

Product Data Sheet

Product Name: AZ-3451
Cat. No.: GC18152

Chemical Properties

Cas. No. 2100284-59-9

Chemical Name (S)-2-(6-bromobenzo[d][1,3]dioxol-5-yl)-N-(4-cyanophenyl)-1-(1-cyclohexylethyl)-1H-benzimidazole-5-carboxamide

SMILES BrC1=CC2=C(OCO2)C=C1C3=NC4=CC(C(NC5=CC=C(C#N)C=C5)=O)=CC=C4N3[C@@H](C)C6CCCCC6

Formula $C_{30}H_{27}BrN_4O_3$ M.Wt 571.46

Solubility Soluble in DMSO 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.

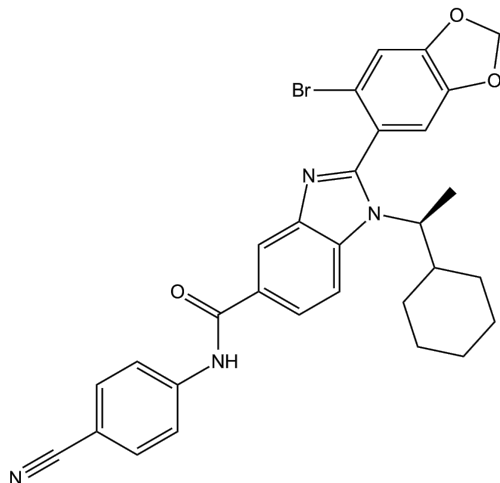
Caution: Product has not been fully validated for medical applications. For research use only.

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Structure



Protocol

Cell experiment [1]:

Cell lines Primary rat chondrocytes

Preparation Method Primary rat chondrocytes were derived from the knee joint cartilage tissue of 1-week-old Sprague-Dawley rats. Up to approximately 80% confluences, cells were treated with 10 μ M AZ-3451 in the presence or absence of 10ng/mL IL-1 β .

Reaction 10 μ M; 48h
Conditions

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Applications 10μM AZ-3451 can effectively inhibit PAR2 expression in chondrocytes. IL-1β increased the inflammatory cytokines and catabolic genes expression, including iNOS, COX2, MMP1, MMP13 and ADAMTS5, while treatment with AZ-3451 alleviated this process. Decreased Collagen II, aggrecan and SOX9 expressions induced by IL-1β were also inhibited by AZ-3451. The IL-1β-treated chondrocytes exerted higher SA-β-gal activity and p16INK4a protein expression compared with the control group, while PAR2 antagonist AZ-3451 significantly prevented this process.

Animal experiment [1]:

Animal models Sprague–Dawley rats

Preparation Method The rat post-traumatic osteoarthritis (PTOA) model was induced by surgical destabilization of the anterior cruciate ligament (ACLT) on the right knee. The rats were randomly divided into three groups. The sham group underwent sham operations with no ligament transection and treated with vehicle (physiological saline). The PTOA group underwent operations and treated with vehicle. The PTOA/AZ-3451 group underwent operations and treated with AZ-3451. For intra-articular injection, AZ-3451 was dissolved in physiological saline (50μg/ml) and rats were given an intra-articular injection (100μl) of AZ-3451 or vehicle twice a week following surgery. Rats were sacrificed at 8 weeks post-OA surgery from each group.

Dosage form 50μg/ml, 100μl; intra-articular injection; twice a week for 8 weeks

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Applications

AZ-3451 treatment group exerted the less cartilage damage and the richer proteoglycan compared to the PTOA group.
AZ-3451 intra-articular injection significantly alleviated OA progression.
AZ-3451 could increase the Beclin1 expression and decrease MMP13 and Cleaved-Caspase 3 expression in rat OA cartilage.
PTOA group exerted higher proportion of chondrocytes apoptosis, while AZ-3451 treatment reversed such pathological change.

References:

[1] Huang X, Ni B, Xi Y, Chu X, Zhang R, You H. Protease-activated receptor 2 (PAR-2) antagonist AZ3451 as a novel therapeutic agent for osteoarthritis. Aging (Albany NY). 2019;11(24):12532-12545.

Background

AZ-3451 is a protease-activated receptor-2 (PAR2) antagonist. PARs are irreversibly activated by proteolytic cleavage of the N-terminus, exposing a tethered peptide ligand that bind to and activates the transmembrane receptor domain (TMD), thereby triggering cellular signaling cascades in response to inflammatory and other stimuli. AZ-3451 binds to a remote allosteric site outside the helical bundle of the PAR2, preventing the conformational rearrangements required for receptor activation and signaling^[1].

In vitro, AZ-3451 (10 μ M; 48h) effectively inhibited PAR2 expression in primary rat chondrocytes and prevented IL-1 β (10ng/mL)-induced inflammatory responses, cartilage degradation, and premature senescence^[2].

In vivo, AZ-3451 (50 μ g/mL; 100 μ L; intra-articular injection; twice weekly for 8 weeks) significantly alleviated osteoarthritis progression in a rat post-traumatic osteoarthritis model, with reduced cartilage damage, increased proteoglycan content, and decreased chondrocyte apoptosis^[2]. AZ-3451 (10mg/kg; s.c.; administered 30min prior to treatment) significantly reduced PAR2 agonist-induced paw edema and decreased mast cell and neutrophil activation in rats^[3].

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- [1] Cheng, Robert K Y et al. "Structural insight into allosteric modulation of protease-activated receptor 2." *Nature* vol. 545,7652 (2017): 112-115.
- [2] Huang X, Ni B, Xi Y, Chu X, Zhang R, You H. Protease-activated receptor 2 (PAR-2) antagonist AZ3451 as a novel therapeutic agent for osteoarthritis. *Aging (Albany NY)*. 2019;11(24):12532-12545.
- [3] Kennedy, Amanda J et al. "Protease-activated receptor-2 ligands reveal orthosteric and allosteric mechanisms of receptor inhibition." *Communications biology* vol. 3,1 782. 17 Dec. 2020.

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