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

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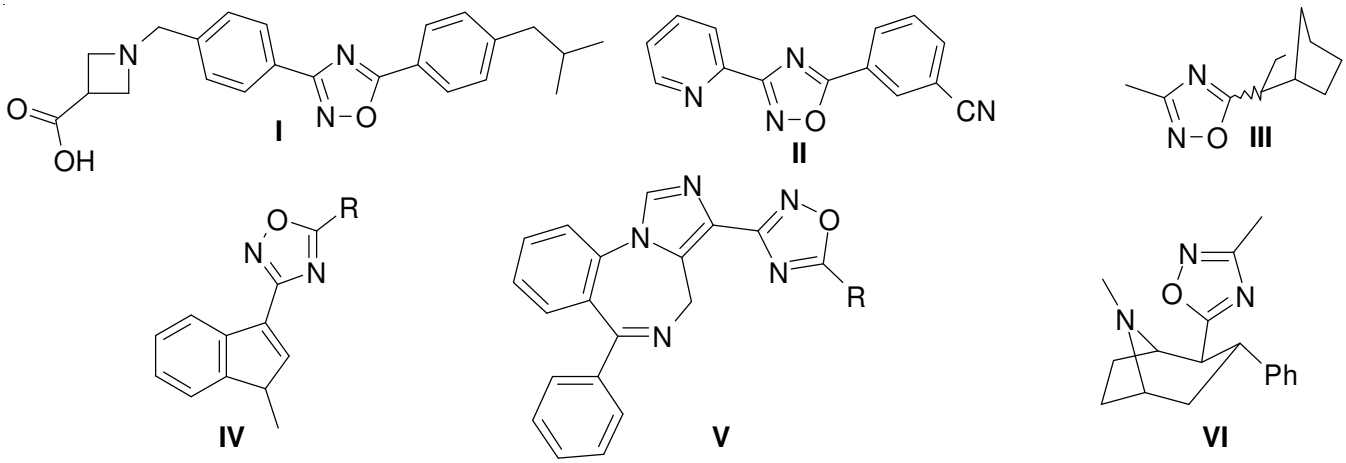
An efficient and high-yielding one-pot synthesis of 3,5-disubstituted-1,2,4-oxadiazoles from indazole carboxylic acid methyl esters and amidoximes is described. In this study a series of novel 3,5-disubstituted-1,2,4-oxadiazoles (**3a-d**), (**4a-d**), (**5a-d**), (**6a-d**), (**7a-d**) were synthesized 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 amides[1] and are found in several drugs and drug leads[2] 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 serotoninergic (5-HT_3) 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 dipeptidomimetics[9], signal transduction inhibitors[10], or cell adhesion inhibitors[11] as antikinetoplastid materials[12], β_3 adrenergic receptor[13], antiinflammatory agents[14], agrochemical and antifungal activities[15-17]. Compounds containing 1,2,4-oxadiazole moieties are also active against HIV integrase inhibitors[18] and antituberculostatic agents[19]. They show activity as growth hormone secretagogues[20] and antitumor agents[21]. They also inhibit SH2 domain of tyrosine kinase[22], monoamine oxidase[23], human nuetrophil elastase[24], human DNA topoisomerases[25]. 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 ^{1}H 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 (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): ^{1}H 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, -OCH_3), 2.62 (s, 3H, -CH_3); ESI-MS *m/z* 196 $(M + H)^+$.

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): ^{1}H 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, -OCH_3), 2.62 (s, 3H, -CH_3); ESI-MS *m/z* 196 $(M + H)^+$.

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): ^{1}H 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, -OCH_3), 2.65 (s, 3H, -CH_3); ESI-MS *m/z* 196 $(M + H)^+$.

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): ^{1}H 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, -OCH_3), 2.34 (s, 3H, -CH_3); ESI-MS *m/z* 196 $(M + H)^+$.

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): ^{1}H 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, -OCH_3), 2.33 (s, 3H, -CH_3); ESI-MS *m/z* 166 $(M + H)^+$.

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): ^{1}H 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, -NH_2), 3.85 (s, 3H, -OCH_3), 2.17 (s, 3H, -CH_3); ESI-MS *m/z* 166 $(M + H)^+$.

