Further Exploration of the Benzimidazole Scaffold as TRPC5 Inhibitors: Identification of 1-Alkyl-2-(pyrrolidin-1-yl)-1H-benzo[d]imidazoles as Potent and Selective Inhibitors

Swagat Sharma†, Juan L. Pablo‡, Kirsten T. Tolentino, Wacey Gallegos, Jennifer Hinman, Madison Beninato, MacKenzie Asche, Anna Greka, and Corey R. Hopkins∗
Table of Contents:

Table 1. PDSP Selectivity 2

$^1$H and $^{13}$C Spectra 4
**Supplemental Table 1.** PDSP Selectivity of select compounds (Compounds tested at 10 µM)

|       | 16f             |       | 9o             |       |
|-------|-----------------|-------|----------------|-------|
|       | Receptor        | Mean %| Receptor       | Mean %|
| 5-HT1A| 0.33            | 5-HT1A| -8.04          |
| 5-HT1B| -13.18          | 5-HT1B| -19.32         |
| 5-HT1D| -20.3           | 5-HT1D| -36.91         |
| 5-HT1E| 0.77            | 5-HT1E| -3.93          |
| 5-HT2A| 59.82           | 5-HT2A| 5.32           |
| 5-HT2B| 96.32           | 5-HT2B| 30.36          |
| Ki    | 258.6 nM        |       |                |
| 5-HT2C| 79.97           | 5-HT2C| 14.42          |
| 5-HT3 | -1.96           | 5-HT3 | -12.44         |
| 5-HT5A| 24.76           | 5-HT5A| -14.99         |
| 5-HT6 | 36.62           | 5-HT6 | 6.5            |
| 5-HT7A| 13.51           | 5-HT7A| -11.23         |
| Alpha1A| -2.69          | Alpha1A| -11.68       |
| Alpha1B| 16.13          | Alpha1B| -7.54         |
| Alpha1D| 10.22          | Alpha1D| -11.06       |
| Alpha2A| 90.23          | Alpha2A| 31.63         |
| Alpha2B| 82.96          | Alpha2B| 18.67         |
| Ki    | 676.7 nM        |       |                |
| Alpha2C| 84.82          | Alpha2C| 16.07         |
| Ki    | 434.3 nM        |       |                |
| Beta1 | 19.53           | Beta1 | -9.19          |
| Beta2 | -10.17          | Beta2 | 0              |
| Brain Site | Value   | Brain Site | Value   |
|------------|---------|------------|---------|
| D1         | 37.8    | D1         | 23.25   |
| D2         | 1.09    | D2         | -11.49  |
| D3         | 40.77   | D3         | 39.31   |
| D4         | 2.14    | D4         | -0.93   |
| D5         | 69.61   | D5         | 48.69   |
| Ki         | 5,661.1 | Ki         | nM      |
| DAT        | 24.3    | DAT        | 19.34   |
| DOR        | -5.69   | DOR        | -11.39  |
| GABAA      | -5.57   | GABAA      | 13.14   |
| GABAA      | -1.19   | GABAA      | 14.18   |
| H1         | 97.85   | H1         | 72.98   |
| Ki         | 6.2 nM  | Ki         | nM      |
| H2         | 83.29   | H2         | 64.13   |
| H3         | -5.56   | H3         | 1.97    |
| H4         | -8.89   | H4         | -16.01  |
| KOR        | 11.13   | KOR        | -11.71  |
| M1         | -16.1   | M1         | -15.52  |
| M2         | 13.73   | M2         | 7.75    |
| M3         | -39.68  | M3         | -31.15  |
| M4         | -7.49   | M4         | -6.19   |
| M5         | 14.48   | M5         | 10.9    |
| MOR        | 12.36   | MOR        | -6.78   |
| NET        | 21.91   | NET        | 39.4    |
|        | PBR   |        | PBR   |        |
|--------|-------|--------|-------|--------|
| SERT   | -8.27 |        | SERT  | -16.85 |
| Sigma 1| -18.76|        | Sigma 1| -19.5  |
| Sigma 2|  54   |        | Sigma 2| 88.88  |
| Ki     |       |        | Ki    | 7,333.3|
|        | nM    |        |        | nM     |
$^{1}$H and $^{13}$C Spectra:

$^{1}$H NMR (400 MHz, CDCl$_3$) δ 7.59 (d, $J = 7.9$ Hz, 1H), 7.23 (dd, $J = 19.6, 6.8$ Hz, 2H), 7.11 (t, $J = 6.8$ Hz, 3H), 7.00 (d, $J = 7.6, 2.1$ Hz, 1H), 6.93 (d, $J = 8.0$ Hz, 1H), 5.17 (d, $J = 5.0$ Hz, 2H), 3.46 (t, $J = 8.8$ Hz, 3H), 2.90 (t, $J = 12.1$ Hz, 2H), 1.64 (d, $J = 13.8$ Hz, 2H), 1.56 (q, $J = 11.5, 10.0$ Hz, 2H), 1.29 (dd, $J = 24.6, 12.5, 8.8$ Hz, 3H), 0.91 (d, $J = 6.6, 1.9$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 158.97, 141.74, 136.51, 135.46, 128.89, 127.52, 126.12, 121.77, 121.18, 117.90, 109.31, 51.27, 47.70, 34.82, 30.65, 23.87.
NMR (600 MHz, CDCl3) δ 7.66 (d, J = 7.9 Hz, 1H), 7.31 (d, J = 13.7 Hz, 6.8 Hz, 3H), 7.19 (d, J = 6.7 Hz, 3H), 7.07 (q, J = 9.5 Hz, 1H), 7.00 (d, J = 7.9 Hz, 1H). 3.20 (s, 2H), 2.62 (g, J = 7.9 Hz, 1H).
$^1$H NMR (400 MHz, CDCl₃): δ 7.59 (d, J = 7.9 Hz, 1H), 7.33 – 7.26 (m, 1H), 7.15 (d, J = 21.8, 8.2 Hz, 2H), 7.74 (t, J = 7.5 Hz, 2H), 6.94 (d, J = 7.9 Hz, 1H), 6.91 (t, J = 7.7 Hz, 1H), 5.34 (s, 2H), 3.59 (q, J = 6.5 Hz, 2H), 2.01 – 1.90 (m, 4H).

$^13$C NMR (100 MHz, CDCl₃): δ 169.97, 158.52, 135.59, 129.26, 127.30, 124.75, 123.94, 122.31, 120.52, 116.48, 108.15, 50.47, 42.08, 25.66.
$^{13}$C NMR (101 MHz, CDCl$_3$): 6 164.49, 162.03, 139.64, 133.64, 130.61, 122.28, 121.36, 120.50, 116.56, 114.78, 113.94, 112.62, 104.26, 30.65, 47.44, 25.65.

$^1$H NMR (400 MHz, CDCl$_3$): 5 7.58 (d, $J = 7.9$ Hz, 1H), 7.30 (td, $J = 8.0$, 5.8 Hz, 1H), 7.17 (td, $J = 7.7$, 1.2 Hz, 1H), 7.06 – 7.01 (m, 1H), 7.00 – 6.99 (m, 3H), 6.87 (dt, $J = 9.7$, 2.2 Hz, 1H), 5.27 (s, 2H), 3.61 – 3.53 (m, 4H), 1.99 – 1.90 (m, 4H).
$^1$H NMR (400 MHz, CDCl$_3$): δ 7.56 (d, J = 7.8 Hz, 1H), 7.19 - 7.08 (m, 3H), 7.06 - 6.98 (m, 3H), 7.19 - 6.95 (d, J = 7.8 Hz, 1H), 5.25 (s, 2H), 3.69 - 3.50 (m, 4H), 1.97 - 1.88 (m, 4H).

