

Supporting Information

## **The Discovery of 3,3'-spiro[azetidine]-2-oxo-indoline Derivatives as Fusion Inhibitors for Treatment of RSV Infection**

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Contents:

1. Chemical synthesis
2. Hep-2 cell protection and cytotoxicity assays
3. *In vivo* PK study
4. *In vivo* Efficacy in the RSV Infection Mouse Model:

## 1. Chemical synthesis

### ■ Supplementary Material

Unless otherwise stated, all reagents and anhydrous solvents were of the highest grade available and were purchased from commercial sources and used without further purification. All NMR spectra were recorded on Bruker Advance III 400 MHz FT-NMR spectrometer with a 5 mm BBO (F) probe or a Varian 400 MHz spectrometer with a  $^1\text{H}/^{19}\text{F}/^{31}\text{P}/^{13}\text{C}$  5 mm PFG 4Nuc probe.  $^1\text{H}$  chemical shifts ( $\delta$ ) were reported in parts per million with  $\text{MeOH-}d_4$ ,  $\text{DMSO-}d_6$ , or  $\text{CDCl}_3$  as the reference standard. Signal multiplicities are represented by s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quadruplet), br (broad), bs (broad singlet), and m (multiplet). Analytical LC-MS analyses were conducted using Shimadzu LC-20AB pumps and an SPD-M20 PDA detector set at 220 and 254 nm, and the MS detection was performed with a MS-2010EV Micromass Platform LC spectrometer in electrospray ionization mode. Analytical SFC-MS analyses were conducted using Mettler pumps and an Agilent G1315B detector set at 190-370 nm, and the MS detection was performed with an Agilent 6110 detector following the detailed column and eluting conditions specified below. Preparative reversed-phase (RP) HPLC was performed using a Gilson 322 pump, a Gilson 156 UV detector set at 220 and 254 nm, and a Gilson GX-281 liquid handler, following the column Boston Green ODS 150\*30\*5u column using gradient mixtures of water/0.1% formic acid and water (10%)/acetonitrile (90%)/0.1% formic acid. Normal-phase silica gel preparative purification was performed using an automated Combi-flash companion from ISCO with pre-packed silica gel cartridges supplied by Santai Technologies Inc. and Agela Inc. SFC separation was performed using a Berger SFC Analytic system on a Column: Chiralpak AD-3 100×4.6mm I.D., 3um; Mobile phase: A:  $\text{CO}_2$  B: ethanol (0.05% DEA); Gradient: from 5% to 40% of B in 4.5min and hold 40% for 2.5 min, then 5% of B for 1 min; Flow rate: 2.8mL/min; Column temperature: 40°C. Chromatographic purifications were performed silica gel (300-400 mesh). Analytical thin-layer chromatography (TLC) was performed using SGF254 TLC plates (0.2-0.25 mm) supplied by Combinol Reagent (Yantai) Co., Ltd. Preparative TLC was performed using SGF254 TLC plates (0.4-0.5 mm) supplied by Yucheng Chemical (Shanghai) Co., Ltd. All of the compounds were established by a variety of LC/MS, and NMR analytical techniques, and purities were >95% for all final products.

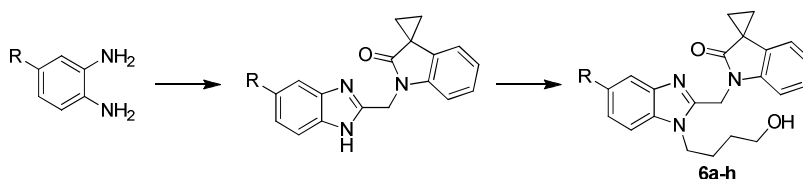
### ■ EXPERIMENTAL SECTION

#### **General Procedure 1 (Preparation of 6a-s): N-alkylation with 4-(2-(chloromethyl)-1H-benzo[d]imidazol-1-yl)butan-1-ol**

To a solution of N-alkylation nucleophilic reagent R-NH (1.0 eq) in DMF was added NaH (1.2 eq)

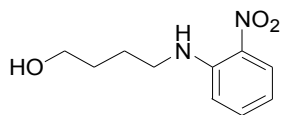
under  $N_2$  at  $0^\circ\text{C}$ , the resulting mixture was stirred at  $0\sim 25^\circ\text{C}$  over 0.5 hr, then 4-(2-(chloromethyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol (1.2 eq) was added thereto. The reaction mixture was stirred at room temperature for 1~4 hrs. The reaction mixture was quenched with water at  $0^\circ\text{C}$ , extracted with EtOAc. The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to give a residue. The residue was subjected to *prep*-HPLC for purification to give the desired product **5a-s**.

**General Procedure 2 (Preparation of 6a-h): substituted benzo[*d*]imidazole cyclization**



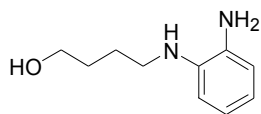
To a solution of varied substituted benzene-1,2-diamine (1.0 eq) in DMF was added DIPEA (1.4 eq) and HATU (1.2 eq), stirred at room temperature for 15 min, followed by 2-(2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)acetic acid (1.0 eq) was added, the mixture stirred at room temperature for 1~4 hrs. Water was added and extracted with EtOAc. The combined organic layer was washed with water and brine, dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give a couple of amide isomers which was used directed for the next step. To the couple of amide isomers was added AcOH, and the resulting mixture was allowed to stir at  $90^\circ\text{C}$  for 1 hr. The mixture was concentrated, and the residue was dissolved in EtOAc, and washed with *aq.*  $\text{NaHCO}_3$ . The combined organic layer was washed with water and brine, dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give the various substituted benzimidazole intermediates. To the substituted benzimidazoles in MeCN was added 4-bromobutyl-1-ol (1.2 eq.), NaI (0.2 eq.),  $\text{K}_2\text{CO}_3$  (2.0 eq.) and stirred at  $80^\circ\text{C}$  for 4~8 hrs till the monitored TLC indicated the starting material was consumed completely. The mixture was filtered and the filtrate was concentrated, purified by silica gel chromatography or SFC separation to give (**6a-h**).

**4-((2-nitrophenyl)amino)butan-1-ol, 2.**



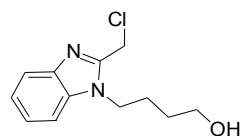
To a solution of 1-fluoro-2-nitrobenzene (6.73 g, 47.75 mmol, 1.0 eq.) in 1,4-dioxane (70 mL) was added 4-aminobutan-1-ol (5.1 g, 57.30 mmol, 1.2 eq.) and triethylamine (7.23 g, 71.63 mmol, 1.5 eq.) sequentially. The resulting solution was stirred at 22 °C for 2 hrs. The mixture was concentrated *in vacuo* and washed with water for twice, extracted with EtOAc. The organic layer was concentrated *in vacuo* to give **3** as yellow oil (9.31g, 92.7%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  8.14 (m, 1H), 8.06 (dd, *J* = 1.3 Hz, 8.6 Hz, 1H), 7.57-7.50 (m, 1H), 7.06 (d, *J* = 8.6 Hz, 1H), 6.71-6.64 (m, 1H), 4.46 (t, *J* = 5.2 Hz, 1H), 3.48 - 3.35 (m, 4H), 1.70-1.62 (m, 2H), 1.57 - 1.46 (m, 2H). HRMS calcd for C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 211.1077, found: 211.1007.

#### 4-((2-aminophenyl)amino)butan-1-ol, **3**.



To a solution of 4-((2-nitrophenyl)amino)butan-1-ol **3** (22.3 g, 106 mmol, 1.0 eq.) in MeOH (250 mL) was added Pd/C (3.0 g, 5% w/w). The resulting solution was stirred at room temperature for 12 hrs under H<sub>2</sub> (1 atm). The mixture was filtered and the filtrates were concentrated *in vacuo* to give **4** as a dark oil (14.7g, 92.7%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.87-6.79 (m, 1H), 6.74-6.64 (m, 3H), 3.67 (t, *J* = 5.9 Hz, 2H), 3.47-3.26 (m, 2H), 3.13 (t, *J* = 6.4 Hz, 2H), 1.78-1.66 (m, 4H). HRMS calcd for C<sub>10</sub>H<sub>16</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 181.1335, found: 181.1261.

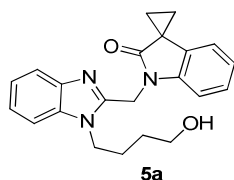
#### 4-(2-(chloromethyl)-1H-benzo[d]imidazol-1-yl)butan-1-ol, **4**.



To a solution of 4-((2-aminophenyl)amino)butan-1-ol, **4** (4.2 g, 23.3 mmol, 1.0 eq.) in 4N HCl (40 mL) was added 2-chloroacetic acid (3.3 g, 35.0 mmol, 1.5 eq.). The resulting solution was refluxed at 80 °C for 2 hrs. The mixture was adjusted pH to 6~7 using saturated aqueous Na<sub>2</sub>CO<sub>3</sub>

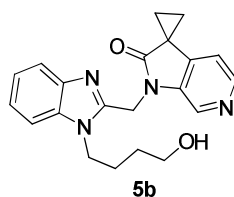
and extracted with EtOAc(100 mL×3). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in *vacuo*. The organic layer was purified by silica gel chromatography (PE:EtOAc=2:1) to give **5** as a light yellow solid (3.1 g, 55.7%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.76 (d, *J* = 7.3 Hz, 1H), 7.41-7.37 (m, 1H), 7.34-7.28 (m, 2H), 4.86 (s, 2H), 4.34-4.28 (m, 2H), 3.72 (t, *J* = 6.1 Hz, 2H), 2.06-1.98 (m, 2H), 1.72-1.63 (m, 2H). HRMS calcd for C<sub>12</sub>H<sub>15</sub>ClN<sub>2</sub>O [M+H]<sup>+</sup>: 239.0946, found: 239.0875.

**1'-((1-(4-hydroxybutyl)-1*H*-benzo[*d*]imidazol-2-yl)methyl)spiro[cyclopropane-1,3'-indolin]-2'-one, **5a**.**



According to general procedure **1**, *spiro*[cyclopropane-1,3'-indolin]-2'-one (100 mg, 1.0 eq ) and 4-(2-(chloromethyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol (180 mg, 1.2 eq) were reacted together in DMF (2 mL). After workup and purification, the title product **5a** was obtained (35 mg, 15.4%) as a white solid. <sup>1</sup>H NMR(400 MHz, Methanol-*d*<sub>4</sub>) δ 7.62 (d, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.29-7.24 (m, 2H), 7.15-7.13 (m, 2H), 6.90-7.05 (m, 2H), 5.34 (s, 2H), 4.32 (t, *J* = 7.6 Hz, 2H), 3.50 (t, *J* = 6.4 Hz, 2H), 1.76-1.66 (m, 6H), 1.60-1.50 (m, 2H). HRMS calcd for C<sub>22</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 362.1863, found: 362.1789.

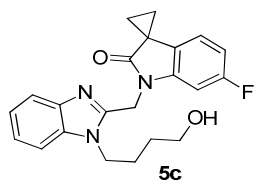
**1'-((1-(4-hydroxybutyl)-1*H*-benzo[*d*]imidazol-2-yl)methyl)spiro[cyclopropane-1,3'-pyrrolo[2,3-*c*]pyridin]-2'(1'*H*)-one, **5b**.**



According to general procedure **1**, *spiro*[cyclopropane-1,3'-pyrrolo[2,3-*c*]pyridin]-2'(1'*H*)-one (70 mg, 1.0 eq.) and 4-(2-(chloromethyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol (114 mg, 1.1 eq.) were reacted together in DMF (1.5 mL). After workup and purification, the title product was obtained

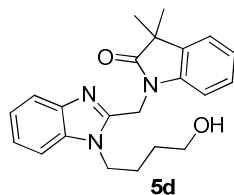
**5b** (40 mg, 25.3%) as a light yellow solid.  $^1\text{H NMR}$  (400 MHz, Methanol- $d_4$ )  $\delta$  8.34 (s, 1H), 8.24 (d,  $J = 4.8$  Hz, 1H), 7.62 (d,  $J = 8.0$  Hz, 1H), 7.55 (d,  $J = 8.0$  Hz, 1H), 7.35-7.29 (m, 1H), 7.29-7.23 (m, 1H), 7.15 (d,  $J = 5.0$  Hz, 1H), 5.42 (s, 2H), 4.39 (t,  $J = 7.7$  Hz, 2H), 3.56 (t,  $J = 6.3$  Hz, 2H), 1.94–1.87 (m, 4H), 1.85–1.75 (m, 2H), 1.65-1.55 (m, 2H). HRMS calcd for  $\text{C}_{21}\text{H}_{22}\text{N}_4\text{O}_2$   $[\text{M}+\text{H}]^+$ : 363.1816, found: 363.1746.

**6'-fluoro-1'-((1-(4-hydroxybutyl)-1*H*-benzo[*d*]imidazol-2-yl)methyl)spiro[cyclopropane-1,3'-indolin]-2'-one, 5c.**



According to general procedure **1**, 6'-fluorospiro[cyclopropane-1,3'-indolin]-2'-one (50 mg, 1.0 eq) and 4-(2-(chloromethyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol (73 mg, 1.1 eq) were reacted together in DMF (1.5 mL). After workup and purification, the title product **5c** was obtained (40 mg, 25.3%) as light yellow solid.  $^1\text{H NMR}$  (400 MHz, Methanol- $d_4$ )  $\delta$  7.69 (d,  $J = 7.6$  Hz, 1H), 7.55 (d,  $J = 7.6$  Hz, 1H), 7.40-7.29 (m, 2H), 7.04-6.97 (m, 2H), 6.77 (t,  $J = 8.0$  Hz, 1H), 5.37 (s, 2H), 4.37 (t,  $J = 8.0$  Hz, 2H), 3.55 (t,  $J = 6.4$  Hz, 2H), 1.76-1.70 (m, 6H), 1.61-1.55 (m, 2H). HRMS calcd for  $\text{C}_{22}\text{H}_{22}\text{FN}_3\text{O}_2$   $[\text{M}+\text{H}]^+$ : 380.1769, found: 380.1696.

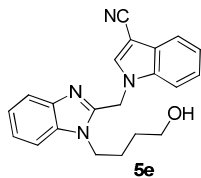
**1-((1-(4-hydroxybutyl)-1*H*-benzo[*d*]imidazol-2-yl)methyl)-3,3-dimethylindolin-2-one, 5d.**



According to general procedure **1**, 3,3-dimethylindolin-2-one (111.0 mg, 1.1 eq) and 4-(2-(chloromethyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol (150.0 mg, 1.0 eq) were reacted together in DMF (3 mL). After workup and purification, the title product was obtained **5d** (20 mg, 8.8%) as light yellow solid.  $^1\text{H NMR}$  (400 MHz, Methanol- $d_4$ )  $\delta$  7.63 (d,  $J = 8.0$  Hz, 1H), 7.53 (d,  $J = 8.0$  Hz, 1H), 7.32-7.07 (m, 6H), 5.27 (s, 2H), 4.37 (t,  $J = 8.0$  Hz, 2H), 3.57 (t,  $J = 8.0$  Hz,

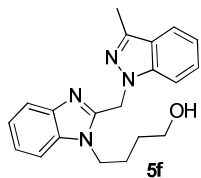
2H), 1.88-1.80 (m, 2H), 1.65-1.59 (m, 2H), 1.43 (s, 6H). HRMS calcd for C<sub>22</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 364.2020, found: 364.1950.

**4-(2-((3-cyclopropyl-1*H*-indol-1-yl)methyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol, 5e.**



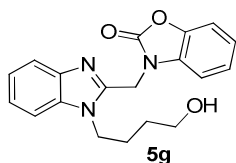
According to general procedure 1, 1,4-(2-(chloromethyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol (100 mg, 1.0 eq.) and 1*H*-indole-3-carbonitrile (71 mg, 1.2 eq.) were reacted together in DMF (2 mL). After workup and purification, the title product was obtained **5e** (72 mg, 49.9%) as yellow solid. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) δ 8.13 (s, 1H), 7.73-7.59 (m, 3H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.36-7.25 (m, 4H), 5.87 (s, 2H), 4.28 (t, *J* = 7.4 Hz, 2H), 3.43 (t, *J* = 5.9 Hz, 2H), 1.53-1.38 (m, 4H). HRMS calcd for C<sub>21</sub>H<sub>20</sub>N<sub>4</sub>O [M+H]<sup>+</sup>: 345.1710, found: 345.1635.

**4-(2-((3-methyl-1*H*-indazol-1-yl)methyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol, 5f.**



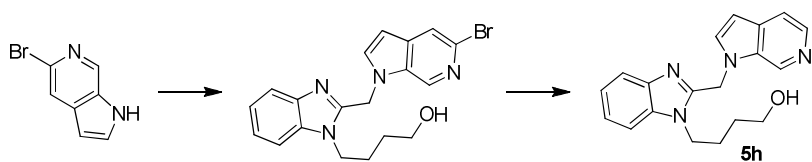
According to general procedure 1, 3-methyl-1*H*-indazole (110 mg) and 4-(2-(chloromethyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol (200 mg) were reacted together in DMF (2 mL). After workup and purification, the title product **5f** was obtained (40 mg, 25.3%) as light yellow solid. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.31-7.29 (m, 1H), 7.16 (t, *J* = 8.0 Hz, 1H), 5.90 (s, 2H), 4.27 (t, *J* = 7.6 Hz, 2H), 3.40 (t, *J* = 5.6 Hz, 2H), 2.57 (s, 3H), 1.38 (t, *J* = 3.6 Hz, 4H). HRMS calcd for C<sub>20</sub>H<sub>22</sub>N<sub>4</sub>O [M+H]<sup>+</sup>: 335.1866, found: 335.1795.

