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MICROWAVE ASSISTED SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF NOVEL 1, 3, 4- OXADIAZOLE DERIVATIVES

Shital A. Chalke*, S.K.Mohite, P.N. Kamble, M.A.Nimbalkar

Rajarambapu College of Pharmacy, Kasegaon, Tal. Walwa, Dist. Sangli, (M S), India

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3-hydroxy-2- Naphthoic acid, 1,3,4- oxadiazole, Antimicrobial Activity, Anti- inflammatory Activity

For Correspondence:

Shital A. Chalke

Rajarambapu College of Pharmacy, Kasegaon, Tal. Walwa, Dist. Sangli, (M S), India

E-mail:

shitalpharma92@gmail.com

ABSTRACT

Oxadiazole derivatives are an important class of heterocyclic compounds, specially sulphur amino substituted oxadiazole reported to possess a wide spectrum of biological activities such as antibacterial, antifugal, analgesic, anti-inflammatory, antioxidant, antitumor, anticancer activities and so on. 1,3,4-oxadiazoles are five membered heterocycles containing one oxygen and two nitrogen atoms at position1, 3 and 4 position respectively. As with the azoles, this is also an electronegative ring system with weak basic characteristics due to the inductive effects of the extra hetero atoms. Oxadiazoles are susceptible to nucleophilic attack as because it readily undergoes ring cleavage with aqueous acid or base hence both carbon positions are substituted (2,5-disubstituted). Microwave assisted synthesis of novel 1,3, 4 – oxadizole derivatives using Naphthoic acid as starting material have been carried out and synthesized compounds have been evaluated for invitro antimicrobial and invitro anti-inflammatory activity.

INTRODUCTION

As resistance to antimicrobial drugs is widespread, there is an increasing need for identification of novel structure leads that may be of use in designing new, potent, and less toxic antimicrobial agents. The multiple pharmacological actions of unique synthetic compounds are a prerequisite for classifying a drug as highly efficacious, because these actions offer possibility of treating various diseases. Heterocyclic compounds are very important compounds which have been found to maintain significant biological activity are represent important moiety in creation of novel medical materials, adversity of biological activities and pharmaceutical uses have been attributed to them such as anti-inflammatory, antifungal, antibacterial, antitumor and analgesic[3,4.]

Oxadiazoles are five membered heterocylic compounds with two nitrogen atoms and one oxygen atom. 1, 3, 4- oxadiazoles are a class of heteocycles which have attracted significant interest in medicinal chemistry and they have a wide range of pharmaceutical and biological activities. The 1, 3, 4- oxadiazoles, 2,5 unsymmetrical disubstituted derivatives have attracted considerable attention because of their biological and electrochemical properties. Numerous studies have been performed with aim of exploring the anti-inflammatory propertiesof 1,3,4-oxadizole analogues. Microwave assisted technique is efficient, eco-friendly and in-expensive method which not only give higher yield but also reduces the reaction time significantly. These studies found that 1, 3, 4 – oxadiazole analogues are equipotent with phenylbutazone and other NSAIDs. Synthesis of Novel 1, 3, 4- oxadiazole analoguaes to investigate their invitro antimicrobial and invitro anti-inflammatory activity.[1,2,3.]

MATERIALS AND METHODS

All the chemicals used were procured from Loba research Lab (Mumbai) and were of AR grade. The equipments used were Microwave (CATALYST), FT-IR (JASCO 4100-FT/IR), JASCO UV Sectrophotometer.

EXPERIMENTAL

Melting points of all compounds was determined by open tube capillary method and was uncorrected. Purity of compounds were checked by thin layer chromatography (TLC) on silicagel-G in solvent system hexane-ethyl acetate and the spots were observed under iodine vapours.

Method of synthesis of 1,3,4- oxadiazole derivatives.

Microwave Method:

I) Synthesis of 3- hydroxy-napthalene- 2- ethyl carboxlate (1)

Mixture of 3-hydroxy-2-naphthoic acid(0.01mole) in absolute ethanol (20ml) was placed in microwave oven and irradiated for 10 min.completion of reaction was monitored by TLC and reaction was cooled .

II) Synthesis of 3-hydroxy- naphthalene-2- carbohydrazide(2)

In a solution of **1**(0.1mol) in absolute ethanol(20ml) was added hydrazine hydrate (0.15mol). This mixture was placed in microwave oven and irradiated for 6 min. The reaction was cooled, solid was filtered, washed with ice cold water, dried and recrystallized from absolute ethanol.

III) Synthesis of 5-(3-hydroxy-2-naphthayl)-2-mercapto-1, 3,4- oxadiazole (3a)

To an ethanolic solution of **2**(0.01mole) was added a solution of potassium hydroxide (0.01mole) in ethanol (5ml), to this carbon disulfide (0.01Mole) was added and reaction mixture was placed in microwave oven and irradiated for 7 min. completion of reaction was monitored by TLC and reaction was cooled .Acidify with hydrochloric acid solid was filtered, dried and recrystallized from absolute ethanol.

