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Progress in research on protein tyrosine kinase inhibitors

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Progress in Research on Protein Tyrosine Kinase Inhibitors

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Abstract. The occurrence and development of tumors are related to the disorder of intracellular signal transduction, especially the disorder of signal transduction pathway of receptor tyrosine kinase (RTK). Protein kinase inhibitors acting on this pathway can suppress the intracellular transmission of proliferation signals of tumor cells, thereby controlling their proliferation. Protein tyrosine kinase-mediated signal transduction pathway is currently an antitumor drug target which is studied by many researchers and demonstrates significant effects. Besides, as the main anti-tumor drug type available on market in recent years, multi-target tyrosine kinase inhibitors can inhibit multiple signal transduction pathways, induce the apoptosis of tumor cells, blocks the formation of new blood vessels, and inhibits the proliferation of tumor cells. Therefore, this paper reviews the relationship between tyrosine kinases and tumors, commercially available typical tyrosine kinase inhibitors, and their application prospects.

Key words: Tyrosine Kinase Inhibitor; Targeted Therapy; Antitumor Drug.

INTRODUCTION

Cancer is a great threat to human health, and antitumor research is a highly challenging and significant area of life science today. At present, the antitumor drugs commonly used in clinical practice are mainly cytotoxic drugs, but such anti-cancer drugs have the disadvantages of poor selectivity, toxic side effects, and drug resistance. With research on the molecular biological mechanism of tumor cell growth, proliferation and regulation further deepening, molecular targeted therapy has become a focus in the development of antitumor drugs because of its high selectivity and small side effects. In particular, some new, highly effective anticancer drugs have become an important direction for the research and development of anti-tumor drugs because they have fewer toxic side effects, use key enzymes of cell signal transduction pathways related to tumor cell proliferation and differentiation as drug screening targets, and act on specific targets.

RELATIONSHIP BETWEEN TYROSINE KINASE AND TUMOR

Tyrosine kinases (TKs) are a class of proteins with tyrosine kinase activity, which can be divided into receptor type and non-receptor type. They can catalyze the transfer of phosphate from ATP to the hydroxyl group of tyrosine residue on many key proteins. Protein tyrosine kinase plays a crucial role in the signal transduction pathway in cells, regulating a series of physiological and biochemical processes such as growth, differentiation and death in cells. However, disorder of tyrosine kinase functions triggers a range of diseases in the body. The data has shown that more than 50% of proto-oncogene and oncogene products have protein tyrosine kinase activity, and their abnormal expression will cause disorder of cell proliferation and regulation, thus leading to tumorigenesis. In addition, abnormal expression of tyrosine kinases is also closely related to tumor invasion and metastasis, tumor angiogenesis and tumor chemo-resistance. Therefore, drug development with tyrosine kinase as a target has become a hot spot for anti-tumor drug research, whose research funding is unmatched by any other non-traditional tumor target1-4.

Bound to the cell membrane, RTK is divided into three parts: extracellular fragment, transmembrane fragment and intracellular fragment among which the intracellular fragment possesses protein tyrosine kinase (PTK) activity.

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Depending on the type of gene, PTK can be divided into two categories: oncogene products and receptors for growth factors. Growth factor receptors include epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR), nerve growth factor receptor (NGFR), type I insulin-like growth Factor receptors (IGFR-1) and the like5, which constitute a so-called "family of receptor tyrosine kinase" growth factor to act as extracellular stimulation signals. When combined with the extracellular fragment of RTK, these growth factors can activate PTK activity in the intracellular fragment.

The receptors for cell growth factors are generally referred to as TPK receptors. When the ligand and the extracellular TPK receptor bind, the phosphorylated TPK receptor can be recognized by the intracellular information substance. As a ligand, the receptor tyrosine kinase, which conducts signal transduction in cells, needs to be bound to the corresponding receptors on cell surface first. Only in this way can it activate downstream signaling molecules to play a biological role and regulate various cell growth factors so as to control cell growth and differentiation.

