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One-Pot Synthesis of Novel 3,5-Disubstituted-1,2,4-oxadiazoles from Indazole Carboxylic Acid Esters and Amidoximes

UDUTHA KUMARA SWAMY^{1,*}, H. RAMA MOHAN¹, U. VIPLAVA PRASAD², T. SURESH¹ and T. LAXMI KUMAR¹

¹Laurus Labs Private Limited, IKP Knowledge Park, Turkapally, Shameerpet, Hyderabad-500 078, India

²Department of Organic Chemistry, Foods, Drugs and Water, Andhra University, Visakhapatnam-530 003, India

*Corresponding author: Fax: +91 40 23480480; Tel: +91 40 30413370; E-mail: kumarudutha@gmail.com

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An efficient and high-yielding one-pot synthesis of 3,5-disubstituted-1,2,4-oxadiazoles from indazole carboxylic acid methyl esters and amidoximes is described. In this study a series of novel 3,5-disubstituted-1,2,4-oxadiazoles (**3a-d**), (**4a-d**), (**5a-d**), (**6a-d**), (**7a-d**) were synthesized using amidoximes **2a-d** and indazole carboxylic acid esters (**3-6**).

Keywords: Amidoximes, Indazole carboxylic acid esters, 1,2,4-Oxadiazoles.

INTRODUCTION

1,2,4-Oxadiazoles are important class of heterocycles due to their biological importance and are stable to physiological environment. 1,2,4-Oxadiazoles have often been used as bioisosteres of esters and amides¹ and are found in several drugs and drug leads² which includes potent sphingosine-1-phosphate-1 (S1P1) agonist (**I**)³, the metabotropic glutamate subtype 5 (mGlu5) receptor (**II**)⁴ and muscarinic receptor (**III**)⁵ for the treatment of Alzheimer's diseases. They can also be found in a number of biologically important molecules, such as serotonergic (5-HT₃) antagonists (**IV**)⁶, benzodiazepine receptor agonists (**V**)⁷ and dopamine ligands (**VI**)⁸. Several papers reported the use of 1,2,4-oxadiazole in a number of

pharmacologically important molecules, including the design of amino acyl-gly dipeptidomimetics⁹, signal transduction inhibitors¹⁰, or cell adhesion inhibitors¹¹ as antiketoplastid materials¹², β_3 adrenergic receptor¹³, antiinflammatory agents¹⁴, agrochemical and antifungal activities¹⁵⁻¹⁷. Compounds containing 1,2,4-oxadiazole moieties are also active against HIV integrase inhibitors¹⁸ and antituberculostatic agents¹⁹. They show activity as growth hormone secretagogues²⁰ and antitumor agents²¹. They also inhibit SH2 domain of tyrosine kinase²², monoamine oxidase²³, human neutrophil elastase²⁴, human DNA topoisomerases²⁵. As discussed above 1,2,4-oxadiazole moiety shows activities in multiple therapeutic areas, hence an attempt was made at first for the synthesis of novel 3-indazolyl-5-aryl-1,2,4-oxadiazoles.

EXPERIMENTAL

Melting points of newly synthesized compounds were determined in an open glass capillary tubes using Buchi/Polman melting point apparatus and are uncorrected. Infrared spectra were recorded in potassium bromide pellets with a Perkin IR spectrometer. All ^1H NMR and ^{13}C NMR spectra were recorded on a BRUCKER 300 MHz instrument respectively. Chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard and the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = double doublet and dt = double triplet. Mass spectra were recorded Agilent-LC-MS instrument giving only M^+ values using ($\text{M}^+ + 1$) mode. TLC was performed with Silica gel GF-254 from Merck & Co., (Germany). Spots were detected under UV-light or in iodine. The following general experimental procedures followed for the synthesis of all compounds.

General procedure-I (Esterification of acid): To a solution of methyl-nitro benzoic acid (0.11 mol) in acetone (200 mL) were added potassium carbonate (0.22 mol) and was stirred at room temperature for 10 min. Dimethyl sulphate (0.13 mol) was added to the reaction mixture. The mixture was then stirred for 4 h at reflux temperature. Reaction was monitored by TLC. After completion, reaction mixture was cooled to room temperature, filtered and washed with acetone. The filtrate was concentrated to get residue and residue was dissolved in ethyl acetate. The organic layer was washed with water three times followed by brine. Organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was triturated with heptane to give corresponding methyl-methyl nitro benzoate.

Methyl-2-methyl-3-nitro-benzoate (15): Compound **15** was prepared from **14** following general procedure-I (98 % yield, Cream colour solid, m.p.: 63-65 °C): ^1H NMR (300 MHz, CDCl_3) 7.99 (dd, 1H, $J = 6.69, 1.11$ Hz, Ar-H), 7.84 (dd, 1H, $J = 7.02, 1.08$ Hz, Ar-H), 7.40 (t, 1H, $J = 7.02$ Hz, Ar-H), 3.94 (s, 3H, $-\text{OCH}_3$), 2.62 (s, 3H, $-\text{CH}_3$); ESI-MS m/z 196 ($\text{M} + \text{H}$) $^+$.

Methyl-3-methyl-4-nitro-benzoate (18): Compound **18** was prepared from **17** following general procedure-I (92 % yield, Light brown colour solid, m.p.: 79-82 °C): ^1H NMR (300 MHz, CDCl_3) 8.03 (s, 1H, Ar-H), 7.98 (d, 2H, $J = 1.26$ Hz, Ar-H), 3.96 (s, 3H, $-\text{OCH}_3$), 2.62 (s, 3H, $-\text{CH}_3$); ESI-MS m/z 196 ($\text{M} + \text{H}$) $^+$.

Methyl-4-methyl-3-nitro-benzoate (21): Compound **21** was prepared from **20** following general procedure-I (96 % yield, Light brown colour solid, m.p.: 48-52 °C): ^1H NMR (300 MHz, CDCl_3) 8.60 (d, 1H, $J = 1.68$ Hz, Ar-H), 8.13 (dd, 1H, $J = 6.24, 1.77$ Hz, Ar-H), 7.43 (d, 1H, $J = 7.98$ Hz, Ar-H), 3.95 (s, 3H, $-\text{OCH}_3$), 2.65 (s, 3H, $-\text{CH}_3$); ESI-MS m/z 196 ($\text{M} + \text{H}$) $^+$.

Methyl-3-methyl-2-nitro-benzoate (24): Compound **24** was prepared from **23** following general procedure-I (90 % yield, Light brown colour solid, m.p.: 71-74 °C): ^1H NMR (300 MHz, CDCl_3) 7.86-7.83 (m, 1H, Ar-H), 7.51-7.42 (m, 2H, Ar-H), 3.89 (s, 3H, $-\text{OCH}_3$), 2.34 (s, 3H, $-\text{CH}_3$); ESI-MS m/z 196 ($\text{M} + \text{H}$) $^+$.

