Frontiers in Health Informatics
ISSN-Online: 2676-7104
www.healthinformaticsjournal.com
2024; Vol 13: Issue 8 Open Ac

Synthesis of Some Novel Derivatives of 1,3,4-Oxadiazole, as Analgesic and Anti-inflammatory Agents

Mrs Amrita Pathak [1] Ms. Neha Sahu[2] Vipin Kumar Tiwari[3], Ms. Khushi Chouksey[4], Ram C Dhakar[5], Sunil Kumar Prajapati[6], Deepak Kumar Jain[7*]

[1,2]Guru Ramdas Khalsa Institute of Science and Technology Pharmacy Barela Jabalpur, MP, 483001
[3]VNS Group of Institutions Faculty of Pharmacy Neelbud Bhopal, MP, 462044
[4]School of Pharmaceutical Sciences, Scope Global Skills University, Misrod Bhopal, MP, 462047
[5]SRG Hospital and Medical College Jhalawar, Rajasthan, 326001
[6]Institute of Pharmacy, Bundelkhand University, Jhansi UP, 284127
[7*]Chetana College of Pharmacy Infront of New Police Station, RLM Campus, Rithore, Khurai, Dist-Sagar, MP, 470117
Corresponding Author Email: jaindeepak2022@gmail.com

ABSTRACT
1,3,4-Oxadiazole derivatives are found to have a wide range of pharmacological activities and attracting the researchers to work on this nucleus. In this continuation of work a series of novel 1,3,4-oxadiazole derivatives were designed, synthesized and evaluated for analgesic and anti-inflammatory activity. The synthesis of target compounds was performed by reaction of 2-furoic carbohydrazide (FH) or toulic hydrazide (TH) with different carboxylic acid in presence of phosphorous oxy chloride. The synthesized compound Oxa-14 exhibited the most potent analgesic and anti-inflammatory activity.
Keywords: Anti-inflammatory, Analgesic, 1,3,4-oxadiazole, Hydrazide.

Introduction
Non-steroidal anti-inflammatory drugs (NSAIDs) form an important class of widely used therapeutic agents due to their anti-inflammatory, analgesic and antipyretic effects. The pharmacological activity of NSAIDs is related to suppression of prostaglandin biosynthesis by inhibiting the enzyme cyclooxygenase (COX). COX is an endogenous enzyme which catalyzes the conversion of arachidonic acid into prostaglandins and thromboxanes. The enzyme exists in at least two isoforms, COX-1 and COX-2. Although both isoforms catalyze the same biochemical transformation, they are subject to a different expression regulation. COX-1 is a constitutive enzyme and is responsible for the physiological function of prostaglandins (PGs) like maintenance of the integrity of the gastric mucosa and provides adequate vascular homeostasis whereas COX-2 is an inducible enzyme and is expressed only after an inflammatory stimulus [1]. With the chronic use of NSAIDs, one prominent side effect is the formation of gastric ulcers. Heterocyclic compounds containing five-membered oxadiazole nucleus possess a diversity of useful biological effects such as antiedema and anti-inflammatory activities. 1,3,4-Oxadiazoles have anti-inflammatory activity by virtue of dual mechanism, that is, inhibiting both COX/LOs to reduce gastric ulcer formation [2]. Literature studies suggest that direct tissue contact of NSAIDs plays an important role in the production of side effects like gastric upset, irritation, and ulceration [3, 4], and the reported literature confirms that gastrointestinal side effects of NSAIDs such as irritation and GI bleeding are due to the presence of a free carboxylic group in the parent drug [5, 6]. Thus, developing new agents with minimum or without side effects is an extensive research area in the present scenario. Our studies and studies of other researchers [6] have shown that derivatization of the carboxylate function of some NSAIDs resulted in an increased anti-inflammatory activity with a reduced ulcerogenic effect. Hence, it is not irrelevant to speculate that replacing the terminal carboxylic function of NSAIDs by oxadiazole ring, a five membered

heterocyclic nucleus, may enhance the anti-inflammatory activity of such compounds. Hence, by incorporating the oxadiazolyl moiety, we hope to get a better anti-inflammatory molecule.

Material and Methods

1.1. Chemicals

All the starting material, solvents and reagents of analytical grade or high purity of commercially available were purchased from local suppliers, Spectrochem, Merch, Aldrich and Sigma.

1.2. Thin Layer Chromatography (TLC)

The purity of the compounds and the reaction progress of the synthesis were checked by thin layer chromatography. TLC was prepared by 5×20 cm aluminum plate coated with silica gel GF254. The synthesized compounds were identified by UV light or reaction with iodine vapors or KMnO4 either ninhydrin.

