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Title: **Synthesis and Pharmacological Evaluation of Substituted Oxadiazlole Derivatives of Ibuprofen**

Shimaju Pandey[1], Versha Percha[2] and Yogita Dobhal [1*]

1 Department of Pharmaceutical Sciences, Sardar Bhagwan Singh PG Institute of Biomedical Sciences & Research, Balawala, Dehradun, Uttarakhand, India.

2 Department of Chemistry, Sardar Bhagwan Singh PG Institute of Biomedical Sciences & Research, Balawala, Dehradun, Uttarakhand, India.

Corresponding Author:

Yogita Dobhal

Email: **yogita_sharma05@rediffmail.com**

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Abstract:

In the present work of synthesis of the oxadiazole derivatives of ibuprofen, first of all the ibuprofen was converted into its conversion to hydrazide. The synthesized hydrazide of ibuprofen was treated with $POCl_3$ and selected (aliphatic and aromatic) acids to form the five final compounds viz. A, B, C, D, E. All compounds were characterized on the basis of IR and ^{1H}NMR spectral data. The 5 analogues were synthesized in order to ascertain the effect of substituted oxadiazole on anti-inflammatory efficacy, which showed good anti-inflammatory activity as compared to parent drug. Furthermore, the SAR studies of the derivatives were important to correlate the pharmacological activity with the proposed new moiety

Keywords: oxadiazole, Ibuprofen, Anti-inflammatory, Characterization, SAR.

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1. Introduction:

NSAIDs are widely used in treatment of various inflammatory disorders. However, long term NSAIDs use has been associated with gastro intestinal ulceration bleeding and nephrotoxicity [1, 2]. These reactions are in both severity and frequency from relatively mild to the more serious and potentially life treating such as gastrointestinal ulceration and hemorrhage [3-5]. The literature survey reveals that several leads aiming at the discovery of new anti-inflammatory has been pushed. The synthetic studies include work on various aryl and hetero aryl alkanoic acid, other acids and their derivatives. A variety of heterocyclic systems, in isolation and fused with other system, have been synthesized, oxadiazole being one of them. NSAIDs are widely used in treatment of various inflammatory disorders such as osteoarthritis, spondylities etc. But they cause adverse effects like gastrointestinal disturbances, bleeding, and nephrotoxicity due to presence of free carboxylic group in the molecule [1, 6]. Thus in the present study, the carboxylic acid group of ibuprofen was temporarily masked by converting to substituted oxadiazole derivatives to impart good anti-inflammatory activity.

Experimental:

Reagents and solvents

Dry methanol, concentrated sulphuric acid, carbon tetrachloride, anhydrous sodium sulphate, hydrazine hydrate, chlorofor, absolute ethanol, 2,4-dichlorobenzoic acid, propionic acid, acetic acid, isobutyric acid, 2-methoxy benzoic acid, petroleum ether, ethyl acetate. Most of the reagents and solvents used are of L.R> grade, manufactured by Rankem, Loba and Himedia.

The purity of compounds was monitored by Thin Layer Chromatography (TLC) using silica gel G as stationary phase and chloroform: methanol (95:5) was used as solvent system. The spots were observed in iodine vapours.

General procedure for synthesis of compounds

The general procedure for synthesis of compounds takes place in following steps [7]

Step 1 - Synthesis of ester

Step 2 - Synthesis of hydrazide

Step 3- Synthesis of oxadiazole derivatives of ibuprofen

Synthesis of ester of ibuprofen

Step 1: Synthesis of Ester

20 gram of drug, 65ml of dry methanol and 2.85 ml of concentrated sulphuric acid was placed in a 250 ml round bottom flask. Reflux mixture

under anhydrous condition for 6 hrs. The mixture was monitored by TLC, using petroleum ether:ethyl acetate as a solvent. On completion of reaction mixture excess of alchol was distilled off on water bath and allowed to cool. Poured the residue into 250 ml separating funnel and extracted with 10-15 ml of carbon tetrachloride, washed with few ml of strong solution of sodiumhydrogen carbonate till all free acids are removed and no further evaluation of CO2 occur and finally dried over magnesium sulphate. Filtered through small flutted filter paper and collected pure ester.

