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Formation and interpretation of new spiro thiadiazines

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ABSTRACT

*Equimolar mixture of substituted triazole **(1)** and substituted aromatic aldehyde were refluxed in presence of alcoholic KOH to yield 4- substituted-banzylidene-amino-5-substituted-4H-1,2,4-triazole-3-thiol **(2)**, which cyclized to form 2H,3H,4H,2-Carbethoxy, 3-substituted, Phenyl,5-substituted-[1,2,4]-triazole [3,4-b] [1,3,4] thiadiazine **(3)** using ethyl chloro acetate and K_2CO_3. Compound **(3)** was undergoes bromination in the presence of iodine which is act as catalyst to form Bromo compound **(4).** Compound **(4)** was further converted into Imino spiro Thiadiazines **(6)**, Hydrazino spiro Thiadiazines **(8)** and spiro Triazolo-thiadiazines **(9)** by reacting with Thiosemicarbazones **(5)**, Thiocarbohydrazones **(7)** and Triazoles **(1)** respectively. The structures of the newly synthesized compounds were confirmed by IR, 1H NMR and mass spectroscopic analysis.*

Keywords: Triazole, Thiosemicarbazones, Thiocarbohydrazones, Thiadiazine and Antimicrobial.

INTRODUCTION

Heterocyclic compounds[1–6] and esp. those containing sulphur and nitrogen atoms possess a wide variety of biological activities and their utility in medicine is very well established.[7–8] Further, the therapeutic effect of 1,2,4-triazole containing compounds have been well studied for a number of pathological conditions including inflammation, cancer, pain, tuberculosis and hypertension.[9–17] In addition, it was reported that 1,3,4-thiadiazine exhibits various biological activities possibly due to the presence of the N–C–S moiety. Moreover, synthesis of triazoles fused to another heterocyclic ring has attracted wide-spread attention due to their diverse applications as antibacterial, antidepressant, antiviral, antitumoral, anti-inflammatory agents, pesticides, herbicides, dyes, lubricant and analytical reagents.[18,19] On the other hand, triazoles fused with six-member ring systems are also found to possess diverse applications in the field of medicine.[20–23] The literature for heterocyclic pharmaceutical agents includes sulphur containing compounds, particularly those incorporating the N–C–S linkage in their skeleton, exhibit a broad spectrum of pharmacological activities such as antimalarial[24], human immuno virus-1 (HIV-1) inhibitors[25] and antimicrobial [26]. These initial reports and our previous work on biologically active spiro-heterocycle stimulated us to integrate thiadiazine moiety in a triazole framework, since these systems possess well documented antimicrobial activity. Here in we report the synthesis of a new series of spiro-thiadiazines and their antimicrobial activity.

MATERIALS AND METHODS

Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The progress of reaction was monitored by thin layer chromatography on silica gel coated aluminum plates (Merck) as adsorbent and UV light as visualizing agent. ^{1}H NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using $CDCl_3$/DMSO-d_6 as solvent and TMS as an internal standard (chemical shifts in δ ppm). C, H, N estimation was recorded on Carlo Erba 1108 (CHN) Elemental Analyzer.

General Procedure:

Synthesis of 4- substitutedbanzylideneamino-5-substituted-4H-1,2,4-triazole-3-thiol (2).

An equimolar mixture of 3-substituted-4-amino-5-mercapto-1,2,4-triazoles (**1)** (0.01 mol) and substituted aromatic aldehyde (0.01 mol) were refluxed for about 4-5 hrs in alcohol (20 ml) as a solvent and KOH (0.01 mol) as a catalyst. The progress of the reaction was monitored on TLC. Upon Completion 3 hrs, the reaction was quenched onto crushed ice. The separated solid was filtered, washed with cold water and crystallized from alcohol, to yield respected (**2)**.

Synthesis of 2H,3H,4H-2-Carbethoxy-3-substitutedphenyl-5-substituted-[1,2,4]-triazole [3,4-b] [1,3,4] thiadiazine (3).

A mixture of **2** (0.01 mol), ethyl chloro acetate (0.01 mol), N, N- Dimethyl formamide (15 ml) and potassium carbonate (0.02 mol) were stirred for 30 mins at room temperature. Then the content was refluxed for 3-4 hrs. The progress of the reaction was monitored on TLC. Upon completion, the content was poured into cold water. Solid thus obtained was filtered, washed with cold water and crystallized from alcohol, to yield respected (**3).**

Synthesis of 3H,4H,2-bromo-2-Carbethoxy,3-(substituted)- Phenyl- 5-substituted-[1,2,4]-triazole [3,4-b] [1,3,4] thiadiazine (4).

