Electronic Supporting Information

Discovery of novel picolinamide-based derivatives as novel VEGFR-2 kinase inhibitors: Synthesis, in vitro biological evaluation and molecular docking

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Contents

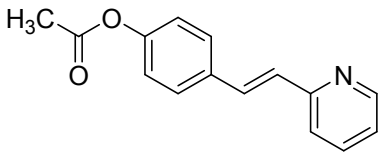
1. General

All the material were purchased from commercial suppliers and used without further purification. All of the solvents were reagent grade and, when necessary, were purified and dried using standard methods. Flash chromatography was performed using silica gel (200-300 mesh). Reactions were monitored by thin layer chromatography on 0.25 mm silica gel plates (60GF-254) and visualized with UV light. The melting points were determined on an electrothermal melting point apparatus and uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were determined on a Bruker ARX-400 MHz spectrometer using TMS as an internal standard in DMSO-d_6 or $CDCl_3$ solutions. Chemical shifts were reported in delta (d) units, parts per million (ppm) downfield from trimethylsilane. High-resolution mass spectra (HRMS) were determined on an Agilent G3250AA LC/MSD TOF mass spectrometer and reported as m/z (relative intensity). The single crystal X-ray diffraction was determined on a Rigaku RAXIS RAPID IP CCD area-detector diffractometer.

2. General procedure for the synthesis of 3a-3b

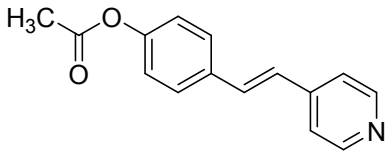
A mixture of picoline **1a-1b** (100 mmol), 4-hydroxybenzaldehyde **2** (12.21 g, 100 mmol), acetic anhydride (20.42 g, 200 mmol) and acetic acid (1.20 g, 20 mmol) in a round bottomed flask equipped with an anhydrous $CaCl_2$ drying tube was heated under reflux for 24 h. Volatile solvent was distilled out and the reaction residue was cooled. The residue was dissolved in CH_2Cl_2 (80 mL), washed with 20% $NaHCO_3$ aqueous solution (80 mL) and distilled water (50 mL×2), respectively. The separated organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated by a rotary evaporator. The crude product was dissolved in hot EtOH and crystallized to afford **3a-3b**.

4-(2-(2-Pyridinyl)ethenyl)phenyl acetate (3a)



White solid (yield 75%), mp: 109.5-110.4 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 4.5 Hz, 1H), 7.69-7.59 (m, 4H), 7.38 (d, *J* = 7.4 Hz, 1H), 7.18-7.11 (m, 4H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.36, 155.42, 150.60, 149.66, 136.57, 134.45, 131.67, 128.11, 128.07, 122.18, 122.13, 121.87, 21.15; HRMS (ESI) m/z: calcd for $C_{15}H_{14}NO_2$ $[M+H]^+$ 240.1019, found 240.1022.

4-(2-(4-Pyridinyl)ethenyl)phenyl acetate (3b)

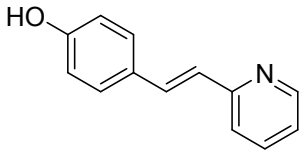


Yellow solid (yield 72%), mp: 160.8-161.5 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (d, *J* = 5.2 Hz, 2H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.58-7.53 (m, 3H), 7.27-7.15 (m, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.57, 151.08, 150.49, 144.63, 134.31, 132.49, 128.56, 126.54, 122.72, 121.31, 21.33; HRMS (ESI) m/z: calcd for $C_{15}H_{14}NO_2$ $[M+H]^+$ 240.1019, found 240.1020.

3. General procedure for the synthesis of 4a-4b

To a solution of **3a-3b** (11.95 g, 50 mmol) in ethanol (80 mL) was added a 2M KOH aqueous solution (12 mL). The mixture was refluxed for 12 h. To the solution was added 1M HCl solution to acidify to pH 5-6. The precipitate was filtered off and recrystallized from ethanol to obtain **4a-4b**.

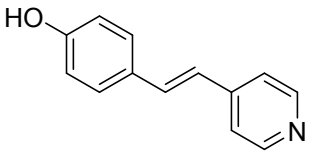
4-(2-(2-Pyridinyl)ethenyl)phenol (4a)



White solid (yield 92%), mp: 217.0-217.7 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.73 (s, 1H), 8.53 (d, *J* = 4.5 Hz, 1H), 7.76-7.71 (m, 1H), 7.58 (d, *J* = 16.1 Hz, 1H), 7.50-7.46 (m, 3H), 7.21-7.17 (m, 1H), 7.08 (d, *J* = 16.1 Hz, 1H), 6.80 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.41, 155.95, 149.81, 137.13, 132.56, 129.04,

127.86, 125.19, 122.25, 122.19, 116.10; HRMS (ESI) m/z: calcd for $C_{13}H_{12}NO$ $[M+H]^+$ 198.0913, found 198.0815.

4-(2-(4-Pyridinyl)ethenyl)phenol (4b)



Yellow solid (yield 94%), mp: 263.5-264.6 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (s, 1H), 8.50 (d, J = 5.1 Hz, 2H), 7.50-7.48 (m, 4H), 7.43 (d, J = 16.4 Hz, 1H), 7.00 (d, J = 16.4 Hz, 1H), 6.81 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.68, 150.34, 145.26, 133.51, 129.12, 127.65, 122.91, 120.94, 116.14; HRMS (ESI) m/z: calcd for $C_{13}H_{12}NO$ $[M+H]^+$ 198.0913, found 198.0818.

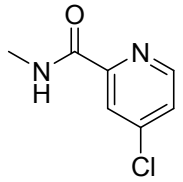
4-Chloropicolinoyl chloride (6)

Anhydrous DMF (0.1 mL) was added to thionyl chloride (100 mL) at 50 ºC under nitrogen. The solution was stirred at 50 ºC for 10 min prior to portionwise addition of picolinic acid **5** (36.93 g, 300 mmol) over 30 min. The solution was heated to reflux for 17 h. The mixture was then cooled to room temperature, diluted with toluene (100 mL), and concentrated under reduced pressure. This process was repeated two additional times to afford **6** as a brown oil that was used in the next step without further purification.

