UNIVERSIDADE DE SÃO PAULO
FACULDADE DE CIÊNCIAS FARMACÊUTICAS
Departamento de Farmácia

Antineoplásicos I

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1 Dificuldades na terapia do câncer

2 Antineoplásicos

2.1 Agentes DNA *cross-linking*

2.2 Antimetabólitos

2.3 Agentes intercalantes

2.4 Inibidores da mitose

Referências bibliográficas

- Roche, V.F. Cancer and chemotherapy. Lemke, T.L.; Williams, D.A. Roche, V.F.; Zito, S.W. **Foye´s Principles of medicinal chemistry**. Filadelfia: Lippincott and Wilkins, 2013, cap.37, p.1199.
- Patrick, G.L. Anticancer agents. In:_____. **An introduction to medicinal chemistry**. Oxford: Oxford University Press, 2013, cap.21, p.514.
- Cunha, M.R.; Parise Filho, R. Antineoplásicos. In: ____. Ferreira, E.I; Barreiro, E.J; Giarolla, J.; Parise Filho, R. **Fundamentos de Química Farmacêutica Medicinal**. 2022, cap.35, p.611.

1 Dificuldades na terapia do câncer

Antineoplásicos

⇩

Fármacos anticrescimento

⇩ ⇩

Células cancerosas multiplicam-se (sofrem mitose) sempre mais rapidamente do que todas as células normais

Atingem também **células normais**, tais como células do sistema hematopoiético, mucosa interna, mucosa oral, folículos capilares e pele

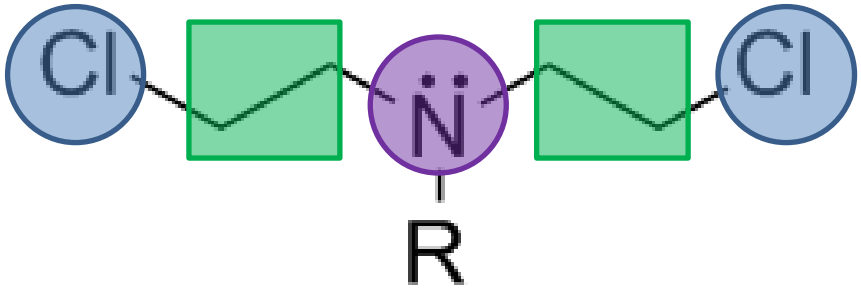
⇩

Leucopenia, trombocitopenia, anorexia, náusea, vômito, alopécia, cistite - podendo ser letais para o paciente

2 Antineoplásicos

2.1 AGENTES DNA *cross-linking*

Bis-β-haloalquilaminas

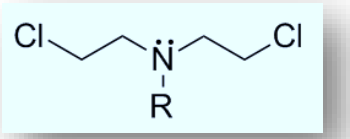


pH fisiológico?

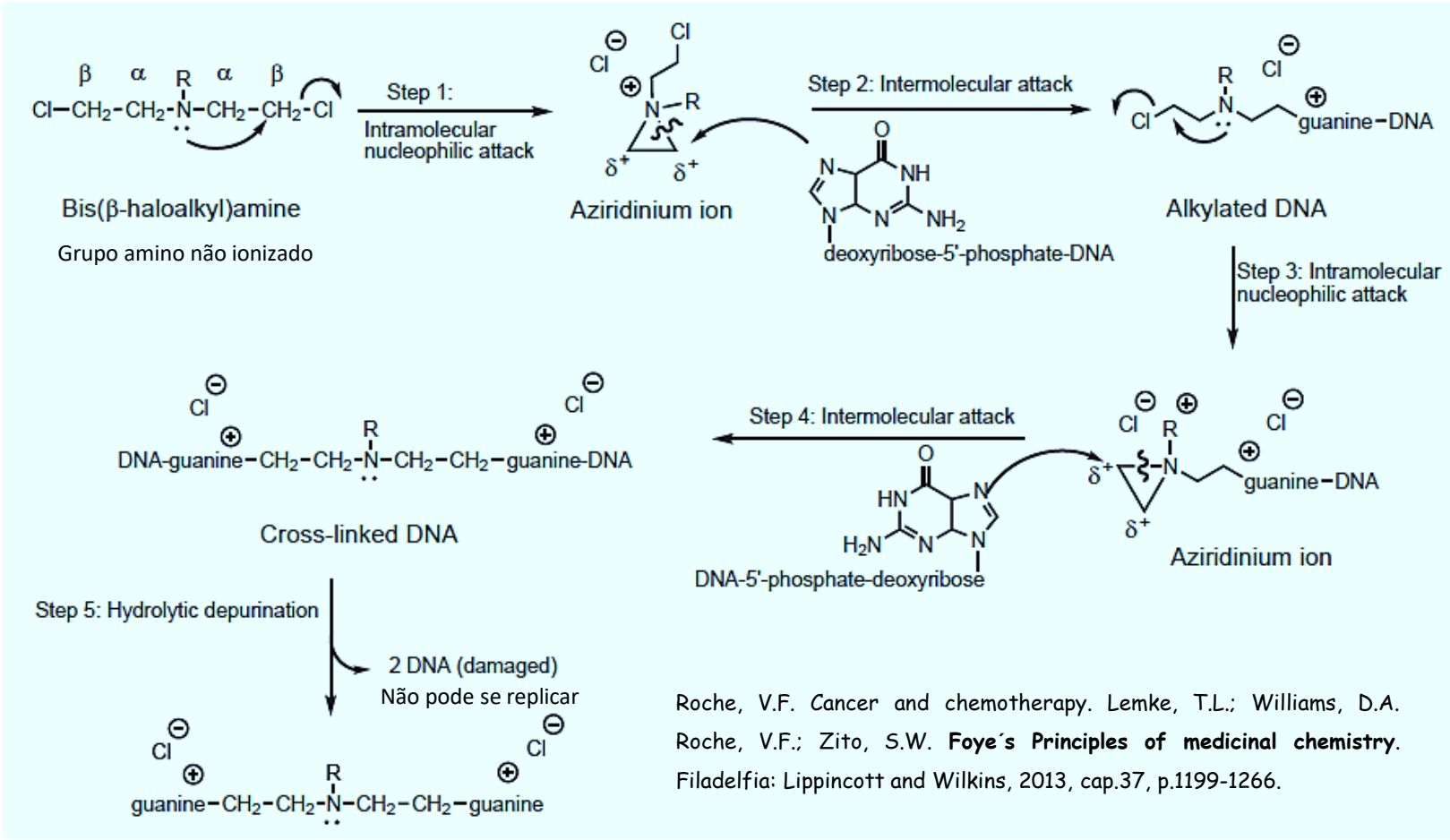
Efeito indutivo negativo → ↓ basicidade da amina

2 Antineoplásicos

2.1 AGENTES DNA *cross-linking*



São compostos extremamente **eletrofílicos** que reagem com grupos **nucleofílicos** do DNA → ligação IRREVERSÍVEL



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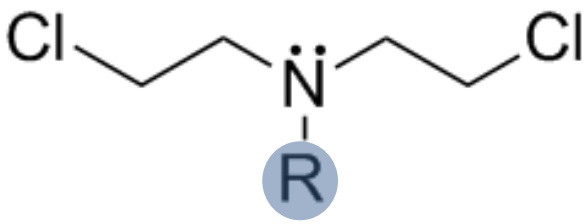
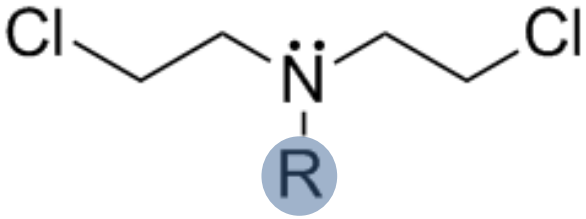
2 Antineoplásicos
2.1 Agentes DNA *cross-linking*
2.1.1 MOSTARDAS NITROGENADAS

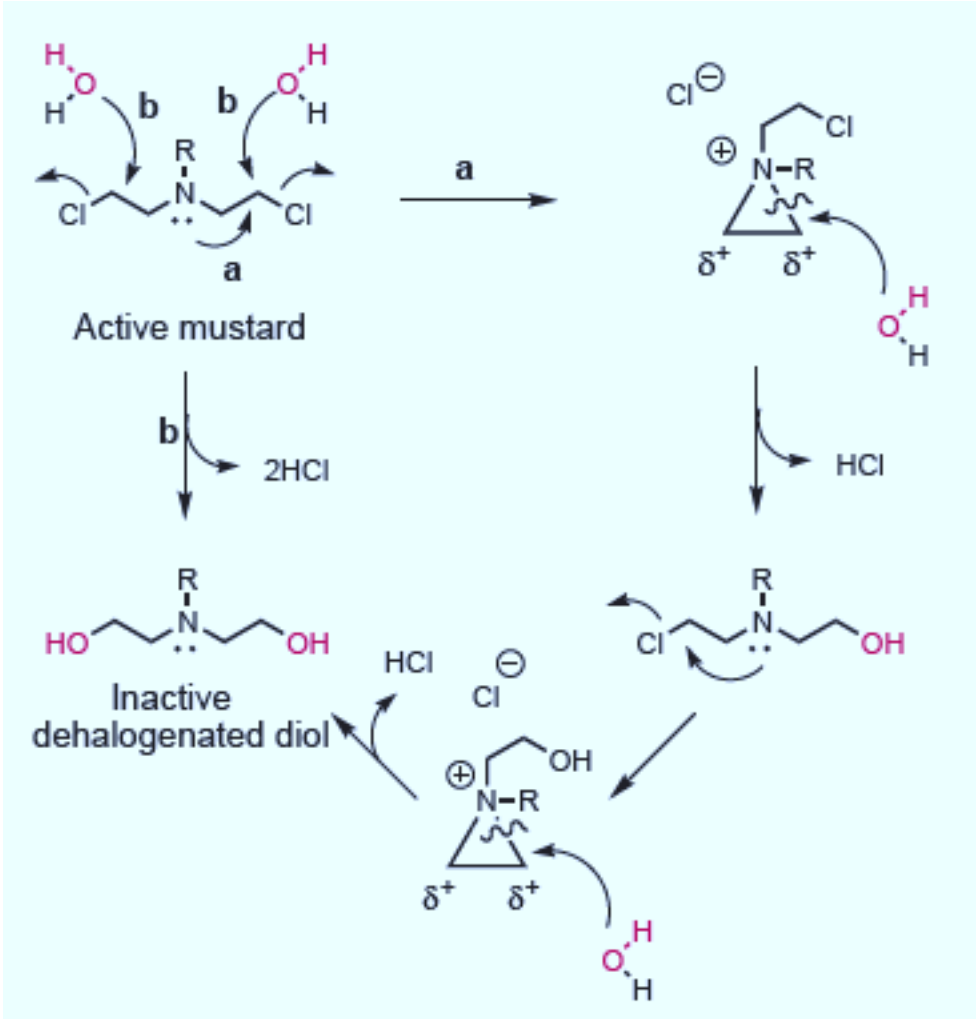


Aminoácidos de enzimas ou receptores de membrana

- ✓ **R** ligado ao **NITROGÊNIO** → reatividade, toxicidade e biodisponibilidade
- ✓ **R alifático** → rapidez da formação do íon aziridínio. **Toxicidade?**
- ✓ **R aromático** → formação do íon aziridínio mais lentamente. **Toxicidade?**