**3-((1-(4-hydroxybutyl)-1*H*-benzo[*d*]imidazol-2-yl)methyl)benzo[*d*]oxazol-2(3*H*)-one, 5g.**



According to general procedure **1**, benzo[*d*]oxazol-2(3*H*)-one (68 mg, 1.2 eq.) and 4-(2-(chloromethyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol (100 mg, 1.0 eq.) were reacted together in DMF (2.0 mL). After workup and purification, the title product **5g** was obtained (23.2 mg, 16.5%) as yellow solid. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) δ 7.62 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.30-7.26 (m, 3H), 7.18-7.15 (m, 3H), 5.42 (s, 2H), 4.41 (t, *J* = 7.6 Hz, 2H), 3.56 (t, *J* = 6.4 Hz, 2H), 1.83-1.77 (m, 2H), 1.64-1.58 (m, 2H). HRMS calcd for C<sub>19</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 338.1499, found: 338.1424.

**4-(2-((1*H*-pyrrolo[2,3-*c*]pyridin-1-yl)methyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol, 5h.**

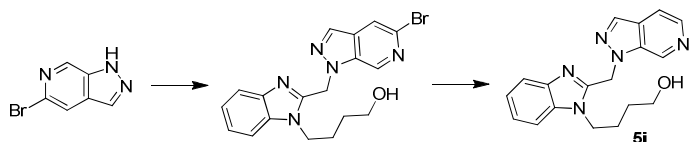


*Step 1.* According to general procedure **1**, 5-bromo-1*H*-pyrrolo[2,3-*c*]pyridine (100.0 mg, 1.1 eq.) and 4-(2-(chloromethyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol (111 mg, 1.0 eq.) were reacted together in DMF (2 mL). After workup, the residue obtained was purified by *prep*-TLC (Developer: EtOAc) to afford the product 4-(2-((5-bromo-1*H*-pyrrolo[2,3-*c*]pyridin-1-yl)methyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol (150mg, 80.8%) as yellow solid. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) δ 8.62 (s, 1H), 7.81 (s, 1H), 7.70-7.66 (m, 2H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.36-7.30 (m, 2H), 6.66 (d, *J* = 2.8 Hz, 1H), 5.89 (s, 2H), 4.28 (t, *J* = 7.6 Hz, 2H), 3.45 (t, *J* = 6.0 Hz, 2H), 1.52-1.42 (m, 4H). HRMS calcd for C<sub>19</sub>H<sub>19</sub>BrN<sub>4</sub>O [M+H]<sup>+</sup>: 399.0815, found: 398.0744.

*Step 2.* To a solution of 4-(2-((5-bromo-1*H*-pyrrolo[2,3-*c*]pyridin-1-yl)methyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol (100 mg, 0.25 mmol) in MeOH (3.0 mL) was added Pd(OH)<sub>2</sub>/C (20 mg, 5% w/w) at 22 °C. The resulting

mixture was stirred at 22°C for 40 min. After the reaction was complete, the mixture was filtered and the filtrate was concentrated to give the crude product. The residue was purified by *prep*-HPLC (0.05% formic acid in water and CAN from 20-55%) to give the title product **5h** (22 mg, 27.4%) as yellow solid. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) δ 9.02(s, 1H), 8.19 (d, *J* = 6.0 Hz, 1H), 7.94 (d, *J* = 2.8 Hz, 1H), 7.87 (d, *J* = 6.0 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.34-7.28 (m, 2H), 6.86 (d, *J* = 3.2 Hz, 1H), 6.00 (s, 2H), 4.33 (t, *J* = 7.6 Hz, 2H), 3.47 (t, *J* = 6.0 Hz, 2H), 1.57-1.48 (m, 4H). HRMS calcd for C<sub>19</sub>H<sub>20</sub>N<sub>4</sub>O [M+H]<sup>+</sup>: 321.1710, found: 321.1635.

**4-(2-((1*H*-pyrazolo[3,4-*c*]pyridin-1-yl)methyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol, 5i.**

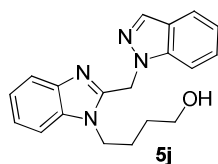


*Step 1.* According to general procedure **1**, 5-bromo-1*H*-pyrazolo[3,4-*c*]pyridine (75 mg, 0.91 eq) and 4-(2-(chloromethyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol (100 mg, 1.0 eq) were reacted together in DMF (2 mL). After workup, the obtained residue was purified by preparation TLC to afford a pair of isomers (90 mg, 16.5%) as yellow solid, which was used directed in the next step. HRMS calcd for C<sub>18</sub>H<sub>18</sub>BrN<sub>5</sub>O [M+H]<sup>+</sup>: 400.0767, found: 400.0692.

*Step 2.* To a solution of 4-(2-((5-bromo-1*H*-pyrazolo[3,4-*c*]pyridin-1-yl)methyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol (60 mg) in MeOH (2 mL) was added Pd(OH)<sub>2</sub>/C (10 mg, 5% w/w) under N<sub>2</sub>. The suspension was degassed under vacuum and purged with H<sub>2</sub> several times, which was stirred at room temperature for 1 hr. The mixture was subjected to *prep*-HPLC (0.05% formic acid in water and CAN from 20-55%) for purification to give the title product **5i** (3.3 mg, 27.4%) as yellow solid. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) δ 9.17 (s, 1H), 8.24 (d, *J* = 4.4 Hz, 2H), 7.81-7.79 (m, 1H), 7.80 (d, *J* = 1.2 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.32-7.24 (m, 2H), 6.13 (s, 2H), 4.38 (t, *J* = 8.0 Hz, 2H), 3.47 (t, *J* = 6.4 Hz, 2H), 1.59-1.46 (m, 4H). HRMS calcd for C<sub>18</sub>H<sub>19</sub>N<sub>5</sub>O

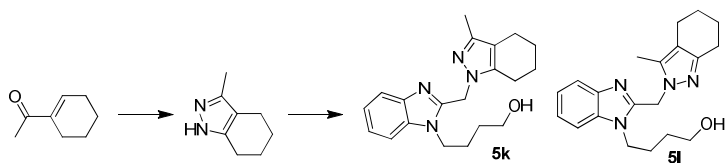
[M+H]<sup>+</sup>: 322.1662, found: 322.1594.

**4-(2-((1*H*-indazol-1-yl)methyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol, 5j.**



According to general procedure 1, 1*H*-indazole(59 mg, 1.2 eq.) and 4-(2-(chloromethyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol (100 mg, 1.0 eq.) were reacted together in DMF (2 mL). After workup and purification, the title product **5j** was obtained (26 mg, 19%) as yellow solid. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) δ 8.09 (s, 1H), 7.77(d, *J* = 8.4 Hz, 1H), 7.76(d, *J* = 5.6 Hz, 2H), 7.48(d, *J* = 8.4 Hz, 1H), 7.39 (t, *J* = 5.6 Hz, 1H), 7.30-7.28 (m, 2H), 7.17 (t, *J* = 5.6 Hz, 1H), 5.97 (s, 2H), 4.29-4.25 (m, 2H), 3.41-3.39 (m, 2H), 1.40-1.36 (m, 4H). HRMS calcd for C<sub>19</sub>H<sub>20</sub>N<sub>4</sub>O [M+H]<sup>+</sup>: 321.1710, found: 321.1635.

**4-(2-((3-methyl-4,5,6,7-tetrahydro-2*H*-indazol-2-yl)methyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol, 5k and 4-(2-((3-methyl-4,5,6,7-tetrahydro-2*H*-indazol-2-yl)methyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol, 5l**



The flasks (50 mL) equipped with magnetic stirrer was charged with 1-(cyclohex-1-en-1-yl)ethanone (1.0 g, 8.06 mmol, 1.0 eq), hydrazine hydrate (2.02 g, 40.3 mmol, 5.0 eq) and EtOH (10 mL). The resulting solution was stirred at 80°C for 18 hr. The solvent was removed directly under vacuum conditions. The residue was charged with dioxane (10 mL) and DDQ (2.01 g, 8.9 mmol, 1.1 eq), and the mixture was refluxed for 6 hrs. Then KOH (20% aq.) and DCM were added to the reaction mixture which stirred for 1 hr. The solvent was separated and the aqueous phase extracted with DCM (50.0 mL×3). The organic layer was

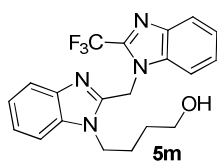
concentrated in vacuum and purified by silica gel chromatography (PE:EtOAc =1:1) to afford 3-methyl-4,5,6,7-tetrahydro-1*H*-indazole (371 mg, 33.73%) as yellow oil.

According to general procedure **1**, 3-methyl-4,5,6,7-tetrahydro-1*H*-indazole (100 mg, 1.0 eq) and 4-(2-(chloromethyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol (190.4 mg, 1.1 eq) were reacted together in DMF (2.0 mL). After workup and purification, the desired product **5k** (17 mg, 7%) and **5l** (14 mg, 6%) was obtained respectively as white solid.

**5k**, <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) δ 7.63 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.33-7.23 (m, 2H), 5.50 (s, 2H), 4.28-4.21 (m, 2H), 3.53-3.46 (m, 2H), 2.50 (t, *J* = 5.9 Hz, 2H), 2.38 (t, *J* = 5.8 Hz, 2H), 2.11 (s, 3H), 1.79-1.65 (m, 4H), 1.55-1.45 (m, 4H). HRMS calcd for C<sub>20</sub>H<sub>26</sub>N<sub>4</sub>O [M+H]<sup>+</sup>: 339.2179, found: 339.2111.

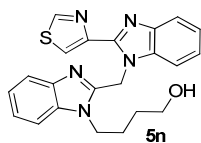
**5l**, <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) δ 7.62 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.32-7.23 (m, 2H), 5.57 (s, 2H), 4.22-4.28 (m, 2H), 3.54-3.48 (m, 2H), 2.58 (t, *J* = 5.9 Hz, 2H), 2.41 (t, *J* = 5.9 Hz, 2H), 2.15 (s, 3H), 1.82-1.70 (m, 4H), 1.56-1.47 (m, 4H). HRMS calcd for C<sub>20</sub>H<sub>26</sub>N<sub>4</sub>O [M+H]<sup>+</sup>: 339.2179, found: 339.2108.

**4-((2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)methyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol, **5m**.**



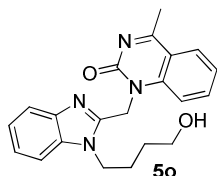
According to general procedure **1**, 2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (94 mg, 1.2 eq.) and 4-(2-(chloromethyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol (100 mg, 1.0 eq.) were reacted together in DMF (2 mL). After workup and purification, the title product **5m** was obtained (56 mg, 34%) as yellow solid. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) δ 7.88 (d, *J* = 6.0 Hz, 1H), 7.59-7.44 (m, 5H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 6.06 (s, 2H), 4.40 (t, *J* = 8.0 Hz, 2H), 3.58 (t, *J* = 6.4 Hz, 2H), 1.91-1.84 (m, 2H), 1.61-1.55 (m, 2H). HRMS calcd for C<sub>20</sub>H<sub>19</sub>F<sub>3</sub>N<sub>4</sub>O [M+H]<sup>+</sup>: 389.1584, found: 389.1509.

**4-(2-((2-(thiazol-4-yl)-1*H*-benzo[*d*]imidazol-1-yl)methyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol, **5n**.**



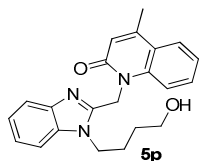
According to general procedure **1**, 4-(1*H*-benzo[*d*]imidazol-2-yl)thiazole (70.46 mg, 1.0 eq.) and 4-(2-(chloromethyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol (100 mg, 1.2 eq.) were reacted together in DMF (2 mL). After workup and purification, the title product **5n** was obtained (30 mg, 17.69%) as white solid.  $^1\text{H NMR}$  (400 MHz, Methanol-*d*<sub>4</sub>)  $\delta$  9.12 (d, *J* = 1.8 Hz, 1H), 8.47 (d, *J* = 1.8 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.59-7.48 (m, 3H), 7.38-7.26 (m, 3H), 7.2 (t, *J* = 8.0 Hz, 1H), 6.52 (s, 2H), 4.38 (t, *J* = 7.5 Hz, 2H), 3.53 (t, *J* = 6.3 Hz, 2H), 1.83-1.74 (m, 2H), 1.57-1.48 (m, 2H). HRMS calcd for C<sub>22</sub>H<sub>21</sub>N<sub>5</sub>OS [M+H]<sup>+</sup>: 404.1540, found: 404.1466.

**1-((1-(4-hydroxybutyl)-1*H*-benzo[*d*]imidazol-2-yl)methyl)-4-methylquinazolin-2(1*H*)-one, **5o**.**



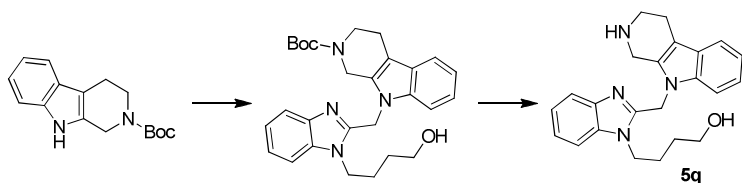
According to general procedure **1**,  
4-methylquinazolin-2(1*H*)-one (56 mg, 1.0 eq.) and  
4-(2-(chloromethyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol (122 mg, 1.46 eq) were reacted together in DMF (2 mL). After workup and purification, the title product **5o** was obtained (91 mg, 71.7%) as pale yellow solid.  $^1\text{H NMR}$  (400 MHz, Methanol-*d*<sub>4</sub>)  $\delta$  8.16 (d, *J* = 8.0 Hz, 1H), 7.78 (t, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.31-7.27 (m, 1H), 7.24-7.18 (m, 1H), 5.85 (s, 2H), 4.47 (t, *J* = 8.0 Hz, 2H), 3.62 (t, *J* = 6.0 Hz, 2H), 2.87-2.85 (m, 3H), 1.99-1.92 (m, 2H), 1.71-1.64 (m, 2H). HRMS calcd for C<sub>21</sub>H<sub>22</sub>N<sub>4</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 363.1816, found: 363.1744.

**1-((1-(4-hydroxybutyl)-1*H*-benzo[*d*]imidazol-2-yl)methyl)-4-methylquinolin-2(1*H*)-one, **5p**.**



According to general procedure 1, 4-methylquinolin-2(1H)-one (100 mg, 1.0 eq.) and 4-(2-(chloromethyl)-1H-benzo[d]imidazol-1-yl)butan-1-ol (165 mg, 1.1 eq.) were reacted together in DMF (2 mL). After workup and purification, the title product **5p** was obtained (30 mg, 13.2%) as pale yellow solid.  $^1\text{H NMR}$  (400 MHz, Methanol- $d_4$ )  $\delta$  7.91 (d,  $J = 8.0$  Hz, 1H), 7.60-7.49 (m, 4H), 7.34-7.20 (m, 3H), 6.69 (s, 1H), 5.91 (s, 2H), 4.43 (t,  $J = 7.6$  Hz, 2H), 3.57 (t,  $J = 6.0$  Hz, 2H), 2.59 (s, 3H), 1.87-1.80 (m, 2H), 1.66-1.60 (m, 2H). HRMS calcd for  $\text{C}_{22}\text{H}_{23}\text{N}_3\text{O}_2$   $[\text{M}+\text{H}]^+$ : 362.1863, found: 362.1789.

**4-(2-((3,4-dihydro-1H-pyrido[3,4-b]indol-9(2H)-yl)methyl)-1H-benzo[d]imidazol-1-yl)butan-1-ol, **5q**.**

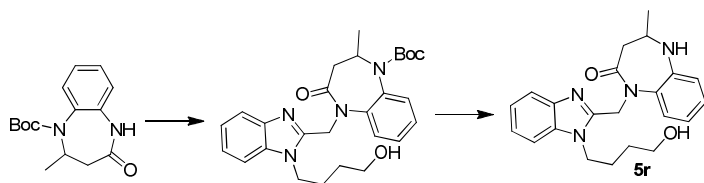


*Step 1.* According to general procedure 1, tert-butyl 3,4-dihydro-1H-pyrido[3,4-b]indole-2(9H)-carboxylate (150 mg, 1.1 eq.) and 4-(2-(chloromethyl)-1H-benzo[d]imidazol-1-yl)butan-1-ol (120 mg, 1.0 eq.) were reacted together in DMF (2 mL). After workup to afford the crude product tert-butyl 9-((1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-2(9H)-carboxylate (240 mg) as yellow oil. HRMS calcd for  $\text{C}_{28}\text{H}_{34}\text{N}_4\text{O}_3$   $[\text{M}+\text{H}]^+$ : 475.2704, found: 475.2633.

*Step 2.* To a solution of the crude (120 mg, 1.0 eq.) in DCM (4 mL) was added TFA (2 mL) at 0°C. The resulting solution was stirred at room temperature for 1 hr. The mixture was concentrated in *vacuo* and the residue was subjected to *prep*-HPLC (0.05% formic acid in water and CAN from 20-55%) for purification to give the title product **5q** (43 mg, 97.7%) as a white solid.  $^1\text{H NMR}$

(400 MHz, Methanol-*d*<sub>4</sub>)  $\delta$  7.62 (d,  $J = 8.0$  Hz, 1H), 7.57-7.50 (m, 3H), 7.33-7.24 (m, 3H), 7.15 (t,  $J = 8.0$  Hz, 1H), 5.74 (s, 2H), 4.23 (s, 2H), 4.17 (t,  $J = 8.0$  Hz, 2H), 3.43 (t,  $J = 8.0$  Hz, 2H), 3.35-3.32 (m, 2H), 3.05-3.02 (m, 2H), 1.42-1.34 (m, 2H), 1.24-1.18 (m, 2H). HRMS calcd for C<sub>23</sub>H<sub>26</sub>N<sub>4</sub>O [M+H]<sup>+</sup>: 375.2179, found: 375.2110.