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): ^{1}H 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, -OCH_3), 3.69 (bs, 2H, -NH_2), 2.20 (s, 3H, -CH_3); ESI-MS *m/z* 166 $(M + H)^+$.

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): ^{1}H 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, -NH_2), 3.8 (s, 3H), 2.16 (s, 3H); ESI-MS *m/z* 166 $(M + H)^+$.

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): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (s, 1H, -CH=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, -OCH_3); 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): ^{1}H 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, -OCH_3); 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): ^{1}H 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, -OCH_3); 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-disubstitued-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-disubstitued-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, ν_{max}, cm^{-1}): 3159 (NH), 1605 (C=N), 1328, 1058, 744; ^{1}H 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, -CH_3); ^{13}C 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, ν_{max}, cm^{-1}): 3193 (NH), 1607 (C=N), 1351, 1044, 745; ^{1}H 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); ^{13}C 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, ν_{max}, cm^{-1}): 3205 (NH), 2943, 1601 (C=N), 1336, 1040, 751; ^{1}H 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, -CH_3); ^{13}C 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, ν_{max}, cm^{-1}): 3196 (NH), 1910, 1603 (C=N), 1462, 1335, 1044, 865, 772; ^{1}H 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); ^{13}C 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, ν_{max}, cm^{-1}): 3141 (NH), 1596 (C=N), 1572, 1341, 1198, 743; ^{1}H 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, -CH_3); ^{13}C 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 $C_{10}H_8N_4O$: 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, ν_{max}, cm^{-1}): 3170 (NH), 1622 (C=N), 1568, 1361, 1193, 740; ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C 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 $C_{15}H_{10}N_4ONa$: 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 2**c** following general procedure-IV method-A (80 % yield). Cream colour solid; IR (KBr, ν_{max}, cm^{-1}): 3118 (NH), 1621 (C=N), 1569, 1361, 961, 750; ^{1}H 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, $-CH_3$); ^{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 $C_{16}H_{12}N_4ONa$: 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, ν_{max}, cm^{-1}): 3161 (NH), 1604 (C=N), 1566, 1362, 961, 754; ^{1}H 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 $C_{15}H_9N_4OF$: 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, ν_{max}, cm^{-1}): 3143 (NH), 2924, 1626 (C=N), 1392, 952, 755; ^{1}H 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, $-CH_3$); ^{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, ν_{max}, cm^{-1}): 3144 (NH), 2928, 1568 (C=N), 1369, 954, 752; ^{1}H 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, ν_{max}, cm^{-1}): 3146 (NH), 2926, 1627, 1603 (C=N), 1370, 955, 756; ^{1}H 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, $-CH_3$); ^{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, ν_{max}, cm^{-1}): 3143 (NH), 2928, 1626 (C=N), 1457, 956, 758; ^{1}H 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, ν_{max}, cm^{-1}): 3211 (NH), 1591 (C=N), 1571, 1333, 940, 774; ^{1}H 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, $-CH_3$); ^{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 $C_{10}H_8N_4O$: 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, ν_{max}, cm^{-1}): 3294 (NH), 1597 (C=N), 1445, 1361, 742, 684; ^{1}H 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, ν_{max}, cm^{-1}): 3434 (NH), 1597 (C=N), 1572, 1354, 754; ^{1}H 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, $-CH_3$); ^{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 $C_{16}H_{12}N_4O$: 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, ν_{max}, cm^{-1}): 3444 (NH), 2868, 1601 (C=N), 1570, 1365, 956, 755; ^{1}H 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, ν_{max}, cm^{-1}): 3266 (NH), 1622 (C=N), 1325, 949, 747; ^{1}H NMR (300 MHz, $CDCl_3$): 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, $-CH_3$); ^{13}C 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, ν_{max}, cm^{-1}): 3314 (NH), 1621 (C=N), 1338, 946, 741; ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C 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, ν_{max}, cm^{-1}): 3291 (NH), 1622 (C=N), 1463, 1332, 753; ^{1}H 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, $-CH_3$); ^{13}C 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, ν_{max}, cm^{-1}): 3273 (NH), 1623 (C=N), 1340, 952, 755; ^{1}H 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); ^{13}C 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): ^{1}H 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, $-CH_3$), 2.33 (s, 3H, $-CH_3$); 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): ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.15 (dd, 1H, *J* = 0.96, 6.54 Hz, Ar-H), 8.01-.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, $-CH_3$); 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): ^{1}H 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, $-CH_3$), 2.37 (s, 3H, $-CH_3$); 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): ^{1}H 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, $-CH_3$); 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): ^{1}H 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,-CH_3), 2.32 (s, 3H, $-CH_3$).; 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): ^{1}H 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, $-CH_3$); 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): ^{1}H 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, $-NH_2$), 2.47 (s, 3H, $-CH_3$), 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): ^{1}H 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, $-NH_2$), 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 dryied at 50 °C under reduced pressure to get compound (**10**) with 95 % yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.42 (s, 1H), 7.79 (s, 1H), 7.59-7.52 (m, 4H), 7.22-7.7.17 (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

