Chemotherapeutic Agents

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Drugs to Treat Neoblastic Agents- Section 5- Miscellaneous Agents

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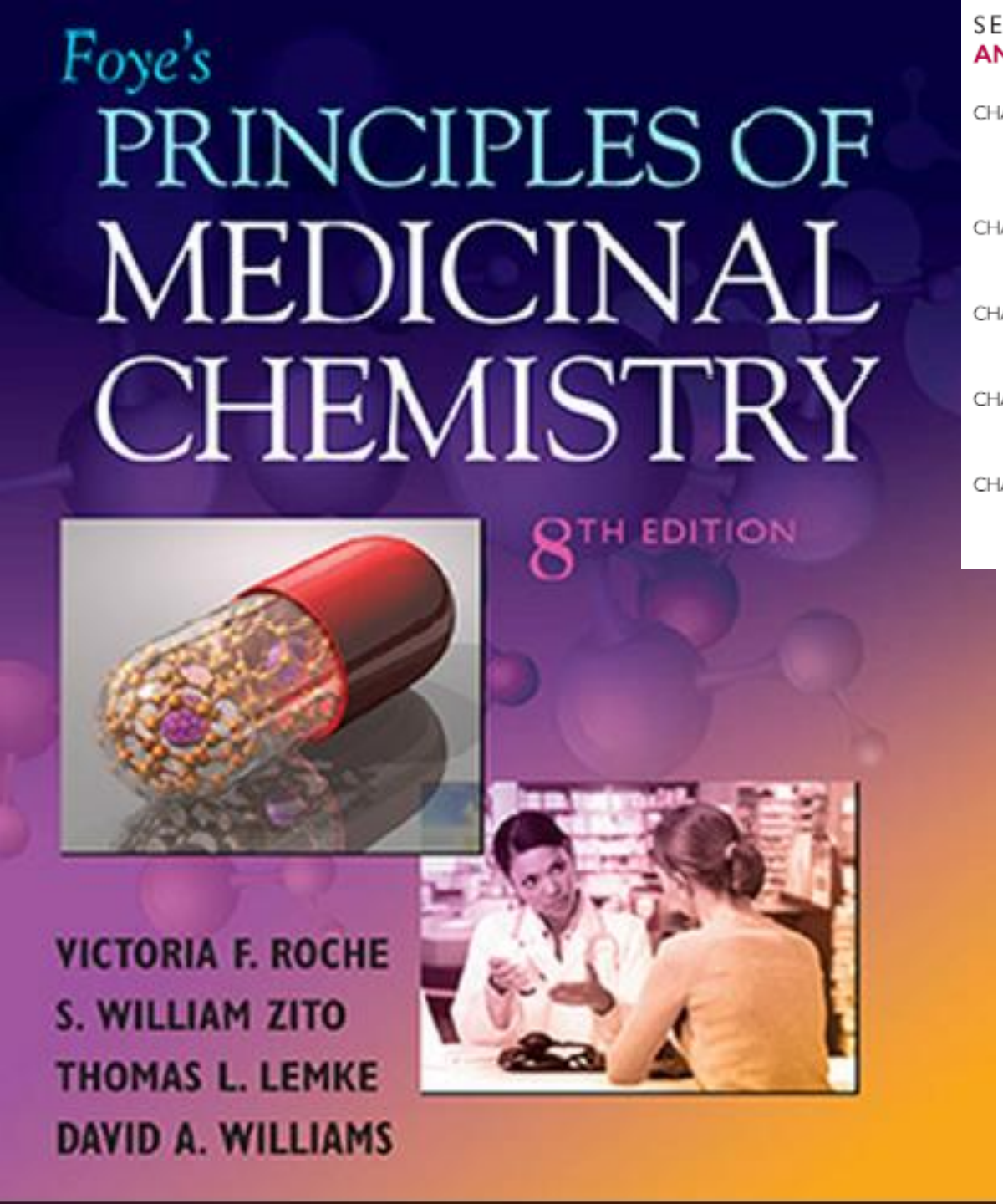


SECTION 7 **DRUGS IMPACTING INFECTIOUS AND NEOPLASTIC DISEASE PROCESSES**

Foye's 2019

Principles of Medicinal Chemistry
by William Foye, 2019

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

Pharmacologic Classification of Chemotherapeutic Agents

I. DNA (cross) linking agents; DNA alkylating agents

II. Antimetabolites

III. DNA topoisomerase poisons & DNA intercalating agents:
Natural alkaloids: III.1.Camptothecins;III.2.Epipodophyllotoxins;
Antibiotics: III.3.Anthracyclines; III.4.Anthracenediones

IV. DNA interacting miscellaneous antibiotics:
IV.1. phenoxazine; IV.2. glycopeptide; IV.3. mitomycin

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

VI. Tyrosine Kinase & Related Inh.

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

Tyrosin Kinase

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

- In normal function:

regulates cell proliferation, differentiation & survival

- In deregulated manner:

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

Tyrosin Kinase (TK)

- Two major types:

Type 1: receptor associated TK

: active conformation

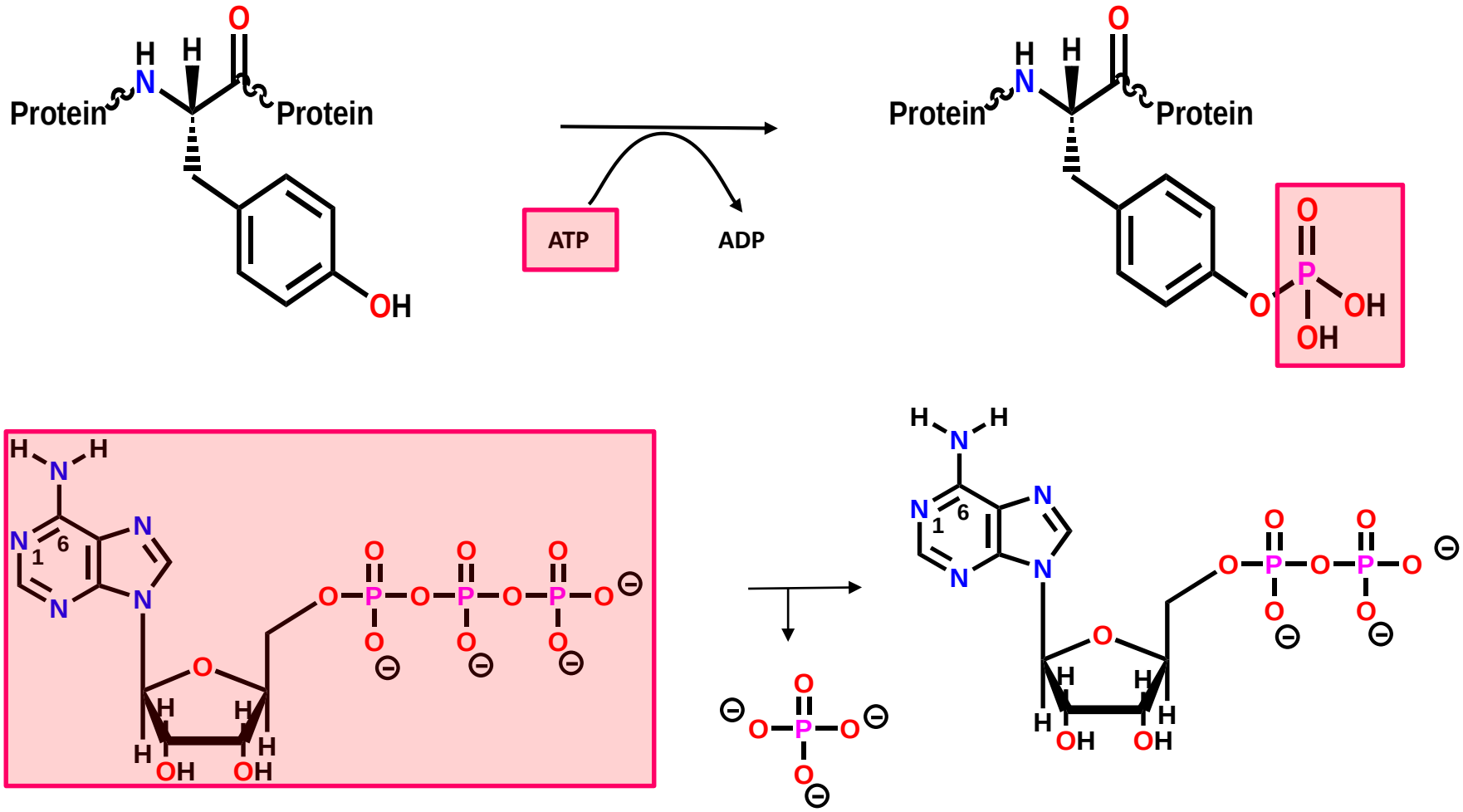
Type 2: membrane-spanning proteins: cellular non-receptor

