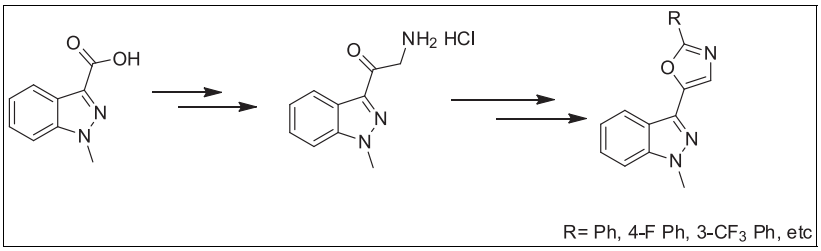
A Facile and Simple Synthesis of Novel 2-(Substituted)-5-(1-methyl-1*H*-indazol-3-yl)-Oxazole Derivatives

E. Vishnu Vardhan Reddy,[a,b]* J. Ramanatham,[c] N. Devanna,[b]
K. Srinivasa Reddy,[a] and D. Rajender[a]

[a]Custom Pharmaceutical Services, Dr Reddys Laboratories Limited, Miyapur, Hyderabad, India
[b]Department of Chemistry, JNT University, Ananthapur, Andhra Pradesh, India
[c]Pfizer Pharmaceuticals India Pvt. Ltd, Turbhe, Navi Mumbai, India, 400705
*E-mail: vishnuvardhanre@drreddys.com

Received May 3, 2011
DOI 10.1002/jhet.1089
Published online 7 March 2013 in Wiley Online Library (wileyonlinelibrary.com).



Novel 2-(substituted)-5-(1-methyl-1*H*-indazol-3-yl)-oxazoles (**13**) were synthesized in moderate yields, from 1-methyl-1*H*-Indazole 3-carboxylic acid (**1**), by converting it into a variety of amides (**12**) and further its heterocyclization. The structures of all the compounds have been elucidated on the basis of IR, ^{1}H-NMR, and HRMS.

J. Heterocyclic Chem., **50**, E221 (2013).

INTRODUCTION

Heterocyclic compounds play an important role in the treatment of various diseases and recent analysis of drugs in late development or on the market shows that 68% of them are heterocyclic compositions. Therefore, it is not surprising that research in the field of synthesis of heterocyclic compounds has gained special attention. Indazole derivatives, which are bioisosteres of indoles, are an important class of compounds in the medicinal area [1]. Compounds containing the indazole skeleton are known to show a variety of biological activities, such as high binding affinity for estrogen receptor [2], inhabitation of protein kinase C-b [3], 5-HT_2, and 5-HT_3 receptor antagonist [4], human immunodeficiency virus (HIV) protease inhibition [5], and anti-tumor activity [6].

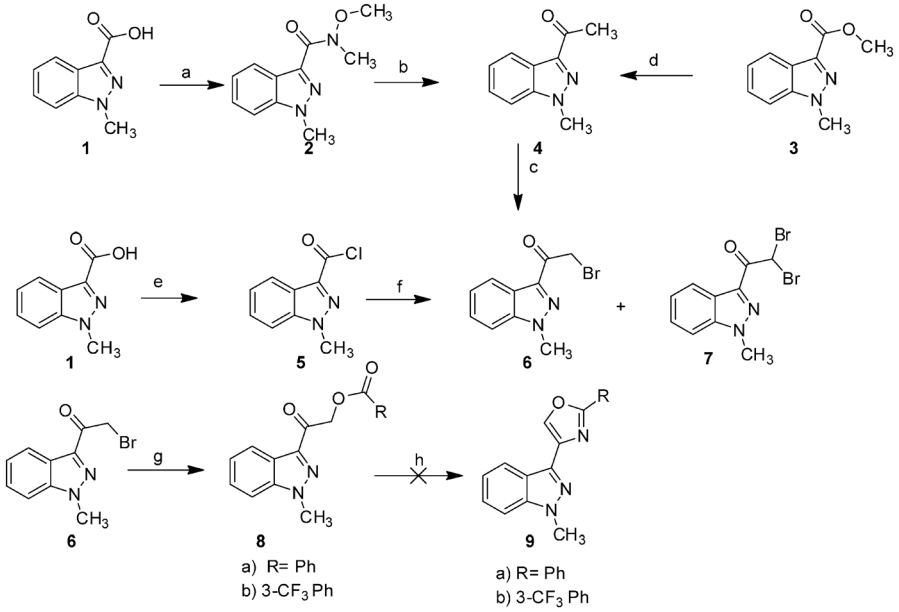
The oxazole heterocycle is a fundamental ring system found in different compounds such as natural products, pharmaceuticals, agrochemicals, peptidomimetics, and polymers [7]. Naturally occurring oxazoles are usually found with a 2,4-substitution pattern [8], a consequence of their biosynthetic assembly from serine residues. However, 2,5-substituted oxazole natural products are also known [9].

Recently, we reported a facile and simple synthesis of novel 1-methyl-2-(2-substituted-oxazol-4-yl)-1*H*-benzimidazole derivatives [10]. As a part of our continuous efforts to synthesize new analogues of nitrogen heterocycles and study their biological activities of these hybrid molecules, we planned to synthesize hybrid molecules containing both indazole and oxazole moieties bound together by a C—C bond which when present together, may have synergistic effects leading to more biologically potent molecules. Herein, in this article, the synthesis of hybrid molecules possessing both indazole and oxazole in their core structure are described.

