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ABSTRACT

A new series of 1,3,4-oxadiazole derivatives **(3a-j)** were synthesized by reacting p-toluic benzhydrazide **(1)** and substituted aromatic aldehydes **(2)** in the presence of ceric ammonium nitrate as catalyst and dichloromethane as a solvent medium. The structures of the new compounds were assigned based on IR, ^{1}H-NMR, and mass spectral data and further evaluated for their *in vitro* anti-inflammatory potential using various protein denaturation methods following bovine serum and egg albumin assay. Some tested compounds **3e, 3f, and 3i** displayed moderate anti-inflammatory activity compared to the standard diclofenac sodium.

Keywords: 1,3,4-Oxadiazole, anti-inflammatory, benzhydrazide, bovine albumin, ceric ammonium nitrate

INTRODUCTION

Heterocyclic compounds are a promising area for synthetic study as well as biological activity. Oxadiazole, a five-membered aromatic ring, is found to be an essential class of heterocyclic compounds. These azoles are composed of oxygen and nitrogen atoms of the general formula $C_2H_2ON_2$. 1,3,4-oxadiazoles are the leading class of compounds in the area of discovery of drugs due to their vast pharmacological activities such as anticancer,[1] antioxidant,[2] anti-arthritic,[3] antibacterial,[4] analgesic,[5] anticonvulsant,[6] and anti-HIV[7]. Moreover, five-membered heterocyclic rings containing nitrogen, carbon, or oxygen at the symmetrical position have been studied deliberately for their various biological activities.[8]

Most of the 1,3,4-oxadiazole derivatives have a significant role in medicinal chemistry. Some of the medicinally essential compounds which are composed of this moiety are raltegravir (HIV-integrase inhibitor drug), fenadiazole (Hypnotic), zibotentan (anticancer), tiodazosin (alpha1-adrenergic antagonist), and furamizole (nitrofuran antibacterial).

Inflammation is the immune system's response to irritants. These irritants can be harmful stimuli or toxic compounds, germs, or damaged cells involving in the accumulation of cells exuding in irritated tissues instigating the healing process.[9] As time follows, inflammation has been considered an effort to fight its impact on the body.[10]

Anti-inflammatory drugs (NSAIDs) have been reported in the market such as indomethacin, Ibuprofen, fenoprofen, fenbufen, and diclofenac, which are the derivatives of propionic acid and acetic acid. However, their clinical uses have been limited by the risk of its gastrointestinal toxicity reported due to the direct proximity of free carboxylic acid with gastrointestinal mucosa, leading to the hindrance of non-selective cyclooxygenase enzyme.[11-15]

1,3,4-oxadiazoles are usually synthesized using carbohydrazides, Schiff bases, and diacylhydrazines. Many oxidizing agents/cyclizing agents are available for their synthesis, namely, phosphorus oxy chloride,[16] iodo benzene diacetate,[17] $FeCl_3$,[18] ceric ammonium nitrate (CAN),[19] chloramine-T,[20] mercuric oxide/iodine, etc.[21]

With the emerging broad spectrum of activities, 1,3,4-oxadiazole draws heedless attention to the researcher. However, after further monitoring and studying the pharmacophore of 1,3,4-oxadiazole, we distinct to synthesize different analogs due to its substitution at the second and the fifth position of the oxadiazole ring.

MATERIALS AND METHODS

All chemicals, including p-toluic benzhydrazide, and solvents were procured from Sigma-Aldrich, Bengaluru, India. The open capillary tube method was employed for determining the melting points. Thin-layer chromatography was used to check the reaction progress using plates of aluminum silica gel 60 F_{245}. The spots were observed under the ultraviolet light chamber. Alpha Bruker FT-IR-Spectrometer was used for recording IR spectra (cm^{-1}). Bruker Avance-II NMR spectrometer (USA) was employed to record

^{1}H-NMR spectra operating at 400 MHz with dimethyl sulfoxide (5%)/$CDCl_3$ as a solvent where TMS served as an internal standard. The recording of the mass spectra was carried out by PerkinElmer gas chromatography–mass spectrometry (USA).

Synthesis of 1,3,4-Oxadiazole Derivatives (3a-j)

p-toluic benzhydrazide **(1)** (0.01M) and substituted aromatic aldehydes **(2)** (0.01M) were dissolved in dichloromethane (30 ml). A pinch of CAN was added, and the contents were refluxed for 10–14 h and cooled to room temperature. The crude product obtained was filtered, washed with water, dried, and recrystallized using alcohol. The physical data of title compounds 1,3,4-oxadiazoles **(3a- j)** are given in Table 1.

