

TP-060: A Chemical Probe for GCLC

Version 1.0 (30th August 2023)

Web link for more details: <https://www.sgc-ffm.uni-frankfurt.de/#!specificprobeoverview/TP-060>

Overview

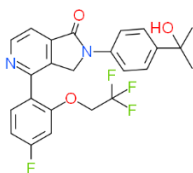
The glucosyltransferase ([GCLC](#)) is responsible for the synthesis of glucosylceramide (GlcCer) from UDP-glucose and ceramide. Glycosphingolipids, generated from GlcCer, are accumulated in various tissues of lysosomal disorders. Prevention of GlcCer synthesis by Glucosylceramide synthase (GCS) inhibitor to reduce toxic glycosphingolipids is one of the validated therapeutic approaches, called substrate reduction therapy (SRT).

Summary

Chemical Probe Name	TP-060
Negative control compound	TP-060n
Target(s) (synonyms)	GCLC (Glutamate-Cysteine Ligase Catalytic Subunit), GCS
Recommended <i>in vitro</i> assay concentration	Use at concentration up to 1 μ M for TP-060 and TP-060n; use with control for best interpretation of data
Suitability for <i>in vivo</i> use and recommended dose	Use at a concentration up to 30 mg/kg; Significant glucosylceramide reduction in the plasma and brain of normal mice by oral administration; Significant glucosylceramide and glycosphingolipids reduction in Gaucher's disease model mice.
Publications	PMID: 35188773 , PMID: 34398463 , PMID: 36341811 (T-036)
<i>In vitro</i> assay(s) used to characterise	GCLC enzymatic assay
Cellular assay(s) for target-engagement	Cellular GlcCer reduction

Chemical Probe & Negative Control Structures and Use

TP-060 Chemical Probe



SMILES: CC(C)(c1ccc(cc1)N1Cc2c(ccnc2c2ccc(cc2OCC(F)(F)F)C1=O)O

InChiKey: OAZAPIKYVGRNCO-UHFFFAOYSA-N

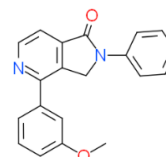
Molecular weight: 460.14 g/mol

Storage: As a dry powder or as DMSO stock solutions (10 mM) at -20 °C.

DMSO stocks beyond 3-6 months or 2 freeze/thaw cycles should be tested for activity before use

Dissolution: Soluble in DMSO up to 10 mM; use only 1 freeze/thaw cycle per aliquot

TP-060n Negative Control



SMILES: COc1cccc(c1)c1c2CN(C(c2ccn1)=O)c1ccccc1

InChiKey: CECLXQDMAJQBCR-UHFFFAOYSA-N

Molecular weight: 316.12 g/mol

Storage: As a dry powder or as DMSO stock solutions (10 mM) at -20 °C.

DMSO stocks beyond 3-6 months or 2 freeze/thaw cycles should be tested for activity before use

Dissolution: Soluble in DMSO up to 10 mM; use only 1 freeze/thaw cycle per aliquot

Chemical Probe Profile

Selectivity:

TP-060 shows a high potency towards the target GCLC (IC_{50} = 31 nM (GCLC enzymatic assay)). The selectivity within the target family is presumed to be high according to the allosteric binding mode. The in house kinase panel (342 kinases at 1 μ M) was clean. Closest hits in the DiscoverX SafetyScan (47 targets at 10 μ M) are SLC6A4 (IC_{50} = 0.31 μ M), HTR1B (EC_{50} = 2.8 μ M), nAChR(a4/b2) Blocker (CHRNA4, IC_{50} = 6.5 μ M).

Potency in Cells and Cellular Target Engagement:

TP-060 was active in the cellular GlcCer reduction assay with EC_{50} = 7.6 nM.