Chemotherapeutic Agents

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Drugs to Treat Neoblastic Agents- Section 5- Miscellaneous Agents

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CHAPTER 33

Drugs Used to Treat Neoplastic Diseases

Victoria F. Roche

Pharmacologic lassification of Chemotherapeutic Agents- Contd.

V. Mitosis inhibitors(antimitotic agents): natural alkaloids

VI. Tyrosine kinase inhibitors & related agents

VII. Angiogenesis inhibitors & Immunomodulators

VIII. Proteasome inhibitor

IX. Histone deacetylase inhibitors

X. Miscellaneous: hormonal, and specific agents

CHAPTER 33

Drugs Used to Treat Neoplastic Diseases

Victoria F. Roche

Drugs covered or mentioned in this chapter:

Tyrosine kinase inhibitors
- Acalabrutinib
- Afatinib
- Alectinib
- Axitinib
- Bosutinib
- Brigatinib
- Cabozantinib
- Ceritinib
- Crizotinib
- Dasatinib
- Erlotinib
- Gefitinib
- Ibrutinib
- Imatinib
- Lapatinib
- Lenvatinib
- Midostaurin
- Neratinib
- Nilotinib
- Omacetaxine mepesuccinate
- Osimertinib
- Pazopanib
- Ponatinib
- Regorafenib
- Ruxolitinib
- Sorafenib
- Sunitinib
- Vandetanib

Serine/threonine kinase inhibitors

MEK inhibitors
- Cobimetinib
- Trametinib

mTOR inhibitors
- Everolimus
- Temsirolimus

Lipid kinase inhibitors

Phosphatidylinositol 3 kinase inhibitors
- Copanlisib
- Idelalisib

IDH1/2 inhibitors
- Enasidenib
- Ivosidenib

BCL-2 inhibitors
- Venetoclax

PARP inhibitors
- Niraparib
- Olaparib
- Rucaparib

Proteasome inhibitors
- Bortezomib
- Carfilzomib
- Ixazomib

Hormone-based antineoplastic agents (representative)

Aromatase inhibitors
- Anastrozole

Antiestrogens

Immunomodulators
- Lenalidomide
- Pomalidomide
- Thalidomide

Histone deacetylase inhibitors
- Belinostat
- Panobinostat
- Romidepsin
- Vorinostat

Topoisomerase poisons

Camptothecins
- Irinotecan
- Topotecan

Epipodophyllotoxins
- Etoposide
- Teniposide

Anthracyclines and anthracenediones
- Aldoxorubicin
- Daunorubicin
- Doxorubicin
- Epirubicin
- Idarubicin
- Mitoxantrone
- Valrubicin

Mitosis inhibitors
- Cabazitaxel
- Docetaxel
- Eribulin

Kinase & Kinase Inhibitors

Tyrosine Kianse

Serine/Threonine Kinase Inhibitors

Tyrosin Kinase

- Estimated to be expressed in more than 80% of human oncogenes and proto-oncogenes

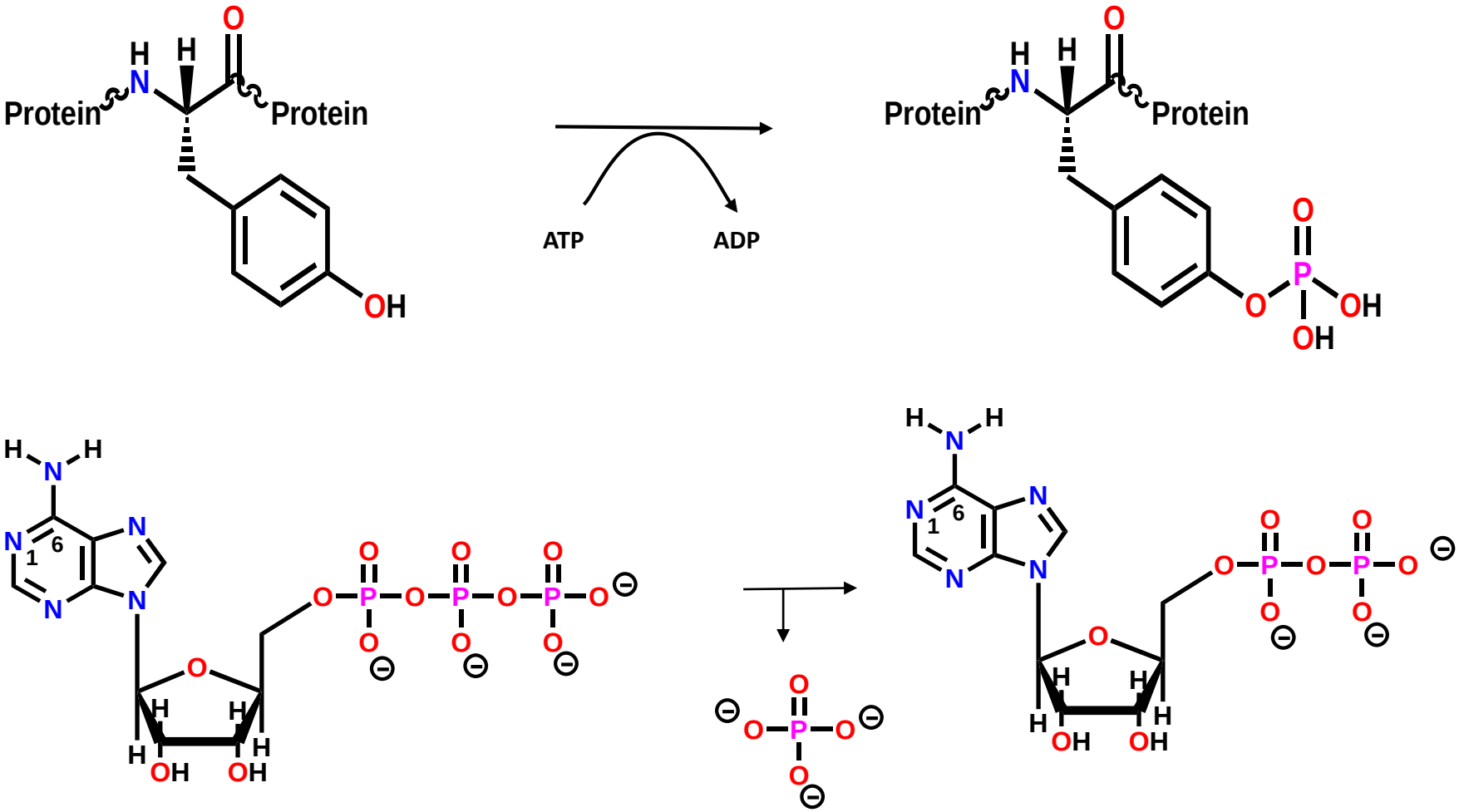
- In normal function:

