

**SYNTHESIS AND CHARACTERIZATION OF 1,3,4- OXADIAZOLE DERIVATIVES:
DERIVED FROM IBUPROFEN**

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Article Received on 13/11/2018

Article Revised on 05/12/2018

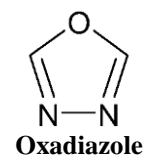
Article Accepted on 26/12/2018

ABSTRACT

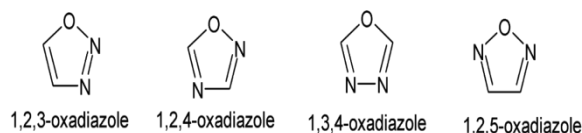
The intent of the study is to broaden derivatives of 1,3,4- oxadiazole. Oxadiazole is a five-member heterocyclic ring which is a resourceful lead compound for crafty potent bioactive agents. Heterocyclic compounds have been an attention-grabbing area for the study of the synthesis and biological activity of novel oxadiazole derivatives for a long time. One of these compounds 1,3,4-Oxadiazole is a resourceful heterocyclic nucleus is a novel molecule which attracts the medicinal chemist to search a new therapeutic molecule. Oxadiazole derivatives were synthesized as per the literature methods, the completion of the reaction will be ascertained by thin layer chromatography. In the present work of synthesis of the oxadiazole derivatives of ibuprofen was to convert its ethyl ester (I) by esterification. This ester was reacted with hydrazine hydrate to give Carbohydrazide of Ibuprofen (II). This Carbohydrazide was treated with CS₂ and KOH in ethanol and it gives 5-{1-[4-(2-methyl propyl) phenyl]ethyl}-1,3,4-oxadiazole-2(3*H*)-thione (III). 5-{1-[4-(2-methyl propyl)phenyl]ethyl}-1,3,4-oxadiazole-2(3*H*)-thione with various 1°/2° amines and formaldehyde in ethanol 1,3,4-oxadiazole derivatives. The purity of the synthesized compounds was confirmed by melting point and TLC on silica gel G. The structure of synthesized compounds was characterized by spectral studies.

KEYWORDS: 1,3,4- oxadiazole, NMR, MP, Ibuprofen, Esterification.**INTRODUCTION**

Chemical pathway as a source of active pharmaceutical ingredients (API) is in use since the development of medicinal chemistry. Synthesis of API is the mainstay of the medicament as helical sources are not sufficient to cater to the need of the growing population. In heterocyclic compounds, the rings are not completely composed of carbon atoms. There may be present one or more heteroatoms in rings. The heterocyclic system of drugs generally has certain substitutions & fictionalization. Heterocyclic compounds are those compounds whose ring contain beside carbon, one or more atoms of another element. The non-carbon atoms in such ring are adopted as heteroatoms. The common heteroatoms are nitrogen, oxygen & sulfur. The important of heterocyclic compounds are present in most of the members of vitamin B complex, antibiotics, alkaloids, amino acids, drugs, dyes, enzyme & genetic material, DNA and having therapeutics use. Heterocyclic compounds having five-member rings containing two carbon atoms, one oxygen, two nitrogen & two double bonds such as oxadiazole.^[1]



The oxadiazole medicate was the main successful chemotherapeutics specialists to be utilized efficiently for the counteractive action and cure of bacterial contamination in individuals. The series of these molecules might be as diverse as 1,2,4-oxadiazole, 1,2,3 oxadiazole, 1,2,5 oxadiazole, 1,3,4 oxadiazole.^[2]



Non-steroidal calming drugs (NSAIDs) are the most normally recommended solutions on the planet. They are utilized for the treatment of suffering, fever, and inflammation, especially joint pain. The expression "non-steroidal" is utilized to recognize these medications from steroids, which, among a wide scope of different impacts, have a comparative eicosanoid-discouraging, mitigating activity. As analgesics, NSAIDs are non-

opiate, NSAIDs are typically shown for the treatment of intense or unending conditions where torment and inflammation are available.