4. General procedure for the synthesis of 7a-7k

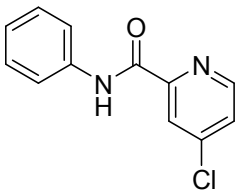
4-Chloropicolinoyl chloride **6** (1.75 g, 10 mmol) was dissolved in dichloromethane (15 mL) and this solution was added dropwise over 30 min to a solution of amine (12 mmol) in dichloromethane (15 mL) held at 0 ºC. After completion of the addition, the reaction mixture was allowed to warm to room temperature and stirring was continued for a further 3 h. The solution was washed with brine (40 mL×2) and the organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by chromatography (ethyl acetate/petroleum ether) on silica gel to afford **7a-7k**.

4-Chloro-*N*-methylpicolinamide (7a)



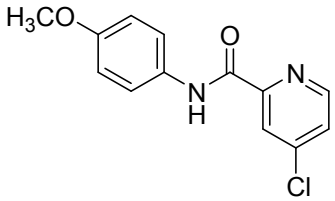
Yellow solid (yield 81%), mp: 41.2-42.0 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 5.2 Hz, 1H), 8.17 (d, *J* = 2.0 Hz, 1H), 7.98 (s, 1H), 7.39 (dd, *J* = 5.2, 2.0 Hz, 1H), 3.01 (d, *J* = 5.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.73, 151.39, 148.94, 145.76, 126.17, 122.67, 26.17; HRMS (ESI) m/z: calcd for $C_7H_8ClN_2O$ $[M+H]^+$ 171.0320, found 171.0323.

4-Chloro-*N*-phenylpicolinamide (7b)



White solid (yield 78%), mp: 79.9-80.6 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 8.54 (d, *J* = 5.2 Hz, 1H), 8.32 (d, *J* = 2.0 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 2H), 7.51 (dd, *J* = 5.2, 2.0 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 2H), 7.19 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.73, 151.31, 148.82, 146.32, 137.42, 129.14, 126.63, 124.61, 123.09, 119.74; HRMS (ESI) m/z: calcd for $C_{12}H_{10}ClN_2O$ $[M+H]^+$ 233.0476, found 233.0479.

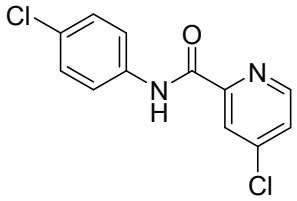
4-Chloro-*N*-(4-methoxyphenyl)picolinamide (7c)



Yellow solid (yield 71%), mp: 84.5-85.2 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 8.52 (d, *J* = 5.2 Hz, 1H), 8.31 (d, *J* = 2.0 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.49 (dd, *J* = 5.3, 2.0 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz,

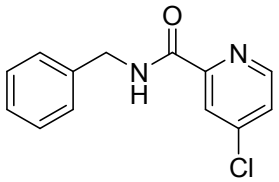
$CDCl_3$) δ 160.48, 156.60, 151.52, 148.80, 146.22, 130.69, 126.44, 122.95, 121.30, 114.30, 55.50; HRMS (ESI) m/z: calcd for $C_{13}H_{12}ClN_2O_2$ $[M+H]^+$ 263.0582, found 263.0585.

4-Chloro-*N*-(4-chlorophenyl)picolinamide (7d)



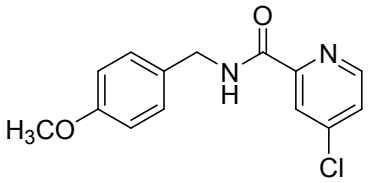
White solid (yield 75%), mp: 137.4-138.1 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 8.53 (d, *J* = 5.2 Hz, 1H), 8.30 (d, *J* = 2.0 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.51 (dd, *J* = 5.2, 2.0 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.76, 151.03, 148.86, 146.37, 136.03, 129.58, 129.15, 126.75, 123.08, 120.93; HRMS (ESI) m/z: calcd for $C_{12}H_9Cl_2N_2O$ $[M+H]^+$ 267.0086, found 267.0088.

***N*-Benzyl-4-chloropicolinamide (7e)**



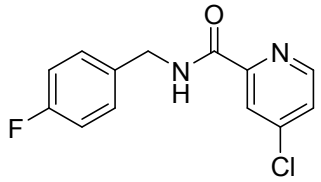
Yellow solid (yield 71%), mp: 70.2-71.0 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 5.2 Hz, 1H), 8.32 (s, 1H), 8.27 (d, *J* = 2.1 Hz, 1H), 7.45 (dd, *J* = 5.2, 2.1 Hz, 1H), 7.38-7.30 (m, 5H), 4.69 (d, *J* = 6.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.06, 151.29, 148.98, 145.91, 137.91, 128.75, 127.85, 127.59, 126.37, 123.03, 43.62; HRMS (ESI) m/z: calcd for $C_{13}H_{12}ClN_2O$ $[M+H]^+$ 247.0633, found 247.0632.

4-Chloro-*N*-(4-methoxybenzyl)picolinamide (7f)



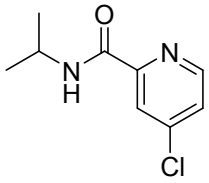
Yellow solid (yield 74%), mp: 54.4-55.0 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 5.2 Hz, 1H), 8.26-8.23 (m, 2H), 7.41 (dd, *J* = 5.2, 1.8 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 4.60 (d, *J* = 6.0 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.93, 159.08, 151.36, 148.95, 145.85, 130.03, 129.22, 126.30, 122.96, 114.11, 55.29, 43.09; HRMS (ESI) m/z: calcd for $C_{14}H_{14}ClN_2O_2$ $[M+H]^+$ 277.0738, found 277.0740.

4-Chloro-*N*-(4-fluorobenzyl)picolinamide (7g)



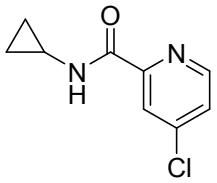
Yellow solid (yield 75%), mp: 78.6-79.2 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 5.3 Hz, 1H), 8.29-8.25 (m, 2H), 7.46 (dd, *J* = 5.3, 1.9 Hz, 1H), 7.36-7.33 (m, 2H), 7.07-7.03 (m, 2H), 4.65 (d, *J* = 6.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.48, 163.07, 151.22, 148.98, 145.97, 133.47, 129.55, 129.47, 126.42, 123.04, 115.69, 115.47, 42.89; HRMS (ESI) m/z: calcd for $C_{13}H_{11}ClFN_2O$ $[M+H]^+$ 265.0538, found 265.0539.