Estabilizar par de elétrons por ressonância





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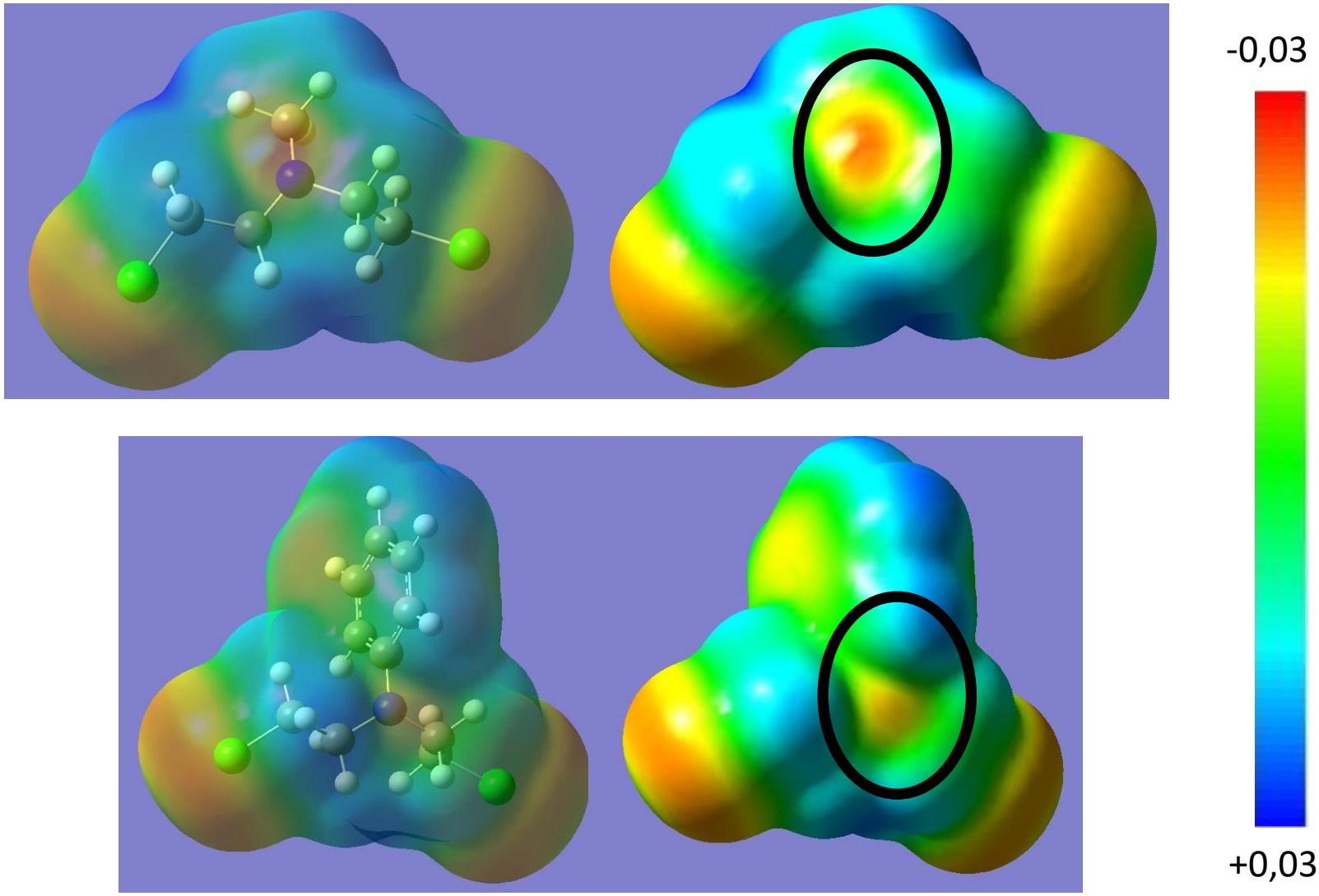
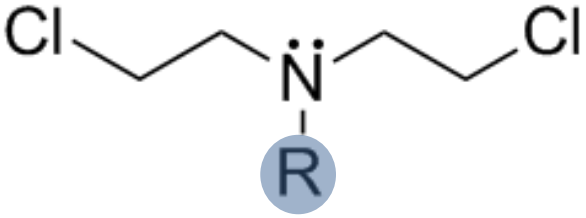
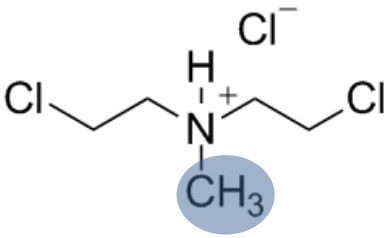
2.1.1 MOSTARDAS NITROGENADAS



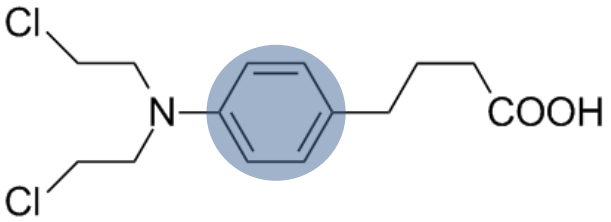
Mapas de potencial eletrostático comparativos entre moléculas com grupo N-CH_3 e N-Ph

2.1.1 MOSTARDAS NITROGENADAS

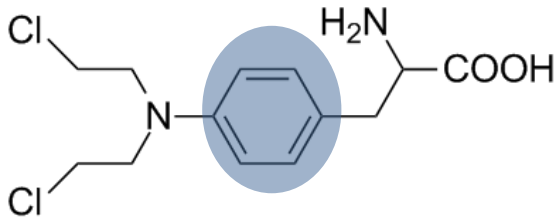




cloridrato de mecloretamina (Mustargen) - Alta reatividade, **muito tóxico**, uso limitado em cânceres hematológicos (IV).

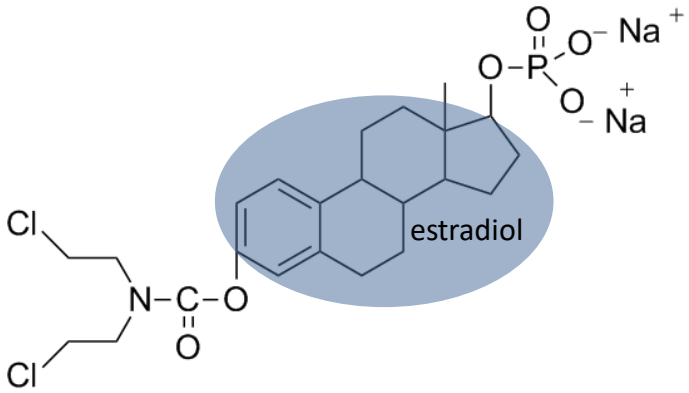


clorambucila (Leukeran) - **Menos reativo**. Administração por **VO**. Usado em leucemia linfoide crônica, linfoma maligno e de Hodgkin.



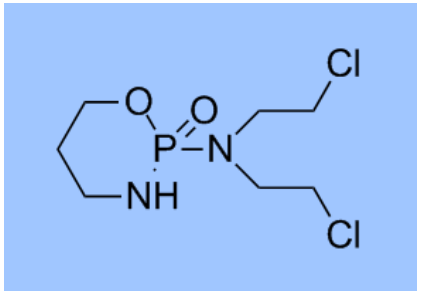
melfalano (Alkeran) - **Menos reativo**. Presença do **aminoácido L-Phe**. Administração por **VO** ou IV.

Transporte para a célula tumoral



fosfato sódico de estramustina (Emcyt) - **PRÓ-FÁRMACO**, administração por **VO**.

2.1.1 MOSTARDAS NITROGENADAS



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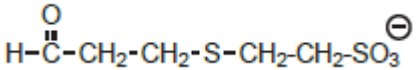
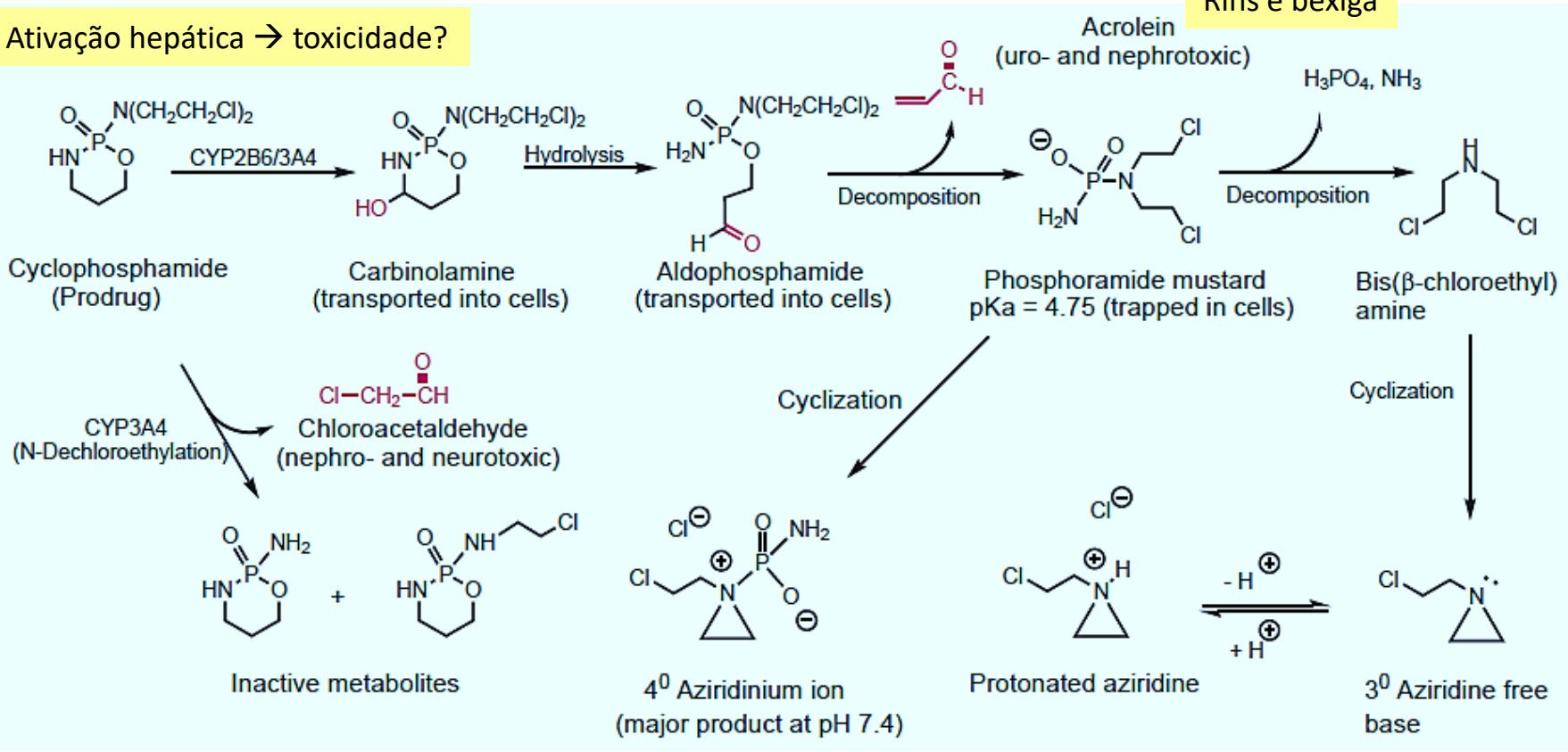
ciclofosfamida (Cytoxan) - **Pró-fármaco**. Uso em cânceres hematológicos e outros



Mesna (Mesnex)

Rins e bexiga

Ativação hepática → toxicidade?



