Schiff bases having a triazole ring bearing a pyridyl moiety are synthesized, and their biological activities are studied

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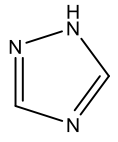
ABSTRACT

The most frequently used organic compounds are Schiff bases. They have been demonstrated to have a broad variety of biological activities. Using a thermal method, the synthesis of a series of imine derivatives 4a-f from Amino triazole thiol (3) as starting material with six different aldehydes. Target compounds' full characterization was achieved using ^{1}H and ^{13}C- NMR, mass spectra, and FT-IR. In the ^{1}H-NMR spectra of compounds (4a-f), an isotope with a proton signal for the CH of the azomethine group that ranged from 8 to 10.30 ppm was observed. Due to labile hydrogen bonds with nitrogen and sulfur, compound 3 exists in two tautomeric forms. Synthesis compounds' antibacterial activity was investigated against the bacteria *Klebsiella*, *E. coli* and, *S. aureus.*

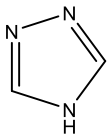
Keywords: Azomethine compounds, pyridine-4-carbohydrazide, Isoniazid, Amino triazole thiol, and Imines

1. Introduction

Organic chemistry in pharmaceutical research is focused on the development of novel, safe, and clinically useful therapeutic agents.[1]. Recently, five-membered heterocyclic compounds have proven to be important as biological activity sites. [2-4]. Nitrogen heterocycles are prevalent in most pharmaceuticals. Beginning with imidazole as an essential component of drug research resulted in the creation of triazole, an imidazole isotope among which the imidazole's carbon atoms are replaced with nitrogen atoms. [5-7]. A modified 1,2,4-triazole ligand was synthesized in this study. Two distinct tautomeric forms of 1,2,4-triazoles exist; 1H(1a) or 4H-[1,2,4]-triazoles(1b).



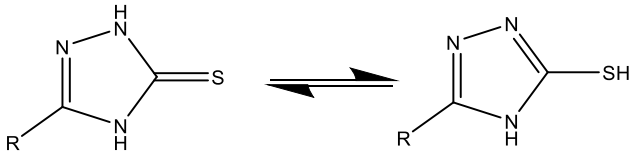
1*H*-1,2,4-triazole
1a



4*H*-1,2,4-triazole
1b

Due to labile hydrogen bonds with nitrogen and sulfur, a pair of tautomeric forms of the [1,2,4]-triazoles-3-thiol are known to exist. It has the tautomeric thione-thiol forms shown below.

Thione is the most common form of this compound (2) [8].



2a 2b

Many medicines and agrochemicals contain 1, 2, 4-triazole. Commercial dragees such as fluconozole and terconazole contain the triazole ring with 1,2,4 substitution. The triazole nucleus participates in a variety of pharmacological actions, including antibacterial, antiviral, and antifungal effects [9].
As a result of condensing carbonyl compounds and primary amines, Schiff bases have an azomethine group [10]. Literature studies have reported the antifungal, antitumor, antibacterial, and anti-inflammatory properties of Schiff bases having a triazole ring [11].
The current study aims to investigate the biological activities of Schiff bases synthesized with a triazole ring having a pyridyl moiety.

2. Experimental section

2.1 Chemicals and Instruments

CDH (Chemical Drug House) in India provided the isoniazid (isonicotinic acid hydrazide). Organic compounds include hydrazine hydrate, potassium hydroxide, carbon disulfide, methanol, ethanol, glacial CH_3COOH, DMSO, anhydrous ether, and Carbonyl compounds (6-methoxy-2-naphthaldehyde, 2-hydroxy-1-naphthaldehyde, 2-oxoacetic acid, 2,2,2-trichloroacetaldehyde, terephthalaldehyde and glutaraldehyde), Open glass capillaries were used to measure the melting points of the produced compounds. The IR spectrum was recorded on an ALPHA FTIR spectrometer (Bruker), A 400 MHz Bruker Avance spectrophotometer was used to record the ^1H and ^{13}C Nuclear Magnetic Resonance spectra, while ESI Jeol SX-102 mass spectrometers were used to record the mass spectra.

2.2 Synthesis methods

2.2.1. Synthesis of 4-Amino-5-pyridin-4-yl-4H-[1,2,4]triazole-3-thiol (3)

The isonicotinohydrazide (13.7 g, 0.1 mol) was dissolved in 150 mL of 98% ethanol that also included 11.2 g, 0.1 mol of KOH., followed by the addition of carbon disulfide (13.17 mL, 0.21 mol). Dilute the mixture with dry diethyl ether (100 mL) after stirring for 16 hours. Under vacuum at 65-70°C, the product is filtered out and dried. A quantitative yield of almost % was obtained from the salt of potassium dithiocarbazate made as previously mentioned. $NH_2NH_2.H_2O$ (0.02 mol, 99%) was gradually added to the water-soluble dithiocarbazic acid potassium salt (100 mL) while mixing and refluxing on a water bath till the release of hydrogen sulfide gas ended. TLC coated with silica gel was used to monitor the reaction. It is acidified with concentrated hydrochloric acid after cooling. To produce 4-amino-3-pyridin-4-yl-1H-1,2,4-triazole-5-thione, the product was refined by recrystallization from ethyl alcohol after being filtered, and rinsed with cold water.
Chemical Formula: $C_7H_7N_5S$; Molecular Weight: 193.23 ; melting point 250-253 °C.; IR (cm^{-1}, KBr):3250 and 3213(NH_2 stretch), 2736(S-H stretch), 1645(C=N stretch) and 637(C-S stretch); ^{1}HNMR (dimethylsulphoxide-d6, δ ppm):5.3(2H,s,NH_2), 8-8.7(4H,aromatic ring) and 14 (1H,s,SH). Fig (1)

2.2.2 The general method of producing Schiff compounds derived from amino triazole thiol (4a-f)

A molar balance of amino triazole thiol and In a 10 mL ethanol solvent containing half mL from acetic acid as a catalyst, the corresponding aldehyde is dissolved. For 6-10 hours, the mixture was warmed at 60°C. Once completed (TLC), we stopped the reaction and kept it at r.t overnight. After filtering, cold ether was used to wash the solid precipitate (20 mL x 3), dried, and purified by recrystallization (hot ethanol) 4a–e.

1- (E)- 4-(((6-methoxynaphthalen-2-yl) methylene) amino)-5-pyridin-4-yl-4H-[1,2,4]-triazole-3-thiol (4a)

Molecular formula: $C_{19}H_{15}N_5OS$; MW: 361.10 ; thin layer chromatography (Retention factor value): 0.65; m.p 264-265°C; IR (cm^{-1}, KBr): 3400 (N-H, stretch); 3091 (C-H, stretch Ar.); 2974(C-H, stretch alph.); 2389(S-H); 1614-1597 (C=N stretch); 1535-1492 (C=C, stretch); 1367 (C-N stretch) as shown in fig.2; ^{1}H NMR (Dimethylsulphoxide-d6, δ ppm): 3.90 (s,3H,(OCH_3), 8.78-7.43 (C-H Ar); 8.84 (s,1H,-N=CH), 14.14(s,1H,(SH)); as shown in fig3 ; ^{13}C-NMR (Dimethylsulphoxide-d6, δ ppm): 175(C-SH);162(C-OCH_3);158 (N=CH); 140-105 (pyridine and phenyl ring); 58 (O-CH_3); as shown in fig.4, (Mass (m/z): 361

2- (E)-1-(((3-mercapto-5-(pyridin-4-yl)-[4H-1,2,4]-triazol-4-yl)imino) methyl) naphthalen-2-ol (4b)