1,3,4-oxadiazole

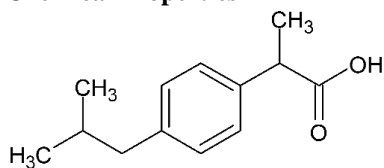
Among the wide variety of heterocycles that have been exposed to developing pharmaceutical important molecules. In the family of heterocyclic compounds, Nitrogen containing heterocycle with oxygen atom i.e. 1,3,4-oxadiazole considered to be an important class of compounds in medicinal chemistry because of their diversified biological application.

1,3,4-oxadiazole derivatives have played a vital role in medicinal chemistry. The 1,3,4-oxadiazole derivatives have been found to exhibit diverse biological activities such as antimicrobial,^[3] anti-HIV,^[4] anthelmintic,^[5] anticancer,^[6] anticonvulsant,^[7] antiviral,^[8] antimalarial,^[9] hypoglycemic,^[10] anti-inflammatory,^[11] analgesic,^[12] antitubercular,^[13] and other biological properties such as genotoxic studies and lipid peroxidation inhibitor.^[14]

Existing NSAIDs causes above mentioned side effects there is a need for exploring newer NSAIDs which are free from these side effects and better potency. Hence the search for a newer and safer anti-inflammatory agent is still very active and essential. In continuation of our work^[15-16] on newer heterocyclic compounds as an anti-inflammatory agent now we have synthesized and characterization 1,3,4-oxadiazole derivatives derived from ibuprofen.

Ibuprofen

Physical / Chemical Properties



Formula: C₁₃H₁₈O₂

Molecular Mass: 206.29 g/mol

The onset of action: 30 min.

Biological half-life: 1.3-3 hr

Metabolism: Liver

Chirality: A Racemic mixture

Melting Point: 76°C

Boiling Point: 157°C

Solubility: Water at 20°C.^[17]

Ibuprofen has been rated as the safest conventional NSAIDs by the spontaneous adverse drug reaction reporting system in the UK. Ibuprofen (400 mg) has been found equally or more efficacious than a combination of Ibuprofen (650 mg) + codeine (60 mg) in relieving dental surgery pain.

Concurrent treatment with ibuprofen has been found to prevent irreversible COX inhibition by low dose Ibuprofen.

Thus, it may antagonize the anti-platelet and cardioprotective effect of low dose Ibuprofen.

Dose: 400-600 mg / day

10 mg / kg (TDS)

Plasma t_{1/2}: 2 hr.^[18]

MATERIAL AND METHODS

Chemicals

Chemicals used in this synthetic work were purchased from Advance Scientific Center Bhopal and Indian Scientific Center Bhopal. They were Carbon disulfide which is used Mfd. in Loba Chemie Laboratory Reagent & Fine Chemicals, Hydrazine hydrate (99%) from Ran Kem RFCL Limited, Ibuprofen from Sunchem India and different secondary amine. All others chemicals of LR Grade from Fisher Scientific Qualigens Fine Chemicals Mumbai.

Instruments

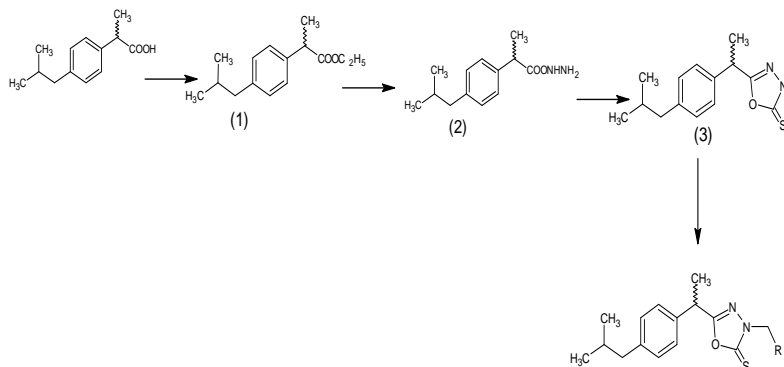
Melting points of the synthesized compound were determined using Thiele tube and Thermionic melting point apparatus and are uncorrected. The ¹HNMR was recorded on Bruker Avance II NMR 300 MHz instruments using appropriated solvent and TMS as an internal standard, chemical shifts are expressed as δ values (ppm) in Anusanadhan laboratory Indor.

