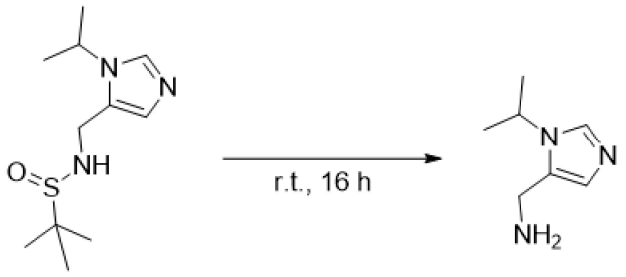
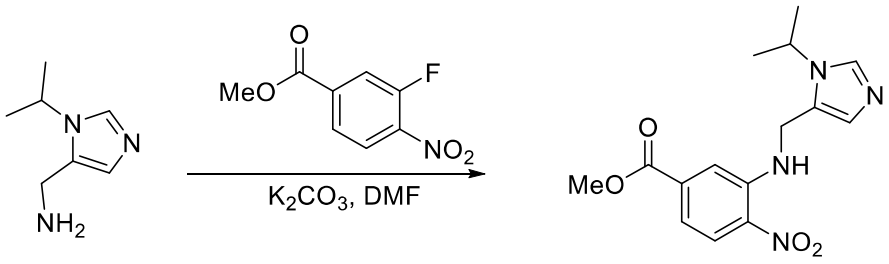
temperature for 2 hours. After completion, water (200 mL×2) was added to quench the reaction, and extracted with ethyl acetate (200 mL). The combined organic layers were washed with brine (200 mL×2), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to obtain N-((1-isopropyl-1H-imidazol-5-yl)methyl)-2-methylpropane-2-sulfoxide amide (4.5 g, 87.5% yield) , LC-MS m/z: 244 $[M+H]^+$.

3). Synthesis of (1-isopropyl-1H-imidazol-5-yl)methanamine:



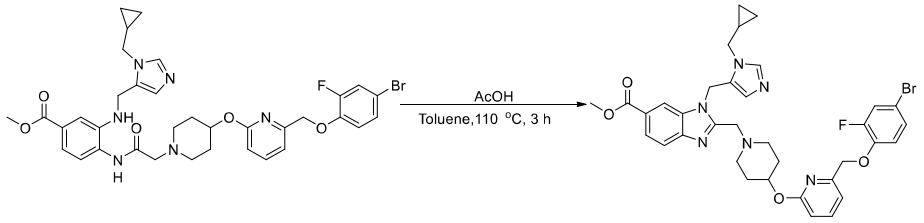
The mixture of N-((1-isopropyl-1H-imidazol-5-yl)methyl)-2-methylpropane-2-sulfoxide amide (4.50 g, 18.44 mmol) and AcOH (50 mL, 3 M in methanol) was stirred for 16 hours at room temperature. After completion, the reaction mixture was concentrated in vacuo to obtain (1-isopropyl-1H-imidazol-5-yl)methanamine (2.4 g, 93.6% yield). LC-MS m/z: 140 $[M+H]^+$.

4). Synthesis of methyl 3-((1-isopropyl-1H-imidazol-5-yl)methyl)amino)-4-nitrobenzoate:



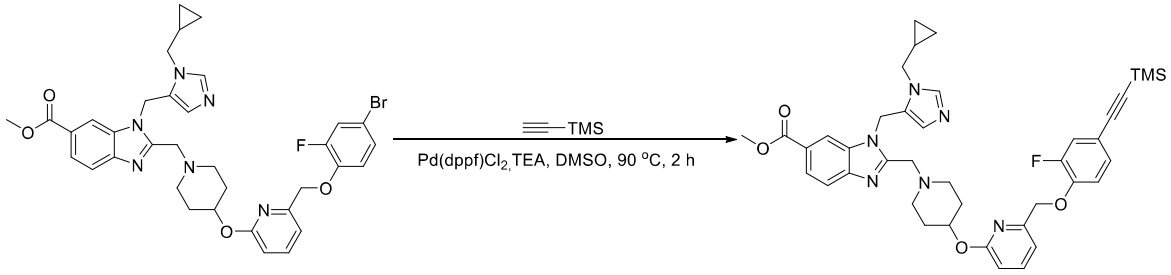
The mixture of (1-isopropyl-1H-imidazol-5-yl)methanamine (3.0 g, 17.27 mmol), methyl 3-fluoro-4-nitrobenzoate (4.14 g, 20.72 mmol) and potassium carbonate (4.79 g, 34.53 mmol) in N,N-dimethylformamide (50 mL) was stirred at room temperature for 16 hours. After completion, it was diluted with water (200 mL) and extracted with ethyl acetate (50 mL×3). The combined organic layers were washed with brine (50 mL×3), dried over anhydrous sodium sulfate, filtered, and concentrated to give a residue in vacuo. The residue was purified by silica gel column chromatography (dichloromethane/methanol=12/1) to obtained methyl 3-((1-isopropyl-1H-imidazol-5-yl)methyl)amino)-4-nitrobenzoate (1.2 g, 21.9% yield). LC-MS m/z: 319 $[M+H]^+$.

5). Synthesis of methyl 4-amino-3-((1-isopropyl-1H-imidazol-5-



The mixture of methyl 4-(2-(4-((6-((4-bromo-2-fluorophenoxy)methyl)pyridin-2-yl)oxy)piperidin-1-yl)acetamido)-3-((1-(cyclopropylmethyl)-1H-imidazol-5-yl)methyl)amino)benzoate (350 mg, 0.48 mmol) in toluene (4 mL) and acetic acid (0.4 mL) was stirred at 110° for 3 hours. After completion, the solvent was removed by concentration to give a residue in vacuo. The residue was purified by silica gel column chromatography (dichloromethane/methanol=20/1) to obtain methyl 2-((4-((6-((4-bromo-2-fluorophenoxy)methyl)pyridin-2-yl)oxy)piperidin-1-yl)methyl)-1-((1-(cyclopropylmethyl)-1H-imidazol-5-yl)methyl)-1H-beno[d]imidazole-6-carboxylate (300 mg, 89.6% yield). LC-MS m/z: 705 $[M+H]^+$.

3). Synthesis of methyl 1-((1-(cyclopropylmethyl)-1H-imidazol-5-yl)methyl)-2-((4-((6-((2-fluoro-4-((trimethylsilyl)ethynyl)phenoxy)methyl)pyridin-2-yl)oxy)piperidin-1-yl)methyl)-1H-benzo[d]imidazole-6-carboxylate:



The mixture of methyl 2-((4-((6- ((4-bromo-2-fluorophenoxy)methyl)pyridin-2-yl)oxy)piperidin-1-yl)methyl)-1-((1-(cyclopropylmethyl)-1H-imidazol-5-yl)methyl)-1H-benzo[d]imidazole-6-carboxylate (150 mg, 0.21 mmol), ethynyltrimethylsilane (206 mg, 2.10 mmol), triethylamine (212 mg, 2.10 mmol) and 1,1'-bisdiphenylphosphinoferrocene palladium dichloride (15 mg, 0.02 mmol) in dry DMSO (5 mL) was purged with nitrogen at room temperature. The resulting mixture was warmed to 90 °C and stirred at 90 °C for 2 hours. After completion, the reaction solution was cooled to room temperature and quenched with water (60 mL), and then extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (20 mL × 3), dried over anhydrous sodium sulfate, filtered, and concentrated to give residue in vacuo. The residue was purified by silica gel column chromatography (dichloromethane/methanol=15/1) to give methyl 1-((1-(cyclopropylmethyl)-1H-imidazol-5-