Support information for

Synthesis of Crizotinib Intermediate via Highly Efficient Catalytic Hydrogenation in Continuous-Flow

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Comparison of physical structure of catalyst

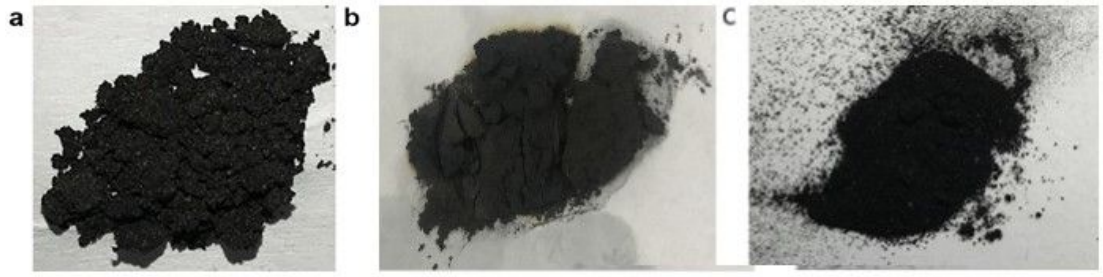


Figure S1. Comparison of catalyst before (a), using(b) and after (c) reaction

Synthesis of Crizotinib

(1) Synthesis of Crizotinib intermediate **III** (*R*)-5-bromo-3-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridine-2-amine

Solution A: 1.79 mmol (0.54 g) of Crizotinib intermediate **II** was dissolved with 6 mL of dichloromethane, stirred and cooled to 10 °C.

Solution B: 1.84 mmol (0.33 g) of NBS (*N*-bromosuccinimide) was dissolved in 1 mL of acetonitrile and cooled to 0 °C.

Solution B was added dropwise to solution A, and the reaction temperature was kept below 10 °C. After the addition of solution B, the reaction was stirred at 25 °C for 30 min, and monitored by TLC. The reaction mixture was added 1 mL of 0.32 mmol sodium thiosulfate solution and stirred for 60 min at 25 °C. The mixture was then separated, where the water was extracted with DCM (2×2 mL). The combined organic phase washed with water, then dried over $MgSO_4$, filtrated, and evaporated. The residue was washed with methanol affording a light yellow solid (0.54 g, 80% yield), m.p.: 102-103 °C(ref.[1], m.p.: 103 °C) ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm 7.66-7.55 (m, 2H), 7.50 (t, J = 8.6 Hz, 1H), 6.77 (d, J = 2.0 Hz, 1H), 6.03 (d, J = 5.8 Hz, 3H), 1.79 (d, J = 6.6 Hz, 3H). HR-MS [ESI]: $C_{13}H_{10}BrCl_2FN_2O$ for $[M+H]^+$, calcd. 380.9398, found 380.9398.

(2) Synthesis of Crizotinib intermediate **IV** tert-butyl(*R*)-4-(4-(6-amino-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridin-3-yl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate.

Crizotinib intermediate **III** (1.3 mmol, 0.50 g), tert-Butyl 4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl]piperidine-1-carboxylate (1.57 mmol, 0.59 g) and tetrabutylammonium bromide (0.012 mmol, 0.39 g), were dissolved in toluene. The resulting solution was added to a solution of cesium carbonate (4.31 mmol, 1.40 g) in

water (3.2 mL). After the replacing with nitrogen, $PdCl_2$(dppf) (0.012 mmol, 0.87 g) was added to the mixture, which was then heated to 80 and agitated for 6 h. The mixture was cooled to 25 °C, and the organic layer was separated, which was diluted with toluene. After the removal of solvent, the residue was recrystallized by *n*-heptane and toluene (1:1) rendering the product as a white solid(0.60 g, 75%), m.p.: 149-150 °C(ref.[1], m.p.: 150 °C) ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm 8.00 (s, 1H), 7.78 (d, J = 1.8 Hz, 1H), 7.64-7.53 (m, 2H), 7.47 (t, J = 8.8 Hz, 1H), 6.93 (d, J = 1.8 Hz, 1H), 6.11 (q, J = 6.6 Hz, 1H), 5.69 (s, 2H), 4.35 (ddd, J = 11.4, 7.4, 3.8 Hz, 1H), 4.06 (d, J = 13.2 Hz, 2H), 2.93 (s, 2H), 2.07-1.99 (m, 2H), 1.80 (dd, J = 17.4, 7.2 Hz, 5H), 1.45 (s, 9H). HR-MS [ESI]: $C_{26}H_{30}Cl_2FN_5O_3$ for $[M+H]^+$, calcd. 550.1791, found 550.1770.