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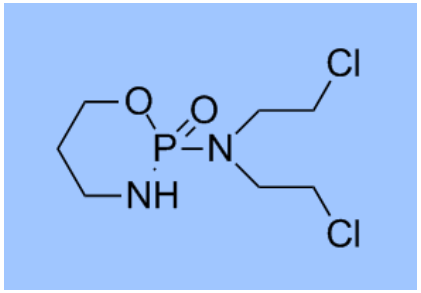
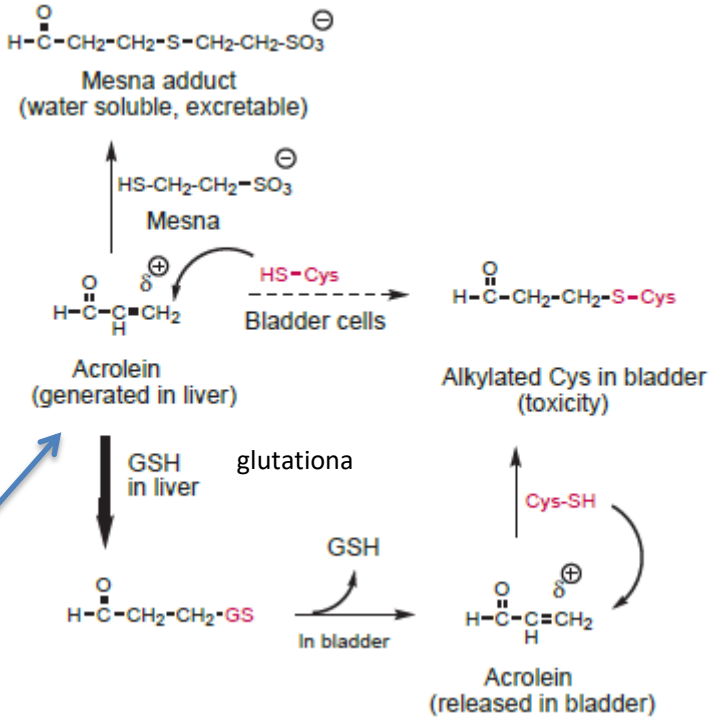
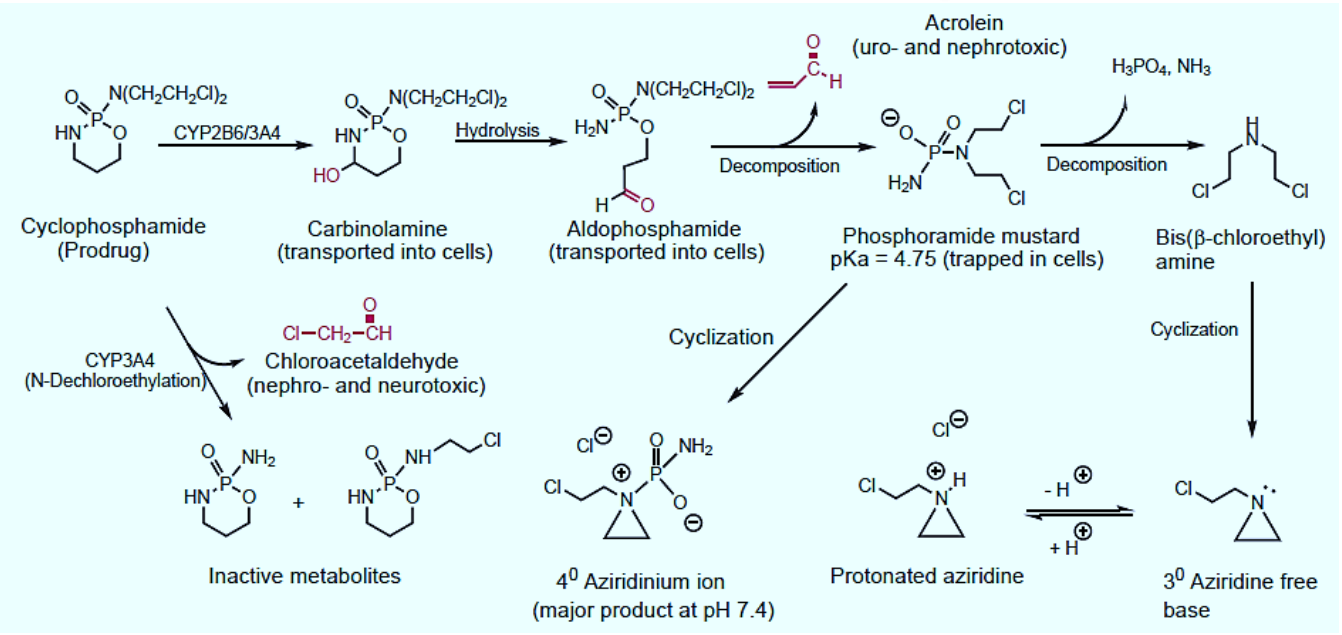


ciclofosfamida (Cytoxan) - Pró-fármaco. Uso em cânceres hematológicos e outros





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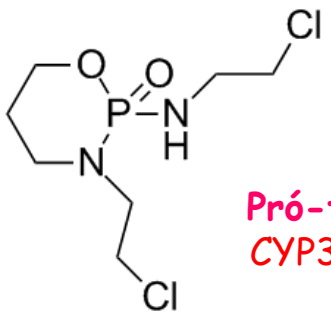
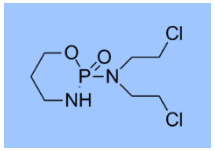
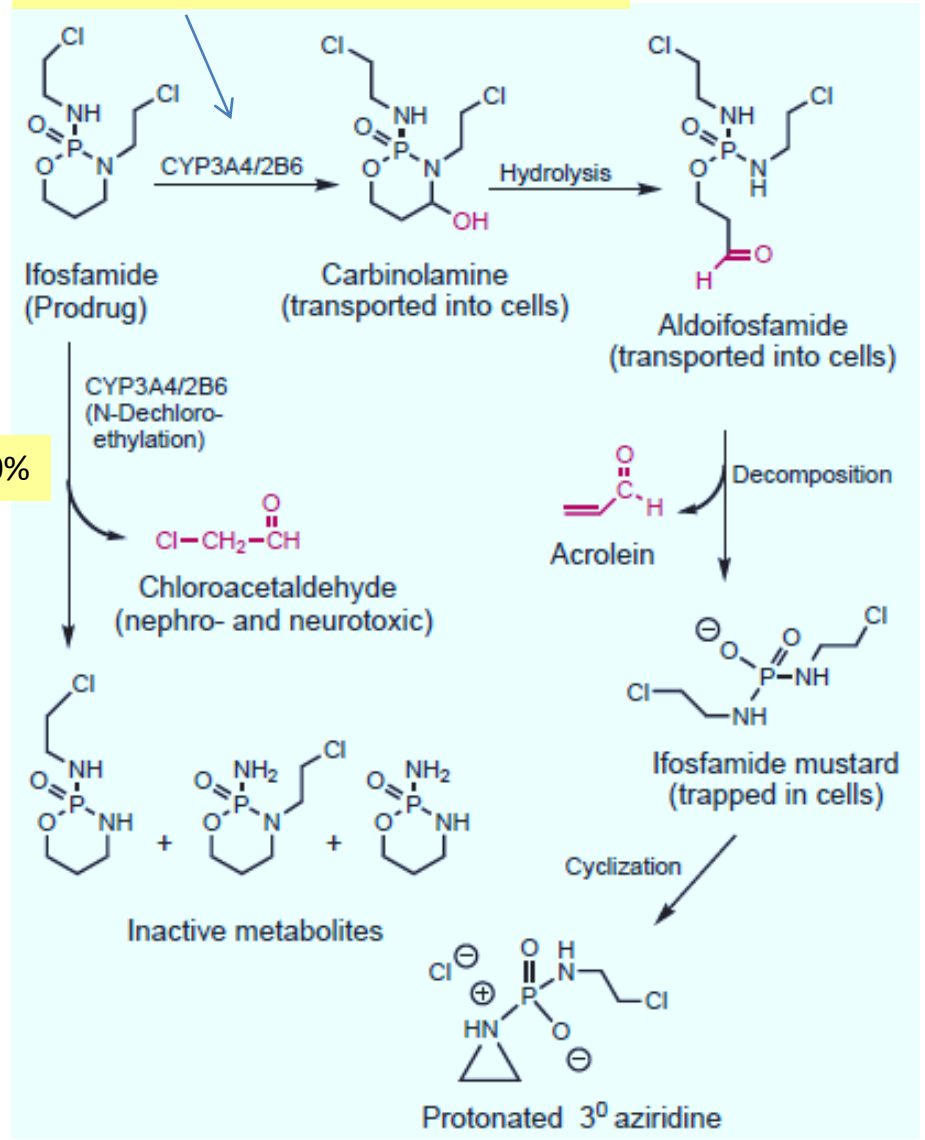




ifosfamida (Ifex)
Pró-farmaco, com ativação via CYP3A4 e CYP2B6. Uso em CA testicular

Ativação mais lenta → doses maiores



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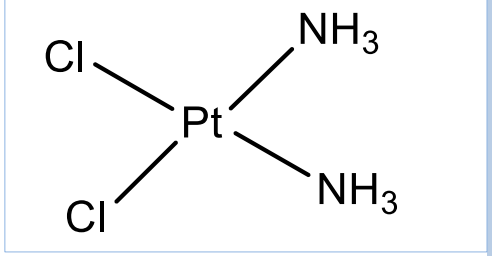
2 Antineoplásicos

2.1 Agentes DNA *cross-linking*

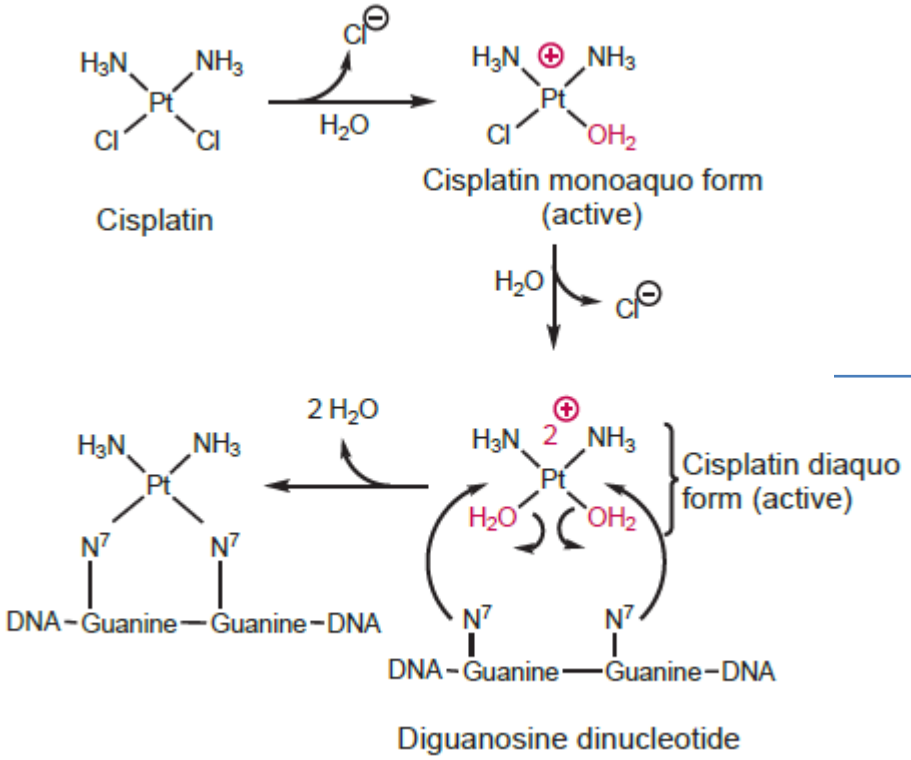
2.1.3 COMPOSTOS DE PLATINA (CISPLATINA)

íman

Metal elétron deficiente → nucleófilos



- ✓ Amplamente utilizado
- ✓ Pt(II) → "*square planar geometry*"
- ✓ Somatória de cargas = zero



