Visible-light-mediated nickel(II)-catalyzed C-N cross-coupling in water: a green and regioselective access for the synthesis of pyrazole-containing compounds

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General Information

All commercial reagents were used as received. All products were isolated by short chromatography on a silica gel (200-300 mesh) column using petroleum ether (60-90°C) and ethyl acetate. $^1$H and $^{13}$C NMR spectra were recorded on Bruker Advance DRX-500 spectrometers at ambient temperature with CDCl$_3$ as solvent and tetramethylsilane (TMS) as the internal standard. All chemical shift values are quoted in ppm and coupling constants quoted in Hz. Compounds for HRMS were analyzed by positive mode electrospray ionization (ESI) using Agilent 6530 QTOF mass spectrometer. The ICP-MS measurement was performed in an Inductively Coupled Plasma Mass Spectrometer of the Elan DRC-e series (PerkinElmer Instruments, USA).

1. Experimental Section

General procedure for the synthesis of substrates 1

A mixture of naphthylamine (10 mmol), pyridine-2-carbonyl chloride (1.05 equiv), NEt$_3$ (3.0 equiv) in anhydrous CH$_2$Cl$_2$ (20 mL) was stirred at room temperature overnight. Water was added and the mixture was extracted with CH$_2$Cl$_2$. The combined organic layer was washed with water and brine, dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The resulting residue was purified by silica gel flash chromatography to give the desired amide products.

General procedure for the synthesis of products 3a-x

Amides 1 (0.2 mmol), pyrazole derivatives 2 (0.4 mmol), NiSO$_4$$\cdot$6H$_2$O (15 mol %), Acr$^+$$-$$Mes$ ClO$_4$ (5 mol%), H$_2$O (0.4 mmol) and H$_2$O (4 mL) were combined in a 25 mL tube. The mixture was then stirred for 24 hours at room temperature under the radiation of 12 W blue LED. After the conversion was completed as indicated by TLC, the mixture was extracted with EtOAc (3 × 5 mL). The collected organic layer was washed with brine, dried with MgSO$_4$, filtered and concentrated in vacuo. The residue was purified directly by flash column chromatography to give the products 3a-x.

General procedure for the synthesis of products 3aa-ad

Amides 1 (0.2 mmol), pyrazole 2a (0.8 mmol), NiSO$_4$$\cdot$6H$_2$O (15 mol %), Acr$^+$$-$$Mes$ ClO$_4$ (5 mol%), H$_2$O$_2$ (0.8 mmol) and H$_2$O (4 mL) were combined in a 25 mL tube. The mixture was then stirred for 48 hours at room temperature under the radiation of 12 W blue LED. After the conversion was completed as indicated by TLC, the mixture was extracted with EtOAc (3 × 5 mL). The collected organic layer was washed with brine, dried with MgSO$_4$, filtered and concentrated in vacuo. The residue was purified directly by flash column chromatography to give the products 3aa-ad.

General procedure for the synthesis of product 4a

Compound 3a (1.0 mmol), NaOH (6.0 mmol) and EtOH (10.0 mL) were combined in a 25 mL tube. The mixture was then stirred for 8 hours at 90°C. After the conversion was completed as indicated by TLC, the mixture was cooled to room temperature and poured into water, extracted with EtOAc (3 × 5 mL). The collected organic layer was washed with brine, dried with MgSO$_4$, filtered and concentrated in vacuo. The residue was purified
directly by flash column chromatography to give the product 4a. Then 1 M HCl was added in aqueous layer until pH 4. The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried with MgSO$_4$, filtered and concentrated in vacuo. The residue was purified directly by flash column chromatography to afford the 2-picolinic acid.

**General procedure for the synthesis of product 5a**

Compound 4a (1.0 mmol), concentrated HCl (1.5 mmol) and water (5.0 mL) were combined in a 25 mL tube at 0 °C. Then, a solution of NaNO$_2$ (1.5 mmol) in water (1.0 mL) was slowly added. After stirring for 15 min, a solution of KI (1.5 mmol) in water (1.0 mL) was slowly added. Then the mixture was warmed to room temperature and stirred for 24 h. Subsequently, the solution was neutralized by adding 2 N NaOH and the organic phase was extracted with EtOAc (3 × 5 mL). The collected organic layer was washed with brine, dried with MgSO$_4$, filtered and concentrated in vacuo. The residue was purified directly by flash column chromatography to give the product 5a.