(**3**) (0.01mol, 3.34gms) was dissolved in 10 ml of glacial acetic acid. A solution of bromine (0.01mol, 0.55 ml) in glacial acetic acid (10ml) was added drop wise with continuous stirring in presence of UV light. The stirring was continued for 1 hr. The reaction mixture was quenched onto ice-cold water and the product was separated out, filtered, washed with cold water, purified by recrystallization from ethanol to **(4).**

Synthesis of thiosemicarbazones (5):

Thiosemicabazones were prepared by the method of Bernstein *et al* [27] as follows:

Representative Procedure

Aromatic aldehyde (0.1 mole) in 100 ml of warm ethanol (95%) and a solution of thiosemicarbazide (0.1 mole) in 100 ml of warm water were refluxed for 30 min. The product separated out immediately when the reaction mixture was allowed to cool at room temperature. It was then filtered, recrystallized from ethanol to obtain thiosemicarbazone of anisaldehyde **(5a).**

Synthesis of 4H, 10H -3,4,9,10 -tetra aza-1,7-dithia -2-(substituted)-benzilidine-imino-5-oxo-11-(substituted)-phenyl-8,9-(3'-substituted)-1,2,4- triazole [4,5-b]-spiro [5.5] undecane-2-ene(6).

An equimolar mixture of compound (4) (0.01mole) and thiosemicarbazone derivative of Aromatic aldehyde (5) (0.01mole) in N,N-Dimethyl formamide (20ml) was refluxed in presence of potassium carbonate (0.02mole, 2.0gms) for about 4-5 hr. The progress of reaction was monitored by TLC. Upon completion, the reaction mixture was quenched onto crushed ice. The product precipitated out was filtered, washed with water, recrystallized from ethanol to obtain the desired product (6).

Synthesis of thiocarbohydrazones (7)

Thiocarbohydrazones were prepared by the method of Kurger and Wilkinson[28] as follows:

Representative Procedure

Thiocarbohydrazide (0.1 mole) was first dissolved in 100 ml of warm water with stirring. Aromatic aldehyde (0.1 mole) in 100 ml of warm ethanol was added to the same solution and the reaction mixture was refluxed for 10 hrs. Upon completion, the reaction mixture was quenched onto ice-cold water. The precipitated product was then filtered and recrystallized from ethanol to yield **(7)**.

Synthesis of 4H, 10H -3,4,9,10 -tetra aza-1,7-dithia -2-(substituted)-benzilidine-hydrazino-5-oxo-11-(substituted)-phenyl-8,9-(3'-substituted)-1,2,4- triazole [4,5-b]-spiro [5.5] undecane-2-ene (8)
An equimolar mixture of compound (4) (0.01 mole) and thiosemicarbazone derivative of aromatic aldehyde (7) (0.01 mole) in N, N- Dimethyl formamide (20 ml) was refluxed in presence of potassium carbonate (0.02 mole, 2.0 gm) for about 4-5 hr. The progress of reaction was monitored by TLC. Upon completion, the reaction mixture was quenched onto crushed ice. The product precipitated, was filtered, washed with water recrystallized from ethanol to yield (8).

Synthesis of 4H,10H-3,4,9,10-tetraza-1,7-dithia-5-oxo-11-(substituted)-phenyl-2,3-(3-substituted)-1,2,4-triazolo[4,5-b],8,9-(3-substituted)-1,2,4-triazolo[4,5-b]spiro[5.5]undecane (9).
An equimolar mixture of compound (4) (0.01 mole) and 3-substituted-4-amino-5-mercapto-1,2,4-triazole (1) (0.01 mole) in N, N- Dimethyl formamide (20 ml) was refluxed in presence of potassium carbonate (0.02 mole, 2.0 gm) for about 4-5 hr. The progress of reaction was monitored by TLC. Upon completion, the reaction mixture was quenched onto crushed ice. The product precipitated out was filtered, washed with water and purified by recrystallization from ethanol to obtain the desired product (9).

Antimicrobial activities:
All the newly synthesized compounds were evaluated for their antibacterial activity against gram-negative bacteria, E coli and P putide and gram-positive, S lactis and B subtilis using disc diffusion method. The zone of inhibition was measured in mm and the activity was compared with standard drug. The antimicrobial data was given in Table **2**.

