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# The Synthesis And Spectral Investigations Of New Derivatives Of 1,3,4-Oxadiazole, 1,3,4-Thiadiazole, And 1,2,4-Triazole

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## ABSTRACT

In this work, various compounds including ring 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,2,4-triazol were synthesized by cyclization of corresponding 1,4-disubstituted thiosemicarbazides from the reactions of hydrazide compounds with alkyl/aryl isothiocyanates. Furthermore, Mannich bases were prepared by thione tautomer form of 1,2,4-triazole and acid derivatives were prepared by thiole tautomer form of 1,2,4-triazole. The solvents, and reactants used in the study were purified according to literature. In addition, the synthesized compounds were also purified because of being importance of purify for characterization of organic compounds. Then these compounds were characterized by performing of melting point, elemental analyses, X-RAY, FT-IR, $^{1}$H-NMR (400MHz), and $^{13}$C-NMR(100MHz). 

## KEYWORDS

1,3,4-Thiadiazole;
1,3,4-Oxadiazole;
1,2,4-Triazole;
Mannich Bases;
Thione-thiole tautomerism.

## INTRODUCTION

The ring-closure reactions of carbohydrazides are well-known and have been thoroughly studied. In these reactions five-membered heterocycles with three heteroatoms such as are formed, 1,3,4-oxadiazoles, 1,3,4-thiadiazoles, and 1,2,4-triazoles[1-3].

1,3,4-oxadiazole, 1,3,4-thiadiazole, and 1,2,4-triazole ring systems are typical planar six-π-electron partially aromatic systems, and are used, along with their derivatives, as starting materials for the synthesis of many heterocycles[4].

Substituted 1,2,4-triazoles have also been actively studied as bridging ligands coordinating through their vicinal N atoms and some have special structure with interesting magnetic properties[5].

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These types of molecules are important for both chemical and pharmacological purposes. Derivatives of 1,2,4-triazoles, 1,3,4-oxadiazoles, and 1,3,4-thiadiazoles are known to exhibit anti-inflammatory[6,7,21], antiviral[8], analgesic[9], antimicrobial[10-12], anticonvulsant[13], and antidepressant activity[14].

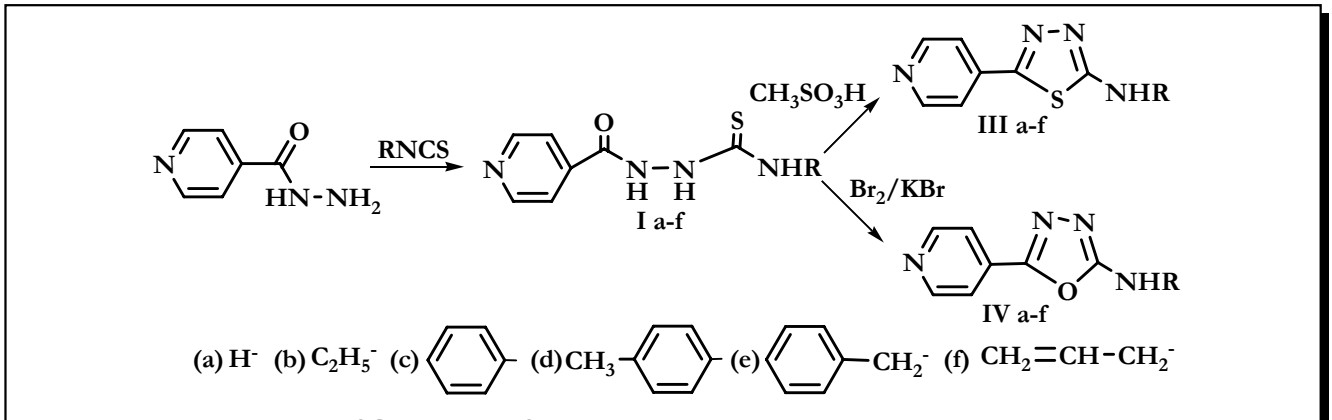
The latter being usually explored by the forced swim test[15,16]. Among the pharmacological profiles of 1,2,4-triazoles, 1,3,4-oxadiazoles, and 1,3,4-thiadiazoles, their antimicrobial, anticonvulsant and antidepressant properties seem to be the best documented. In addition there are some studies on electronic structures and thiole-thione tautomeric equilibrium of heterocyclic thione derivatives[1,17,18].

New changing problems in plant protection technology have promoted research to discover more efficient pesticides. In particular the development of herbicides, now an unavoidable means to selectively control the growth of weeds, resulted in a whole range of azoles exhibiting high levels of activity, application flexibility, crop tolerance and low levels of toxicity to mammals[19].

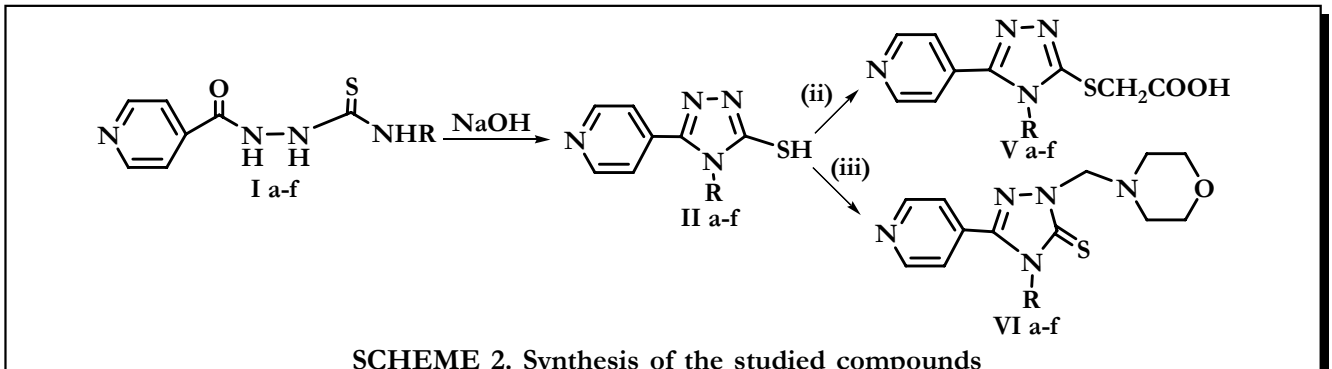
In view of the potential biological activity of members of the 1,2,4-triazole, 1,3,4-oxadiazole, and 1,3,4-thiadiazole ring systems. It was of interest to us to prepare the title compounds as possible drugs effective against tropical diseases[20].