Regulated cell proliferation, differentiation, and survival

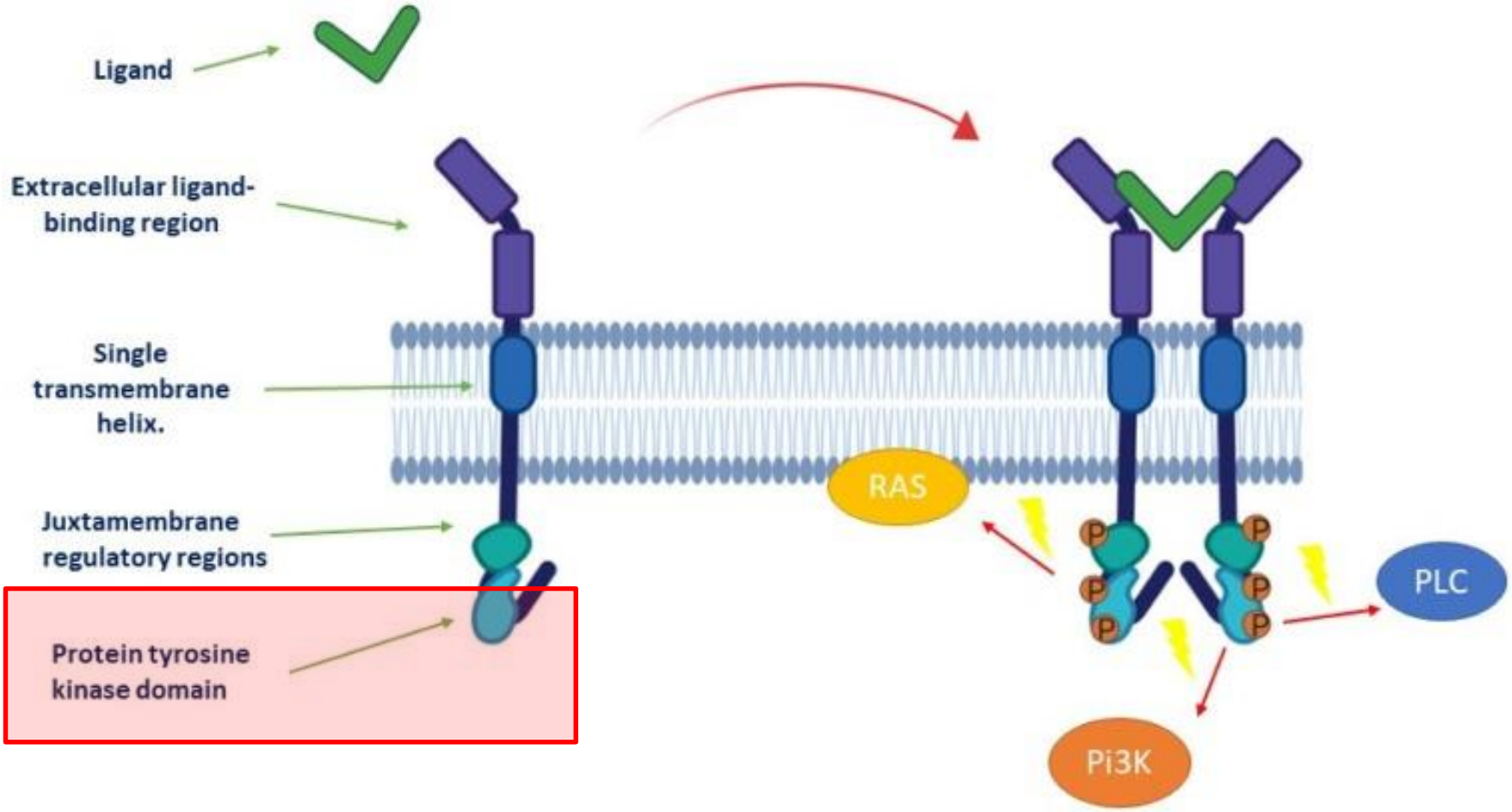
- In deregulated manner:

Accelerate cell signaling cascades and cellular growth, induce tumors, augment antiapoptotic processes: confer resistance to chemotherapeutic agents

Chemical Function of Tyrosin Kinase



TK & Its Ligand in Schematic Image



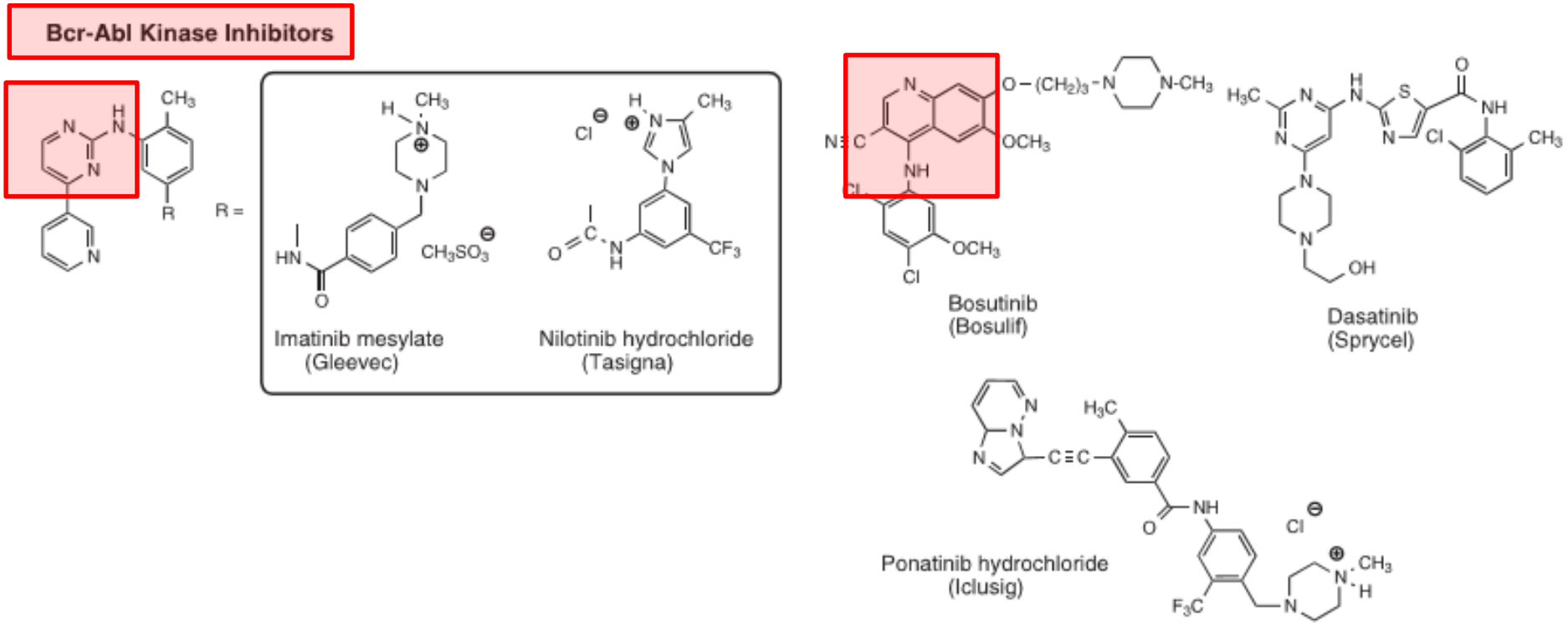
VI. Tyrosine Kinase & Related Inh.

- Bcr-Abl Inhibitors
- EGFR & EGFR/HER2 Inhibitors
- VEGFR Inhibitors
- ALK & Bruton Kinase Inhibitors
- mTor Inhibitors

Types of Kinase & Kinase Related enzymes

- Non/receptor
- Involved in GLC & FA metabolism
- ATP associated

VI. Bcr-Abl Kinase Inhibitors

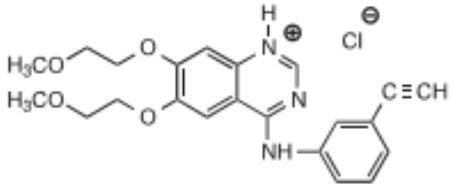


*Inhibits multiple kinases; **Irreversible kinase inhibitor

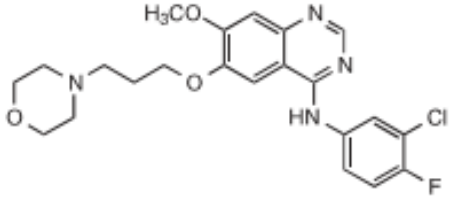
Figure 33.1 Tyrosine kinase inhibitors.

VI. EGFR/HER Kinase Inhibitors

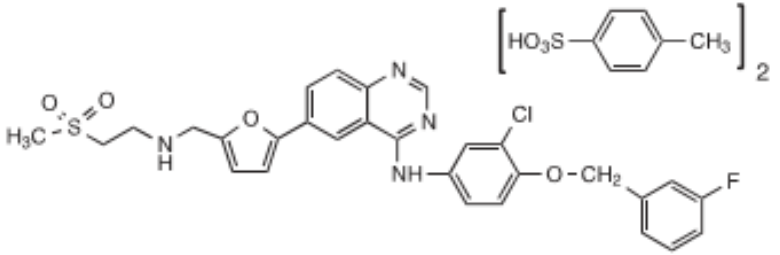
EGFR/HER Kinase Inhibitors



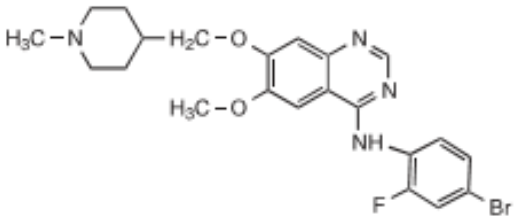
Erlotinib hydrochloride (Tarceva)