: inactive conformation

:Extracellular ligand binding domain &

Intracellular catalytic (kinase) domain:

Chemical Function of Tyrosine Kinase



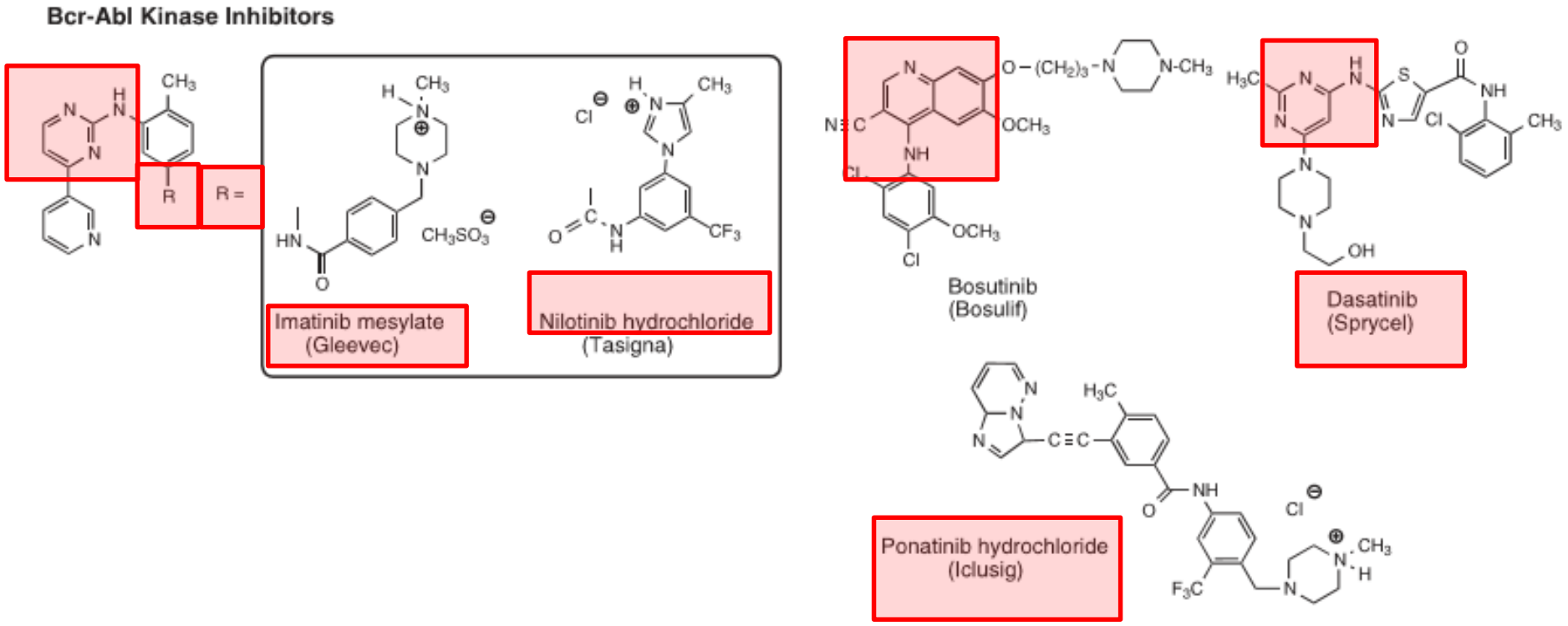
TKIs

- Receptors for TKI:
- the highly conserved ATP binding domain
- Hydrophobic domain:
- ✓ a depression or groove rich in Ile, Leu, Ala & Val in the "hinge region"
- Five potential binding pockets surrounds this site:
- ✓ degree of selectivity
- TKIs:

Type 1: EGFR, VEGFR,
human growth factor receptor 2 (HER2), PDGFR

Type 2: Bcr-Abl, SRC

VI. Bcr-Abl Kinase Inhibitors

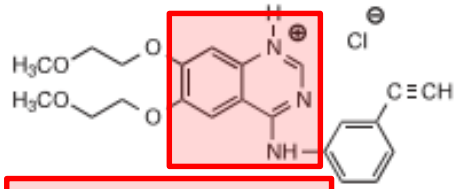


*Inhibits multiple kinases; **Irreversible kinase inhibitor

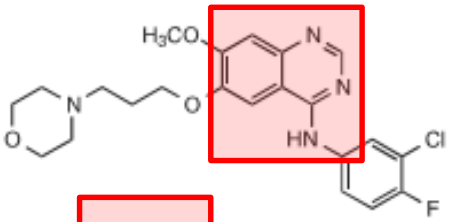
Figure 33.1 Tyrosine kinase inhibitors.