RESULTS AND DISCUSSION

Based on our previous experience on facile and simple synthesis of novel 1-methyl-2-(2-substituted-oxazol-4-yl)-1*H*-benzimidazole derivatives [10], we attempted to make 4-(1-methyl-1*H*-indazol-3-yl)-2-substituted oxazole (**9**) starting from 1-methyl-1*H*-indazole-3-carboxylic acid (**1**) (Scheme 1). Acid chloride (**5**) was prepared *in-situ* from acid (**1**) and thionyl chloride in toluene medium [11]. The obtained acid chloride (**5**) was reacted with tetra-methyl silane (TMS) diazomethane at room temperature for 16 h and the reaction mass was quenched with 48% aq. HBr solution to get the corresponding mono-bromo compound (**6**). We developed an alternative, mild and flexible strategy, owing to the safety challenges of the diazo compounds, for the preparation of bromo compound, **6**. 1-Methyl-1*H*- indazole-3-carboxylic methyl ester (**3**) was reacted with the methyl magnesium bromide or iodide leading to the 3-acetyl indazole derivative (**4**). **4** was alternatively prepared from **1** by the coupling with *N*,*O*-dimethyl hydroxylamine hydrochloride, EDC hydrochloride, and pyridine as base in THF at room temperature which furnished the Weinreb amide (**2**). **2** when reacted with 5 mol equivalents of methyl magnesium bromide or iodide gave **4** in a higher yield. Subsequently, bromination of **4** with

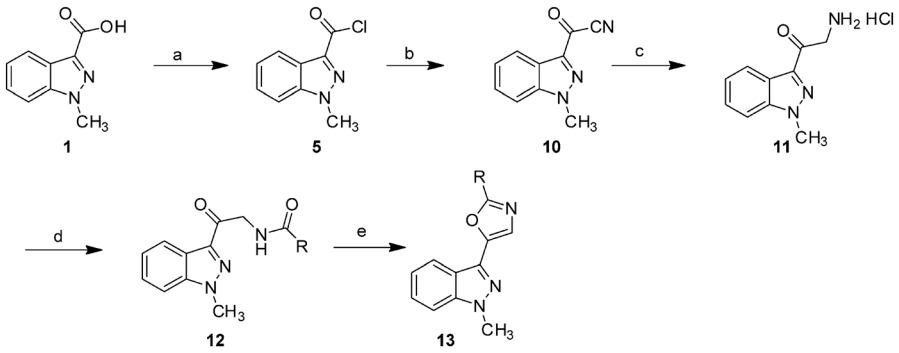
Scheme 1. Reagent and conditions: (a) NH(OMe)Me.HCl, pyridine, EDC.HCl, THF, 0°C–RT; (b) MeMgI/Br, THF, 0–5°C, 1 h; (c) $CuBr_2$, CHCl3, ethyl acetate, 70–80°C, 16 h; (d) MeMgI/Br, THF, 0–5°C, 1 h; (e) $SOCl_2$, toluene, 55–60°C, 3 h; (f) $TMSCHN_2$, 48% HBr, RT, 16 h; (g) RCOOH, TEA, acetone, RT, 30–60 min; (h) acetamide, BF_3-etherate, ethyl acetate, reflux, 48 h; (or) ammonium acetate, acetic acid, 100°C, 48 h.



copper (II) bromide in chloroform and ethyl acetate mixture led to the corresponding mono-bromo derivative (**6**) along with small percentage of dibromo derivative (**7**). The bromo derivative (**6**) was converted to corresponding ester (**8**) in the presence of triethyl amine in acetone medium. Attempts to convert the obtained ester (**8**) to the corresponding oxazole (**9**) under Cornforth conditions [12] and BF_3-etherate at different temperatures, different solvent media [13] were unsuccessful. This could be because of the amide formation with the carboxylate moiety displacing the heterocyclic alcoholic group as seen in common for the esters.

Eventually, we planned to synthesize 2-(substituted)-5-(1-methyl-1*H*-indazol-3-yl)-oxazole (**13**) instead of 4-(1-methyl-1*H*-indazol-3-yl)-2-substituted oxazole (**9**) (Scheme 2). 1-Methyl-3-indazolyl chloride (**5**) was treated with CuCN to prepare the corresponding nitrile derivative (**10**). As **10** was unstable, it was immediately reduced with Pd/C under hydrogen atmosphere to the corresponding amine and was isolated as its hydrochloride salt (**11**). The amine hydrochloride derivative (**11**) was converted to the corresponding amides (**12**) with moderate to good yields by reacting with suitable acid chlorides or acids based on its ease of use or commercial availability. Thus, the amides (**12a–c)** were synthesized by treating the corresponding acid chloride in presence of TEA [14], while the amides (**12d–h)** where synthesized by coupling amine hydrochloride derivatives **(11)** with corresponding acids in presence of EDC hydrochloride. The amides (**12a–h**) were then converted to the corresponding oxazole (**13a–h**) by reacting with phosphorous oxychloride at elevated temperatures under solvent free reaction conditions [15].

Scheme 2. Reagent and conditions: (a) $SOCl_2$, toluene, 55–60°C, 3 h; (b) CuCN, CH_3CN, toluene, TBAI, 80–85°C, 12 h; (c) acetic acid, Pd/C,H_2 50–55 psi, 8–10 h; (d) RCOCl, Et_3N, DCM, RT, 3–4 h; or RCOOH, EDC.HCl, RT, 1–3 h; (e) $POCl_3$, 50–60°C, 3–12 h.



CONCLUSION

In conclusion, we have developed a simple, operationally friendly process for the synthesis of 2-(substituted)-5-(1-methyl-1*H*-indazol-3-yl)oxazole derivatives with moderate to good yields. As a part of these studies, a number of 2-substituted oxazole derivatives have been synthesized and biological evaluation of these molecules are under progress, which will be reported in due course of time.