2-(4-bromophenyl)-5-p-tolyl-1,3,4-oxadiazole(3a)

$C_{15}H_{11}BrN_2O$. Mol. wt.: 315.16. % Yield: 72. M.P: 185–187°C. FT-IR (KBr, cm^{-1}): 1090 (C-O-C), 1555 (C=C), 1628 (C=N), 3028 (C-H). ^{1}H-NMR ($CDCl_3$): δ 2.51 (s, CH_3, 3H), 7.33–8.43 (m, Ar-H, 8H). LC–MS: m/z: 315.16(M^+).

2-(4-nitrophenyl)-5-p-tolyl-1,3,4-oxadiazole(3b)

$C_{15}H_{11}N_3O_3$ Mol. wt.: 281.27. %Yield: 68. M.P:190–192°C. FT-IR (KBr, cm^{-1}): 1079 (C-O-C), 1527 (C=C), 1632 (C=N), 3049 (C-H). ^{1}H-NMR ($CDCl_3$): δ 2.39 (s, CH_3, 3H), 7.34–8.57 (m, Ar-H, 8H). LC–MS: m/z:281.27 (M^+).

2-(4-chlorophenyl)-5-p-tolyl-1,3,4-oxadiazole(3c)

$C_{15}H_{11}ClN_2O$ Mol. wt.: 270.71. %Yield: 64. M.P: 255–257°C FT-IR (KBr, cm^{-1}): 1071 (C-O-C), 1555 (C=C), 1629 (C=N), 3047 (C-H).1H-NMR (CDCl3): δ 2.38 (s, CH3, 3H), 7.32–8.45 (m, Ar-H, 8H). LC–MS: m/z: 270.71(M+1).

N,N-dimethyl-4-(5-p-tolyl-1,3,4-oxadiazol-2-yl)aniline(3d)

$C_{17}H_{17}N_3O$ Mol. wt.: 279.34. %Yield: 76. M.P: 230–232°C. FT-IR (KBr, cm^{-1}): 1097(C-O-C), 1555 (C=C), 1606 (C=N), 3003 (C-H). ^{1}H-NMR ($CDCl_3$): δ 2.51 (s, CH_3, 3H), 2.98 (s, $2XCH_3$, 6H), 7.33–8.43 (m, Ar-H, 8H). LC–MS: m/z: 279.34(M^+).

2-(3,4-dimethoxyphenyl)-5-p-tolyl-1,3,4-oxadiazole(3e)

$C_{17}H_{16}N_2O_3$ Mol. wt.: 296.32. % Yield: 74. M.P: 228–230°C. FT-IR (KBr, cm^{-1}): 1099 (C-O-C), 1545 (C=C), 1628 (C=N), 3007 (C-H). ^{1}H-NMR ($CDCl_3$): δ 2.48 (s, CH_3, 3H), 3.36 (s, $2XOCH_3$, 7H), 7.47–7.81 (m, Ar-H, 7H). LC–MS: m/z: 296.32(M^+).

4-(5-p-tolyl-1,3,4-oxadiazol-2-yl) phenol (3f)

$C_{15}H_{12}N_2O_2$ Mol. wt.: 252.27. % Yield: 69. M.P: 210–212°C. FT-IR (KBr, cm^{-1}): 1066 (C-O-C), 1525 (C=C), 1601 (C=N), 3057 (C-H). 3401 (OH). ^{1}H-NMR ($CDCl_3$): δ 2.50 (s, CH_3, 3H), 6.75–8.31 (m, Ar-H, 8H), 11.47(s, OH, 1H).LC–MS: m/z: 252.27 (M^+).

2-(5-p-tolyl-1,3,4-oxadiazol-2-yl) phenol (3g)

$C_{15}H_{12}N_2O_2$ Mol. wt.: 252.27. %Yield: 68. M.P: 205–207°C. FT-IR (KBr, cm^{-1}): 1081 (C-O-C), 1526 (C=C), 1608 (C=N), 3077 (C-H). 3439 (OH). ^{1}H-NMR ($CDCl_3$): δ 2.38 (s, CH_3, 3H), 6.83–8.34 (m, Ar-H, 8H), 11.57 (s, OH, 1H). LC–MS: m/z:252.27 (M^+).

