

## Supporting Information

### **Aminopyridyl/pyrazinyl spiro[indoline-3,4'-piperidine]-2-ones As Highly Selective and Efficacious c-Met/ALK Inhibitors**

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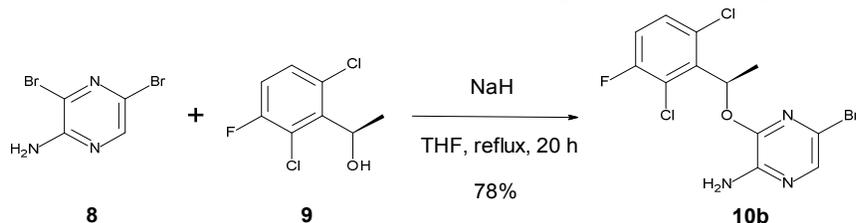
# These authors contributed equally to this work.

## **Experimental**

### ***General Synthetic and Analytical Chemistry Methods:***

All chemicals were obtained from Aladdin or J&K. Solvents were purified and dried by standard procedures, and stored over 4-Å molecular sieves. Reactions were monitored by TLC using SILG/UV 254 silica-gel plates. Flash chromatography (FC): silica gel (SiO<sub>2</sub>; 40 μm, 230-400 mesh). <sup>1</sup>H-NMR spectra: Bruker Digital NMR Spectrometer, rep. δ in ppm, *J* in Hz. EI-MS: Waters ZQ4000. Elemental analysis was carried out using Vario EL III Element Analyzer.

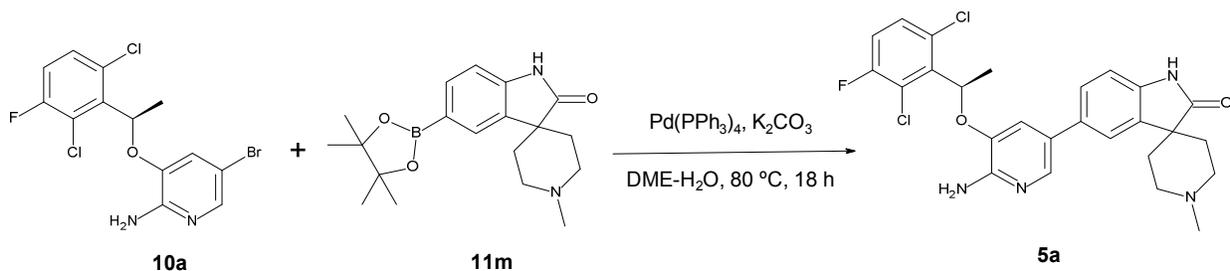
### **5-Bromo-3-[(1*R*)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]pyrazin-2-amine (10b)**



At 0 °C, NaH (80 mg, 60% in mineral oil, 2 mmol) was added to a solution of (1*R*)-1-(2,6-dichloro-3-fluorophenyl)ethanol (**9**, 418 mg, 2 mmol) in anhydrous THF (6 mL). After stirred at

the same temperature for 30 min, a solution of 2-amino-3,5-dibromopyrazine (**8**, 506 mg, 2 mmol) in THF (6 mL) was added. The resulting mixture was warmed to room temperature and stirred under reflux for 20 h. TLC showed the reaction was complete. After cooled down to room temperature, water (10 mL) was added and the mixture was extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, dried over MgSO<sub>4</sub>, and concentrated to dryness. The residue was purified by column chromatography eluted with 1-3% MeOH in hexanes to afford 594 mg of the desired product **10b** (yield: 78%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 1.83 (d, *J* = 7.2 Hz, 3 H), 5.12 (s, br, 2 H), 6.73 (q, *J* = 6.8 Hz, 1 H), 7.05 (t, *J* = 8.0 Hz, 1 H), 7.28 (dd, *J* = 4.8, 8.8 Hz, 1 H), 7.58 (s, 1 H). MS: *m/z* (ESI<sup>+</sup>) 379.83 [M+H<sup>+</sup>, <sup>35</sup>Cl, <sup>35</sup>Cl, <sup>79</sup>Br], 381.81 [M+H<sup>+</sup>, <sup>35</sup>Cl, <sup>35</sup>Cl, <sup>81</sup>Br], 383.79 [M+H<sup>+</sup>, <sup>35</sup>Cl, <sup>37</sup>Cl, <sup>81</sup>Br].