**1-((1-(4-hydroxybutyl)-*1H*-benzo[*d*]imidazol-2-yl)methyl)-4-methyl-4,5-dihydro-*1H*-benzo[*b*][1,4]diazepin-2(3H)-one, 5r.**



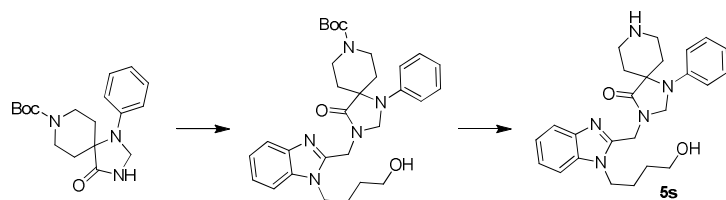
*Step 1.* According to general procedure 1, tert-butyl 2-methyl-4-oxo-2,3,4,5-tetrahydro-*1H*-benzo[*b*][1,4]diazepine-1-carboxylate (130 mg, 1.0 eq.) and 4-(2-(chloromethyl)-*1H*-benzo[*d*]imidazol-1-yl)butan-1-ol (136 mg, 1.2 eq.) were reacted together in DMF (1.5 mL). After workup, the residue obtained was purified by *prep*-TLC to afford the product

tert-butyl-5-((1-(4-hydroxybutyl)-*1H*-benzo[*d*]imidazol-2-yl)methyl)-2-methyl-4-oxo-2,3,4,5-tetrahydro-*1H*-benzo[*b*][1,4]diazepine-1-carboxylate (110 mg, 48.8%) as a pale yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.79 (d,  $J = 7.6$  Hz, 1H), 7.30-7.16 (m, 3H), 7.05-6.98 (m, 1H), 6.75 (d,  $J = 8.0$  Hz, 1H), 6.63 (d,  $J = 8.0$  Hz, 1H), 6.36 (d,  $J = 7.6$  Hz, 1H), 5.43 (d,  $J = 15.2$  Hz, 1H), 4.59 (d,  $J = 15.2$  Hz, 1H), 4.30-4.20 (m, 1H), 3.86-3.78 (m, 2H), 3.72-3.60 (m, 1H), 2.74-2.70 (m, 1H), 3.33-2.20 (m, 1H), 1.67-1.62 (m, 5H), 1.42 (s, 9H), 1.36 (t,  $J = 6.4$  Hz, 3H). HRMS calcd for C<sub>27</sub>H<sub>34</sub>N<sub>4</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 479.2653, found: 479.2578.

*Step 2.* To a solution of tert-butyl 5-((1-(4-hydroxybutyl)-*1H*-benzo[*d*]imidazol-2-yl)methyl)-2-methyl-4-oxo-2,3,4,5-tetrahydro-*1H*-benzo[*b*][1,4]diazepine-1-carboxylate (100 mg, 1.0 eq.) in CF<sub>3</sub>COOH/DCM (5 mL) was stirred at 20°C for 2 hrs, The reaction was quenched with water, The aqueous phase was basified with *aq.*NaHCO<sub>3</sub> till pH = 8 and extracted with EtOAc (50 mL×2). The combined organic layer was

dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated to give crude product. The crude product was subjected to HPLC (0.05% formic acid in water and CAN from 20-55%) for purification to give the title product **5r** (20 mg, 25%) as white solid. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) δ 7.64 (d, *J* = 7.2 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.29-7.25 (m, 2H), 7.90 (d, *J* = 8.0 Hz, 1H), 6.69-6.62 (m, 3H), 4.69-4.63 (m, 2H), 4.29-4.18 (m, 4H), 3.95-3.85 (m, 1H), 2.81 (dd, *J* = 3.6, 14.0 Hz, 1H), 2.44-2.39 (m, 1H), 1.99-1.92 (m, 2H), 1.79-1.75 (m, 2H), 1.30 (d, *J* = 6.0 Hz, 3H). HRMS calcd for C<sub>22</sub>H<sub>26</sub>N<sub>4</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 379.2129, found: 379.2055.

**3-((1-(4-hydroxybutyl)-1*H*-benzo[*d*]imidazol-2-yl)methyl)-1-phenyl-1,3,8-triazaspiro[4.5]decane-4-one, **5s**.**

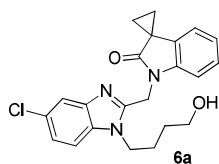


*Step 1.* According to general procedure **1**, tert-butyl tert-butyl 4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decane-8-carboxylate (80 mg, 1.0 eq.) and 4-(2-(chloromethyl)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol (75 mg, 1.2 eq.) were reacted together in DMF (1 mL). After workup to afford the crude product tert-butyl 3-((1-(4-hydroxybutyl)-1*H*-benzo[*d*]imidazol-2-yl)methyl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decane-8-carboxylate (110 mg) as yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.75(d, *J* = 6.8 Hz, 1H), 7.40-7.38 (m, 1H), 7.31-7.29 (m, 2H), 7.22-7.18 (m, 2H), 6.84 (t, *J* = 7.2 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 2H), 4.93 (s, 2H), 4.80 (s, 2H), 4.33 (t, *J* = 8.0 Hz, 2H), 3.73 (t, *J* = 6.0 Hz, 2H), 1.94 (t, *J* = 7.6 Hz, 2H), 1.73-1.58 (m, 7H), 1.50 (s, 12H). HRMS calcd for C<sub>30</sub>H<sub>39</sub>N<sub>5</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 534.3075, found: 534.3001.

*Step 2.* To a solution of tert-butyl tert-butyl 3-((1-(4-hydroxybutyl)-1*H*-benzo[*d*]imidazol-2-yl)methyl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decane-8-carboxylate (100 mg, 1.0 eq.) in TFA/DCM (5 mL) was stirred at 20°C for 2 hrs. After the reaction was complete, the mixture was concentrated to remove TFA and DCM, The residue

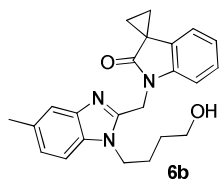
was diluted with THF (2 mL) and added LiOH (23 mg, 0.94 mmol, 5 eq.). The mixture was stirred at 20°C for 3 hrs. The reaction was quenched with water. The mixture was extracted with EtOAc (50 mL×2). The combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated to give crude product. The crude product was subjected to *prep*-HPLC (0.05% formic acid in water and CAN from 20-55%) to give the title product **5s** (20 mg, 24.5%) as a white solid. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) δ 7.65(d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.33-7.28 (m, 4H), 7.03-6.96 (m, 3H), 4.99 (s, 2H), 4.87 (s, 2H), 4.41 (t, *J* = 7.6 Hz, 2H), 3.86-3.79 (m, 2H), 3.61 (t, *J* = 6.4 Hz, 2H), 3.40 (d, *J* = 9.6 Hz, 2H), 2.65-2.58 (m, 2H), 2.14 (d, *J* = 14.8 Hz, 2H), 1.95-1.91 (m, 2H), 1.65-1.62 (m, 2H). HRMS calcd for C<sub>25</sub>H<sub>31</sub>N<sub>5</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 434.2551, found: 434.2479.

**1'-((5-chloro-1-(4-hydroxybutyl)-1*H*-benzo[*d*]imidazol-2-yl)methyl)spiro[cyclopropane-1,3'-indolin]-2'-one, **6a**.**



According to general procedure **2**, to afford the product **6a** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.68 (d, *J* = 1.8 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 1H), 7.27 (dd, *J* = 1.9, 8.7 Hz, 1H), 7.19-7.14 (m, 2H), 7.05-6.97 (m, 2H), 5.29 (s, 2H), 4.48 (s, 1H), 4.31 (t, *J* = 7.7 Hz, 2H), 3.42-3.37 (m, 2H), 1.69-1.60 (m, 6H), 1.47-1.40 (m, 2H). HRMS calcd for C<sub>22</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 396.1473, found: 396.1402.

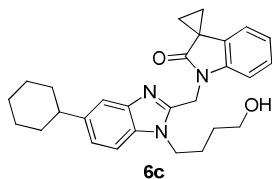
**1'-((1-(4-hydroxybutyl)-5-methyl-1*H*-benzo[*d*]imidazol-2-yl)methyl)spiro[cyclopropane-1,3'-indolin]-2'-one, **6b**.**



According to general procedure **2**, to afford the product **6b** as a white solid. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) δ 7.86 (d, *J* = 9.28 Hz, 1H), 7.48-7.58 (m, 2H), 7.27-7.37 (m, 1H), 7.06-7.22 (m,

3H), 5.67 (s, 2H), 4.56-4.67 (m, 2H), 3.62 (t,  $J = 6.16$  Hz, 2H), 2.68 (s, 1H), 2.56 (s, 3H), 1.99 (td,  $J = 7.84, 15.43$  Hz, 2H), 1.74-1.86 (m, 4H), 1.58-1.71 (m, 2H). HRMS calcd for  $C_{23}H_{25}N_3O_2$   $[M+H]^+$ : 376.2020, found: 376.1948.

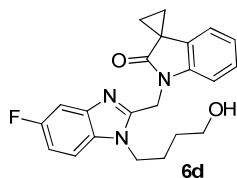
**1'-((5-cyclohexyl-1-(4-hydroxybutyl)-1*H*-benzo[*d*]imidazol-2-yl)methyl)spiro[cyclopropane-1,3'-indolin]-2'-one, 6c.**



To the solution of **6h** (300 mg, 0.68 mmol, 1.0 eq.), cyclohex-1-en-1-ylboronic acid (103 mg, 0.82 mmol, 1.2 eq.),  $Pd(PPh_3)_4$  (61 mg, 0.07 mmol, 0.1 eq.) and  $Na_2CO_3$  (108 mg, 1.02 mmol, 1.5 eq.) in DMF (1 mL) was stirred under microwave at  $90^\circ C$  under  $N_2$  protection over 4 hrs. The reaction was quenched with water, extracted with EA. The combined organic layers were washed with water, dried over  $Na_2SO_4$ , concentrated in vacuum. The residue was purified *via* column chromatography (PE/EA=1:1) to afford 150 mg of light yellow oil.

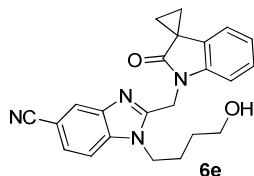
The oil was dissolved in MeOH (4 mL) and Pd/C (30 mg, 5% w/w) was added. The mixture was stirred under  $H_2$  balloon at room temperature overnight. The reaction mixture was filtered and the filtrate was concentrated in vacuum. The residue was purified by *prep*-HPLC (0.05% formic acid in water and CAN from 20-65%) purification to afford the desired compound **6c** (40 mg, 13% yield) as a white solid.  $^1H$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  7.91–7.84 (m, 1H), 7.54-7.41 (m, 4H), 7.32 (s, 1H), 7.21 (d,  $J = 8.5$  Hz, 1H), 6.03 (s, 2H), 4.36 (t,  $J = 7.5$  Hz, 2H), 3.56 (t,  $J = 6.3$  Hz, 2H), 2.62-2.52 (m, 1H), 1.91-1.69 (m, 7H), 1.61-1.24 (m, 11H). HRMS calcd for  $C_{28}H_{33}N_3O_2$   $[M+H]^+$ : 444.2646, found: 444.2572.

**1'-((5-fluoro-1-(4-hydroxybutyl)-1*H*-benzo[*d*]imidazol-2-yl)methyl)spiro[cyclopropane-1,3'-indolin]-2'-one, 6d.**



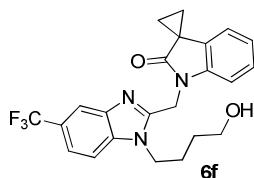
According to general procedure **2**, to afford the product **6d** as a white solid.  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  7.57-7.50 (m, 1H), 7.35-7.32 (m, 1H), 7.20-7.01 (m, 5H), 5.37 (s, 2H), 4.36 (t,  $J$  = 7.6 Hz, 2H), 3.54 (t,  $J$  = 6.4 Hz, 2H), 1.77-1.69 (m, 6H), 1.59-1.57 (m, 2H). HRMS calcd for  $\text{C}_{22}\text{H}_{22}\text{FN}_3\text{O}_2$   $[\text{M}+\text{H}]^+$ : 380.1769, found: 380.1699.

**1-(4-hydroxybutyl)-2-((2'-oxospiro[cyclopropane-1,3'-indolin]-1'-yl)methyl)-1H-benzo[d]imidazole-5-carbonitrile, 6e.**



According to general procedure **2**, to afford the product **6e** as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.10 (s, 1H) 7.50-7.53 (q,  $J$  = 12Hz, 1H) 7.46-7.48 (d,  $J$  = 8Hz, 1H) 7.38-7.40 (d,  $J$  = 8.4Hz, 1H) 7.19-7.23 (t,  $J$  = 16Hz, 1H) 7.00-7.04 (t,  $J$  = 16 Hz, 1H) 6.80-6.83 (d,  $J$  = 7.2Hz, 1H) 5.32 (s, 2H) 4.31-4.35 (t,  $J$  = 15.6Hz, 2H) 3.64-3.68 (q,  $J$  = 15.6Hz, 2H) 1.79-1.81 (m,  $J$  = 7.6Hz, 2H) 1.71-1.75 (m,  $J$  = 15.6Hz, 2H) 1.61-1.65 (m,  $J$  = 13.6 Hz, 2H) 1.58-1.59 (m,  $J$  = 4Hz, 2H). HRMS calcd for  $\text{C}_{23}\text{H}_{22}\text{N}_4\text{O}_2$   $[\text{M}+\text{H}]^+$ : 387.1816, found: 387.1741.

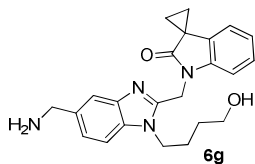
**1'-((1-(4-hydroxybutyl)-5-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)methyl)spiro[cyclopropane-1,3'-indolin]-2'-one, 6f.**



According to general procedure **2**, to afford the product **6f** as a pale white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.00 (s, 1H), 7.84 (d,  $J$  = 8.5 Hz, 1H), 7.60 (d,  $J$  = 8.0 Hz, 1H), 7.21 - 7.14 (m, 2H), 7.07-6.98 (m, 2H), 5.37 (s, 2H), 4.39 (t,  $J$  = 7.7 Hz, 2H), 3.38 (t,  $J$  = 6.4 Hz, 2H),

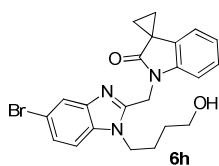
1.71-1.59 (m, 6H), 1.49-1.40 (m, 2H). HRMS calcd for C<sub>23</sub>H<sub>22</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 430.1737, found: 430.1665.

**1'-((5-(aminomethyl)-1-(4-hydroxybutyl)-1*H*-benzo[*d*]imidazol-2-yl)methyl)spiro[cyclopropane-1,3'-indolin]-2'-one, **6g**.**



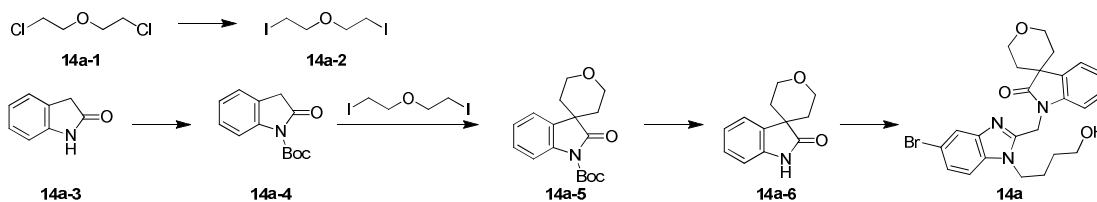
According to general procedure **2**, to afford the product **6g** as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  8.84 (s, 1H), 7.71 (s, 1H), 7.55-7.57 (d, *J* = 8.4Hz, 1H), 7.33-7.35 (d, *J* = 8.4Hz, 1H), 7.12-7.13 (d, *J* = 3.2Hz, 2H), 7.00-7.02 (d, *J* = 7.2Hz, 1H), 6.95-6.96 (d, *J* = 4.8Hz, 2H), 5.26 (s, 2H), 4.78 (s, 1H), 4.25-4.29 (m, *J* = 15.2Hz, 2H), 4.05 (s, 1H), 4.13-4.13 (d, *J* = 3.2Hz, 2H), 1.65(s, 2H), 1.57-1.64(m, *J* = 28.8Hz, 4H), 1.41-1.36 (m, *J* = 21.2Hz, 2H). HRMS calcd for C<sub>23</sub>H<sub>26</sub>N<sub>4</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 391.2129, found: 391.2055.

**1'-((5-bromo-1-(4-hydroxybutyl)-1*H*-benzo[*d*]imidazol-2-yl)methyl)spiro[cyclopropane-1,3'-indolin]-2'-one, **6h**.**



According to general procedure **2**, to afford the product **6h** as a white solid. <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>)  $\delta$  7.77 (s, 1H), 7.42-7.53 (m, 2H), 7.08-7.26 (m, 2H), 7.13-7.23 (m, 2H), 5.28 (s, 2H), 4.27-4.35 (m, 2H), 3.46-3.55 (m, 2H), 1.65-1.80 (m, 6H), 1.47-1.57 (m, 2H). HRMS calcd for C<sub>22</sub>H<sub>22</sub>BrN<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 440.0968, found: 440.0898.

**1-((5-bromo-1-(4-hydroxybutyl)-1*H*-benzo[*d*]imidazol-2-yl)methyl)-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one, **14a****



### Step 1 1-iodo-2-(2-iodoethoxy)ethane (14a-2)

To a mixture of compound 14a-1 (10 g, 70 mmol, 1.0 eq.) and NaI (30 g, 0.2 mol, 2.8 eq.) was stirred in acetone (100 mL) at 55 °C for 18 hours. The mixture was washed with water and extracted with EtOAc (3 times). The organic layer was washed with water and NaHCO<sub>3</sub>(aq.). The organic layer was dried over by Na<sub>2</sub>SO<sub>4</sub>. The organic layer was removed under reduce pressure to afford crude product 16 g (70.2% yield). The crude product which was used next step without further purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.24 (t, *J*=6.72 Hz, 4 H) 3.59 - 3.65 (m, 1 H) 3.71 - 3.80 (m, 5 H).

