Abstract

Protein kinases are enzymes that covalently modify proteins by attaching phosphate groups (from ATP) to serine, threonine, and/or tyrosine residues. In so doing, the functional properties of the protein kinase’s substrates are modified. Protein kinases transduce signals from the cell membrane into the interior of the cell. Such signals include not only those arising from ligand-receptor interactions but also environmental perturbations (i.e., cell stretch or shear stress). Ultimately, the activation of signaling pathways results in the reprogramming of gene expression through the direct regulation of transcription factors or protein translation. Protein kinases regulate most aspects of normal cellular function. The pathophysiological dysfunction of protein kinase signaling pathways underlies the molecular basis of many cancers and of several manifestations of cardiovascular disease, such as hypertrophy, ischemia/reperfusion injury, angiogenesis. Given their roles in such a wide variety of disease states, protein kinases are rapidly becoming extremely attractive targets for drug discovery. The development of selective protein kinase inhibitors that can block or modulate diseases caused by abnormalities in these signaling pathways is widely considered a promising approach for drug development.

Key words: protein kinase, signaling pathway, cell function.

Introduction: Targets: Generally, the "target" is the naturally existing cellular or molecular structure involved in the pathology of interest that the drug-in-development is meant to act on. There is a distinction between "established" and "new" target.
"Established targets" are those for which there is a good scientific understanding, supported by a lengthy publication history, of both how the target functions in normal physiology and how it is involved in human pathology. This does not imply that the mechanism of action of drugs that are thought to act through a particular established targets is fully understood.

"New targets" are all those targets that are not "established targets" but which have been the subject of drug discovery. These typically include newly discovered proteins, or proteins whose function has now become clear as a result of basic scientific research.¹

**Protein Kinase**

A protein kinase is an enzyme that transfers a phosphate group from a donor molecule (usually ATP) to hydroxyl group of amino acid residue of a protein (phosphorylation). Phosphorylation results in conformational change of the target protein and effect the protein function².

Protein kinase act directly by involving a biological response immediately after activation or by initiating branching or linear cascades of signal amplification and integration causing eventual biological response³.

![Figure-1](image)

**Figure-1**

Protein kinases transduce signals from the cell membrane into the interior of the cell. Protein kinases regulate most aspects of normal cellular function. The pathophysiological dysfunction of protein kinase signaling pathways underlies the molecular basis of many cancers and of several manifestations of cardiovascular disease, such as hypertrophy and other types of left ventricular remodeling, ischemia/reperfusion injury, angiogenesis, and atherogenesis⁴.
Mechanism of action

Due to their integrative role of phosphorylating specific proteins essential for modifying different biological processes kinases are involved in a number of “signal transduction mechanisms”\textsuperscript{5,6}.

Signal transduction is the process by which an extracellular signalling molecule activates a membrane receptor that in turn alters the intracellular molecule creating a response\textsuperscript{7}. The chemical signal binds to the outer portion of the receptor, changing its shape and conveying another signal inside the cell\textsuperscript{8}.

The movement of signals can be simple. Upon ligand interaction, allow signals to be passed in the form of small ion movement, either into or out of the cell. These ion movements result in changes in the electrical potential of the cells that, in turn, propagates the signal along the cell\textsuperscript{9}.

More complex signal transduction involves the coupling of ligand-receptor interactions to many intracellular events. These events include phosphorylations by tyrosine kinases and/or serine/threonine kinases. Protein phosphorylations change enzyme activities and protein conformations. The eventual outcome is an alteration in cellular activity and changes in the program of genes expressed within the responding cells\textsuperscript{10}.

