



ISSN: 0976-3031

Available Online at <http://www.recentscientific.com>

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 8, Issue, 4, pp. 16379-16383, April, 2017

**International Journal of
Recent Scientific
Research**

DOI: 10.24327/IJRSR

Review Article

PROTEIN KINASE INHIBITORS IN CANCER TREATMENT: A REVIEW

Lata C. Potey* and Satish Kosalge

Hi-Tech College of Pharmacy Chandrapur

DOI: <http://dx.doi.org/10.24327/ijrsr.2017.0804.0139>

ARTICLE INFO

Article History:

Received 15th January, 2017
Received in revised form 25th
February, 2017
Accepted 23rd March, 2017
Published online 28th April, 2017

Key Words:

Protein kinases, Growth Blockers,
Tyrosine Kinase Inhibitors, Cancer.

ABSTRACT

Protein kinases have important role in cell proliferation & differentiation of cell. They involved in diverse biological processes like growth, differentiation, metabolism and apoptosis in response to external and internal stimuli, mediator of signaling cascade. Tyrosine kinases are enzymes that selectively phosphorylates tyrosine residue in different substrates. Over expression of these tyrosine kinases receptor cause development of human cancer. So lot of work is done to understand role of tyrosine kinases in the pathophysiology of cancer. Defective regulation of growth processes plays a role in the genesis and progression of most type of cancer. Oncogenic activation of tyrosine kinase due to mutation, autocrine-paracrine stimulation in cancer cells can be blocked by selective tyrosine kinase inhibitors and thus considered as a promising approach for treatment of cancer. This review describes the role of growth factors in development of cancer & the role of TK inhibitors or growth blockers on treating cancer. This review article describes the mechanism of action, structures, and side effects of potent protein kinase inhibitors.

Copyright © Lata C. Potey and Satish Kosalge, 2017, this is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

A protein kinase is a kinase enzyme that modifies other proteins by chemically adding phosphate groups to them (phosphorylation). Phosphorylation usually results in a functional change of the target protein (substrate) by changing enzyme activity, cellular location, or association with other proteins. The human genome contains about 500 protein kinase genes and they constitute about 2% of all human genes.^[1] Up to 30% of all human proteins may be modified by kinase activity, and kinases are known to regulate the majority of cellular pathways, especially those involved in signal transduction. Protein kinases are also found in bacteria and plants.

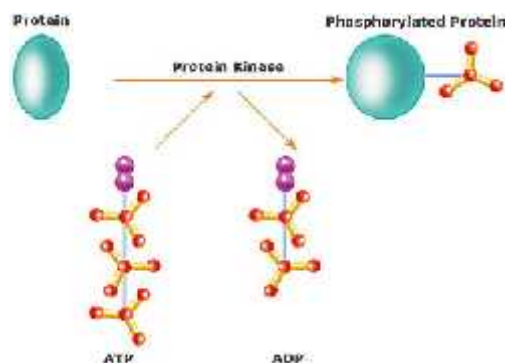


Figure 1 Protein Phosphorylation

Protein Kinase Group

The human protein kinase family is divided into the following groups:

- AGC kinases - containing PKA, PKC and PKG.
- CaM kinases - containing the calcium/calmodulin-dependent protein kinases.
- CK1 - containing the case in kinase 1 group.
- CMGC- containing CDK, MAPK, GSK3 and CLK kinases.
- STE - containing the homologs of yeast Sterile 7, Sterile 11, and Sterile 20 kinases.
- TK - containing the tyrosine kinases.
- TKL - containing the tyrosine-kinase like group of kinases.

A protein kinase inhibitor is a type of enzyme inhibitor that can block the action of protein kinases. Protein kinases add a phosphate group to a protein in a process called phosphorylation, which can turn a protein on or off and therefore affect its level of activity and function. Protein kinase inhibitors can be subdivided according to the amino acid on a protein that they add the phosphate to (e.g serine, threonine or tyrosine) in order to inhibit phosphorylation of that amino acid. Kinases mostly act on both serine and threonine, but tyrosine kinase acts on tyrosine only and some dual-specificity kinases act on all three of these amino acid residues. Some protein kinases also phosphorylate other amino acids, such as histidine kinases that act on histidine residues.

