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ChemTech

International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol. 3, No.1, pp 178-184 Jan-Mar 2011

Synthesis of Schiff bases of 2-amino-5-aryl-1, 3,4-thiadiazole And its Analgesic, Anti-Inflammatory,Anti-Bacterial and Anti-Tubercular Activity

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Abstract: Schiff Bases of 2-amino-5-aryl-1, 3, 4-thiadiazole derivatives have been synthesized with different aromatic aldehyde. 1, 3, 4-thiadiazole derivatives were prepared by the reaction of thiosemicarbazide, sodium acetate and aromatic aldehyde. The structures of the titled Schiff bases were elucidated by IR and ^{1}H NMR spectral measurements. All the compounds were evaluated for their analgesic activity against swiss albino mice, anti-inflammatory activity against Wister albino rats. The compounds showed significant antibacterial activity against *Staphylococcus aureus* (gram-positive) bacteria *and E. coli* (gram-negative) bacteria and antitubercular activity against *Mycobacterium tuberculosis.*

Keywords: 1,3,4-thiadiazole, Schiff base, Analgesic, Anti-inflammatory, Anti-Bacterial and Anti-tubercular Activity.

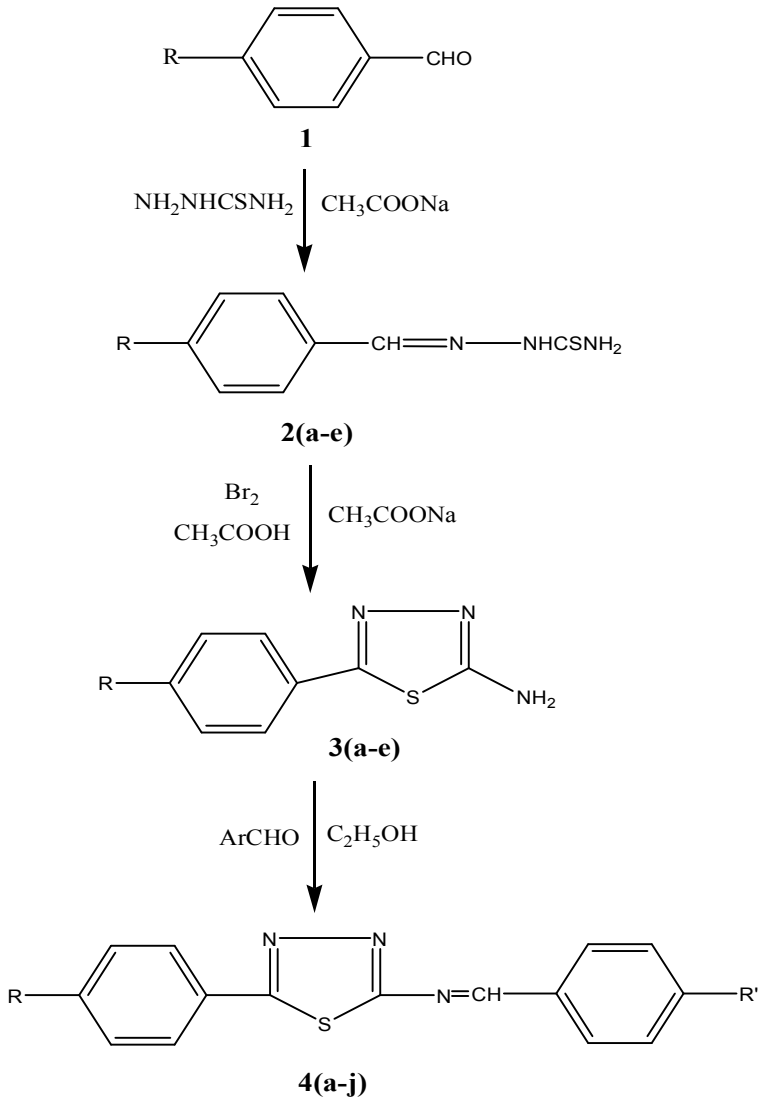
Introduction

Several five membered aromatic systems having three hetero atoms at symmetrical position have been studied because of their interesting physiological properties. The derivatives of 1, 3, 4-thiadiazole was known to possess various pharmacological activities like anti-inflammatory[1-4], analgesic[5-6] , antimicrobial[7-11], anti-tubercular[12-13], anti-convulsant[14] activities. Other activities that are reporting in thiadiazole containing drugs include diuretic[15] , anthelmintic[16], anticancer[17-18] and antiplatelet[19] activities. 2-amino-1, 3, 4-thiadiazole are used as antitumour drugs and their acetazolamide derivatives show diuretic activity. Some of their derivatives used as carbonic anhydrase inhibitors and antiparkinsonian agents. The derivatives showed considerable promise as remedies for infection in the gastrointestinal tract. 1, 3, 4-thiadiazoles are also used as pesticidal, herbicidal, amoebicidal, CNS depressant, and antiviral.