$^1$C NMR (101 MHz, CDCl$_3$): δ 163.39, 160.95, 156.56, 141.52, 135.72, 132.48, 127.38, 122.14, 120.35, 116.59, 116.03, 115.81, 110.23, 50.63, 47.23, 25.64.
$^{13}$C NMR (101 MHz, CDCl$_3$): δ 156.83, 141.91, 139.68, 135.86, 135.91, 130.29, 127.88, 125.06, 123.93, 122.14, 120.33, 116.70, 108.15, 50.65, 47.37, 25.65.

$^1$H NMR (600 MHz, CDCl$_3$): δ 7.55 (d, $J = 7.9$ Hz, 1H), 7.25 (d, $J = 5.6$ Hz, 2H), 7.20 – 7.12 (m, 2H), 7.06 – 6.98 (m, 2H), 6.94 (d, $J = 7.8$ Hz, 1H), 5.24 (s, 2H), 3.58 – 3.49 (m, 4H), 1.99 – 1.86 (m, 4H).
$^1$H NMR (400 MHz, CDCl$_3$) δ 7.56 (d, $J$ = 7.9 Hz, 1H), 7.32 – 7.28 (m, 2H), 7.16 (d, $J$ = 7.6, 1.2 Hz, 1H), 7.08 (d, $J$ = 8.2 Hz, 2H), 7.02 (d, $J$ = 7.6, 1.1 Hz, 1H), 6.93 (d, $J$ = 7.9 Hz, 1H), 5.24 (s, 2H), 3.59 – 3.49 (m, 4H), 1.97 – 1.89 (m, 4H).

$^1$C NMR (101 MHz, CDCl$_3$) δ 166.63, 140.64, 135.74, 135.37, 133.46, 129.16, 127.16, 122.17, 120.35, 116.64, 108.17, 50.63, 47.28, 25.64.
$^{13}$C NMR (101 MHz, CDCl$_3$) δ 159.07, 128.60, 126.93, 122.14, 120.45, 116.24, 114.38, 108.44, 55.51, 50.65, 47.35, 25.56.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.59 (d, $J = 7.8$ Hz, 1H), 7.19 – 7.12 (m, 1H), 7.02 (d, $J = 8.2$ Hz, 4H), 6.88 – 6.82 (m, 2H), 5.24 (s, 2H), 3.78 (s, 3H), 3.62 – 3.57 (m, 4H), 1.99 – 1.90 (m, 4H).
$^3$C NMR (101 MHz, CDCl$_3$): δ 156.83, 153.84, 151.38, 149.97, 141.96, 135.88, 128.81, 122.01, 121.39, 120.21, 110.66, 113.78, 108.19, 50.32, 50.58, 46.97, 35.64.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.54 (d, $J = 7.9$ Hz, 1H), 7.15 (td, $J = 7.6$, 1.3 Hz, 1H), 7.02 (td, $J = 7.6$, 1.1 Hz, 1H), 6.97 – 6.79 (m, 4H), 5.19 (s, 2H), 3.86 (s, 3H), 3.59 – 3.51 (m, 4H), 1.97 – 1.89 (m, 4H).
\[^{13}C\ NMR\ (101\ MHz,\ CDCl\text{ }3)\ \delta\ 156.41,\ 137.30,\ 135.81,\ 133.71,\ 129.63,\ 125.65,\ 122.04,\ 120.33,\ 116.35,\ 108.49,\ 50.62,\ 47.65,\ 25.65,\ 21.07.\]

\[^{1}H\ NMR\ (400\ MHz,\ CDCl\text{ }3)\ \delta\ 7.57\ (d, J=7.6\ Hz, 1H),\ 7.15\ (dd, J=12.6, 7.9\ Hz, 3H),\ 7.06\ -\ 6.94\ (m, 4H),\ 5.25\ (s, 2H),\ 3.64\ -\ 3.54\ (m, 4H),\ 2.33\ (s, 3H),\ 1.97\ -\ 1.88\ (m, 4H).\]
$\text{HNMR (400 MHz, CDCl}_3\): 8 7.57 (d, J = 7.9 Hz, 1H), 7.14 - 7.14 (m, 2H), 7.07 - 7.00 (m, 1H), 6.93 - 6.80 (m, 3H), 5.27 (s, 2H), 3.56 - 3.49 (m, 4H), 1.98 - 1.89 (m, 4H).