EXPERIMENTAL

General methods. ^{1}H-NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ on a Mercury plus Varian 400 MHz spectrometers. Proton chemical shifts (δ) are relative to TMS (δ 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), and m (multiplet). Coupling constants (*J*) are given in hertz. Melting points were determined using a scientific open capillary melting point apparatus and are uncorrected. Mass spectra were obtained from Triple Quad 6410 Mass Spectrometer. Thin layer chromatography was performed on silica gel plates (SRL 230–400 mesh). All the solvents used are commercially available and were distilled before use.

General procedure for 1-methyl-1*H*-indazole-3-carboxylic acid methoxy-methyl-amide (Weinreb amide) (2). To a solution of 1-methyl-1*H*-indazole-3-carboxylic acid (**1**) (20 g, 0.0693 mol) in THF (200 mL) was added *N*,*O*-dimethylhydroxylamine hydrochloride (12.2 g, 0.124 mol) at room temperature. The mixture was cooled to 0°C and pyridine (20.2 mL, 0.249 mol) was added. The reaction mixture was stirred initially for 1.5 h at 0°C and then room temperature for 1 h. Pyridine (18.49 mL, 0.227 mol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (43.5 g, 0.227 mol) were successively added and the reaction mixture was stirred overnight. After completion of the reaction, water (500 mL) was added to the reaction mixture and extracted with ethyl acetate. Organic layer was washed with water, dried over a sodium sulfate and concentrated under vacuum to get viscous liquid of **2**. (20.0 g. Yield = 79.0%).

Compound 2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ_H 8.0 (d, *J* = 7.8 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.25–7.49 (m, 2H), 4.13 (s, 3H), 3.78 (s, 3H), 3.44 (s, 3H); electrospray ionisation-mass spectrometric (ESI-MS) (*m*/*z*): 220.2 (*M*+1).

General procedure for 1-(1-methyl-1*H*-indazol-3-yl) ethanone (4) from 2. To a stirred solution of 1-methyl-1*H*-indazole-3-carboxylic acid methoxy methyl amide (**2**) (10 g, 0.045 mol) in THF (100 mL) was added 1.5*M* solution of methyl magnesium iodide in ether (152 mL, 0.22 mol) at 0–5°C under nitrogen atmosphere and stirred for about 1 h at room temperature. The reaction mass was quenched with saturated aqueous NH_4Cl solution and further extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The crude material was purified by column chromatography on silica gel (EtOAc/hexane) to get the pure title compound **4** (9.5 g, yield = 59.7%).

Compound 4. Solid, m.p. 91–93°C; IR (KBr, *v*): 2940, 1661, 1473, 1302; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.37 (d, *J* = 7.8 Hz, 1H), 7.43–7.44 (m, 2H), 7.31–7.34 (m, 1H), 4.15 (s, 3H), 2.71 (s, 3H). ^{13}C-NMR (5 MHz, $CDCl_3$): ppm, δ 194.5, 142.0, 141.1, 126.7, 123.4, 122.8, 122.5, 109.1, 36.1, 26.6; ESI-MS (*m*/*z*): 175 (*M*+1).

General procedure for 2-bromo-1-(1-methyl-1*H*-indazol-3-yl)-ethanone (6) from 4. To a solution of 1-(1-methyl-1*H*-indazol-3-yl)-ethanone (**4**) (1.0 g, 5.7 mmol) in a mixture of chloroform (20 mL) and ethyl acetate (20 mL) was added copper (II) bromide (2.3 g, 10.33 mmol) and stirred at 70–80°C for 16 h. After completion of reaction, as monitored by TLC, reaction mixture was cooled to room temperature and filtered the solid. The filtrate was concentrated under reduced pressure. Both monobromo (**6**) and dibromo (**7**) compounds were separated by column chromatography on silica gel after eluting with toluene/hexane (0.8 g, yield = 55%).

Compound 6. Solid, m.p. 91–94°C; IR (KBr, *v*): 2925, 1663, 1471; ^{1}H-NMR (400 MHz, DMSO-d_6): δ_H 8.16 (d, *J* = 8.3 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.39–7.57 (m, 2H), 4.86 (s, 2H), 4.21 (s, 3H); ESI-MS (*m*/*z*): 253.1 (*M*+1).

Compound 7. Solid, m.p. 150–152°C; IR (KBr, *v*): 2939, 1682, 1470; ^{1}H-NMR (400 MHz, DMSO-d_6): δ_H 8.19 (dd, *J* = 1.1 Hz, *J* = 8.0 Hz, 1H), 7.9 (d, *J* = 8.4, 1H), 7.57–7.59 (m, 1H), 7.54 (s, 1H), 7.45–7.49 (m, 1H), 4.25 (s, 3H); ^{13}C-NMR (50 MHz, DMSO-d_6): ppm, 181.7, 141.3, 134.8, 127.5, 124.8, 122.8, 121.0, 111.4, 40.9, 36.8. ESI-MS (*m*/*z*): 333 (*M*+1).

General procedure for synthesis of ester (8). A mixture of 2-bromo-1-(1-methyl-1*H*-indazol-3-yl)-ethanone (**6**) (0.5g 1.0 mol), corresponding carboxylic acid (1.0 mol), triethylamine (0.59 g, 5.92 mmol), and acetone (10 mL) were stirred at 25–35°C for 30–60 min. After completion of reaction, as monitored by TLC, triethylamine hydro bromide was filtered and filtrate was distilled off under vacuum. The residue was washed with water, and purified by column chromatography on silica gel (EtOAc/hexane) to give the pure title compound.