### 5-[6-Amino-5-[(1*R*)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]-3-pyridyl]-1'-methylspiro[indoline-3,4'-piperidine]-2-one (**5a**)

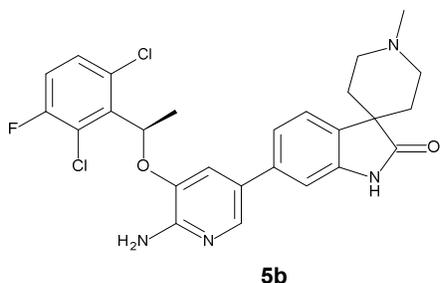


To a mixture of 5-bromo-3-[(1*R*)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]-2-aminopyridine<sup>1</sup> (**10a**, 75.8 mg, 0.2 mmol), 1'-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[indoline-3,4'-piperidine]-2-one<sup>2</sup> (**11m**, 82 mg, 0.24 mmol), and potassium carbonate (82.9 mg, 0.6 mmol) in DME/water (4/1, 2.0 ml) was added Pd(PPh<sub>3</sub>)<sub>4</sub> (11.6 mg, 0.01 mmol). The resulting mixture was bubbled into nitrogen for 2 min, then stirred at 80 °C for 18 h. LC-MS showed the reaction was complete. After cooled down to room temperature, the mixture was diluted with water (5 mL) and extracted with DCM (3 × 10 mL). The organic phases were combined, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated to give the crude product, which was purified by silica gel column chromatography eluted with 7 M ammonia in methanol/DCM (5/95) to afford the target product (88.6 mg, yield: 86%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 1.86 (d, *J* = 6.4 Hz, 3 H), 1.93-2.02 (m, 4 H), 2.44 (s, 3 H), 2.66-2.72 (m, 2 H), 2.89-2.93 (m, 2 H), 4.87 (s, br, 2 H), 6.11 (q, *J* = 6.4 Hz, 1 H), 6.88 (d, *J* = 8.0 Hz, 1 H), 6.94 (d, *J* = 1.2 Hz, 1 H), 7.06 (t, *J* = 8.4 Hz, 1 H), 7.19 (dd, *J*

= 1.2, 8.0 Hz, 1 H), 7.31 (m, 1 H), 7.36 (s, 1 H), 7.66 (s, br, 1 H), 7.80 (d,  $J = 2.0$  Hz, 1 H). MS:  $m/z$  (ESI<sup>+</sup>) 515.05 [M+H<sup>+</sup>, <sup>35</sup>Cl, <sup>35</sup>Cl], 517.03 [M+H<sup>+</sup>, <sup>35</sup>Cl, <sup>37</sup>Cl]. Anal. Calcd. for C<sub>26</sub>H<sub>25</sub>Cl<sub>2</sub>FN<sub>4</sub>O<sub>2</sub>: C, 60.59; H, 4.89; N, 10.87; Cl, 13.76; F, 3.69. Found: C, 60.45; H, 4.80; N, 10.94; Cl, 13.96; F, 3.75.

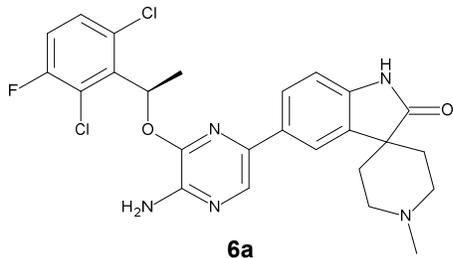
The following compounds were prepared according to the same procedure for synthesizing compound **5a**:

**6-[6-Amino-5-[(1R)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]-3-pyridyl]-1'-methyl-spiro[indoline-3,4'-piperidine]-2-one (5b)**