1.3. Melting Point

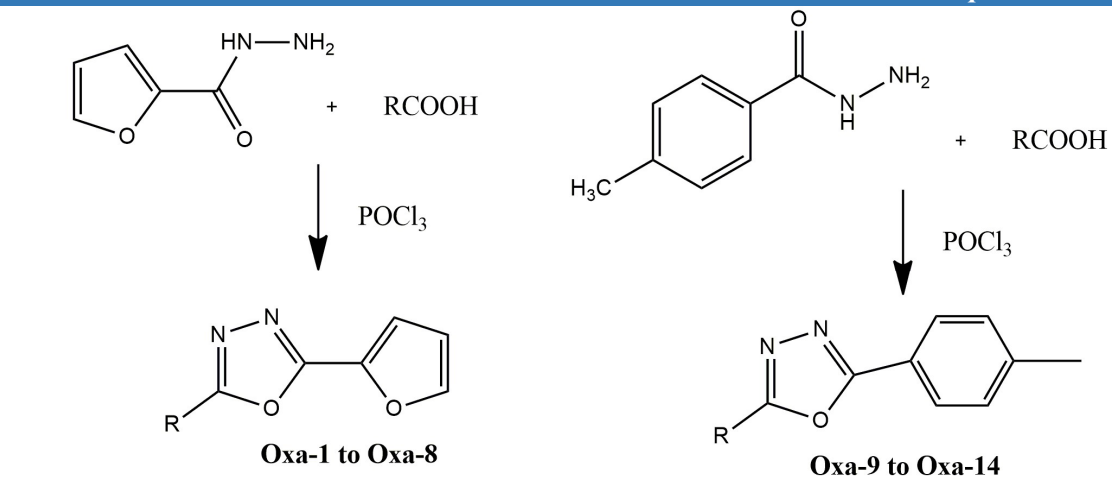
Melting point of the synthesized compounds are uncorrected by using electrothermal and digital labtronics melting point apparatus.

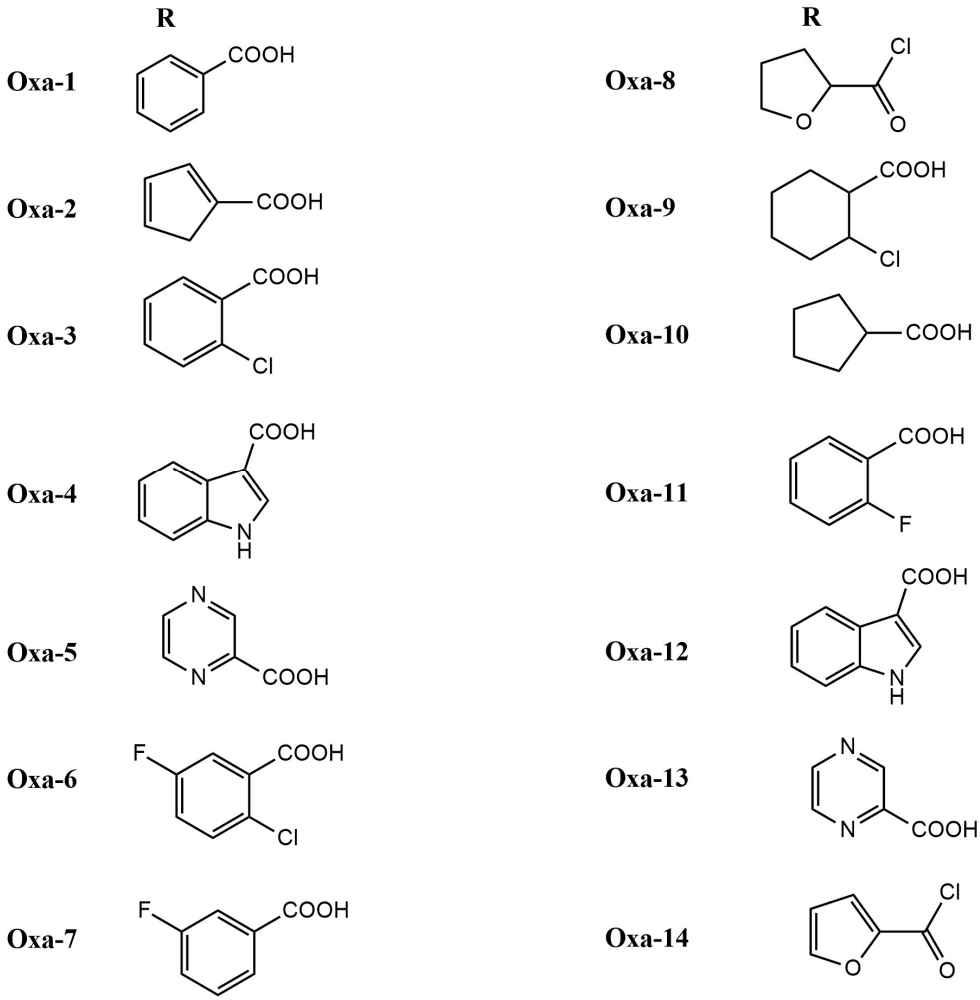
1.4. Spectral Data

Infrared spectral data of all the synthesized compounds were recorded using KBr pellet discs (400-4000 cm-1) on Perkin Elmer instrument Proton NMR and carbon NMR spectra's of all the synthesized compounds were recorded on Bruker 300 either 400 MHz spectrometer using DMSO-d6 or $CDCl_3$ as solvents and tetramethylsilane as internal standard. Chemical shift values are referred as ppm on scale and coupling constant were given in hertz (Hz). The multiplicity of the peaks were appeared as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets), tt (triplet of triplet), multiplet (m), Mass spectra were reported on Therma LCQ Deca XP MAX at 70 eV or Waters UPLC-UPD mass spectrometer.