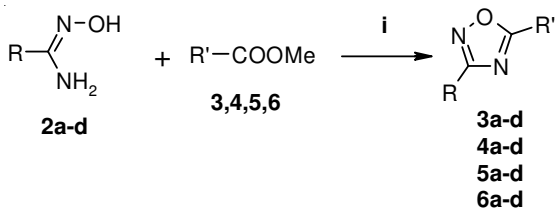
to 25 °C. Reaction mixture was concentrated to dryness to get residue. The residue was dissolved in dichloromethane (76 mL) and aluminum chloride (165.7 mmol) was added slowly to the reaction mixture maintaining the temperature below 25 °C. After complete addition the reaction mixture was refluxed for 3 h and reaction progress was monitored by TLC. After completion, reaction mixture was cooled to 0 °C and diluted with chilled water (152 mL). The reaction was further stirred for 1 h and organic layer was separated. Aqueous layer was extracted with dichloromethane and combined organic layers were washed with dil. HCl and brine. Organic layer was concentrated to dryness under reduced pressure to give compound **12** (91 % yield). Light brown colour solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.60 (s, 1H), 7.87 (d, 2H, *J* = 8.49 Hz), 7.75-7.69 (m, 3H), 7.61 (d, 1H, *J* = 6.81 Hz), 7.45 (d, 1H, *J* = 7.89 Hz), 7.24-7.20 (m, 1H).

Synthesis of compound 13: A solution of compound **12** (13.7 mmol) in acetic acid (45.0 mL) and conc. hydrochloric acid (6.6 mL) was heated to 90 to 100 °C for 1 h. Reaction mixture was concentrated under reduced pressure. Acetic acid (45 mL) was added to the residue and heated to 115 °C for 1 h and cooled to room temperature and stirred for 1 h. The solid obtained was filtered and washed with acetic acid followed by water. The product was dryied at 60 °C under reduced pressure to give compound **13** (85 % yield). Light yellow colour solid, m.p.: >220 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.77 (s, 1H, -NH), 12.0 (s, 1H, -COOH), 8.05 (d, 1H, *J* = 8.16 Hz, Ar-H), 7.62 (d, 1H, *J* = 8.43 Hz, Ar-H), 7.43-7.38 (m, 1H, Ar-H), 7.28-7.23 (m, 1H, Ar-H).; ESI-MS *m/z* 177 $(M + H)^+$.

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): ^{1}H 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, -CH_3); ESI-MS *m/z* 177 $(M + H)^+$.

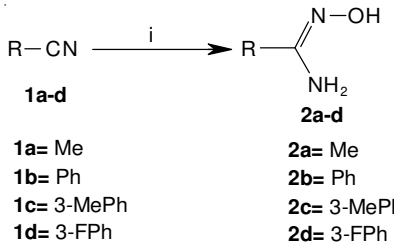
RESULTS AND DISCUSSION

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 pyridine[26]. A recent report has been described by the use of tetrabutylammonium fluoride (TBAF) to promote the cyclization of O-acylamidoximes in good yields[27]. Amidoximes were prepared form 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 reported[30] recently with moderate to good yields. Due to importance of 1,2,4-oxadiazoles and indazoles in the pharmaceutical area prompted us to synthesize 3-aryl/alkyl-5-indazolyl-1,2,4-oxadiazoles (**Scheme-I**, Table-1) from amidoximes.