Molecular formula: $C_{18}H_{13}N_5OS$; MW: 347.08; thin layer chromatography (Retention factor value): 0.55; m.p 270-271°C ; IR (cm^{-1}, KBr): 3419 (N-H Str.); 3062 (C-H, stretch .Ar); 3043 (C-H, stretch Ar); 2883(CH=N);2632 (S-H stretch); 1620-1577(C=N, stretch); 1465 (C=C, stretch); 1379 (C-N stretch); 1240 (C-O stretch) as shown in fig. 5 ; ^{1}H NMR (Dimethylsulphoxide-d6, δ ppm): 7.24-8.68((=C-H phenyl ring),8.74-876((=C-H pyridine ring), 10.24(s,1H,(-N=CH),11.21(s,1H,(O-H), 14.41(s,1H,(S-H)); as shown fig. 6; ^{13}C NMR (Dimethylsulphoxide-d6, δ ppm):165(C-SH);160(C-OH) 152 (N=CH, pyridine ring); 150 (N=CH triazole ring); ; 138 (N=CH Schiff base); 135-100 (CH=CH phenyl ring) asshown in fig. 7; Mass (m/z): 347

3- (E)-2-(((3-mercapto-5-(pyridin-4-yl)-[4H-1,2,4]-triazol-4-yl)) imino)acetic acid (4c)

Molecular formula: $C_9H_7N_5O_2S$; MW: 249.03; TLC (Retention factor value): 0.73; m.p 230 °C, IR (cm^{-1}, KBr): 3253 (N-H Stretch); 3149-3034 (C-H stretch .Ar); 2889 (N=C-H stretch.); 2580 (S-H stretch.); 1600 (N=CH stretch.); 1554(C=N stretch.); 1494-1419 (CH=CH Ar; 1365 (C-N stretch.); 1217 (C-O stretch) as shown in fig. 8; ^{1}H NMR (Dimethylsulphoxide-d6, δ ppm): 7.77(=C-H pyridine ring) , 8.02 (-N=CH), 8.72 (N=CH pyridine ring); 14.22,(s,1H(S-H)), as shown in fig. 9 : ^{13}C-NMR (Dimethylsulphoxide-d6, δ ppm): 162 (COOH); 151 (C-SH); 145 (CH=N); 132-120(C =C, pyridine ring) as shown fig. 10; Mass (m/z): 249

4- (E)-5-(pyridin-4-yl)-4-((2,2,2-trichloroethylidene) amino)-[4H-1,2,4]-triazole-3-thiol (4d)

Molecular formula: $C_9H_6Cl_3N_5S$; MW: 322.59; TLC (Retention factor value): 0.66; m.p 268°C; IR (cm^{-1}, KBr): 3439 (N-H Stretch); 3088-3034 (C-H stretch Ar); 2868(N=C-H stretch), 2364 (S-H stretch); 1614(N=CH stretch); 1597(C=N stretch); 1552-1494 (CH=CH Ar; 1365 (C-N stretch), 688 (C-S, stretch); 831 (C-Cl stretch) as shown in fig. 11; ^{1}H NMR (Dimethylsulphoxide-d6, δ ppm): 8.78-8.75(=C-H, pyridine ring) ; 8.01 (s,1H,N=CH); 8.01-8.76(=C-H, pyridine ring); 14.16,(s,1H,(S-H)); as shown in fig. 12; ^{13}C NMR (Dimethylsulphoxide-d6, δ ppm): 150.86(C-SH); 145(N=CH) as shown in fig. 13; Mass (m/z): 320.59

5- 4,4'-(((1E,5E)-pentane-1,5-diylidene)bis(azaneylylidene))bis(5-(pyridin-4-yl)-4H-[1,2,4]-triazole-3-thiol) (4e)

Molecular formula: $C_{19}H_{18}N_{10}S_2$; MW: 450.54; TLC (Retention factor value): 0.60; m.p 260°C;; IR (cm^{-1}, KBr): 3433 (-N-H Stretch); 3074-3049 (C-H stretch Ar); 2945-2931 (C-H stretch alphatic); 2870 (CH=N stretch); 2428 (SH stretch); 1614(CH=N stretch); 1598 (CH=N of pyridine ring); 1552-1490(C=C stretch Ar); 1367 (C-N stretch); 688 (C-S str.) as shown in fig. 14; ^{1}H NMR (Dimethylsulphoxide-d6, δ ppm): 1.52-1.04 ($(CH_2)_3$, 8.35 (N=CH); 8.76(N=CH of pyridine ring) 9.60 (N=CH);14.10(s,1H,(SH)); as shown in fig. 15 ; ^{13}C-NMR (Dimethylsulphoxide-d6, δ ppm): 178 (N=CH); 150 (C-SH); 131 (C6 ring of pyridine); 119 (C2, ring of pyridine);62(CH_2-C=N);32(CH2) as shown in fig. 16; Mass (m/z): 450.

2.3 Antibacterial study.[12]

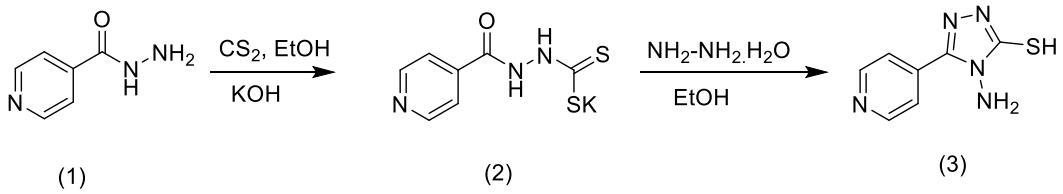
The disc diffusion techniques were demonstrated to have undergone antimicrobial tests. In vitro tests were performed on compounds (4a, 4b, 4c, 4d, 4e, and 4f) to see whether they had any antibacterial activity against *S. aureus, Klebsiella, and E. coli*. This hole in the agar plate was filled with (0.1 ml) of a synthesis compound after it had been injected uniformly and shallowly from a broth culture of

the tested microorganisms in a properly spread-out solidified medium. In order to treat antibiotic bacteria, the chemical was synthesised at concentrations of 1000, 500, 250, and 100 ppm. Ampicillin was employed as an example. Dimethyl sulfoxide was employed as the solvent to achieve unprecedented hole files with DMSO as the controller

3.1 Synthesis of compounds

In accordance with the synthesis scheme (3-1), the intermediates and target compounds were synthesized. The potassium dithiocarbazinate (2) salt is acquired from the treatment of the isonicotinohydrazide [13] in a potassium hydroxide medium with CS_2 and is converted to amino [1,2,4]triazole thiol (3) [14] by hydrazine handling.

3- Results and discussion



Scheme (3-1)

