

Supporting Information:

Pd(II)-Catalyzed *gamma*-C(sp³)-H Alkynylation of Amides: A selective functionalization of R chain of amides R¹C(O)NHR

Vinod G. Landge, Ayisha Parveen, Avanashiappan Nandakumar, and Ekambaram Balaraman*

*¹Organic Chemistry Division, Dr. Homi Bhabha Road, CSIR-National Chemical Laboratory
(CSIR-NCL), Pune - 411008, India.*

Contents

1. General Information	S2
2. Experimental Section	S2-S3
3. Synthetic Application	S3-S4
4. Rate Order Determination	S5-S7
5. Characterization Data	S7-S21
6. References	S21
7. Spectra	S22-S76

1. General Information

All catalytic experiments were carried out using standard Schlenk techniques. All solvents were reagent grade or better. Deuterated solvents were used as received. Toluene was refluxed over sodium/benzophenoneketyl and distilled under argon atmosphere and stored over sodium. Metal complexes and other chemicals used in catalysis reactions were used without additional purification. Thin layer chromatography (TLC) was performed using silica gel precoated glass plates, which were visualized with UV light at 254 nm or under iodine. Column chromatography was performed with SiO₂ (SilicycleSiliaflash F60 (230-400 mesh). ¹H NMR (400 or 500 MHz), ¹³C{¹H} NMR (100 MHz) spectra were recorded on the NMR spectrometer. Deuterated chloroform was used as the solvent, and chemical shift values (δ) are reported in parts per million relative to the residual signals of this solvent [δ 7.26 for ¹H (chloroform-d), δ 77.2 for ¹³C{¹H} (chloroform-d). Abbreviations used in the NMR follow-up experiments: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. GC analysis was carried out using a HP-5 column (30 m, 0.25 mm, 0.25μ). Mass spectra were obtained on a GCMS-QP 5000 instruments with ionization voltages of 70 eV. High resolution mass spectra (HRMS) were obtained on a High-resolution mass spectra (HRMS) were obtained by fast atom bombardment (FAB) using a double focusing magnetic sector mass spectrometer and electron impact (EI) ionization technique (magnetic sector-electric sector double focusing mass analyzer). HPLC analysis was performed on Agilent Technologies 1260 Infinity with UV detector.

2. Experimental Section

2.1 Synthesis of the Starting Materials

Picolinamides were prepared by the reaction of picolinic acid with the corresponding amines.^{S1,S2,S3} The (bromoethynyl)triisopropylsilane (**2**) was prepared by previously reported AgNO₃-catalyzed bromination of (triisopropylsilyl)acetylene with *N*-bromosuccinimide.^{S4}

2.2 General Procedure

To an oven-dried 10 mL screw-capped vial, picolinamide (0.25 mmol), (bromoethynyl)triisopropylsilane **2** (0.27 mmol), Pd(OAc)₂ (10 mol%), Ag₂CO₃ (2 equiv), and toluene (1 mL) were added under a gentle stream of argon. The mixture was stirred for 18 hrs at 130 °C (bath temperature) followed by cooling to room temperature. The mixture was filtered through a celite pad with several washings (3 x 3 mL dichloromethane) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: pet ether/EtOAc) to afford the desired alkynylated product **3**.

3. Synthetic Application

Synthesis of **4a** (Removal of Directing Group)

To a suspension of the starting **3a** (0.15 mmol, 1.0 equiv) in THF (1.5 mL) was added water (1.5 mL) followed by 12M HCl (0.37 mL) and the mixture was stirred for 5 minutes at rt. Zinc dust (145 mg, 2.24 mmol, 15 equiv) was then added in three portions and the mixture was stirred at rt. After 1.5 h, the reaction was filtered through a celite plug. The filtrate was transferred to a separating funnel with 2M NaOH (50 mL) and extracted twice with DCM (2 x 50 mL). The combined organic phase was dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: MeOH/DCM) to afford the desired product **4a** (33 mg, 80%, yellow liquid).

Synthesis of **4b**^{S4}

To an oven-dried 10 mL screw-capped vial, amide **3a** (38 mg, 0.1 mmol), ethyl acrylate (20 mg, 0.15 mmol), [Cp*RhCl₂]₂ (5 mol%), Cu(OAc)₂ (2 equiv), and toluene (1 mL) were added under a gentle stream of argon. The mixture was stirred for 24 hrs at 130 °C (bath temperature) followed by cooling to room temperature. The mixture was filtered through a celite pad with several washings (3 x 3 mL dichloromethane) and concentrated *in vacuo*. The residue

was purified by column chromatography on silica gel (eluent: pet ether/EtOAc) to afford the desired product **4b** (34 mg, 72%, yellow liquid).

Synthesis of **4c**

The corresponding compound **3a** (500 mg, 1.3mmol) was dissolved in THF and 1.0 M TBAF in THF (1.5 equiv) was then added at 0 °C with constant stirring. The reaction progress was monitored by TLC. The mixture was diluted with water extracted with EtOAc, dried over anhydrous Na₂SO₄, filtered and evaporated *in vacuo*. The obtained crude product was purified by column chromatography to afford the desired terminal alkyne **4c** (294 mg, 99%, yellow liquid).

Synthesis of **4e**

Under argon atm, **3a** (prepared by the above mentioned procedure) (34 mg, 0.15 mmol), iodobenzene (39 mg, 0.18 mmol), PdCl₂ (5 mol%), CuI (2.5 mol%), Et₃N (1 mL) were charged to a 25 mL Schlenk tube. The reaction mixture was stirred at 50 °C for 12 hrs. The mixture was filter through celite and concentrated *in vacuo*. The obtained crude product was purified by column chromatography to afford **4e** (43 mg, 90%, white solid).

Synthesis of **4d**

Under argon atm, **3a** (34 mg, 0.15 mmol, 1.0 equiv), CuI (10 mol %) and 3-methyl benzyl azide (20 mg, 0.15 mmol, 1.0 equiv) were dissolved in DMF (1 mL) and stirred at 60 °C for 16 hrs. After completion of the reaction saturated aq. NH₄Cl solution (5 mL) was added and the mixture was extracted with dichloromethane (3 x 5 mL) and dried over anhydrous Na₂SO₄. After complete evaporation of the solvent, the obtained crude product was purified by column chromatography to afford **4d** (49 mg, 87%, yellow solid).

4 Rate Order Determination

The rate order of the alkynylation reaction with various reaction components was determined by the initial rate method. The data of the concentration of the product vs time (min) plot was fitted linear with Origin Pro 8. The slope of the linear fitting represents the reaction rate. The order of the reaction was then determined by plotting the log(rate) vs log(conc) for a particular component.

5.1 Rate order determination for 3a.

To determine the order of the alkynylation reaction on **1a**, the initial rates at different initial concentrations of **1a** were recorded. The final data was obtained by averaging the results of three independent runs for each experiment.

To an oven-dried 10 mL screw-capped vial, (bromoethynyl)triisopropylsilane **2** (71 mg, 0.27 mmol), Pd(OAc)₂ (6 mg, 10 mol%), AgOAc (149 mg, 2 equiv), specific amount of **1a** (as shown in table S1), n-decane (38.4 mg, 0.27 mmol) as internal standard and toluene (2 mL) were added under a gentle stream of argon. The mixture was stirred at 130 °C (bath temperature). At regular intervals, the reaction vessel was cooled to ambient temperature and an aliquot of sample was withdrawn to the GC vial. The sample was diluted with EtOAc and subjected to GC analysis. The concentration of the product **3a** obtained in each sample was determined with respect to the internal standard n-decane.