Compound 8a. Solid, m.p. 138–140°C; IR (KBr, *v*): 3265, 1714, 1683, 1282; ^{1}H-NMR (400 MHz, DMSO-d_6): δ_H 8.14 (d, *J* = 7.8 Hz, 1H), 8.07 (d, *J* = 7.3 Hz, 2H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.72–7.74 (m, 1H), 7.55–7.61 (m, 3H), 7.38–7.42 (m, 1H), 5.74 (s, 2H), 4.23 (s, 3H); ESI-MS (*m*/*z*): 295.2 (*M*+1).

Compound 8b. Solid, m.p. 127–129°C; IR (KBr, *v*): 3398, 1738, 1706,1616; ^{1}H-NMR (400 MHz, DMSO-d_6): δ_H 8.36 (d, *J* = 7.6 Hz, 1H), 8.3 (s, 1H), 8.12–8.15 (m, 2H), 7.87–7.88 (m, 2H), 7.40–7.57 (m, 2H), 5.80 (s, 2H), 4.24 (s, 3H); ESI-MS (*m*/*z*): 363.2 (*M*+1).

General procedure for 1-methyl-1*H*-indazole-3-carbonyl cyanide (10). A mixture of 1-methyl-1*H*-indazole-3-carboxylic acid (**1**) (10.0 g, 0.0565 mol), thionyl chloride (12.4 mL, 0.17 mol), DMF (catalytic), and toluene (100 mL) was heated for 3 h at 55–60°C. Excess thionyl chloride was removed at 60°C under vacuum and crude compound triturated with hexanes to afford acid chloride **5**.

To a well stirred mixture of copper (I) cyanide (4.98 g, 0.05 mol), toluene (24 mL) and acetonitrile (72 mL) was added 1-methyl-1*H*-indazole-3-carbonyl chloride (**5**) (8.0 g, 0.04 mol) in toluene (24 mL) at room temperature under nitrogen atmosphere. Tetra-butyl ammonium iodide (3.0 g, 8.22 mmol) was added to reaction mass and heated to 80–85°C for 12 h. Reaction mass was diluted with toluene and filtered through celite. The filtrate was evaporated under reduced pressure below 50°C and material directly taken into for next step without any further purification.

Compound (10). IR (KBr, *v*): 3445, 2942, 2223, 1741, 1651; ^{1}H-NMR (400 MHz, DMSO-d_6): δ_H 8.1 (d, *J* = 8.2 Hz, 1H), 7.95 (d, *J* = 8.6 Hz, 1H), 7.50–7.66 (m, 2H), 4.32 (s, 3H).

General procedure for 2-amino-1-(1-methyl-1*H*-indazol-3-yl)-ethanone hydrochloride (11). The 1-methyl-1*H*-indazole-3-carbonyl cyanide (**10**) (7.6 g, 0.041 mol) in acetic acid (500 mL) was treated with hydrogen in presence of 10% Pd/C (0.76 g) at 50–55 psi for 8–10 h. The reaction mixture was filtered over celite and the filtrate was concentrated under reduced pressure at below 65°C. To the residue, 15% IPA-HCl (100 mL) was added and stirred for 30 min at 25–35°C. The solid obtained was filtered, washed with IPA, and dried under reduced pressure at 50°C which offered a reddish brown color solid of **11** (5 g, yield 40% from acid (**1**)).

Compound (11). Solid, m.p. 272–275°C; ^{1}H-NMR (400 MHz, DMSO-d_6): 8.52 (bs, 2H), 8.18 (d, J = 8.3 Hz, 1H), 7.87 (d, J = 8.3 Hz, 1H), 7.42–7.59 (m, 2H), 4.52 (s, 2H), 4.23 (s, 3H); ^{13}C-NMR (50 MHz, DMSO-d_6): ppm, 188.1, 141.3, 138.9, 127.7, 124.8, 122.2, 122.38, 111.6, 44.6, 37.1; high resolution mass spectrometry (HRMS) (m/z): $[M + H]^+$ calcd for$[C_{10}H_{12}N_3O]^+$ 190.0980, found: 190.0988.

General procedure for *N*-[2-(1-methyl-1*H*-indazol-3-yl)-2-oxo-ethyl]-substituted amide from acid chloride (12a–c). To a suspension of 2-amino-1-(1-methyl-1*H*-indazol-3-yl)-ethanone hydrochloride (**11**) (1.0 g, 4.4 mmol) in dichloromethane (10 mL) was added triethylamine (1.34 g, 13.3 mmol) followed by corresponding acid chloride (4.66 mmol) at 0–5°C and stirred for appropriate time (see Table 1) at room temperature. After ensuring the completion of reaction by TLC, the mixture was quenched with water and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure below 40°C. The crude compound on trituration with diethyl ether gave as the title compounds (see Table 1).

General procedure for *N*-[2-(1-methyl-1*H*-indazol-3-yl)-2-oxo-ethyl]-substituted amide from acid (12d–h). To a suspension of 2-amino-1-(1-methyl-1*H*-indazol-3-yl)-ethanone hydrochloride (**11**) (1.0 g, 4.4 mmol) in dichloromethane (10 mL) was added corresponding acid (4.88 mmol) at 0–5°C. *N*-Methyl pyrrolidinone (1.34 g, 13.3 mmol) followed by 1-(3-dimethyl amino propyl)-3-ethylcarbodiimide hydrochloride (1.0 g, 5.21 mmol) were added to the above reaction mixture and stirred for appropriate time (see Table 1) at room temperature. After completion of the reaction, as confirmed by TLC, the mixture was taken into water, extracted with dichloromethane and dried over anhydrous sodium sulfate. The solvent was removed under vacuum to afford the crude compound which on trituration with diethyl ether gave the pure title compounds (see Table 1).