### Step 2 tert-butyl 2-oxoindoline-1-carboxylate (14a-4)

To a mixture of compound 14a-3 (20 g, 0.15 mol, 1.0 eq.) and DMAP (3.4g, 0.028 mol, 0.19 eq.) in MeCN (200 mL) at 26 °C. Then (Boc)<sub>2</sub>O (41.9 g, 0.192 mol, 1.3 eq.) was added dropwise at 26 °C. The mixture was stirred at 26 °C for 16 hours. The solvent was removed and washed with water. The mixture was extracted with EtOAc. The organic layer was washed with water and brine. The organic layer was dried over and concentrated. The crude product was purified by silica gel chromatography(PE : Ethyl acetate = 70 : 1) to afford 12g (34.2% yield) of compound 14a-4. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.67 (s, 9 H) 3.68 (s, 2 H) 7.17 (d, *J*=7.52Hz, 1 H) 7.26 (s, 1 H) 7.30 - 7.37 (m, 1 H) 7.81 (d, *J*=8.28 Hz, 1 H).

### Step 3 tert-butyl 2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-1-carboxylate (14a-5)

To a mixture of compound 14a-4 (4.395 g, 18.842 mmol, 1.0 eq.), compound 14a-2 (6.035 g, 18.517 mmol, 1.0 eq.) and Cs<sub>2</sub>CO<sub>3</sub> (24.098 g, 73.691 mmol, 4.0 eq.) in DMF (50 mL) was stirred at -20 °C for 16 h. The mixture was washed with water and extracted with EtOAc (3 times). The organic layer was washed with water and NaHCO<sub>3</sub>(aq.). The organic layer was dried over and concentrated. The crude product was purified by silica gel chromatography (PE : Ethyl acetate=25:1) to afford

2.455g (43.8% yield) of compound **14a-5**. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.62 - 1.69 (m, 9 H) 1.79 - 1.89 (m, 2 H) 1.93 (dd, *J*=10.03, 4.40 Hz, 2 H) 3.91 (dt, *J*=11.92, 4.20 Hz, 2 H) 4.19 - 4.31 (m, 2 H) 7.20 (d, *J*=7.32 Hz, 1 H) 7.27 - 7.37 (m, 2 H) 7.83 (d, *J*=8.08 Hz, 1 H).

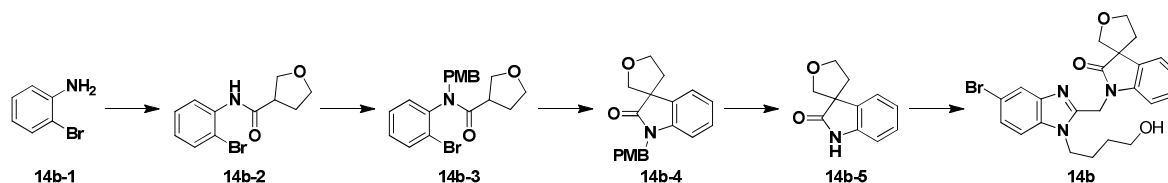
**Step 4 2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one (14a-6)**

To a solution of TFA (7 ml) in DCM (14 mL) was stirred at 26 °C. The solution was added dropwise into compound **14a-5** at 26 °C. The solution was stirred at 26 °C for 30 min. The solution was with NaHCO<sub>3</sub> (aq.) and extracted with EtOAc 3 times. The organic layer was washed with brine. The organic layer was dried over and concentrated. The crude product was purified by silica gel chromatography (PE : Ethyl acetate :DCM = 1 : 1 : 1) to afford 900 mg (56.3% yield) of compound **14a-6**. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.78 - 2.01 (m, 4 H) 3.93 (dt, *J*=11.58, 4.92 Hz, 2 H) 4.24 (ddd, *J*=11.85, 7.55, 4.40 Hz, 2 H) 6.90 (d, *J*=7.72 Hz, 1 H) 7.00 - 7.12 (m, 1 H) 7.23 (t, *J*=7.94 Hz, 1 H) 7.36 (d, *J*=7.52 Hz, 1 H) 7.94 (br. s., 1 H).

**Step 5**  
**1-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one (14a)**

To a mixture of compound **14a-6** (300 mg, 1.476 mmol, 1.0 eq.) in DMF (50 mL) was added NaH (79 mg, 1.9 mmol, 1.3 eq.) at 26 °C. The mixture was stirred at 26 °C for 20 min. Then, to this solution, compound **7** (470 mg, 1.480 mmol, 1.0 eq.) was added. The mixture was stirred at 26 °C for 1.5 hours. The mixture was with NH<sub>4</sub>Cl (aq.) and extracted with EtOAc (3 times). The organic layer was washed with brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduce pressure afford crude product. The crude product was purified by preparative HPLC (0.05% formic acid in water and CAN from 20-65%) to afford 280 mg (39.2% yield) of **14a**. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.94 (d, *J*=1.00 Hz, 1 H), 7.52 (d, *J*=7.76 Hz, 1 H), 7.40 (d, *J*=7.52 Hz, 2 H), 7.30-7.21 (m, 2H), 7.14 - 7.06 (m, 1 H), 5.24 (s, 2 H), 4.41-4.16 (m, 4 H), 4.05-3.90 (m, 2H), 3.72 (t, *J*=5.92 Hz, 2 H), 1.94-1.88 (m, 4H), 1.76-1.65 (m, 4H). HRMS calcd for C<sub>24</sub>H<sub>26</sub>BrN<sub>3</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 484.1230, found: 484.1155.

**1'-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)-4,5-dihydro-2H-spiro[furan-3,3'-indolin]-2'-one, 14b**



**Step 1 N-(2-bromophenyl)tetrahydrofuran-3-carboxamide (14b-2)**

To a stirred solution of tetrahydrofuran-3-carboxylic acid (8.02 g, 70 mmol) in DCM (50 mL) was added oxalyl dichloride (10 mL). And the mixture was stirred at 25 °C for 2 hours. The solvent was removed, then the residue was dissolved in DCM (50 mL). To this solution, 14b-1 (12 g, 70 mmol) and Et<sub>3</sub>N (20 g, 210 mmol) were added. The mixture was stirred at 25 °C for 2 hours. The mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc, washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The crude was purified by column chromatography on silica gel (eluting with PE/EA = 15:1) to give 14 g of compound 14b-2 (74 % yield).

**Step 2 N-(2-bromophenyl)-N-(4-methoxybenzyl)tetrahydrofuran-3-carboxamide (14b-3)**

To a stirred solution of **14b-2** (5.4 g, 20 mmol) in DMF (40 mL) was added NaH (1.6 g, 40 mmol) and PMBCl (4.68 g, 30 mmol). The mixture was stirred at 25 °C for 12 hours. The reaction was quenched with water, extracted with EtOAc, washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The crude was purified by column chromatography on silica gel (eluting with PE / Ethyl acetate = 4:1) to give 8.0 g of compound **14b-3** (100 % yield).

**Step 3 1'-(4-methoxybenzyl)-4,5-dihydro-2H-spiro[furan-3,3'-indolin]-2'-one (14b-4)**

To a solution of compound **14b-3** (2.5 g, 6.4 mmol) in dioxane (6 mL) were added tricyclohexylphosphine (700 mg, 2.5 mmol) and t-BuONa (1.75 g, 12.5 mmol). To this solution, Pd(OAc)<sub>2</sub> (275 mmol, 1.22 mmol) was added. And the mixture was subjected to microwave at 75 °C for 40 mins. The mixture was filtered and extracted with EtOAc, concentrated and the residue was purified by column chromatography on silica gel (eluting with PE / Ethyl acetate = 10:

1) to give 1.2 g of compound **14b-4** (61 % yield).

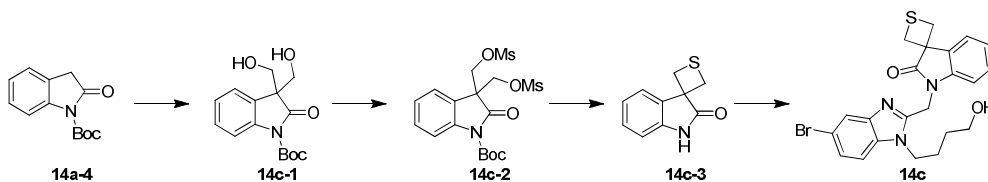
#### Step 4 4,5-dihydro-2H-spiro[furan-3,3'-indolin]-2'-one (**14b-5**)

To a stirred solution of compound **14b-4** (2.0 g, 6.5 mmol) in CF<sub>3</sub>SO<sub>3</sub>H(10 mL) was added. The mixture was stirred at 25 °C for 2 hours. The reaction was quenched with water, extracted with EtOAc, washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The crude was purified by column chromatography on silica gel (eluting with PE/EA = 5:1) to give 0.96 g of compound **14b-5** (80% yield).

#### Step 5 4,5-dihydro-2H-spiro[furan-3,3'-indolin]-2'-one (**14b**)

To a stirred solution of compound **14b-5** (378 mg, 2.0 mmol) in DMF (10 mL) were added 4-(5-bromo-2-(chloromethyl)-1H-benzo[d]imidazol-1-yl)butan-1-ol (634 mg, 2.0 mmol) and NaH (120 mg, 3.0 mmol). The mixture was stirred at 25 °C for one hour. Then the reaction was quenched with H<sub>2</sub>O, extracted with EtOAc, washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was dissolved in DMSO (5 mL). The crude was purified by Prep-HPLC (0.05% formic acid in water and CAN from 20-65%) to obtain the target product **14b** (450 mg, 48% yield). <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400MHz) δ 7.97-7.93 (m, 2H), 7.84-7.82 (d, *J* = 8.2 Hz, 1H), 7.50-7.48 (d, *J* = 7.2 Hz, 1H), 7.40-7.37 (m, 1H), 7.25-7.23 (m, 1H), 7.14-7.112 (d, *J* = 7.2 Hz, 1H), 5.62 (s, 2H), 4.68-4.66 (m, 2H), 4.29-4.27 (m, 1H), 4.26-4.24 (m, 1H), 4.11-4.09 (d, *J* = 8.8 Hz, 1H), 4.04-4.02 (d, *J* = 8.8 Hz, 1H), 3.67-3.64 (m, 2H), 2.58-2.54 (m, 1H), 2.34-2.31 (m, 1H), 2.08-2.04 (m, 2H), 1.72-1.68 (m, 2H). HRMS calcd for C<sub>23</sub>H<sub>24</sub>BrN<sub>3</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 470.1074, found: 470.1003.

#### 1-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)spiro[indoline-3,3'-thietan]-2-one, **14c**



#### Step 1 tert-butyl 3,3-bis(hydroxymethyl)-2-oxindoline-1-carboxylate (**14c-1**)

An aqueous 37% HCHO solution (11.3 mL) was added to a mixture of **14a-4** (12 g, 1.0 eq) and Na<sub>2</sub>CO<sub>3</sub> (1.0 g, 0.2 eq) in dioxane (100 mL), after finished the mixture was stirred at room temperature for 2 h. The solvent was removed and the residue was purified by column chromatography (PE: Ethyl acetate = 3: 1) to obtain the target product (10 g, 66% yield) as white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ: 7.92-7.67 (m, 1H), 7.41-7.36 (m, 2H), 7.24-7.22 (m, 1H), 4.79-4.71 (m, 1H), 4.07-3.98 (m, 4H), 1.67 (s, 9H).

### **Step 2 tert-butyl 3,3-bis(((methylsulfonyl)oxy)methyl)-2-oxindoline-1-carboxylate (14c-2)**

To a solution of **14c-1** (12 g, 1.0 eq) in DCM (100 mL) in ice-water bath was added Et<sub>3</sub>N (37.5 mL, 2.0 eq) through a syringe followed by MsCl (11.7 g, 2.0 eq) also through a syringe, after finished the resulting mixture was stirred at 0 °C for 2.5 h. After being checked with TLC, the solvent was removed under reduced pressure and the residue was purified by column chromatography (PE: Ethyl acetate = 5: 1) to obtain the target product (7 g, 38% yield) as a colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz) δ: 7.90-7.88 (d, *J* = 8.0 Hz, 1H), 7.45-7.41 (m, 2H), 7.28-7.24 (m, 1H), 4.60-4.57 (d, *J* = 10.0 Hz, 2H), 4.48-4.46 (d, *J* = 10.0 Hz, 2H), 2.92 (s, 6H), 1.65 (s, 9H).

### **Step 3 spiro[indoline-3,3'-thietan]-2-one (14c-3)**

A mixture of **14c-2** (8 g, 1.0 eq), Na<sub>2</sub>S (2.12 g 1.5eq) in DMF (50 mL) was stirred at 105 °C for 16 h. After cooling, the mixture was poured into ice-water and saturated NH<sub>4</sub>Cl aqueous solution, extracted with EA (100 mL × 3), the combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated, and purified by column chromatography (PE: Ethyl acetate = 4 : 1) to obtain the target product (1.4 g, 41% yield) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz) δ 7.98-7.96 (d, *J* = 7.2 Hz, 1H), 7.81 (brs, 1H), 7.23-7.19 (m, 1H), 7.11-7.08 (m, 1H), 6.82-6.81 (d, *J* = 7.6 Hz, 1H), 3.82-3.79 (d, *J* = 9.6 Hz, 2H), 3.13-3.10 (d, *J* = 9.6 Hz, 2H).

### **Step**

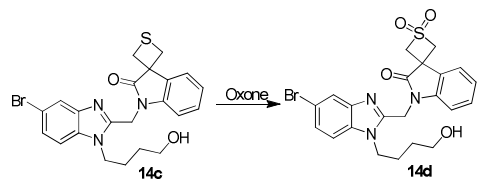
**4**

### **1-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)spiro[indoline-3,3'-thietan]-2-one (14c)**

To a mixture of **14c-3** (80 mg, 1.1 eq) in DMF (4 mL) was added NaH (11 mg, 1.2 eq) in ice-water

bath, after stirred at room temperature for 10 min, 4-(5-bromo-2-(chloromethyl)-1H-benzo[d]imidazol-1-yl)butan-1-ol (120 mg, 1.0 eq) was added, after finished the resulting solution was stirred at room temperature for 16 h. The reaction solution was added cold water and extracted with EtOAc (30mL × 2), the combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated and the residue was further purified by Prep-HPLC (0.05% formic acid in water and CAN from 20-65%) to obtain the target product (85 mg, 47% yield). <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400MHz) δ: 8.22-8.20 (d, *J* = 7.2 Hz, 1H), 7.89-7.87 (m, 2H), 7.76-7.74 (d, *J* = 8.8 Hz, 1H), 7.40-7.38 (m, 1H), 7.32-7.28 (m, 1H), 7.10-7.08 (d, *J* = 7.6 Hz, 1H), 5.53 (s, 2H), 4.63-4.59 (t, *J* = 7.6 Hz, 2H), 3.90-3.88 (d, *J* = 9.6 Hz, 2H), 3.66-3.63 (t, *J* = 6.4 Hz, 2H), 3.27-3.24 (d, *J* = 9.6 Hz, 2H), 2.03-2.00 (m, 2H), 1.72-1.66 (m, 2H). HRMS calcd for C<sub>22</sub>H<sub>22</sub>BrN<sub>3</sub>O<sub>2</sub>S [M+H]<sup>+</sup>: 472.0689, found: 472.0615.

**1-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)spiro[indoline-3,3'-thietan]-2-one 1',1'-dioxide, 14d**



**Step**

**1**

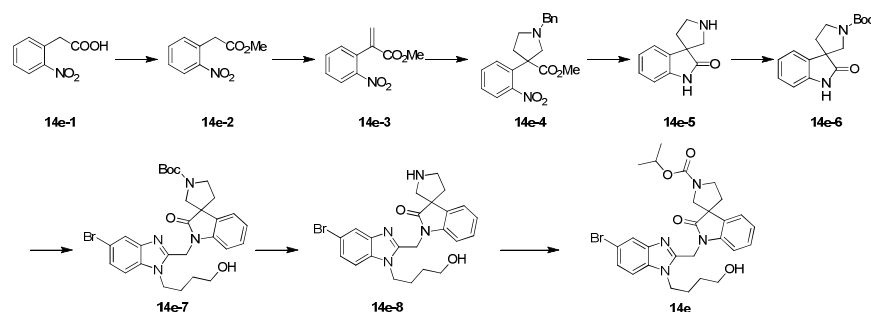
**1-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)spiro[indoline-3,3'-thietan]-2-one 1',1'-dioxide (14d)**

To a stirred ice-cooled solution of compound **14c** (100 mg, 1.0 eq) in a mixture of water (0.8 mL), methanol (5.4 mL), and acetone (1.6 mL) was added Oxone (320 mg, 2.0 eq), after finished the reaction mixture was stirred at room temperature for overnight. The mixture was poured into saturated aqueous NH<sub>4</sub>Cl solution and extracted with EtOAc, the combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure, then the residue was purified by Prep-HPLC (0.05% formic acid in water and CAN from 20-65%) to obtain the target product (30 mg, 25.7%). <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ: 7.94-7.92 (d, *J* = 7.6 Hz, 1H), 7.82-7.76 (m, 2H), 7.66-7.64 (m,

1H), 7.39 (m, 1H), 7.29-7.27 (m, 1H), 7.12-7.10 (d,  $J = 8.0$  Hz, 1H), 5.51 (s, 2H), 4.79-4.75 (m, 2H), 4.58-4.54 (m, 2H), 4.43-4.39 (m, 2H), 3.66-3.63 (m, 2H), 2.04-1.96 (m, 2H), 1.72-1.65 (m, 2H). HRMS calcd for  $C_{22}H_{22}BrN_3O_4S$   $[M+H]^+$ : 504.0587, found: 504.0515.

