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Microwave Induced Synthesis of some substituted 2-amino thiadiazines as a prospective antimicrobial agents.

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ABSTRACT

A series of some newly substituted 2-amino thiadiazines have been synthesized using environmentally benign procedure. Neat reactants are subjected to microwave irradiation using of PEG-600 as a solvent. The structures of the synthesized compounds are characterized by elemental and spectral analysis. The newly prepared compounds have been subjected as antimicrobial activity against various strains of bacteria and fungus.

Key words: Microwave irradiation, 2-amino thiadiazine, antimicrobial activity, PEG-600.

INTRODUCTION

The usage of microwave energy to accelerate the organic reactions is of increasing interest in the use of environmentally benign reagent and conditions[1-2]. Synthesis under microwave irradiations can be achieved coveniently and particularly using solvent free procedure[3]. The use of solvent less reaction condition in organic synthesis leads to clean, efficient, eco-friendly, economical technology and is integral part of green chemistry [4-8].

Microwave activation as a non-conventional energy source has become an important method that can be used to carry out a wide range of reactions within shorter reaction time and with high yields especially in the absence of solvents[9-11]. Microwave assisted synthesis of heterocycles have attracted immense attention due to simplicity and enhanced reaction rate[12].

Synthesis and characterization of pyrazoline derivatives has been a developing field within the realm of heterocyclic chemistry. Pyrazoline have been used extensively as important synthons in the organic chemistry and drug designing. Several pyrazoline derivatives have been found to possess considerable biological activities such as antimicrobial[13], anticonvulsants[14], antiinflammatory[15], analgesic[16], antipyretic[17], antitumor[18], insecticidal[19] and antidepressant activities[20]. Pyrazolines have played a crucial role in the development of theory in heterocyclic chemistry and also used extensively in organic synthesis. The design and development of procedures for the generation of new heterocycles is of growing interest. 2-amino thiadiazines are well-known for their soil fungicide [21], antimicrobial [22] and antiparasitic activity[23].

Therefore it was thought worthwhile to synthesize some newly 2-amino thiadiazine derivatives using this synthon, under non-conventional microwave assisted synthesis under liquid phase. Substituted acetyl pyrazolines (1a-g) were

treated with thiosemicarbazide and sodium hydroxide in presence of polyethylene glycol-600 as solvent under MWI resulted in the formation of substituted 2-amino thiadiazines [24-25].

Furthermore reaction under microwave irradiation is clean, efficient, eco-friendly, easy work-up and using fewer amount of solvent makes the process economical viable. The purity of compounds was monitored by TLC using silica g el-G as adsorbent and benzene-ethyl acetate (9:1v/v) as the eluent. The structure of the newly synthesized compounds was confirmed by elemental and spectral (IR, ^{1}H-NMR, Mass) analysis which are summarized in Table-I and II respectively.

