 7.63-7.53 (m, 5H, $C\text{-}H)_{ar}$, 5.80 (s, 2H, NH_2). ^{13}C-NMR (d_6-DMSO) δ/ppm: 178.02 (C=S), 160.00 $(CH=N)_{imine}$, 152.10 $(C=N)_{triazole}$, 133.70 $(C=C)_{ar}$, 132.54 $(C=C)_{ar}$, 129.51 $(C=C)_{ar}$, 128.37 $(C=C)_{ar}$. IR (cm^{-1}): 3394, 3281/3191 (NH_2/NH), 3137 $(C\text{-}H)_{ar}$, 1654 $\nu(CH=N)_{imine}$, 1636 $\nu(C=N)_{triazole}$, 1602-1461 $(C=C)_{ar}$, 1268 (C=S). Anal. Calcd. %, for $C_9H_9N_5S$ (M_r = 219.27): C 49.30, H 4.14, N 31.94, S 14.62; found: C 49.37, H 4.18, N 31.98, S 14.70.

2.3.2. (E)-4-amino-3-((3,4-dimethoxybenzylidene)amino)-1*H*-1,2,4-triazole-5(4*H*)-thione (3b)

Light green crystals (75 %), melting point 252-254˚C. ^{1}H-NMR (d_6-DMSO) δ/ppm: 13.85 (s, 1H, NH), 8.10 (s, 1H, $CH=N)_{imine}$, 7.46-7.23 (m, 3H, $C\text{-}H)_{ar.}$, 5.82 (s, 2H, NH_2), 3.90 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3). ^{13}C-NMR (d_6-DMSO) δ/ppm: 187.23 (C=S), 163.32 $(CH=N)_{imine}$, 151.32, ($\underline{C}$-OCH_3), 150.67 ($\underline{C}$-OCH_3), 148.42 (C=N), 129.98 $(C=C)_{ar}$, 125.79 $(C=C)_{ar}$, 119.07 $(C=C)_{ar}$, 118.34 $(C=C)_{ar}$, 117.63 $(C=C)_{ar}$, 58.24 (OCH_3). IR (cm^{-1}): 3392, 3259/3189 (NH_2/NH), 3103 $(C\text{-}H)_{ar}$, 2953 $(C\text{-}H)_{aliph,}$ 1651 $\nu(CH=N)_{imine}$, 1601 $\nu(C=N)_{triazole}$, 1572-1462 $(C=C)_{ar}$, 1269 (C=S). Anal. Calcd. %, for $C_{11}H_{13}N_5O_2S$ (M_r = 279.32): C 47.30, H 4.69, N 25.07, S 11.48; found: C 47.53, H, 4.76, N 25.14, S 11.70.

2.3.3. (E)-4-amino-3-((4-(dimethylamino)benzylidene)amino)-1*H*-1,2,4-triazole-5(4*H*)-thione (3c)

Yellow crystals (80 %), melting point 226-228˚C. ^{1}H-NMR (d_6-DMSO) δ/ppm: 8.12 (s, 1H, $CH=N)_{imine}$, 7.25 (d, 2H, J = 7.60 Hz, $C\text{-}H)_{ar}$, 6.85 (d, 2H, J = 7.60 Hz, $C\text{-}H)_{ar}$, 5.85 (s, 2H, NH_2), 3.15 (s, 6H, CH_3). ^{13}C-NMR (d_6-DMSO) δ/ppm: 190.16 (C=S), 165.23 $(CH=N)_{imine}$, 155.33 $(C=N)_{triazole}$, 153.48 ($\underline{C}$-NCH_3), 133.15 $(C=C)_{ar}$, 125.38 $(C=C)_{ar}$, 111.42 $(C=C)_{ar}$, 40.24 ($N(CH_3)_2$). IR (cm^{-1}): 3112, 3061 $(C\text{-}H)_{ar}$, 2845 $(C\text{-}H)_{aliph}$, 1660 $\nu(CH=N)_{imine}$, 1642 $\nu(C=N)_{triazole}$, 1618-1458 $(C=C)_{ar}$, 1271 (C=S). Anal. Calcd. %, for $C_{11}H_{14}N_6S$ (M_r = 262.33): C 50.36, H 5.38, N 32.04, S 12.22; found: C 50.45, H, 5.42, N 32.13, S 12.38.

2.3.4. (E)-4-amino-3-((2-hydroxybenzylidene)amino)-1*H*-1,2,4-triazole-5(4*H*)-thione (3d)