General procedure-II (Reduction of nitro group to amine): To a solution of corresponding nitro compound (0.10

mol) in ethanol (200 mL) was added Fe (0.40 mol) and heated to reflux. Aqueous NH_4Cl (50 mL, 1.00 mol) was added slowly drop by drop to the reaction mixture at reflux temperature. After complete addition reaction, mixture was refluxed for 4 h. Reaction was monitored by TLC. After completion, reaction mixture was cooled to room temperature, filtered and washed with ethanol. The filtrate was concentrated to get residue and the residue was dissolved in ethyl acetate. The organic layer was washed with water three times, followed by brine. Organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was triturated with heptane to give corresponding methyl aminobenzoate.

Methyl-3-amino-2-methyl-benzoate (16): Compound **16** was prepared from compound **15** following general procedure-II (86 % yield, brown colour low-melting solid): ^1H NMR (300 MHz, CDCl_3) 7.20 (dd, 1H, $J = 6.54, 1.23$ Hz, Ar-H), 7.05 (t, 1H, $J = 7.86$ Hz, Ar-H), 6.81 (dd, 1H, $J = 7.23, 0.63$ Hz, Ar-H), 3.87 (s, 3H, $-\text{OCH}_3$), 2.33 (s, 3H, $-\text{CH}_3$); ESI-MS m/z 166 ($\text{M} + \text{H}$) $^+$.

Methyl-4-amino-3-methyl-benzoate (19): Compound **19** was prepared from compound **18** following general procedure-II (80 % yield, brown color solid, m.p.: 115-120 °C): ^1H NMR (300 MHz, CDCl_3) δ 7.73 (d, 2H, $J = 9.00$ Hz, Ar-H), 6.62 (d, 1H, $J = 8.07$ Hz, Ar-H), 4.99 (bs, 2H, $-\text{NH}_2$), 3.85 (s, 3H, $-\text{OCH}_3$), 2.17 (s, 3H, $-\text{CH}_3$); ESI-MS m/z 166 ($\text{M} + \text{H}$) $^+$.

Methyl-3-amino-4-methyl-benzoate (22): Compound **22** was prepared from compound **21** following general procedure-II (88 % yield, light brown colour solid, m.p.: 115-120 °C): ^1H NMR (300 MHz, CDCl_3) 7.38-7.33 (m, 2H, Ar-H), 7.09 (d, 1H, $J = 7.71$ Hz, Ar-H), 3.87 (s, 3H, $-\text{OCH}_3$), 3.69 (bs, 2H, $-\text{NH}_2$), 2.20 (s, 3H, $-\text{CH}_3$); ESI-MS m/z 166 ($\text{M} + \text{H}$) $^+$.

Methyl-2-amino-3-methyl-benzoate (25): Compound **25** was prepared from **24** following general procedure-II (85 % yield, Light brown colour low melting solid): ^1H NMR (300 MHz, CDCl_3) δ 7.79-7.76 (m, 1H, Ar-H), 7.20-7.16 (m, 1H, Ar-H), 6.60 (dd, 1H, $J = 7.47, 0.45$ Hz, Ar-H), 5.82 (bs, 2H, $-\text{NH}_2$), 3.8 (s, 3H), 2.16 (s, 3H); ESI-MS m/z 166 ($\text{M} + \text{H}$) $^+$.

General procedure-III (Synthesis of indazole carboxylic acid methyl ester (4,5,6)): Methyl-amino benzoate (0.10 mol) was dissolved in acetic acid (320 mL) and was cooled to 15 to 20 °C, solution of sodium nitrite (0.12 mol) in demineralized water (16 mL) was slowly added over a period of 0.5 h. After complete addition reaction temperature was increased to 25 to 30 °C and stirring was continued for 2-3 h. The progress of the reaction was monitored by TLC. After completion, reaction mass was filtered and residue washed with acetic acid. Filtrate was concentrated under reduced pressure at below 60 °C to get residue. To the residue demineralized water was added at room temperature and stirred for 0.5 h. The solid obtained was filtered and washed with water. Crude product was dried under vacuum at 60 °C for 2 h. Crude product was taken in to 5 % ethyl acetate-*n*-hexane solution and stir for 1 h at room temperature. Solid was filtered and washed with 5 % ethyl acetate-*n*-hexane mixture. The product was dried under vacuum at below 80 °C to give corresponding indazoles.

Indazole-4-carboxylic acid methyl ester (4): Compound **4** was prepared from compound **16** following general procedure-III (80 % yield, brown colour solid, m.p.: 150-154 °C): ^1H NMR (300 MHz, CDCl_3) δ 8.60 (s, 1H, $-\text{CH}=\text{N}$), 7.96 (dd,

1H, $J = 6.66, 0.66$ Hz, Ar-H), 7.73 (d, 1H, $J = 8.40$ Hz, Ar-H), 7.48 (dd, 1H, $J = 7.32, 1.05$ Hz, Ar-H), 4.03 (s, 3H, -OCH₃); ESI-MS m/z 177 (M + H)⁺.

Indazole-5-carboxylic acid methyl ester (5): Compound **5** was prepared from compound **19** following general procedure-III (85 % yield, brown color solid, m.p.: >220 °C): ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.38 (s, 1H, -NH), 8.47 (t, 1H, $J = 0.78$ Hz, -CH=N), 8.23 (t, 1H, 1.17 Hz, Ar-H), 7.89 (dd, 1H, $J = 7.17, 1.62$ Hz, Ar-H), 7.61-7.58 (m, 1H, Ar-H), 3.84 (s, 3H, -OCH₃); ESI-MS m/z 177 (M + H)⁺.

Indazole-6-carboxylic acid methyl ester (6): Compound **6** was prepared from compound **22** following general procedure-III (83 % yield, brown color solid, m.p.: 140-144 °C): ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.42 (s, 1H, -NH), 8.16 (t, 2H, $J = 10.35$ Hz, Ar-H), 7.86 (d, 1H, $J = 8.46$ Hz, Ar-H), 7.65 (dd, 1H, $J = 7.17, 1.32$ Hz, Ar-H), 3.86 (s, 3H, -OCH₃); ESI-MS m/z 177 (M + H)⁺.

