Design, synthesis and characterization of 1*H*-pyridin-4-yl-3,5-disubstituted indazoles and their AKT inhibition activity

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Abstract. A new series of 1*H*-pyridin-4-yl-3,5-disubstituted indazoles and their derivatives were synthesized by the reaction of 5-Bromo-1-(2-cyano-pyridin-4-yl)-1*H*-indazole-3-carboxylic acid diethylamide with aryl boronic acids by Suzuki coupling reaction in the presence of Pd(OAc)₂ and CsF. All the new compounds have been characterized by spectral data. The title compounds were subsequently evaluated for their Akt kinase activity.

Keywords. 1*H*-pyridin-4-yl-3,5-disubstituted indazoles; Suzuki reaction; Akt kinase activity.

1. Introduction

In organic synthesis, Palladium-catalysed new carbon–carbon bond formation from aryl halides with organo boronic acids via Suzuki coupling reaction has been proved to be an important method. The 2010 Nobel Prize in chemistry was awarded jointly to Ei-ichi Negishi, Akira Suzuki and Richard F. Heck for developing new methods for connecting carbon atoms together, which are key steps in building complex and bioactive molecules. However, the Suzuki reaction provides a reliable method for the preparation of biaryl derivatives.¹ Recently, Migliorini *et al.*² reported the application of the Suzuki reaction to synthesis of novel 5-substituted pyrrole and thiophenyl indazole in good yields.

Indazole and pyridine are highly utilized moieties and are found in active compounds having proportion such as male contraception, anti-cancer,³ anti-viral,⁴ cytotoxic⁵ and Akt inhibition⁶ (figure 1). In regulating cellular growth and survival, the kinase Akt is a key signalling node and is an important target for drug development. The first indazole-based scaffold was reported by Abott Group⁶ (figure 1). Indazole derivatives bearing aryl or *O*-aryl groups on the 5 position have been prepared and identified as potent, kinase inhibitors⁷ selective glucocorticoid receptor agonists, antagonists⁸ and

as anti-cancer compounds.⁹ Also 2,4-disubstituted pyridine derivatives play a vital role in biological activity, especially mono methyl amide function activity at 2 position, prepared and identified as biologically active anti-cancer¹⁰ compounds. As part of our ongoing research on indazoles¹¹ and pyridines,¹² we were interested in coupling the two moieties and incorporating the different aryl groups on 5 position of indazole ring through Suzuki coupling and conversion of –CN to mono methyl amide at 2 position of pyridine ring. Thus, by incorporating aryl groups on 5 position and mono methyl amide function at 2 position may lead to synthesis of more significant Akt inhibitors than the existing ones (figure 2).

2. Experimental

2.1 General information

All reagents were obtained commercially and were of the highest commercial quality and used without further purification. Solvents were freshly distilled and used. Melting points were determined in open capillaries and are uncorrected. TLC or HPLC routinely checked for the purity of all compounds. IR spectra were recorded on a Perkin–Elmer model 2000 instrument in KBr phase. ¹H-NMR (400 MHz) and ¹³C-NMR (100 MHz) spectra were recorded in CDCl₃ or DMSO using Bruker instrument and mass spectra were recorded on a Perkin–Elmer mass spectrometer operating at 70 eV.

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Figure 1. Indazole and pyridine scaffold cytotoxic and Akt inhibitors.

2.2 Synthesis by Suzuki reaction

General procedure for the preparation of 5-arylsubstituted-1-(2-cyanopyridin-4-yl)-*N,N*-diethyl-1*H*-indazole-3-carboxamide **7(a)**.

Method A: To a solution of 5-bromo-1-(2-cyanopyridin-4-yl)-1*H*-indazole-3-carboxylic acid diethylamide **5** (5 g, 0.0125 mol), 4-methoxyphenylboronic acid **6a** (3.8 g, 0.025 mol) in DMF (90 mL), palladium acetate (0.56 g, 0.0025 mol), cesium fluoride (3.8 g, 0.025 mol) and water (10 mL) were added at room temperature. Reaction mass was heated to 100°C and maintained for 2 h at 95–100°C. Upon completion of reaction, the reaction mass was quenched into ice water (200 mL) and dichloromethane (200 mL). The organic layer was separated and dried over Na_2SO_4 and distilled off the solvent to get the crude product, which was purified by column chromatography.

