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Synthesis of some new substituted 1,2,4-triazole-5-thiol-1,3,4-thiadiazole and 1,3-thiazine derivatives

B. Venugopala Rao[1*], V. S. Hariharakrishnana[1] and P. K. Dubey[2]

[1]*Dissymmetrix Pvt. Ltd, IDA, Uppal, Hyderabad, A.P., India*
[2]*Department of Chemistry, College of Engineering, J.N.T. University, Hyderabad, A.P., India*

ABSTRACT

*Reaction of 2-(4-Aminophenyl)-N-methylethanesulfonamide **(1)** with thiophosgene in chloroform gives 2-(4-Isothiocyanatophenyl)-N-methylethanesulfonamide **(2),** which on reaction with 4-pyridine carboxylic acid hydrazide gives 2-Isonicotinoyl-N-(4-(2-(N-methylsulfamoyl) ethyl) phenyl) hydrazine carbothio amide **(3)**. Treatment of **3** in alkaline and acidic media, gives the corresponding 1,2,4-triazole-5-thiols **(4)** and 1,3,4-thiadiazoles **(5)** respectively. Condensation of **2** with 3-aminopropan-1-ol in THF and followed by cyclisation in presence of conc. hydrochloric acid gives 1,3-thiazine **(6)**. All the synthesized compounds were characterized by their FT-IR, ^{1}H-NMR and mass spectral data.*

Keywords: 1,2,4-Triazole, 1,3,4-Thiadiazole, 1,3-Thiazine, 4-Pyridine carboxylic acid hydrazide, 3-Aminopropan-1-ol.

INTRODUCTION

1,2,4-Triazoles, 1,3,4-thiadiazoles and their derivatives an important class of organic compounds having biological activity with diverse applications in pharmaceutical and agrochemicals [1-3], including anti-microbial [4-5], antifungal [6-7], antibacterial [8], and anti-inflammatory [9]. 1,3-thiazines also have been reported to exhibit a Varity of biological activities in the medical and pharmaceutical chemistry [10-11]. Hence, it was thought worth while to synthesize new 1,2,4-triazole, 1,2,4-thidiazoles and 1,3-thiazine derivatives containing hetero aryl sulfonyl methyl functionality as potentially biologically active compounds. In this paper, we report the synthesis of some new 1,2,4-triazole-5-thiole, 1,2,4-thiadiazole and 1,3-thiazine derivatives bearing pyridyl and benzene methane sulfonamide substituents. The synthetic scheme of these compounds is shown in scheme-1.

MATERIALS AND METHODS

All the reagents used for reactions are of L.R. Grade. Solvents were routinely distilled before use. IR spectra were recorded as KBr pellets on Thermo Nicolet Avatar 330 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a 100 MHz Varian or 200 MHz Tecmag instruments using TMS as internal standard. Melting points are uncorrected and were determined in open capillaries on Mettler FP-90 apparatus. TLC was recorded on Merck silica gel 60 F_{254} Plates and spots were detected using iodine chamber or U.V lamp at 254nm.

Synthesis of isothiocynates (2a-c).

A mixture of **1a-c** (10.0 g, 0.046 mol), chloroform (60 ml) and water (50 ml) was cooled to about 10 ^{O}C. Thiophosgen (7.3 g, 0.063 mol) was added drop wise to the reaction mixture with continuous stirring at 10-20 ^{O}C. After addition, the mixture was stirred at room temperature for 3 hours. The progress of the reaction was monitored by TLC. Allowed the reaction mass to settle for 15 minutes, separated the organic layer and washed the organic layer with excess of water and finally with brine solution. The organic layer was dried over anhydrous Na_2SO_4 and distilled off the solvent under reduced pressure. The residue was stirred with hexane (20 ml) for 1 hour at room temperature. The solid was filtered, washed with hexane to give pure compound **2a-c**.

2-(4-Isothiocyanatophenyl)-N-methylethanesulfonamide (2a).

Yield: 60 %, m.p: 166-168 ^{O}C; IR (KBr, cm^{-1}) 3306 (-NH); 2185 and 2140 (-N=C=S); 1310 and 1122 (-SO_2); ^{1}H NMR (DMSO-d^6/TMS) at δ 2.50 (d, 3H, CH_3), 3.00-3.20 (t, 2H, CH_2), 3.40-3.50 (t, 2H, CH_2), 7.00 (d, 1H, NH, D_2O Exchangeable), 7.60 (d, 2H, Ar-H), 8.20 (d, 2H, Ar-H); (M+1): 257.

