World Journal of
Medicinal Chemistry

IDAAM Publications

World J Med Chem 2024; 1(1): 5-9

RESEARCH ARTICLE

Microwave assisted synthesis of some novel 1,3,4-oxadiazole analogues as potent anti-inflammatory agents

AKSHAY R YADAV[1]*

[1]Department of Pharmaceutical Chemistry, Rajarambapu College of Pharmacy, Kasegaon, Maharashtra-415404, India

***Author for Correspondence:** *Email:*akshayyadav24197@gmail.com

ARTICLE DETAILS

Article history:
Received on 18 February 2021
Modified on 22 September 2022
Accepted on 30 September 2022

Keywords:
1,3,4-oxadiazole,
Microwave irradiation,
Inflammation,
Anti-inflammatory activity.

ABSTRACT

The present study depicts synthesis of a series of some novel 1,3,4-oxadiazole. The compounds were evaluated for their anti-inflammatory activity. 1,3,4-oxadiazole derivatives are very well-known biologically active N-containing heterocycles and represent a versatile lead molecule for designing potential bioactive agents. The widespread use of 1,3,4-oxadiazoles as a scaffold in medicinal chemistry establishes this moiety as a member of the privileged structures class. This pharmacological activity evaluation revealed that, among all the compounds screened, compound code 3a was found to have promising anti-inflammatory activity.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) were known as important class of therapeutic agents for the alleviation of pain and inflammation. The pharmacological activity of NSAIDs is due to the inhibition of prostaglandins biosynthesis from arachidonic acid through inhibiting cyclooxygenases (COXs)[1]. However, long term use of NSAIDs was associated with several side effects such as gastrointestinal mucosal damage, bleeding, intolerance, and renal toxicity. The gastrointestinal (GI) damage from NSAIDs generally attributes to two factors, *i.e.*, local irritation by the carboxylic acid moiety, common to most NSAIDs (topical effect) and decreased tissue prostaglandins production which maintains GI health and homeostasis[2]. Therefore, synthetic approaches based upon chemical modification of NSAIDs were taken with theaim of improving NSAID safety profile[3]. The core 1,3,4-oxadiazole structure generally attracted widespread attention because of the diversity of biological activity as they showed anti-inflammatory, analgesic, antitumor, antimicrobial, hypoglycemic, and antitubercular activities. One of the first synthetic organic compounds that used as an important drug and having a 1,3,4-oxadiazole nucleus. Thus, our main objective is to design novel derivatives to be further explored as powerful and novel anti-inflammatory lead candidates. Some of these derivatives contain acidic centers with further esterification aiming to decrease the local side effects that might be attained by its acidic moieties. The synthesized compounds were evaluated for their anti-inflammatory activity. Inflammation is a central part of the response to injury and infection in the immune system. It may become problematic if the inflammatory process continues for too long. External infections involving the skin and wound are the most frequent complications affecting humans and animals[4-6].The compounds containing a heterocyclic ring play an important role among organic compounds with biological activity used as drugs in human, veterinary medicine or as insecticides and pesticides in agriculture[7]. Microwave assisted organic synthesis has as a new "lead" in the organic synthesis. The technique offers clean, simple, efficient, fast and economic for the synthesis of a number of organic molecules such reaction has new tool in the organic synthesis[7,8]. Conventional method of organic synthesis usually requires longer heating