General procedure for 2-(substituted)-5-(1-methyl-1*H*-indazol-3-yl)-oxazoles (13a-h). *N*-[2-(1-Methyl-1*H*-indazol-3-yl)-2-oxo-ethyl]-substituted amide (1.38 mmol) and phosphorous oxychloride (5 mL) were stirred for appropriate time (see Table 2) at 50–60°C under nitrogen atmosphere. After completion of the reaction, as monitored by TLC, excess phosphorous oxychloride was distilled off. Water was added to the residue and extracted with dichloromethane (DCM). The organic layer was washed with 5% aqueous HCl solution followed by 5% $NaHCO_3$ solution and dried over anhydrous sodium sulfate. The solvent was removed under vacuum and residue was purified by flash chromatography using a 25:75 gradient of ethyl acetate/hexane to afford the pure compounds (see Table 2).

Spectral data. ***3,4-dichloro-N-(2-(1-methyl-1H-indazol-3-yl)-2-oxoethyl)benzamide (12a).*** Solid, m.p. 202–205°C; IR (KBr, v): 3416, 3405, 1669, 1654, 1541; ^{1}H-NMR (400 MHz, DMSO-d_6): δ_H 9.13 (t, J = 5.4 Hz, 1H), 8.15–8.17 (m, 2H), 7.92 (dd, J = 1.9 Hz, J = 8.3 Hz, 1H), 7.80–7.90 (m, 2H), 7.37–7.56 (m, 2H), 4.85 (d, J = 5.8 Hz, 2H), 4.23 (s, 3H); HRMS (m/z): $[M + H]^+$ calculated for $[C_{17}H_{14}N_3O_2Cl_2]^+$ 362.0463. Found: 362.0448.

2-(3,4-dichlorophenyl)-5-(1-methyl-1H-indazol-3-yl)oxazole (13a). Solid, m.p. 143–146°C; IR (KBr, v): 3115, 2939, 1594, 1494, 1474; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 8.20 (d, J = 8.3 Hz, 1H), 8.18 (s, 1H), 8.07 (d, J = 8.3, 1H), 7.98 (s, 1H), 7.85(d, J = 8.8 Hz, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.32–7.55 (m, 2H), 4.15 (s, 3H); HRMS (m/z): $[M + H]^+$ calculated for $[C_{17}H_{12}N_3OCl_2]^+$ 344.0357. Found: 344.0349.

4-fluoro-N-(2-(1-methyl-1H-indazol-3-yl)-2-oxoethyl)benzamide (12b). Solid, m.p. 152–154°C; IR (KBr, v): 3500, 3305, 1683, 1644, 1503; ^{1}H-NMR (400 MHz, DMSO-d_6): δ_H 8.93 (t, J = 5.3 Hz, 1H), 8.16 (d, J = 8.1 Hz, 1H), 7.99–8.02 (m, 2H), 7.83 (d, J = 8.5 Hz, 1H), 7.52–7.53 (m, 1H), 7.32–7.40 (m, 3H), 4.8 (d, J = 5.4 Hz, 2H), 4.23 (s, 3H); HRMS (m/z): $[M + H]^+$ calculated for $[C_{17}H_{15}N_3O_2F]^+$ 312.1148. Found: 312.1133.

2-(4-fluorophenyl)-5-(1-methyl-1H-indazol-3-yl)oxazole (13b). Solid, m.p. 182–185°C; IR (KBr, v): 3120, 1595, 1495, 1321; ^{1}H-NMR (400 MHz, DMSO-d_6): δ_H 8.14–8.19 (m, 3H), 7.92 (s, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.50–7.54 (m, 1H), 7.43 (t, J = 8.8 Hz, 2H), 7.31–7.34 (m, 1H), 4.15 (s, 3H); ^{13}C-NMR (50 MHz, DMSO-d_6): ppm, δ159.5, 146.3, 140.9, 132.1, 128.8, 128.7, 127.2, 124.9, 123.7, 122.1, 120.8, 120.4, 116.9, 116.4, 110.6, 36.0; HRMS (m/z): $[M + H]^+$ calculated for $[C_{17}H_{13}N_3OF]^+$ 294.1043. Found: 294.1050.

N-[2-(1-Methyl-1H-indazol-3-yl)-2-oxo-ethyl]-benzamide (12c). Solid, m.p. 148–151°C; IR (KBr, v): 3283, 3062, 1690, 1621, 1541; ^{1}H-NMR (400 MHz, DMSO-d_6): δ_H 8.8 (t, J = 5.8 Hz, 1H), 8.17 (d, J = 7.8 Hz, 1H), 7.82–7.94 (m, 3H), 7.37–7.55 (m, 5H), 4.85 (d, J = 5.8 Hz, 2H), 4.23 (s, 3H); ^{13}C-NMR (50 MHz, DMSO-d_6): ppm, δ 190.7, 166.5, 140.7, 139.3, 133.9, 131.3, 128.3, 127.2, 126.9, 123.8, 121.8, 121.2, 110.7, 45.9, 36.4; HRMS (m/z): $[M + H]^+$ calculated for $[C_{17}H_{16}N_3O_2]^+$ 294.1243. Found: 294.1240.

5-(1-Methyl-1H-indazol-3-yl)-2-phenyloxazole (13c). Solid, m.p. 148–151°C; IR (KBr, v): 3118, 2926, 1722,1599; ^{1}H-NMR (400 MHz, DMSO-d_6): δ_H 8.2 (d, J = 8.1 Hz, 1H), 8.11–8.14 (m, 2H), 7.93 (s, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.31–7.63 (m, 5H), 4.16 (s, 3H); ^{13}C-NMR (50 MHz, DMSO-d_6): ppm, δ 159.9, 145.8, 140.5, 131.8, 130.6, 129.2, 126.8, 126.6, 125.9, 124.6, 121.6, 121.8, 120.5, 120.0, 110.3, 35.7; HRMS (m/z): $[M + H]^+$ calculated for $[C_{17}H_{14}N_3O]^+$ 276.1137. Found: 276.1139.

