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SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL STUDY OF THIADIAZOLE DERIVATIVES.

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ABSTRACT

Thiadiazoles are five membered heterocycles containing two nitrogen and one sulphur atom. 3,4-dihydropyrimidin-2(1H)-thione is pharmacologically active compound that has been shown to possess various biological activities. In the present study, some Schiff bases of 1,3,4-thiadiazole derivatives of 3,4-dihydropyrimidin-2(1H)-thione are prepared by conventional as well as by microwave heating method and studied for their antibacterial activities. Cyclocondensation of substituted benzoic acid and thiosemicarbazide in presence of $POCl_3$ under reflux condition gave amino thiadiazole derivatives. Various amino thiadiazoles on further condensation with dihyropyrimidin-2-thione gave final product. The structure of the synthesized compounds is confirmed by IR, NMR and Mass spectra. Synthesized compounds are tested for their antibacterial activities. All the synthesized compounds posses moderate antibacterial activity against *E. coli* and *S. aureus* bacteria.

KEYWORDS: *1,3,4- Thiadiazole, dihydropyrimidin-2-thione, shiff's base, antibacterial activity, microwave irradiation, green synthesis*

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INTRODUCTION

1,3,4- Thiadiazole derivatives possess a wide range of therapeutic activities like antimicrobial[1], antifungal[2], antimycobacterial[3], antileshmanial[4] analgesic, anti-inflammatory[5], antidepressant[6], antipsychotic and anticonvulsant[7]. 1,3,4-Thiadiazole derivatives exhibit interesting invitro[9] and invivo[10] antitumor activities. Different mechanisms of action are attributed to the antitumor activity of 1,3,4- thiadiazole ring such as inhibited DNA and RNA synthesis specifically without appreciably affecting protein synthesis[11], inhibition of carbonic anhydrase[12]. 3,4-dihydropyrimidin-2(1H)-ones and 3,4-dihydropyrimidin-2(1H)-thiones have recently emerged as important target molecule due to their therapeutic and pharmacological properties[13] such as their antivira1[14] , antimitotic[15], anticarcinogenic, antihepertensive[16], and noteworthy as calcium channel modulators[17]. Microwave assisted organic synthesis[18] (MAOS) has emerged a new lead in synthetic Organic Chemistry. This technique is simple fast and economic for the synthesis of a large number of organic molecules. An important advantage of technology include high accelerated rate of reaction. Microwave assisted organic synthesis is considered as an important approach in green chemistry because it is environmentally friendly. This technology is used in laboratory medicinal chemistry and drug industry. Schiff bases are important intermediates for the synthesis of various bioactive products. They are also fundamental material for the synthesis of various Schiff base ligands which are used as chiral auxiliaries in asymmetric synthesis. In the present work we have synthesized some Schiff bases of amino 1,3,4-thiadizole derivatives by conventional method as well as microwave irradiation method and studied their antibacterial activities.

MATERIALS AND METHODS

Thiosemicarbazide was purchased from Loba Chemicals. Substituted benzoic acids and phosphorous oxychloride were purchased from sd fine chemicals. Hexane and ethyl acetate used for thin layer chromatography were of Loba and PCL chemicals respectively. . The melting point of the compounds were determined in open head capillary. IR spectra were recorded on Shimadzu Hyper IR Instruments (FTIR-8400). ^{1}H-NMR were recorded on Bruker 300 MHz, FT-NMR Spectrometer with TMS as internal standard. All reactions were carried out in oven dried or flame dried glassware. All the compounds were checked for their purity by thin layer chromatography (TLC).

Experimental

Synthesis of 5-phenyl-1, 3,4-thiadiazol-2-amine (compound 1)[19]

Compound 1 was prepared by the reported method[19]. The mixture of Benzoic acid (0.016 mol), thiosemicarbazide (0.016 mol) and 5ml of $POCl_3$ was heated in boiling water bath for 2 hrs. After cooling down to room temperature, ice cold water was added. Then again dilute NaOH was added till precipitate was formed. It was filtered and washed with cold water and dried, the crude product was recrystallized from ethanol.