1.5. General procedure for synthesis of 2,5-disubtituted 1,3,4-oxadiazole derivatives

An equimolar mixture of 2-furoic carbohydrazide (FH) or toulic hydrazide (TH) with different carboxylic acid was refluxed with phosphorous oxy chloride for 2–4 h. Reaction mixture was concentrated through rotatary evaporator, the residue was quenched with ice water, washed with sodium hydrogen carbonate, and the solid separated was filtered off, washed with water and with cold ethanol to give 1,3,4-oxadiazole derivatives as per reported procedure (**Scheme 1**) [7].





Scheme 1: Synthesis of different derivatives of 2,5-disubtituted 1,3,4-oxadiazole derivatives

1.5.1. Synthesis of 2-phenyl-5-(furan-2-yl)-1,3,4-oxadiazole (Oxa-1)

Compound Oxa-1 was synthesized using an equimolar mixture of 2-furoic carbohydrazide (FH) with

cyclohexanoic acid in $POCl_3$ was refluxed with phosphorous oxy chloride (10 vol) for 2–4 h. Reaction mixture was concentrated through rotary evaporator, the residue was quenched with ice water, washed with sodium hydrogen carbonate, and the solid separated was filtered off, washed with water and cold ethanol to give 1,3,4-oxadiazole derivatives as per the reported procedure.

1.5.2. Synthesis of 2-cyclopentyl-5-(furan-2-yl)-1,3,4-oxadiazole (Oxa-2)

Compound Oxa-2 was synthesized similar to the preparation of compound Oxa-1 from starting material furoic hydrazide (FH) and cyclopentonoic acid in $POCl_3$. The reaction was carried out at 110ºC for 3h.

1.5.3. Synthesis of 2-(2-chlorobenzyl)-5-(furan-2-yl)-1,3,4-oxadiazole (Oxa-3)

Compound Oxa-3 was synthesized similar to the preparation of compound Oxa-1from starting material furoic hydrazide (FH) and 2-fluoro phenyl acetic acid in $POCl_3$. The reaction was carried out of 110ºC for 3h.

1.5.4. Synthesis of 2-(indol-3-yl) methyl)-5-(furan-2-yl)-1,3,4-oxadiazole (Oxa-4)

Compound Oxa-4 was synthesized similar to the preparation of compound Oxa-1 from starting material furoic hydrazide (FH) and indole 3- acetic acid in $POCl_3$.

1.5.5. Synthesis of 2-(furan-2-yl)-5-(pyrazin-2-yl)-1,3,4-oxadiazole (Oxa-5)

Compound Oxa-5 was synthesized similar to the preparation of compound Oxa-1 from starting material furoic hydrazide (FH) and pyrazine carboxylic acid in $POCl_3$.

1.5.6. Synthesis of 2-(2-chloro, 5-fluorophenyl)-5-(furan-2-yl)-1,3,4-oxadiazole (Oxa-6)

Compound Oxa-6 was synthesized similar to the preparation of compound Oxa-1 from starting material furoic hydrazide (FH) and 2,5-difluoro benzoic acid in $POCl_3$.

1.5.7. Synthesis of 2-(5-fluorophenyl)-5-(furan-2-yl)-1,3,4-oxadiazole (Oxa-7)

Compound Oxa-7 was synthesized similar to the preparation of compound Oxa-1 from starting material furoic hydrazide (FH) and cyclohexane dicarboxylic acid in $POCl_3$.

1.5.8. Synthesis of 2-(furan-2-yl)-5-(2-(furan-2-yl) vinyl)-1,3,4- oxadiazole (Oxa-8)

Compound Oxa-8 was synthesized similar to the preparation of compound Oxa-1 from starting material furoic hydrazide (FH) and 2-furyl acrylic acid in $POCl_3$.

1.5.9. Synthesis of 2-choro phenyl-5-(p-tolyl)-1,3,4-oxadiazole (Oxa-9)

Compound Oxa-9 was synthesized similar to the preparation of compound Oxa-1 from starting material toulic hydrazide (TH) and cyclohexanoic acid in $POCl_3$.

1.5.10. Synthesis of 2-cyclopentyl-5-(p-tolyl)-1,3,4-oxadiazole (Oxa-10)

Compound Oxa-10 was synthesized similar to the preparation of compound Oxa-1 from starting material toulic hydrazide (TH) and 2-cyclo pentatonic acid in POCl3.

1.5.11. Synthesis of 2-(2-fluorobenzyl)-5-(p-tolyl)-1,3,4-oxadiazole (Oxa-11)

Compound Oxa-11 was synthesized similar to the preparation of compound Oxa-1 from starting material toulic hydrazide (TH) and 3-fluoro phenyl acetic acid in $POCl_3$.

1.5.12. Synthesis of 2-((1H-indol-3-yl) methyl)-5-(p-tolyl)-1,3,4-oxadiazole (Oxa-12)

Compound Oxa1-12 was synthesized similar to the preparation of compound Oxa-1 from starting material toulic hydrazide (TH) and indole 3- acetic acid in $POCl_3$.