**General procedure for the cycle experiment of catalyst-in-water**

Amides 1a (0.2 mmol), pyrazole derivatives 2a (0.4 mmol), NiSO$_4$•6H$_2$O (15 mol %), Acr$^-$–Mes ClO$_4^-$ (5 mol %), H$_2$O$_2$ (0.4 mmol) and H$_2$O (4 mL) were combined in a 25 mL tube. The mixture was then stirred for 24 hours at room temperature under the radiation of 12 W blue LED. After the conversion was completed as indicated by TLC, the water in the flask was extracted directly, using EtOAc (3 × 5 mL) in which the nickel(II) salt is insoluble. According to the difference of the solubility to nickel(II) salt and organic product in H$_2$O and EtOAc, catalyst-in-water (contains nickel(II) salt and H$_2$O) could be retrieved by an easy phase separation from the organic layer. And the retrieved catalyst-in-water was reutilized in the next round by the addition of starting materials.
Table S1 Conditions screening$^{a,b}$

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<td>2</td>
<td>Acr$^-$–Mes ClO$_4$^-</td>
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<td>Ir(ppy)$_3$</td>
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Table S2 ICP-Ms analysis on product for Ni content

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2. Characterization of Products

**N-(4-(1H-pyrazol-1-yl)naphthalen-1-yl)picolinamide (3a)**

Faint yellow solid (45 mg, 72% yield), M.p. 148-149 °C. $^1$H NMR (500 MHz, CDCl$_3$) δ 10.89 (s, 1H), 8.70 (d, $J = 4.2$ Hz, 1H), 8.50 (d, $J = 8.1$ Hz, 1H), 8.35 (d, $J = 7.8$ Hz, 1H), 8.15 (d, $J = 8.5$ Hz, 1H), 7.93 (td, $J = 7.7$, 1.7 Hz, 1H), 7.84 (d, $J = 1.8$ Hz, 1H), 7.81 (d, $J = 8.5$ Hz, 1H), 7.78 (d, $J = 2.3$ Hz, 1H), 7.63 (t, $J = 7.2$ Hz, 1H), 7.58 (d, $J = 8.1$ Hz, 1H), 7.56 – 7.51 (m, 2H), 6.54 (t, $J = 2.1$ Hz, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 162.41, 149.84, 148.27, 140.91, 138.00, 134.23, 133.27, 132.00, 130.10, 127.38, 127.10, 126.88, 126.84, 124.29, 123.73, 122.70, 120.75, 117.51, 106.61. HRMS (ESI): Calculated for C$_{19}$H$_{14}$N$_4$O$^+$: 315.1241 [M+H]$^+$, Found: 315.1243.

**N-(4-(1H-pyrazol-1-yl)naphthalen-1-yl)pyrazine-2-carboxamide (3b)**

Faint yellow solid (43 mg, 69% yield), M.p. 153-154 °C. $^1$H NMR (500 MHz, CDCl$_3$) δ 10.40 (s, 1H), 9.52 (d, $J = 1.1$ Hz, 1H), 8.81 (d, $J = 2.4$ Hz, 1H), 8.63 (dd, $J = 2.2$, 1.6 Hz, 1H), 8.39 (d, $J = 8.1$ Hz, 1H), 8.03 (d, $J = 8.5$ Hz, 1H), 7.80 – 7.75 (m, 2H), 7.72 (d, $J = 2.2$ Hz, 1H), 7.58 (dd, $J = 11.3$, 4.0 Hz, 1H), 7.53 (d, $J = 8.1$ Hz, 2H), 6.48 (t, $J = 2.1$ Hz, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 160.05, 146.87, 143.86, 143.36, 141.54, 139.94, 133.71, 131.43, 130.82, 128.99, 126.38, 126.18, 125.79, 123.39, 122.49, 119.33, 117.03, 105.58. HRMS (ESI): Calculated for C$_{18}$H$_{13}$N$_5$O$^+$: 316.1193 [M+H]$^+$, Found: 316.1188.

**N-(4-(1H-pyrazol-1-yl)naphthalen-1-yl)-3-methylpicolinamide (3c)**

Faint yellow solid (39 mg, 60% yield), M.p. 155-156 °C. $^1$H NMR (500 MHz, CDCl$_3$) δ 11.09 (s, 1H), 8.50 (d, $J = 4.1$ Hz, 1H), 8.40 (d, $J = 8.1$ Hz, 1H), 8.09 (d, $J = 8.5$ Hz, 1H), 7.77 (d, $J = 1.8$ Hz, 1H), 7.71 (d, $J = 2.2$ Hz, 2H), 7.63 (d, $J = 7.7$ Hz, 1H), 7.56 (d, $J = 7.7$ Hz, 1H), 7.52 – 7.47 (m, 2H), 7.37 (dd, $J = 7.7$, 4.6 Hz, 1H), 6.47 (t, $J = 2.0$ Hz, 1H), 2.80 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 162.80, 145.65, 144.52, 140.51, 139.75, 135.50, 133.28, 132.90, 132.57, 130.88, 129.05, 126.17, 125.84, 125.31, 123.08, 122.63, 119.83,
HRMS (ESI): Calculated for C_{20}H_{16}N_{4}O^{+}: 329.1397 [M+H]^{+}, Found: 329.1394.