Yield: 82%. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 1.86 (d,  $J = 6.4$  Hz, 3 H), 1.91-1.95 (m, 2 H), 1.97-2.03 (m, 2 H), 2.45 (s, 3 H), 2.65-2.72 (m, 2 H), 2.89-2.95 (m, 2 H), 5.12 (s, br, 2 H), 6.12 (q,  $J = 6.4$  Hz, 1 H), 6.94-7.00 (m, 3 H), 7.06 (t,  $J = 8.4$  Hz, 1 H), 7.31 (m, 1 H), 7.35 (d,  $J = 7.2$  Hz, 1 H), 7.90 (d,  $J = 2.0$  Hz, 1 H), 9.28 (s, br, 1 H). MS:  $m/z$  (ESI<sup>+</sup>) 515.05 [M+H<sup>+</sup>, <sup>35</sup>Cl, <sup>35</sup>Cl], 517.03 [M+H<sup>+</sup>, <sup>35</sup>Cl, <sup>37</sup>Cl]. Anal. Calcd. for C<sub>26</sub>H<sub>25</sub>Cl<sub>2</sub>FN<sub>4</sub>O<sub>2</sub>: C, 60.59; H, 4.89; N, 10.87; Cl, 13.76; F, 3.69. Found: C, 60.67; H, 4.98; N, 10.74; Cl, 13.49; F, 3.48.

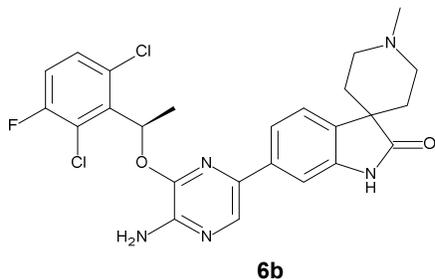
**5-[5-Amino-6-[(1R)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]pyrazin-2-yl]-1'-methyl-spiro[indoline-3,4'-piperidine]-2-one (6a)**



Yield: 54%. <sup>1</sup>H-NMR (CD<sub>3</sub>OD, 400 MHz):  $\delta$  (ppm) 1.85 (d,  $J = 6.8$  Hz, 3 H), 1.85-1.88 (m, 2 H), 1.97-2.04 (m, 2 H), 2.46 (s, 3 H), 2.76-2.82 (m, 2 H), 2.97-3.02 (m, 2 H), 6.74 (q,  $J = 6.4$  Hz, 1 H), 6.85 (d,  $J = 8.0$  Hz, 1 H), 7.15 (t,  $J = 8.4$  Hz, 1 H), 7.41 (dd,  $J = 4.8, 9.2$  Hz, 1 H), 7.54 (dd,  $J$

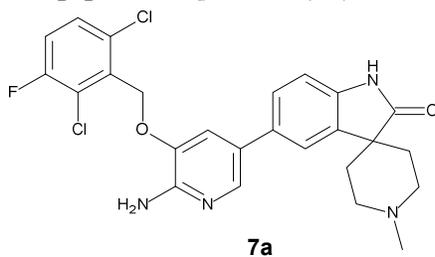
= 1.6, 8.0 Hz, 1 H), 7.69 (d,  $J = 1.8$  Hz, 1 H), 7.81 (dt,  $J = 2.0, 8.0$  Hz, 1 H), 7.87 (s, 1 H). MS:  $m/z$  (ESI<sup>+</sup>) 515.92 [M+H<sup>+</sup>, <sup>35</sup>Cl, <sup>35</sup>Cl], 517.90 [M+H<sup>+</sup>, <sup>35</sup>Cl, <sup>37</sup>Cl]. Anal. Calcd. for C<sub>26</sub>H<sub>25</sub>Cl<sub>2</sub>FN<sub>4</sub>O<sub>2</sub>·0.5H<sub>2</sub>O: C, 57.15; H, 4.80; N, 13.33; Cl, 13.50; F, 3.62. Found: C, 57.38; H, 4.66; N, 13.01; Cl, 13.62; F, 3.53.