4-Chloro-*N*-isopropylpicolinamide (7h)



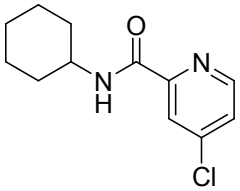
Yellow solid (yield 72%), mp: 41.3-42.2 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 5.2 Hz, 1H), 8.19 (d, *J* = 2.2 Hz, 1H), 7.80 (s, 1H), 7.41 (dd, *J* = 5.2, 2.2 Hz, 1H), 4.30-4.22 (m, 1H), 1.28 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.14, 151.66, 148.82, 145.81, 126.11, 122.78, 41.54, 22.70; HRMS (ESI) m/z: calcd for $C_9H_{12}ClN_2O$ $[M+H]^+$ 199.0633, found 199.0636.

4-Chloro-*N*-cyclopropylpicolinamide (7i)



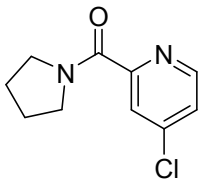
Yellow solid (yield 76%), mp: 100.2-101.0 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 5.2 Hz, 1H), 8.19 (d, *J* = 2.1 Hz, 1H), 7.98 (s, 1H), 7.42 (dd, *J* = 5.2, 2.1 Hz, 1H), 2.96-2.91 (m, 1H), 0.88 (td, *J* = 7.1, 5.1 Hz, 2H), 0.66 (td, *J* = 7.1, 5.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.40, 151.26, 148.85, 145.87, 126.30, 122.63, 22.60, 6.56; HRMS (ESI) m/z: calcd for $C_9H_{10}ClN_2O$ $[M+H]^+$ 197.0476, found 197.0477.

4-Chloro-*N*-cyclohexylpicolinamide (7j)



Pink solid (yield 72%), mp: 116.6-117.3 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 5.2 Hz, 1H), 8.20 (d, *J* = 2.1 Hz, 1H), 7.87 (s, 1H), 7.41 (dd, *J* = 5.2, 2.1 Hz, 1H), 4.00-3.92 (m, 1H), 2.03-1.98 (m, 2H), 1.78-1.74 (m, 2H), 1.68-1.63 (m, 1H), 1.48-1.38 (m, 2H), 1.36-1.22 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.04, 151.75, 148.82, 145.80, 126.08, 122.82, 48.30, 32.98, 25.55, 24.81; HRMS (ESI) m/z: calcd for $C_{12}H_{16}ClN_2O$ $[M+H]^+$ 239.0946, found 239.0949.

4-Chloro-2-(pyrrolidin-1-yl-carbonyl)pyridine (7k)

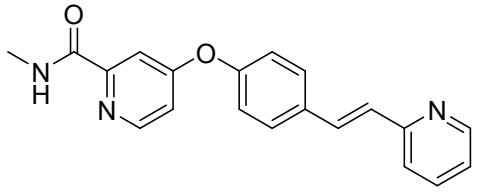


Brown oil (yield 71%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 5.2 Hz, 1H), 7.84 (s, 1H), 7.32 (d, *J* = 5.2 Hz, 1H), 3.68 (dt, *J* = 28.1, 6.4 Hz, 4H), 1.90 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.00, 155.73, 148.86, 144.96, 124.92, 124.47, 49.05, 47.01, 26.58, 23.94; HRMS (ESI) m/z: calcd for $C_{10}H_{12}ClN_2O$ $[M+H]^+$ 211.0633, found 211.0637.

5. General procedure for the synthesis of 8a-8v

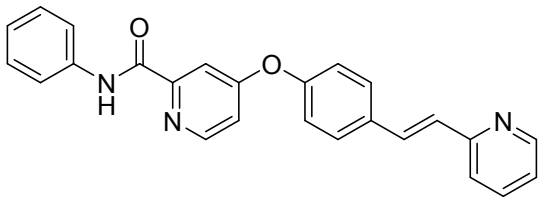
A mixture of **4a-4b** (1 mmol) and **7a-7k** (1 mmol) were suspended in DMF (5 ml), then copper powder (6.4 mg, 0.1 mmol) and cesium carbonate (815 mg, 2.5 mmol) were added. The reaction mixture was held at 110 ºC under nitrogen for 6 h, and then diluted with ethyl acetate (30 ml). The organic layer was washed with brine (25 mL×3), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by chromatography (ethyl acetate/petroleum ether) on silica gel to afford **8a-8v**.

***N*-Methyl-4-(4-(2-(2-pyridinyl)ethenyl)phenoxy)picolinamide (8a)**



Brown solid (yield 64%), mp: 79.0-79.6 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 4.1 Hz, 1H), 8.40 (d, *J* = 5.5 Hz, 1H), 8.03 (s, 1H), 7.77 (d, *J* = 2.5 Hz, 1H), 7.70-7.62 (m, 4H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.19-7.09 (m, 4H), 6.99 (dd, *J* = 5.5, 2.5 Hz, 1H), 3.02 (d, *J* = 5.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.96, 164.47, 155.33, 153.78, 152.37, 149.75, 149.64, 136.63, 134.30, 131.47, 128.93, 128.19, 122.25, 122.20, 120.99, 114.34, 110.52, 26.13; HRMS (ESI) m/z: calcd for $C_{20}H_{18}N_3O_2$ $[M+H]^+$ 332.1394, found 332.1396.

