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Synthesis and Biological Activity of New 4-(Pyridin-4-yl)-(3-methoxy-5-methylphenyl)-1*H*-pyrazoles Derivatives as ROS Receptor Tyrosine Kinase Inhibitors

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A series of new 4-(pyridin-4-yl)-(3-methoxy-5-methylphenyl)-1*H*-pyrazoles (**6a-k** & **7a-l**) has been rationally designed based on the structure of the lead compound **KIST301080**, a selective ROS receptor tyrosine kinase inhibitor, in order to study the activity of ROS of this new class of inhibitors. The compounds were synthesized and screened against ROS kinase, where compound **6h** showed moderate inhibitory activity with an IC_{50} value of 6.25 μM. The study emphasized the importance of the acetonitrile group at the pyrazole ring and also the importance of having a hydrogen bond donor on the distal phenyl ring linked to the pyridine moiety.

Key Words : 1*H*-pyrazoles, ROS receptor, Tyrosine kinase inhibitor, Cancer

Introduction

Receptor tyrosine kinases (RTKs) are important players in the process of signal transduction and cellular communication. They act as the cell surface receptors for a number of important growth factors and hormones. The dysregulation and over-expression of such kinases results in the continuous switch-on of the substantial signaling cascade which is generally associated with physiological abnormalities inform of different diseases including cancer.

ROS kinase is one of the last two remaining orphan receptor tyrosine kinases with an as yet unidentified ligand. The normal functions of human ROS kinase in different body tissues have not been fully identified so far.[1] However, the ectopic expression, as well as the production of variable mutant forms of ROS kinase has been reported in a number of cancers, such as glioblastoma multiforme,[2] and non-small cell lung cancer,[3] suggesting a role for ROS kinase in deriving such tumors. A number of research findings have also linked ROS kinase to different cardiovascular diseases, suggesting possible implications of this kinase in diseases other than cancer.[4-6]

The first selective inhibitors for ROS RTK on 45 kinases have been recently developed by our research group, where compound **KIST301072** with an IC_{50} of 199 nM was initially discovered,[7] followed by the development of more simplified and equipotent derivative "**KIST301080**" with an IC_{50} value of 209 nM (Figure 1).[8] These two compounds represent new promising leads for the development of more potent and more selective ROS kinase inhibitors, and following this discovery, it was important to explore this new chemical scaffold, in order to have a clear picture about the structure activity relationship (SAR) of this new group of

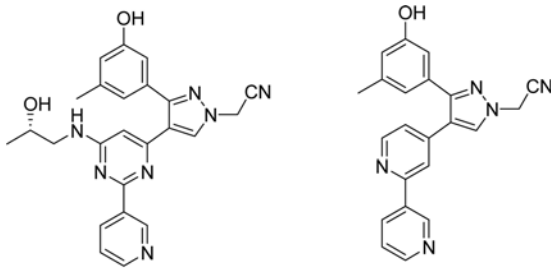
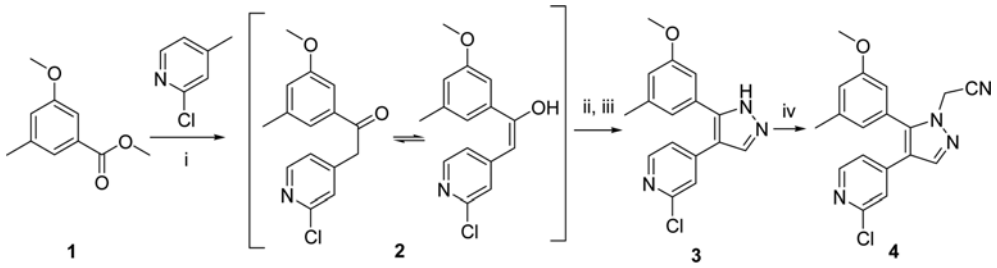


Figure 1. Structure of the lead compounds **KIST301072** and **KIST301080**.

ROS kinase inhibitors. Accordingly, a new series of 4-(pyridin-4-yl)-(3-methoxy-5-methylphenyl)-1*H*-pyrazoles (**6a-k** & **7a-l**) has been designed and synthesized. The chemical modifications in the new series were focused on the substituents at the pyridine-4-yl moiety and the 1*H*-position of the pyrazole ring. The synthesized final compounds were screened against ROS kinase to explore the effect of the new modifications on their kinase inhibitory activity.