2-phenyl-5-p-tolyl-1,3,4-oxadiazole(3h)

$C_{15}H_{12}N_2O$ Mol. wt.: 236.27. % Yield: 75. M.P: 216–218°C. FT-IR (KBr, cm^{-1}): 1023 (C-O-C), 1541 (C=C), 1602 (C=N), 3059 (C-H). ^{1}H-NMR ($CDCl_3$): δ 2.39 (s, CH_3, 3H), 6.91–9.64 (m, Ar-H, 8H). LC–MS: m/z:236.27 (M^+).

2-(4-methoxyphenyl)-5-p-tolyl-1,3,4-oxadiazole(3i)

$C_{16}H_{14}N_2O_2$ Mol. wt.: 266.29. % Yield: 77. M.P: 246–248°C. FT-IR (KBr, cm^{-1}): 1098(C-O-C), 1554 (C=C), 1626 (C=N), 3051 (C-H). ^{1}H-NMR ($CDCl_3$): δ 2.50 (s, CH_3, 3H), 3.81 (s, OCH_3, 3H), 7.62–8.39 (m, Ar-H, 8H). LC–MS: m/z: 266.29 (M^+).

2-(4-fluorophenyl)-5-p-tolyl-1,3,4-oxadiazole(3j)

$C_{15}H_{11}FN_2O$ Mol. wt.: 254.26. % Yield: 67. M.P: 263–265°C. FT-IR (KBr, cm^{-1}): 1083 (C-O-C), 1561 (C=C), 1630 (C=N), 3032 (C-H). ^{1}H-NMR ($CDCl_3$): δ 2.38 (s, CH_3, 3H), 7.28–8.45 (m, Ar-H, 8H). LC–MS: m/z: 254.26 (M^+).

Hydrazones can be mediated in synthesis of 1,3,4-oxadiazoles by cyclization -oxidation reaction by using CAN as catalyst using DCM as solvent. The possible mechanism is depicted in the following Figure 1.[22]

In vitro Anti-inflammatory Activity

Bovine serum albumin denaturation assay[23]

About 5% w/v aqueous solution of serum bovine albumin was prepared. Test solution (0.5 mL) was prepared using 0.05 mL of different concentrations (10–50 µg/mL) of synthesized

Table 1: Physical of 1,3,4-oxadiazole derivatives (3a-j)

Compound	R-CHO	Molecular formula	Molecular weight	MP (°C)	Yield (%)
3a	4-Br	$C_{15}H_{11}BrN_2O$	315.16	185–187	72
3b	4-NO_2	$C_{15}H_{11}N_3O_3$	281.27	190–192	68
3c	4-Cl	$C_{15}H_{11}ClN_2O$	270.71	255–257	64
3d	4-N $(CH_3)_2$	$C_{17}H_{17}N_3O$	279.34	230–232	76
3e	3,4-$(OCH_3)_2$	$C_{17}H_{16}N_2O_3$	296.32	228–230	74
3f	4-OH	$C_{15}H_{12}N_2O_2$	252.27	210–212	69
3g	2-OH	$C_{15}H_{12}N_2O_2$	252.27	205–07	68
3h	C_6H_5	$C_{15}H_{12}N_2O$	236.27	216–218	75
3i	4-OCH_3	$C_{16}H_{14}N_2O_2$	266.29	246–248	77
3j	4-F	$C_{15}H_{11}FN_2O$	254.26	263–265	67

