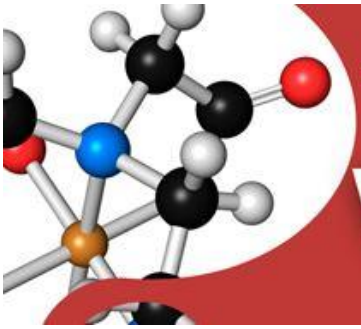

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TargetMol®
A DRUG SCREENING EXPERT

WIKIMOLE

PROMOZIONE *Ver. 2024/01*
VALIDITA' *dal 01/05/2024 al 31/07/2024*
CODICE *WIKIMOLE*

Molecole in focus e in promozione

Acquista una delle molecole in focus, presenti nelle pagine seguenti, abbinando un qualsiasi altro prodotto del catalogo TargetMol:
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Molecole in focus

Codice	CAS - Nome	Descrizione	Research Area	Mechanism of Action	Biological Applications / Clinical Research
T2154	133407-82-6 MG-132	MG-132, catalog number: T2154, also known as Z-LLL-al or Z-Leu-Leu-Leu-CHO, is a 26S proteasome inhibitor with an IC50 of 100 nM. It exhibits cell permeability and reversibility. MG-132 is capable of inducing apoptosis.	Epigenetics, regulation of gene expression and cell division, proliferation , molecular biology	The 26S proteasome is one of the most important protein degradation systems in cells, also known as the Ubiquitin-Proteasome System (UPS). This system mainly consists of two parts: the ubiquitination system and the proteasome. Ubiquitination system: This system involves the covalent attachment of ubiquitin molecules to target proteins, marking these proteins as targets for degradation. This process involves ubiquitin-activating enzymes and ubiquitin-conjugating enzymes, which work together to attach ubiquitin to specific proteins, forming polyubiquitin chains. Proteasome: This system is mainly composed of 20S core particles and 19S regulatory particles that bind to them, forming a 26S complex. The 26S proteasome is the primary intracellular protease responsible for degrading proteins that have been tagged with ubiquitin. It plays a crucial role in maintaining the quality of intracellular proteins and regulating protein levels by recognizing, deconstructing, and degrading ubiquitinated proteins.	The 26S proteasome maintains cellular protein homeostasis by clearing abnormal, aging, or excessive proteins. It participates in the regulation of cellular life cycles, stress responses, and metabolic regulation, among other physiological processes. MG-132, as an inhibitor of the 26S proteasome, can disrupt the normal function of this system, providing important tools and information for research in cell biology and molecular biology. Additionally, the apoptosis of cancer cells is closely related to the activity of the ubiquitin-proteasome pathway. MG132 can induce cell apoptosis through various intermediate pathways, playing a crucial role in anti-tumor therapy.
TP2030	10047-33-3 Gastrin I, human	Gastrin I, human, Catalog Number TP2030, also known as Gastrin I (human) or Gastrin 1, is an endogenous peptide produced in the stomach. It increases gastric pepsinogen and gastric acid secretion in rats through the CCK2 receptor.	Organiod (gastrointestinal, liver, pancreas)	Gastrin is an important gastrointestinal hormone mainly secreted by G cells. G cells are typical open-type cells, most abundant in the gastric antrum, followed by the gastric fundus, duodenum, and jejunum. Gastrin I is one of the earliest discovered subtypes of gastrin. Gastrin affects almost the entire gastrointestinal tract. It can promote the synthesis of DNA, RNA, and proteins in the mucosa of the gastric acid gland area and duodenal mucosa, thereby promoting mucosal cell growth and proliferation. The main functions of gastrin include: 1. Stimulating the synthesis of DNA, RNA, and proteins in the mucosa of the gastric acid gland area and duodenal mucosa, thereby promoting mucosal cell growth and proliferation. 2. Stimulating parietal cells to secrete hydrochloric acid and chief cells to secrete pepsinogen. 3. Stimulating gastric antrum and intestinal movement, delaying gastric emptying. 4. Stimulating the secretion of pancreatic juice, bile, and intestinal juice.	In the culture process of gastrointestinal organs, gastrin I can promote gastric acid secretion, proliferation, and repair of gastric mucosal cells. It also simulates the physiological environment in the body, helping to maintain the normal development and function of gastric organs. Therefore, in the culture process of gastrointestinal organs, gastrin I is often added as an auxiliary factor to the culture medium.

