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MICROWAVE ASSISTED AS A PART OF GREEN CHEMISTRY FOR THE SYNTHESIS OF NOVEL OXADIAZOLE DERIVATIVES

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1 hydroxy 2 naphthoic acid, Para anisic acid, Phosphorus oxychloride, Microwave assisted synthesis, Antimicrobial activity

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ABSTRACT

Green chemistry is a new and rapid emerging branch of chemistry. The concept of green chemistry incorporates a new approach to synthesize, processing and application of chemical substance in such a manner that to reduce the damage of health and environment. An effective synthesis and preparation of 2,5-disubstituted 1, 3, 4- oxadiazole derivatives by using microwave technique. In microwave assisted technique gives high yield, time consuming as well as effective, ecofriendly and inexpensive. The synthesized compound was characterized by using IR (JASCO 4100-FT/IR) Mass (QP 2013 Shimadzu) and NMR. 1, 3, 4-oxadiazole showed prominent antimicrobial activity in comparison to standard drug was used.

INTRODUCTION

Microwave irradiation provides a higher yield, these are also a time consuming process. The microwave synthesis includes all types of chemical reactions such as addition, elimination, cycloadditions, fragmentations etc.[1] This new approach are also known as Environmentally benign chemistry, Clean chemistry, Atom economy, Benign-by-design chemistry. Azole derivatives are the important class of the heterocyclic compounds. The heterocyclic compounds like oxadiazole and triazole etc. Heterocyclic compounds having five membered ring containing two carbon atom, one oxygen, two nitrogen and two double bonds such as oxadiazole. 1, 3, 4 oxadiazole derivatives have played a vital role in the medicinal chemistry.[2] 2, 5- disubstituted 1, 3, 4- oxadiazole has been synthesized using microwave irradiation methods. The synthesized compound shows a broad spectrum of pharmacological activities like antimicrobial, anti-inflammatory, anti tuberculosis, anti analgesic, anticancer etc.[3-4]

Many of the scientists have reported that the microwave methods yields more quantity of derivative and also are time consuming; hence an attempt was made to perform synthesis by microwave method which is fast and eco friendly process.

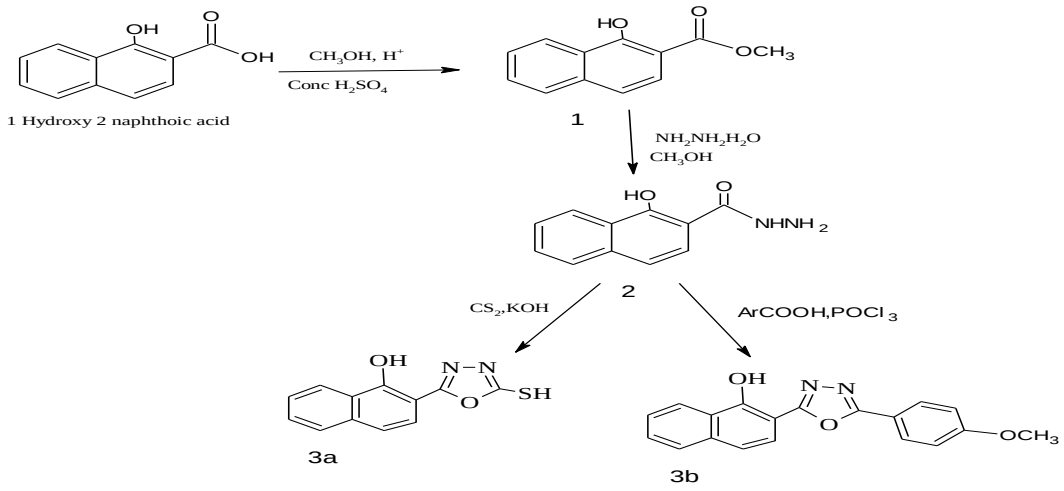
MATERIALS AND METHODS

Material- 1 hydroxy 2 naphthoic acids were obtained from *SIGMA ALDRICH* and other chemicals are purchased from Loba Reaserch Lab (Mumbai). All chemicals are AR grade.

Methods- Microwave Technique (Catalyst)

Experimental work [5,6,7,8]

Melting Points of all compounds was determined by open tube capillary method and wad uncorrected Purity and reaction completion of compounds were checked by Thin Layer Chromatography using silica gel- G.



Where- ArCOOH is Para Anisic acid etc.

