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Synthesis of some new biologically active 1,3,4-oxadiazolyl nitroindoles and a modified Fischer indole synthesis of ethyl nitro indole-2-carboxylates

B. Narayana,[a,*] B. V. Ashalatha,[a] K. K. Vijaya Raj,[a] J. Fernandes[b] and B. K. Sarojini[c]

[a]*Department of Post-Graduate Studies and Research in Chemistry, Mangalore University, Mangalagangotri 574 199, India*
[b]*Department of Pharmaceutical Chemistry, N.G.S.M. Institute of Pharmaceutical Sciences, Mangalore 574 005, India*
[c]*Department of Chemistry, P.A. College of Engineering, Mangalore 574 153, India*

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Abstract—An efficient and modified synthesis of ethyl-4-nitro/5-nitro/6-nitro and 7-nitroindole-2-carboxylates is described. Carbohydrazides of corresponding ethyl nitroindole-2-carboxylates underwent smooth one-step transformation to 1,3,4-oxadiazolyl nitroindoles (**4a**–**l**) on reaction with aromatic carboxylic acids in the presence of phosphorus oxychloride. An alternate method to synthesize 1,3,4-oxadiazolyl nitroindoles is also described. Among the newly synthesized 1,3,4-oxadiazolyl nitroindoles, a few compounds are studied for anti-inflammatory activity.

1. Introduction

The indole derivatives display a wide range of biological activities. This is exemplified by the amino acid tryptophan, the hormones serotonin and melatonin, the anti-inflammatory drug indomethacin, the psychotropic drug LSD and the anti-tumour agent vinblastine.[1] Accordingly, the synthesis of indole derivatives has long been a topic of fundamental interest to organic and medicinal chemists. The Fischer indole synthesis is the most widely used method for the preparation of indole derivatives.[2] However, two major drawbacks of Fischer indole synthesis are lower yield and numerous by-products.[3] The synthesis of ethyl esters of 4/6/5/7-nitro-indole-2-carboxylic acids carried out according to Fischer indole synthesis resulted in mixtures of ethyl 4-nitro/6-nitro-indole-2-carboxylates, ethyl 5-nitroindole-2-carboxylate and ethyl 7-nitro indole-2-carboxylate and these cyclizations were carried out at elevated temperatures (125–195 °C). The separation between ethyl-4-nitro and 6-nitro indole-2-carboxylate was done by differential recrystallization in benzene, which is carcinogenic.[4,5]

During our initial trials for the cyclization of ethyl pyruvate nitrophenyl hydrazones (**1a**–**c**) to ethyl-nitroindole-2-carboxylates (**2a**–**d**) as per the reported procedure,[4,5] we faced the problem of charring of compounds and yields obtained were very low. But these cyclizations when carried out at temperatures in the range of 50–60 °C and maintained for 4 h, and after workup and recrystallization from ethyl acetate instead of benzene, resulted in better yields and purer compounds. These compounds on reaction with hydrazine hydrate yielded corresponding acid hydrazides (**3a**–**d**). The formation of acid hydrazides is confirmed by recording the IR spectrum.

The chemistry of substituted 1,3,4-oxadiazoles and their derivatives received considerable attention during the last decade as potential anti-inflammatory, analgesic, CNS-stimulanting, anticonvulsive, anticancer, diuretic and antihypertensive agents.[6–12] Anti-inflammatory activity of indole derivatives is extensively studied in recent years.[13–16] Incorporation of potential indole moiety may enhance biological activity of 1,3,4-oxadiazole derivatives. Hence it is thought worthwhile to synthesize

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* Corresponding author. Tel.: +91 8242287262; fax: +91 8242287367; e-mail: nbadiadka@yahoo.co.uk

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1,3,4-oxadiazolyl nitroindoles and study their anti-inflammatory activity.

2. Chemistry

4/6/5/7-Nitroindole-2-carbohydrazides (**3a–d**) underwent smooth one-step reaction with aromatic carboxylic acids in the presence of phosphorus oxychloride (method-1) to give 2-[5-(aryl)-1,3,4-oxadiazol-2-yl]-4-nitro/6-nitro/5-nitro/7-nitro indoles (**4a–l**) (Scheme 1). The structures of the newly synthesized compounds are confirmed by recording IR, ^{1}H NMR, mass spectra and elemental analysis.

