Synthesis of Schiff Bases of 2-amino-5-aryl-1,3,4-thiadiazole and Its Analgesic, Anti-Inflammatory and Anti-Bacterial Activity

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Received 05 May 2011; Accepted 21 July 2011

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 ¹H 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.

Keywords: 1, 3, 4-thiadiazole, Analgesic, Anti-inflammatory and Anti-Bacterial 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 antibacterial¹, analgesic², anti-inflammatory^{3, 4}, anti-convulsant⁵, antimicrobial⁶ activities. Other activities that are reporting in thiadiazole containing drugs include anticancer⁷, anti-tubercular⁸, diuretic⁹ and anthelmintic¹⁰ 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 patent literature. The derivatives of 1,3,4-thiadiazoles were tested for their cytotoxic potential using A549 (lung adenocarcinoma) 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 and antibacterial activity. Their synthesis are outlined in scheme 1. The structures of the compounds were established on the basis of their IR and ^1H 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

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. ¹H NMR (CDCl₃) on a Bruker 300MHz spectrometer using TMS as an internal reference (chemical shift in δ ppm). The physical data of the compounds prepared are presented in Table 1.

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 ₃ O ₂ S	155	62 %	13.37	10.19
4B	OH	OH	C ₁₅ H ₁₄ N ₃ O ₂ S	214	58 %	14	10.66
4C	Cl	OH	C ₁₅ H ₁₃ N ₃ OSCl	188	45 %	13.20	10.06
4D	NO ₂	OH	C ₁₅ H ₁₃ N ₄ O ₃ S	170	48 %	17.02	9.72
4E	N(CH ₃) ₂	OH	C ₁₇ H ₁₉ N ₄ OS	185	51 %	17.12	9.78
4F	OCH ₃	NO ₂	C ₁₆ H ₁₅ N ₄ O ₃ S	138	54 %	16.32	9.32
4G	OH	NO ₂	C ₁₅ H ₁₃ N ₄ O ₃ S	194	38 %	17.02	9.72
4H	Cl	NO ₂	C ₁₅ H ₁₂ N ₄ O ₂ SCl	205	43 %	16.13	9.22
4I	NO ₂	NO ₂	C ₁₅ H ₁₂ N ₅ O ₄ S	148	54 %	19.55	8.93
4J	N(CH ₃) ₂	NO ₂	C ₁₇ H ₁₈ N ₅ O ₂ S	197	36 %	19.66	8.98

Synthesis of thiosemicarbazone 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 until 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 ¹H NMR (CDCl₃), δ 6.8-7.5 (m, 4H, Ar-H), δ 3.73(t, 3H of OCH₃), δ 5.0 (s, 1H of OH), δ 2.85 (t, 3H of CH₃), δ 2.0(t, 2H, NH₂). 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 ¹H NMR (CDCl₃), δ 6.79-7.31(m, 4H, Ar-H), δ 4.0(t, 2H, NH₂), δ 5.0 (s, 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 ¹H NMR (CDCl₃), δ 6.83-7.37(m, 4H, Ar-H), δ 6.8-7.4 (m, 4H, C₆H₅CH=N), δ 5.0 (s, 1H, OH), δ 8.1(s, 1H, C₆H₅CH=N), δ 3.73 (t, 3H, OCH₃). 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, ¹H 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 δ 6.8-7.5 (m, 4H, Ar-H), δ 3.73(t, 3H of OCH₃), δ 5.0 (s, 1H of OH), δ 2.85(t, 3H of CH₃), δ 2.0(t, 2H, NH₂). 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; 3385-3201 cm⁻¹, C-O stretching; 1096-1027 cm⁻¹, N=O stretching; 1674-1633 cm⁻¹. The NMR spectrum of the compound 3a showed δ 6.79-7.31(m, 4H, Ar-H), δ 4.0(t, 2H, NH₂), δ 5.0(s, 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; 949-937 cm⁻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 δ 6.83-7.37 (m, 4H, Ar-H), δ 6.8-7.4 (m, 4H, C₆H₅CH=N), δ 5.0 (s, 1H, OH), δ 8.1(s, 1H, C₆H₅CH=N), δ 3.73 (t, 3H, OCH₃) that indicated the presence of aromatic protons. The IR, ¹H 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 2. Anti –Bacterial Activity of 1, 3, 4-thiadiazole derivatives against *S. aureus*.

S. No.	Comp.	<i>S. aureus</i> (+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

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 3. Anti –Bacterial Activity of 1, 3, 4-thiadiazole derivatives against *E.coli*.

S. No.	Comp.	<i>E. coli</i> (-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

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	Dosemg/kg	Paw diameter (mm)						% of inhibition
		0 hr	1hr	2hr	3hr	4hr	5hr	
Control	--	0.79±0.042 3	0.925±0.022 3	1.3±0.01 8	2.062±0. 033	2.358±0. 042	2.568±0.0 20	--
Std	10	0.810±0.01 4	0.978±0.012	1.10±0.0 11	0.978±0. 014	0.952±0. 011	0.951±0.0 6	72.55
4a	30	0.775±0.01 3	0.915±0.025	1.240±0. 038	1.523±0. 033	1.830±0. 015	1.638±0.0 38	23
4b	30	0.801±0.01 2	0.925±0.014	1.095±0. 022	1.19±0.0 9	1.395±0. 013	1.330±0.0 42	48
4c	30	0.682±0.02 0	0.855±0.015 0	0.922±0. 011	1.252±0. 034	1.401±0. 038	1.502±0.0 42	31
4d	30	0.725±0.02 5	1.425±0.048 5	1.655±0. 032	1.757±0. 089	1.548±0. 0455	1.422±0.0 35	29
4e	30	0.621±0.03 2	0.952±0.042 5	1.28±0.0 18	2.238±0. 033	2.445±0. 0252	2.728±0.0 21	14
4f	30	0.752±0.01 4	1.102±0.012 1	1.225±0. 041	1.445±0. 014	1.278±0. 0128	1.052±0.0 72	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±0.0 45	16
4h	30	0.628±0.04 5	0.952±0.054 8	1.221±0. 035	1.542±0. 012	1.667±0. 0212	1.438±0.0 55	24
4i	30	0.722±0.08 2	1.208±0.022 1	1.432±0. 052	1.566±0. 043	1.732±0. 0368	1.652±0.0 25	20
4j	30	0.998±0.52 8	1.118±0.048 5	1.332±0. 042	1.654±0. 011	1.55±0.0 445	1.477±0.0 78	35

Conclusion

A total of 10 compounds were synthesized with good yields. All synthesized compounds exhibited analgesic, anti-inflammatory and antibacterial activity. 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 were compounds **4b**, **4c**, **4f** and **4j**.

The synthesized compounds were screened in-vitro anti-bacterial against *S. aureus* Gram (+ve) and *E. coli* Gram (-ve) bacteria which is common for most of the 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.

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 1H NMR studies.

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