1.5.13. Synthesis of 2-(pyrazin-2-yl)-5-(p-tolyl)-1,3,4-oxadiazole (Oxa-13)

Compound Oxa-13 was synthesized similar to the preparation of compound Oxa-1 from starting material toulic hydrazide(TH) and pyrazine carboxylic acid in $POCl_3$.

1.5.14. Synthesis of 2-(2-(furan-2-yl)vinyl)-5-(p-tolyl)-1,3,4-oxadiazole (Oxa-14)

Compound Oxa-14 was synthesized similar to the preparation of compound Oxa-1 from starting material toulic hydrazide (TH) and furyl 2- acrylic acid in $POCl_3$.

1.6. Structural analysis of the compounds

1.6.1. 2-phenyl-5-(furan-2-yl)-1,3,4-oxadiazole (Oxa-1)

Pale yellow solid, mp 100ºC; yield 78%. IR (KBr, cm^{-1}): 1410, 1450, and 1520 (for oxadiazole) 1630 (C = N), 1018 (C-O-C), 1536 (C = C), 1354 (C-N str) and 2931, 2857 (CH_2 str). ^1H NMR ($CDCl_3$, 300 MHz): δ 1.79 - 2.13 (10H, m), 2.94 - 2.99 (m, 1H), 6.56 - 6.57 (1H, m), 7.10 -7.11 (1H, d), 7.60 - 7.61 (1H, d) 13C. NMR ($CDCl_3$, 300 MHz): δ 165.4, 154.8, 151.3, 147.3, 116.4, 112.7, 35.2, 30.1, 29.2, 25.4. LC/ESI: m/z value 219 (M+1).

1.6.2. 2-cyclopentyl-5-(furan-2-yl)-1,3,4-oxadiazole (Oxa-2)

Brown solid, mp 86ºC; yield 81%. IR (KBr, cm^{-1}): 1410, 1452, and 1527 (for oxadiazole) 1631 (C = N, 1018 (C-O-C), 1566 (C = C), 2959, 2874 (CH_2 str) and 1304 (C-N str). 1H NMR ($CDCl_3$, 300 MHz): δ 1.68-2.17 (8H, m), 3.32-3.41 (1H, m), 6.57-6.59 (1H, m), 7.12-7.13(1H, d), 7.62 (1H, d). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 165.9, 153.5, 151.3, 145.1, 115.9, 111.7, 37.2, 32.1, 23.7. LC/ESI: m/z value 205 (M+1).

1.6.3. 2-(2-chlorobenzyl)-5-(furan-2-yl)-1,3,4-oxadiazole (Oxa-3)

Brown solid, mp 92ºC; yield 75%. IR (KBr, cm^{-1}): 1452, 1492, and 1517 (for oxadiazole), 1629 (C = N), 1011 (C-O-C), 1581 (C = C), 1357 (C-N Str), 3039 (Ar-H mono substituted), 754 (C-H bend), 1229 (C-F str). ^1H NMR ($CDCl_3$, 300 MHz): δ 4.30 (s, 2H), 6.56 - 6.57 (m, 1H), 7.05 -7.15 (m, 3H 7.23 (d 1H J = 2.4 Hz), 7.26 -7.34 (m, 2H), 7.60 -7.61 (m, 1H). ^{13}CNMR ($CDCl_3$, 300 MHz) : δ 163.7, 161.9, 159.5, 158.0, 145.5, 139.3, 130.8, 129.5, 124.4, 120.8, 115.5, 113.9, 24.8. LC/ ESI: m/z value 245 (M+1).

1.6.4. 2-(indol-3-yl) methyl)-5-(furan-2-yl)-1,3,4-oxadiazole (Oxa-4)

Orange solid, MP 110ºC; yield 72%. IR (KBr, cm^{-1}): 1452, 1517 and 1563 (for oxadiazole), 3368 (N - N str for indole), 1630 (C= N), 1012 (C-O-C), 2923, 2855 (CH_2 Str), ^{1}HNMR (CDCl3, 300 MHz): δ 4.41 (s, 2H), 7.06-7.07 (m, 1H), 7.13-7.22 (m, 3H),7.37 (d, 2H, J = 6Hz), 7.58 (d, 1H), 7.68 (d, 1H, J = 5.7 Hz) ,8.45 (s, 1H, NH). 13C NMR (CDCl3, 300 MHz): δ 165.8, 157.3, 147.7, 137.6, 135.8, 127.8, 120.5, 120.3, 116.7, 114.1, 111.7, 30.5. LC / ESI: m/z value 266 (M+1).