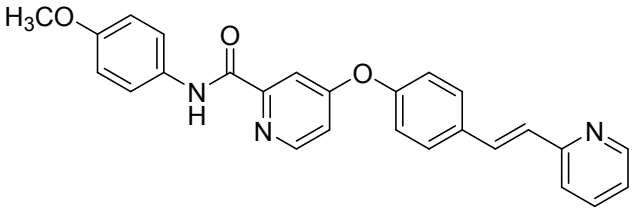
***N*-Phenyl-4-(4-(2-(2-pyridinyl)ethenyl)phenoxy)picolinamide (8b)**



White solid (yield 69%), mp: 167.2-167.9 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 8.65 (d, *J* = 4.2 Hz, 1H), 8.49 (d, *J* = 5.2 Hz, 1H), 7.87 (d, *J* = 2.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.73-7.66 (m, 4H), 7.43-7.38 (m, 3H), 7.21-7.14 (m, 5H), 7.07 (dd, *J* = 5.2, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.32, 161.51, 155.33,

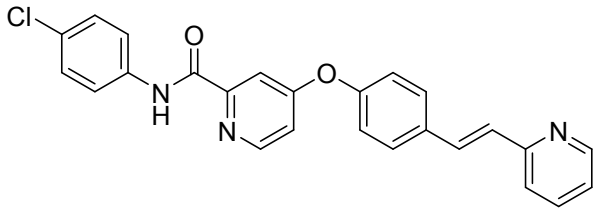
153.64, 152.22, 149.68, 149.67, 137.67, 136.65, 134.49, 131.42, 129.08, 129.00, 128.31, 124.35, 122.28, 122.24, 121.09, 119.62, 114.67, 110.65; HRMS (ESI) m/z: calcd for $C_{25}H_{20}N_3O_2$ $[M+H]^+$ 394.1550, found 394.1555.

***N*-(4-Methoxyphenyl)-4-(4-(2-(2-pyridinyl)ethenyl)phenoxy)picolinamide (8c)**



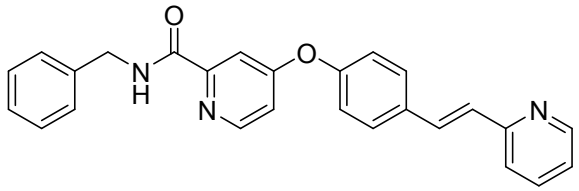
Yellow solid (yield 54%), mp: 168.8-169.5 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 8.63 (d, *J* = 4.0 Hz, 1H), 8.46 (d, *J* = 5.5 Hz, 1H), 7.85 (d, *J* = 2.5 Hz, 1H), 7.70-7.64 (m, 6H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.19-7.12 (m, 4H), 7.04 (dd, *J* = 5.5, 2.5 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.26, 161.22, 156.40, 155.31, 153.70, 152.39, 149.62, 136.67, 134.43, 131.49, 130.97, 130.90, 128.98, 128.83, 128.24, 122.25, 121.14, 121.06, 114.53, 114.23, 110.57, 55.47; HRMS (ESI) m/z: calcd for $C_{26}H_{22}N_3O_3$ $[M+H]^+$ 424.1656, found 424.1656.

***N*-(4-Chlorophenyl)-4-(4-(2-(2-pyridinyl)ethenyl)phenoxy)picolinamide (8d)**



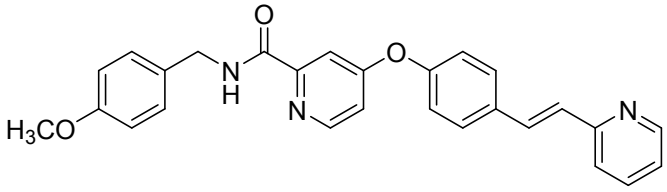
Yellow solid (yield 62%), mp: 218.3-219.1 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.64 (d, *J* = 3.8 Hz, 1H), 8.48 (d, *J* = 5.5 Hz, 1H), 7.85 (d, *J* = 2.5 Hz, 1H), 7.74-7.66 (m, 6H), 7.43-7.34 (m, 3H), 7.19-7.07 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.37, 161.53, 155.32, 153.60, 151.91, 149.67, 136.64, 136.27, 134.56, 131.42, 130.88, 129.29, 129.09, 129.00, 128.83, 128.36, 122.24, 121.06, 120.82, 114.78, 110.70; HRMS (ESI) m/z: calcd for $C_{25}H_{19}ClN_3O_2$ $[M+H]^+$ 428.1160, found 428.1161.

***N*-Benzyl-4-(4-(2-(2-pyridinyl)ethenyl)phenoxy)picolinamide (8e)**



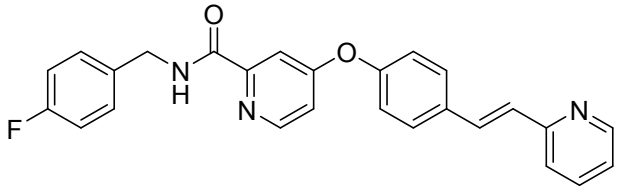
Yellow oil (yield 67%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 4.3 Hz, 1H), 8.41-8.37 (m, 2H), 7.80 (d, *J* = 2.3 Hz, 1H), 7.68-7.62 (m, 4H), 7.40-7.28 (m, 6H), 7.17-7.09 (m, 4H), 7.00 (dd, *J* = 5.4, 2.3 Hz, 1H), 4.64 (d, *J* = 6.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.99, 163.80, 155.34, 153.73, 152.23, 149.81, 149.67, 138.16, 136.61, 134.36, 131.43, 128.95, 128.68, 128.27, 127.83, 127.46, 122.25, 122.20, 121.02, 114.51, 110.69, 43.55; HRMS (ESI) m/z: calcd for $C_{26}H_{22}N_3O_2$ $[M+H]^+$ 408.1707, found 408.1709.

_N_-(4-Methoxybenzyl)-4-(4-(2-(2-pyridinyl)ethenyl)phenoxy)picolinamide (8f)



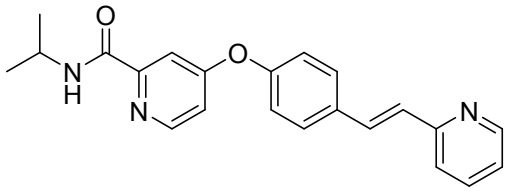
Yellow oil (yield 64%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.4 Hz, 1H), 8.36-8.33 (m, 2H), 7.78 (d, *J* = 2.4 Hz, 1H), 7.66-7.59 (m, 4H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.26 (d, *J* = 8.5 Hz, 2H), 7.14-7.06 (m, 4H), 6.96 (dd, *J* = 5.5, 2.4 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 2H), 4.55 (d, *J* = 6.0 Hz, 2H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.94, 163.68, 158.99, 155.31, 153.72, 152.30, 149.79, 149.63, 136.60, 134.32, 131.42, 130.27, 129.19, 128.93, 128.24, 122.24, 122.19, 120.99, 114.45, 114.06, 110.63, 55.25, 43.01; HRMS (ESI) m/z: calcd for $C_{27}H_{24}N_3O_3$ $[M+H]^+$ 438.1812, found 438.1815.