**6-[5-Amino-6-[(1R)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]pyrazin-2-yl]-1'-methylspiro[indoline-3,4'-piperidine]-2-one (6b)**



Yield: 67%. <sup>1</sup>H-NMR (CD<sub>3</sub>OD, 400 MHz):  $\delta$  (ppm) 1.85 (d,  $J = 6.8$  Hz, 3 H), 1.88-1.96 (m, 4 H), 2.48 (s, 3 H), 2.76-2.82 (m, 2 H), 2.98-3.05 (m, 2 H), 6.75 (q,  $J = 6.4$  Hz, 1 H), 7.16 (t,  $J = 8.8$  Hz, 1 H), 7.31 (d,  $J = 2.0$  Hz, 1 H), 7.36-7.43 (m, 3 H), 7.88 (s, 1 H). MS:  $m/z$  (ESI<sup>+</sup>) 515.99 [M+H<sup>+</sup>, <sup>35</sup>Cl, <sup>35</sup>Cl], 517.90 [M+H<sup>+</sup>, <sup>35</sup>Cl, <sup>37</sup>Cl]. Anal. Calcd. for C<sub>26</sub>H<sub>25</sub>Cl<sub>2</sub>FN<sub>4</sub>O<sub>2</sub>·0.33H<sub>2</sub>O: C, 57.48; H, 4.76; N, 13.41; Cl, 13.57; F, 3.64. Found: C, 57.62; H, 4.71; N, 13.64; Cl, 13.50; F, 3.74.

**5-[6-Amino-5-[(2,6-dichloro-3-fluorophenyl)methoxy]-3-pyridyl]-1'-methylspiro[indoline-3,4'-piperidine]-2-one (7a)**



Yield: 85%. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 1.92-2.02 (m, 4 H), 2.43 (s, 3 H), 2.65-2.71 (m, 2 H), 2.90-2.91 (m, 2 H), 4.92 (s, br, 2 H), 5.52 (s, 2 H), 6.89 (d,  $J = 8.4$  Hz, 1 H), 6.90 (d,  $J = 1.2$  Hz, 1 H), 7.06 (t,  $J = 8.0$  Hz, 1 H), 7.21 (dd,  $J = 1.2, 8.0$  Hz, 1 H), 7.31 (m, 1 H), 7.37 (s, 1 H), 7.79 (s, br, 1 H), 7.80 (d,  $J = 2.0$  Hz, 1 H). MS:  $m/z$  (ESI<sup>+</sup>) 501.06 [M+H<sup>+</sup>, <sup>35</sup>Cl, <sup>35</sup>Cl], 503.04



reaction was complete. Methanol (50 mL) was added to quench the excess borane. Solvents and trimethyl borate by-product were evaporated under reduced pressure to dryness. The same process was repeated one more time to afford a viscous oil product (**12a**, 2.1 g, yield: 75%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 2.09 (t, *J* = 6.4 Hz, 1 H), 4.97 (d, *J* = 6.4 Hz, 2 H), 7.09 (t, *J* = 8.8 Hz, 1 H), 7.32 (dd, *J* = 4.8, 9.1 Hz, 1 H). MS: *m/z* (ESI<sup>+</sup>) 193.08 [M-H<sup>+</sup>, <sup>35</sup>Cl, <sup>35</sup>Cl], 195.12 [M-H<sup>+</sup>, <sup>35</sup>Cl, <sup>37</sup>Cl].

### **3-[(2,6-Dichloro-3-fluorophenyl)methoxy]-2-nitropyridine (12c):**

At rt under N<sub>2</sub>, to a solution of (2,6-dichloro-3-fluorophenyl)methanol (**12a**, 1.95 g, 10 mmol), 3-hydroxyl-2-nitropyridine (**12b**, 1.54 g, 11 mmol), and PPh<sub>3</sub> (3.409 g, 13 mmol) in dry THF (80 ml) was added isopropyl azodicarboxylate (DIAD, 2.63 g, 13 mmol) dropwise. After addition, addition, the reaction mixture was stirred at 0 °C for 16 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography eluted with petroleum ether/ethyl acetate (4:1) to give the desired product (**12c**) as a white solid (2.85 g, yield: 90%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 5.45 (s, 2 H), 7.20 (dd, *J* = 8.0, 9.2 Hz, 1 H), 7.37 (dd, *J* = 4.8, 9.2 Hz, 1 H), 7.59 (dd, *J* = 4.4, 8.4 Hz, 1 H), 7.74 (dd, *J* = 1.2, 8.4 Hz, 1 H), 8.17 (dd, *J* = 1.6, 4.4 Hz, 1 H). MS: *m/z* (ESI<sup>+</sup>) 316.89 [M+H<sup>+</sup>, <sup>35</sup>Cl, <sup>35</sup>Cl], 318.89 [M+H<sup>+</sup>, <sup>35</sup>Cl, <sup>37</sup>Cl].