**N-(4-(1H-pyrazol-1-yl)naphthalen-1-yl)isoquinoline-1-carboxamide (3d)**

Faint yellow solid (34 mg, 47% yield), M.p. 148-149 °C. $^{1}$H NMR (500 MHz, CDCl$_3$) $\delta$ 11.27 (s, 1H), 9.82 (d, $J = 8.1$ Hz, 1H), 8.66 (d, $J = 5.5$ Hz, 1H), 8.53 (d, $J = 8.1$ Hz, 1H), 8.23 (d, $J = 8.5$ Hz, 1H), 7.96 – 7.92 (m, 2H), 7.86 – 7.75 (m, 5H), 7.67 (t, $J = 7.6$ Hz, 1H), 7.60 – 7.55 (m, 1H), 6.56 (t, $J = 2.0$ Hz, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 162.93, 146.25, 139.82, 139.09, 136.77, 133.19, 132.47, 130.87, 129.79, 129.09, 128.15, 126.80, 126.47, 126.24, 126.14, 126.01, 125.94, 124.25, 123.16, 122.62, 119.92, 116.65, 105.45. HRMS (ESI): Calculated for C$_{23}$H$_{16}$N$_{4}$O$^{+}$: 365.1397 [M+H]$^{+}$, Found: 365.1392.

**N-(4-(1H-pyrazol-1-yl)naphthalen-1-yl)quinoline-2-carboxamide (3e)**

Faint yellow solid (38 mg, 52% yield), M.p. 169-170 °C. $^{1}$H NMR (500 MHz, CDCl$_3$) $\delta$ 11.10 (s, 1H), 8.55 (d, $J = 8.1$ Hz, 1H), 8.47 (d, $J = 8.4$ Hz, 1H), 8.43 (d, $J = 8.5$ Hz, 1H), 8.30 (d, $J = 8.4$ Hz, 1H), 8.26 (d, $J = 8.5$ Hz, 1H), 7.96 (d, $J = 8.1$ Hz, 1H), 7.85 (d, $J = 7.7$ Hz, 3H), 7.81 (d, $J = 2.2$ Hz, 1H), 7.70 (t, $J = 6.4$ Hz, 2H), 7.62 (d, $J = 8.1$ Hz, 1H), 7.60 (d, $J = 7.4$ Hz, 1H), 6.56 (t, $J = 2.0$ Hz, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 161.49, 148.59, 145.32, 139.84, 137.08, 133.24, 132.20, 130.86, 129.47, 129.07, 128.66, 128.60, 127.36, 126.87, 126.27, 126.03, 125.90, 123.26, 122.65, 119.64, 117.82, 116.54, 105.48. HRMS (ESI): Calculated for C$_{23}$H$_{16}$N$_{4}$O$^{+}$: 365.1397 [M+H]$^{+}$, Found: 365.1391.

**N-(4-(3-methyl-1H-pyrazol-1-yl)naphthalen-1-yl)picolinamide (3i)**

Faint yellow solid (43 mg, 66% yield), M.p. 160-161 °C. $^{1}$H NMR (600 MHz, CDCl$_3$) $\delta$ 10.88 (s, 1H), 8.73 (d, $J = 4.5$ Hz, 1H), 8.49 (d, $J = 8.0$ Hz, 1H), 8.37 (d, $J = 7.7$ Hz, 1H), 8.15 (d, $J = 8.5$ Hz, 1H), 7.96 (t, $J = 7.6$ Hz, 1H), 7.88 (d, $J = 8.4$ Hz, 1H), 7.67 (d, $J = 1.9$ Hz, 1H), 7.60 – 7.55 (m, 1H), 7.48 (t, $J = 7.6$ Hz, 1H), 6.56 (t, $J = 2.0$ Hz, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 162.61, 148.57, 145.29, 139.80, 137.06, 133.22, 132.19, 130.87, 129.47, 129.07, 128.66, 128.60, 127.36, 126.87, 126.27, 126.03, 125.90, 123.26, 122.65, 119.64, 117.82, 116.54, 105.48. HRMS (ESI): Calculated for C$_{23}$H$_{16}$N$_{4}$O$^{+}$: 365.1397 [M+H]$^{+}$, Found: 365.1391.
Hz, 1H), 7.64 (t, J = 7.6 Hz, 1H), 7.59 – 7.54 (m, 3H), 6.32 (d, J = 1.9 Hz, 1H), 2.44 (s, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) δ 162.34, 150.14, 149.85, 148.22, 137.88, 134.35, 132.86, 132.59, 130.06, 127.21, 126.93, 126.77, 126.75, 124.37, 123.55, 122.60, 120.60, 117.50, 106.30, 13.75. HRMS (ESI): Calculated for C$_{20}$H$_{16}$N$_{4}$O$: 329.1397$ [M+H]$^+$, Found: 329.1391.