## RESULTS AND DISCUSSION

The synthesized of the title compounds was accomplished as shown in SCHEME 1, 2, and 3. Synthetic methods for preparation of the title heterocycles from the isothiocyanate adducts of hydrazides are known. The treatment of isonicotinohydrazide with isothiocyanates gave thiosemicarbazides **(1a-f)**, respectively, in nearly quantitative yields. On the treatment of thiosemicarbazides **(1a-f)** with aqueous sodium hydroxide, 1,2,4-triazole derivatives were obtained in 75-85% yields **(2a-f)**. A short reflux of thiosemicarbazides in sulfuric acid, furnished the thiadiazole derivatives, via water elimination **(3a-f)**. The some product were obtained when methanesulfonic acid was used according to Method B. With iodine in KI solution(5%), compounds **(4a-f)** could be cyclized to oxadiazoles in good yields.




**SCHEME 1: Synthesis of the studied compounds**




**SCHEME 2. Synthesis of the studied compounds**

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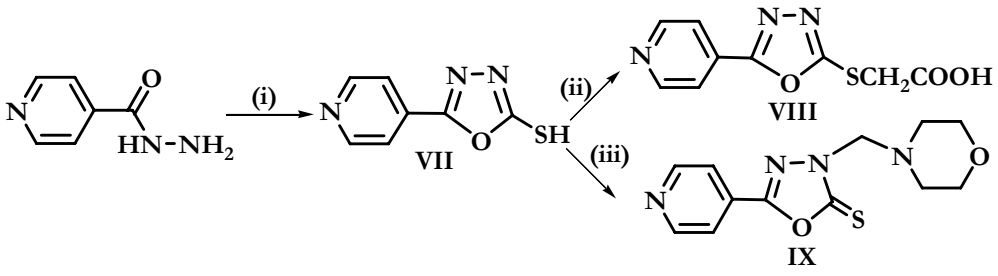


(i) : KOH (ii) : $Na_2CO_3$, $BrCH_2COOC_2H_5$, hydrolysis (iii) :$H_2CO$, $R_2NH$

**SCHEME 3: Synthesis of the studied compounds**

All spectral data are in accordance with assigned structures. IR spectra of compounds **(2a-f, 3a-f, and 4a-f)** no absorption bands were deducted at about 1688-1640 $cm^{-1}$, and 1274-1240 $cm^{-1}$ indicating the absence of C=O, and S=O groups of N-substituted-2-isonicotinoylhydrazinecarbothioamide which is an evidence for the cyclization reaction.

In the $^1$H-NMR spectra, N-H protons of acylthiosemicarbazides derivatives **(1a-f)** were observed at 7.90-8.15, 9.20-9.45, and 10.10-10.24 ppm. The compounds having, triazole **(2a-f)**, thiadiazole **(3a-f)**, oxadiazole **(4a-f)** ring, N-H protons were seen at about 8.60-10.78, 8.62-10.80, 13.60-14.10 ppm respectively. The $^1$H-NMR spectrum of **(6a-f)**, and **(9)** shows apair of triplets δ=2.60-2.80(J=4.46), and 3.70-3.90(J=4.42) for morpholine ring. The $^1$HNMR spectrum of **(5a-f)**, and **(8)** shows singled δ=3.60-2.80ppm for the a S-$CH_2$-COOH methylene groups, and δ=10.68-12.10 shows an broad carboxylic OH at room temperature in DMSO-$d_6$.

$^{13}$CNMR spectrum of substituted thiosemi carbazides shows δ=186-182, 160-156 ppm for the S=O, and C=O groups. Oxadiazole, thiadiazole, and triazole were seen at about δ=150-154,160-169 ppm for the carbons of five membered ring.

In the X-ray single crystallographic analysis, the intra- and intermolecular hydrogen bonds indicated by dashed lines. In the these compounds **(2c, 2f, 6f)**, the planer triazole ring is effectively coplanar with the benzene ring, which facilitates the formation of two intramolecular interactions N-H…S(leading to a thione tautomer in the solid state), and C-H…N. Intermolecular N-H…S interactions lead to the formation of dimmers. The crystal packing is stabilized by N..H-N and C..H-S type hydrogen bonds

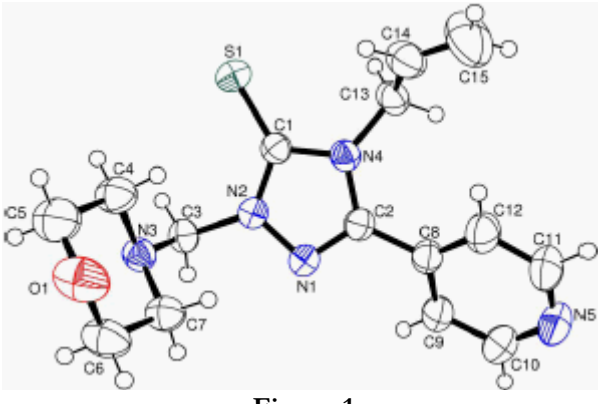


**Figure 1**

Figure 1 A drawing of **(6f)**, showing the atomic numbering SCHEME. Displacement ellipsoids are drawn at the 40% probability level and H atoms are shown as small spheres of arbitrary radii. Crystallographic data(excluding structure factors) for the structure in this paper, have been publication in the Acta Cryst[22-24]. or [E-mail: acetin74@hotmail.com]

## EXPERIMENTAL

Melting points were determined in open capillary tubes on a digital gallenkamp melting point apparatus and are uncorrected. The IR spectra were recorded for KBr disks with a Mattson 1000 FTIR spectrometer. $^1$HNMR spectra were recorded on a Varian-Mercury-Plus 400MHz $^1$HNMR, 100MHz $^{13}$CNMR spectrometer in DMSO-$d_6$ with TMS as an internal standard. Elemental analyses were done on a LECO-CHNS-938. Starting materials was obtained from fluka or aldrich.

### General procedure for the synthesis of 2-isonicotinoyl-N-substitutedhydrazine carbo-thio amide(1a-f)

0.01 mole of isonicotinohydrazide(1.37g) in 50mL of absolute ethanol was heated until it dissolved. 0.01mole appropriate substituted isothiocyanate derivatives was added and the mixture were refluxed for 5h. After the completion of the reaction, the crude product which precipitated on cooling was filtered, washed with diethyl ether, dried and crystallized from suitable solvents.