Method B: To a solution of 5-bromo-1-(2-cyanopyridin-4-yl)-1*H*-indazole-3-carboxylic acid diethylamide **5** (0.5 g, 0.0012 mol), 4-isobutylphenylboronic acid **6e** (0.447 g, 0.0025 mol) in DMF (5 mL), tetrakis (triphenylphosphine)palladium(0) (0.2 g, 0.00017 mol), sodium carbonate (0.254 g, 0.0023 mol) and water (0.75 mL) were added at room temperature. Reaction mass was heated to 100°C and maintained for 12–14 h at 95–100°C. Upon completion of reaction, the reaction mass was quenched into ice water (200 mL) and dichloromethane (200 mL). The organic layer was separated and dried over Na_2SO_4 and distilled off the solvent to get the crude product, which was purified by column chromatography.

Method C: To a solution of 5-bromo-1-(2-cyanopyridin-4-yl)-1*H*-indazole-3-carboxylic acid diethylamide **5** (0.2 g, 0.0005 mol), 4-isobutylphenylboronic acid **6e** (0.178 g, 0.001 mol) in DMF (3 mL), $dppf.PdCl_2$

Figure 2. Graph showing % activity of AKT kinase.

(0.08 g, 0.0001 mol), sodium carbonate (0.106 g, 0.001 mol) and water (0.4 mL) were added at room temperature. Reaction mass was heated to 100°C and maintained for 13–15 h at 95–100°C. Only 50–60% conversion was observed. Reaction mass was quenched into ice water (15 mL) and dichloromethane (30 mL). The organic layer was separated and dried over Na₂SO₄ and distilled off the solvent to get the crude product, which was purified by column chromatography.

2.2a 1-(2-cyanopyridin-4-yl)-N,N-diethyl-5-(4-methoxyphenyl)-1H-indazole-3-carboxamide (7a): Yield (77.36%); mp 117–120°C; IR (KBr): 1607.74 (C=O), 2238.49 (CN) (cm⁻¹); ¹H NMR (400 MHz, CDCl₃): δ 1.32–1.37 (m, 6H), 3.64–3.82 (qd, 4H), 3.84 (s, 3H), 6.94 (d, 2H, *J* = 8.55 Hz), 7.54 (d, 2H, *J* = 8.56 Hz), 7.73 (d, 1H, *J* = 8.71 Hz), 7.85 (d, 1H, *J* = 8.80 Hz), 7.96 (dd, 1H, *J*₁ = 1.68, *J*₂ = 5.50 Hz), 8.16 (d, 1H, *J* = 1.29 Hz), 8.31 (s, 1H), 8.77 (d, 1H, *J* = 5.52 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 12.83, 14.76, 40.93, 43.42, 55.27, 110.78, 114.23, 116.71, 116.82, 119.24, 120.66, 127.15, 128.28, 128.61, 132.21, 135.14, 137.29, 137.73, 144.08, 147.36, 152.29, 159.31, 161.94; ms: *m/z* 426.2 (M)⁺. Anal. Calcd. for C₂₅H₂₃N₅O₂: C, 70.57; H, 5.45; N, 16.46. Found. C, 70.56; H, 5.41; N, 16.48.