Table S1. Rate of cobalt-catalyzed alkynylation reaction at different initial concentration of 1a.

Experiment	Amount of 1a (gm)	Initial concentration of 1a [M]	Initial Rate [Mmin ⁻¹] x 10 ⁻³
1	0.060	0.147	0.397
2	0.090	0.220	0.544
3	0.119	0.294	0.729
4	0.150	0.367	0.864

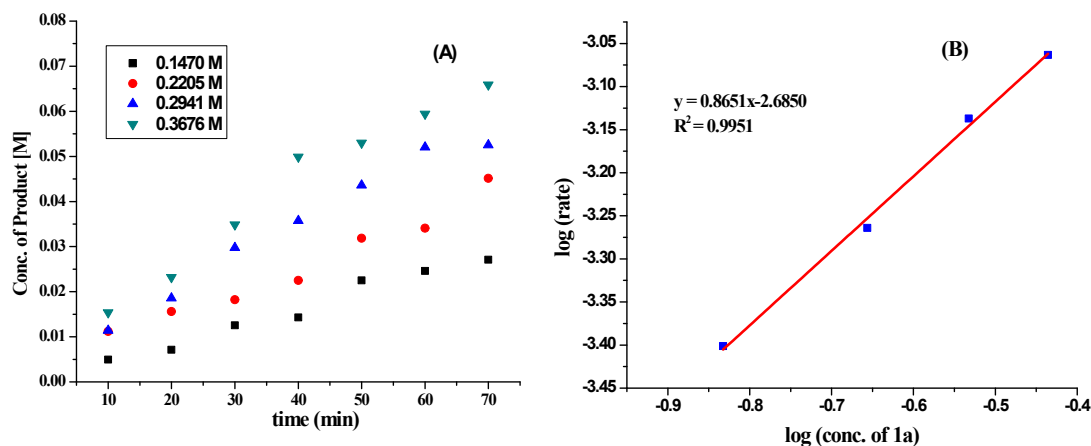


Figure S1. (A) Time-dependent formation of **3a** at different initial concentration of **1a**. (B) Plot of $\log(\text{rate})$ vs $\log(\text{conc. of } \mathbf{1a})$.

5.2 Rate order determination for (bromoethynyl)triisopropylsilane (**2**).

To determine the order of the alkylation reaction on (bromoethynyl)triisopropylsilane (**2**), the initial rates at different initial concentrations of (bromoethynyl)triisopropylsilane were recorded. The final data was obtained by averaging the result of three independent runs for each experiment.

Representative procedure was followed, employing **1a** (80 mg, 0.27mmol), $\text{Pd}(\text{OAc})_2$ (6 mg, 10 mol%), AgOAc (149 mg, 2 equiv), specific amount of (bromoethynyl)triisopropylsilane **2** (as shown in table S2), n-decane (38.4 mg, 0.27 mmol) as internal standard and toluene (2 mL).

Table S2. Rate of alkylation reaction at different initial concentration of **2**.

Experiment	Amount of 2a (gm)	Initial concentration of 2a [M]	Initial Rate [Mmin ⁻¹] x 10 ⁻³
1	0.076	0.146	0.242
2	0.152	0.293	0.597
3	0.228	0.440	0.728
4	0.304	0.558	0.987

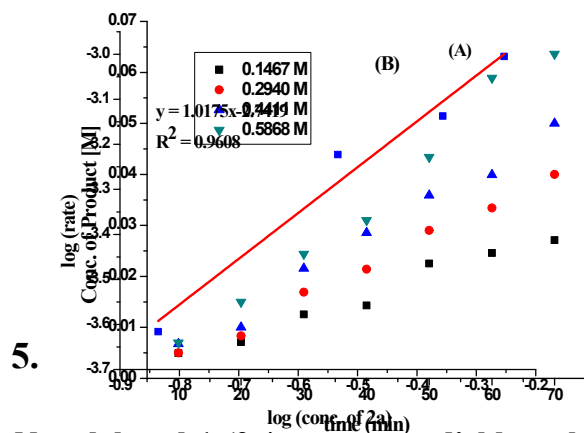
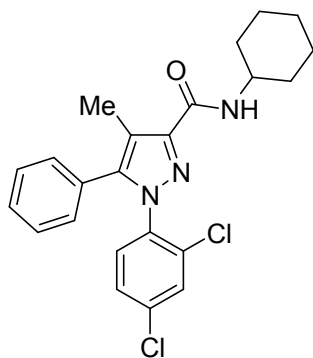


Figure S2. (A) Time-dependent formation of **3a** at different initial concentration of **2**. (B) Plot of $\log(\text{rate})$ vs $\log(\text{conc. } 2)$.

5.

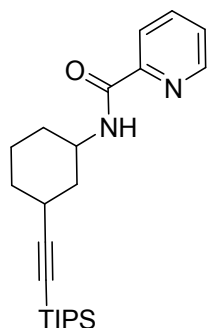
Characterization Data

N-cyclohexyl-1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-1H-pyrazole-3-carboxamide (**1u**)^{S5}



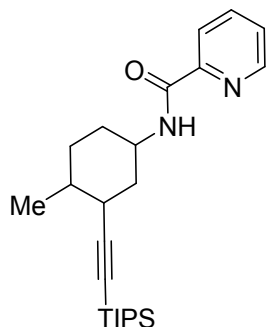
^1H NMR (500MHz, *CHLOROFORM-d*) δ ppm 7.41 (d, $J = 1.1$ Hz, 1 H), 7.34 - 7.22 (m, 5 H), 7.13 (td, $J = 2.8, 3.9$ Hz, 2 H), 6.85 (d, $J = 8.0$ Hz, 1 H), 4.02 - 3.87 (m, 1 H), 2.42 - 2.32 (m, 3 H), 2.10 - 1.96 (m, 2 H), 1.76 (td, $J = 3.4, 13.4$ Hz, 2 H), 1.70 - 1.57 (m, 1 H), 1.50 - 1.36 (m, 2 H), 1.32 - 1.19 (m, 4 H). ^{13}C NMR (126MHz, *CHLOROFORM-d*) δ ppm 162.0, 145.2, 144.2, 136.3, 135.7, 133.1, 130.7, 130.2, 129.6, 128.9, 128.6, 128.5, 127.7, 117.5, 47.9, 33.2, 25.6, 25.1, 9.5. HRMS (EI): m/z Calcd for $[\text{M}+\text{H}]$ $\text{C}_{23}\text{H}_{24}\text{ON}_3\text{Cl}_2$: 428.1291; Found: 428.1289

N-(2-(((triisopropylsilyl)ethynyl)cyclohexyl)picolinamide (**3a**)



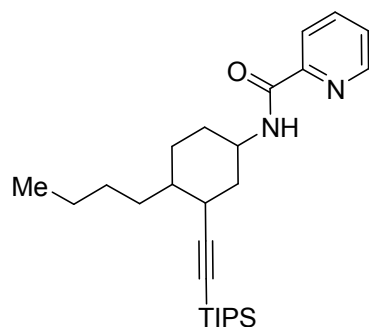
82 mg, 85% isolated yield. $R_f = 0.32$ (hexane/EtOAc = 9/1). Yellow liquid. ^1H NMR (500MHz, *CHLOROFORM-d*) δ ppm 8.54 (d, $J = 4.2$ Hz, 1 H), 8.20 (d, $J = 8.0$ Hz, 1 H), 7.93 (d, $J = 8.0$ Hz, 1 H), 7.84 (dt, $J = 1.7, 7.7$ Hz, 1 H), 7.47 - 7.37 (m, 1 H), 4.06 - 3.86 (m, 1 H), 2.54 - 2.42 (m, 1 H), 2.37 (d, $J = 12.6$ Hz, 1 H), 2.10 - 1.93 (m, 2 H), 1.84 (td, $J = 3.1, 13.5$ Hz, 1 H), 1.46 - 1.22 (m, 4 H), 1.04 (s, 21 H). ^{13}C NMR (126MHz, *CHLOROFORM-d*) δ ppm 163.3, 150.0, 147.9, 137.3, 126.1, 122.3, 112.1, 79.5, 77.3, 76.7, 47.6, 39.4, 32.5, 32.3, 29.8, 24.4, 18.6, 11.2. HRMS (EI): m/z Calcd for $[\text{M}+\text{H}]$ $\text{C}_{20}\text{H}_{31}\text{N}_2\text{OSi}$: 343.2200; Found: 343.2200.