(3) Synthesis of Crizotinib (*R*)-3-(1-(2, 6-dichloro-3-fluorophenyl)ethoxy)-5-(1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)pyridin-2-amine

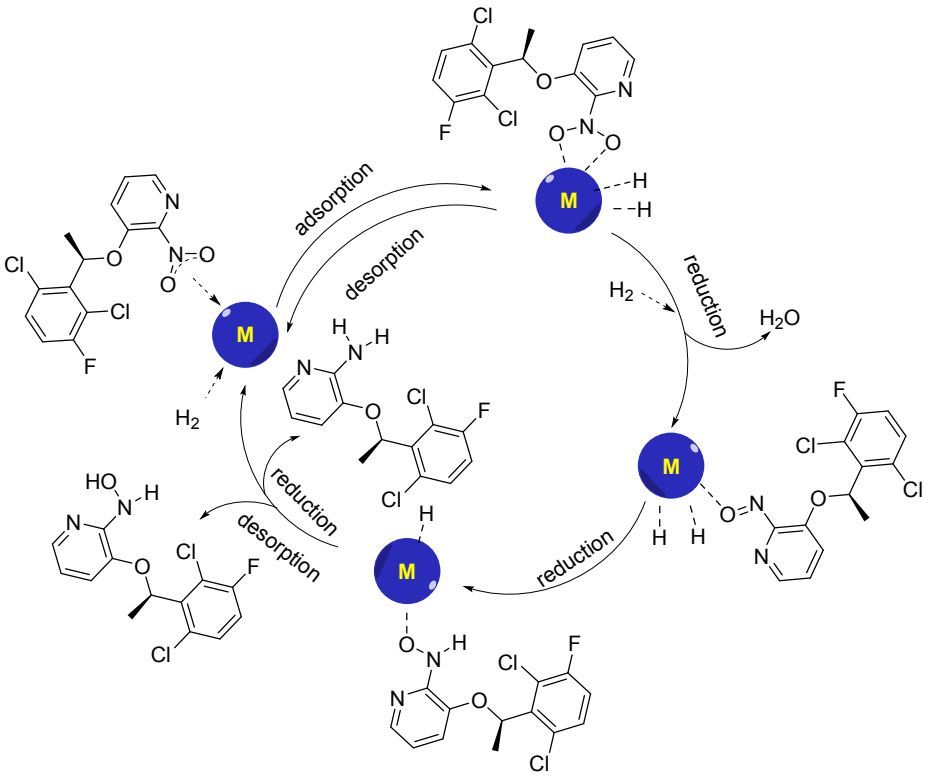
Crizotinib intermediate IV (1.13 mmol, 0.62 g) was dissolved in 5 mL DCM keeping between -5– 0 °C, which was then slowly add 16.9 mmol HCl of 1,4-dioxane solution. After the addition, the mixture was warmed to 25°Cand stirred for 4 h. After the reaction, the solid was filtered and dissolved in 10 mL water, and the pH was adjusted to 10 with sodium carbonate. The aqueous phase was extracted with DCM, and the organic phase was washed saturated aqueous $NaHCO_3$ and brine. The extract was dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. The solid was slurried with 2 mL of acetonitrile at 0 °C for 2 h, filtered and dried to give Crizotinib as a white solid (0.45 g, 88%), m.p.: 190-192 °C (ref.[1], m.p.: 192 °C) ^{1}H NMR (400 MHz, Chloroform-d) δ/ppm 7.80 (d, J = 1.8 Hz, 1H), 7.60 (s, 1H), 7.54 (s, 1H), 7.34 (dd, J = 8.8, 4.8 Hz, 1H), 7.08 (t, J = 8.4 Hz, 1H), 6.91 (d, J = 1.8 Hz, 1H), 6.11 (q, J = 6.8 Hz, 1H), 4.83 (s, 2H), 4.24 (ddd, J = 11.6, 7.6, 4.0 Hz, 1H), 3.29 (dt, J = 12.8, 3.4 Hz, 2H), 2.81 (td, J = 12.4, 2.4 Hz, 2H), 2.26-2.15 (m, 2H), 2.04-1.83 (m, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.01, 161.05, 154.63, 144.00, 142.05, 140.69, 140.63, 139.66, 139.59, 135.77, 133.96, 133.93, 128.45, 126.33, 126.18, 124.22, 122.67, 119.64, 77.18, 64.43, 50.33, 38.82, 23.82. HR-MS [ESI]: $C_{21}H_{22}Cl_2FN_5O$ for $[M+H]^+$, Calculated 450.1266, found 450.1278.