1-(4-Isothiocyanatophenyl)-N-methylmethanesulfonamide (2b).

Yield: 55 %, m.p: 146-148 ^{O}C; IR (KBr, cm^{-1}) 3306 (-NH); 2140 and 2140 (-N=C=S); 1310 and 1122 (-SO_2); ^{1}H NMR (DMSO-d^6/TMS) at δ 2.60 (d, 3H, CH_3), 4.40 (s, 2H, CH_2), 7.00 (d, 1H, NH D_2O Exchangeable), 7.50 (d, 2H, Ar-H), 8.30 (d, 2H, Ar-H); (M+1): 243.

1-(4-Isothiocyanatobenzylsulfonyl)pyrrolidine (2c).

Yield: 65 %, m.p: 141-143 ^{O}C; IR (KBr, cm^{-1}) 2150 (-N=C=S); 1310 and 1122 (-SO_2); ^{1}H NMR (DMSO-d^6/TMS) at δ 1.90 (m, 4H, pyrrolidine), 3.20 (m, 4H, pyrrolidine), 4.40 (s, 2H, CH_2), 7.70-7.80 (m, 4H, Ar-H); (M+1): 283.

Synthesis of hydrazine carbothioamides (3a-c).

4-pyridine carboxylic acid hydrazide (0.004 mol) was dissolved in absolute ethanol (80.0ml). A solution of substituted methane sulfonamide isothiocyanate **(2a-c)** (0.004 mol) in absolute ethanol was added into the solution of hydrazide with continuous stirring. The reaction mixture was refluxed by monitoring on TLC for completion of reaction. After the completion of the reaction, the mixture was cooled to room temperature. The resultant white solid was filtered and recrystallized from methanol to get pure compounds **(3a-c)**.

2-Isonicotinoyl-N-(4-(2-(N-methylsulfamoyl) ethyl) phenyl) hydrazine carbothio amide (3a).

Yield: 75 %, m.p: 150-155 °C; IR (KBr, cm^{-1}) 3309 (-NH), 1693 (C=O), 1257 (-C=S), 1292 and 1118 (-SO_2); ^{1}H NMR (DMSO-d^6/TMS) at δ 2.50 (d, 3H, CH_3), 2.9-3.00 (t, 2H, CH_2), 3.40-3.50 (t, 2H, CH_2), 7.00 (d, 1H, NH, D_2O Exchangeable), 7.20-7.40 (m, 4H, Ar-H), 7.90 (d, 2H,

pyridine ring protons), δ 8.80 (d, 2H, pyridine ring protons), 9.90 (d, 2H, NH-NH protons), 10.90 (s, 1H, NH).; (M+1): 349.

2-isonicotinoyl-N-(4-(N-methylsulfamoylmethyl) phenyl) hydrazine carbothioamide (3b).
Yield: 80 %, m.p: 182-184 °C; IR (KBr, cm^{-1}) 3310 (-NH), 1697 (C=O), 1255 (-C=S), 1296 and 1118 ($-SO_2$); ^1H NMR (DMSO-d^6/TMS) at δ 2.60 (d, 3H, CH_3), 4.40 (s, 2H, CH_2), 7.00 (s, ^1H, NH, D_2O Exchangeable), 7.20-7.40 (m, 4H, Ar-H), 7.90 (d, 2H, pyridine ring protons), δ 8.80 (d, 2H, pyridine ring protons), 9.90 (d, 2H, NH-NH protons), 11.00 (s, 1H, NH, D_2O Exchangeable).; (M+1): 380.

2-Isonicotinoyl-N-(4-((pyrrolidin-1-ylsulfonyl)methyl) phenyl) hydrazine carbothioamide (3c).
Yield: 80 %; m.p: 160-163 ^OC; IR (KBr, cm^{-1}) 1698 (C=O), 1257 (-C=S), 1292 and 1118 ($-SO_2$); ^1H NMR (DMSO-d^6/TMS) at δ 1.90 (m, 4H, pyrrolidine), 3.20 (m, 4H, pyrrolidine), 4.40 (s, 2H, CH_2), 7.20-7.40 (m, 4H, Ar-H), 7.90 (d, 2H, pyridine ring protons), δ 8.80 (d, 2H, pyridine ring protons), 9.80 (d, 2H, NH-NH protons), 10.90 (s, 1H, NH, D_2O Exchangeable).; (M+1): 420.

