

## **Data Sheet**

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 Product Name
 :
 SK-124

 Cat. No.
 :
 PC-49563

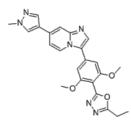
 CAS No.
 :
 2760404-50-8

 Molecular Formula
 :
 C<sub>23</sub>H<sub>22</sub>N<sub>6</sub>O<sub>3</sub>

 Molecular Weight
 :
 430.468

Target : Salt Inducible Kinase (SIK)

**Solubility**: 10 mM in DMSO



## **Biological Activity**

SK-124 (SK124) is a potent, selective, orally active **SIK2/SIK3** inhibitor with IC50 of 8.8/11.3 nM in cell-based NanoBRET assays, 15-fold selectivity versus SIK1.

SK-124 potently inhibits SIK2/SIK3 with IC50 of 0.41/1.2 nM in radioisotope kinase assays, respectively.

SK-124 displays acceptable oral bioavailability in mice, robust stability in human, rat, and mouse liver microsomes, no inhibition of cytochrome P450 enzymes.

SK-124 exhibits no significant off-target activities at 10  $\mu$ M in the Eurofins SafetyScreen44 panel, PDGFR $\alpha$  (IC50=15.8 nM) is the major off-target kinase.

SK-124 engages endogenous SIK2 in murine osteocyte-like Ocy454 cells, reduces phosphorylation of SIK substrates HDAC4/HDAC5 and CRTC2 in murine Ocy454 and human Saos2 cells, promotes CRTC2 (EC50=128 nM in ) and HDAC5 nuclear translocation, and regulated SIK target gene [SOST and TNFSF11 (also known as RANKL)] expression in a PTH-like manner without causing cytotoxicity.

Oral SK-124 (40 mg/kg) treatment increased P1NP and C terminal telopeptide (CTX) compared with oral vehicle solution in a manner similar to that of once-daily subcutaneous PTH treatmentparathyroid hormone (PTH).

3 wk of 40 mg/kg SK-124 treatment led to changes consistent with intermittent PTH therapy and inducible SIK2/SIK3 deletion including increased trabecular bone in the primary spongiosa (PS), modest growth plate expansion, and increased TRAP-positive osteoclasts in the proximal tibia.

## References

Sato T, et al. *Proc Natl Acad Sci U S A*. 2022 Dec 13;119(50):e2214396119.

Caution: Product has not been fully validated for medical applications. Lab Use Only!

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