Results and Discussion

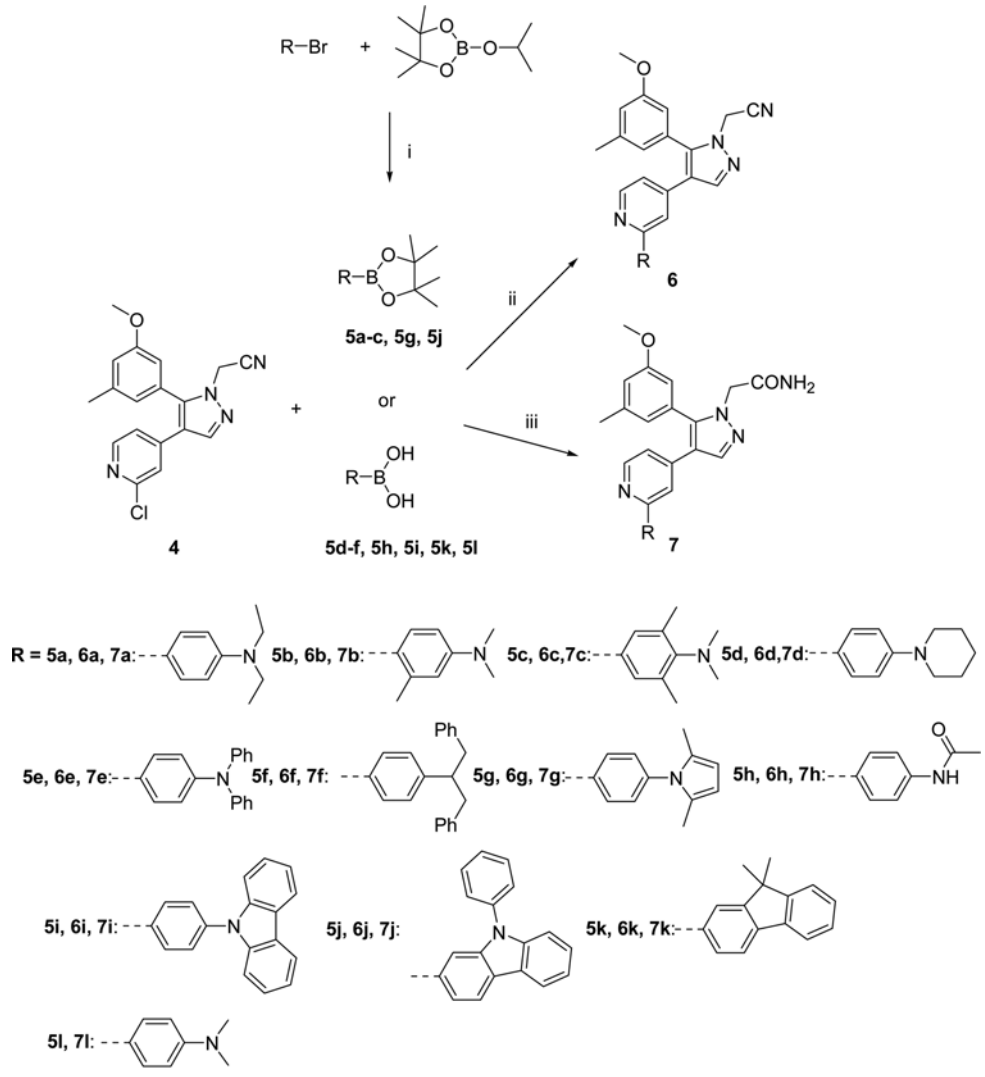
The synthesis of the target compounds started with the preparation of the key ester, methyl 3-methoxy-5-methylbenzoate (**1**) as illustrated in literature.[7,8] In Scheme 1, the benzoate ester **1** underwent a nucleophilic attack at its carboxylic carbon by the activated methylene group of 2-chloro-4-methyl-pyrimidine. The activation of this methyl group into an active methylene was achieved by dropwise addition of lithium bis(trimethylsilyl)amide (LHMDS) in dry THF at room temperature.[8] The resulted tautomeric α,β-



