(*E*)-3-(Cyclobutylamino)acrylonitrile (3.8 g, crude product) was dissolved in dichloromethane (50 mL), then DBU (4.9 g, 32.394 mmol) was added. Dimethyl but-2-ynedioate (6.9 g, 48.591 mmol) was slowly added dropwise at 0°C. After the addition was completed, the mixture was maintained at 0°C and continuted to stir to react for 0.5 h. The reaction solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: petroleum ether/ethyl acetate=1/2) to obtain methyl 5-cyano-1-cyclobutyl-2-oxo-1,2-dihydropyridine-4-carboxylate, yield 31.9%; ESI-MS (m/z): 233.0 $[M+H]^+$.

step c): Preparation of 3-amino-5-cyclobutyl-1*H*-pyrrolo[3,4-c]pyridine-1,6(5*H*)-dione

Methyl 5-cyano-1-cyclobutyl-2-oxo-1,2-dihydropyridine-4-carboxylate (2.4 g, 10.345 mmol) and a ammonia methanol solution (25 mL) were added to a sealed tube. The mixture was stirred to react at room temperature overnight. The reaction solution was filtered, and the filter cake was dried to obtain 3-amino-5-cyclobutyl-1*H*-pyrrolo[3,4-*c*]pyridine-1,6(5*H*)-dione (yield 97.9%); ESI-MS (m/z): 218.0 $[M+H]^+$.

step d): Preparation of (*R*)-5-cyclobutyl-3-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-1*H*-pyrrolo[3,4-*c*] pyridine-1,6(5*H*)-dione

3-amino-5-cyclobutyl-1*H*-pyrrolo[3,4-*c*]pyridine-1,6(5*H*)-dione (800 mg, 3.687 mmol), (*R*)-1-(3-(difluoromethyl)-2-fluorophenyl)ethan-1-amine hydrochloride (912 mg, 4.055 mmol) and ethanol (30 mL) were added to a reaction flask. The mixture was warmed to 80°C and reacted for 16 h. After the reaction was completed, the mixture was cooled to room temperature and

concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: dichloromethane/methanol=97/3) to obtain (*R*)-5-cyclobutyl-3-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-1*H*-pyrrolo[3,4-*c*]pyridine-1,6(5*H*)-dione, yield 56.5%; ESI-MS (m/z): 390.0 $[M+H]^+$.

step e): Preparation of (*R*)-6-cyclobutyl-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2,6-dihydropyrido[3,4-*d*]pyridazine-1,7-dione

(*R*)-5-cyclobutyl-3-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-1*H*-pyrrolo[3,4-*c*]pyridine-1,6(5*H*)-dione (810 mg, 2.082 mmol) and ethanol (20 mL) were added to a reaction flask. Hydrazine hydrate (260 mg, 4.165 mmol, 80%) was added dropwise at 0°C. After the addition was completed, the reaction was maintained at 0°C for another 2 h. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: dichloromethane/methanol = 97/3) to obtain (*R*)-6-cyclobutyl-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2,6-dihydropyrido[3,4-*d*]pyridazine-1,7-dione, with a yield of 38.0%; ESI-MS (m/z): 405.2 $[M+H]^+$.

step f): (*R*)-1-chloro-6-cyclobutyl-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)pyrido[3,4-*d*]pyridazin-7(6*H*) -one

(*R*)-6-cyclobutyl-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-2,6-dihydropyrido[3,4-*d*]pyridazine-1,7-dione (320 mg, 0.792 mmol), DIPEA (153 mg, 1.188 mmol), phosphorus oxychloride (364 mg, 2.376 mmol) and acetonitrile (50 mL) were added to a reaction flask. Under nitrogen protection, the mixture was warmed to 105°C and reacted for 2 h. The reaction solution was

cooled to room temperature, quenched with saturated aqueous sodium bicarbonate solution (50 mL), and extracted with dichloromethane (50 mL × 3). The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate/petroleum ether = 4/1) to obtain (*R*)-1-chloro-6-cyclobutyl-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)pyrido[3,4-*d*]pyridazin-7(6*H*)-one, yield 43.4%; ESI-MS (m/z): 423.0 $[M+H]^+$.

step g): Preparation of (*R*)-6-cyclobutyl-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-1- (4-methylpiperazin-1-yl)pyrido[3,4-*d*]pyridazin-7(6*H*)-one

(*R*)-1-Chloro-6-cyclobutyl-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)pyrido[3,4-*d*]pyridazin-7(6*H*)-one (50 mg, 0.118 mmol), N-methylpiperazine (24 mg, 0.237 mmol) and 1,4-dioxane (2 mL) were added to a reaction flask. The mixture was warmed to 120ºC and reacted for 1h in a microwave reactor. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC (separation method 3) to obtain (*R*)-6-cyclobutyl-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-1-(4-methylpiperazin-1-yl)pyrido[3,4-*d*]pyridazin-7(6*H*)-one, yield 18.0%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (s, 1H), 7.63 (t, *J* = 7.2 Hz, 2H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 52.0 Hz, 1H), 6.41 (s, 1H), 5.65-5.56 (m, 1H), 5.22-5.11 (m, 1H), 3.07-2.89 (m, 4H), 2.49-2.41 (m, 8H), 2.22 (s, 3H), 1.93-1.83 (m, 2H), 1.56 (d, *J* = 7.2 Hz, 3H); ESI-MS (m/z): 487.0 $[M+H]^+$.