

COMPOUND USED AS KINASE INHIBITOR AND APPLICATION THEREOF

TECHNICAL FIELD

The invention relates to the technical field of medicine, in particular to a compound used as a kinase inhibitor, a preparation method thereof, and a use for preparing a medicament for treating diseases mediated by kinase such as ROS1, NTRK, ALK, etc.

BACKGROUND OF THE INVENTION

Tropomyosin receptor kinase (TRK) family belongs to transmembrane receptor tyrosine kinases (RTKs), which are involved in regulating synaptic growth and function maintenance, memory generation and development, and protecting neurons from damage, etc. in mammalian nervous system. TRK kinase is a kind of nerve growth factor receptor. Its family consists of Tropomyosin-related kinase A (TRKA), Tropomyosin-related kinase B (TRK B) and Tropomyosin-related kinase C (TRK C), which are highly homologous and encoded by NTRK 1, NTRK 2 and NTRK 3 genes, respectively. Complete TRK kinase consists of extracellular domain, transmembrane domain and intracellular domain. Like other RTKs, the extracellular domain of TRK kinase binds with corresponding ligands to form dimer, which can cause autophosphorylation of intracellular domain of TRK kinase to activate its kinase activity and further activate downstream signal transduction pathway. TRK kinase affects cell proliferation, differentiation, metabolism and apoptosis through downstream pathways such as Ras/MAPK, PI3K/AKT and PLC γ . When the NTRKs gene is fused or mutated, the extracellular receptor is altered or eliminated (Greco, A. et. al, Mol. Cell. Biol. 1995, 15, 6118; Oncogene 1998, 16, 809), but the fused or mutated TRK protein is in a highly activated kinase activity state without ligand binding, which can continuously activate the downstream signal transduction pathway, causing the regulation disorder of the downstream signal pathway of TRK kinase, inducing cell proliferation and promoting the occurrence and development of tumor. NTRKs gene fusion occurs in a variety of solid tumors in adults and children, including breast cancer, colorectal cancer, non-small cell lung cancer, papillary thyroid cancer, Spitz-like melanoma, glioma and various sarcomas, etc. In common cancers, such as non-small cell lung cancer and colorectal cancer, the incidence of NTRK gene fusion is lower, about 1%-3%, but in some rare cancers, such as infantile fibrosarcoma and secretory breast cancer, the incidence of NTRK gene fusion can reach more than 90%. The earliest TPM3-TRKA fusion protein was found in colon cancer cells. Later, more types of NTRK fusion proteins such as CD74-NTRKA, MPRIP-NTEKA, QKI-NTRKB, ETV6-NTRKC, BTB1-NTRKC, etc. were found in different clinical tumor patients such as breast cancer, non-small cell lung cancer, papillary thyroid cancer, Spitz-like melanoma, glioma, etc..Therefore, in recent years, NTRK fusion protein has become an effective anti-cancer target, and has become a hot spot in the research and development of anti-cancer drugs. With the further understanding of TRK kinase in recent years, more TRK fusion protein types and mutation types have been found (Russo, M. et. al Cancer Discovery, 2016, 6, 36; Drilon, A. et. al, Annals of Oncology, 2016, 27, 920), so it is urgent to develop new NTRK inhibitors with better activity and wider effects in clinic, so