**2-Isonicotinoylhydrazine carbothioamide (1a)**

According to the procedure described **(1a-f).** Yield:1.47g, (75%); m.p. 305°C; IR(KBr) $\nu_{max}/cm^{-1}$: 3317-3156, 3105-3041, 1692, 1275; $^{1}$HNMR (DMSO-d6) δ/ppm:7.84 (s, 2H), 7.77(dd, J=5.87, 1.47, 2H), 8.75(dd, J=6.23, 1.47, 2H), 9.42(br, 1H), 10.66(br, 1H); $^{13}$CNMR(DMSO-d6) δ/ppm:182.67, 165.07, 150.78, 140.31, 122.0; Anal.calcd. for $C_7H_8N_4OS$:C 42.85, H 4.11, N 28.55 %; found:C 42.79, H 4.13, N 28.52 %.

**N-Ethyl-2-isonicotinoylhydrazinecarbothioamide (1b)**

According to the procedure described **(1a-f).** Yield: 1.79g,(80%), m.p. 190-192°C; IR(KBr) $\nu_{max}/cm^{-1}$:3200-3080, 3100-3060, 3000-2800, 1692, 1641, 1243; $^{1}$HNMR(DMSO-d6) δ/ppm:1.04(t, J=6.93, 3H), 3.47(q, J=6.60, 2H), 7.80(dd, J=6.23, 1.47, 2H), 8.60(t, J=5.13, 1H), 8.74(dd, J=5.87, 1.47, 2H), 9.34 (br, 1H), 10.61(br, 1H); $^{13}$CNMR(DMSO-d6) δ/ppm: 181.94, 165.14, 150.85, 140.24, 122.34, 39.24, 15.13; Anal.Calcd. for $C_9H_{12}N_4OS$: C 48.20, H 5.39, N 24.98 %; found: C 48.21, H 5.38; N 24.97 %.

**2-Isonicotinoyl-N-phenylhydrazinecarbothioamide(1c)**

According to the procedure described **(1a-f).** Yield: 2.31g, (85%); m.p. 194-196°C; IR(KBr) $\nu_{max}/cm^{-1}$: 3272-3124, 3105-3030, 1686, 1615, 1255; $^{1}$HNMR(DMSO-d6) δ/ppm:7.15(t, J=7.34, 1H), 7.32(t, J=7.60, 2H), 7.37-7.35(m, 2H), 7.84(dd, J=5.87, 1.47, 2H), 8.76(dd, J=6.23, 1.47, 2H), 9.80(br, 1H), 9.86(br, 1H), 10.80(br, 1H); $^{13}$CNMR (DMSO-d6) δ/ppm:181.99, 165.18, 150.88, 140.29, 139.80, 125.92, 128.76, 126.66, 122.38; Anal.Calcd. for $C_{13}H_{13}N_4OS$: C 57.34, H 4.44, N, 20.57 %. found: C 57.32, H 4.43, N 20.55 %.

**2-Isonicotinoyl-N-(4-methylphenyl) hydrazine carbothioamide(1d)**

According to the procedure described **(1a-f)**. Yield:2.29g, (80%); m.p. 200-201°C; IR(KBr) $\nu_{max}/cm^{-1}$:3285-3100, 3100-3010, 2960-2840, 1680, 1620, 1262; $^{1}$HNMR(DMSO-d6) δ/ppm:2.26 (s, 3H), 7.12(d, J=8.43, 2H), 7.28(d, J=6.96, 2H), 7.84(dd, J=5.87, 1.47, 2H), 8.76(dd, J=6.23, 1.47, 2H), 9.75(br, 1H), 9.80(br, 1H), 10.83(br, 1H); $^{13}$CNMR (DMSO-d6) δ/ppm:181.82, 165.18, 150.86, 140.30, 137.21, 135.10, 129.24, 126.75, 1230, 21.26; Anal. Calcd. for $C_{14}H_{14}N_4OS$: C 58.72, H, 4.93, N 19.57 %; found: C 58.73, H 4.95, N 19.56 %.

**N-Benzyl-2-isonicotinoylhydrazinecarbothioamide(1e)**

According to the procedure described **(1a-f)**. Yield: 2.29g, (80%); m.p.238-241°C; IR(KBr) $\nu_{max}/cm^{-1}$:3278-3100, 3100-3010, 2980-2820, 1686, 1610, 1260; $^{1}$HNMR(DMSO-d6) δ/ppm:4.73(d, J=5.87, 2H) 7.19-7.22(m, 1H), 7.27(s, 4H), 7.84(dd, J=6.23, 1.47, 2H), 8.73(s, 1H), 8.75(dd, J=6.23, 1.47, 2H), 8.75(Br, 1H), 9.56(Br, 1H), 10.72(Br, 1H); Anal.calcd. for $C_{14}H_{14}N_4OS$: C 58.72, H 4.93, N 19.57 %. found:C 58.74, H 4.92, N 19.59 %.

**N-Allyl-2-isonicotinoylhydrazinecarbothioamide (1f)**

According to the procedure described **(1a-f)**. Yield: 1.77g, (75%); m.p. 227-230°C; IR(KBr) $\nu_{max}/cm^{-1}$:3278-3100, 3100-3010, 2980-2820, 1686, 1610, 1260; $^{1}$HNMR(DMSO-d6) δ/ppm: 4.08 (t, J=5.50, 2H) 5.04(dd, 1H, Jcis=7.80, 1.47), 5.12 (dd, 1H, Jt=15.40, 1.83), 5.80(dq, 1H, J= 11.13, 5.13), 7.84(dd, J=6.23, 1.47, 2H), 8.73(s, 1H), 8.75(dd, J=6.23, 1.47, 2H), 8.75(br, 1H), 9.56(br, 1H), 10.72(br, 1H); Anal.calcd. for $C_{1O}H_{12}N_4OS$: C 50.83, H 5.12, N 23.71 %; found:C 50.80, H 5.10, N 23.72 %.

**General procedure for the synthesis of 4-substituted-5-pyridin-4-yl-4H-1,2,4-triazole-3-thiol(2a-f)**

A solution of 0.01 mole **(1a-f)** in 50mL 1N NaOH solution was heated under reflux for 5h. The mixture was cooled and acidified to pH 3 with concentrated hydrochloric acid was added. The precipitate was filtered and washed several times with distilled water. The pure compounds were obtained following crystallization from suitable solvent.

**5-pyridin-4-yl-4H-1,2,4-triazole-3-thiol (2a)**

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According to the procedure described, **(2a-f)**. Yield: 1.42g, (80%); m.p.>350°C; IR(KBr) $\nu_{max}$/cm$^{-1}$: 3430-3270, 3120-3000, 1248, 1615; $^1$H-NMR (DMSO-d6) δ/ppm:3.55(s, 1H), 7.78(dd, J=5.87, 1.83, 2H), 8.52(dd, J=6.23, 1.47, 2H); $^{13}$CNMR (DMSO-d6) δ/ppm:169.84, 157.38, 150.47, 140.16, 120.303; Anal.calcd. for $C_7H_6N_4S$: C 47.18, H 3.39, N 31.44 %; found:C 47.16, H 3.41, N 31.48 %.