1.6.5. 2-(furan-2-yl)-5-(pyrazin-2-yl)-1,3,4-oxadiazole (Oxa-5)

Pale yellow solid, mp 152ºC; yield 85%. IR (KBr, cm^{-1}): 1418, 1452 and 1520 (for oxadiazole) 1616 (C = N), 1012 (C-O-C), 2924, 2856 (CH_2 str), 3119 (Ar-H). ^{1}HNMR ($CDCl_3$, 300 MHz): δ 6.67- 6.65 (1H, m), 7.71 - 7.72 (1H, d), 7.36 (1H, dd, J = 4.8 Hz), 8.77 (2H, m, J = 1.6 Hz), 9.53 (1H, d, J = 1.6 Hz). ^{13}CNMR ($CDCl_3$, 300 MHz): δ 161.2, 158.6, 146.4, 144.6, 144.2, 141.8, 139.4, 138.8, 115.3, 112.3. LC/ ESI: m/z value 215 (M+1)

1.6.6. 2-(2-chloro, 5-fluorophenyl)-5-(furan-2-yl)-1,3,4-oxadiazole (Oxa-6)

White solid, mp 127ºC; yield 79%. IR (KBr, cm^{-1}): 1442, 1518 and 1555 (for oxadiazole) 1629 (C = N) 1008 (C-O-C), 2923, 2856 (CH_2 str), 3079 (Ar-H), 1235 (C-F str), 864,767 (Meta di-substituted). ^1H NMR ($CDCl_3$, 300 MHz): δ 6.65 (dd, 1H, J = 2.2, 3.7 Hz), 7.01 (tt, 1H, J = 1.9 Hz), 7.23 (d, 1H), 7.64 - 7.702 (m, 3H). ^{13}CNMR ($CDCl_3$, 300 MHz): δ 165.5, 160.8, 158.4, 157.5, 139.5, 129.6, 119.8, 118.3, 116.7, 114.8, and 113.9. LC/ ESI: m/z value 249 (M+1).

1.6.7. 2-(5-fluorophenyl)-5-(furan-2-yl)-1,3,4-oxadiazole (Oxa-7)

Pale yellow solid, mp 118ºC; yield 72%. IR (KBr, cm^{-1}): 1452, 1518 and 1564 (for oxadiazole) 1635 (C = N), 1015 (C-O-C), 2923, 2858 (CH_2 str), ^{1}HNMR ($CDCl_3$, 300 MHz): δ 1.79- 1.87 (m, 2H), 2.01-2.07 (m, 2H), 2.21-2.40 (m, 4H), 3.01 - 3.25 (m, 2H), 6.56 - 6.59 (m, 2H), 7.12-7.14 (m, 2H),7.61 - 7.62 (m, 2H). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 170.2, 157.8, 149.6, 138.5, 115.7, 111.3, 38.3, 35.2, and 28.5. LC/ ESI: m/z value 353 (M+1).

1.6.8. 2-(furan-2-yl)-5-(2-(furan-2-yl) vinyl)-1,3,4- oxadiazole (Oxa-8)

Brown solid, mp 123ºC; yield 69 %. IR (KBr, cm^{-1}): 1518, 1455, and 1399 (for oxadiazole), 1635 (C = N), 1015 (C-O-C), 2926, 2855 (CH_2 str). ^{1}HNMR ($CDCl_3$, 300 MHz); δ 6.43 (d, 1H, J = 1.5 Hz), 6.55 (d, 2H, J = 3.3 Hz), 6.85 (d, 1H, J = 8.4 Hz), 7.14 (d, 1H, J=3.3 Hz), 7.33 (d, 1H, J = 3.5 Hz), 7.45 (d, 1H),7.58 (d, 1H). ^{13}CNMR (CDC_{l3}, 300 MHz): δ 161.3, 157.5, 151.3, 147.8, 145.4, 139.6, 116.7,

115.1, 112.7. LC/ ESI: m/z value 229 (M+1).

1.6.9. 2-choro phenyl-5-(p-tolyl)-1,3,4-oxadiazole (Oxa-9)

White solid, MP 92ºC; yield 82%. IR (KBr, cm^{-1}): 1496, 1445 and 1410 (for oxadiazole), 1592 (C = N), 1014 (C-O-C), 2933, 2855 (CH_2 str). ^{1}HNMR ($CDCl_3$, 300 MHz): δ 1.26 - 1.47 (3H, m), 1.63 - 1.78 (3H, m), 1.86 -1.91 (2H, m), 2.12 - 2.18 (2H, m), 2.46 (S, 3H), 2.9 - 3.04 (m, 1H), 7.32 (d, 2H, J = 7.8 Hz), 7.92 (d, 2H, J = 8.1 Hz). ^{13}CNMR ($CDCl_3$ 300 MHz) δ; 168.6, 163.3, 140.9, 128.8, 125.7, 128.3, 120.3, 41.9, 39.4, 38.5, 34.1, 29.1, 21.5. LC/ESI: m/z value 243(M+1).

1.6.10. 2-cyclopentyl-5-(p-tolyl)-1,3,4-oxadiazole (Oxa-10)

Brown crystalline, MP 85ºC; yield 73%. IR (KBr, cm^{-1}): 1498, 1448 and 1401 (for oxadiazole), 1605 (C = N), 1012 (CO-C), 2954, 2870 (CH_2 str), ^{1}HNMR ($CDCl_3$, 300 MHz): δ 1.64 - 2.13 (m, 8H), 2.34 (s, 3H), 3.25 -3.36 (m, 1H), 7.15 - 7.27 (d, 2H), 7.93 - 7.96 (d, 2H). ^{13}CNMR ($CDCl_3$, 300 MHz); 169.8, 164.7, 141.8, 129.6, 127.2, 121.4, 36, 30.9, 30.3, 25.4, 21.5. LC/ESI: m/z value 229 (M+1).