Chemical Synthesis

The title compounds were synthesized as given in the scheme. Ibuprofen was refluxed with absolute ethanol in presence of Conc.

Sulphuric acid gave ester(I), this on reaction with hydrazine hydrate (99%) in absolute ethanol gave carbohydrazide (II), this compound was refluxed with CS₂ in ethanol in presence of KOH gave 5-{1-[4-(2-methyl propyl)phenyl]ethyl}-1,3,4-oxadiazole-2-thiol (III). The title compound (IVa-e) were synthesized by reaction of 5-{1-[4-(2-methyl propyl)phenyl]ethyl}-1,3,4-oxadiazole-2(3H)-thione. with various primary/secondary amine in presence of formaldehyde.

Scheme 1



RESULT AND DISCUSSION

Synthesis

The sequence of the reaction employed for the synthesis of the title compound is outlined in Scheme 1. The physicochemical data and spectral data of the different synthesized compounds are given in Table 1-2.

The Ibuprofen was converted to its ethyl esters (I) by esterification. The purity of the compound was confirmed by melting point, TLC and structure were confirmed by a chemical test and $^1\text{H-NMR}$ spectral data. This was further supported by $^1\text{H-NMR}$ spectral data with δ value at 1.84 (7H, CH₃) 2.44 (2H, CH₂) 4.14 (3H, CH) 7.21 (4H, Ar) reveals the confirmation of structure.

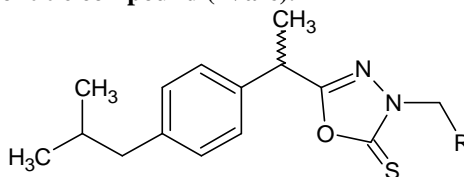
This ethyl ester was reacted with hydrazine hydrate, gave Carbohydrazide (II). The purity of these compound was confirmed by melting point, TLC and structure were confirmed by $^1\text{H-NMR}$ spectral data. This was supported by $^1\text{H-NMR}$ spectral data with δ value at 1.36(s,4H,

CH₃) 2.44(2H, CH₃) 7.06-7.22 (m,4H, Ar) reveals the confirmation of structure.

This Carbohydrazide was treated with CS₂/KOH in ethanol gave 5-{1-[4-(2-methyl propyl)phenyl]ethyl}-1,3,4-oxadiazole-2(3H)-thione (III). The purity of the compound was confirmed by melting point, TLC and structure were confirmed by $^1\text{H-NMR}$ spectral data. This was supported by $^1\text{H-NMR}$ spectral data with δ value at 1.84 (s,4H, CH₃) 2.44 (d, 2H, CH₂) 5.29 (t, 1H, N-H) 7.03-7.12 (m, 4H, Ar) reveals the confirmation of structure.

Treatment of 5-{1-[4-(2-methyl propyl)phenyl]ethyl}-1,3,4-oxadiazole-2(3H)-thione (III). With various 2°/1° amines in presence of formaldehyde gave the title compounds IV a-e. The purity of these compounds was assessed by melting point, TLC and Structure were confirmed by $^1\text{H-NMR}$. Physicochemical data and spectral data of the different synthesized title compounds (IV a-e) are given in Table 1-2.

Table No.1: Physico-chemical data of title compound (IV a-e).



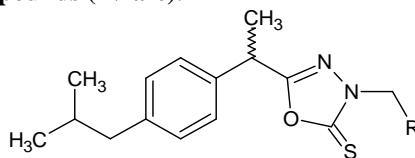
Compound	R	M.P.(C)	% Of Yield	Rf*	Molecular Formula
IV a		112-114	78.2	0.35	C ₁₆ H ₂₁ N ₃ O ₄ S
IV b		83-85	72.1	0.31	C ₁₇ H ₂₃ N ₃ O ₃ S
IV c		165-167	79.8	0.42	C ₁₀ H ₁₄ N ₂
IV d		76-78	65.9	0.32	C ₁₆ H ₂₃ N ₃ O ₃ S
IV e		192-194	70.6	0.43	C ₂₄ H ₂₃ N ₃ O ₃ S

All compound was recrystallized by ethanol.