Validation of Mechanism

Through the confirmation of the intermediate molecular weight by LC-MS, we confirmed the reaction mechanism of the catalytic hydrogenation of Crizotinib intermediate I. The data as follows: 1). Retention time (RT) *of* (R)-(3-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridine-2-yl)hydroxylamine is 20.15 min and molecular weight is 315.7, with two isotopic peaks of chlorine, 317.7 and 318.7, respectively. 2). RT of (R)-3-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridine-2-amine is 22.78 min and molecular

weight is 299.9. 3). RT of (R)-3-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)-2-nitrosopyridine retention is 29.75 min and molecular weight is 313.8.

According to the mechanism reported by Horiuti Polanyi, the aromatic nitro compound is adsorbed on the surface of the metal catalyst, and the nitrogen-oxygen double bond of the nitro group is complexed with the metal, so that the nitrogen-oxygen double bond is pulled up, and the bond energy is weakened. At the same time, hydrogen molecules were also adsorbed on the surface of the catalyst, and bond cracks occurred on the surface of the catalyst, and active hydrogen atoms were obtained. The reactive hydrogen is inserted directly between the nitrogen-oxygen bonds, binding with the nitrogen to form the amino group, while losing a molecule of water to form a hydroxylamine-like compound with oxygen atoms complexing with the metal. The hydroxylamine compounds can be divided into two pathways to synthesize the corresponding aromatic hydroxylamine and aromatic amine compounds, and then the aromatic amine or aromatic hydroxylamine desorbs from the catalyst surface and leaves the catalyst surface to form the corresponding products (Scheme S1). If the aromatic hydroxylamine compound failed to desorb from the catalyst surface, it would be further reduced to the corresponding aromatic amines. If the aromatic amine compound could not be desorbed from the catalyst, the active site of the catalyst would be gradually covered and the catalyst slowly loses its activity.



Scheme S1. Conformed mechanism of catalytic hydrogenation of Crizotinib intermediate