Codice	CAS - Nome	Descrizione	Research Area	Mechanism of Action
T1870	146986-50-7 Y-27632	Y-27632, catalog number T1870, is a selective inhibitor of ROCK-I and ROCK-II, exhibiting oral bioavailability and ATP competitiveness. Y-27632 can also inhibit apoptosis of dissociation-induced mouse prostate stem cells or progenitor cells, commonly used in stem cell research and organoid culture.	cancer, glaucoma, asthma, erectile dysfunction, insulin resistance, neurodegeneration, osteoporosis, renal failure, fibrosis, and graft-versus-host disease.	
T1725	129830-38-2 Y-27632 2HCl	Y-27632 2HCl, catalog number T1725, also known as Y-27632 dihydrochloride or trans-4-[(R)-1-aminoethyl]-N-(4-pyridyl)cyclohexanecarboxamide dihydrochloride, is the dihydrochloride salt form of Y-27632, exerting the same inhibitory effects as Y-27632.		
T3031	909910-43-6 A 83-01 .	A 83-01, catalog number T3031, also known as ALK5 Inhibitor IV, is an inhibitor of TGF-β type I receptors ALK5, ALK4, and ALK7 (IC50 = 12/45/7.5 nM). A 83-01 promotes the reprogramming of mouse fibroblasts into induced pluripotent stem cells (iPSCs). It can also be used for organoid culture.	Organiod	

Biological Applications / Clinical Research

Y-27632/Y-27632 2HCl, as a ROCK inhibitor, has significant applications not only in diseases like cancer but also in organoid culture and stem cell research, contributing to the maintenance of cell survival and functionality, thus holding crucial value in various fields.

Common applications:

1) Cryopreservation of stem cells: Y-27632 helps prevent dissociation-related cell apoptosis during the low-temperature preservation of stem cells and enhances cell viability post-thaw.

2) Pancreatic ductal adenocarcinoma organoid culture: Y-27632 serves as a supplement to the culture medium.

3) Mouse embryonic stem cells: Y-27632 inhibits the Rho kinase (Rho) in these cells.

4) Human embryonic stem cells and induced pluripotent stem cells (iPSCs): Y-27632 inhibits Rho-associated protein kinase (ROCK).

These diverse applications highlight the versatility and importance of Y-27632/Y-27632 2HCl in various research settings, promising advancements in cell biology and regenerative medicine.
There are many small molecules used in reprogramming, which can be categorized into four types: metabolic regulators, epigenetic modifiers, signaling modulators, and aging inhibitors. In this issue, we introduce three commonly used small molecule signaling modulators in reprogramming:

1) A 83-01 and SB-431542 inhibit the activity of TGF-β type I receptors ALK5/4/7 kinases. TGF-β plays a crucial role in stem cell culture. Stem cells possess active paracrine functions and can secrete a large amount of transforming