Colourless crystals (78 %), melting point 230-232˚C. ^{1}H-NMR (d_6-DMSO) δ/ppm: 12.98 (1H, NH), 9.10 (s, 1H, OH), 8.50 (s, 1H, $CH=N)_{imine}$, 7.46 (d, 1H, *J* = 7.51 Hz, $C-H)_{ar}$, 7.33 (t, 1H, *J* = 7.52 Hz, $C-H_{ar}$), 6.95 (t, 1H, *J* = 7.52 Hz, $C-H)_{ar}$, 6.02 (d,1H, *J* = 7.52 Hz, $C-H)_{ar}$, 5.62 (s, 2H, NH_2). ^{13}C-NMR (d_6-DMSO) δ/ppm: 185.00 (C=S), 165.32 $(CH=N)_{imine}$, 163.18 (C-OH), 152.76 $(C=N)_{triazole}$, 131.01 $(C=C)_{ar}$, 130.00 $(C=C)_{ar}$, 120.00 $(C=C)_{ar}$, 118.03 $(C=C)_{ar}$, 117.68 $(C=C)_{ar}$. IR (cm^{-1}): 3454(s) (OH), 3385, 326373171 (NH_2/NH), 3069 $(C-H)_{ar}$, 1637 $\nu(CH=N)_{imine}$, 1617 $\nu(C=N)_{triazole}$, 1566-1472 $(C=C)_{ar}$, 1244 (C=S). Anal. Calcd. %, for $C_9H_9N_5OS$ (M_r = 235.27): C 45.95, H 3.86, N 29.77, S 13.63; found: C 45.98, H 3.90, N 29.73, S 13.70.

3. RESULTS AND DISCUSSION

3.1. FT–IR Measurements of 2 and 3a-d

The IR spectroscopy data are given in Table 1 for **2** and **3a-d** (Figures A1-A5). The band of ν(OH) stretching vibration in the aromatic ring was observed at 3454 cm^{-1} and a band showing extensive H-bond interaction was also observed at 2974 cm^{-1} in the same region for **3d**. The NH_2 group gives two N-H vibration absorption bands, asymmetrical and symmetrical. Asymmetrical stretching vibration is observed at higher frequency than the symmetrical one. Asymmetrical (ν_{as}) and symmetrical (ν_s) stretching vibrations of NH_2 group were found to be 3385 and 3297 cm^{-1} for **2**. These bands were located in the range of 3394-3385 and 3281-3259 cm^{-1}, respectively in the IR spectra of compounds **3a-d**. It has been reported in the literature that N-H asymmetrical and symmetrical vibrations of the triazole-based compound are observed at 3331 and 3253 cm^{-1} [42]. The N-H vibration band of 1,2,4-triazole was found as 3182 cm^{-1} for **2**, 3191 cm^{-1} for **3a,** 3189 cm^{-1} for **3b** and 3171 cm^{-1} for **3d**. This band was not observed in compound **3c** due to the very rapid thione-thiol tautomerism exchange. Aromatic ν(C-H) stretching vibration bands were observed at 3137 cm^{-1} for **3a**, 3103 cm^{-1} for **3b,** 3112 and 3061 cm^{-1} for **3c** and 3069 cm^{-1} for **3d**. Sharp absorption bands belonging to imine groups ν(CH=N) of compounds **3a-d** showing Schiff base formation were observed in the range of 1660-1637 cm^{-1}.

Table 1. Some selected IR^a frequencies (cm^{-1}) of the prepared compounds **2** and **3a-d**.

Comp	O-H	NH_2/ NH	$(C-H)_{ar}$	$(C-H)_{aliph}$	CH=N	C=N	C=C	C=S
2		3385(w) 3297(w) 3182(w)				1651(s)		1269(m)
3a		3394(w)) 3281(w) 3191(w)	3137(w)		1654(s)	1636(s)	1602-1461(s)	1268(m)
3b		3392(w) 3259(w) 3189(w)	3103(w)	2974(w)	1652(s)	1636(s)	1620-1457(s)	1277(m)
3c			3112(w) 3061(w)	2845(w)	1660(s)	1642(s)	1618-1458(s)	1271(m)
3d	3454(s)	3385(w) 3263(w) 3171(w)	3069(w)		1637(s)	1617(s)	1566-1472(s)	1244(m)

[a] ATR technique.
w: weak, m: medium, s: sharp.

IR spectroscopy is of great importance in the structure analysis of triazoles. Stretching vibration bands observed at 1572 and 1562 cm^{-1} for C=N group are characteristic bands for the triazole ring [43, 44]. The stretching vibration bands of ν(C=N) for compound **2** and **3a-d** were observed at 1651 cm^{-1} and 1642-1617 cm^{-1}, respectively. The aromatic vibration bands of ν(C=C) were exhibited in the range of 1602-1461 cm^{-1} for **3a**, 1620-1457 cm^{-1} for **3b**, 1618-1458 cm^{-1} **3c** and 1566-1472 cm^{-1} for **3d**. The IR spectrum is also important in elucidating the thione-thiol tautomeric structures of **2** and **3a-d** compounds (Figure 3).

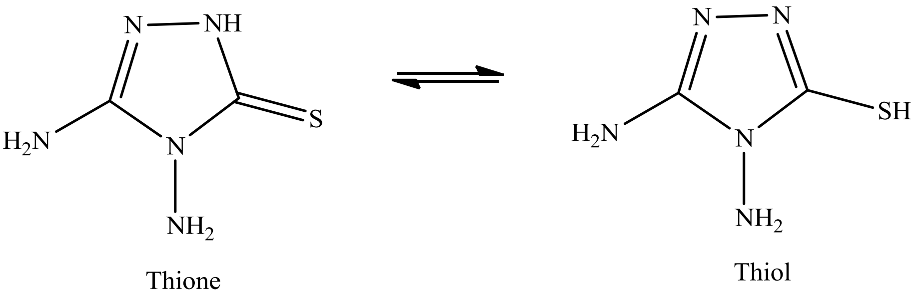


Figure 3. Tautomeric forms of **2**.