![Figure 2- signal transduction](image)

Protein phosphorylation is implicated in proliferation, differentiation, secretion, apoptosis and thus effect cellular response to a variety of hormones, cytokines and neurotransmitters\textsuperscript{11}.
**Regulation:** Kinases are turned on or off by phosphorylation, by binding of activator proteins or inhibitor proteins, or small molecules, or by controlling their location in the cell relative to their substrates; this is via phosphorylation in active centre (intrasterical regulation), by other protein kinases (trans-phosphorylation) or itself (cis-phosphorylation/ autophosphorylation).\(^{13}\)

**Structure:** Eukaryotic protein kinases are enzymes that belong to a very extensive family of proteins that share a conserved catalytic core.\(^{14}\) There are a number of conserved regions in the catalytic domain of protein kinases. In the N-terminal extremity of the catalytic domain there is a glycine-rich stretch of residues in the vicinity of a lysine amino acid, which has been shown to be involved in ATP binding. In the central part of the catalytic domain, there is a conserved aspartic acid, which is important for the catalytic activity of the enzyme.\(^{15,16}\)

![Figure 3-structure of protein kinases](image)

**Chemical activity**

Most kinases act on both serine and threonine, others act on tyrosine, and a number (dual-specificity kinases) act on all three.\(^{17}\) There are also protein kinases that phosphorylate other amino acids, including histidine kinases that phosphorylate histidine residue.\(^{18}\) Protein kinases are specific to both receptor or non-receptor classes of tyrosine and serine/threonine.

**Receptor tyrosine kinase**

- Epidermal growth factor receptor
- Platelet derived growth factor receptor
- Nerve growth factor receptor
- Insulin like growth factor receptor
Non receptor tyrosine kinase

- Src and Src family
- Abl and BCR-Abl
- C-terminal Src kinase

Receptor serine/Threonine kinase

- Transforming growth factor receptor

Non Receptor serine/Threonine kinase

- cAMP dependent protein kinase
- Cyclin dependent kinases (CDK1,CDK2)
- Mitogen activated protein kinases
- Protein kinase-C
- Phosphoinositol-3-kinase

2. TYPES OF PROTEIN KINASES

1. Protein kinase A (PKA)
2. Protein kinase C (PKC)
3. Ca^{2+}/calmodulin dependent protein kinase (CaMK)
4. Mitogen activated protein kinase (MAPK)
5. Tyrosine specific protein kinase
6. Histidine specific protein kinase

1. PROTEIN KINASE A (PKA)

Structure

It consists of two domains, a small domain with several β sheet structures and a larger domain containing several α helices. The binding sites for substrate and ATP are located in the catalytic cleft between the domains (or lobes). When ATP and substrate bind, the two lobes rotate so that the terminal phosphate group...
of the ATP and the target amino acid of the substrate move into the correct positions for the catalytic reaction to take place\textsuperscript{19}.

**Function**

PKA phosphorylates other proteins, altering their function. As protein expression varies from cell type to cell type, the proteins that are available for phosphorylation will depend upon the cell in which PKA is present. Thus, the effects of PKA activation vary with cell type.

**Table -1:**

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Organ/ System</th>
<th>Stimulators ligands --&gt; G\textsubscript{x}-GPCRs or PDE inhibitors</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>myocyte (cardiac muscle)</td>
<td>muscular system</td>
<td>norepinephrine --&gt; β-adrenergic receptor</td>
<td>sequester Ca\textsubscript{2+} in sarcoplasmic reticulum phosphorylates phospholamban\textsuperscript{20}</td>
</tr>
<tr>
<td>hepatocyte</td>
<td>liver</td>
<td>epinephrine --&gt; β-adrenergic receptor glucagon --&gt; Glucagon receptor</td>
<td>produce glucose stimulate glycogenolysis phosphorylate glycogenphosphorylase (activating it) phosphorylate Acetyl-CoA carboxylase (inhibiting it) inhibit glycogenesis phosphorylate glycogen synthase (inhibiting it)\textsuperscript{21}</td>
</tr>
<tr>
<td>principal cells in kidney</td>
<td>kidney</td>
<td>Vasopressin --&gt; V2 receptor theophylline (PDE inhibitor)</td>
<td>exocytosis of aquaporin 2 to apical membrane\textsuperscript{22,23}.</td>
</tr>
</tbody>
</table>
2. PROTEIN KINASE C (PKC)

Protein kinase C is actually a family of protein kinases that require Ca\textsuperscript{2+}, diacylglycerol, and a phospholipid such as phosphatidyl -choline for activation. Thus, protein kinase C is activated through the same signal transduction pathway as phospholipase C.