Scheme-I: General synthesis of 3,5-disubstituted oxadiazole; Conditions: (i) K_2CO_3, toluene, 110 °C. (R=Me (2a); Ph (2b); 3-Me-Ph (2c); 3F-Ph (2d); R^1=3-ind (3), 4-ind (4), 5-ind (5), 6-ind (6))

The precursor amidoximes **2a-d** were synthesized from corresponding nitriles with hydroxylamine hydrochloride in the presence of base such as potassium carbonate in methanol by stirring at room temperature for 6 h to yield amidoximes in the range of 80-90 % (**Scheme-II**).



Scheme-II: Synthesis of amidoximes; Conditions: (i) Hydroxylamine. Hydrochloride, Methanol, K_2CO_3, room temperature

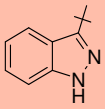
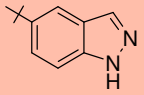
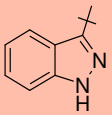
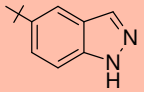
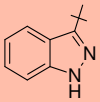
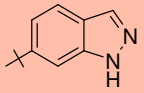
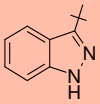
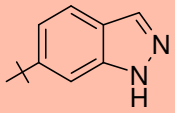
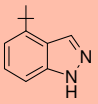
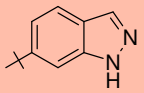
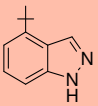
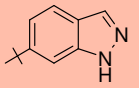
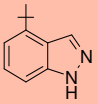
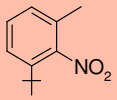
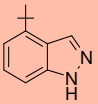
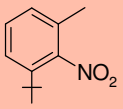
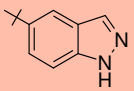
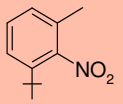
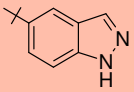
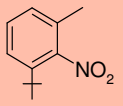
Various indazole carboxylic acid methyl esters **3,4,5,6** were treated with amidoximes **2a-d** in solvents such as DMF, NMP, ethanol and toluene using different bases such as TEA, DIPEA, pyridine, $NaHCO_3$, K_2CO_3, tBuOK and NaH to optimize reaction conditions. We have observed that K_2CO_3 as base and toluene as solvent at 110 °C for 6 to 12 h resulted in formation 3,5-disubstitued-1,2,4-oxadiazoles (**3,4,5,6**) (**Scheme-III-VI**) in high yields and good purity.

Indazole-3-carboxylic acid methyl ester (**3**) was prepared starting from phenyl hydrazine (**8**) and 4-bromobenzaldehyde (**9**) (**Scheme-III**). Phenyl hydrazine was treated with 4-bromobenzaldehyde to result 4-bromobenzalde-hydephenylhydrazone (**10**) in quantitative yields. Reaction of compound **10** with oxalylchoride provides an intermediate **11**, which upon treatment with aluminum chloride resulted in 4-bromobenzylideneaminoisatine (**12**) in good yields. Hydrolysis followed by rearrangement of compound **12** produces the indazole-3-carboxylic acid (**13**). Compound **13** was treated with dimethylsulphate in presence of potassium carbonate in acetone at reflux temperature to give desired indazole -3-carboxylic acid methyl ester (**3**) in good yields. The overall yields were improved by using 4-bromobenzaldehyde when compared with benzaldehyde.

The 5-(3-indazolyl)-1,2,4-oxadiazole series **3a-d** (**Shecme-III**) were synthesized from compound **3**; compound **3** was treated with amidoximes **2a-d** in the presence of potassium carbonate in toluene at reflux for **6-8** h and resulted in compounds **3a-d** in good yields.