2.3 General procedure for the preparation of 5-arylsubstituted-methyl 4-(3-diethylcarbamoyl)-1H-indazol-1-ylpicolinate (8a)

To a solution of 1-(2-cyanopyridin-4-yl)-N,N-diethyl-5-(4-methoxyphenyl)-1H-indazole-3-carboxamide **7a** (1.6 g, 0.0037 mol) in methanol (40 mL), thionyl chloride was added at 30–40°C over a period of 15–20 min. Reaction mass was heated to 60–64°C and maintained for 12 h. Upon completion of reaction, the solvent was distilled off under vacuum at 50°C to get the crude. To the crude, water (5 mL) and ethyl acetate (15 mL) were added and stirred for 30 min at room temperature. The organic layer was separated and washed with brine solution (2 mL). Organic solvent was distilled off to get the solid.

2.3a Methyl 4-(3-(diethylcarbamoyl)-5-(4-methoxyphenyl)-1H-indazol-1-yl)picolinate (8a): Yield (88%); mp 138–142°C; IR (KBr): 1727.33 (C=O) (cm⁻¹); ¹H NMR (400 MHz, CDCl₃): δ 1.33–1.41 (td, 6H, *J*₁ = 7.14, *J*₂ = 7.01 Hz), 3.65 (q, 2H), 3.79 (q, 2H), 3.87 (s, 3H), 4.08 (s, 3H), 6.99 (d, 2H, *J* = 8.52 Hz), 7.06 (d, 2H, *J* = 8.52 Hz), 7.79 (dd, 1H, *J*₁ = 8.68, *J*₂ = 1.12 Hz), 7.97 (m, 2H), 8.39 (s, 1H), 8.65 (d, 1H,

J = 1.76 Hz), 8.86 (d, 1H, *J* = 5.32 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 12.85, 14.72, 40.96, 43.47, 53.15, 55.28, 110.86, 114.21, 115.99, 117.53, 120.73, 127.08, 128.40, 132.65, 137.09, 137.99, 143.42, 147.80, 149.56, 151.18, 159.24, 162.24, 165.21; ms: *m/z* 459.2 (M)⁺.

2.4 General procedure for the preparation of 5-arylsubstituted-N,N-diethyl-1-(2-(methylcarbamoyl)pyridin-4-yl)-1H-indazole-3-carboxamides 9(a)

Method A: To a solution of methyl 4-(3-(diethylcarbamoyl)-5-(4-methoxyphenyl)-1H-indazol-1-yl)picolinate **8a** (1.3 g, 0.0028 mol) in methanol, mono methylamine gas was bubbled into reaction mass at 25–40°C and maintained for 30 min. Upon completion of reaction, the solvent was distilled off to get the crude. To the crude, water (5 mL) and ethyl acetate (20 mL) were added and stirred for 30 min. The organic layer was separated and washed with brine solute (2 mL). The organic layer was dried over Na₂SO₄ and distilled off the solvent to get solid, which was slurred in hexane (5 mL) and filtered and washed with hexane (5 mL).

Method B: To a solution of 5-bromo-N,N-diethyl-1-(2-(methylcarbamoyl)pyridin-4-yl)-1H-indazole-3-carboxamide **11** (0.55 g, 0.00116 mol), 4-methoxyphenylboronic acid **6a** (0.35 g, 0.0023 mol) in DMF (5 mL), palladium acetate (0.05 g, 0.00022 mol), cesium fluoride (3.8 g, 0.0025 mol) and water (0.75 mL) were added at room temperature. Reaction mass was heated to 100°C and maintained for 12 h at 95–100°C. Reaction was not completed (60–70% completed). The mass was quenched into ice water (15 mL) and dichloromethane (30 mL) at 15–20°C. The organic layer was separated and dried over Na₂SO₄ and distilled off the organic solvent to get the crude product, which was purified by column chromatography.