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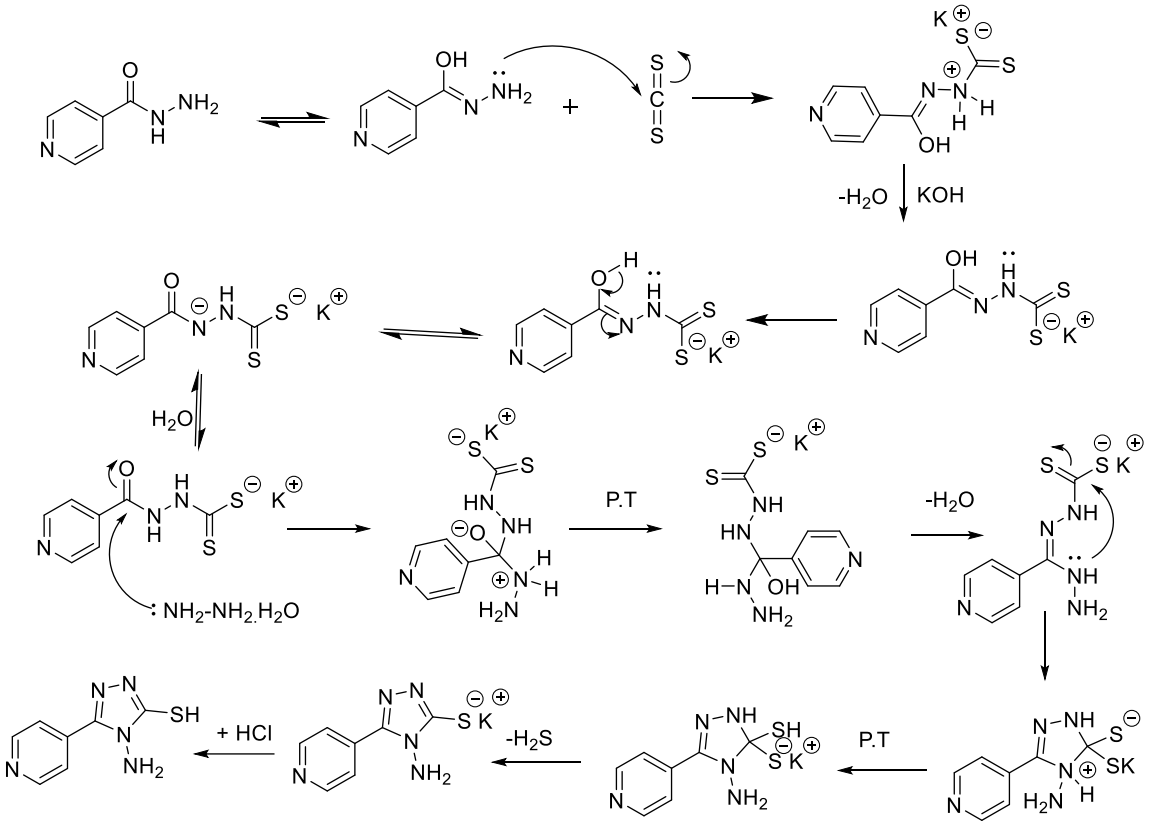
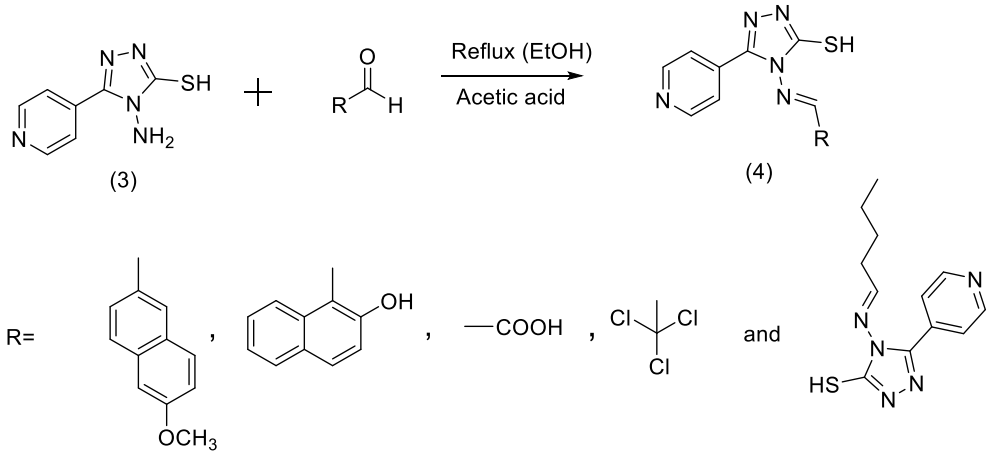
Scheme (3-2 illustrated of the reaction pathway for the production of a compound (3).



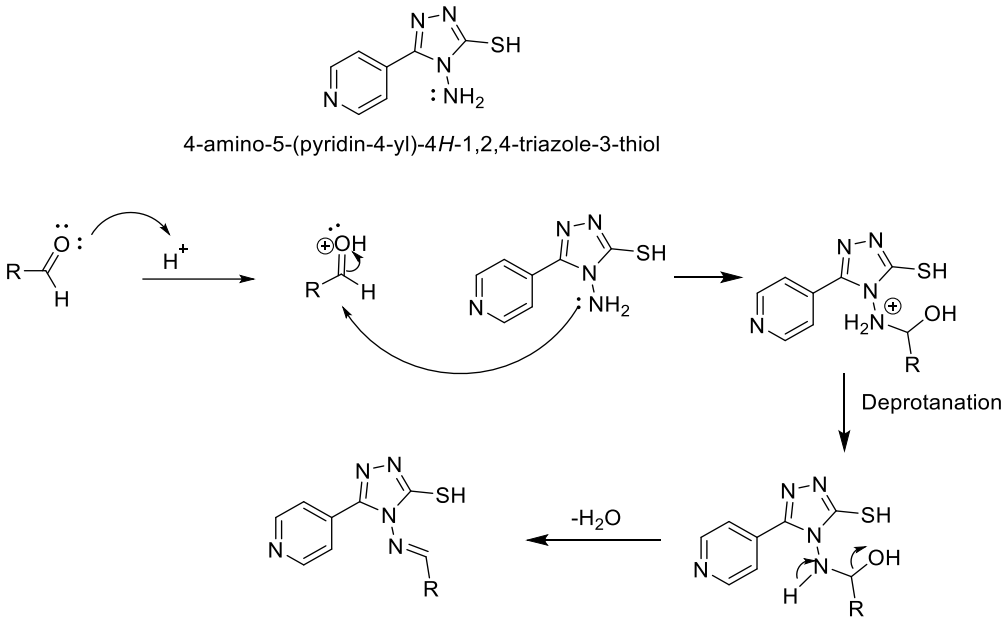
Scheme (3-2)

The synthesis of Schiff base compounds is achieved from the reaction of compound 3 with six different aldehydes [15]. Scheme (3-3) provides the structures of the prepared substances. The prepared compounds were characterized by FT-IR, ^{1}H, and ^{13}C-NMR, and MS (EI). All compounds showed solubility in CH_3CN, EtOH and DMSO, and less in acetone and methanol.



Scheme(3-3)

The reaction process for the preparation of compound (4) was shown in the scheme. (3-4).



Scheme (3-4)

FT-IR and NMR analysis confirmed the formation of compound 3. The triazole ring was formed because the infrared spectra of compounds (4a–f) displayed the unique absorption bands of (C-N) and (Azomethine group) of the triazole unit at (1313–1365 cm^{-1} and 1562–1598 cm^{-1}), respectively. The CH of the azomethine group's proton signal was visible as an isotope range from 8 to 10.30 ppm in the proton nuclear magnetic resonance spectra of compounds (4a-f), while the -SH group was present in compounds (4b, 4d, and 4e). At 14.11–14.41 ppm, these compounds showed the singlet signal of the (S–H) proton on the triazole ring. Compounds (4a, 4c, and 4f) have triazole rings that are thiols since there is no (C=S and N-H) absorption.

3.2 Biological activity

The restraint zones generated by the compounds prepared in the culture medium, which contain three types of bacteria, *Klebsiella*, *Staph aureus* and *E. coli*, were examined. Where the concentration (1000PPM) was used for all compounds, the 4a compound had the greatest biological activity for three types of bacteria. Also, compounds 4d and 4e had inhibitory activity for the two types of bacteria used (*Klebsiella* and *E.Coli*), while compound 4c was effective against *Klebsiella*. While 4b compound did not possess any inhibitory activity. The results are listed in Table (3.1).

Table (3.1): Inhibition Zones of synthesized compounds.

Comp. Symbol	Inhibition zone (mm) *Klebsiella*	Inhibition zone (mm) *Staphylococcuse*	Inhibition zone (mm) ***E . coli***
4a	17 mm	19 mm	20 mm
4b	-	-	-
4c	9 mm	-	-
4d	13 mm	-	20mm
4e	12 mm	-	16 mm

4. Conclusion

In conclusion, starting materials of 4-amino-3-(4-pyridyl)-5-mercapto-4H-[1,2,4]-triazole 3 were used to create a new series of triazole Schiff base derivatives 4a-f. FT-IR, NMR and mass spectra (EI) were applied to fully characterize the compounds that were made. The findings suggested that the thermal method produced more pure products in greater quantities. As active pharmaceutical agents, these brand-new Schiff bases may be utilized. These Schiff bases could be used to make a variety of biologically active heterocycles and ligands for making useful coordination compounds, and from the findings, we deduced that some substances have good biological activity against two Gram-positive and one Gram-negative variety of bacteria.