$N$-(4-(3-phenyl-1H-pyrazol-1-yl)naphthalen-1-yl)picolinamide (3j)

Faint yellow solid (48 mg, 62% yield), M.p. 173-174 °C. $^1$H NMR (500 MHz, CDCl$_3$) δ 10.91 (s, 1H), 8.76 – 8.73 (m, 1H), 8.55 (d, J = 8.1 Hz, 1H), 8.39 (d, J = 7.8 Hz, 1H), 8.18 (d, J = 8.5 Hz, 1H), 7.96 (dd, J = 10.3, 3.4 Hz, 4H), 7.81 (d, J = 2.3 Hz, 1H), 7.68 (d, J = 8.2 Hz, 2H), 7.58 – 7.54 (m, 2H), 7.43 (d, J = 7.8 Hz, 2H), 7.34 (d, J = 7.3 Hz, 1H), 6.86 (d, J = 2.3 Hz, 1H). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 162.36, 152.87, 149.83, 148.24, 137.90, 134.22, 133.24, 133.22, 130.05, 127.98, 127.33, 127.06, 126.83, 126.79, 125.91, 124.37, 123.72, 122.62, 120.63, 117.47, 103.91. HRMS (ESI): Calculated for C$_{25}$H$_{18}$N$_{4}$O$: 391.1553$ [M+H]$^+$, Found: 391.1546.

$N$-(4-(4-methyl-1H-pyrazol-1-yl)naphthalen-1-yl)picolinamide (3m)

Faint yellow solid (48 mg, 74% yield), M.p. 148-149 °C. $^1$H NMR (600 MHz, CDCl$_3$) δ 10.87 (s, 1H), 8.71 (d, J = 4.3 Hz, 1H), 8.49 (d, J = 8.1 Hz, 1H), 8.36 (d, J = 7.8 Hz, 1H), 8.15 (d, J = 8.5 Hz, 1H), 7.96 – 7.92 (m, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.66 – 7.62 (m, 2H), 7.57 – 7.53 (m, 4H), 2.23 (s, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 162.35, 149.82, 148.22, 141.56, 137.86, 134.43, 132.85, 130.54, 129.91, 127.14, 126.93, 126.81, 126.75, 124.39, 123.34, 122.58, 120.62, 117.53, 117.03, 8.96. HRMS (ESI): Calculated for C$_{20}$H$_{16}$N$_{4}$O$: 329.1397$ [M+H]$^+$, Found: 329.1398.

$N$-(4-(4-bromo-1H-pyrazol-1-yl)naphthalen-1-yl)picolinamide (3n)
Faint yellow solid (40 mg, 51% yield), M.p. 172-173 °C. $^1$H NMR (500 MHz, CDCl$_3$) δ 10.93 (s, 1H), 8.74 (d, $J = 4.7$ Hz, 1H), 8.54 (d, $J = 8.1$ Hz, 1H), 8.38 (d, $J = 7.8$ Hz, 1H), 8.18 (d, $J = 8.5$ Hz, 1H), 7.98 (td, $J = 7.7$, 1.6 Hz, 1H), 7.82 - 7.77 (m, 3H), 7.68 (s, 1H), 7.59 (d, $J = 8.1$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 161.33, 148.73, 147.22, 140.41, 136.90, 132.65, 132.46, 132.42, 130.87, 128.69, 126.51, 126.14, 125.81, 125.65, 122.79, 121.62, 119.70, 116.16, 93.43. HRMS (ESI): Calculated for C$_{19}$H$_{13}$BrN$_4$O$: 393.0346 [M+H]$^+$, Found: 393.0345.

**N-(4-(4-iodo-1H-pyrazol-1-yl)naphthalen-1-yl)picolinamide (3o)**

![Structure](image)

Faint yellow solid (53 mg, 60% yield), M.p. 144-145 °C. $^1$H NMR (600 MHz, CDCl$_3$) δ 10.95 (s, 1H), 8.76 (d, $J = 4.2$ Hz, 1H), 8.55 (d, $J = 8.1$ Hz, 1H), 8.40 (d, $J = 7.8$ Hz, 1H), 8.20 (d, $J = 8.5$ Hz, 1H), 8.01 - 7.98 (m, 1H), 7.86 (d, $J = 7.2$ Hz, 2H), 7.81 (d, $J = 8.4$ Hz, 1H), 7.71 - 7.68 (m, 1H), 7.62 - 7.58 (m, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 162.32, 149.71, 145.85, 137.93, 136.13, 133.65, 129.69, 127.52, 127.15, 126.83, 126.65, 123.83, 123.78, 122.65, 120.71, 117.17, 57.57. HRMS (ESI): Calculated for C$_{19}$H$_{13}$IN$_4$O$: 441.0207 [M+H]$^+$, Found: 441.0200.

