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Review Article

# A review on macrocyclic kinase inhibitors in clinical trials

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ABSTRACT

Macrocyclic kinase inhibitors have high binding affinity and selectivity towards a variety of kinases including mammalian target of rapamycin complex 1/2, janus kinases/ Fms like tyrosine kinase, cyclin-dependent kinases and anaplastic lymphoma kinase1. Recently, few macrocyclic kinase inhibitors have entered clinical trial for treatment different types of cancers including leukemia, non-small cell lung cancer, myelofibrosis, breast cancer, glioblastoma and lymphoma. Of them, ridaforomilus has completed Phase III clinical trial and is waiting to be approved for treatment of breast cancer and advanced leukemia. Pacritinib is also currently being tested in phase III clinical trial for treatment of myelofibrosis and, loratinib is being evaluated for advanced ALK gene positive nonsmall cell lung carcinoma. The broad-spectrum cyclin-dependent kinases inhibitor, TGO2, has also entered phase II clinical trial for treatment of glioblastoma and advanced leukemia.



## 1. Introduction

Protein kinases are enzymes that transfer a phosphate group to a protein while phosphatases remove a phosphate group from protein. Together, these two enzymatic processes modulate numerous activities of proteins in a cell, often in response to an external stimulus. Approximately 538 known kinases are encoded in the human genome, and these kinases maintain cellular function by turning protein function on, while corresponding phosphatases reverse this action.[1]

Recent advances in our understanding of the fundamental molecular mechanisms underlying cancer cell signaling have elucidated a crucial role for kinases in the carcinogenesis and metastases of various types of cancer. Since most protein kinases promote cell proliferation, survival and migration, when constitutively overexpressed, or active, they are also associated with oncogenesis.[2]

Genome-wide studies of kinase mutations have revealed genetically inherited variants of specific kinases are causally associated with cancer initiation, promotion, progression as well as recurrence.[3] Over the last three decades, multiple human malignancies have been identified to be associated with modulation and dysfunction of protein and lipid kinases and deactivated phosphatases on account of chromosomal reshuffling and genetic mutations.[4] Apart from the oncological issues, dysregulation of kinases has been demonstrated in many human disorders including immune, neurological and infectious diseases.[5]

Kinome, the complete set of protein kinases encoded in its genome has become an attractive target for the treatment of numerous types of cancer. Single and multiple kinase inhibitors, both synthetic and natural molecules, are now targeted therapeutic strategies for treatment of human malignancies. Apart from this wide range of kinase-based drug targets, inhibition of distinct kinase signaling pathways can be less cytotoxic to non-cancerous cells, thus presenting the selective killing of tumor cells with considerably lower

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toxic manifestations.[6]

Targeting the kinases harboring oncogenic transformational capacity and metastasis has led to a notable change in the clinical management of cancer. Hundreds of kinases play overlapping and intricate roles in cell transformation, tumor initiation, survival and proliferation. Diving kinases while justifying their coinciding functionalities is difficult. However, in order to understand and discuss their oncogenic undertakings, they can be vaguely categorized based on their hallmark roles in cancer.[3]

### *1.1. Macrocyclic kinase inhibitors*

The structural homology within kinase families poses challenges for developing selective small molecule inhibitors.[4] A chemistry-driven approach utilizes macrocycles, capitalizing on their unique features to generate novel molecular scaffolds. This focused rational strategy explores relatively under-explored chemical space. Macrocycles, with well-defined three-dimensional shapes, enhance selectivity by fitting into the DFG-in conformation of target kinase ATP-binding sites. Cyclization reduces conformational freedom, lowering the entropy cost of binding and increasing free energy. While macrocycles offer a compromise between preorganization and flexibility, reports suggest favorable impacts on properties crucial for drugs. Despite their complexity, macrocycles may exhibit unique selectivity profiles in therapeutic areas, from malignancies to autoimmune disorders. However, their non-compliance with drug-like properties limits widespread adoption in drug discovery. This review discusses ongoing efforts in designing and synthesizing macrocyclic kinase inhibitors, presenting those in clinical trials after almost two decades of research.[7,8]

### *1.2. **mTOR** kinase*

mTOR is a protein kinase belongs to the family of phosphatidylinositol-3-kinase-related kinases (PIKKs) that phosphorylates threonine and serine residues in its substrates, is a central controller of cell growth, proliferation and metabolism.[9] Cumulative evidence indicates that mTOR acts as a 'master switch' of cellular anabolic and catabolic processes, regulating the rate of cell growth and proliferation by virtue of its ability to sense mitogen, energy and nutrient levels.[10]