time, tedious apparatus setup which result in higher cost of process and the excessive use of solvents or reagents lead to environmental pollution. This technique is considered as important approach toward green chemistry because this technique is more environments friendly and this technology is used in the laboratory and has the potential to have a large impact on the fields of combinatorial chemistry. The microwave reactions were performed using microwave assisted synthesis on microwave, the reactions were worked up extensively to obtain a pure form of product which was isolated using literature work-up procedures. Microwave heating is the best process due to the microwave couple directly with the molecule that are present in the mixture, leading to fast rise in temperature, faster reaction and cleaner chemistry. The microwave is also called as green chemistry because it does not produce any hazardous material like gas fumes or heating using external energy source. In the discovery of effective medicines for prevention and treatment, an outbreak of coronavirus disease (COVID-19) caused by the novel extreme acute respiratory syndrome coronavirus-2 (SARS-CoV-2) poses an unprecedented obstacle. The proximity to the patient during dental care, high generation of aerosols, and the identification of SARS-CoV-2 in saliva have suggested the oral cavity as a potential reservoir for COVID-19 transmission. Given the rapid pace of scientific research and clinical data provided by the large number of people who are rapidly infected with SARS-CoV-2, clinicians need reliable evidence of good medical care for this infection, as it is simple to do in-silico analysis in the initial stage with the aid of molecular docking software with help of chemical structure of compound. It is necessary to enhance both enzymatic stability and membrane permeation in the formulating drug delivery system for protein and peptide drugs. Soon, someday, you might be making your own drugs at home. That is because researchers have adapted a 3D printer from basic, readily available medicinal active agents fed into a drug delivery system.

MATERIALS AND METHODS

All chemicals and solvent procured from commercial sources, purified and dried using standard procedures from literature whenever required the reagents were purchased from Research lab, Mumbai .and issued from store department of Rajarambapu College of Pharmacy, Kasegaon. and solvents were purified by distillation and residual water was removed. The test compounds 1,3,4-oxadiazole derivatives 3a-d were synthesized in our laboratory. Melting point of synthesized compounds was determined by open capillary tubes.

Chemistry

Synthesis of pyridyl-3-carbohydrazide

A mixture of Pyridine-3-carboxylic acid ethyl ester8 (0.1 mol), and hydrazine hydrate (99%) (0.1 mol), in absolute alcohol (50ml) was refluxed for about 4hrs. The excess of solvent was removed and the residue was poured into ice cold water (125ml). The solid which is obtained was recrystallized from ethanol to get white crystalline product. Yield-85%, Mp 162^{0}C, IR (KBr): 1612 (C=N), 1670(C=O), 3048 (-CH of pyridyl).

General procedure for the synthesis of 2-aryl-5-pyridyl-1,3,4-oxadiazoles

A mixture of nicotinic hydrazide [0.01mol] and various aromatic acids [0.01mol] in presence of $POCl_3$ [8ml] were refluxed for 8-14hrs in an oil bath. The contents were cooled and poured into crushed ice. It was neutralized with $NaHCO_3$ solution and the resulting solid was filtered, dried and recrystallized from ethanol.

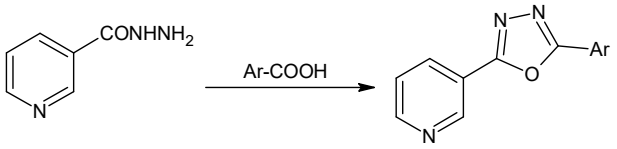

Figure 1: Synthetic scheme of title compound

Table 1: Physical data of 2-aryl-5-pyridyl-1,3,4-oxadiazoles (3a-d)

Compound Code	Ar-COOH	MP (^{0}C)	Yield (%)
3a	Benzoic acid	118-120	79
3b	p-chloro Benzoic acid	125-127	84
3c	o-amino Benzoic acid	115-117	65
3d	3,5-dinitrosalicyclic acid	129-131	92

Anti-inflammatory Evaluation

a. Protein denaturation using egg albumin

The sample mixture (10 ml) consists of 0.4 ml of egg albumin (from fresh egg), 0.6ml of phosphate buffered solution (pH 6.4) and 4ml of test sample 50 µg/ml and 100µg/ml of final concentration. The same DMSO volume acts as control and the

sample mixtures were then incubated for 15-20min at (37ºC ± 2). Then set at 70ºC for 5 min. With the assistance of the ostwald viscometer, their viscosity was determined. Diclofenac sodium has been used as reference drug in an absorption and viscosity determine similarly as standard drug at the final concentration of 50µg/ml and 100µg/ml. They were measured at 660nm (JASCO UV spectrophotometer) after cooling the sample by using the vehicle as blank. The percentage of protein denaturation inhibition was calculated[9,10].The % inhibition of protein denaturation was calculated by using the following formula:

$$\%\ inhibition\ protein\ denaturation = \frac{Absorbance\ of control - Absorbance\ of\ test}{Absorbance\ of\ control}$$

b. Protein denaturation using bovine serum albumin (BSA)

