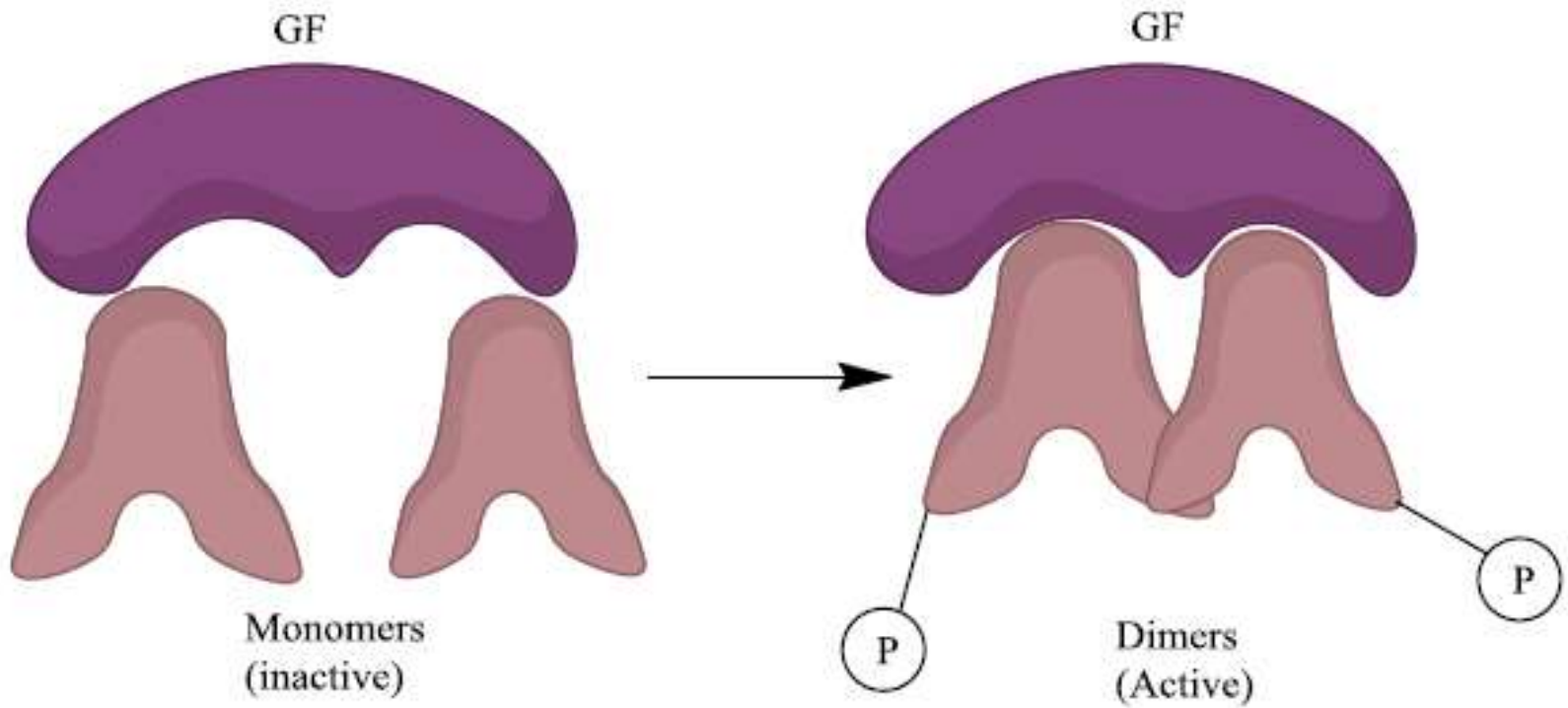
Tyrosine kinase inhibitors

- They are new agents, the first one was in 2000, and they were developed under more detailed understanding of cancer.
- The third group of anticancer agents is "Protein Tyrosine Kinase Inhibitors (PTKIs)", which are discovered recently.
- Protein Tyrosine Kinase receptors are growth factor receptors that bind to Growth factors released by damaged cells to promote the multiplication of nearby cells.
- Upon binding, PTK receptors will be activated by "Dimerization" and then "TransPhosphorylation" to phosphorylate other enzymes. The question now how these receptors are involved in cancers?