Codice	CAS - Nome	Descrizione	Research Area	Mechanism of Action	Biological Applications / Clinical Research
T1726	301836-41-9 SB-431542.	SB-431542, catalog number T1726, also known as SB 431542 or 4-[4-(1,3-benzodioxol-5-yl)-5-(2-pyridinyl)-1H-imidazol-2-yl]benzamide hydrate, is a selective inhibitor of transforming growth factor-beta (TGF-β) type I receptor ALK5, with an IC50 of 94 nM. It also exhibits inhibitory activity against ALK4 and ALK7 to some extent, with no inhibitory effect on other proteins. SB-431542 is commonly used for inducing differentiation in stem cells.			growth factors through exosomes. TGF-β promotes stem cell proliferation, aiding in the maintenance of their numbers. A 83-01 and SB-431542, as TGF-β inhibitors, are commonly used to inhibit the differentiation of iPSCs and maintain the self-renewal of cells in vitro. A 83-01 is generally used for the culture of gastrointestinal, hepatic, prostatic, and mammary organoids, while SB-431542 is typically used for the culture of lung and inner ear organoids. 2) SB 202190 is a potent p38 MAPK kinase inhibitor that can induce human embryonic stem cells to differentiate into cardiac muscle cells and promote the self-renewal of neural stem cells. It can be used for the culture of gastrointestinal, mammary, and prostatic organoids.
T2301	152121-30-7 SB 202190	SB 202190, catalog number T2301, also known as FHPI, is a selective inhibitor of p38 MAPK. It inhibits p38α and p38β2 with IC50 values of 50 nM and 100 nM, respectively. Additionally, it has demonstrated efficacy in rescuing memory impairments and exhibits anticancer activity. SB 202190 can also be used in organoid culture.			
T3015	763113-22-0 Olaparib	Olaparib, catalog number T3015, also known as AZD2281 or KU0059436, is a small molecule inhibitor of PARP1/PARP2. It exhibits selectivity and oral activity. Additionally, Olaparib also possesses activity in inducing autophagy and mitochondrial autophagy. Note: PARP stands for poly (ADP-ribose) polymerase.	breast cancer, ovarian cancer		Olaparib, marketed under the brand name Lynparza®, is an approved PARP inhibitor used to treat ovarian cancer and breast cancer patients carrying BRCA mutations. For these patients, specific gene mutations like BRCA disrupt other DNA repair pathways, making them particularly sensitive to PARP inhibitors. Treating ovarian and breast cancer patients carrying BRCA mutations is a common application of PARP inhibitors. Additionally, PARP inhibitors have shown therapeutic potential in other cancer types and non-oncological diseases. Approved PARP inhibitors on the market include Olaparib, Rucaparib, Niraparib, Talazoparib, etc.

Codice	CAS - Nome	Descrizione	Research Area	Mechanism of Action	Biological Applications / Clinical Research
T2310	252917-06-9 CHIR-99021	CHIR-99021, catalog number T2310, also known as Laduviglusib or CT99021, is a highly selective inhibitor of GSK-3α/β (Glycogen synthase kinase 3), with IC50 values of 10 nM and 6.7 nM, respectively. It is also an effective activator of the Wnt/β-catenin signaling pathway. Additionally, CHIR-99021 can induce autophagy and enhance self-renewal in mouse and human embryonic stem cells.	type 2 diabetes, Alzheimer's disease, inflammation, cancer, addiction, and bipolar disorder.		CHIR-99021 is a highly selective inhibitor of GSK-3α/β, which are regulators of the Wnt signaling pathway. By inhibiting GSK-3α/β, CHIR-99021 promotes the activation of the Wnt signaling pathway, thereby influencing the self-renewal and differentiation of stem cells. For example, human pluripotent stem cell (hPSC)-derived organoids such as Heart Forming Organoids (HFOs) represent a complex, highly structured in vitro model of early heart, gut, and vascular system development. These organoids are commonly used in teratogenic research, gene function analysis, and drug discovery studies. CHIR-99021 and IWP2 (Catalog No. T2702) are typically used during the establishment of this model for cell differentiation. As research progresses, scientists have found that CHIR-99021 significantly enhances the quantity and functionality of stem cells, showing promising applications across various stem cell types. The scope of CHIR-99021's applications continues to expand. Apart from its use in the field of stem cells, CHIR-99021 also demonstrates potential therapeutic value in neurodegenerative diseases, tumors, and metabolic disorders. In neurodegenerative diseases, CHIR-99021 can inhibit the generation and aggregation of beta-amyloid proteins, thereby slowing the progression of conditions like Alzheimer's disease. In the field of tumors, CHIR-99021 can modulate tumor cell proliferation and apoptosis, inhibiting tumor growth and metastasis. Additionally, CHIR-99021 can improve symptoms of metabolic disorders such as diabetes and obesity, promoting metabolic balance in the body.
T2310L	1797989-42-4 CHIR-99021 HCl	CHIR-99021 HCl, catalog number T2310L, is the hydrochloride salt form of CHIR-99021.			
T10765	1860875-51-9 Eragidomide	Eragidomide, Catalog number T10765, also known as CC-90009 or Cereblon modulator 1, is a selective cereblon (CRBN) E3 ubiquitin ligase modulator with specificity towards GSPT1. It acts through molecular glue, selectively targeting GSPT1 for ubiquitination and proteasomal degradation via the CRL4CRBN pathway.	Haematological Oncology Prostate Cancer Immune Microenvironment New drug discovery targeting protein degradation	E3 ubiquitin ligases play a crucial role in protein degradation. Ubiquitin (Ub) is a small protein consisting of approximately 76 amino acids with a molecular weight of around 8.5 kDa, and it is widely present in all eukaryotic cells. The process in which ubiquitin is covalently attached to target proteins, under the catalytic action of a series of enzymes, is known as ubiquitination. This is a highly regulated post-translational modification of proteins that not only participates in protein degradation but also plays a	The human body encodes over 600 different E3 ubiquitin ligases, but currently, only about 10 publicly disclosed E3 ligases are used in protein degradation research. Among them, two E3 ligases, CRBN and VHL12, have entered the clinical stage for protein degradation studies. Eragidomide (CC-90009) and Mezigdomide (CC-92480) are both CRBN E3 ligase modulators (CELMoD), exhibiting potent anti-tumor and immunomodulatory effects. They particularly induce immune-stimulatory effects and enhanced anti-tumor activity against multiple myeloma