_N_-(4-Fluorobenzyl)-4-(4-(2-(2-pyridinyl)ethenyl)phenoxy)picolinamide (8g)



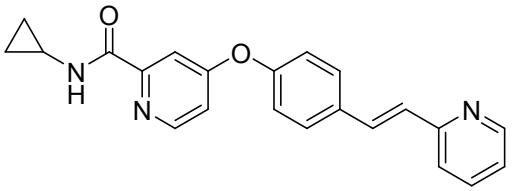
Yellow solid (yield 59%), mp: 135.9-136.4 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.3 Hz, 1H), 8.43-8.36 (m, 2H), 7.78 (d, *J* = 2.3 Hz, 1H), 7.67-7.60 (m, 4H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.32-7.28 (m, 2H), 7.16-7.07 (m, 4H), 7.02-6.98 (m, 3H), 4.59 (d, *J* = 6.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.02, 163.84, 163.37, 160.92, 155.31, 153.67, 152.08, 149.82, 149.64, 136.63, 134.37, 134.01, 133.97, 131.42, 129.53, 129.45, 128.94, 128.26, 122.24, 121.02, 115.58, 115.37, 114.55, 110.68, 42.80; HRMS (ESI) m/z: calcd for $C_{26}H_{21}FN_3O_2$ $[M+H]^+$ 426.1612, found 426.1616.

***N*-Isopropyl-4-(4-(2-(2-pyridinyl)ethenyl)phenoxy)picolinamide (8h)**



Yellow oil (yield 60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 4.1 Hz, 1H), 8.39 (d, *J* = 5.5 Hz, 1H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.76 (d, *J* = 2.3 Hz, 1H), 7.68-7.61 (m, 4H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.16-7.08 (m, 4H), 6.98 (dd, *J* = 5.5, 2.3 Hz, 1H), 4.28-4.20 (m, 1H), 1.27 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.97, 162.87, 155.37, 153.78, 152.63, 149.68, 149.64, 136.54, 134.31, 131.42, 128.90, 128.25, 122.20, 122.15, 120.97, 114.32, 110.50, 41.43, 22.70; HRMS (ESI) m/z: calcd for $C_{22}H_{22}N_3O_2$ $[M+H]^+$ 360.1707, found 360.1711.

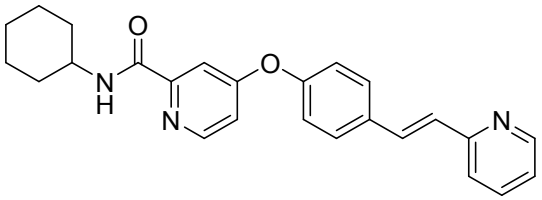
***N*-Cyclopropyl-4-(4-(2-(2-pyridinyl)ethenyl)phenoxy)picolinamide (8i)**



White solid (yield 68%), mp: 155.4-156.0 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (d, *J* = 4.9 Hz, 1H), 8.58 (d, *J* = 4.1 Hz, 1H), 8.48 (d, *J* = 5.6 Hz, 1H), 7.77-7.70 (m, 4H), 7.52-7.50 (m, 2H), 7.31-7.18 (m, 4H), 7.14 (dd, *J* = 5.6, 2.5 Hz, 1H), 2.93-2.86 (m, 1H), 0.67 (d, *J* = 5.7 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.70, 164.96, 155.31, 153.72, 152.86, 150.77, 149.92, 137.14, 134.55, 131.34, 129.51, 128.85,

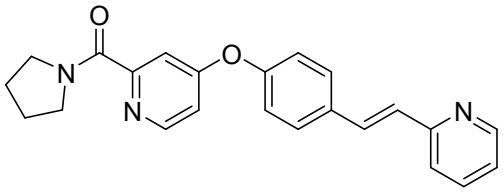
122.85, 122.81, 121.48, 114.87, 109.76, 23.36, 6.26; HRMS (ESI) m/z: calcd for $C_{22}H_{20}N_3O_2$ $[M+H]^+$ 358.1550, found 358.1552.

***N*-Cyclohexyl-4-(4-(2-(2-pyridinyl)ethenyl)phenoxy)picolinamide (8j)**



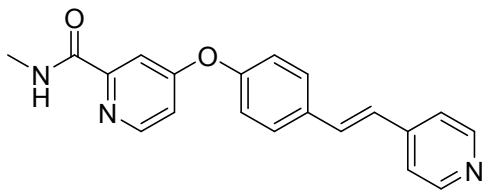
White solid (yield 63%), mp: 132.7-133.5 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (d, J = 3.1 Hz, 1H), 8.52 (d, J = 5.6 Hz, 1H), 8.42 (d, J = 8.5 Hz, 1H), 7.78-7.70 (m, 4H), 7.54-7.48 (m, 2H), 1H), 7.33-7.16 (m, 5H), 3.77-3.73 (m, 1H), 1.78-1.52 (m, 5H), 1.41-1.06 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.79, 162.54, 155.32, 153.75, 153.01, 150.82, 149.93, 137.20, 134.57, 131.33, 129.53, 128.87, 122.87, 122.84, 121.51, 114.92, 109.88, 48.44, 32.58, 25.52, 25.17; HRMS (ESI) m/z: calcd for $C_{25}H_{26}N_3O_2$ $[M+H]^+$ 400.2020, found 400.2021.

4-(4-(2-(2-Pyridinyl)ethenyl)phenoxy)-2-(pyrrolidin-1-yl-carbonyl)pyridine (8k)



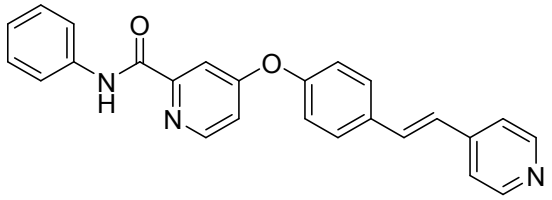
Yellow solid (yield 65%), mp: 132.9-133.8 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (d, J = 4.7 Hz, 1H), 8.50 (d, J = 5.7 Hz, 1H), 7.80-7.70 (m, 4H), 7.54 (d, J = 7.8 Hz, 1H), 7.33-7.18 (m, 5H), 7.08 (dd, J = 5.7, 2.5 Hz, 1H), 3.59 (t, J = 6.6 Hz, 2H), 3.47 (t, J = 6.6 Hz, 2H), 1.81 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.34, 165.12, 156.93, 155.32, 153.73, 150.68, 149.95, 137.27, 134.52, 131.34, 129.55, 128.84, 122.90, 121.59, 113.63, 111.43, 48.91, 46.88, 26.49, 23.93; HRMS (ESI) m/z: calcd for $C_{23}H_{22}N_3O_2$ $[M+H]^+$ 372.1707, found 372.1710.