The derivatives of 1, 3, 4-thiadiazoles are active against a panel of 3 cell line i.e. lung, breast and CNS cancer. They also showed good cytotoxicity against SI leukaemia and SF-268 CNS cancer. 2-5-Dimercapto- 1, 3, 4-thiadiazoles such as corrosion inhibition, vulcanization acceleration, prevention of sunburn and darkening of photographic developers are recorded in the patient literature. The derivatives of 1,3,4-thiadiazoles were tested for their cytotoxic potential using A549 (lung adrenocarcinoma) cells in the presence of fetal bovine serum.

1, 3, 4-thiadiazoles also showing mild antihistaminic activity. N-[5-(amino- sulphonyl)-1,3,4-thiadiazole- 2-yl] acetamide is effective in the control of fluid secretion (glaucoma), in the treatment of convulsive disorder (epilepsy) and in the promotion of diuresis in the instances of abnormal fluid retention (cardiac oedema).

In view of the above mentioned fact we synthesized biologically important heterocyclic compounds. We are describing synthesis of Schiff bases of 1, 3, 4-thiadiazoles derivatives and evaluation of their analgesic, anti-inflammatory, antibacterial and antitubercular activity. Their synthesis are outlined in scheme 1. The structures of the compounds were established on the basis of their IR and ^{1}H NMR spectral data.



R = OCH_3	R' = OH	R = OCH_3	R' = NO_2
R = OH	R' = OH	R = OH	R' = NO_2
R = Cl	R' = OH	R = Cl	R' = NO_2
R = NO_2	R' = OH	R = NO_2	R' = NO_2
R = $N(CH_3)_2$	R' = OH	R = $N(CH_3)_2$	R' = NO_2

Table 1:Characterization data of Compounds

Comp.	R	R'	Mol. Formula	M.P. (°C)	Yield %	N % Found	S % Found
4A	OCH_3	OH	$C_{16}H_{16}N_3O_2S$	155	62 %	13.37	10.19
4B	OH	OH	$C_{15}H_{14}N_3O_2S$	214	58 %	14	10.66
4C	Cl	OH	$C_{15}H_{13}N_3OSCl$	188	45 %	13.20	10.06
4D	NO_2	OH	$C_{15}H_{13}N_4O_3S$	170	48 %	17.02	9.72
4E	$N(CH_3)_2$	OH	$C_{17}H_{19}N_4OS$	185	51 %	17.12	9.78
4F	OCH_3	NO_2	$C_{16}H_{15}N_4O_3S$	138	54 %	16.32	9.32
4G	OH	NO_2	$C_{15}H_{13}N_4O_3S$	194	38 %	17.02	9.72
4H	Cl	NO_2	$C_{15}H_{12}N_4O_2SCl$	205	43 %	16.13	9.22
4I	NO_2	NO_2	$C_{15}H_{12}N_5O_4S$	148	54 %	19.55	8.93
4J	$N(CH_3)_2$	NO_2	$C_{17}H_{18}N_5O_2S$	197	36 %	19.66	8.98

Experimental

Melting points were determined in open capillary tubes. Purity of the compounds were checked by TLC (Thin layer Chromatography) on silica gel plates and spots were visualized by exposure to iodine vapours. IR spectra (KBr, cm-[1]) were recorded on Perkins Elmer Infrared-283 FTIR. ^{1}H NMR (CDCl3) on a Bruker 300MHz spectrometer using TMS as an internal reference (chemical shift in ppm). The physical data of the compounds prepared are presented in Table 1.

Synthesis of thiosemicarbazide 2**(a):**

Thiosemicarbazide (0.01 M) and Crystalline sodium acetate (0.02 M) were taken in RB Flask , 8-10 ml of water and 0.5 gm of aldehyde was added slowly with continuous stirring. The mixture was turbid so added methanol untill clear solution obtained shake mixture for few minutes and allowed to stand. Thiosemicarbazone precipitated from the cold solution. Filter off the precipitate and recrystallize with ethanol. **2a** IR (KBr) 3290(C-H), 1157(C-C), 1691(C=N), 1249 (C=S), 3070.78 (N-H). **2a** ^{1}H NMR ($CDCl_3$), 6.8-7.5 (4H, Ar-H), 3.73(1H of OCH_3), 5.0 (1H of OH), 2.85(1H of CH_3), 2.0(2H, NH_2) . Other compounds **2(a-e)** were prepared similarly and their characterization data are recorded in Table 1.