All receptor tyrosine kinases are type I membrane proteins whose molecules have similar topologies: glycosylated extracellular receptor ligand domain, hydrophobic single-transmembrane domain, and intracellular catalytic domain of tyrosine kinases and regulatory sequences. The differences between different receptor tyrosine kinases mainly lie in the extracellular receptor ligand domain and there is high homology between the intracellular tyrosine kinase domains. The ligand should be bound to the corresponding receptor tyrosine kinase, which will result in dimerization of the receptor and further promote auto-phosphorylation or cross-phosphorylation of the specific receptor tyrosine residues in the receptor's intracellular region, thereby activating downstream signal transduction pathway. The occurrence and development of many tumors are closely related to the abnormal expression of tyrosine kinases.

COMMERCIALLY AVAILABLE TYPICAL TYROSINE KINASE INHIBITORS

Tumor growth does not depend solely on a receptor or signaling pathway, which determines that drugs acting only on a single target can't completely kill tumor cells. Compared with single-target drugs, multi-target tyrosine kinase inhibitors have more advantages, for example, avoiding drug interactions and having more comprehensive effects. Multi-target tyrosine kinase inhibitors are small molecule inhibitors that can penetrate the cell membrane and target specific sites of tumor cells and / or peripheral endothelium and vascular kinase receptors, thereby blocking the signal transduction pathway of cell proliferation6. Compared with drug injections of macromolecular, monoclonal antibody, small molecular multi-target tyrosine kinase inhibitors can be made into oral preparations, which are convenient to take and favored by medical researchers and patients, becoming a hot spot in anti-tumor drug research around the world.

Imatinib

Imatinib is a first-generation / old-generation targeted drug developed and sold by Novartis AG in Switzerland for the treatment of chronic myelogenous leukemia, gastrointestinal stromal tumors and other cancers. As a tyrosine kinase inhibitor used in the treatment of various cancers, it is used to treat chronic myelogenous leukemia / chronic myeloid leukemia (CML), gastrointestinal stromal tumors (GISTs) and some other malignancies, which act most effectively on the treatment for chronic myelogenous leukemia with a Philadelphia chromosomal translocation. By 2011, the drug has been approved by the US FDA for the treatment of 10 different cancers. Chronic myelogenous leukemia appears because the chromosomes 9 and 22 break a short segment and then switch places. This translocation results in abnormal function of bone marrow cells and a large number of abnormal white blood cells and the translocated chromosome is also called "Philadelphia chromosome". Imatinib can effectively inhibit the Philadelphia chromosome gene, so that the phosphorylation reaction cannot be catalyzed, thereby leading to the dysfunction of chromosome and inhibiting the proliferation of abnormal white blood cells. Imatinib can be bond to the active site of tyrosine kinase to blocks its activity7

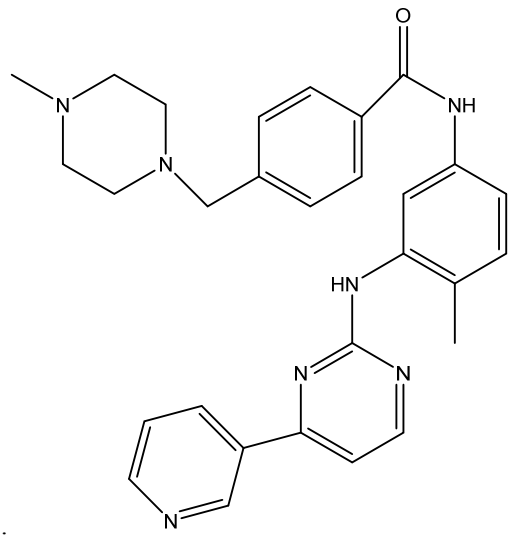

FIGURE 1. Structure of Imatinib

Sorafenib

Sorafenib, a patented drug of Bayer AG, USA, is a novel multi-target oral drug for the treatment of tumors, whose primary development goal is to treat gastrointestinal stromal tumors and metastatic renal cell carcinoma that are unresponsive or intolerant to standard therapy8. It can selectively targets the receptrs of certain proteins which are thought to play a molecular switch-like role in tumor growth. The above indications have been granted the "fast track" approval by the Food and Drug Administration in the United States, which approved the use of Sorafenib in advanced kidney cancer and unresectable hepatocellular carcinoma in 2005 and 2007 respectively9. Meanwhile, China Food and Drug Administration approved its sales on the market in 2006.

