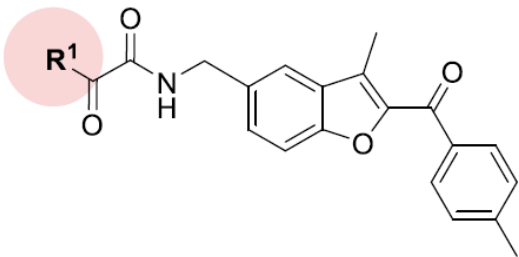
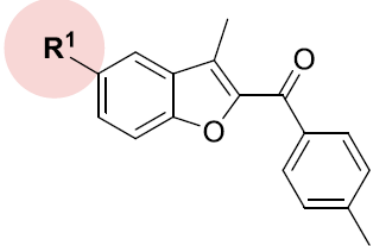


# Supplementary Figure 1

*R*<sup>1</sup> oxo-acetic acid SAR



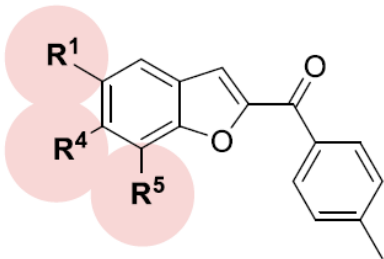
| ESC Code   | R <sup>1</sup>   | EPAC1<br>(pIC <sub>50</sub> ) | EPAC1<br>(E <sub>max</sub> ) | EPAC2<br>(pIC <sub>50</sub> ) | EPAC2<br>(E <sub>max</sub> ) |
|------------|------------------|-------------------------------|------------------------------|-------------------------------|------------------------------|
| ESC1000851 | OH               | 4.9                           | 88                           | 5.1                           | 102                          |
| ESC1000852 | OE <sub>t</sub>  | < 4.0                         | 16                           | < 4.0                         | 18                           |
| ESC1001771 | OMe              | 4.3                           | 50                           | < 4.0                         | 46                           |
| ESC1001772 | NHMe             | < 4.0                         | 18                           | 4.0                           | 54                           |
| ESC1001793 | NMe <sub>2</sub> | < 4.0                         | -4                           | < 4.0                         | -2                           |
| ESC1001895 | CH <sub>3</sub>  | < 4.0                         | 8                            | < 4.0                         | 1                            |



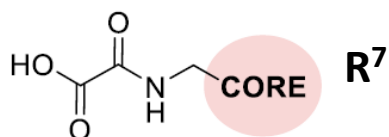
| ESC Code   | R <sup>1</sup> | EPAC1<br>(pIC <sub>50</sub> ) | EPAC1<br>(E <sub>max</sub> ) | EPAC2<br>(pIC <sub>50</sub> ) | EPAC2<br>(E <sub>max</sub> ) |
|------------|----------------|-------------------------------|------------------------------|-------------------------------|------------------------------|
| ESC1000853 |                | < 4.0                         | 14                           | < 4.0                         | 8                            |
| ESC1000854 |                | < 4.0                         | 7                            | < 4.0                         | 16                           |
| ESC1000915 |                | < 4.0                         | 9                            | < 4.0                         | 35                           |
| ESC1000960 |                | < 4.0                         | -6                           | < 4.0                         | 29                           |
| ESC1001000 |                | < 4.0                         | 4                            | < 4.0                         | 4                            |
| ESC1001622 |                | < 4.0                         | 12                           | < 4.0                         | 7                            |
| ESC1001634 |                | < 4.0                         | 10                           | < 4.0                         | 6                            |
| ESC1001650 |                | < 4.0                         | 8                            | < 4.0                         | 4                            |
| ESC1001696 |                | < 4.0                         | 6                            | < 4.0                         | 12                           |
| ESC1001702 |                | < 4.0                         | 0                            | < 4.0                         | 2                            |
| ESC1001792 |                | < 4.0                         | 3                            | < 4.0                         | 0                            |
| ESC1001889 |                | < 4.0                         | -2                           | < 4.0                         | -1                           |
| ESC1001918 |                | < 4.0                         | 37                           | < 4.0                         | 19                           |