*Corresponding author: **Lata C. Potey**
Hi-Tech College of Pharmacy Chandrapur

Phosphorylation is often a required step in the growth of some cancers and inflammatory disorders, meaning inhibition of the enzymes that trigger phosphorylation provides an approach to treating such diseases. One example of a drug being used in this way is the tyrosine kinase inhibitor dasatinib, which is used as an anticancer therapy in several forms of leukemia. Another agent currently being tested in clinical trials for polycystic kidney disease is PLX5568. Tyrosine kinase inhibitors are particularly important agents because these high-affinity cell surface receptors play a critical role in the progression of many cancers.

Tyrosine kinases are involved in various cell functions including cell signalling, cell growth and cell division. In some forms of cancer, these enzymes are present in high levels or overactive and inhibiting them can prevent the proliferation of cancer cells. Tyrosine kinase inhibitors therefore provide an important form of targeted therapy in the fight against cancer.

Growth Factors

Growth factors are chemicals produced by the body that control cell growth. There are many different types of growth factors and they all work in different ways. Some tell cells what type of cells they should become (how they should specialize). Some make cells grow and divide into new cells. Some tell cells to stop growing or to die¹. Growth factors work by plugging in to receptors on the cell surface. This sends a signal to the inside of the cell, which sets off a chain of complicated chemical reactions.

There are a number of different growth factors. Examples include

- Epidermal growth factor (EGF)-controls cell growth
- Vascular endothelial growth factor (VEGF)-controls blood vessel development
- Platelet derived endothelial growth factor (PDGF)-controls blood vessel development and cell growth
- Fibroblast growth factor(FGF)-controls cell growth

Each growth factor works by attaching to the corresponding receptor on the cell surface. For example, EGF binds to epidermal growth factor receptor (EGFR).

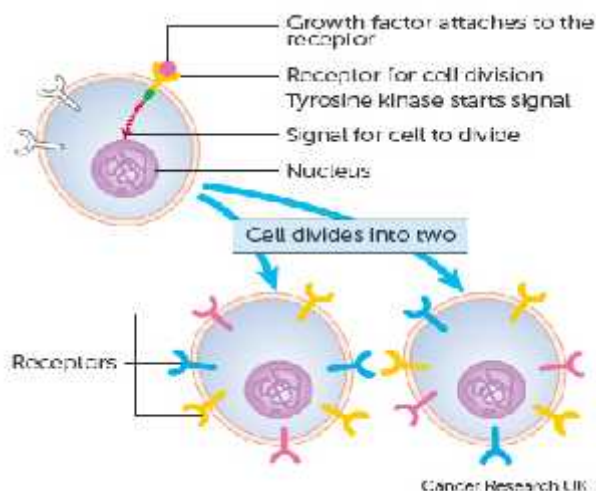


Figure 2 Growth Factors Bind to Receptor Causing Cell Division

A cancer growth blocker blocks the growth factors that trigger the cancer cells to divide and grow. Scientists are looking at different ways of doing this such as

- Lowering levels of the growth factor in the body
- Blocking the growth factor receptor on the cancer cell
- Blocking the signals inside the cell that start up when the growth factor triggers the receptor

Most of these treatments work by blocking the signalling processes that cancer cells use to divide. Cancer cells are often very sensitive to growth factors. So if we can block them, we can stop some types of cancer from growing and dividing. Scientists are developing different inhibitors for the different types of growth factors.

A Tyrosine Kinase Inhibitor (TKI)

These are the pharmaceutical drug that inhibits tyrosine kinases. Tyrosine kinases are enzymes responsible for the activation of many proteins by signal transduction cascades. The proteins are activated by adding a phosphate group to the protein (phosphorylation), a step that TKIs inhibit. TKIs are typically used as anticancer drugs. For example, they have substantially improved outcomes in chronic myelogenous leukemia².

They are also called tyrophostins, the short name for “tyrosinephosphorylation inhibitor”, originally coined in a 1988 publication, which was the first description of compounds inhibiting the catalytic activity of the epidermal growth factor receptor (EGFR). The 1988 study was the first demonstration of a systematic search and discovery of small-molecular-weight inhibitors of tyrosine phosphorylation, which do not inhibit protein kinases that phosphorylateserine or threonine residues and can discriminate between the kinase domains of the EGFR and that of the insulin receptor. It was further shown that in spite of the conservation of the tyrosine-kinase domains one can design and synthesize tyrophostins that discriminate between even closely related protein tyrosine kinases such as EGFR and its close relative HER2.