### **3-[(2,6-Dichloro-3-fluorophenyl)methoxy]pyridin-2-amine (12d):**

A mixture of 3-[(2,6-dichloro-3-fluorophenyl)methoxy]-2-nitropyridine (**12c**, 2.537 g, 8 mmol) iron powder (3.575g, 64 mmol) in EtOH (15 mL) was vigorously stirred at 90 °C (oil bath), and 0.8 mL of 1 M HCl (aq) was added through a syringe. After 10 min, another 0.8 mL of 1 M HCl (aq) was added. Stirring was continued for 30 min. TLC showed the reaction was complete. After cooled down to room temperature, the reaction mixture was filtered through a Celite pad, and the residue was washed with ethanol (3 × 10 mL). The combined organic phases were combined and evaporated to dryness to afford the desired product (**12d**) as a pale brown solid (2.182 g, yield: 95%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 4.65 (s, br, 2 H), 5.31 (s, 2 H), 6.66 (dd, *J* = 5.2, 8.0 Hz, 1 H), 7.14 (dd, *J* = 1.2, 8.0 Hz, 1 H), 7.18 (dd, *J* = 8.4, 9.2 Hz, 1 H), 7.37 (dd, *J* = 4.8, 8.8 Hz, 1 H), 7.73 (dd, *J* = 1.6, 5.6 Hz, 1 H). MS: *m/z* (ESI<sup>+</sup>) 286.95 [M+H<sup>+</sup>, <sup>35</sup>Cl, <sup>35</sup>Cl], 288.85 [M+H<sup>+</sup>, <sup>35</sup>Cl, <sup>37</sup>Cl].

**5-Bromo-3-[(2,6-dichloro-3-fluorophenyl)methoxy]pyridin-2-amine (13):**

At 0 °C, NBS (0.908 g, 5.1 mmol) was added in portions to a solution of 3-[(2,6-dichloro-3-fluorophenyl)methoxy]pyridin-2-amine (**12d**, 1.436 g, 5 mmol) in acetonitrile (20 mL). The resulting mixture was stirred at the same temperature for 30 min. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography to give the desired product (**13**) as a white solid (1.098 g, yield: 60%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 4.68 (s, br, 2 H), 5.28 (s, 2 H), 7.21 (dd, *J* = 8.0, 8.8 Hz, 1 H), 7.24 (dd, *J* = 2.0 Hz, 1 H), 7.39 (dd, *J* = 4.8, 9.2 Hz, 1 H), 7.78 (d, *J* = 2.0 Hz, 1 H). MS: *m/z* (ESI<sup>+</sup>) 364.83 [M+H<sup>+</sup>, <sup>35</sup>Cl, <sup>35</sup>Cl, <sup>79</sup>Br], 366.77 [M+H<sup>+</sup>, <sup>35</sup>Cl, <sup>37</sup>Cl, <sup>79</sup>Br or <sup>35</sup>Cl, <sup>35</sup>Cl, <sup>81</sup>Br], 368.69 [M+H<sup>+</sup>, <sup>37</sup>Cl, <sup>37</sup>Cl, <sup>79</sup>Br or <sup>35</sup>Cl, <sup>37</sup>Cl, <sup>81</sup>Br].