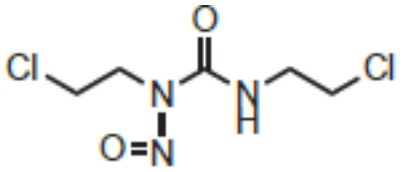
Mudança de conformação DNA

~~Ligação hidrogênio com pares de bases~~

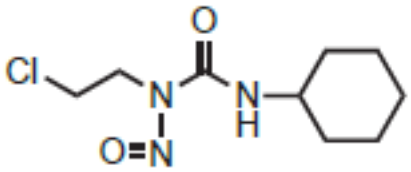
2 Antineoplásicos

2.1 Agentes DNA *cross-linking*

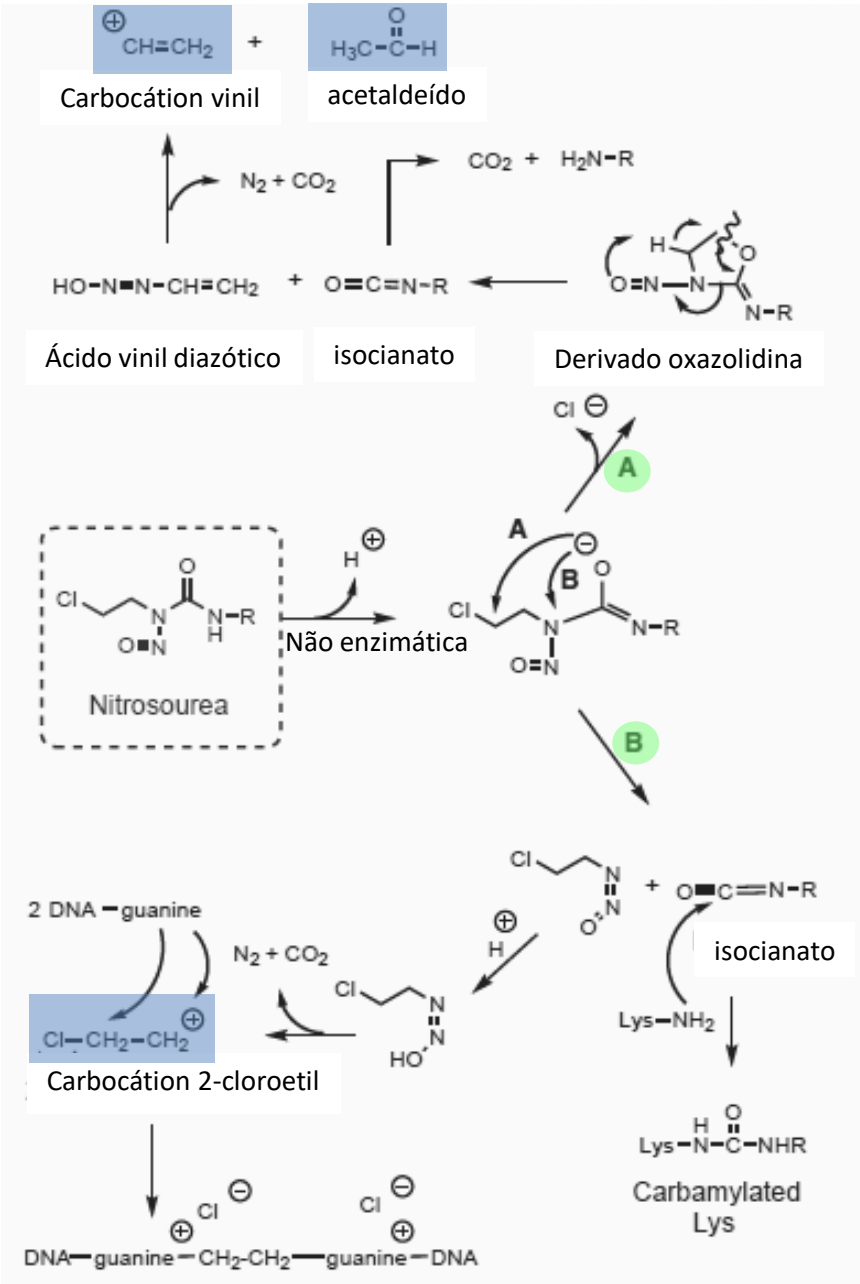
2.1.4 Nitrosureia



carmustina



lomustina



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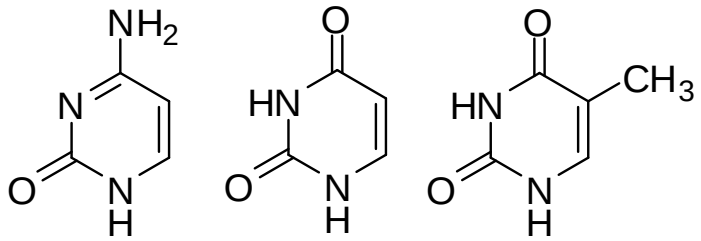
2 Antineoplásicos
2.2 ANTIMETABÓLITOS

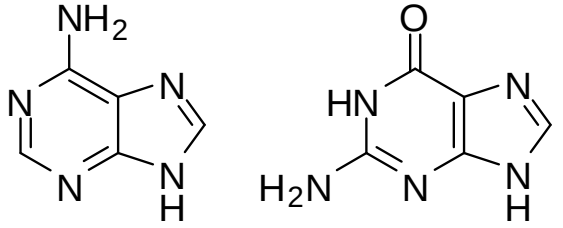
- ✓ Fármacos tem **semelhanças** estruturais com **substratos** endógenos
- ✓ Atuam em **enzimas** envolvidas na síntese de nucleotídeos → inibição do DNA ou síntese defeituosa
- ✓ Classificações:

1. **Antimetabólitos de pirimidinas**
2. **Antimetabólitos de purinas**



citosina uracila timina

Antimetabólito de pirimidina

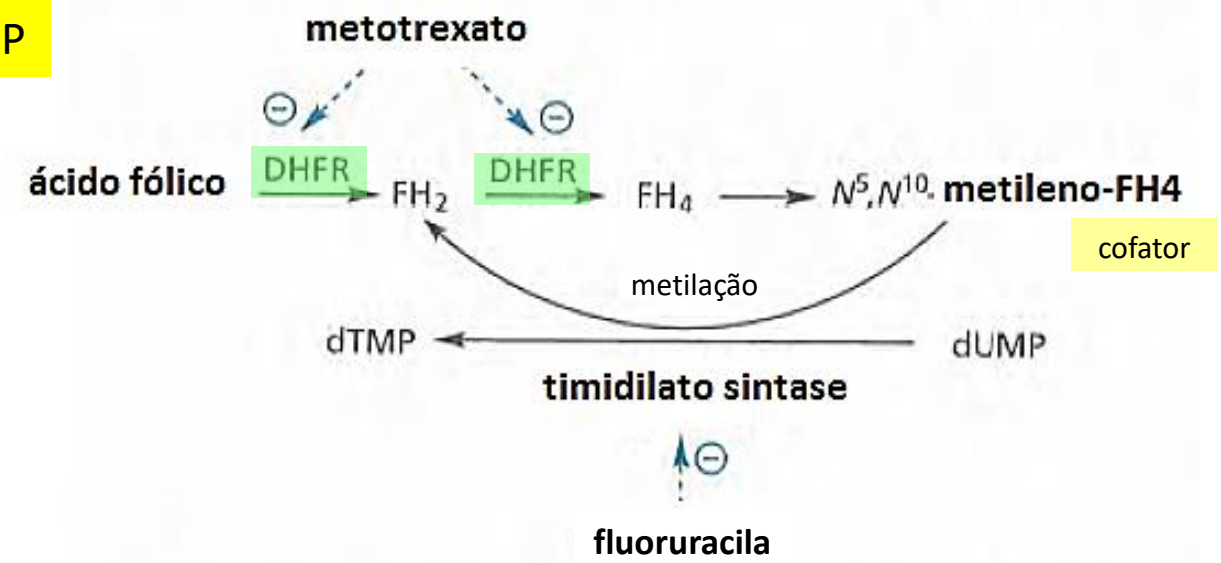


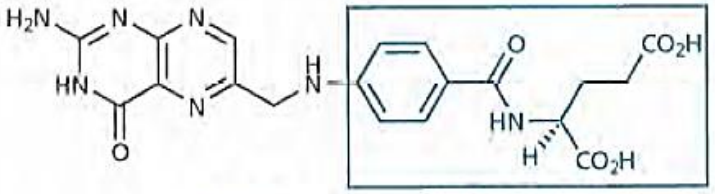
adenina guanina

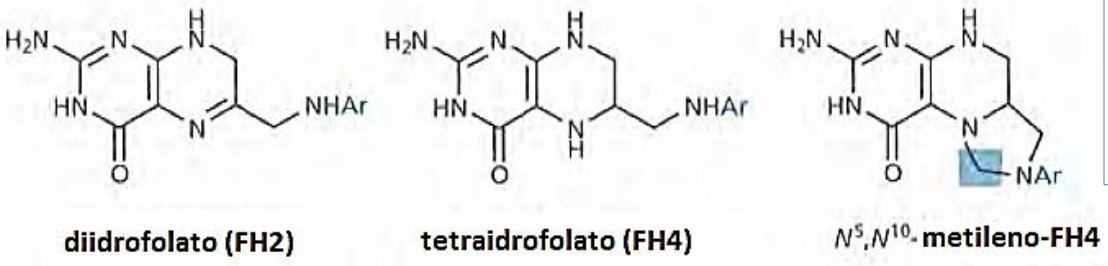
Antimetabólito de purina

2.2.1 INIBIDORES DA DIIDROFOLATO REDUTASE: antagonista de pirimidina

DHFR crucial → FH4 → dTMP







DHFR: **diidrofolato redutase**

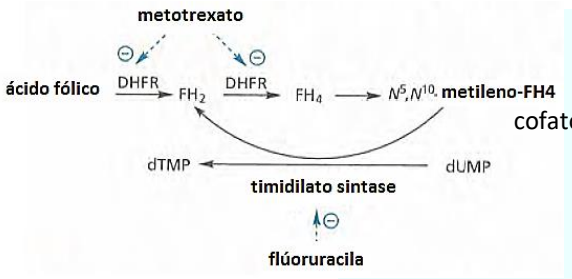
FH_2: diidrofolato

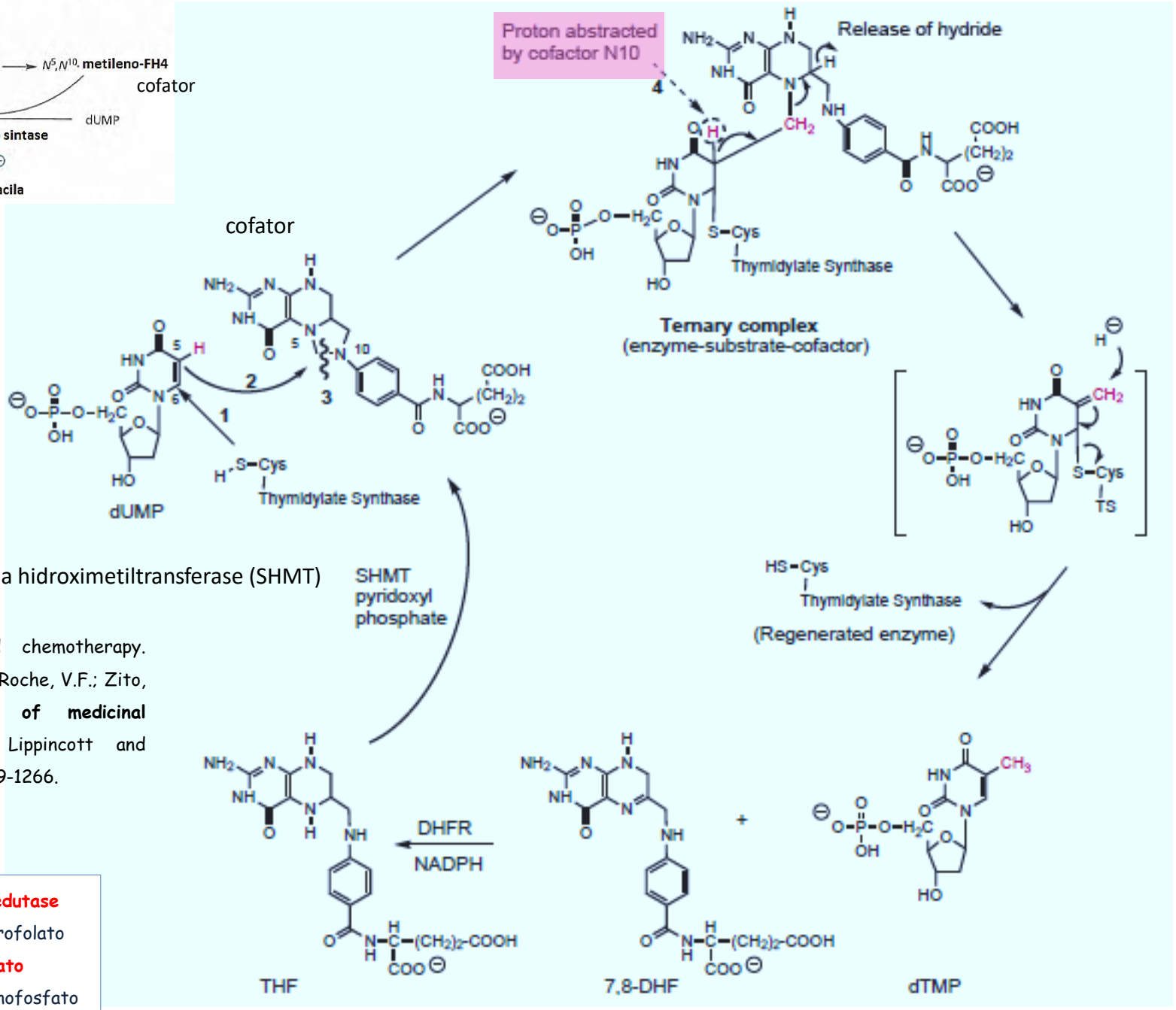
FH_4: **tetraidrofolato**

dUMP: desoxiuridina monofosfato

dTMP: desoxitimidina monofosfato

Patrick, G.L. Anticancer agents. In:_____. **An introduction to medicinal chemistry**. Oxford: Oxford University Press, 2013, cap.21, p.514-576