***N*-(4-methyl-2-((triisopropylsilyl)ethynyl)cyclohexyl)picolinamide (3b)**



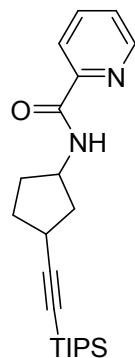
75 mg, 75% isolated yield. $R_f = 0.32$ (hexane/EtOAc = 9/1). Yellow liquid. ^1H NMR (500MHz, *CHLOROFORM-d*) δ ppm 8.55 - 8.49 (m, 1 H), 8.19 (d, $J = 8.0$ Hz, 1 H), 7.88 - 7.78 (m, 1 H), 7.45 - 7.33 (m, 1 H), 2.81 - 2.70 (m, 1 H), 2.20 - 2.02 (m, 2 H), 2.02 - 1.96 (m, 1 H), 1.86 - 1.64 (m, 3 H), 1.61 (d, $J = 9.2$ Hz, 2 H), 1.13 - 1.09 (m, 4 H), 1.08 - 0.98 (m, 22 H). ^{13}C NMR (126MHz, *CHLOROFORM-d*) δ ppm 163.5, 163.4, 150.1, 150.0, 147.9, 137.3, 137.2, 126.0, 126.0, 122.3, 122.2, 111.2, 110.8, 81.6, 80.6, 47.7, 47.1, 39.4, 37.2, 37.2, 33.5, 33.3, 33.2, 32.7, 31.4, 29.3, 27.3, 20.4, 18.6, 11.2. . HRMS (EI): m/z Calcd for $[\text{M}+\text{H}]$ $\text{C}_{24}\text{H}_{39}\text{N}_2\text{OSi}$: 399.2826; Found: 399.2827.

***N*-(4-butyl-2-((triisopropylsilyl)ethynyl)cyclohexyl)picolinamide (3c)**



76 mg, 69% isolated yield. R_f = 0.32 (hexane/EtOAc = 9/1). Yellow liquid. ^1H NMR (500MHz, *CHLOROFORM-d*) δ ppm 8.53 (dd, J = 4.6, 9.2 Hz, 1 H), 8.20 (dd, J = 3.4, 7.6 Hz, 1 H), 8.00 - 7.77 (m, 2 H), 7.50 - 7.32 (m, 1 H), 3.93 (dtd, J = 4.2, 7.9, 12.0 Hz, 1 H), 2.40 (dd, J = 2.3, 12.6 Hz, 1 H), 2.23 (d, J = 2.3 Hz, 1 H), 2.14 - 1.96 (m, 1 H), 1.96 - 1.85 (m, 1 H), 1.80 - 1.71 (m, 1 H), 1.71 - 1.56 (m, 2 H), 1.54 - 1.39 (m, 2 H), 1.39 - 1.17 (m, 8 H), 1.14 - 0.96 (m, 23 H), 0.96 - 0.84 (m, 3 H). ^{13}C NMR (126MHz, *CHLOROFORM-d*) δ ppm 163.4, 150.0, 147.9, 137.3, 137.2, 126.0, 125.9, 122.3, 122.2, 111.3, 80.8, 47.7, 41.9, 39.7, 35.8, 34.1, 34.0, 32.7, 32.1, 32.0, 29.9, 27.2, 26.1, 22.6, 22.5, 18.6, 14.1, 11.3, 11.2. HRMS (EI): m/z Calcd for $[\text{M}+\text{H}]$ $\text{C}_{24}\text{H}_{39}\text{N}_2\text{OSi}$: 441.3296; Found: 441.3293.

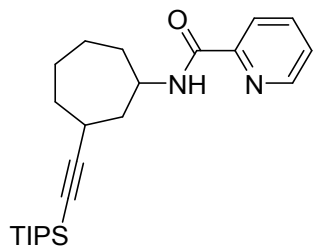
***N*-(2-((triisopropylsilyl)ethynyl)cyclopentyl)picolinamide (3d)**



80 mg, 87% isolated yield. R_f = 0.32 (hexane/EtOAc = 9/1). Yellow liquid. ^1H NMR (500MHz, *CHLOROFORM-d*) δ ppm 8.52 (d, J = 4.6 Hz, 1 H), 8.27 - 8.05 (m, 2 H), 7.84 (dt, J = 1.5, 7.6 Hz, 1 H), 7.41 (dd, J = 5.0, 6.5 Hz, 1 H), 4.50 (d, J = 7.2 Hz, 1 H), 2.87 (t, J = 7.2 Hz, 1 H), 2.55 - 2.37 (m, 1 H), 2.16 (dd, J = 5.5, 7.4 Hz, 1 H), 2.07 - 1.97 (m, 1 H), 1.97 - 1.86 (m, 1

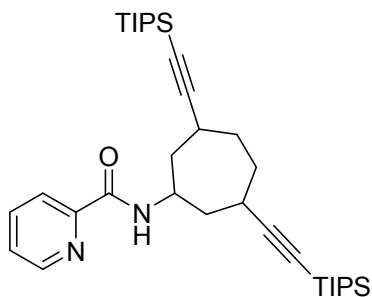
H), 1.86 - 1.65 (m, 3 H), 1.09 - 1.00 (m, 22 H). ^{13}C NMR (126MHz, *CHLOROFORM-d*) δ ppm 163.8, 149.9, 147.9, 137.2, 126.0, 122.1, 112.7, 80.3, 50.1, 41.1, 32.5, 32.5, 29.7, 18.7, 18.6, 11.2. HRMS (EI): m/z Calcd for $[\text{M}+\text{H}]$ $\text{C}_{22}\text{H}_{35}\text{N}_2\text{OSi}$: 371.2513; Found: 371.2516.