1.6.11. 2-(2-fluorobenzyl)-5-(p-tolyl)-1,3,4-oxadiazole (Oxa-11)

Pale yellow solid, MP 92ºC; yield 78%. IR (KBr, cm^{-1}): 1491, 1456 and 1411 (for oxadiazole), 1595 (C = N), 1010 (C-O-C), 3029, 2933 (CH_2 str). ^{1}HNMR ($CDCl_3$, 300 MHz): δ 2.32 (s, 3H), 4.21 (s, 2H), 6.97 - 7.14 (m, 3H) 7.23 - 7.28 (m, 4H), 7.94 (d, 2H, J = 8.1 Hz). 13C NMR ($CDCl_3$, 300 MHz) 165.5, 163.8, 161.5, 139.7, 136.5, 129.7, 128.6, 126.8, 123.4, 121.5, 117.4, 112.7, 33.9, 21.3 .LC/ ESI: m/z value 269 (M+1).

1.6.12. 2-((1H-indol-3-yl) methyl)-5-(p-tolyl)-1,3,4-oxadiazole (Oxa-12)

Dark brown solid, M.P. 110ºC; yield 56%. IR (KBr, cm^{-1}): 1495, 1455 and 1420 (for oxadiazole), 1606 (C = N), 1010 (C-O-C), 3049, 2923 (CH_2 str). ^{1}HNMR ($CDCl_3$, 300 MHz): δ 2.34 (s, 3H), 4.34 (s, 2H), 7.02-7.17 (m, 1H), 7.15 - 7.18 (m, 3H), 7.26 (d, 1H, J = 8 Hz), 7.33 (d, 1H, J = 8.1 Hz), 7.65 (d, 1H, J = 7.8 Hz), 7.79 (d, 2H, J = 8.1Hz), 7.94 (d, 1H, J = 8.1 Hz), 8.21 (s, 1H). ^{13}CNMR ($CDCl_3$, 300 MHz): 165.6, 163.9, 139.8, 137.4, 135.7, 129.6, 127.8, 126.8, 123.9, 122.2, 120.5, 120.3, 111.7, 104, 31.2, 21.6. LC/ ESI: m/z value 276 (M+1).

1.6.13. 2-(pyrazin-2-yl)-5-(p-tolyl)-1,3,4-oxadiazole (Oxa-13)

Yellow solid, M.P. 73ºC; yield 83%. IR (KBr, cm^{-1}): 1489, 1453 and 1419 (for oxadiazole), 1606 (C = N), 1015 (C-O-C), 2923, 2855 (CH_2 Str), ^{1}HNMR ($CDCl_3$ 300 MHz): δ 2.3 (s, 3H), 7.28 (d, 2H, J = 8.4 Hz), 8.02 (2H, d), 8.70 (m, 2H), 9.45 (d, 1H, J = 1.2 Hz). ^{13}CNMR ($CDCl_3$, 300 MHz): 166.0, 161.7, 146.2, 144.5, 143.0, 139.7, 129.8, 127.2, 120.3, 21.6. LC/ESI: m/z value 239 (M+1).

1.6.14. Synthesis of 2-(2-(furan-2-yl)vinyl)-5-(p-tolyl)-1,3,4-oxadiazole (Oxa-14)

Brown solid, M.P. 85ºC; yield 65%. IR (KBr cm^{-1}): 1581, 1491 and 1456 (for oxadiazole), 1625 (C = N), 1007 (C-O-C), 2966, 2855 (CH_2 Str). ^{1}HNMR ($CDCl_3$, 300 MHz): δ 2.36 (s, 3H), 6.43 (m, 1H, J = 3.3, 1.8 Hz), 6.54 (d, 1H, J = 3.3 Hz), 6.89 (d, 1H, J = 16.2 Hz), 7.25 (d, 2H, J = 8.1 Hz), 7.30 (d, 1H, J = 16.2 Hz), 7.45 (d, 1H, J = 1.5 Hz) ,7.91 (d, 2H, J = 8.1Hz). ^{13}CNMR ($CDCl_3$, 300 MHz): 163.9, 151.0, 144.4, 142.2, 129.7, 126.8, 125.4, 121.0, 113.5, 112.3, 107.7, 21.5. LC/ ESI: m/z value 253 (M+1).

1.7. Pharmacological Activity

1.7.1. Analgesic activity

(a) Animal

Swiss strain Mice (20-28 g) were group housed (n= 6) under a standard 12 h light/dark cycle and controlled conditions of temperature and humidity (25±2 °C, 55–65%). Rats received standard rodent chow and water *ad libitum*. Mice were acclimatized to laboratory conditions for 7 days before carrying out the experiments. All the experiments were carried in a noise-free room between 08.00 to 15.00 h. Separate group (n=6) of Mices was used for each set of experiments. The animal studies were approved by the Institutional Animal Ethics Committee (IAEC), constituted for the purpose of control and supervision of experimental animals by Ministry of Environment and Forests, Government of India,

New Delhi, India.

(c) Chemicals

The chemicals used in this study were Rofecoxib, Diclofenac and Tramadol. The solvents and reagents obtained were used as received.