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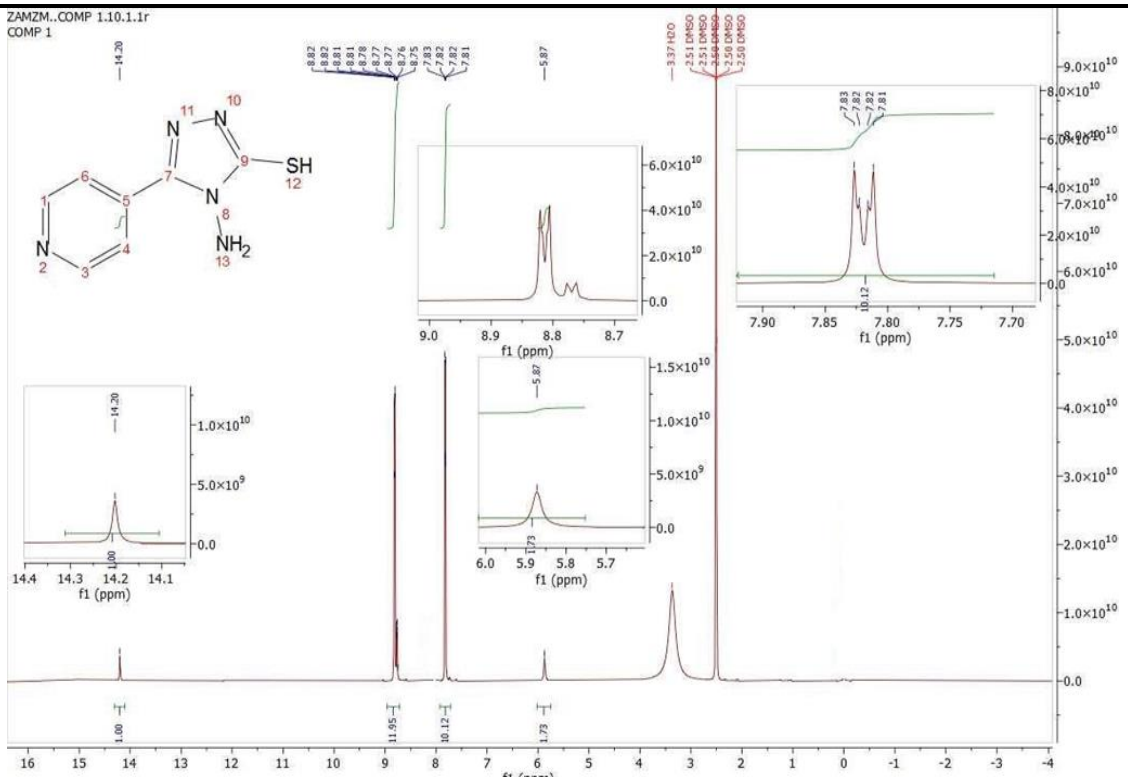

Fig 1: 1H-NMR spectrum of 4-Amino-5-pyridin-4-yl-4H-[1,2,4]triazole-3-thiol

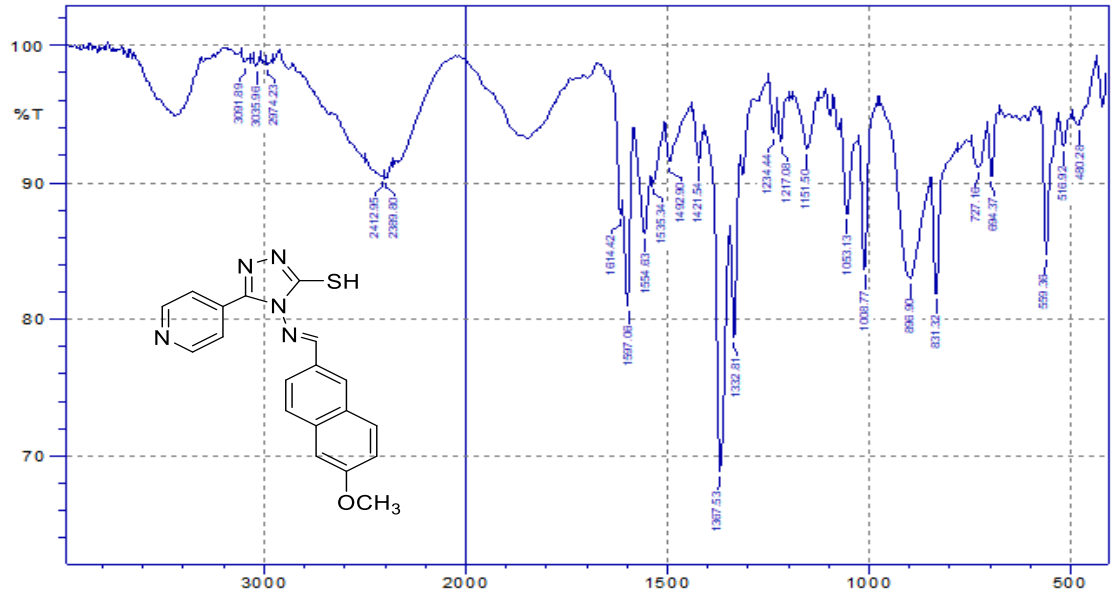

Fig 2: IR spectrum of E)- 4-(((6-methoxynaphthalen-2-yl) methylene) amino)-5-pyridin-4-yl-4H-[1,2,4]-triazole-3-thiol

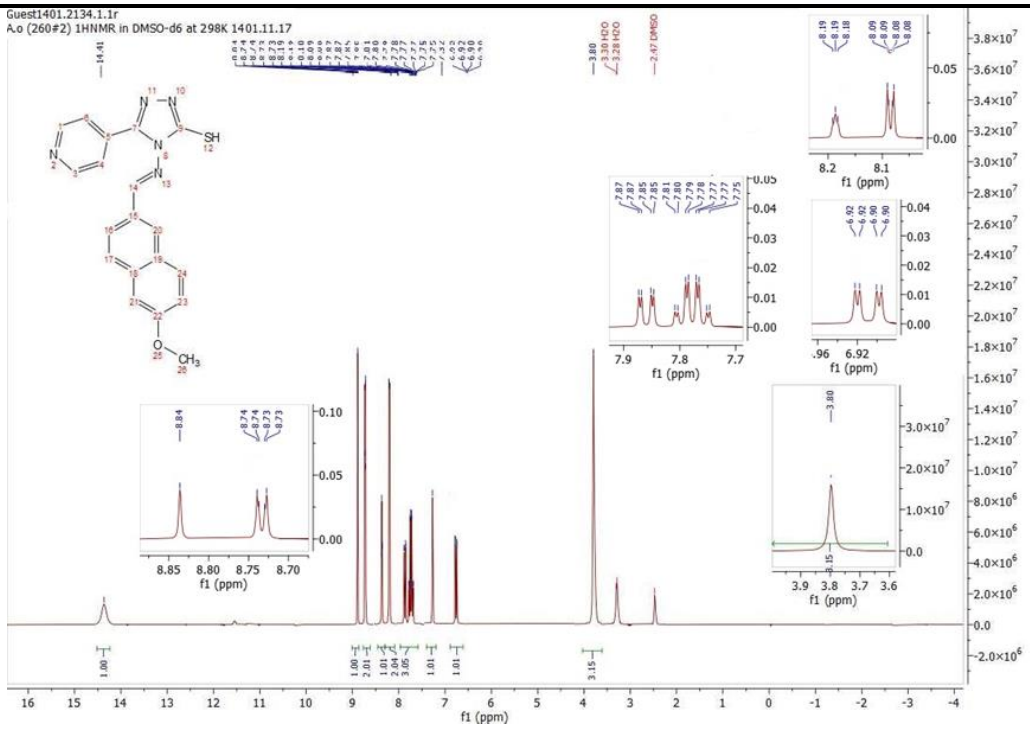

Fig 3: 1H-NMR spectrum of E)- 4-(((6-methoxynaphthalen-2-yl) methylene) amino)-5-pyridin-4-yl-4H-[1,2,4]-triazole-3-thiol