Reaction conditions and reagents: (i) LHMDS, THF, N_2, rt, 24 h, 72%; (ii) DMF-DMA, 90 °C, 12 h; (iii) hydrazine hydrate, abs. EtOH, rt, 2 h, 81%; (iv) K_2CO_3, iodoacetonitrile, acetone, reflux, 3 h, 23%

Scheme 1. Synthesis of Intermediate **4**.

unsaturated ketone **2** was then converted to the required pyrazole derivative **4** through two successive steps.[8] In the first step, compound **2** was heated with excess *N,N*-dimethylformamide dimethylacetal for 12 h, and the resulted product was taken to the next step without further purification, where it was cyclized with hydrazine monohydrate in absolute ethanol into the pyrazole derivative **3**. The reaction of the resulted pyrazole **3** with iodoacetonitrile in



Reaction conditions and reagents: (i) *n*-BuLi, dry THF, N_2, -78 °C to rt, 12h; (ii) $Pd(PPh_3)_2Cl_2$, K_2CO_3, N_2, CH_3CN/H_2O (4:1), reflux, 2 h; (iii) $Pd(PPh_3)_2Cl_2$, K_2CO_3, N_2, CH_3CN/H_2O (1:1), reflux, 12 h.

Scheme 2. Synthesis of target compounds **6a-k** and **7a-l**.

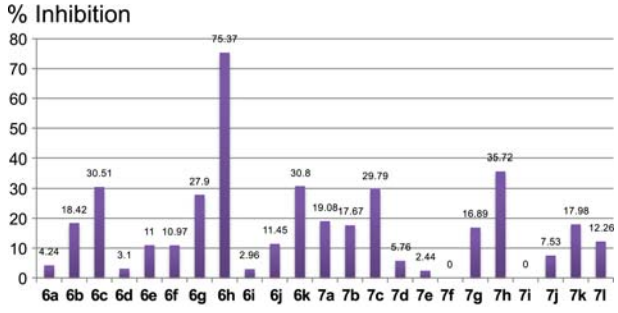


Figure 2. % of ROS enzyme inhibition exerted by single dose concentration of 20 μM.

the presence of excess potassium carbonate produced the key intermediate **4**.

In Scheme 2, compounds **6a-k** were obtained through a series of Suzuki couplings for the key intermediate **4** with a group of dioxoborolans or arylboronic acids in the presence of dichlorobis(triphenylphosphine) Pd(II) and potassium carbonate in a mixed solvent of THF and H_2O (4:1, v/v) under reflux for 2 h, while compounds **7a-l** were obtained by coupling of **4** with a group of dioxoborolans or arylboronic acids in a mixed solvent of THF and H_2O (1:1, v/v) and under reflux of 12 h, where the nitrile group was easily hydrolyzed under the influence of the coupling conditions into amide. The dioxoborolans used for the synthesis of compounds **6a-c**, **6g**, **6j**, **7a-c**, **7g** and **7j** were synthesized by the reaction of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane with the appropriate aryl bromide as showed in Scheme 2,[9] while the boronic acids which were used for the synthesis of compounds **6d-f**, **6h-i**, **6k**, **7d-f**, **7h-i** and **7k-l** are commercially available.

Kinase assays were performed at Reaction Biology Corporation using the "HotSpot" assay platform. All the final compounds were tested in a 10-dose IC_{50} mode with 3 fold serial dilutions starting at 20 μM, using Staurosporine as a positive control. The reaction was carried out at 10 μM ATP concentration. By comparing the inhibition percentages exerted by the tested compounds at the highest test concentration (20 μM), it was clear that the reduction of the acetonitrile group in compound **6** into the corresponding amide in compound **7** was associated generally with a drop in activity (Figure 2). The inhibitions observed by the tested compounds at 20 μM concentration were all below 40% except for compound **6h** (with an acetamidophenyl group at distal pyridine moiety), which showed an inhibition of ~75%, and an IC_{50} of 6.25 μM.

The unique feature of this compound is the presence of a hydrogen-bond donor group (the acetamido functionality) at its pyridine terminal. This suggests the presence of a hydrogen bond acceptor amino acid residue at this area of ROS kinase binding pocket, which is close enough to the group carried by the distal pyridine to interact through hydrogen bonding.