Product characterization data：

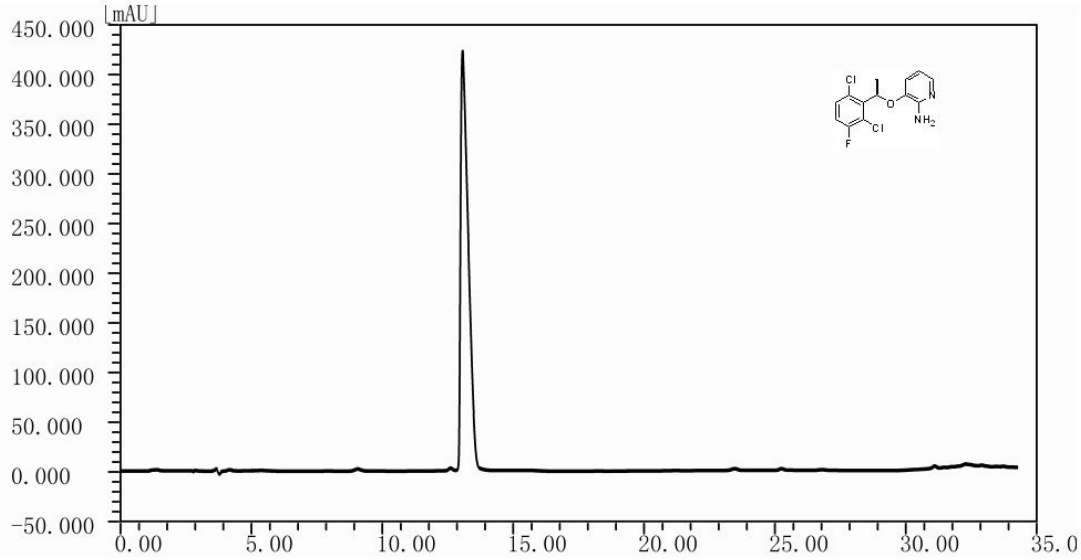


Figure S2. Purity of Crizotinib intermediate **II**

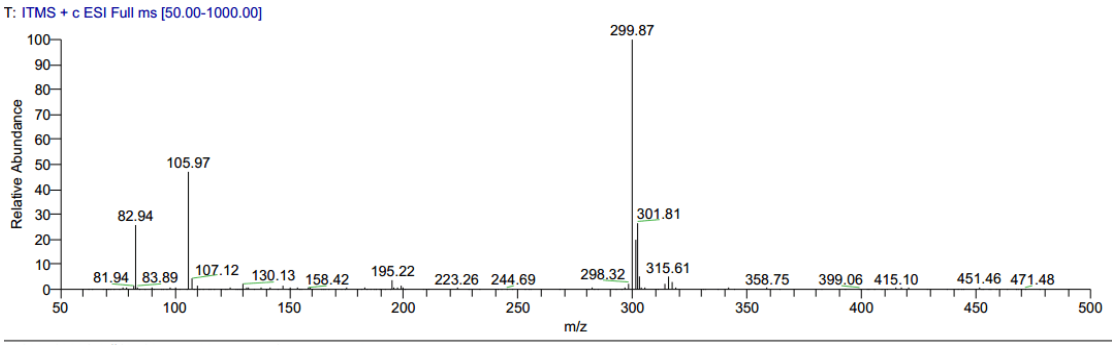


Figure S3. MS of Crizotinib intermediate **II**

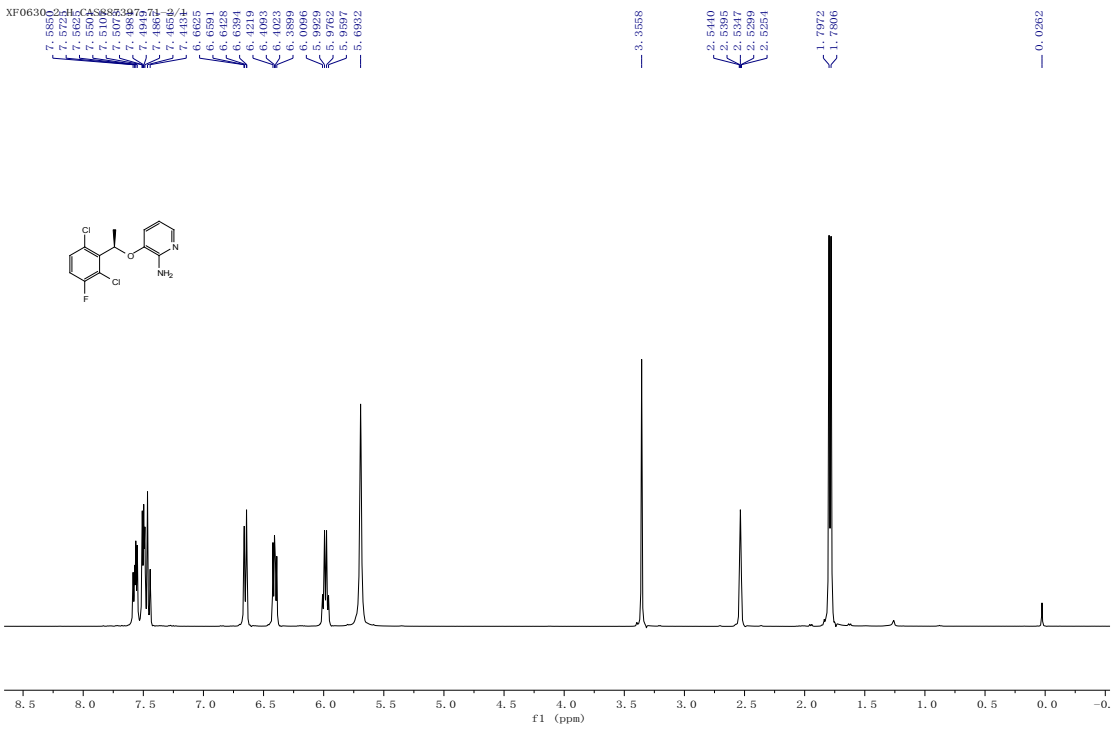


Figure S4. ^{1}H NMR of Crizotinib intermediate **II**

Mass Spectrum List Report

Analysis Info

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Sample Name	XF20190123001	Instrument	compact 8255754.20167
Comment			