***N*-(2-((triisopropylsilyl)ethynyl)cycloheptyl)picolinamide (3e)**



78 mg, 78% isolated yield. R_f = 0.32 (hexane/EtOAc = 9/1). Yellow liquid. ^1H NMR (500MHz, *CHLOROFORM-d*) δ ppm 8.52 (d, J = 4.2 Hz, 1 H), 8.19 (d, J = 8.0 Hz, 1 H), 8.14 (d, J = 8.0 Hz, 1 H), 7.83 (dt, J = 1.5, 7.8 Hz, 1 H), 7.41 (dd, J = 4.8, 6.7 Hz, 1 H), 4.22 (td, J = 4.6, 9.2 Hz, 1 H), 2.83 - 2.71 (m, 1 H), 2.28 (td, J = 3.4, 14.1 Hz, 1 H), 2.06 (ddd, J = 3.8, 6.9, 13.7 Hz, 1 H), 1.95 - 1.85 (m, 2 H), 1.84 - 1.64 (m, 5 H), 1.59 - 1.45 (m, 1 H), 1.14 - 0.96 (m, 21 H). ^{13}C NMR (126MHz, *CHLOROFORM-d*) δ ppm 162.9, 150.1, 147.9, 137.2, 126.0, 122.2, 113.1, 80.6, 77.3, 76.7, 48.9, 41.4, 35.5, 34.9, 29.4, 25.8, 24.3, 18.6, 11.2. HRMS (EI): m/z Calcd for $[\text{M}+\text{H}]$ $\text{C}_{24}\text{H}_{39}\text{N}_2\text{OSi}$: 399.2826; Found: 399.2827.

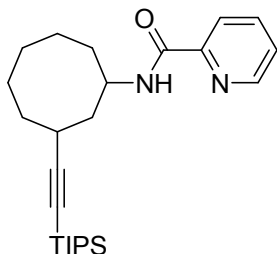
***N*-(3,6-bis((triisopropylsilyl)ethynyl)cycloheptyl)picolinamide (3e')**



14 mg, 10% isolated yield. R_f = 0.32 (hexane/EtOAc = 10/1). Yellow liquid. ^1H NMR (500MHz, *CHLOROFORM-d*) δ = 8.52 (d, J = 4.6 Hz, 1 H), 8.35 - 8.11 (m, 2 H), 7.84 (t, J = 7.1 Hz, 1 H), 7.41 (dd, J = 5.3, 6.5 Hz, 1 H), 4.43 - 4.22 (m, 1 H), 2.75 (t, J = 8.6 Hz, 2 H), 2.30 (td, J = 3.7, 14.0 Hz, 2 H), 2.19 - 1.98 (m, 4 H), 1.97 - 1.75 (m, 3 H), 1.11 - 0.99 (m, 42 H). ^{13}C NMR

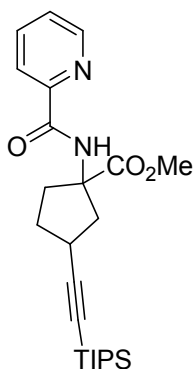
(126MHz, *CHLOROFORM-d*) δ = 162.9, 150.0, 147.9, 137.2, 126.0, 122.3, 112.5, 81.1, 47.2, 41.3, 32.8, 29.3, 18.6, 11.2.

***N*-(2-((triisopropylsilyl)ethynyl)cyclooctyl)picolinamide (3f)**



74 mg, 72% isolated yield. R_f = 0.32 (hexane/EtOAc = 9/1). Yellow liquid. ^1H NMR (400MHz, *CHLOROFORM-d*) δ ppm 8.54 (d, J = 4.3 Hz, 1 H), 8.20 (d, J = 7.9 Hz, 1 H), 8.08 (d, J = 7.9 Hz, 1 H), 7.84 (t, J = 7.0 Hz, 1 H), 7.42 (dd, J = 4.9, 7.3 Hz, 1 H), 4.19 (dd, J = 4.3, 7.9 Hz, 1 H), 2.84 (dd, J = 4.0, 7.0 Hz, 1 H), 2.22 - 2.09 (m, 1 H), 2.06 - 1.92 (m, 3 H), 1.92 - 1.65 (m, 5 H), 1.61 (br. s., 5 H), 1.10 - 0.97 (m, 22 H). ^{13}C NMR (101MHz, *CHLOROFORM-d*) δ ppm 162.9, 150.2, 148.0, 137.3, 126.0, 122.2, 113.4, 79.9, 48.3, 39.3, 33.8, 31.9, 30.2, 26.8, 23.4, 22.5, 18.6, 11.2. HRMS (EI): m/z Calcd for $[\text{M}+\text{H}]$ $\text{C}_{25}\text{H}_{41}\text{N}_2\text{OSi}$: 413.1983; Found: 413.2985.

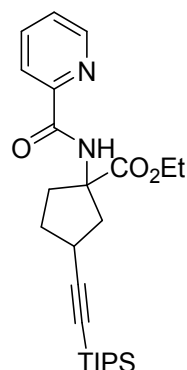
Methyl 1-(picolinamido)-3-((triisopropylsilyl)ethynyl)cyclopentanecarboxylate (3g)



93 mg, 87% isolated yield. R_f = 0.32 (hexane/EtOAc = 9/1). Yellow liquid. ^1H NMR (500MHz, *CHLOROFORM-d*) δ ppm 8.55 (brs., 1 H), 8.51 (brs., 1 H), 8.15 (d, J = 7.2 Hz, 1 H), 7.84 (brs., 1 H), 7.44 (brs., 1 H), 3.74 (brs., 3 H), 3.08 (brs., 1 H), 2.85 - 2.76 (m, 1 H), 2.51 - 2.39 (m, 1 H), 2.35 - 2.24 (m, 1 H), 2.24 - 2.14 (m, 2 H), 2.02 (d, J = 8.0 Hz, 1 H), 1.00 (br. s., 21 H). ^{13}C NMR (126MHz, *CHLOROFORM-d*) δ ppm 174.0, 164.1, 149.5, 148.0, 137.3, 126.3,

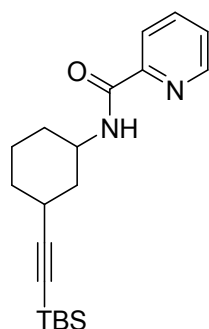
122.1, 111.4, 80.7, 65.1, 52.7, 44.9, 37.2, 33.1, 30.5, 18.6, 11.2. HRMS (EI): m/z Calcd for $[M+H]^+$ $C_{24}H_{37}N_2O_3Si$: 429.2568; Found: 429.2568.

Ethyl 1-(picolinamido)-3-((triisopropylsilyl)ethynyl)cyclopentanecarboxylate (3h)



91 mg, 82% isolated yield. R_f = 0.32 (hexane/EtOAc = 9/1). Yellow liquid. 1H NMR (500MHz, *CHLOROFORM-d*) δ ppm 8.65 - 8.47 (m, 2 H), 8.15 (d, J = 8.0 Hz, 1 H), 7.84 (dt, J = 1.5, 7.6 Hz, 1 H), 7.43 (dd, J = 5.0, 6.9 Hz, 1 H), 4.21 (q, J = 7.1 Hz, 2 H), 3.08 (t, J = 7.6 Hz, 1 H), 2.80 (dd, J = 8.4, 13.7 Hz, 1 H), 2.50 - 2.36 (m, 1 H), 2.34 - 2.26 (m, 1 H), 2.26 - 2.13 (m, 2 H), 2.02 (dd, J = 8.0, 12.6 Hz, 1 H), 1.24 (t, J = 7.1 Hz, 4 H), 1.08 - 0.89 (m, 21 H). ^{13}C NMR (126MHz, *CHLOROFORM-d*) δ ppm 173.4, 164.0, 149.6, 148.0, 137.2, 126.2, 122.0, 111.5, 80.7, 65.1, 61.5, 44.8, 37.1, 33.2, 30.6, 18.6, 14.1, 11.2. HRMS (EI): m/z Calcd for $[M+H]^+$ $C_{25}H_{39}N_2O_3Si$: 443.2724; Found: 443.2727.