## isopropyl

### 1-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)-2-oxospiro[indoline-3,3'-pyrrolidine]-1'-carboxylate, **14e**



#### Step 1 methyl 2-(2-nitrophenyl)acetate (**14e-2**)

The compound **14e-1** (60 g, 0.33 mol) was stirring in 300 mL of methanol. Sulfuric acid (1 mL) was added and the mixture heated to reflux. After 14 h, the mixture was cooled and evaporated under reduced pressure to give clear yellow oil. The oil was brought up in EtOAc and washed up with saturated  $NaHCO_3$ . The organic layers were dried and evaporated to afford the compound **14e-2** (64g, 99.07%), which was used directly.  $^1H$  NMR (400MHz,  $CDCl_3$ )  $\delta$  8.11 (d,  $J=7.9$  Hz, 1H), 7.63 - 7.56 (m, 1H), 7.50 - 7.44 (m, 1H), 7.35 (d,  $J=7.5$  Hz, 1H), 4.02 (s, 2H), 3.71 (s, 3H).

#### Step 2 methyl 2-(2-nitrophenyl)acrylate (**14e-3**)

To a solution of the compound **14e-2** (52 g, 0.27 mol) in toluene (416 mL) was added HCHO (20.8 g, 0.63 mol),  $Bu_4NI$  (3.95 g, 10.66 mmol) and  $K_2CO_3$  (109.2 g, 0.8 mol) at room temperature. The resulting mixture was stirred for 12 h at  $80^\circ C$ . After cooling to room temperature, water (500 mL) was added and the aqueous phase was extracted with EtOAc(500 mL  $\times$  2). The collected organic extracts were dried, filtered and concentrated under reduced pressure to give the crude product, which was purified by flash chromatography to afford the compound **3** (51.2g, 92.5%).  $^1H$  NMR (400MHz,  $CDCl_3$ )  $\delta$  8.12 (d,  $J=7.9$  Hz, 1H), 7.65 (dt,  $J=1.3, 7.5$  Hz, 1H), 7.57 - 7.49 (m, 1H), 7.39

(dd,  $J=1.1, 7.7$  Hz, 1H), 6.54 (s, 1H), 5.88 (s, 1H), 3.78 - 3.67 (m, 3H).

### Step 3 methyl 1-benzyl-3-(2-nitrophenyl)pyrrolidine-3-carboxylate (14e-4)

To the solution of compound **14e-3** (6.2 g, 29.01 mmol) and TFA (66 mg, 46.26 mmol) in  $\text{CHCl}_3$  (5 mL) was added a solution of N-benzyl-1-methoxy-N-((trimethylsilyl)methyl)methanamine (8.25 g, 34.79 mmol) in  $\text{CHCl}_3$  (25 mL) at  $0^\circ\text{C}$  and the reaction solution was stirred at  $70^\circ\text{C}$  for 12 h. After cooling to room temperature, saturated  $\text{NaHCO}_3$  (100 mL) was added and the aqueous phase was extracted with DCM (50 mL  $\times$  2). The collected organic extracts were dried, filtered and concentrated under reduced pressure to give the crude product, which was purified by flash chromatography to afford the compound **14e-4** (7.4g, 75%).  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  7.88 (dd,  $J=0.9, 7.9$  Hz, 1H), 7.77 (d,  $J=7.5$  Hz, 1H), 7.61 - 7.53 (m, 1H), 7.41 - 7.30 (m, 5H), 7.30 - 7.24 (m, 1H), 3.78 - 3.71 (m, 1H), 3.67 - 3.55 (m, 4H), 3.37 - 3.27 (m, 1H), 3.10 - 2.99 (m, 2H), 2.82 (d,  $J=10.6$  Hz, 1H), 2.69 - 2.57 (m, 1H), 2.19 - 2.04 (m, 1H).

### Step 4 methyl 1-benzyl-3-(2-nitrophenyl)pyrrolidine-3-carboxylate (14e-5)

To a solution of **14e-4** (4.9 g, 14.5 mmol) in MeOH (1 L) was added Pd/C (1.0 g) and the suspension was degassed under vacuum and purged  $\text{H}_2$  three times. The mixture was stirred at  $50^\circ\text{C}$  under the atmosphere of  $\text{H}_2$  at 50 psi for 4 h. The mixture was filtrated and evaporated under the reduced pressure to afforded the compound **14e-5** (2.7 g, 99.2%), which was used directly.

### Step 5 tert-butyl 2-oxospiro[indoline-3,3'-pyrrolidine]-1'-carboxylate (14e-6)

To a solution of **14e-5** (2.8 g, 14.8 mmol) and  $\text{Et}_3\text{N}$  (4.67 mL) in DCM (20 mL) was added to  $\text{Boc}_2\text{O}$  (2.9 g, 13.3mmol) dropwise at  $0^\circ\text{C}$ . The mixture was stirred at the temperature. After 20 min, the mixture was washed up with water and the organic layers was evaporated under reduced pressure and separated by silica gel column chromatography using (PE:EA=20:1- PE:EA=3:1) to afforded the compound **14e-6** (1.4g, 36.8%).  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  7.59 - 7.46 (m, 1H), 7.14 - 7.06 (m, 1H), 6.99 (t,  $J=7.3$  Hz, 1H), 6.84 (d,  $J=7.5$  Hz, 1H), 3.83 - 3.61 (m, 3H), 3.59 - 3.45 (m, 1H), 2.40 - 2.29 (m, 1H), 1.98 (s, 1H), 1.46 - 1.31 (m, 9H).

**Step****6****tert-butyl****1-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)-2-oxospiro[indoline-3,3'-pyrrolidine]-1'-carboxylate (14e-7)**

To a mixture of Compound **14e-6** (0.5 g, 1.74 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.7 g, 7.29 mmol) in CH<sub>3</sub>CN (20 mL) was added to Compound 4-(5-bromo-2-(chloromethyl)-1H-benzo[d]imidazol-1-yl)butan-1-ol (0.60 g, 1.91 mmol) and the mixture was refluxed for 10 h. The mixture was filtered and the filtrate was evaporated under reduced pressure and separated by gel column chromatography using (PE : Ethyl acetate=20:1 PE : Ethyl acetate=1:1) to afford the compound **14e-7** (0.38g, 38.5%) as a white solid. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 7.85 (d, *J*=1.3 Hz, 1H), 7.51 - 7.39 (m, 1H), 7.31 (dd, *J*=1.5, 8.6 Hz, 1H), 7.22 - 7.18 (m, 1H), 7.15 (d, *J*=8.4 Hz, 1H), 7.10 (d, *J*=6.6 Hz, 1H), 7.03 - 6.97 (m, 1H), 5.38 (d, *J*=15.4 Hz, 1H), 5.24 - 5.09 (m, 1H), 4.93 (d, *J*=15.4 Hz, 1H), 4.35 - 4.24 (m, 1H), 4.25 - 4.19 (m, 1H), 4.15 - 3.95 (m, 1H), 3.89 - 3.74 (m, 2H), 3.72 - 3.59 (m, 4H), 3.48 (br. s., 1H), 2.44 - 2.27 (m, 1H), 2.19 - 2.07 (m, 1H), 1.74 (d, *J*=8.8 Hz, 2H), 1.63 - 1.49 (m, 3H), 1.48 - 1.34 (m, 9H).

**Step****7****1-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)spiro[indoline-3,3'-pyrrolidin]-2-one (14e-8)**

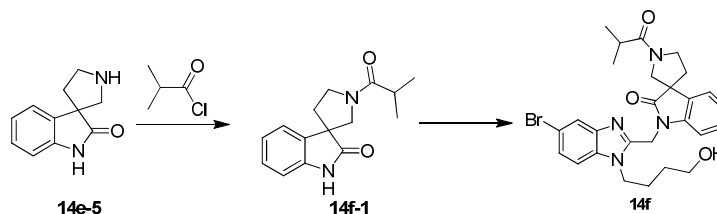
To a solution of **14e-7** (0.16 g, 0.282 mmol) in CH<sub>3</sub>OH (3 mL) was added to HCl/CH<sub>3</sub>OH (1 mol/L, 120 mL) dropwise at room temperature. The mixture was stirred at room temperature for 5 h and evaporated under reduced pressure to afford **14e-8** (0.13g, 98.5%) as a white solid. <sup>1</sup>H NMR (400MHz, CD<sub>3</sub>OD) δ 7.88 (d, *J*=11.0 Hz, 1H), 7.79 - 7.71 (m, 1H), 7.57 (d, *J*=7.5 Hz, 1H), 7.44 - 7.38 (m, 1H), 7.29 - 7.23 (m, 1H), 7.14 (d, *J*=7.9 Hz, 1H), 5.56 (s, 2H), 4.62 (t, *J*=7.7 Hz, 2H), 3.86 - 3.73 (m, 3H), 3.72 - 3.58 (m, 3H), 2.65 - 2.55 (m, 1H), 2.53 - 2.41 (m, 1H), 2.04 (quin, *J*=7.6 Hz, 2H), 1.74 - 1.63 (m, 2H).

**Step****8****isopropyl****1-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)-2-oxospiro[indoline-3,3'-p**

### pyrrolidine]-1'-carboxylate (**14e**)

To a solution of **14e-8** (90 mg, 0.192 mmol) and Et<sub>3</sub>N (96.9 mg, 0.96 mmol) in DCM (10 mL) was added to isopropyl carbonochloridate (23.4 mg, 0.192mmol) dropwise at -10 °C. After 10 mins, the mixture was washed up with saturated NH<sub>4</sub>Cl and extract with EtOAc and the organic layers was evaporated under reduced pressure and separated by TLC using (Ethyl acetate : CH<sub>3</sub>OH = 40 : 1) to afford compound **14e** (56mg, 52.8%). <sup>1</sup>H NMR (400MHz, MeOH-d<sub>4</sub>) δ 7.73 (s, 1H), 7.52 - 7.46 (m, 1H), 7.43 - 7.38 (m, 1H), 7.26 (dd, *J*=7.3, 19.2 Hz, 2H), 7.13 - 7.05 (m, 2H), 5.35 - 5.23 (m, 2H), 5.00 - 4.87 (m, 1H), 4.37 (t, *J*=7.5 Hz, 2H), 3.92 - 3.52 (m, 6H), 2.49 - 2.36 (m, 1H), 2.33 - 2.17 (m, 1H), 1.85 (br. s., 2H), 1.72 - 1.51 (m, 2H), 1.33 - 1.23 (m, 6H). HRMS calcd for C<sub>27</sub>H<sub>31</sub>BrN<sub>4</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 555.1601, found: 555.1527.

### 1-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)-1'-isobutyrylspiro[indoline-3,3'-pyrrolidin]-2-one, **14f**



#### Step 1 1'-isobutyrylspiro[indoline-3,3'-pyrrolidin]-2-one (**14f-1**)

To a solution of **14e-5** (0.55 g, 2.928 mmol) and Et<sub>3</sub>N(0.887 g, 8.782 mmol) in DCM(25 mL) was added to isobutyryl chloride (0.312 g, 2.975 mmol) at 0°C. After 10 min, the mixture was washed up with saturated NH<sub>4</sub>Cl and extracted with EA, concentrated under reduced pressure to afford the compound **14f-1** (0.750 g, 99.3%) as white oil. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 8.49 - 8.20 (m, 1H), 7.20 - 7.13 (m, 1H), 7.08 (dd, *J*=3.3, 7.3 Hz, 1H), 7.04 - 6.95 (m, 1H), 6.93 - 6.79 (m, 1H), 4.12 - 3.54 (m, 4H), 2.78 - 2.33 (m, 2H), 2.31 - 1.96 (m, 1H), 1.18 - 1.04 (m, 6H).

#### Step

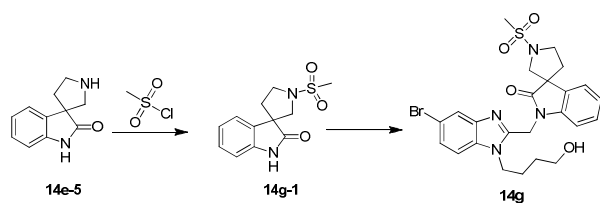
2

### 1-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)-1'-isobutyrylspiro[indoline-3,3'-pyrrolidin]-2-one, (**14f**)

To a mixture of **14f-1** (0.264 g, 1.023 mmol) and 4-(5-bromo-2-(chloromethyl)-1H-benzo

[d]imidazol-1-yl)butan-1-ol (0.356 g, 1.126 mmol), K<sub>2</sub>CO<sub>3</sub> (0.430 g, 3.070 mmol) in CH<sub>3</sub>CN (10 mL) was reflux for 12 h. The mixture was filter and the filtered was concentrated under reduced pressure and separated by TLC(Ethyl acetate : MeOH = 20 : 1) to afford the compound **14f** (0.24 g, 43.6%) as white solid. <sup>1</sup>H NMR (400MHz, DMSO-d<sub>6</sub>) δ 7.78 (s, 1H), 7.56 (dd, *J*=2.6, 8.8 Hz, 1H), 7.44 - 7.28 (m, 2H), 7.28 - 7.14 (m, 2H), 7.09 - 7.02 (m, 1H), 5.27 - 5.15 (m, 2H), 4.49 - 4.41 (m, 1H), 4.30 (t, *J*=7.1 Hz, 2H), 4.01 - 3.76 (m, 2H), 3.73 - 3.53 (m, 2H), 3.45 - 3.35 (m, 2H), 2.84 - 2.56 (m, 1H), 2.42 - 2.06 (m, 2H), 1.69 (br. s., 2H), 1.49 - 1.38 (m, 2H), 1.05 (t, *J*=7.3 Hz, 3H), 1.01 - 0.91 (m, 3H). HRMS calcd for C<sub>27</sub>H<sub>31</sub>BrN<sub>4</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 539.1652, found: 539.1582.

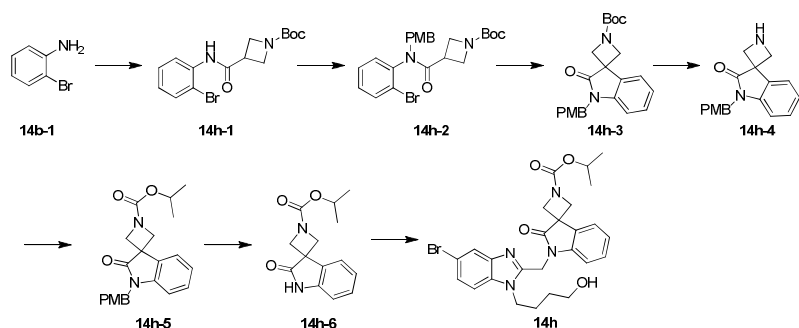
**1-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)-1'-(methylsulfonyl)spiro[indoline-3,3'-pyrrolidin]-2-one, *14g***



1-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)-1'-(methylsulfonyl)spiro[indoline-3,3'-pyrrolidin]-2-one was prepared by the common procedure as compound **14f** starting with **14e-5**, methanesulfonyl chloride and 4-(5-bromo-2-(chloromethyl)-1H-benzo[d]imidazol-1-yl)butan-1-ol. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 7.85 (d, *J*=1.8 Hz, 1H), 7.43 (d, *J*=7.5 Hz, 1H), 7.32 (dd, *J*=1.8, 8.8 Hz, 1H), 7.23 (d, *J*=7.9 Hz, 2H), 7.15 (d, *J*=8.4 Hz, 1H), 7.07 - 7.02 (m, 1H), 5.24 - 5.08 (m, 2H), 4.27 - 4.13 (m, 2H), 3.80 - 3.70 (m, 2H), 3.68 - 3.53 (m, 4H), 2.94 (s, 3H), 2.37 (td, *J*=6.4, 12.8 Hz, 1H), 2.23 (td, *J*=7.5, 12.8 Hz, 1H), 1.78 - 1.68 (m, 2H), 1.62 - 1.53 (m, 2H). HRMS calcd for C<sub>24</sub>H<sub>27</sub>BrN<sub>4</sub>O<sub>4</sub>S [M+H]<sup>+</sup>: 547.1009, found: 547.0938.

**isopropyl**

**1'-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxospiro[azetidine-3,3'-indoline]-1-carboxylate, *14h***



### Step 1 tert-butyl 3-((2-bromophenyl)carbamoyl)azetidine-1-carboxylate (14h-1)

To a mixture of 1-(tert-butoxycarbonyl)azetidine-3-carboxylic acid (5.85 g, 29.07 mmol, 1.0 eq.) in THF (50 mL) was added CDI (4.95 g, 30.52 mmol, 1.05 eq.) at room temperature. The mixture was refluxed for 90 mins. Then compound **14b-1** (5.0 g, 29.07 mmol, 1.0 eq.) was added at room temperature. The mixture was refluxed overnight. The mixture was concentrated and the residue was extracted with EtOAc and H<sub>2</sub>O. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by silica gel chromatography (PE:EtOAc=3:1) to afford 5 g (48.4 % yield) of compound **14h-1** as colorless oil. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>), δ 8.35 (d, *J* = 7.9 Hz, 1H), 7.66 (br. s., 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.34 (t, *J* = 7.7 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 4.29 - 4.14 (m, 4H), 3.46 - 3.34 (m, 1H), 1.46 (s, 9H).

