**Supplemental Material**

# A 'Target-Class' Screen To Identify Activators Of Two-Pore Domain Potassium (K2P) Channels

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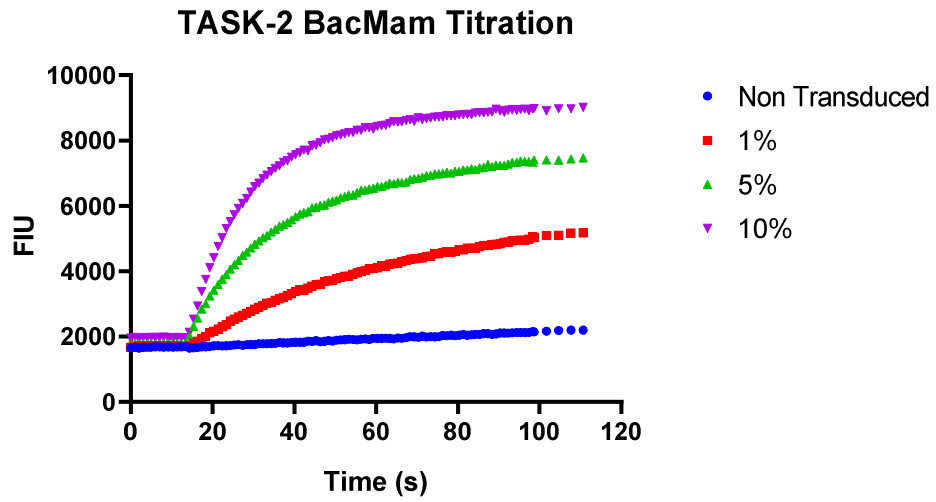
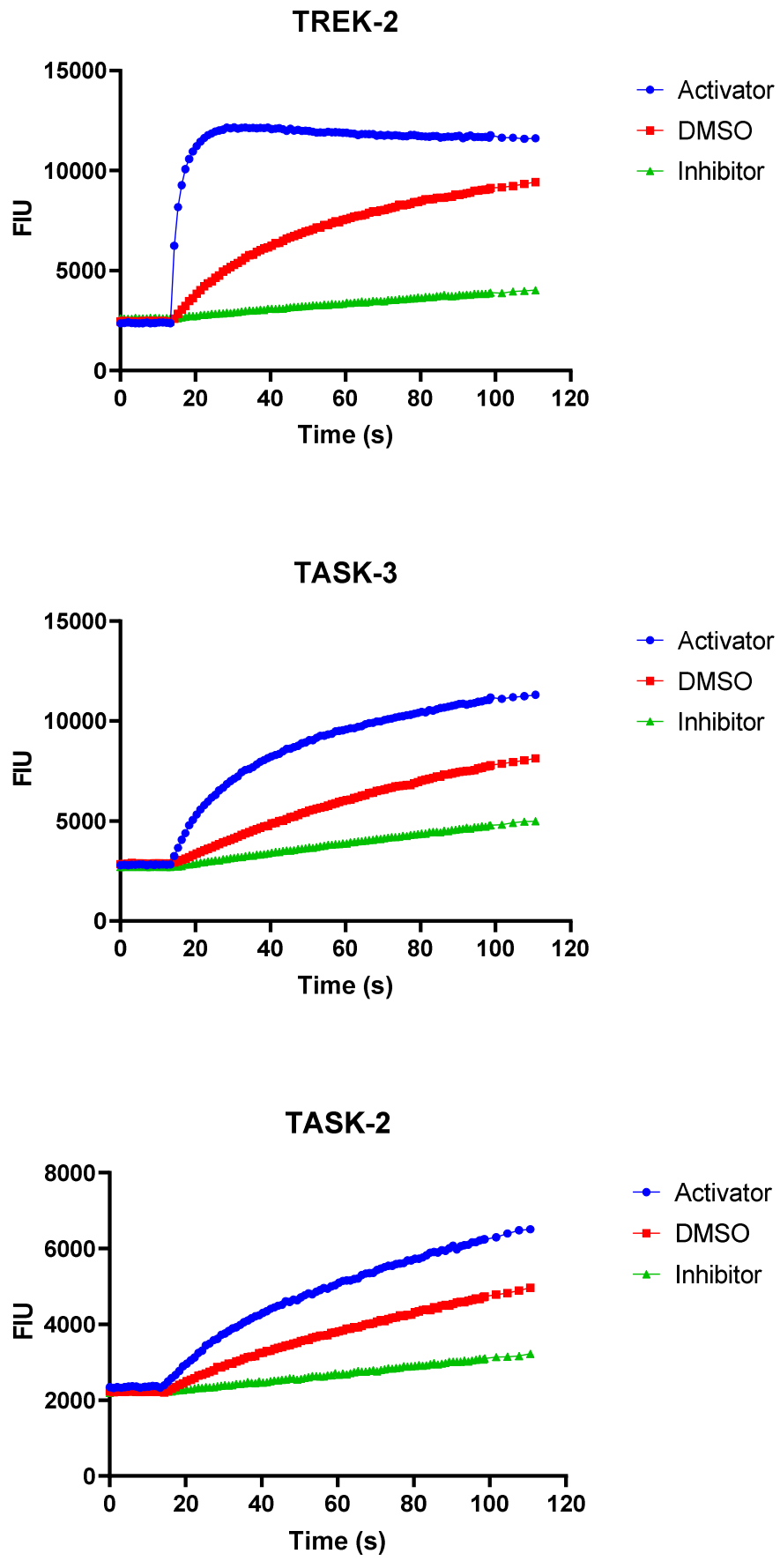
**A**