VI. EGFR/HER Kinase Inhibitors

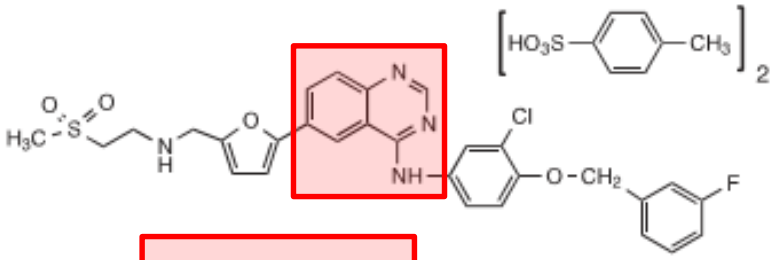
EGFR/HER Kinase Inhibitors



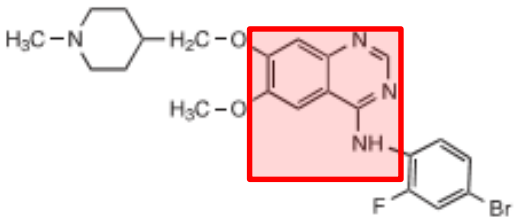
Erlotinib hydrochloride (Tarceva)



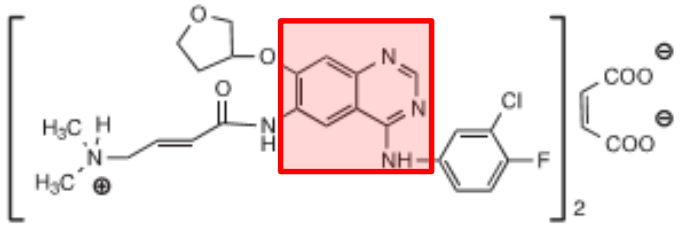
Gefitinib (Iressa)



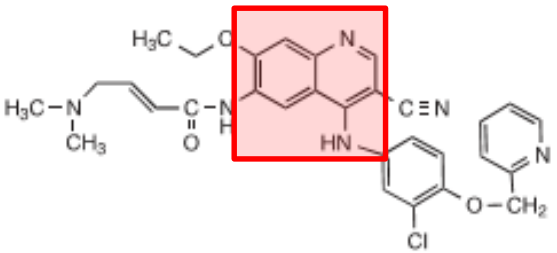
Lapatinib ditosylate (Tykerb)



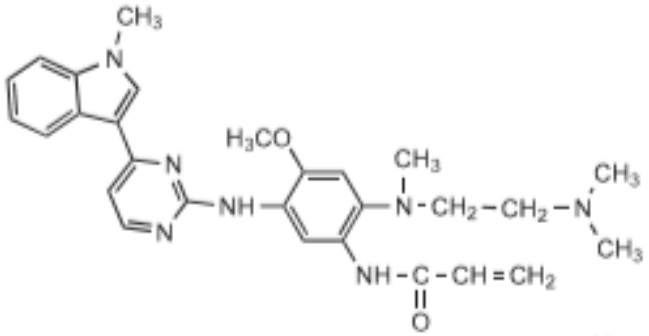
Vandetanib (Caprelsa)*



Afatinib dimaleate (Gilotrif)**



Neratinib (Nerlynx)**



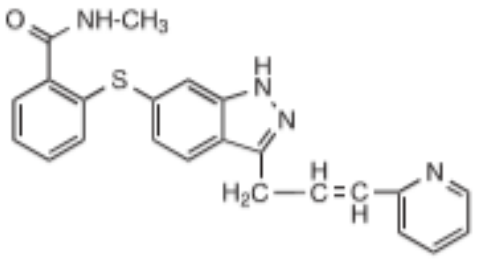
Osimertinib (Tagrisso)**

*Inhibits multiple kinases; **Irreversible kinase inhibitor

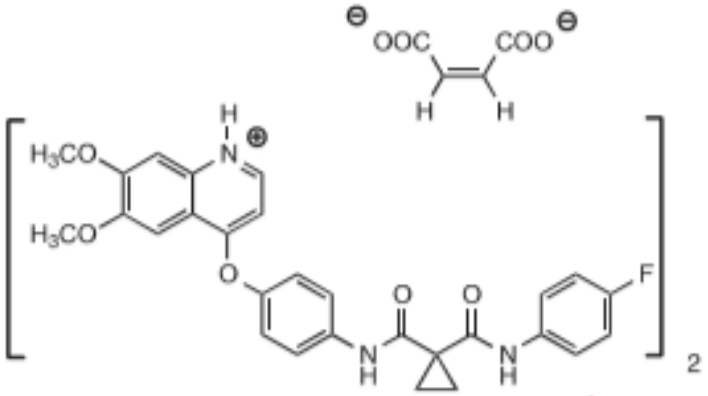
Figure 33.1 Tyrosine kinase inhibitors.

VI. VEGFR Kinase Inhibitors

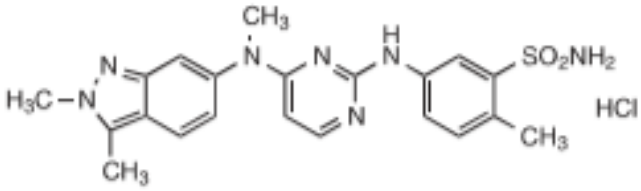
VEGFR kinase inhibitors



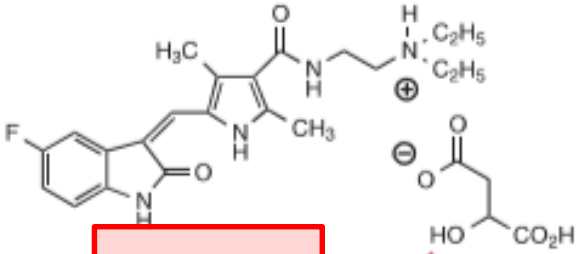
Axitinib (Inlyta)



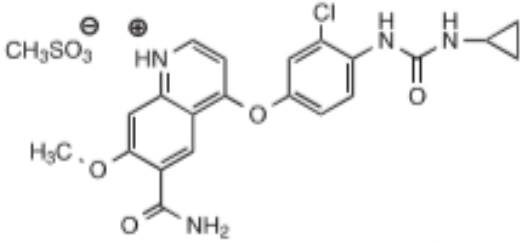
Cabozantinib maleate (Exelixis)*



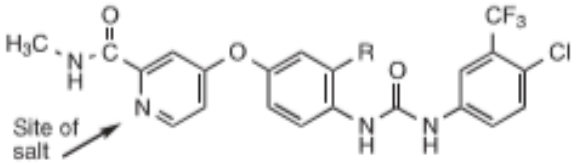
Pazopanib hydrochloride (Votrient)*



Sunitinib malate (Sutent)*



Lenvatinib mesylate (Lenvima)*



Sorafenib tosylate (R = H, tosylate = $C_7H_7SO_3^-$) (Nexavar)*

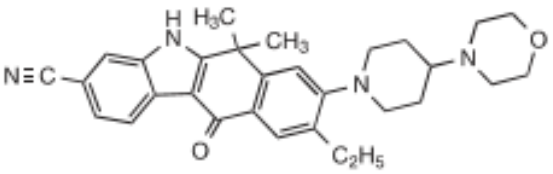
Regorafenib (R = F) (Stivarga)*

*Inhibits multiple kinases; **Irreversible kinase inhibitor

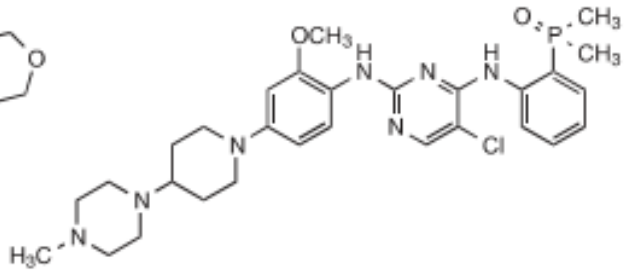
Figure 33.1 Cont'd

VI. ALK & Bruton Tyr Kinase Inhibitors

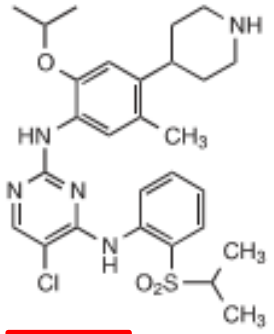
ALK inhibitors



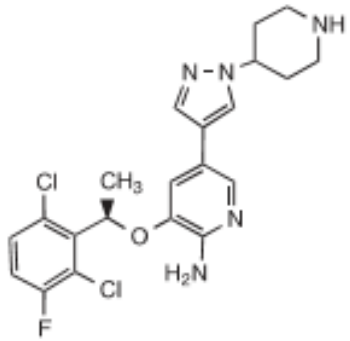
Alectinib (Alecensa)