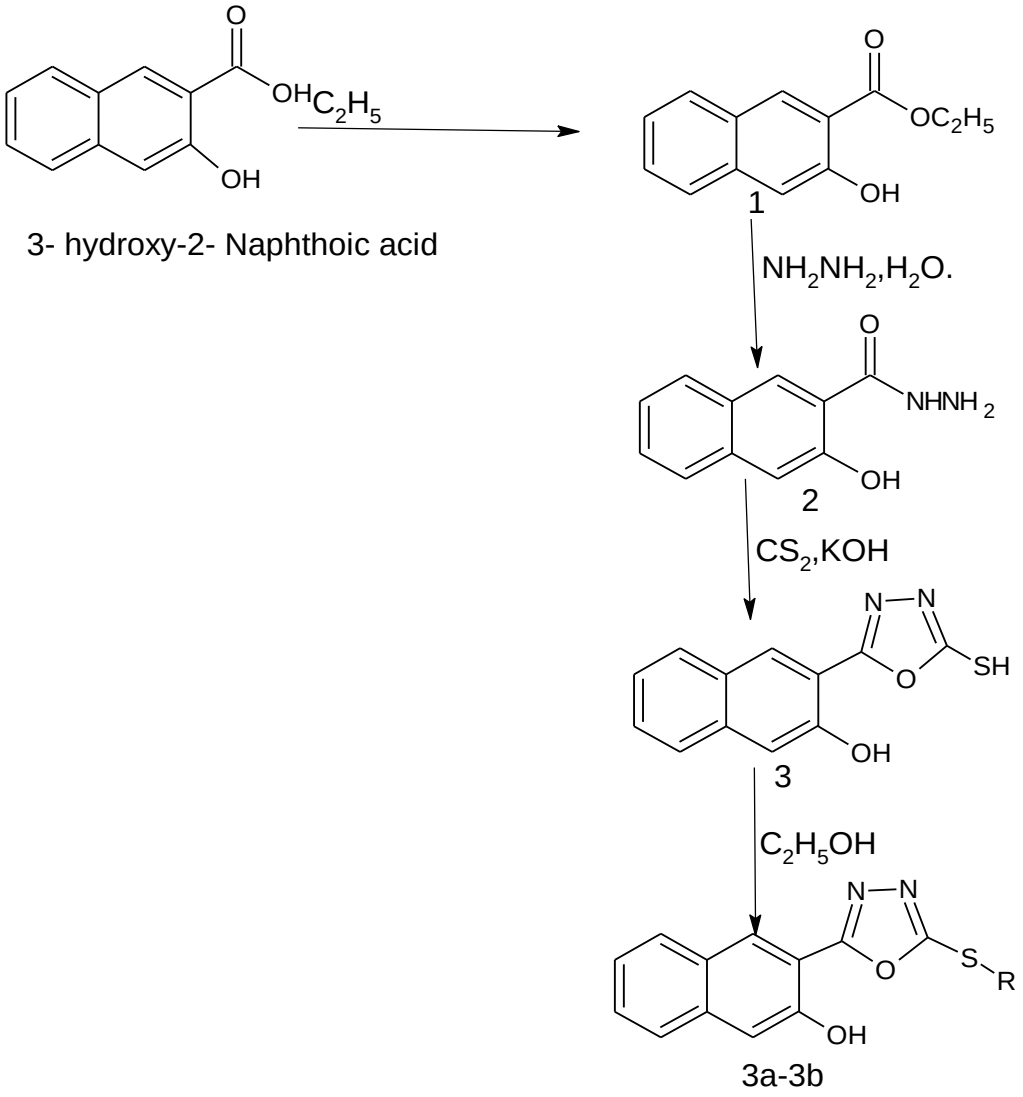
IV) Synthesis of 3-{5-[(4-aminophenyl)sulfanyl]-1,3,4-oxadiazol-2-yl}naphthalene-2-ol.($3a_1$).

To an ethanolic solution of 3a(0.01mole) was added aniline solution(0.01mole).and reaction mixture was placed in microwave oven and irradiated for 12 min.Completion of reaction was monitored by TLC and reaction was cooled. Solid was filtered, dried and recrystallized from absolute ethanol.

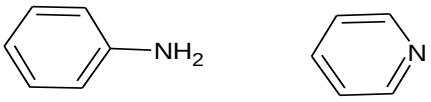
V) Synthesis of 3-[5-(pyridin-4-ylsulfanyl)-1,3,4-oxadiazol-2-yl]naphthalen-2-ol

To an ethanolic solution of 3a(0.01mole) was added pyridine solution(0.01mole).and reaction mixture was placed in microwave oven and irradiated for 10 min. Completion of reaction was monitored by TLC and reaction was cooled. Solid was filtered, dried and recrystallized from absolute ethanol.

REACTIONSCHEME:[5,6,7,8.]



Where R=



The melting points were determined the observations are mentioned in table I.