- If we looked closely at these receptors, they are membrane receptors (integral proteins). At resting state (inactive state) they are monomers, if they got attached to a growth factor they become dimers (Dimerization by the growth factor), this process makes the two forms approach each other a close distance , and each one phosphorylates the other (trans phosphorylation)


GF
GF
Monomers
(inactive)
P
P
Dimers
(Active)

- The phosphorylated form of the receptor is now active and phosphorylates other
- proteins & enzymes, once that happens, a sequence of phosphorylation starts (EX: Enzyme A then B,C..) which finally gets to the nucleus of the cell and cause propagation of signaling of multiplication .

Tyrosine Kinase Inhibitors

- MOA
- • Deregulated tyrosine kinase (TK) activity is associated with many neoplastic diseases. Inhibiting the enzyme halts TK-induced cell division and antiapoptotic actions.
- • TKs are classified as receptor-associated and cellular (nonreceptor). TK targets for antineoplastic tyrosine kinase inhibitors (TKIs) include EGFR, VEGFR, HER2, PDGRF, and Bcr-Abl.
- • Bcr-Abl is a cellular TK.

- Some cells are able to produce their own growth factors and stimulate their own growth this is called autocrine stimulation:
- For example
- Glioblastomas produce Platlet Derived Growth Factors or PDGF
- Sarcomas produce Tumor Growth Factor Alpha or TGF α as well as Epidermal Growth Factor Receptor (EGFR)

- "BCR-ABL Kinase" is an example; and CML (chronic myelocytic leukemia) is the result of its mutation. More than 90% of CML cases are caused by a chromosomal abnormality that causes the formation of a so-called Philadelphia chromosome, the ligand is co-transcripted with the receptor and the complex produced causes permanent switching on to the receptor. Other examples are: KIT, JAK1 (involved in some blood cancers), JAK2, JAK3, and FGFR1 (involved in certain leukemia's).

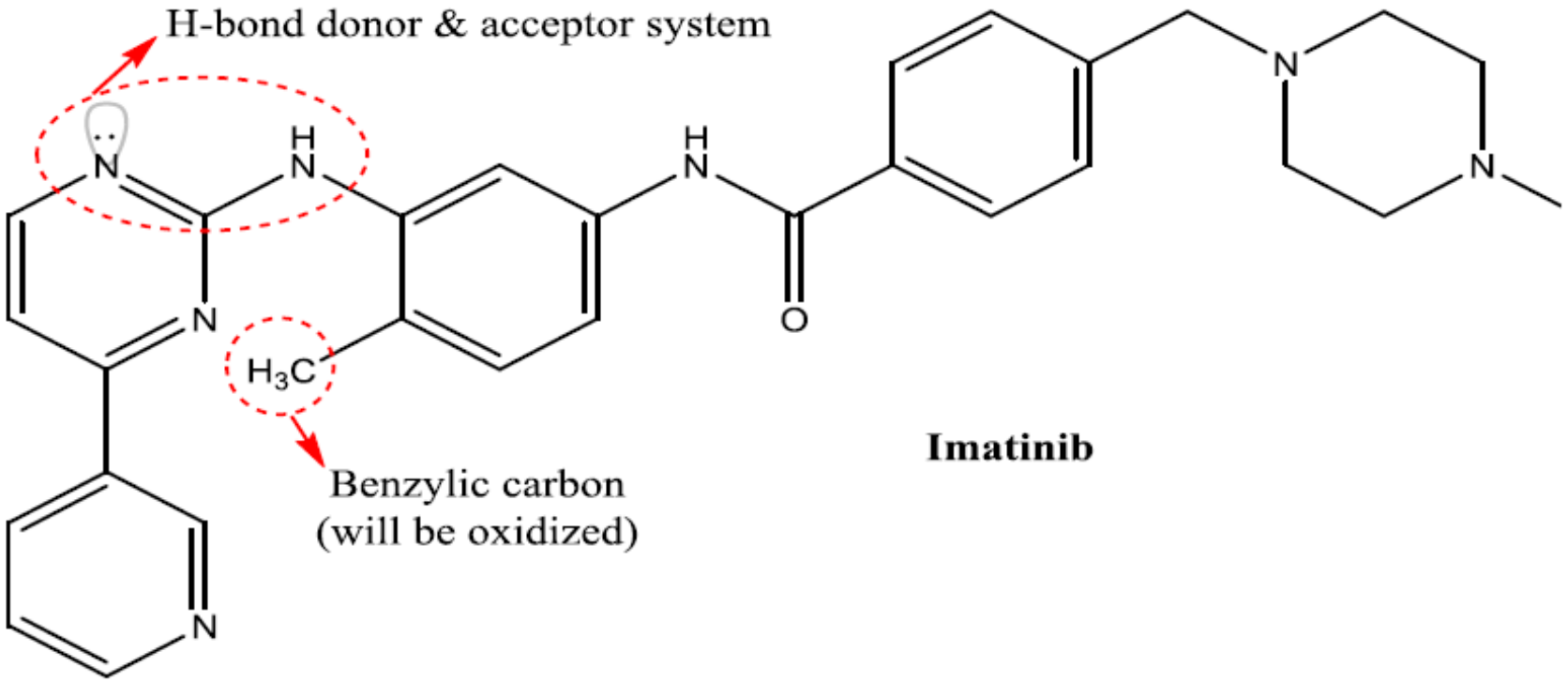
- All of TK receptor to work needs transphosphorylation (mentioned above);
- phosphorylation needs ATP ;), so! We need an ATP analogue that competes with ATP in these receptor’s binding sites.
- We can do nothing to stop the Growth factor! First it's a large protein and