Stretching vibration band of C=S group gives characteristic band for thione at 1258 cm^{-1} [45], 1189 cm^{-1} [46] and 1166 cm^{-1} [47] cm^{-1}. The indicator of the synthesized **2** and **3a-d** compounds in the form of thione is the formation of a sharp C=S vibration band at 1269 cm^{-1}.and in the range of 1271-1244 cm^{-1}, respectively. Because the C=S bond is weaker than the C=N bond and is observed at lower frequency [48, 49]. The examinations on the thione-thiol tautomer have shown that the predominant form in the gas phase and solution is the thione tautomer [**Hata! Yer işareti tanımlanmamış.**].

3.2. ^{1}H-NMR and ^{13}C-NMR spectra of 2 and 3a-d.

NMR (^{1}H and ^{13}C) spectra of compounds **2** and **3a-d** (Figures A1-A5) were taken in DMSO-d$_6$ solvent at 25 °C and TMS was used as internal standard. NMR (^{1}H and ^{13}C) assignments were given in Table 2 and 3 for compounds **2** and **3a-d**. Compound **2** can exist in two tautomeric forms, 4,5-diamino-4*H*-1,2,4-triazole-3-thiol and 3,4-diamino-1*H*-1,2,4-triazole-5(4*H*)-thione. The spectral analysis of compound **2** exhibits that it exists in the second form. It was determined that the peak observed at δ 12.42 ppm in the ^{1}H-NMR spectrum belonged only to NH instead of SH. Confirmation of this comes from the absence of the ν(S-H) absorption band, which should be observed at 2500 cm^{-1} in the IR spectrum. The ^{1}H NMR spectrum of **2** also displayed two singlets with intensity of 2H for two NH$_2$ group protons at δ 5.23 (C-NH$_2$) and δ 5.95 ppm (N-NH$_2$). The NMR spectra of **3a, 3b** and **3d** exhibited downfield signal with 1H intensity appearing at δ 13.73, 13.85 and 12.98 ppm, respectively were attributed to the NH proton. This peak was not observed in compound **3c** because of the rapid exchange of thione-thiol tautomerism. The peak observed at 5.23 ppm in the starting material (**2**) for NH$_2$ protons attached to a carbon atom of triazole ring was not observed in the new **3a-d**. In addition, the observation of a new peak of CH=N proton in **3a-d** indicates the formation of Schiff Bases. The CH=N proton in the **3a-d** compounds appeared in the range of 8.50-8.05 ppm.

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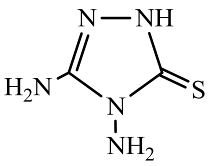
These data are in good agreement with the values (8.62 and 9.69 ppm) of similar compounds [50, 51]. If the formation of Schiff base was with the NH_2 group attached to the nitrogen atom in the 1,2,4-triazole ring, the CH=N proton should have been observed in the lower field due to the disshielding of C=S group [**Hata! Yer işareti tanımlanmamış.**, 52]. It was understood that a singlet with 1H intensity observed at δ 9.10 ppm in the NMR spectrum of **3d** belonged to the OH proton of the aromatic ring. The differently substituted aromatic rings protons in compounds **3a-d** were observed in the range δ 7.63-6.02 ppm. On the other hand NH_2 moieties on 1,2,4-triazole rings of Schiff bases **3a-d** were shifted downfield (δ 5.95-5.62 ppm) when compared to the chemical shift of NH_2 group in compound **2** (δ 5.23 ppm). The protons of NH_2 and OH groups were observed at 5.78 and 10.21 ppm, respectively in similar compounds [**Hata! Yer işareti tanımlanmamış.**, 50]. Two singlets for two OCH_3 protons with 3H intensity each have been seen at 3.90 and 3.85 ppm for compound **3b**. A singlet for $N(CH_3)_2$ protons with 6H intensity was observed at 3.15 ppm for compound **3c**.

Table 2. ^{1}HNMR chemical shifts (ppm) with coupling constants and assignments for compounds **2** and **3a-d**.