Conclusions

In conclusion, the study of a new series of ROS kinase inhibitors was carried out, where a series of 23 compounds was synthesized and screened against the enzyme. The study has showed that the reduction of the acetonitrile group to an amide reduces the inhibitory activity, and that a hydrogen-bond donor group at the distal pyridine moiety is important for good activity. This interesting part of ROS kinase inhibitors' structure (the distal pyridine ring) needs to be further explored, and accordingly a new series of inhibitors is being designed currently by our group to explore more the effect of varying hydrogen bond donors at the distal pyridine moiety on kinase inhibitory activity.

Experimental

Materials. ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) were recorded on a Bruker Avance 300 spectrometer with TMS as an internal standard. The IR spectra were recorded on Perkin Elmer Spectrum GX spectrometer. Melting points were taken on a Thomas-Hoover capillary melting apparatus and were uncorrected. Column chromatography was performed on Merck silica gel 60 (230 - 400 mesh). TLC was carried out using glass sheets precoated with silica gel 60 F254 prepared by E. Merck. All the commercially available reagents were obtained from Aldrich and Tokyo Kasei Chemicals and generally used without further purification.

General Procedure for the Synthesis of 5a-c, 5g, and 5j. *n*-BuLi (1.6 mL, 2.57 mmol, 1.6 M/Hexane) was added dropwise *via* syringe at −78 °C to solution of aryl bromide (2.34 mmol) in dry THF (30 mL) under N_2. Stirring was continued at −78 °C for 1 h, then 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.48 g, 2.57 mmol) was added slowly to the reaction mixture, the resulting mixture was allowed to warm to room temperature and stirred at this temperature for 12 h. The mixture was taken up in water and neutralized with aqueous 5% HCl solution, followed by extraction with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and evaporated under vacuum. The crude product was purified by column chromatography (silica gel, ethyl acetate-hexane) to yield the pure product.

***N,N*-Diethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenamine (5a).** Yield: (0.32 g, 50%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (t, J = 7.1 Hz, 6H), 1.24 (s, 12H), 3.3 (q, J = 7.0 Hz, 4H), 6.57 (d, J = 9.0 Hz, 2H), 7.59 (d, J = 8.7 Hz, 2H).

***N,N*,3-Trimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenamine (5b).** Yield: (0.54 g, 87%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 12H), 2.44 (s, 3H), 2.89 (s, 6H), 6.44 (d, J = 7.5 Hz, 2H), 7.59 (d, J = 8.4 Hz, 1H).

***N,N*,2,6-Tetramethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenamine (5c).** Yield: (0.43 g, 67%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, J = 6.0 Hz, 12H), 2.21 (d, J = 6.0 Hz, 6H), 2.73 (d, J = 6.0 Hz, 6H), 7.39 (s, 2H).

2,5-Dimethyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrrole (5g). Yield: (0.45 g, 64 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 12H), 2.09 (s, 6H), 5.96 (s, 2H), 7.27 (d, *J* = 7.8 Hz, 2H), 7.96 (d, *J* = 7.8 Hz, 2H).

9-Phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9*H*-carbazole (5j). Yield: (0.54 g, 63%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.4 (s, 12H), 7.32-7.35 (m, 1H), 7.41-7.47 (m, 2H), 7.5-7.55 (m, 1H), 7.6-7.7 (m, 4H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.89 (s, 1H), 8.21 (dd, *J* = 9.0 and 2.6 Hz, 2H).

General Procedure for the Synthesis of 6a-k. To a mixture of 2-(4-(2-chloropyridin-4-yl)-5-(3-methoxy-5-methylphenyl)-1*H*-pyrazol-1-yl)acetonitrile (**4**) (50 mg, 0.15 mmol), the appropriate dioxoborolans or aryl boronic acid **5** (0.18 mmol), dichlorobis(triphenylphosphine)Pd(II) (3 mg, 0.005 mmol) and K_2CO_3 (21 mg, 0.15 mmol) was placed in a mixed solvent of acetonitrile and water (4:1, 5 mL). N_2 gas was bubbled into this mixture for 15 min, and then the mixture was refluxed while stirring under N_2 atmosphere for 2 h. The reaction mixture was cooled to at room temperature, and then poured into ice water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and evaporated under vacuum. The crude product was purified by column chromatography (silica gel, ethyl acetate-hexane) to yield the pure product.