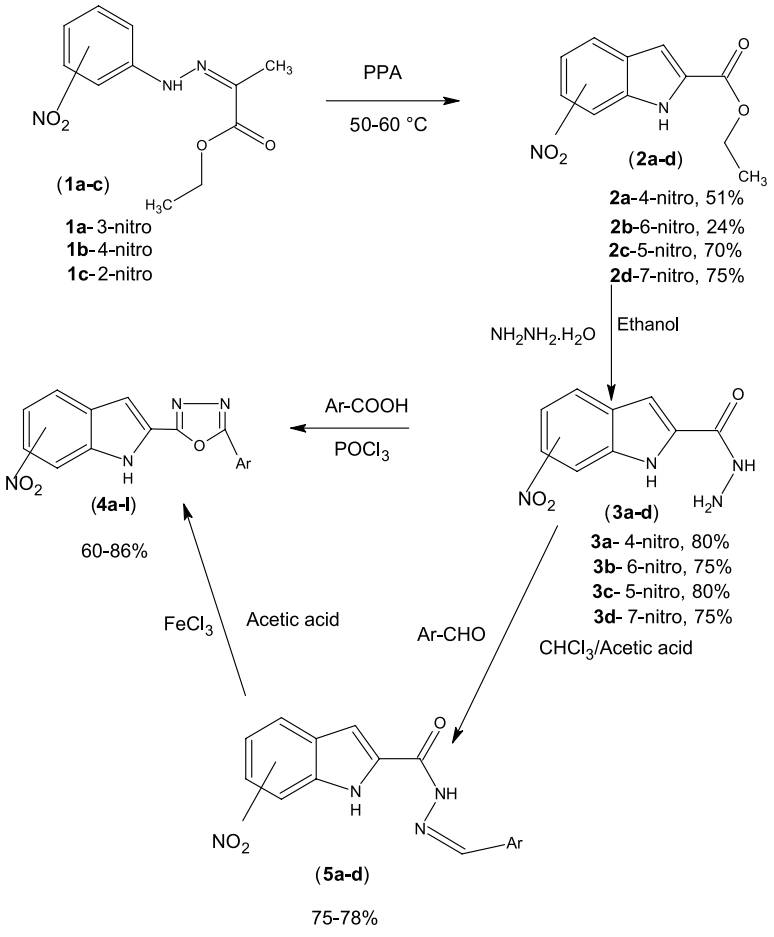
4-Nitroindole-2-carbohydrazide (**3a**), 6-nitroindole-2-carbohydrazide (**3b**), 5-nitroindole-2-carbohydrazide (**3c**) and 7-nitroindole-2-carbohydrazide (**3d**) were treated with corresponding aromatic aldehydes in chloroform with a catalytic amount of acetic acid. The compounds were confirmed by recording the IR and mass spectra. The characterization data are given in Experimental section. The Schiff bases of ethyl-4/6/5/7-nitroindole-2-carbohydrazides (**5a–d**) on cyclization in the presence of $FeCl_3$ (method-2) yielded **4a**, **4d**, **4f** and **4l**. Spectral data of the compounds **4a**, **4d**, **4f**, and **4l** are given in Experimental section (Tables 1 and 2).

3. Pharmacology

3.1. Anti-inflammatory activity

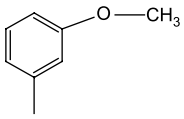
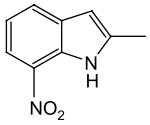
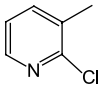
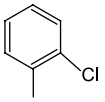
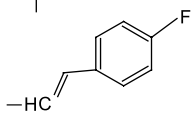
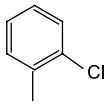
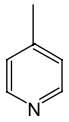
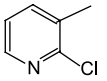
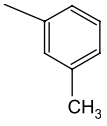
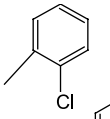
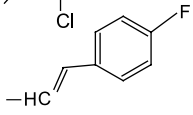
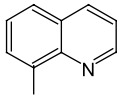
Six of the newly synthesized compounds **4a**, **4c–f** and **4k** were evaluated for their anti-inflammatory activity against carrageenin-induced acute paw edema in rats weighing 150–200 g.[17–20] Carrageenin, 0.1 ml (1% w/v solution prepared in 0.9% NaCl solution) was injected underneath the subplantar region. Indomethacin, 1.5 mg/kg body weight per oral (suspended in 0.3% CMC) was used as the standard drug. Compounds **4a**, **4c–f** and **4k** (5.0 mg/kg body weight) were suspended in 0.3% CMC and administered to rats by the oral route.