even if we did! It will get inactivated by peptidases.

- Protein tyrosine kinase inhibitors have an advantage which is:
- Less side affects those traditional anticancer agents, NO bone marrow

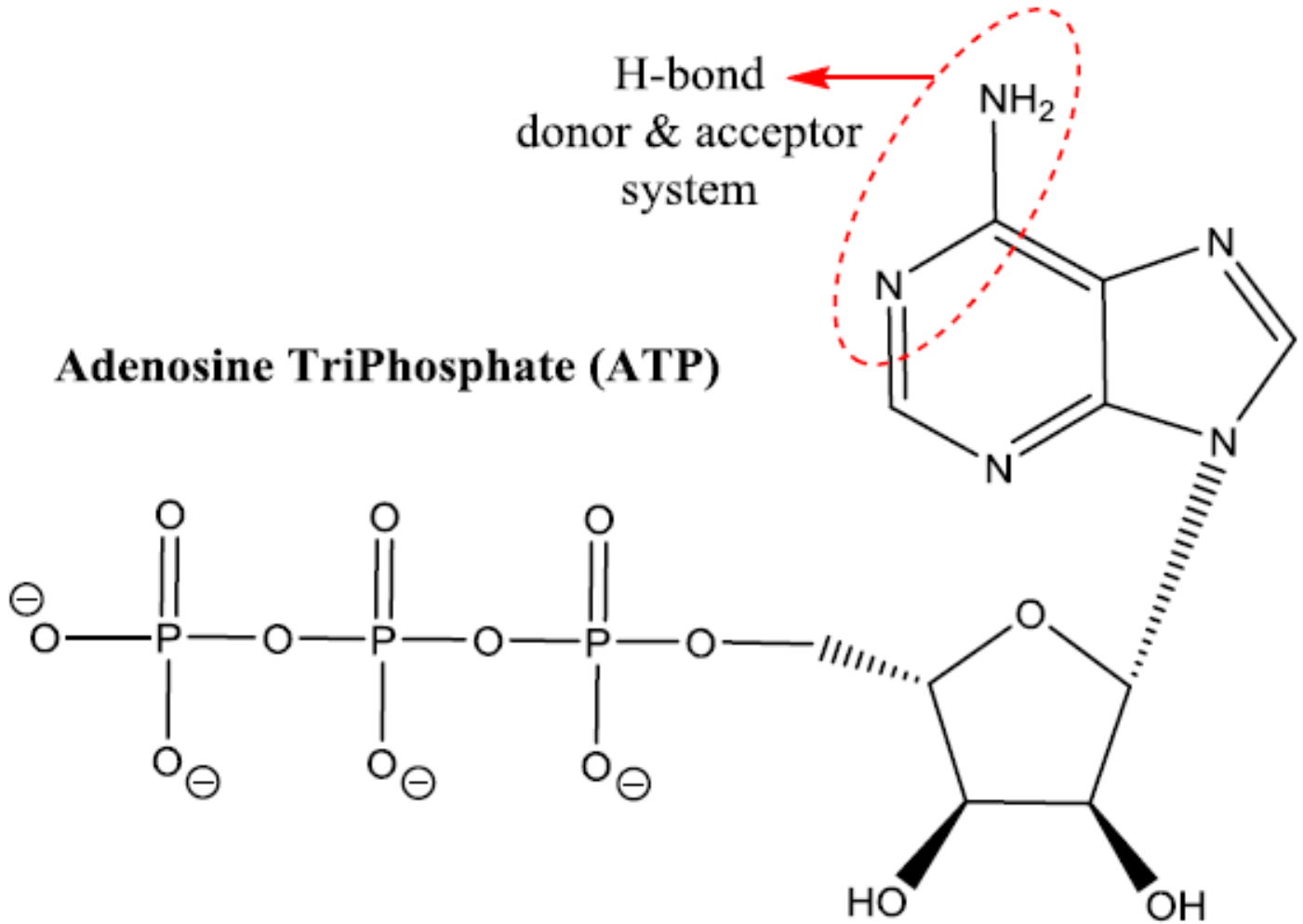
suppression, GI bleeding, hair loss or the overall toxicity

