

## Supplemental Data

### Materials and Methods

**Synthesis and characterization of *N*-{(3*R*,4*S*)-3-[4-(5-cyano-2-thienyl)phenyl]tetrahydro-2*H*-pyran-4-yl}propane-2-sulfonamide (PF-4778574).** A mixture of *N*-[(3*R*,4*S*)-3-(4-iodophenyl)tetrahydro-2*H*-pyran-4-yl]propane-2-sulfonamide (25 mmol), 5-cyanothiophene-2-boronic acid pinacol boronate ester (30 mmol), (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) chloride (1.3 mmol) and tribasic potassium phosphate (75 mmol) in 20% H<sub>2</sub>O in 2-methyl-THF (125 mL) was evacuated and backfilled with N<sub>2</sub> three times. The reaction was heated to 75 °C until starting material was consumed, as determined by the periodic HPLC analysis of reaction mixture aliquots, and then concentrated *in vacuo*. The residue was reconstituted in H<sub>2</sub>O and extracted with EtOAc, the pooled organic extract was washed with saturated aqueous NaCl, dried over MgSO<sub>2</sub>, filtered and concentrated by rotary evaporation. The residue was purified by flash chromatography using a 120 g silica gel RediSep<sup>®</sup> column (eluant: 20–100% EtOAc in heptane) to afford PF-4778574 (9.7 g, 99%) as a pale yellow foam. Mp: 118–120 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.84 (d, *J* = 6.4 Hz, 3H), 1.13 (d, *J* = 7.2 Hz, 3H), 1.77 (m, 1H), 2.29 (m, 1H), 2.60 (m, 1H), 2.75 (td, *J* = 10.8, 10.8, 4.4 Hz, 1H), 3.46 (t, *J* = 11.2 Hz, 1H), 3.57 (ddd, apparent td, *J* = 12.0, 12.0, 1.6 Hz, 1H), 3.71 (m, 1H), 3.95 (dd, *J* = 11.6, 4.8 Hz, 1H), 4.05 (dd, *J* = 12.0, 4.4 Hz, 1H), 4.12 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 3.6 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 4.0 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 16.3, 16.4, 36.1, 50.2, 54.3, 55.6, 67.4, 72.7, 108.7, 114.5, 123.6, 127.0, 129.5, 132.0, 138.7, 140.2, 151.2; ESI: [M-H]<sup>+</sup> = 389.2; elemental analysis

Shaffer CL, Hurst RS, Scialis RJ, Osgood SM, Bryce DK, Hoffmann WE, Lazzaro JT, Hanks AN, Lotarski S, Weber ML, Liu J, Menniti FS, Schmidt CJ and Hajós M  
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calculated for  $C_{19}H_{22}N_2O_3S_2$  C: 58.44, H: 5.68, N: 7.17; found, C: 58.38, H: 5.55, N: 7.16;

optical rotation:  $+0.226^\circ$ ;  $[\alpha]^{20} = +61^\circ$  (c = 0.74,  $CH_2Cl_2$ ).

## Results

### Mouse Neuropharmacokinetics Data.

PF-4778574: CD-1 Mouse Single-dose Neuropharmacokinetics Data (0.178 mg/kg, SC)

| Time (h) | Cp (ng/mL) |      |      |    | Cb (ng/g) |      |      |    | Cb,u (nM) |       |       |    |
|----------|------------|------|------|----|-----------|------|------|----|-----------|-------|-------|----|
|          | #1M        | #2M  | Mean | SD | #1M       | #2M  | Mean | SD | #1M       | #2M   | Mean  | SD |
| 0.5      | 15.1       | 16.3 | 15.7 |    | 18.3      | 19.3 | 18.8 |    | 0.914     | 0.964 | 0.939 |    |
| fu,p     | 0.0570     |      |      |    |           |      |      |    |           |       |       |    |
| fu,b     | 0.0195     |      |      |    |           |      |      |    |           |       |       |    |
| MW       | 390.5      |      |      |    |           |      |      |    |           |       |       |    |