Codice	CAS - Nome	Descrizione	Research Area	Mechanism of Action	Biological Applications / Clinical Research
T10703	2259648-80-9 Mezigdomide	Mezigdomide, Catalog number T10703, alias CC-92480, is a novel and selective CRBN E3 ubiquitin ligase modulator. It functions in the form of a molecular glue to recruit IKZF1 and ZFP91 targets to the CRL4CRBN E3 ubiquitin ligase, leading to their ubiquitination and degradation.		vital role in regulating cellular functions. Ubiquitination typically involves the coordinated action of three enzymes: E1 ubiquitin-activating enzyme, E2 ubiquitin-conjugating enzyme, and E3 ubiquitin ligase. The process is as follows: 1. Ubiquitin-activating enzyme (E1) activates the ubiquitin molecule using ATP as an energy source. 2. E1 transfers the activated ubiquitin molecule to the ubiquitin-conjugating enzyme (E2). 3. Ubiquitin ligase (E3) facilitates the transfer of ubiquitin from the E2 enzyme to a specific lysine residue on the target protein. In summary, the coordinated action of ubiquitin ligases allows ubiquitin molecules to be covalently attached to target proteins, thereby regulating the function, stability, and localization of proteins. E3 ubiquitin ligases, as a critical final step, hold significant importance in the field of protein degradation and provide powerful tools for the development of novel drugs.	cells. Currently, they are undergoing clinical trials as potential treatments for diseases such as multiple myeloma. CELMoD stands for Cereblon E3 Ligase Modulator, and it is a small molecule that can bind to E3 ligases (such as CRBN). Subsequently, it recruits new substrate proteins for ubiquitination and proteasomal degradation. GSPT1, also known as G1 to S phase transition 1, is a crucial translation termination factor significantly overexpressed in various cancer tissues and cells. Molecular glue refers to a small molecule that can bind to E3 ligases (e.g., CRBN) and then recruit new substrate proteins for ubiquitination and proteasomal degradation.

Codice	CAS - Nome	Descrizione	Research Area	Mechanism of Action
T11125	1467157-21-6 Durlobactam sodium salt	Durlobactam sodium salt, catalog number T11125, is the sodium salt form of Durlobactam, also known as ETX2514, Duobatan sodium, and Durobatan sodium. It is a beta-lactamase inhibitor with varying degrees of inhibition against beta-lactamases of classes A, C, and D. Durlobactam sodium salt can be used for research on multidrug-resistant Gram-negative bacteria, including Acinetobacter baumannii.	Gram-negative bacteria study	Beta-lactamases are enzymes produced by certain bacteria, categorized into four classes (A, B, C, and D). These enzymes contribute to bacterial multidrug resistance by inactivating beta-lactam antibiotics, such as penicillins, cephalosporins, monobactams, and carbapenems. Beta-lactam antibiotics constitute a widely used class of antibiotics characterized by a common four-membered core structure known as a beta-lactam ring. Beta-lactamases hydrolyze the beta-lactam ring, rendering the antibiotics ineffective and leading to bacterial resistance. Gram-negative bacteria commonly produce beta-lactamases, and clinically relevant organisms include members of the Acinetobacter–Calcoaceticus–Baumannii (ACB) complex. The rapid acquisition of multidrug resistance, encompassing fluoroquinolones, aminoglycosides, cephalosporins, and carbapenems, by the ACB complex limits therapeutic options, posing a significant global public health threat. The development of drugs targeting such bacteria is of crucial clinical importance.