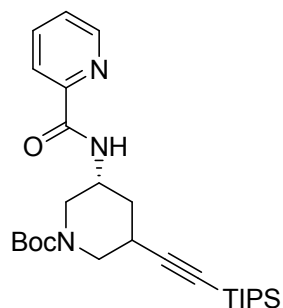
***N*-(2-((tert-butyldimethylsilyl)ethynyl)cyclohexyl)picolinamide(3i)**



56 mg, 65% isolated yield. R_f = 0.32 (hexane/EtOAc = 9/1). Yellow liquid. 1H NMR (500MHz, *CHLOROFORM-d*) δ ppm 8.53 (d, J = 4.6 Hz, 1 H), 8.19 (d, J = 7.6 Hz, 1 H), 7.95 (d, J = 8.0 Hz, 1 H), 7.84 (dt, J = 1.5, 7.6 Hz, 1 H), 7.41 (dd, J = 5.0, 6.9 Hz, 1 H), 4.02 - 3.83 (m, 1

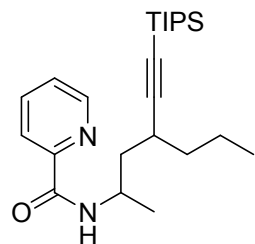
H), 2.52 - 2.40 (m, 1 H), 2.34 (d, $J = 12.6$ Hz, 1 H), 2.09 - 1.94 (m, 2 H), 1.88 - 1.78 (m, 1 H), 1.44 - 1.21 (m, 4 H), 0.90 (s, 10 H), 0.06 (s, 6 H). ^{13}C NMR (126MHz, *CHLOROFORM-d*) δ ppm 163.3, 150.0, 147.9, 137.3, 126.0, 122.2, 110.7, 81.9, 47.5, 39.1, 32.3, 32.2, 29.6, 26.0, 24.2, 16.4, -4.5. HRMS (EI): m/z Calcd for $[\text{M}+\text{H}]$ $\text{C}_{20}\text{H}_{31}\text{N}_2\text{OSi}$: 343.2200; Found: 343.2200.

(3*R*)-tert-butyl 3-(picolinamido)-5-((triisopropylsilyl)ethynyl)piperidine-1-carboxylate (3j)



99 mg, 82% isolated yield. $R_f = 0.32$ (hexane/EtOAc = 7/3). Yellow liquid. ^1H NMR (500MHz, *CHLOROFORM-d*) δ ppm 8.53 (d, $J = 4.2$ Hz, 1 H), 8.19 (d, $J = 7.6$ Hz, 1 H), 7.96 (d, $J = 8.4$ Hz, 1 H), 7.85 (t, $J = 7.2$ Hz, 1 H), 7.56 - 7.36 (m, 1 H), 4.30 (br. s., 2 H), 4.15 - 3.91 (m, 1 H), 2.75 - 2.59 (m, 2 H), 2.45 (d, $J = 12.2$ Hz, 1 H), 1.52 - 1.43 (m, 9 H), 1.13 (dd, $J = 5.0, 7.2$ Hz, 2 H), 1.09 - 0.93 (m, 21 H). ^{13}C NMR (126MHz, *CHLOROFORM-d*) δ ppm 163.7, 154.3, 149.6, 147.9, 137.3, 126.3, 122.2, 107.7, 81.9, 80.3, 48.5, 48.0, 45.0, 37.7, 28.8, 28.3, 18.8, 18.8, 18.5, 12.5, 11.4, 11.0. HRMS (EI): m/z Calcd for $[\text{M}+\text{H}]$ $\text{C}_{27}\text{H}_{44}\text{N}_3\text{O}_3\text{Si}$: 486.3146; Found: 486.3150.

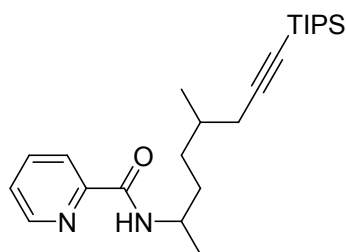
***N*-(4-((triisopropylsilyl)ethynyl)heptan-2-yl)picolinamide (3k)**



45 mg, 45% isolated yield. $R_f = 0.32$ (hexane/EtOAc = 9/1). Yellow liquid. ^1H NMR (500MHz, *CHLOROFORM-d*) δ ppm 8.54 (d, $J = 4.2$ Hz, 1 H), 8.21 (d, $J = 7.6$ Hz, 1 H), 7.91 (d, $J = 6.9$ Hz, 1 H), 7.87 - 7.78 (m, 1 H), 7.42 (dd, $J = 5.3, 6.9$ Hz, 1 H), 4.48 - 4.25 (m, 1 H), 2.59 -

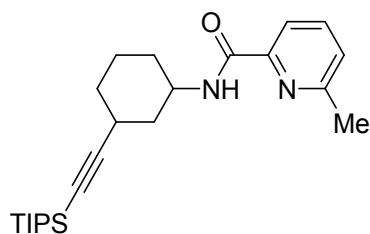
2.48 (m, 1 H), 1.92 - 1.84 (m, 1 H), 1.84 - 1.77 (m, 1 H), 1.77 - 1.65 (m, 1 H), 1.61 (br. s., 2 H), 1.50 - 1.41 (m, 3 H), 1.38 - 1.29 (m, 4 H), 1.13 - 1.02 (m, 23 H), 0.94 - 0.90 (m, 4 H). ¹³C NMR (126MHz, *CHLOROFORM-d*) δ ppm 163.5, 150.3, 147.9, 137.3, 126.0, 122.2, 111.9, 81.4, 76.8, 44.5, 42.7, 37.6, 30.0, 21.1, 20.3, 18.6, 13.9, 11.3. HRMS (EI): m/z Calcd for [M+H] C₂₄H₄₁N₂OSi: 401.2983; Found: 401.2985.

***N*-(7-methyl-1-(triisopropylsilyl)oct-1-yn-4-yl)picolinamide (3l)**



30 mg, 30% isolated yield. R_f = 0.32 (hexane/EtOAc = 9/1). Yellow liquid. ¹H NMR (500MHz, *CHLOROFORM-d*) δ ppm 8.46 (d, J = 4.2 Hz, 2 H), 8.19 (d, J = 8.0 Hz, 1 H), 7.82 (dt, J = 1.5, 7.6 Hz, 1 H), 7.39 (dt, J = 1.0, 6.2 Hz, 1 H), 4.19 (d, J = 8.4 Hz, 1 H), 2.52 (s, 1 H), 2.45 (d, J = 17.5 Hz, 2 H), 2.03 (d, J = 6.5 Hz, 2 H), 1.65 - 1.55 (m, 2 H), 1.41 (t, J = 9.0 Hz, 1 H), 1.32 - 1.21 (m, 1 H), 1.19 - 0.95 (m, 25 H). ¹³C NMR (126MHz, *CHLOROFORM-d*) δ ppm 163.7, 150.3, 147.8, 137.0, 125.8, 122.3, 108.9, 84.2, 77.3, 76.7, 52.4, 48.3, 42.9, 40.3, 38.8, 28.1, 27.3, 18.6, 11.3. HRMS (EI): m/z Calcd for [M+H] C₂₄H₄₁N₂OSi: 401.2983; Found: 401.2978.