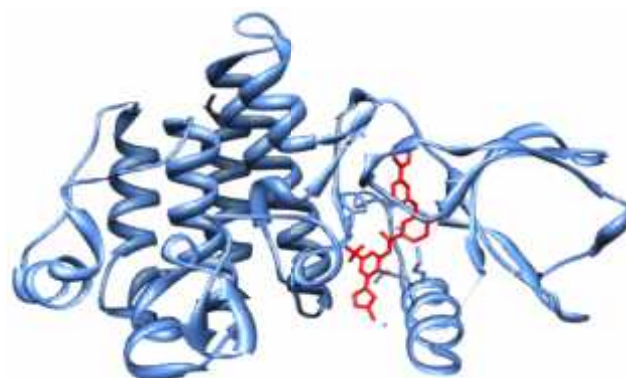


Figure 3 Crystal structure of the second generation Bcr-Abl tyrosine-kinase inhibitor nilotinib (red) in complex with anAbl kinase domain (blue). Nilotinib is used to treat chronic myelogenous leukemia (CML), a hematological malignancy.

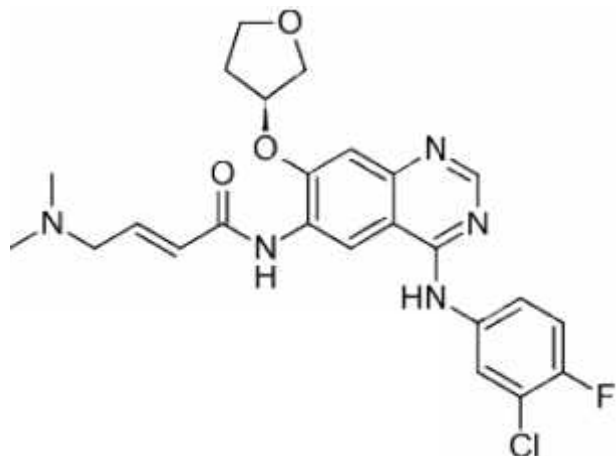
General Mechanism of Action

TKIs operate by four different mechanisms: they can compete with adenosine triphosphate (ATP), the phosphorylating entity, the substrate or both or can act in an allosteric fashion, namely bind to a site outside the active site, affecting its activity by a conformational change.⁵ Recently TKIs have been shown to

deprive tyrosine kinases of access to the Cdc37-Hsp90 molecular chaperone system on which they depend for their cellular stability, leading to their ubiquitylation and degradation.^[9] Signal transduction therapy can in principle also apply for non-cancer proliferative diseases and for inflammatory conditions.^[10] Until now TKIs have not been developed for the treatment of such conditions.

Drugs

AFATINIB



Mechanism of action

Afatinib is a protein kinase inhibitor that also irreversibly inhibits human epidermal growth factor receptor 2 (Her2) and epidermal growth factor receptor (EGFR) kinases. Afatinib is not only active against EGFR mutations targeted by first generation tyrosine-kinase inhibitors (TKIs) like Erlotinib or Gefitinib, but also against mutations such as T790M which are not sensitive to these standard therapies.⁶ Because of its additional activity against Her2, it is being investigated for breast cancer as well as other EGFR and Her2 driven cancers.