2-(4-(2-(4-(Diethylamino)phenyl)pyridin-4-yl)-5-(3-methoxy-5-methylphenyl)-1*H*-pyrazol-1-yl)acetonitrile (6a). Yield: (34 mg, 50%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (t, *J* = 7.1 Hz, 6H), 2.32 (s, 3H), 3.32 (q, *J* = 7.0 Hz, 4H), 3.72 (s, 3H), 4.85 (s, 2H) 6.59-6.84 (m, 6H), 7.40 (s, 1H), 7.61 (d, *J* = 8.7 Hz, 2H), 7.90 (s, 1H), 8.35 (d, *J* = 5.1 Hz, 1H).

2-(4-(2-(4-(Dimethylamino)-2-methylphenyl)-2,3-dihydropyridin-4-yl)-5-(3-methoxy-5-methylphenyl)-1*H*-pyrazol-1-yl)acetonitrile (6b). Yield: (38 mg, 58%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.09 (s, 3H), 2.31 (s, 3H), 2.89 (s, 6H), 3.72 (s, 3H), 4.84 (s, 2H), 6.48-6.52 (m, 2H), 6.63 (s, 1H), 6.70 (s, 1H), 6.82 (s, 1H), 6.94-6.95 (m, 1H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.86 (s, 1H), 8.44 (d, *J* = 5.1 Hz, 1H).

2-(4-(2-(4-(Dimethylamino)-3,5-dimethylphenyl)-2,3-dihydropyridin-4-yl)-5-(3-methoxy-5-methyl phenyl)-1*H*-pyrazol-1-yl)acetonitrile (6c). Yield: (36 mg, 53%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.24 (s, 6H), 2.34 (s, 3H), 2.75 (s, 6H), 3.73 (s, 3H), 4.87 (s, 2H), 6.67 (s, 1H), 6.74 (s, 1H), 6.88 (s, 1H), 6.98 (d, *J* = 5.1 Hz, 1H), 7.26 (s, 2H), 7.37 (s, 1H), 7.93 (s, 1H), 8.44 (d, *J* = 5.1 Hz, 1H).

2-(5-(3-Methoxy-5-methylphenyl)-4-(2-(4-(piperidin-1-yl)phenyl)pyridin-4-yl)-1*H*-pyrazol-1-yl)acetonitrile (6d). Yield: (30 mg, 42%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62-1.75 (m, 6H), 2.44 (s, 3H), 3.29 (t, *J* = 5.3 Hz, 4H), 3.85 (s, 3H), 4.98 (s, 2H), 6.77 (s, 1H), 6.84 (s, 1H), 6.97-7.00 (m, 4H), 7.53 (s, 1H), 7.74 (d, *J* = 9 Hz, 2H), 8.03 (s, 1H), 8.5 (d, *J* = 5.1 Hz, 1H).

2-(4-(2-(4-(Diphenylamino)phenyl)pyridin-4-yl)-5-(3-methoxy-5-methylphenyl)-1*H*-pyrazol-1-yl)acetonitrile (6e). Yield: (53 mg, 64%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H), 3.60 (s, 3H), 4.74 (s, 2H), 6.54-7.49 (m, 19H), 7.80 (s, 1H), 8.28 (s, 1H).

2-(4-(2-(4-(Dibenzylamino)phenyl)pyridin-4-yl)-5-(3-methoxy-5-methylphenyl)-1*H*-pyrazol-1-yl)acetonitrile (6f). Yield: (74 mg, 86%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.70 (s, 3H), 4.62 (s, 4H), 4.85 (s, 2H), 6.64 (s, 1H), 6.69-6.71 (m, 3H), 6.80-6.82 (m, 2H), 7.17-7.21 (m, 5H), 7.24-7.28 (m, 5H), 7.39 (s, 1H), 7.58 (d, *J* = 8.9 Hz, 2H), 7.88 (s, 1H), 8.35 (d, *J* = 5.2 Hz, 1H).