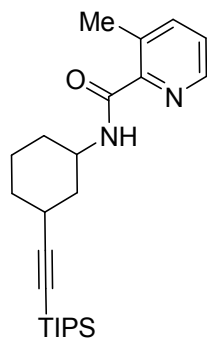
6-methyl-*N*-(2-((triisopropylsilyl)ethynyl)cyclohexyl)picolinamide (3m)



63 mg, 63% isolated yield. R_f = 0.32 (hexane/EtOAc = 9/1). Yellow liquid. ¹H NMR (500MHz, *CHLOROFORM-d*) δ ppm 8.08 - 7.93 (m, 2 H), 7.73 (t, J = 7.6 Hz, 1 H), 7.29 (s, 1 H), 3.95 (td, J = 3.7, 12.1 Hz, 1 H), 2.59 (s, 3 H), 2.54 - 2.44 (m, 1 H), 2.39 (d, J = 12.6 Hz, 1 H), 2.05 (t, J = 13.0 Hz, 2 H), 1.90 - 1.79 (m, 1 H), 1.47 - 1.26 (m, 4 H), 1.12 - 0.94 (m, 21 H). ¹³C NMR (126MHz, *CHLOROFORM-d*) δ ppm 163.5, 157.0, 149.3, 137.4, 125.7, 119.3, 112.1, 79.4,

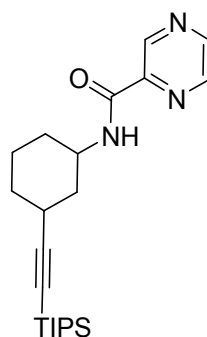
47.6, 39.4, 32.6, 32.4, 29.8, 24.5, 24.2, 18.6, 11.2. HRMS (EI): m/z Calcd for $[M+H]$ $C_{24}H_{39}N_2OSi$: 399.2826; Found: 399.2827.

3-methyl-*N*-(2-(((triisopropylsilyl)ethynyl)cyclohexyl)picolinamide (3n)



75 mg, 75% isolated yield. R_f = 0.32 (hexane/EtOAc = 9/1). Yellow liquid. 1H NMR (500MHz, $CHLOROFORM-d$) δ ppm 8.37 (d, J = 4.2 Hz, 1 H), 8.03 (d, J = 8.0 Hz, 1 H), 7.57 (d, J = 7.6 Hz, 1 H), 7.29 (dd, J = 4.6, 8.0 Hz, 1 H), 3.97 - 3.80 (m, 1 H), 2.74 (s, 3 H), 2.52 - 2.42 (m, 1 H), 2.36 (d, J = 12.2 Hz, 1 H), 2.02 (t, J = 12.8 Hz, 2 H), 1.83 (td, J = 3.2, 13.4 Hz, 1 H), 1.45 - 1.21 (m, 4 H), 1.10 - 0.95 (m, 22 H). ^{13}C NMR (126MHz, $CHLOROFORM-d$) δ ppm 165.1, 147.3, 145.3, 140.8, 135.4, 125.5, 112.2, 79.4, 47.4, 39.5, 32.6, 32.4, 29.8, 24.4, 20.5, 18.6, 11.2. HRMS (EI): m/z Calcd for $[M+H]$ $C_{24}H_{39}N_2OSi$: 399.2826; Found: 399.2827.

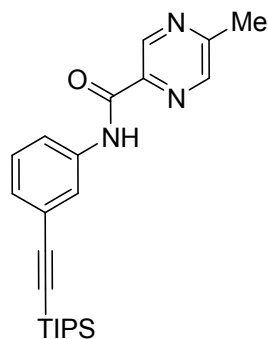
***N*-(2-(((triisopropylsilyl)ethynyl)cyclohexyl)pyrazine-2-carboxamide (3o)**



61 mg, 63% isolated yield. R_f = 0.32 (hexane/EtOAc = 8/2). Yellow liquid. 1H NMR (500MHz, $CHLOROFORM-d$) δ ppm 9.42 (s, 1 H), 8.76 (d, J = 2.3 Hz, 1 H), 8.53 (s, 1 H), 7.71 (d, J = 8.0 Hz, 1 H), 3.99 (d, J = 8.0 Hz, 1 H), 2.57 - 2.47 (m, 1 H), 2.38 (d, J = 11.8 Hz, 1 H), 2.10 - 2.02 (m, 3 H), 1.87 (td, J = 3.0, 13.4 Hz, 1 H), 1.48 - 1.25 (m, 4 H), 1.17 - 1.09 (m, 2 H), 1.09 - 0.96

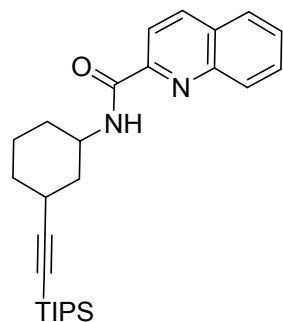
(m, 20 H). ^{13}C NMR (126MHz, *CHLOROFORM-d*) δ ppm 162.0, 147.2, 144.5, 144.5, 142.4, 111.8, 79.7, 47.7, 39.2, 32.4, 32.2, 29.6, 24.2, 18.6, 11.2. HRMS (EI): m/z Calcd for $[\text{M}+\text{H}]$ $\text{C}_{22}\text{H}_{36}\text{N}_3\text{OSi}$: 386.2622; Found: 386.2621.

5-methyl-*N*-(2-((triisopropylsilyl)ethynyl)cyclohexyl)pyrazine-2-carboxamide (3p)



74 mg, 75% isolated yield. R_f = 0.32 (hexane/EtOAc = 8/2). Yellow liquid. ^1H NMR (500MHz, *CHLOROFORM-d*) δ ppm 9.26 (s, 1 H), 8.36 (s, 1 H), 7.63 (d, J = 8.0 Hz, 1 H), 4.05 - 3.86 (m, 1 H), 2.65 (s, 3 H), 2.53 - 2.41 (m, 1 H), 2.36 (d, J = 12.6 Hz, 1 H), 2.07 - 1.97 (m, 2 H), 1.89 - 1.79 (m, 1 H), 1.46 - 1.29 (m, 3 H), 1.29 - 1.22 (m, 1 H), 1.11 - 0.92 (m, 22 H). ^{13}C NMR (126MHz, *CHLOROFORM-d*) δ ppm 162.3, 156.9, 143.4, 142.1, 141.8, 111.9, 79.6, 47.6, 39.3, 32.4, 32.3, 29.7, 24.3, 21.8, 18.6, 11.2. HRMS (EI): m/z Calcd for $[\text{M}+\text{H}]$ $\text{C}_{23}\text{H}_{38}\text{N}_3\text{OSi}$: 400.2779; Found: 400.2777.

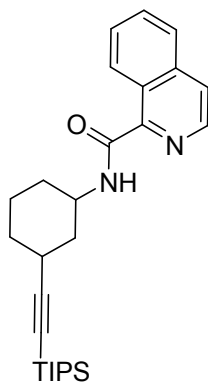
***N*-(2-((triisopropylsilyl)ethynyl)cyclohexyl)quinoline-2-carboxamide (3q)**



67 mg, 62% isolated yield. R_f = 0.32 (hexane/EtOAc = 9/1). Yellow liquid. ^1H NMR (500MHz, *CHLOROFORM-d*) δ ppm 8.35 - 8.21 (m, 2 H), 8.20 - 8.04 (m, 2 H), 7.87 (d, J = 8.4 Hz, 1 H), 7.76 (t, J = 7.6 Hz, 1 H), 7.67 - 7.53 (m, 1 H), 4.08 - 3.92 (m, 1 H), 2.57 - 2.48 (m, 1

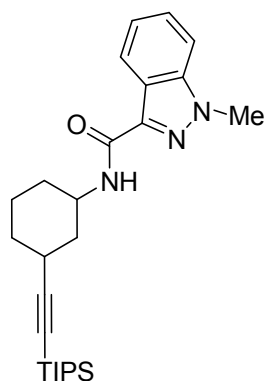
H), 2.43 (d, $J = 12.6$ Hz, 1 H), 2.15 - 1.99 (m, 2 H), 1.93 - 1.82 (m, 1 H), 1.53 - 1.29 (m, 4 H), 1.14 - 0.94 (m, 21 H). ^{13}C NMR (126MHz, *CHLOROFORM-d*) δ ppm 163.5, 149.9, 146.4, 137.4, 130.0, 129.6, 129.3, 127.8, 127.7, 118.9, 112.1, 79.5, 47.8, 39.5, 32.6, 32.4, 29.8, 24.5, 18.6, 11.2. HRMS (EI): m/z Calcd for [M-H] $\text{C}_{27}\text{H}_{37}\text{N}_2\text{OSi}$: 433.2670; Found: 433.2666.