B


TREK-2
15000
10000
5000
0
FIU
0
20
40
60
80
100
120
Time (s)
Activator
DMSO
Inhibitor
TASK-3
15000
10000
5000
0
FIU
0
20
40
60
80
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Time (s)
Activator
DMSO
Inhibitor
TASK-2
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Time (s)
Activator
DMSO
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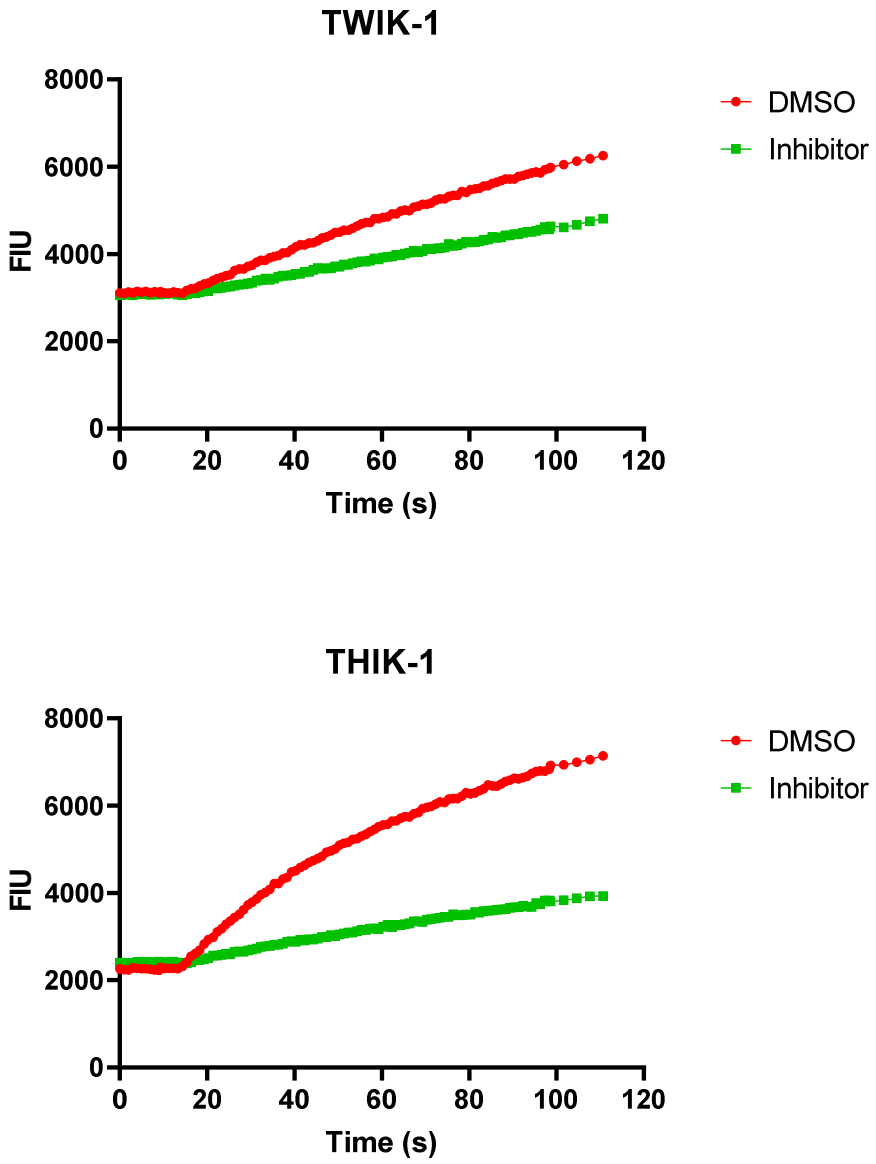