Structure

Protein kinase C enzymes consist of an N-terminal regulatory domain and a C-terminal catalytic domain. The kinases are inactive in the absence of activating agents, due to autoinhibition of the regulatory domain. They can be activated by tumor promotors such as tetradecanoyl-phorbol-acetate (TPA) or by the cofactors Ca\textsuperscript{2+}, diacylglycerol, and a phospholipid

**Function:** A multiplicity of functions have been ascribed to PKC. PKC is involved in receptor desensitization, in modulating membrane structure events, in regulating transcription, in mediating immune responses, in regulating cell growth, and in learning and memory.

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Organ/system</th>
<th>Activators</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smooth muscle cell (vascular)</td>
<td>Circulatory system</td>
<td>5-HT → 5-HT2A receptor</td>
<td>Vasoconstriction\textsuperscript{23}</td>
</tr>
<tr>
<td>Smooth muscle cell (GI tract)</td>
<td>Digestive system</td>
<td>5-HT → 5-HT2A/5HT2B receptor</td>
<td>Contraction\textsuperscript{24,25}</td>
</tr>
<tr>
<td>Neurons in CNS</td>
<td>Nervous system</td>
<td>5-HT → 5-HT2A receptor</td>
<td>Neuronal excitation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acetyl choline → M1 receptor</td>
<td>Memory\textsuperscript{26,27}</td>
</tr>
</tbody>
</table>

Table 2
3. **Ca\textsuperscript{2+}/CALMODULIN –DEPENDENT PROTEIN KINASE(CaMK)**

Also called \textit{CaM kinase} regulated by the Ca\textsuperscript{2+}/calmodulin complex. These kinases show a memory effect on activation. Two types of CaM kinases are:

- **Specialized CaM kinases.** An example is the myosin light chain kinase (MLCK) that phosphorylates myosin, causing muscles to contract.

- **Multifunctional CaM kinases.** Also collectively called \textit{CaM kinase II}, which play a role in many processes, such as neurotransmitter secretion, transcription factor regulation, and glycogen metabolism.

**Structure**

The CaM kinases consist of an N-terminal catalytic domain, a regulatory domain, and an associative domain. In the absence of Ca\textsuperscript{2+}/calmodulin, the catalytic domain is autoinhibited by the regulatory domain, which contains a pseudosubstrate sequence. Upon activation by Ca\textsuperscript{2+}/calmodulin, the activated CaM kinases autophosphorylate each other in an intermolecular reaction\textsuperscript{28}.

**Function**

Due to its ability for autophosphorylation, CaMK activity can outlast the intracellular calcium transient that is needed to activate it. In neurons, this property is important for the induction of synaptic plasticity. Pharmacological inhibition of CaMKII blocks the induction of long-term potentiation. Upon activation, CaMKII phosphorylates postsynaptic glutamate receptors and thus changes the electrical properties of the synapse\textsuperscript{28}.

4. **MITOGEN ACTIVATED PROTEIN (MAP) KINASE**

Mitogen-activated protein kinases (are serine/threonine-specific protein kinases that respond to extracellular stimuli (mitogens, osmotic stress, heat, shock and pro-inflammatory cytokines) and regulate various cellular activities, such as gene expression, mitosis, differentiation, proliferation, and cell survival/apoptosis\textsuperscript{29}.
Activation: MAP kinases are activated within the protein kinase cascades called “MAPK cascade”. Each one consists of three enzymes, MAP kinase, MAP kinase kinase (M KK, MEK, or MAP2K) and MAP kinase kinase kinase (MKKK, MEKK or MAP3K) that are activated in series.

5. **TYROSINE SPECIFIC PROTEIN KINASES**

Tyrosine-specific protein kinases phosphorylates tyrosine amino acid residue and like serine/threonine-specific kinases are used in signal transduction. They act primarily as growth factor receptors; some examples:

- Platelet derived growth factor (PDGF) receptor;
- Epidermal growth factor (EGF) receptor;
- Insulin receptor and insulin-like growth factor (IGF1) receptor.