The animals were weighed and numbered into six groups and each group contained six animals. A mark was made on the hind paw (left) just beyond the tibio-tarsal junction, so that every time the paw was dipped in the mercury column up to the fixed mark constant paw volume was ensured. The initial paw volume of each rat was noted (all the six groups) by the mercury displacement method. To the first group was administered saline and to the second group was administered indomethacin orally. The third, fourth, fifth, and sixth groups were administered the test compounds **4a**, **4c–f** and **4k** orally



Scheme 1.

Table 1. Characterization data of (**4a–l**)

Compound no.	Position of NO_2	Ar	Yield (%)[a]	MP (°C)	Nature of crystals	% Nitrogen	
						Found	Calcd
4a	4		80[b] 69[c]	180–182	Yellow crystals	16.5	16.66
4b	4		70	226–228	Light yellow crystals	21.49	21.53
4c	4		85	>250	Yellow crystals	20.49	20.53
4d	6		87[b] 72[c]	>250	Yellow crystals	16.40	16.47
4e	6		75	>250	Yellow crystals	16.04	15.99
4f	5		86[b] 72[c]	>250	Brown crystals	16.38	16.47
4g	5		78	>250	Brown crystals	22.83	22.79
4h	5		76	194–196	Dark brown crystals	20.50	20.49
4i	7		75	222–225	Yellow crystals	17.43	17.48
4j	7		75	210–212	Yellow crystals	16.48	16.44
4k	7		60	240–242	Beige crystals	16.05	15.99
4l	7		68[b] 65[c]	250	Brown micro-crystals	19.56	19.59

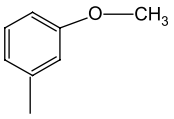
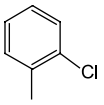
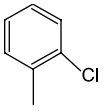
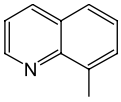
[a] Yields refer to single runs and are given for isolated products.
[b] Yield by method-1.
[c] Yield by method-2.

(5.0 mg/kg, suspended in 0.3% CMC). After 30 min, 0.1 ml of 1% (w/v) carrageenin was injected in the subplantar region of the left paw in all drug-treated groups (group I–IV). Immediately after the injection of carrageenin, paw volumes were measured in a mercury plethysmograph. Thereafter the paw volume was measured at 1, 2 and 3 h. The amount of edema in the drug-treated groups was compared in relation to the control group with the corresponding time intervals. The percentage of inhibition by the drugs was calculated using the formula,

$$\% \text{ of edema inhibition} = 100 - (V_{\text{test}}/V_{\text{control}}) \times 100,$$

where V_{control} = volume of paw edema in the control group; V_{test} = volume of paw edema in the drug treated group.

Table 2. Characterization data of (**5a–d**)

Compound No	Position of NO_2	Ar	Yield (%)[a]	MP °C	Nature of crystals	% Nitrogen	
						Found	Calcd
5a	4		78	>250	Yellow crystals	16.53	16.55
5b	6		75	>250	Light yellow crystals	16.38	16.34
5c	5		78	>250	Light yellow crystals	16.30	16.34
5d	7		78	>250	Light yellow crystals	19.39	19.48

[a] Yields refer to single runs and are given for isolated products.

Table 3. Anti-inflammatory activity screening of compounds **4a**, **4c–f** and **4k**: Carrageenin-induced rat paw edema

Group	Dose	Paw edema volume, Mean ± SE (ml)	% Decrease in paw edema (anti-inflammatory activity)
Control (Carrageenin alone)	0.1 ml/kg	0.42 ± 0.0089	—
Indomethacin	1.5 mg/kg p.o (suspended in 0.3% CMC)	0.163 ± 0.00843	60.04
4a	5.0 mg/kg p.o (suspended in 0.3% CMC)	0.26 ± 0.00549	35.0
4c	5.0 mg/kg p.o (suspended in 0.3% CMC)	0.22 ± 0.00281	46.07
4d	5.0 mg/kg p.o (suspended in 0.3% CMC)	0.19 ± 0.0033	52.5
4e	5.0 mg/kg p.o (suspended in 0.3% CMC)	0.22 ± 0.00840	46.07
4f	5.0 mg/kg p.o (suspended in 0.3% CMC)	0.21 ± 0.00343	48.5
4k	5.0 mg/kg p.o (suspended in 0.3% CMC)	0.21 ± 0.00666	48.5

Vehicle: 5% Gum acacia. Animals: Albino rats. Weights: 150–200 g. Route of administration: Oral. No of animals in each group: 6.
$P < 0.001$ versus indomethacin.

