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Synthesis, Characterization and Anti-microbial Screening of Novel Substituted thiadiazole5-aminotetrazoles

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Abstract: An efficient and green synthesis of substituted thiadiazole5-aminotetrazoles has been prepared in situ by reaction of cyanogen bromide and sodium azide to generate a cynogenazide as an intermediate in acetonitrile. The cyclization reaction of cynogenazide and substituted thiadiazoles containing primary amines in acetonitrile-water solvent media, gave the intermediate 1-substituted 5-aminotetrazoles in good yield. In addition, to further evaluate the role of synthesized molecules for antimicrobial activities, and it's found that compound 3c and 3g shows a good antimicrobial for broad range of bacterial and fungal pathogens.

Keywords: Tetrazoles, thiosemicarbazide, aromatic carboxylic acids, antimicrobial screening

1. INTRODUCTION

Five membered heterocycles are well known for their biological properties[1]. Currently, the most widely used substituted amino tetrazoles have been investigated for their use organic and inorganic materials[2], high energy density materials[3] and significant therapeutic properties. The sulfur atom of the thiadiazole imparts liposolubility and mesoionic nature reported as anti-parasitic, anti-convulsant and anti-coagulant[4], anti-microbial[5], anti-cancer[6], anti-inflammatory[7,8]anti-tubercular [9]. Various research study reported that the 1,3,4-thiadiazole derivatives has pharmacological properties like anti-fungal[10], diuretic[11], anthelmintic activity[12], anti-tumor[13], anti-diabetic [14], anti-platelet[15].

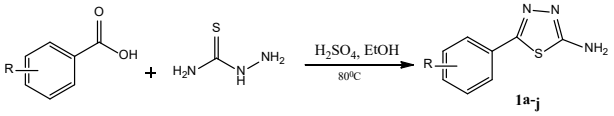
Outstanding pharmacological importance of 1,3,4-thiadiazole derivatives attracts researchers to find new synthetic routes or synthesis the novel molecules. Hence, considering above importance of substituted thiadiazoles

containing tetrazoles, the development of new synthetic approaches with unusual reaction conditions continues to be an active area of research.

2. Results and Discussion Chemistry

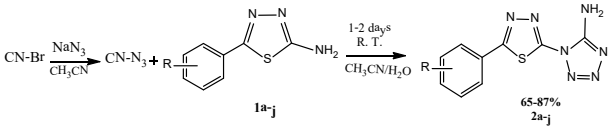
In continuation with our work in expansion of new methods for synthesis of heterocyclic compounds [16], herewith we are reported an efficient and green protocol for the synthesis substituted thiadiazole-5-aminotetrazoles. Firstly synthesized substituted thiadiazoleamine from anethanolic solution of aromatic carboxylic acid was added to aqueous solution of thiosemicarbazide with constant starring; few drop of conc. sulphuric acid was added and reflux the reaction mixture for 4-5 hours at 80-90^{0}C**(Scheme 1).**

Then cyanogen bromide and sodium azide was dissolved in 10 ml dry acetonitrile at 0°C.



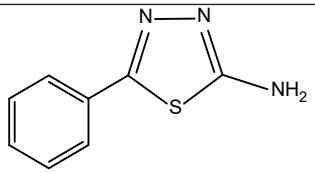
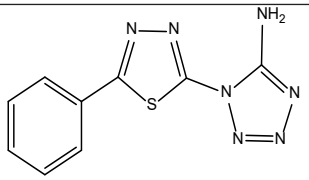
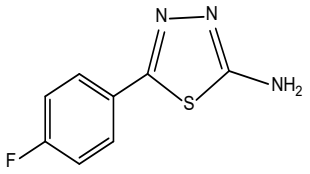
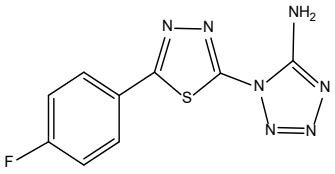
Scheme 1: Synthesis of 5-aryl-1,3,4-thiadiazol-2-amine in ethanol