As the first multi-target oral tyrosine kinase inhibitor that targets Raf, Sorafenib has dual anti-tumor effects. On the one hand, it can directly inhibit tumor growth by inhibiting the RAF/MEK/ERK signal transduction pathway. On the other hand, Sorafenib can block the formation of tumor neovascularization by inhibiting vascular endothelial growth factor receptors and PDGF receptors.

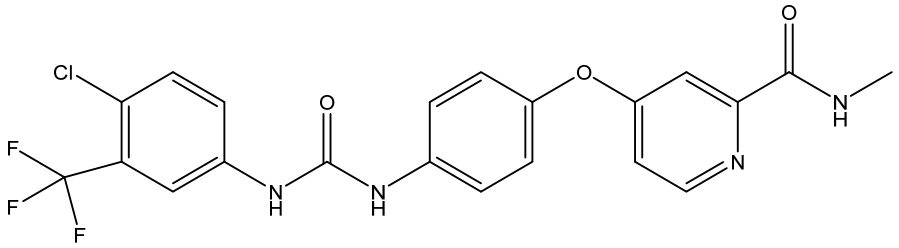

FIGURE 2. Structure of Sorafenib

Sunitinib

As an oral small molecular multi-target receptor tyrosine kinase inhibitor, Sunitinib was approved by the FDA on January 26, 2006 for the treatment of gastrointestinal stromal tumors and metastatic renal cell carcinoma that are unresponsive or intolerant to standard therapy. It is the first drug approved for the treating two types of cancer at the same time10. Sunitinib inhibits cellular signaling by targeting multiple receptor tyrosine kinases. Typical receptors include platelet-derived growth factor R-chain (PDGF-R) and vascular endothelial growth factor receptor (VEGFRs), which play important roles in tumor angiogenesis and cell proliferation. These simultaneous inhibitions cause a reduction in tumor vascularization and apoptosis in the cancer, ultimately leading to tumor shrinkage. Besides, Sunitinib also inhibits the KIT gene (CD117)11, which is a receptor tyrosine kinase that causes most gastrointestinal

stromal tumors when the mutation is inappropriately activated12. As a second-line therapy, Sunitinib is recommended for cancer patients with mutations in the KIT gene, who may be resistant to Imatinib or have reduced drug tolerance13-14. In addition, Sunitinib can inhibit other receptor tyrosine kinases15 including: RET, CSF-1R, and flt3. Since it targets many different receptors, Sunitinib also cause many side effects such as chiropody, stomatitis and other cutaneous poisonings.

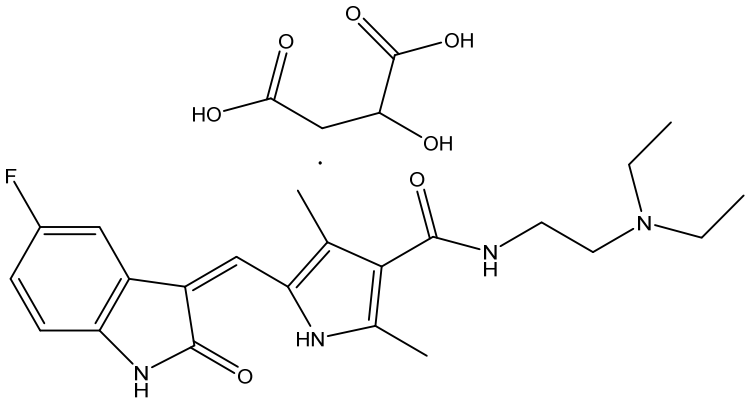

FIGURE 3. Structure of Sunitinib

Nilotinib

Nilotinib is the second-generation / new-generation target drug developed and sold by Novartis AG for the treatment of chronic myelogenous leukemia. The drug is safe and has a good effect on the drug resistance caused by Imatinib in patients with chronic myelogenous leukemia / chronic leukemia16. In a study, 92% of patients (suffering drug resistance or drug retardation) returned to the normal level of white blood cells through a five-month treatment17. It is a tyrosine kinase inhibitor that mainly inhibits such kinases as BCR-ABL 18, KIT, LCK, EPHA3, EPHA8, DDR1, DDR2, PDGFRB, MAPK11, and ZAK. In 2007, this drug was approved by the US FDA for the treatment of chronic myelogenous leukemia. Later in 2009, the European Union EMA approved of its treating chronic myelogenous leukemia. In 2011, it was approved for sale in Hong Kong.