Step 2-Synthesis of hydrazide of ibuprofen methyl ester

8 ml of ester 2-(4-isobutyl phenyl) propionate and 2.63ml of hydrazine hydrate were placed in 100ml round bottom flask,containing sufficient amount of dry methanol.Refluxed the mixture for 6 hrs under anhydrous condition.The reaction was monitored by T.L.C using chloroform, methanol(95:5) as solvent system. Spots were observed in iodine vapours. After completion of reaction, excess amount of alcohol was distilled off on a waterbath and the solution was kept in freezer until white crystals of hydrazide were obtained. Obtained white crystals of hydrazide were collected, dried and recrystallized from ethyl alcohol and yield was obtained 3 gm

Step 3-Synthesis of substituted oxadiazole derivatives of ibuprofen

Step 3 (A). 2-(1-(4-isobutylphenyl)ethyl)-5-methyl- 1,3,4- oxadiazole

The mixture of hydrazide and acetic acid in phosphorus oxychloride(5ml) was refluxed for 8-10 hrs.The content was cooled and poured onto crushed ice made alkaline by sodium carbonate solution(5%) and the resulting solid was filtered,dried and recrystallized from a mixture of ethanol: DMF.

IR. Vmax cm=3100(C-H aromatic),2940(C-H aliphatic),1615(C=C aromatic),1110(C-O stretching); 1H NMR CDCL3 (300 MHz) δ:0.82 (d,6H,J=6Hz(CH3)2 CH), 1.42 (3H,d,J=8Hz CH3CH, 2.09 (m,1H,(CH3)2CHCH2), 2.15 (S,3H, CH3), 2.32 (m,2H (CH3)2CHCH2), 2.48 (S,3H CH3CH), 3.70 (1H,q, CH3CH), 7.83(m,2H, ArH,5.,6.), 7.48 (m,4H ArH), 7.92 (S,1H,ArH 5).

Step 3 (B). 2-ethyl-5-(1-(4-isobutylphenyl) ethyl) - 1,3,4- oxadiazole

The mixture of hydrazide and propionic acid in phosphorus oxychloride(5ml) was refluxed for 8-10 hrs.The content was cooled and poured onto crushed ice made alkaline by sodium carbonate solution(5%) and the resulting solid was filtered, dried and recrystallized from a

mixture of ethanol: DMF.

IR.V_{max} cm=3100(C-H aromatic),2940(C-H aliphatic),1615(C=C aromatic),1110(C-O stretching); $_1$H NMR $CDCL_3$ (300 MHz) δ:0.82 (d,6H,J=6Hz$(CH_3)_2$ CH), 1.42 (3H,d,J=8Hz CH_3CH, 1.92 (τ,3H,J=2Hz CH_2 CH_3), 2.09 (m,1H,$(CH_3)_2CHCH_2$), 2.18 (q,2H CH_2CH_3), 2.32 (m,2H $(CH_3)_2CHCH_2$), 2.48 (δ,3H CH_3CH), 3.70 (1H,q, CH_3CH), 7.83 (m,2H,ArH,5,6), 7.48 (m,4H ArH), 7.92 (S,1H,ArH 5).

Step 3 (C). 2-(1-(4-isobutylphenyl) ethyl)-5-isopropyl- 1,3,4- oxadiazole

The mixture of hydrazide and isobutyric acid in phosphorus oxychloride(5ml) was refluxed for 8-10 hrs.The content was cooled and poured onto crushed ice made alkaline by sodium carbonate solution(5%) and the resulting solid was filtered, dried and recrystallized from a mixture of ethanol: DMF.

IR.V_{max} cm=3100(C-H aromatic),2940(C-H aliphatic),1615(C=C aromatic),1110(C-O stretching); $_1$H NMR $CDCL_3$ (300 MHz) δ:0.82 (d,6H,J=6Hz$(CH_3)_2$ CH), 1.42 (3H,d,J=8Hz CH_3CH, 1.83 (d,6H CH-$(CH_3)_2$), 1.93 (q,m,1H, $CH(CH_3)_2$) 2.09 (m,1H,$(CH_3)_2CHCH_2$), 2.32 (m,2H $(CH_3)_2CHCH_2$), 2.48 (S,3H CH_3CH), 3.70(1H,q, CH_3CH), 7.83 (m,2H,ArH,5.,6.), 7.48 (m,4H ArH), 7.92(S,1H,ArH 5).