General procedure-IV (Synthesis of 1,2,4-oxadiazoles):

Method-A: To a mixture of indazole carboxylic acid ester (2.8 mmol) and amidoxime (2.8 mmol) in toluene (7.5 mL) was added potassium carbonate (5.6 mmol). Reaction mixture was heated to reflux for 6 to 12 h and reaction progress was monitored by TLC. After completion, reaction mixture was cooled to room temperature and filtered. Filtrate was concentrated to get residue and dissolved in ethyl acetate. Resulting mixture was washed with water and brine. The organic phase dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the resulting residue was chromatographed on silica gel, elution with hexane-ethyl acetate (4:1) to give corresponding 3,5-disubstituted-1,2,4-oxadiazole.

Method-B: To a mixture of indazole carboxylic acid (3.02 mmol) and amidoxime (3.02 mmol) in dichloromethane (7.5 mL) was added DCC (3.02 mmol) and HOBT (3.02 mmol). Reaction mixture was stirred at rt for 4 h and reaction progress was monitored by TLC. After completion, reaction mixture was filtered. Filtrate was concentrated to get residue and the residue dissolved in pyridine (2.5 mL). The reaction mixture was heated to reflux for 4 h. Reaction mixture diluted with water and extracted in to ethyl acetate. The organic phase was washed with water and brine. The organic phase dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the resulting residue was chromatographed over silica gel, elution with hexane-ethyl acetate (4:1) resulted corresponding 3,5-disubstituted-1,2,4-oxadiazole.

3-Methyl-5-(3-indazolyl)-1,2,4-oxadiazole (3a): Compound **3a** was prepared from compound **3** and amidoxime **2a** following general procedure-IV method-A (80 % yield). Cream color solid; IR (KBr, $\nu_{\max}$, cm⁻¹): 3159 (NH), 1605 (C=N), 1328, 1058, 744; ¹H NMR (300 MHz, DMSO-*d*₆) δ 14.17 (s, 1H, -NH), 8.19 - 8.15 (m, 1H, Ar-H), 7.72 (d, 1H, $J = 8.4$ Hz, Ar-H), 7.53-7.48 (m, 1H, Ar-H), 7.39-7.34 (m, 1H, Ar-H), 2.46 (s, 3H, -CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 170.60, 167.69, 141.28, 130.25, 127.62, 123.57, 121.54, 120.72, 111.66, 11.62; ESI-MS m/z 201 (M + H)⁺.

3-Phenyl-5-(3-indazolyl)-1,2,4-oxadiazole (3b): Compound **3b** was prepared from compound **3** and amidoxime **2b** following general procedure-IV method-A (85 % yield). Cream coloured solid; IR (KBr, $\nu_{\max}$, cm⁻¹): 3193 (NH), 1607 (C=N), 1351, 1044, 745; ¹H NMR (300 MHz, DMSO-*d*₆) δ 14.26 (s,

1H, -NH), 8.33 (d, 1H, $J = 8.2$ Hz, -CH=N), 8.17 (dd, 2H, $J = 1.80, 3.6$ Hz, Ar-H), 7.75 (d, 1H, $J = 8.40$ Hz, Ar-H), 7.63-7.59 (m, 3H, Ar-H), 7.56 (t, 1H, $J = 7.80$ Hz, Ar-H), 7.44 (t, 1H, $J = 7.80$ Hz, Ar-H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 171.25, 168.37, 141.34, 132.01, 130.19, 129.63, 127.72, 127.57, 126.55, 123.73, 121.73, 120.89, 111.73; ESI-MS m/z 263 (M + H)⁺.

3-(3-Methylphenyl)-5-(3-indazolyl)-1,2,4-oxadiazole (3c): Compound **3c** was prepared from compound **3** and amidoxime **2c** following general procedure-IV method-A (80 % yield). Cream color solid; m.p.: 215-218 °C; IR (KBr, $\nu_{\max}$, cm⁻¹): 3205 (NH), 2943, 1601 (C=N), 1336, 1040, 751; ¹H NMR (300 MHz, DMSO-*d*₆) δ 14.25 (s, 1H, -NH), 8.33 (d, 1H, $J = 8.10$ Hz, -CH=N), 7.98 (t, 2H, $J = 4.6$ Hz, Ar-H), 7.75 (d, 1H, $J = 8.4$ Hz, Ar-H), 7.57-7.40 (m, 4H, Ar-H), 2.42 (s, 3H, -CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 171.14, 168.41, 141.31, 138.99, 132.60, 129.46, 127.93, 127.69, 126.47, 124.71, 123.68, 121.71, 120.91, 111.68, 21.26; ESI-MS m/z 277 (M + H)⁺.

3-(3-Fluorophenyl)-5-(3-indazolyl)-1,2,4-oxadiazole (3d): Compound **3d** was prepared from compound **3** and amidoxime **2d** following general procedure-IV method-A (70 % yield). Pale brown color solid; m.p.: >200 °C; IR (KBr, $\nu_{\max}$, cm⁻¹): 3196 (NH), 1910, 1603 (C=N), 1462, 1335, 1044, 865, 772; ¹H NMR (300 MHz, DMSO-*d*₆) δ 14.27 (s, 1H, -NH), 8.34 (d, 1H, $J = 8.10$ Hz, -CH=N), 8.01 (d, 1H, $J = 7.80$ Hz, Ar-H), 7.94-7.89 (m, 1H, Ar-H), 7.75 (d, 1H, $J = 8.40$ Hz, Ar-H), 7.71-7.63 (m, 1H, Ar-H), 7.57-7.40 (m, 3H, Ar-H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 171.44, 167.51, 167.48, 164.31, 161.07, 141.31, 131.98, 131.87, 130.04, 128.75, 128.63, 127.72, 123.75, 121.73, 120.90, 119.07, 118.79, 114.39, 114.07, 111.69; ESI-MS m/z 281 (M + H)⁺.

3-Methyl-5-(4-indazolyl)-1,2,4-oxadiazole (4a): Compound **4a** was prepared from compound **4** and amidoxime **2a** following general procedure-IV method-A (75 % yield). Cream colour solid; m.p.: 195-197 °C; IR (KBr, $\nu_{\max}$, cm⁻¹): 3141 (NH), 1596 (C=N), 1572, 1341, 1198, 743; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.60 (s, 1H, -NH), 8.50 (s, 1H, -CH=N), 7.95 (dd, 1H, $J = 7.95, 0.6$ Hz, Ar-H), 7.89 (d, 1H, $J = 8.4$ Hz, Ar-H), 7.57 (dd, 1H, $J = 7.2, 8.1$ Hz, Ar-H), 2.46 (s, 3H, -CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 174.59, 168.01, 140.78, 133.42, 126.34, 122.30, 119.74, 115.89, 115.50, 11.69; HRMS: m/z (M + H) calcd. for C₁₀H₈N₄O: 201.0776; Found (M + H)⁺: 201.0774; ESI-MS m/z 201 (M + H)⁺.