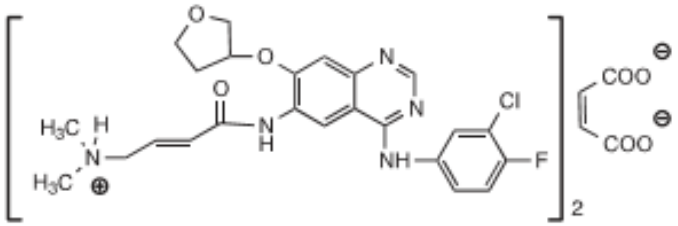
Gefitinib (Iressa)



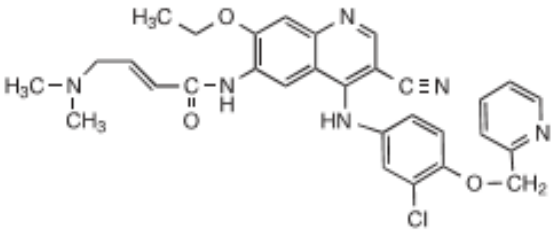
Lapatinib ditosylate (Tykerb)



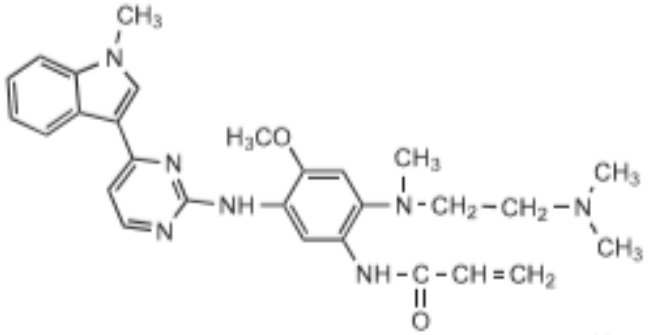
Vandetanib (Caprelsa)*



Afatinib dimaleate (Gilotrif)**



Neratinib (Nerlynx)**



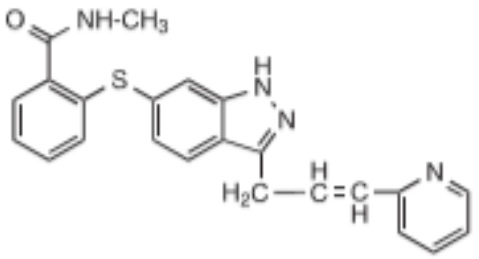
Osimertinib (Tagrisso)**

*Inhibits multiple kinases; **Irreversible kinase inhibitor

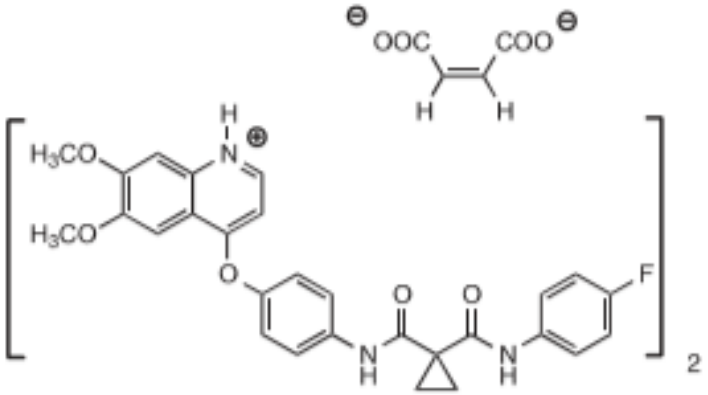
Figure 33.1 Tyrosine kinase inhibitors.

VI. VEGFR Kinase Inhibitors

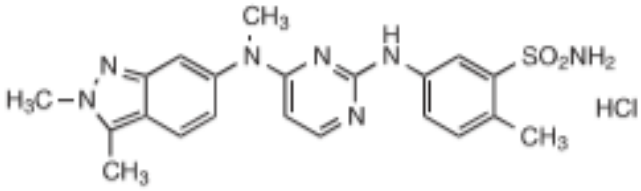
VEGFR kinase inhibitors



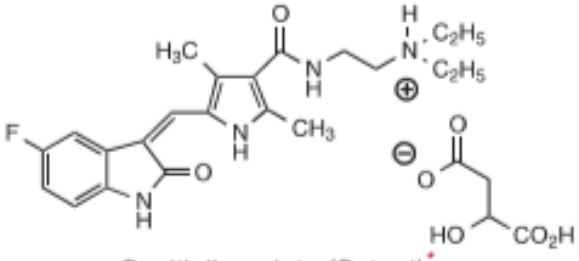
Axitinib (Inlyta)



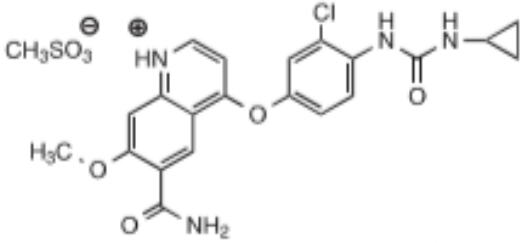
Cabozantinib maleate (Exelixis)*



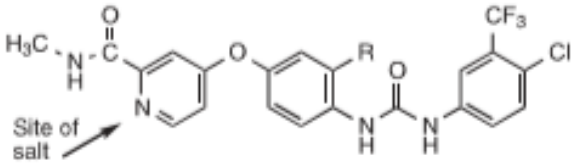
Pazopanib hydrochloride (Votrient)*



Sunitinib malate (Sutent)*



Lenvatinib mesylate (Lenvima)*



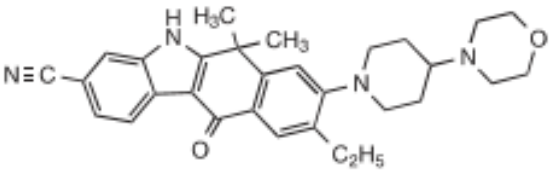
Sorafenib tosylate (R = H, tosylate = $C_7H_7SO_3$) (Nexavar)*
Regorafenib (R = F) (Stivarga)*

*Inhibits multiple kinases; **Irreversible kinase inhibitor

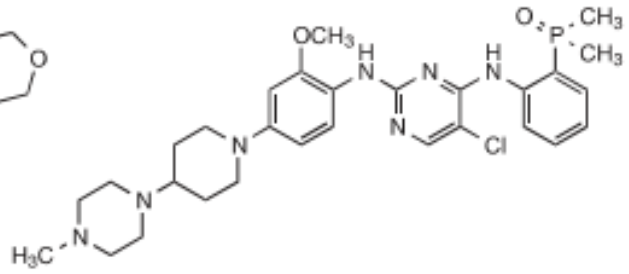
Figure 33.1 Cont'd

VI. ALK & Bruton Tyr Kinase Inhibitors

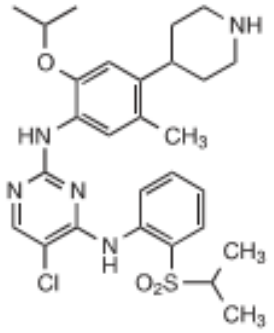
ALK inhibitors



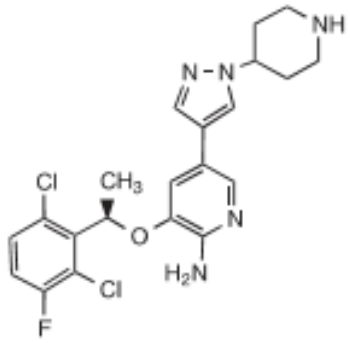
Alectinib (Alecensa)



Brigatinib (Alunbrig)*

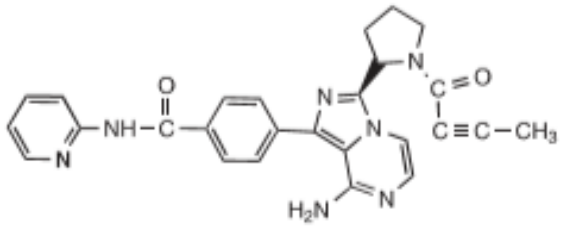


Ceritinib (Zykadia)