Brigatinib (Alunbrig)*

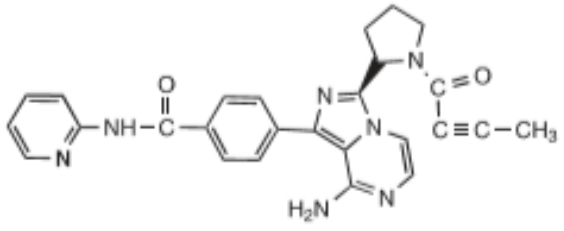


Ceritinib (Zykadia)

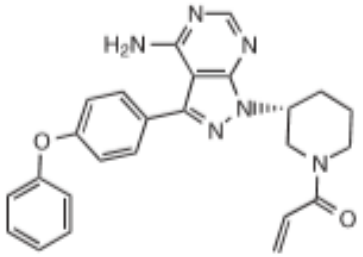


Crizotinib (Xalkori)*

Bruton tyrosine kinase inhibitors

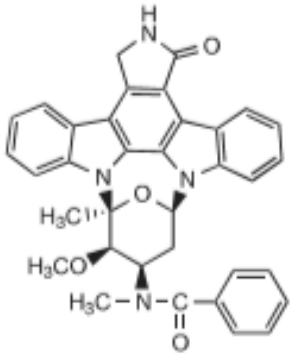


Acalabrutinib (Calquence)**



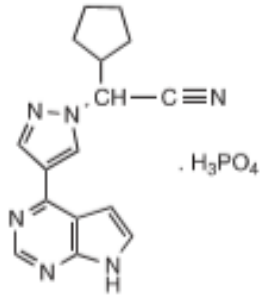
Ibrutinib (Imbruvica)**

FLT3 kinase inhibitor



Midostaurin (Rydapt)*

JAK inhibitor

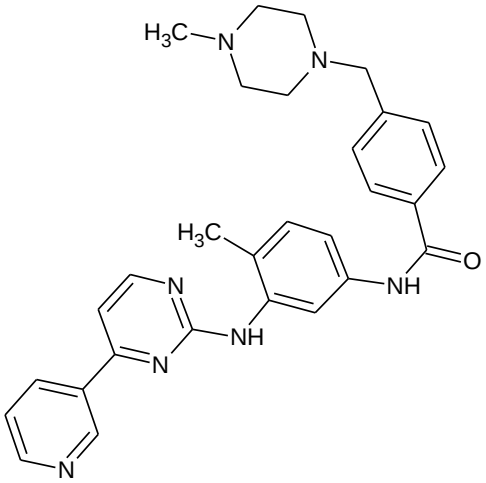


Ruxolitinib phosphate (Jakafi)

*Inhibits multiple kinases; **Irreversible kinase inhibitor

Figure 33.1 Cont'd

TKI: Imatinib



- Mesylate salt: $CH_3SO_3^-$
- CYP3A4- mediated N-dealkylation:

  equally active Desmethyl metabolite
- With large water of glass and with food to minimize GI distress

Interactions Between Bcr-Abl Tyr Kinase & Related Inhibitors

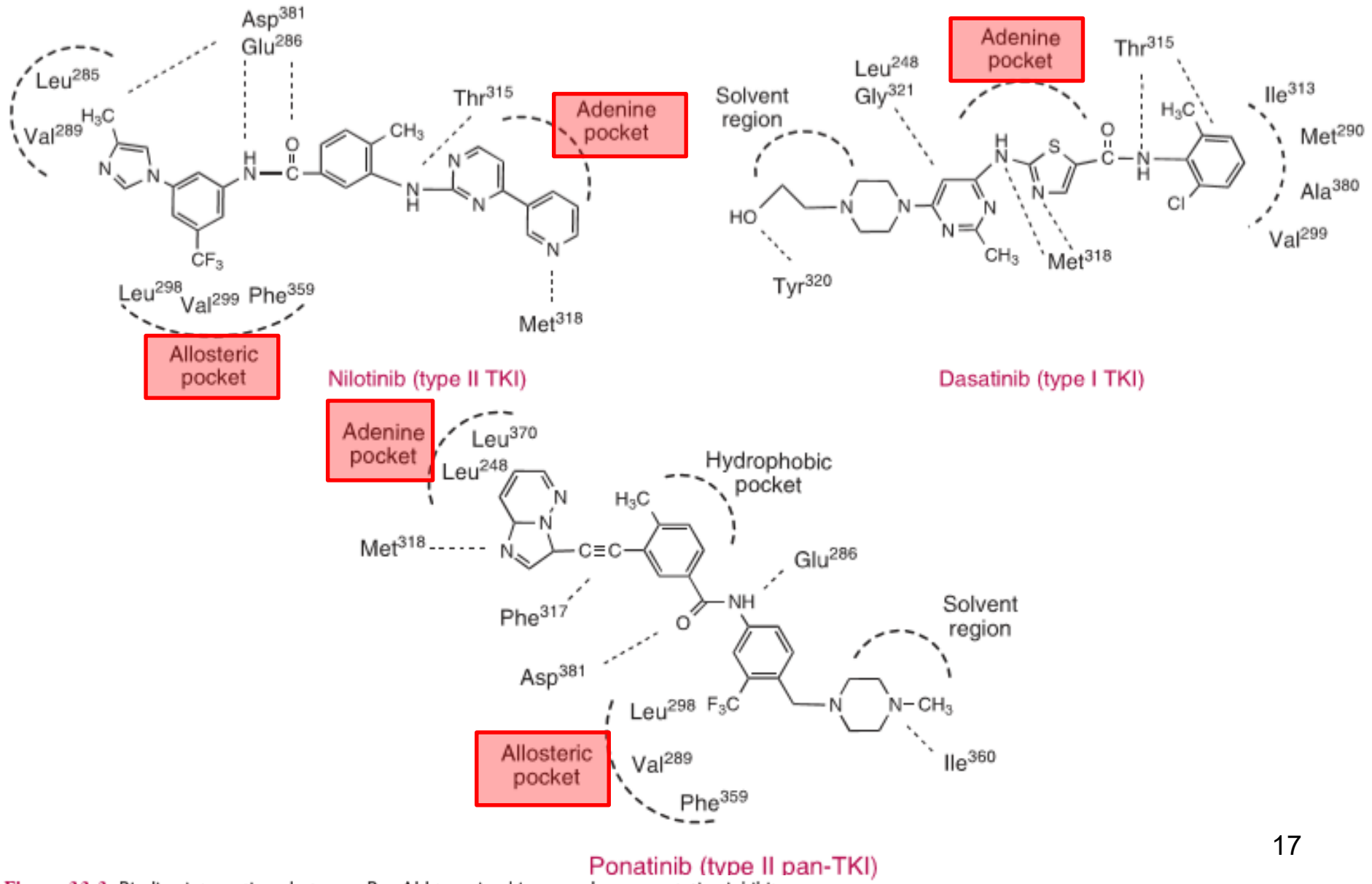


Figure 33.3 Binding interactions between Bcr-Abl tyrosine kinase and representative inhibitors.