3-Phenyl-5-(4-indazolyl)-1,2,4-oxadiazole (4b): Compound **4b** was prepared from compound **4** and amidoxime **2b** following general procedure-IV method-A (85 % yield). Light brown colour solid; m.p.: 192-194 °C; IR (KBr, $\nu_{\max}$, cm⁻¹): 3170 (NH), 1622 (C=N), 1568, 1361, 1193, 740; ¹H NMR (300 MHz, CDCl₃) δ 10.56 (bs, 1H, -NH), 8.89 (s, 1H, -CH=N), 8.24 (dd, 2H, $J = 7.2, 3.6$ Hz, Ar-H), 8.15 (d, 1H, $J = 7.2$, Ar-H), 7.78 (d, 1H, $J = 8.4$ Hz, Ar-H), 7.60-7.54 (m, 4H, Ar-H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 174.80, 168.96, 140.48, 135.46, 131.18, 128.80, 127.50, 126.83, 126.53, 122.71, 120.44, 116.68, 114.37; HRMS: m/z (M + Na) calcd. for C₁₅H₁₀N₄ONa: 285.0752; Found (M + Na)⁺: 285.0796; ESI-MS m/z 263 (M + H)⁺.

3-(3-Methylphenyl)-5-(4-indazolyl)-1,2,4-oxadiazole (4c): Compound **4c** was prepared from compound **4** and

amidoxime **2c** following general procedure-IV method-A (80 % yield). Cream colour solid; IR (KBr, $\nu_{\max}$, cm^{-1}): 3118 (NH), 1621 (C=N), 1569, 1361, 961, 750; ^1H NMR (300 MHz, DMSO- d_6): δ 10.35 (s, 1H, -NH), 8.89 (s, 1H, -CH=N), 8.15 (d, 1H, $J = 7.5$ Hz, Ar-H), 8.05 (d, 2H, $J = 9.0$ Hz, Ar-H), 7.77 (d, 1H, $J = 8.4$ Hz, Ar-H), 7.57 (dd, 1H, $J = 8.1, 7.5$ Hz, Ar-H), 7.46-7.35 (m, 2H, Ar-H), 2.48 (s, 3H, -CH₃); ^{13}C NMR (75 MHz, DMSO- d_6): δ 175.10, 168.68, 140.77, 139.00, 133.73, 132.60, 129.46, 127.93, 126.48, 126.33, 124.70, 122.47, 119.86, 116.09, 115.44, 21.25; HRMS: m/z (M + Na) calcd. for C₁₆H₁₂N₄ONa: 299.0909; Found (M + Na)⁺: 299.0919; ESI-MS m/z 277 (M + H)⁺.

3-(3-Fluorophenyl)-5-(4-indazolyl)-1,2,4-oxadiazole (**4d**):

Compound **4d** was prepared from compound **4** and amidoxime **2d** following general procedure-IV method-A (70 % yield). Half-white colour solid; IR (KBr, $\nu_{\max}$, cm^{-1}): 3161 (NH), 1604 (C=N), 1566, 1362, 961, 754; ^1H NMR (300 MHz, DMSO- d_6): δ 13.63 (s, 1H, -NH), 8.70 (s, 1H, -CH=N), 8.04 (t, 2H, $J = 4.5$ Hz, Ar-H), 7.95 (d, 2H, $J = 8.5$ Hz, Ar-H), 7.70-7.57 (m, 2H, Ar-H), 7.52-7.45 (m, 1H, Ar-H); ^{13}C NMR (75 MHz, DMSO- d_6): δ 175.34, 167.69, 167.66, 164.25, 161.01, 140.81, 133.58, 131.83, 131.72, 129.71, 128.60, 126.19, 123.65, 123.61, 122.48, 119.78, 118.96, 118.68, 116.25, 115.18, 114.31, 114.00; HRMS: m/z (M) calcd. for C₁₅H₉N₄OF: 280.2636; Found (M)⁺: Not ionized; ESI-MS m/z 281 (M + H)⁺.

3-Methyl-5-(5-indazolyl)-1,2,4-oxadiazole (**5a**):

Compound **5a** was prepared from compound **5** and amidoxime **2a** following general procedure-IV method-A (65 % yield). Light yellow colour solid; m.p.: 204-205 °C; IR (KBr, $\nu_{\max}$, cm^{-1}): 3143 (NH), 2924, 1626 (C=N), 1392, 952, 755; ^1H NMR (300 MHz, DMSO- d_6): δ 13.49 (s, 1H, -NH), 8.58 (s, 1H, -CH=N), 8.27 (s, 1H, Ar-H), 8.00 (dd, 1H, $J = 8.7, 1.5$ Hz, Ar-H), 7.71 (d, 1H, $J = 8.7$ Hz, Ar-H), 2.39 (s, 3H, -CH₃); ^{13}C NMR (75 MHz, DMSO- d_6): δ 175.71, 167.85, 141.67, 135.70, 125.23, 123.25, 122.48, 116.19, 111.71, 11.63; ESI-MS m/z 201 (M + H)⁺.

3-Phenyl-5-(5-indazolyl)-1,2,4-oxadiazole (**5b**):

Compound **5b** was prepared from compound **5** and amidoxime **2b** following general procedure-IV method-A (75 % yield). Cream colour solid; m.p.: 204-205 °C; IR (KBr, $\nu_{\max}$, cm^{-1}): 3144 (NH), 2928, 1568 (C=N), 1369, 954, 752; ^1H NMR (300 MHz, DMSO- d_6): δ 13.53 (s, 1H, -NH), 8.70 (s, 1H, -CH=N), 8.32 (s, 1H, Ar-H), 8.13-8.08 (m, 3H, Ar-H), 7.77 (d, 1H, $J = 8.8$ Hz, Ar-H), 7.61-7.57 (m, 3H, Ar-H); ^{13}C NMR (75 MHz, DMSO- d_6): δ 176.46, 168.53, 141.78, 135.83, 131.92, 129.60, 127.45, 126.72, 125.40, 123.31, 122.86, 116.05, 111.79; ESI-MS m/z 263 (M + H)⁺.