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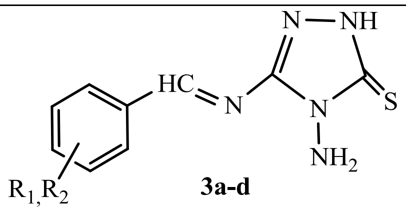

3a-d

Comp	NH	OH	$(CH=N)_{imine}$	$(C\text{-}H)_{ar}$	$C\text{-}NH_2$	$N\text{-}NH_2$	OCH_3 or $N(CH_3)_2$
2	12.42 (s, 1H)				5.23 (s, 2H)	5.95 (s, 2H)	
3a	13.73 (s, 1H)		8.05 (s, 1H)	7.63-7.53 (m, 5H)		5.80 (s, 2H)	
3b	13.85 (s, 1H)		8.10 (s, 1H)	7.46-7.23 (m, 3H)		5.82 (s, 2H)	3.90 (s, 3H) 3.85 (s, 3H)
3c			8.12 (s, 1H)	7.25 (d, 2H ^3J= 7.60 Hz) 6.85 d, 2H ^3J= 7.60 Hz)		5.85 (s, 2H)	3.15 (s, 6H)
3d	12.98 (s, 1H)	9.10 (s, 1H)	8.50 (s, 1H)	7.46 (d, 1H, ^3J= 7.51 Hz) 7.33 (t, 1H, ^3J= 7.52 Hz) 6.95 (t, 1H, ^3J= 7.52 Hz) 6.02 (d,1H, ^3J= 7.52 Hz)		5.62 (s, 2H)	

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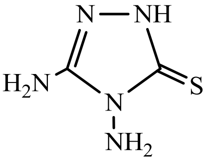
Thiol and thione tautomers can also be characterized by the ^{13}C NMR spectra. In the ^{13}C NMR spectra of the compounds, the peak of the C=S carbon atom was observed at 163.87 ppm for **2**, 178.02 ppm for **3a**, 187.23 ppm for **3b**, 190.16 ppm for **3c** and 185.00 ppm for **3d**. Carbon atoms of CH=N and C=N groups also showed down field signals in the ranges of 165.32-160.00 and 155.33-148.42 ppm, respectively for **3a-d**. Substituted carbons resonated at 151.32 and 150.67 ppm for **3b**, at 153.48 ppm for **3c** and at 163.18 ppm for **3d**. Compound **2** shows a signal at 152.75 ppm for C=N group carbon of triazole ring. This band was observed in the range of aromatic ring carbons (C=C) were observed in the aromatic region for the Schiff bases in the range 133.70-128.37 ppm for **3a**, 129.98-117.63 ppm for **3b**, 133.15-111.42 ppm for **3c** and 131.01-117.68 ppm for **3d**. A peak has been seen at 58.24 ppm for OCH_3 carbons in the ^{13}C NMR spectrum of **3b**. ^{13}C NMR spectrum of **3c** showed a peak at 40.24 ppm for two CH_3 carbons.

Table 3. ^{13}C NMR chemical shifts (ppm) and assignments for compound **2** and **3a-d**.



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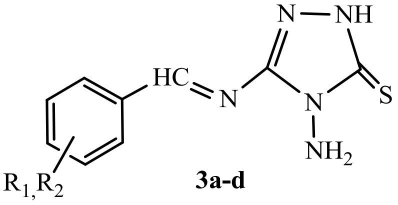

3a-d

Comp	C=S	$(CH=N)_{imine}$	$C\text{-}OCH_3$ $C\text{-}N(CH_3)_2$ C-OH	$(C=N)_{triazole}$	$(C=C)_{ar}$	OCH_3 or CH_3
2	163.87			152.75		
3a	178.02	160.00		152.10	133.70-128.37	
3b	187.23	163.32	151.32 and 150.67	148.42	129.98-117.63	58.24
3c	190.16	165.23	153.48	155.33	133.15-111.42	40.24
3d	185.00	165.32	163.18	152.76	131.01-117.68	

4. CONCLUSIONS

In conclusion, we have synthesized **2** from the starting materials **1** and hydrazine hydrate. New Schiff bases of **2** with various aromatic aldehydes have also been prepared. All of the synthesized compounds were characterized by spectral (IR, ^{1}H and ^{13}C NMR), and elemental analysis. The results obtained from the analyzes are compatible with the proposed structure of **2** and newly synthesized compounds **3a-d** as shown in Figures 1 and 2.

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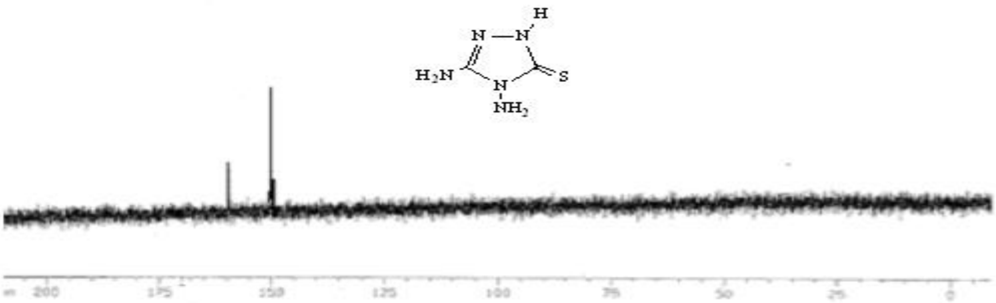
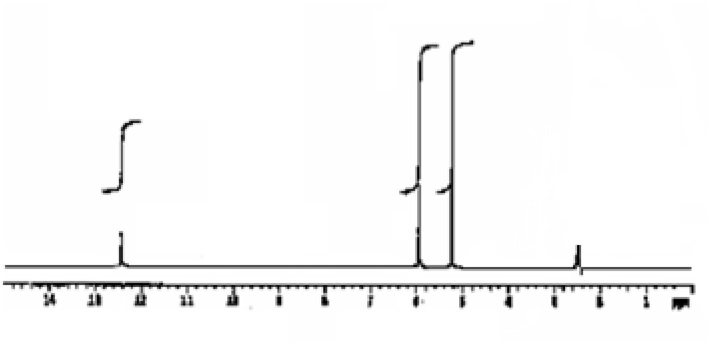
APPENDICES