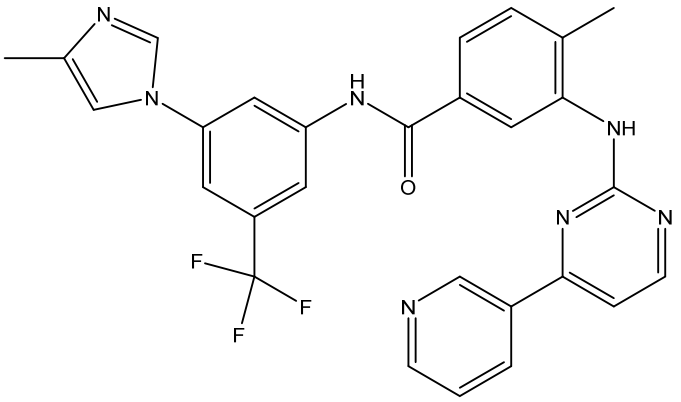

FIGURE 4. Structure of Nilotinib

Vandetanib

Vandetanib, which is a synthetic aniline quinazoline compound, is an oral small molecular multi-target tyrosine kinase inhibitor (TKI) that acts on cell receptors such as the vascular endothelial growth factor receptor (VEGFR), the epidermal growth factor receptor (EGFR), and the RET-tyrosine kinase19. It can also selectively inhibit other tyrosine

kinases as well as serine / threonine kinases, and conducts multi-target signal blocking. Vandetanib is therefore a multi-channel tumor signaling inhibitor that inhibits vascular endothelial cell proliferation and tumor cell growth. It was approved by FDA for the treatment of unresectable, locally advanced or metastatic medullary thyroid carcinoma in April, 2011.

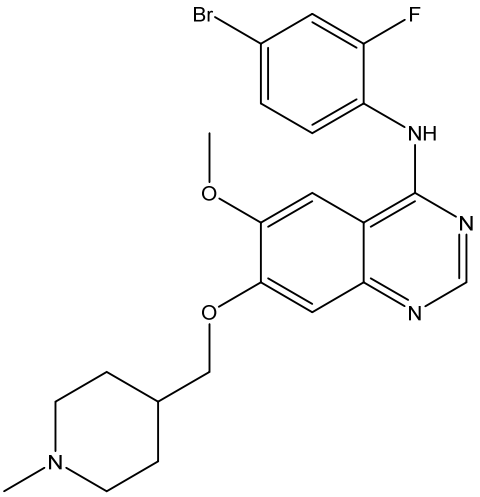

FIGURE 5. Structure of vandetanib

Lapatinib

Lapatinib is a small molecular oral epidermal growth factor tyrosine kinase inhibitor produced by GlaxoSmithKline. Approved for sale by FDA in March 2007, it is combined with Capecitabine for the treatment of breast cancer patients with metastatic or invasive HER-2 overexpression that have been treated with steroids, taxanes and trastuzumab. In January, 2010 FDA approved its combination with letrozole to treat er-positive and HER-2-positive postmenopausal advanced breast cancer. Lapatinib mainly acts on the Epidermal Growth Factor Receptor (EGFR) EGFR which has an important effect on cancer cell growth. If the receptors of cancer cells are over-expressed or over-activated, the cancer cells will grow in large numbers, which in turn will increase the difficulty of healing and the chance of recurrence. In addition to blocking the type 1 receptor (EGFR), lapatinib can also block the role of the type 2 receptor (HER2). And this dual inhibitory effect can effectively cut off the downstream signaling of tyrosine kinase, thereby terminating the rapid proliferation of cancer cells. Since about 20 to 30% of breast cancer patients have excessive expression of type 1 and type 2 receptors, lapatinib can effectively slow the progression of cancer 20.