3-(3-Methylphenyl)-5-(5-indazolyl)-1,2,4-oxadiazole (**5c**):

Compound **5c** was prepared from compound **5** and amidoxime **2c** following general procedure-IV method-A (70 % yield). Off-white colour solid; IR (KBr, $\nu_{\max}$, cm^{-1}): 3146 (NH), 2926, 1627, 1603 (C=N), 1370, 955, 756; ^1H NMR (300 MHz, DMSO- d_6): δ 13.53 (s, 1H, -NH), 8.70 (s, 1H, -CH=N), 8.32 (s, 1H, Ar-H), 8.11 (d, 1H, $J = 8.8$ Hz, Ar-H), 7.89 (d, 2H, $J = 12.1$ Hz, Ar-H), 7.76 (d, 1H, $J = 8.7$ Hz, Ar-H), 7.49-7.40 (m, 2H, Ar-H), 2.46 (s, 3H, -CH₃); ^{13}C NMR (75 MHz, DMSO- d_6): δ 176.37, 168.57, 141.79, 138.97, 135.83, 132.52, 129.47, 127.85, 126.66, 125.39, 124.59, 123.32, 122.83, 116.07, 111.76, 21.25; ESI-MS m/z 277 (M + H)⁺.

3-(3-Fluorophenyl)-5-(5-indazolyl)-1,2,4-oxadiazole (**5d**):

Compound **5d** was prepared from compound **5** and amidoxime **2d** following general procedure-IV method-A (60 % yield). Light yellow colour solid; IR (KBr, $\nu_{\max}$, cm^{-1}): 3143 (NH), 2928, 1626 (C=N), 1457, 956, 758; ^1H NMR (300 MHz, DMSO- d_6): δ 13.54 (s, 1H, -NH), 8.71 (s, 1H, -CH=N), 8.32 (s, 1H, Ar-H), 8.09 (t, 1H, $J = 8.76$, Ar-H), 7.94 (d, 1H, $J = 7.8$ Hz, Ar-H), 7.85-7.76 (m, 2H, Ar-H), 7.69-7.62 (m, 1H, Ar-H), 7.50-7.44 (m, 1H, Ar-H); ^{13}C NMR (75 MHz, DMSO- d_6): δ 176.75, 167.67, 164.30, 161.06, 141.84, 135.88, 132.04, 131.93, 128.96, 128.84, 125.42, 123.69, 123.66, 123.32, 122.99, 119.03, 118.75, 115.87, 114.27, 113.96, 111.83; ESI-MS m/z 281 (M + H)⁺.

3-Methyl-5-(6-indazolyl)-1,2,4-oxadiazole (**6a**):

Compound **6a** was prepared from compound **6** and amidoxime **2a** following general procedure-IV method-A (85 % yield). Light yellow colour solid; IR (KBr, $\nu_{\max}$, cm^{-1}): 3211 (NH), 1591 (C=N), 1571, 1333, 940, 774; ^1H NMR (300 MHz, DMSO- d_6): δ 13.51 (s, 1H, -NH), 8.22 (d, 2H, $J = 7.4$ Hz, -CH=N), 7.98 (d, 1H, $J = 8.4$ Hz, Ar-H), 7.77 (dd, 1H, $J = 8.4, 1.2$ Hz, Ar-H), 2.41 (s, 3H, -CH₃); ^{13}C NMR (75 MHz, DMSO- d_6): δ 175.58, 168.00, 139.64, 134.35, 125.47, 122.28, 121.08, 119.27, 110.73, 11.60; HRMS: m/z (M + H) calcd. for C₁₀H₈N₄O: 201.0776; Found (M + H)⁺: 201.0766; ESI-MS m/z 201 (M + H)⁺.

3-Phenyl-5-(6-indazolyl)-1,2,4-oxadiazole (**6b**):

Compound **6b** was prepared from compound **6** and amidoxime **2b** following general procedure-IV method-A (90 % yield). Brown colour solid; IR (KBr, $\nu_{\max}$, cm^{-1}): 3294 (NH), 1597 (C=N), 1445, 1361, 742, 684; ^1H NMR (300 MHz, DMSO- d_6): δ 13.56 (s, 1H, -NH), 8.37 (s, 1H, -CH=N), 8.26 (s, 1H, Ar-H), 8.11 (t, 1H, $J = 4.8$ Hz, Ar-H), 8.03 (d, 1H, $J = 8.4$ Hz, Ar-H), 7.88 (d, 1H, $J = 8.1$ Hz, Ar-H), 7.61 (t, 4H, $J = 3.9$, Ar-H); ^{13}C NMR (75 MHz, DMSO- d_6): δ 176.35, 168.66, 139.63, 134.41, 132.01, 129.62, 127.48, 126.57, 125.62, 122.42, 120.98, 119.45, 111.11; ESI-MS m/z 263 (M + H)⁺.

3-(3-Methylphenyl)-5-(6-indazolyl)-1,2,4-oxadiazole (**6c**):

Compound **6c** was prepared from compound **6** and amidoxime **2c** following general procedure-IV method-A (75 % yield). Off-white colour solid; m.p.: >220 °C; IR (KBr, $\nu_{\max}$, cm^{-1}): 3434 (NH), 1597 (C=N), 1572, 1354, 754; ^1H NMR (300 MHz, DMSO- d_6): δ 13.5 (s, 1H, -NH), 8.36 (s, 1H, -CH=N), 8.25 (s, 1H, Ar-H), 8.02 (d, 1H, $J = 8.4$ Hz, Ar-H), 7.93-7.86 (m, 3H, Ar-H), 7.51-7.41 (m, 2H, Ar-H), 2.41 (s, 3H, -CH₃); ^{13}C NMR (75 MHz, DMSO- d_6): δ 176.25, 168.70, 139.67, 139.01, 134.41, 132.62, 129.50, 127.86, 126.48, 125.61, 124.63, 122.40, 121.00, 119.45, 111.05, 21.25; HRMS: m/z (M + H) calcd. for C₁₆H₁₂N₄O: 277.1089; Found (M + H)⁺: 277.1265; ESI-MS m/z 277 (M + H)⁺.

3-(3-Fluorophenyl)-5-(6-indazolyl)-1,2,4-oxadiazole (**6d**):

Compound **6d** was prepared from compound **6** and amidoxime **2d** following general procedure-IV method-A (72 % yield). Cream colour solid; m.p.: >220 °C; IR (KBr, $\nu_{\max}$, cm^{-1}): 3444 (NH), 2868, 1601 (C=N), 1570, 1365, 956, 755; ^1H NMR (300 MHz, DMSO- d_6): δ 13.58 (s, 1H, -NH), 8.37 (s, 1H, -CH=N), 8.26 (s, 1H, Ar-H), 8.02 (t, 1H, $J = 8.1$ Hz, Ar-H), 7.97-7.94 (m, 2H, Ar-H), 7.89-7.82 (m, 2H, Ar-H), 7.69-7.62 (m, 1H, Ar-H), 7.51-7.45 (m, 1H, Ar-H); ^{13}C NMR (75 MHz, DMSO- d_6): δ 176.57, 167.78, 167.74, 164.27, 161.02, 139.70,

134.32, 131.98, 131.87, 128.74, 128.63, 125.66, 123.67, 123.63, 122.40, 120.76, 119.41, 119.06, 118.78, 114.26, 113.95, 111.23; ESI-MS m/z 281 (M + H)⁺.