Spectral Data of **4H, 10H -3,4,9,10 -tetra aza-1,7-dithia -2-(4-methoxy)-benzilidine-imino-5-oxo-11-(4-methoxy)-phenyl-8,9-(3'-methyl)-1,2,4- triazole [4,5-b]-spiro [5.5] undecane-2-ene (6a).**
Yield: 65 %; m.p. =223-25°C: IR (cm^{-1}): 3274 (N-H), 1749 (C=O), ^{1}H NMR(DMSO-d_6,δ/ ppm): 2.35(s, 3H, CH_3), 3.73(s, 6H, 2×OCH_3), 4.67(s, 1H, NH), 5.29(s, 1H, CH) 7.17-8.01(m, 4H, Ar- H), 9.05(s, 1H, CH), 9.98(s, 1H, NHC=O). ^{13}C NMR (DMSO-d_6, δ/ ppm): 14.39(CH_3), 55.17(2×OCH_3), 64.14(CH), 80.67(C-S), 119.21-132.78(Ar-C), 148.21(C=N), 154.39(C=N), 160.29(C=N), 163.74(C=N), 188.24(C=O). Anal. Calcd for $C_{22}H_{21}N_70_3S_2$: C,53.34;H,4.24;N,19.79%.Found: C,53.31;H,4.21;N,19.75%.

Spectral Data of **4H, 10H -3,4,9,10 -tetra aza-1,7-dithia -2-(4-hydroxy)-benzilidine-imino-5-oxo-11-phenyl-8,9-(3'-ethyl)-1,2,4- triazole [4,5-b]-spiro [5.5] undecane-2-ene (6ai).**
Yield: 72 %; m.p. =178-80°C: IR (cm^{-1}): 3482 (OH), 3247 (N-H), 1765 (C=O), ^{1}H NMR(DMSO-d_6,δ/ ppm): 1.35(t, 3H, CH_3), 2.24(q, 2H, CH_2), 4.67(s, 1H, NH), 5.25(s, 1H, CH), 6.35(s, 1H, OH) 7.01-8.12(m, 9H, Ar- H), 9.16s, 1H, CH), 10.14(s, 1H, NHC=O). ^{13}C NMR (DMSO-d_6,δ/ppm): 15.49(CH_3), 20.14(CH_2), 64.81(CH), 80.77(C-S), 118.84-132.27(Ar-C), 148.11(C=N), 154.78(C=N), 161.01(C=N), 162.71(C=N), 191.49(C=O). Anal. Calcd for $C_{21}H_{19}N_70_2S_2$: C,54.19;H,4.08;N,21.07%.Found: C,54.16;H,4.05;N,21.04%.

Spectral Data of **4H, 10H -2,4,9,10 -tetra aza-1,7-dithia -3-(4-methoxy)-benzilidine-hydrazino-5-oxo-11-(4-methoxy)-phenyl-8,9-(3'-methyl)-1,2,4- triazole [4,5-b]-spiro [5.5] undecane-2-ene (81a).**
Yield: 74 %; m.p. =202-204°C: IR (cm^{-1}): 3331 (N-H), 1755 (C=O), ^{1}H NMR(DMSO-d_6,δ/ ppm): 2.15(s, 3H, CH_3), 3.68(s, 6H, 2×OCH_3), 4.58(s, 1H, NH), 5.31(s, 1H, CH) 7.07-8.12(m, 8H, Ar- H), 9.05(s, 1H, CH), 9.98(s, 1H, NH), 10.47(s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ/ ppm): 14.74(CH_3), 56.85(2×OCH_3), 64.34(CH), 80.98(C-S), 118.37-134.97(Ar-C), 149.64(C=N), 155.74C=N), 161.31(C=N), 164.27(C=N), 189.94(C=O). Anal. Calcd for $C_{22}H_{22}N_80_3S_2$: C,51.76;H,4.31;N,21.96%.Found: C,51.73;H,4.28;N,21.93%.

Spectral Data of **4H, 10H -2,4,9,10 -tetra aza-1,7-dithia -3-(4-methoxy)-benzilidine-hydrazino-5-oxo-11-(4-hydroxy)-phenyl-8,9-(3'-ethyl)-1,2,4- triazole [4,5-b]-spiro [5.5] undecane-2-ene (81aa).**
Yield:62 %; m.p. =202-204°C: IR (cm^{-1}): 3378(OH), 3287 (N-H), 1757 (C=O), ^{1}H NMR(DMSO-d_6,δ/ ppm): 1.35(t, 3H, CH_3), 2.34(q, 2H, CH_2), 3.75(s, 3H, OCH_3), 4.67(s, 1H, NH), 5.25(s, 1H, CH), 6.35(s, 1H, OH) 7.01-8.12(m, 8H, Ar- H), 9.16s, 1H, CH), 10.14(s, 1H, NH), 10.86(s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ/ ppm): 15.17(CH_3), 20.01(CH_2), 54.72(OCH_3), 64.81(CH), 81.71(C-S), 114.24-134.21(Ar-C), 147.23(C=N), 152.01(C=N), 162.12(C=N), 161.45(C=N), 190.12(C=O). Anal. Calcd for $C_{22}H_{22}N_80_3S_2$: C,51.76;H,4.31;N,21.96%.Found: C,51.73;H,4.28;N,21.93%.