Synthesis of 1-[4-(furan-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]ethanone (compound 2)[13]

Furfuraldehyde (1mol), acetyl acetone (1mol) and thiourea (1.5 mol) were taken in ethanol and added with few drops dilute HCl and heated in water bath for 8 hrs. Then completion of reaction was checked with TLC (ethyl acetate + hexane 9:1). The reaction mixture was poured in ice cold water, solid obtained was filtered and washed with sufficient water and recrystallization from methanol.

Synthesis of 4-(furan-2-yl)-5-[(1E)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)ethanimidoyl]-3,4-dihydropyrimidine-2(1H)-thione(compounds 3a-j)3-i. Conventional method

Compounds 3a-j were synthesized according to the literature procedure.[22] In a round bottom flask, Compound 1 (1 mol) and dihydropyrimidin-2-thione(1 mol) were dissolved in ethanol then few drops of glacial acetic acid were added. The reaction mixture was refluxed for about 5 hrs. Progress of the reaction was checked with TLC (Hexane: Ethyl acetate – 4:1) Then it was cooled with ice cold water. It was filtered and washed with cold water and dried, the crude product was recrystallized from ethanol.

Microwave irradiation method

Microwave assisted synthesis was according to the literature procedure.[22] A mixture of Compound 1 (1mol), Compound 2 (1 mol), and few drops of glacial acetic acid as an energy transfer medium and acid catalyst were added in a hard glass tube and irradiated in domestic microwave oven at an appropriate power and time. Completion of the reaction was monitored by TLC, mixture was cooled and poured with ice cold water. And the resulting Solid filtered dried and recrystallized from ethanol.

Reaction scheme

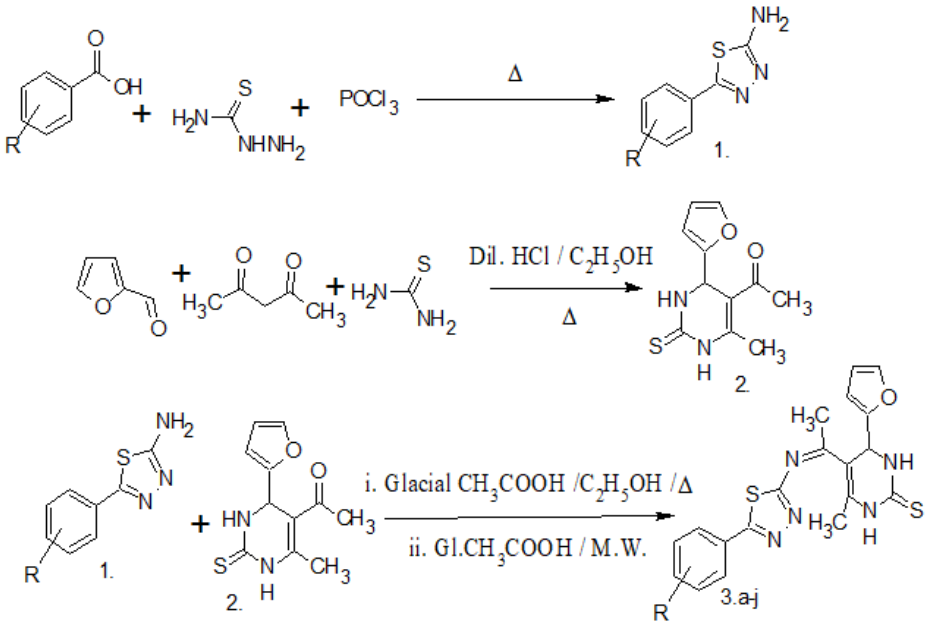

Figure 1
Reaction Scheme for the synthesis of thiadiazole derivatives.

Table 1
Synthesis 3a-j under conventional and microwave heating

ENTRY	R	Conventional heating		Microwave heating		
		Time in hours	% yields*	Microwave power in watt	Time in min	% yield*
3a	H	5	55	300	3	92
3b	R-CH_3O	5	49	300	3	90
3c	P-NO_2	5	52	450	6	84
3d	4-Cl	5	72	300	3.5	94
3e	4-OH	5	79	300	3	93
3f	2-Cl	5	71	300	3	91
3g	CH=CH	5	68	450	5	86
3h	2-OH	5	59	300	3.5	88
3i	4-CH_3	5	73	300	3.5	89
3j	3-CH_3	5	59	300	3	87

****Yields refer to purified compounds, compounds(3a-j) are synthesized by conventional as well as microwave heating method.***