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

TABLE-1

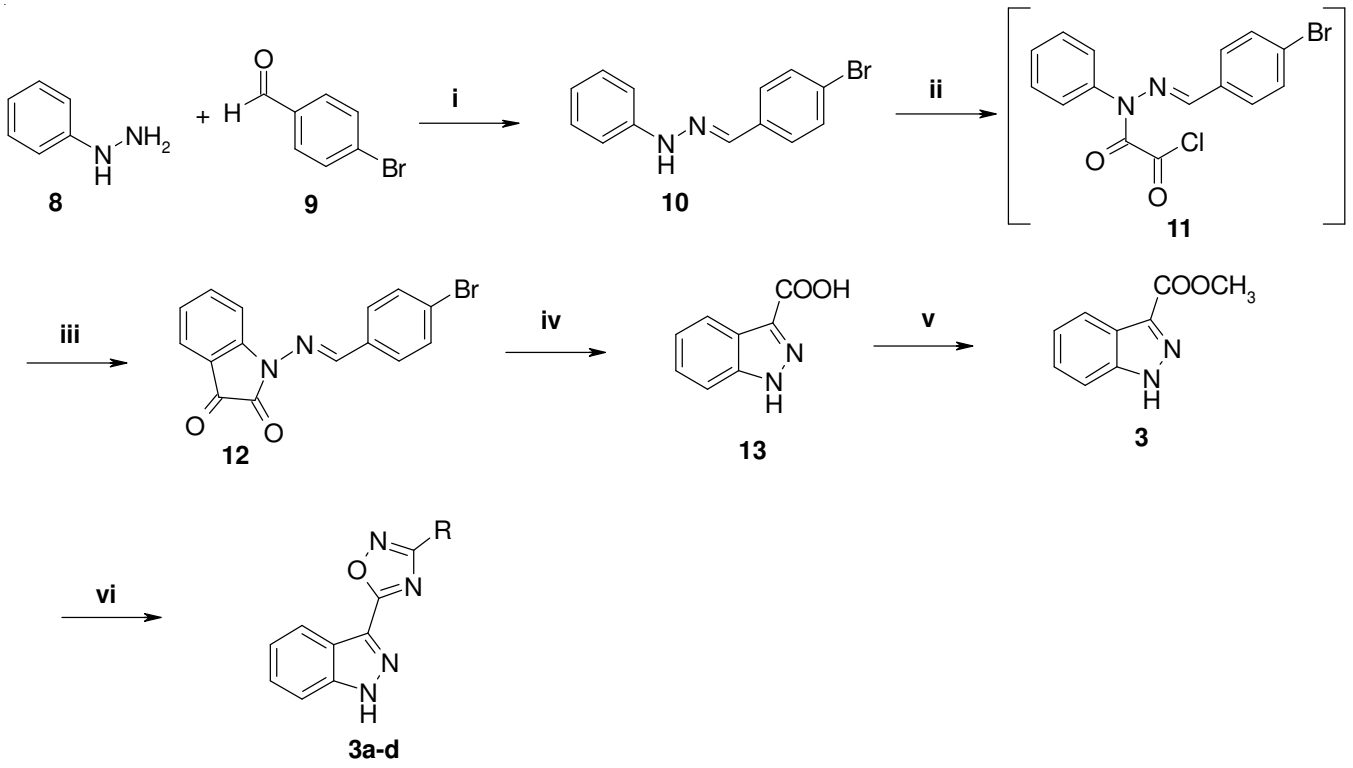
Entry	R	R^1	Product	Yield (%)[a]	Entry	R	R^1	Product	Yield (%)[a]
1	CH_3 (**2a**)	 3	**3a**	80	11	3-CH_3Ph (**2c**)	 5	**5c**	70
2	Ph (**2b**)	 3	**3b**	85	12	3-FPh (**2d**)	 5	**5d**	60
3	3-CH_3Ph (**2c**)	 3	**3c**	80	13	CH_3 (**2a**)	 6	**6a**	85
4	3-FPh (**2d**)	 3	**3d**	75	14	Ph (**2b**)	 6	**6b**	90
5	CH_3 (**2a**)	 4	**4a**	75	15	3-CH_3Ph (**2c**)	 6	**6c**	75
6	Ph (**2b**)	 4	**4b**	85	16	3-FPh (**2d**)	 6	**6d**	72
7	3-CH_3Ph (**2c**)	 4	**4c**	80	17	CH_3 (**2a**)	 24	**27a**	72
8	3-FPh (**2d**)	 4	**4d**	70	18	Ph (**2b**)	 24	**27b**	79
9	CH_3 (**2a**)	 5	**5a**	65	19	3-CH_3Ph (**2c**)	 24	**27c**	80
10	Ph (**2b**)	 5	**5b**	75	20	3-FPh (**2d**)	 24	**27d**	71

[a]Purified products.