**4-Ethyl-5-pyridin-4-yl-4H-1,2,4-triazole-3-thiol (2b)**

According to the procedure described, **(2a-f)**. Yield:1.75g, (85%); m.p. 290-293°C; IR(KBr) $\nu_{max}$/cm$^{-1}$:3446-3330, 3130-3040, 2980-2900, 1256, 1647; $^1$HNMR(DMSO-d6) δ/ppm:1.24 (t, J=6.96, 3H ), 4.32(q, J=6.62, 2H), 7.79-7.80(m, 2H), 8.73-8.74(m, 2H); Anal.calcd. for $C_9H_{10}N_4S$:C 52.41, H 4.89, N 27.16 %; Found:C 52.44, H 4.92, N 27.15 %.

**4-Phenyl-5-pyridin-4-yl-4H-1,2,4-triazole-3-thiol (2c)**

According to the procedure described, **(2a-f)**. Yield: 2.29g, (90%); m.p. 297-298°C; IR(KBr) $\nu_{max}$/cm$^{-1}$: 3135-3015, 2893, 1614; $^1$HNMR(DMSO-d6) δ/ppm: 7.21(dd, J=6.23, 1.47, 2H), 7.32-7.39(m, 2H), 7.50-7.53(m, 3H), 8.55(dd, J=6.23, 1.83, 2H); $^{13}$CNMR(DMSO-d6) δ/ppm: 169.92, 150.75, 149.01, 134.83, 133.87, 130.47, 130.20, 129.34, 122.59; Anal.calcd. for $C_{13}H_{11}N_4S$: C 61.40, H 3.96, N 22.03 %; found: C 61.41, H 3.98, N 22.03 %.

**4-(4-Methylphenyl)-5-pyridin-4-yl-4H-1,2,4-triazole-3-thiol (2d)**

According to the procedure described, **(2)**. Yield: 2.28g, 85%, mp 273-274°C. IR(KBr) $\nu_{max}$/cm$^{-1}$: 3426-3320, 3160-3020, 2940-2980, 1256, 1618 cm$^{-1}$. $^1$HNMR(DMSO-d6): δ 2.35(s, 3H), 7.23(dd, J=6.23, 1.47, 2H), 7.27(d, J=8.07, 2H), 7.31(d, J= 7.96, 2H), 8.56(dd, J=6.23, 1.83, 2H) ppm. $^{13}$CNMR(DMSO-d6):δ 170.00, 150.78, 149.13, 140.09, 133.93, 132.25, 130.70, 129.02, 122.56, 21.51 ppm. Anal.calcd. for $C_{14}H_{13}N_4S$: C, 62.66; H, 4.51; N, 20.88. Found:C, 62.67; H, 4.51; N, 20.89.

**4-Benzyl-5-pyridin-4-yl-4H-1,2,4-triazole-3-thiol (2e)**

According to the procedure described, **(2a-f)**. Yield: 2.28g, (85%); m.p. 273-274°C. IR(KBr) $\nu_{max}$/cm$^{-1}$: 3140-3020, 2990-2900, 2934-2565, 1644; $^1$HNMR(DMSO-d6) δ/ppm: 5.45 (s, 2H) 7.04 (d, J=8.53, 2H), 7.20-7.27(m, 3H), 7.71(d, J=6.24, 2H), 8.74(d, J=5.47, 2H); $^{13}$CNMR(DMSO-d6) δ/ppm: 169.67, 149.45, 149.12, 136.06, 135.98, 129.40, 128.36, 127.25, 123.64, 47.51; Analcalcd. for $C_{14}H_{13}N_4S$:C 62.66, H 4.51, N 20.88 %; found:C 62.65, H 4.52, N 20.88 %.

**4-Allyl-5-pyridin-4-yl-4H-1,2,4-triazole-3-thiol (2f)**

According to the procedure described, **(2a-f)**. Yield: 1.74g, (80%); m.p. 222-224°C; IR(KBr) $\nu_{max}$/cm$^{-1}$:3110-3060, 2925-2560, 1624, 975-910; $^1$HNMR(DMSO-d6) δ/ppm:4.08(t, J=5.49, 2H) 4.83 (dd, 1H, Jt =17.23, 1.10), 5.12(dd, 1H, Jcis=9.33, 1.10), 5.80(dq, J=9.90, 5.13, 1H), 7.88(dd, J=6.23, 1.83, 2H), 8.74(dd, J=5.87, 1.47, 2H); $^{13}$CNMR (DMSO-d6) δ/ppm:168.91, 151.17, 149.92, 134.12, 132.36, 122.85, 118.00, 46.67; Anal.calcd. for $C_{10}H_{10}N_4S$: C 55.02, H 4.62, N 25.67 %; found:C 55.00, H 4.63, N 25.66 %.

**General procedure for the synthesis of N-substituted-5-Pyridin-4-yl-1,3,4-thiadiazol-2-amine (3a-f)**

**Method A**

0.01mole of substituted thiosemicarbazides **(1a-f)** was dissolved in 25mL of toluene and methanesulfonic acid(0.015m, 0.975mL) was added drop wise in 10 minutes and refluxed 1h. The mixture was neutralized with ammonium hydroxide under ice cooling. The precipitate was filtered off and washed with water.

**Method B**

1,4-disubstituted-3-thiosemicarbazide **(1a-f)** (0.01m) was added portion wise to 5mL of concentrated sulfuric acid at °C with continuous stirring. The reaction mixture was stirred further for 3h. at room temperature and then allowed to stand overnight. Neutralization with diluted sodium hydroxide precipitated a crude solid, which was filtered and washed with water. The crude product was then recrystallized from a mixture of acetic acid and water(1:2).

**5-Pyridin-4-yl-1,3,4-thiadiazol-2-amine (3a)**

According to the procedure described, **(3a-f)**. Yield: 0.71g, (40%); m.p. 127°C; IR(KBr) $\nu_{max}$/cm$^{-1}$: 3220-3170, 3110, 1621; $^1$HNMR(DMSO-d6) δ/ppm: 7.50(br, 2H), 7.68(dd, J=6.23, 1.83, 2H), 8.70(d,

J=5.86, 2H); Anal.calcd. for $C_7H_6N_4S$: C 47.18, H 3.39, N 31.44 %; found:C 47.17, H 3.40, N 31.46 %.