3-Methyl-5-(7-indazolyl)-1,2,4-oxadiazole (7a): Compound **7a** was prepared from compound **28a** following general procedure-III (78 % yield). Cream colour solid; m.p.: >220 °C; IR (KBr, $\nu_{\max}$, cm⁻¹): 3266 (NH), 1622 (C=N), 1325, 949, 747; ¹H NMR (300 MHz, CDCl₃): δ 13.38 (s, 1H, -NH), 8.29 (d, 1H, J = 1.38, -CH=N), 8.14 (d, 2H, J = 7.32, Ar-H), 7.35 (q, 1H, J = 7.47, Ar-H), 2.46 (s, 3H, -CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆): δ 173.47, 167.87, 136.31, 135.21, 127.20, 126.87, 125.07, 120.90, 106.60, 11.67; ESI-MS m/z 201 (M + H)⁺.

3-Phenyl-5-(7-indazolyl)-1,2,4-oxadiazole (7b): Compound **7b** was prepared from compound **28b** following to general procedure-III (81 % yield). Cream coloured solid; m.p.: >220 °C; IR (KBr, $\nu_{\max}$, cm⁻¹): 3314 (NH), 1621 (C=N), 1338, 946, 741; ¹H NMR (300 MHz, CDCl₃): δ 13.55 (s, 1H, -NH), 8.39 (t, 2H, J = 4.50 Hz, Ar-H), 8.35 (s, 1H, -CH=N), 8.22 (dd, 2H, J = 7.5, 3.9 Hz, Ar-H), 7.61 (t, 3H, J = 3.60 Hz, Ar-H), 7.39 (t, 1H, J = 7.50 Hz, Ar-H); ¹³C NMR (75 MHz, DMSO-*d*₆): δ 173.75, 168.68, 136.32, 135.32, 132.04, 129.42, 128.07, 127.21, 126.50, 125.16, 120.97, 106.64; ESI-MS m/z 263 (M + H)⁺.

3-(3-Methylphenyl)-5-(7-indazolyl)-1,2,4-oxadiazole (7c): Compound **7c** was prepared from compound **28c** following general procedure-III (76 % yield). Light brown color solid; m.p.: >220 °C; IR (KBr, $\nu_{\max}$, cm⁻¹): 3291 (NH), 1622 (C=N), 1463, 1332, 753; ¹H NMR (300 MHz, DMSO-*d*₆): δ 13.52 (s, 1H, -NH), 8.36 (s, 1H, -CH=N), 8.24-8.17 (m, 4H, Ar-H), 7.50-7.35 (m, 3H, Ar-H), 2.48 (s, 3H, -CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆): δ 173.61, 168.71, 138.84, 136.30, 135.32, 132.60, 129.26, 128.52, 127.16, 125.11, 120.93, 106.54, 21.26; ESI-MS m/z 277 (M + H)⁺.

3-(3-Fluorophenyl)-5-(7-indazolyl)-1,2,4-oxadiazole (7d): Compound **7d** was prepared from compound **28d** following general procedure-III (72 % yield). Brown color solid; m.p.: >220 °C; IR (KBr, $\nu_{\max}$, cm⁻¹): 3273 (NH), 1623 (C=N), 1340, 952, 755; ¹H NMR (300 MHz, DMSO-*d*₆): δ 13.59 (s, 1H, -NH), 8.43-8.38 (m, 1H, -CH=N), 8.36 (d, 1H, J = 1.20 Hz, Ar-H), 8.24-8.15 (m, 3H, Ar-H), 7.68-7.61 (m, 1H, Ar-H), 7.51-7.44 (m, 1H, Ar-H), 7.40 (t, 1H, J = 8.10 Hz, Ar-H); ¹³C NMR (75 MHz, DMSO-*d*₆): δ 173.82, 167.83, 164.51, 161.28, 136.25, 135.33, 131.70, 131.59, 128.74, 128.62, 127.37, 127.15, 125.15, 123.82, 123.78, 120.95, 119.03, 118.75, 115.54, 115.23, 106.34; ESI-MS m/z 281 (M + H)⁺.

3-Methyl-5-(2-nitro-3-methylphenyl)-1,2,4-oxadiazole (27a): Compound **27a** was prepared from compound **24** and amidoxime **2a** following general procedure-IV method-A (72 % yield): ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.04 (dd, 1H, J = 0.96, 6.63 Hz, Ar-H), 7.83-7.71 (m, 2H, Ar-H), 2.39 (s, 3H, -CH₃), 2.33 (s, 3H, -CH₃); ESI-MS m/z 220 (M + H)⁺.

3-Phenyl-5-(2-nitro-3-methylphenyl)-1,2,4-oxadiazole (27b): Compound **27b** was prepared from compound **24** and amidoxime **2b** following general procedure-IV method-A (79 % yield): ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.15 (dd, 1H, J = 0.96, 6.54 Hz, Ar-H), 8.01-0.98 (m, 2H, Ar-H), 7.87-7.75 (m, 2H, Ar-H), 7.61-7.58 (m, 3H, Ar-H), 2.36 (s, 3H, -CH₃); ESI-MS m/z 282 (M + H)⁺.

3-(3-Methyl-phenyl)-5-(2-nitro-3-methylphenyl)-1,2,4-oxadiazole (27c): Compound **27c** was prepared from compound **24** and amidoxime **2c** according to general procedure-IV method-A (80 % yield): ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.15 (dd, 1H, J = 0.99, 6.51 Hz, Ar-H), 7.87-7.75 (m, 4H, Ar-H), 7.46 (dd, 2H, J = 7.02, 0.60 Hz, Ar-H), 2.39 (s, 3H, -CH₃), 2.37 (s, 3H, -CH₃); ESI-MS m/z 300 (M + H)⁺.

3-(3-Fluoro-phenyl)-5-(2-nitro-3-methylphenyl)-1,2,4-oxadiazole (27d): Compound **27d** was prepared from compound **24** and amidoxime **2d** following general procedure-IV method-A (71 % yield): ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.16 (dd, 1H, J = 0.93, 6.66 Hz, Ar-H), 7.88-7.62 (m, 5H, Ar-H), 7.53-7.49 (m, 1H, Ar-H), 2.37 (s, 3H, -CH₃); ESI-MS m/z 300 (M + H)⁺.