***N*-(2-(((triisopropylsilyl)ethynyl)cyclohexyl)isoquinoline-1-carboxamide (3r)**



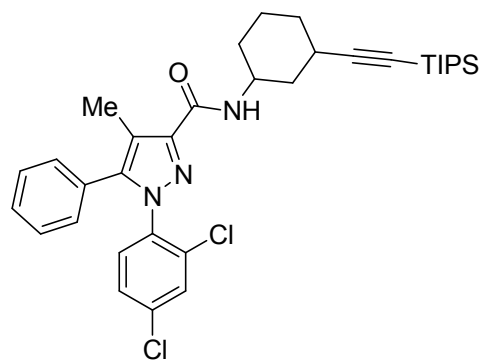
81 mg, 75% isolated yield. $R_f = 0.32$ (hexane/EtOAc = 9/1). Yellow liquid. ^1H NMR (500MHz, *CHLOROFORM-d*) δ ppm 9.60 (d, $J = 8.4$ Hz, 1 H), 8.45 (d, $J = 5.3$ Hz, 1 H), 8.12 (d, $J = 8.4$ Hz, 1 H), 7.84 (d, $J = 8.0$ Hz, 1 H), 7.79 (d, $J = 5.3$ Hz, 1 H), 7.75 - 7.64 (m, 2 H), 4.08 - 3.92 (m, 1 H), 2.60 - 2.48 (m, 1 H), 2.44 (d, $J = 12.6$ Hz, 1 H), 2.10 (d, $J = 12.2$ Hz, 1 H), 2.03 (d, $J = 13.0$ Hz, 1 H), 1.87 (td, $J = 3.1, 13.5$ Hz, 1 H), 1.50 - 1.26 (m, 4 H), 1.08 - 0.93 (m, 21 H). ^{13}C NMR (126MHz, *CHLOROFORM-d*) δ ppm 165.2, 148.4, 140.1, 137.4, 130.4, 128.6, 127.9, 127.0, 126.7, 124.2, 112.1, 79.5, 47.7, 39.4, 32.6, 32.3, 29.8, 24.4, 18.6, 11.2. HRMS (EI): m/z Calcd for [M-H] $\text{C}_{27}\text{H}_{37}\text{N}_2\text{OSi}$: 433.2670; Found: 433.2666.

1-methyl-*N*-(2-(((triisopropylsilyl)ethynyl)cyclohexyl)-1H-indazole-3-carboxamide (3s)



49 mg, 45% isolated yield. R_f = 0.32 (hexane/EtOAc = 9/1). Yellow liquid. ^1H NMR (500MHz, *CHLOROFORM-d*) δ ppm 8.38 (d, J = 8.4 Hz, 1 H), 7.48 - 7.37 (m, 2 H), 7.29 (d, J = 7.2 Hz, 1 H), 6.88 (d, J = 8.4 Hz, 1 H), 4.09 (s, 3 H), 4.05 - 3.93 (m, 1 H), 2.58 - 2.46 (m, 1 H), 2.42 (d, J = 12.6 Hz, 1 H), 2.14 - 1.97 (m, 2 H), 1.90 - 1.77 (m, 1 H), 1.47 - 1.24 (m, 4 H), 1.10 - 0.94 (m, 22 H). ^{13}C NMR (126MHz, *CHLOROFORM-d*) δ ppm 161.7, 141.2, 137.3, 126.8, 122.9, 122.8, 122.5, 112.2, 109.0, 79.4, 47.2, 39.6, 35.9, 32.5, 29.8, 24.4, 18.6, 11.2. HRMS (EI): m/z Calcd for $[\text{M}+\text{H}]$ $\text{C}_{26}\text{H}_{40}\text{N}_3\text{OSi}$: 438.2935; Found: 438.2935.

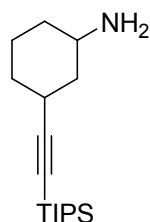
1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-*N*-(2-((triisopropylsilyl)ethynyl)cyclohexyl)-1H-pyrazole-3-carboxamide (3t)



83 mg, 55% isolated yield. R_f = 0.32 (hexane/EtOAc = 8/2). Yellow liquid. ^1H NMR (500MHz, *CHLOROFORM-d*) δ ppm 7.21 - 7.10 (m, 7 H), 7.04 - 6.93 (m, 2 H), 6.68 (d, J = 8.0 Hz, 1 H), 3.87 - 3.71 (m, 1 H), 2.37 - 2.30 (m, 1 H), 2.26 - 2.18 (m, 4 H), 1.95 - 1.81 (m, 2 H), 1.71 - 1.63 (m, 1 H), 1.29 - 1.22 (m, 1 H), 1.21 - 1.03 (m, 5 H), 0.96 - 0.89 (m, 22 H). ^{13}C NMR (126MHz, *CHLOROFORM-d*) δ ppm 162.0, 144.9, 144.2, 136.2, 135.7, 133.1, 130.6, 130.2, 129.6, 128.8, 128.6, 128.5, 127.7, 117.6, 112.2, 79.4, 47.3, 39.6, 32.5, 32.4, 29.8, 24.5, 18.6,

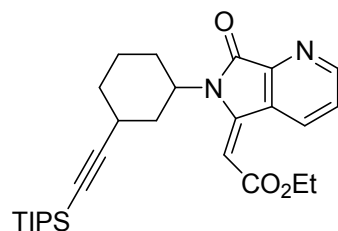
18.5, 11.3, 11.2, 9.5. HRMS (EI): m/z Calcd for $[M+H]^+ C_{34}H_{44}ON_3Cl_2Si$: 608.2625; Found: 608.2623.

2-((triisopropylsilyl)ethynyl)cyclohexanamine (4a)



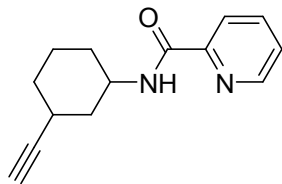
1H NMR (500MHz, *CHLOROFORM-d*) δ ppm 5.00 (brs., 3 H), 2.97 (br. s., 1 H), 2.33 (d, J = 12.2 Hz, 1 H), 2.05 (d, J = 6.1 Hz, 1 H), 1.96 (brs., 2 H), 1.82 (brs., 1 H), 1.38 - 1.26 (m, 4 H), 1.06 - 1.02 (m, 21 H). ^{13}C NMR (126MHz, *CHLOROFORM-d*) δ ppm 111.1, 80.2, 49.7, 38.1, 32.1, 31.2, 29.4, 23.8, 18.6, 11.2. HRMS (EI): m/z Calcd for $[M+H]^+ C_{17}H_{34}Si$: 280.2455; Found: 280.2457.