Interactions Between EGFR/HER Kinase & Related Inhibitors

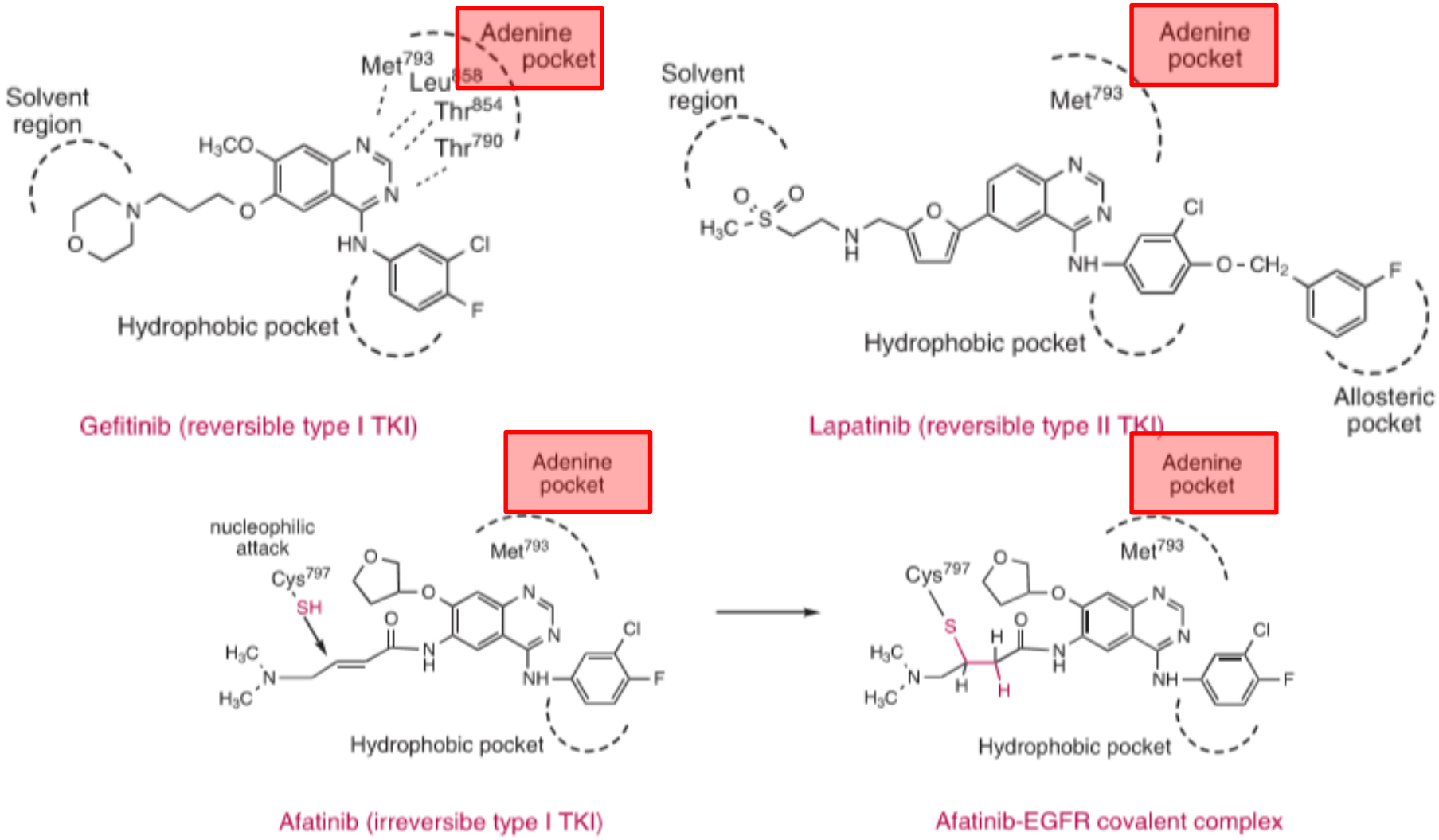
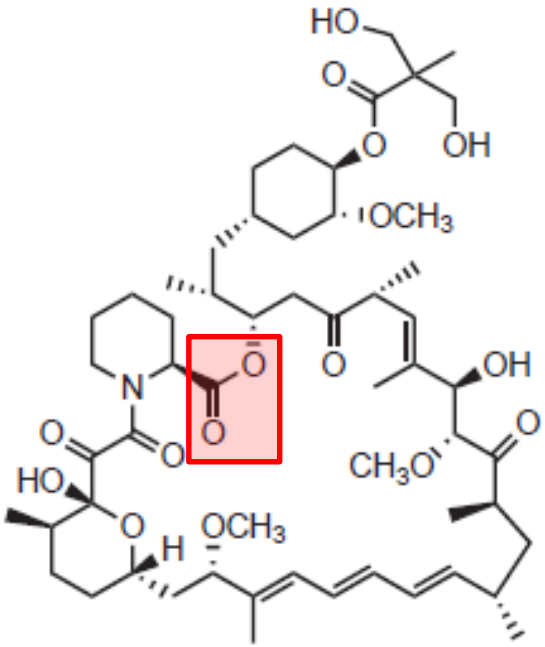


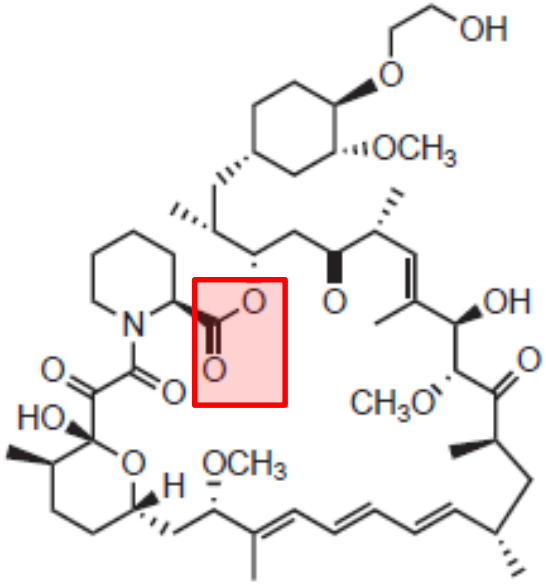
Figure 33.5 Binding interactions between EGFR/HER2 tyrosine kinase and representative inhibitors.

