SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF NOVEL 1, 3, 4-THIADIAZOLE DERIVATIVES

Jessy E. Mathew[1]*, Vachala Dinakaran [1], K.K. Srinivasan[1], Pankaj C Jain[1], M.R. Metha[2]

[1] Department of Pharmaceutical Chemistry, Manipal College of Pharmaceutical Sciences, Madav Nagar, Manipal-576104, India.

[2] Senior group leader, Nicholas Piramal India Ltd, Digwal-502 321, India.

*for Correspondence

Dr. (Mrs) Jessy E. Mathew M.Pharm., Ph.D
Associate Professor
Dept of Pharmaceutical Chemistry
College of Pharmaceutical Sciences
MAHE, Madav Nagar, Manipal-576 104

Telephone:(0820) 2922482
Extn:22482
Fax :91-0820-2571998
Email : jessyjamesmathew@yahoo.co.in

Summary

In the present study, a new series of 2, 5-disubstituted-1, 3, 4-thiadiazole derivatives were synthesized from thiosemicarbazides by condensing with different aromatic acids. The chemical structures of compounds were established on the basis of elemental and spectral data analysis. These compounds were screened for their antimicrobial activity at the level of 40µg/ml against seven organisms. Only the compounds 2-(3',4',5'-trihydroxyphenyl)-5-(4'-methoxyphenylamino)-1,3,4-thidiazole (PA2) and 2-(3'-pyridinyl)-5-(4'-methoxy phenyl amino)-1,3,4-thidiazole (PA3) showed good antibacterial activity against *S.sonnei* and *P.aeruginosa*, remaining compounds showed resistance to these organisms. Compounds 2-(3',4',5'-trihydroxyphenyl)-5-(4'-methoxy phenylamino)-1,3,4-thidiazole (PA2), 2-(3'-pyridyl)-5-(4'-methoxyphenylamino)-1, 3, 4-thidiazole (PA3) and 2-(3'-pyridinyl)-5-(4'-bromophenylamino)-1,3,4-thidiazole (BA3) showed better spectrum of antimicrobial activity.

Key words: thiadiazole, thiosemicarbazides, cyclization, antimicrobial activity.

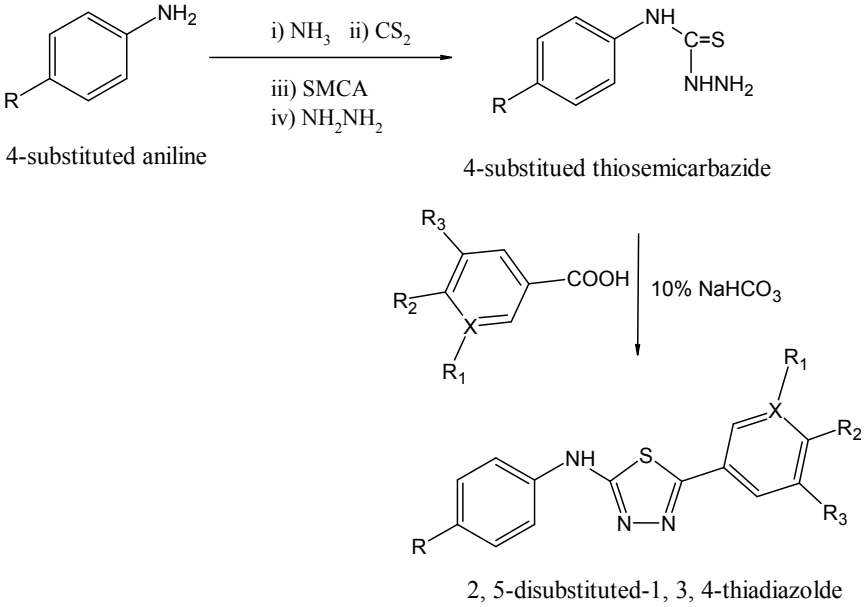
Introduction

Following the discovery of 1, 3, 4-thiadiazole nucleus, numerous of structural modifications have been made to increase their biological activities. 1, 3, 4-thiadiazole derivatives display quite a broad spectrum of biological activities such as antimicrobial (1-3), anticonvulsant (4), antimycotic (5), anti-inflammatory (6), antiviral (7), antitubercular (8), analgesic (9). Several methods have been described for the synthesis of 1, 3, 4-thiadiazoles (10-11). Among these, the cyclization of thiosemicarbazide derivatives with different acids has reported to be a good strategy resulting in good yields. There are antimicrobial agents having different structures are frequently used in treatment of microbial infections. However, there is an increasing resistance to these drugs. Moreover, some of azole derivatives used as common antibiotics such as Amphotericin B posses a toxic effect on humans as well as their antimicrobial effects. To overcome the development of drug resistance, it is crucial to synthesize a new class of antimicrobials possessing different chemical properties from those of used commonly. In view of these facts, the aim of this present study is to synthesize and pursue the antimicrobial activity of the synthesized compounds containing 1, 3, 4-thiadiazole derivatives. The cyclization of 4-substituted phenyl thiosemicarbazides with different acid in presence of base gave the novel 1, 3, 4-thiadiazoles.