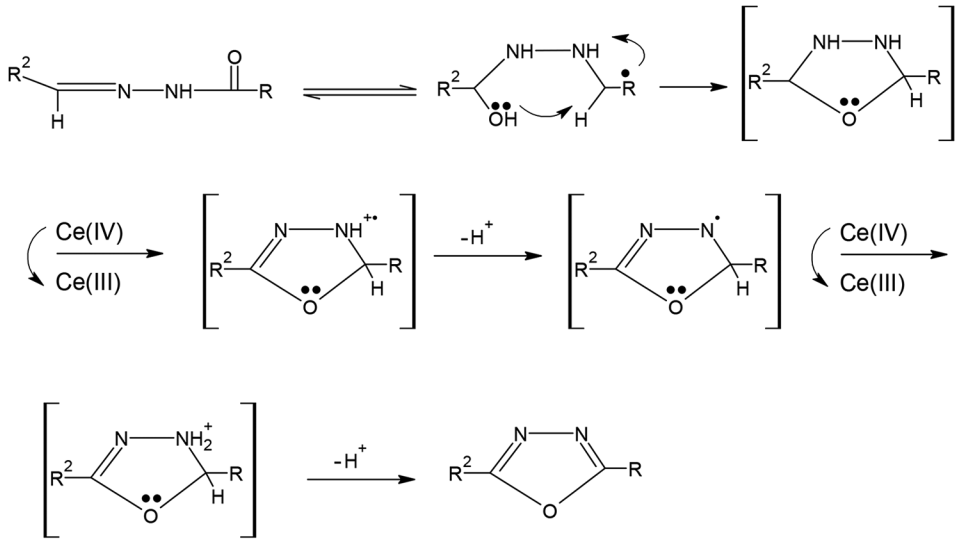


Figure 1: Mechanism involved in the reaction

compounds **(3a-j)** and 0.45 mL of bovine serum albumin and was mixed thoroughly. 0.45 mL of the 5% w/v aqueous solution of serum bovine albumin, that is, 5%w/v, along with 0.05 mL of distilled H_2O, was used as a control solution. 0.05 mL of test compounds (3a-j) along with 0.45 mL of distilled water is taken as the product control. 0.05 mL of diclofenac sodium and 0.45 mL of the 5% w/v aqueous solution of serum bovine albumin were taken as a standard. 1 N HCl was prepared and use to adjust the pH of the above solutions, that is, test, control, product control, and standard to pH 6.3. The above solutions were incubated at 37°C for 20 min, further heated for 3 min at 57°C. 2.5 mL of phosphate buffer was added after the incubation period to the above solution, and the absorbance was read at 416 nm using an ELISA plate reader. All the tests were carried out in triplicates. The results of the bovine serum albumin denaturation assay (3a-j) are shown in Table 2. Percentage inhibition of denaturation was expressed as IC_{50} (μM) (Figure 2). Percentage inhibition of denaturation was calculated using the formula.

% inhibition = 100 × [Vt/Vc–1]

Egg albumin Denaturation Assay[23]

A 5 ml of test solution consists of egg albumin (0.2 ml) prepared from hen's egg and different concentrations (10–50 µg/ml) of test compounds **(3a-j)**. A 5 ml of the control solution consists of 0.2 ml of egg albumin and distilled H_2O. A 5 ml of the standard solution consists of different concentrations of diclofenac sodium (2 ml and 0.2 ml of egg albumin). A 2 ml phosphate buffer of pH 6.4 is added to both the control, test solution, and standard solution. The above solution was incubated at 37 ± 2°C for 15 min, further heated at 70°C for 5 min. The absorbance was measured at 660 nm using an ELISA plate reader. All the tests were carried out in triplicates. The results of the egg albumin denaturation assay (3a-j) are shown in Table 3. Percentage inhibition of denaturation was expressed as IC_{50} (μM) (Figure 3). Percentage inhibition of denaturation was calculated using the formula.

% inhibition = 100 × [Vt/Vc–1]