2-(4-(2-(4-(2,5-Dimethyl-1*H*-pyrrol-1-yl)phenyl)pyridin-4-yl)-5-(3-methoxy-5-methylphenyl)-1*H*-pyrazol-1-yl)acetonitrile (6g). Yield: (53 mg, 75%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.98 (s, 6H), 2.34 (s, 3H), 3.74 (s, 3H), 4.88 (s, 2H), 5.84 (s, 2H), 6.68 (s, 1H), 6.75 (s, 1H), 6.86 (s, 1H), 6.98 (d, *J* = 4.8 Hz, 1H), 7.2 (d, *J* = 8.7 Hz, 2H), 7.56 (s, 1H), 7.81 (d, *J* = 8.1 Hz, 2H), 7.95 (s, 1H), 8.46 (d, *J* = 4.8 Hz, 1H).

***N*-(4-(4-(1-(Cyanomethyl)-5-(3-methoxy-5-methylphenyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)phenyl)acetamide (6h).** Yield: (49 mg, 74%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.09 (s, 3H), 2.31 (s, 3H), 3.72 (s, 3H), 4.87 (s, 2H), 6.65 (s, 1H), 6.72 (s, 1H), 6.85 (s, 1H), 6.95 (dd, *J* = 1.5 and 1.2 Hz, 1H), 7.43 (s, 1H), 7.5 (d, *J* = 8.7 Hz, 2H), 7.65 (d, *J* = 8.7 Hz, 2H), 7.78 (s, 1H), 7.92 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H).

2-(5-(3-Methoxy-5-methylphenyl)-4-(2-(9-phenyl-9*H*-carbazol-2-yl)pyridin-4-yl)-1*H*-pyrazol-1-yl)acetonitrile (6i). Yield: (38 mg, 47%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3H), 3.74 (s, 3H), 4.88 (s, 2H), 6.70 (s, 1H), 6.76 (s, 1H), 6.87 (s, 1H), 7.02 (d, *J* = 4.2 Hz, 1H), 7.20-7.25 (m, 2H), 7.32-7.40 (m, 4H), 7.55-7.59 (m, 3H), 7.95 (d, *J* = 8.7 Hz, 3H), 8.08 (d, *J* = 7.5 Hz, 2H), 8.5 (d, *J* = 5.1 Hz, 1H).

2-(4-(2-(4-(9*H*-Carbazol-9-yl)phenyl)pyridin-4-yl)-5-(3-methoxy-5-methylphenyl)-1*H*-pyrazol-1-yl)acetonitrile (6j). Yield: (63 mg, 78%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3H), 3.73 (s, 3H), 4.86 (s, 2H), 6.66 (s, 1H), 6.72 (s, 1H), 6.83 (s, 1H), 6.92 (d, *J* = 4.5 Hz, 1H), 7.21-7.25 (m, 1H), 7.33-7.43 (m, 3H), 7.52-7.57 (m, 6H), 7.93 (d, *J* = 7.5 Hz, 2H), 8.09 (d, *J* = 7.9 Hz, 2H), 8.42 (d, *J* = 4.9 Hz, 1H).

2-(4-(2-(9,9-Dimethyl-9*H*-fluoren-2-yl)pyridin-4-yl)-5-(3-methoxy-5-methylphenyl)-1*H*-pyrazol-1-yl)acetonitrile (6k). Yield: (65 mg, 87%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 6H), 2.34 (s, 3H), 3.74 (s, 3H), 4.87 (s, 2H), 6.70-7.05 (m, 4H), 7.18-7.67 (m, 8H), 7.96 (s, 1H), 8.50 (s, 1H).

General Procedure for the Synthesis of 7a-l. To a mixture of 2-(4-(2-chloropyridin-4-yl)-5-(3-methoxy-5-methylphenyl)-1*H*-pyrazol-1-yl)acetonitrile (**4**) (50 mg, 0.15 mmol), the appropriate dioxoborolans or aryl boronic acid **5** (0.18 mmol), dichlorobis(triphenylphosphine)Pd(II) (3 mg, 0.005 mmol) and K_2CO_3 (21 mg, 0.15 mmol) was placed in a mixed solvent of acetonitrile and water (1:1, 5 mL). N_2 gas was bubbled into this mixture for 15 min, and then the mixture was refluxed while stirring under N_2 atmosphere for 12 h. The reaction mixture was cooled to at room temperature, and then poured into ice water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and evaporated under vacuum.