(c) Eddy's hot plate technique

Eddy's hot plate technique was used to carry out analgesic activity [8]. 77 Adult albino mice of either sexes, weighing 25-35 g, were grouped, each of six animals. A suspension of the test compounds (20 mg/kg) and Tramadol/Diclofenac/Rofecoxib (20 mg/kg) were administered intra peritoneal to the mice groups. The control group was treated equivalent volume of the vehicle. Mice were placed for testing on the surface of a hot-plate apparatus maintained at 55 ± 0.5ºC after 3 or 4 h of injection. The basal activity time of all animals against thermal heat was noted. The animals showing for paw licking or jumping activity (displayed earlier) in 6 to 8 sec was considered for the study. To avoid injuries to the paws, 15 sec was considered as a cut off time as highest analgesic activity. The hotplate latency was taken as a measure of the analgesic activity, the mean licking time ± S.E. was calculated for each group [8].

1.7.2. Anti-Inflammatory Activity

(a) Animal

Wistar strain Albino rat (150-200 gm)were group housed (n= 6) under a standard 12 h light/dark cycle and controlled conditions of temperature and humidity (25±2 °C, 55–65%). Rats received standard rodent chow and water *ad libitum*. Mice were acclimatized to laboratory conditions for 7 days before carrying out the experiments. All the experiments were carried in a noise-free room between 08.00 to 15.00 h. Separate group (n=6) of Mices was used for each set of experiments. The animal studies were approved by the Institutional Animal Ethics Committee (IAEC), constituted for the purpose of control and supervision of experimental animals by Ministry of Environment and Forests, Government of India, New Delhi, India.

(b) Chemicals

The chemicals used in this study were carrageenan, Rofecoxib, Diclofenac and Tramadol. The solvents and reagents obtained were used as received.

(c) Winter et *al*., method

All the designed structures were screened for anti-inflammatory activity by using Winter et al., proposed carrageenan-induced rat paw edema method. All the animals divided into group of six animals in the random fashion. Prior to experiment animals were fasted for 24 h and only free acess to water. 0.5 % CMC solution was administered to control group and remaining group animals were administered with the test compounds and reference drugs diclofenac or tramadol or rofecoxib (20 or 200 mg/kg p.o). 1% carrageenan solution was prepared in saline water and 0.1 ml prepared solution was injected subcataneously in to the right hind paw sub-planar region of each rat, 30 minutes after the administration of test and reference drug. Digital plethysmometer (Orchid life sciences) was used to measure right hind paw volume before and after 3 and 4 h of carrageenan injection [9, 10].

Anti-inflammatory activity (% inhibition) = [(Vc – Vt)/Vc] × 100.

Where (Vc): edema volume in control group, (Vt): edema volume in test compounds

Results and Discussion

1.8. Analgesic activity

Analgesic activity of compounds Oxa-1 to Oxa-14 was performed using Eddy's hot plate technique. The compounds showed analgesic activity ranging from 44.33 to 53.90% (**Table 1**), whereas the standard drug Tramadol showed 56.25% inhibition. It was interesting to note that the compound Oxa-14 exhibited highest activity (58.80) among test compound also manifested anti-inflammatory activity. Compound Oxa-13 (57.34) and Oxa-2 (53.90) also exhibited higher activity.

Table 1 Data of Analgesic activity of synthesized compounds Oxa-1 to Oxa-14

Comp	Hind paw lick ±SEM		% Inhibition
	Pre-treatment 0 h (s)	After 4 h (s)	After 4 h
Control	12.20±0.35	12.82±0.26*	
Tramadol	12.70±0.23	5.58±0.17*	56.25*
Oxa-1	12.68±0.27	6.26±0.13*	50.78*
Oxa-2	12.70±0.19	5.66±0.26*	53.90*
Oxa-3	12.32±0.28	6.80±0.25	46.87*
Oxa-4	12.47±0.34	7.10±0.11*	44.33*
Oxa-5	12.38±0.27	6.20±0.19*	51.56*
Oxa-6	12.40±0.40	6.70±0.16	47.65
Oxa-7	12.33±0.38	6.76±0.25	47.65
Oxa-8	12.58±0.27	6.06±0.17*	52.34*
Oxa-9	12.57±0.27	6.07±0.17*	53.34*
Oxa-10	12.42±0.31	6.50±0.18*	49.21
Oxa-11	12.45±0.30	7.66±0.11*	42.33*
Oxa-12	12.65±0.27	6.46±0.13*	48.78*
Oxa-13	12.56±0.27	7.06±0.17*	57.34*
Oxa-14	12.72±0.12	6.66±0.26*	58.80*

Data are Mean ±SD; *p<0.01 followed by Dunnet's test (n=6)

1.9. Acute Anti-inflammatory activity

All the compounds from scheme-I (Oxa-1 to Oxa-14) were tested for their anti-inflammatory activity and assayed at the initial dose of 100 mg/kg i.p. As a reference substance in experiment diclofenac sodium was used. None of the tested derivatives induce direct signs of toxicity or mortality in the animals subjected to experiment. All the title compounds exhibited anti-inflammatory activity. Out of fourteen tested compounds four compounds (Oxa-14, Oxa-13, Oxa-3 and Oxa-1) showed a highly significant anti-inflammatory activity. Activity for tested compound was observed in the range of 34.65% to 67.34%. Reference drug diclofenac exhibited 74.20% inhibition (**Table 2**) after 4 hr. The most active compound was Oxa-12 that produced a highly significant inhibition 67.34%.