Dysregulation of mTOR and other proteins in the signaling pathway often occurs in a variety of human malignant diseases and the tumor cells have shown higher susceptibility to mTOR inhibitors than normal cells. For example, activation of the mTOR pathway was noted in squamous cancers.[11] adenocarcinomas,[12] bronchioloalveolar carcinomas.[13] colorectal cancers,[14] astrocytomas[15] and glioblastomas.[16] These findings indicate a potential role of dysregulated mTOR signaling in tumorigenesis and support the currently ongoing clinical development of mTOR inhibitors as a potential tumor-selective therapeutic strategy.

Rapamycin, a first-generation mTOR inhibitor, forms a complex with FKBP12, binding selectively to the FRB domain and allosterically inhibiting mTORC1. Despite mTOR's presence in both mTORC1 and mTORC2, rapamycin only affects mTORC1. Its clinical use as an anticancer agent is limited by poor water solubility and stability. Rapalogs, improved derivatives with enhanced pharmacokinetics and reduced immunosuppression, are explored in cancer treatment. Examples include temsirolimus and everolimus, designed for oral administration. Ridaforolimus, a rapamycin-40-O-yl ester, demonstrates greater stability and is tested in clinical trials for various tumors, showing promising results in phase 3 trials for advanced soft tissue and bone sarcomas.[14–20]

Structure of ridaforomilus.

## 2. The Janus kinases (JAK) and FLT3

Janus kinases (Jaks), comprising JAK1, JAK2, JAK3, and TYK2, are non-receptor tyrosine kinases. While Jak1, Jak2, and Tyk2 are widely expressed in mammals, Jak3 is mainly found in hematopoietic cells. Jaks, typically located in endosomes and the plasma membrane due to their association with cytokine receptors, play a crucial role in cytokine signaling. Upon cytokine binding, receptor dimerization triggers autophosphorylation of associated JAK proteins, initiating a cascade that involves Signal Transducer and Activator of Transcription (STAT) proteins transducing signals to the nucleus for gene expression regulation. Mutations in the JAK-STAT pathway are implicated in autoimmune and malignant conditions. JAK3 and TYK2 mutations cause immunodeficiency, while JAK2 and STAT3 polymorphisms contribute to autoimmune diseases. Acquired mutations in JAK2 are prevalent in myeloproliferative neoplasms like polycythemia vera and essential thrombocythemia.[21–23]

FLT3, a class III receptor tyrosine kinase, is part of the RTK family, including c-KIT, FMS, PDGFRA, and PDGFRB. Class III RTKs have extracellular immunoglobulin G-like motifs with ligand-binding and tyrosine kinase domains. Upon ligand binding, FLT3 undergoes homodimerization, leading to activation and signal transduction through PI3K and MAPK pathways. Expressed in early hematopoietic progenitor cells, FLT3 is crucial for normal hematopoiesis and B-lymphopoiesis. Although not essential for granulopoiesis, FLT3 plays a significant role in leukemia cell functions, promoting proliferation, differentiation, and survival. FLT3 is overexpressed in various leukemias, with FLT3-ITD being more common than TKD mutations. FLT3 inhibition shows a beneficial effect in wild-type FLT3 AML, and FLT3

mutations, especially FLT3-ITD, are prevalent in acute promyelocytic leukemia.[24–26]

Pacritinib, a low molecular weight, macrocyclic compound, exhibits a unique kinome profile inhibiting multiple JAK/FLT signaling pathway members. Demonstrating specificity for JAK/STAT signaling, pacritinib inhibits wild-type and mutant JAK2, FLT3, and mutant FLT3. Notably, it lacks inhibition for JAK1, potentially reducing side effects associated with therapy. In Phase I/II studies, pacritinib showed tolerability up to 500 mg q.d. The Phase II study in patients with intermediate- and high-risk MF revealed spleen volume reduction in 31% of patients and improved MF symptom scores. Common toxicities included grade 1 or 2 diarrhea and nausea. Ongoing Phase III studies (PERSIST-1) evaluate pacritinib's efficacy and safety in MF patients.[27–33]