GatekeeperThr790

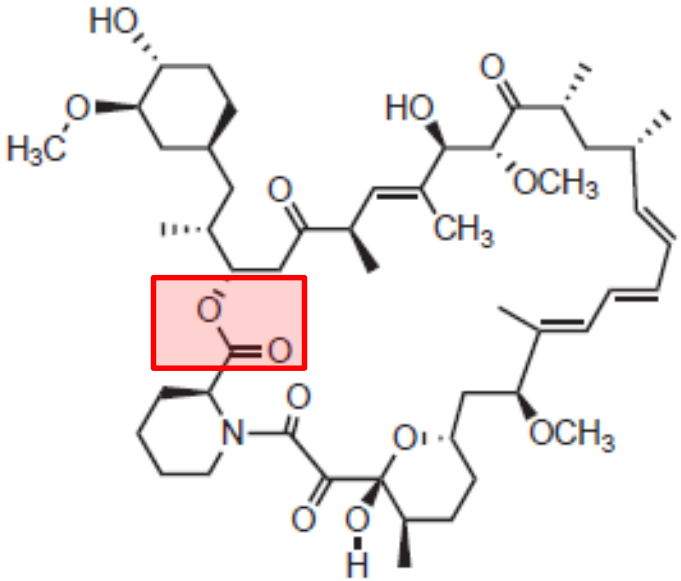
VI. mTOR Inhibitors



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

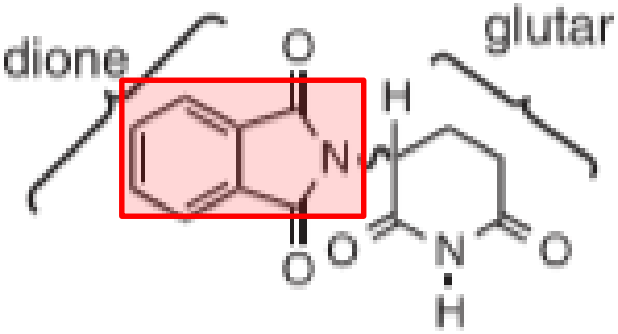
IX. Histone deacetylase inhibitors

X. Miscellaneous: hormonal, and specific agents

VIII. Immunomodulators

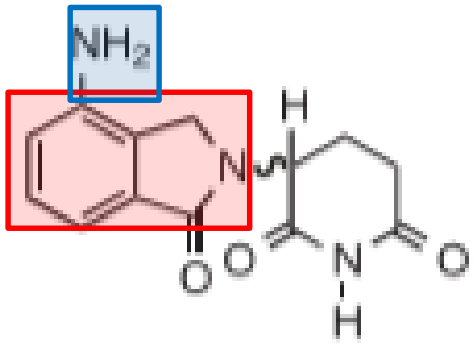
isoindole-1,3-dione

glutarimide

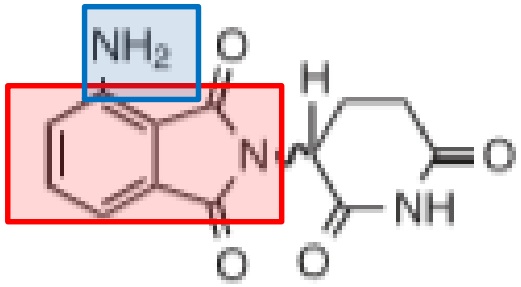


iso-indole
Or
phthalimide

Thalidomide
(Thalomid)



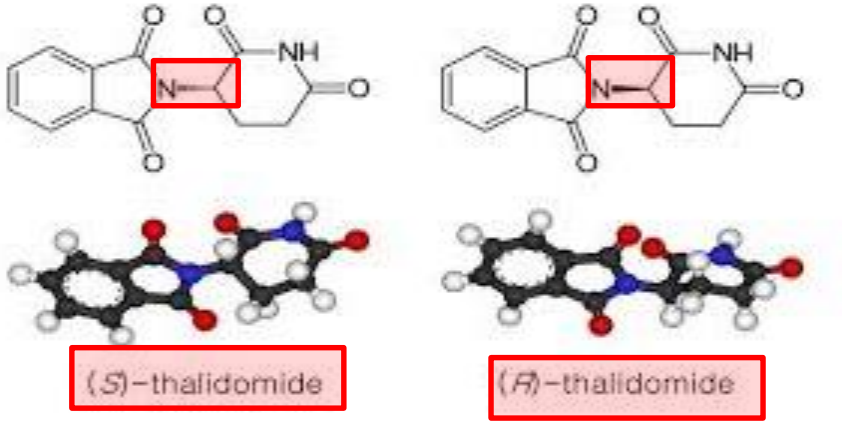
Lenalidomide
(Revlimid)

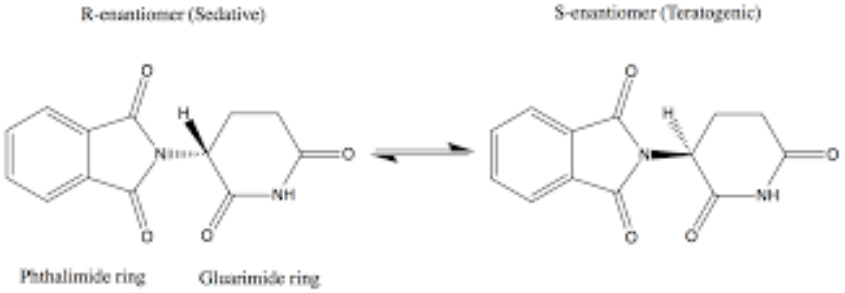


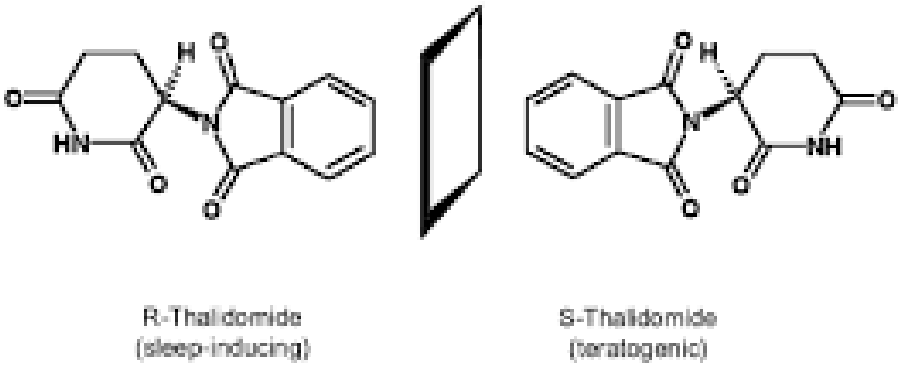
Pomalidomide (Pomalyst)