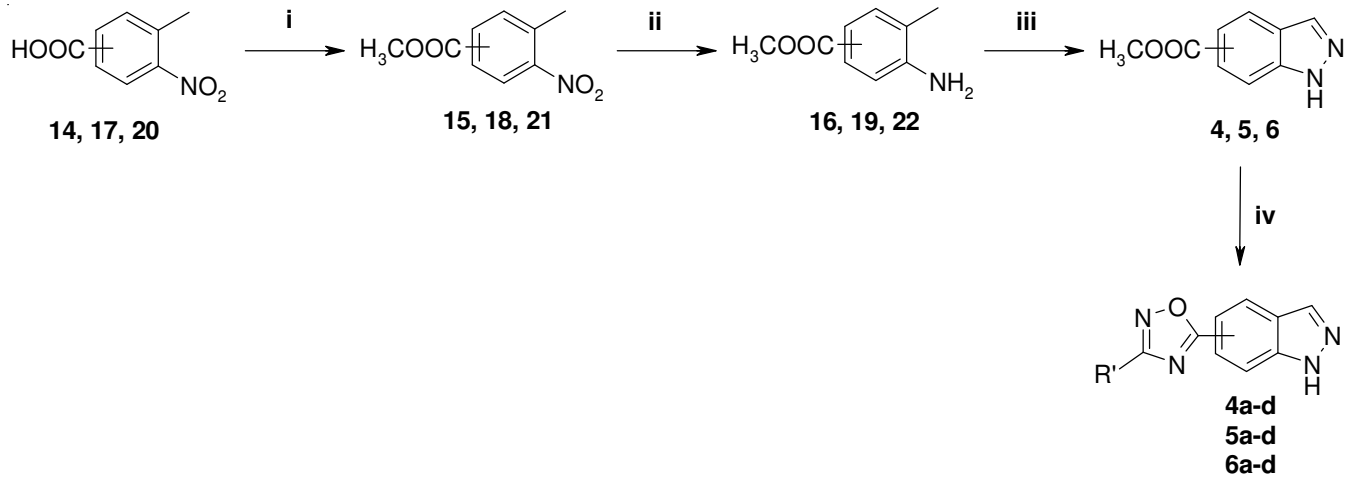
17, **20**) (**Scheme-IV**); compound **14**, **17**, **20** were converted to methyl ester (**15**, **18**, **21**) with dimethylsulphate in presence of potassium carbonate in acetone at reflux temperature. The compound nitro ester **15**, **18**, **21** were treated with Fe / NH_4Cl at reflux temperature to affordcorresponding **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