2.4a N,N-diethyl-5-(4-methoxyphenyl)-1-(2-(methylcarbamoyl)pyridin-4-yl)-1H-indazole-3-carboxamide (9a): Yield (74%); mp 142–144°C; IR (KBr): 1682.96 (C=O), 3374.61 (NHCH₃) (cm⁻¹); ¹H-NMR (400 MHz, CDCl₃): δ 1.32–1.41 (td, 6H, *J*₁ = 6.94, *J*₂ = 7.06, Hz), 3.09 (d, 3H, *J* = 5.04 Hz), 3.65 (q, 2H), 3.79 (q, 2H), 3.86 (s, 3H), 6.98 (d, 2H, *J* = 8.58 Hz), 7.61 (d, 2H, *J* = 8.58 Hz), 7.76 (dd, 1H, *J*₁ = 8.76, *J*₂ = 1.02 Hz), 7.91 (dd, 1H, *J*₁ = 5.34, *J*₂ = 1.96 Hz), 8.01 (d, 1H, *J* = 8.84 Hz), 8.09 (q, 1H), 8.39 (s, 1H), 8.65 (d, 1H, *J* = 5.35 Hz), 8.70 (d, 1H, *J* = 1.52 Hz); ¹³C-NMR (100 MHz, CDCl₃): δ 12.85, 14.74, 26.14, 40.95, 43.48, 55.27, 111.15, 112.73, 114.18, 116.94,

120.60, 127.02, 128.30, 128.41, 132.75, 136.95, 138.07, 143.17, 148.07, 149.53, 151.77, 159.18, 162.34, 164.22; ms: m/z 458.2 (M)⁺. Anal. Calcd. for C₂₆H₂₇N₅O₃: C, 68.25; H, 5.95; N, 15.31. Found C, 68.20; H, 5.92; N, 15.30.

2.5 Preparation of methyl 4-(5-bromo-3-(diethylcarbamoyl)-1H-indazol-1-yl) picolinate **10**

To a solution of 5-bromo-1-(2-cyanopyridin-4-yl)-1H-indazole-3-carboxamide **5** (4 g, 0.010 mol) in methanol, thionyl chloride (7.1 g, 0.060 mol) was added at 25–40°C over a period of 15 min. Reaction mass was heated to 64°C and maintained for 24 h. After completion of reaction, the solvent was distilled off the solvent to get the crude product. To the crude product water (20 mL) and ethyl acetate (50 mL) were added and stirred for 20 min. The organic layer is separated and washed with brine solution (5 mL). The organic layer is dried over Na₂SO₄ and distilled off the solvent to get the desired product, which is slurred in hexane and filtered at room temperature.

Yield (71.75%); mp 153–155°C; IR (KBr): 1743.72 (C=O) (cm⁻¹); ¹H-NMR (400 MHz, CDCl₃): δ (td, 6H, J_1 = 7.06, J_2 = 6.95 Hz), 3.63 (q, 2H), 3.79 (q, 2H), 4.10 (s, 3H), 7.65 (dd, 1H, J_1 = 8.98, J_2 = 1.72 Hz), 7.80 (d, 1H, J = 8.96 Hz), 7.92 (dd, 1H, J_1 = 5.12, J_2 = 2.0 Hz), 8.47 (d, 1H, J = 1.12 Hz), 8.58 (d, 1H, J = 1.89 Hz), 8.88 (d, 1H, J = 5.41 Hz); ¹³C-NMR (100 MHz, CDCl₃): δ 12.75, 14.66, 41.12, 43.41, 53.17, 111.78, 116.17, 117.20, 117.75, 126.29, 127.93, 131.90, 137.63, 142.37, 147.40, 149.68, 151.27, 161.53, 165.02; ms: m/z 431.1 (M)⁺, 431.2 (M)⁺², 433.9 (M)⁺³. Anal. Calcd. for C₁₉H₁₉BrN₄O₂: C, 52.91; H, 4.44; N, 12.99; Found C, 52.90; H, 4.45; N, 12.98.