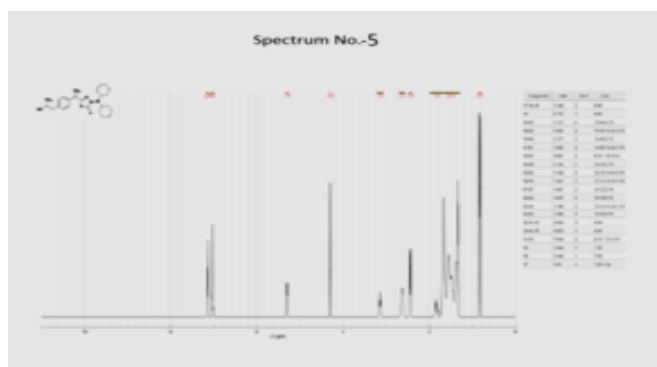
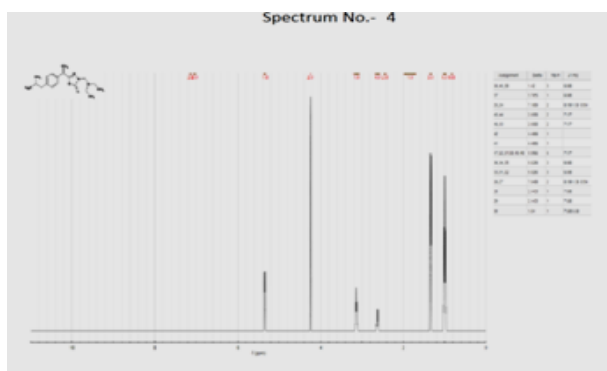
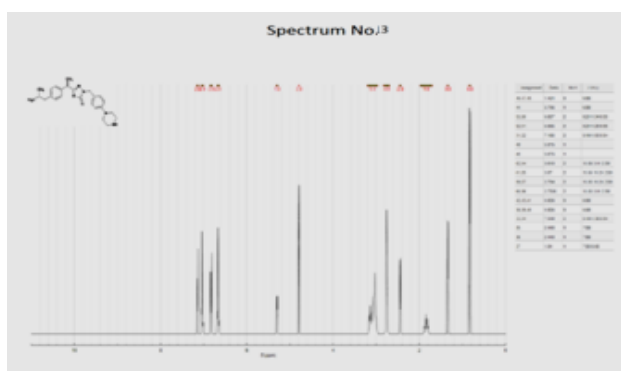
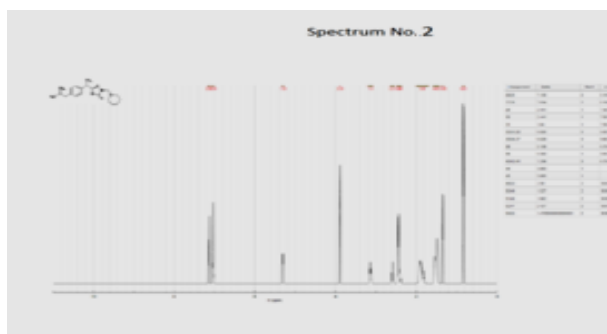
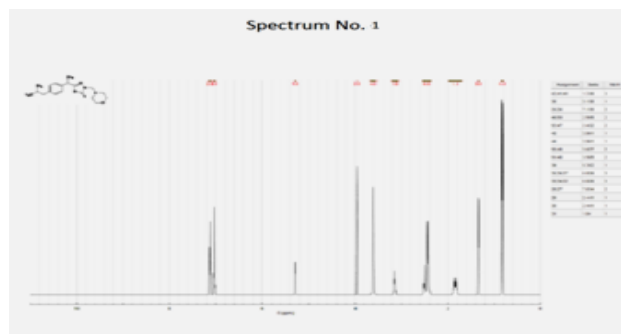
Stationary phase* - silica gel G.