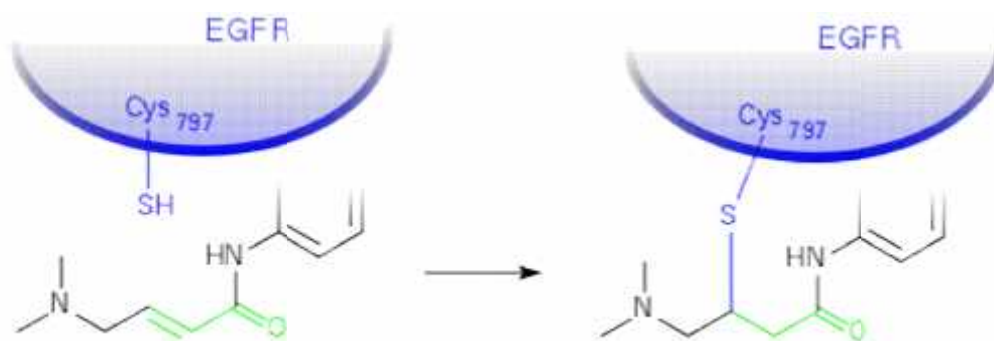
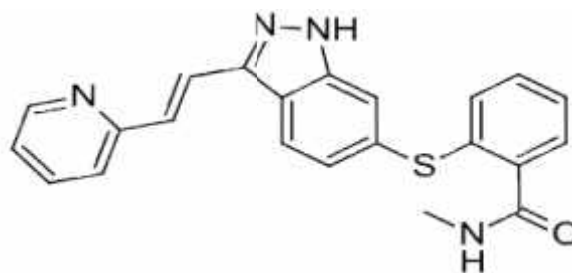


Figure 4 Afatinib binds to cysteine number 797 of the epidermal growth factor receptor (EGFR) via a Michael addition (IC₅₀ = 0.5 nM).[12]

Medical Uses

It has received regulatory approval for use as a treatment for non-small cell lung cancer, although there is emerging evidence to support its use in other cancers such as breast cancer.⁶

AXITINIB



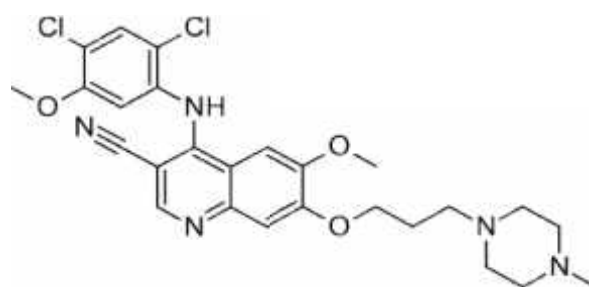
Mechanism of Action

Its primary mechanism of action is thought to be Vascular endothelial growth factor receptor 1-3, c-KIT and PDGFR inhibition, this, in turn, enables it to inhibit angiogenesis (the formation of new blood vessels by tumours).⁷ It was also proposed that it might act by inducing autophagy, as some other tyrosine kinase inhibitors, like sorafenib. It has also been shown to bind (in a different conformation from the VEGF binding) to the BCR-ABL fusion protein, specifically inhibiting the drug-resistant T315I mutant isoform.

Adverse Effects

Diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, hand-foot syndrome, weight decreased, vomiting, asthenia, and constipation are the most common side effects occurring in more than 20% of patients.⁷

BOSUTINIB



Mechanism of action

It is an ATP-competitive Bcr-Abl tyrosine-kinase inhibitor with an additional inhibitory effect on SRC family kinases (including Src, Lyn and Hck).^{[9][10]} Bosutinib inhibited 16 of 18 imatinib-resistant forms of Bcr-Abl expressed in murine myeloid cell lines, but did not inhibit T315I and V299L mutant cells.^[9]

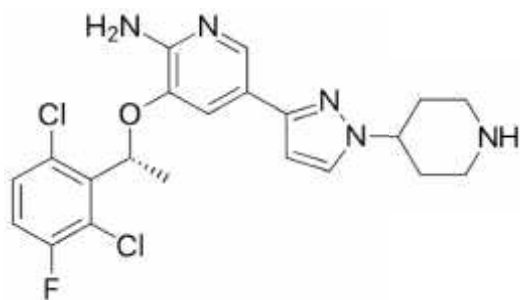
Medical Uses

Bosutinib received US FDA and EU European Medicines Agency approval on September 4, 2012 and 27 March 2013 respectively for the treatment of adult patients with Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) with resistance, or intolerance to prior therapy.