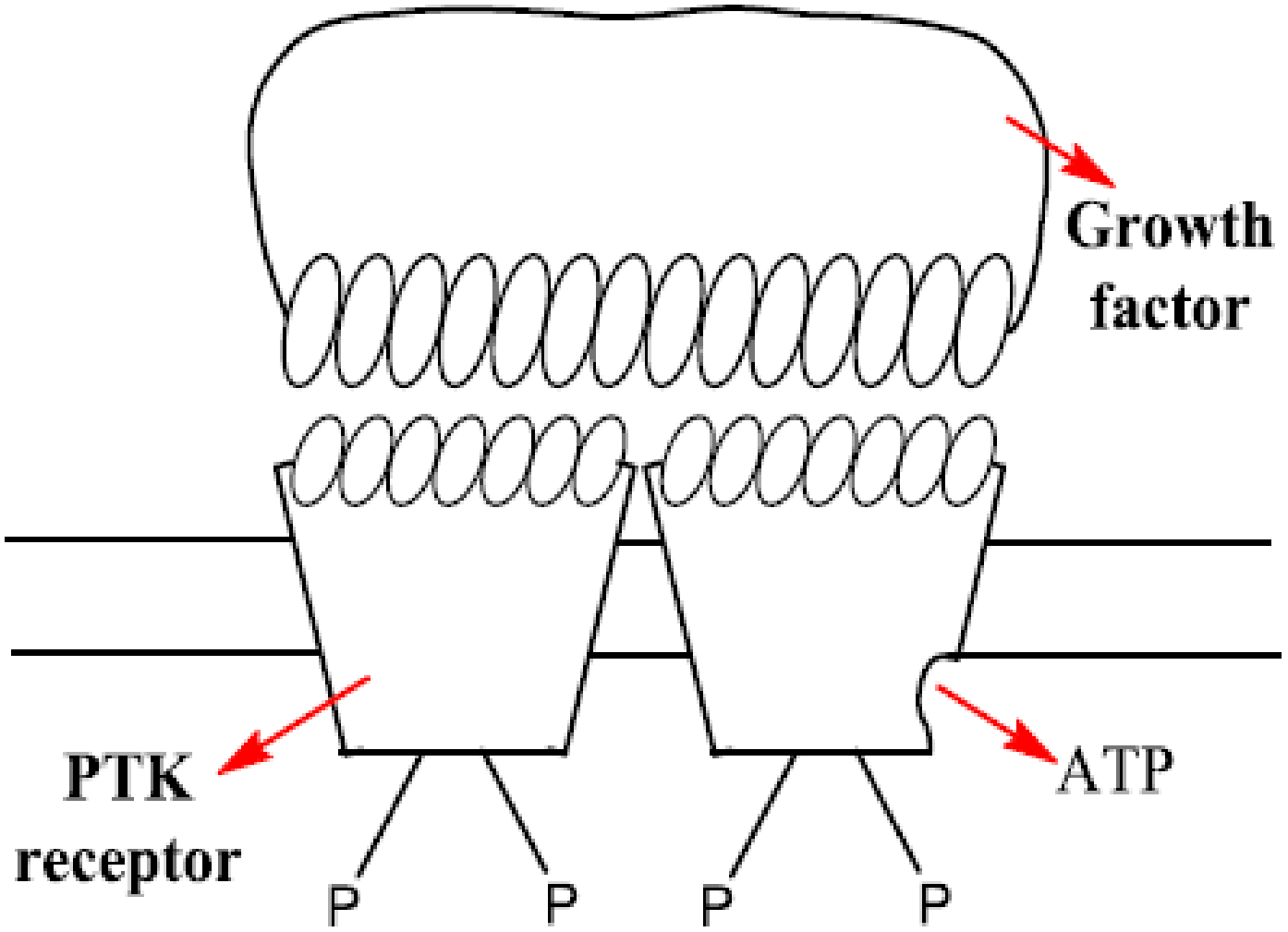
"Imatinib", Gleevec® is the first one.