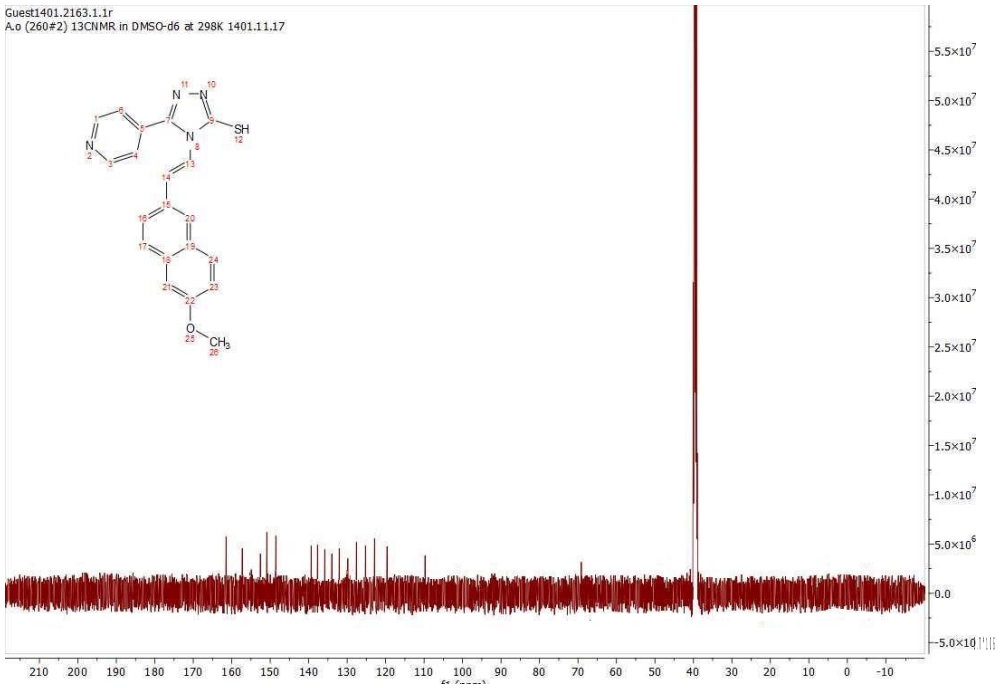

Fig 4: 13C-NMR specrum of E)- 4-(((6-methoxynaphthalen-2-yl) methylene) amino)-5-pyridin-4-yl-4H-[1,2,4]-triazole-3-thiol

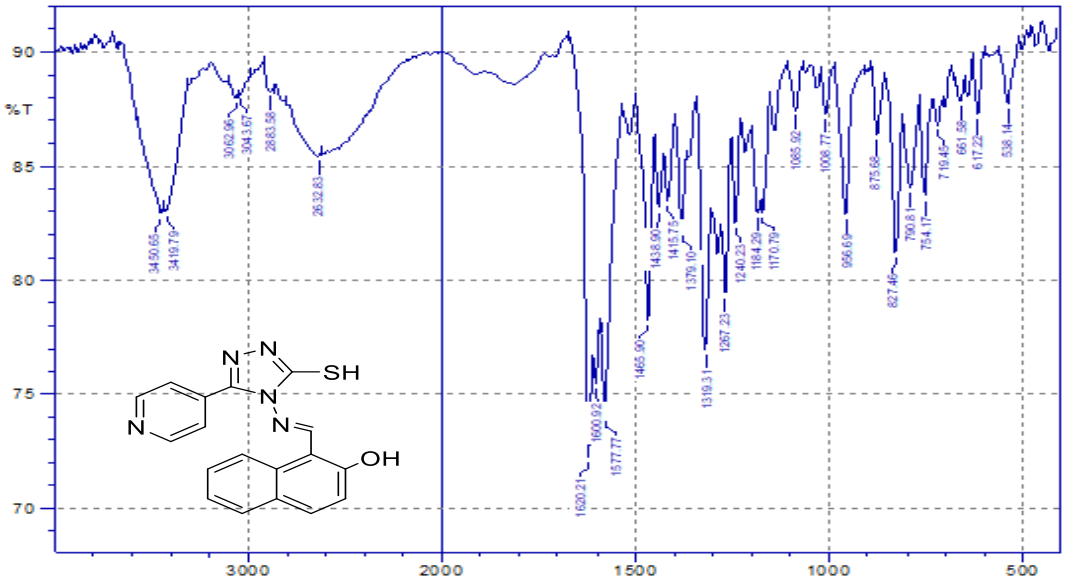

Fig5: IR spectrum of (E)-1-(((3-mercapto-5-(pyridin-4-yl)-[4H-1,2,4]-triazol-4-yl)imino) methyl) naphthalen-2-ol

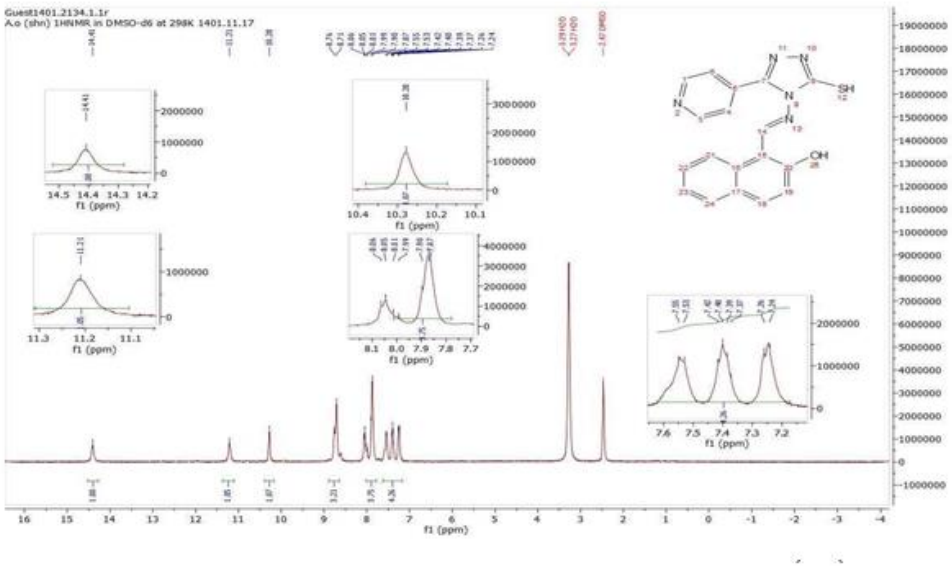

Fig 6: 1H-NMR spectrum of (E)-1-(((3-mercapto-5-(pyridin-4-yl)-[4H-1,2,4]-triazol-4-yl)imino) methyl) naphthalen-2-ol

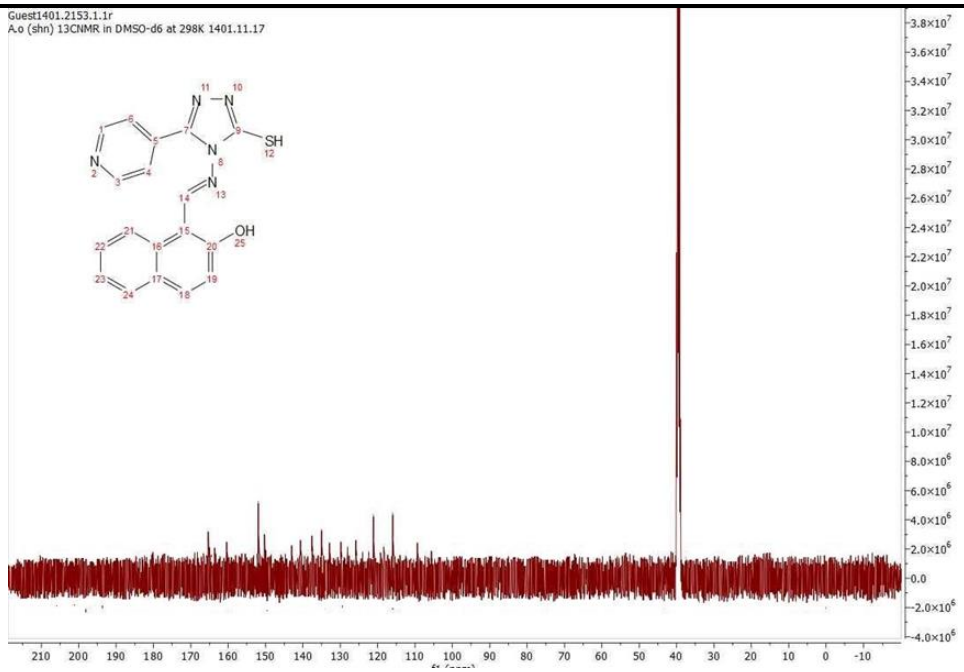

Fig 7: 13C-NMR spectrum of (E)-1-(((3-mercapto-5-(pyridin-4-yl)-[4H-1,2,4]-triazol-4-yl)imino) methyl) naphthalen-2-ol