**N-Ethyl-5-pyridin-4-yl-1,3,4-thiadiazol-2-amine (3b)**

According to the procedure described, **(3a-f)**.Yield: 0.93g, (45%); m.p. 239-241°C; IR(KBr) $\nu_{max}$/$cm^{-1}$:3310-3130, 3110-3034, 2912, 1615; $^1$H-NMR(DMSO-d6) δ/ppm:1.16(t, J=7.32, 3H), 4.09 (q, J=7.33, 2H), 7.70(dd, J=5.87, 1.47, 2H), 8.80 (dd, J= 5.87, 1.47, 2H); $^{13}$CNMR(DMSO-d6) δ/ppm: 168.16, 151.28, 149.68, 134.25, 123.17, 40.03, 14.10; Anal.calcd. for $C_9H_{10}N_4S$: C 52.41, H 4.89, N 27.16%; found: C 52.43, H 4.90, N 27.15 %.

**N-Phenyl-5-pyridin-4-yl-1,3,4-thiadiazol-2-amine (3c)**

According to the procedure described, **(3a-f)**. Yield: 1.27g, (50%); m.p. 197-199°C; IR(KBr) $\nu_{max}$/ $cm^{-1}$:3340-3120, 3092-3000, 1615; $^1$HNMR(DMSO-d6) δ/ppm: 7.03(t, J=7.33, 1H), 7.36(d, J=7.33, 2H), 7.37(t, J=7.36, 2H), 7.70(d, J=5.87, 2H), 8.8(d, J= 6.23, 2H), 10.8(s, 1H); $^{13}$CNMR(DMSO-d6) δ/ppm: 166.04, 151.49, 151.29, 140.91, 137.86, 129.89, 123.19, 121.29, 118.49; Anal.calcd. for $C_{13}H_{11}N_4S$: C 61.40, H 3.96, N 22.03 %; found: C 61.42, H 3.97, N 22.04%.

**N-(4-Methylphenyl)-5-pyridin-4-yl-1,3,4-thia diazol-2-amine (3d)**

According to the procedure described, **(3a-f)**.Yield: 1.29g, (48%); m.p. 205-207°C; IR(KBr) $\nu_{max}$/$cm^{-1}$: 3300-3130, 3040-3010, 2925-2816, 1628; $^1$HNMR (DMSO-d6) δ/ppm:2.25(s, 3H), 7.17 (d, J=8.06, 2H), 7.50(d, J=8.43, 2H), 7.70(s, 2H), 8.72(s, 2H), 10.70 (s, 1H); $^{13}$CNMR(DMSO-d6) δ/ppm: 166.26, 155.60, 151.30, 138.52, 137.86, 132.29, 130.29, 121.25, 118.63; Anal.calcd. for $C_{14}H_{13}N_4S$: C 62.66, H 4.51, N 20.88%; found: C 62.65, H 4.50, N 20.87%.

**N-Benzyl-5-pyridin-4-yl-1,3,4-thiadiazol-2-amine (3e)**

According to the procedure described, **(3a-f)**. Yield: 1.15g. (43%); m.p. 135°C; IR(KBr) $\nu_{max}$/$cm^{-1}$: 3271-3200, 3100-3010, 3000-2925, 1610; $^1$HNMR (DMSO-d6) δ/ppm:4.55 (d, J=5.86, 2H), 7.24-7.38 (m, 5H), 7.70 (dd, J=5.23, 1.83, 2H), 8.70 (d, J=5.50, 2H), 8.72 (t, J=5.86, 1H); Anal.calcd. for $C_{14}H_{13}N_4S$: C 62.66, H 4.51, N 20.88%; found: C 62.67, H 4.53, N 20.89%.

**N-Allyl-5-pyridin-4-yl-1,3,4-thiadiazol-2-amine (3f)**

According to the procedure described, **(3a-f)**. Yield: 0.98g, (45%); m.p. 181-183°C; IR(KBr) $\nu_{max}$/ $cm^{-1}$:3430-3320, 3090-3040, 1630, 975-910; $^1$HNMR(DMSO-d6) δ/ppm:4.80(t, J=5.49, 2H), 5.18(m, 2H), 5.84(dq, J=9.90, 5.13, 1H), 7.28(dd, J=6.23, 1.83, 2H), 8.36(s, 1H), 8.62(dd, J=5.87, 1.47, 2H); Anal.calcd. for $C_{10}H_{10}N_4S$: C 55.02, H 4.62, N 25.67%; found: C 55.01, H 4.64, N 25.66%.

**General procedure for the synthesis of N-substituted-5-Pyridin-4-yl-1,3,4-oxadiazol-2-amine (4a-f)**

The appropriate thiosemicarbazides **(1a-f)** (0.01m) was suspended in 100mL of ethanol and to this, 5mL of 5N NaOH was gradually added with cooling and shaking. To the clear solution iodine in KI solution(5%) was gradually added with stirring until the color of iodine persisted at room temperature. The mixture was refluxed on a steam bath and more KI solution was carefully added until a permanent tinge of excess iodine was obtained. The mixture was gradually poured over crushed ice(100g), and the solid mass which separated our was removed by filtration, washed with water, dried, and washed with warm carbon disulfide.

**5-Pyridin-4-yl-1,3,4-oxadiazol-2-amine (4a)**

According to the procedure described, **(4a-f)**. Yield: 0.89g, (55%); m.p. 135°C; IR(KBr) $\nu_{max}$/$cm^{-1}$: 3300-3160, 3120-3000, 1620; $^1$HNMR(DMSO-d6) δ/ppm:7.43(br, 2H), 7.68(dd, J=6.23, 1.83, 2H), 8.70 (d, J=5.86, 2H); $^{13}$CNMR(DMSO-d6) δ/ppm:166.80, 152.38, 145.22, 134.24, 123.10; Anal.calcd. for $C_7H_6N_4O$: C 51.85, H 3.73, N 34.55%; found: C 51.83, H 3.73, N 34.56%.

**N-Ethyl-5-pyridin-4-yl-1,3,4-oxadiazol-2-amine (4b)**

According to the procedure described, **(4a-f)**. Yield: 0.86g, (45%); m.p. 131-132°C; IR(KBr) $\nu_{max}$/ $cm^{-1}$:3285, 3090-3000, 2970-2900, 1634; $^1$HNMR (DMSO-d6) δ/ppm:1.13(t, J=7.33, 3H), 3.31(2H), 7.71(br, 1H), 7.87(dd, J=6.23, 1.47, 2H), 8.80(dd,

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J= 5.87, 1.47, 2H); $^{13}$CNMR(DMSO-d6) δ/ppm: 164.64, 156.55, 151.49, 123.73, 119.44, 38.12, 15.23; Anal.calcd. for $C_9H_{10}N_4O$: C 56.83, H 5.30, N 29.46%; found: C 56.84, H 5.33, N 29.46%.