**N-(4-(3,5-dimethyl-1H-pyrazol-1-yl)naphthalen-1-yl)picolinamide (3p)**

![Structure](image)

Faint yellow solid (44 mg, 65% yield), M.p. 155-156 °C. $^1$H NMR (500 MHz, CDCl$_3$) δ 10.92 (s, 1H), 8.72 (dd, $J = 4.1$, 0.6 Hz, 1H), 8.55 (d, $J = 8.0$ Hz, 1H), 8.37 (d, $J = 7.8$ Hz, 1H), 8.16 (d, $J = 8.5$ Hz, 1H), 7.96 (td, $J = 7.7$, 1.6 Hz, 1H), 7.63 (t, $J = 7.7$ Hz, 1H), 7.54 (dd, $J = 10.1$, 5.5 Hz, 3H), 7.37 (d, $J = 8.4$ Hz, 1H), 6.08 (s, 1H), 2.36 (s, 3H), 2.07 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 161.26, 148.82, 147.99, 147.19, 140.74, 136.84, 132.38, 131.79, 130.55, 126.31, 125.85, 125.72, 125.60, 124.70, 123.16, 121.56, 119.53, 116.19, 104.35, 12.65, 10.43. HRMS (ESI): Calculated for C$_{21}$H$_{18}$N$_4$O$: 343.1553 [M+H]$^+$, Found: 343.1549.
**N-(4-(4-bromo-3,5-dimethyl-1H-pyrazol-1-yl)naphthalen-1-yl)picolinamide (3q)**

Faint yellow solid (50 mg, 60% yield), M.p. 179-180 °C. $^1$H NMR (600 MHz, CDCl$_3$) δ 10.95 (s, 1H), 8.72 (d, $J$ = 4.7 Hz, 1H), 8.57 (d, $J$ = 8.0 Hz, 1H), 8.37 (d, $J$ = 7.8 Hz, 1H), 8.17 (d, $J$ = 8.5 Hz, 1H), 7.96 (t, $J$ = 7.7 Hz, 1H), 7.65 (t, $J$ = 7.6 Hz, 1H), 7.54 (dd, $J$ = 14.2, 8.0 Hz, 3H), 7.37 (d, $J$ = 8.4 Hz, 1H), 2.36 (s, 3H), 2.08 (s, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 162.32, 149.74, 148.24, 147.64, 139.89, 137.91, 133.86, 132.53, 131.17, 127.58, 127.06, 126.83, 125.78, 123.84, 122.62, 120.69, 117.08, 94.97, 12.53, 10.91. HRMS (ESI): Calculated for C$_{21}$H$_{17}$BrN$_4$O: 421.0659 [M+H]$^+$, Found: 421.0644.

**N-(4-(4-iodo-3,5-dimethyl-1H-pyrazol-1-yl)naphthalen-1-yl)picolinamide (3r)**

Faint yellow solid (60 mg, 64% yield), M.p. 182-183 °C. $^1$H NMR (600 MHz, CDCl$_3$) δ 10.94 (s, 1H), 8.70 (d, $J$ = 4.3 Hz, 1H), 8.56 (d, $J$ = 8.0 Hz, 1H), 8.35 (d, $J$ = 7.7 Hz, 1H), 8.16 (d, $J$ = 8.5 Hz, 1H), 7.94 (t, $J$ = 7.6 Hz, 1H), 7.63 (t, $J$ = 7.6 Hz, 1H), 7.52 (d, $J$ = 8.0 Hz, 3H), 7.35 (d, $J$ = 8.4 Hz, 1H), 2.36 (s, 3H), 2.11 (s, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 162.32, 150.85, 149.70, 148.24, 143.34, 137.91, 133.86, 132.71, 131.11, 127.60, 127.08, 126.84, 126.56, 125.74, 123.83, 122.61, 120.70, 117.07, 63.59, 14.29, 12.56. HRMS (ESI): Calculated for C$_{21}$H$_{17}$IN$_4$O: 469.0520 [M+H]$^+$, Found: 469.0521.