The reaction mixture was consisting of of test compoundand G-max (50:50 ratio) at different concentrations and 1% of aqueous solution of bovine albumin. The samples were incubated at 37°C for 20 min and then heated at 57°C for 20 min. After cooling the samples, the absorbance of turbidity was measured at 660 nm[11,12].The % inhibition of protein denaturation was calculated by using the following formula:

$$\%\ inhibition\ protein\ denaturation = \frac{Absorbance\ of control - Absorbance\ of\ test}{Absorbance\ of\ control}$$

RESULTS AND DISCUSSION

Chemistry

Pyridyl-3-carbohydrazide prepared by mixture of Pyridine-3-carboxylic acid ethyl and hydrazine hydrate in absolute alcohol was refluxed for about 4hrs. The excess of solvent was removed and the residue was poured into ice cold water. The solid which is obtained was recrystallized from ethanol to get white crystalline product. In next step, 2-aryl-5-pyridyl-1, 3, 4-oxadiazoles were synthesized by adding mixture of nicotinic hydrazide and various aromatic acids in presence of $POCl_3$ were refluxed for 8-14 hrs in an oil bath. The contents were cooled and poured into crushed ice. It was neutralized with $NaHCO_3$ solution and the resulting solid was filtered, dried and recrystallized from ethanol.

Anti-inflammatory Evaluation

a. Protein denaturation using egg albumin

In current study in-vitro results confirmed anti-inflammatory activity of new series of 1,3,4-oxadiazoles derivatives by denaturation of proteins which is a well documented cause of inflammation. Several anti-inflammatory drugs shown dose dependent ability to inhibit thermally induced protein denaturation. Ability of 1,3,4-oxadiazoles is to bring down thermal denaturation of protein is possibly a contributing factor for its anti-inflammatory activity. The data of our studies suggests that compound code 3a shows significant anti-inflammatory activity.

b. Protein denaturation using bovine serum albumin (BSA)

The autoantigen production in inflammation is due to denaturation of protein and several studies reveal that protein denaturation is one of the reasons for inflammation. Protein denaturation is a process in which proteins lose their tertiary structure and secondary structure by application of external stress or compound, such as strong acid or base, a concentrated inorganic salt, an organic solvent, or heat. Most biological proteins lose their biological function when denatured. The results suggest that compound code 3c shows significant anti-inflammatory activity.

Table 2: Anti-inflammatory activity of 1,3,4-oxadiazoles derivatives (3a-d) measuring the percentage inhibition

Sr. No	Compound Code	% of inhibition of protein denaturation		Viscosity (cps)	
		50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml
1	3a	75.67	78.23	0.58	0.60
2	3b	60.87	64.91	0.35	0.38
3	3c	55.01	56.12	0.41	0.48
4	3d	60.12	66.72	0.51	0.54
5	Diclofenac	80.34	82.49	0.60	0.65