Immunomodulatory agents used in multiple myeloma

Stereochemistry of Thalidomide







Metabolism of Thalidomide

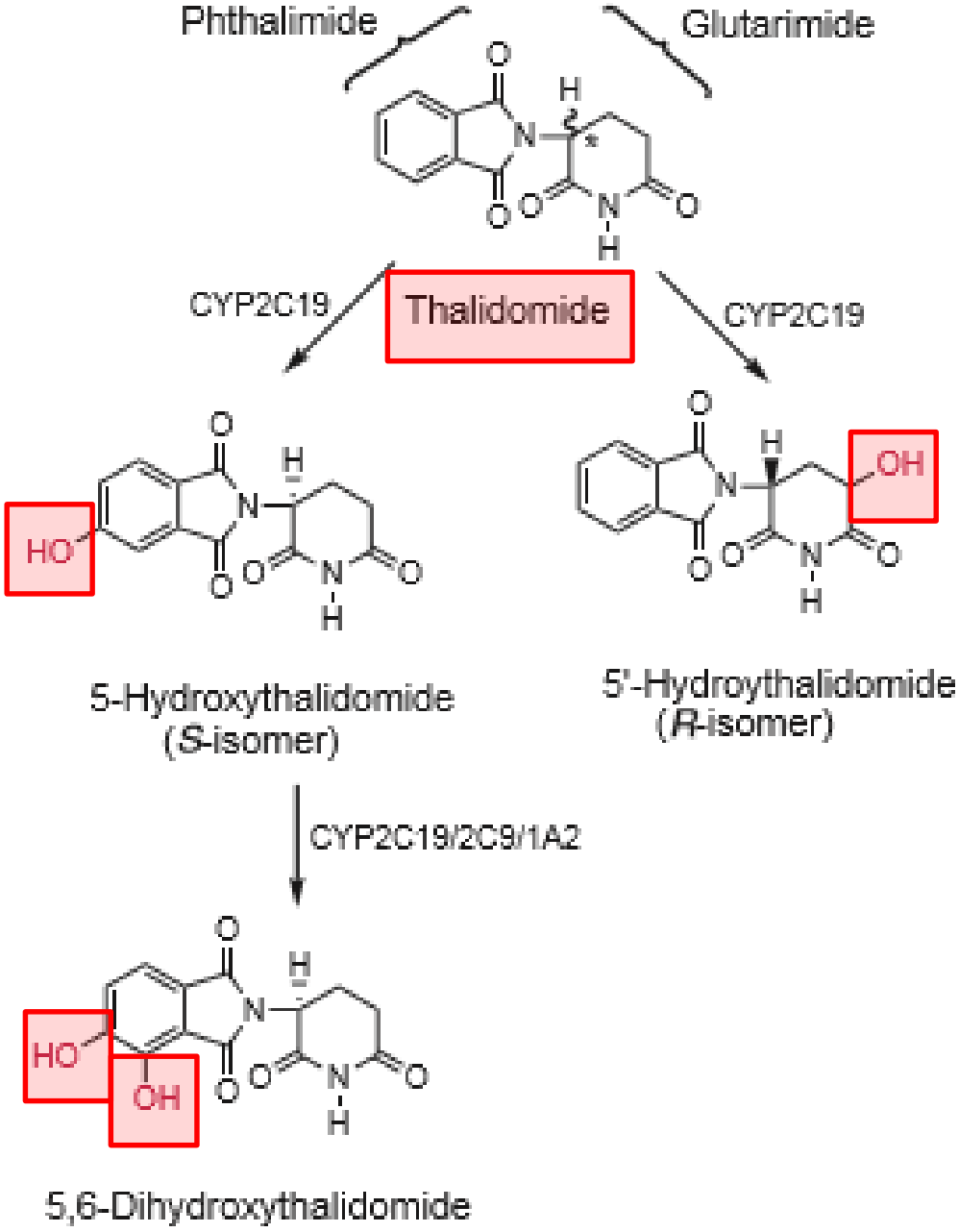


FIGURE 37.56 CYP2C19-mediated thalidomide metabolism.

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

Proteasome

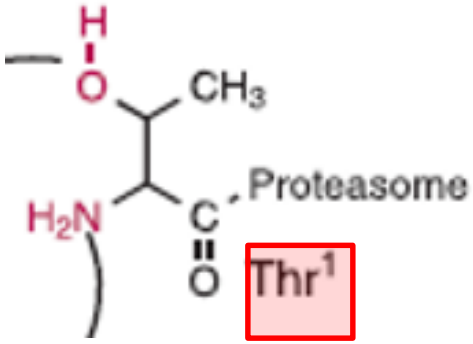
- Clear cells of cytoplasmic regulatory proteins
- By cleaving them into short peptides:
- Ubiquitin Proteasome Pathway (UPP): regulates cell processes in stress & immune response, transcription, cell-cycle differentiation, apoptosis, …
- 26S proteasome as recognition site for ubi-quitinated Prs
- ATP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