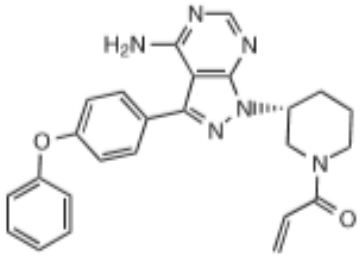


Crizotinib (Xalkori)*

Bruton tyrosine kinase inhibitors

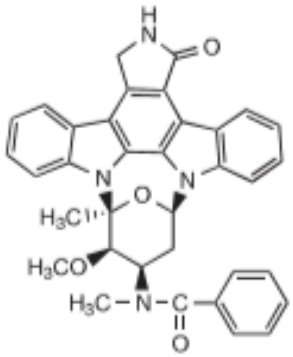


Acalabrutinib (Calquence)**



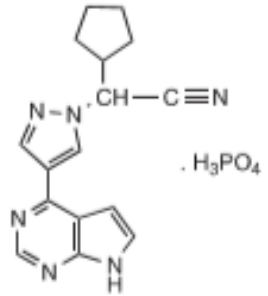
Ibrutinib (Imbruvica)**

FLT3 kinase inhibitor



Midostaurin (Rydapt)*

JAK inhibitor



Ruxolitinib phosphate (Jakafi)

*Inhibits multiple kinases; **Irreversible kinase inhibitor

Figure 33.1 Cont'd

Interactions Between EGFR/HER Kinase

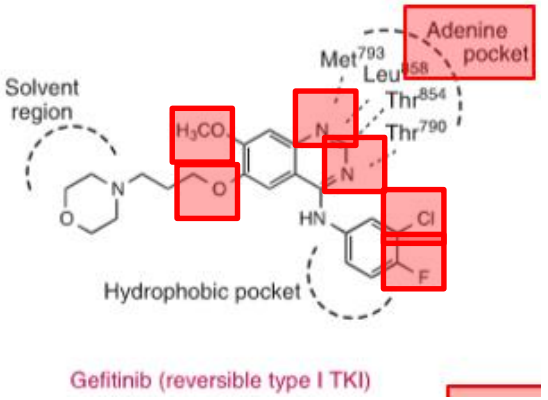
- Reversible:

✓ 4-anilino-quinazoline: 2 critical hydrogen bonds: N1 & N3

✓ Oxygen containing at C6

✓ Ether containing at C7

✓ EWG at m/p of aniline:



F: improve hydrophobic interaction

larger substituents: broadens TK specificity to HER2

- Irreversible:

✓ Michael alkylating group: electrophilic group: Cys-SH attack

GatekeeperThr790

VEGFR TK Inhibitors

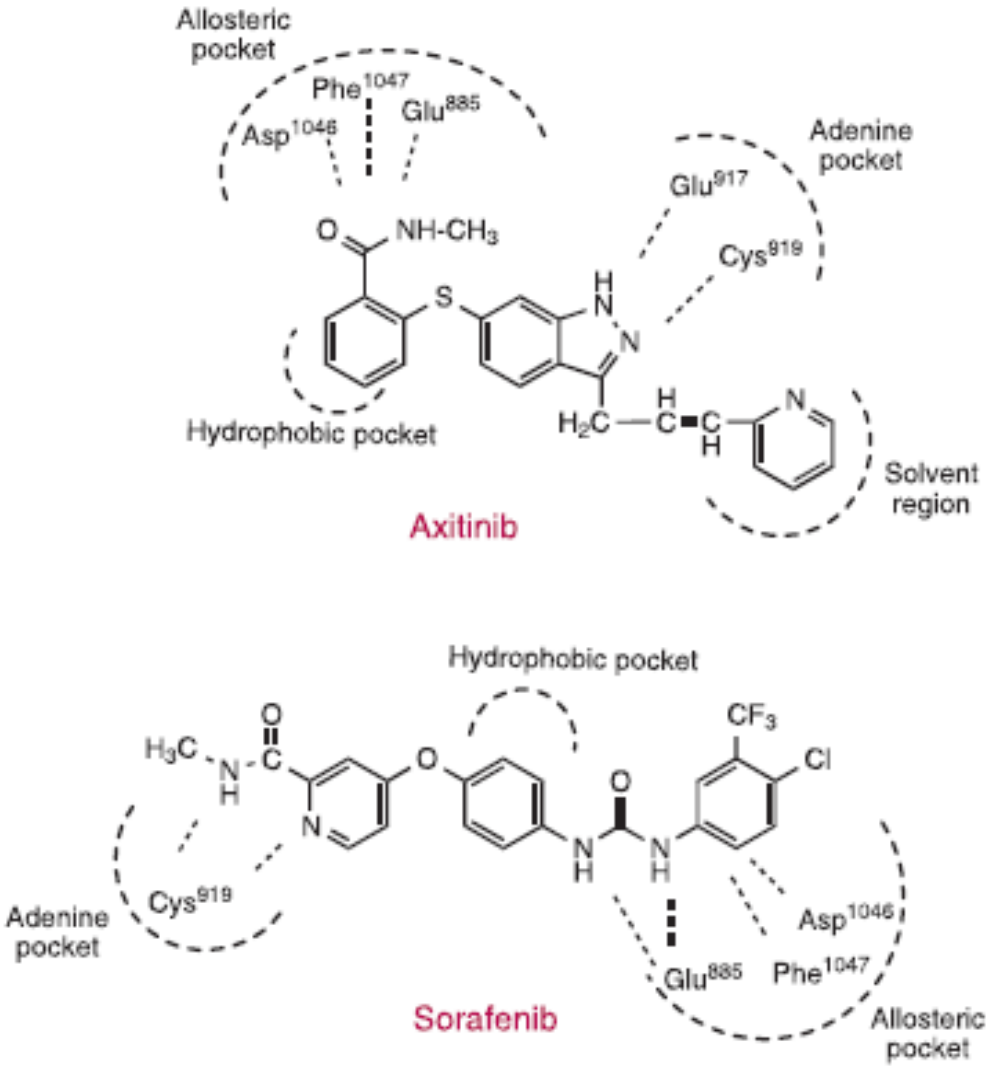
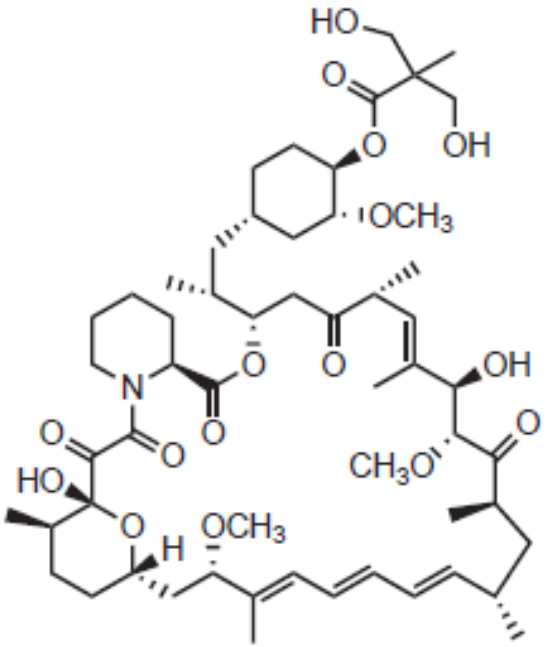
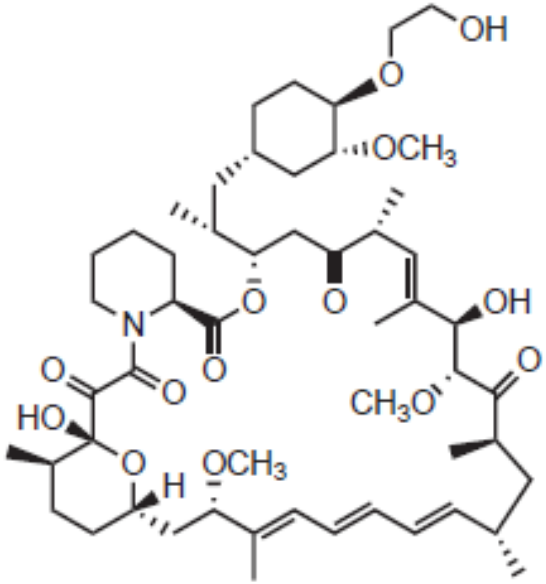


Figure 33.8 Binding interactions between VEGFR tyrosine kinase and representative inhibitors.