2-(4-(2-(4-(Diethylamino)phenyl)pyridin-4-yl)-5-(3-methoxy-5-methylphenyl)-1*H*-pyrazol-1-yl)acetamide (7a). Yield: (20 mg, 28%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (t, *J* = 6.9 Hz, 6H), 2.29 (s, 3H), 3.33 (q, *J* = 6.8 Hz, 4H), 3.69 (s, 3H), 4.64 (s, 2H), 5.82 (s, 1H), 6.21 (s, 1H), 6.59-6.65 (m, 4H), 6.80 (s, 2H), 7.40 (s, 1H), 7.61 (d, *J* = 8.7 Hz, 2H), 7.92 (s, 1H), 8.35 (d, *J* = 5.1 Hz, 1H).

2-(4-(2-(4-(Dimethylamino)-2-methylphenyl)-2,3-dihydropyridin-4-yl)-5-(3-methoxy-5-methylphenyl)-1*H*-pyrazol-1-yl)acetamide (7b). Yield: (36 mg, 52%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.09 (s, 3H), 2.27 (s, 3H), 2.89 (s, 6H), 3.69 (s, 3H), 4.60 (s, 2H), 5.86 (s, 1H), 6.21 (s, 1H), 6.47-6.57 (m, 3H), 6.63 (s, 1H), 6.77 (s, 1H), 6.95 (d, *J* = 5.1 Hz, 1H), 7.17 (t, *J* = 7.2 Hz, 1H), 7.88 (s, 1H), 8.42 (d, *J* = 5.4 Hz, 1H).

2-(4-(2-(4-(Dimethylamino)-3,5-dimethylphenyl)-2,3-dihydropyridin-4-yl)-5-(3-methoxy-5-methyl phenyl)-1*H*-pyrazol-1-yl)acetamide (7c). Yield: (34 mg, 48%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.24 (s, 6H), 2.31 (s, 3H), 2.76 (s, 6H), 3.70 (s, 3H), 4.65 (s, 2H), 5.73 (s, 1H), 6.19 (s, 1H), 6.60, (s, 1H), 6.7 (s, 1H), 6.84 (s, 1H), 6.99 (d, *J* = 4.2 Hz, 1H), 7.25 (s, 2H), 7.37 (s, 1H), 7.95 (s, 1H), 8.43 (d, *J* = 5.1 Hz, 1H).

2-(5-(3-Methoxy-5-methylphenyl)-4-(2-(4-(piperidin-1-yl)phenyl)pyridin-4-yl)-1*H*-pyrazol-1-yl)acetamide (7d). Yield: (35 mg, 50%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63-1.73 (m, 6H), 2.39 (s, 3H), 3.27 (t, *J* = 5.1 Hz, 4H), 3.79 (s, 3H), 4.73 (s, 2H) 5.76 (s, 1H), 6.28 (s, 1H), 6.68 (s, 1H), 6.75 (s, 1H), 6.90-6.97 (m, 4H), 7.51 (s, 1H), 7.71 (d, *J* = 8.6 Hz, 2H), 8.03 (s, 1H), 8.47 (d, *J* = 5.1 Hz, 1H).

2-(4-(2-(4-(Diphenylamino)phenyl)pyridin-4-yl)-5-(3-methoxy-5-methylphenyl)-1*H*-pyrazol-1-yl)acetamide (7e). Yield: (16 mg, 19%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3H), 3.76 (s, 3H) 4.70 (s, 2H), 5.94 (s, 1H), 6.27 (s, 1H), 6.66-6.98 (m, 4H), 7.29-7.59 (m, 12H), 8.01 (s, 2H), 8.15 (s, 2H), 8.48 (s, 1H).

2-(4-(2-(4-(Dibenzylamino)phenyl)pyridin-4-yl)-5-(3-methoxy-5-methylphenyl)-1*H*-pyrazol-1-yl)acetamide (7f). Yield: (20 mg, 23%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.26 (s, 3H), 3.65 (s, 3H), 4.62 (s, 6H), 5.72 (s, 1H), 6.18 (s, 1H), 6.56-6.81 (m, 6H), 7.18-7.58 (m, 13H), 7.90 (s, 1H), 8.33 (s, 1H).