The results were expressed as % inhibition of edema over the untreated control group.

Table 3 shows the effect of drug and extract treatment on carrageenin-induced edema. The percentage of inhibition was compared with that of the standard drug indomethacin.

4. Discussion

An insight into the anti-inflammatory activity with respect to the chemical structure reveals that compounds **4d** and **4f** bearing a 2-chlorophenyl moiety, and compound **4k** bearing a 4-fluoro cinnamyl moiety, exhibited good anti-inflammatory activity at a dose of 5.0 mg/kg in comparison with the standard drug indomethacin. Compound **4c** bearing a 2-chloronicotinyl moiety and compound **4e** bearing a 4-fluorocinnamyl moiety have shown moderate anti-inflammatory activity and the compound **4a** bearing a 3-methoxyphenyl moiety has shown mild anti-inflammatory activity. There is further scope to investigate the effect of nitro group and its orientation to the anti-inflammatory activity. In the present study, the studies are being done at 5.0 mg/kg of different test compounds. So there is further scope to carry out the study at different doses and also compare the activity with other non-steroidal anti-inflammatory drugs.

5. Experimental

5.1. Preparation of ethyl-4/6-nitro indole-2-carboxylate (*2a–b*)[5]

Ethylpyruvate-3-nitro phenylhydrazone (2 g, 0.00796 mol) was taken in 10 g polyphosphoric acid and kept under stirring for proper mixing. The reaction mass was slowly heated to 50–60 °C and maintained for 4 h. Progress of the reaction was monitored by TLC. The reaction mass was cooled and 100 ml of DM water was added to break the lumps till it became a slurry. The solid was filtered and washed with water. The dried crude was charcoalized in ethyl acetate filtered over hyflo and slowly cooled to room temperature and kept overnight under stirring. After one more recrystallization from ethyl acetate, ethyl-4-nitro indole-2-carboxylate (**2a**) was obtained as yellow crystals with a yield of 0.96 g (51%) mp 226–228 °C (lit.,[5] 228–230 °C).

Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.4; H, 4.3; N, 11.96. Found: C, 56.20, H, 4.52; N, 12.04.

The ethyl acetate mother liquor from which ethyl-4-nitro indole-2-carboxylate was isolated, was concentrated and kept under stirring overnight at room temperature. The solid obtained was filtered and again recrystallized from ethyl acetate. Ethyl-6-nitro indole-2-carboxylate (**2b**) was isolated as light yellow needles with a yield of 0.43 g (24%) mp 194–196 °C (lit.[5] 195–197 °C).

Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.4; H, 4.3; N, 11.96. Found: C, 56.38, H, 4.52; N, 12.20.

5.2. Preparation of ethyl-5-nitro indole-2-carboxylate (2c)[5]

Ethylpyruvate-4-nitrophenylhydrazone (2 g, 0.00796 mol) was taken in 10 g of polyphosphoric acid and kept under stirring for proper mixing. The reaction mass was slowly heated to 50–60 °C and maintained for 4 h. Progress of the reaction was monitored by TLC. The reaction mass was cooled and 100 ml of DM water was added to break the lumps till it became a slurry. The solid was filtered and washed with water. The dried crude was recrystallized from ethyl acetate. The product was obtained as yellow crystals with a yield of 1.29 g (70%), mp 219–222 °C (lit.,[5] 220–223 °C).

Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.4; H, 4.3; N, 11.96. Found: C, 56.39, H, 4.42; N, 12.04.

5.3. Preparation of ethyl-7-nitro indole-2-carboxylate (2d)[5]

Ethylpyruvate-2-nitrophenylhydrazone (2 g, 0.00796 mol) was taken in 10 g of polyphosphoric acid and kept under stirring for proper mixing. The reaction mass was slowly heated to 50–60 °C and maintained for 4 h. Progress of the reaction was monitored by TLC. The reaction mass was cooled and 100 ml of DM water was added to break the lumps till it became a slurry. The solid was filtered and washed with water. The dried crude was recrystallized from ethyl acetate. The product was obtained as yellow crystals with a yield of 1.39 g (75%), mp 92–93 °C (lit.,[5] 92–93 °C).

Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.4; H, 4.3; N, 11.96. Found: C, 56.46, H, 4.48; N, 12.02.

5.4. General method for the preparation of 4/6/5/7-nitro indole-2-carbohydrazide (3a–d)

Ethyl-4/6/5/7-nitro indole-2-carboxylate (2.34 g, 0.01 mol) in 25 ml of absolute ethanol was refluxed with 1.0 ml of hydrazine hydrate for 2 h. After the completion of the reaction by TLC, the reaction mixture was cooled to room temperature. The separated solid was filtered, washed with cold ethanol and recrystallized from ethanol.

5.4.1. 4-Nitro indole-2-carbohydrazide (3a). The product was obtained as yellow micro-crystals with a yield of 1.76 g (80%), mp 280 °C (dec). Molecular formula: $C_9H_8N_4O_3$, IR (KBr): 3325 cm^{-1} ($-NH_2$), 1722 and 1635 cm^{-1} ($-CONH_2$) and 1544.9 cm^{-1} ($-NO_2$).

Anal. Calcd for $C_9H_8N_4O_3$: C, 49.09; H, 3.66; N, 25.45. Found: C, 49.1, H, 3.67; N, 25.42.

5.4.2. 6-Nitro indole-2-carbohydrazide (3b). The product was obtained as yellow micro-crystals with a yield of 1.65 g (75%), mp 292 °C (dec). Molecular formula: $C_9H_8N_4O_3$, IR (KBr): 3388 cm^{-1} ($-NH_2$), 1654 and 1615 cm^{-1} ($-CONH_2$) and 1546 cm^{-1} ($-NO_2$).

Anal. Calcd for $C_9H_8N_4O_3$: C, 49.09; H, 3.66; N, 25.45. Found: C, 49.11, H, 3.65; N, 25.44

5.4.3. 5-Nitro indole-2-carbohydrazide (3c). The product was obtained as brown crystals with a yield of 1.76 g (80%), mp >250 °C. Molecular formula: $C_9H_8N_4O_3$, IR (KBr): 3324 cm^{-1} (–NH), 1635 and 1724 cm^{-1}($-CONH_2$) and 1544 cm^{-1} ($-NO_2$).

Anal. Calcd for $C_9H_8N_4O_3$: C, 49.09; H, 3.66; N, 25.45. Found: C, 49.09, H, 3.67; N, 25.41.

5.4.4. 7-Nitro indole-2-carbohydrazide (3d). The product was obtained as yellow micro-crystals with a yield of 1.65 g (75%), mp 230–232 °C. Molecular formula: $C_9H_8N_4O_3$, IR (KBr): 3325 cm^{-1} ($-NH_2$), 1635.5 and 1722.3 cm^{-1} ($-CONH_2$) and 1544.9 cm^{-1} ($-NO_2$).

Anal. Calcd for $C_9H_8N_4O_3$: C, 49.09; H, 3.66; N, 25.45. Found: C, 49.06, H, 3.67; N, 25.44.

5.5. Preparation of Schiff bases (5a–d)

4/6/5/7-Nitro indole-2-carbohydrazide (2.20 g, 0.01 mol) in 22 ml of chloroform was refluxed with 0.01 mol of aromatic aldehydes for 4 h in the presence of one drop of acetic acid. The solvent was removed by distillation. The solid was collected and recrystallized from methanol–dimethyl formamide mixture.

5.5.1. *N*′-[(3-Methoxyphenyl)methylene]-4-nitro-1*H*-indole-2-carbohydrazide (5a). Molecular formula: $C_{17}H_{14}N_4O_4$; MS: *m/z* 338 (M^+, *I* = 20%), *m/z* 205 ($C_9H_7N_3O_3$, *I* = 80%), *m/z* 188 ($C_9H_5N_2O_3$, *I* = 100%); IR (KBr): 3398 cm^{-1} (–NH–), 3053 cm^{-1} ($-CH_3$), 2949 and 2848 cm^{-1} (–CH), 1656 cm^{-1} (–C=O), 1545 cm^{-1} ($-NO_2$).