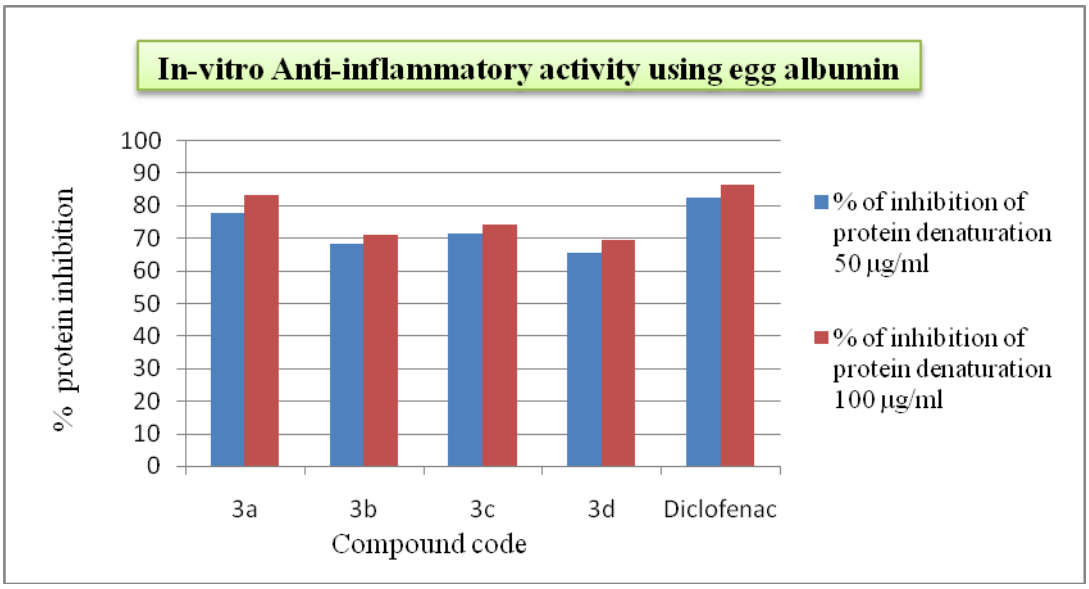

Figure 2: Anti-inflammatory activity of synthesized compounds (3a-d) using egg albumin

Table 3: Anti-inflammatory activity of 1,3,4-oxadiazoles derivatives (3a-d) measuring the percentage inhibition

Sr. No	Compound code	% of inhibition of protein denaturation	
		50 µg/ml	100 µg/ml
1	3a	77.54	82.91
2	3b	68.29	70.71
3	3c	71.14	73.97
4	3d	65.20	69.32
5	Diclofenac	82.39	86.12

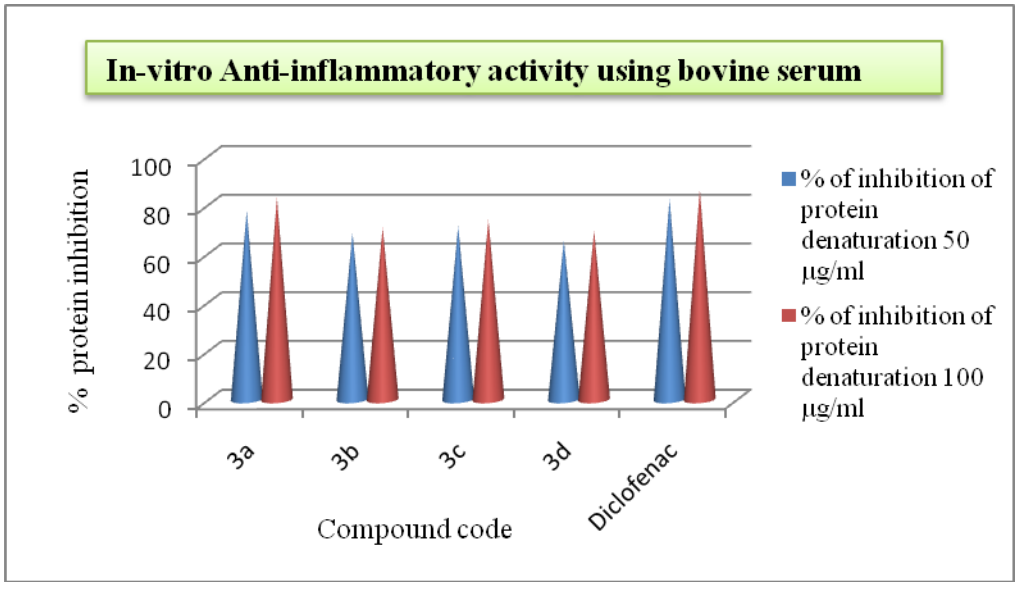

Figure 3: Anti-inflammatory activity of synthesized compounds (3a-d) using bovine serum