Step 3 (D). 2-(1-(4-isobutylphenyl)ethyl)-5-(2-methoxyphenyl)- 1,3,4- oxadiazole (3D)

The mixture of hydrazide and 2-methoxybenzoic acid in phosphorus oxychloride(5ml) was refluxed for 8-10 hrs. The content was cooled and poured onto crushed ice made alkaline by sodium carbonate solution (5%) and the resulting solid was filtered, dried and recrystallized from a mixture of ethanol: DMF.

IR.V_{max} cm=3100(C-H aromatic),2940(C-H aliphatic),1615(C=C aromatic),1110(C-O stretching); $_1$H NMR $CDCL_3$ (300 MHz) δ:0.82 (d,6H, J=6Hz $(CH_3)_2$ CH), 1.42(3H,d,J=8Hz CH_3CH, 2.09 (m,1H,$(CH_3)_2CHCH_2$), 2.32 (m,2H $(CH_3)_2CHCH_2$), 2.48 (S,3H CH_3CH), 3.70 (1H,q, CH_3CH), 3.86 (S,3H OMe), 7.48 (m,4h ArH), 7.60 (m,4H ArH 3.,4.,5.,6.)

Step 3 (E). 2-(2, 4-dichlorophenyl)-5-(1-(4-isobutylphenyl)ethyl)-1,3,4- oxadiazole

The mixture of hydrazide and 2,4-dichlorobenzoic acid in phosphorus oxychloride(5ml) was refluxed for 8-10 hrs.The content was cooled and poured onto crushed ice made alkaline by sodium carbonate solution(5%) and the resulting solid was filtered,dried and recrystallized from a mixture of ethanol: DMF.

IR. Vmax cm=3100(C-H aromatic),2940(C-H aliphatic),1615(C=C aromatic),1110(C-O stretching); 1H NMR CDCL3 (300 MHz) δ:0.82(d,6H,J=6Hz(CH3)2 CH), 1.42(3H,d,J=8Hz CH3CH, 2.09(m,1H,(CH3)2CHCH2), 2.32(m,2H (CH3)2CHCH2), 2.48(S,3H CH3CH), 3.70(1H,q, CH3CH), 7.83(m,2H,ArH,5.,6.), 7.48(m,4H ArH), 7.92(S,1H,ArH 5).