2-(4-(2-(4-(2,5-Dimethyl-1*H*-pyrrol-1-yl)phenyl)pyridin-4-yl)-5-(3-methoxy-5-methylphenyl)-1*H*-pyrazol-1-yl)acetamide (7g). Yield: (25 mg, 35%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.99 (s, 6H), 2.30 (s, 3H), 3.71 (s, 3H), 4.66 (s, 2H), 5.71 (s, 1H), 5.85 (s, 2H), 6.17 (s, 1H), 6.50 (d, *J* = 18.6 Hz, 2H) , 6.82 (s, 1H), 6.99 (d, *J* = 3.6 Hz, 1H), 7.20 (d, *J* = 6.9 Hz, 2H), 7.55 (s, 1H), 7.80 (d, *J* = 7.8 Hz, 2H), 7.97 (s, 1H), 8.46 (d, *J* = 4.5 Hz, 1H).

2-(4-(2-(4-Acetamidophenyl)pyridin-4-yl)-5-(3-methoxy-5-methylphenyl)-1*H*-pyrazol-1-yl)acetamide (7h). Yield: (27 mg, 40%); ^{1}H NMR (300 MHz, CD_3OD) δ 2.16 (s, 3H), 2.38 (s, 3H), 3.79 (s, 3H), 4.75 (s, 2H), 6.85 (s, 2H), 7.00 (s, 1H), 7.25 (d, *J* = 5.1 Hz, 1H), 7.53-7.66 (m, 5H), 8.14 (s, 1H), 8.39 (d, *J* = 5.1 Hz, 1H).

2-(5-(3-Methoxy-5-methylphenyl)-4-(2-(9-phenyl-9*H*-carbazol-2-yl)pyridin-4-yl)-1*H*-pyrazol-1-yl)acetamide (7i). Yield: (46 mg, 54%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3H), 3.71 (s, 3H), 4.67 (s, 2H), 5.65 (s, 1H), 6.18 (s, 1H), 6.63 (s, 1H), 6.70 (s, 1H), 6.83 (s, 1H), 7.04 (d, *J* = 4.4 Hz, 1H), 7.18-7.24 (m, 2H), 7.35-7.39 (m, 4H), 7.56-7.59 (m, 3H), 7.94-7.99 (m, 3H), 8.08 (d, *J* = 7.6 Hz, 2H), 8.5 (d, *J* = 5 Hz, 1H).

2-(4-(2-(4-(9*H*-Carbazol-9-yl)phenyl)pyridin-4-yl)-5-(3-methoxy-5-methylphenyl)-1*H*-pyrazol-1-yl)acetamide (7j). Yield: (46 mg, 70%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.81 (s, 3H), 3.70 (s, 3H), 4.65 (s, 2H), 5.43 (s, 1H), 6.17 (s, 1H), 6.59 (s, 1H), 6.65 (s, 1H), 6.79 (s, 1H), 6.93 (d, *J* = 4.4 Hz, 1H), 7.19-7.25 (m, 1H), 7.31-7.35 (m, 2H), 7.4-7.44 (m, 1H), 7.51-7.57 (m, 6H), 7.95 (s, 2H), 8.08 (d, *J* = 8.4 Hz, 2H), 8.42 (d, *J* = 5.2 Hz, 1H).

2-(4-(2-(9,9-Dimethyl-9*H*-fluoren-2-yl)pyridin-4-yl)-5-(3-methoxy-5-methylphenyl)-1*H*-pyrazol-1-yl)acetamide (7k). Yield: (46 mg, 60%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 6H), 2.31 (s, 3H), 3.70 (s, 3H), 4.65 (s, 2H), 5.83 (s, 1H), 6.20 (s, 1H), 6.64-7.66 (m, 12H), 7.97 (s, 1H), 8.49 (s, 1H).

2-(4-(2-(4-(Dimethylamino)phenyl)pyridin-4-yl)-5-(3-methoxy-5-methylphenyl)-1*H*-pyrazol-1-yl)aceto-nitrile (7l). Yield: (33 mg, 50%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.04 (s, 6H), 3.80 (s, 3H), 4.74 (s, 2H), 5.57 (s, 1H), 6.27 (s, 1H), 6.68 (s, 1H), 6.76 (d, *J* = 6.8 Hz, 3H), 6.91-6.95 (m, 2H), 7.51 (s, 1H), 7.73 (d, *J* = 8.8 Hz, 2H), 8.03 (s, 1H), 8.47 (d, *J* = 5.2 Hz, 1H).

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