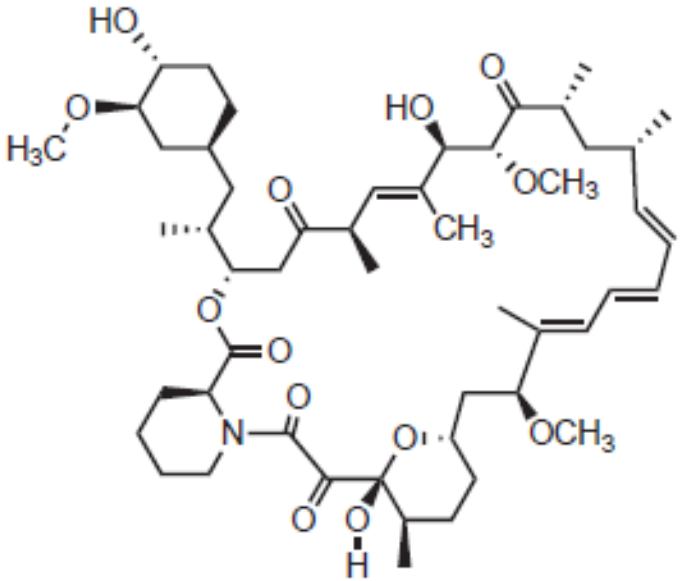
VI. mTOR Inhibitors



Temsirolimus (Torisel)



Everolimus (Afinitor)



Rapamycin

FIGURE 37.53 mTOR inhibitors.

Pharmacologic lassification of Chemotherapeutic Agents- Contd.

V. Mitosis inhibitors(antimitotic agents): natural alkaloids

VI. Tyrosine kinase inhibitors & related agents

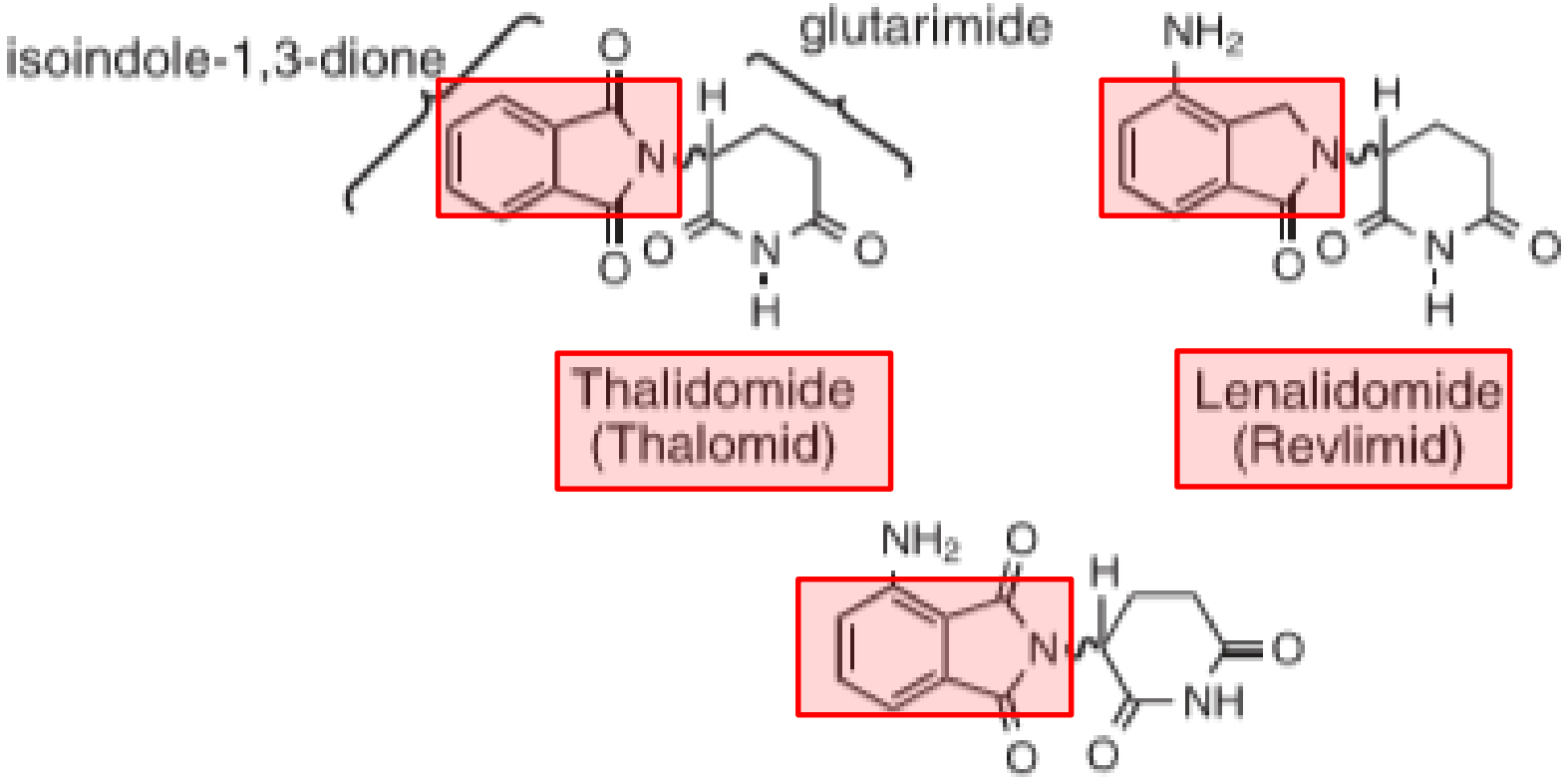
VII. Angiogenesis inhibitors & Immunomodulators

VIII. Proteasome inhibitor

IX. Histone deacetylase inhibitors

X. Miscellaneous: hormonal, and specific agents

VIII. Immunomodulators



Immunomodulatory agents used in multiple myeloma

Metabolism of Thalidomide

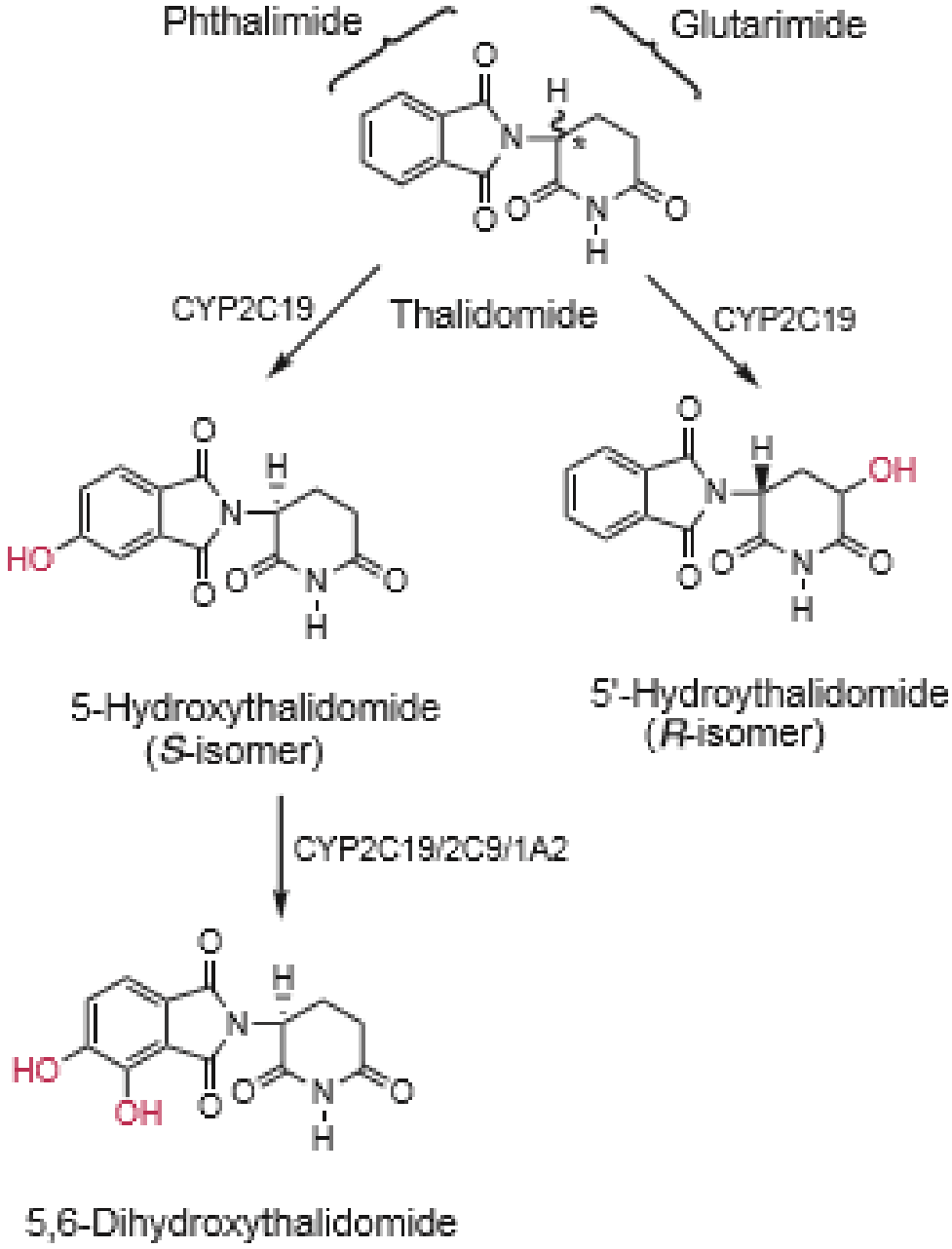


FIGURE 37.56 CYP2C19-mediated thalidomide metabolism.