Synthesis of 1,2,4-trizole-5-thiol (4a-c).
Thiosemicarbazide **(3a-c)** (3 mmol) was added portion wise to (25 ml) of 2N sodium hydroxide solution. The reaction mixture was refluxed, and the completion of the reaction was monitored by TLC. Cool the reaction mass to room temperature and filtered. The filtrate was acidified with 2N hydrochloric acid to pH 2. The precipitated solid was filtered, washed thoroughly with water, dried. The crude compound was recrystallized from ethanol/water (4:1) to get compounds of **(4a-c).**

2-(4-(3-Mercapto-5-(pyridin-4-yl)-4H-1,2,4-triazol-4-yl)phenyl)-N-methylethanesulfonamide (4a)
Yield: 80 %; m.p: 248-250 °C; IR (KBr, cm^{-1}) 3337 (-NH) 2626 (broad -SH) 1322 and 1130 ($-SO_2$); ^1H NMR (DMSO-d^6/TMS) at δ 2.60 (d, 3H, CH_3), 2.9-3.00 (t, 2H, CH_2), 3.40-3.50 (t, 2H, CH_2), 7.00 (d, 1H, NH, D_2O Exchangeable), 7.20-7.40 (m, 4H, phenyl ring protons), 7.60 (d, 2H, pyridine ring protons), δ 8.70 (d, 2H, pyridine ring protons), 14.20 (s, 1H, SH, D_2O Exchangeable); (M+1): 376.

1-(4-(3-Mercapto-5-(pyridin-4-yl)-4H-1,2,4-triazol-4-yl)phenyl)-N-methylmethanesulfonamide (4b).
Yield: 80 %; m.p: 260-262 °C; IR (KBr, cm^{-1}) 3325 (-NH) 2616 (broad -SH) 1315 and 1110 ($-SO_2$); ^1H NMR (DMSO-d^6/TMS) at δ 2.60 (d, 3H, CH_3), 4.40 (s, 2H, CH_2), 7.00 (d, 1H, NH, D_2O Exchangeable), 7.20-7.40 (m, 4H, phenyl ring protons), 7.60 (d, 2H, pyridine ring protons), δ 8.70 (d, 2H, pyridine ring protons), 14.10 (s, 1H, SH, D_2O Exchangeable); (M+1): 362.

5-(pyridin-4-yl)-4-(4-((pyrrolidin-1-ylsulfonyl)methyl)phenyl)-4H-1,2,4-triazole-3-thiol (4c).
Yield: 80 %; m.p: < 260 ^OC; IR (KBr, cm^{-1}) 2526 (broad -SH) 1318 and 1115 ($-SO_2$) ; ^1H NMR (DMSO-d^6/TMS) at 1.90 (m, 4H, pyrrolidine), 3.20 (m, 4H, pyrrolidine), 4.40 (s, 2H, CH_2), 7.20-7.40 (m, 4H, phenyl ring protons), 7.60 (d, 2H, pyridine ring protons), δ 8.70 (d, 2H, pyridine ring protons), 14.10 (s, 1H, SH, D_2O Exchangeable); (M+1): 402

Synthesis of 1,2,4-thiadiazole (5a-c).
Thiosemicarbazide **(3a-c)** (0.2 g, 0.6 mmol) was added portion wise to (25 ml) of conc. sulfuric acid at 0 °C with continuous stirring. The reaction mixture was stirred further for 3 h at room

temperature, poured the reaction mass into crushed ice and stirred for 30 mints. Filtered the product and recrystallized from a mixture of acetic acid and water (1:1) to get compounds **(5a-c).**

N-Methyl-2-(4-(5-(pyridin-4-yl)-1,3,4-thiadiazol-2-ylamino) phenyl) ethane sulfonamide (5a).
Yield: 80 %; m.p: < 300 °C; IR (KBr, cm^{-1}) 3301 (-NH) 1326 and 1119 (-SO_2); ^{1}H NMR (DMSO-d^6/TMS) at δ 2.70 (d, 3H, CH_3), 2.9-3.00 (t, 2H, CH_2), 3.30-3.40 (t, 2H, CH_2), 7.00 (d, 1H, NH D_2O Exchangeable), 7.20-7.60 (dd, 4H, Ar-H), 7.80 (d, 2H, pyridine ring protons), δ 8.70 (d, 2H, pyridine ring protons), 10.80 (s, 1H, NH, D_2O Exchangeable), (M+1): 376.