5.5.2. *N*′-[(2-Chlorophenyl)methylene]-6-nitro-1*H*-indole-2-carbohydrazide (5b). Molecular formula: $C_{16}H_{11}ClN_4O_3$, MS: *m/z* 342 (M^+, *I* = 10%), *m/z* 205 ($C_9H_7N_3O_3$, *I* = 84%), *m/z* 188 ($C_9H_5N_2O_3$, *I* = 100%); IR (KBr): 3399 cm^{-1} (–NH–), 2945 and 2843 cm^{-1} (–CH), 1659 cm^{-1} (–C=O), 1545 cm^{-1} ($-NO_2$), 1058 cm^{-1} (Ar–Cl).

5.5.3. *N*′-[(2-Chlorophenyl) methylene]-5-nitro-1*H*-indole-2-carbohydrazide (5c). Molecular formula: $C_{16}H_{11}ClN_4O_3$, MS: *m/z* 342 (M^+, *I* = 12%), *m/z* 205 ($C_9H_7N_3O_3$, *I* = 86%), *m/z* 188 ($C_9H_5N_2O_3$, *I* = 100%); IR (KBr): 3399 cm^{-1} (–NH–), 2945 and 2843 cm^{-1} (–CH), 1659 cm^{-1} (–C=O), 1545 cm^{-1} ($-NO_2$), 1058 cm^{-1} (Ar–Cl).

5.5.4. 7-Nitro-*N*′-[(quinolin-7-yl) methylene]-1*H*-indole-2-carbohydrazide (5d). Molecular formula: $C_{19}H_{13}N_5O_3$, MS: *m/z* 359 (M^+, *I* = 5%), *m/z* 155 ($C_{10}H_5N_2$, *I* = 40%), *m/z* 142 ($C_{10}H_9N$, *I* = 20%); IR (KBr): 3399 cm^{-1} (–NH–), 2945 and 2843 cm^{-1} (–CH), 1659 cm^{-1} (–C═O), 1545 cm^{-1} ($–NO_2$).

5.6. Preparation of 2-[5-(aryl)-1,3,4-oxadiazol-2-yl]-4-nitro-1*H*-indoles (4a–c), 2-[5-(aryl)-1,3,4-oxadiazol-2-yl]-6-nitro-1*H*-indoles (4d–e), 2-[5-(aryl)-1,3,4-oxadiazol-2-yl]-5-nitro-1*H*-indoles (4f–h) and 2-[5-(aryl)-1,3,4-oxadiazol-2-yl]-7-nitro-1*H*-indoles (4i–l)

Method-1: A mixture of 4-nitro, 6-nitro, 5-nitro, or 7-nitroindole-2-carbohydrazide (0.001 mol), aromatic carboxylic acid (0.0015 mol) in 4 ml of phosphorus oxychloride was refluxed on an oil bath for 6 h. The excess phosphorus oxychloride was distilled under reduced pressure. The cooled reaction mass was then poured into ice cold water with stirring. The separated solid was filtered and washed with sodium bicarbonate solution and then with water. The product was then recrystallized from ethanol–dimethylformamide mixture.

Method-2: The appropriate Schiff bases (**5a–d**), (0.01 mol) were dissolved in glacial acetic acid (100 ml) and ferric chloride (4 g in 100 ml) was added to it with stirring. The mixture was stirred for 1 h and diluted with water. The solid obtained was filtered, washed with water, dried and recrystallized in ethanol–dimethylformamide mixture.

5.6.1. 2-[5-(3-Methoxyphenyl)-1,3,4-oxadiazol-2-yl]-4-nitro-1*H*-indole (4a). Molecular formula: $C_{17}H_{12}N_4O_4$, MS: *m/z* 336 (M^+, *I* = 60%); ^1H NMR ($CDCl_3$–DMSO); δ 3.89 (s, 3H, $–CH_3$), δ 7.07–7.09 (m, 2H, Ar–H), δ 7.38 (t, 1H, Ar–H), δ 7.52 (s, 1H, Ar–H), δ 7.87–7.95 (m, 2H, Ar–H), δ 8.11–8.16 (m, 2H, Ar–H), δ 12.73 (s, –NH–).

5.6.2. 4-Nitro-2-[5-(7-nitro-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]-1*H*-indole (4b). Molecular formula: $C_{18}H_{10}N_6O_5$, MS: *m/z* 390 (M^+, *I* = 10%), *m/z* 220 (*I* = 80%, $C_9H_8N_4O_3$); ^1H NMR ($CDCl_3$–DMSO); δ 7.27 (t, 1H, Ar–H), δ 7.35 (s, 1H, Ar–H), δ 8.07$_{(J = 7.8)}$ (d, 1H, Ar–H), δ 8.27$_{(J = 8.1)}$ (d, 1H, Ar–H), δ 10.40 (s, 1H, –NH–).