Scheme

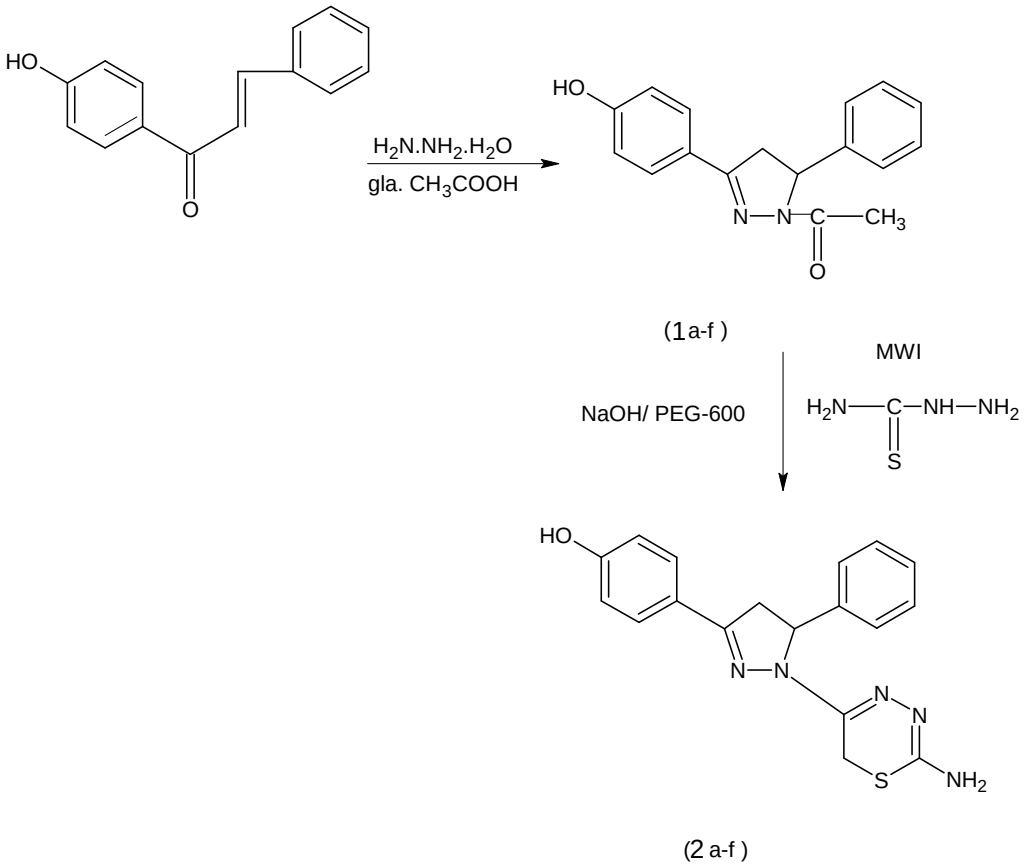

Table I Characterization data of newly synthesized compound 2-amino thiadiazines (2a-f):

S.No.	Compound	Ar	Molecular formula (mol. wt.)	M.P. (^{0}C)	Reaction Time (MWI)		Yield %
					Power (watt.)	Time (min.)	
1.	2a	H	$C_{18}H_{17}N_5OS$ (351)	120	180	3	78
2.	2b	4-$N(CH_3)_2$	$C_{20}H_{22}N_6OS$ (394)	123	180	4	81
3.	2c	4-Cl	$C_{18}H_{16}N_5OSCl$ (385.5)	138	180	3	85
4.	2d	3,4-$(OCH_3)_2$	$C_{20}H_{21}N_5O_3S$ (411)	165	180	3	80
5.	2e	4-OCH_3	$C_{19}H_{19}N_5O_2S$ (381)	135	180	5	75
6.	2f	3,4,5-$(OCH_3)_3$	$C_{21}H_{23}N_5O_4S$ (441)	126	180	3	

Table II Spectral data of newly synthesized compounds (2a-f):

Compound	Spectral data
2a	IR (KBr, υ cm^{-1}) : 3553 (OH), 3294-3146 (NH_2), 1600-1413 (C=C, C=N), 711 (C-S-C) ^{1}H-NMR ($CDCl_3$,δppm) : 9.97 (s, 1H, OH), 9.84 (s, 2H, NH_2), 2.68 (s, 2H, CH_2 of thiadiazine), 3.34-3.39 (dd, 1H, H_a), 3.81-3.89 (dd, 1H, H_b), 5.36-5.43 (dd, 1H, H_x), 6.81-7.38 (m, 9H, Ar-H), Mass (FAB, m/z) : 351 $M^{+\cdot}$ (100)
2b	IR (KBr, υ cm^{-1}) : 3472(OH), 3012 (NH_2), 1611-1459(C=C, C=N), 708(C-S-C), ^{1}H-NMR ($CDCl_3$,δppm) : 9.84 (s, 1H, OH), 9.73 (s, 2H, NH_2), 2.63 (s, 2H, CH_2 of thiadiazine), 2.83-3.08 (dd, 1H, H_a), 3.29-3.31 (dd, 1H, H_b), 5.33-5.38 (dd, 1H, H_x), 6.57-7.31 (m, 8H, Ar-H), Mass (FAB, m/z) : 394 $M^{+\cdot}$ (100)
2d	IR (KBr, υ cm^{-1}) : 3413 (OH), 3063 (NH_2), 1599-1415(C=C, C=N), 711(C-S-C), ^{1}H-NMR ($CDCl_3$,δppm) : 9.87 (s, 1H, OH), 9.85 (s, 2H, NH_2), 2.69 (s, 2H, CH_2 of thiadiazine), 2.17 (s, 6H, OCH3), 3.37-3.42 (dd, 1H, H_a), 3.82-3.94 (dd, 1H, H_b), 5.38-5.43 (dd, 1H, H_x), 6.68-7.34 (m, 7H, Ar-H), Mass (FAB, m/z) : 411 $M^{+\cdot}$ (100
2e	IR (KBr, υ cm^{-1}) : 3391 (OH), 3010 (NH_2), 1610-1453 (C=C,C=N), 720-696 (C-S-C) ^{1}H-NMR ($CDCl_3$,δppm) : 9.95 (s, 1H, OH), 9.86 (s, 2H, NH_2), 2.64 (s, 2H, CH_2 of thiadiazine), 2.17 (s, 3H, OCH_3), 3.33-3.39 (dd, 1H, H_a), 3.79-3.89 (dd, 1H, H_b), 5.36-5.43 (dd, 1H, H_x), 6.81-7.38 (m, 8H, Ar-H), Mass (FAB, m/z) : 381 $M^{+\cdot}$(100)
2f	IR (KBr, υ cm^{-} IR (KBr, υ cm^{-1}) : 3405 (OH), 2936 (NH_2), 1592-1423 (C=C, C=N), 695 (C-S-C), ^{1}H-NMR ($CDCl_3$,δppm) : 9.91 (s, 1H, OH), 9.84 (s, 2H, NH_2), 2.62 (s, CH_2 of thiadiazine), 2.17 (s, 9H, OCH_3), 3.34-3.36 (dd, 1H, H_a), 3.78-3.89 (dd, 1H, H_b), 5.37-5.48 (dd, 1H, H_x), 6.75-7.34 (m, 6H, Ar-H), Mass (FAB, m/z) : 441 $M^{+\cdot}$ (100)