Spectral Data of **4H,10H-3,4,9,10-tetraza-1,7-dithia-5-oxo-11-(4-methoxy)-phenyl-2,3-(3-methyl)-1,2,4-triazolo[4,5-b],8,9-(3-methyl)-1,2,4-triazolo[4,5-b]spiro[5.5]undecane (82a).**
Yield: 71%; m.p. =157-59°C: IR (cm^{-1}): 3247(N-H), 1737(C=O), ^{1}H NMR(DMSO-d_6,δ/ ppm): 2.46(s, 6H, 2×CH_3), 3.71(s, 3H, OCH_3), 4.59(s, 1H, CH), 7.29-7.91(m, 4H, Ar- H), 9.17(s, 1H, NH), 10.42(s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ/ ppm): 14.12(CH_3), 19.47(CH_3), 54.23(CH), 65.27(OCH_3), 75.51(C-S), 123.74-134.19(Ar-C), 148.61 (C=N), 152.14(C=N), 157.71(C=N), 159.47(C=N), 184.39(C=O). Anal. Calcd for $C_{16}H_{16}N_80_2S_2$: C,46.15;H,3.84; N,26.92%. Found: C,46.12;H,3.81;N,26.88%.

Spectral Data of **4H,10H-3,4,9,10-tetraza-1,7-dithia-5-oxo-11-(4-methoxy)-phenyl-2,3-(3-ethyl)-1,2,4-triazolo[4,5-b],8,9-(3-methyl)-1,2,4-triazolo[4,5-b]spiro[5.5]undecane (82f).**
Yield: 70%; m.p. =149-51°C: IR (cm^{-1}): 3278(N-H), 1742(C=O), ^{1}H NMR(DMSO-d_6,δ/ ppm): 1.34(s, 3H, CH_3), 2.34 (t, 3H, CH_3), 2.89(q, 2H, CH_2), 3.71(s, 3H, OCH_3), 4.71 (s, 1H, CH), 6.97-7.84(m, 4H, Ar-H), 8.92 (s, 1H, NH), 10.01 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ/ ppm): 12.26(CH_3), 15.41(CH_2), 18.68(CH_3) 52.17(CH), 62.49(OCH_3), 78.86(C-S), 122.36-133.78(Ar-C), 148.47(C=N), 152.14(C=N), 154.49(C=N), 158.27(C=N), 183(C=O). Anal. Calcd for $C_{17}H_{18}N_80_2S_2$: C,47.44;H,4.18;N,26.04%.Found: C,47.41;H,4.15;N,26.01%.