Pharmacologic lassification of Chemotherapeutic Agents- Contd.

V. Mitosis inhibitors(antimitotic agents): natural alkaloids

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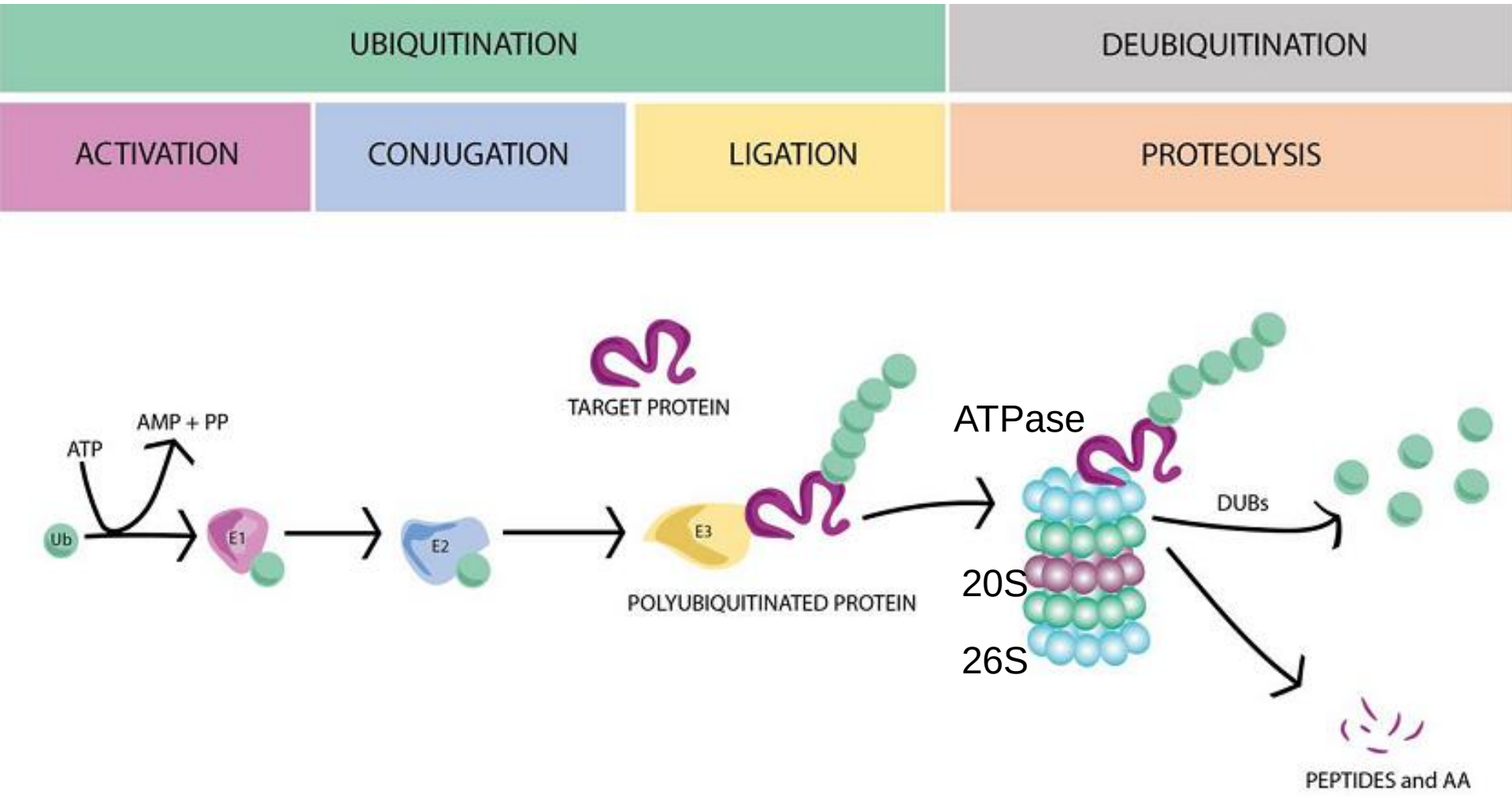
Proteasome

- Clear cells of cytoplasmic regulatory proteins
- By cleaving them into short peptides:
- Ubiquitin Proteasome Pathway (UPP): regulates cell processes in stress & immune response, transcription, cell-cycle differentiation, apoptosis, …
- 26S proteasome as recognition site for ubi-quitinated Prs
- ATP dependent 19S regulatory unit
- 26S is transferred to 20S (core particle) proteolytic domain:Thr1(OH)
- Inhibition of this process: induce apoptosis
- Inhibitors: ir/reversible

✓ dipeptide: bortezomib; ixazomib

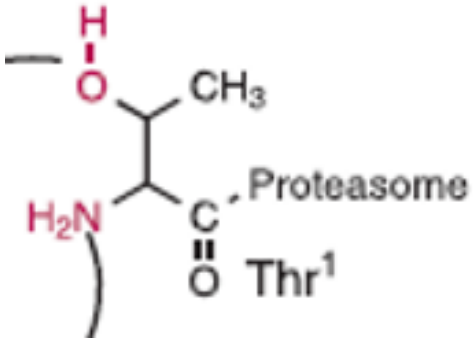
✓ tetrapeptide: carfilzomib

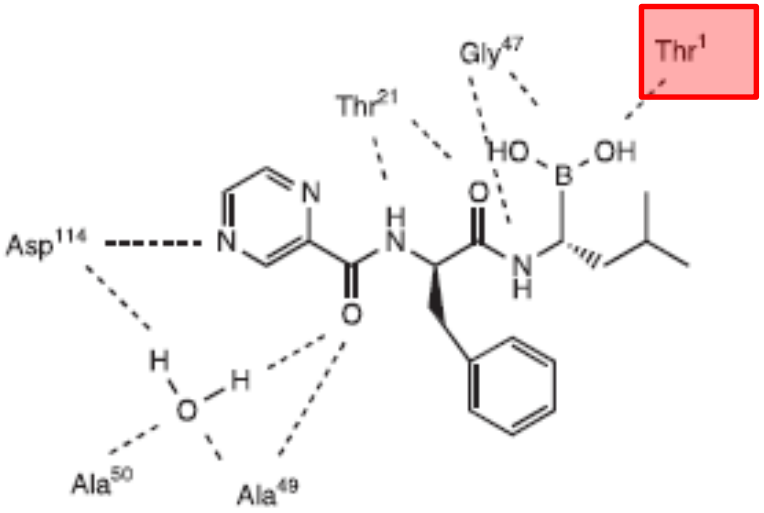
Ubiquitin Proteasome Pathway (UPP)