**Figure S1.** Raw FLIPR data. (A) Exemplar data for TASK-2 demonstrating the response to DMSO at a range of concentrations of TASK-2 BacMam. (B) Exemplar data for each target demonstrating the response to an activator (where available) inhibitor and DMSO. Pre-addition baselines were established for 13 seconds prior to the addition of 2mM thallium and fluorescence measured to 110 seconds. Channel activity was then measured as the rate of fluorescence increase following thallium addition. The time points used in the rate calculation for each target were as follows; TREK-2 (13-19s), TASK-2 (15-28s), TASK-3 (14-24s), TWIK-1 (18-36s), THIK-1 (18-36s). FIU represents fluorescence intensity units.

| | TWIK-1 | TASK-2 | TASK-3 | TREK-2 |
|---|---|---|---|---|
| **Mol Wt** | 213 - 505 | 248 - 395 | 201 - 429 | 242 - 489 |
| **AlogP** | 2.6 – 5.4 | 1.1 – 4.2 | 2.3 – 5.4 | 1.9 – 6.1 |
| **TPSA** | 26 - 121 | 29 - 85 | 12 - 96 | 18 - 127 |
| **SFI**[1] | 3.6 – 9.0 | 2.3 – 5.3 | 2.9 – 7.1 | 3.4 – 7.2 |
| **QED**[2] | 0.38 – 0.91 | 0.67 – 0.91 | 0.64 – 0.84 | 0.29 – 0.87 |

**Table S1:** Compound physicochemical property ranges for Index Set hits. SFI represents the Solubility Forecast Index, a simple predictive metric using the summation of calculated LogD (at pH 7.4) and the number of aromatic rings as a means of forecasting the likelihood of achieving good levels of solubility. QED represents the Quantitative Estimate of Druglikeness, a score which integrates a balance of eight key physicochemical properties as a general tractability indicator, representing the overall similarity of compound properties to those of the majority of orally available drugs. Properties were summarised following the removal of compounds with undesirable structural features.

**References:**


1. Hill, A. P.; Young, R. J. Getting Physical with Drug Discovery; a Contemporary Perspective on Solubility and Hydrophobicity. *Drug Discov. Today* **2010,** *15*, 648-655.
2. Bickerton, G. R.; Paolini, G. V.; Besnard, J.; et al. Quantifying the Chemical Beauty of Drugs. *Nat. Chem.* **2012,** *4*, 90-98.