A) Microwave method-[7, 9]

Synthesis of 1- hydroxy- naphthalene-2- ethyl carboxylate (1)

1 hydroxy 2 naphthoic acid (0.15mole) in absolute methanol (30ml) was added concentrated sulfuric acid (1ml) where taken in 250 ml round bottom flask fitted with reflux condenser. The reaction mixture was refluxed for 10 min. the reaction completion was established by thin layer chromatography. After the reaction mixture was poured into a separating funnel containing distilled water (30ml). Diethyl ether (15ml) was added to separating funnel and mixture was neutralized by concentrated aq.10% $NaHCO_3$ solution. Lower aq. layer was discarded and upper ether layer containing required ester. Melting Point: 198°C.

Synthesis of 1 hydroxy- naphthalene- 2- carbohydrazide (2)

In a solution of **1** (0.018mole) in absolute methanol (30ml) was added hydrazine hydrate (0.018mole) mixture was refluxed for 8 min. the reaction was monitored by TLC. Excess methanol was distilled off and cold distilled water was added along with shaking till the appearance of precipitated. The carbohydrazide were filtered, washed with distilled water, dried and recrystallized with ethanol. Melting Point: 196°C.

Synthesis of 2-(5-mercapto-1, 3, 4-oxadiazol-2-yl)-1-naphthol (3a)

The carbohydrazide (0.015mole) were dissolved in absolute ethanol (30ml). Potassium hydroxide (0.5 g, 0.01mole) in water 5ml under stirring. To this, carbon disulphide (0.76g, 0.01mole) was added and the reaction mixture was refluxed till the evolution of H_2S ceased. Reaction was monitored by TLC. After complete reaction the mixture was diluted with distilled water (25ml) and acidified with dil. HCl to a P^H of 2. The precipitated product was then filtered, washed with distilled water and recrystallized from ethanol. Melting Point: 172°C.

Synthesis of 2-[5-(4-methoxyphenyl) - 1, 3, 4-oxadiazol-2-yl]-1-naphthol (3b)

The mixture of **2** (0.005mole) and appropriate aromatic acids (0.005mole) were dissolved in phosphorus oxychloride (0.025mole) and refluxed for 10 min on a steam bath, then reaction mixture was cooled to room temperature and neutralized with ice cold solution of 10% $NaHCO_3$.The solid was filtered, washed with water, dried recrystallized from ethanol. Melting Point: 180°C.

Table 1- Time of reaction, Percentage yield and properties of synthesized compounds

Compounds	Melting Point($^{\circ}$C)	RF Value	Microwave Method		Molecular Formula
			Time (min)	Yield (%)	
1	198	0.90	10	77.21	$C_{12}H_{10}O_3$
2	196	0.74	8	63.26	$C_{11}H_{10}N_2O_2$
3a	172	0.71	15	69.45	$C_{12}H_8N_2SO_2$
3b	180	0.8	10	65.56	$C_{19}H_{14}N_2O_3$

Pharmacological studies

The compounds were evaluated for their invitro antimicrobial activity against *E. coli, S. aureus, B. subtilis* and *S. typhi* by disk diffusion method was performed using MacConkeys agar and Nutrient agar medium. Each compound was tested at a concentration at 100µg/ml in DMSO. The zone of inhibition was measured after 24 h incubation at 37°C.

***In vitro* antimicrobial activity-**[7, 9, 10]

The synthesized compound were tested against microorganism including gram positive bacteria; *Bacillus subtilis, staphylococcus aureus* and gram negative bacteria against *Escherichia coli, pseudomonas auerginosa,* The stock solution of compounds were prepared in DMSO. Suspension of test organism was freshly prepared in 1 ml of sterile normal saline and was standardized to 10^7 CFU/ml. 100ml suspension of organism was seeded on culture plates, in each agar plate 3 well were prepared. The 100ug/ml of each dilution of compounds was poured into wells. Ciprofloxacin were used as a standard drug employed at a concentration 100 µg/ml. Control was maintained for strain pure solvent (DMSO) was incubated into well. The plates were incubated at 37^0C and zone of inhibition were measured at the end of 24 hours.