Synthesis of 2-Amino-5-aryl-1, 3, 4-thiadiazole 3**(a) :**

Thiosmicarbazone **2a** (0.01 M) and Sodium acetate (0.02 M) were dissolved in 30-40 ml of glacial acetic acid taken in a round-bottom flask equipped with a separating funnel for the addition of bromine. Bromine (0.7 ml in 5 ml glacial acetic acid) was added slowly to it, while stirring magnetically. After half an hour stirring, the solution was poured on crushed ice. The resulting solid was separated, dried and recrystallized from ethanol. **3a** IR (KBr) 3201(C-H), 1170(C-C), 1624(C=N), 1567(N=C), 949(C-S), 3385(O-H), 1096(C-O), 1674(N=O). **3a** ^{1}H NMR ($CDCl_3$) , 6.79-7.31(4H, Ar-H), 4.0(2H, NH_2), 5.0(1H, OH). Other compounds **3(a-e)** were prepared similarly and their characterization data are recorded in Table 1.

Synthesis of Schiff bases of 2-amino-5-aryl-1, 3, 4-thiadiazole **4(a):**

A solution of 3a (0.01 M) was prepared in 20 ml alcohol in a round bottom flask. Required aldehyde (0.01 M) dissolved in 15 ml alcohol, was then added to it. The mixture was refluxed for 5-6 hr. The volume of alcohol was reduced to half by distillation under reduced pressure. The resulting solution was poured on crushed ice. The precipitate which got separated was dried and recrystallized from ethanol. **4a** IR (KBr) 3385(C-H), 1157(C-C), 1691(C=N), 1567(N=C), 949 (C-S) , 3201(O-H), 1096(C-O), 1674(N=O). **4a** ^{1}H NMR ($CDCl_3$), 6.83-7.37(4H, Ar-H), 6.8-7.4 (4H, C_6H_5CH=N), 5.0 (1H, OH), 8.1(1H, C_6H_5CH=N), 3.73 (1H, OCH_3). Other compounds **4(a-j)** were prepared similarly and their characterization data are recorded in Table 1.

Result and Discussion

The newly synthesized compounds of Schiff bases of 2-amino-5-aryl-1, 3, 4-thiadiazole **4(a-j)** were characterized by using IR, ^{1}H NMR spectroscopy. The IR spectrum of the compounds **2(a-e)** showed peaks at 3290-3271 cm^{-1} ,N-H stretching; 2935-2932 cm^{-1} ,C-C stretching; 1170-1157 cm^{-1} , C=N stretching; 1691-1624 cm^{-1} ,C=S stretching; 1249-1216 cm^{-1} . The NMR spectrum of the compound **2a** showed 6.8-7.5 (4H, Ar-H), 3.73(1H of OCH_3), 5.0 (1H of OH), 2.85(1H of CH_3), 2.0(2H, NH_2). The IR spectrum of the compounds **3(a-e)** showed peaks at 3201-3192 cm^{-1} , C-C stretching; 1170-1155 cm^{-1} , C=N stretching; 1624-1598 cm^{-1} , N=C stretching; 1567-1550 cm^{-1}, C-S stretching; 949-937 cm^{-1}, O-H stretching; 3385-3201cm^{-1}, C-O stretching; 1096-1027 cm^{-1}, N=O stretching; 1674-1633 cm^{-1}. The NMR spectrum of the compound **3a** showed 6.79-7.31(4H, Ar-H), 4.0(2H, NH_2), 5.0(1H, OH). The IR spectrum of the compounds **4(a-j)** showed peaks at 3385-3290 cm^{-1} , C-C stretching; 1157-1150 cm^{-1}, C=N stretching; 1691-1649 cm^{-1}, N=C stretching; 1567-1552 cm^{-1} , C-S stretching; 949-937cm^{-1} O-H stretching; 3521-3443 cm^{-1} , C-O stretching; 1096-1022 cm^{-1}, N=O stretching; 1674-1633 cm^{-1}. The NMR spectrum of the compound 4a showed 6.83-7.37 (4H, Ar-H), 6.8-7.4 (4H, C_6H_5CH=N), 5.0 (1H, OH), 8.1(1H, C_6H_5CH=N), 3.73 (1H, OCH_3) that indicated the presence of aromatic protons. The IR, ^{1}H NMR showing the various functional groups present in the synthesized compounds.