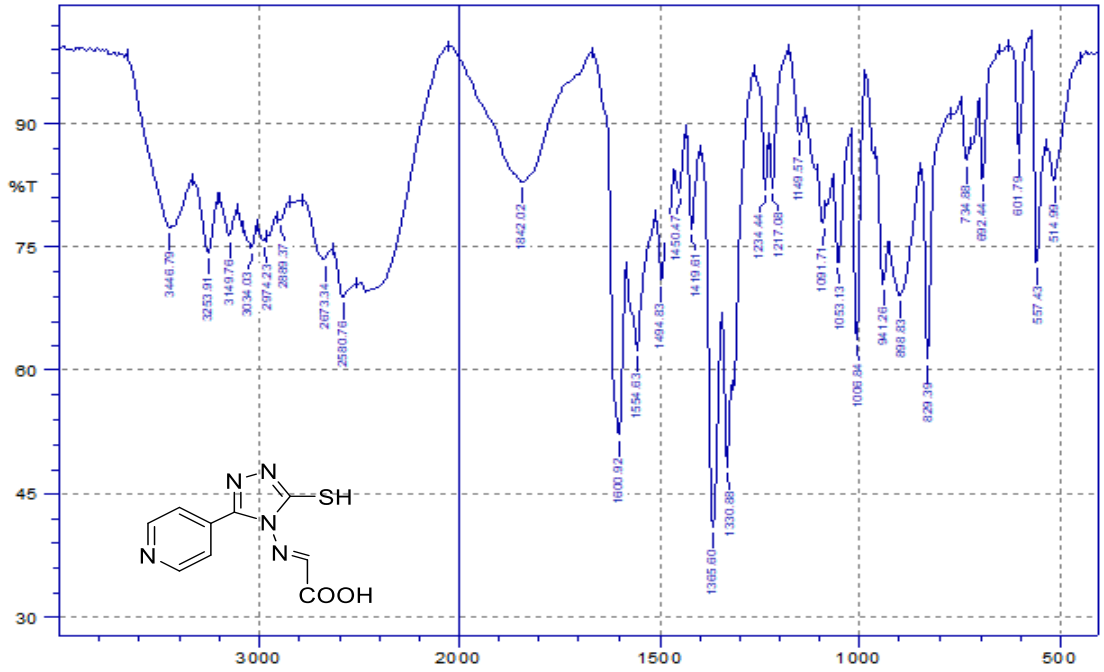

Fig 8: IR spectrum of (E)-2-(((3-mercapto-5-(pyridin-4-yl)-[4H-1,2,4]-triazol-4-yl)) imino)acetic acid

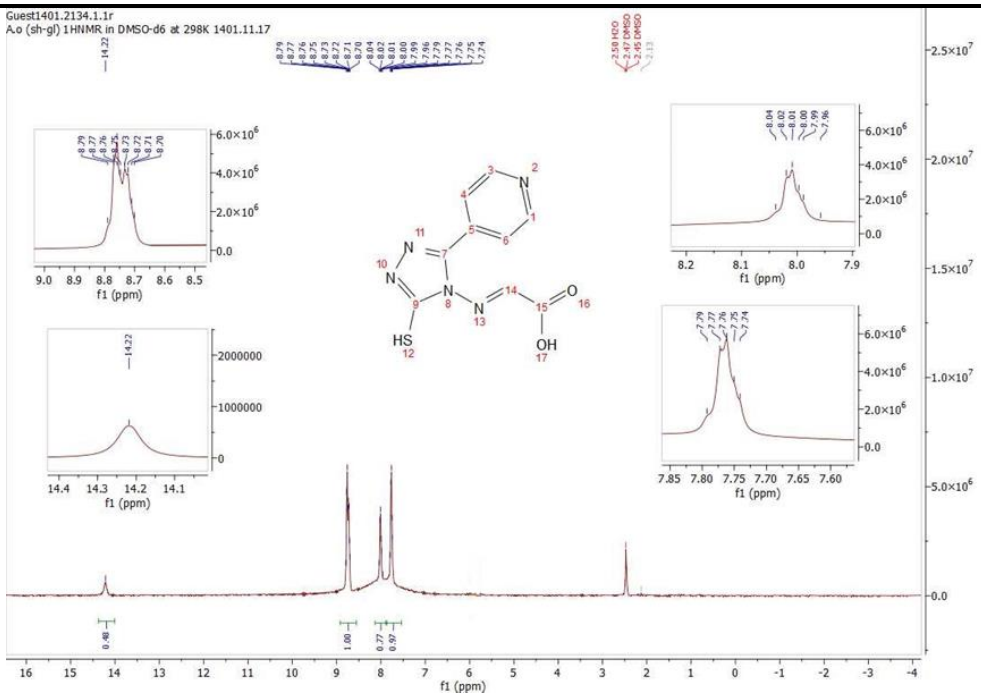

Fig 9: 1H-NMR spectrum of (E)-2-(((3-mercapto-5-(pyridin-4-yl)-[4H-1,2,4]-triazol-4-yl)) imino)acetic acid

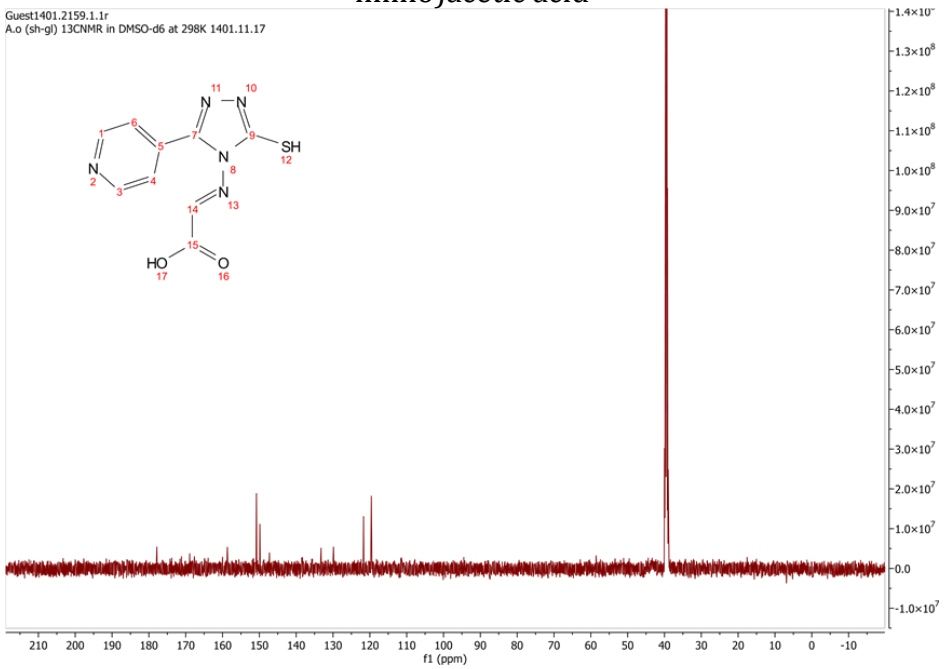

Fig 10: 13C-NMR spectrum of (E)-2-(((3-mercapto-5-(pyridin-4-yl)-[4H-1,2,4]-triazol-4-yl)) imino)acetic acid