N-Methyl-1-(4-(5-(pyridin-4-yl)-1,3,4-thiadiazol-2-ylamino) phenyl) methane sulfonamide (5a-c).
Yield: 80 %; m.p: < 270 °C; IR (KBr, cm^{-1}) 3310 (-NH), 1326 and 1119 (-SO_2); ^{1}H NMR (DMSO-d^6/TMS) at δ 2.60 (d, 3H, CH_3), 4.40 (s, 2H, CH_2), 7.00 (d, 1H, NH, D_2O Exchangeable), 7.20-7.60 (m, 4H, Ar-H), 7.80 (d , 2H, pyridine ring protons), δ 8.80 (d, 2H, pyridine ring protons), 10.80 (s, 1H, NH), D_2O Exchangeable); (M+1): 362.

5-(pyridin-4-yl)-N-(4-((pyrrolidin-1-ylsulfonyl)methyl)phenyl)-1,3,4-thiadiazol-2-amine (5c).
Yield: 80 %; m.p: <270 °C; IR (KBr, cm^{-1}) 1316 and 1109 (-SO_2); ^{1}H NMR (DMSO-d^6/TMS) at δ 1.90 (m, 4H, pyrrolidine), 3.20 (m, 4H, pyrrolidine), 4.40 (s, 2H, CH_2), 7.20-7.60 (m, 4H, Ar-H), 7.80 (d, 2H, pyridine ring protons), δ 8.80 (d, 2H, pyridine ring protons), 10.80 (s, 1H, NH, D_2O Exchangeable); (M+1): 402.

Synthesis of 1,3-thiazine-2-amine (6a-c).
Substituted methanesulfonamide isothiocyanate **(2a-c)** was added portion wise to a mixture of tetrahydrofuron (35 ml) and 4-aminobutane-1-ol (1.28 gm) at room temperature. The reaction mixture was stirred further for 1 h at 50-55 °C and completion of the reaction monitored by TLC. After the completion of the reaction, the mixture was cooled to room temperature and added conc. HCl (3.8 gm). The reaction mixture was refluxed by monitoring on TLC for completion of reaction. After the completion of the reaction, the mixture was concerted under vacuum at 90 °C. To the resultant crude was added water and adjusted to neutral pH with sodium bicarbonate, filtered and recrystallized from methanol to get pure compounds **(6a-c)**.

2-(4-(5,6-dihydro-4H-1,3-thiazin-2-ylamino)phenyl)-N-methylethanesulfonamide (7a).
Yield: 65 %; m.p: 184-187 °C; IR (KBr, cm^{-1}) 3288 (-NH), 1625 (C=N) 1310 and 1150 (-SO_2); ^{1}H NMR (DMSO-d^6/TMS) at δ 1.80 (m, 2H, CH_2), 2.6 (d, 3H, CH_3), 2.80 (t, 2H, CH_2), 3.00 (m, 2H, CH_2), 3.20 (t, 2H, CH_2), 3.40 (m, 2H, CH_2), 6.90 (s, 1H, NH, D_2O Exchangeable), 7.20-7.60 (m, 4H, phenyl ring protons), 8.40 (s, 1H, NH, D_2O Exchangeable); MS (m/z) 314 (M+1);

1-(4-(5,6-dihydro-4H-1,3-thiazin-2-ylamino)phenyl)-N-methylmethanesulfonamide (7b).
Yield: 70 %; m.p; 152-155 °C; IR (KBr, cm^{-1}) 3278 (-NH), 1624 (C=N) 1310 and 1150 (-SO_2); ; ^{1}H NMR (DMSO-d^6/TMS) at δ 1.90 (m, 2H, CH_2), 2.6 (d, 3H, CH_3), 2.90 (m, 2H, CH_2), 3.50 (m, 2H, CH_2), 4.20 (s, 2H, CH_2), 6.90 (d, 1H, NH D_2O Exchangeable), 7.20-7.60 (m, 4H, Ar-H), 8.40 (s, 1H, NH, D_2O Exchangeable); MS (m/z) 300 (M+1);

N-(4-((pyrrolidin-1-ylsulfonyl)methyl)phenyl)-5,6-dihydro-4H-1,3-thiazin-2-amine (7c).
Yield: 68 %; m.p: 142-145 °C; IR (KBr, cm^{-1}) 1625 (C=N) 1310 and 1150 (-SO_2); ^{1}H NMR (DMSO-d^6/TMS) at δ 1.90-2.20 (m, 6H, pyrrolidine and thiazine ring), 3.20-3.80 (m, 8H,

pyrrolidine and thiazine ring), 4.40 (s, 2H, CH_2), 7.20-7.60 (m, 4H, Ar-H), 8.80 (s, 1H, NH, D_2O Exchangeable); (M+1): 340.