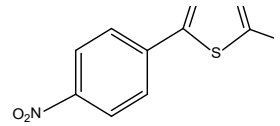
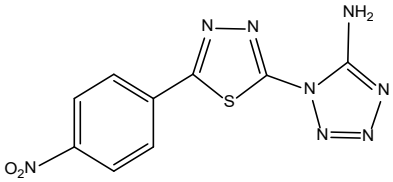
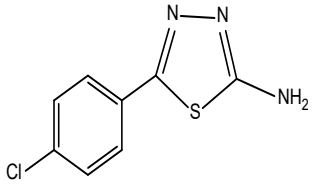
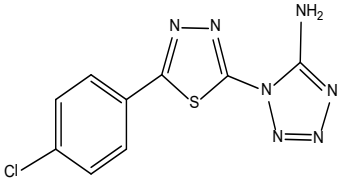
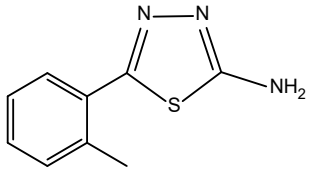
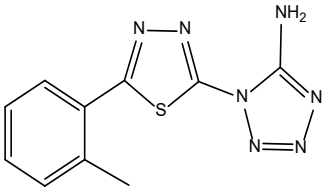
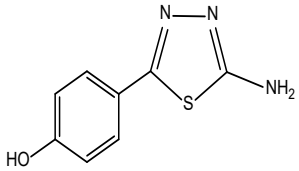
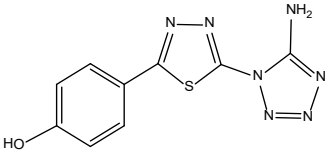
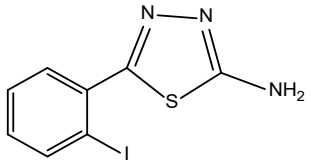
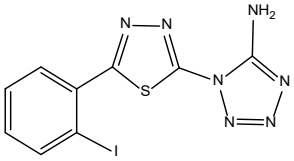
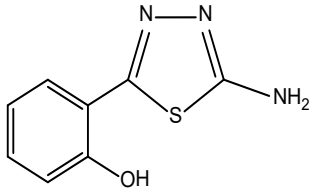
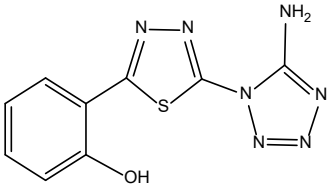
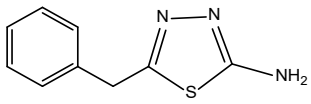
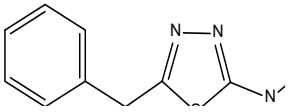
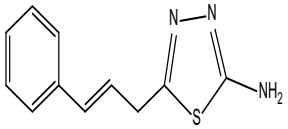
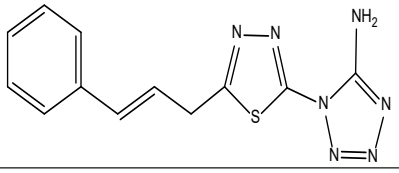
The reaction mixture was stirred at 0−15 °C for 4 hours. The inorganic salt was filtered off. The solution is added to a suspension containing substituted 5-aryl-1,3,4-thiadiazol-2-amine in 15 ml water at 0°C. After 1–2 days stirring at ambient temperature, the progress of reaction was monitored by TLC. After completion of reaction, the solvent was dried in air. The solid product of 1-(5-aryl-1,3,4-thiadiazol-2-yl)-1H-tetrazol-5-amine was filtered and recrystallized by using ethanol. The analytical and spectral data of obtained compounds is obtained (**Scheme 2).**



Scheme 2: Synthesis of 1-(5-aryl-1,3,4-thiadiazol-2-yl)-1H-tetrazol-5-amine

Table 1: Synthesis of substituted 1-(5-aryl-1,3,4-thiadiazol-2-yl)-1H-tetrazol-5-amine derivatives

Entry	1a-j	Azide	2a-j	Time (h)	M.P. (^{o}C)	Yield[b] (%)
a		$CN-N_3$		36	135	87
b		$CN-N_3$		48	142	75

c		$CN-N_3$		24	258	68
d		$CN-N_3$		48	238	80
e		$CN-N_3$		24	180	65
f		$CN-N_3$		48	140	78
g		$CN-N_3$		24	168	67
h		$CN-N_3$		36	138	81
i		$CN-N_3$		24	170	70
j		CN-N_3		48	225	69

2.2 Biology

2.2.1. Antibacterial and antifungal activity:

All synthesized 1-(5-aryl-1,3,4-thiadiazol-2-yl)-1H-tetrazol-5-amine derivatives were screened in vitro for the antibacterial and antifungal activity. Antibacterial activity was evaluated against Gram positive and Gram negative bacterial pathogens. *Staphylococcusaureus, Bacilluscereus, Bacillusmegaterium*, *Micrococcusglutamicum, Bacillussubtilis* were Gram positive pathogens used in this study. *Escherichiacoli, Salmonellatyphi, Shigellaboydii, Enterobacteraerogenes, Pseudomonasaerogenosa*, *Salmonellaabony* were the used Gram negative pathogens. Antifungal activities of synthesized compounds were determined against Aspergillus*niger, Saccharomycescereviseae*, *Candidaalbicans* fungal pathogens. Tetracyclin and fluconazol were used as standard antibacterial and antifungal drug respectively. DMSO was used as control solvent. The antimicrobial activity of synthesized compounds was determined by agar well diffusion method as described [17,18].

Antimicrobial activity was confirmed if the zone around the agar well was observed. Zones were measured and recorded. The results of compound **3c** and **3g** were as good as the standard drug, so these two compounds might serve as a good antimicrobial for broad range of bacterial and fungal pathogens.

Table 2 : Antibacterial activity of Substituted thiadiazole5- derivatives.