PF-4778574: C57BL/6J Mouse Single-dose Neuropharmacokinetics Data (0.178 mg/kg, SC)

| Time (h) | Cp (ng/mL) |      |      |      | Cb (ng/g) |      |      |      | Cb,u (nM) |     |      |      |      |      |      |
|----------|------------|------|------|------|-----------|------|------|------|-----------|-----|------|------|------|------|------|
|          | #1M        | #2M  | #3M  | Mean | SD        | #1M  | #2M  | #3M  | Mean      | SD  | #1M  | #2M  | #3M  | Mean | SD   |
| 0.5      | 31.4       | 28.1 | 18.9 | 26.1 | 6.5       | 24.7 | 29.1 | 37.6 | 30.5      | 6.6 | 1.23 | 1.45 | 1.88 | 1.52 | 0.33 |
| fu,p     | ND         |      |      |      |           |      |      |      |           |     |      |      |      |      |      |
| fu,b     | 0.0195     |      |      |      |           |      |      |      |           |     |      |      |      |      |      |
| MW       | 390.5      |      |      |      |           |      |      |      |           |     |      |      |      |      |      |

ND = Not determined

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## Sprague-Dawley Rat Neuropharmacokinetics Data.

### PF-4778574: Sprague-Dawley Rat Single-dose Neuropharmacokinetics Data (1 mg/kg, SC)

|                    |         | Plasma                    | Brain                    | CSF                         | Plasma                   | Brain                    | CSF                      |
|--------------------|---------|---------------------------|--------------------------|-----------------------------|--------------------------|--------------------------|--------------------------|
| Time (h)           |         | C <sub>p</sub><br>(ng/mL) | C <sub>b</sub><br>(ng/g) | C <sub>CSF</sub><br>(ng/mL) | C <sub>p,u</sub><br>(nM) | C <sub>b,u</sub><br>(nM) | C <sub>CSF</sub><br>(nM) |
| 0.25               |         | 105                       | 70.3                     | 2.66                        | 12.8                     | 3.51                     | 6.81                     |
| 0.5                |         | 69.4                      | 70.2                     | 2.21                        | 8.46                     | 3.51                     | 5.66                     |
| 1.0                |         | 61.7                      | 66.4                     | 2.01                        | 7.52                     | 3.32                     | 5.15                     |
| 2.0                |         | 19.9                      | 31.8                     | 0.930                       | 2.43                     | 1.59                     | 2.38                     |
| 4.0                |         | <LLOQ                     | <LLOQ                    | <LLOQ                       |                          |                          |                          |
| 8.0                |         | <LLOQ                     | <LLOQ                    | <LLOQ                       |                          |                          |                          |
| AUC <sub>0-2</sub> | ng*h/mL | 122                       | 131                      | 3.46                        |                          |                          |                          |
| AUC Extrap         | ng*h/mL | 131                       | 150                      | 5.40                        |                          |                          |                          |
| C <sub>max</sub>   | ng/mL   | 105                       | 70.3                     | 2.66                        |                          |                          |                          |
| T <sub>max</sub>   | h       | 0.3                       | 0.3                      | 0.3                         |                          |                          |                          |
| t <sub>1/2</sub>   | h       | 0.7                       | 0.8                      | 1.3                         |                          |                          |                          |
| f <sub>u,p</sub>   | 0.0476  |                           |                          |                             |                          |                          |                          |
| f <sub>u,b</sub>   | 0.0195  |                           |                          |                             |                          |                          |                          |
| MW                 | 390.5   |                           |                          |                             |                          |                          |                          |

LLOQ = Lower limit of quantification

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## Sprague-Dawley Rat Single Intravenous Bolus Pharmacokinetics Data.