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	1.8 Bar
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Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	9.0 l/min
Scan End	1300 m/z	Set Charging Voltage	2000 V	Set Divert Valve	Waste
		Set Corona	0 nA	Set APCI Heater	0 °C

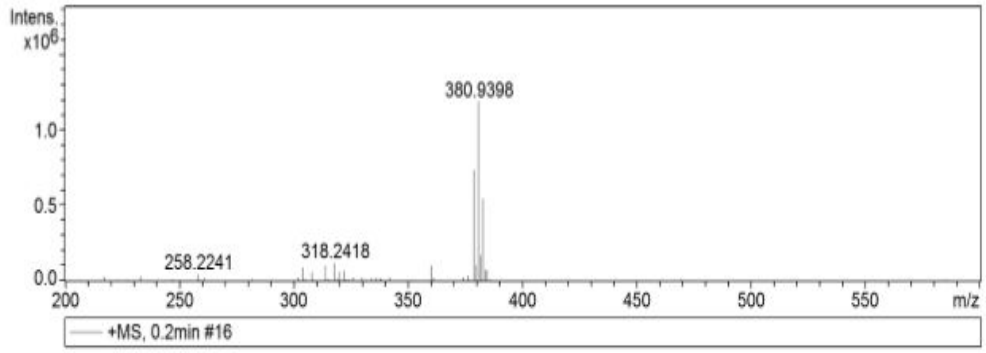


Figure S5. MS of (*R*)-5-bromo-3-(1-(2, 6-dichloro-3-fluorophenyl)ethoxy)pyridine-2-amine

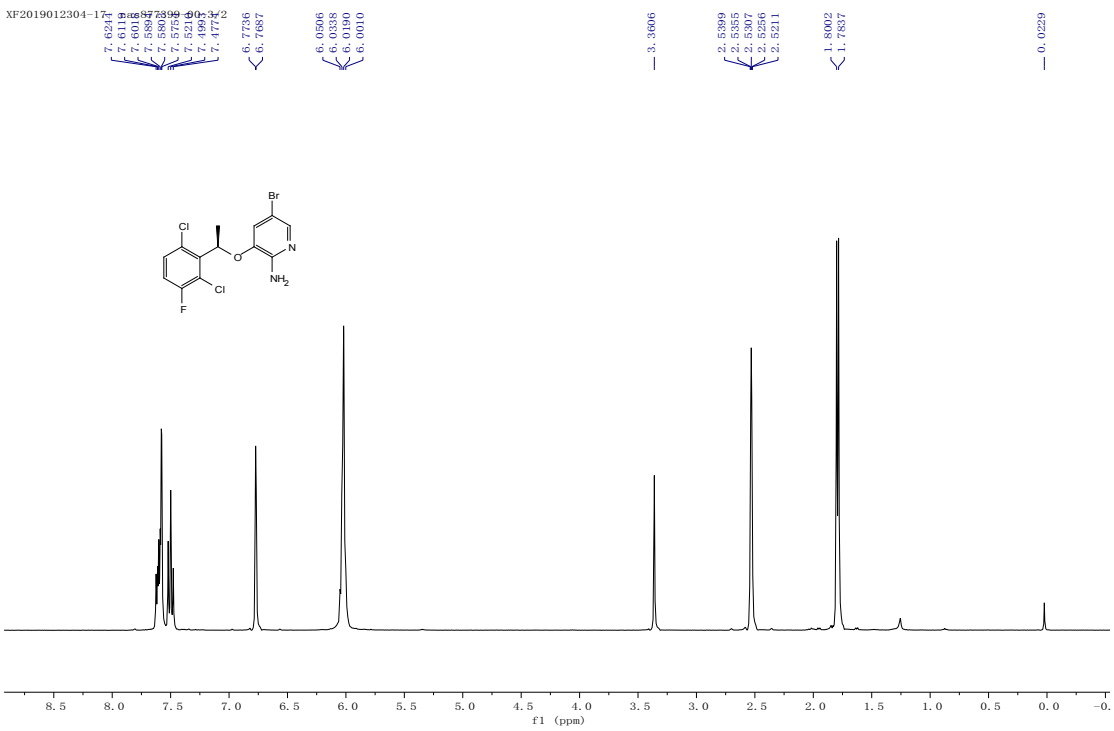


Figure S6. ^{1}H NMR of(*R*)-5-bromo-3-(1-(2, 6-dichloro-3-fluorophenyl)ethoxy)pyridine-2-amine