***N*-Methyl-4-(4-(2-(4-pyridinyl)ethenyl)phenoxy)picolinamide (8l)**



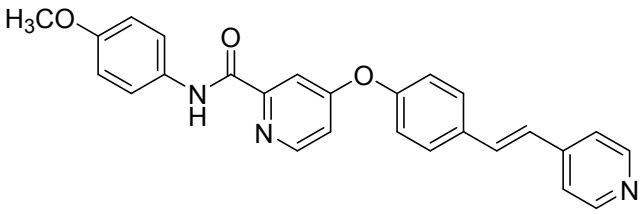
Yellow solid (yield 64%), mp: 210.2-211.0 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (d, J = 4.6 Hz, 1H), 8.59-8.53 (m, 3H), 7.80 (d, J = 8.5 Hz, 2H), 7.62-6.57 (m, 3H), 7.45 (d, J = 2.2 Hz, 1H), 7.30-7.25 (m, 3H), 7.20 (dd, J = 5.5, 2.2 Hz, 1H), 2.80 (d, J = 4.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.72, 164.18, 153.97, 153.02, 150.99, 150.49, 144.63, 134.39, 132.36, 129.64, 126.79, 121.68, 121.40, 114.93, 109.71, 26.48; HRMS (ESI) m/z: calcd for $C_{20}H_{18}N_3O_2$ $[M+H]^+$ 332.1394, found 332.1398.

***N*-Phenyl-4-(4-(2-(4-pyridinyl)ethenyl)phenoxy)picolinamide (8m)**



Yellow solid (yield 68%), mp: 214.4-215.2 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1H), 8.62-8.50 (m, 3H), 7.84-7.77 (m, 3H), 7.63 (d, J = 8.0 Hz, 2H), 7.41-7.28 (m, 5H), 7.17-7.00 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.21, 161.46, 153.98, 152.27, 150.18, 149.70, 144.43, 137.64, 133.95, 131.88, 129.09, 128.96, 126.49, 124.39, 121.21, 120.90, 119.61, 114.83, 110.49; HRMS (ESI) m/z: calcd for $C_{25}H_{20}N_3O_2$ $[M+H]^+$ 394.1550, found 394.1553.

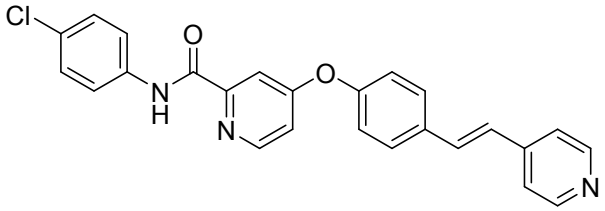
***N*-(4-Methoxyphenyl)-4-(4-(2-(4-pyridinyl)ethenyl)phenoxy)picolinamide (8n)**



Yellow solid (yield 62%), mp: 192.0-192.7 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H), 8.64-8.63 (m, 3H), 7.83-7.78 (m, 4H), 7.64-7.56 (m, 4H), 7.32-7.27 (m,

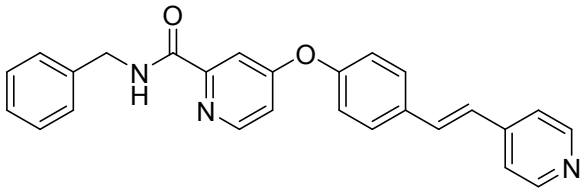
4H), 6.92 (d, J = 8.8 Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.97, 161.86, 159.93, 156.25, 153.95, 153.00, 150.98, 150.46, 134.48, 132.35, 131.78, 129.67, 126.87, 122.23, 121.71, 115.41, 115.31, 114.28, 110.18, 55.66; HRMS (ESI) m/z: calcd for $C_{26}H_{22}N_3O_3$ $[M+H]^+$ 424.1656, found 424.1659.

***N*-(4-Chlorophenyl)-4-(4-(2-(4-pyridinyl)ethenyl)phenoxy)picolinamide (8o)**



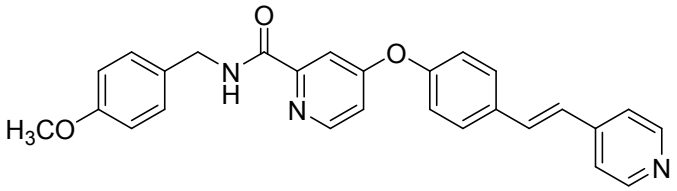
Yellow solid (yield 70%), mp: 221.6-222.2 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 8.64-8.49 (m, 3H), 7.82 (d, J = 2.5 Hz, 1H), 7.74-7.62 (m, 4H), 7.41-7.31 (m, 5H), 7.17-7.00 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.25, 161.49, 153.94, 151.97, 150.11, 149.72, 144.43, 136.24, 134.02, 131.87, 129.35, 129.11, 128.96, 128.83, 126.55, 121.18, 120.81, 114.93, 110.55; HRMS (ESI) m/z: calcd for $C_{25}H_{19}ClN_3O_2$ $[M+H]^+$ 428.1160, found 428.1164.