Look at its structure, you will see a signature found in all of PTKIs which is the system of hydrogen bond donor and acceptor, this system makes these inhibitors compete with ATP at the binding pocket of the PTK receptors because ATP molecules also have this system.

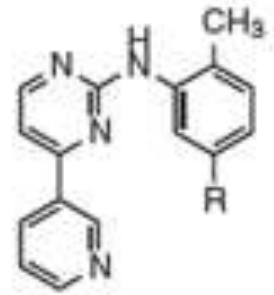
n better tolerated.



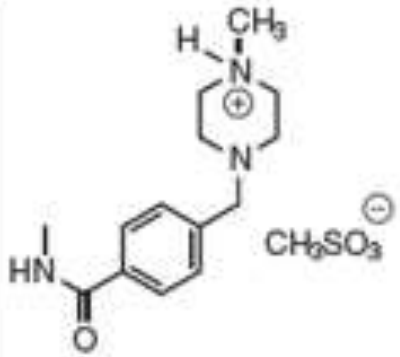

Growth
factor
PTK
receptor
ATP
P
P
P
P

- • TKIs bind to the ATP-binding domain of their specific TK enzyme.
- • Type 1 inhibitors bind to the active conformation.
- Type 2 inhibitors have highest affinity for the inactive conformation.
- • Type 2 inhibitors show the greater TK selectivity.
- • The TKI binding site is primarily hydrophobic and spans a “hinge region” that connects the N and C termini of the protein.
- • The binding site residues of several TKIs have been identified. (For specifics, refer to Figure 37.49, Chapter 37 in *Foye’s Principles of Medicinal Chemistry, Seventh Edition.*)

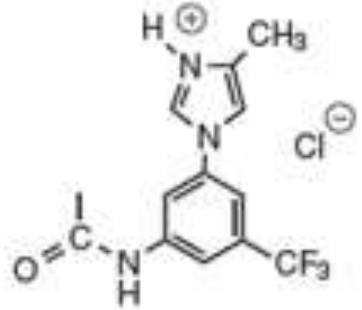
Bcr-Abl kinase inhibitors:



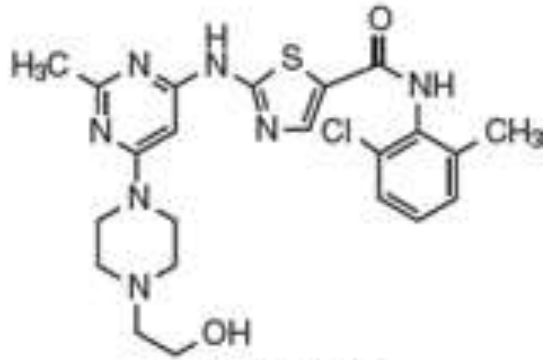
R =



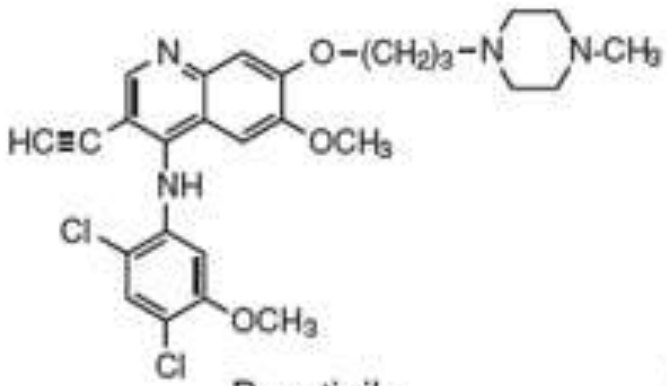
Imatinib mesylate
(Gleevec)