Adverse Effects

- Diarrhoea (~82%)
- Nausea
- Myelosuppression
- Vomiting (~37%)
- Abdominal pain
- Raised ALT
- Raised AST
- Rash
- Arthralgia (joint pain)
- Fever
- Oedema
- Fatigue
- Cough
- Headache
- Reduced appetite
- Respiratory tract infection

CRIZOTINIB



Mechanism of action

Crizotinib has an aminopyridine structure, and functions as a protein kinase inhibitor by competitive binding within the ATP-binding pocket of target kinases. About 4% of patients with non-small cell lung carcinoma have a chromosomal rearrangement that generates a fusion gene between EML4 ('echinoderm microtubule-associated protein-like 4') and ALK ('anaplastic lymphoma kinase'), which results in constitutive kinase activity that contributes to carcinogenesis and seems to drive the malignant phenotype. The kinase activity of the fusion protein is inhibited by crizotinib.⁸ Patients with this gene fusion are typically younger non-smokers who do not have mutations in the epidermal growth factor receptor gene (EGFR). Crizotinib is currently thought to exert its effects through modulation of the growth, migration, and invasion of malignant cells. Other studies suggest that crizotinib might also act via inhibition of angiogenesis in malignant tumors.

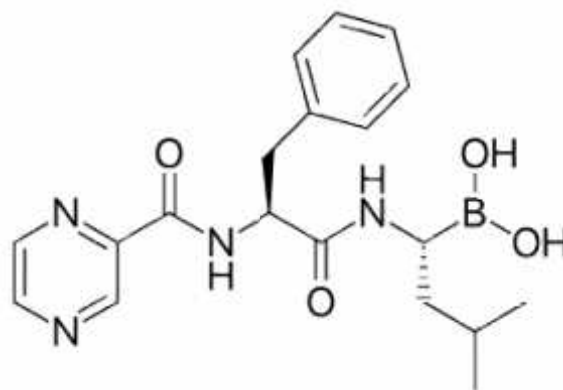
Common side effects

More than 10 in every 100 people have one or more of these.

- Vision changes happen in about 6 out of 10 people (60%) and can include blurred vision, double vision, flashing lights, and seeing dark spots called floaters-let your doctor or nurse know if you have any eyesight changes
- Diarrhoea can happen in up to 6 out of 10 people (60%)-drink plenty of fluids and tell your doctor or nurse if diarrhoea becomes severe, or continues for more than 3 days
- Feeling or being sick occurs in about 5 out of 10 people (50%) but it is usually well controlled with anti sickness medicines
- Constipation happens in about 4 out of 10 people (40%) - your doctor or nurse may give you laxatives to help prevent this but do tell them if you are constipated for more than 3 days
- An increased risk of getting an infection from a drop in white blood cells-it is harder to fight infections and you can become very ill. You may have headaches, aching muscles, a cough, a sore throat, pain passing urine, or you may feel cold and shivery. If you have a severe infection this can be life threatening. Contact your treatment centre straight away if you have any of these effects or if your temperature goes above 38°C
- Loss of appetite happens in more than 2 out of 10 people (27%)
- Tiredness (fatigue) occurs in 2 in 10 people (20%) during and after treatment
- Dizziness
- Taste changes
- Tiredness and breathlessness due to a drop in red blood cells (anaemia)-you may need a blood transfusion
- Fluid buildup-let your doctor or nurse know if you get swollen ankles, indigestion or difficulty in swallowing
- Nerve pain
- Abdominal pain
- A sore mouth happens in 1 out of 10 people (10%)
- Loss of fertility- you may not be able to become pregnant or father a child after treatment with this drug. Talk to your doctor

Proteasome Inhibitors

Proteasomes are tiny, barrel shaped structures found in all cells. They help break down proteins that the cell doesn't need into smaller parts.



The cell can then use them to make new proteins that it does need. Drug treatments that block proteasomes from working are called proteasome inhibitors. They cause a buildup of unwanted proteins in the cell, which makes the cancer cells die¹.

Bortezomib is a proteasome inhibitor used to treat myeloma. You have it as an injection through a tube into a vein.

Bortezomib

Structure

The drug is an N-protected dipeptide and can be written as Pyz-Phe-boroLeu, which stands for pyrazinoic acid, phenylalanine and Leucine with a boronic acid instead of a carboxylic acid. Peptides are written N-terminus to C-terminus, and this convention is used here even though the "C-terminus" is a boronic acid instead of a carboxylic acid.