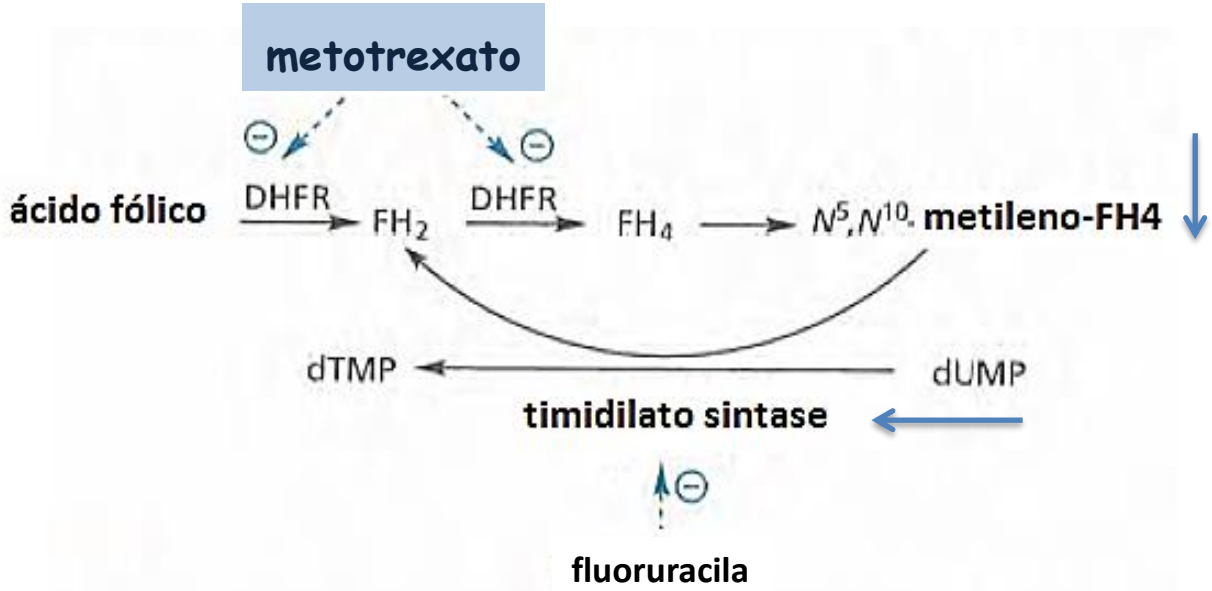


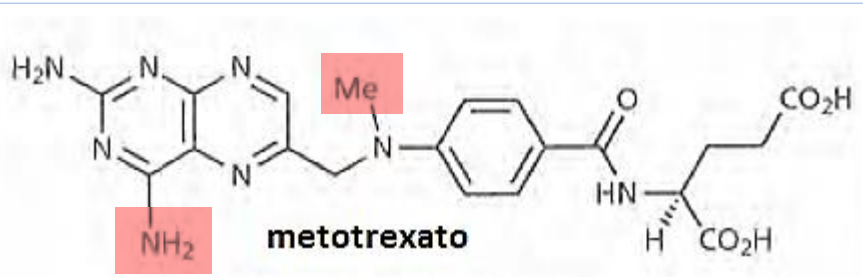
Serina hidroximetiltransferase (SHMT)

Roche, V.F. Cancer and chemotherapy. Lemke, T.L.; Williams, D.A. Roche, V.F.; Zito, S.W. **Foye´s Principles of medicinal chemistry**. Filadelfia: Lippincott and Wilkins, 2013, cap.37, p.1199-1266.

DHFR: **diidrofolato redutase**
FH_2 ou 7,8-DHF: diidrofolato
FH_4: **tetraidrofolato**
dUMP: desoxiuridina monofosfato
dTMP: desoxitimidina monofosfato

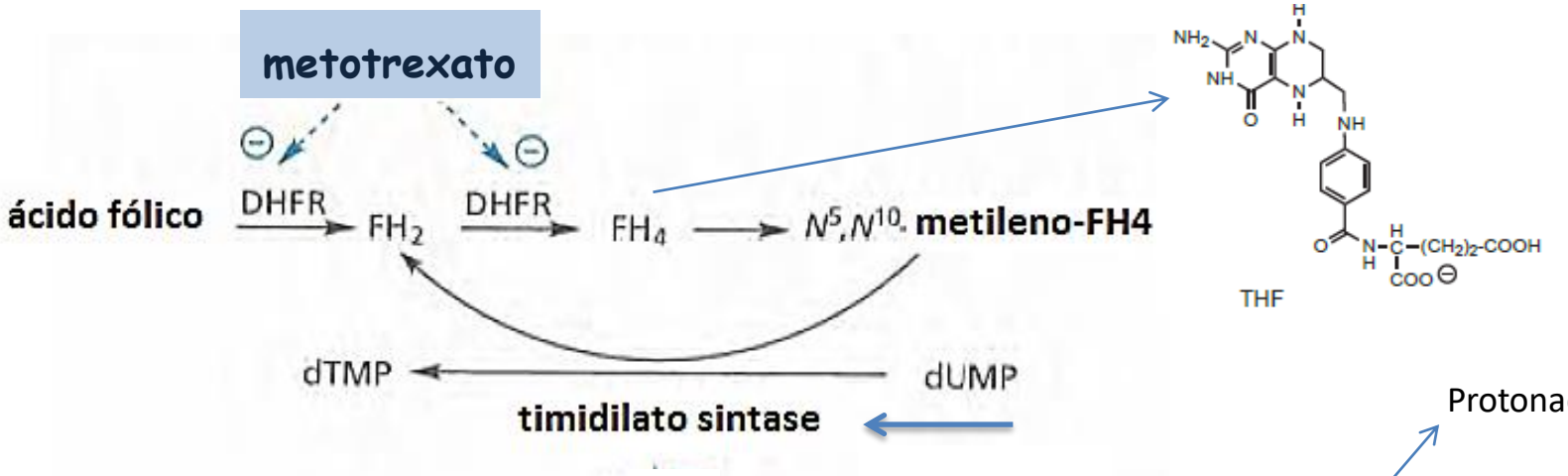
2.2.1 INIBIDORES DA DIIDROFOLATO REDUTASE



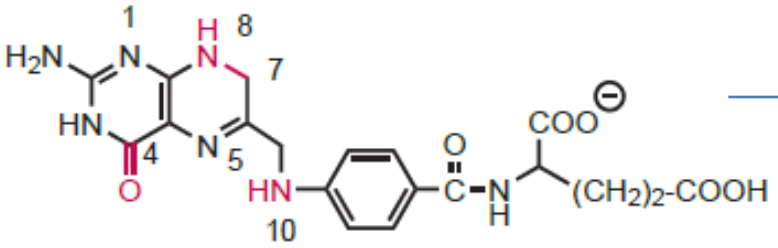


- ✓ Antimetabólito mais utilizado na quimioterapia
- ✓ **Inibidor da diidrofolato redutase**
- ✓ Redução da síntese desoxitimidina monofosfato (dTMP)

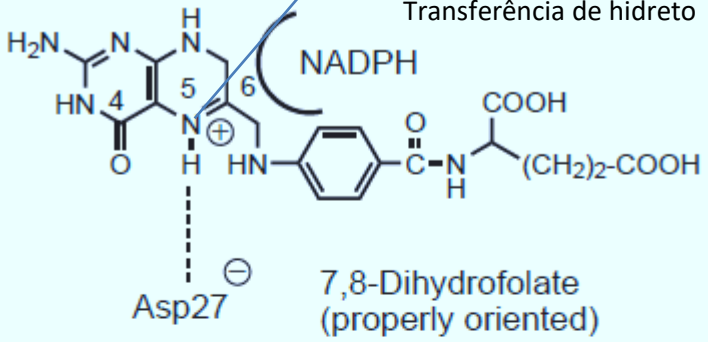
Patrick, G.L. Anticancer agents. In:_____. **An introduction to medicinal chemistry**. Oxford: Oxford University Press, 2013, cap.21, p.514-576