Structure

Included in a number of the structural features that can be recognized in all protein tyrosine kinases are an ATP binding site, three residues that are thought to be associated with the function of the third phosphate group (often called the gamma-phosphate group) of an ATP molecule bound to the enzyme, and a possible catalytic site of the enzyme that is an amino acid. Also very common among protein tyrosine kinases are two peptide sequences.

Function

Tyrosine kinases function in a variety of processes, pathways, and actions, and is responsible for key events in the body. The receptor tyrosine kinases function in transmembrane signaling, whereas tyrosine kinases within the cell function in signal transduction to the nucleus. Tyrosine kinase activity in the nucleus involves cell-cycle control and properties of transcription factors. In this way, in fact, tyrosine kinase activity is involved in mitogenesis, or the induction of mitosis in a cell; proteins in the cytosol and proteins in the nucleus are phosphorylated at tyrosine residues during this process.

6. **HISTIDINE-SPECIFIC PROTEIN KINASE**

Histidine kinases are structurally distinct from most other protein kinases and are found mostly in prokaryotes as part of two-component signal transduction mechanisms. A phosphate group from ATP is first
added to a histidine residue within the kinase, and later transferred to an aspartate residue on a 'receiver domain' on a different protein, or sometimes on the kinase itself. The aspartyl phosphate residue is then active in signaling.

SCREENING AND DESIGN

Drug discovery involves screening and design against a chosen or biological target.

Screening: The process of finding a new drug against a chosen target for a particular disease usually involves high-throughput screening (HTS), wherein large libraries of chemicals are tested for their ability to modify the target. For example, if the target is a protein kinase, the chemicals will be tested for their ability to inhibit that kinase.

Another important function of HTS is to show how selective the compounds are for the chosen target. The ideal is to find a molecule which will interfere with only the chosen target, but not other, related targets. To this end, other screening runs will be made to see whether the "hits" against the chosen target will interfere with other related targets - this is the process of cross-screening. Cross-screening is important, because the more unrelated targets a compound hits, the more likely that off-target toxicity will occur with that compound.

It is more often observed that several compounds are found to have some degree of activity, and if these compounds share common chemical features, one or more pharmacophores can be developed. At this point, medicinal chemists will attempt to use structure-activity relationships (SAR) to improve certain features of the lead compound:

- increase activity against the chosen target
- improve the "drug-like" or ADME properties of the molecule.
- reduce activity against unrelated target

HTS is a commonly used method for novel drug discovery. It is often possible to start from a molecule which already has some of the desired properties. Such a molecule might be extracted from a natural product or even be a drug on the market. Other methods, such as virtual high throughput screening, where screening is done using computer-generated models.
Design

Drug design, also sometimes referred to as rational drug design, which is the inventive process of finding new medications based on the knowledge of the biological target\textsuperscript{36}. The drug is most commonly an organic small molecule which activates or inhibits the function of a biomolecule such as a protein which in turn results in a therapeutic benefit to the patient.

In the most basic sense, drug design involves design of small molecules that are complementary in shape and charge to the biomolecular target to which they interact and therefore will bind to it\textsuperscript{37}.

There are two types of drug design:

- Ligand based drug design
- Structure based drug design

**Ligand based**

Ligand-based drug design (or indirect drug design) relies on knowledge of other molecules that bind to the biological target of interest. These other molecules may be used to derive a pharmacophore model which defines the minimum necessary structural characteristics a molecule must possess in order to bind to the target\textsuperscript{38}. Alternatively, a quantitative structure-activity relationship (QSAR) in which a correlation between calculated properties of molecules and their experimentally determined biological activity may be derived. These QSAR relationships in turn may be used to predict the activity of new analogs.

![Figure 4 - Flow charts of two strategies of structure-based drug design](image-url)

*Figure 4 - Flow charts of two strategies of structure-based drug design*
Structure-based drug design (or **direct drug design**) relies on knowledge of the three-dimensional structure of the biological target obtained through methods such as x-ray crystallography or NMR spectroscopy. If an experimental structure of a target is not available, it may be possible to create a homology model of the target based on the experimental structure of a related protein.