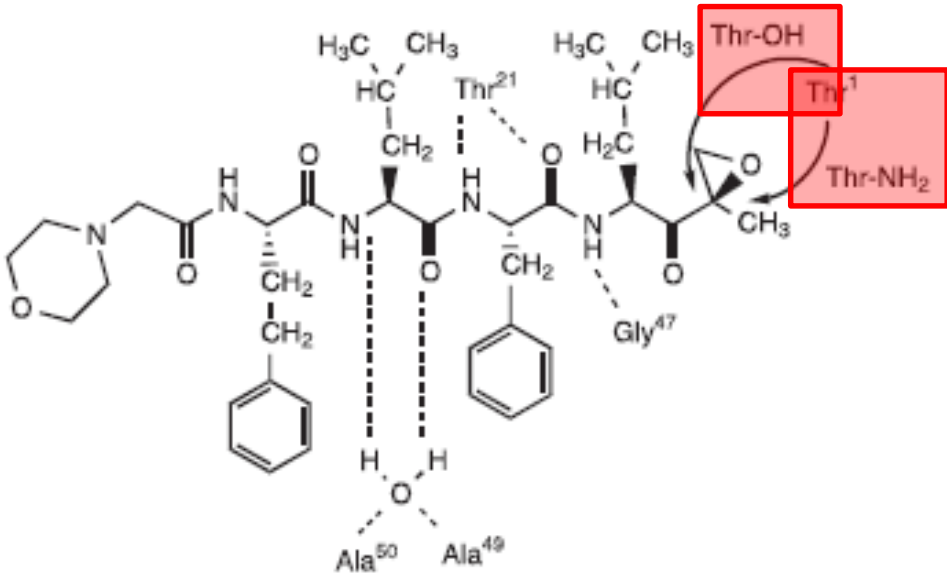
Proteasome Interaction Points

- Thr1: critical portion
- Asp114:
- ✓ secondly critical for bortezomib





Bortezomib-proteasome (yeast) interactions



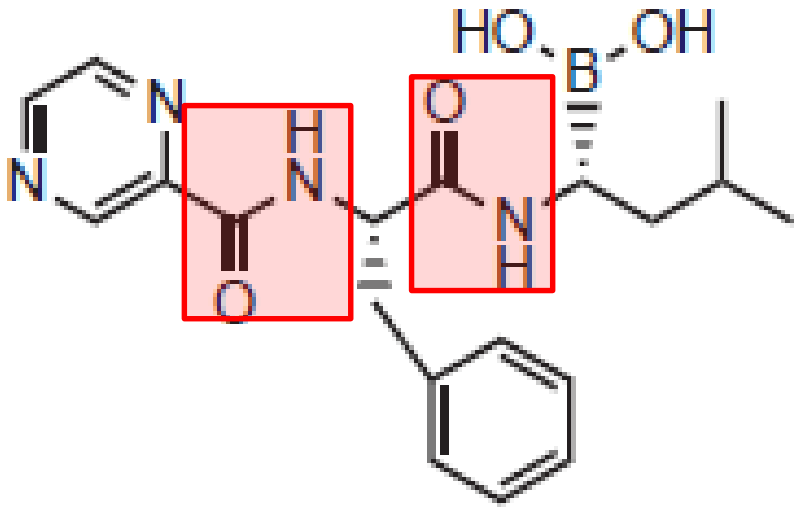
Carfilzomib-proteasome (human) interactions

Figure 33.21 Proteasome-inhibitor interactions.

SRAm

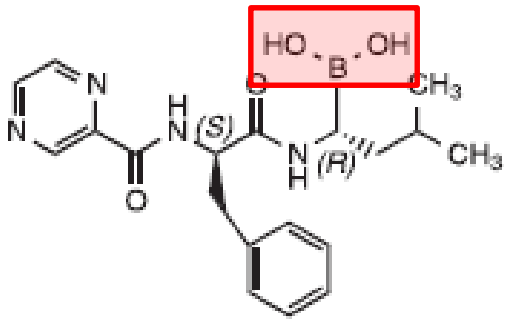
Proteasome Inhibitor

- Chemistry: peptide +/- boron derivative

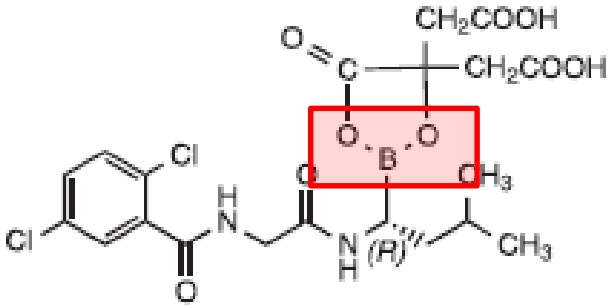


Bortezomib (Velcade)

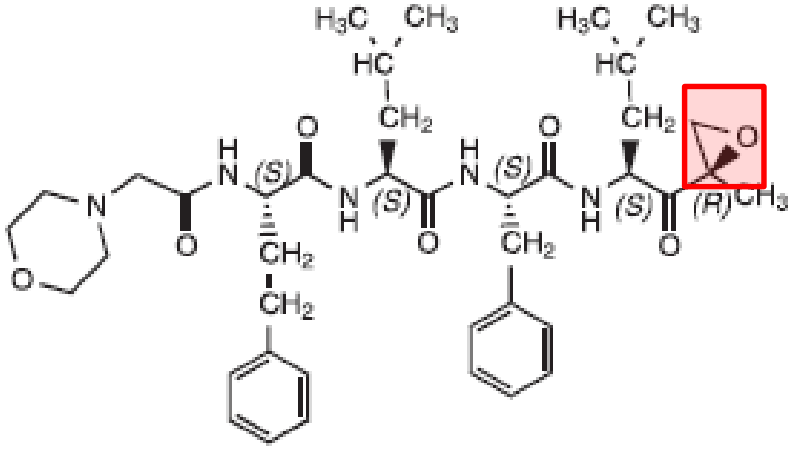
Proteasome Inhibitors



Bortezomib (Velcade)



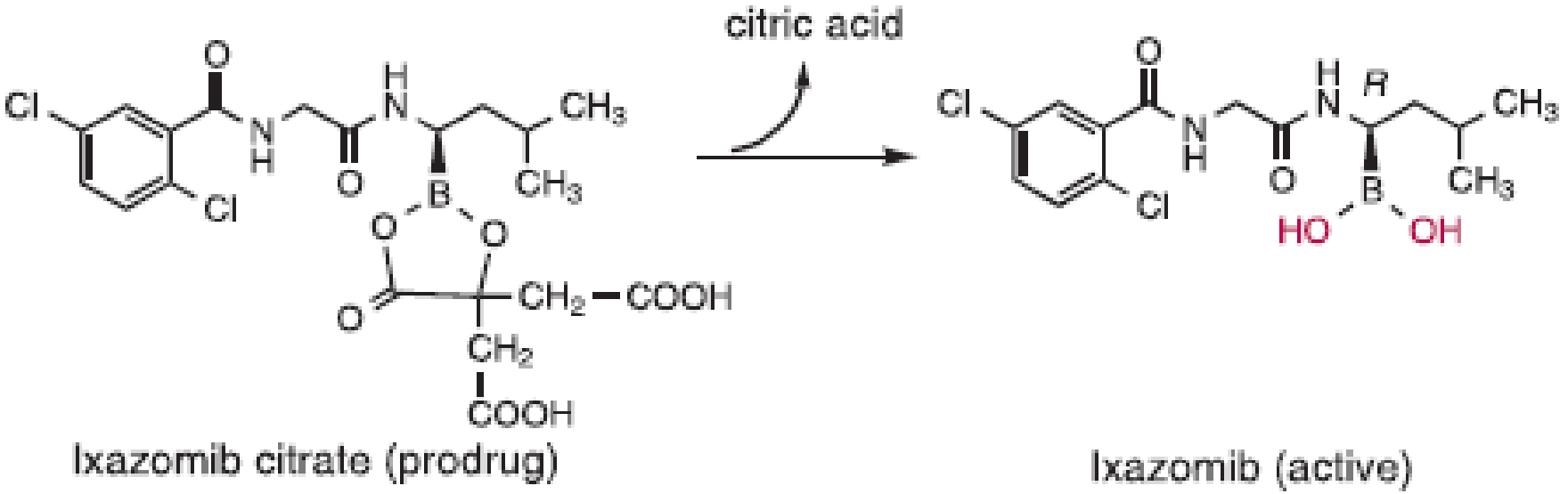
Ixazomib citrate (Ninlaro)



Carfilzomib (Kyprolis)

