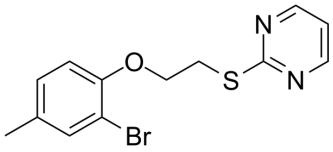
ZLN024

Cat. No.:	HY-16708
CAS No.:	723249-01-2
Molecular Formula:	$C_{13}H_{13}BrN_2OS$
Molecular Weight:	325.22
Target:	AMPK
Pathway:	Epigenetics; PI3K/Akt/mTOR
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	ZLN024 is an AMPK allosteric activator. ZLN024 directly activates recombinant AMPK α1β1γ1, AMPK α2β1γ1, AMPK α1β2γ1 and AMPK α2β2γ1 heterotrimer with EC_{50}s of 0.42 μM, 0.95 μM, 1.1 μM and 0.13 μM, respectively.

IC_{50} & Target			
	AMPK α2β2γ1 0.13 μM (EC50)	AMPK α1β1γ1 0.42 μM (EC50)	AMPK α2β1γ1 0.95 μM (EC50)

In Vitro

ZLN024 allosterically stimulates active AMPK heterotrimers and the inactive α1 subunit truncations α1 (1-394) and α1 (1-335) but not α1 (1-312). AMPK activation by ZLN024 requires the pre-phosphorylation of Thr-172 by at least one upstream kinase and protects AMPK Thr-172 against dephosphorylation by PP2Cα. ZLN024 activates AMPK in L6 myotubes and stimulates glucose uptake and fatty acid oxidation without increasing the ADP/ATP ratio. Using the established scintillation proximity assay (SPA) assay, random screening against the AMPK α1β1γ1 heterotrimer is performed and a new AMPK activator, ZLN024 is found. ZLN024 directly activates recombinant AMPK α1β1γ1 and its homologue α2β1γ1 in a concentration-dependent manner. ZLN024 increases the activity of α1β1γ1 by 1.5-fold and has an EC_{50} of 0.42 μM, and it increases the activity of α2β1γ1 by 1.7-fold with an EC_{50} of 0.95 μM. ZLN024 also directly activates recombinant AMPK α1β2γ1, by 1.7-fold with an EC_{50} of 1.1 μM; and AMPK α2β2γ1, by 1.6-fold with an EC_{50} of 0.13 μM[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

C57BKS db/db mice are administered a 15 mg/kg/day dose of ZLN024 by daily gavage for 5 weeks; 250 mg/kg/day Metformin (Met) is used as a positive control. During the treatment period, there is no significant alteration in food intake and body weight compared with the vehicle group. After 4 weeks of treatment, ZLN024 improves glucose tolerance. ZLN024 reduces the fasting blood glucose by 15%. Liver tissue weight, triacylglycerol and the total cholesterol content are decreased[1].

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PROTOCOL

Kinase Assay [1]

Before the scintillation proximity assay (SPA) assay, 200 nM recombinant AMPK protein (α1β1γ1, α2β1γ1, α1β2γ1, α2β2γ1, α1(1-394), α1(1-335), α1(1-312)) is constructed, expressed, purified and fully phosphorylated. The SPA reactions are performed in 96-well plates in a final volume of 50 μL containing 20 mM Tris-HCl, pH 7.5, 5 mM $MgCl_2$, 1 mM DTT, 2 μM biotin-SAMS, 2 μM ATP and 7.4×10^3 Bq/well [γ-^{33}P]ATP. The reactions are initiated by the addition of 50 nM recombinant AMPK protein to the reaction solutions, followed by incubation at 30°C for 2 hr. The reactions are then terminated by the addition of 40 μL of stop solution containing 80 μg Streptavidin-coated SPA beads per well, 50 mM EDTA and 0.1% Triton X-100 in

	PBS, pH 7.5, followed by incubation for 1 hr. Finally, 160 μL of suspension solution containing 2.4 M CsCl, 50 mM EDTA and 0.1% Triton X-100 in PBS, pH 7.5, is added to the reaction solution to suspend the SPA beads completely. The SPA signals are measured in a Wallac Microbeta plate counter 30 min later[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] C57BKS ***db/db*** mice are maintained under a 12 hr light-dark cycle with free access to water and food. At 8 weeks of age, male db/db mice are randomly assigned to the various treatment groups by body weight and glucose levels (n=6-8). The treatment groups for the 5-week chronic study are as follows: vehicle (0.5% methylcellulose), ZLN024 (15 mg/kg) and Metformin (250 mg/kg). The treatments are orally administered once daily. The body weights and food intake are measured daily. After 5 weeks of treatment, the mice are killed after a final dose, and the tissues are collected for further analysis. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell Death Differ. 2022 Jan 29.

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REFERENCES

[1]. Zhang LN, et al. Novel small-molecule AMP-activated protein kinase allosteric activator with beneficial effects in db/db mice. PLoS One. 2013 Aug 20;8(8):e72092.

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