Antimicrobial activity

The synthesized compounds were evaluated for their antibacterial activity against bacterial strain *S. aureus* (Gram +ve) and *E. coli* (Gram -ve) by cup plate diffusion method at 1000, 500, 250 µg/mL concentration. Ofloxacin were used as standard drugs for antibacterial activity. The minimal inhibitory concentration (MICs, µg/mL) of the tested compounds are recorded in Table 2 and 3.

Table No 2: Anti –Bacterial Activity of 1, 3, 4-thiadiazole derivatives against *S. aureus*

S. No.	Comp.	*S. aureus* (+ve) Zone of inhibition (mm)			
		1000µg/ml	500µg/ml	250µg/ml	Ofloxacin (Std. drug) 1000µg/ml
1	**4a**	18	14	11	22
2	**4b**	16	13	10	20
3	**4c**	19	13	9	22
4	**4d**	18	14	11	22
5	**4e**	19	16	10	22
6	**4f**	17	15	9	21
7	**4g**	16	15	7	22
8	**4h**	16	13	7	22
9	**4i**	17	15	9	22
10	**4j**	19	15	12	21

Table No 3: Anti –Bacterial Activity of 1, 3, 4-thiadiazole derivatives against *E.coli*

S. No.	Comp.	*E. coli* (-ve) Zone of inhibition (mm)			
		1000µg/ml	500µg/ml	250µg/ml	Ofloxacin (Std. drug) 1000µg/ml
1	**4a**	16	13	9	22
2	**4b**	18	15	12	20
3	**4c**	17	13	11	22
4	**4d**	16	15	11	22
5	**4e**	17	16	10	22
6	**4f**	18	13	10	21
7	**4g**	16	15	7	22
8	**4h**	18	13	8	22
9	**4i**	17	13	9	22
10	**4j**	18	15	10	21

Analgesic activity

The synthesized compounds were evaluated for their analgesic activity in swiss albino mice by using hot plate method using Pentazocine as standard drug.

Anti-inflammatory Activity

The synthesized compounds were evaluated for their anti-inflammatory activity in Wister albino rats by Carrageenan induced paw edema method using Indomethacin as standard drug.

Table: 4

Treatment Group	Dose mg/kg)	Reaction time (sec)				
		15(min)	30(min)	45(min)	60(min)	90(min)
Control(vehicle)	10	2.0 ± 0.3	2.6 ± 0.4	2.3 ± 0.2	1.7 ± 0.2	1.3 ± 0.2
Pentazocine	30	4.6 ± 0.5	6.0 ± 0.3	6.3 ± 0.7	8.6 ± 0.7	10.6 ± 0.2
4a	30	2.1 ± 0.4	3.3 ± 0.4	4.4 ± 0.2	3.7 ± 0.8	3.9 ± 0.4
4b	30	2.2 ± 0.4	3.0 ± 0.3	2.7 ± 0.2	3.4 ± 0.3	3.2 ± 1.7
4c	30	2.3 ± 0.3	3.47 ± 0.2	4.32 ± 0.4	3.22 ± 0.5	4.9 ± 0.1
4d	30	1.7 ± 0.1	2.5 ± 0.4	2.67 ± 0.2	3.34 ± 0.4	3.90 ± 0.3
4e	30	2.4 ± 0.3	3.77 ± 0.3	3.8 ± 0.1	3.2 ± 0.4	3.7 ± 0.2
4f	30	1.5 ± 0.2	2.1 ± 0.1	1.8 ± 0.3	2.4 ± 0.5	2.3 ± 0.1
4g	30	2.5 ± 0.6	2.2 ± 0.2	2.4 ± 0.5	2.7 ± 0.7	2.9 ± 0.6
4h	30	2.6 ± 0.4	2.4 ± 0.3	2.8 ± 0.3	3.1 ± 0.4	2.9 ± 0.3
4i	30	2.1 ± 0.3	2.6 ± 0.5	3.2 ± 0.2	3.1 ± 0.2	2.9 ± 0.4
4j	30	1.9 ± 0.5	2.5 ± 0.6	2.9 ± 0.8	3.2 ± 0.1	2.7 ± 0.2