Compound	Molecular Formula	Rf value	Melting Point	Practical Yield
1	$C_{13}H_{12}O_3$	0.9	144-146^{0}C	75%
2	$C_{11}H_{11}N_2O_2$	0.22	126-128^{0}C	80%
3	$C_{12}H_8N_2O_2S$	0.72	168-170^{0}C	70%
3a	$C_{18}H_{14}N_3O_2S$	0.5	216-218^{0}c	73%
3b	$C_{17}H_{12}N_3O_2$	0.7	210-212^{0}c	71%

UV spectroscopy

λ**max** in nm of compound 3a= 305nm

λ**max** in nm of compound 3b= 340nm.

IR Spectroscopy :

1. **Synthesis of 3-{5-[(4-aminophenyl)sulfanyl]-1,3,4-oxadiazol-2-yl}naphthalene-2-ol.**
   Ar-H str -3052, OHstr- 3330, NH str- 3350,C-O-C str- 1042, CH Str - 2920, (C=N)str-1541, c-s str 2590.
2. **Synthesis of 3-[5-(pyridin-4-ylsulfanyl)-1,3,4-oxadiazol-2-yl]naphthalen-2-ol**
   Ar-H str -3060, OHstr- 3332, NH str- 3352,C-O-C str- 1045, CH Str - 2920, (C=N)str-1541, c-s str 2590, C=N str- 1432.

RESULT AND DISCUSSION

Microwave assisted synthesis can make an impact in several areas of drug discovery and is not only confined to areas related to organic synthesis. Microwave technology is also being used in target discovery, screening, pharmacokinetics and even in the clinic. Synthesized compound were characterized by UV spectroscopy and IR spectroscopy. Synthesized compounds were evaluated for invitro antimicrobial and invitro- anti-inflammatory activity.

PHARMACOLOGICAL ACTIVITIES

Antimicrobial Activities

Antibacterial Activity [6,7]

The synthesized compounds were evaluated for their *in-vitro* antibacterial activity against strain *Bacilus substilis* and *Escherichia coli.* Disk diffusion method was performed using Nutrient agar medium. Stock solutions of the compounds were prepared in dimethyl sulphoxide (DMSO). Suspension of test organism was freshly prepared in 1ml of sterile normal saline solution and was standardized to 10^7 CFU/ml.100ml suspension of organism was seeded on culture plates. Then in each agar plate 3 well were prepared .100 µg/ml of each dilution of compounds were transferred to the wells. Standard drug Ciprofloxacin was 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. Observations of zone of inhibition are noted in table 2.

Antifungal Activity

Synthesized compounds were evaluated for their invitro antifungal activity against strain Candida albicans. Disk diffusion method was performed using saboraud's agar medium. Stock solutions of the compounds were prepared in dimethyl sulphoxide (DMSO). Suspension of test organism was freshly prepared in 1ml of sterile normal saline solution and was standardized to 10^7 CFU/ml.100ml suspension of organism was seeded on culture plates. Then in each agar plate 3 well were prepared .100 µg/ml of each dilution of compounds were transferred to the wells. 100 µg/ml of each dilution of compounds were transferred to the wells. Standard drug Fluconazole was 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. Observations of zone of inhibition are noted in table.

Table No 2

Compound Code	Zone of inhibition (mm)								
	Staphylococcus aureus			*Escherichia coli*			*Candida albicans*		
	50 µg/ml	100 µg/ml	150 µg/ml	50 µg/ml	100 µg/ml	150 µg/ml	50 µg/ml	100 µg/ml	150 µg/ml
3a	5	7	9	3	8	11	7	11	14
$3a_1$	3	6	8	2	7	13	8	10	11
$3a_2$	2	5	11	4	6	10	9	13	12
Standard	-	10	-	-	10	-	-	10	-

IN VITRO ANTI- INFLAMMATORY ACTIVITY

Evaluation invitro anti- inflammatory activity by protein Denaturation method [9]

The mixture (10ml) consisted of 0.4ml of egg albumin (from fresh hen's egg), 5.6ml of phosphate buffered solution (PBS, pH 6.4) and 4ml of varying concentration of test samples so that final concentration become 50 µg/ml ,100 µg/ml. Similar volume of DMSO served as control. Then the mixtures were incubated at (37°c ± 2) for 15 min. and then heated at 70°c for 5min. After cooling, their absorbance was measured at 660nm (JASCO UV Sectrophotometer) by using vehicle as blank and their viscosity was determined by using Ostwald viscometer. Diclofenac sodium at the final concentration of 50 µg/ml ,100 µg/ml was used as reference drug and treated similarly for determination of absorbance and viscosity. The % inhibition of protein denaturation was calculated by using the following formula, and results noted in table no 3

$$\% \text{ inhibition protein denaturation} = \frac{\text{abs of control- abs of test}}{\text{abs of control}} \times 100$$

Table No 3

Compound Code	Percentage of protein Denaturation		Viscosity (cps)	
	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml
3a	65%	70%	0.72	0.53
$3a_1$	55%	75%	0.83	0.64
$3a_2$	52%	72%	0.92	0.45

CONCLUSION

Microwave is a convenient way toward the goal of green/sustainable chemistry, and is strongly recommended to use in organic preparations. The research study reports the successful microwave assisted synthesis. The synthesized compounds 3,3a,3b shows good antimicrobial activity and good anti-inflammatory activity.

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