ML402

Cat. No.: HY-104027

CAS No.: 298684-44-3

Molecular Formula: $C_{14}H_{14}ClNO_2S$

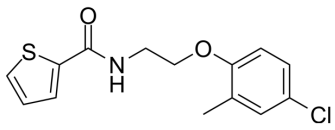
Molecular Weight: 295.78

Target: Potassium Channel

Pathway: Membrane Transporter/Ion Channel

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 100 mg/mL (338.09 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	3.3809 mL	16.9045 mL	33.8089 mL
5 mM	0.6762 mL	3.3809 mL	6.7618 mL
10 mM	0.3381 mL	1.6904 mL	3.3809 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (8.45 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (8.45 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

ML402, a thiophene-carboxamide, is a selective K_{2P}2.1(TREK-1) and K_{2P}10.1(TREK-2) activator. ML402 is inactive against K_{2P}4.1(TRAAK)[1].

IC_{50} & Target

TREK-1/2[1]

In Vitro

Xenopus oocyte two-electrode voltage-clamp measurements show that ML335 and ML402 activate K_{2P}2.1 and K_{2P}10.1 but not K_{2P}4.1(14.3±2.7 μM, K_{2P}2.1-ML335; 13.7±7.0 μM, K_{2P}2.1-ML402; 5.2±0.5 μM, K_{2P}10.1-ML335; and 5.9±1.6 μM, K_{2P}10.1-ML402). The K_{2P} modulator pocket has a single difference among TREK subfamily members at the cation-π interaction position, K_{2P}2.1 Lys271, which is also a lysine in K_{2P}10.1 but a glutamine in K_{2P}4.1.Swapping the Lys271 equivalent between

$K_{2P}2.1$ and $K_{2P}4.1$ results in a clear phenotype reversal for ML335 and M402 activation. $K_{2P}2.1$ (K271Q) is insensitive to ML335 and ML402, whereas $K_{2P}4.1$ (Q258K) responds to both with a similar EC_{50} to $K_{2P}2.1$ (14.3±2.7 μM, $K_{2P}2.1$-ML335; 16.2±3.0 μM, $K_{2P}4.1$(Q258K)-ML335; 13.7±7.0 μM, $K_{2P}2.1$-ML402; 13.6±1.5 μM, $K_{2P}4.1$ (Q258K)-ML402) but with a lower magnitude response than $K_{2P}2.1$[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]

$K_{2P}2.1_{cryst}$ ML335 and ML402 complex crystals grow in the same conditions as $K_{2P}2.1_{cryst}$, but the protein is incubated for at least 1 h with 2.5 mM of activator (including ML 402) before setting the crystal plates. ML335 and ML402 are insoluble in aqueous solutions, so they are dissolved in 100% DMSO at a concentration of 500 mM. Then each compound is diluted 1:100 in SEC buffer to 5 mM concentration, giving a milky solution. This solution is mixed 1:1 to $K_{2P}2.1_{cryst}$ previously concentrating to 12 mg/mL. The $K_{2P}2.1_{cryst}$ ML402 mixture results in a clear solution, while the mixture with ML335 is slightly milky. The samples are briefly centrifuged in a table-top centrifuge (10,000×g) to remove any insoluble material before setting the crystal plates. Dose-response experiments are carried by first preparing a DMSO stock solution of each activator (including ML402) at a concentration of 100 mM. Owing to the low solubility of the compounds the highest test concentrations in recording solution are 100 μM and 80 μM for ML335 and ML402, respectively. Other concentrations are prepared by serial dilutions of the 100 μM solution in recording buffer supplementing with 0.1% DMSO[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Lolicato M, et al. K2P2.1 (TREK-1)-activator complexes reveal a cryptic selectivity filter binding site. Nature. 2017 Jul 20;547(7663):364-368.

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