Compounds→ / Pathogens↓	3a	3b	3c	3d	3e	3f	3g	3h	3i	3j	Standard
S.abony	16	14	-	-	-	-	16	-	10	12	28
B.subtilis	07	15	-	14	-	-	07	12	-	-	22
E.aerogenes	13	12	14	-	15	-	19	-	14	10	30
C.albicans	14	14	-	-	-	-	24	14	-	-	22
S.typhi	07	14	-	06	-	-	13	-	-	-	18
P.aerogenosa	12	11	-	-	09	-	23	13	14	-	20
E.Coli	11	10	15	-	-	-	15	-	-	-	24
B.megaterium	15	12	-	10	-	-	15	-	11	13	18
S.aureus	08	14	13	-	-	-	15	-	-	-	24
A.niger	11	12	-	-	15	-	22	-	12	-	24
S.cerevisiae	13	08	-	-	-	-	17	-	-	-	16
S.boydii	12	09	-	-	-	-	15	08	-	-	20
M.glutamicus	12	09	08	14	14	-	11	-	13	11	15
B.cereus	13	10	-	-	-	-	14	05	-	-	14

3. Experimental

All chemicals were purchased from commercial suppliers and used without further purification. All solvents were treated according to the standard procedure. The progress of the reactions was monitored by TLC. ^{1}H NMR (400 MHz) and ^{13}C (100 MHz) spectra were recorded with tetramethylsilane as the internal standard.

1.1 General procedure for synthesis of substituted Thiadiazoles amines:

An ethanolic solution of aromatic carboxylic acid (10mmole) was added to aqueous solution of thiosemicarbazide (10mmole) with constant starring; few drop of conc. $H_2SO_4$was added and reflux the reaction mixture for 4-5 hours at 80-90^{0}C. The progress of reactions was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The reaction mixture was poured on crushed ice, basify with 10% Na_2CO_3 solution, filter the crude product and recrystallized in ethanol to obtain corresponding substituted thiadiazole containing amine with high yield.

1.2 General procedure for synthesis of substituted Thiadiazolestetrazole amine:

At 0°C, (10mmole) cyanogen bromide was dissolved in 10 ml dry acetonitrile to which was added (20mmole) sodium azide. The reaction mixture was stirred at 0−15 °C for 4 hours. The inorganic salt was filtered off. The solution is added to a suspension containing 10mmol substituted thiadiazolestetrazole amine in 15 ml water at 0°C. After 1–2 days stirring at ambient temperature, the solvent was dried in air. The product was washed with water and acetonitrile. The crude product was extracted from ethyl acetate, washed with water and brine solution. The organic layer was dried over anhydrous sodium sulphate. Then, the solvent ethyl acetate was evaporated under reduced pressure. The crude product was recrystallized in ethanol to obtain corresponding substituted thiadiazole containing amine with high yield.

1.3 Spectral data of selected compounds:

1-(5-phenyl-1,3,4-thiadiazol-2-yl)-1H-tetrazol-5-amine (Entry 1):

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.14 (s, 2H), 7.27 (d, 2H), 7.57 (m, 2H), 8.15 (m, 1H);
^{13}C NMR ($CDCl_3$, 100 MHz): δ 128.85, 131.47, 132.95, 133.90, 156.46, 163.18, 176.32.

1-(5-(4-fluorophenyl)-1,3,4-thiadiazol-2-yl)-1H-tetrazol-5-amine (Entry 2):

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.8(s, 2H), 7.30 (m, 2H), 7.68 (m, 2H);
^{13}C NMR ($CDCl_3$, 100 MHz): δ 118.51, 128.8, 130.70, 155.98, 162.41, 166.23, 176.23.

1-(5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl)-1H-tetrazol-5-amine(Entry 3):

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26(s, 2H), 8.68 (d, 2H), 8.74 (d, 2H);
^{13}C NMR ($CDCl_3$, 100 MHz): δ 122.11, 128.85, 141.17, 147.52, 156.82, 162.24, 175.65.

1-(5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl)-1H-tetrazol-5-amine(Entry 4):

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.03 (s, 2H), 8.51 (d, 2H), 8.56 (d, 2H);
^{13}C NMR ($CDCl_3$, 100 MHz): δ 127.76, 128.92, 130.06, 134.05, 156.21, 162.61, 174.15.

1-(5-o-tolyl-1,3,4-thiadiazol-2-yl)-1H-tetrazol-5-amine (Entry 5):

^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.53 (s, 3H), 6.92 (s, 2H), 7.65 (m, 4H);
^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.03, 126.68, 127.76, 128.38, 128.80, 136.06, 137.15, 156.00, 162.03, 174.15.

4. Conclusion

In conclusion, we have reported an efficient and green protocol for synthesis of various novel substituted 5-aminotetrazoles from thiadiazole amine and cyanogen bromide in presence of acetonitrile/water as solvent. The present protocol has several advantages over earlier reported. This will be alternative and highly useful method for preparation of novel substituted 5-aminotetrazoles.

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