MATERIALS AND METHODS

All the melting points reported are uncorrected and were taken in open capillaries. The IR spectra were recorded on Shimadzu FT-IR spectrometer using KBr (υ cm^{-1}). The 1H-NMR spectra were taken on Bruker DRx-600 spectrometer using TMS (Tetra methyl silane) as internal standard and $CDCl_3$ as solvent. All chemical shift values were recorded as δppm. Mass spectra (FAB) were recorded on Jeol Sx-600 mass spectrometer using m-nitro benzyl alcohol as matrix. The purity of compounds was checked by TLC using silica gel-G adsorbent and benzene-ethyl acetate (9:1 v/v) as the eluent. All the transformations were carried out in domestic microwave oven Samsung 30N.

General procedure for the synthesis of 3,5-diaryl acetyl pyrazolines (1a-f):
4-hydroxy chalcone (0.01 mole) was dissolved in glacial acetic acid (10mL) then added hydrazine hydrate (0.015 mole) and subjected to microwave irradiation for 2-4 minutes at power 600 watts. After completion of reaction as indicated by TLC, the reaction mixture was cooled to room temperature, it was then poured into ice cold water, the separated solid was filtered wash with water, dried, recrystallized from methanol to obtain compound (1a-f) in (85-90%) yield.

General procedure for synthesis of substituted 2-amino thiadiazines (2a-f):
A mixture of acetyl pyrazoline (0.01mole), thiosemicarbazide (0.015 mole) and sodium hydroxide (1.0gm) in presence of polyethylene glycol-600 was irradiated under microwave at 180 watt. for 2-5 minutes with interruption after each 30 sec. After completion of reaction as indicated by TLC, the reaction mixture was cooled to room temperature and poured into ice cold water, neutralized with dil. HCl to obtained solid mass, which was filtered wash with water, dried and recrystallized from methanol to obtained compounds (2a-f).

RESULTS AND DISCUSSION

Newly substituted 2-amino thiadiazines were prepared by non-conventional microwave irradiation in presence of PEG-600. The chemical synthesis initiates with the reaction of 4-hydroxy chalcone with hydrazine hydrate and glacial acetic acid to yield 3,5-diaryl acetyl pyrazolines (1a-f).

Newly synthesized substituted 2-amino thiadiazines were prepared by the cyclization of compound (1) with thiosemicarbazide in presence of base to obtain compounds (2a-f). The products obtained were characterized on the

basis of their analytical and spectral data and the identity of the newly synthesized compounds was checked by m.p. and TLC. The IR spectra of compounds (2a-f) exhibited major absorption bands at 3553-3391 (-OH str.), 3294-3146 (-NH str.), 1610-1453 (C=C, C=N), and 711 (C-S-C str.).

Antimicrobial activity:-

All the newly synthesized 2-amino thiadiazines were screened in vitro for their antimicrobial activities. Synthesized compounds were screened for their antibacterial activity against Bacillus, Pseudomonas, K.pneumoniae, E.Coli and antifungal activity against C. albicans and Aspergillus N. at concentration 250µg/mL using Ciprofloxacin and Flucazole as standard drug respectively. The antibacterial activity was checked by measuring zone of inhibition. All the compounds were found to be active against all strains of pathogens. By visualizing the antimicrobial activity data it could be observed that many of the compounds possess significant activity. The results for biological screening are tabulated in Table III.

Table III:- Biological screening results of compounds (2a-f), Zone of inhibition in (mm):-

	Antibacterial activity				Antifungal activity	
Compound	***Bacillus***	***Pseudomonas***	***K. pneumoniae***	***E.Coli***	***C. albicans***	***Aspergillus N.***
2a	13	12	16	12	10	10
2b	16	14	23	15	12	16
2c	12	14	18	14	16	16
2d	18	10	13	10	18	17
2e	15	13	15	13	14	19
2f	14	13	17	12	18	10
Ciprofloxacin	36	36	36	36	-	-
Flucazole	-	-	-	-	28	28

CONCLUSION

In above synthetic scheme we use microwave irradiation technique. The reaction under microwave irradiation is clean, efficient, economic easy, eco-friendly, easy work-up, shorter reaction time and are an integral part of green chemistry. The purity of compounds was checked by TLC. The structure of the newly synthesized compounds were confirmed by spectral data (IR, PMR, Mass). Some compounds show potential antibacterial and antifungal activity.

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