(*E*)-ethyl 2-(7-oxo-6-(2-((triisopropylsilyl)ethynyl)cyclohexyl)-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-ylidene)acetate (4b)



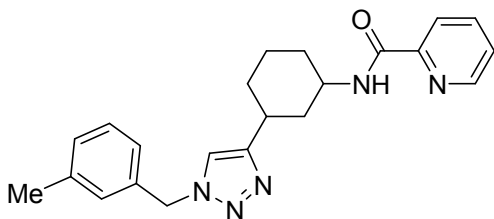
1H NMR (500MHz, *CHLOROFORM-d*) δ ppm 9.34 (dd, J = 1.0, 8.2 Hz, 1 H), 8.82 (d, J = 3.8 Hz, 1 H), 7.53 (dd, J = 4.8, 8.2 Hz, 1 H), 5.96 (brs., 1 H), 4.31 (q, J = 7.0 Hz, 2 H), 2.48 (d, J = 9.5 Hz, 3 H), 2.14 - 1.98 (m, 2 H), 1.98 - 1.87 (m, 1 H), 1.78 (d, J = 12.6 Hz, 1 H), 1.56 - 1.33 (m, 6 H), 1.08 - 0.98 (m, 22 H). ^{13}C NMR (126MHz, *CHLOROFORM-d*) δ ppm 165.8, 165.0, 152.8, 148.3, 135.9, 128.7, 126.4, 111.2, 80.2, 60.9, 35.6, 32.1, 30.9, 28.4, 25.3, 18.6, 18.3, 14.3, 11.2. HRMS (EI): m/z Calcd for $[M+H]^+ C_{28}H_{41}N_2O_3Si$: 481.2881; Found: 481.2875.

***N*-(2-ethynylcyclohexyl)picolinamide (4c)**



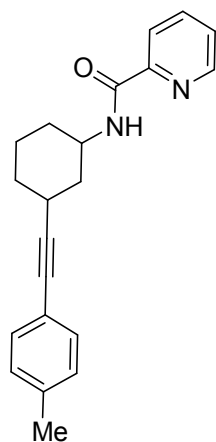
^1H NMR (500MHz, *CHLOROFORM-d*) δ ppm 8.53 (d, $J = 4.2$ Hz, 1 H), 8.19 (d, $J = 7.6$ Hz, 1 H), 8.11 - 7.89 (m, 1 H), 7.83 (dt, $J = 1.5, 7.6$ Hz, 1 H), 7.45 - 7.30 (m, 1 H), 4.03 - 3.88 (m, 1 H), 2.52 - 2.37 (m, 1 H), 2.32 (d, $J = 12.6$ Hz, 1 H), 2.11 - 1.93 (m, 3 H), 1.93 - 1.75 (m, 1 H), 1.48 - 1.24 (m, 4 H). ^{13}C NMR (126MHz, *CHLOROFORM-d*) δ ppm 163.3, 150.0, 147.9, 137.3, 126.0, 122.2, 87.5, 68.1, 47.3, 38.7, 32.2, 32.0, 28.2, 23.9. HRMS (EI): m/z Calcd for $[\text{M}+\text{H}]$ $\text{C}_{14}\text{H}_{17}\text{N}_2\text{O}$: 229.1335; Found: 229.1335.

***N*-(2-(1-(3-methylbenzyl)-1H-1,2,3-triazol-4-yl)cyclohexyl)picolinamide (4d)**



^1H NMR (500MHz, *CHLOROFORM-d*) δ ppm 8.51 (d, $J = 4.6$ Hz, 1 H), 8.18 (d, $J = 8.0$ Hz, 1 H), 7.95 (d, $J = 8.0$ Hz, 1 H), 7.82 (t, $J = 7.6$ Hz, 1 H), 7.40 (dd, $J = 5.3, 6.9$ Hz, 1 H), 7.27 - 7.21 (m, 1 H), 7.19 - 7.10 (m, 2 H), 7.10 - 7.00 (m, 2 H), 5.43 (s, 2 H), 4.07 (dt, $J = 3.8, 7.8$ Hz, 1 H), 2.98 - 2.77 (m, 1 H), 2.41 (d, $J = 12.2$ Hz, 1 H), 2.33 (s, 3 H), 2.18 - 2.05 (m, 2 H), 2.03 - 1.88 (m, 2 H), 1.61 - 1.51 (m, 1 H), 1.47 - 1.37 (m, 2 H), 1.36 - 1.27 (m, 1 H). ^{13}C NMR (126MHz, *CHLOROFORM-d*) δ ppm 163.3, 152.5, 150.0, 147.9, 138.8, 137.3, 134.7, 129.3, 128.9, 128.7, 126.0, 125.1, 122.1, 119.3, 54.0, 48.2, 38.9, 34.3, 32.5, 32.0, 24.6, 21.3. HRMS (EI): m/z Calcd for $[\text{M}+\text{H}]$ $\text{C}_{22}\text{H}_{26}\text{N}_4\text{O}$: 376.2132; Found: 376.2130.

***N*-(2-(p-tolylethynyl)cyclohexyl)picolinamide (4e)**



^1H NMR (500MHz, *CHLOROFORM-d*) δ ppm 8.45 (d, $J = 4.2$ Hz, 1 H), 8.20 (d, $J = 7.6$ Hz, 1 H), 8.15 - 8.03 (m, 1 H), 7.83 (dt, $J = 1.5, 7.6$ Hz, 1 H), 7.47 - 7.32 (m, 1 H), 7.32 - 7.21 (m, 2 H), 7.08 (d, $J = 8.0$ Hz, 2 H), 4.13 - 3.95 (m, 1 H), 2.78 - 2.62 (m, 1 H), 2.42 - 2.28 (m, 4 H), 2.07 - 1.96 (m, 2 H), 1.90 (dd, $J = 3.8, 9.9$ Hz, 1 H), 1.59 - 1.42 (m, 3 H), 1.42 - 1.30 (m, 1 H). ^{13}C NMR (126MHz, *CHLOROFORM-d*) δ ppm 163.4, 150.0, 147.9, 137.5, 137.2, 131.4, 128.9, 126.0, 122.2, 120.7, 92.2, 77.3, 76.7, 47.3, 38.7, 32.2, 32.1, 28.9, 23.7, 21.4. HRMS (EI): m/z Calcd for $[\text{M}+\text{H}]$ $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}$: 319.1805; Found: 319.1805.

6. References

- S1. Nadres, E. T. F.; Santos, G. I.; Shabashov, D.; Daugulis, O. *J. Org. Chem.* **2013**, 78, 9689-9714.
- S2. Zhang S. Y.; He G., Nack W.A.; Zhao Y.; Li Q.; Chen G., *J. Am. Chem. Soc.* **2013**, 135, 2124-2127.
- S3. Xu J. W.; Zhang Z. Z.; Rao W. H.; Shi B. F., *J. Am. Chem. Soc.* **2016**, 138, 10750-10753.
- S4. Jiang M. X.-W.; Rawat M.; Wulff W. D., *J. Am. Chem. Soc.* **2004**, 126, 5970-5971.
- S5. Gajbhiye, J.M.; More N. A., Patil M. D.; Ummanni R.; Kotapalli S. S.; Yogeeswari P.; Sriram D.; Masand V. H., *Med Chem Res*, **2015**, 24, 2960–2971.

7. Spectra