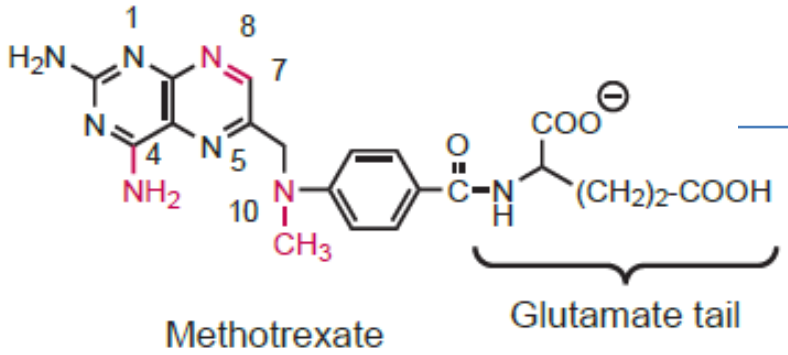


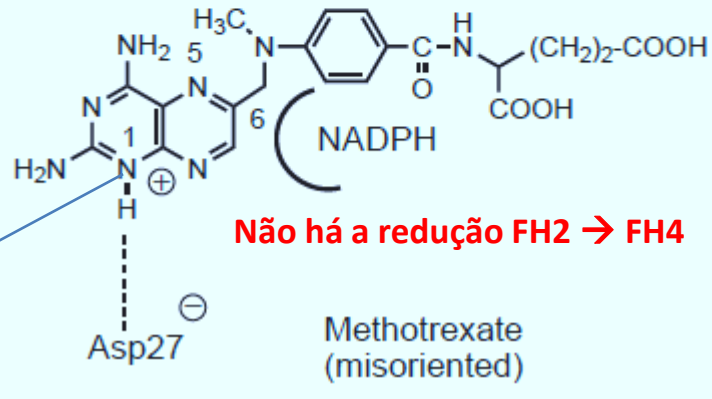
Protonação Glu30 DHFR



Transferência de hidreto







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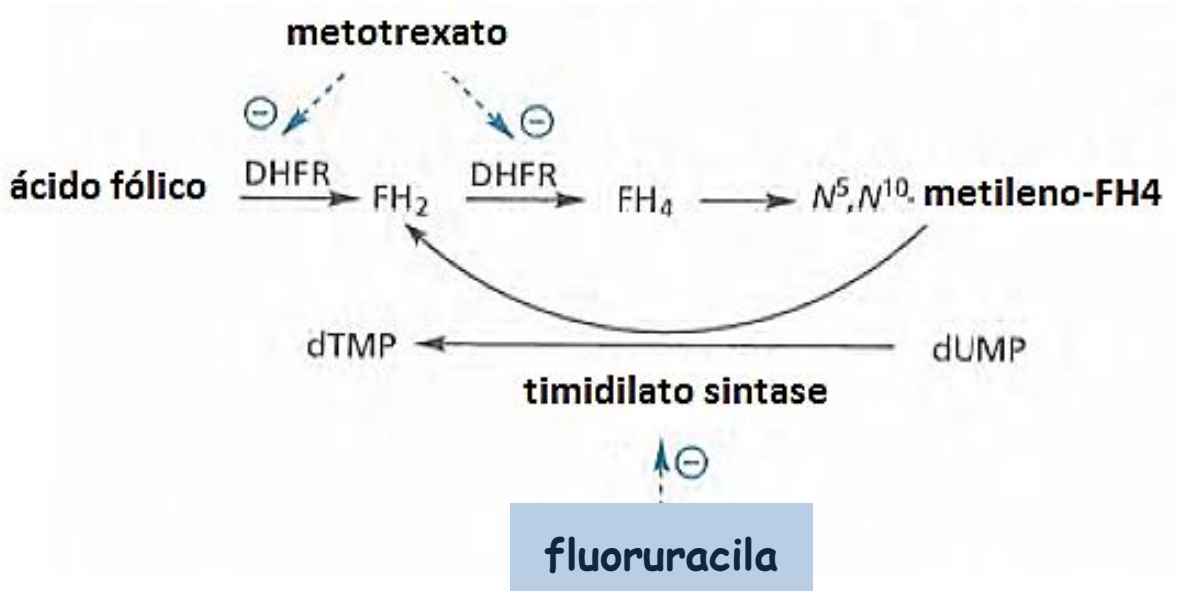
Roche, V.F. Cancer and chemotherapy. Lemke, T.L.; Williams, D.A. Roche, V.F.; Zito, S.W. **Foye´s Principles of medicinal chemistry**. Filadelfia: Lippincott and Wilkins, 2013, cap.37, p.1199-1266.

2.2.2 INIBIDORES DA TIMIDALATO SINTASE



- ✓ Antimetabólito direto
- ✓ A presença de **F** em **C5** impede que o complexo **fármaco-cofator-enzima** se desfaça
- ✓ Administrado IV: câncer de mama e TGI

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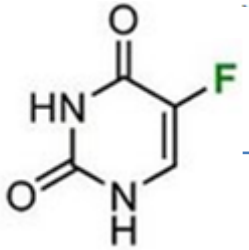
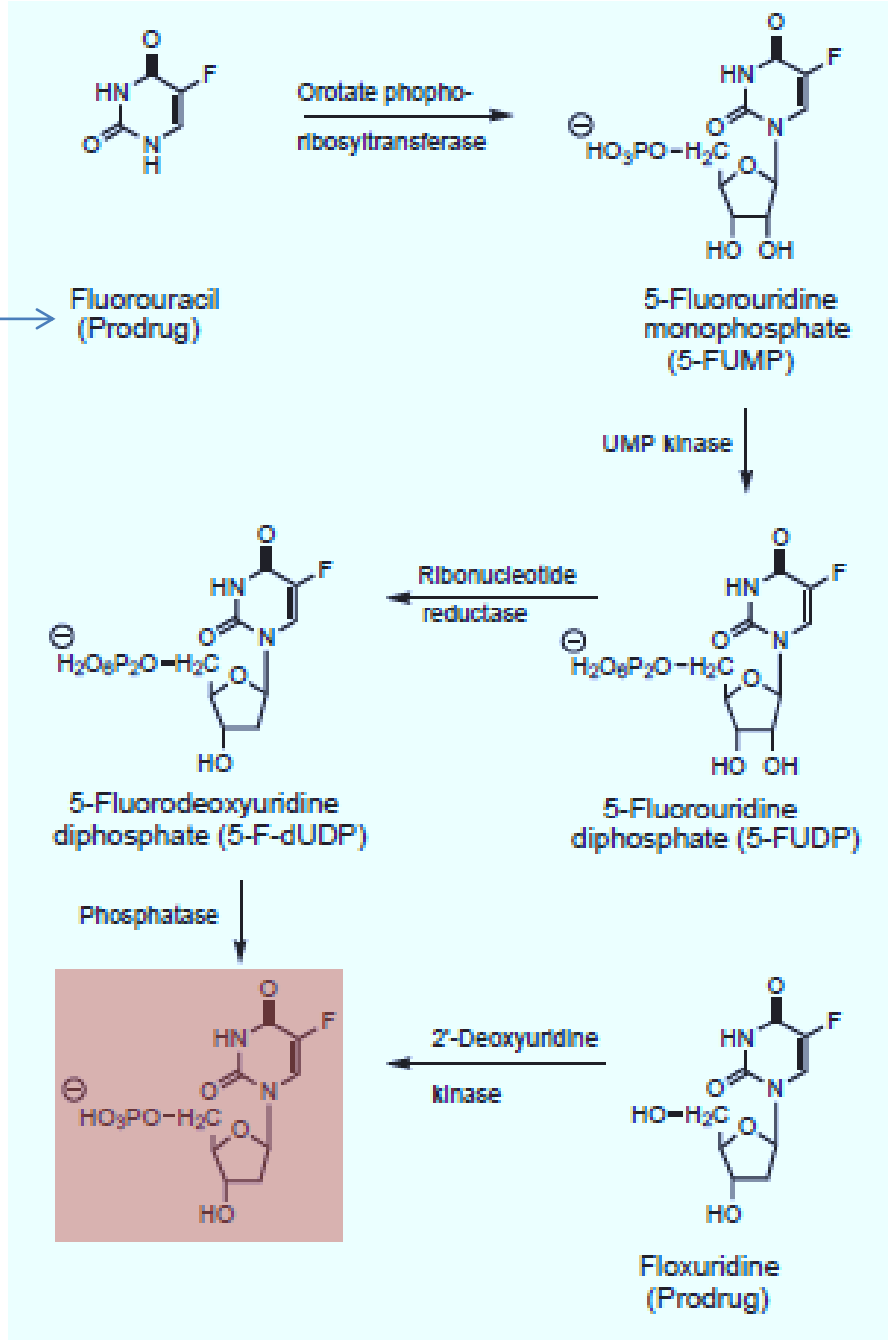
2.2.2 INIBIDORES DA TIMIDALATO SINTASE



fluoruracila

Pró-fármaco



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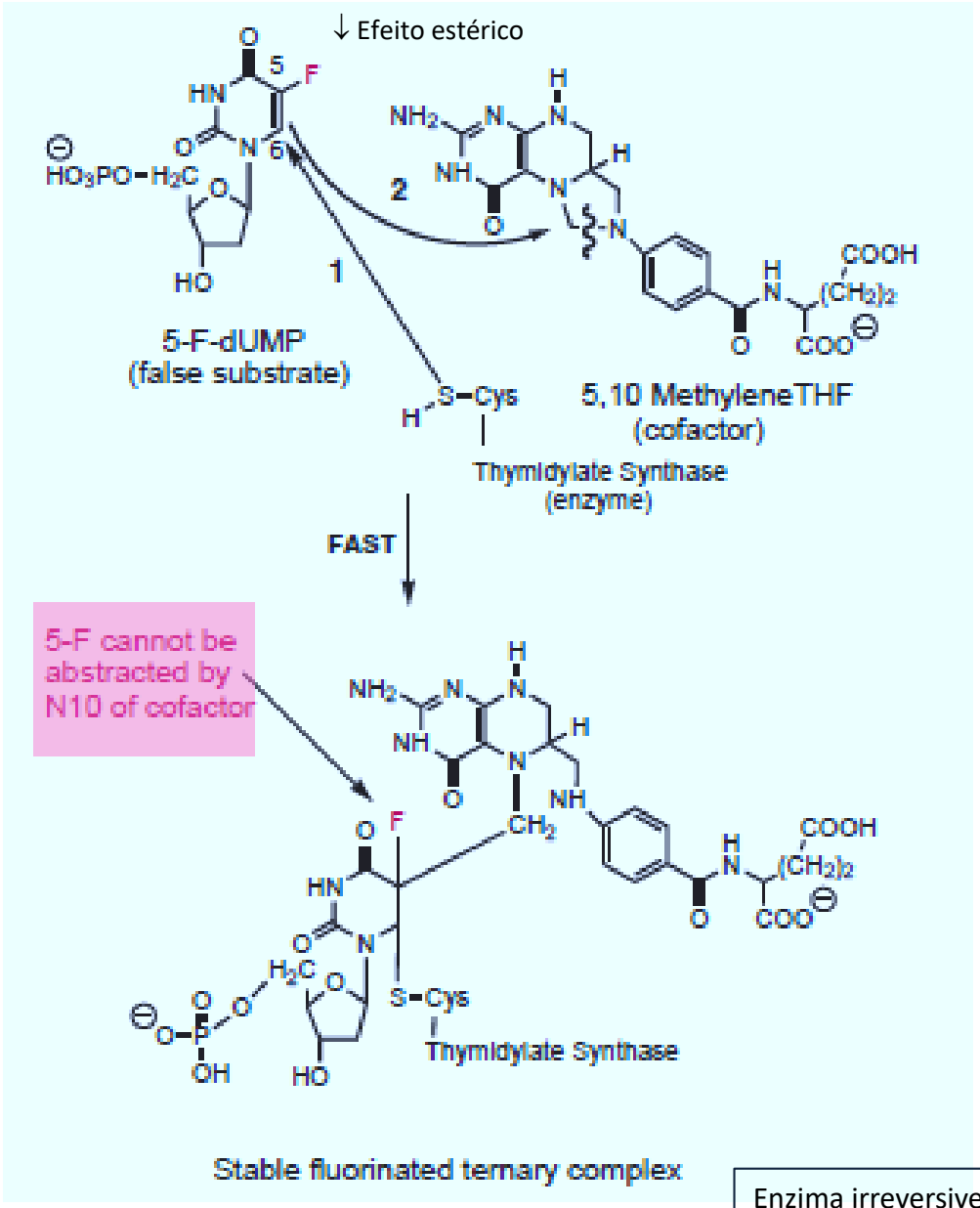
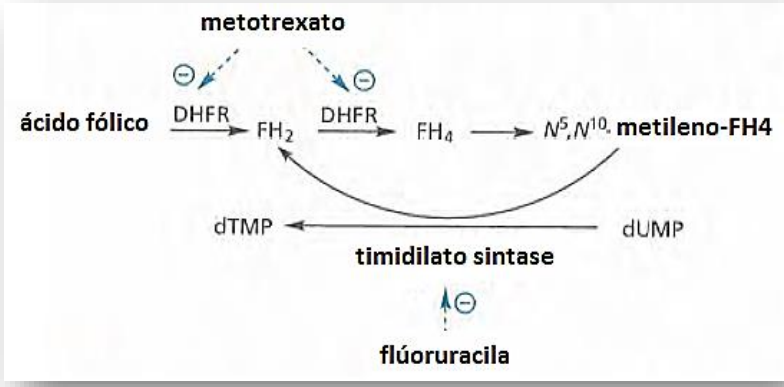
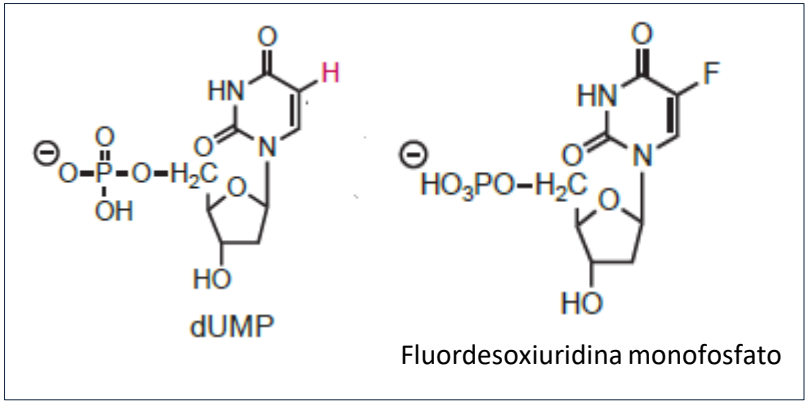