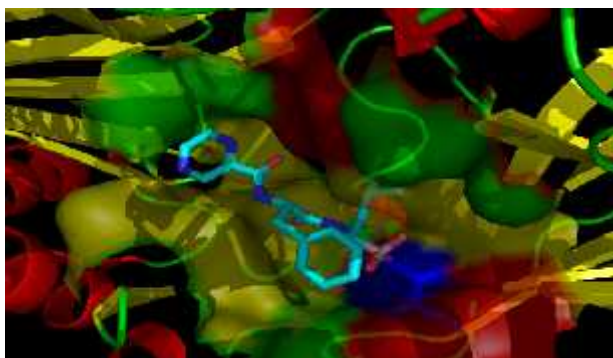


Figure 5 Bortezomib bound to the core particle in a yeast proteasome. The bortezomib molecule is in the center colored by atom type (boron = pink, carbon = cyan, nitrogen = blue, oxygen = red), surrounded by the local protein surface. The blue patch is catalytic threonine residue whose activity is blocked by the presence of bortezomib.

Mechanism of action

The boron atom in bortezomib binds the catalytic site of the 26S proteasome^[6] with high affinity and specificity. In normal cells, the proteasome regulates protein expression and function by degradation of ubiquitylated proteins, and also cleanses the cell of abnormal or misfolded proteins. Clinical and preclinical data support a role in maintaining the immortal phenotype of myeloma cells, and cell-culture and xenograft data support a similar function in solid tumor cancers. While multiple mechanisms are likely to be involved, proteasome inhibition may prevent degradation of pro-apoptotic factors, permitting activation of programmed cell death in neoplastic cells dependent upon suppression of pro-apoptotic pathways.

Recently, it was found that bortezomib caused a rapid and dramatic change in the levels of intracellular peptides that are produced by the proteasome.^[7] Some intracellular peptides have been shown to be biologically active, and so the effect of bortezomib on the levels of intracellular peptides may contribute to the biological and/or side effects of the drug.

Tyrosine kinases as targets for anticancer agents

Protein kinase catalyzed protein phosphorylation, is the most general and frequent mechanism by which almost all cellular function are reversibly regulated. Due to better understanding of pathophysiology of cancer shown that tyrosine kinases found upstream or downstream of epidemiological relevant oncogenes or tumor suppressors, in particular the receptor tyrosine kinases. More attention is given to tyrosine kinase that catalyzes the 49 phosphorylation of specific tyrosine residue¹⁰.

Target Site of action

Inhibiting the activity of tyrosine kinases by low molecular weight compounds capable of interfering with either ligand binding (in the 50 case of receptor tyrosine kinases) or with protein substrate (in 51 case of non receptor tyrosine kinase) has proved to be difficult. Although the bisubstrate inhibitor approach offered promise, but with very little practical progress. Approaches to generate noncompetitive or allosteric inhibitors have also failed. The ATP 52 competitive inhibitors appear to be the target of choice.

References

1. Cancer Research UK.
2. Yaish P, Gazit A, Gilon C, Levitzki A (1988). "Blocking of EGF-dependent cell proliferation by EGF receptor kinase inhibitors". *Science*. 242 (4880): 933-935.
3. Gazit A, Osherov N, Posner I, Yaish P, Poradosu E, Gilon C, Levitzki A (1991). "Tyrophostins. 2. Heterocyclic and alpha-substituted benzylidenemalonitrile tyrophostins as potent inhibitors of EGF receptor and ErbB2/neu tyrosine kinases". *J Med Chem*. 34 (6): 1896-907.
4. Osherov N, Gazit A, Gilon C, Levitzki A (1993). "Selective inhibition of the epidermal growth factor and HER2/neu receptors by tyrophostins". *J Biol Chem*. 268 (15): 11134-42.
5. Bari SB*, Adhikari S, Surana SJ, "Tyrosine Kinase Receptor Inhibitors: A New Target for Anticancer Drug Development", *Journal of Pharma Sci Tech* 2012;

How to cite this article:

Lata C. Potey and Satish Kosalge.2017, Protein Kinase Inhibitors in Cancer Treatment: A Review. *Int J Recent Sci Res*. 8(4), pp. 16379-16383. DOI: <http://dx.doi.org/10.24327/ijrsr.2017.0804.0139>