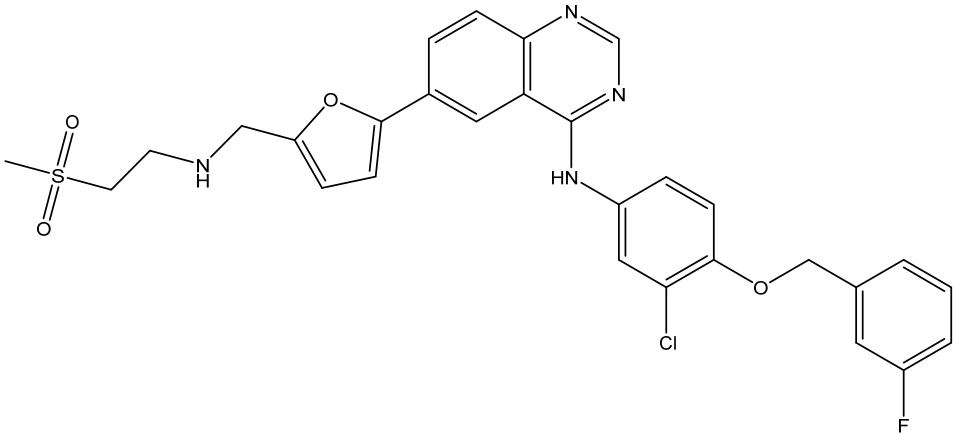

FIGURE 6. Structure of lapatinib

Pazopanib

Pazopanib, a novel oral angiogenesis inhibitor developed by GlaxoSmithKline that interferes with the neovascularization required for the survival and growth of stubborn tumors, targets vascular endothelial growth factor receptor (VEGFR) and works by inhibiting neovascularization of tumor blood supply. It is suitable for the treatment of advanced renal cell carcinoma (a type of renal cancer in which cancer cells are found in the renal tubules), soft tissue sarcoma (STS), epithelial ovarian cancer, and non-small cell lung cancer (NSCLC). 21-24 Based on a phase III clinical trial, FDA approved its use in treating soft tissue sarcomas that had previously received chemotherapy in April 2012.

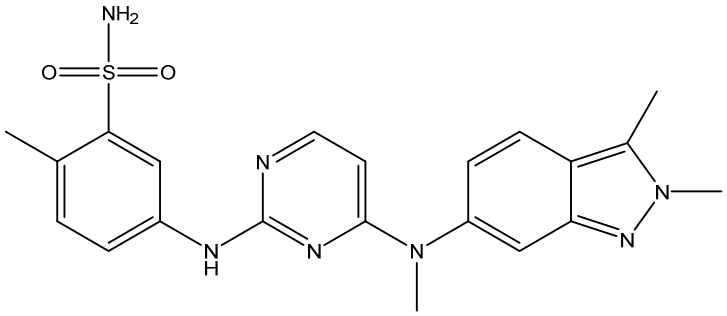

FIGURE 7. Structure of Pazopanib

Axitinib

Axitinib, also known as Inlyta, is a second-generation VEGFR inhibitor approved by the FDA in January 2012 for the treatment of advanced renal cell carcinoma on which other medicines had no effect. Axitinib is a potent and selective VEGFR1, 2, 3 TKI, which can block endothelial cell survival, microtubule formation, and inhibit downstream signaling through nitric oxide synthase, Akt, and extracellular signal-regulated kinase. At present, this product has been used in Phase II clinical trials in the treatment of a variety of tumors such as adrenal cortical tumors, hepatocellular carcinoma, soft tissue tumors, and lung cancer.