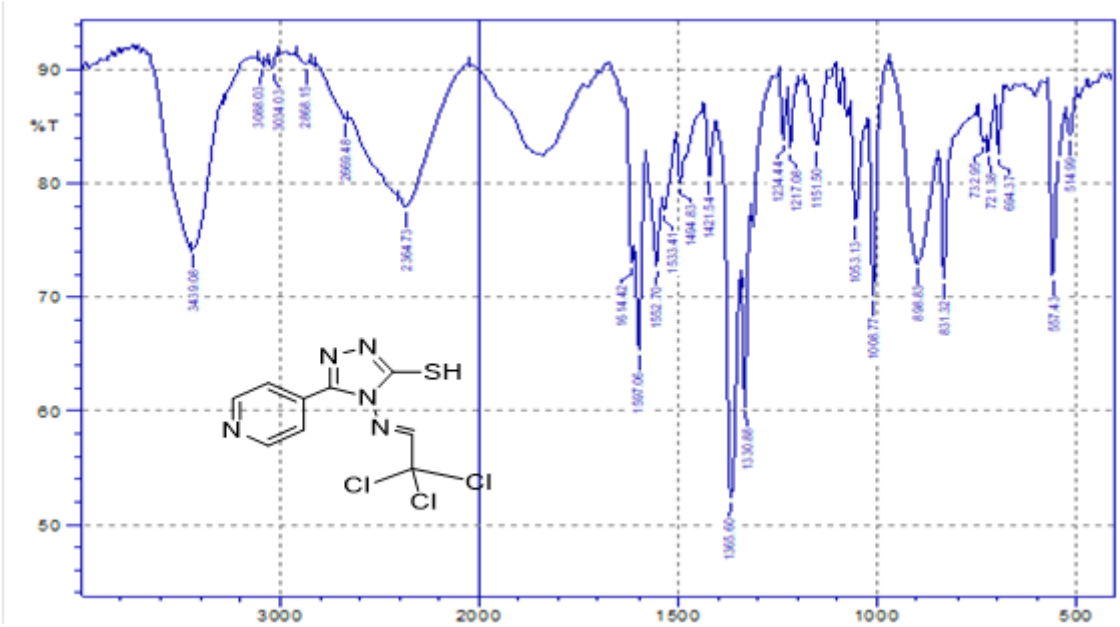

Fig 11: IR spectrum of (E)-5-(pyridin-4-yl)-4-((2,2,2-trichloroethylidene) amino)-[4H-1,2,4]-triazole-3-thiol

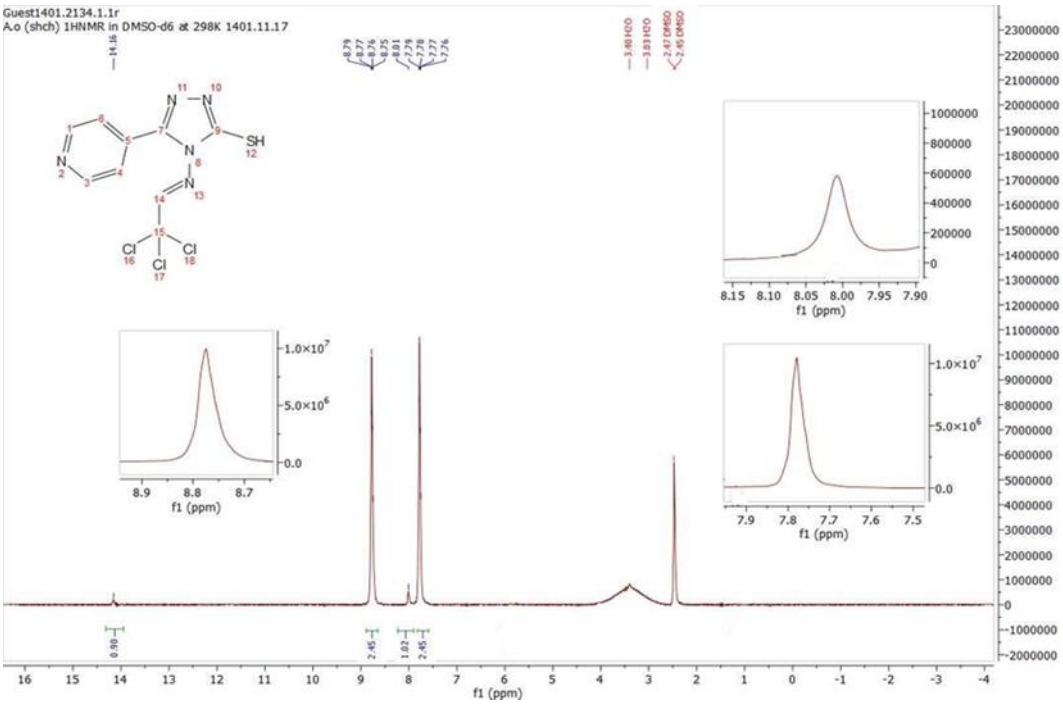

Fig 12 : 1H-NMR spectrum of (E)-5-(pyridin-4-yl)-4-((2,2,2-trichloroethylidene) amino)-[4H-1,2,4]-triazole-3-thiol

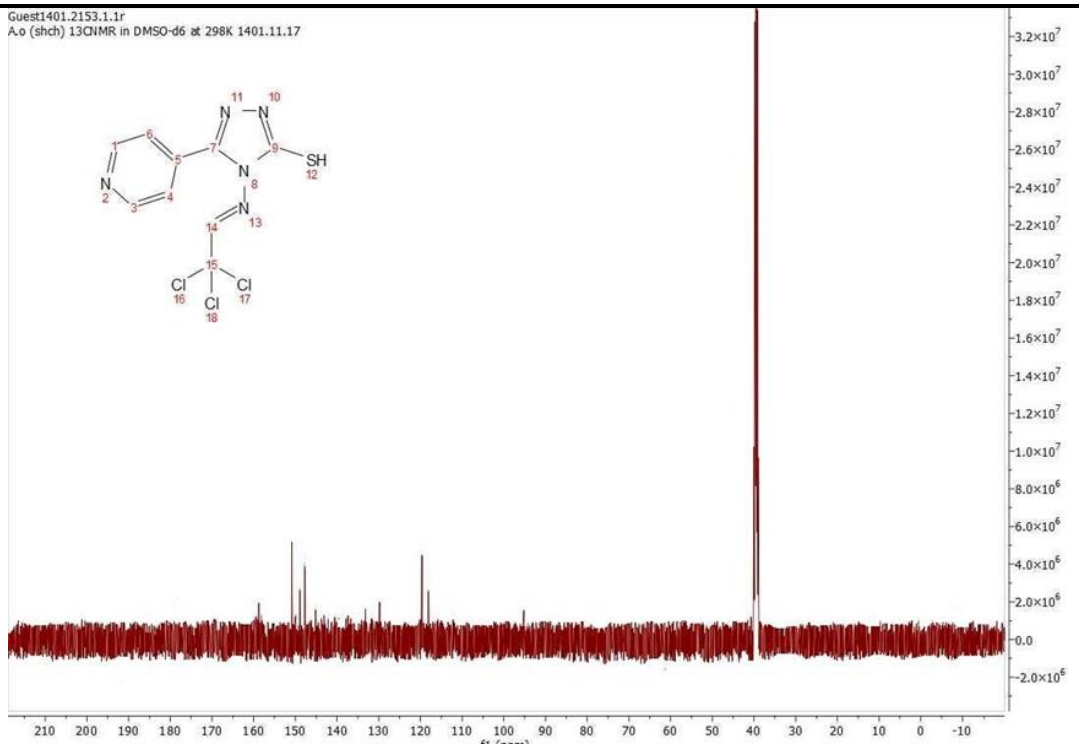

Fig 13: 13C-NMR spectrum of (E)-5-(pyridin-4-yl)-4-((2,2,2-trichloroethylidene) amino)-[4H-1,2,4]-triazole-3-thiol