2.6 Preparation of 5-bromo-N,N-diethyl-1-(2-(methylcarbamoyl)pyridin-4-yl)-1H-indazole-3-carboxamide (**11**)

To a solution of methyl 4-(5-bromo-3-(diethylcarbamoyl)-1H-indazol-1-yl) picolinate **10** (3 g, 0.0069) in methanol (50 mL), mono methylamine gas was bubbled into reaction mass at 25–40°C and maintained for 30 min. Upon completion of reaction, the solvent was distilled off to get the crude. To the crude, water (10 mL) and ethyl acetate (50 mL) were added and stirred for 30 min. The organic layer was separated and washed with brine solution (5 mL). The organic layer was dried over Na₂SO₄ and the solvent was distilled off to get the solid. Yield: (83.5%); mp 152.8–154.9°C; IR

(KBr): 1745.65 (C=O), 3334.10 (NHCH₃) (cm⁻¹). ¹H-NMR (400 MHz, CDCl₃): δ 1.30–1.40 (td, 6H, J_1 = 7.06, J_2 = 6.92 Hz), 3.07 (d, 3H, J = 5.04 Hz), 3.61 (q, 2H), 3.78 (q, 2H), 7.60 (dd, 1H, J_1 = 8.86, J_2 = 1.28 Hz), 7.82 (m, 2H), 8.10 (d, 1H, J = 4.2 Hz), 8.45 (d, 1H, J = 1.0 Hz), 8.60 (d, 1H, J = 1.52 Hz), 8.65 (d, 1H, J = 8.32 Hz); ¹³C-NMR (400 MHz, CDCl₃): δ 12.76, 14.68, 26.14, 41.11, 43.34, 112.08, 112.86, 117.08, 117.10, 126.12, 127.86, 131.72, 137.64, 142.07, 147.60, 149.65, 151.85, 161.61, 164.0; ms: m/z 430.2 (M)⁺, 432.2 (M)⁺², 433 (M)⁺³. Anal. Calcd. for C₁₉H₂₀BrN₅O₂: C, 53.03; H, 4.68; N, 16.28. Found C, 53.01; H, 4.69; N, 16.29.

3. Biological evaluation of newly synthesized compounds

3.1 AKT kinase inhibition assay

The kinase inhibition assay was performed using Akt kinase assay kit from Cell Signalling Technologies, USA, according to manufacturer's protocol. Akt kinase was immunoprecipitated with Anti-AKT antibody provided in the kit from K562, chronic myelogenous leukaemia, cells. Inhibitory studies of the compounds on AKT kinase was performed at a final concentration of 10 μM (dissolved in DMSO) in duplicates in presence of GSK-β as the substrate for AKT. The enzyme activity was monitored by reading absorbance at 450 nm using TMB as the substrate for the HRP-tagged secondary antibody. The % activity was determined as a fraction of control (only DMSO).

4. Results and discussion

4.1 Chemistry

We herein report a general and novel synthesis of 1H-pyridin-4yl-3,5-disubstituted indazoles via Suzuki coupling in good yields. The synthesis starts

Table 1. Screening of Pd catalyst and base for Suzuki coupling reaction.

Sl.no	Pd(cat)/base/solvent	Temp(°C)	Yield (%)
1	Pd(pph ₃) ₄ /Na ₂ CO ₃ /DMF	95–100	86
2	PdCl ₂ (dppf)/Na ₂ CO ₃	95–100	60
3	Pd(OAc) ₂ /Na ₂ CO ₃ /DMF	85–100	85
4	Pd(OAc) ₂ /CsF/DMF	95–100	92

Table 2. Synthesis of 5-arylsubstituted-1-(2-cyanopyridin-4-yl)-*N,N*-diethyl-1*H*-indazole-3-carboxamide (**7a–f**) by Suzuki coupling.

Sl.no	Product	Time(h)	M.p.(°C)	Yield (%)
1	7a	2	117–120	77.36
2	7b	12	157–161	60.09
3	7c	5	164–165	77.36
4	7d	10	130–135	67.28
5	7e	10	106–109	90.02
6	7f	7	180–182	68.23

from 5-bromo-1-(2-cyano-pyridin-4-yl)-1*H*-indazole-3-carboxylic acid diethylamide **5**, which is prepared according to our own procedure.¹³