Using the structure of the biological target, candidate drugs that are predicted to bind with high affinity and selectivity to the target may be designed using interactive graphics.

**INHIBITORS**

Inhibitor molecules bind to enzymes to reduce their activity. Reducing enzyme activity can disable a pathogen or correct an incorrectly functioning system; as such, many enzyme inhibitors are developed to be used as drugs for the general public.

**Protein kinase inhibitors:** A protein kinase inhibitor is a type of enzyme inhibitor that specifically blocks the action of one or more protein kinases. Hence, they can be subdivided or characterised by the amino acids whose phosphorylation is inhibited: most kinases act on both serine and threonine, the tyrosine kinases act on tyrosine, and a number (dual-specificity kinases) act on all three. There are also protein kinases that phosphorylate other amino acids, including histidine kinases that phosphorylate histidine residues.

Currently there are several drugs launched or in development that target protein kinases and the receptors that activate them:

<table>
<thead>
<tr>
<th>Name</th>
<th>Target</th>
<th>Company</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>VEGF</td>
<td>Genentech</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>BIBW 2992</td>
<td>EGFR/Erb2</td>
<td>Boehringer Ingelheim</td>
<td>Small molecule</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Erb1</td>
<td>Imclone/BMS</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Bcr-Abl</td>
<td>Novartis</td>
<td>Small molecule</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Erb2</td>
<td>Genentech/Roche</td>
<td>Monoclonal antibody</td>
</tr>
</tbody>
</table>
### Tyrosine-kinase inhibitors (TKI)

A tyrosine-kinase inhibitor (TKI) is a pharmaceutical drug that inhibits tyrosine kinases, enzymes responsible for the activation of signal transduction cascades (through phosphorylation of various proteins). TKIs are typically used as anti-cancer drugs. They are also called “tyrphostins”.$^{45}$

Tyrphostins 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. Signal transduction therapy can in principle also apply for non-cancer proliferative diseases and for inflammatory conditions.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target(s)</th>
<th>Company</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>EGFR</td>
<td>AstraZeneca</td>
<td>Small molecule</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>VEGF</td>
<td>Genentech</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>Pegaptanib</td>
<td>VEGF</td>
<td>OSI/Pfizer</td>
<td>RNA Aptamer</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>multiple targets</td>
<td>Onyx/Bayer</td>
<td>Small molecule</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>multiple targets</td>
<td>BMS</td>
<td>Small molecule</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>multiple targets</td>
<td>Pfizer</td>
<td>Small molecule</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Erb1</td>
<td>Genentech/Roche</td>
<td>Small molecule</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>Bcr-Abl</td>
<td>Novartis</td>
<td>Small molecule</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Erb1/Erb2</td>
<td>GSK</td>
<td>Small molecule</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>EGFR</td>
<td>Amgen</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>RET/VEGFR/EGFR</td>
<td>AstraZeneca</td>
<td>Small molecule</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>VEGFR2/PDGFR/c-kit</td>
<td>GlaxoSmithKline</td>
<td>Small molecule</td>
</tr>
<tr>
<td>Mubritinib</td>
<td></td>
<td>Takeda</td>
<td>Small molecule</td>
</tr>
</tbody>
</table>

**Table 3**
TKI are some specific kind of proteins that forward the message by adding phosphate group to special aminoacids in the chains to carry on the whole system. Its command over communication process gives an immense action in terms of controlling the cellular structure, cell communication, & cell growth while turning them “on” & simultaneously allowing them to perform their individual tasks.

1. **APPLICATIONS**

   **a. In the treatment of cancer**

   Tyrosine kinases are particularly important today because of their implications in the treatment of cancer. A mutation that causes certain tyrosine kinases to be constitutively active has been associated with several cancers.

   Enhanced activity, of the enzyme has been implicated in the dearrangement of the function of certain systems, such as cell division. Also included are numerous diseases related to local inflammation such as atherosclerosis and psoriasis, or systemic inflammation such as sepsis and septic shock.