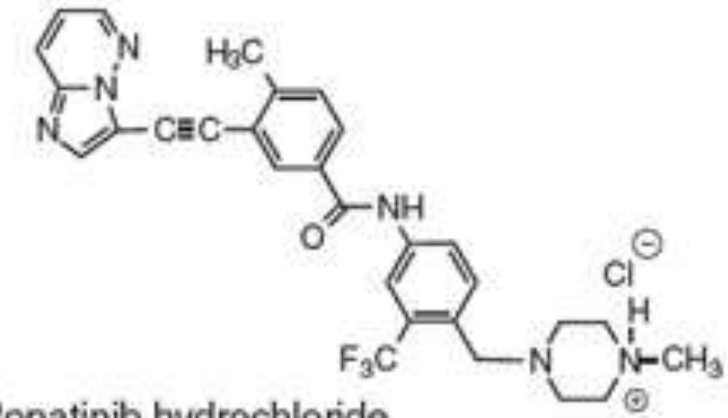
Nilotinib hydrochloride
(Tasigna)



Dasatinib
(Sprycel)



Bosutinib
(Bosulif)



Ponatinib hydrochloride
(Iclusig)

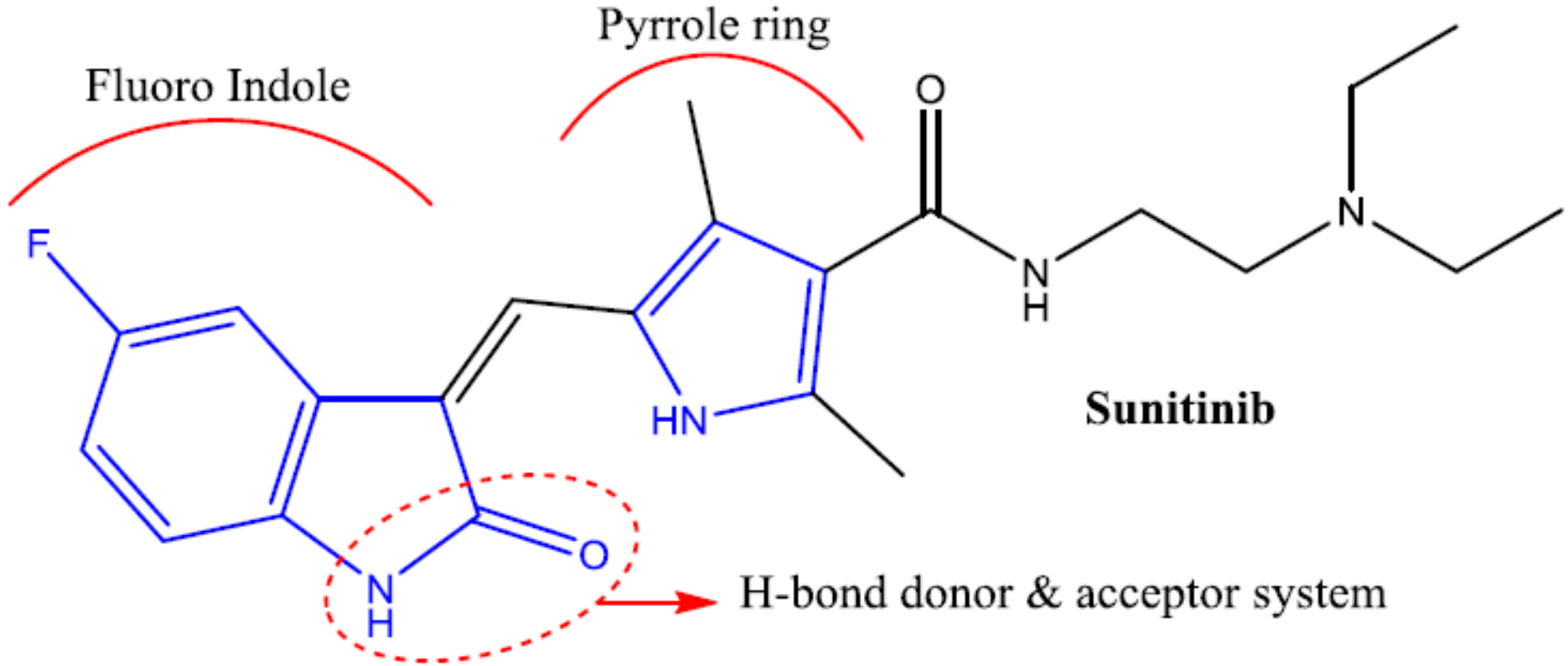
	Indications	Dosage Form	Therapeutic Issues
Bcr-Acl Inhibitors			
Bosutinib	Imatinib-resistant chronic myelogenous leukemia (CML)	Tablets	Administer with food. GI and hepatotoxicity possible
Dasatinib	Ph⁺ CML, imatinib-resistant acute lymphoblastic leukemia (ALL)	Tablets	May take with food and water if GI distress occurs. Fluid retention, hemorrhage, QT interval prolongation possible.
Imatinib	Ph⁺ CML, ALL, gastrointestinal stromal tumors (GIST)	Tablets	Take with food and water to minimize GI distress. Edema and hepatotoxicity possible
Nilotinib	Imatinib-resistant CML	Capsules	Black Box Warning: QT interval prolongation leading to sudden death
Ponatinib	Imatinib-resistant CML and ALL	Tablets	Black Box Warning: vascular occlusion, heart failure, hepatotoxicity
EGFR Inhibitors			
Afatinib	Nonsmall cell lung cancer	Tablets	GI, hepatic, and dermatologic toxicity possible
Erlotinib	Nonsmall cell lung cancer, pancreatic cancer	Tablets	24% increase in clearance in smokers demands dose increase. Food increases bioavailability from 60–100%
Lapatinib	HER2 positive breast cancer	Tablets	Black Box Warning: Potentially fatal hepatotoxicity
Vandetanib	Medullary thyroid cancer	Tablets	Black Box Warning: QT interval prolongation leading to sudden death