3-Methyl-5-(2-amino-3-methylphenyl)-1,2,4-oxadiazole (28a): Compound **28a** was prepared from compound **27a** following general procedure-II (79 % yield): ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.02 (dd, 1H, J = 6.96, 0.63 Hz, Ar-H), 7.81-7.69 (m, 2H, Ar-H), 2.38 (s, 3H, -CH₃), 2.32 (s, 3H, -CH₃); ESI-MS m/z 190 (M + H)⁺.

3-Phenyl-5-(2-amino-3-methylphenyl)-1,2,4-oxadiazole (28b): Compound **28b** was prepared from compound **27b** following general procedure-II (86 % yield): ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.11-8.07 (m, 2H, Ar-H), 7.75 (dd, 1H, J = 6.99, 1.14 Hz, Ar-H), 7.62-7.57 (m, 3H, Ar-H), 7.27 (t, 1H, J = 6.63 Hz, Ar-H), 6.67 (t, 1H, J = 7.89 Hz, Ar-H), 2.19 (s, 3H, -CH₃); ESI-MS m/z 252 (M + H)⁺.

3-(3-Methyl-phenyl)-5-(2-amino-3-methylphenyl)-1,2,4-oxadiazole (28c): Compound **28c** was prepared from compound **27c** following general procedure-II (89 % yield): ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.88 (d, 2H, J = 8.94 Hz, Ar-H), 7.76 (dd, 1H, J = 7.05, 1.05 Hz, Ar-H), 7.50-7.40 (m, 2H, Ar-H), 7.27 (t, 1H, J = 5.73 Hz, Ar-H), 6.66 (t, 1H, J = 7.83 Hz, Ar-H), 6.12 (s, 2H, -NH₂), 2.47 (s, 3H, -CH₃), 2.19 (s, 3H); ESI-MS m/z 266 (M + H)⁺.

3-(3-Fluoro-phenyl)-5-(2-amino-3-methylphenyl)-1,2,4-oxadiazole (28d): Compound **28d** was prepared from compound **27d** following general procedure-IV method-A (80 % yield): ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.95-7.85 (m, 2H, Ar-H), 7.73 (t, 1H, J = 7.14, 0.87 Hz, Ar-H), 7.68-7.60 (m, 1H, Ar-H), 7.50-7.43 (m, 1H, Ar-H), 7.26 (d, 1H, J = 6.90 Hz, Ar-H), 6.73 (s, 2H, -NH₂), 6.65 (t, 1H, J = 7.86, 7.41 Hz, Ar-H), 2.18 (s, 3H); ESI-MS m/z 270 (M + H)⁺.

Synthesis of compound 10: To a solution of phenyl hydrazine (**8**) (92.5 mmol) in water (100.0 mL) 4-bromobenzaldehyde (**9**) (92.5 mmol) was added slowly over a period of 1 h at room temperature. The solution was stirred for 2 h at same temperature and reaction mixture was cooled to 15 °C. The obtained solid was filtered and washed with isopropyl alcohol. The product was dried at 50 °C under reduced pressure to get compound (**10**) with 95 % yield. ¹H NMR (300 MHz, DMSO-*d*₆): δ 10.42 (s, 1H), 7.79 (s, 1H), 7.59-7.52 (m, 4H), 7.22-7.17 (m, 2H), 7.06-7.03 (m, 2H), 6.75 (t, 1H, J = 7.26 Hz); ESI-MS m/z 277 (M + 2)⁺.

Synthesis of compound 12: To a solution of oxalyl chloride (76.0 mmol) in dichloromethane (76.0 mL) was added compound **10** (69.0 mmol) in dichloromethane (152.0 mL) slowly over a period of 1 h at reflux temperature. This solution was stirred for 3 h at same temperature and reaction mixture was cooled

Synthesis of compound 3: Compound **3** was prepared from **13** following general procedure-III (95 % yield, light yellow colour solid, m.p.: 160-165 °C): ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.89 (s, 1H, -NH), 8.06 (d, 1H, *J* = 8.13 Hz, Ar-H), 7.64 (d, 1H, *J* = 8.40 Hz, Ar-H), 7.46-7.40 (m, 1H, Ar-H), 7.32-7.26 (m, 1H, Ar-H), 3.90 (s, 3H, -CH₃); ESI-MS *m/z* 177 (M + H)⁺.

1,2,4-Oxadiazoles are most commonly synthesized from amidoximes and carboxylic acid derivatives in two steps. In the first step amidoximes were coupled with the activated acids to get O-acylamidoximes. In the second step intramolecular dehydrative cyclization results in 1,2,4-oxadiazoles^{9-11, 24, 27-29}. These approaches generally require longer reaction times. O-acylamidoximes were also prepared from amidoximes and were coupled with carboxylic acids in the presence of coupling reagents such as EDC, DCC or DIC. The cyclization reaction of O-acylamidoximes is promoted either by heat or by bases such as NaH, NaOEt or pyridine²⁶. A recent report has been described by the use of tetrabutylammonium fluoride (TBAF) to promote the cyclization of O-acylamidoximes in good yields²⁷. Amidoximes were prepared from corresponding nitriles by treatment with hydroxylamine in methanol at room temperature. In an attempt to improve on these procedures, microwave-assisted 1,2,4-oxadiazole synthesis has been reported³⁰ recently with moderate to good yields. Due to importance of 1,2,4-oxadiazoles and indazoles in the pharmaceutical

$$\begin{array}{c}
 \text{R}-\text{C}(\text{NH}_2)=\text{N}-\text{OH} \\
 \text{2a-d}
 \end{array}
 + \text{R}'-\text{COOMe}
 \xrightarrow{\text{i}}
 \begin{array}{c}
 \text{R}-\text{C}(\text{N}=\text{O})=\text{N}-\text{R}' \\
 \text{3a-d} \\
 \text{4a-d} \\
 \text{5a-d} \\
 \text{6a-d}
 \end{array}$$

$$\text{R-CN} \xrightarrow{\text{i}} \text{R}-\text{C}(\text{NH}_2)=\text{N-OH}$$

1a-d **2a-d**

1a= Me **2a=** Me
1b= Ph **2b=** Ph
1c= 3-MePh **2c=** 3-MePh
1d= 3-FPh **2d=** 3-FPh

Indazole-carboxylic acid methyl ester (**4**, **5**, **6**) were prepared starting from respective 2-methyl-nitrobenzoic acid (**14**,

TABLE-1

Entry	R	R ¹	Product	Yield (%) ^a	Entry	R	R ¹	Product	Yield (%) ^a
1	CH ₃ (2a)		3a	80	11	3-CH ₃ Ph (2c)		5c	70
2	Ph (2b)		3b	85	12	3-FPh (2d)		5d	60
3	3-CH ₃ Ph (2c)		3c	80	13	CH ₃ (2a)		6a	85
4	3-FPh (2d)		3d	75	14	Ph (2b)		6b	90
5	CH ₃ (2a)		4a	75	15	3-CH ₃ Ph (2c)		6c	75
6	Ph (2b)		4b	85	16	3-FPh (2d)		6d	72
7	3-CH ₃ Ph (2c)		4c	80	17	CH ₃ (2a)		27a	72
8	3-FPh (2d)		4d	70	18	Ph (2b)		27b	79
9	CH ₃ (2a)		5a	65	19	3-CH ₃ Ph (2c)		27c	80
10	Ph (2b)		5b	75	20	3-FPh (2d)		27d	71

^aPurified products.