5.6.3. 2-[5-(2-Chloropyridin-3-yl)-1,3,4-oxadiazol-2-yl]-4-nitro-1*H*-indole (4c). Molecular formula: $C_{15}H_8ClN_5O_3$; MS: *m/z* 340 (M^+, *I* = 10%), *m/z* 220 (*I* = 80%, $C_9H_8N_4O_3$); IR (KBr): 3427.5 and 3232.5 cm^{-1} (–NH–), 1330 cm^{-1} (═C–O–), 1058 cm^{-1} (Ar–Cl).

5.6.4. 2-[5-(2-Chlorophenyl)-1,3,4-oxadiazol-2-yl]-6-nitro-1*H*-indole (4d). Molecular formula: $C_{16}H_9ClN_4O_3$; MS: *m/z* 340 (M^+, *I* = 42%), *m/z* 139 (*I* = 100%, *o*-Cl-C_6H_4CN); IR (KBr): 3297 cm^{-1} (–NH–), 1589 cm^{-1} ($–NO_2$), 1342 cm^{-1} (═C–O–), 1058 cm^{-1} (Ar–Cl); ^1H NMR ($CDCl_3$–DMSO): δ 7.47 (s, 1H, Ar–H), δ 7.59–7.75 (m, 3H, Ar–H), δ 7.89$_{(J = 8.86)}$ (d, 1H, Ar–H), δ 7.97$_{(J = 10.5)}$ (d, 1H, Ar–H), δ 8.15$_{(J = 6.28)}$ (d, 1H, Ar–H), δ 8.15 (s, 1H, Ar–H), δ 8.13 (s, 1H, –NH–).

5.6.5. 2-{5-[2-(4-Fluorophenyl)vinyl]-1,3,4-oxadiazol-2-yl}-6-nitro-1*H*-indole (4e). Molecular formula: $C_{18}H_{11}FN_4O_3$; MS: *m/z* 347 (M−1, *I* = 15%), *m/z* 189 (*I* = 10%, $C_8H_5N_3O_2$); *m/z* 149 (*I* = 30%, C_9H_6FO).

5.6.6. 2-[5-(2-Chlorophenyl)-1,3,4-oxadiazol-2-yl]-5-nitro-1*H*-indole (4f). Molecular formula: $C_{16}H_9ClN_4O_3$; MS: *m/z* 340 (M^+, *I* = 5%), *m/z* 139 (*I* = 100%, *o*-Cl-C_6H_4CN); IR (KBr): 3297 cm^{-1} (–NH–), 1589 cm^{-1} ($–NO_2$), 1342 cm^{-1} (C–O), 1058 cm^{-1} (Ar–Cl).

5.6.7. 5-Nitro-2-(5-pyridin-4-yl-1,3,4-oxadiazol-2-yl)-1*H*-indole (4g). Molecular formula: $C_{15}H_9N_5O_3$; MS: *m/z* 307 (M^+, *I* = 50%); ^1H NMR ($CDCl_3$–DMSO): δ 7.40 (dd, 2H, Ar–H), δ 7.8 (dd, 2H, Ar–H), δ 8.0 (dd, 2H, Ar–H), δ 8.8 (s, 1H, Ar–H), δ 8.9 (s, 1H, Ar–H), δ13.16 (s, 1H, –NH–).

5.6.8. 2-[5-(2-Chloropyridin-3-yl)-1,3,4-oxadiazol-2-yl]-5-nitro-1*H*-indole (4h). Molecular formula: $C_{15}H_8ClN_5O_3$; MS: *m/z* 340 (M^+, *I* = 80%); ^1H NMR ($CDCl_3$–DMSO): δ 7.60 (m, 3H, Ar–H), δ 7.8 (s, 1H, Ar–H), δ 8.02 (dd, 1H, Ar–H), δ 8.15 (dd, 1H, Ar–H), δ 8.6 (s, 1H, Ar–H), 12.5 (s, 1H, –NH–).