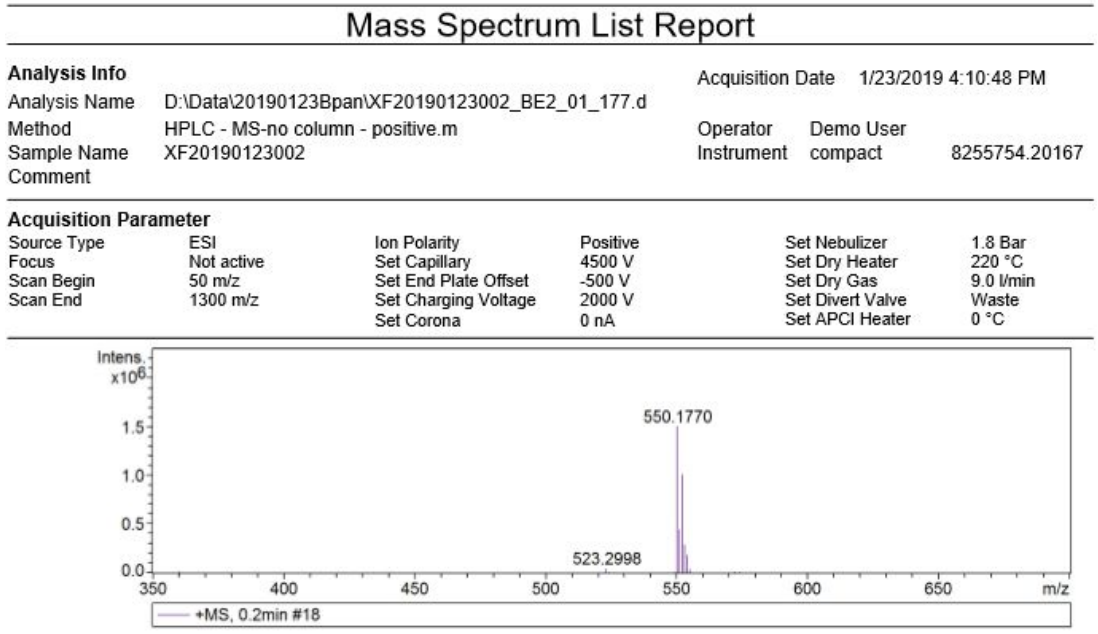


Figure S7. MS of tert-butyl(*R*)-4-(4-(6-amino-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridin-3-yl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate