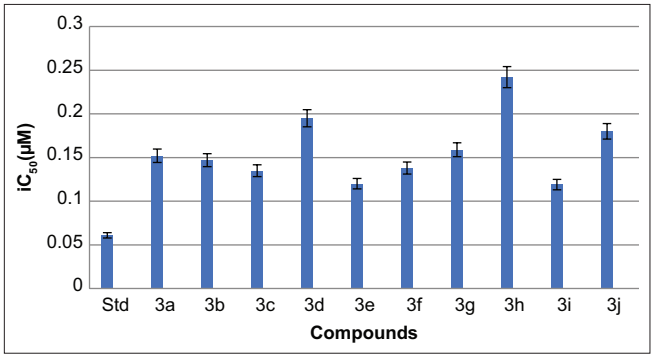


Figure 2: Bovine serum albumin assay

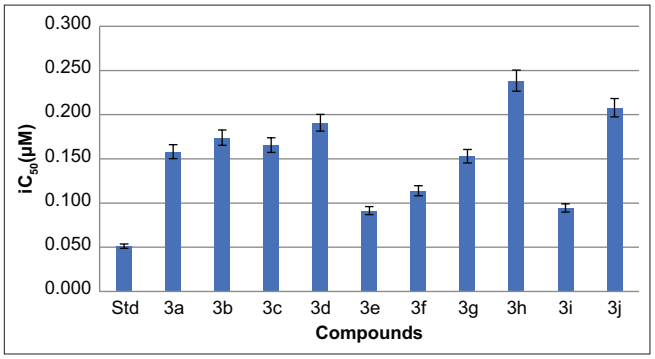


Figure 3: Egg albumin denaturation assay

RESULTS AND DISCUSSION

Chemistry

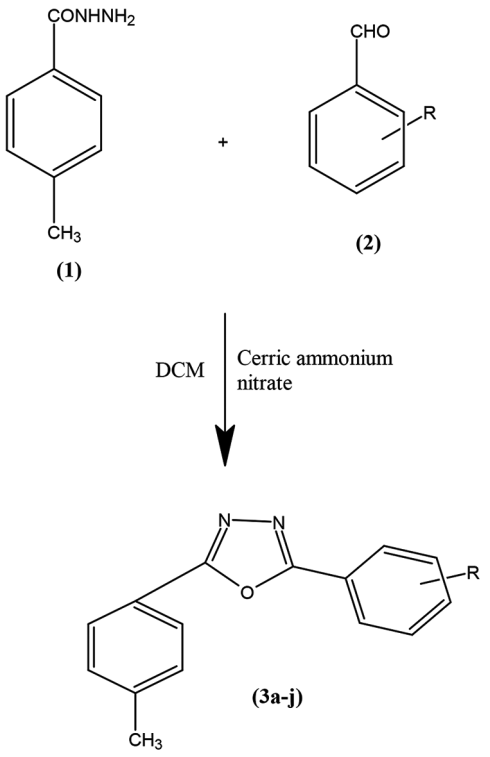
In the present work, a new series of 1,3,4-oxadiazoles **(3a-j)** were synthesized using CAN as an oxidative catalyst. The outline of the work is depicted in **Scheme 1.** p-toluic benzhydrazide **(1)** was employed as a starting material to synthesize 1,3,4-oxadiazole analogs substituted at the second and fifth position of the oxadiazole ring. The hydrazide was made to react with different

Table 2: Data of bovine serum albumin denaturation assay of compounds (3a-j)

Con.	Percentage inhibition										
	Std.	3a	3b	3c	3d	3e	3f	3g	3h	3i	3j
10 µg/ml	17.70±0.12	13.54±0.18	13.54±0.03	9.375±0.44	25±0.26	7.29±0.32	9.37±0.42	9.37±0.27	27.08±0.43	16.66±0.33	20.83±0.22
20 µg/ml	20.83±0.08	15.62±0.23	20.83±0.34	12.5±0.32	38.54±0.22	19.79±0.35	20.83±0.32	19.79±0.10	38.54±0.38	20.83±0.36	29.16±0.32
30 µg/ml	62.50±0.23	20.83±0.32	30.20±0.43	32.29±0.07	40.62±0.34	20.83±0.44	33.33±0.24	30.20±0.18	40.62±0.50	32.29±0.27	40.62±0.43
40 µg/ml	76.04±0.21	32.29±0.29	41.66±0.28	43.75±0.22	51.04±0.42	35.41±0.54	43.75±0.27	40.62±0.23	51.04±0.47	42.70±0.19	51.04±0.39
50 µg/ml	79.16±0.36	47.9 1±0.23	47.91±0.02	53.12±0.32	64.58±0.21	64.58±0.28	56.25±0.30	48.95±0.32	64.58±0.44	66.66±0.15	64.58±0.34
IC_{50z}(µg/ml)	19.29±0.20	48.04±0.24	41.39±0.19	36.66±0.22	54.54±0.28	35.68±0.22	34.82±0.31	40.20±0.19	57.14±0.33	31.62±0.17	45.71±0.35
IC_{50} (µM)	0.061±0.20	0.152±0.24	0.147±0.19	0.135±0.22	0.195±0.28	0.120±0.22	0.138±0.31	0.159±0.19	0.242±0.33	0.119±0.17	0.180±0.35

Table 3: Data of egg albumin denaturation assay of compounds (3a-j)