Table 2- Antimicrobial activity of synthesized compound

Compounds	Zone of inhibition in mm (*Bacillus subtilis)*		
	100 µg/ml	300 µg/ml	500 µg/ml
3a	8	10	15
3b	7	9	17
Ciprofloxacin	29	-	-
Control	-	-	-
compound	Zone of inhibition in mm (*Escherichia coli)*		
	100 µg/ml	300 µg/ml	500 µg/ml
3a	14	15	16
3b	5	10	15
Ciprofloxacin	34	-	-
Control	-	-	-

RESULTS AND DISCUSSION

Experimental

I. Synthesis of 1- hydroxy- naphthalene-2- ethyl carboxylate (1)

II. Synthesis of 1- hydroxy- naphthalene- 2- carbohydrazide (2)

III. Synthesis of 2-(5-mercapto-1, 3, 4-oxadiazol-2-yl)-1-naphthol (3a)

IV. Synthesis of 2-[5-(4-methoxyphenyl) - 1, 3, 4-oxadiazol-2-yl]-1-naphthol (3b)

The step 1 reaction afforded the yield of product in the range of 77.21% and time taken by the method is 10 min.

In step 2 reaction the yield of product in the range of 63.26% and time taken by the method is 8 min.

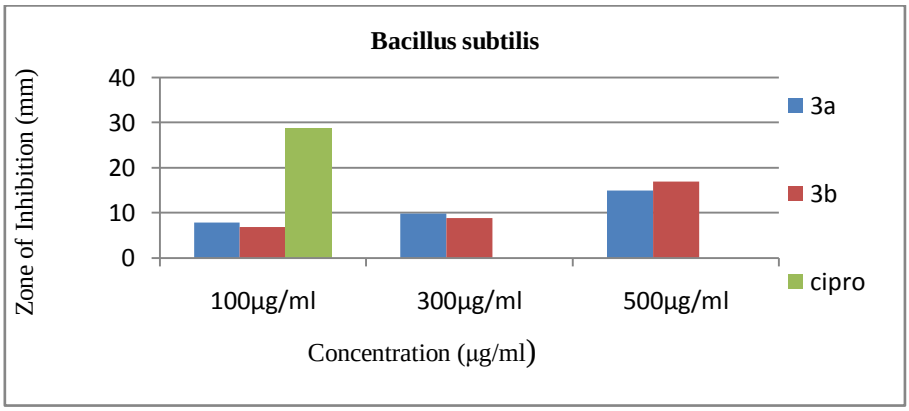
In step 3a and 3b reactions afforded the yield of products in the range of 69.45% and 65.56% and time taken by the method is 15 and 10 min respectively.

IR, MASS, NMR Spectra studies

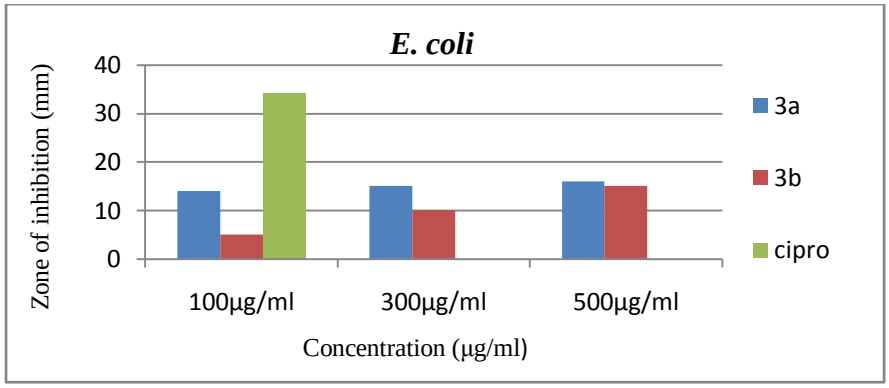
The structural elucidation of synthesized compounds was done by the interpretation of IR, MASS and NMR spectra's. All the compounds show satisfactory results.

Pharmacological studies

The antimicrobial activity of synthesized compounds 3a, 3b was carried out by disc diffusion method and screening against *E. Coli*, and *Bacillus Subtilis.* Ciprofloxacin were used as a standard drug. Synthesized compounds show considerably antimicrobial activity.



Graph 1. The antimicrobial activity of synthesized compound against *bacillus subtilis.*



Graph 2. The antimicrobial activity of synthesized compound against *Escherichia coli*

CONCLUSION

The preparation of oxadiazole by microwave method takes only 10-15 min for the completion of reaction. The yield of microwave is higher. The microwave method is suitable and reduces the damage of health and environment also. The 1,3,4 oxadiazole compound was characterized by physicochemical properties like melting point, RF value, and also gives the good and satisfactory antimicrobial activity. These data reveals that the microwave assisted synthesis is eco-friendly, inexpensive as well as reduce the reaction time.

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