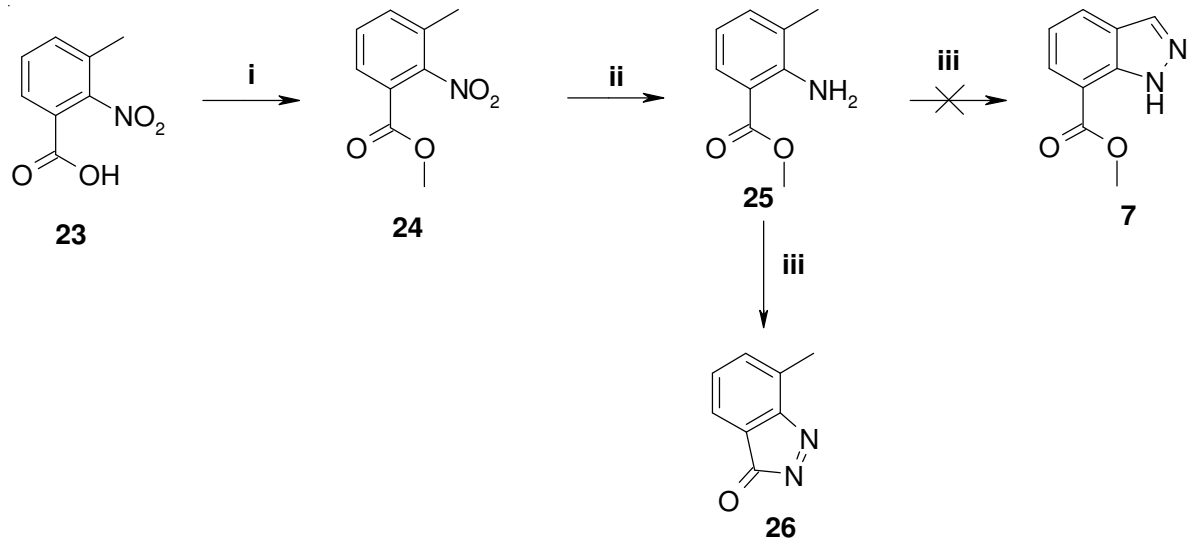


Scheme-IV: Synthesis of 5-indazolyl-1,24-oxadiazole; Conditions: (i) K_2CO_3, DMS, Acetone, reflux; (ii) Fe, NH_4Cl, EtOH, H_2O, 65 to 75 °C; (iii) Isoamylnitrite, Ac_2O, KOAc, $CHCl_3$, Reflux or $NaNO_2$, AcOH, H_2O, rt; (iv) Amidoxime (**2a-d**, **a** = Me, **b** = Ph, **c** = 3-MePh, 4-3-FPh), K_2CO_3, toluene, 110 °C; (iii)

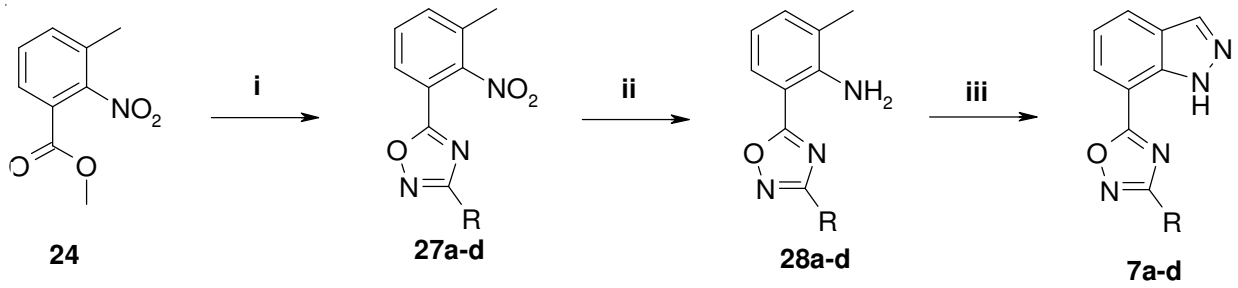
ester (**24**) with dimethyl sulphate in presence of potassium carbonate in acetone at reflux temperature (**Scheme-V**). Compound **24** was treated with Fe/NH_4Cl at reflux temperate to get compound **25** in good yields. Compound **25** was treated with sodium nitrite to get corresponding hydrazine 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 from 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 isoamylnitrite, 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-disubstitued-1,2,4-oxazidazoles 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) Isoamylnitrite, Ac_2O, KOAc, $CHCl_3$, Reflux or $NaNO_2$, AcOH, H_2O, rt

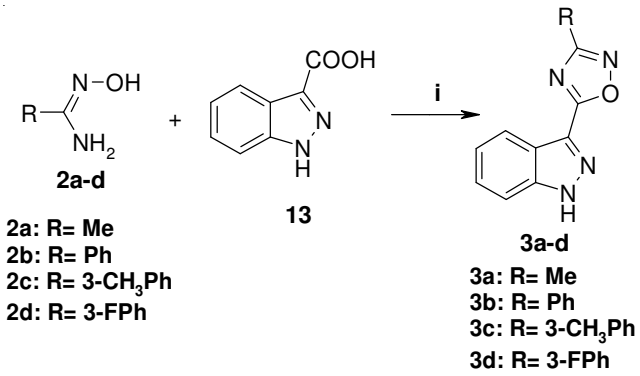


Scheme-VI: Synthesis of 5-(7-indazolyl)-1,2-4-oxadiazoles; **Conditions:** (i) Amidoxime (**2a-d**, **a = Me**, **b = Ph**, **c = 3-MePh**, **d = 3-FPh**), K_2CO_3, Toluene, 110 °C; (iii) Fe, NH_4Cl, EtOH, H_2O, 65 to 75 °C; (iv) (a) Isoamylnitrite, Ac_2O, KOAc, $CHCl_3$, Reflux or (b) $NaNO_2$, AcOH,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

[a]Purified products



2a: R= Me
2b: R= Ph
2c: R= 3-CH_3Ph
2d: R= 3-FPh

3a: R= Me
3b: R= Ph
3c: R= 3-CH_3Ph
3d: R= 3-FPh

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.

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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