Table 2: Data of anti-inflammatory activity of synthesized compounds

Comp	Paw vol. (sec) Mean ± SEM			
	3 hr	4 hr	% Inhibition After 3h	% inhibition After 4h
STD Diclofenac Sodium	0.75±0.16	0.54±0.08	61.92	74.20
CNT Normal saline	1.97±0.18	2.02±0.21	-	-
Oxa-1	0.98±0.10	0.75±0.16	50.25	62.87
Oxa-2	1.25±0.20	0.86±0.17	36.54	57.42*
Oxa-3	0.95±0.16	0.70±0.07	51.77	65.34*
Oxa-4	0.92±0.08	0.92±0.03	53.29	54.45*
Oxa-5	1.10±0.12	0.98±0.08	44.16	51.48
Oxa-6	0.88±0.21	0.95±0.09	55.32	52.97
Oxa-7	1.42±0.26	1.18±0.19	27.91	41.58*

Oxa-8	1.23±0.34	1.32±0.10	37.56	34.65
Oxa-9	1.18±0.30	1.12±0.20	40.10	44.55
Oxa-10	1.41±0.28	1.12±0.19	26.91	40.58*
Oxa-11	0.86±0.20	0.92±0.09	55.31	51.97
Oxa-12	1.22±0.10	0.84±0.17	34.54	51.40*
Oxa-13	0.96±0.14	0.71±0.07	51.70	66.32*
Oxa-14	0.97±0.15	0.72±0.07	52.77	67.34*

Conclusion

The present study entitled "Synthesis of Some Novel Derivatives of 1,3,4-Oxadiazole, As analgesic and Anti-inflammatory Agents" was carried out to synthesize and to screen the newly derivatives of 1,3,4-oxadiazole for its analgesic and Anti-inflammatory activity. The melting point of the synthesized compounds was determined by open capillary method. The purity and progress of reaction were monitored by thin layer chromatography. All the newly synthesized compounds were then identified for their structure and functional groups by using various analytical studies like IR, Mass and 1HNMR spectra. The newly synthesized compounds were evaluated for the analgesic; anti-inflammatory activity was performed *in- vivo*. The both results were correlated by percentage of inhibition. All the synthesized derivatives of 1,3,4-odaizole show significant analgesic, anti-inflammatory activity.

References

1. Palomer A., Cabré F., Pascual J., Campos J., Trujillo M. A., Entrena A., Gallo M. A., García L., Mauleón D., and Espinosa A., Identification of novel cyclooxygenase-2 selective inhibitors using pharmacophore models, *Journal of Medicinal Chemistry*. (2002) 45, no. 7, 1402–1411, 2-s2.0-0037187425.
2. Omar F. A., Mahfouz N. M., and Rahman M. A., Design, synthesis and antiinflammatory activity of some 1,3,4-oxadiazole derivatives, *European Journal of Medicinal Chemistry*. (1996) 31, no. 10, 819–825, 2-s2.0-0029802439.
3. Lanza F. L., A guideline for the treatment and prevention of NSAID-induced ulcers, *American Journal of Gastroenterology*. (1998) 93, no. 11, 2037–2046, 2-s2.0-0032468069,
4. Buttgereit F., Burmester G. R., and Simon L. S., Gastrointestinal toxic side effects of nonsteroidal anti-inflammatory drugs and cyclooxygenase-2-specific inhibitors, *American Journal of Medicine*. (2001) 110, no. 3, 135–195.
5. Metwally K. A., Yaseen S. H., Lashine E.-S. M., El-Fayomi H. M., and El-Sadek M. E., Non-carboxylic analogues of arylpropionic acids: synthesis, anti-inflammatory activity and ulcerogenic potential, *European Journal of Medicinal Chemistry*. (2007) 42, no. 2, 152–160, 2-s2.0-33847106971.
6. Husain A., Khan M. S. Y., Hasan S. M., and Alam M. M., 2-Arylidene-4-(4-phenoxy-phenyl)but-3-en-4-olides: synthesis, reactions and biological activity, European Journal of Medicinal Chemistry. (2005) 40, no. 12, 1394–1404, 2-s2.0-27744559326.
7. Raghunath B, Toche Ravindra A & Janrao, 2015, 'Synthesis, Chacterization and antimicrobial evaluation of novel urea,sulphonamide, acetamide 3,4 dihydropyrazino[1,2-a]indol-1(2H)-one dereivatives', Arab. J. Chem.
8. R.A. Turner, Screening Methods in Pharmacology, Academic Press, New York, London, (1965) 100.
9. J.G. Hardman, L.E. Lombard, A.G. Gilman, Goodmann and Gilman's – The Pharmacological basis of Therapeutics, Mcgraw Hill, New York, (2001) 688-689.
10. C.A. Winter, E.T. Risley, G.W. Nuss, Carrageenin-induced edema in hind paw of the rat as an assay for antiinflammatory drugs, Proc. Soc. Exp. Biol. Med. 3 (1962) 544-547.