Table: 5

Groups	Dose mg/kg	Paw diameter (mm)						% of inhibition
		0 hr	1hr	2hr	3hr	4hr	5hr	
Control	--	0.79±0.0423	0.925±0.0223	1.3±0.018	2.062±0.033	2.358±0.042	2.568±0.020	--
Std	10	0.810±0.014	0.978±0.012	1.10±0.011	0.978±0.014	0.952±0.011	0.951±0.06	72.55
4a	30	0.775±0.013	0.915±0.025	1.240±0.038	1.523±0.033	1.830±0.015	1.638±0.038	23
4b	30	0.801±0.012	0.925±0.014	1.095±0.022	1.19±0.09	1.395±0.013	1.330±0.042	48
4c	30	0.682±0.020	0.855±0.0150	0.922±0.011	1.252±0.034	1.401±0.038	1.502±0.042	31
4d	30	0.725±0.025	1.425±0.0485	1.655±0.032	1.757±0.089	1.548±0.0455	1.422±0.035	29
4e	30	0.621±0.032	0.952±0.0425	1.28±0.018	2.238±0.033	2.445±0.0252	2.728±0.021	14
4f	30	0.752±0.014	1.102±0.0121	1.225±0.041	1.445±0.014	1.278±0.0128	1.052±0.072	43
4g	30	0.87±0.32	1.11±0.0152	1.205±0.62	1.523±0.015	1.728±0.0128	1.875±0.045	16
4h	30	0.628±0.045	0.952±0.0548	1.221±0.035	1.542±0.012	1.667±0.0212	1.438±0.055	24
4i	30	0.722±0.082	1.208±0.0221	1.432±0.052	1.566±0.043	1.732±0.0368	1.652±0.025	20
4j	30	0.998±0.528	1.118±0.0485	1.332±0.042	1.654±0.011	1.55±0.0445	1.477±0.078	35

Anti-Tubercular Activity

The synthesized compounds were evaluated for their anti-tubercular activity by Rema plate method.

Conclusion

A total of l0 compounds were synthesized with good yields. All synthesized compounds exhibited analgesic, anti-inflammatory, antibacterial and antituberculosis activities at various MIC levels. The compound **4a, 4b, 4c** and **4e** were shown significant analgesic activity against swiss albino mice. The compounds which shown good anti-inflammatory activity against Wister albino rats was compounds **4b, 4c, 4f** and **4j.**

The synthesized compounds were screened *in-vitro* anti-bacterial with *S. aureus* Gram (+ve) and *E. coli* Gram (-ve) bacteria which is cause for common cold and cough and some of the other diseases. Few compounds like compounds **4a, 4d, 4e** and **4j** were shows good anti-bacterial activity against *S. aureus* Gram (+ve) and compounds **4b, 4d, 4e** and **4j** were shows good anti-bacterial activity against *E. coli* Gram (-ve) bacteria.

The synthesized compounds for anti-tubular activity against *Mycobacterium tuberculosi*s (organism).The **MIC** of synthesized compounds **4c, 4e, 4f** and **4i** were shown positive response at minimum concentration as compared to other compounds. Further explored of the all the compounds **4c, 4e** and **4j** were shown comparatively significant activity.

Acknowledgement:

The authors would like to express their gratitude and thanks to the Head, Dept. of Pharmaceutical Chemistry, Nandha College of Pharmacy and research institute, Erode for necessary facilities for this research work. I would like to thank **IIT, Chennai Tamilnadu** for their immense help in Scanning ^{1}H NMR studies.

Table : 6

Comp	Conc. of Test Sample/ Minimum Inhibitory Concentration (MIC) Colour Change							
	1.25 mg/mL	2.5 mg/mL	3.75 mg/mL	5.0 mg/mL	6.25 mg/mL	7.5 mg/mL	8.75 mg/mL	10.0 mg/mL
4a	-------	-------	**Blue Colour to Pink**	-------	-------	-------	-------	-------
4b	-------	-------	-------	-------	-------	**Blue Colour to Pink**	-------	-------
4c	-------	**Blue Colour to Pink**	-------	-------	-------	-------	-------	-------
4d	-------	-------	-------	-------	**Blue Colour to Pink**	-------	-------	-------
4e	-------	**Blue Colour to Pink**	-------	-------	-------	-------	-------	-------
4f	-------	**Blue Colour to Pink**	-------	-------	-------	-------	-------	-------
4g	-------	-------	**Blue Colour to Pink**	-------	-------	-------	-------	-------
4h	-------	-------	-------	-------	**Blue Colour to Pink**	-------	-------	-------
4i	-------	**Blue Colour to Pink**	-------	-------	-------	-------	-------	-------
4j	-------	-------	-------	-------	-------	-------	-------	**Blue Colour to Pink**

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