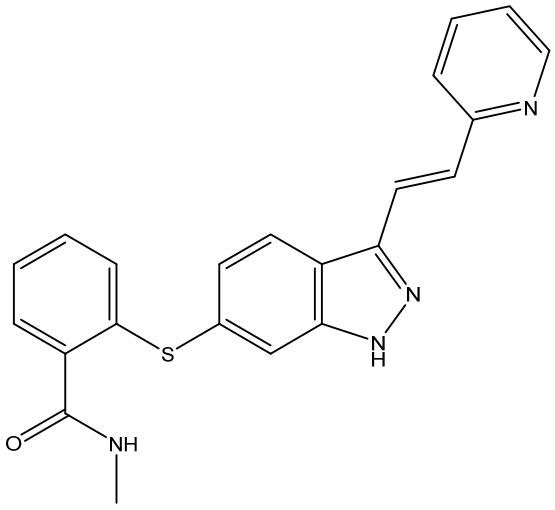

FIGURE 8. Structure of Axitinib

Ruxolitinib

Ruxolitinib is a drug for the treatment of intermediate or high-risk myelofibrosis, a type of myeloproliferative disorder that affects the bone marrow, 25-26 and for polycythemia vera (PCV) when there has been an inadequate response to or intolerance of hydroxyurea.27-28Ruxolitinib is a janus kinase inhibitor with selectivity for subtypes JAK1 and JAK2 of this enzyme.29-30 Ruxolitinib inhibits dysregulated JAK signaling associated with myelofibrosis. JAK1 and JAK2 recruit signal transducers and activators of transcription (STATs) to cytokine receptors leading to modulation of gene expression. The phase III Controlled Myelofibrosis Study with Oral JAK Inhibitor-I (COMFORT-I) and COMFORT-II trials showed significant benefits by reducing spleen size and relieving debilitating symptoms.31-34 In November 2011, ruxolitinib was approved by the U.S. Food and Drug Administration (FDA) for the treatment of intermediate or high-risk myelofibrosis based on results of the COMFORT-I and COMFORT-II Trials.35 In 2014, it was approved in polycythemia vera (PCV) when there has been an inadequate response to or intolerance of hydroxyurea, based on the RESPONSE trial.36, 28.

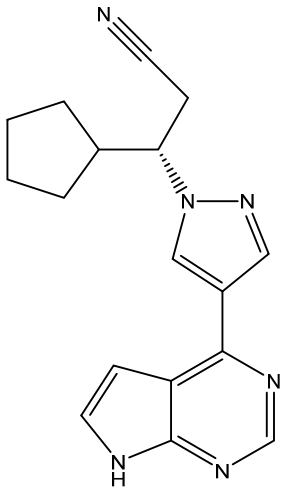

FIGURE 9. Structure of Ruxolitinib

PROSPECTS

Although small molecular tyrosine kinase inhibitors have made great progress in the treatment of cancer, they are still confronted by some challenges. First, mutations in tumor cell genes cause resistance problems in small molecular kinase inhibitors. According to the time of drug resistance, it is divided into primary drug resistance and acquired drug resistance. These small molecular tyrosine kinase inhibitors demonstrate good curative effect in the dominant population of a few gene mutations, but they are not as effective as traditional chemotherapy (chemotherapy) for many other patients. Therefore, genetic testing should be routinely taken before the application of the drugs, which incurs high cost. Second, there appeal some side effects and interaction between the drugs. Although their adverse side effects are lighter compared with the traditional cytotoxic chemotherapeutic drugs, research has shown that tyrosine kinase inhibitors are detrimental to metabolism and the endocrine system. For instance, there might appear severe adverse reactions such as dermal toxicity, interstitial pneumonia, hypothyroidism, prolonged QT interval, reversible posterior leukoencephalopathy syndrome, etc.37 Most of the TKIs metabolize through the liver CYP3A4 enzyme, so the combination with a strong CYP3A4 inhibitor may increase the pharmacological activity of the substrate, while long-term combination with a strong CYP3A4 inducer may reduce substrate activity and require increased drug use38. Third, how to find a balance point between multi-target tyrosine kinase inhibitors and increased kinase selectivity is still in question. The forth question remains to be solved is how to accurately predict the toxicity and pharmacokinetic properties of compounds before clinic trials so as to accelerate new drug development and avoid repeated waste. The discovery and expansion of the tertiary structure of protein kinases, X-ray crystal structures and the “ATP-binding sites”, and the invention and application of advanced technologies such as large-scale rapid screening, combinatorial chemistry, and genetic engineering have accelerated the development of small molecular protein tyrosine kinase

inhibitors39. It is believed that in the near future, small molecular tyrosine kinase inhibitors will overcome multidrug resistance of tumors, actualize multi-target inhibition, and realize the safety evaluation and individualized administration of small molecular TKIs, playing a much more significant role in the field of cancer treatment.

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