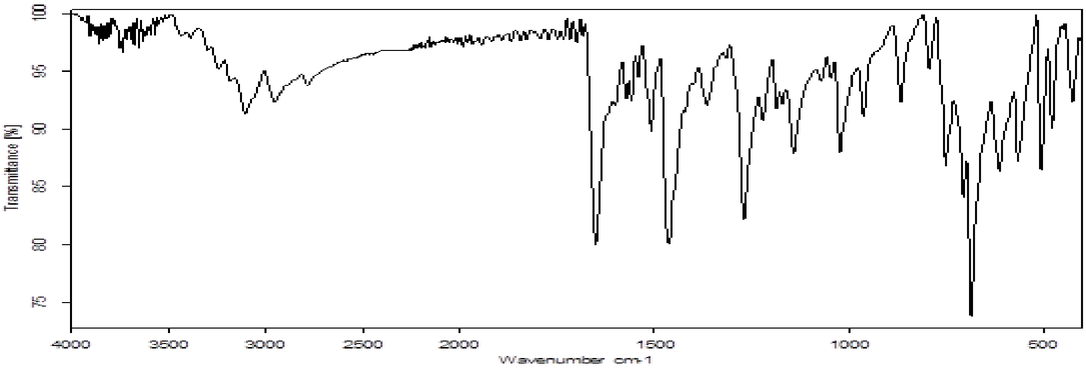
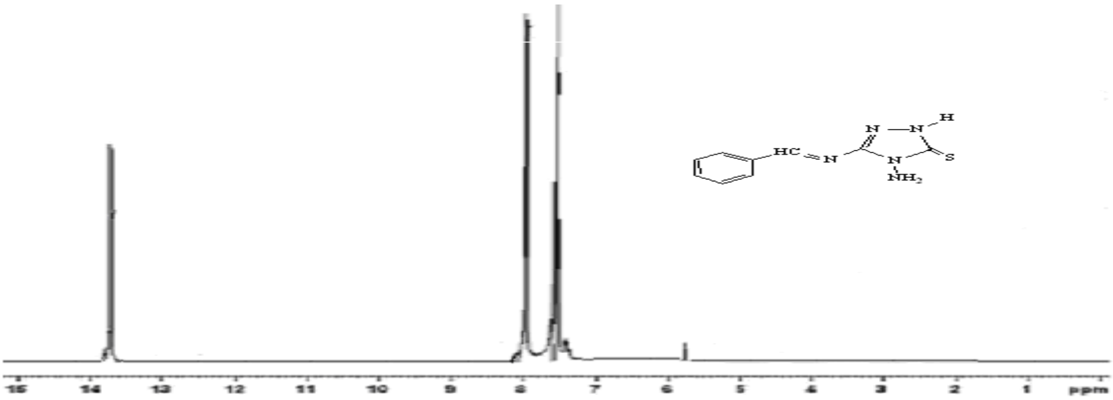
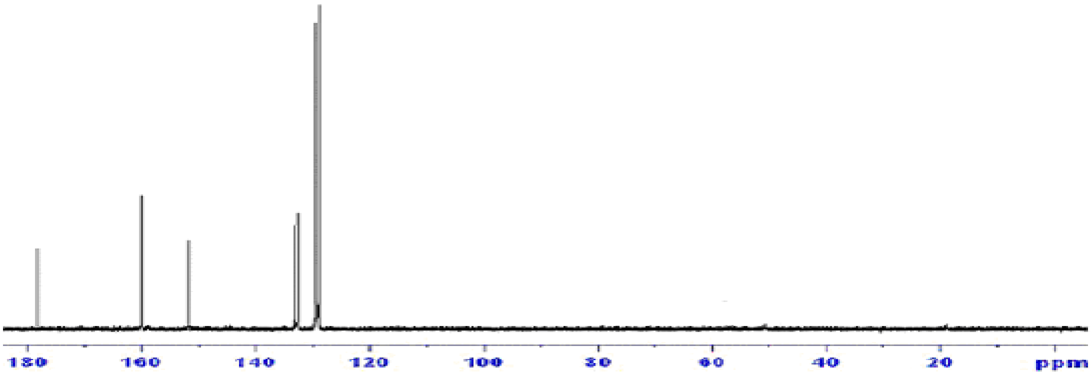


Figure A1. ^{1}H and ^{13}C NMR and IR spectra of **2**.