**Molecular docking.** Molecular docking was performed with Surflex-Dock program that is interfaced with Sybyl 7.3. The programs adapted an empirical scoring function and a patented searching engine.<sup>3-4</sup> Ligand was docked into the corresponding protein's binding site guided by protomol, which is an idealized representation of a ligand that makes every potential interaction with binding sites. In this work, the protomol was established by ligand from the crystal structure of c-Met (PDB code: 2WGJ). Beginning of docking, all the water and ligands were removed and the random hydrogen atoms were added. Then the receptor structure was minimized in 10,000 cycles with Powell method in Sybyl 7.3. All the compounds were constructed using Sketch Molecular module. Hydrogen and Gasteiger-Hückel charges were added to every molecular. Then their geometries are optimized by conjugate gradient methods in Tripos force field. The energy convergence criterion is 0.001 kcal/mol. Default values are chosen to finish this work except that the threshold was 1 when the protomol was generated.

**Kinase Selectivity.** Kinase selectivity screening was performed by DiscoverX in their scanEDGE<sup>SM</sup> 97-kinase panel.<sup>5</sup>

**Biochemical Assays.** Biochemical IC<sub>50</sub>'s against c-Met, ALK, and AXL were determined by Reaction Biology Corp in their proprietary nanoliter kinase assay.<sup>6</sup>

**Cell Mechanistic Assay for c-Met.** MKN-45 cells (from Riken Cell Bank of Japan) were cultured in RPMI 1640 medium containing 10% FCS and pretreated for 1 h at 37 °C with increasing concentrations of compound or DMSO. Cells were then lysed in RIPA buffer containing appropriate inhibitors. Western blotting was carried out following standard procedures and probed with the following antibodies: anti-phosphor c-Met (pYpYpY1230/1234/1235), anti-c-Met (Cell Signaling Technologies Inc.), following the manufacturer's protocol. Total cellular protein loadings were semi-quantified by probing with anti-GAPDH.

**Cell Mechanistic Assays for c-Met, ALK, and AXL.** These assays were performed by ProQinase GmbH.<sup>7</sup>

**Cell Culture and Reagents.** U87MG human glioma cell line and GTL-16 human gastric carcinoma cell line were obtained from the China Center for Type Culture Collection (Shanghai, China). H1993 and H441 non-small cell lung carcinoma cell lines were from JENNIO biological technology (Guangzhou, China). All cell lines were maintained in DMEM (Gibco), supplemented with 10% fetal bovine serum (FBS, Gibco), and 1% penicillin-streptomycin at 37 °C with humidified 5% carbon dioxide.

**Cell Proliferation Assay.** Logarithmically growing tumor cells were transferred to 96-well flat-bottomed plates and cultured overnight before exposure to compound **5b (SMU-B)** at concentrations ranging from 0 to 10 μM for 48h. MTT (5 mg/mL) was then added to each well and cells were continued to incubate for 4 h at 37 °C. The resulting crystals were dissolved in DMSO before measurement of absorbance at 490 nm with a plate microreader (Bio-Rad). The percentage of cell growth inhibition was calculated as follows:

$$\text{Cell inhibitory ratio (\%)} = [(A_{490} \text{ control} - A_{490} \text{ sample}) / A_{490} \text{ control}] \times 100\%$$

The concentration of compound **5b (SMU-B)** resulting in 50% growth inhibition (IC<sub>50</sub>) was calculated.

**Pharmacokinetics Study.** BALB/c mice were divided randomly for intravenous (5 mg/kg) or oral (20 mg/kg) administration. Blood samples were collected from all animals at predetermined

time points with heparin as the anticoagulant, and then centrifuged. The resulting plasma samples were stored at approximately -20 °C until analysis. Concentrations of compound **5b** (SMU-B) in biological samples were quantitatively determined by UPLC-MS/MS analysis.

### **In vivo Studies:**

**Animals.** Female nu/nu BALB/c nude mice (3-4 weeks old) were acclimated to the animal housing facility for 1 week before studies. All experimental procedures conformed to the Animal Management Rules of the Chinese Ministry of Health and were approved by Animal Care and Use Committee of the Southern Medical University.