$\text{13C NMR (101 MHz, CDCl}_3\): 8 163.1, 160.6, 156.5, 135.5, 132.4, 130.8, 128.1, 122.3, 120.4, 117.3, 116.7, 114.9, 107.9, 80.3, 45.5, 25.6.}$
$^1$H NMR (400 MHz, CDCl$_3$) δ 7.56 (d, $J = 7.9$ Hz, 1H), 7.20 - 7.13 (m, 2H), 7.06 - 7.01 (m, 2H), 6.84 (d, $J = 8.2$ Hz, 1H), 5.94 (s, 2H), 3.06 - 3.51 (m, 3H), 1.99 - 1.89 (m, 4H).

$^1$C NMR (101 MHz, CDCl$_3$) δ 160.70, 158.23, 156.60, 141.70, 135.40, 134.28, 128.27, 125.15, 122.23, 128.40, 116.75, 116.20, 107.96, 56.67, 56.64, 23.65.
$^1$C NMR (101 MHz, CDCl$_3$): δ 162.72, 160.24, 156.54, 141.69, 135.53, 131.08, 129.02, 122.48, 120.52, 119.31, 116.76, 114.51, 107.92, 90.39, 44.34, 2.56.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.58 (d, $J = 7.9$ Hz, 1H), 7.47 (dd, $J = 8.6, 2.7$ Hz, 1H), 7.18 (d, $J = 7.6$ Hz, 1H), 7.12 (dd, $J = 8.2, 2.7$ Hz, 1H), 7.03 (d, $J = 7.6$ Hz, 1H), 6.96 (dd, $J = 8.8, 5.2$ Hz, 1H), 6.88 (d, $J = 7.8$ Hz, 1H), 5.82 (s, 1H), 3.52 (t, $J = 6.6$, 5.4, 3.0 Hz, 2H), 1.96 – 1.39 (m, 4H).
$^1$H NMR (400 MHz, CDCl$_3$) δ 7.90 (d, $J = 7.7$ Hz, 3H), 7.68 (d, $J = 7.5$ Hz, 1H), 7.52 (q, $J = 7.6$ Hz, 1H), 7.11 (s, $J = 7.7$ Hz, 1H), 6.81 (d, $J = 7.7$ Hz, 1H), 6.52 (d, $J = 8.1$ Hz, 1H), 3.49 (s, 4H), 1.91 (d, $J = 11.9$, 5.8 Hz, 3H).
$^{13}$C NMR (126 MHz, CDCl$_3$): δ 157.50, 136.69, 134.10, 122.91, 129.80, 128.91, 125.96, 121.86, 118.87, 116.25, 52.77, 25.70.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.89 (d, $J = 8.0$ Hz, 1H), 7.60 (dd, $J = 8.4$, 3.4 Hz, 2H), 7.49 (t, $J = 7.5$ Hz, 1H), 7.33 (d, $J = 7.8$ Hz, 2H), 7.24 (dd, $J = 7.8$, 1.3 Hz, 3H), 7.19 (dd, $J = 7.6$, 1.2 Hz, 1H), 7.10 (d, $J = 7.7$, 4 Hz, 1H), 7.75 (d, $J = 6.7$, 5.4, 3.0 Hz, 4H), 2.02 – 1.97 (m, 4H).
$^{13}$C NMR (126 MHz, CDCl$_3$): δ 158.12, 141.63, 135.18, 134.00, 133.39, 129.00, 127.85, 121.05, 121.72, 118.64, 109.57, 54.75, 51.90, 46.37, 33.10, 25.96, 22.33, 18.30.