- Imatinib usually used to treat CML (BCR-ABL tyrosine Kinase inhibitor), and usually the
- disease has two phases:
- 1) The Chronic phase 3-5 years, only minor clinical symptoms appear in the patents and
- the number of WBCs increases above 50,000, here the remission rate is 100% if the patient
- takes his medication chronically.
- 2) The Blast phase : develops within 8 months to 1 year after the chronic phase, a massive
- increase in the number of WBCs occurs then bone marrow damage and death, the remission
- rate is 60% if the patient takes his medication chronically.
- (NOTE: CML chronic myelogenous leukemia, CLL chronic lymphoblastic leukemia, and some GIT cancers are more likely chronic diseases that requires
- chronic or maintenance treatments as DM or HTN, and the remission happens as long as the patient takes his medication).

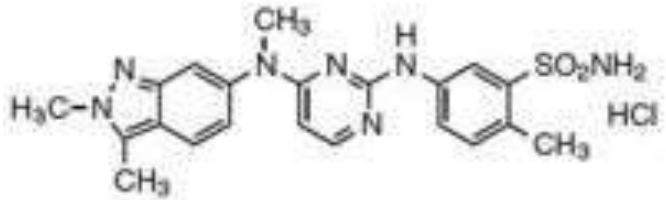
- Imatinib usually used in the chronic phase, it has less side effects (minor bone marrow suppression and GI disturbance may occur in some individuals 1-2%), it's totally absorbed orally (100% bioavailable), well distributed, metabolized by cyp450 oxidation of the benzylic carbon and eliminated in the urine and bile.

"Sunatinib" is the second example; it has fluoro-Indol and a Pyrrole ring. The system of hydrogen bond donor and acceptor makes it an ATP analogue; it’s the same as Imatinib. Orally available, well distributed, and mainly eliminated in the feces.

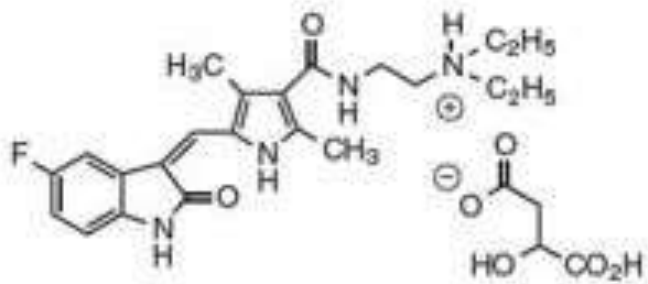
It used to treat CML, RCC (Renal Cell Carcinoma), and some of GIT cancers. It considered "Multi-target PTK inhibitor"; inhibits many of PTK receptors (and remember that sometimes the cancer involves many types of mutations in the PTK receptor) but at the same time it has more activity against some PTK receptors than others.