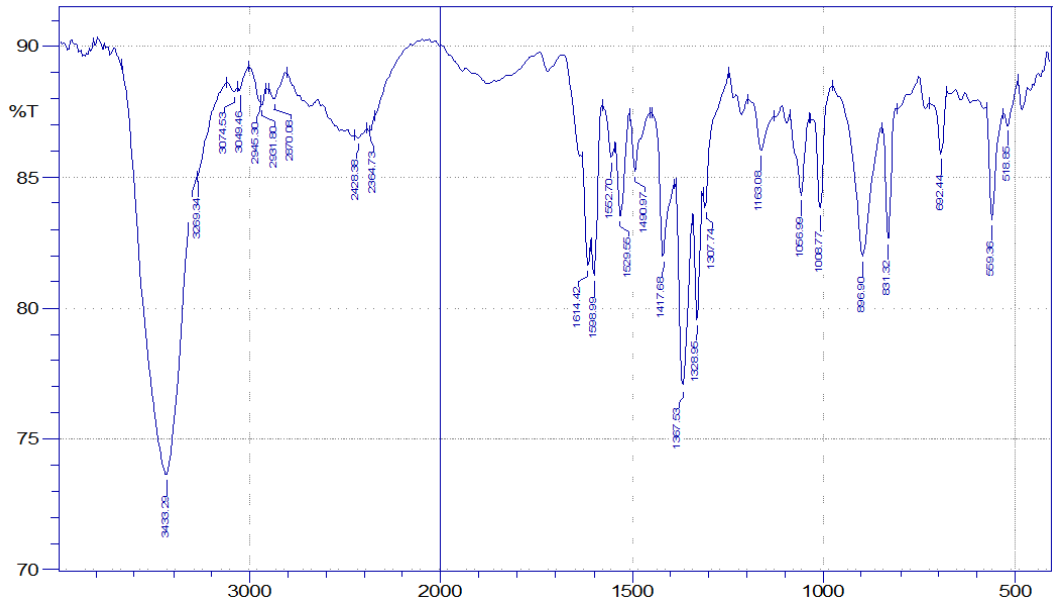

Fig 14: IR spectrum of 4,4'-(((1E,5E)-pentane-1,5-diylidene)bis(azaneylylidene))bis(5-(pyridin-4-yl)-4H-[1,2,4]-triazole-3-thiol)

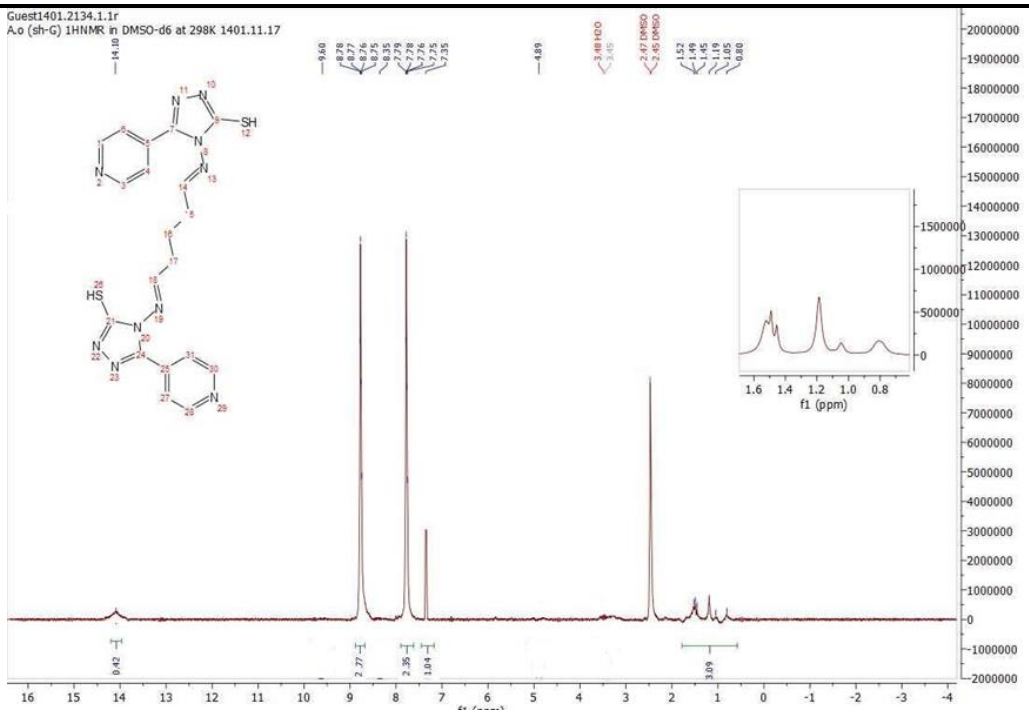

Fig 15 : 1H-NMR spectrum of 4,4'-(((1E,5E)-pentane-1,5-diylidene)bis(azaneylylidene))bis(5-(pyridin-4-yl)-4H-[1,2,4]-triazole-3-thiol)

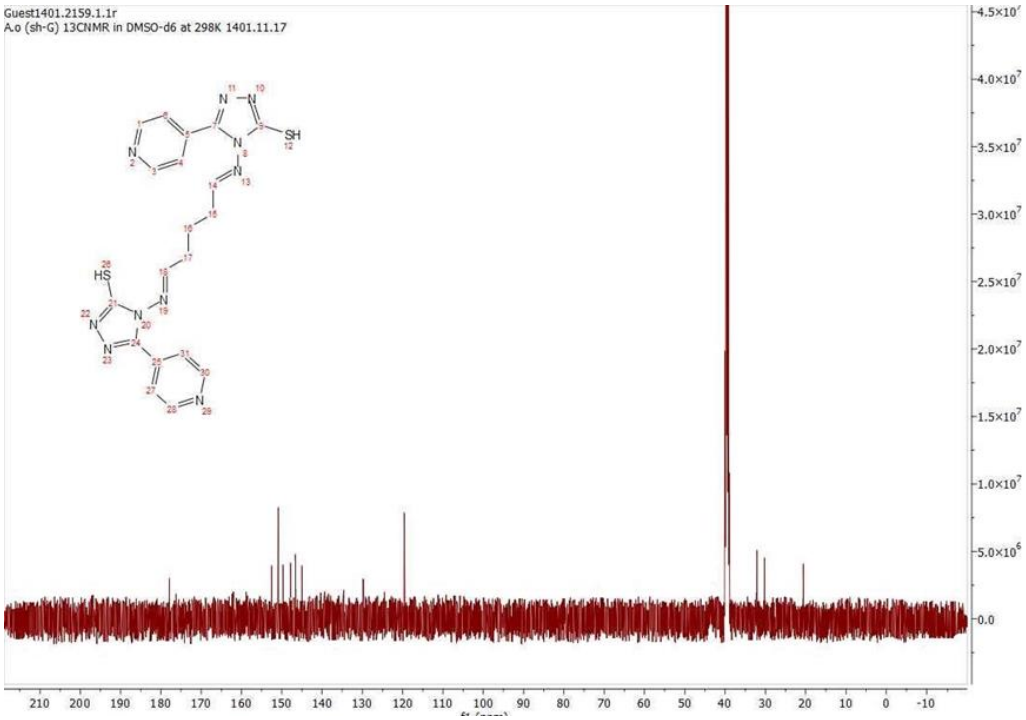

Fig 16: 13C-NMR spectrum of 4,4'-(((1E,5E)-pentane-1,5-diylidene)bis(azaneylylidene))bis(5-(pyridin-4-yl)-4H-[1,2,4]-triazole-3-thiol)