# Supplementary Figure 3

Analogues with substitution at R<sup>4</sup> and R<sup>5</sup>



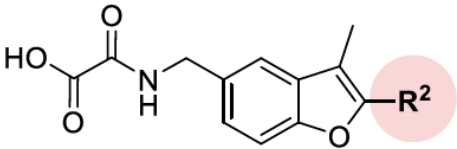
| ESC Code   | R <sup>1</sup> | R <sup>4</sup> | R <sup>5</sup>  | EPAC1 (pIC <sub>50</sub> ) | EPAC2 (pIC <sub>50</sub> ) |
|------------|----------------|----------------|-----------------|----------------------------|----------------------------|
| ESC1001742 |                | H              | H               | 5.0                        | 4.5                        |
| ESC1001896 | H              |                | H               | < 4.0                      | 4.4                        |
| ESC1001954 |                | OMe            | H               | < 4.0                      | 4.2                        |
| ESC1001955 |                | H              | OMe             | 4.9                        | 4.7                        |
| ESC1001956 |                | H              | NH <sub>2</sub> | 4.3                        | 4.5                        |



| ESC Code   | CORE | EPAC1<br>(pIC <sub>50</sub> ) | EPAC2<br>(pIC <sub>50</sub> ) |
|------------|------|-------------------------------|-------------------------------|
| ESC1001264 |      | <4.0                          | <b>4.4</b>                    |
| ESC1001466 |      | <4.0                          | <b>4.1</b>                    |
| ESC1001486 |      | <4.0                          | <4.0                          |
| ESC1001487 |      | <4.0                          | <4.0                          |
| ESC1001549 |      | <4.0                          | <4.0                          |
| ESC1001568 |      | <4.0                          | <4.0                          |
| ESC1001596 |      | <4.0                          | <4.0                          |
| ESC1001597 |      | <4.0                          | <4.0                          |

Supplementary Figure 5

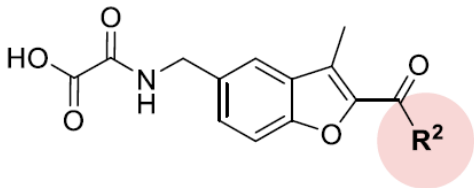
Alternative R<sup>2</sup> linkers



| ESC Code   | R <sup>2</sup> | EPAC1<br>(pIC <sub>50</sub> ) | EPAC2<br>(pIC <sub>50</sub> ) | ESC Code   | R <sup>2</sup> | EPAC1<br>(pIC <sub>50</sub> ) | EPAC2<br>(pIC <sub>50</sub> ) |
|------------|----------------|-------------------------------|-------------------------------|------------|----------------|-------------------------------|-------------------------------|
| ESC1000851 |                | 4.9                           | 5.1                           | ESC1001581 |                | 4.0                           | 4.6                           |
| ESC1001536 |                | 4.3                           | 4.7                           | ESC1001547 |                | < 4.0                         | 4.7                           |

Supplementary Figure 6

R<sup>2</sup> aryl and heteroaryl ketone substituents



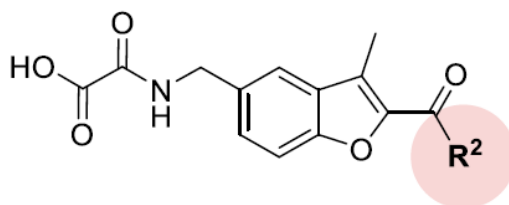
| ESC Code   | R <sup>2</sup> | EPAC1 (pIC <sub>50</sub> ) | EPAC2 (pIC <sub>50</sub> ) | ESC Code   | R <sup>2</sup> | EPAC1 (pIC <sub>50</sub> ) | EPAC2 (pIC <sub>50</sub> ) |
|------------|----------------|----------------------------|----------------------------|------------|----------------|----------------------------|----------------------------|
| ESC1000851 |                | 4.9                        | 5.1                        | ESC1001548 |                | 4.3                        | 4.7                        |
| ESC1000906 |                | 4.6                        | 5.1                        | ESC1001595 |                | 4.9                        | 5.2                        |
| ESC1000907 |                | 4.7                        | 4.8                        | ESC1001602 |                | 4.9                        | 4.9                        |
| ESC1001536 |                | 4.3                        | 4.7                        | ESC1001604 |                | 4.8                        | 5.1                        |
| ESC1001621 |                | 4.8                        | 4.7                        |            |                |                            |                            |