Biological Applications / Clinical Research

Durlobactam is a novel broad-spectrum intravenous beta-lactamase inhibitor commonly used in combination with beta-lactam antibiotics, particularly Sulbactam. Sulbactam is an intravenous beta-lactam antibiotic with intrinsic antibacterial activity against Acinetobacter baumannii complex (ABC) infections.

In May 2023, Sulbactam/Durlobactam (XACDURO®) received FDA approval in the United States for patients aged 18 and older, indicated for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) caused by susceptible strains of ABC. This medication is a combination product designed to address infections caused by the Acinetobacter baumannii–Calcoaceticus–Baumannii complex. The use of Durlobactam prevents the degradation of Sulbactam by beta-lactamases produced by ABC, enhancing its efficacy.In the Phase 3 clinical trials of Sulbactam/Durlobactam, the effectiveness and safety of Sulbactam/Durlobactam in comparison to the combination of Imipenem-Cilastatin-Relebactam (ICR) with Colistin were evaluated for the treatment of severe infections caused by carbapenem-resistant Acinetobacter baumannii (ABC).

The study randomized 181 patients, with 125 patients confirmed to have carbapenem-resistant ABC strains included in the primary efficacy analysis. In the Sulbactam/Durlobactam group of 63 patients, the 28-day all-cause mortality rate was 12 cases (19%), while in the Colistin group of 62 patients, it was 20 cases (32%). The incidence of renal toxicity was significantly lower in the Sulbactam/Durlobactam group compared to Colistin (as shown in the figure below), and the incidence of severe adverse events was also lower in the Sulbactam/Durlobactam group than the Colistin group.

Codice	CAS - Nome	Descrizione	Research Area	Mechanism of Action
T11408	2212020-52-3 Orforglipron	GLP-1RA and SGLT-2i are new diabetes medications that have gained widespread attention due to their cardiovascular and renal benefits brought to patients with type 2 diabetes (T2D). Orforglipron, also known as LY3502970, is a GLP-1 receptor agonist. It is used in research related to obesity and T2D.	Obesity T2D	
T72061	2937344-16-4 BI-2493	BI-2493, catalog number:T72061, is a highly selective pan-KRAS inhibitor and a structural analogue of BI-2865. It exhibits similar anti-tumor activity to BI-2865, inhibiting tumor cell growth, and is used in research related to cancer diseases.	Pan-KRAS Inhibitors	

Biological Applications / Clinical Research

Orforglipron belongs to a new class of chemically synthesized oral non-peptide drugs that exhibit effective anti-diabetic effects by enhancing glucose-dependent insulin secretion and improving energy balance. In preclinical models, orforglipron has shown promising efficacy in lowering elevated blood glucose levels in experimental animals and exhibits favorable pharmacokinetic characteristics for oral administration. Currently, Orforglipron, as a medication for improving blood sugar control in adults and managing chronic body weight (weight loss) in adults, initiated Phase 3 clinical trials in September 2023. Results from the Phase 1 clinical study of Orforglipron indicate its GLP-1-like effects, making it a potential treatment for obesity and type 2 diabetes, comparable to other GLP-1 analogs. Phase 2 clinical data suggests that Orforglipron treatment significantly reduces blood sugar and body weight, without any clinically inconsistent adverse events compared to other GLP-1 receptor agonists. Its pharmacokinetic profile allows for once-daily oral administration, without dietary restrictions on food or water, providing a potentially safe and effective oral treatment option for patients with type 2 diabetes (T2D) and other indications. The current mainstream method of administration is subcutaneous injection; however, oral medications offer greater convenience and accessibility, eliminating the fear of injections for some patients.