Pyrrole ring
Fluoro Indole
F
O
N
H
N
HN
O
N
H
Sunitinib
H-bond donor & acceptor system

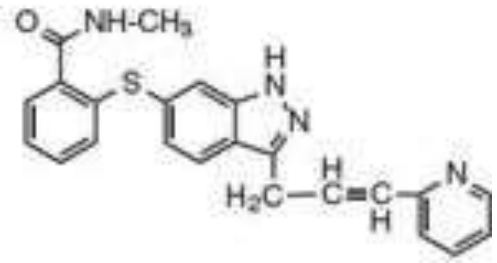
VEGFR kinase inhibitors:



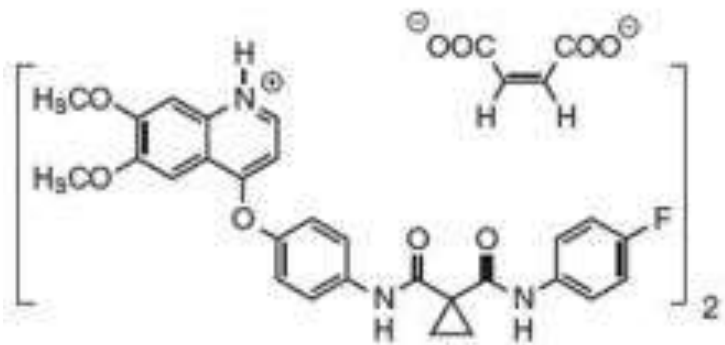
Pazopanib hydrochloride
(Votrient)



Sunitinib malate
(Sutent)

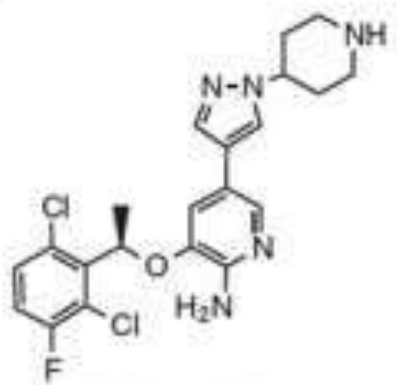


Axitinib (Inlyta)

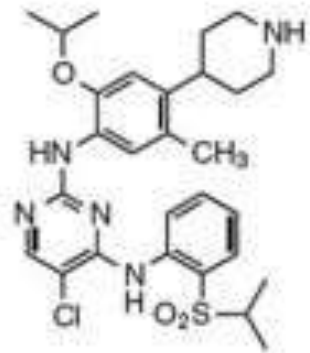


Cabozantinib maleate (Exelixis)

ALK Inhibitors:

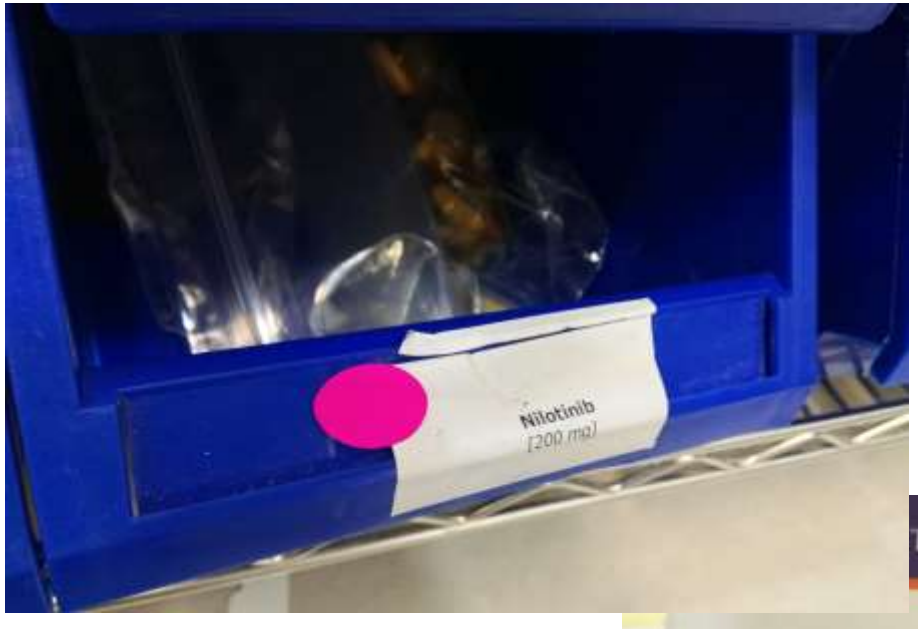


Crizotinib (Xalkori)



Ceritinib (Zykadia)

Some tyrosine kinase inhibitors in KHCI



Some tyrosine kinase inhibitors in KHCl

- K