$^1$H NMR (499 MHz, CDCl$_3$): δ 7.68 (dd, J = 25.6, 7.9 Hz, 1H), 7.32 – 7.28 (m, 2H), 7.25 – 7.20 (m, 1H), 7.17 – 7.09 (m, 3H), 7.09 (d, J = 7.9 Hz, 1H), 5.33 – 5.16 (m, 2H), 3.51 – 3.43 (m, 3H), 3.09 (dd, J = 12.1, 10.4, 4.5 Hz, 2H), 1.89 – 1.75 (m, 3H), 1.70 – 1.60 (m, 2H), 1.52 – 1.48 (m, 1H), 1.02 (dd, J = 12.8, 6.4 Hz, 3H).
$^{13}$C NMR (126 MHz, CDCl$_3$) 158.92, 141.77, 135.24, 135.00, 134.62, 129.13, 127.53, 121.98, 121.35, 118.10, 109.14, 51.34, 47.15, 34.03, 30.67, 21.87.

$^1$H NMR (400 MHz, CDCl$_3$) 8 7.65 (d, $J$ = 7.9 Hz, 1H, 7.33 - 7.27 (m, 2H), 7.23 - 7.17 (m, 1H), 7.15 - 7.06 (m, 2H), 6.97 (d, $J$ = 7.9 Hz, 1H), 3.17 (s, 2H), 3.05 (d, $J$ = 12.5 Hz, 2H), 2.99 (d, $J$ = 12.3, 2.2 Hz, 2H), 1.72 (dd, $J$ = 17.7, 1.9 Hz, 2H), 1.65 - 1.54 (m, 1H), 1.36 (ddd, $J$ = 26.4, 12.4, 3.8 Hz, 2H), 1.00 (d, $J$ = 6.5 Hz, 3H).
$\text{N}$

$\text{Cl}$

$\text{16c}$

$\text{O}$

$\text{O}$

$\text{1H NMR (400 MHz, CDCl$_3$):} \delta$ 7.66 (d, $J = 7.9$ Hz, 3H), 7.35 (d, $J = 8.4$ Hz, 2H), 7.30 - 7.25 (m, 1H), 7.22 - 7.17 (m, 1H), 7.09 (d, $J = 8.2$ Hz, 3H), 5.84 (s, 2H), 3.82 - 3.76 (m, 4H), 3.22 - 3.24 (m, 4H).
$\text{Cl}$

$1^3$C NMR (126 MHz, CDCl$_3$): $\delta$ 157.12, 142.35, 135.62, 135.40, 133.29, 129.00, 127.38, 121.01, 120.38, 117.14, 108.38, 56.71, 52.42, 47.11, 33.56, 23.05, 20.14.

$\text{Cl}$

$\text{N}$

$\text{N}$

$\text{16d}$

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.69 (d, $J = 7.9$ Hz, 1H), 7.29 (dd, $J = 7.5$, 5.9 Hz, 2H), 7.21 - 7.16 (m, 1H), 7.10 (d, $J = 8.4$ Hz, 2H), 7.08 - 7.03 (m, 1H), 6.98 (d, $J = 7.8$ Hz, 1H), 5.22 (dd, $J = 5.6$, 17.3 Hz, 2H), 4.14 - 4.25 (m, 1H), 3.61 - 3.53 (m, 1H), 3.23 (dd, $J = 8.7$, 3.8 Hz, 1H), 2.19 (dd, $J = 8.8$, 8.6, 3.9 Hz, 1H), 1.97 - 1.81 (m, 2H), 1.63 - 1.54 (m, 1H), 1.24 (d, $J = 6.1$ Hz, 3H).

$\text{Cl}$

$\text{N}$

$\text{N}$

$\text{16d}$
$^{13}$C NMR (126 MHz, CDCl$_3$): δ 157.11, 142.33, 135.61, 133.39, 133.39, 128.28, 127.37, 121.91, 120.38, 117.14, 108.38, 56.71, 52.42, 47.11, 39.41, 35.56, 25.05, 20.13.