   Research has shown that protein phosphorylation occurs on residues of tyrosine by both transmembrane receptor- and membrane-associated protein tyrosine kinases in normal cells. Phosphorylation plays a significant role in cellular signalling that regulates the number and variety of growth factors.

   Incorrect tyrosine kinase function can lead to non-small cell lung cancer. BCR-ABL is a constitutively activated tyrosine kinase that is associated with chronic myeloid leukemia. It is possible that an inhibitor of tyrosine kinase could be a viable option for the treatment of cancers. In this case, Gefitinib is the inhibitor of cancer.

   The successful agent that inhibits the protein kinases without targeting the ATP binding sites are monoclonal antibodies such as Trastuzumab.

   **b. In the treatment of cardiac diseases**

   CaMKII inhibition is effective in suppressing arrhythmias, as well as reducing hypertrophic response upon inhibition of the CaMKII δC isoform indicating that inhibition of CaMKII, particularly the δC isoform, would reduce cardiac dysfunction which also inhibit calcineurin because of its involvement in cardiac dysfunction.
Activation of Protein kinase C (PKC) in diabetic cardiomyopathy and cardiac hypertrophy reveals that different PKC inhibitors may prevent these diseases as some of these agents have been found effective in attenuating abnormal cardiomyocyte function. However, inhibition of the PKC-ε isoform would also prevent its cardioprotective effects whereas inhibition of the PKC-δ isoform may augment cardioprotection.

Although delaying the development of cardiac dysfunction in HF and prevention of cardiac hypertrophy have been demonstrated upon inhibiting PI3K, it is emphasized that this signal transduction pathway is mainly involved in cardioprotection and thus its enhancement by various interventions has the potential for therapeutic use. Finally, p38 MAPK inhibition has been shown to prevent cardiac remodeling, increase resistance to I/R injury, and improve myocardial function.

Tyrosine kinase-mediated phosphorylation has also been noted to attenuate apoptosis during cardioprotection which was prevented by its non-specific inhibitor, genistein. From this it is important to emphasize that inhibition of different protein kinase targets may prevent their cardioprotective effects.

c. In anti-diabetic chemotherapy

AMPK is a global target as it regulates different diversified signals in metabolic pathways. On the basis of the merits associated with this target, an ideal AMPK activator is expected to increase muscle glucose transport and muscle insulin sensitivity; enhance fat oxidation in muscle and liver; inhibit hepatic gluconeogenesis; decrease cholesterol and triglyceride synthesis in liver and should be devoid of problems associated with present antidiabetic drugs (gastrointestinal problem, body weight increase, etc.).

Three different kinds of AMPK activators have been reported so far. First, PPARγ activators, rosiglitazone and pioglitazone, which activate AMPK without direct binding but by increasing cellular AMP/ATP ratio. Second, AICAR, an analogue of natural activator AMP, which activates AMPK through direct binding followed by allosteric modification. Lastly, metformin, anAMPK activator which does not affect AMP/ATP ratios or bind to AMPK, but acts through an unknown mechanism.

**DRUGS THAT ACT AS PROTEIN KINASE INHIBITORS**

- IMATINIB
- SUNITINIB
- DASATINIB
- GEFITINIB
- NILOTINIB

IMATINIB\textsuperscript{57}

**Description:** agents that act by inhibiting particular tyrosine kinase enzymes, instead of non-specifically inhibiting rapidly dividing cells.

**Structure**

![Chemical structure of IMATINIB](image)

**Categories**
- Antineoplastic Agents
- Protein Kinase Inhibitor

**IUPAC name**

N-(4-methyl-3-\{4-(pyridin-3-yl)pyrimidin-2-yl\}amino)phenyl)-4-[(4-methylpiperazin-1-yl)methyl]benzamide.

**Indication**

For the treatment Philadelphia chromosome positive chronic myeloid leukaemia and malignant gastrointestinal stromal tumors (GIST).

