

QPCT/L dual inhibitor

BI-3614

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Summary

BI-3614 is a highly selective, equipotent orthosteric inhibitor of QPCT and QPCTL and thus qualifies as an *in vitro* tool compound suitable for cell-based studies.

Chemical Structure

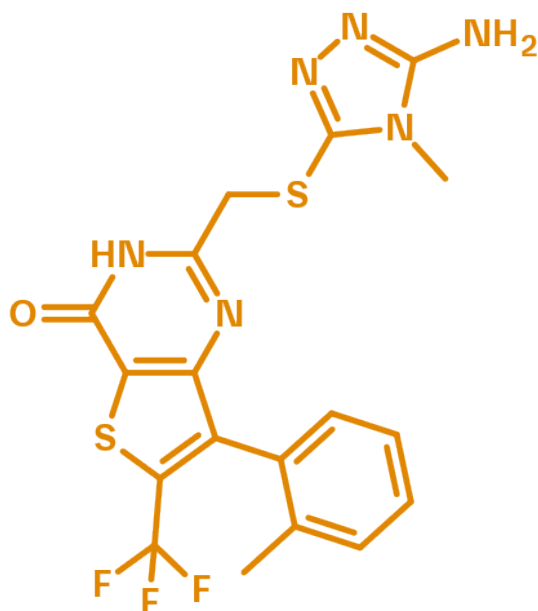


Figure 1: 2D structure of BI-3614, a QPCT/L inhibitor

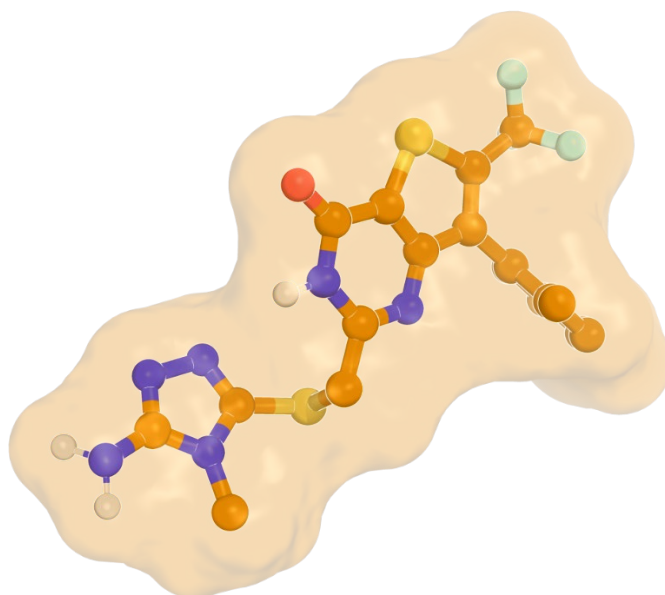


Figure 2: 3D Model of the bioactive conformation of BI-3614, based on a co-XRay structure with a closely related ligand

Highlights

BI-3614 is a potent and highly selective dual QPCT and QPCTL inhibitor suitable for complex *in vitro* investigations as it shows significantly improved cellular potency of previously described compounds. BI-9692 can be used as negative control.

Target information

BI-3614 is a potent and highly selective dual QPCT and QPCTL inhibitor¹. QPCT and QPCTL are enzymes responsible for the cyclization of N-terminal glutamine (Q) into pyroglutamate (pE)². QPCT is secreted and plays an important role by stabilization A β -peptides and thus increased oligomerization and plaque deposition through Q to pE post-translational modification³. QPCTL is Golgi-bound and is reported to catalyze the Q to pE transformation on a diverse set of chemokines, such as CCL2⁴, and fractalkine CX3CL1⁵. Recently, two independent studies identified CD47 as a QPCTL substrate^{6,7}. In this case, the seemingly small pE-modification by QPCTL is essential to establish the protein-protein interaction of CD47 with SIRPa, also known as the “don’t eat me”-signal of tumor cells. Thus, pharmacological inhibition of QPCT and QPCTL has the potential to modulate disease processes across a range of neurological, inflammatory, fibrotic, and oncological indications.



Figure 2: Model of the complex of BI-3614 with QPCTL, based on a co-XRay structure with a closely related ligand¹

In vitro activity

BI-3614 is a potent dual QPCT and QPCTL inhibitor with single-digit nanomolar potency on both enzymes. The compound is also highly potent in cellular assays using either Raji or A549 cells and inhibits the binding of its substrate CD47 to SIRP α . It is cross-reactive on the respective mouse and dog enzymes.

Probe name / Negative control	BI-3614	BI-9692
MW [Da] ^a	452.5	463.5
Human QPCT (IC ₅₀) [nM] ¹	2.5	1,889
Human QPCTL (IC ₅₀) [nM] ¹	4.0	3,255
Mouse QPCTL (IC ₅₀) [nM] ^b	6.3	4,738
Dog QPCTL (IC ₅₀) [nM] ^b	3.7	3,384
Cell. CD47/SIRP α Raji Reporter Assay (IC ₅₀) [nM] ¹	74	>10,000
Cell. CD47/SIRP α A549 Reporter Assay (IC ₅₀) [nM] ⁸	32	>10,000

^a The molecule is supplied in salt form; for the molecular weight of the salt, please refer to the vial label.