**N-(4-(1H-benzo[d][1,2,3]triazol-1-yl)naphthalen-1-yl)picolinamide (3s)**

Faint yellow solid (32 mg, 44% yield), M.p. 152-153 °C. $^1$H NMR (500 MHz, CDCl$_3$) δ 11.05 (s, 1H), 8.77 (d, $J$ = 4.7 Hz, 1H), 8.70 (d, $J$ = 8.1 Hz, 1H), 8.41 (d, $J$ = 7.8 Hz, 1H), 8.27 (d, $J$ = 8.6 Hz, 1H), 8.22 (d, $J$ = 8.1 Hz, 1H), 8.00 (td, $J$ = 7.7, 1.6 Hz, 1H), 7.75 (d, $J$ = 8.1 Hz, 1H), 7.73 – 7.70 (m, 1H), 7.60 – 7.57 (m, 1H), 7.53 (dd, $J$ = 14.8, 7.8 Hz, 2H), 7.47 (d, $J$ = 7.8 Hz, 2H), 7.35 (d, $J$ = 8.0 Hz, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 162.42, 149.68,
N-(4-(4-methyl-1H-pyrazol-1-yl)naphthalen-1-yl)isoquinoline-1-carboxamide (3t)

Faint yellow solid (37 mg, 49% yield), M.p. 159-160 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\)
11.24 (s, 1H), 9.82 (d, \(J = 7.9\) Hz, 1H), 8.65 (d, \(J = 5.5\) Hz, 1H), 8.50 (d, \(J = 8.0\) Hz, 1H), 8.21 (d, \(J = 8.4\) Hz, 1H), 7.94 – 7.90 (m, 3H), 7.77 (ddd, \(J = 7.8, 6.3, 1.5\) Hz, 2H), 7.68 – 7.63 (m, 2H), 7.59 (dd, \(J = 11.7, 7.9\) Hz, 3H), 2.24 (s, 3H).

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\)
162.94, 146.28, 140.53, 139.10, 136.75, 133.44, 132.14, 129.76, 129.54, 129.51, 128.97, 128.12, 126.80, 126.45, 126.19, 126.10, 126.00, 125.87, 124.21, 123.32, 122.32, 119.90, 116.77, 7.93. HRMS (ESI): Calculated for C\(_{22}\)H\(_{15}\)N\(_5\)O\(^+\): 366.1349 [M+H]\(^+\), Found: 366.1343.

N-(4-(4-bromo-1H-pyrazol-1-yl)naphthalen-1-yl)isoquinoline-1-carboxamide (3u)

Faint yellow solid (29 mg, 33% yield), M.p. 184-185 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\)
11.24 (s, 1H), 9.74 (d, \(J = 8.0\) Hz, 1H), 8.59 (d, \(J = 5.5\) Hz, 1H), 8.48 (d, \(J = 8.1\) Hz, 1H), 8.16 (d, \(J = 8.5\) Hz, 1H), 7.87 (t, \(J = 6.0\) Hz, 2H), 7.73 (dd, \(J = 13.4, 8.9\) Hz, 5H), 7.61 (t, \(J = 7.1\) Hz, 1H), 7.54 (dd, \(J = 7.6, 5.1\) Hz, 2H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\)
162.93, 146.12, 140.40, 139.09, 136.77, 132.99, 132.41, 131.58, 130.90, 129.82, 128.74, 128.21, 126.75, 126.51, 126.47, 126.11, 126.03, 124.33, 122.77, 122.74, 120.02, 116.38, 93.42. HRMS (ESI): Calculated for C\(_{23}\)H\(_{15}\)BrN\(_4\)O\(^+\): 443.0502 [M+H]\(^+\), Found: 443.05009.

N-(4-(4-iodo-1H-pyrazol-1-yl)naphthalen-1-yl)isoquinoline-1-carboxamide (3v)
Faint yellow solid (38 mg, 39% yield), M.p. 169-170 °C. $^{1}$H NMR (500 MHz, CDCl$_3$) δ 11.23 (s, 1H), 9.73 (d, $J = 7.9$ Hz, 1H), 8.58 (d, $J = 5.5$ Hz, 1H), 8.47 (d, $J = 8.1$ Hz, 1H), 8.15 (d, $J = 8.5$ Hz, 1H), 7.85 (d, $J = 6.7$ Hz, 2H), 7.78 (d, $J = 4.2$ Hz, 2H), 7.72 (d, $J = 8.4$ Hz, 3H), 7.60 (t, $J = 7.1$ Hz, 1H), 7.53 (d, $J = 8.1$ Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 162.91, 146.11, 144.82, 139.08, 136.76, 135.12, 132.97, 132.25, 129.81, 128.72, 128.19, 126.74, 126.48, 126.45, 126.09, 126.02, 126.00, 124.31, 122.76, 122.74, 119.99, 116.34, 56.52. HRMS (ESI): Calculated for C$_{23}$H$_{15}$IN$_4$O$^+$: [M+H]$^+$ 491.0364, Found: 491.0368.