Materials and methods

Synthesis of 2, 5-disubstituted-1, 3, 4-thiadiazole derivatives

The starting material 4'-substitued thiosemicarbazides were synthesized from 4'-substitued aniline by a known procedure (12). A mixture of 4-substituted aniline (0.4mol) and 30ml methanol was placed in round bottom flask. It was basified with 80ml of ammonia. Carbondisulfide (32ml) was added drop wise under stirring and allowed to stand for 1h at room temperature. Sodiummonochloroacetate (0.4mol) was added in one portion under stirring followed by addition of hydrazine hydrate (50%, 8ml) at 25º. After stirring for 1h at room temperature, it was concentrated to the half volume and then added to 50ml cold water. Crude thiosemicarbazide was collected by filtration and Recrystallized from ethanol. The mixture of the synthesized thiosemicarbazide (0.01mol) and aromatic carboxylic acid (0.0125mol) was heated in dry state at 180-200ºC for 2h. The reaction mixture was cooled and added with 20ml of sodium bicarbonate solution. Crude final product was obtained by filtration and recrystallized from ethanol. The scheme was given in figure 1.



Synthesis of 2,5-disubstituted-1,3,4-thiadiazole derivatives.

Test organism and drugs used

Pure cultures of test organisms *Escherichia coli, Bacillus pumilis, Staphylococcus aureus Shigella sonnei, Proteus vulgaris, Pseudomonas aeroginosa,* and *Aspergillus niger* were procured from the central drugs laboratory (Kolkata, India). All the organisms were maintained on agar slant stocks and were subsequently sub cultured into newly prepared nutrient agar slants. Gentamycin and Griseofulvin were used as a standard in antibacterial and antifungal studies respectively.

Antimicrobial activity

All the synthesized compounds were screened for antimicrobial activity by cup-plate method (13). The antibacterial activity of the compounds was tested against *Staphylococcus aureus , Bacillus pumilis, Pseudomonas vulgaris, Shigella sonnei , Proteus vulgaris* and *Escherichia coli* using nutrient agar media. The antifungal activity of the compounds was tested against *Aspergillus niger* using sabouraud dextrose agar media. The sterilized medium was poured in to petri dishes and allowed to solidify. On the surface of the media microbial suspension was spread with the help of sterilized triangular loop. A stainless steel cylinder of 8mm diameter (pre-sterilized) was used to bore the cavities. All the synthesized compounds were placed serially in the cavities with the help of micropipette and allowed to diffuse for 1h. Dimethylformamide (DMF) was used as a solvent for all compounds and as control. Then the plates were incubated for 24 h and 48 h at 37 ± 1^0 to observe for antibacterial and antifungal activity respectively. The diameter of zone of inhibition against bacteria and fungi were observed. The results were presented in Table-2.

Results and conclusion

A new series of 2, 5-disubstituted-1, 3, 4-thiadiazole derivatives were synthesized from thiosemicarbazides by condensing with different aromatic acids. The physico chemical properties were given in table 1.

Table 1: Physical data of 2, 5-disubstituted-1, 3, 4-thiadiazole derivatives.

Cpd code	X	R	R_1	R_2	R_3	Molecular formula	% yield	Mp (ºC)	λ max	R_f value
PA1	-	OCH_3	-	-	-	$C_8H_{11}N_3OS$	57.7	138	244.5	0.45
PA2	C	OCH_3	OH	OH	OH	$C_{15}H_{14}N_3O_4S$	41.8	227	324.6	0.41
PA3	N	OCH_3	H	H	H	$C_{14}H_{12}N_4OS$	40.7	202	266	0.28
PA4	C	OCH_3	H	H	NO_2	$C_{15}H_{12}N_4O_3S$	45.8	221	269.7	0.51
BA1	-	Br	-	-	-	C_7H_8BrNS	62.8	180	237.8	0.37
BA2	C	Br	H	H	NH_2	$C_{14}H_{11}BrN_4S$	45.6	218	315.4	0.33
BA3	C	Br	H	H	H	$C_{14}H_{10}BrN_3OS$	49.5	209	328.2	0.52

The compounds were tested in vitro for their antimicrobial activity against seven microorganisms belonging to bacteria and fungi classes. The antimicrobial activity was done at 40µg/ml concentration by cup and plate method. The data were given in table-2.

Table 2: Antimicrobial activity of 2, 5-disubstituted-1,3,4-thiadiazole derivatives.

Drug Treatment 40µg/ml	Zone of inhibition in mm						
	E.coli	*B.pumilis*	*S.aureus*	*S.sonnei*	*P.vulgaris*	*P.aeruginosa*	*A.niger*
PA1	-	7	11	-	10	-	18
PA2	-	-	11	15	13	-	16
PA3	9	-	12	-	12	12	-
PA4	9	-	13	-	-	-	-
BA1	8	-	-	-	-	-	-
BA2	10	-	-	-	-	-	-
BA3	8	9	9	-	9	-	16
Gentamicin	20	16	22	22	22	20	-
Griseofulvin	-	-	-	-	-	-	22
control	-	-	-	-	-	-	-

'-' indicates resistance.