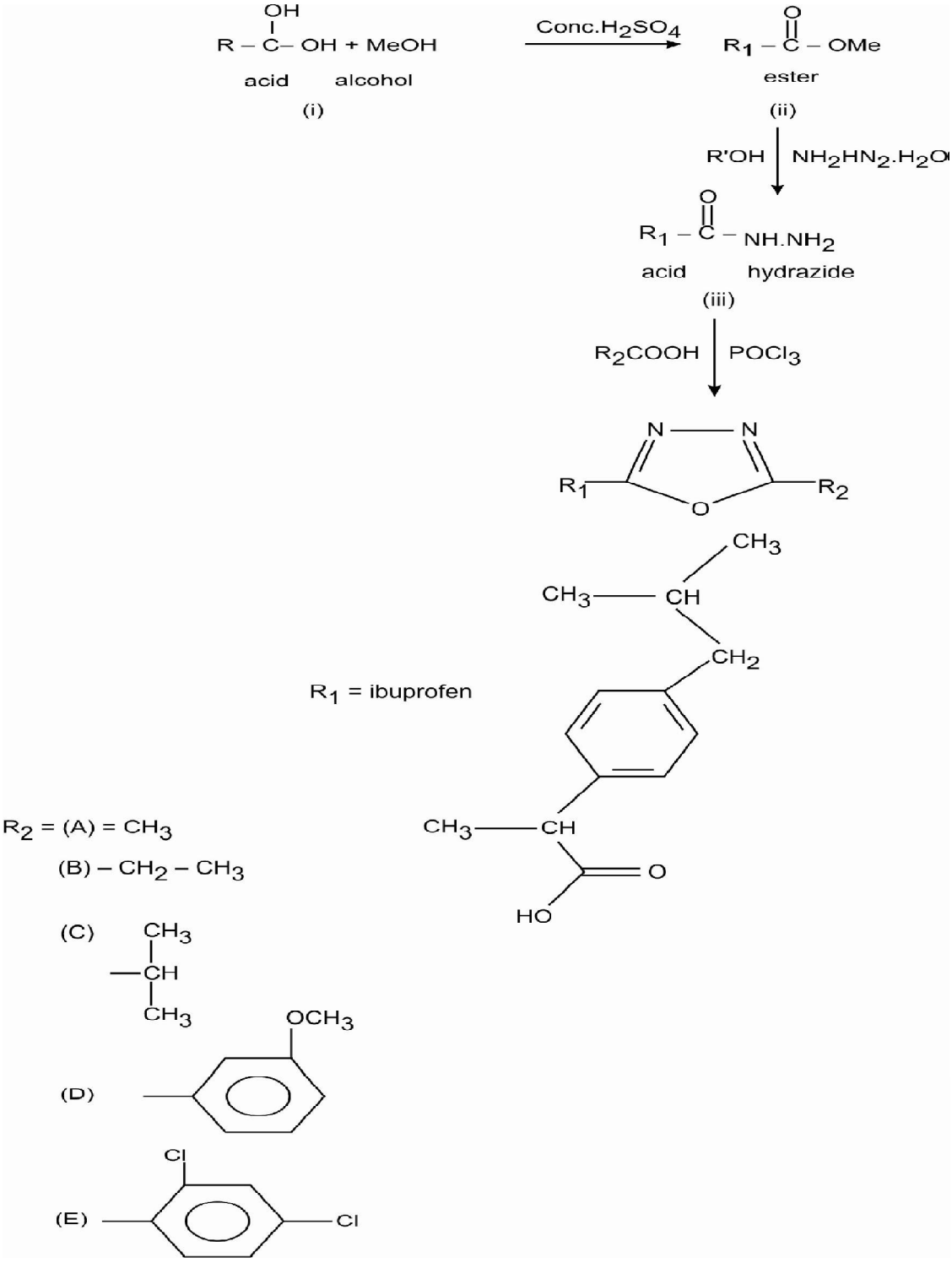
Pharmacological study

The animals were weighed and numbered them. A mark was made on the right hind paw just beyond tibio tarsal junction, so that every time the paw was dipped in the mercury (Hg) column up to the fixed mark to ensure constant paw volume. The initial volume was noted of each rat by mercury (Hg) displacement method.0.1% suspension of carrageenan in sodium C.M.C was prepared. The volume of 0.1% was injected into the sub-planter region of left hind paw of each rat. The standard drug (50mg/kg b.wt) and the test drugs at dose level of (50mg/kg b.wt) were administered orally by gavages ,half hour prior to carrageenan administration to the animals. After 2hrs of carrageenan administration, the paw volume of control and drug treated rats was recorded by Plethysmograph. Edema was calculated as the difference between the two measurements. Inhibition of swelling was determined by the comparing the change in hind paw volume in compounds and vehicle-treatedmrats. The anti-inflammatory activity was determined as the percentage of inhibition of inflammation after. It was induced by carrageenan. The percentage inhibition was calculated by using the formula:

$$\% \text{ inhibition} = \frac{\text{Mean paw inflammation of control - Mean paw inflammation of test}}{\text{Mean paw inflammation of control}} \times 100$$

Results and Discussion:

Schematic Representation



Synthesis of Substituted Oxadiazlole Derivatives of Ibuprofen:

Various oxadiazole were synthesized and characterized by TLC. All compounds were characterized on the basis of IR and HNMR spectral data.

STEP 1:- Synthesis of ester of ibuprofen

The ester was synthesized from acid by refluxing ibuprofen with dry alcohol and few ml. of **H_2SO_4** under the anhydrous condition for 6 hrs. Reaction monitored by T.L.C. on completion of reaction mixture excess of alcohol was distilled of and allowed to cool. Extracted with carbon tetra chloride and washed with strong solution of sodium hydrogen carbonate. Dried

over anhydrous magnesium sulphate. The ester of ibuprofen was obtained, which was used further.

STEP 2:- Synthesis of hydrazide of ibuprofen

The equimolar quantity of ester and hydrazine hydrate was refluxed for 6 hrs. with adding of methanol. Evaporated of excess of alcohol and poured solution into ice cold water. The solid mass was obtained, purified that with ethyl alcohol.

STEP 3 :- Synthesis of substituted oxadiazole derivatives

A mixture of hydrazide and different substituted acids was refluxed for 10 hrs. in **POCl**3 (10ml.). The contend was cooled and poured onto crushed ice made alkaline by sodium carbonate solution (5%) and resulting solids was filtered, dried and recrystalized from a mixture of ethanol.