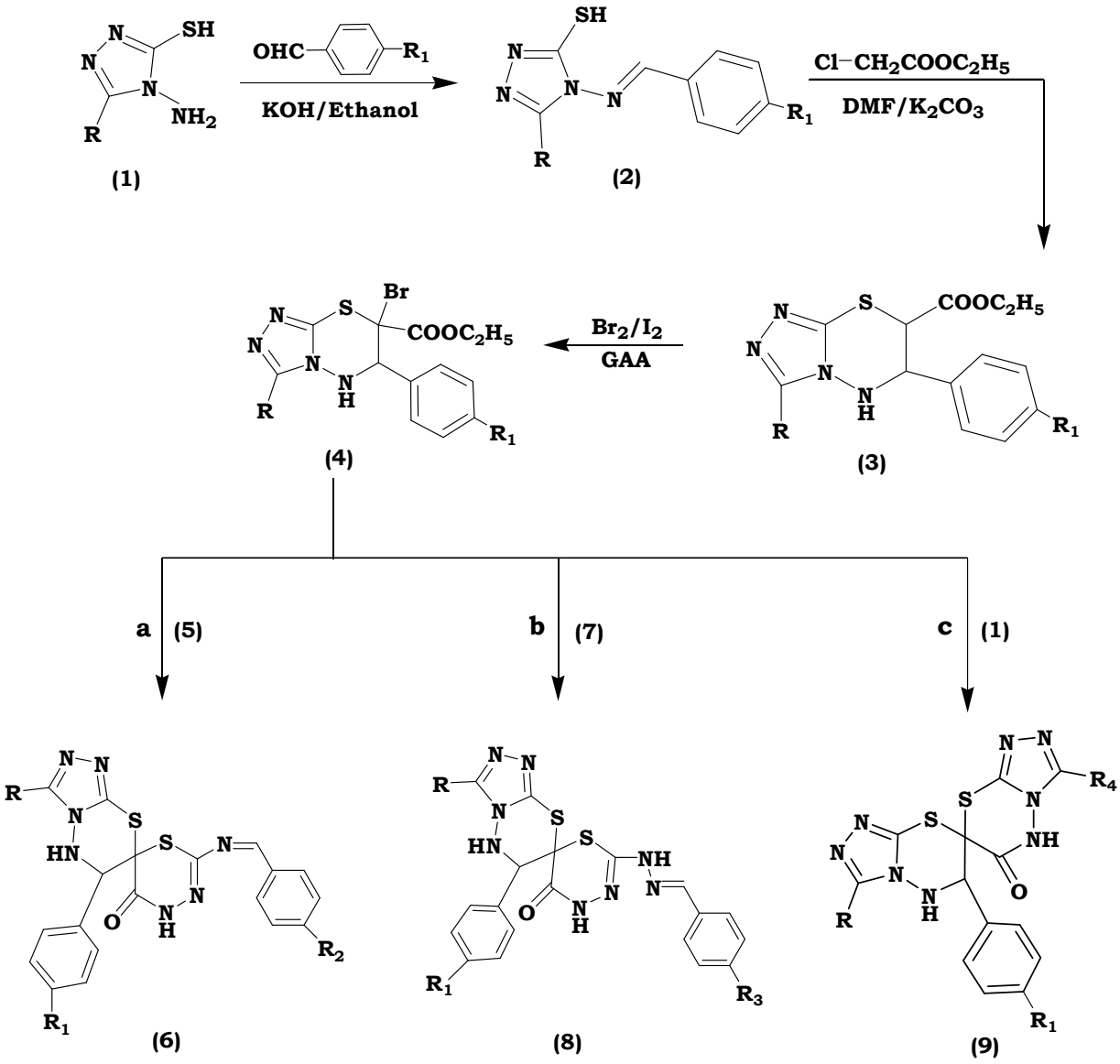
Table 1.Characterization of the some selected synthesized compounds

Compound	R	R_1	$R_2/R_3/R_4$	Melting point (°C)	Yield (%)
79a	-CH_3	4-OCH_3	4-OCH_3	223-25	69
79f	-CH_3	4-OCH_3	4-OH	168-70	83 84/794 68/8
79aa	-C_2H_5	4-OH	4-OCH_3	223-25	68
79ad	-C_2H_5	4-H	4-OCH_3	201-03	70
81a	-CH_3	4-OCH_3	4-OCH_3	202-04	74 85/87894 7692/9
81c	-CH_3	4-OH, 3-OCH_3 OCH_3OCH_3	4-OCH_3	191-93	68
81ab	-C_2H_5	4-OH, 3-OCH_3 OCH_3OCH_3	4-OCH_3	184-86	63
82a	-CH_3	4-OCH_3	-CH_3	157-59	71 85/894 72/9
82l	-C_2H_5	4-OH	-CH_3	149-51	74
82o	-C_2H_5	4-H	-CH_3	173-75	63
**All the compounds gave satisfactory elemental analysis.*					

Table 2. Antimicrobial activities of some newly synthesized compounds

Compounds	Inhibition Zone (mm)			
	Gram-negative		Gram-positive	
	E.coli	***P.Putide***	***B.Subtilis***	***S.lactis***
79a	17	18	17	17
79f	24	23	18	16
79aa	21	20	20	20
79ad	18	18	15	17
81a	23	20	17	15
81c	20	22	20	18
81ab	23	21	18	17
82a	18	17	15	16
82l	24	23	21	20
82o	22	20	18	18
Ciprofloxacin	25	24	24	22
DMSO	0	0	0	0

General Scheme:-



a =Thiosemicarbazones/DMF/K2CO3
b =Thiocarbohydrazones/DMF/K2CO3
c =Triazoles/DMF/K2CO3

RESULTS AND DISCUSSION

Compound (3) was formed by treating 4- substitutedbanzylideneamino-5-substituted-4H-1,2,4-triazole-3-thiol (2) with using ethylchloroacetate and K_2CO_3, which was brominated to yield compound (4) and then condensed with Thiosemicarbazones, Thiocarbohydrazones and Triazoles in the presence of N,N-Dimethyl formamide and Potassium carbonate yielded compound (6), (8) and (9).The formation of the all compounds was confirmed using different spectroscopic techniques.

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