***N*- Benzyl-4-(4-(2-(4-pyridinyl)ethenyl)phenoxy)picolinamide (8p)**



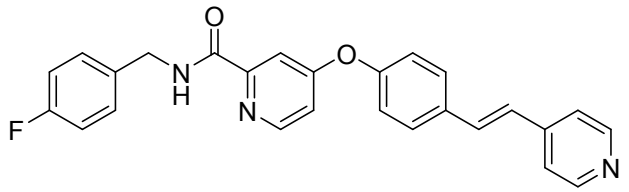
Yellow solid (yield 58%), mp: 118.6-119.2 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 5.9 Hz, 2H), 8.42-8.39 (m, 2H), 7.78 (d, J = 2.5 Hz, 1H), 7.61 (d, J = 8.6 Hz, 2H), 7.40-7.30 (m, 8H), 7.14 (d, J = 8.6 Hz, 2H), 7.05-6.99 (m, 2H), 4.66 (d, J = 6.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.91, 163.74, 154.10, 152.29, 150.19, 149.83, 144.42, 138.11, 133.84, 131.90, 128.91, 128.69, 127.84, 127.49, 126.43, 121.14, 120.86, 114.67, 110.56, 43.58; HRMS (ESI) m/z: calcd for $C_{26}H_{22}N_3O_2$ $[M+H]^+$ 408.1707, found 408.1711.

***N*-(4-Methoxybenzyl)-4-(4-(2-(4-pyridinyl)ethenyl)phenoxy)picolinamide (8q)**



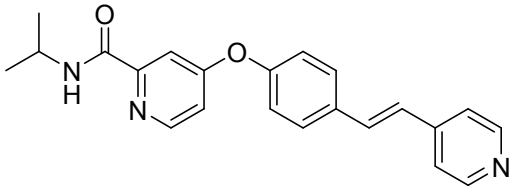
Yellow solid (yield 60%), mp: 134.0-134.8 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 5.4 Hz, 2H), 8.39-8.32 (m, 2H), 7.77 (d, *J* = 2.2 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 5.6 Hz, 2H), 7.32-7.27 (m, 3H), 7.11 (d, *J* = 8.5 Hz, 2H), 7.02-6.96 (m, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 4.57 (d, *J* = 6.0 Hz, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.86, 163.63, 159.02, 154.08, 152.34, 150.15, 149.82, 144.43, 133.79, 131.90, 130.23, 129.20, 128.91, 126.37, 121.12, 120.88, 114.62, 114.08, 110.51, 55.28, 43.04; HRMS (ESI) m/z: calcd for $C_{27}H_{24}N_3O_3$ $[M+H]^+$ 438.1812, found 438.1811.

_N_-(4-Fluorobenzyl)-4-(4-(2-(4-pyridinyl)ethenyl)phenoxy)picolinamide (8r)



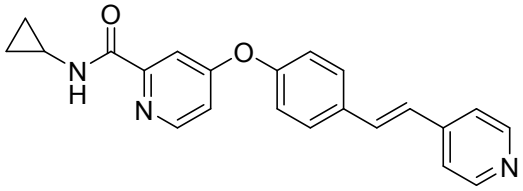
White solid (yield 67%), mp: 95.5-96.2 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 5.0 Hz, 2H), 8.42-8.39 (m, 2H), 7.77 (d, *J* = 2.3 Hz, 1H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 5.1 Hz, 2H), 7.35-7.30 (m, 3H), 7.13 (d, *J* = 8.5 Hz, 2H), 7.05-6.99 (m, 4H), 4.61 (d, *J* = 6.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.94, 163.77, 163.41, 154.04, 152.15, 150.18, 149.85, 144.42, 133.97, 133.93, 133.86, 131.88, 129.55, 129.46, 128.92, 126.44, 121.15, 120.88, 115.62, 115.41, 114.73, 110.54, 42.84; HRMS (ESI) m/z: calcd for $C_{26}H_{21}FN_3O_2$ $[M+H]^+$ 426.1612, found 426.1613.

_N_-Isopropyl-4-(4-(2-(4-pyridinyl)ethenyl)phenoxy)picolinamide (8s)



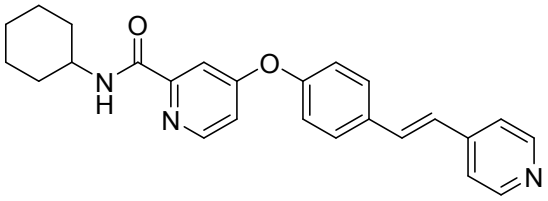
Yellow solid (yield 60%), mp: 174.7-175.5 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66-8.40 (m, 3H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.73 (d, *J* = 2.1 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.39-7.27 (m, 3H), 7.10 (d, *J* = 8.5 Hz, 2H), 7.01-6.95 (m, 2H), 4.26-4.21 (m, 1H), 1.27 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.85, 162.82, 154.12, 152.68, 150.16, 149.68, 144.28, 133.78, 131.83, 128.86, 126.42, 121.08, 114.48, 110.36, 41.45, 22.69; HRMS (ESI) m/z: calcd for $C_{22}H_{22}N_3O_2$ $[M+H]^+$ 360.1707, found 360.1709.

***N*-Cyclopropyl-4-(4-(2-(4-pyridinyl)ethenyl)phenoxy)picolinamide (8t)**



Green solid (yield 59%), mp: 209.9-210.8 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58-8.37 (m, 3H), 8.03 (d, *J* = 3.9 Hz, 1H), 7.73 (d, *J* = 2.5 Hz, 1H), 7.59-7.57 (m, 3H), 7.33-7.28 (m, 2H), 7.10 (d, *J* = 7.9 Hz, 2H), 7.00-6.94 (m, 2H), 2.93-2.89 (m, 1H), 0.85 (d, *J* = 3.5 Hz, 2H), 0.64 (d, *J* = 3.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.81, 165.08, 154.07, 152.30, 149.71, 149.44, 143.94, 133.84, 131.72, 128.83, 126.60, 121.07, 114.57, 110.29, 23.39, 6.29; HRMS (ESI) m/z: calcd for $C_{22}H_{20}N_3O_2$ $[M+H]^+$ 358.1550, found 358.1554.

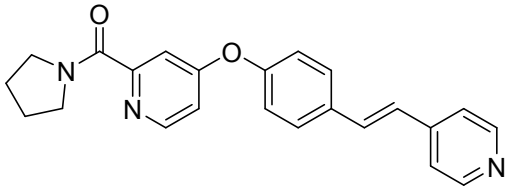
***N*-Cyclohexyl-4-(4-(2-(4-pyridinyl)ethenyl)phenoxy)picolinamide (8u)**



White solid (yield 65%), mp: 160.3-161.3 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56-8.52 (m, 3H), 8.42 (d, *J* = 8.5 Hz, 1H), 7.77 (d, *J* = 7.4 Hz, 2H), 7.59-7.54 (m, 3H), 7.47 (d, *J* = 2.5 Hz, 1H), 7.26-7.18 (m, 4H), 3.78-3.71 (m, 1H), 1.79-1.53 (m, 5H), 1.42-1.09 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.74, 162.53, 154.00, 153.03, 150.86, 150.46, 144.62, 134.33, 132.32, 129.59, 126.75, 121.54, 121.31,

115.01, 109.90, 48.44, 32.57, 25.52, 25.17; HRMS (ESI) m/z: calcd for $C_{25}H_{26}N_3O_2$ $[M+H]^+$ 400.2020, found 400.2023.