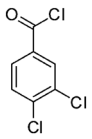
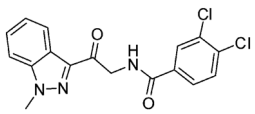
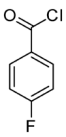
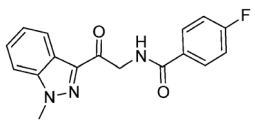
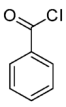
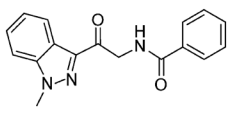
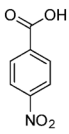
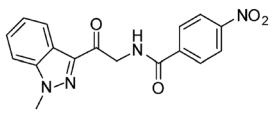
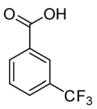
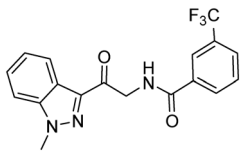
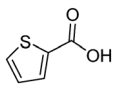
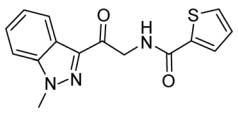
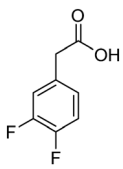
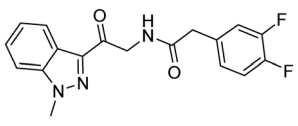
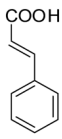
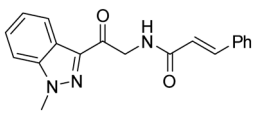
N-[2-(1-Methyl-1H-indazol-3-yl)-2-oxoethyl]-4-nitrobenzamide (12d). Solid, m.p. 210–212°C; IR (KBr, v): 3323, 2947, 1693, 1635, 1595; ^{1}H-NMR (400 MHz, DMSO-d_6): δ_H 9.26 (t, J = 5.3 Hz, 1H), 8.37 (d, J = 8.8 Hz, 2H), 8.15–8.17 (m, 3H), 7.84 (d, J = 8.8 Hz, 1H), 7.37–7.56 (m, 2H), 4.89 (d, J = 5.4 Hz, 2H), 4.2 (s, 3H); HRMS (m/z): $[M + H]^+$ calculated for $[C_{17}H_{15}N_4O_4]^+$ 339.1093. Found: 339.1078.

5-(1-Methyl-1H-indazol-3-yl)-2-(4-nitrophenyl)oxazole (13d). Solid, m.p. 202–205°C; IR (KBr, v): 3114, 1734, 1605, 1593, 1333, 1314; ^{1}H-NMR (400 MHz, DMSO-d_6): δ_H 8.40–8.42 (m, 2H), 8.33–8.35 (m, 2H), 8.21 (d, J = 8.3, 1H), 8.06 (s, 1H), 7.7 (d, J = 8.8 Hz, 1H), 7.33–7.56 (m, 2H), 4.16 (s, 3H); HRMS (m/z): $[M + H]^+$ calculated for $[C_{17}H_{13}N_4O_3]^+$ 321.0988. Found: 321.0994.

N-(2-(1-Methyl-1H-indazol-3-yl)-2-oxoethyl)-3-(trifluoromethyl) benzamide (12e). Solid, m.p. 140–142°C; IR (KBr, v): 3421, 1678, 1661, 1512; ^{1}H-NMR (400 MHz, DMSO-d_6): δ_H 9.22 (t, J = 5.4 Hz, 1H), 8.29 (s, 1H), 8.24 (d, J = 7.5 Hz, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 8.1Hz 1H), 7.84 (d, J = 8.6 Hz, 1H), 7.78 (t, J = 7.5 Hz, 1H), 7.37–7.56 (m, 2H),

Table 1

Preparation of amide (**12**) by reacting amine hydrochloride (**11**) with carboxylic acid or acid chloride.

Entry	Acid or acid chloride	Amide (**12**)	Yield[a] (%)	Time (h)	M.p. (°C)
a			50	4	202–205
b			56	4	152–154
c			64	3	148–151
d			56	3	210–212
e			50	1	140–142
f			45	1	161–163
g			52	1	146–149
h			43	1	188–190

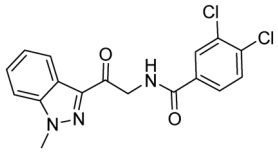
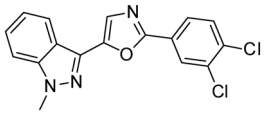
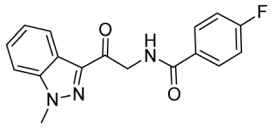
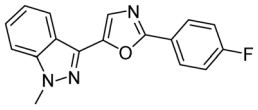
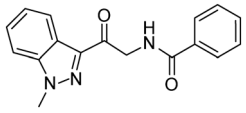
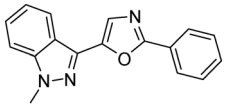
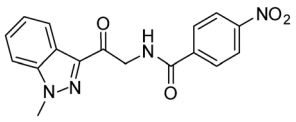
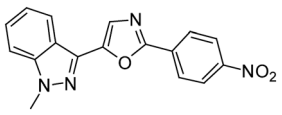
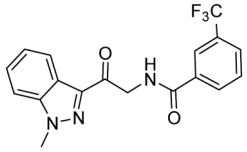
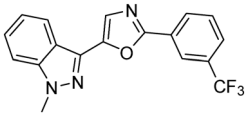
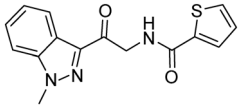
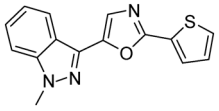
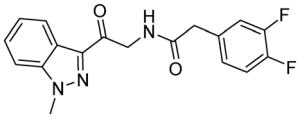
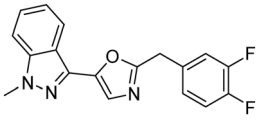
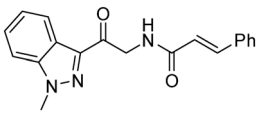
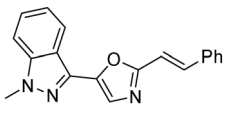
[a]Yields refer to isolated pure products characterized by IR, NMR, and HRMS.