### Step 2 tert-butyl 3-((2-bromophenyl)(4-methoxybenzyl)carbamoyl)azetidine-1-carboxylate (14h-2)

To a solution of compound **14h-1** (5.0 g, 14.08 mmol, 1.0 eq.) in DMF (50 mL) was added NaH (676 g, 16.89 mmol, 1.2 eq.) at 0°C. The mixture was stirred at 0°C for 10 mins and at room temperature for 10 mins. PMBCl (2.42 g, 15.48 mmol, 1.1 eq.) was added at 0°C. The mixture was stirred at 0°C for 10 mins and at room temperature for 2 h. TLC analysis showed the reaction was complete. The mixture was extracted with EtOAc and H<sub>2</sub>O. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by silica gel chromatography (PE : EtOAc = 5 : 1) to afford 6.5 g (97.2 % yield) of compound **14h-2** as white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.69 (dd, *J* = 1.9, 7.7 Hz, 1H), 7.25 - 7.16 (m, 2H), 7.10 (d, *J* = 8.5 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 6.65 (dd, *J* = 2.0, 7.3 Hz, 1H), 5.56 (d, *J* = 14.1 Hz, 1H), 4.29 (br.

s., 1H), 4.00 (d,  $J = 14.3$  Hz, 2H), 3.79 (s, 3H), 3.72 (br. s., 1H), 3.56 (br. s., 1H), 3.10 - 3.01 (m, 1H), 1.41 (s, 9H).

**Step 3 tert-butyl 1'-(4-methoxybenzyl)-2'-oxospiro[azetidine-3,3'-indoline]-1-carboxylate (14h-3)**

To a solution of compound **14h-2** (1.63 g, 3.42 mmol, 1.0 eq.) in toluene (5 mL) was added *i*-Pr-PEPPSI (163 mg, cat.), *t*-BuONa (493 mg, 5.13 mmol, 1.5 eq.). The mixture was stirred at 110°C under microwave for 30 mins. TLC analysis showed the STM was consumed. The mixture was extracted with EtOAc and H<sub>2</sub>O. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by silica gel chromatography (PE:EtOAc=10:1) to afford 3.7 g (68.6 % yield) of compound **14h-3** as yellow oil. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>)  $\delta$  7.59 (d,  $J = 7.3$  Hz, 1H), 7.32 - 7.26 (m, 3H), 7.15 (t,  $J = 8.0$  Hz, 1H), 6.89 (d,  $J = 8.5$  Hz, 2H), 6.82 (d,  $J = 7.8$  Hz, 1H), 4.89 (s, 2H), 4.47 (d,  $J = 8.3$  Hz, 2H), 4.13 (d,  $J = 8.0$  Hz, 2H), 3.82 (s, 3H), 1.55 (s, 9H).

**Step 4 1'-(4-methoxybenzyl)spiro[azetidine-3,3'-indolin]-2'-one (14h-4)**

To a solution of compound **14h-3** (500 mg, 1.27 mmol, 1.0 eq.) in DCM (5 mL) was added TFA (2.5 mL) at room temperature. The resulting solution was stirred at room temperature for 1 hour. TLC analysis showed the STM was consumed. The pH was adjusted to 7 using saturated Na<sub>2</sub>CO<sub>3</sub> solution. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to afford 360 mg (96.5 % yield) of compound **14h-4** as yellow oil. <sup>1</sup>H NMR (400MHz, DMSO-*d*<sub>6</sub>)  $\delta$  7.73 (d,  $J = 7.3$  Hz, 1H), 7.28 - 7.17 (m, 3H), 7.09 (t,  $J = 8.0$  Hz, 1H), 6.94 - 6.81 (m, 3H), 4.79 (s, 2H), 4.00 (d,  $J = 7.3$  Hz, 2H), 3.69 (s, 3H), 3.55 (d,  $J = 7.3$  Hz, 2H).

**Step 5 isopropyl 1'-(4-methoxybenzyl)-2'-oxospiro[azetidine-3,3'-indoline]-1-carboxylate (14h-5)**

To a solution of compound **14h-4** (360 mg, 1.22 mmol, 1.0 eq.) in DCM (4 mL) was added TEA (371 mg, 3.67 mmol, 3.0 eq.) at room temperature. Isopropyl carbonochloridate (164 mg, 1.34 mmol, 1.1 eq.) was added dropwise at 0°C. The mixture was stirred at room temperature for 1 hour.

TLC analysis showed the STM was consumed. The mixture was extracted with DCM and H<sub>2</sub>O. The combined organic layers were washed with HCl (1 N), saturated Na<sub>2</sub>CO<sub>3</sub> solution, H<sub>2</sub>O, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to afford 460 mg (99.1 % yield) of compound **14h-5** as yellow oil. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 7.55 (d, *J* = 7.3 Hz, 1H), 7.26 - 7.19 (m, 3H), 7.11 (t, *J* = 8.0 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 7.8 Hz, 1H), 5.01 - 4.95 (m, 1H), 4.84 (s, 2H), 4.46 (d, *J* = 8.0 Hz, 2H), 4.13 (d, *J* = 8.0 Hz, 2H), 3.78 (s, 3H), 1.29 (d, *J* = 6.3 Hz, 6H).

#### **Step 6 isopropyl 2'-oxospiro[azetidine-3,3'-indoline]-1-carboxylate (14h-6)**

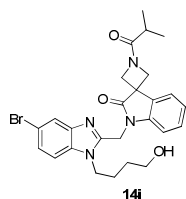
To a solution of compound **14h-5** (350 mg, 0.92 mmol, 1.0 eq.) in CH<sub>3</sub>CN (10.5 mL) and H<sub>2</sub>O (3.5 mL) was added (NH<sub>4</sub>)<sub>2</sub>Ce(NO<sub>3</sub>)<sub>6</sub> (3.03 g, 5.52 mmol, 6.0 eq.) and 2,6-dicarboxypyridine 1-oxide (1.01 g, 5.52 mmol, 6.0 eq.). The mixture was stirred at room temperature for 2 hours. TLC analysis showed the reaction was complete. The mixture was extracted with EtOAc and saturated Na<sub>2</sub>CO<sub>3</sub> solution. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by silica gel chromatography (PE:EtOAc=4:1) to afford 70 mg (29.3 % yield) of compound **14h-6** as yellow oil. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 7.67 (br. s., 1H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.32 - 7.27 (m, 1H), 7.18 - 7.11 (m, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.03 - 4.94 (m, 1H), 4.43 (d, *J* = 8.0 Hz, 2H), 4.15 - 4.09 (m, 2H), 1.31 - 1.26 (d, *J* = 4.0 Hz, 6H).

#### **Step 7 isopropyl 1'-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxospiro[azetidine-3,3'-indoline]-1-carboxylate (14h)**

To a solution of compound **14h-6** (70 mg, 0.269 mmol, 1.0 eq.) in DMF (2 mL) was added NaH (13 mg, 0.323 mmol, 1.2 eq.) at 0°C. The resulting solution was stirred at 0°C for 10 mins and at room temperature for 10 mins. 4-(5-bromo-2-(chloromethyl)-1H-benzo[d]imidazol-1-yl)butan-1-ol (94 mg, 0.296 mmol, 1.1 eq.) was added at 0°C, the mixture was stirred at 0°C for 10 mins and at room temperature overnight. The mixture was extracted with EtOAc and H<sub>2</sub>O. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was subjected to prep-HPLC (0.05% formic acid in water and CAN from 20-65%) for purification

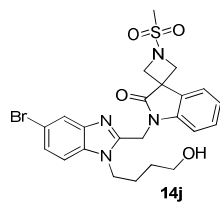
to afford 37 mg (25.3 % yield) of **14h** as white solid.  $^1\text{H NMR}$  (400MHz, Methanol- $d_4$ )  $\delta$  7.72-7.62 (m, 2H), 7.52 (d,  $J = 8.0$  Hz, 1H), 7.45-7.40 (m, 1H), 7.31-7.24 (m, 1H), 7.22-7.15 (m, 1H), 6.97 (d,  $J = 7.78$  Hz, 1H), 5.29 (s, 2H), 4.98-4.93 (m, 1H), 4.45-4.32 (m, 4H), 4.20 (d,  $J = 7.78$  Hz, 2H), 3.60 (t,  $J = 6.27$  Hz, 2H), 1.93 – 1.85 (m, 2H), 1.67-1.56 (m, 2H), 1.29 (d,  $J = 6.27$  Hz, 6H). HRMS calcd for  $\text{C}_{26}\text{H}_{29}\text{BrN}_4\text{O}_4$   $[\text{M}+\text{H}]^+$ : 541.1445, found: 541.1373.

**1'-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)-1-isobutyrylspiro[azetidine-3,3'-indolin]-2'-one, 14i**



1'-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)-1-isobutyrylspiro[azetidine-3,3'-indolin]-2'-one (**14i**) was prepared by the common procedure as compound **14h** starting with **14h-4** and isobutyryl chloride.  $^1\text{H NMR}$  (400MHz, MeOH- $d_4$ )  $\delta$  7.73 - 7.70 (m, 1H), 7.70 - 7.66 (m, 1H), 7.57 - 7.52 (m, 1H), 7.48 - 7.42 (m, 1H), 7.34 - 7.28 (m, 1H), 7.24 - 7.18 (m, 1H), 7.03 - 6.98 (m, 1H), 5.37 - 5.27 (m, 2H), 4.68 - 4.64 (m, 1H), 4.56 - 4.51 (m, 1H), 4.47 - 4.36 (m, 3H), 4.26 - 4.21 (m, 1H), 3.65 - 3.59 (m, 2H), 2.73 - 2.65 (m, 1H), 1.96 - 1.85 (m, 2H), 1.70 - 1.59 (m, 2H), 1.23 - 1.14 (m, 6H). HRMS calcd for  $\text{C}_{26}\text{H}_{29}\text{BrN}_4\text{O}_3$   $[\text{M}+\text{H}]^+$ : 525.1496, found: 525.1421.

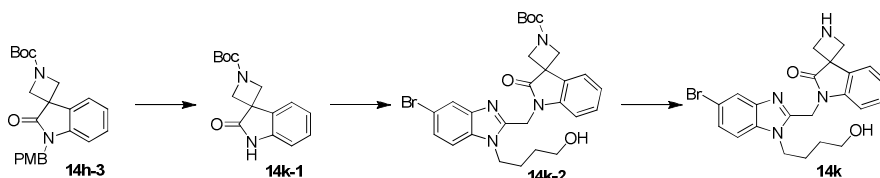
**1'-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)-1-(methylsulfonyl)spiro[azetidine-3,3'-indolin]-2'-one, 14j**



1'-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)-1-(methylsulfonyl)spiro[azetidine-3,3'-indolin]-2'-one (**14j**) was prepared by the common procedure as compound **14h** starting with **14h-4** and Methanesulfonyl chloride.  $^1\text{H NMR}$  (400MHz, MeOH- $d_4$ )  $\delta$  7.93 - 7.88 (m, 1H), 7.87 - 7.85 (m, 1H), 7.84 - 7.80 (m, 1H), 7.80 - 7.74 (m, 1H), 7.43 - 7.35 (m, 1H), 7.34 - 7.26 (m,

1H), 7.11 - 7.03 (m, 1H), 5.58 (s, 2H), 4.62 (s, 2H), 4.42 (d,  $J=8.5$  Hz, 2H), 4.20 (d,  $J=8.3$  Hz, 2H), 3.65 (t,  $J=6.1$  Hz, 2H), 3.13 (s, 3H), 2.11 - 1.99 (m, 2H), 1.78 - 1.60 (m, 2H). HRMS calcd for  $C_{23}H_{25}BrN_4O_4S$   $[M+H]^+$ : 533.0853, found: 533.0782.

**1'-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)spiro[azetidine-3,3'-indoline]-2'-one, 14k**



**Step 1 tert-butyl 2'-oxospiro[azetidine-3,3'-indoline]-1-carboxylate (14k-1)**

To a solution of compound **14h-3** (3.68 g, 9.34 mmol, 1.0 eq.) in  $CH_3CN$  (108 mL) and  $H_2O$  (36 mL) was added  $(NH_4)_2Ce(NO_3)_6$  (20.47 g, 37.36 mmol, 4.0 eq.). The mixture was stirred at room temperature for 2 hours. The mixture was extracted with EtOAc and  $H_2O$ . The combined organic layers were washed with brine, dried over  $Na_2SO_4$ , filtered and concentrated. The residue was purified by silica gel chromatography (PE:EtOAc=3:1) to afford 500 mg (19.5 % yield) of compound **14k-1** as yellow oil.  $^1H$  NMR (400MHz,  $CDCl_3$ )  $\delta$  7.96 (br. s., 1H), 7.54 (d,  $J=7.3$  Hz, 1H), 7.31 - 7.27 (t,  $J=8.0$  Hz, 1H), 7.18 - 7.09 (t,  $J=8.0$  Hz, 1H), 6.90 (d,  $J=7.8$  Hz, 1H), 4.39 (d,  $J=8.3$  Hz, 2H), 4.11 - 4.06 (m, 2H), 1.50 (s, 9H).

**Step 2 tert-butyl 1'-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxospiro[azetidine-3,3'-indoline]-1-carboxylate (14k-2)**

To a solution of compound **14k-1** (500 mg, 2.69 mmol, 1.0 eq.) in DMF (5 mL) was added NaH (129 mg, 3.22 mmol, 1.2 eq.) at  $0^\circ C$ . The resulting solution was stirred at  $0^\circ C$  for 10 mins and at room temperature for 10 mins. 4-(5-bromo-2-(chloromethyl)-1H-benzo[d]imidazol-1-yl)butan-1-ol was added at  $0^\circ C$ , the mixture was stirred at  $0^\circ C$  for 10 mins and at room temperature overnight. The mixture was extracted with EtOAc and  $H_2O$ . The combined organic layers were washed with brine, dried over  $Na_2SO_4$ , filtered and concentrated. The residue was purified by silica gel

chromatography (PE : EtOAc = 1 : 1) to afford 350 mg (23.5 % yield) of **14k-2** as white solid. <sup>1</sup>H NMR (400MHz, MeOH-*d*<sub>4</sub>) δ 7.69 (d, *J* = 1.3 Hz, 1H), 7.65 (d, *J* = 7.3 Hz, 1H), 7.55 - 7.49 (d, *J* = 8.0 Hz, 1H), 7.45 - 7.40 (m, 1H), 7.27 (t, *J* = 8.0 Hz, 1H), 7.18 (t, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 7.8 Hz, 1H), 5.29 (s, 2H), 4.44 - 4.33 (m, 4H), 4.16 (d, *J* = 8.0 Hz, 2H), 3.60 (t, *J* = 6.1 Hz, 2H), 1.92 - 1.84 (m, 2H), 1.67 - 1.59 (m, 2H), 1.51 (s, 9H).

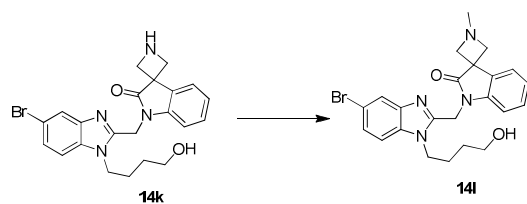
### Step

3

#### 1'-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)spiro[azetidine-3,3'-indolin]-2'-one (**14k**)

To a solution of compound **14k-2** (330 mg, 0.59 mmol, 1.0 eq.) in MeOH (2 mL) was added HCl/MeOH (4N, 2 mL) dropwise at 0°C. The resulting solution was stirred at 0°C for 10 mins and at room temperature for 1 hour. TLC analysis showed the STM was consumed. The pH was adjusted to 7 using saturated Na<sub>2</sub>CO<sub>3</sub> solution. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to afford 200 mg (74.1 % yield) of **14k** as white solid. <sup>1</sup>H NMR (400MHz, MeOH-*d*<sub>6</sub>) δ 7.93 (d, *J* = 7.3 Hz, 1H), 7.90 - 7.84 (m, 2H), 7.74 (d, *J* = 10.0 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 5.57 (s, 2H), 4.62 (t, *J* = 7.8 Hz, 2H), 4.56 - 4.49 (m, 2H), 4.47 - 4.39 (m, 2H), 3.66 (t, *J* = 6.0 Hz, 2H), 2.06 (m, 2H), 1.74 - 1.67 (m, 2H). HRMS calcd for C<sub>22</sub>H<sub>23</sub>BrN<sub>4</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 455.1077, found: 455.1001.

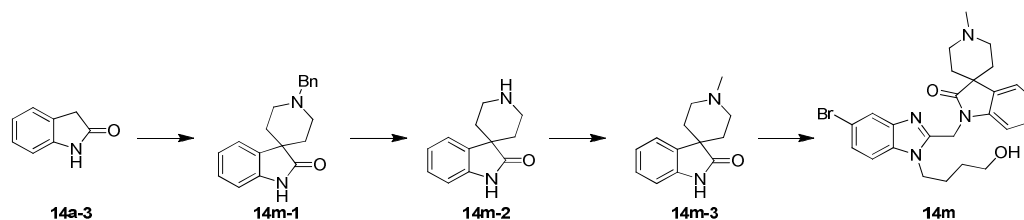
#### 1'-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)-1-methylspiro[azetidine-3,3'-indolin]-2'-one, **14l**



To a solution of compound **14k** (180 mg, 0.40 mmol, 1.0 eq.) in MeOH (2 mL) was added AcOH (3 drops) and HCHO (36 mg, 1.186 mmol, 3.0 eq.) at room temperature. The resulting solution was stirred at rt for 30 mins. NaBH<sub>3</sub>CN (75 mg, 1.186 mmol, 3.0 eq.) was added at room temperature.