17, 20 (Scheme-IV); compound **14, 17, 20** were converted to methyl ester (**15, 18, 21**) with dimethylsulphate in presence of potassium carbonate in acetone at reflux temperature. The compound nitro ester **15, 18, 21** were treated with Fe / NH₄Cl at reflux temperature to afford corresponding **16, 19, 22** in good yields. Products **16, 19, 22** were treated with sodium nitrite to get hydrazine followed by cyclization results in indazole-carboxylic acid methyl ester (**4, 5, 6**) (Scheme-IV).

5-Indazolyl-1,2,4-oxadiazole **4a-d, 5a-d, 6a-d** (Scheme-IV) were synthesized from compound **4, 5, 6**; compound **4, 5, 6** were treated with amidoximes **2a-d** in the presence of potassium carbonate in toluene resulted in good yields.

Synthesis of 7-indazolyl-1,2,4-oxadiazoles were unsuccessful to get the desired product when we adopted regular procedure to make the indazoles followed by oxadiazoles. 2-Methyl-3-nitro-benzoic acid (**23**) was converted to methyl

Scheme-III: Synthesis of 5-(3-indazolyl)-1,2,4-oxadiazole; Conditions: (i) Water, 25 to 35 °C, 95 %; (ii) Oxalyl chloride, DCM, reflux; (iii) AlCl_3 , DCM, reflux, 91 % for two steps; (iv) Conc. HCl , AcOH , 95 °C, 85 %; (v) K_2CO_3 , DMS, Acetone, reflux, 95 %; (vi) Amidoxime (**2a-d**, **a** = Me, **b** = Ph, **c** = 3-MePh, **d** = 3-FPh), K_2CO_3 , Toluene, reflux

Scheme-IV: Synthesis of 5-indazolyl-1,2,4-oxadiazole; Conditions: (i) K_2CO_3 , DMS, Acetone, reflux; (ii) Fe , NH_4Cl , EtOH , H_2O , 65 to 75 °C; (iii) Isoamyl nitrite, Ac_2O , KOAc , CHCl_3 , Reflux or NaNO_2 , AcOH , H_2O , rt; (iv) Amidoxime (**2a-d**, **a** = Me, **b** = Ph, **c** = 3-MePh, 4-3-FPh), K_2CO_3 , toluene, 110 °C; (iii)

ester (**24**) with dimethyl sulphate in presence of potassium carbonate in acetone at reflux temperature (**Scheme-V**). Compound **24** was treated with $\text{Fe}/\text{NH}_4\text{Cl}$ at reflux temperature to get compound **25** in good yields. Compound **25** was treated with sodium nitrite to get corresponding hydrazine followed by cyclization to get indazole-7-carboxylic acid methyl ester (**7**) was unsuccessful (**Scheme-V**). The hydrazine found at step-3 reacted with the adjacent ester group to form cyclic hydrazone (**26**). Hence a different approach was attempted to make these analogues as discussed below.

In the modified approach construction of the oxadiazole ring was carried out first and later we carried out indazole

ring formation. Compound **24** was treated with amidoxime (**2a-d**) in presence of potassium carbonate in toluene at reflux temperature to provide oxadiazole (**27a-d**). Nitro group of compound **27a-d** was reduced with iron and ammonium chloride in ethanol at reflux temperature to produce corresponding amines **28a-d**, which on reaction with isoamyl nitrite, Ac_2O and potassium acetate in chloroform at reflux gave the desired 5-(7-indazolyl)-1,2,4-oxadiazoles (**7a-d**) (**Scheme-VI**, Table-2).

As an alternative, we have also studied the synthesis of 3,5-disubstituted-1,2,4-oxadiazoles 3,4,5,6,7 (**Scheme-VII**), using amidoximes **2a-d** and carboxylic acid **13** in presence of coupling agents such as DCC, EDC and HOBT and found that

Scheme-V: Synthesis of methyl-7-indazole carboxylic acid (**7**); Conditions: (i) DMS, K_2CO_3 , Acetone, Reflux, 90 %; (ii) Fe, NH_4Cl , EtOH, H_2O , 65 to 75 °C, 85 %; (iii) Isoamyl nitrite, Ac_2O , KOAc, $CHCl_3$, Reflux or $NaNO_2$, AcOH, H_2O , rt

Scheme-VI: Synthesis of 5-(7-indazolyl)-1,2,4-oxadiazoles; **Conditions:** (i) Amidoxime (**2a-d**, **a** = Me, **b** = Ph, **c** = 3-MePh, **d** = 3-FPh), K_2CO_3 , Toluene, 110 °C; (iii) Fe, NH_4Cl , EtOH, H_2O , 65 to 75 °C; (iv) (a) Isoamyl nitrite, Ac_2O , KOAc, $CHCl_3$, Reflux or (b) $NaNO_2$, AcOH, H_2O , rt.

TABLE-2

Entry	R	Product	Yield (%) ^a
1	CH ₃	7a	78
2	Ph	7b	81
3	3-MePh	7c	76
4	3-FPh	7d	72

^aPurified products

Conclusion

The work presented here demonstrates a straight forward and mild procedure for an efficient synthesis of 3,5-disubstituted-1,2,4-oxadiazoles using potassium carbonate as base and toluene as solvent. A variety of esters can be used to expand the scope of substituents around the oxadiazole ring. We have also successfully demonstrated the synthesis of all the positional isomers of indazolyl (3-7 positions) oxadiazoles in good yields. The high pharmacological importance of indazoles and oxadiazoles prompted us to synthesize these derivatives.

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Scheme-VII: Synthesis of 3-indazolyl-1,2,4-oxadiazoles; Conditions: (i) (a) DCC, HOBt, DCM, rt; (b) Pyridine, reflux.

the yields of oxadiazoles were much lower when compared with K_2CO_3 toluene procedure from corresponding esters.

All new compounds **3**, **4**, **5**, **6**, **7** were thoroughly characterized by 1H and ^{13}C NMR, Mass and IR spectra.

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