PF-4778574: Sprague-Dawley Rat Single IV Bolus Pharmacokinetics Data (0.2 mg/kg)

| Time (h)         | Cp (ng/mL) |       |       |      |      | Cb,u (nM) |       |       |       |       |
|------------------|------------|-------|-------|------|------|-----------|-------|-------|-------|-------|
|                  | #1M        | #2M   | #3M   | Mean | SD   | #1M       | #2M   | #3M   | Mean  | SD    |
| 0.083            | 40.4       | 26.9  | 42.4  | 36.6 | 8.4  | 2.17      | 1.44  | 2.27  | 1.96  | 0.45  |
| 0.167            | 28.6       | 16.5  | 31.3  | 25.5 | 7.9  | 1.53      | 0.885 | 1.68  | 1.37  | 0.42  |
| 0.25             | 22.3       | 12.2  | 19.2  | 17.9 | 5.2  | 1.20      | 0.654 | 1.03  | 0.960 | 0.277 |
| 0.5              | 9.83       | 6.30  | 8.56  | 8.23 | 1.79 | 0.527     | 0.338 | 0.459 | 0.441 | 0.096 |
| 1                | 2.96       | 0.985 | 2.27  | 2.07 | 1.00 | 0.159     | 0.053 | 0.122 | 0.111 | 0.054 |
| 2                | <LLOQ      | <LLOQ | <LLOQ |      |      |           |       |       |       |       |
| 4                | <LLOQ      | <LLOQ | <LLOQ |      |      |           |       |       |       |       |
| 6                | <LLOQ      | <LLOQ | <LLOQ |      |      |           |       |       |       |       |
| 8                | <LLOQ      | <LLOQ | <LLOQ |      |      |           |       |       |       |       |
| 12               | <LLOQ      | <LLOQ | <LLOQ |      |      |           |       |       |       |       |
| fu,p             | 0.0476     |       |       |      |      |           |       |       |       |       |
| fu,b             | 0.0195     |       |       |      |      |           |       |       |       |       |
| MW               | 390.5      |       |       |      |      |           |       |       |       |       |
| SD rat Cb,u:Cp,u | 0.44       |       |       |      |      |           |       |       |       |       |

LLOQ = Lower limit of quantification

## Beagle Dog Single Oral Dose Pharmacokinetics Data.

### PF-4778574: Beagle Dog Single Oral Dose Pharmacokinetics Data (0.1 mg/kg)

| Time (h) | Cp (ng/mL) |      |      |    | Cb,u (nM) |      |      |    |
|----------|------------|------|------|----|-----------|------|------|----|
|          | #1M        | #2F  | Mean | SD | #1M       | #2F  | Mean | SD |
| 0.25     | 2.80       | 42.4 | 22.6 |    | 0.250     | 3.79 | 2.02 |    |
| 0.5      | 6.05       | 66.0 | 36.0 |    | 0.541     | 5.90 | 3.22 |    |
| 1        | 46.0       | 39.8 | 42.9 |    | 4.12      | 3.56 | 3.84 |    |
| 2        | 31.5       | 27.0 | 29.3 |    | 2.82      | 2.42 | 2.62 |    |
| 4        | 24.3       | 17.6 | 21.0 |    | 2.17      | 1.57 | 1.87 |    |

fu,p 0.0685  
 fu,b ND  
 MW 390.5  
 Beagle dog Cb,u:Cp,u 0.51

### PF-4778574: Beagle Dog Single Oral Dose Pharmacokinetics Data (0.2 mg/kg)

| Time (h) | Cp (ng/mL) |      |    | Cb,u (nM) |      |    |
|----------|------------|------|----|-----------|------|----|
|          | #3F        | Mean | SD | #3F       | Mean | SD |
| 0.25     | 20.9       |      |    | 1.87      |      |    |
| 0.5      | 122        |      |    | 10.9      |      |    |
| 1        | 121        |      |    | 10.8      |      |    |
| 2        | 67.1       |      |    | 6.00      |      |    |
| 4        | 39.4       |      |    | 3.52      |      |    |