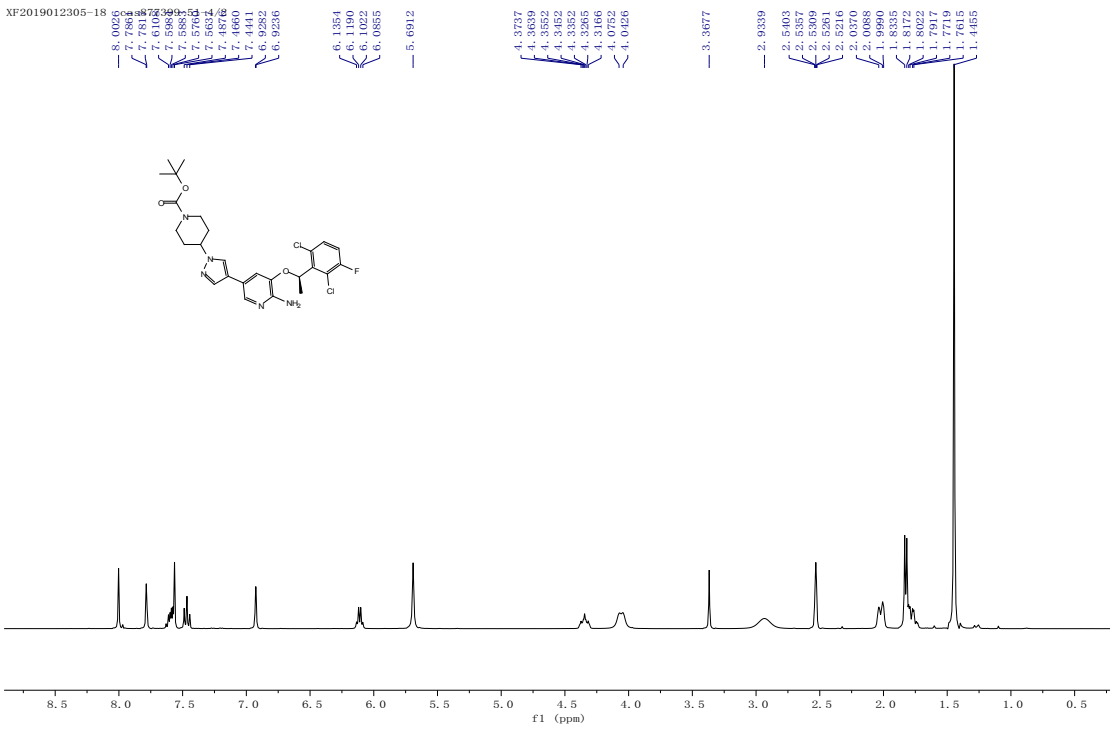
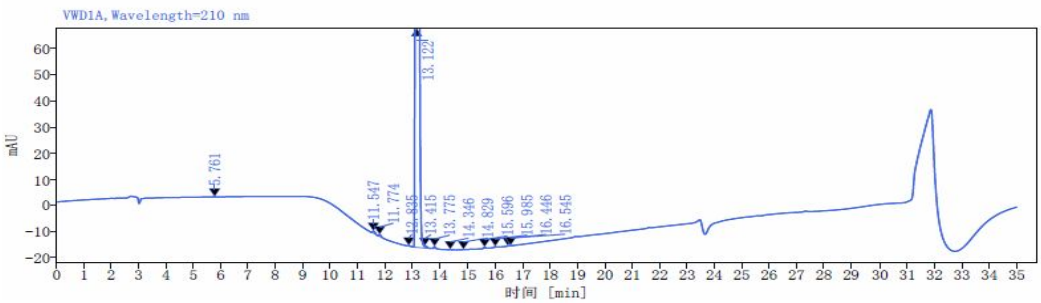


Figure S8. ^{1}H NMR of tert-butyl(*R*)-4-(4-(6-amino-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridin-3-yl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate



信号: VWD1A, Wavelength=210 nm

保留时间 [min]	类型	峰宽 [min]	峰面积	高度	峰面积%	名称
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11.547	MM m	0.10	5.01	0.84	0.079	
11.774	MM m	0.08	3.87	0.74	0.061	
12.835	MM m	0.12	1.30	0.18	0.020	
13.122	BM m	0.10	6317.89	1022.44	99.625	
13.415	MB m	0.11	4.50	0.71	0.071	
13.775	MM m	0.06	3.08	0.77	0.049	
14.346	MM m	0.06	0.48	0.12	0.008	
14.829	MM m	0.06	0.35	0.09	0.005	
15.596	MM m	0.07	2.11	0.47	0.033	
15.985	MM m	0.07	1.62	0.36	0.026	
16.446	MM m	0.07	0.60	0.13	0.009	
16.545	MM m	0.08	0.65	0.12	0.010	
		总和	6341.67			

Figure S9. HPLC of (*R*)-3-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)-5-(1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)pyridin-2-amine