RESULTS AND DISCUSSION

The required starting materials, substituted 2-(4-Aminophenyl)-N-methylethanesulfonamide were synthesized from 1-(2-bromoethyl)-4-nitrobenzene, as per a reported procedure [12]. Thus 1-(2-bromoethyl)-4-nitrobenzene was reacted with sodium sulfite to obtain sodium 2-(4-nitrophenyl)ethanesulfonic acid, which was converted to the 2-(4-nitrophenyl)ethanesulfonyl chloride by reacting with thionyl chloride. Treatment of 2-(4-nitrophenyl)ethanesulfonyl chloride with excess of aliphatic and cyclic amines gave corresponding nitro methane sulfonamide. The latter compounds were then hydrogenated using palladium on carbon as a catalyst in methanol to yield corresponding amino methane sulfonamide derivatives.

Pyridinecarboxylic acid hydrazide was prepared by treatment of the corresponding pyridinecarboxylic acid with hydrazine hydrate as per the reported procedure [13]. 1-(4-Aminophenyl)-N-methyl methane sulfonamide **(1a)** was treated with thiophosgene in chloroform to give a new product 1-(4-isothiocyanatophenyl)-N-methyl methane sulfonamide **(2a).** The characteristic peaks at 2185 and 2140 cm^{-1} in IR spectrum of **2a** can be attributed to N=C=S group.

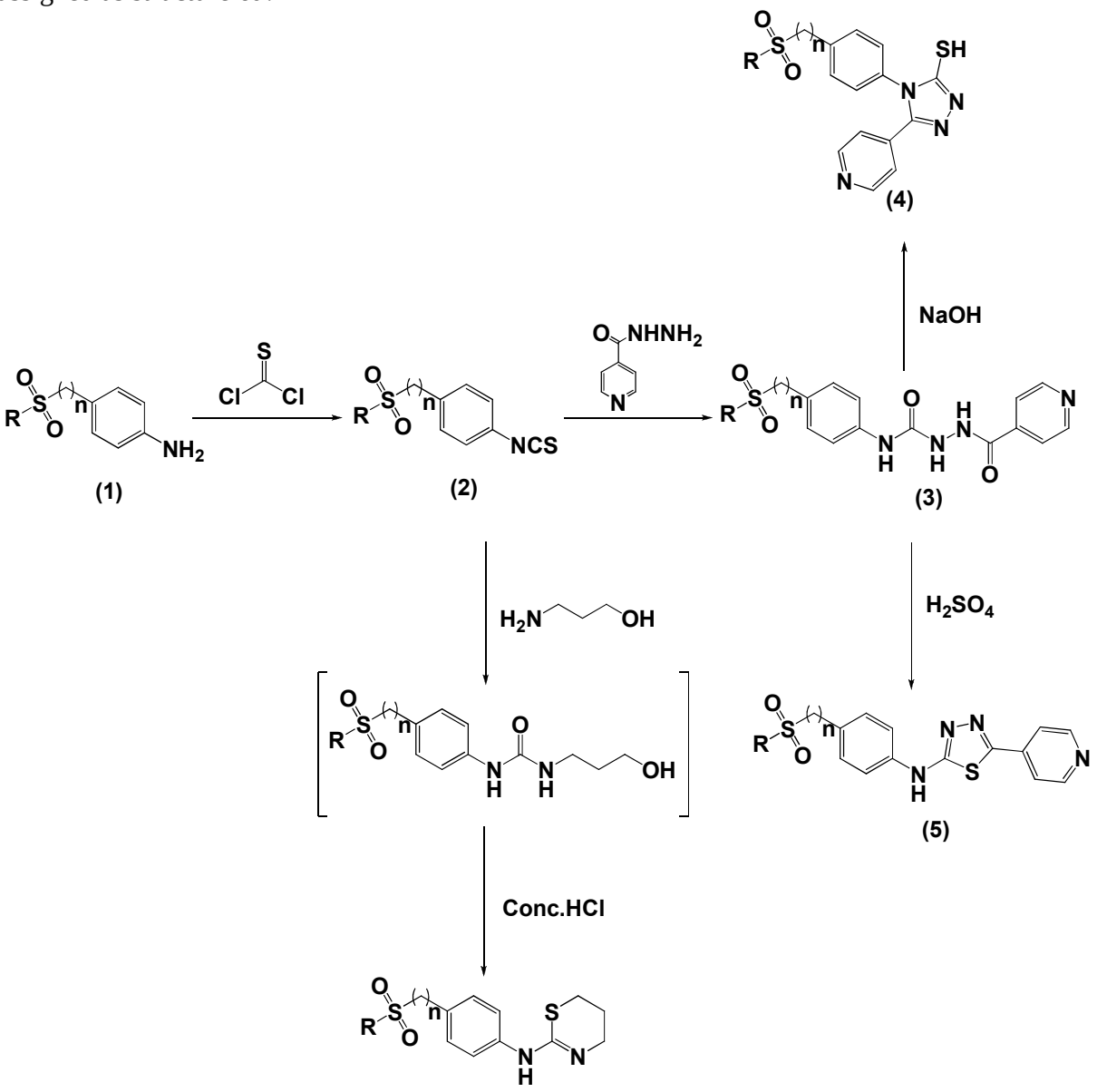
Condensation of **2a** with pyridine carboxylic acid hydrazide in methanol gave a new compound 2-isonicotinoyl-N- (4-(N-methylsulfamoylmethyl) phenyl) hydrazine carbothioamide **(3a)**. The infrared spectra of **3a** showed a characteristic peak at 1292 cm^{-1} which can be attributed to C=S group. A peak at 1693 cm^{-1} confirming the carbonyl group. It's ^{1}H-NMR spectrum showed signals at δ 9.7 and 9.8 confirmed the protons of –NH-NH. The signal at δ 10.8 is of –NH proton between thioketone and aromatic groups.