5.6.9. 2-[5-(3-Methyl phenyl)-1,3,4-oxadiazol-2-yl]-7-nitro-1*H*-indole (4i). Molecular formula: $C_{17}H_{12}N_4O_3$; MS: *m/z* 320 (M^+, *I* = 100%), *m/z* 189 ($C_9H_7N_3O_2$, *I* = 16%), *m/z* 119 (C_8H_9N, *I* = 97%), *m/z* 91 (C_7H_7, *I* = 25%) ^1H NMR ($CDCl_3$–DMSO): δ 2.48 (s, 3H, $–CH_3$), δ 7.31–7.41 (m, 3H, Ar–H), δ 7.52 (s, 1H, Ar–H), δ 7.9 (s, 1H, Ar–H), δ 8.15$_{(J = 7.84)}$ (d, 1H, Ar–H), δ 8.24$_{(J = 8.15)}$ (d, 1H, Ar–H), δ 8.15 (s, 1H, Ar–H), δ 11.9 (s, 1H, –NH–).

5.6.10. 2-[5-(2-Chlorophenyl)-1,3,4-oxadiazol-2-yl]-7-nitro-1*H*-indole (4j). Molecular formula: $C_{16}H_9ClN_4O_3$; MS: *m/z* 340 (M^+, *I* = 63%), *m/z* 189 ($C_9H_7N_3O_2$, *I* = 25%), *m/z* 139 (C_7H_6ClN, *I* = 100%); IR (KBr): 3298 cm^{-1} (–NH–), 1598 cm^{-1} ($–NO_2$), 1342 cm^{-1} (C–O), 1054 cm^{-1} (Ar–Cl).

5.6.11. 2-{5-[2-(4-Fluorophenyl)vinyl]-1,3,4-oxadiazol-2-yl}-7-nitro-1*H*-indole (4k). Molecular formula: $C_{18}H_{11}FN_4O_3$; MS: *m/z* 349 (M^+, *I* = 100%), *m/z* 189 ($C_9H_7N_3O_2$, *I* = 40%,) *m/z* 149 (C_9H_8FN, *I* = 66%) *m/z* 121 (C_8H_6F, *I* = 50%); ^1H NMR ($CDCl_3$–DMSO): δ 7.18 (dd, 2H, –HC═CH–), δ 7.35 (t, 1H, Ar–H), δ 7.50 (s, 1H, Ar–H), δ 7.72–7.78 (m, 4H, Ar–H), δ 8.14$_{(J = 7.73)}$ (d, 1H, Ar–H), δ 8.26$_{(J = 8.08)}$ (d, 1H, Ar–H), δ 11.65 (s, 1H, –NH–).

5.6.12. 8-[5-(7-Nitro-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]quinoline 4l. Molecular formula: $C_{19}H_{11}N_5O_3$; MS: *m/z* 357 (M^+, *I* = 98%), *m/z* 311 ($M–NO_2$, *I* = 22%), *m/z* 187 ($C_{10}H_9N_3O$, *I* = 20%), *m/z* 156 ($C_{10}H_8N_2$, *I* = 100%), *m/z* 143 ($C_{10}H_9N$, *I* = 25%); ^1H NMR ($CDCl_3$–DMSO): δ 7.35 (t, 1H, Ar–H), δ 7.74 (dd, 1H, Ar–H), δ 7.84$_{(J = 7.83)}$ (d, 1H, Ar–H), δ 7.89$_{(J = 4.6)}$ (d, 1H, Ar–H), δ 8.15$_{(J = 7.95)}$ (d, 1H, Ar–H), δ 8.28 (dd, 2H, Ar–H), δ 8.57 (m, 2H, Ar–H), δ 9.18 (s, 1H, Ar–H), δ 11.76 (s, 1H, –NH).

6. Conclusion

In conclusion, we developed a smooth one-step synthesis of 2-[5-(aryl)-1,3,4-oxadiazol-2-yl]-4-nitro-1*H*-indoles, 2-[5-(aryl)-1,3,4-oxadiazol-2-yl]-5-nitro-1*H*-indoles, 2-[5-(aryl)-1,3,4-oxadiazol-2-yl]-6-nitro-1*H*-indoles and 2-[5-(aryl)-1,3,4-oxadiazol-2-yl]-7-nitro-1*H*-indoles. In the present work, the Fischer indole cyclization was modified by considerably reducing the temperature to 50–60 °C and maintaining the reaction for 4–5 h. The synthesized compounds **4d** and **4f** bearing a 2-chlorophenyl moiety, and compound **4k** bearing a 4-fluoro cinnamyl moiety, exhibited good anti-inflammatory activity at a dose of 5.0 mg/kg in comparison with the standard drug indomethacin.

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