Study of Antibacterial Activity[20]

Synthesized compounds(3a-j)were tested for the antibacterial activity against Gram +ve (*Escherichia coli*) and Gram –ve bacteria (*Staphylococcus aureus*). The neutrient agar medium was prepared by using bactotryptone (4g), Broth (3.9 g) less than 2%, NaCl (2.9 g) in 100 ml of water (2.9%). After 18 hours the exponentially growing culture of the 2 bacteria in nutrient broth at 37^{0}C were diluted in sterile broth. From each of these diluted culture, 1 ml was added to 100 ml sterilized and cooled nutrient agar media to give a final bacterial culture. The plates were set at room temperature and later dried at 37 ^{0}C for 20 hours. Paper discs (6mm, punched from whatmann no 41 paper) were used for the assays. Discs were soaked in DMF and placed on the inoculated agar media at regular intervals of 6-7 cm, care was taken to ensure that excess solution was not on the discs. All the samples were taken in triplicates. The plates were incubated at 37 ^{0}C in an inverted fusion. Activity has been determined by zone showing complete inhibition (mm). Growth inhibition was calculated with reference to positive control. Results of antibacterial activity are given in table-2.

Table 2
Antibacterial activity of synthesized compounds (3a-j)

Compounds	R	Activity index Zone Of Inhibition (mm)*	
		Eschericha coli Gram(+)	*Staphylococcus aureus* Gram(-)
3a	H	9	10
3b	R-CH_3O	10	9
3c	P-NO_2	8	11
3d	4-Cl	12	9
3e	4-OH	11	10
3f	2-Cl	13	11
3g	CH=CH	12	10
3h	2-OH	9	10
3i	4-CH_3	12	14
3j	3-CH_3	14	9
Standard	Erythromycin	24	22

Antibacterial activity in terms of zone of inhibition in mm.

RESULTS

In the present research work, a series of various substituted thiadiazole derivatives are synthesized by conventional as well as microwave heating method. All these compounds are tested for their purity by TLC and melting point. The structure of these compounds is confirmed by IR, NMR, GC-Ms analysis. The microwave assisted organic synthesis required less time and also percentage yield was more compared with conventional method. All synthesized compound arre screened for antimicrobial activities. Compound 3j shows maximum activity for *E.Coli* and compound 3i shows maximum activity for *S.Aureus* bacteria.

DISCUSSION

Schiff's bases of 1,3,4-thiadiazole derivatives of dihydropyrimidine-2-thione are prepared by conventional heating as well as microwave irradiation method. Results are given in table-1. The reactions which are carried out by microwave heating method have given higher yields of the product as compared to the conventional heating method. Microwave assisted reactions are fast, clean and green synthesis[21] because it requires shorter reaction time, and byproducts are not formed. 2-Amino-1,3,4-thiadiazoles with various substituent containing electron donating and electron withdrawing groups are used. Yields of the compounds containing electron donating group are slightly high in conventional as well as in microwave heating methods as compared to the compounds containing electron withdrawing groups. Antibacterial activities of the synthesized compounds are given in table-2. All synthesized compounds shows good to moderate antibacterial activity against both, *E.Coli* and *S.Aureus* bacteria. Compound 3j shows maximum zone of inhibition while compound 3c shows minimum zone of inhibition for gram positive *E. coli* bacteria. . Compound 3i containing 4-CH_3 substituent at benzene ring of thiadiazole shows maximum zone of inhibition against gram negative *S.Aureus* bacteria.

CONCLUSION

Thiadiazole derivatives of dihydropyrimidin-2-thiones are synthesized by conventional as well as by microwave assisted synthesis method. Microwave assisted synthesis have given better yields as compared to conventional method. Higher yield of microwave assisted synthesis is attributed to dielectric heating due dipolar polarization of the molecules. As this technique requires shorter reaction time, yields of the product are high, and workup procedure is also simple, it is considered as green technique. Due to the prevention of pollution by eliminating the generation of waste, microwave technique is beneficial for the society for the control of pollution as well as energy saving tool as the reaction time is decreased from hours to few minute. Synthesized compounds are active against gram positive and gram negative bacteria, hence these compounds can be further explored for detailed pharmacological investigations

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CONFLICT OF INTEREST

Conflict of interest declared none.

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