The reaction of 5-bromo-1-(2-cyano-pyridin-4-yl)-1*H*-indazole-3-carboxylic acid diethylamide **5** with aryl boronic acids **6(a–f)** through Suzuki reaction in the presence of different bases (CsF/Na₂CO₃) and different Pd catalysts such as Pd(pph₃)₄ or Pd(dppf)Cl₂

or Pd(OAc)₂ gave 5-arylsubstituted-1-(2-cyanopyridin-4-yl)-*N,N*-diethyl-1*H*-indazole-3-carboxamides **7(a–f)** in good yields. The best conditions were observed in the presence of Pd(OAc)₂ and CsF (see table 1) and the results are tabulated in table 2. Later **7(a–f)** was converted into 5-arylsubstituted-methyl 4-(3-(diethylcarbamoyl)-1*H*-indazol-1-yl) picolinate **8(a–f)** in presence of thionyl chloride and methanol

Table 3. Synthesis of 5-arylsubstituted-*N,N*-diethyl-1-(2-(methylcarbamoyl)pyridin-4-yl)-1*H*-indazole-3-carboxamides **9(a, b, c, e, f)**.

Sl.no	Product	M.p.(°C)	Yield (%)
1	9a	142–144	74
2	9b	145–147	80
3	9c	161–164	73
4	9e	143–145	78
5	9f	178–180	72

Scheme 1. Synthesis of 5-arylsubstituted-*N,N*-diethyl-1-(2-(methylcarbamoyl) pyridin-4-yl)-1*H*-indazole-3-carboxamide **9**.

in 80–90% yields. Finally **8(a–f)** was reacted with mono methylamine gas in methanol at 25–40°C to give the corresponding 5-arylsubstituted-*N,N*-diethyl-1-(2-(methylcarbamoyl) pyridin-4-yl)-1*H*-indazole-3-carboxamide **9(a–f)** in good yields. These results are tabulated in table 3 and schematically represented in scheme 1.

Based on the successful results, we next explored the scope of the Suzuki reaction to synthesize 5-arylsubstituted-*N,N*-diethyl-1-(2-(methylcarbamoyl) pyridin-4-yl)-1*H*-indazole-3-carboxamides **9** from 5-bromo-1-(2-cyano-pyridin-4-yl)-1*H*-indazole-3-carboxylic acid diethylamide **5** in a different manner. The 5-arylsubstituted-*N,N*-diethyl-1-(2-(methylcarbamoyl) pyridin-4-yl)-1*H*-indazole-3-carboxamides were synthesized by initial conversion of nitrile **5** to methyl ester **10**. Later, compound **10** was reacted with aryl

boronic acids **6** in the presence of $\text{Pd}(\text{pPh}_3)_4/\text{Na}_2\text{CO}_3$; $\text{Pd}(\text{OAc})_2/\text{CsF}$ to give the corresponding coupling

Table 4. AKT kinase inhibitory concentration (10 μM) against chronic myelogenous leukaemia cell line (K562).

Compound	%Inhibition
7a	24.04
7b	NA
7c	NA
7d	NA
7f	20.0
9a	20.81
9b	18.0
9c	19.0
9e	NA
9f	NA
10	24.52

products in moderate to good yields (40–60%) (scheme 1).

4.2 Biological activity

The Akt inhibition efficiency of the newly synthesized compounds has been assessed using Akt activity assay kit. Results of the assay demonstrated a maximum of 24% inhibition by compounds **7a** and **10** (table 4). Further, structure activity studies on compounds **7f**, **9a**, **9b** and **9c** might help in improving the Akt kinase inhibitory activity.

5. Conclusion

We have synthesized 5-arylsubstituted-*N,N*-diethyl-1-(2-methylcarbamoyl)pyridine-4-yl)-1*H*-indazole-3-carboxamides and found that only **7a**, **7f**, **9a**, **9b**, **9c** and **10** exhibit moderate inhibition. Further studies are necessary to obtain better Akt kinase inhibitory activity.

Supplementary Information

The electronic supplementary information can be seen at www.ias.ac.in/chemsci.

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