SGC-CK2-2: A Chemical Probe for CK2

Version 1.0 (4th May 2023)

Web link for more details: https://www.thesgc.org/chemical-probes/SGC-CK2-2

Overview

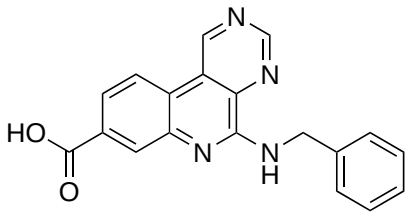
Casein kinase 2 (CK2, CSNK2) is a highly conserved and ubiquitously expressed serine/threonine kinase for which more than 300 substrates have been identified. Accordingly, a plethora of diverse functions and roles in disease have been ascribed to CK2. Indications for which CK2 inhibition has been investigated as therapeutically beneficial include different cancers, SARS-CoV-2, and neuroinflammation. A clinical stage CK2 inhibitor, silmitasertib (CX-4945), has been evaluated in clinical trials for advanced cholangiocarcinoma and SARS-CoV-2.

Summary

Chemical Probe Name	SGC-CK2-2
Negative control compound	SGC-CK2-2N
Target(s) (synonyms)	CK2, CSNK2
Recommended cell assay concentration	Use at concentration of 5 µM (and ≤ 10 µM) for SGC-CK2-2 and SGC-CK2-2N; use with control for best interpretation of data.
Suitability for *in* vivo use and recommended dose	SGC-CK2-2 was not tested *in vivo*
Publications	10.1021/acsmedchemlett.2c00530; 10.26434/chemrxiv-2022-05jcz
Orthogonal chemical probes	SGC-CK2-1
In vitro assay(s) used to characterise	Radiometric enzymatic assays
Cellular assay(s) for target-engagement	NanoBRET

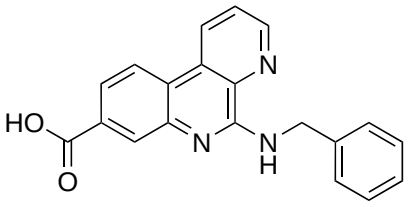
Chemical Probe & Negative Control Structures and Use

SGC-CK2-2: Chemical Probe



SMILES: OC(C1=CC2=NC(NCC3=CC=CC=C3)=C4N=CN=CC4=C2C=C1)=O
InChiKey: HEVVNKYNJCSHFA-UHFFFAOYSA-N
Molecular weight: 330.35
Storage: Stable as a solid at room temperature. DMSO stock solutions (up to 10 mM) are stable at -20°C.
Dissolution: Soluble in DMSO up to 100 mM

SGC-CK2-2N: Negative Control



SMILES: OC(C1=CC2=NC(NCC3=CC=CC=C3)=C4N=CC=CC4=C2C=C1)=O
InChiKey: VBKHXXPYOSWXSA-UHFFFAOYSA-N
Molecular weight: 329.36
Storage: Stable as a solid at room temperature. DMSO stock solutions (up to 10 mM) are stable at -20°C.
Dissolution: Soluble in DMSO up to 10 mM

Chemical Probe Profile

In vitro Potency & Selectivity:

SGC-CK2-2 was profiled in the KINOMEscan assay against 403 wild-type kinases at 1 µM. Only 3 kinases showed PoC <10 giving an S_{10}(1 µM) = 0.007. When the PoC <35 fraction was examined, 13 kinases were included (S_{35}(1 µM) = 0.032). Potential off-targets within the S_{35}(1 µM) fraction were tested via biochemical enzymatic assays plus NanoBRET target engagement assays for CK2α and CK2α'. SGC-CK2-2 binds to CK2α and CK2α'with PoC = 0.1 and PoC = 0.2, respectively, in the corresponding DiscoverX assays and demonstrated IC_{50} = 3.0 nM and IC_{50} < 1.0 nM in the respective CK2α and CK2α' enzymatic assays (Eurofins). The closest off-target kinase based on enzymatic potency is HIPK2 (IC_{50} = 600 nM, 200-fold selectivity window).

Potency in Cells and Cellular Target Engagement:

SGC-CK2-2 displayed an IC_{50} = 920 nM and IC_{50} = 200 nM in the CK2α and CK2α' NanoBRET assays, respectively, using HEK293 cells.

Our CK2 chemical probe is not broadly proliferative. It was profiled up to 10 µM in MDA-MB-231 cells, and at 1 µM in small panels of multiple myeloma (including some with resistance), Ewings sarcoma, and chordoma cell lines. A PAMPA assay was used to demonstrate that SGC-CK2-2 has good cellular permeability.