SKI2852

Cat. No.: HY-19325

CAS No.: 1346554-47-9

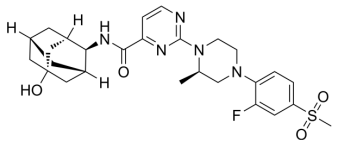
Molecular Formula: $C_{27}H_{34}FN_5O_4S$

Molecular Weight: 543.65

Target: 11β-HSD

Pathway: Metabolic Enzyme/Protease

Storage: Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description

SKI2852 is a potent, selective and orally active 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitor with IC_{50}s of 1.6 nM and 2.9 nM against mHSD1 and hHSD1, respectively[1].

IC_{50} & Target

IC50: 1.6 nM (mHSD1), 2.9 nM (hHSD1)[1]

In Vitro

SKI2852 inhibits 11β-HSD1 with an IC_{50} of 4.4 ± 0.5 nM in HEK293 cells stably transfected with human 11β-HSD1 cDNA[1].
The amide carbonyl group of SKI2852 established a central hydrogen bond interaction with the hydroxyl side chain of Ser170, one of the key residues (Ser170, Tyr183, and Lys 187) that define the catalytic triad for 11β-HSD1 activity[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

SKI2852 (20 mg/kg; oral; once daily for 25 days) significantly reduces blood glucose and HbA1c levels and improved the lipid profiles in ob/ob mice[1].
In Vivo PK Data for SKI2852[1]

species	iv[a]				po[b]			
	CL (L/kg/h)	V_{ss} (L/kg)	$t_{1/2}$ (h)	AUC (μg × h/mL)	C_{max} (μg/mL)	t_{max} (h)	AUC (μg × h/mL)	F (%)
mouse[c]	0.42	1.1	1.7	2.35	2.21	1.0	11.26	96
rat[c]	0.93	2.1	1.8	1.12	1.02	1.3	3.39	60
dog[d]	0.36	2.4	4.7	1.47	1.12	2.1	11.52	98

[a]10% hydroxylpropyl-β-cyclodextrin was used as vehicle. [b]0.5% methylcellulose and 1% Tween80 was used as vehicle. [c] Dosed iv at 1 mg/kg, po at 5mg/kg. [d]Dosed iv at 0.5 mg/kg, po at 4 mg/kg.
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	ob/ob mice, diet-induced obesity (DIO) model[1]
Dosage:	20 mg/kg
Administration:	Oral, once daily for 25 days
Result:	Efficiently reduced postprandial glucose and/or blood HbA1c levels and suppressed hepatic mRNA levels of gluconeogenic enzymes. Clearly enhanced hepatic and whole-body insulin sensitivities in a hyperinsulinemic-euglycemic clamp experiment in DIO mice.

Animal Model:	C57BL/6 mice, rats and dogs[1]
Dosage:	0.5 or 4 mg/kg
Administration:	IV or PO (Pharmacokinetic Analysis)
Result:	Showed good pharmacokinetic profiles.

REFERENCES

[1]. Ryu JH, et al. Discovery of 2-((R)-4-(2-Fluoro-4-(methylsulfonyl)phenyl)-2-methylpiperazin-1-yl)-N-((1R,2s,3S,5S,7S)-5-hydroxyadamantan-2-yl)pyrimidine-4-carboxamide (SKI2852): A Highly Potent, Selective, and Orally Bioavailable Inhibitor of 11β-Hydroxysteroid Dehydrogenase Type 1 (11β-HSD1). J Med Chem. 2016 Nov 23;59(22):10176-10189.

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