4.90 (d, J = 5.3 Hz, 2H), 4.23 (s, 3H); ^{13}C-NMR (50 MHz, DMSO-d_6): ppm, δ 190.6, 165.6, 140.9, 139.5, 134.9, 131.5, 130.0, 129.7, 129.1, 128.2, 127.2, 126.8, 124.1, 121.4, 110.9, 46.2, 36.6; HRMS (m/z): $[M + H]^+$ calculated for $[C_{18}H_{15}N_3O_2F_3]^+$ 362.1116. Found: 362.1120.

5-(1-Methyl-1H-indazol-3-yl)-2-(3-(trifluoromethyl)phenyl) oxazole (13e). Solid, m.p. 171–173°C; IR (KBr, v): 3133, 2949, 1600, 1339, 1168, 1124; ^{1}H-NMR (500 MHz, DMSO-d_6) δ_H 8.41 (d, J = 7.6 Hz, 1H), 8.31 (s, 1H), 8.19 (d, J = 8.2 Hz, 1H), 8.01 (s, 1H), 7.94–7.95 (m, 1H), 7.84–7.87 (m, 1H), 7.76

Table 2

Preparation of 2-(substituted)-5-(1-methyl-1*H*-indazol-3-yl)-oxazole derivatives (**13**) by reacting **12** with $POCl_3$.

Entry	Amide (**12**)	Product (**13**)	Yield[a] (%)	Time (h)	M.p. (°C)
a			69	12	143–146
b			53	12	182–185
c			63	3	148–151
d			67	3	202–205
e			63	3	171–173
f			53	3	149–150
g			56	3	97–98
h			53	4	146–148

[a]Yields refer to isolated pure products characterized by IR, NMR, and HRMS.

(d, J = 8.5 Hz, 1H), 7.33–7.55 (m, 2H), 4.16 (s, 3H); HRMS (*m*/*z*): $[M + H]^+$ calculated for $[C_{18}H_{13}N_3OF_3]^+$ 344.1011. Found: 344.1009.

***N*-(2-(1-Methyl-1*H*-indazol-3-yl)-2-oxoethyl)thiophene-2-carboxamide (12f).** Solid, m.p. 161–163°C; IR (KBr, *v*): 3417, 3089, 1671, 1648, 1524; ^{1}H-NMR (400 MHz, DMSO-d_6):δ_H 8.92 (t, J = 5.9 Hz, 1H), 8.17 (d, J = 7.8, 1H), 7.79–7.88 (m, 3H), 7.37–7.55 (m, 2H), 7.19–7.21 (m, 1H), 4.82 (d, J = 5.8 Hz, 2H), 4.22 (s, 3H); ^{13}C-NMR (50 MHz, DMSO-d_6): ppm, δ 190.4, 161.4, 140.7, 139.3, 130.7, 128.3, 127.7, 126.8, 127.7, 126.8, 123.7, 121.8, 121.1, 110.6, 45.6, 36.3; HRMS (*m*/*z*): $[M + H]^+$ calculated for $[C_{15}H_{14}N_3O_2S]^+$ 300.0807. Found: 300.0807.

***5*-(1-Methyl-1*H*-indazol-3-yl)-2-(thiophen-2-yl)oxazole (13f).** Solid, m.p. 149–150°C; IR (KBr, *v*): 3112, 2933, 1602, 1492, 1344, 1298, 1256; ^{1}H-NMR (400 MHz, DMSO-d_6): δ_H 8.15

(d, *J* = 7.9 Hz, 1H), 7.9 (s, 1H), 7.84–7.86 (m, 2H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.52 (t. *J* = 7.9 Hz, 1H), 7.27–7.34 (m, 2H), 4.15 (s, 3H); ^{13}C-NMR (50 MHz, DMSO-d_6): ppm, δ 156.2, 145.1, 140.4, 131.5, 129.6, 128.8, 128.4, 128.0, 126.7, 124.4, 121.6, 120.3, 119.9, 110.1, 40.7; HRMS (*m*/*z*): [*M* + H]$^+$ calculated for $[C_{15}H_{12}N_3OS]^+$ 282.0701. Found: 282.0714.

2-(3,4-Difluorophenyl)-N-(2-(1-methyl-1H-indazol-3-yl)-2-oxoethyl)acetamide (12g). Solid, m.p. 146–149°C; IR (KBr, *v*): 3304, 3074, 1690, 1636, 1549, 1519; ^{1}H-NMR (500 MHz, DMSO-d_6): δ_H 8.49 (t, *J* = 5.4 Hz, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.37–7.54 (m, 4H), 7.15–7.17 (m, 1H), 4.70 (d, *J* = 5.4 Hz, 2H), 4.19 (s, 3H), 3.59 (s, 2H); ^{13}C-NMR (50 MHz, DMSO-d_6): ppm, δ 190.6, 170.0, 140.7, 139.2, 133.9, 126.9, 125.9, 123.8, 121.8, 121.2, 118.1, 117.8, 117.2, 116.8, 110.7, 45.5, 36.4; HRMS (*m*/*z*): [*M* + H]$^+$ calcd for $[C_{18}H_{16}N_3O_2F_2]^+$ 344.1211. Found: 344.1200.