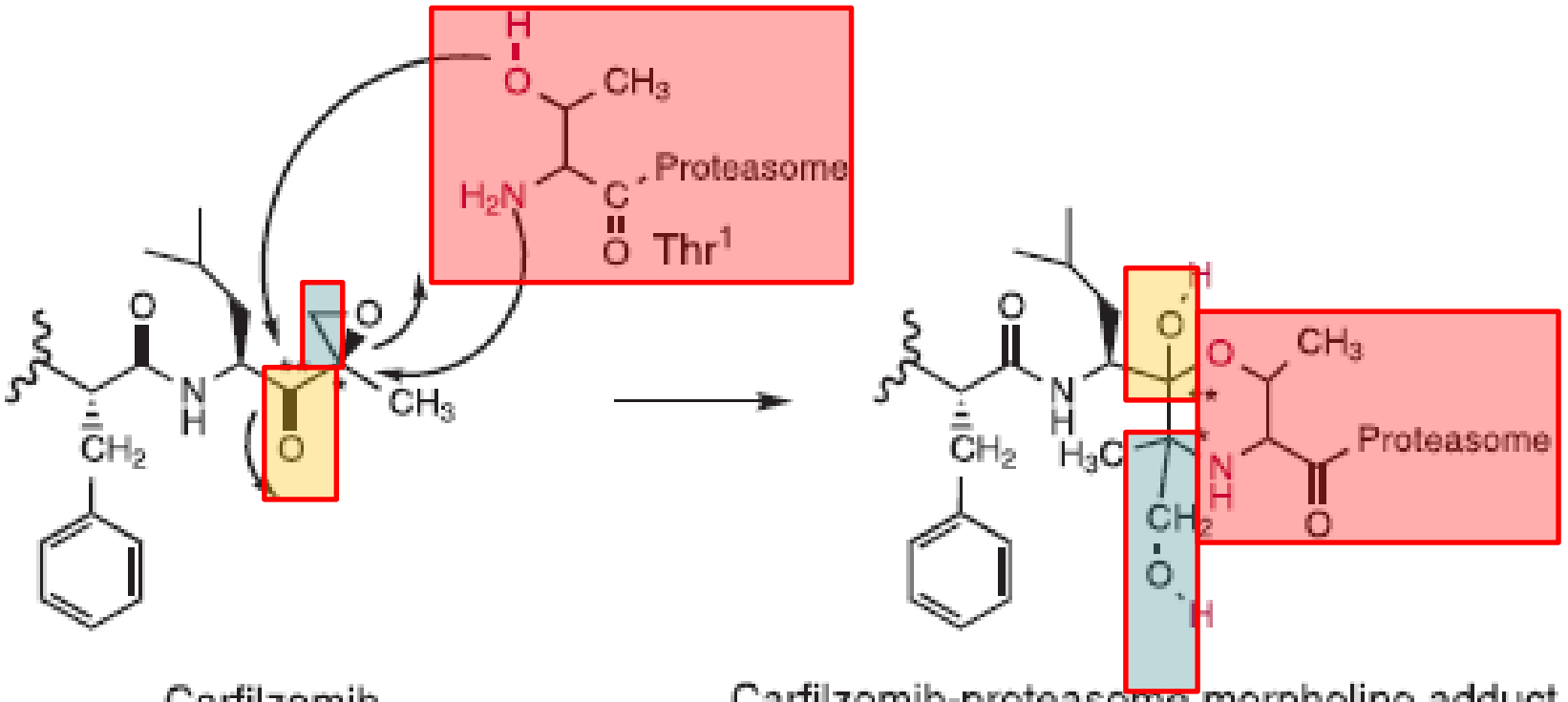
Figure 33.20 Proteasome inhibitors.

Ixazomib: Irreversible Proteasome Inhibitor



Carfilzomib: Irreversible Proteasome Inhibitor

- Consider Thr to provide morpholino adduct.



Pharmacologic lassification of Chemotherapeutic Agents- Contd.

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VIII. Proteasome inhibitor

IX. Histone deacetylase inhibitors

X. Miscellaneous: hormonal, and specific agents

VII. Histone Deacetylase & Inhibitors

- Histones: highly basic: Lys rich: basic & cationic
- Process DNA into nucleosomes for chromatin formation
- Substrate for HAT & HDAC
- HAT: provides more open chromatin conformation:

✓ allowing transcription factors to readily access DNA

✓ initiate RNA synthesis

- HDAC inhibitors:

✓ keeps the chromatin in relaxed conformation

✓ blocks transcriptional repression

✓ provide tumor suppression

VII. Histone Deacetylase in Cancer

- Excessive histone acetylation

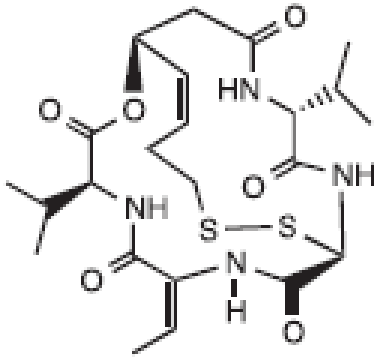
✓ associated with an aggressive neoplastic diseases

- Reduction in the extent of Lys acetylation of selected histones is also common in cancer

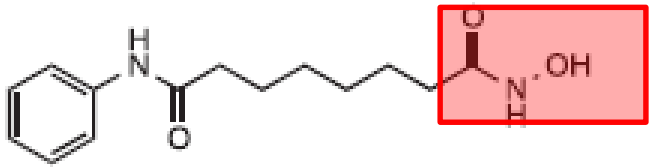
- HDAC: 3 of 4 classes require Zn^{2+} as cofactor

VII. Histone Deacetylase Inhibitors

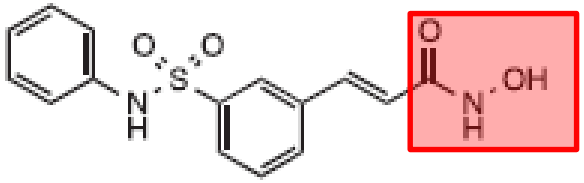
- Chemistry: depsipeptide or hydroxamic acid



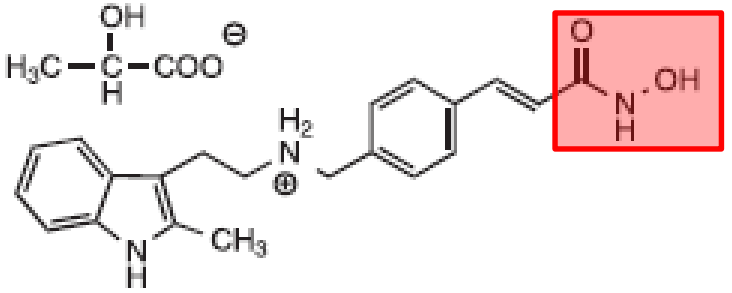
Romidepsin (Istodax)



Vorinostat (Zolinza)



Belinostat (Beleodaq)

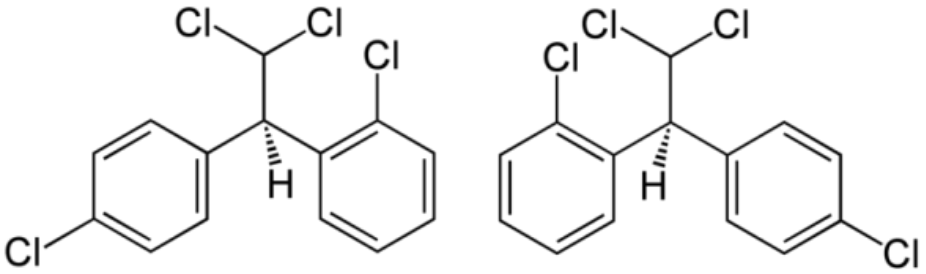


Panobinostat lactate (Farydak)

Figure 33.23 Histone deacetylase inhibitors (HDACi).

IX. Miscellaneous Anticancer Agents

- Mitotan: alters steroid metabolism;
  suppress adrenal cortex;
  hypocortisolism



- Retinoids: Tretinoin; Alitretinoin: block cell cycle;
  induce apoptosis

Pharmacologic lassification of Chemotherapeutic Agents- Contd.

V. Mitosis inhibitors(antimitotic agents): natural alkaloids

VI. Tyrosine kinase inhibitors & related agents

VII. Angiogenesis inhibitors & Immunomodulators

VIII. Proteasome inhibitor

IX. Histone deacetylase inhibitors

X. Miscellaneous: hormonal, and specific agents

IX. Miscellaneous Mechanisms of Action for Anticancer Agents

- Hormone therapy:
- ✓ anti-estrogen / anti-androgen; GnRH analog
- Enzyme therapy: L-Asparaginase in leukemia
- Human protein modifiers: recombinant agents: Interleukin-2; IFN
- Epidermal Growth Factor (EGF); VEGF
- Cancer vaccines
- Gene therapy: SiRNA
- Telomerase agents