CONCLUSION

We have described an efficient and benign synthesis of 1,3,4-oxadiazoles systems gives more yields and requires less time by microwave method. 1,3,4-oxadiazoles is the key intermediate in the formation of these heterocyclic compounds. All the synthesized compounds have been investigated for their anti-inflammatory activity. With our newly synthesized compounds, it is evident that compound code 3a have shown excellent anti-inflammatory activity. Accordingly, this novel class of new 1,3,4-oxadiazoles derivatives reported from our laboratory, emerge as a valuable lead series with great potential to be used as anti-inflammatory agents, and as promising candidates for further efficacious evaluation.

ACKNOWLEDGEMENT

I express my sincere thanks to Vice-principal Prof. Dr. S. K. Mohite for providing me all necessary facilities.

REFERENCES

[1] Talley JJ, Brown DL, Carter JS, Graneto MJ, Koboldt CM, Masferrer JL. 4-[5-Methyl-3-phenylisoxazol-4-yl]-benzenesulfonamide, Valdecoxib: a potent and selective inhibitor of COX-2. J Med Chem. 2000; 43: 775-7.

[2] Ottana R, Maccari R, Barreca MT, Bruno G, Rotondo A, Rossi A, *et al*. 5-Arylidene-2-imino-4-thiazolidinones: design and synthesis of novel anti-inflammatory agents. Bioorg Med Chem. 2005; 13: 4243-52.

[3] Warner TD, Giuliano F, Vaynovie I, Bukasa A, Mitchell JA, Vave JR. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full *in vitro* analysis. Proc Natl AcadSci [USA]. 1999; 96: 7563-8.

[4] Xie WL, Chipman JG, Robertson DL, Erikson RL, Simmons DL. Expression of a mitogen-responsive gene encoding prostaglandin synthase is regulated by mRNA splicing. Proc Natl AcadSci [USA] 1991; 88: 2692-6.

[5] Kujubu DA, Fletcher BS, Vamum BC, Lim RW, Herschman HR. TIS10, a phorbolester tumor promoter-inducible mRNA from Swiss 3T3 cells, encodes a novel prostaglandin synthase/cyclooxygenase homologue. J Biol Chem. 1991; 266: 12866-72.

[6] Dannhardt G, Kiefer W. Cyclooxygenase inhibitors–current status and future prospects. Eur J Med Chem. 2001; 36: 109-26.

[7] Habeeb AG, Rao P, Knaus ED. Design and Synthesis of 4,5-Diphenyl-4-isoxazolines: Novel Inhibitors of Cyclooxygenase-2 with Analgesic and Antiinlammatory Activity. J Med Chem. 2001; 44: 2921-7.

[8] Yadav A, Mohite S, Magdum C. Synthesis, Characterization and Biological Evaluation of Some Novel 1,3,4-Oxadiazole Derivatives as Potential Anticancer Agents. Int. j. sci. res. sci. technol. 2020; 7(2): 275-282.

[9] Yadav A, Mohite S. Design, synthesis and characterization of some novel benzamide derivatives and it's pharmacological screening. Int. j. sci. res. sci. technol. 2020; 7(2), 68-74.

[10] Chitruk A, Yadav A Rode P, Mohite S, Magdum C. Microwave assisted synthesis, antimicrobial and anti-inflammatory potential of some novel 1,2,4-triazole derivatives. Int. j. sci. res. sci. technol. 2020; 7(4): 360-367.

[11] Ghumrel S, Sawant M, Jadhav V, Kadam V, Sonawane N, Ramaiya M. Assessment of *in-vitro* anti-inflammatory activity of *cynodondactylon*and acyclovir showing synergistic effect by albumin denaturation and membrane stabilization assay. Mod Appro Drug Des. 2017; 1(2): 1-5.

[12] Mirke N, Shelke P, Malavdkar P, Jagtap P. *In vitro* protein denaturation inhibition assay of *eucalyptus globulus*and *glycine max* for potential anti-inflammatory activity. Innov Pharm Pharmacother. 2020;8(2):28-31.