

Product Name: SAFit2
Cat. No.: GC34093

Cas. No. 1643125-33-0

SMILES O=C(N1[C@@H](CCCC1)C(O[C@@H](C2=CC(OCN3CCOCC3)=CC=C2)CCC4=CC(OC)=C(OC)C=C4)=O)[C@@H](C5CC(CCC5)C6=CC(OC)=C(OC)C(OC)=C6

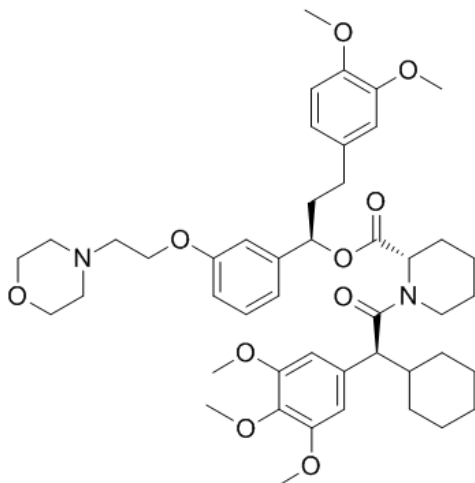
Formula	C ₄₆ H ₆₂ N ₂ O ₁₀	M.Wt	802.99
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Solubility	DMSO : 125 mg/mL (155.67 mM);Water : < 0.1 mg/mL (insoluble)	Storage	Store at -20°C
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General tips	For obtaining a higher solubility , please warm the tube at 37 °C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.
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Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.
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Structure



Cell experiment [1]:

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Cell lines	ICR mouse pancreatic β cells
Preparation Method	ICR mouse pancreatic β cells were grown in DMEM medium supplemented with 10% fetal bovine serum, 100U/ml penicillin, and 0.1mg/ml streptomycin in 5% CO ₂ at 37°C. Cells were treated with DMSO or SAFit2 (1 μ M) for 48h and the mRNA expression levels of Nkx6.1, Mafa, Ins1 and ins2 were analyzed.
Reaction Conditions	1 μ M; 48h
Applications	SAFit2 treatment significantly enhanced the levels of Nkx6.1, Mafa, Ins1 and ins2 in mouse pancreatic β cells.

Animal experiment [2]:

Animal models	C57Bl/6N mice
Preparation Method	Male C57Bl/6N mice (8 weeks old) were kept in temperature-controlled (21°C-25°C) and humidity-maintained (40%-70%) room with a 12-h light/dark cycle. Water and food were provided freely. For inducing neuropathic pain in mice, a spared nerve injury (SNI) surgery was performed under anesthesia to establish neuroinflammation. During the surgery, the sciatic nerve was exposed by a blunt dissection at the level of the knee joint. Then, two of the three sciatic nerve branches, the common peroneal and tibial branches, were ligated with 6/0 non-sterile silk thread and cut distally from the ligature, leaving the sural nerve branch intact. Contact with the sural nerve branch was avoided to prevent stretching or harm. Afterwards, the muscle and skin are closed in two layers. Mice were treated intraperitoneally with either 10mg/kg SAFit2 or vehicle (PBS supplemented with 5% PEG400, 5% Tween and 0.7% ethanol) twice daily on six consecutive days starting on day five after surgery. For the determination of the mechanical withdrawal threshold, a dynamic plantar test was used.

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Dosage form 10mg/kg; twice a day for 6 days; i.p.

Applications SAFit2 treatment reduced nerve injury-induced mechanical hypersensitivity in mice.

References:

- [1] D'Arrigo P, Digregorio M, Romano S, et al. The splicing FK506-binding protein-51 isoform plays a role in glioblastoma resistance through programmed cell death ligand-1 expression regulation[J]. Cell Death Discovery, 2019, 5(1): 137.
- [2] Wedel S, Mathoor P, Rauh O, et al. SAFit2 reduces neuroinflammation and ameliorates nerve injury-induced neuropathic pain[J]. Journal of neuroinflammation, 2022, 19(1): 254.

Background

SAFit2 is a potent inhibitor of FK506-binding protein 51 (FKBP51), with the K_i value of 6nM^[1]. SAFit2 can reduce the phosphorylation levels of the inhibitory complex α (I κ B α) and p65, as well as decrease the levels of chemokines and cytokines, thereby inhibiting the inflammatory response^[2]. SAFit2 has been widely used as a pharmacological probe for FKBP51 to alleviate pain and regulate neuroinflammation in animals^[3].

In vitro, SAFit2 treatment (60nM) for 4 days reduced PD-L1 expression and inhibited cell growth in mouse glioblastoma (GBM) cells^[4]. Treatment with 1 μ M SAFit2 for 48 hours can improve the function of isolated mouse β cells and upregulate the mRNA expression levels of Nkx6.1, Mafa, Ins1 and ins2^[5].

In vivo, SAFit2 treatment via intraperitoneal injection twice daily at a dose of 10mg/kg for 6 days restored lipid signaling and metabolism in the neural tissue of mice after nerve injury^[6]. Administering 10mg/kg SAFit2 by intraperitoneal injection twice a day for 6 consecutive days can alleviate mechanical hyperalgesia induced by paclitaxel in mice^[7]. A single intraperitoneal injection of 20mg/kg SAFit2, administered over a period of 4 hours, reduced the anxiety-like behaviors in female rats during the early stage of cocaine self-administration withdrawal^[8].

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References:

- [1] Gaali S, Feng X, Hähle A, et al. Rapid, structure-based exploration of pipecolic acid amides as novel selective antagonists of the FK506-binding protein 51[J]. Journal of medicinal chemistry, 2016, 59(6): 2410-2422.
- [2] Buffa V, Knaup F H, Heymann T, et al. Analysis of the selective antagonist SAFit2 as a chemical probe for the FK506-binding protein 51[J]. ACS Pharmacology & Translational Science, 2023, 6(3): 361-371.
- [3] Si Y, Zhao X, Wu L, et al. Inhibition of the NFATc2/FKBP5 axis alleviates microglial neuroinflammation by regulating arachidonic acid metabolism in Parkinson's disease[J]. Brain, Behavior, and Immunity, 2026: 106296.
- [4] D'Arrigo P, Digregorio M, Romano S, et al. The splicing FK506-binding protein-51 isoform plays a role in glioblastoma resistance through programmed cell death ligand-1 expression regulation[J]. Cell Death Discovery, 2019, 5(1): 137.
- [5] Liu N, Li R, Cao J, et al. The inhibition of FKBP5 protects β -cell survival under inflammation stress via AKT/FOXO1 signaling[J]. Cell death discovery, 2023, 9(1): 247.
- [6] Wedel S, Hahnefeld L, Alnouri M W, et al. The FKBP51 inhibitor SAFit2 restores the pain-relieving C16 dihydroceramide after nerve injury[J]. International journal of molecular sciences, 2022, 23(22): 14274.
- [7] Wedel S, Hahnefeld L, Schreiber Y, et al. SAFit2 ameliorates paclitaxel-induced neuropathic pain by reducing spinal gliosis and elevating pro-resolving lipid mediators[J]. Journal of neuroinflammation, 2023, 20(1): 149.
- [8] Connelly K L, Wolsh C C, Barr J L, et al. Sex differences in the effect of the FKBP5 inhibitor SAFit2 on anxiety and stress-induced reinstatement following cocaine self-administration[J]. Neurobiology of stress, 2020, 13: 100232.

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