3a, on cyclisation in basic medium gave a new compound 1-(4-(3-mercapto-5- (pyridin-4-yl)-4H-1, 2,4-triazol-4-yl) phenyl)-N-methyl methane sulfonamide **(4a)**. The IR spectrum of **4a** showed a peak at 2626 cm^{-1} attributed to SH. The signal at δ 14.20 in its ^{1}H-NMR confirmed the proton of -SH. Its mass spectrum showed molecular ion at m/z 362 which further confirmed the structure.

3a, on cyclization in acidic medium gave a new compound N-methyl-1-(4-(5-(pyridin-4-yl)-1,3,4-thiadiazol-2-ylamino)phenyl)methane sulfonamide **(5a)**. Absence of carbonyl absorption and presence of –NH group at 3440 cm^{-1} in its IR spectrum supports the assigned structure of **5a** and further confirmed by ^{1}H-NMR and mass spectral fragmentation.

2a, was further reacted with 4-aminobutan-1-ol in refluxing tetrahydrofuran to give 1-(4-(3-(4-hydroxybutyl)thioureido)phenyl)-N-methyl ethane sulfonamide, wich on cyclisation in hydrochloric acid yield 2-(4-(5,6-Dihydro-4H-1,3-thiazin-2-yl amino) phenyl) -N-methyl ethane sulfonamide **(6a)**. Its ^{1}H NMR (DMSO-d_6/TMS) spectrum showed signals at δ 1.80 (m, 2H, CH_2), 2.6 (d, 3H, CH_3), 2.80 (t, 2H, CH_2), 3.00 (m, 2H, CH_2), 3.20 (t, 2H, CH_2), 3.40 (m, 2H, CH_2), 6.90 (s, 1H, NH, D_2O Exchangeable), 7.20-7.60 (m, 4H, phenyl ring protons), 8.40 (s,

1H, NH, D_2O Exchangeable); (M+1); 314. Based on the above spectral data, the compound was assigned as structure **6a**.



1a, 2a, 3a, 4a, 5a, 6a, : R = -NHCH$_3$, n = 2

1b, 2b, 3b, 4b, 5b, 6b, : R = -NHCH$_3$, n = 1

1c, 2c, 3c, 4c, 5c,6c, : R = Pyrrolidine, n = 1

Scheme-I

CONCLUSION

As a conclusion, we have prepared some pyridyl and benzene methane/ethane sulfonamide substitued 1,2,4-triazole, 1,3,4-thiadiazoles and 1,3-thiazine derivatives. Further studies are desirable to evaluate their biological activities.

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