The mixture was stirred at room temperature overnight. After the reaction was completed. The mixture was subjected to prep-HPLC (0.05% formic acid in water and CAN from 20-55%) for purification to afford 60 mg (32.4 % yield) of **14l** as white solid.  $^1\text{H}$  NMR (400MHz, MeOH- $d_6$ )  $\delta$  7.99 - 7.84 (m, 3H), 7.75 (d,  $J$  = 8.8 Hz, 1H), 7.42 (t,  $J$  = 8.0 Hz, 1H), 7.32 (t,  $J$  = 8.0 Hz, 1H), 7.08 (d,  $J$  = 7.8 Hz, 1H), 5.59 (s, 2H), 4.77 - 4.70 (m, 2H), 4.63 (t,  $J$  = 7.7 Hz, 2H), 4.51 (d,  $J$  = 11.3 Hz, 1H), 4.38 (d,  $J$  = 11.5 Hz, 1H), 3.66 (t,  $J$  = 5.9 Hz, 2H), 3.24 - 3.11 (m, 3H), 2.11 - 2.03 (m, 2H), 1.77 - 1.64 (m, 2H). HRMS calcd for  $\text{C}_{23}\text{H}_{25}\text{BrN}_4\text{O}_2$   $[\text{M}+\text{H}]^+$ : 469.1234, found: 469.1164.

**1-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)-1'-methylspiro[indoline-3,4'-piperidin]-2-one, *14m***



**Step 1 1'-benzylspiro[indoline-3,4'-piperidin]-2-one (**14m-1**)**

To a mixture of **14a-3** (5 g, 1.0 eq) in THF (50 mL) was added NaHMDS (187.8 mL, 5 eq) dropwise at  $-60^\circ\text{C}$ , the mixture was stirred at this temperature for 0.5h, then compound N-benzyl-2-chloro-N-(2-chloroethyl)ethanamine (13.1 g, 1.5 eq) was added and the reaction mixture was stirred for another 18hs. The reaction solution was poured into ice-water and extracted with EtOAc(100mL\*2), the combined organic layer was washed with water and brine, dried over  $\text{Na}_2\text{SO}_4$ , concentrated and purified by column chromatography to give **14m-1** (2 g, 18.2% yield).  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.76 (brs, 2H), 7.43-7.39 (m, 3H), 7.37-7.33 (m, 2H), 7.28-7.27 (m, 1H), 7.23-7.21 (m, 1H), 7.05-7.03 (m, 1H), 7.89-7.87 (d,  $J$  = 8.0 Hz, 1H), 3.70 (s, 2H), 2.97-2.94 (m, 2H), 2.74-2.72 (m, 2H), 2.03-2.00 (m, 2H), 1.89-1.85 (m, 2H).

**Step 2 spiro[indoline-3,4'-piperidin]-2-one (**14m-2**)**

To a mixture of **14m-1** (1.3 g, 1.0 eq) in MeOH (50 mL) was added Pd/C (0.4 g), and the resulting solution was stirred at  $60^\circ\text{C}$  under  $\text{H}_2$  at 55 Psi for 2 days. The reaction mixture was filtered and concentrated to give **14m-2** (0.9 g, 89% yield).  $^1\text{H}$  NMR (400MHz, DMSO- $d_6$ )  $\delta$ : 10.52 (brs, 1H),

7.34-7.33 (m, 1H), 7.22-7.19 (m, 1H), 7.01-6.98 (m, 1H), 6.88-6.86 (m, 1H), 3.38-3.33 (m, 2H), 3.16-3.12 (m, 2H), 1.95-1.88 (m, 2H), 1.83-1.79 (m, 2H).

### Step 3 1'-methylspiro[indoline-3,4'-piperidin]-2-one (**14m-3**)

To a solution of spiro[indoline-3,4'-piperidin]-2-one (0.2 g, 0.99 mmol, 1.0 eq), 2,2,2-trifluoroacetic acid (1 mL, make the solution PH=3) in MeOH (15 mL) was added formaldehyde (0.148 g, 4.94 mmol, 5.0 eq), then the mixture was stirred at room temperature for 20min, then Sodium cyanoborohydride (0.37 g, 5.93 mmol) was added to the solution, the mixture was stirred at 40<sup>0</sup>C for 12hs. After being checked by TLC, the mixture was quenched with water, extracted with EtOAc, the combined organic layer was washed with brine, dried over anhydrous sodium sulfate, concentrated under reduce pressure, and the residue was purified by flash chromatography with PE/EtOAc = 1:1 ~ EtOAc/MeOH = 10:1 to obtain the target product (0.2 g, 95% yield) as a grey oil.

### Step

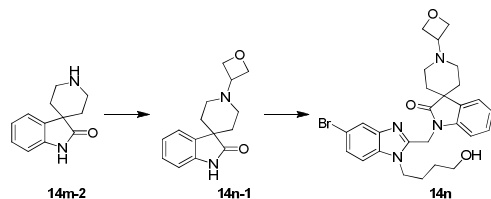
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### 1-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)-1'-methylspiro[indoline-3,4'-piperidin]-2-one (**14m**)

To a mixture of **14m-3** (150 mg, 0.69 mmol, 1.1 eq) in DMF (3 mL) was added NaH (18 mg, 0.76 mmol, 1.2eq) at 0<sup>0</sup>C, after stirred at room temperature for 10 min, 4-(5-bromo-2-(chloromethyl)-1H-benzo[d]imidazol-1-yl)butan-1-ol (200 mg, 0.63 mmol, 1.0 eq) was added, then the resulting solution was stirred at room temperature for 16hs. The reaction solution was added cold water and extracted with EtOAc (30mL\*2), the combined organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated and purified by Prep-HPLC (0.05% formic acid in water and CAN from 20-65%) to obtain the target product **14m** (7 mg, 2.2% yield).  
<sup>1</sup>H NMR (400MHz, MeOH-*d*<sub>4</sub>) δ: 7.81 (s, 1H), 7.70-7.68 (m, 1H), 7.59-7.57 (m, 1H), 7.41-7.39 (m, 1H), 7.35-7.33 (m, 1H), 7.21-7.19 (m, 1H), 7.12-7.10 (m, 1H), 5.418 (s, 2H), 4.54-4.50 (m, 2H), 3.87-3.80 (m, 2H), 3.64-3.61 (m, 2H), 3.56-3.53 (m, 2H), 3.00 (s, 3H), 2.49-2.43 (m, 2H), 2.24-2.20 (m, 2H), 2.02-1.96 (m, 2H), 1.66-1.64 (m, 2H). HRMS calcd for C<sub>25</sub>H<sub>29</sub>BrN<sub>4</sub>O<sub>2</sub>

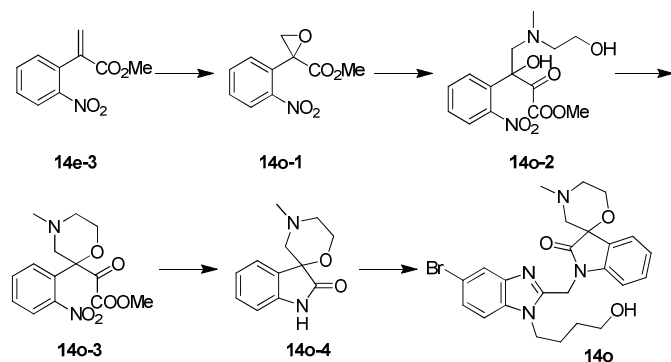
[M+H]<sup>+</sup>: 497.1547, found: 497.1476.

**1-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)-1'-(oxetan-3-yl)spiro[indoline-3,4'-piperidin]-2-one, *14n***



1-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)-1'-(oxetan-3-yl)spiro[indoline-3,4'-piperidin]-2-one was prepared by the common procedure as compound **14m** starting with **14m-2**, oxetan-3-one and 4-(5-bromo-2-(chloromethyl)-1H-benzo[d]imidazol-1-yl)butan-1-ol. <sup>1</sup>H NMR (400MHz, DMSO-d<sub>6</sub>) δ 7.77 (s, 1H), 7.57-7.50 (m, 2H), 7.38-7.36 (m, 1H), 7.21-7.198 (m, 1H), 7.15-7.13 (m, 1H), 7.09-7.03 (m, 1H), 5.19 (s, 2H), 4.58-4.56 (m, 3H), 4.50-4.48 (m, 2H), 4.30 (m, 2H), 3.35-3.32 (m, 4H), 2.68 (m, 2H), 1.83 (m, 4H), 1.69 (m, 2H), 1.45 (m, 2H). HRMS calcd for C<sub>27</sub>H<sub>31</sub>BrN<sub>4</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 539.1652, found: 539.1583.

**1-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)-4'-methylspiro[indoline-3,2'-morpholin]-2-one, *14o***



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**Step 1 methyl 2-(2-nitrophenyl)oxirane-2-carboxylate (**14o-1**)**

To a solution of **14e-3** (4 g, 19.28 mmol) in CHCl<sub>3</sub> (24 mL) was added to m-CPBA (13.36 g, 77.2 mmol) at 0 °C. The mixture was stirred at 70 °C for 12 h. then saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> was added and washed up with saturated NaHCO<sub>3</sub>. The organic layers was dried with Na<sub>2</sub>SO<sub>4</sub> and filter,

evaporated under reduced pressure to afford the crude product and purity by silica gel column chromatography (PE : Ethyl acetate = 50 : 1-PE : Ethyl acetate = 30 : 1) to give compound **14o-1** (2 g, 46.5%) as an orange oil. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 8.19 - 8.10 (m, 1H), 7.73 - 7.58 (m, 2H), 7.54 - 7.46 (m, 1H), 3.77 - 3.70 (m, 1H), 3.69 - 3.62 (m, 3H), 2.91 (d, *J*=6.2 Hz, 1H).

**Step 2 methyl 3-hydroxy-4-((2-hydroxyethyl)(methyl)amino)-3-(2-nitrophenyl)-2-oxobutanoate (14o-2)**

To a solution of compound **14o-1** (1 g, 4.48 mmol) and 2-(methylamino)ethanol (0.528 g, 8.96 mmol) in MeOH (20 mL) was stirred at 50 °C for 10 h. The mixture was evaporated under reduced pressure and separated by silica gel column chromatography using (PE: Ethyl acetate = 10 : 1-PE : Ethyl acetate = 3 : 1) to afford compound **14o-2** (0.68 g, 50.9%) as orange oil. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 7.96 (dd, *J*=8.0, 14.3 Hz, 2H), 7.66 (t, *J*=7.7 Hz, 1H), 7.53 - 7.46 (m, 1H), 3.86 - 3.79 (m, 1H), 3.78 - 3.71 (m, 4H), 3.70 - 3.64 (m, 1H), 2.97 - 2.88 (m, 1H), 2.84 - 2.75 (m, 2H), 2.37 (s, 3H).

**Step 3 methyl 2-(4-methyl-2-(2-nitrophenyl)morpholin-2-yl)-2-oxoacetate (14o-3)**

To a mixture of compound **14o-2** (0.38 g, 1.275 mmol) and tris(3,6-dioxahetyl)amine (5.0 mg, 0.0153 mmol), KOH(0.286 g, 5.1mmol) in 1,4-dioxiane (4 mL) was added to TsCl (0.322 g, 1.6 mmol) in 1,4-dioxiane (5 mL) at room temperature. The mixture was stirred at room temperature for 10h. The mixture was filter and the filtrated was evaporated under reduced pressure and separated by silica gel column chromatography using (PE : Ethyl acetate = 10 : 1-PE : Ethyl acetate = 2 : 1) to afford crude **14o-3** (0.16 g). <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 7.60 - 7.50 (m, 3H), 7.50 - 7.43 (m, 1H), 3.93 - 3.87 (m, 1H), 3.86 - 3.83 (m, 3H), 3.65 - 3.50 (m, 1H), 3.18 - 3.05 (m, 1H), 2.99 - 2.86 (m, 1H), 2.44 (t, *J*=4.8 Hz, 2H), 2.34 (s, 3H).

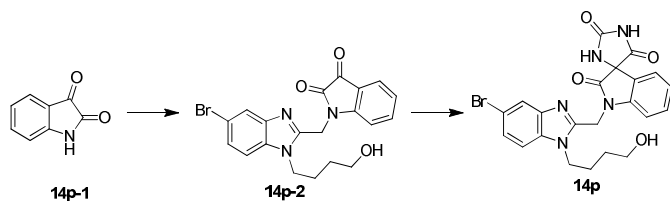
**Step 4 4'-methylspiro[indoline-3,2'-morpholin]-2-one (14o-4)**

To a solution of compound **14o-3** (0.2 g, 0.65 mmol) and Pd/C (0.2 g) in MeOH (100 mL) was stirred at 50 °C for 2 h. The mixture was filter and the filtrated was evaporated under reduced pressure to give crude product compound **14o-4** (0.13 g).

**1-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)-4'-methylspiro[indoline-3,2'-morpholin]-2-one (14o)**

To a mixture of compound **14o-4** (0.124 g, 0.569 mmol) and  $K_2CO_3$  (0.294 g, 1.707 mmol) in  $CH_3CN$  (4mL) was added to compound 7 (0.19 g, 0.626 mmol) and reflux for 7h. The mixture was filter and the filtrated was evaporated under reduced pressure and separated by TLC using (Ethyl acetate:MeOH=10:1) to afford **14o** (0.1 g, 37.6%) as a white solid.  $^1H$  NMR (400MHz,  $CDCl_3$ )  $\delta$  7.85 (s, 1H), 7.57 (d,  $J=7.5$  Hz, 1H), 7.37 (d,  $J=7.9$  Hz, 1H), 7.31 (d,  $J=8.4$  Hz, 1H), 7.25 - 7.21 (m, 1H), 7.14 (d,  $J=8.4$  Hz, 1H), 7.03 - 6.94 (m, 1H), 5.27 (d,  $J=15.4$  Hz, 1H), 4.99 (d,  $J=15.4$  Hz, 1H), 4.39 - 4.10 (m, 2H), 3.97 (br. s., 1H), 3.59 (br. s., 2H), 2.71 - 2.42 (m, 4H), 2.24 (s, 3H), 1.74 - 1.51 (m, 4H), 1.47 - 1.41 (m, 1H). HRMS calcd for  $C_{24}H_{27}BrN_4O_3$   $[M+H]^+$ : 499.1339, found: 499.1268.

**1'-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)spiro[indolizidine-4,3'-indoline]-2,2',5-trione, 14p**



**Step 1 1-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)indoline-2,3-dione (14p-2)**

To a solution of compound **14p-1** (400 mg, 26.22 mmol, 1.0 eq.) in DMF (8 mL) was added NaH (125.6 mg, 5.24mmol, 2eq.) at 0 °C for 30 min. Then, the compound 2 (624.8 g, 26.228 mmol, 1.0 eq.) was added and the mixture was stirred overnight at room temperature. TLC show one new point and no material. The resulting solution was added water and extracted with EtOAc. The organic layer was washed with brine. The organic layer was dried over with  $NaSO_4$  and concentrated. The residue was purified by silica gel (PE : Ethyl acetate = 3 : 1) to afford compound **14p-2** (517.2 mg, 46.2 %) .  $^1H$  NMR (400MHz,  $MeOH-d_4$ )  $\delta$  7.91 (s, 1H), 7.62 - 7.53 (m, 3H), 7.41 (d,  $J=8.2$  Hz,

1H), 7.24 (d, 1H), 7.14 - 7.11 (t,  $J=8.0$  Hz 1H), 5.25 (s, 2H), 4.28 (t, 2H), 3.67 (t, 2H), 1.85 - 1.77 (m, 2H), 1.68 - 1.64 (m, 2H)

## Step

2

### **1'-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)spiro[imidazolidine-4,3'-indoline]-2,2',5-trione (14p)**

To a mixture of compound **14p-2** (390.0 mg, 0.91 mmol, 1.0 eq.) in EtOH : H<sub>2</sub>O = 2 : 1 (6 mL) was added (NH<sub>4</sub>)<sub>2</sub>CO<sub>3</sub> (401.5 mg, 6.37 mmol, 7.0 eq.) and KCN(94.6 mg, 1.45mmol, 1.1 eq). The mixture was stirred at reflux for 2 h. The mixture poured into NaOH aq and EtOAc, then the solution was extracted with EtOAc and water. The combined organic layer was drying (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The mixture was subjected to prep-HPLC (0.05% formic acid in water and CAN from 20-65%) for purification to afford 66.5 mg (15.4 % yield) of **14p** as white solid. 1H NMR (400MHz, MeOH-*d*<sub>4</sub>)  $\delta$  7.98 - 7.94 (s, 1H), 7.87 (d,  $J=8.2$  Hz, 1H), 7.75 (dd, 1H), 7.55 - 7.44 (m, 2H), 7.31 - 7.25 (m, 2H), 5.64 - 5.50 (m, 2H), 4.61 - 4.52 (m, 2H), 3.67 - 3.55 (m, 2H), 2.03 - 1.92 (m, 2H), 1.69 - 1.58 (m, 2H). HRMS calcd for C<sub>22</sub>H<sub>20</sub>BrN<sub>5</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 498.0771, found: 498.0697.

## **2. Hep-2 cell protection and cytotoxicity assays:**

Hep-2 cells and the RSV Long strain were obtained from the American Type Culture Collection (Manassas, Va.). The Hep-2 cells were cultured in DMEM/F-12 medium supplemented with 10% fetal bovine serum (FBS), 100 units/mL penicillin, and 100 units/mL streptomycin.

An assay for cell protection against RSV was used to screen for compounds that inhibit RSV-induced CPE in tissue culture. The Hep-2 cells were seeded into 384-well plates at a density of  $1.5 \times 10^3$  cells per well and incubated at 37°C and 5% CO<sub>2</sub> overnight. Next day, complete DMEM/F-12 medium containing diluted compounds (final DMSO concentration of 0.5%) and virus at a concentration of 100 50% tissue culture infective doses (TCID<sub>50</sub>)/well were added. TheHEp-2cells were then cultured at 37°C and5% CO<sub>2</sub> for 5 days. A series of uninfected HEp-2

cells containing test compounds were run in parallel to assess the cytotoxicities of the test compounds. Cell viability and cytotoxicity were determined by adding 6  $\mu$ L of cell counting kit 8. The absorbance values were read on a Microplate reader (Molecular Device). EC<sub>50</sub> and CC<sub>50</sub> values of compounds were determined by dose-response curves plotted with Graph Pad Prism software.