Conc.	Percentage inhibition										
	Std.	3a	3b	3c	3d	3e	3f	3g	3h	3i	3j
10 µg/ml	20.83±0.32	18.75±0.40	32.29±0.26	30.20±0.43	30.21±0.08	12.5±0.23	16.66±0.06	19.79±0.15	9.37±0.16	32.29±0.19	8.33±0.28
20 µg/ml	53.12±0.43	30.20±0.24	35.41±0.18	32.29±0.32	34.37±0.26	32.2±0.44	22.91±0.23	25.00±0.33	15.6±0.17	43.75±0.24	18.75±0.11
30 µg/ml	62.5±0.34	28.12±0.13	45.83±0.25	43.75±0.37	38.54±0.12	41.66±0.37	47.91±0.42	27.08±0.12	23.9±0.13	42.70±0.32	32.29±0.21
40 µg/ml	64.58±0.13	41.66±0.16	66.66±0.22	64.58±0.18	59.37±0.27	54.16±0.23	54.16±0.18	41.66±0.34	25.0±0.54	43.75±0.34	33.33±0.43
50 µg/ml	68.75±0.19	42.70±0.20	67.70±0.09	69.79±0.33	64.58±0.27	64.58±0.28	58.33±0.22	55.20±0.30	41.66±0.41	68.75±0.39	37.5±0.41
IC_{50} (µg/ml)	16.31±0.21	49.82±0.24	48.97±0.14	44.85±0.26	53.33±0.32	27.10±0.12	28.72±0.21	38.57±0.29	56.33±0.33	25.14±0.21	52.85±0.27
IC_{50} (µM)	0.051±0.21	0.158±0.24	0.174±0.14	0.166±0.26	0.191±0.32	0.091±0.12	0.114±0.21	0.153±0.29	0.238±0.33	0.094±0.21	0.208±0.27



Scheme 1: Synthetic scheme of 1,3,4-oxadiazole derivatives

substituted aromatic aldehydes **(2)**, which undergo selective cyclization in the presence of cerium ammonium nitrate (CAN) as a catalytic medium and dichloromethane as a solvent to furnish the formation of final 1,3,4-oxadiazole derivatives. Dichloromethane acts as an excellent solvent medium and CAN as a tenable and uncontaminated catalytic agent. The purity of the compounds was ascertained by TLC and recrystallization techniques. The physicochemical data of the synthesized compounds are listed in Table 1. All the synthesized compounds were acquired in good yields between 64% and 77%.

The postulated structures of the 1,3,4-oxadiazoles were confirmed by FT-IR, ^{1}H-NMR, and mass spectral data. The FT-IR spectrum of compound **3a** showed an absorption band at 3028 cm^{-1} attributed to the C-H stretching. The other stretching vibrations at 1628 and 1555 cm^{-1} correspond to C=N and C=C groups, respectively. The absence of the carbonyl group of the hydrazide in the region of 1640–1680 cm^{-1} clearly indicates the oxadiazole ring formation. Formation of the compound **3a** was further confirmed by the ^{1}H-NMR spectrum, wherein the presence of aromatic protons was observed in the region of δ7.33–8.43 ppm. A sharp singlet was observed at δ2.51 ppm, indicating the presence of methyl protons. Further, the molecular ion peak at 315.16 [M+] in the mass spectrum of the compound confirmed the proposed structure.

Biological Evaluation

Denaturation of proteins is a well-reported cause of Inflammation; hence, the denaturation of egg and bovine serum albumin by the synthesized analogs of 1,3,4-oxadiazole was demonstrated as an attempt to evaluate its anti-inflammatory potential.

In the assay of bovine serum albumin method, all the tested compounds exhibited moderate-to-weak inhibitory efficacy at a concentration of 10–50 μg/ml. Compounds **3c, 3e, 3f, and 3i** showed moderate inhibition, compared to the standard drug (diclofenac sodium) at their micromolar concentrations. Compounds **3c** and **3f** showed moderate inhibition at the same micromolar concentration, that is, 0.13 μM. Furthermore, compounds **3e** and **3i** showed moderate inhibition at a concentration of 0.12 μM. This may be attributed due to the presence of electron-donating groups, which are present at the third/fourth position of the aromatic ring. All the other tested compounds showed very weak activity [Table 2].

In the case of egg serum albumin denaturation assay, most of the tested compounds exhibited moderate activity when compared to the standard diclofenac sodium. Compounds **3e, 3i, and 3f** showed moderate activity, and it is due to the presence of electron-donating groups such as methoxy and hydroxyl at position fourth [Table 3]. These compounds showed activity at low micromolar levels (0.091, 0.094, and 0.114, respectively) when compared to the other tested compounds. All the other compounds showed very weak activity in comparison to the standard.

From both activity profiles, it is clear that only those compounds with electron-donating capacity are exhibiting moderate activity, while the electron-withdrawing groups are showing weak activity toward the protein denaturation assay.

CONCLUSION

A new series of disubstituted 1,3,4-oxadiazoles at the second and fifth positions were synthesized, and spectral data confirmed their structures. Compounds with electron-donating groups showed moderate inhibitory anti-inflammatory activity in both the tested methods. CAN is an effective catalyst in the synthesis of proposed title compounds. It offers many advantages like available in solid form, non-irritant, reaction conditions are simple, easy to handle, a specific product, excellent yield, without any side products, compared to other oxidative/cyclizing agents.

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