4-(4-(2-(4-Pyridinyl)ethenyl)phenoxy)-2-(pyrrolidin-1-yl-carbonyl)pyridine (8v)



Yellow solid (yield 59%), mp: 184.6-185.3 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (d, J = 5.1 Hz, 2H), 8.50 (d, J = 5.6 Hz, 1H), 7.78 (d, J = 8.3 Hz, 2H), 7.60-7.55 (m, 3H), 7.27-7.23 (m, 3H), 7.17 (d, J = 2.5 Hz, 1H), 7.09 (dd, J = 5.6, 2.5 Hz, 1H), 3.60 (t, J = 6.7 Hz, 2H), 3.46 (t, J = 6.8 Hz, 2H), 1.83 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.36, 165.08, 156.95, 153.99, 150.73, 150.48, 144.66, 134.30, 132.38, 129.61, 126.72, 121.62, 121.34, 113.70, 111.45, 48.91, 46.87, 26.48, 23.94; HRMS (ESI) m/z: calcd for $C_{23}H_{22}N_3O_2$ $[M+H]^+$ 372.1707, found 372.1708.

6. Crystal X-ray diffraction for 8b and 8l

Crystals of **8b** and **8l** suitable for X-ray diffraction analysis were obtained by the slow evaporation of an ethyl acetate/dichloromethane solution of **8b** and **8l** at room temperature. The single crystal X-ray diffraction measurements were conducted on a Rigaku Saturn CCD area-detector diffractometer at 113 K using graphite monochromated MoKα radiation (λ = 0.71073 Å) in the ω and φ scanning mode. An empirical absorption correction was applied using the ABSCOR program. All structures were solved by direct methods using the SHELXS program and refined by full matrix least-squares on F^2 using the SHELXL program. All of the hydrogen atoms were geometrically fixed using the riding model. The crystallographic data of **8b** (CCDC number 1588889) and **8l** (CCDC number 1588886) were given in **Table 1**.

Table 1. Crystallographic data for **8b** and **8l**

Entry	**8b**	**8l**
Empirical formula	$C_{25}H_{19}N_3O_2$	$C_{20}H_{17}N_3O_2$
Formula weight	393.43	331.36

Temperature	113 K	113 K
Wavelength	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic
Unit cell dimensions	a = 5.4568 (7)	a = 9.949 (2)
	b = 7.5939 (5)	b = 15.604 (3)
	c = 45.622 (3)	c = 11.098 (2)
	α= 90	α= 90
	β= 90	β= 104.703 (4)
	γ= 90	γ= 90
Volume	1890.5 (3)	1666.5 (6)
Z	4	4
Calculated density	1.382 Mg m^{-3}	1.321 Mg m^{-3}
Absorption coefficient	0.090 mm^{-1}	0.087 mm^{-1}
F(000)	824.0	696.0
Crystal size	0.20×0.18×0.12 mm^{-3}	0.22×0.18×0.16 mm^{-3}
Data/restraints/parameters	3864/1/275	3778/0/230
Goodness-of-fit on F2	1.079	1.044
R indices (all data)	R_1=0.0298, wR_2=0.0743	R_1=0.0389, wR_2=0.1047

7. Biological evaluation

The antiproliferative activity was tested by CCK assay on A549 and HepG2 cell lines. The cell lines were obtained from Chinese Center for Disease Control and Prevention (Beijing, China). Briefly, cells were plated in 96-well plates at a concentration of 5×10^3 cells/well, and then incubated for 24 h in an atmosphere of 5% CO_2 at 37 °C. Compounds were respectively dissolved in DMSO to make stock solutions at a concentration of 2.0×10^{-3} mol/L, and then the cells were treated with the diluted stock solutions at various concentrations (50, 25, 12.5, 6.25, 3.125, 1.6525 and 0.78125 μM). After 48 h treatment, the old medium was discarded and washed by PBS, then 10% CCK-8 solution was added to each well and the cells were further incubated for 2 h at 37 °C and with 5% CO_2. Absorbance values were determined by a microplate reader (PerkinElmer, USA) at 450 nm. The IC_{50} values were calculated from a log plot of percent of control versus concentration.

The inhibitory activity of VEGFR-2 was measured by use of the ADP-Glo™ kinase assay. It measured inhibitory activity by quantitating the amount of ATP remaining in solution after a kinase reaction. The general procedure was as the

following: Kinase was incubated with substrate, ATP and variable concentrations of target compounds in a buffer containing 40 mM Tris, 10 mM $MgCl_2$, 0.1 mg/mL BSA, 1 mM DTT in a 384-well plate. The kinase reaction was allowed to proceed at 30 ˚C for 1 h, and then cooled for 5 min at room temperature. ADP-Glo reagent was added to stop the reaction and consumed the remaining ADP for 40 min, followed by another 30 min incubation with kinase detection reagent. The luminescence signal was measured by a VICTOR multilabel plate reader (PerkinElmer, USA). The signal was correlated with the amount of ATP present in the reaction and was inversely correlated with the kinase activity. The IC_{50} value was determined as the concentration causing half-maximal percent activity.

8. Molecular docking

Molecular docking was performed using AutoDock 4.2 that used the Lamarckian genetic algorithm (LGA) to explore the full range of ligand conformational flexibility with partial flexibility of the receptor. The crystal structure of VEGFR-2 in complex with Sorafenib (PDB code: 4ASD) was retrieved from the Brookhaven Protein Data Bank, and the crystal structure of VEGFR-2 was extracted from the PDB file. AutoDock Tool was used to assign polar hydrogens and Gasteiger charges. AutoGrid 4 was used to create affinity grid maps for all atom types. The docked conformations were generated using the LGA and the rest of the parameters were set to their default values. The model analysis was performed using the Discovery Studio 2016.