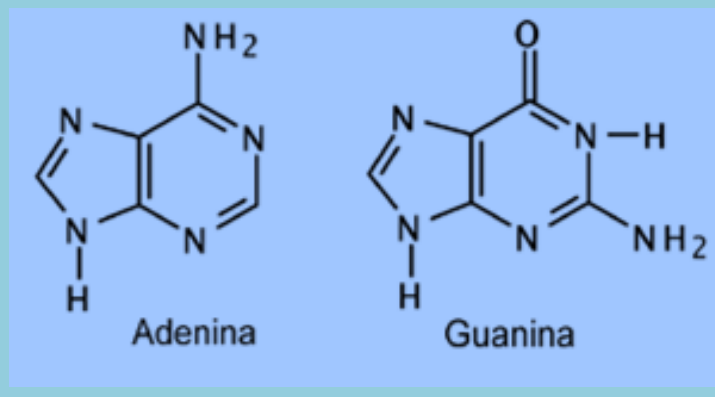


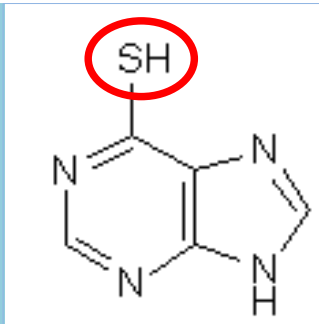
Roche, V.F. Cancer and chemotherapy. Lemke, T.L.; Williams, D.A. Roche, V.F.; Zito, S.W. **Foye´s Principles of medicinal chemistry**. Filadelfia: Lippincott and Wilkins, 2013, cap.37, p.1199-1266; Patrick, G.L. Anticancer agents. In:_____. **An introduction to medicinal chemistry**. Oxford: Oxford University Press, 2013, cap.21, p.514-576

Enzima irreversivelmente inibida → não há formação de dTMP → morte celular

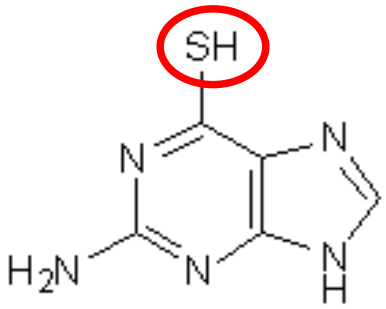
2.2 Antimetabólitos

2.2.3 ANTIMETABÓLITO DE PURINAS

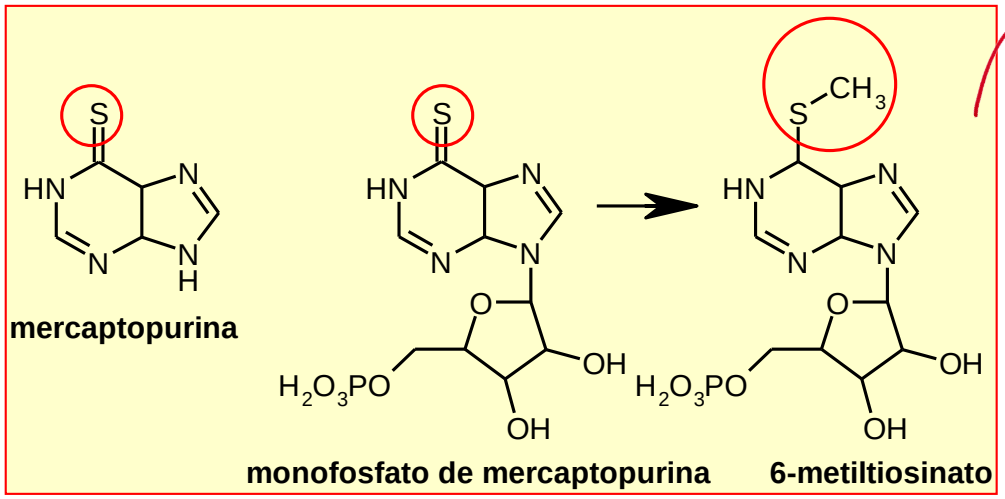




6-mercaptopurina



6- tioguanina



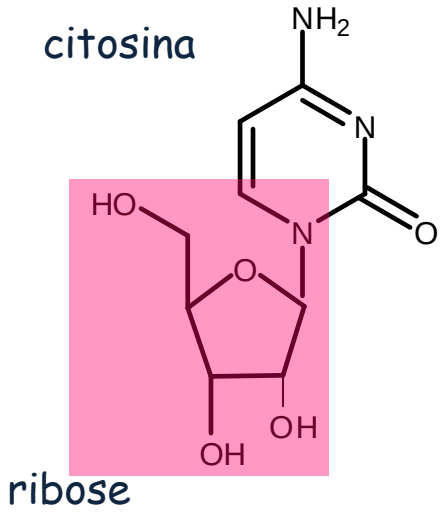
Inibição da amidofosforibosil - transferase

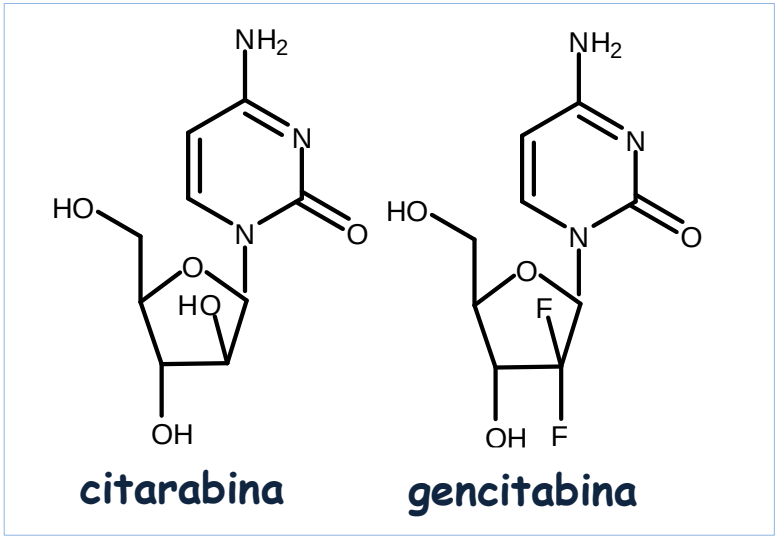
↓

Efeito citotóxico

2.2 Antimetabólitos

2.2.3 ANTIMETABÓLITO – Inibidores da elongação do DNA

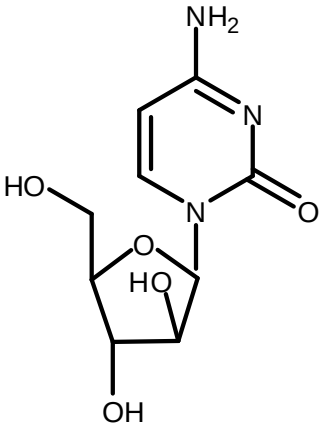




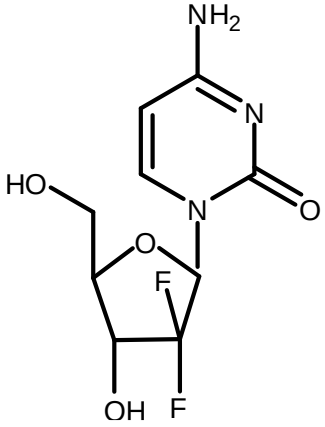
- ✓ Inibem a **DNA polimerase**
- ✓ Trifosfatos → ativos
- ✓ Na forma de trifosfatos, são incorporados ao DNA e interrompem sua elongação e/ou inibem enzimas necessárias à sua síntese

2.2 Antimetabólitos

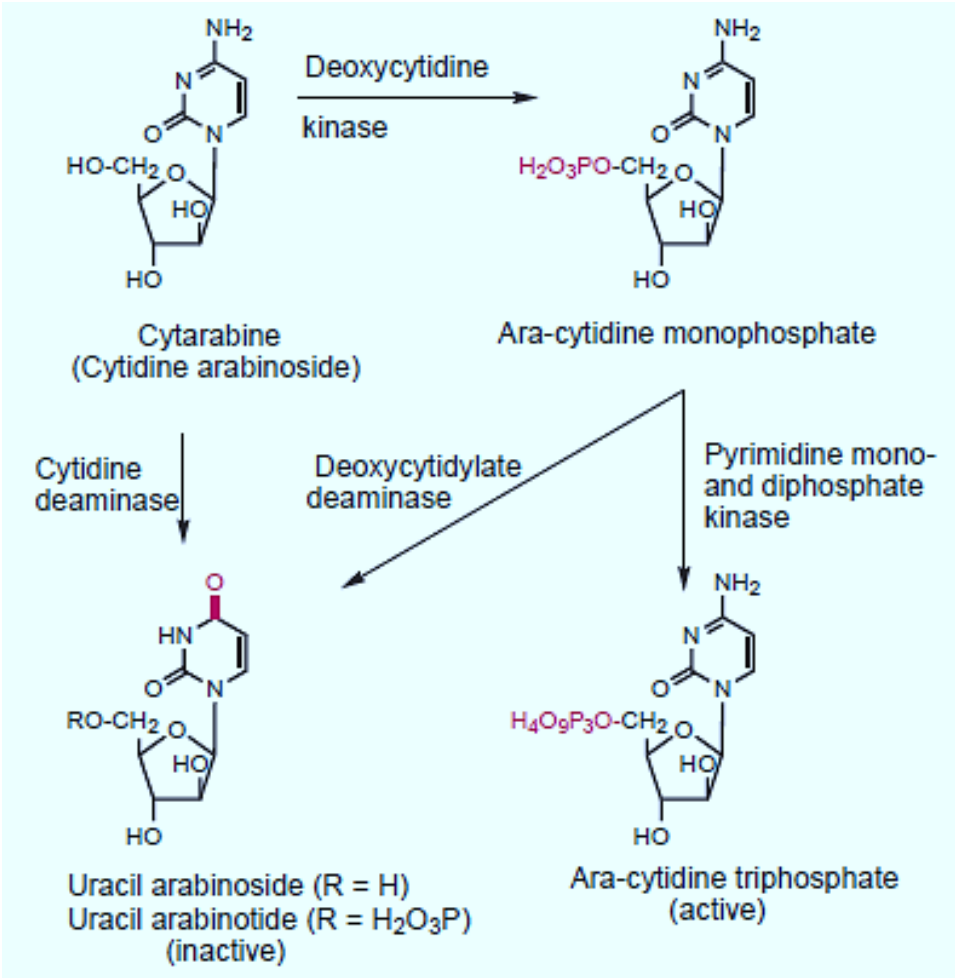
2.2.3 ANTIMETABÓLITO – Inibidores da elongação do DNA



citarabina



gencitabina



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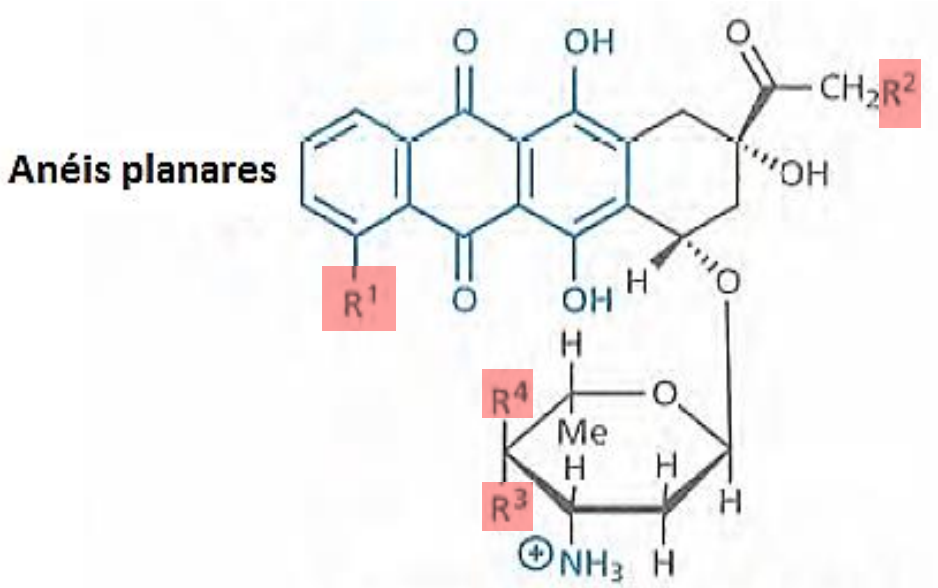
2 Antineoplásicos
2.3 Agentes intercalantes
2.3.1 ANTRACICLINAS



antraciclinas	R^1	R^2	R^3	R^4
doxorrubicina	OMe	OH	OH	H
epirrubicina	OMe	OH	H	OH
daunorrubicina	OMe	H	H	OH
idarrubicina	H	H	H	OH