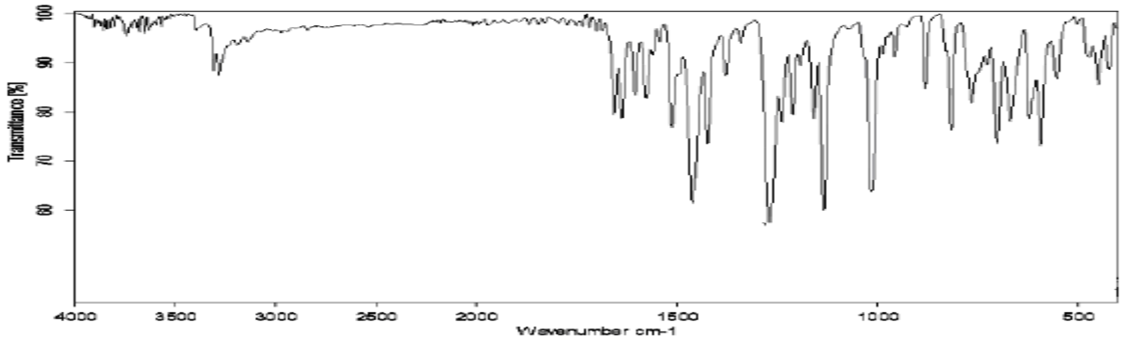
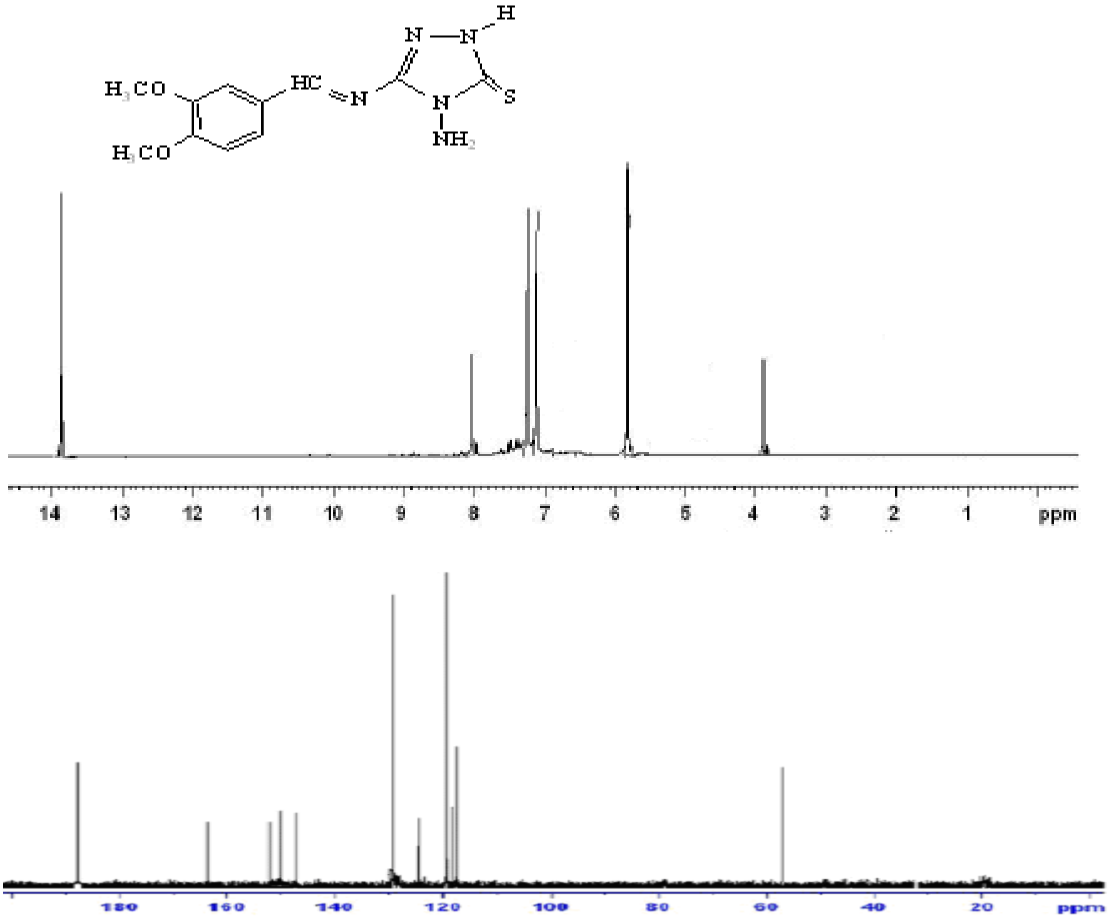


Figure A2. ^{1}H and ^{13}C NMR and IR spectra of **3a**.