R<sup>2</sup> cycloalkyl and heteroalkyl ketone substituents

| ESC Code   | R <sup>3</sup> | R <sup>2</sup> | EPAC1 (pIC <sub>50</sub> ) | EPAC2 (pIC <sub>50</sub> ) | Fsp <sup>3</sup> | LE   | LipE |
|------------|----------------|----------------|----------------------------|----------------------------|------------------|------|------|
| ESC1000851 | Me             |                | 4.9                        | 5.1                        | 0.15             | 0.26 | 2.6  |
| ESC1001531 | Me             |                | 4.1                        | 4.4                        | 0.31             | 0.26 | 2.8  |
| ESC1001653 | Me             |                | 4.8                        | <b>5.8</b>                 | <b>0.52</b>      | 0.23 | 2.2  |
| ESC1001866 | i-Pr           |                | <b>5.4</b>                 | 4.5                        | 0.23             | 0.27 | 2.5  |
| ESC1001908 | i-Pr           |                | 4.7                        | 4.1                        | <b>0.45</b>      | 0.24 | 3.6  |
| ESC1001920 | i-Pr           |                | 5.0                        | 4.7                        | <b>0.48</b>      | 0.26 | 2.1  |

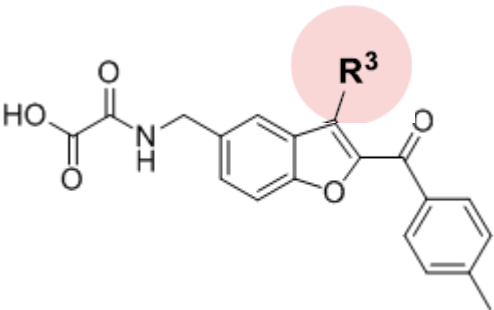
# Supplementary Figure 7

*R*<sup>2</sup> Amide substituents



| ESC Code   | $R^2$ | EPAC1<br>(pIC <sub>50</sub> ) | EPAC2<br>(pIC <sub>50</sub> ) |
|------------|-------|-------------------------------|-------------------------------|
| ESC1001605 |       | 4.4                           | 4.6                           |
| ESC1001607 |       | 4.1                           | 4.1                           |
| ESC1001608 |       | <4.0                          | <4.0                          |
| ESC1001609 |       | <4.0                          | <4.0                          |
| ESC1001610 |       | <4.0                          | <4.0                          |
| ESC1001693 |       | <4.0                          | 4.4                           |
| ESC1001694 |       | <4.0                          | 4.3                           |
| ESC1001711 |       | 4.7                           | 5.1                           |
| ESC1001876 |       | 4.6                           | 5.1                           |
| ESC1001877 |       | 4.4                           | 4.6                           |
| ESC1001878 |       | 4.4                           | 4.7                           |

Supplementary Figure 8



3-Substituted benzofuran analogues

| SY000<br>→ | ESC Code   | R <sup>3</sup> | EPAC1<br>(pIC <sub>50</sub> ) | EPAC2<br>(pIC <sub>50</sub> ) |
|------------|------------|----------------|-------------------------------|-------------------------------|
|            | ESC1000851 | Me             | 4.9                           | 5.1                           |
| SY009<br>→ | ESC1001588 | O <i>i</i> -Pr | 4.2                           | 4.4                           |
|            | ESC1001628 | OMe            | 4.5                           | 4.6                           |
|            | ESC1001652 | Et             | 5.3                           | 5.3                           |
|            | ESC1001742 | H              | 5.0                           | 4.5                           |
|            | ESC1001860 | <i>c</i> -Pr   | 5.0                           | 4.8                           |
|            | ESC1001866 | <i>i</i> -Pr   | 5.4                           | 4.5                           |
|            | ESC1001867 | <i>i</i> -Bu   | 5.2                           | 4.7                           |
|            | ESC1001903 | <i>c</i> -Hex  | 5.0                           | 4.3                           |
|            | ESC1001919 | 4Cl-Ph         | 4.9                           | 4.1                           |