$N$-(4-(4-iodo-1H-pyrazol-1-yl)naphthalen-1-yl)-3-methylpicolinamide (3w)

Faint yellow solid (26 mg, 29% yield), M.p. 167-168 °C. $^{1}$H NMR (500 MHz, CDCl$_3$) δ 11.19 (s, 1H), 8.55 (d, $J = 4.0$ Hz, 1H), 8.48 (d, $J = 8.1$ Hz, 1H), 8.15 (d, $J = 8.5$ Hz, 1H), 7.83 (d, $J = 9.7$ Hz, 2H), 7.76 (d, $J = 8.4$ Hz, 1H), 7.70 (d, $J = 7.6$ Hz, 1H), 7.63 (d, $J = 7.5$ Hz, 1H), 7.56 (t, $J = 7.6$ Hz, 2H), 7.43 (dd, $J = 7.7$, 4.6 Hz, 1H), 2.86 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 162.70, 145.49, 144.76, 144.42, 140.58, 135.53, 135.11, 133.02, 131.99, 128.65, 126.40, 125.98, 125.78, 125.35, 122.71, 122.67, 119.91, 115.95, 56.48, 19.80. HRMS (ESI): Calculated for C$_{20}$H$_{15}$IN$_4$O$^+$: 455.0364 [M+H]$^+$, Found: 455.0361.

$N$-(4-(4-iodo-1H-pyrazol-1-yl)naphthalen-1-yl)quinoline-2-carboxamide (3x)

Faint yellow solid (30 mg, 31% yield), M.p. 173-174 °C. $^{1}$H NMR (500 MHz, CDCl$_3$) δ 11.14 (s, 1H), 8.57 (d, $J = 8.1$ Hz, 1H), 8.46 (q, $J = 8.5$ Hz, 2H), 8.29 (dd, $J = 15.6$, 8.5 Hz, 2H), 7.97 (d, $J = 8.2$ Hz, 1H), 7.89 – 7.86 (m, 1H), 7.86 (d, $J = 2.2$ Hz, 2H), 7.82 (d, $J = 8.5$ Hz, 1H), 7.72 (d, $J = 8.2$ Hz, 2H), 7.61 (t, $J = 7.5$ Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 161.52, 148.52, 144.86, 139.77, 137.16, 135.21, 135.13, 133.00, 132.35, 129.52, 128.87, 127.42, 126.90, 126.54, 126.21, 125.82, 124.05, 122.88, 122.81, 119.74, 117.84, 116.34, 56.55. HRMS (ESI): Calculated for C$_{23}$H$_{15}$IN$_4$O$^+$: 491.0364 [M+H]$^+$, Found: 491.0359.
N-(4-(1H-pyrazol-1-yl)phenyl)picolinamide (3aa)

White solid (22 mg, 42% yield), M.p. 143-144 °C. $^1$H NMR (500 MHz, CDCl$_3$) δ 10.12 (s, 1H), 8.63 (d, $J = 4.7$ Hz, 1H), 8.31 (d, $J = 7.8$ Hz, 1H), 7.92 – 7.88 (m, 4H), 7.73 – 7.70 (m, 3H), 7.52 – 7.49 (m, 1H), 6.47 (t, $J = 2.1$ Hz, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 161.00, 148.58, 146.99, 139.94, 136.75, 135.51, 135.19, 125.67, 125.57, 121.43, 119.46, 118.91, 106.52. HRMS (ESI): Calculated for C$_{15}$H$_{12}$N$_4$O$^+$: 265.1084 [M+H]$^+$, Found: 265.1084.

N-(2-chloro-4-(1H-pyrazol-1-yl)phenyl)picolinamide (3ab)

White solid (22 mg, 37% yield), M.p. 152-153 °C. $^1$H NMR (500 MHz, CDCl$_3$) δ 10.75 (s, 1H), 8.77 (d, $J = 9.0$ Hz, 1H), 8.68 (d, $J = 4.1$ Hz, 1H), 8.31 (d, $J = 7.8$ Hz, 1H), 7.94 (d, $J = 7.7$ Hz, 1H), 7.90 (dd, $J = 11.4$, 2.5 Hz, 2H), 7.73 (d, $J = 1.6$ Hz, 1H), 7.62 (dd, $J = 9.0$, 2.5 Hz, 1H), 7.52 (dd, $J = 7.6$, 4.8 Hz, 1H), 6.49 – 6.47 (m, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 162.19, 149.51, 148.33, 141.33, 137.71, 136.38, 133.08, 126.75, 126.67, 124.26, 122.47, 121.47, 120.19, 117.95, 107.96. HRMS (ESI): Calculated for C$_{15}$H$_{11}$ClN$_4$O$^+$: 299.0694 [M+H]$^+$, Found: 299.0697.