Mobile phase – Diethyl ether: ethyl acetate (5:5), Visualizing agent - iodine vapors

Table No. 2: Spectral data of the compounds (IV a-e).



Compound	R	¹ H NMR spectra (CDCl ₃ , δ, ppm)
IV a		7.13(m, 7H, Ar-H), 5.30(s,1H, N-H), 3.96(s,2H,N-CH ₂ -N), 3.96-3.62 (s, 2H,CH ₂ of ibuprofen),3.58(t,4H,morpholine),2.43(t,4H, morpholine). Spectrum No-01.
IV b		7.13-7.03 (m,7H,Ar-H),5.30 (s,1H,N-H),3.89 (s,2H,N-CH ₂ -N), 3.13(s,2H,CH ₂ of Ibuprofen),2.59(t,2H,Piperidine) 2.44-2.42(m,4H,Piperidine). Spectrum No-2
IV c		7.18-7.04(m,7H,Ar-H),6.83-6.66 (s,1H,N-H), 5.07 (s, 2H,N-CH ₂ -N),3.70 (s,2H,CH ₂ of Ibuprofen),2.75 (t,4H,1-phenyl piperazin), 1.84(m,2H,1-phenylpiperazin), 1.42(m,4H,1-phenylpiperazin)Spectrum No- 3
IV d		7.18-7.04(m,7H,Ar-H),4.40 (s,1H,N-H),3.70 (s,2H,N-CH ₂ -N),2.65(s,2H,CH ₂ of Ibuprofen),2.44 (m,4H,CH ₂ ,CH ₂), 1.84-1.42(t,6H,CH ₃ ,CH ₃). Spectrum No-4
IV e		7.04-6.99(m,17H,Ar-H),3.72(s,1H,N-H), 3.16 (s,2H,N,CH ₂ ,N),2.44(s, 2H,CH ₂ of Ibuprofen)1.84-1.72 (m,2H,CH ₂ ,CH ₂), 1.48-1.37 (t,6H,CH ₃ ,CH ₃). Spectrum No-5



CONCLUSION

An oversized figure of the non-steroidal anti-inflammatory drug is undertaken clinically to care for acute and frequent provocative disorders. Non-steroidal anti-inflammatory drugs are the generally normally prescribed pills in the world. They are old in dealing with pain, fever and inflammation, predominantly arthritis. The investigation involves the synthesis of 1,3,4-oxadiazole derivatives from NSAIDs drug ibuprofen.

Ibuprofen was converted to its ethyl ester (I) by esterification. This ester was reacted with hydrazine hydrate to give Carbohydrazide of Ibuprofen (II). This Carbohydrazide was treated with CS₂ and KOH in ethanol to give 5-{1-[4-(2-methyl propyl)phenyl]ethyl}-1,3,4-oxadiazole-2(3*H*)-thione (III). 5-{1-[4-(2-methyl propyl) phenyl] ethyl}-1,3,4-oxadiazole-2(3*H*)-thione with various 1°/2° amines and formaldehyde in ethanol 1,3,4-oxadiazole derivatives. The purity of the synthesized compounds was confirmed by melting point and TLC on silica gel G. The structures of synthesized compounds were characterized by spectral studies.

The structure (III) was ascertained by detailed ¹HNMR spectral data with δ value at 1.84(s, 1H, NH of oxadiazole), 2.44 (m, 7H, Ar-H of Ibuprofen), 5.29 (s, 1H, N-H of Ibuprofen), 7.03-7.12 (s, 2H, CH₂). Structure of the title compounds (IV a-e) was ascertained by detailed ¹HNMR spectral data. The presence of multiplet between δ 7.03 to 5.30 of Ar-H of Ibuprofen, singlet between 6.58 to 4.40 of N-H of Ibuprofen, singlet between 5.08-3.16 of CH₂ (H-CH₂-N), singlet between 3.96 to 2.42 of CH₂ of Ibuprofen and 3.16 to 1.37 of various amines reveals confirmation of structures.

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

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