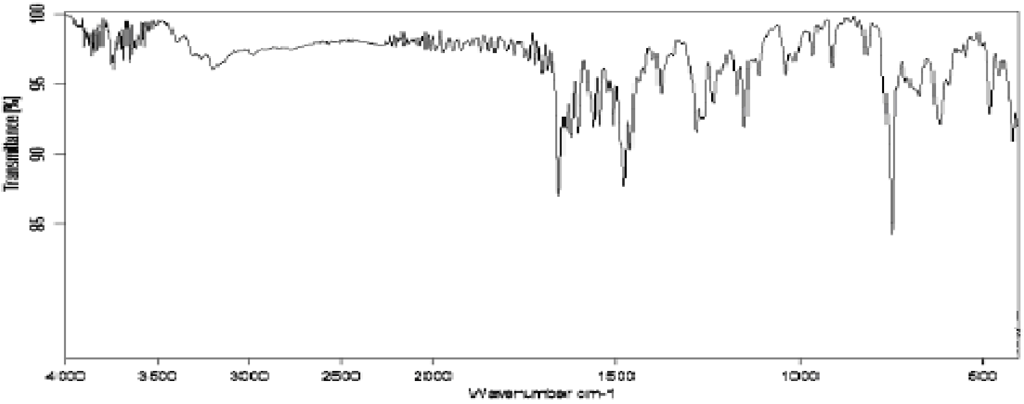
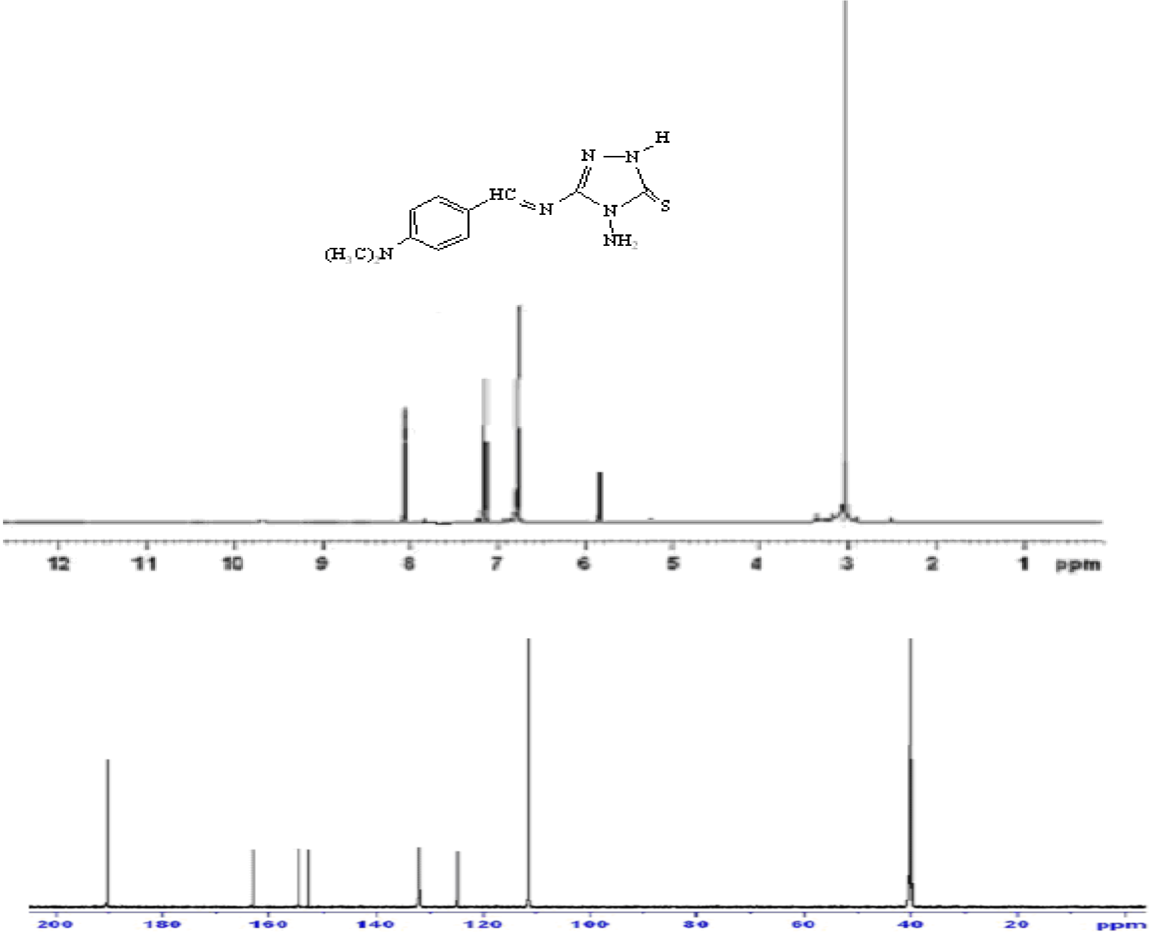


Figure A3. ^{1}H and ^{13}C NMR and IR spectra of **3b**.