2-(3,4-Difluorobenzyl)-5-(1-methyl-1H-indazol-3-yl)oxazole (13g). Solid, m.p. 97–98°C; IR (KBr, *v*): 3117, 3058, 1607, 1566, 1516; ^{1}H-NMR (500 MHz, DMSO-d_6): δ_H 8.0 (d, *J* = 8.2 Hz, 1H), 7.69–7.71 (m, 2H), 7.41–7.51 (m, 3H), 7.23–7.28 (m, 2H), 4.30 (s, 2H), 4.09 (s, 3H); HRMS (*m*/*z*): [*M* + H]$^+$ calculated for $[C_{18}H_{14}N_3OF_2]^+$ 326.1105. Found: 326.1118.

N-(2-(1-methyl-1H-indazol-3-yl)-2-oxoethyl)cinnamamide (12h). Solid, m.p. 188–190°C; IR (KBr, *v*): 3224, 1686, 1668,1649; ^{1}H-NMR (400 MHz, DMSO-d_6): δ_H 8.52 (t, *J* = 5.9, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.61 (d, *J* = 6.8 Hz, 2H), 7.52–7.55 (m, 6H), 6.86 (d, *J* = 15.7 Hz, 1H), 4.83 (d, *J* = 5.9 Hz, 2H), 4.2 (s, 3H); HRMS (*m*/*z*): [*M* + H]$^+$ calculated for $[C_{19}H_{18}N_3O_2]^+$ 320.1399. Found: 320.1394.

(E)-5-(1-Methyl-1H-indazol-3-yl)-2-styryloxazole (13h). Solid, m.p. 146–148°C; IR (KBr, *v*): 3121, 1602, 1520; ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H 8.18 (d, *J* = 8.2 Hz, 1H), 7.9 (s, 1H), 7.8 (d, *J* = 7.6 Hz, 2H), 7.5 (d, *J* = 8.2 Hz, 1H), 7.64 (d, *J* = 16.4 Hz, 1H), 7.27–7.54 (m, 6H), 4.15 (s, 3H); HRMS (*m*/*z*): [*M* + H]$^+$ calcd for $[C_{19}H_{16}N_3O]^+$ 302.1293. Found: 302.1294.

Acknowledgments. The authors thank Dr. Reddy's Laboratories Ltd for supporting this work. The authors also thank Dr. Vilas Dahanukar, Dr. Suju Joseph, and Dr. Syam Kumar for their constant help and encouragement. Cooperation extended by all colleagues of analytical division is greatly acknowledged.

REFERENCES AND NOTES

[1] Cerecetto, H.; Gerpe, A.; Gonzalez, M.; Aran, V. J.; deocariz, C. O. Mini-Rev Med Chem 2005, 5, 869.

[2] Angelis, M. D.; Stossi, F.; Carlson, K. A.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. J Med Chem 2005, 48, 1132.

[3] Zhang, H. C.; Derian, C. K.; McComsey, D. F.; White, K. B.; Ye, H.; Hecker, L. R.; Li, J.; Addo, M. F.; Croll, D.; Eckardt, A. J.; Smith, C. E.; Li Q.; Cheung, W. M.; Conway, B. R.; Emanuel, S.; Demarest, K. T.; Andrade-Gordon, P.; Damiano, B. P.; Maryanoff, B. E. J Med Chem 2005, 48, 1725.

[4] May, J. A.; Dantanarayana, A. P.; Zinke, P. W.; McLaughlin, M. A.; Sharif, N. A. J Med Chem 2006, 49, 318.

[5] Han, W.; Pelletier, J. C.; Hodge C. N. Bioorg Med Chem Lett 1998, 8, 3615.

[6] Showalter, H. D. H.; Angelo, M. M.; Berman, E. M.; Kanter, G. D.; Ortwine, D. F.; Ross-Kesten, S. G.; Sercel, A. D.; Turner, W. R.; Werbel, L. M.; Worth D. F.; Elslager, E. F.; Leopald, W. R.; Shillis, J. L. J Med Chem 1988, 31, 1527.

[7] Palmer, D. C.; Taylor, E. C. The Chemistry of Heterocyclic Compounds. Oxazoles: Synthesis, Reactions, and Spectroscopy, Parts A & B; Wiley: New Jersey, 2004; p 60.

[8] Roy, R. S.; Gehring, A. M.; Milne, J. C.; Belshaw, P. J.; Walsh, C. T. Nat Prod Rep 1999, 16, 249.

[9] Fresneda, P. M.; Castaneda, M.; Blug, M.; Molina, P. Synlett, 2007, 324.

[10] Vishnu, E.; Bhanu Prakash, P.; Sandip, K.; Ramanatham, J.; Devanna, N. Synth Commun 2010, 40, 414.

[11] Bermudez, J.; Fake, C. S.; Joiner, G. I.; Joiner, K. A.; King, F. D.; Miner, W. D. J Med Chem 1990, 33, 1924.

[12] Cornforth, J. W.; Cornforth, R. H. J Chem Soc 1953, 93.

[13] Pei, W.; Li, S.; Nie, X.; Li, Y.; Jian, P.; Bingzi, C.; Jie, W.; Xiulin, Y. Synthesis 1998, 1298.

[14] Dalip, K.; Swapna, S.; Gautam, P.; Rao, V. S. Tetrahedron Lett 2008, 49, 867.

[15] Miyake, F.; Hashimoto, M.; Tonsiengsom, S.; Yakushijin, K.; Horane, D. Tetrahedron 2010, 66, 4888.