**Mechanism of action**

![Diagram of IMATINIB's mechanism of action](image)

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**Figure 5**
In chronic myelogenous leukemia, the Philadelphia chromosome leads to a fusion protein of abl with bcr (breakpoint cluster region), termed bcr-abl. As this is now a constitutively active tyrosine kinase, imatinib is used to decrease bcr-abl activity. Imatinib works by binding close to the ATP binding site of bcr-abl, locking it in a closed or self-inhibited conformation, and therefore inhibiting the enzyme activity of the protein semi-competitively. This fact explains why many BCR-ABL mutations can cause resistance to imatinib by shifting its equilibrium toward the open or active conformation. Imatinib also inhibits the abl protein of non-cancer cells but cells normally have additional redundant tyrosine kinases which allow them to continue to function even if abl tyrosine kinase is inhibited.

Toxicity

Side effects include nausea, vomiting, diarrhea, loss of appetite, dry skin, hair loss, swelling (especially in the legs or around the eyes) and muscle cramps.

Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Increased hepatic toxicity of both agents.</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Clarithromycin, may increase the serum concentration of imatinib.</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Erythromycin may increase the serum concentration of imatinib.</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>The imidazole increases the levels of imatinib.</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>The imidazole increases the levels of imatinib.</td>
</tr>
</tbody>
</table>

**SUNITINIB**

Description

Sunitinib is an oral, multi-targeted receptor tyrosine kinase (RTK) inhibitor used for the treatment of renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumor (GIST). It inhibits cellular signaling by targeting multiple RTKs. These include all platelet-derived growth factor receptors (PDGF-R) and vascular endothelial growth factor receptors (VEGF-R).
Angiogenesis Inhibitors and Antineoplastic agents

Structure

![Chemical Structure](image)

IUPAC Name

N-[2-(diethylamino)ethyl]-5-{|[(3Z)-5-fluoro-2-oxo-2,3-dihydro-1H-indol-3-ylidene]methyl}|-2,4-dimethyl-1H-pyrrole-3-carboxamide.

Mechanism of action

Sunitinib is a small molecule that inhibits multiple RTKs, some of which are implicated in tumor growth, pathologic angiogenesis, and metastatic progression of cancer. Sunitinib was evaluated for its inhibitory activity against a variety of kinases (>80 kinases) and was identified as an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). Sunitinib inhibition of the activity of these RTKs has been demonstrated in biochemical and cellular assays, and inhibition of function has been demonstrated in cell proliferation.

Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Possible decrease in sunitinib levels.</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Possible increase in sunitinib levels.</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Possible decrease in sunitinib levels.</td>
</tr>
</tbody>
</table>
Itraconazole Possible increase in sunitinib levels.
Ketoconazole Possible increase in sunitinib levels.
Phenobarbital Possible decrease in sunitinib levels.

**DASATINIB**

**Description:** Dasatinib is an oral dual BCR/ABL and Src family tyrosine kinase inhibitor approved for use in patients with chronic myelogenous leukemia (CML). The main targets of Dasatinib, are BCRABL, SRC, Ephrins and GFR.

**Category**
- Protein Kinase Inhibitor

**Structure**

![Structure of Dasatinib](image)

**IUPAC Name**

N-(2-chloro-6-methylphenyl)-2-\{(6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-yl)amino\}-1,3-thiazole-5-carboxamide.

**Mechanisms of action:** Dasatinib, at nanomolar concentrations, inhibits the following kinases: BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EPHA2, and PDGFRβ. Based on modeling studies, dasatinib is predicted to bind to multiple conformations of the ABL kinase. In vitro, dasatinib was active in leukemic cell lines representing variants of imatinib mesylate sensitive and resistant disease. Dasatinib inhibited the growth of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) cell lines overexpressing BCR-ABL.
Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>Omeprazole may decrease the serum level of Dasatinib.</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Phenobarbital may decrease the serum level and efficacy of dasatinib.</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Phenytoin may decrease the serum level and efficacy.</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>Ranitidine may decrease the serum level of dasatinib.</td>
</tr>
</tbody>
</table>

**GEFITINIB**

**Description**

Gefitinib is a drug used in the treatment of certain types of cancer. gefitinib selectively targets the mutant proteins in malignant cells. It is marketed by AstraZeneca.