The intermediate 4'-methoxy Phenyl thiosemicarbazide (PA1) showed good antifungal activity. Compounds 2-(3', 4', 5'-trihydroxyphenyl)-5-(4'-methoxy phenyl amino)-1, 3, 4-thidiazole (PA2) and 2-(3'-pyridinyl)-5-(4'-methoxy phenyl amino)-1, 3, 4-thidiazole (PA3) showed antibacterial activity against *S.sonnei* and *P.aeruginosa* respectively. Remaining all other compounds showed resistance to these two organisms.

On the whole, compounds 2-(3', 4', 5'trihydroxyphenyl)-5-(4'-methoxyphenylamino)-1, 3, 4-thidiazole (PA2), 2-(3'-pyridyl)-5-(4'-methoxyphenylamino)-1, 3, 4-thidiazole (PA3) and 2-(4'-hydroxyphenyl)-5-(4'-bromophenylamino)-1, 3, 4-thidiazole (BA3) showed good antimicrobial activity.

Finally on the basis of the observations, it can be concluded that the presence of 4'-methoxyphenylamino substituted compounds were showing good spectrum of activity than 4'-bromosubstituted compounds. 3', 4', 5'trihydroxyphenyl, unsubstituted phenyl ring and pyridyl substitutions at 2nd position in 1, 3, 4-thiadiazoles enhances antimicrobial activity.

Acknowledgement

The authors are thankful to MAHE, Manipal University, Manipal, for providing necessary facilities to carry out the research.

References

1. Ashour F.A, Habib N.S, el Taibbi M, el Dine S, el Dine A.S. Synthesis of 1,3,4-thiadiazoles, imidazo[2,1-b]1,3,4-thiadiazoles and thiadiazolo[3,2-a]pyrimidines derived from benzimidazole as potential antimicrobial agents. Farmaco 1990; 45(12):1341-1349.
2. Mamolo M.G, Vio L, Banfi E. Synthesis and antimicrobial activity of some 2,5-disubstituted 1,3,4,-thiadiazole derivatives. Farmaco 1996; 51(1): 71-74.
3. Habib N.S, Abdel-Hamid S, El-Hawash M. Synthesis of benzimidazole derivatives as potential antimicrobial agents. Farmaco 1989; 44:1225-1232.
4. Chapleo C.B, Myers M, Myers P.L, Saville J.F, Smith A.C, Stillings M.R, Tulloch I.F, Walter D.S, Welbourn A.P, Substituted 1,3,4-thiadiazoles with anticonvulsant activity. J Med Chem 1986; 29(11), 2273-2280.
5. Dogan H.N, Duran A, Rollas S, Sener G, Uysal M.K, Gülen D. Synthesis of new 2,5-disubstituted-1,3,4-thiadiazoles and preliminary evaluation of anticonvulsant and antimicrobial activities. Bioorg Med Chem 2002;10**:**2893-2898.
6. Kadi A.A, El-Brollosy N.R, Al-Deeb O.A, Habib E.E, Ibrahim T.M, El-Emam A.A. Synthesis, antimicrobial, and anti-inflammatory activities of novel 2-(1-adamantyl)-5-substituted-1,3,4-oxadiazoles and 2-(1-adamantylamino)-5-substituted-1,3,4-thiadiazoles. Eur J Med Chem 2007; 42(2): 235-239.
7. Jones D.H, Slack R, Squires S, Wooldridge K.H. Antiviral Chemotherapy. I. The Activity of Pyridine and Quinoline Derivatives against Neurovaccinia in Mice. J Med Chem 1965; 8: 676-680.
8. Nilufer Solak, Sevim Rollas. Synthesis and antituberculosis activity of 2-(aryl/alkylamino)-5-(4-aminophenyl)-1,3,4-thiadiazoles and their Schiff bases. ARKIVOC 2006;173-181.
9. Sughen J.K, Yologe T. Medicinal applications of indole derivatives. Pharm Acta Helv 1978; 58: 64-68.

10.Varvarasou A, Siatra-Papastaikoudi T, Tsotunis A, Tsatili-Kakoulidou A, Vamvakides A. Synthesis, lipophilicity and biological evaluation of indole-containing derivatives of 1,3,4-thiadiazole and 1,2,4-triazole Farmaco 1998; 53: 320-326.
11.Collin X, Sauleau A, Coulon J. 1,2,4-Triazolo mercapto and aminonitriles as potent antifungal agents**.** Bioorg Med Chem 2003;13: 2601-2605.
12.Hirpara S.B, Parikh K.A, Merja B.C, Parekh H.H. Synthesis of 2-methoxy-5-methylphenyl thiosemicarbazide: A versatile molecule for the synthesis of thiadiazoles poseesing multiple biological activities. Indian J Chem 2003; 42B:1172-1175.
13.Gillespie SH. Medical Microbiology-Illustrated. 1st edn., UK: Butterworth Heinemann, 1994.