Anti-inflammatory activity

The anti-inflammatory activity of ibuprofen and its derivative was measured by their ability to inhibit carrageenan induced paw swelling in rats. From table no. 8 it is cleared that ibuprofen, the reference drug was found to inhibit 76.64% of edema produced by injecting 0.01%(w/v) of carrageenan after 2hrs. The result demonstrated that all derivatives of ibuprofen, compound A,B,C,D,E have anti-inflammatory activity showing 83.1%, 70.7%, 59.4%, 68.8%, 85% inhibition respectively. It was observed that derivative compound A, B, C, D have lower and compound E have higher (85%) activity than parent drug ibuprofen (Table 1).

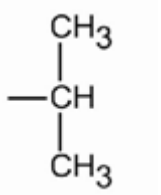
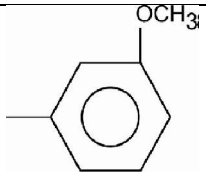
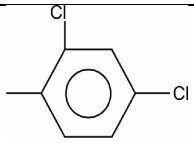
S. No	Compounds	No. of animals	Mean Inflammation (ml)+S.D	%Inhibition of Inflammation
1	**Control**	**5**	0.616±0.139	**-**
2	**Ibuprofen**	**5**	0.144±0.138	76.64%
3	**A**	**5**	0.104±0.071	83.1%
4	**B**	**5**	0.180±0.103	70.7%
5	**C**	**5**	0.256±0.153	59.4%
6	**D**	**5**	0.192±0.088	68.8%
7	**E**	**5**	0.092±0.049	**85%**

Table 1. Effect of oxadiazole derivatives on carrageenan induced paw oedema

Preliminary Structure Activity Relationship of Substituted Oxadiazole Derivatives of Ibuprofen:

The structure activity relationship studies play an important role in traditional drug-design. The synthesis of new structures and their biological evaluation are correlated which can be useful in proposing hypothetical structures for target binding sites and receptor topological features. The analogues of ibuprofen were synthesized and biologically evaluated for establishing preliminary SAR insight. Ibuprofen is a potent anti-inflammatory agent. Chemically it is a derivative of propionic acid with phenyl isobutyl functionality. The 5 analogues were synthesized in order to ascertain the effect of substituted oxadiazole on anti-inflammatory efficacy. The structure of substituted oxadiazole derivative of ibuprofen is as follows (Table 2).

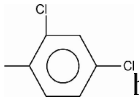
Table 2. The structural variations and their biological activities

Compounds	Structural Variations (R)	Biological Activity
Ibuprofen	-	76.6%
A	-CH3	83.1%
B	$-CH_2-CH_3$	70.7%
C		59.4%
D		68.8%
E		85%

Among the series COOH group of Ibuprofen is replaced by oxadiazole moiety substituted by methyl,ethyl and isopropyl group in aliphatic series at and by 2,4-dichloro aryl and 2-methoxyaryl group in aromatic series at position 2 of oxadiazole moiety. It was observed when substituted by 2-methyl oxadiazole inflammation was inhibited upto 83% even more than standard ibuprofen (76.6%) followed by ethyl oxadiazole (70.7%) and isopropyl oxadiazole (59.4%) among aromatic series substituted by[2,4-dichloro aryl] substituted oxadiazole (85%) replacing COOH group of ibuprofen showed much more anti-inflammatory potential followed followed by 2-methyl,2-methoxyaryl,2- ethyl and 2-isopropyl substitution. Further work on this drug could lead to development of new anti-inflammatory drug.

Conclusion:

The substituted oxadiazole were prepared by condensation of hydrazide with different acid using POCL3 as solvent by the help synthetic method as outlined in scheme. All the compounds prepared were adequately

characterized by their elemental analysis, spectral (IR, ^{1H}NMR) data. The compounds were screened for their anti-inflammatory activity by hind paw method. The standard drug ibuprofen (50mg/kg body weight) and test drugs (50mg/kg body weight) were used. In ibuprofen, the COOH group is replaced by substituted oxadiazole derivatives which showed percentage inhibition (83.1, 70.7, 59.4, 68.8, 85) comparable to the parent drug (76). Thus, replacing COOH group of NSAIDS by substituted oxadiazole increased percentage inhibition of inflammation. Thus it could be concluded from the present study that out of forming all screened compounds, compound E having group  have enhanced activity which is also confirmed by structure activity relationship studies among the series. Further work on this drug could lead to development of new anti-inflammatory drug.

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