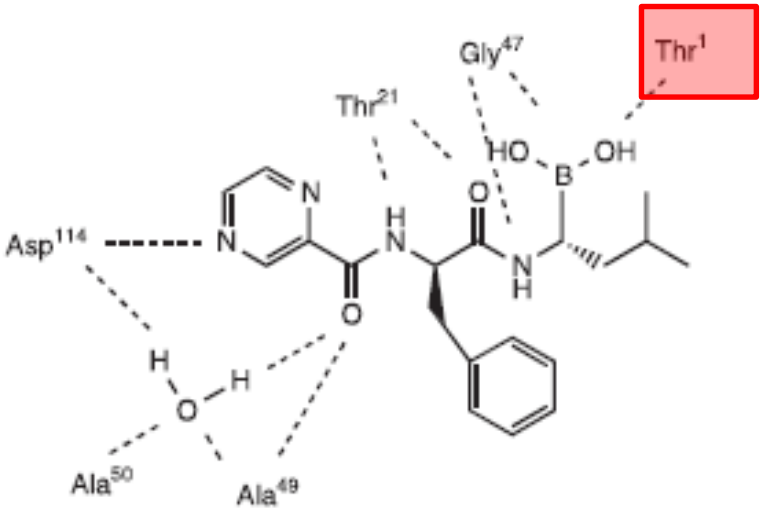
✓ dipeptide: bortezomib; ixazomib

✓ tetrapeptide: carfilzomib

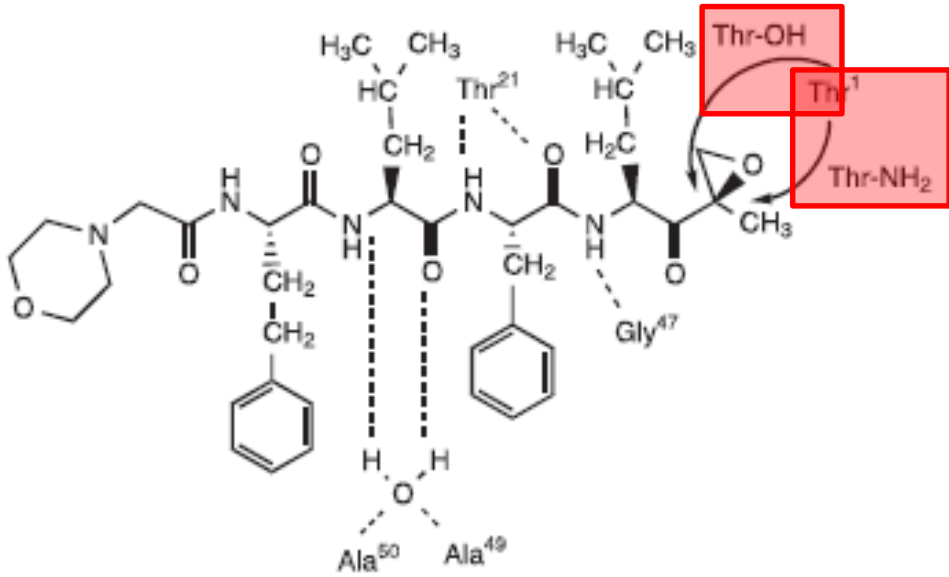
Proteasome Interaction Points

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





Bortezomib-proteasome (yeast) interactions



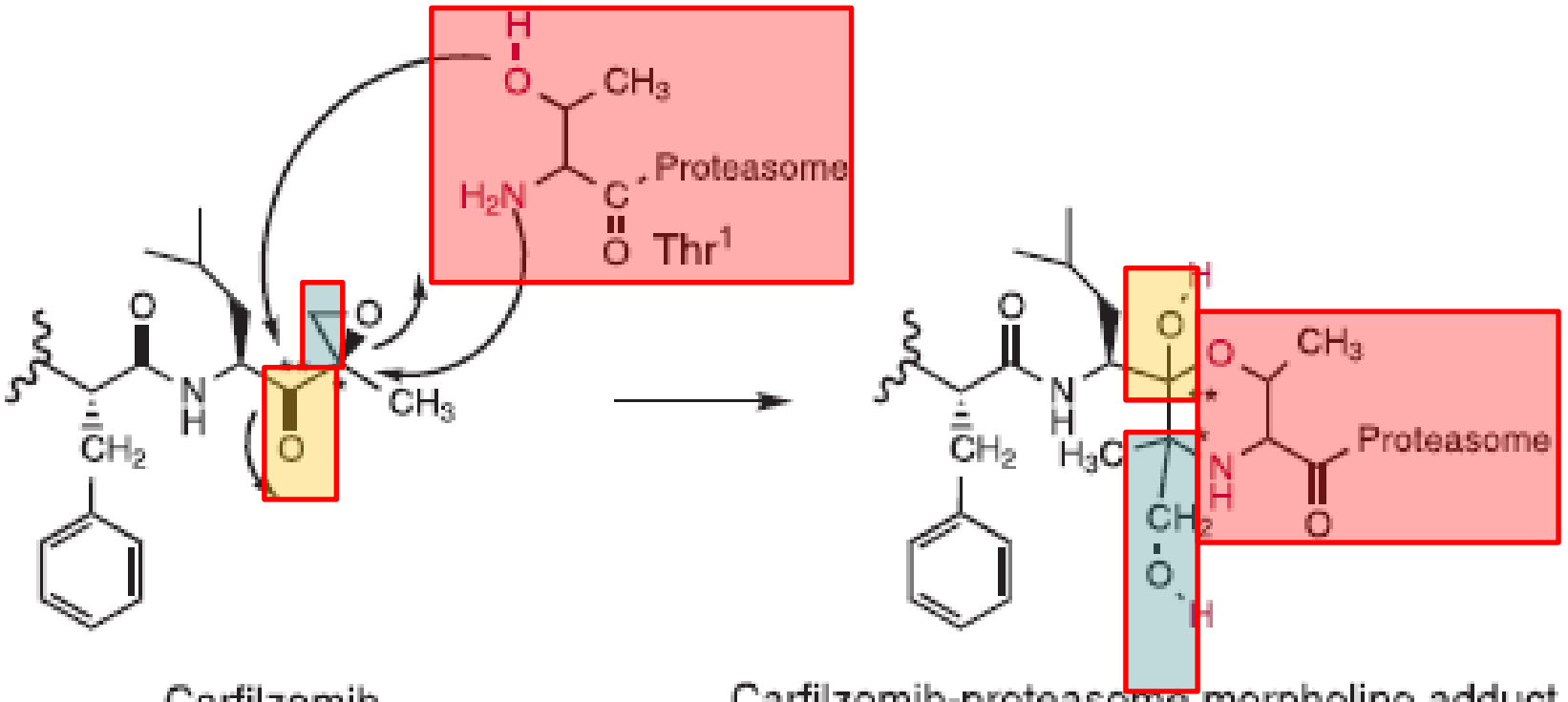
Carfilzomib-proteasome (human) interactions

Figure 33.21 Proteasome-inhibitor interactions.

SRAm

Carfilzomib: Irreversible Proteasome Inhibitor

- Consider Thr to provide morpholino adduct.



Pharmacologic lassification of Chemotherapeutic Agents- Contd.

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VI. Tyrosine kinase inhibitors & related agents

VII. Angiogenesis inhibitors & Immunomodulators

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:

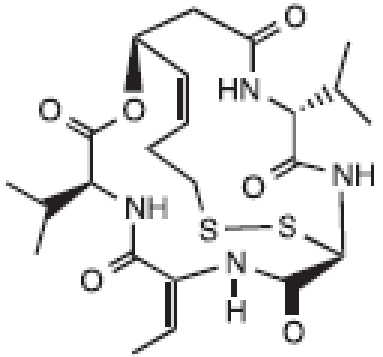
✓ keeps the chromatin in relaxed conformation

✓ blocks transcriptional repression

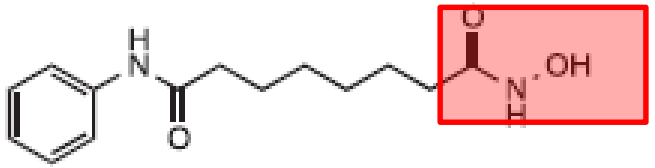
✓ provide tumor suppression

VII. Histone Deacetylase Inhibitors

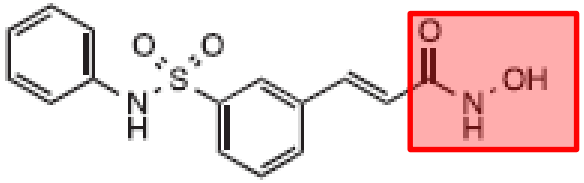
- Chemistry: depsipeptide or hydroxamic acid



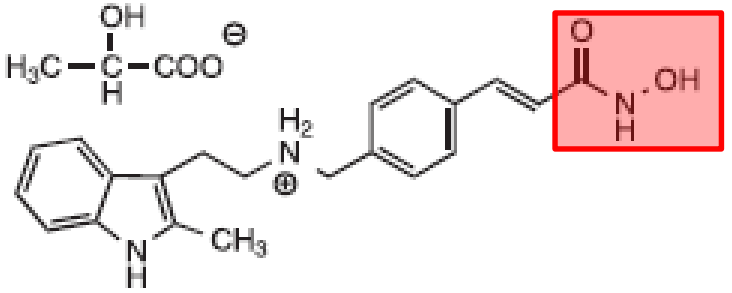
Romidepsin (Istodax)



Vorinostat (Zolinza)



Belinostat (Beleodaq)



Panobinostat lactate (Farydak)

Figure 33.23 Histone deacetylase inhibitors (HDACi).

Pharmacologic lassification of Chemotherapeutic Agents- Contd.

V. Mitosis inhibitors(antimitotic agents): natural alkaloids

VI. Tyrosine kinase inhibitors & related agents

VII. Angiogenesis inhibitors & Immunomodulators

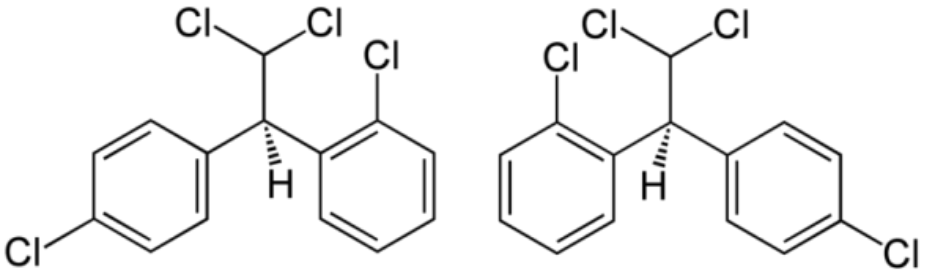
VIII. Proteasome inhibitor

IX. Histone deacetylase inhibitors

X. Miscellaneous: hormonal, and specific agents

IX. Miscellaneous Anticancer Agents

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



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