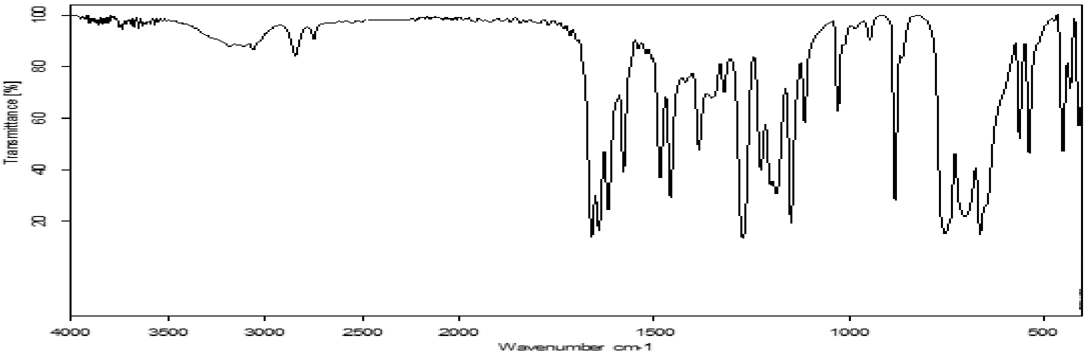
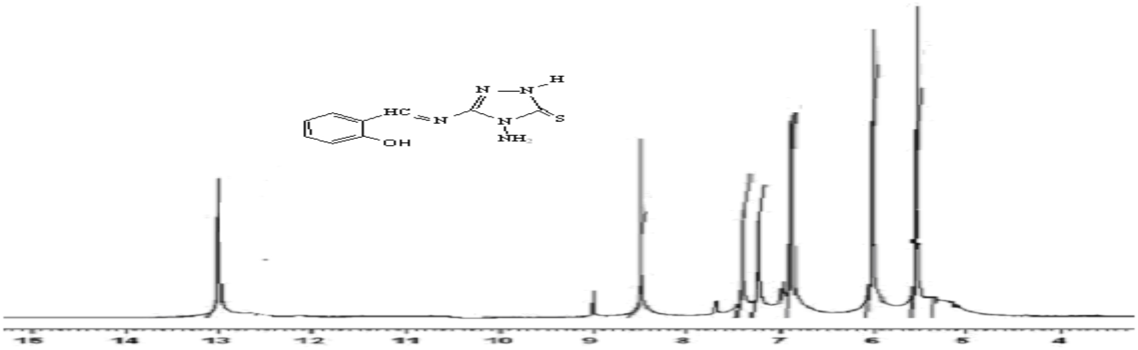
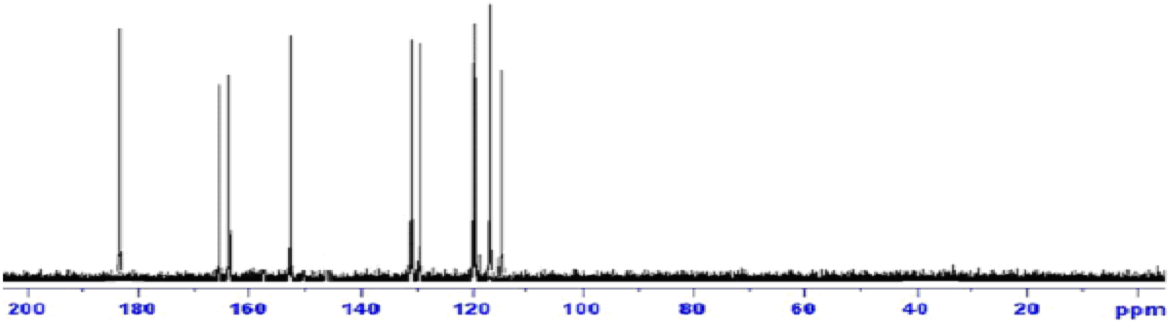


Figure A4. ^{1}H and ^{13}C NMR and IR spectra of **3c**.





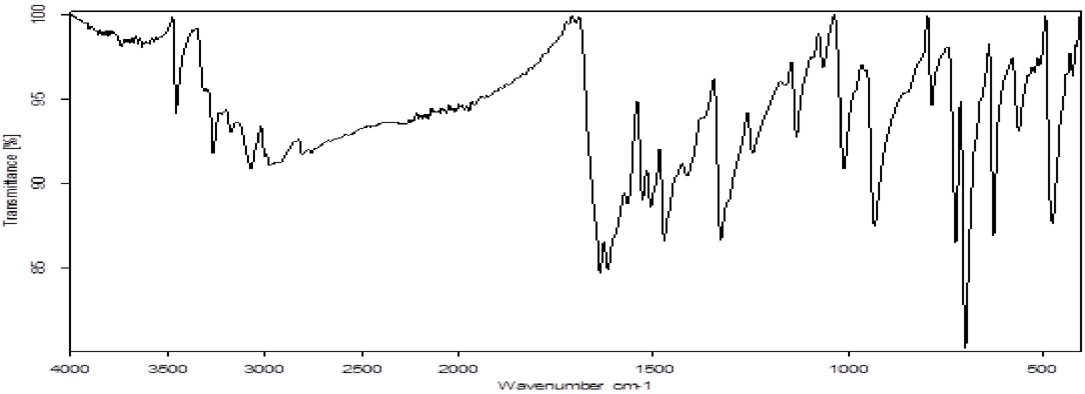


Figure A5. ^{1}H and ^{13}C NMR and IR spectra of **3d**.