

## **Supporting Information**

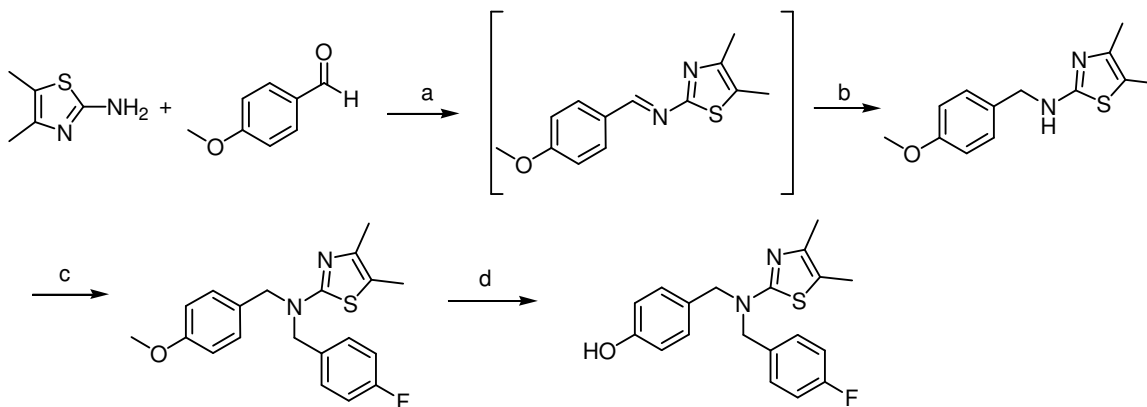
### **Discovery and Characterization of Non-ATP Site Inhibitors of the Mitogen Activated Protein (MAP) Kinases**

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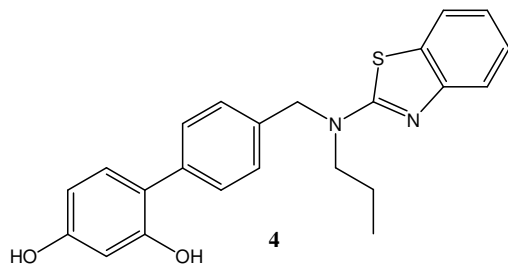
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Supplemental scheme S1<sup>a</sup>.



<sup>a</sup>Reagents and conditions: (a) AcOH, toluene, reflux; (b)  $\text{NaBH}_4$ , EtOH; (c) NaH, 4-fluorobenzyl bromide, DMF; (d)  $\text{BBr}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78\text{ }^\circ\text{C}$  to room temperature.

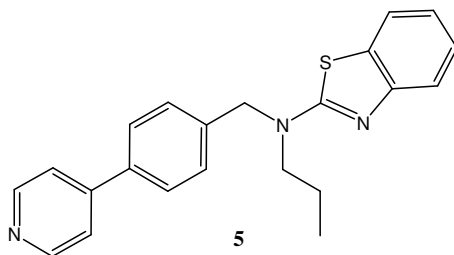
## Supplemental synthesis S1.



### **4'-[(Benzothiazol-2-yl-propyl-amino)-methyl]-biphenyl-2,4diol**

The title compound was synthesized using the same method as compound **2** with yield 55%.  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  7.73 (d,  $J=7.80\text{Hz}$ , 2H), 7.36 - 7.58 (m, 3H), 7.17 - 7.39 (m, 3H), 6.81 - 7.17 (m, 2H), 6.39 (d,  $J=2.37\text{Hz}$ , 2H), 6.28 (dd,  $J_1=8.14$ ,  $J_2=2.37$  Hz, 1 H), 4.79 (s, 2H), 3.49 (t, 2H), 1.46 - 1.86 (m, 2H), 0.91 (t,  $J=7.29\text{Hz}$ , 3H);  $^{13}\text{C}$  NMR (100MHz, DMSO- $d_6$ )  $\delta$  167.7 (C), 157.7 (C), 155.2 (C), 152.7 (C), 137.9 (C), 134.2 (C), 130.7 (CH), 130.4 (C), 128.9 (CH), 126.7 (CH), 125.8 (CH), 120.9 (CH), 120.7 (CH), 118.5 (C), 118.2 (CH), 106.9 (CH), 103.0 (CH), 53.2(CH $_2$ ), 52.5(CH $_2$ ), 20.1(CH $_2$ ), 11.0 (CH $_3$ ); MS (ESI)  $m/z$  391[M+H] $^+$ , 389 [M-H] $^-$ . Anal calcd for C $_{23}$ H $_{22}$ N $_2$ O $_2$ S•0.15H $_2$ O: C, 70.26; H, 5.72; N, 7.12. Found: C, 70.18; H, 5.50; N, 7.18.

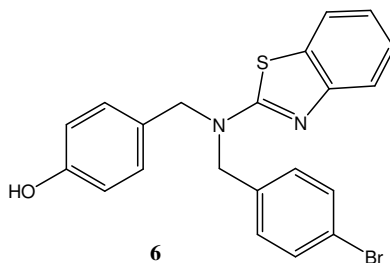
## Supplemental synthesis S2.