The latest data from Phase 2 clinical trials show that different doses of Orforglipron, when taken orally, can significantly reduce patient weight by up to approximately 13% at 26 weeks and around 15% at 36 weeks. This study not only sets the stage for future Phase 3 weight loss clinical trials but also rejuvenates the weight loss market. The Phase 3 clinical trial plans to enroll 1576 patients with type 2 diabetes and is expected to be completed by July 2025.
(1) KRAS-Specific Inhibitors
KRAS inhibitors can bind to the KRAS protein, rendering it in an inactive state. As mentioned earlier, KRASG12C mutant inhibitors (sotorasib & Adagrasib) irreversibly bind to KRAS, marking a pivotal milestone in clinical drug discovery. However, for another common mutation, KRASG12D (found in 33% of KRAS mutant tumors), there are currently no clinical drugs. Several inhibitors targeting KRASG12D are still in the development stage, with

Codice	CAS - Nome	Descrizione	Research Area	Mechanism of Action
T72062	2937327-93-8 BI-2865	BI-2865, catalog number:T72062, is a non-covalent inhibitor with pan-KRAS potential. This inhibitor induces the inactivation of common KRAS oncoproteins (BI-2865 targets KRAS WT, G12C, G12D, G12V, and G13D mutants) without the need for covalent anchoring to specific mutant amino acids.		
T6013	187389-52-2 Z-VAD(OMe)-FMK	Z-VAD(OMe)-FMK is a cell-permeable and irreversible pan-caspase inhibitor. It inhibits cleavage of PARP, preventing apoptosis when used at 10-50 μM.	Neurological disorders (epilepsy, Parkinson's, etc.) Inflammatory diseases (rheumatoid arthritis, sepsis) AIDS Obesity, diabetes Liver disease Breast cancer, lung cancer, etc.	Z-VAD (OMe)-FMK and Z-VAD (OH)-FMK are both caspase inhibitors, but the differences in their chemical structures lead to distinct properties and modes of action. Z-VAD (OMe)-FMK is a cell-permeable, irreversible caspase inhibitor that can inhibit caspases and apoptosis in tumor cells in vitro. The methyl ester compound undergoes hydrolysis by endogenous esterase activity upon entering the cell, generating the biologically active form. Therefore, pre-treatment with esterase is required when using it with isolated, purified, or recombinant caspases. On the other hand, Z-VAD (OH)-FMK is a carboxylic acid compound that can be directly added to cell culture media without the need for esterase pre-treatment.
T7020	161401-82-7 Z-VAD (OH)-FMK	Z-VAD-FMK (Caspase Inhibitor VI) is an irreversible pan-caspase inhibitor.		

Biological Applications / Clinical Research

MRTX1133 (Catalog No. T9303) being a prominent candidate.
Preclinical research results demonstrate the specific inhibitory activity of MRTX1133 in various tumor cell lines carrying the KRASG12D mutation. The drug has received FDA approval for a new drug clinical trial application and entered Phase I/II clinical trials in 2023. Although there is considerable research on KRAS mutations, an effective and widely applicable clinical drug has yet to be found. Hence, new methods are needed to identify a class of novel selective KRAS inhibitors.

(2) Pan-KRAS Inhibitors
More than 100 mutation sites have been identified in RAS subtypes, with prominent mutation hotspots at G12, G13, and Q61. However, KRAS-specific inhibitor targets only G12C or G12D mutants, limiting clinical applications. To address these limitations, research teams have begun developing small molecule pan-KRAS inhibitors.
Pan-KRAS inhibitors deactivate common KRAS cancer proteins without the need for covalent anchoring to specific mutant amino acids. These inhibitors can prevent reactivation through nucleotide exchange by preferentially targeting the non-active state of KRAS. Representative examples include BI-2865 and its analogue BI-2493.
Z-VAD-FMK, as a broad-spectrum inhibitor of Caspase, plays a crucial role in apoptosis research. Numerous preclinical studies, both in vitro and in vivo, indicate that Caspase primarily acts as an inflammatory and apoptotic mediator in various pathologies. Consequently, several Caspase inhibitors have been patented for their anti-inflammatory and apoptotic functions. However, due to factors such as drug toxicity, their application is currently limited to preclinical research. Although some studies propose novel therapeutic approaches using nanoparticle delivery systems and CRISPR/Cas9 gene editing to improve drug delivery and reduce drug-induced toxicity, targeting individual Caspases separately, these remain short-term solutions. Because the lack of Caspase activity can increase the crosstalk between cell death and inflammatory pathways, there are concerns about the long-term efficacy of Caspase inhibitors. If inhibitors increase the risk of cell death and inflammatory reactions, they may exacerbate diseases. Therefore, it is crucial to clearly determine the specific mechanisms of action of Caspase inhibitors in preclinical models.

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