fu,p 0.0685  
 fu,b ND  
 MW 390.5  
 Beagle dog Cb,u:Cp,u 0.51

### PF-4778574: Beagle Dog Single Oral Dose Pharmacokinetics Data (0.25 mg/kg)

| Time (h) | Cp (ng/mL) |      |    | Cb,u (nM) |      |    |
|----------|------------|------|----|-----------|------|----|
|          | #4M        | Mean | SD | #4M       | Mean | SD |
| 0.25     | 98.2       |      |    | 8.79      |      |    |
| 0.5      | 174        |      |    | 15.6      |      |    |
| 1        | 154        |      |    | 13.8      |      |    |
| 2        | 135        |      |    | 12.1      |      |    |
| 4        | 70.5       |      |    | 6.31      |      |    |

fu,p 0.0685  
 fu,b ND  
 MW 390.5  
 Beagle dog Cb,u:Cp,u 0.51

ND = not determined

## Cynomolgus Monkey Single Subcutaneous Dose Pharmacokinetics Data.

### PF-4778574: Cynomolgus Monkey Single Subcutaneous Dose Pharmacokinetics Data (0.1 mg/kg)

| Time (h) | Cp (ng/mL) |       |      |    | Cb,u (nM) |       |       |    |
|----------|------------|-------|------|----|-----------|-------|-------|----|
|          | #3M        | #4M   | Mean | SD | #3M       | #4M   | Mean  | SD |
| 0.25     | 11.9       | 5.65  | 8.78 |    | 1.95      | 0.925 | 1.44  |    |
| 0.5      | 22.1       | 15.4  | 18.8 |    | 3.62      | 2.52  | 3.07  |    |
| 1        | 29.1       | 20.9  | 25.0 |    | 4.77      | 3.42  | 4.09  |    |
| 2        | 24.5       | 21.9  | 23.2 |    | 4.01      | 3.59  | 3.80  |    |
| 4        | 9.20       | 8.01  | 8.6  |    | 1.51      | 1.31  | 1.41  |    |
| 6        | 3.06       | 2.70  | 2.9  |    | 0.501     | 0.44  | 0.472 |    |
| 24       | <LLOQ      | <LLOQ |      |    |           |       |       |    |

fu,p 0.0876  
 fu,b ND  
 MW 390.5  
 Cynomolgus monkey Cb,u:Cp,u 0.73

### PF-4778574: Cynomolgus Monkey Single Subcutaneous Dose Pharmacokinetics Data (0.32 mg/kg)

| Time (h) | Cp (ng/mL) |       |      |    | Cb,u (nM) |        |      |    |
|----------|------------|-------|------|----|-----------|--------|------|----|
|          | #1M        | #2M   | Mean | SD | #1M       | #2M    | Mean | SD |
| 0.25     | 37.4       | 9.44  | 23.4 |    | 6.12      | 1.55   | 3.84 |    |
| 0.5      | 80.5       | 20.3  | 50.4 |    | 13.2      | 3.32   | 8.25 |    |
| 1        | 109        | 30.0  | 69.5 |    | 17.8      | 4.91   | 11.4 |    |
| 2        | 147        | 57.3  | 102  |    | 24.1      | 9.38   | 16.7 |    |
| 4        | 136        | 48.7  | 92.4 |    | 22.3      | 7.98   | 15.1 |    |
| 6        | 114        | 40.4  | 77.2 |    | 18.7      | 6.62   | 12.6 |    |
| 24       | 23.1       | 0.497 | 11.8 |    | 3.78      | 0.0814 | 1.93 |    |

fu,p 0.0876  
 fu,b ND  
 MW 390.5  
 Cynomolgus monkey Cb,u:Cp,u 0.73

ND = Not determined

LLOQ = Lower limit of quantification