**N-Phenyl-5-pyridin-4-yl-1,3,4-oxadiazol-2-amine (4c)**

According to the procedure described, **(4a-f)**. Yield: 1.43g, (60%); m.p. 133-134°C; IR(KBr) $\nu_{max}$/cm$^{-1}$: 3285-3180, 3170-3000, 1622; $^1$HNMR(DMSO-d6) δ/ppm:6.93(t, J=7.33, 1H), 7.30(d, J=7.33, 2H), 7.39(t, J=7.40, 2H), 7.80(dd, J=6.23, 1.47, 2H), 7.92 (br, 1H), 8.78(dd, J= 5.87, 1.47, 2H); Anal.calcd. for $C_{13}H_{11}N_4O$: C 65.54, H 4.23, N 23.52%; found: C 65.51, H 4.26, N 23.53%.

**N-(4-Methylphenyl)-5-pyridin-4-yl-1,3,4-oxadiazol-2-amine(4d)**

According to the procedure described, **(4a-f)**. Yield: 1,39g, (55%); m.p. 128-129°C; IR(KBr) $\nu_{max}$/cm$^{-1}$:3365-3140, 3110-2850, 1618; $^1$HNMR(DMSO-d6) δ/ppm: 7.14(d, J=8.43, 2H), 7.28(d, J=6.96, 2H), 7.80(dd, J=6.23, 1.47, 2H), 7.82(br, 1H), 8.78(dd, J=5.87, 1.47, 2H); Anal.calcd. for $C_{14}H_{13}N_4O$: C 66.65, H 4.79, N 22.21%; found: C 66.63, H 4.81, N 22.22%.

**N-Benzyl-5-pyridin-4-yl-1,3,4-oxadiazol-2-amine (4e)**

According to the procedure described, **(4a-f)**. Yield: 26g, (50%); m.p. 137-139°C; IR(KBr) $\nu_{max}$/cm$^{-1}$:3225-3100, 3080-2930, 1626; $^1$HNMR(DMSO-d6) δ/ppm:7.20(s, 5H), 7.86(dd, J=6.23, 1.47, 2H), 8.84(dd, J= 5.87, 1.47, 2H), 9.86(br, 1H); Anal.calcd. for $C_{14}H_{13}N_4O$:C 66.65, H 4.79, N 22.21%; found: C 66.64, H 4.80, N 22.24%.

**N-Allyl-5-pyridin-4-yl-1,3,4-oxadiazol-2-amine (4f)**

According to the procedure described, **(4a-f)**. Yield: 1.21g, (60%); m.p. 130°C; IR(KBr) $\nu_{max}$/cm$^{-1}$: 3225-3100, 3130-2910, 1611, 975-920; $^1$HNMR (DMSO-d6) δ/ppm: 4.18(t, J=5.49, 2H), 4.85(dd, 1H, Jt =17.23, 1.10), 5.12(dd, Jcis=9.33, 1.10, 1H), 5.82(dq, J=9.90, 5.13, 1H), 7.80(dd, J=6.23, 1.47, 2H), 8.89(dd, J= 5.87, 1.47, 2H), 10.4(br, 1H); Anal.calcd. for $C_{10}H_{10}N_4O$: C 59.40, H 4.98, N 27.71%; found: C 59.42, H 4.99, N 27.70%.

**General procedure for the synthesis of [(4-substituted-5-pyridin-4-yl-4H-1,2,4-triazol-3-yl)thio] acetic acid(5a-f)**

A solution of the 0.01mole triazole **(2a-f)** and sodium hydroxide (0.01m, 0.4g) in 30mL ethanol was refluxed for 0.5h. To this solution, ethylbromoacetate(0.01m, 1.65g) was added, and the resulting mixture refluxed for 4 hour. After cooling, the solution was poured on ice and the solid mass thus separated recrystallized from suitable solvent.

**Ethyl [(5-pyridin-4-yl-4H-1,2,4-triazol-3-yl)thio] acetate(5a)**

According to the procedure described, **(5a-f)**. Yield: 1.85g, (70%); m.p. >375°C; IR(KBr) $\nu_{max}$/cm$^{-1}$: 3490-3233, 3120-3000, 2970-2867, 1742, 1610; $^1$HNMR($D_2O$) δ/ppm: 1.07(t, J=7.33, 3H), 3.42(q, J=6.96, 2H), 3.78(s, 2H), 7.78(d, J=6.23, 2H), 8.22 (d, J=5.83, 2H); Anal.calcd. for $C_{11}H_{12}N_4O_2S$:C 49.99, H 4.58, N 21.20%; found:C 49.97, H 4.59, N 21.22%.

**[(4-Ethyl-5-pyridin-4-yl-4H-1,2,4-triazol-3-yl) thio]acetic acid(5b)**

According to the procedure described, **(5a-f)**. Yield: 2.03g, (77%); m.p. >375°C; IR(KBr) $\nu_{max}$/cm$^{-1}$: 3558-3100, 3120-2887, 1716, 1615; $^1$HNMR($D_2O$) δ/ppm: 1.20(t, J=6.96, 3H), 4.05(q, J=7.33, 2H), 3.83(s, 2H), 7.58(dd, J=6.23, 1.47, 2H), 8.64(d, J=5.87, 2H); $^{13}$CNMR($D_2O$) δ/ppm:175.20, 166.87, 152.00, 149.89, 135.01, 123.50, 40.70, 38.25, 14.58; Anal.calcd. for $C_{11}H_{12}N_4O_2S$: C 49.99, H 4.58, N 21.20%; found:C 50.02, H 5.01, N 21.20%.

**[(4-Phenyl-5-pyridin-4-yl-4H-1,2,4-triazol-3-yl) thio]acetic acid (5c)**

According to the procedure described, **(5a-f)**. Yield: 2.59g, (83%); m.p. >375°C; IR(KBr) $\nu_{max}$/cm$^{-1}$: 3452, 3100-2896, 1728, 1615; $^1$HNMR(DMSO-d6) δ/ppm: 3.78(s, 2H), 7.58(dd, J=6.23, 1.47, 2H), 7.40-7.44(m, 2H ), 7.58-7.60(m, 3H), 8.64(dd, J=5.86, 1.47, 2H); Anal.calcd. for $C_{15}H_{12}N_4O_2S$:C 57.68, H 3.87, N 17.94%; found: C 57.69, H 3.90, N 17.92%.

