

Product Data Sheet

Product Name: SAFit1
Cat. No.: GC33699

Chemical Properties

Cas. No. 1643125-32-9

SMILES O=C(N1[C@@H](CCCC1)C(O[C@@H](C2=CC(OCC(O)=O)=CC=C2)CCC3=CC(OC)=C(OC)C=C3)=O)[C@@H](C4CCCCC4)C5=CC(OC)=C(OC)C(OC)=C5

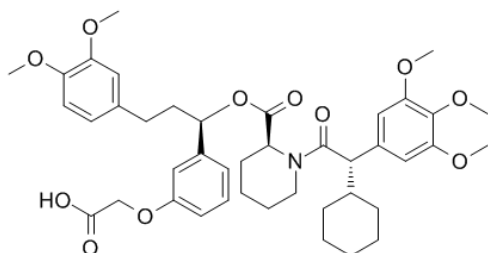
Formula $C_{42}H_{53}NO_{11}$ M.Wt 747.87

Solubility Methanol : 125 mg/mL (167.14 mM); DMSO : 62.5 mg/mL (83.57 mM); Water : < 0.1 mg/mL (insoluble)
Storage Store at -20°C

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.

Shipping Condition Evaluation sample solution : ship with blue ice All other available size: ship with RT, or blue ice upon request.

Structure



Protocol

Cell experiment [1]:

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Cell lines murine microglia SIM-A9 cell

Preparation Method For the preparation of whole-cell lysates, confluent SIM-A9 cell cultures treated with the SAFit1 for 16h. Subsequently, supernatants of cell lysis were prepared for an SDS-PAGE system and analyzed by immunoblotting.

Reaction Conditions 0.4, 0.2, 1 μ M; 16h

Applications SAFit1 interfered with the cellular functions of FKBP51 and inhibited IKK α phosphorylation.

Animal experiment [2]:

Animal models male Balb/C mice

Preparation Method Twelve male Balb/C mice were housed at Jubilant Animal House facility (having 12/12h light/dark cycles with controlled humidity and temperature) for seven days before performing pharmacokinetic study. Mice were fasted for 4h (during the fasting period animals had free access to water) on the day of pharmacokinetic study. Mice received SAFit1 (30mg/kg) and SAFit2 (30mg/kg) as a cassette dose orally. Blood samples (100 μ L) were collected at pre-determined time points (0.083, 0.17, 0.25, 0.5, 1, 2, 4, 8, 10 and 24h) from retro-orbital plexus.

Dosage form 30mg/kg; oral administration.; one dose

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Applications

Following oral administration SAFit1 maximum concentration (C_{max}) in plasma (1467ng/mL) attained at 0.5h (T_{max} , time to reach C_{max}) indicating the rapid absorption from gastrointestinal tract. The $AUC_{0-\infty}$ (area under curve from time zero to infinity) was found to be 1851ng $\times$ h/mL for SAFit1.

References:

- [1] Voll A M, Meyners C, Taubert M C, et al. Macrocyclic FKBP51 Ligands Define a Transient Binding Mode with Enhanced Selectivity. *Angew Chem Int Ed Engl.* 2021 Jun 7; 60(24): 13257-13263.
- [2] Gabani B B, Sulochana S P, Siddesh A H, et al. Validated LC-MS/MS Method for Simultaneous Quantitation of SAFit-1 and SAFit-2 in Mice Plasma: Application to a Pharmacokinetic Study. *Drug Res (Stuttg).* 2020 Jul;70(7):325-332.

Background

SAFit1 is a FK506 binding protein 51 (FKBP51)-specific inhibitor with a K_i value of $4 \pm 0.3nM$ ^[1]. The selective inhibition of FKBP51 using SAFit1 has emerged as a possible treatment for chronic pain, obesity-induced diabetes, or depression^{[2][3]}.

In vitro, SAFit1 (1-1000nM) effectively stimulated neurite growth in two neuronal cell lines, specifically the mouse N2a line and the human SH-SY5Y line, as well as in primary hippocampal neurons. The active concentration range of SAFit1 is very wide^[1]. The NanoBRET assay shows that SAFit1 (1-100000nM) treated HEK293T cells transiently expressing FKBP51-NLuc for 2h dose-dependently competed with a fluorescent NanoBRET tracer, which indicated that SAFit1 was able to engage FKBP51 inside cells. SAFit1 (0.4, 0.2, 1 μ M) incubated murine microglia SIM-A9 cells for 16h could engage FKBP51 in cells and inhibited IKK α phosphorylation in a dose-dependent manner^[4]. A375 melanoma incubated in the presence of 20nM SAFit1 for 5h decreased transcript and protein levels of the receptor type I of TGF- β (T β RI) and reduced the protein expression of phosphorylated (p)-Smad2,3. SAFit1 finally inhibited FKBP51-dependent TGF- β pro-tumoral function in vitro^[5].

In vivo, mice received SAFit1 (30mg/kg) and SAFit2 (30mg/kg) as a cassette dose orally in a

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pharmacokinetic study. The experimental results showed that the maximum concentration ($C_{\max}$) of SAFit1 in mice was 1467ng/mL, and the time to reach $C_{\max}$ was 0.5 hours, indicating that SAFIT1 was absorbed quickly in the gastrointestinal tract^[6].

References:

- [1] Gaali S, Kirschner A, Cuboni S, et al. Selective inhibitors of the FK506-binding protein 51 by induced fit. *Nat Chem Biol.* 2015 Jan;11(1):33-7.
- [2] Sidibeh C O, Pereira M J, Abalo X M, et al. FKBP5 expression in human adipose tissue: potential role in glucose and lipid metabolism, adipogenesis and type 2 diabetes. *Endocrine.* 2018 Oct;62(1):116-128.
- [3] Knaup F H, Meyners C, Sugiarto W O, et al. Structure-Based Discovery of a New Selectivity-Enabling Motif for the FK506-Binding Protein 51. *J Med Chem.* 2023 Apr 27;66(8):5965-5980.
- [4] Voll A M, Meyners C, Taubert M C, et al. Macrocyclic FKBP51 Ligands Define a Transient Binding Mode with Enhanced Selectivity. *Angew Chem Int Ed Engl.* 2021 Jun 7; 60(24): 13257-13263.
- [5] Marrone L, Giacomo V D, Malasomma C, et al. Exploring the potential of selective FKBP51 inhibitors on melanoma: an investigation of their in vitro and in vivo effects. *Cell Death Discov.* 2025 Apr 3;11(1):138.
- [6] Gabani B B, Sulochana S P, Siddesh A H, et al. Validated LC-MS/MS Method for Simultaneous Quantitation of SAFit-1 and SAFit-2 in Mice Plasma: Application to a Pharmacokinetic Study. *Drug Res (Stuttg).* 2020 Jul;70(7):325-332.

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