**Structure**

![Gefitinib Structure](image)

**Categories**

- Antineoplastic Agents
- Protein kinase inhibitors

**IUPAC Name**

N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(morpholin-4-yl)propoxy]quinazolin-4-amine.

**Mechanism of action:** Gefitinib inhibits the epidermal growth factor receptor (EGFR) tyrosine kinase by binding to the adenosine triphosphate (ATP)-binding site of the enzyme. Thus the function of the EGFR tyrosine kinase in activating the Ras signal transduction cascade is inhibited; and malignant cells are inhibited. EGFR is overexpressed (lung and breast cancers) leads to inappropriate activation of the apoptotic Ras signal transduction cascade, eventually leading to uncontrolled cell proliferation.
Toxicity

The acute toxicity of gefitinib up to 500 mg in clinical studies has been low. Symptoms of overdose include diarrhea and skin rash.

Drug interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butobarbital</td>
<td>The CYP3A4 inducer, butobarbital, may decrease the serum concentration and therapeutic effects of gefitinib.</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>This CYP3A4 inhibitor increases levels/toxicity of gefitinib.</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>This CYP3A4 inhibitor increases levels/toxicity of Gefitinib.</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>This potent CYP3A4 inhibitor increases levels/toxicity of gefitinib.</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>This CYP3A4 inhibitor increases levels/toxicity of gefitinib.</td>
</tr>
</tbody>
</table>

**NILOTINIB**

Description

Nilotinib, also known as AMN107, is a tyrosine kinase inhibitor under investigation as a possible treatment for chronic myelogenous leukemia (CML). nilotinib has a relatively favorable safety profile and shows activity in cases of CML resistant to treatment with imatinib.

Structure

![Structure diagram](image-url)
Categories

- Anti cancer agent

Mechanism of action

Chronic myelogenous leukaemia (CML) is caused by the BCR-ABL oncogene. Nilotinib inhibits the tyrosine kinase activity of the BCR-ABL protein. Nilotinib fits into the ATP-binding site of the BCR-ABL protein with higher affinity than imatinib, over-riding resistance caused by mutations. The ability of AMN107 to inhibit TEL-platelet-derived growth factor receptor-beta (TEL-PDGFRbeta), which causes chronic myelomonocytic leukaemia, suggests potential use of AMN107 for myeloproliferative diseases characterised by these kinase fusions. AMN107 also inhibits the c-Kit receptor kinase, at pharmacologically achievable concentrations, supporting potential utility in the treatment of mastocytosis, and gastrointestinal stromal tumours.

Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus</td>
<td>May cause additive QTc-prolonging effects.</td>
</tr>
<tr>
<td></td>
<td>Concomitant therapy is contraindicated.</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>decrease the therapeutic effect of Tamoxifen by Decreasing the production of active metabolites.</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>May cause additive QTc-prolonging effects.</td>
</tr>
<tr>
<td></td>
<td>Concomitant therapy should be avoided.</td>
</tr>
<tr>
<td>Toremifene</td>
<td>May cause additive QTc-prolonging effects.</td>
</tr>
<tr>
<td></td>
<td>Concomitant therapy is contraindicated.</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Nilotinib may decrease the effect of tramadol by decreasing active metabolite production.</td>
</tr>
</tbody>
</table>

Conclusion

Kinase inhibitors described above illustrate the potential of signal transduction in drug discovery where understanding of cell biology events has allowed to identify druggable targets which play a critical role in
diseases for which chemists are able to design potent and selective inhibitors with promising therapeutic applications. The drug discovery strategy has enormous potential since, on one hand proteins that will be identified as key players in pathological conditions which will be up or down regulated directly or indirectly by kinases. On other hand the design and synthesis of selective potent cell permeable drug like inhibitors of kinases is within the scope of chemists current expertise.

References


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44. http://www.nature.com/nrd/journal/v8/n9/full/nrd2871.html "Factors underlying sensitivity of cancers to small-molecule kinase inhibitors".


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