^b Mouse QPCTL and Dog QPCTL enzymatic activity assay was performed analogous to human QPCTL enzymatic activity assay^{1,8}

In vitro DMPK and CMC parameters

BI-3614 is an in-vitro tool compound with a good solubility at neutral pH, moderate permeability and high stability towards metabolism by microsomal or hepatic pathways.

Probe name / Negative control	BI-3614	BI-9692
logD @ pH 2, 11	1.7, 0.3	3.6, 0.9
Solubility @ pH 6.8 [μ g/mL]	46	<1.0
Caco-2 permeability AB ^a @ pH 7.4 [$\times 10^{-6}$ cm/s]	3.3	34.0
Caco-2 efflux ratio	4.2	0.6
MDCK permeability P _{appAB} ^b @ 1 μ M [10^{-6} cm/s]	1.2 (PGP ^c) / 0.1 (BCRP ^d)	6
MDCK efflux ratio	1.8 (PGP) / 21.1 (BCRP)	3.8
Microsomal stability (human/mouse/rat) [% Q _H]	<23 / <23 / 24	59 / 81 / 73
Hepatocyte stability (human/mouse/rat) [% Q _H]	11 / <12 / 16	30 / 77 / 84

Plasma Protein Binding (human/mouse/rat) [%]	99.6 / 98.0 / 99.9	99.9 / 99.4 / 99.6
CYP 3A4 (IC ₅₀) [μM]	15.7	2.5
CYP 2C8 (IC ₅₀) [μM]	16.0	20.3
CYP 2C9 (IC ₅₀) [μM]	43.4	29.6
CYP 2C19 (IC ₅₀) [μM]	>50	>50
CYP 2D6 (IC ₅₀) [μM]	>50	>50

^aAB = apical-to-basolateral transport

^bP_{appAB} = apparent permeability coefficient in the apical-to-basolateral (AB) transport direction

^cPGP = P-glycoprotein (ABCB1) efflux transporter

^dBCRP = Breast Cancer Resistance Protein (ABCG2) efflux transporter

Negative control

BI-9692, a structurally close analog, can be used as negative control.

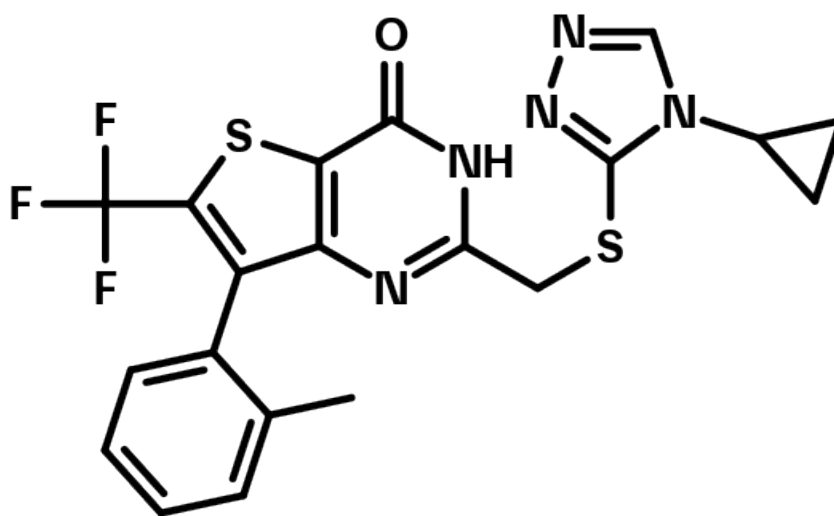


Figure 4: BI-9692 which serves as a negative control.

Selectivity

BI-3614 inhibited none of the targets at a concentration of 10 μ M to more than 50% in the SafetyScreen44™ or in a 38 kinase-panel at DiscoverX®. Negative control BI-9692 did not show inhibition of any of the targets in the 38 kinase-panel at DiscoverX® and showed inhibition of 2 out of 44 tested targets in the SafetyScreen44™ by greater than 50% @ 10 μ M (KAPPA(KOP): 66% and MU/H: 71%).

Selectivity data available	BI-3614	BI-9692
SafetyScreen44™ with kind support of  eurofins	Yes	Yes
DiscoverX®	Yes	Yes

Reference molecules

Commercially available QPCT/L inhibitors such as varoglutamstat⁹ or SEN-177¹⁰ show significantly inferior cellular potencies (IC₅₀>1 μ M). Another recently described QPCT/L inhibitor QP-5038 with improved cellular potency is now commercially available¹¹.

Supplementary data

2D structure files can be downloaded free of charge from [openMe](#).

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