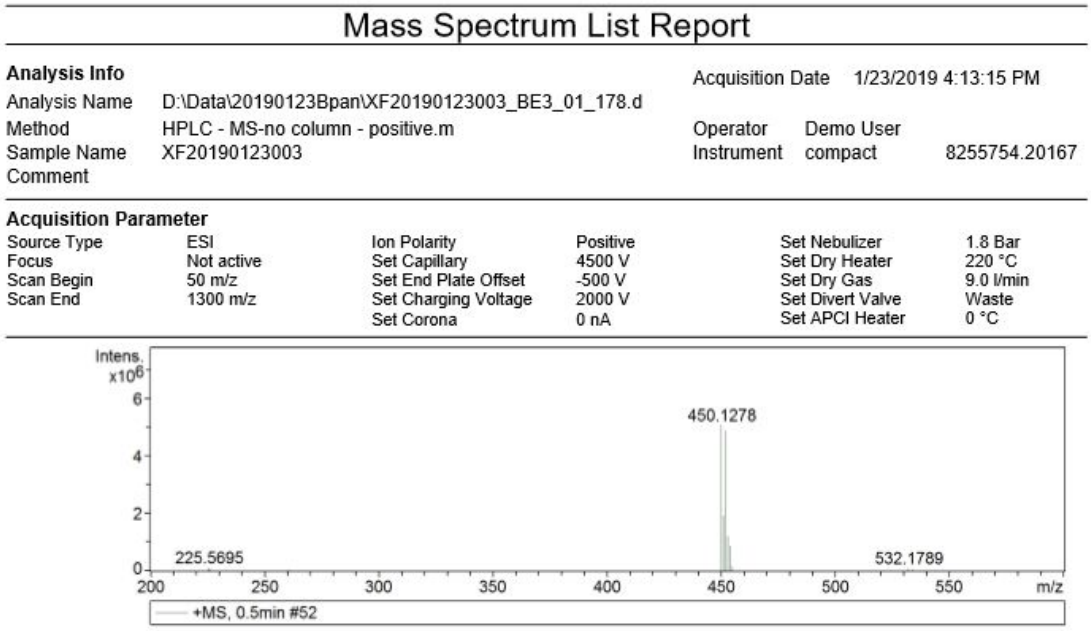

Figure S10. MS of (*R*)-3-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)-5-(1-(piperidin-4-yl)-1*H*-pyrazol-4-yl) pyridin-2-amine

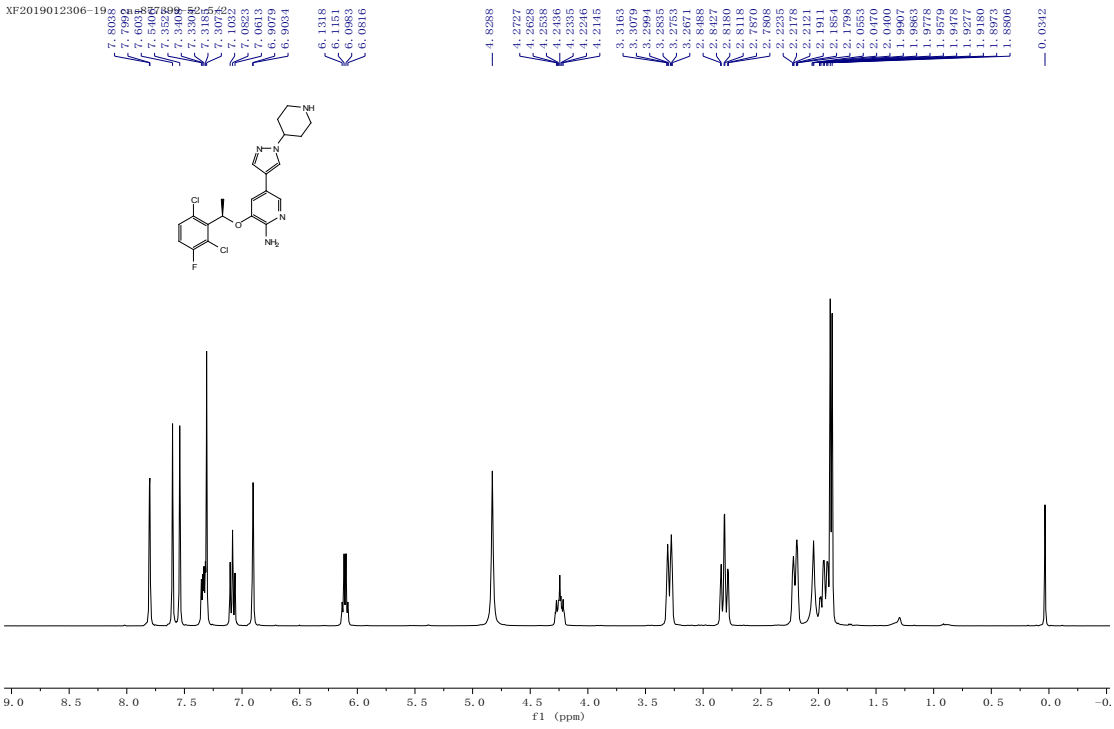

Figure S11. ^{1}H NMR of (*R*)-3-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)-5-(1-(piperidin-4-yl)-1*H*-pyrazol-4-yl)pyridin-2-amine

References:

[1] Zhang, G. Y.; Li, P. C.; Liu, D. F.; Guan, J. X.; Gong, P.; Xu, L. Y. Improved synthesis of Crizotinib. *Chin. J. Med. Chem.*, 2014, 24(6): 445-449.