**{[4-(4-Methylphenyl)-5-pyridin-4-yl-4H-1,2,4-triazol-3-yl]thio}acetic acid (5d)**

According to the procedure described, **(5a-f)**. Yield: 2.18g, (67%); m.p. >375°C; IR(KBr) $\nu_{max}$/cm$^{-}$

[1]: 3497-3120, 3100-2966, 1730, 1628; [1]HNMR($D_2O$) δ/ppm: 2.21(s, 3H), 3.78(s, 2H), 6.18-6.20(m, 2H), 6.70(d, J=8.05, 2H), 7.72(d, J=5.86, 1.47, 2H), 8.68 (dd, J=6.23, 1.47, 2H); Anal.calcd. for $C_{16}H_{14}N_4O_2S$: C 58.88, H 4.32, N 17.17%; found: C 58.90, H 4.35, N 17.17%.

**[(4-Benzyl-5-pyridin-4-yl-4H-1,2,4-triazol-3-yl) thio]acetic acid(5e)**

According to the procedure described, **(5a-f)**. Yield: 1.99g, (61 %); m.p. >375°C; IR(KBr) $\nu_{max}$/ $cm^{-1}$: 3520-3310, 3080-2932, 1718, 1615; [1]HNMR (DMSO-d6) δ/ppm:1.05(t, J=6.96, 3H), 3.46(q, J=7.33, 2H), 3.73(s, 2H), 5.34(s, 2H), 6.95-6.97(m, 2H), 7.23-7.32(m, 3H), 7.58(dd, J=6.23, 1.47, 2H), 8.64(dd, J=5.86, 1.47, 2H); Anal.calcd. for $C_{16}H_{14}N_4O_2S$: C 58.88, H 4.32, N 17.17%; found: C 58.89, H 4.33, N 17.16%.

**Ethyl[(4-allyl-5-pyridin-4-yl-4H-1,2,4-triazol-3-yl) thio]acetate (5f)**

According to the procedure described, **(5a-f)**. Yield: 1.52g, (55%); m.p. >375°C; IR(KBr) $\nu_{max}$/$cm^{-1}$:3400-3150, 3080-2902, 1765, 1623, 975-910; [1]HNMR($D_2O$) δ/ppm:1.06 (t, J=7,33, 3H), 3.42(q, J=6.97, 2H), 3.76(s, 2H), 4.45(d, J=4.87, 2H), 4.65 (m, 1H), 4.97(d, Jt=11.02, 1H), 5.64(dq, J=6.63, 5.13, 1H), 7.88(dd, J=6.23, 1.83, 2H), 8.74(dd, J=5.87, 1.47, 2H); Anal.calcd. for $C_{14}H_{16}N_4O_2S$:C 55.25, H 5.30, N 18.41%; found: C 55.23, H 5.30, N 18.38%.

**General procedure for the synthesis of 2-(Morpholin-4-ylmethyl)4-substituted-5-pyridin-4-yl-2,4-dihydro-3H-1,2,4-triazole-3-thione (6a-f)**

A slurry consisting 0.002mole of **(2a-f)**, ethanol (10mL) and (0.003mole, 0.289mL) 37% formalin was made. To this(0.002m, 0.174mL) morpholine was added drop wise, with cooling and shaking. The reaction mixture was allowed to stand at room temperature for 1h. With occasional shaking after which it was warmed on a steam bath for 0.5h. At the end of period the contents were cooled and the product obtained was recrystallized from suitable solvent.

**2-(Morpholin-4-ylmethyl)-5-pyridin-4-yl-2,4-dihydro-3H-1,2,4-triazole-3-thione (6a)**

According to the procedure described, **(6a-f)**. Yield: 1.44g, (52%); m.p. 183-184°C; IR(KBr) $\nu_{max}$/ $cm^{-1}$:3270, 3120-3040, 2942-2842, 1618, 1258; [1]HNMR(DMSO-d6) δ/ppm:2.78(t, J=4.40, 4H), 3.60(t, J=4.40, 4H), 5.12(s, 2H), 5.64(br, 1H), 7.78 (dd, J=5.87, 1.47, 2H). 8.76(dd, J=5.87, 1.47, 2H); Anal.calcd. for $C_{12}H_{15}N_5OS$: C 51.97, H 5.45, N 25.25%; found: C 52.00, H 5.46, N 25.23%.

**4-Ethyl-2-(morpholin-4-ylmethyl)-5-pyridin-4-yl-2,4-dihydro-3H-1,2,4-triazole-3-thione (6b)**

According to the procedure described, **(6a-f)**. Yield: 1.74g, (57%); m.p. 195-197°C; IR(KBr) $\nu_{max}$/ $cm^{-1}$:3100-3040, 2965-2860, 1610, 1252; [1]HNMR(DMSO-d6) δ/ppm: 1.24(t, J=6.96, 3H), 2.72(t, J=4.40, 4H), 3.66(t, J=4.40, 4H), 4.08(q, J=7.32, 2H), 5.10(s, 2H), 7.76(dd, J=5.87, 1.47, 2H). 8.74(dd, J=5.87, 1.47, 2H); Anal.calcd. for $C_{14}H_{19}N_5OS$: C 55.06, H 6.27, N 22.93%; found: C 55.05, H 6.27, N 22.94%.

**2-(Morpholin-4-ylmethyl)-4-phenyl-5-pyridin-4-yl-2,4-dihydro-3H-1,2,4-triazole-3-thione (6c)**

According to the procedure described, **(6a-f)**. Yield: 1.69g, (48%); m.p. 182-185°C; IR(KBr) $\nu_{max}$/ $cm^{-1}$:3133-3014, 2963-2850, 1608, 1254; [1]HNMR (DMSO-d6) δ/ppm: 2.80(t, J=4.45, 4H), 3.56(t, J=4.40, 4H), 5.17(s, 2H), 7.42-7.43(m, 2H), 7.50-7.53(m, 3H), 7.51(d, J=6.23, 2H), 8.55(d, J=6.23, 2H); [13]CNMR(DMSO-d6) δ/ppm:170.84, 150.78, 147.71, 135.11, 133.54, 130.59, 129.79, 129.35, 122.80, 69.94, 66.81, 50.92; Anal.calcd. for $C_{18}H_{20}N_5OS$: C 61.17, H 5.42, N 19.81%; found: C 61.15, H 5.43, N 19.80%.