### 3. *In vivo* PK study

#### ■ General information

The purpose of this study was to determine the pharmacokinetics of compounds in female Balb/c-Mouse following a single intravenous bolus and oral gavage administration of the testing compound, their concentrations in plasma were determined by LC-MS/MS.

#### ■ Test Article Formulations

10% HP- $\beta$ -CD in saline or DMSO: PEG400: water = 5:40:55 was used as vehicle for IV and PO. The concentration prepared for both IV and PO was at 1 mg/mL for compound BMS433771, while IV at 1 mg/mL and PO at 2 mg/mL for compound of 14h. Appropriate amount of test article was accurately weighed into an appropriate container, added with appropriate amount of vehicle to obtain a nearly clear solution. The IV dosing solution was further sterile-filtered through 0.22  $\mu$ m filter before dosing.

#### ■ Experimental Design

Animals were randomly assigned to 4 treatment groups based on body weight before the first dosing. The experimental design was summarized below:

Group No.	No. of animals (gender)	Treatment					
		Test Article	Dose (mg/kg)	Dose Volume (mL/kg)	Conc. (mg/mL)	Vehicle	Dose Route
1	3 female	BMS-433771	1	1	1	10% HP- $\beta$ -CD in saline	IV
2	3 female		10	5	2		PO
3	3 female	14h	1	1	1	DMSO: PEG400: water = 5:40:55	IV
4	3 female		10	5	2		PO
Test article storage: Desiccated at 4°C			Food returned: N/A				
Overnight Fast of Animals: Fasted			Comments: N/A.				

#### ■ Samples Collection and Processing

The schedule for sample collection is shown in the table below:

Group	Matrix	Time-points
1 and 3	Plasma	0.083, 0.25, 0.5, 1, 2, 4, 8 and 24 hours post-dose
2 and 4	Plasma	0.25, 0.5, 1, 2, 4, 8 and 24 hours post-dose

Each blood sample (about 0.02 mL) was collected via submandibular vein puncture (or other suitable blood collection site). Actual sample collection times were recorded in the study records. The acceptable deviation of blood collection was  $\pm 1$  min for sample collected within 1 hour postdose and 5% of the nominal time for other timepoints. All blood samples were transferred into pre-labeled plastic microcentrifuge tubes containing K<sub>2</sub>-EDTA (0.5M) as anti-coagulant. After blood was collected, the samples were processed for plasma by centrifugation at approximately 4°C, 3000 g for 15 minutes, and then quick frozen over dry ice and kept at -60°C or lower until LC-MS/MS analysis.

■ **LC-MS/MS method:**

A calibration curve with 7 non-zero calibration standards was applied for the existing method including LLOQ. A set of QC samples consisting of low, middle, and high concentration were applied for the existing method.

■ **Sample analysis:**

In general, one calibration curve with 2 sets of QC samples consisting of low, middle, and high concentration were applied if sample numbers were less than 48. If sample numbers were more than 48, then two calibration curves with 2 sets of QC samples were applied.

■ **Acceptance criteria:**

Linearity:  $\geq 75\%$  STDs are back calculated to within  $\pm 20\%$  of their nominal values in biofluid and within 25% of their nominal values in tissue and feces sample.

Accuracy:  $\geq 67\%$  all QC samples are back calculated to within  $\pm 20\%$  of their nominal values for biofluid and within 25% of their nominal values for tissue and feces samples.

Specificity: The mean calculated concentration in the single blank matrix should be no more than 0.5 times the LLOQ.

Sensitivity: Plasma sample is recommended to be quantified against corresponding own matrix calibration curves and the LLOQ will be tried to target  $\leq 3$  ng/mL. Any adjustment of LLOQ will inform sponsor in advance.

Carryover: the mean calculated carry-over concentration in the single blank matrix immediately after the highest standard injection should be less than LLOQ. If the carryover couldn't meet the criteria, then the percent of carryover should be estimated following in-house bioanalytical SOP.

#### ■ Data analysis and reporting

Plasma concentration versus time data were analyzed by non-compartmental approaches using the WinNonlin software program (version 6.3, Pharsight, Mountain View, CA). Pharmacokinetic parameters, including (where data allows), but not necessarily limited to,  $C_0$ ,  $T_{1/2}$ ,  $V_{dss}$ ,  $Cl$ ,  $AUC_{0-last}$ ,  $AUC_{0-inf}$ ,  $MRT_{0-last}$ ,  $MRT_{0-inf}$  for IV group;  $C_{max}$ ,  $T_{max}$ ,  $T_{1/2}$ ,  $AUC_{0-last}$ ,  $AUC_{0-inf}$ ,  $MRT_{0-last}$ ,  $MRT_{0-inf}$ , Bioavailability (%) for PO groups was calculated.

**Result 1: Mouse PK profile of single dosing of BMS-433771 and compound 14h.**

Study Details				
Administered compound	BMS-433771		compound 14h	
Species	Female Balb/c mouse, fasted		Female Balb/c mouse, fasted	
Study Group	IV	PO	IV	PO
Nominal dose (mg/kg)	1.0	10.0	1.0	10.0
Nominal dose (µmol/kg)	2.65	26.5	1.85	18.5
Administered dose (mg/kg)	1.39	11.2	1.07	10.5
Administered dose (µmol/kg)	3.68	29.7	1.98	19.4
Formulation	1 mg/mL in 10% HP-β-CD in saline, solution.	1 mg/mL in 10% HP-β-CD in saline, solution.	1 mg/mL in DMSO:PEG400:water=5:40:55, solution.	2 mg/mL in DMSO:PEG400:water=5:40:55, solution.
Bioanalytical Details				
Analyte compound	BMS-433771		14h	
Molecular weight	377		541	
Formular weight	377		541	
Salt factor	1.0		1.0	
Purity	98%		98%	
Analytical technique	LC-MS/MS		LC-MS/MS	
Matrix	Plasma (EDTA-K <sub>2</sub> )		Plasma (EDTA-K <sub>2</sub> )	
Plasma LLOQ (nM)	2.65		1.85	

Bioavailability of BMS433771 in Mouse															
IV (nM)								PO (nM)							
IV Time (h)	M1 <sup>a</sup>	M2	M3	Mean IV		SD	CV (%)	PO Time (h)	M4	M5	M6	Mean PO		SD	CV (%)
0.0833	906	3233	2676	<b>2954</b>	±	ND	ND	0.25	1545	2112	2636	<b>2098</b>	±	<b>546</b>	<b>26.0</b>
0.25	472	872	1129	<b>1000</b>	±	ND	ND	0.5	522	1256	1129	<b>969</b>	±	<b>392</b>	<b>40.5</b>
0.5	607	189	281	<b>235</b>	±	ND	ND	1	225	376	196	<b>266</b>	±	<b>96.7</b>	<b>36.4</b>
1	652	64.9	55.9	<b>60.4</b>	±	ND	ND	2	45.8	52.2	43.5	<b>47.2</b>	±	<b>4.52</b>	<b>9.58</b>
2	60.4	13.7	12.2	<b>13.0</b>	±	ND	ND	4	23.3	46.1	40.0	<b>36.5</b>	±	<b>11.78</b>	<b>32.3</b>
4	7.63	3.44	20.0	<b>11.7</b>	±	ND	ND	8	BQL	BQL	BQL	<b>ND</b>	±	ND	ND
8	BQL	BQL	BQL	<b>ND</b>	±	ND	ND	24	BQL	BQL	BQL	<b>ND</b>	±	ND	ND
24	BQL	BQL	BQL	<b>ND</b>	±	ND	ND								
PK Parameters	M1	M2	M3	Mean IV		SD	CV (%)	PK Parameters	M4	M5	M6	Mean PO		SD	CV (%)
No. points used for T <sub>1/2</sub>	3	3	3	<b>3</b>	±	--	--	No. points used for T <sub>1/2</sub>	3	3	3	<b>3</b>	±	--	--
C <sub>0</sub> (nM)	1256	6223	4120	<b>5171</b>	±	ND	ND	C <sub>max</sub> (nM)	1545	2112	2636	<b>2098</b>	±	<b>546</b>	<b>26.0</b>
T <sub>1/2</sub> (h)	0.489	0.739	2.67 <sup>b</sup>	<b>1.71</b>	±	ND	ND	T <sub>max</sub> (h)	0.250	0.250	0.250	<b>0.250</b>	±	0	0
V <sub>dss</sub> (L/kg)	3.23	1.10	3.77	<b>2.44</b>	±	ND	ND	T <sub>1/2</sub> (h)	0.997 <sup>b</sup>	1.14 <sup>b</sup>	1.51 <sup>b</sup>	<b>1.21</b>	±	0.263	21.6
Cl (mL/min/kg)	64.4	68.1	65.5	<b>66.8</b>	±	ND	ND	T <sub>last</sub> (h)	4.00	4.00	4.00	<b>4.00</b>	±	--	--
T <sub>last</sub> (h)	4.00	4.00	4.00	<b>4.00</b>	±	--	--	AUC <sub>0-last</sub> (nM.h)	784	1303	1225	<b>1104</b>	±	<b>280</b>	<b>25.3</b>
AUC <sub>0-last</sub> (nM.h)	948	898	860	<b>879</b>	±	ND	ND	AUC <sub>0-inf</sub> (nM.h)	818	1379	1312	<b>1170</b>	±	<b>306</b>	<b>26.2</b>
AUC <sub>0-inf</sub> (nM.h)	954	902	937	<b>919</b>	±	ND	ND	MRT <sub>0-last</sub> (h)	0.771	0.756	0.662	<b>0.73</b>	±	0.0588	8.06
MRT <sub>0-last</sub> (h)	0.815	0.250	0.343	<b>0.296</b>	±	ND	ND	MRT <sub>0-inf</sub> (h)	0.962	1.02	1.03	<b>1</b>	±	0.0367	3.65
MRT <sub>0-inf</sub> (h)	0.837	0.270	0.959	<b>0.615</b>	±	ND	ND	AUC <sub>0-inf</sub> /AUC <sub>0-last</sub> (%)	104	106	107	<b>106</b>	±	1.41	1.33
AUC <sub>0-inf</sub> /AUC <sub>0-last</sub> (%)	101	100	109	<b>105</b>	±	ND	ND	Bioavailability (%) <sup>c</sup>	11.0	18.6	17.7	<b>15.8</b>	±	4.13	26.2

ND = Not determined (Parameters not determined due to inadequately defined terminal elimination phase)

BQL = Below the lower limit of quantitation (LLOQ)

a: The data grey highlighted (animal M1) was excluded during average calculation due to its abnormal PK profile. Some of the formulation was probably leaked subcutaneously during intravenous dosing.

b: The linear regression coefficient of the concentration value on the terminal phase is less than 0.9, T<sub>1/2</sub> might not be accurately estimated.

c: Bioavailability (%) was calculated with AUC<sub>0-inf</sub> and nominal dose.

Bioavailability of compound 14h in Mouse															
IV (nM)								PO (nM)							
IV Time (h)	M1	M2	M3	Mean IV		SD	CV (%)	PO Time (h)	M4	M5	M6	Mean PO		SD	CV (%)
0.0833	1516	1502	1463	<b>1494</b>	±	27.7	1.85	0.25	3195	4064	2697	<b>3319</b>	±	692	20.8
0.25	1016	868	1049	<b>978</b>	±	96.4	9.86	0.5	2771	3140	2253	<b>2721</b>	±	445	16.4
0.5	687	549	757	<b>664</b>	±	106	16.0	1	2290	2180	1775	<b>2082</b>	±	271	13.0
1	272	303	497	<b>357</b>	±	122	34.2	2	1463	1474	1310	<b>1415</b>	±	91.9	6.49
2	66.5	86.6	158	<b>104</b>	±	47.8	46.2	4	1165	669	639	<b>824</b>	±	296	35.9
4	5.60	12.9	29.7	<b>16.1</b>	±	12.4	77.0	8	62.6	169	167	<b>133</b>	±	60.8	45.8
8	4.10	2.05	5.37	<b>3.84</b>	±	1.68	43.7	24	BQL	BQL	BQL	<b>ND</b>	±	ND	ND
24	BQL	BQL	BQL	<b>ND</b>	±	ND	ND								
PK Parameters	M1	M2	M3	Mean IV		SD	CV (%)	PK Parameters	M4	M5	M6	Mean PO		SD	CV (%)
No. points used for T <sub>1/2</sub>	3	3	3	<b>3</b>	±	--	--	No. points used for T <sub>1/2</sub>	3	3	3	<b>3</b>	±	--	--
C <sub>0</sub> (nM)	1852	1976	1728	<b>1852</b>	±	124	6.69	C <sub>max</sub> (nM)	3195	4064	2697	<b>3319</b>	±	692	20.8
T <sub>1/2</sub> (h)	1.69 <sup>a</sup>	1.15	1.27	<b>1.37</b>	±	0.284	20.6	T <sub>max</sub> (h)	0.250	0.250	0.250	<b>0.250</b>	±	0.00	0.00
Vd <sub>ss</sub> (L/kg)	1.51	1.61	1.53	<b>1.55</b>	±	0.0551	3.56	T <sub>1/2</sub> (h)	1.25 <sup>a</sup>	1.93	2.03	<b>1.74</b>	±	0.424	24.4
Cl (mL/min/kg)	30.6	31.0	22.2	<b>27.9</b>	±	4.97	17.8	T <sub>last</sub> (h)	8.00	8.00	8.00	<b>8.00</b>	±	--	--
T <sub>last</sub> (h)	8.00	8.00	8.00	<b>8.00</b>	±	--	--	AUC <sub>0-last</sub> (nM.h)	8376	8015	6764	<b>7718</b>	±	846	11.0
AUC <sub>0-last</sub> (nM.h)	997	992	1379	<b>1122</b>	±	222	19.8	AUC <sub>0-inf</sub> (nM.h)	8489	8486	7252	<b>8076</b>	±	714	8.84
AUC <sub>0-inf</sub> (nM.h)	1007	995	1389	<b>1130</b>	±	224	19.8	MRT <sub>0-last</sub> (h)	2.33	2.25	2.44	<b>2.34</b>	±	0.0996	4.26
MRT <sub>0-last</sub> (h)	0.723	0.836	1.08	<b>0.881</b>	±	0.184	20.9	MRT <sub>0-inf</sub> (h)	2.43	2.72	3.01	<b>2.72</b>	±	0.293	10.7
MRT <sub>0-inf</sub> (h)	0.820	0.866	1.15	<b>0.944</b>	±	0.176	18.7	AUC <sub>0-inf</sub> /AUC <sub>0-last</sub> (%)	101	106	107	<b>105</b>	±	3.08	2.93
AUC <sub>0-inf</sub> /AUC <sub>0-last</sub> (%)	101	100	101	<b>101</b>	±	0.332	0.329	Bioavailability (%) <sup>b</sup>	75.1	75.1	64.2	<b>71.5</b>	±	6.31	8.84

ND = Not determined (Parameters not determined due to inadequately defined terminal elimination phase)

BQL = Below the lower limit of quantitation (LLOQ)

a: The adjusted linear regression coefficient of the concentration value on the terminal phase is less than 0.9, t(1/2) might not be accurately estimated.

b: Bioavailability (%) was calculated with average AUC<sub>0-inf</sub> and nominal dose.

#### 4. *In vivo* Efficacy in the RSV Infection Mouse Model:

Animal protocols were approved by the WuXi AppTec Institutional Animal Care and Use Committee (IACUC). Treatment of animals strictly obeyed the guideline of WuXi AppTec IACUC. IACUC and animal facility of WuXi AppTec is a certificated organization by AAALAC.

BALB/c mice (~16-20 g, female, specific pathogen free) were housed in individual cages. The animals were randomly distributed into dose groups. The animals were immuno-suppressed by IP injection of cyclophosphamide at the dosage of 100 mg/kg on day -6 and day -1, and thereafter, treated with vehicle, BMS433771 or **14h** 1 hr prior to infection via oral route following the study design indicated below (Supp. Table 1). BMS433771 and **14h** were prepared in 5% DMSO, 60% PEG 400 and 35% H<sub>2</sub>O (vehicle) and administered at 10 mL/kg to each animal.

Supp. Table 1: Study design

Group	Study drug	Number of animals	Route of administration	Dose (mg/kg)	Dosing regimen
1	Vehicle	7	PO	0	QD, from day 0 to
2	BMS433771	7	PO	50	day 3, with first
3	<b>14h</b>	7	PO	5	dose given at 1 h
4	<b>14h</b>	7	PO	15	prior to RSV
5	<b>14h</b>	7	PO	50	inoculation.

\*: define the RSV inoculation day as day 0.

Mice were infected with RSV strain A2 (Lot. Number: WX-20121023) by intranasal administration of  $6.0 \times 10^4$  PFU in 50  $\mu$ L of DMEM/F12 medium to each mouse which was deeply anesthetized

with IP injection of pentobarbital of 75 mg/kg. Animals were treated with vehicle or test articles and monitored on a daily basis of body weight and body weight change from day 0 to day 4. On day 4 post-infection, animals were euthanized by CO<sub>2</sub> asphyxiation and the lungs were removed and weighed, snap frozen on dry ice in Hanks balanced salt solution containing 0.21 M sucrose, 25 mM HEPES, and 5 mM sodium L-glutamate, supplemented with 20 U of penicillin G/ml, 20 µg of streptomycin/ml, and 0.05 µg of amphotericin B, in a volume equal to 10 times of the lung weight (vol./wt). The lung tissues were thawed and homogenized with tissue lyser (Qiagen) to release the cell-associated virus, and then centrifuged at 2000 g for 5 min at 4°C. The resulting supernatant samples were immediately titrated for RSV infectivity in HEp-2 cells following the standard method of plaque assay. Final RSV lung titers for each animal were calculated as PFU (plaque forming unit) and were expressed as log<sub>10</sub>.