### Benzothiazole-2-yl-propyl-(4-pyridin-4-yl-benzyl)-amine

Reductive-amination of 2-aminobenzothiazole and 4-pyridin-4-yl-benzaldehyde yielded benzothiazol-2-yl-(4-bromo-benzyl)-amine, which was alkylated with propyl bromide in the same method as compound **2** and followed by Suzuki coupling with 4-pyridyl boronic acid to give the title compound with 53% yield.  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$ , 8.62 (d,  $J=6.0\text{Hz}$ , 2H), 7.79 (d,  $J=6.0\text{Hz}$ , 2H), 7.73 (d,  $J=6.0\text{Hz}$ , 1H), 7.68 (d,  $J=6.0\text{Hz}$ , 2H), 7.48 - 7.744 (m, 3H), 7.26 (t,  $J=6.0\text{Hz}$ , 1H), 7.05 (t,  $J=6.0\text{Hz}$ , 1H), 4.87 (s, 2H), 3.51 (d,  $J=6.0\text{Hz}$ , 2H), 1.73-1.67 (m, 2H), 0.91(t,  $J=6.0\text{Hz}$ , 3H);  $^{13}\text{C}$  NMR (100MHz, DMSO- $d_6$ )  $\delta$  167.7 (C), 152.5 (C), 151.8 (C), 145.4(CH), 140.4(C), 134.3 (C), 130.4 (C), 128.2 (CH), 127.8 (CH), 125.9 (CH), 122.6 (CH), 121.0 (CH), 120.9 (CH), 118.3 (CH), 53.1(CH<sub>2</sub>), 52.5(CH<sub>2</sub>), 20.2(CH<sub>2</sub>), 11.0 (CH<sub>3</sub>); MS (ESI)  $m/z$  360[M+H]<sup>+</sup>, 358 [M-H]<sup>-</sup>. Analysis calculated for C<sub>22</sub>H<sub>21</sub>N<sub>3</sub>S•0.15H<sub>2</sub>O: C, 72.96; H, 5.93; N, 11.6. Found: C, 73.01; H, 5.80; N, 11.4.

### Supplemental synthesis S3.



#### 4-[[Benzothiazol-2-yl-(4-bromo-benzyl)-amino]-methyl]-phenol

The compound was synthesized using 2-aminobenzothiazole as starting material in the same method as compound **2** & **3** with 62% yield.  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  9.40 (s, 1H), 7.73 (d,  $J=7.80\text{Hz}$ , 1H), 7.53 (m, 2H), 7.46 (d,  $J=7.80\text{Hz}$ , 1H), 7.20 - 7.33 (m, 3H), 7.14 (d,  $J=8.48\text{Hz}$ , 2H), 7.06 (td,  $J_1=8.48$ ,  $J_2=3.0\text{Hz}$ , 1H), 6.72 (d,  $J=8.48\text{Hz}$ , 2H), 4.72 (s, 2H), 4.64 (s, 2H);  $^{13}\text{C}$  NMR (100MHz, DMSO- $d_6$ ),  $\delta$  167.9 (C), 156.9 (C), 152.4 (C), 136.3(C), 131.4 (CH), 130.6 (CH), 129.5 (CH), 129.0 (CH), 126.4 (C), 125.9 (CH), 121.0 (CH), 120.3 (C), 118.4 (CH), 112.6(C), 115.4 (CH), 53.5 ( $\text{CH}_2$ ), 52.5 ( $\text{CH}_2$ ); MS (ESI)  $m/z$  425 $[\text{M}+\text{H}]^+$ , 423  $[\text{M}-\text{H}]^-$ . Analysis calculated for  $\text{C}_{21}\text{H}_{17}\text{BrN}_2\text{OS}$ : C, 59.30; H, 4.03; N, 6.59. Found: C, 59.15; H, 3.84; N, 6.63.

**Supplemental Table S1.****Crystallographic statistics for apo Jnk-1 and Jnk-1/compound 3 complex**

|                             | Apo-JNK1- $\alpha$ 1<br>(jnk1-pepJIP1) | Complex with<br>compound 3 |
|-----------------------------|--|----------------------------|
| <b>PDB entry</b>            | 3O17                                   | 3O2M                       |
| <b>Data collection</b>      |  |                            |
| Space group                 | P3 <sub>2</sub> 21                     | P3 <sub>2</sub> 21         |
| Unit cell (a,b,c) (Å)       |  |                            |
| a = b =                     | 155.85                                 | 158.38                     |
| c =                         | 124.49                                 | 123.96                     |
| Resolution (Å)              | 3.0                                    | 2.7                        |
| Unique reflections          | 35007                                  | 49665                      |
| Completeness (%)            | 98.9(99.9)                             | 99.3(97.3)                 |
| Average I/ $\sigma$ (I)     | 39.8(3.2)                              | 36.1(4.1)                  |
| Rsym (%)                    | 4.6(36.3)                              | 6.8(34.7)                  |
| <b>Structure refinement</b> |  |                            |
| Rcryst                      | 0.247                                  | 0.242                      |
| Rfree                       | 0.298                                  | 0.281                      |
| R.m.s.d.                    |  |                            |
| Bonds (Å)                   | 0.008                                  | 0.018                      |
| Angles (°)                  | 1.46                                   | 1.75                       |

Supplemental Table S2.

## Crystallographic statistics for p38 $\alpha$ /compound 10 complex

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**PDB entry** 3NEW

### Data collection

Space group *P*2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>

Unit cell (a,b,c) (Å)

a = 64.9

b = 74.4

c = 77.9

Resolution (Å) 49.9–2.5

Unique reflections 13311

Completeness (%) 99.3 (95.5)

Average *I*/ $\sigma$ (*I*) 8.1 (2.2)

R<sub>sym</sub> (%) 6.7 (38.9)

(values in parentheses are those for the highest resolution bin)

### Structure refinement

R<sub>cryst</sub> 0.214

R<sub>free</sub> 0.306

R.m.s.d.

Bonds (Å) 0.037

Angles (°) 2.7