**4-(4-Methylphenyl)-2-(morpholin-4-ylmethyl)-5-pyridin-4-yl-2,4-dihydro-3H-1,2,4-triazole-3-thione (6d)**

According to the procedure described, **(6a-f)**. Yield: 1.55g, (42%); m.p. 193-195°C; IR(KBr) $\nu_{max}$/ $cm^{-1}$:3100-3040, 2963-2842, 1609, 1254 $cm^{-1}$. [1]HNMR(DMSO-d6) δ/ppm:2.35(s, 3H), 2.78(t, J=4.45, 4H), 3.58(t, J=4.40), 5.16(s, 2H), 7.30-7.31(m, 4H), 7.51(dd, J=5.87, 1.47, 2H). 8.55(dd, J=5.87, 1.47, 2H); [13]CNMR(DMSO-d6) δ/ppm: 170.93, 150.81, 147.46, 140.23, 133.61, 132.74, 130.71, 129.05, 122.80, 69.92, 66.80, 50.92, 21.50; Anal.calcd. for $C_{19}H_{22}N_5OS$: C 62.10, H 5.76, N 19.06%; found: C 62.11, H 5.77, N 19.07%.

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**4-Benzyl-2-(morpholin-4-ylmethyl)-5-pyridin-4-yl-2,4-dihydro-3H-1,2,4-triazole-3-thione (6e)**

According to the procedure described, **(6a-f).** Yield: 2.13g, (58%); m.p. 147°C;. IR(KBr) $\nu_{max}/cm^{-1}$: 3182-3041, 2952-2842, 1612, 1256; $^{1}$HNMR (DMSO-d6) δ/ppm: (t, J=4.45, 4H), 3.58 (t, J=4.40, 4H), 7.01(s, 2H), 7.02(s, 2H), 7.27(s, 5H), 7.58(dd, J=6.23, 1.47, 2H). 8.65(dd, J=5.87, 1.47, 2H); $^{13}$CNMR(DMSO-d6) δ/ppm: 169.11, 151.15, 149.05, 135.89, 133.71, 129.37, 128.40, 127.26, 122.99, 71.80, 66.67, 51.00, 48.47; Anal.calcd. for $C_{19}H_{22}N_5OS$: C 62.10, H 5.76, N 19.06%; found: C 62.13, H 5.75, N 19.07%.

**4-Allyl-2-(morpholin-4-ylmethyl)-5-pyridin-4-yl-2,4-dihydro-3H-1,2,4-triazole-3-thione (6f)**

According to the procedure described, **(6a-f)**. Yield: 1.52g, (48%); m.p. 134°C; IR(KBr) $\nu_{max}/cm^{-1}$: 3099-3011, 2960-2829, 1614, 1258, 975-910; $^{1}$HNMR($D_2O$) δ/ppm: 2.70(t, J=4.40, 4H), 3.31(s, 2H), 3.54(t, J=4.40, 4H), 4.81(dd, Jcis =6.23, 1.10, 1H), 4.86(s, 1H), 5.81(dq, J=9.90, 5.13, 1H), 5.14 (s, 2H), 7.55 (dd, J=5.23, 1.83, 2H), 8.55 (dd, J=5.23, 1.47, 2H); $^{13}$CNMR(DMSO-d6) δ/ppm: 169.83, 151.22, 148.74, 133.72, 132.12, 123.06, 117.15, 69.82, 66.74, 50.95, 47.74; Anal.calcd. for $C_{15}H_{18}N_5OS$: C 56.76, H 6.03, N 22.06%; found: C 56.77, H 6.04, N 22.05%.

**5-Pyridin-4-yl-1,3,4-oxadiazole-2-thiol (7)**

Isonicotinohydrazide(0.05m, 6.86g) was dissolved in 50mL of ethanol, sodium hydroxide (0.05mole, 2.0g), and carbon disulfide(0.05mole, 3.3mL) were added. The mixture was refluxed for 3 hours. The solvent was evaporated under reduced pressure. The residue was dissolved in water and filtered, the filtrate was acidified and filtered. The precipitate was crystallized from mixture of ethanol-dioxane(5:1) Yield: 4.85g, (54%); m.p. 279-280C; IR(KBr) $\nu_{max}/cm^{-1}$: 3443-3220, 3131-3000, 3000-2883, 1252, 1621; $^{1}$HNMR(DMSO-d6) δ/ppm: 7.78 (dd, J=6.23, 1.83, 2H). 8.78(d, J=5.83, 2H); $^{13}$CNMR(DMSO-d6) δ/ppm: 182.05, 159.88, 151.47, 132.44, 119.291; Anal.calcd. for $C_7H_5N_3OS$: C 46.92, H 2.81, N 23.45%; found: C 46.93, H 2.81, N 23.44%.

**[(5-Pyridin-4-yl-1,3,4-oxadiazol-2-yl)thio] acetic acid (8)**

A solution of the 5-pyridin-4-yl-1,3,4-oxadiazole-2-thiol(0.01m, 1.79g), and sodium hydroxide (0.01m, 0.4g) in 30mL ethanol was refluxed for 0.5h. To this solution, ethylbromoacetate(0.01m, 1.65g) was added, and the resulting mixture refluxed for 4 h. After cooling, the solution was poured on ice and the solid mass thus separated recrystallized from a mixture of ethanol-water(4:1). Yield: 1.47g, (62%); m.p. >375°C; IR(KBr) $\nu_{max}/cm^{-1}$: 3516-3246, 3131-2925, 1800-1660, 1610; $^{1}$HNMR(DMSO-d6) δ/ppm: 3.79 (s, 2H), 7.28(dd, J=6.23, 1.83, 2H), 8.78 (d, J=5.83, 2H); Anal.calcd. for $C_9H_7N_3O_3S$: C 45.57, H 2.97, N 17.71%; found:C 45.56, H 2.98, N 17.704%.

**3-(Morpholin-4-ylmethyl)-5-pyridin-4-yl-1,3,4-oxadiazole-2(3H)-thion(9)**

A slurry consisting(0.002mole, 0.358g) 5-pyridin-4-yl-1,3,4-oxadiazole-2-thiol, ethanol(10mL) and (0.003mole, 0.289mL) 37% formalin was made. To this morpholine (0.002m, 0.174mL) was added dropwize, with cooling and shaking. The reaction mixture was allowed to stand at room temperature for 1h. with occasional shaking after which it was warmed on a steam bath for 0.5 h. At the end of period the contents were cooled and the product obtained was recrystallized from dioxane. Yield: 0.21g, (38%); m.p. 336-337°C; IR(KBr) $\nu_{max}/cm^{-1}$: 3080-3020, 2970-2820, 1256; $^{1}$HNMR(DMSO-d6) δ/ppm:2.78(t, J=4.45, 4H), 3.58(t, J=4.40, 4H), 5.16 (s, 2H), 7.22(dd, J=5.87, 1.47, 2H), 8.58(dd, J=5.87, 1.47, 2H); Anal.calcd. for $C_{12}H_{14}N_4O_2S$: C 51.78, H 5.07, N 20.13%; found: C 51.78, H 5.09, N 20.14%.

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