### 2.1. Cyclin-dependent kinases

The cell cycle, vital for cell duplication, is controlled by cyclin-dependent kinases (CDKs). CDKs, belonging to the CMGC kinase group, are regulated by cyclins. In humans, there are 20 CDK family members, with five (CDK1, CDK2, CDK3, CDK4, and CDK6) directly driving the cell cycle. Cyclins, which vary in activity throughout the cycle, activate specific CDKs. D-type cyclins act in mid to late G1, phosphorylating the cell cycle inhibitor pRb. Cyclin A appears at the G1/S boundary, activating CDK2 and CDK1 for G2 progression. B-type cyclins, like cyclin B1 and CDK1, drive cells into mitosis. During mitosis, transcription inhibition correlates with increased phosphorylation of RNA polymerase II (RNAPII) and transcription factors. CDK7, CDK8, and CDK9, members of the CDK superfamily, are associated with transcription initiation complexes. CDK7, through the CDK7-cyclin H-MAT1 complex, may link cell cycle regulation to transcription. Recent studies suggest p16INK4A may influence cell cycle progression through CDK7-mediated CTD phosphorylation. CDK8 negatively regulates CDK7 and TFIIH. CDK9, associated with RNAPII transcription complexes, shows increased activity during cell activation. PMA/PHA activation of lymphocytes demonstrates cell type-specific CDK9-cyclin T1 activation, promoting cell cycle progression.[34–38] SB1317 (TG02) is a broad-spectrum CDK inhibitor, targeting CDK1, 2, 7, and 9. Its inhibitory activity against both transcriptional CDKs and cell-cycle regulatory CDKs enhances apoptotic induction in tumor cells. Additionally, TG02 effectively inhibits the MAPK ERK5, crucial for multiple myeloma proliferation and survival. In multiple myeloma cells, TG02 induces cell-cycle arrest and apoptosis by depleting or cleaving antiapoptotic proteins. It synergizes with other antimyeloma drugs, inhibits tumor growth in xenograft models, and enhances bortezomib and lenalidomide activity in vivo. TG02, potent against JAK2 and TYK2 in the Janus kinase family, exhibits over 240-fold selectivity for JAK2 over JAK3. In preclinical studies, TG02 demonstrates efficacy against various tumor cell lines, induces G1 cell cycle arrest and apoptosis, and shows sensitivity in primary cultures from leukemia patients. In vivo, TG02 accumulates in tumor tissues, effectively blocking CDK and STAT signaling, leading to tumor regression in leukemia models and prolonged survival in disseminated AML models. These findings suggest TG02's therapeutic potential for a wide range of hematological malignancies.[39–43]

### 2.2. Anaplastic lymphoma kinase and ROS

Anaplastic lymphoma kinase 1 (ALK-1) belongs to the insulin receptor tyrosine kinase family (RTK) encoded by the ALK gene. This family includes receptors like PDGF, EGF, HER2/neu, insulin, and IGF-1, which regulate cellular growth and may lead to neoplastic transformation when mutated or expressed improperly. Although ligands for ALK like pleiotrophin, midkine, and heparin have been identified, the detailed understanding of ALK receptor activation remains incomplete. In mice, ALK protein expression is observed in specific brain regions during early development, but ALK knockout mice show normal growth and lifespans, with implications for frontal cortex and hippocampus function in adults. The ALK rearrangement, identified in non-small cell lung cancer (NSCLC), involves fusion with partners like EML4, HIP1, and TPR, activating Ras/MAPK, PI3K/AKT, and JAK/STAT pathways. This fusion gene has also been associated with Hodgkin lymphoma, and ALK mutations are found in anaplastic large cell lymphoma (ALCL), rhabdomyosarcoma, inflammatory myofibroblastic pseudotumor, neuroblastoma, and non-small cell lung cancer. In preclinical models, ALK inhibition has shown significant antitumor efficacy. In clinical settings, tyrosine kinase inhibitors like crizotinib, alectinib, and ceritinib targeting ALK have demonstrated remarkable effectiveness and improved prognosis in patients with ALK-rearranged NSCLC (45, 63-68). ROS proto-oncogene 1, receptor tyrosine kinase (ROS1), found on chromosome 6q22.1, is part of the tyrosine kinase insulin receptor gene subfamily. It is highly expressed in various tumor cells and encodes a protein with tyrosine kinase activity. ROS1 has been identified in different human cancers such as ovarian cancer, angiosarcoma, NSCLC, cholangiocarcinoma, inflammatory myofibroblastoma, glioblastoma multiforme, and spitzoid melanoma. Its prevalence makes ROS1 an appealing therapeutic target in cancer treatment. Tyrosine kinase inhibitors (TKIs) like crizotinib, which negatively impact cell proliferation in ROS1 fusion cases, have shown significant antitumor activity. Crizotinib was FDA-approved in 2016 for treating advanced ROS1-rearranged NSCLC.[44–47]