N-(5-(1H-pyrazol-1-yl)-[1,1'-biphenyl]-2-yl)picolinamide (3ac)

White solid (33 mg, 48% yield), M.p. 158-159 °C. $^1$H NMR (600 MHz, CDCl$_3$) δ 10.36 (s, 1H), 8.77 (d, $J = 9.6$ Hz, 1H), 8.38 (d, $J = 4.1$ Hz, 1H), 8.26 (d, $J = 7.8$ Hz, 1H), 7.95 (d, $J = 2.4$ Hz, 1H), 7.88 – 7.85 (m, 1H), 7.73 – 7.71 (m, 3H), 7.52 (d, $J = 3.2$ Hz, 4H), 7.49 – 7.46 (m, 1H), 7.39 (ddd, $J = 7.5$, 4.8, 1.1 Hz, 1H), 6.49 – 6.47 (m, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 161.01, 148.77, 146.97, 139.98, 136.51, 136.25, 135.26, 132.63, 132.33, 128.44, 128.01, 127.24, 125.72, 125.23, 121.23, 120.42, 120.14, 117.85, 106.55. HRMS (ESI): Calculated for C$_{21}$H$_{16}$N$_4$O$^+$: 341.1397 [M+H]$^+$, Found: 341.1392.
**N-(4-(1H-pyrazol-1-yl)phenyl)-3-methylpicolinamide (3ad)**

![Chemical Structure](image)

White solid (28 mg, 51% yield), M.p. 131-132 °C. $^1$H NMR (600 MHz, CDCl$_3$) δ 10.36 (s, 1H), 8.46 (d, $J$ = 4.0 Hz, 1H), 7.91 (d, $J$ = 2.3 Hz, 1H), 7.87 (d, $J$ = 8.8 Hz, 2H), 7.72 (s, 1H), 7.70 (d, $J$ = 8.8 Hz, 2H), 7.66 (d, $J$ = 7.7 Hz, 1H), 7.38 (dd, $J$ = 7.7, 4.5 Hz, 1H), 6.50 – 6.44 (m, 1H), 2.83 (s, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$) δ 163.50, 146.48, 145.26, 141.44, 140.87, 136.57, 136.31, 136.29, 126.14, 120.39, 119.86, 107.44, 20.80. HRMS (ESI): Calculated for C$_{16}$H$_{14}$N$_4$O$^+$: 279.1241 [M+H]$^+$, Found: 279.1247.

**4-(1H-pyrazol-1-yl)naphthalen-1-amine (4a)**

![Chemical Structure](image)

Light brown solid (186 mg, 89% yield), M.p. 88-89 °C. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.78 (d, $J$ = 7.7 Hz, 1H), 7.72 (d, $J$ = 1.6 Hz, 1H), 7.62 (d, $J$ = 2.2 Hz, 1H), 7.50 (d, $J$ = 9.5 Hz, 1H), 7.41 (t, $J$ = 8.3 Hz, 2H), 7.27 (d, $J$ = 7.9 Hz, 1H), 6.70 (d, $J$ = 7.9 Hz, 1H), 6.42 (t, $J$ = 2.1 Hz, 1H), 4.26 (s, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 142.10, 139.29, 130.95, 129.58, 128.07, 126.13, 124.47, 123.41, 122.59, 122.44, 119.96, 107.03, 104.92. HRMS (ESI): Calculated for C$_{13}$H$_{11}$N$_3$O$^+$: 210.1026 [M+H]$^+$, Found: 210.1031.

**1-(4-iodonaphthalen-1-yl)-1H-pyrazole (5a)**

![Chemical Structure](image)

Faint yellow solid (240 mg, 75% yield), M.p. 123-124 °C. $^1$H NMR (500 MHz, CDCl$_3$) δ 8.17 (d, $J$ = 8.5 Hz, 1H), 8.14 (d, $J$ = 7.8 Hz, 1H), 7.84 (d, $J$ = 1.3 Hz, 1H), 7.77 – 7.72 (m, 2H), 7.61 (t, $J$ = 7.7 Hz, 1H), 7.55 – 7.51 (m, 1H), 7.24 (d, $J$ = 7.9 Hz, 1H), 6.55 – 6.51 (m, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 140.13, 137.24, 135.55, 133.91, 131.55, 130.73, 128.76, 127.43, 126.99, 123.02, 122.90, 105.81, 99.03. HRMS (ESI): Calculated for C$_{13}$H$_9$IN$_3^+$: 320.9886 [M+H]$^+$, Found: 320.9883.
3. Copies of $^1$H and $^{13}$C NMR Spectra

3a $^1$H NMR

3a $^{13}$C NMR
$3b \textsuperscript{1}^H \text{NMR}$

$3b \textsuperscript{13}C \text{NMR}$
3e $^1$H NMR

3e $^{13}$C NMR
$^1\text{H NMR}$

$^{13}\text{C NMR}$
3j $^1$H NMR

3j $^{13}$C NMR
3p $^1$H NMR

3p $^{13}$C NMR
$3r^1H$ NMR

$3r^{13}C$ NMR
3s $^1$H NMR

3s $^{13}$C NMR
$^{1}H$ NMR

$^{13}C$ NMR
$5a^{\text{H}}$ NMR

$5a^{\text{13C}}$ NMR