**Pharmacodynamics Studies.** *In vivo* target modulation studies were carried out in mice bearing GTL-16 tumor xenografts by determining the effects of compound **5b** (SMU-B) on c-Met signaling pathway. The tumor volume was measured with electronic Vernier calipers every other day, and tumor volume was calculated as its length $\times$ width<sup>2</sup>/2. When tumors reached a volume of  $\sim$ 100 mm<sup>3</sup>, mice were then separated into four subgroups with three animals in each group and given compound **5b** (SMU-B) orally at designated doses and dosing schedules. At designated times following compound **5b** (SMU-B) administration, mice were euthanized, and their tumors were resected. Tumors were snap frozen and pulverized using a liquid nitrogen-cooled cryomortar and pestle, protein lysates were generated, and protein concentrations were determined using a BCA assay. The level of proteins was determined using Western Blot method.

**Tumor Growth Inhibition.** When tumors reached a volume of  $\sim$ 150 mm<sup>3</sup>, mice were randomly divided into three groups (n = 6) and compound **5b** (SMU-B) or vehicle was administered once a day (q.d.) *via* oral gavage for 2 weeks. The tumor volume was recorded every other day. Tumor volume was expressed on indicated days as the mean tumor volume  $\pm$  SD. Percent (%) inhibition values were measured on the last day of study (day 15). Percent (%) tumor growth inhibition (TGI) =  $100 \times (1 - V_{\text{Treated}} / V_{\text{Control}})$ . The body weight of each mouse was monitored daily, and expressed as the mean  $\pm$  SD. After 2 weeks of treatment, mice were sacrificed and individual tumors were weighed.

### **Supporting Information References.**

- (1) de Koning, P. D.; McAndrew, D.; Moore, R.; Moses, I. B.; Boyles, D. C.; Kissick, K.; Stanchina, C. L.; Cuthbertson, T.; Kamatani, A.; Rahman, L.; Rodriguez, R.; Urbina, A.; Sandoval, A.; Rose, P. R. Fit-for-purpose development of the enabling route to crizotinib (PF-02341066). *Org. Process Res. Dev.* **2011**, *15*, 1018-1026.
- (2) Ye, L.; Tian, Y.; Li, Z.; Jin, H.; Zhu, Z.; Wan, S.; Zhang, J.; Yu, P.; Zhang, J.; Wu, S. Design, synthesis and molecular docking studies of some novel spiro[indoline-3,4']-2-ones as potent c-Met inhibitors. *Eur. J. Med. Chem.* **2012**, *50*, 370-375.
- (3) Jain, A. N. Surflex: Fully automatic flexible molecular docking using a molecular similarity-based search engine. *J. Med. Chem.* **2003**, *46*, 499-511.
- (4) Jain, A. N. Surflex-Dock 2.1: Robust performance from ligand energetic modeling, ring flexibility, and knowledge-based search. *J. Comput. Aided Mol. Des.* **2007**, *21*, 281-306.
- (5) Fabian, M. A.; Biggs III, W. H.; Treiber, D. K.; Atteridge, C. E.; Azimioara, M. D.; Benedetti, M. G.; Carter, T. A.; Ciceri, P.; Edeen, P. T.; Floyd, M.; Ford, J. M.; Galcin, M.; Gerlach, J. L.; Grotzfeld, R. M.; Herrgard, S.; Insko, D. E.; Insko, M. A.; Lai, A. G.; Lélias, J.-M.; Mehta, S. A.; Milanov, Z. V.; Velasco, A. M.; Wodicka, L. M.; Patel, H. K.; Zarrinkar, P. P.; Lockhart, D. J. A small molecule-kinase interaction map for clinical kinase inhibitors. *Nat. Biotechnol.* **2005**, *23*, 329-336.
- (6) Ma, H.; Horiuchi, K. Y.; Wang, Y.; Kucharewicz, S. A.; Diamond, S. L. Nanoliter homogenous ultra-high throughput screening microarray for lead discoveries and IC<sub>50</sub> profiling. *Assay Drug Dev. Technol.* **2005**, *3*, 177-187.
- (7) Cellular Phosphorylation Assays: <http://www.proqinase.com/content/view/61> (accessed May 22, 2013).