Lorlatinib (PF-06463922) is a 3rd-generation macrocyclic inhibitor designed for ALK/ROS1 in cancer

therapy, featuring a new chemical structure. Developed by Pfizer, this oral inhibitor exhibits strong and selective activity against ALK and ROS1 kinases, showcasing promising antineoplastic effects. It surpasses the potency and efficacy of FDA-approved TKIs like crizotinib, ceritinib, and alectinib. In ongoing phase III clinical trials, lorlatinib is being evaluated for ALKþ/ROS1þ NSCLC patients, irrespective of CNS metastases or prior TKI treatment. Derived from crizotinib, lorlatinib addresses clinical resistance, offering improved CNS exposure and safety. Its macrocyclic structure enhances metabolic stability and reduces P-gp efflux. In preclinical studies, lorlatinib demonstrated activity against crizotinib-resistant tumors, with complete regression observed. Importantly, lorlatinib is well-tolerated, showing robust activity against various mutations in both ALK and ROS1.[44–49]

## 3. Future Perspectives

Macrocyclic kinase inhibitors have shown improvements in potency over uncyclized counterparts through conformational restriction. There is evidence that macrocyclization intrinsically varies the selectivity profiles of acyclic precursor pharmacophores. Generally, improved solubility and decreased ADMET liabilities have been achieved without detriment to target kinase's biological activity in multiparameter optimizations, by strategic functionalization of the macrocyclic scaffolds.

A fruitful area for further research would be to achieve more efficient macrocyclic ligands, through addressing multiple properties by crafting of functionality within the scaffold itself. For example, a macrocycle could improve target potency through conformational restriction, while also incorporating polar functionality within the core cycle, which could improve physicochemical properties such as solubility and also directly interact with the kinase protein target through hydrogen bonding or charge–charge interactions. With strategic positioning of this additional functionality, which could be controlled through spatial organization using a fixed macrocyclic scaffold, changes in selectivity against related kinase targets could also be achieved. To further advance the field of macrocycles kinase inhibitors in medicinal chemistry, the progress in synthetic methods available to generate macrocycles needs to be continued.

In the next few years, I would anticipate that the discovery of macrocyclic kinase inhibitors will become routine and a significant number of macrocyclic kinase inhibitor molecules would be found in late-stage clinical trials. There are several cases of this occurring, for example, pacritinib (SB1518) is completing Phase II evaluation. It is reasonable to expect that one or more macrocycles kinase inhibitors will come into clinical use in the next decade. I suggest that in the future the insilico prediction of macrocyclic conformations and their interactions with kinase proteins will become more robust, reducing the barrier to incorporation of these scaffolds earlier in the drug-discovery process.

## 4. Summary

In this review, novel emerging class of macrocyclic kinase inhibitors that have entered clinical trial are discussed. Macrocyclic kinase inhibitors are designed and synthesized and found to have activity for mTOR, JAK2, CDK2, FLT3 and ALK1/ROS1 Kinases. These enzymes are implicated in important pathways of carcinogenesis affecting the JAK/STAT signaling pathway, cell cycle, mutated FLT3-ITD and ALK1, which are prevalent in cancer. Combination of those targets was proposed as a compelling strategy for the treatment of hematological malignancies with later expansion into solid tumors.

Ridaforolimus (AP23573; MK-8669) is a novel rapamycin analogue that selectively targets mTOR andcurrently, it completes phase III clinical trial. Pacritinib is a novel JAK inhibitor with dual activity against JAK2 and FLT3. It has activity in patients with mylofibrosis, including those with anemia and thrombocytopenia, and is currently being tested in Phase III clinical trials. TG02 is a novel chemical entity with broad spectrum activity against oncogenic CDKs, with the additional benefit of targeting JAK2 and FLT3, the two kinases that are key to the etiology of several hematopoietic malignancies. Compared with mono-targeted reference inhibitors, TG02 is more consistently anti-proliferative across tumor cell lines as well as primary diseased cells. TG02's unique kinase spectrum and favorable pharmacological profile provide the rationale for its current evaluation in patients with advanced leukemias.

Lorlatinib has attracted significant attention because of its potent antitumor effects against both systemic and intracranial lesions in preclinical and Phase I/II studies. A Phase III study to compare the efficacy of lorlatinib with crizotinib as a first-line treatment in patients with advanced ALK-positive NSCLC is currently underway.

## 5. Source of Funding

None.

## 6. Conflict of Interest

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