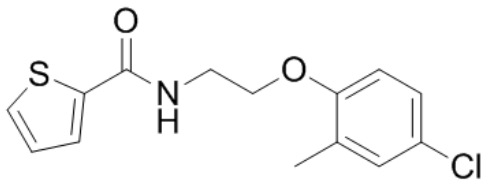
Product Data Sheet

Product Name: ML402
Cat. No.: GC31062

Chemical Properties

Cas. No.	298684-44-3		
SMILES	O=C(C1=CC=CS1)NCCOC2=CC=C(Cl)C=C2C		
Formula	$C_{14}H_{14}ClNO_2S$	M.Wt	295.78
Solubility	DMSO : 150 mg/mL (507.13 mM)	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 °C and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20°C for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		

Structure



Protocol

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Kinase experiment: K2P2.1cryst ML335 and ML402 complex crystals grow in the same conditions as K2P2.1cryst, 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 K2P2.1cryst previously concentrating to 12 mg/mL. The K2P2.1cryst 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].

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.

Background

ML402 is a selective TREK-1 activator.

Xenopus oocyte two-electrode voltage-clamp measurements show that ML335 and ML402 activate K2P2.1 and K2P10.1 but not K2P4.1(14.3±2.7 μM, K2P2.1-ML335; 13.7±7.0 μM, K2P2.1-ML402; 5.2±0.5 μM, K2P10.1-ML335; and 5.9±1.6 μM, K2P10.1-ML402). The K2P modulator pocket has a single difference among TREK subfamily members at the cation-π interaction position, K2P2.1 Lys271, which is also a lysine in K2P10.1 but a glutamine in K2P4.1.Swapping the Lys271 equivalent between K2P2.1 and K2P4.1 results in a clear phenotype reversal for ML335 and M402 activation. K2P2.1 (K271Q) is insensitive to ML335 and ML402, whereas K2P4.1 (Q258K) responds to both with

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a similar EC50 to K2P2.1 (14.3±2.7 μM, K2P2.1-ML335; 16.2±3.0 μM, K2P4.1(Q258K)-ML335; 13.7±7.0 μM, K2P2.1-ML402; 13.6±1.5 μM, K2P4.1 (Q258K)-ML402) but with a lower magnitude response than K2P2.1[1].

[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.