Agentes intercalantes

- ✓ Anéis planares **intercalam** na dupla hélice do DNA
- ✓ Inibição **topoisomerase II** (processos de replicação)
- ✓ Seletividade para células que se dividem rapidamente

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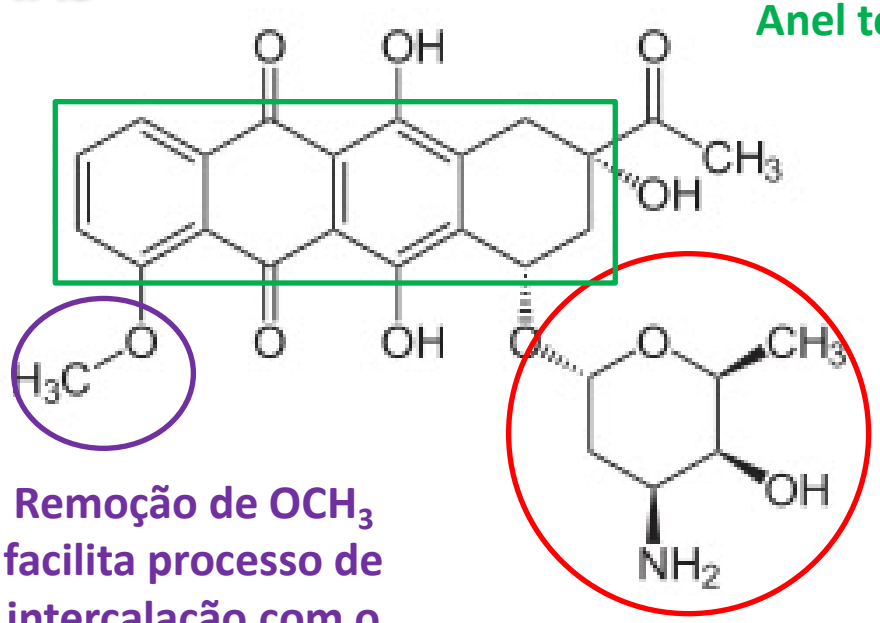
2.3 Agentes intercalantes

2.3.1 ANTRACICLINAS

Anel tetracíclico

Porção aglicona da antraciclina



Remoção de OCH_3 facilita processo de intercalação com o DNA (planar)

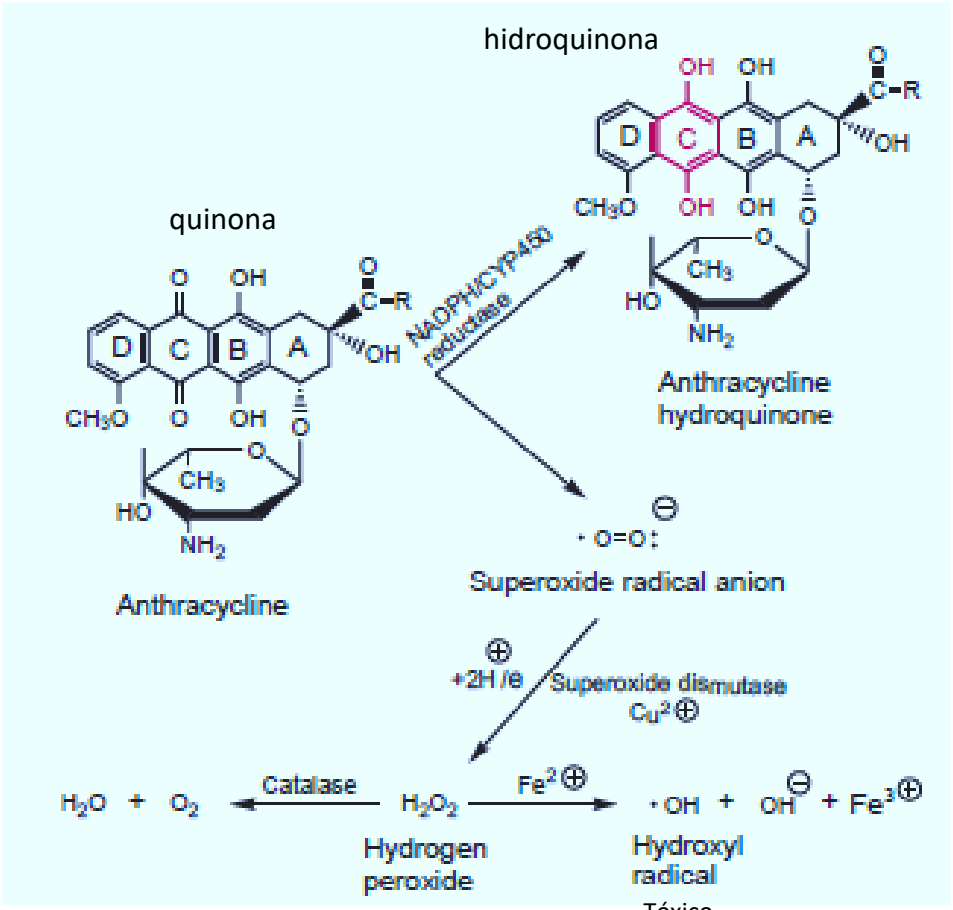
L-daunosamina (açúcar)
Participação importante na especificidade do processo de intercalação com DNA

-Resíduo fosfato aniônico do DNA

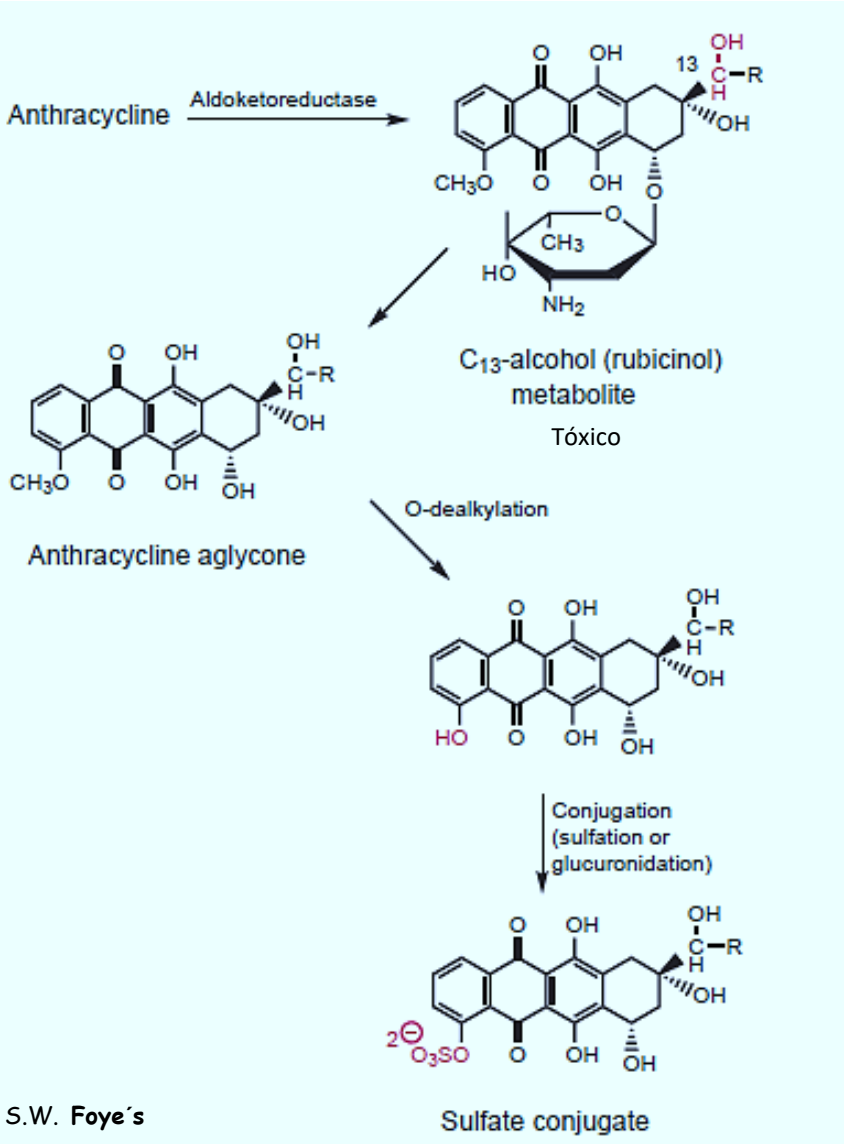
Complexo ternário fármaco-enzima-DNA

2.3.1 ANTRACICLINAS

Mecanismos propostos para a cardiotoxicidade



Cardiotoxicidade crônica



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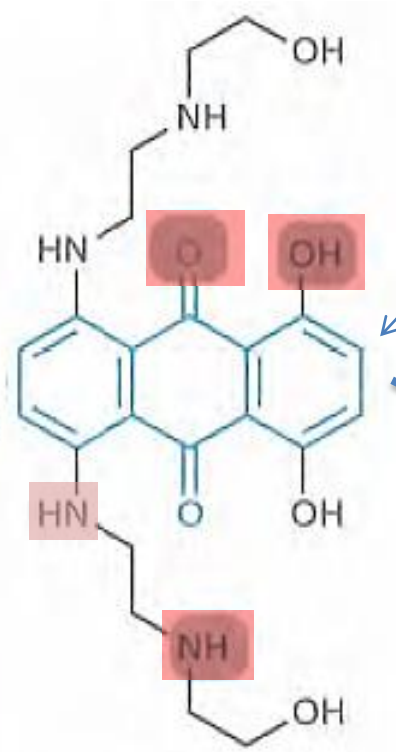
2.3 Agentes intercalantes
2.3.1 ANTRACICLINAS



Sistema de anéis planares

cardiotoxicidade

mitoxantrona

- ✓ Análogo **sintético** mais simples
- ✓ Molécula simétrica
- ✓ Relação estrutura-atividade: O, OH e NH → importantes para atividade

Estabilidade do anel quinona

↓

ligação hidrogênio intramolecular

↓

Resistência NADPH/CYP450 redutase

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2 Antineoplásicos
2.3 Agentes intercalantes
2.3.1 ANTRACICLINAS

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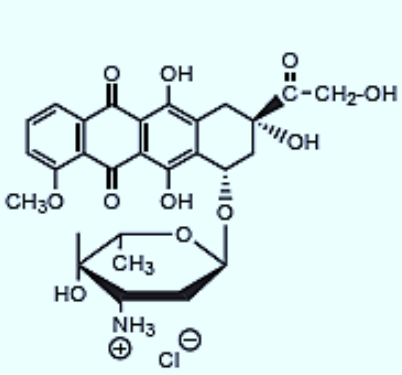
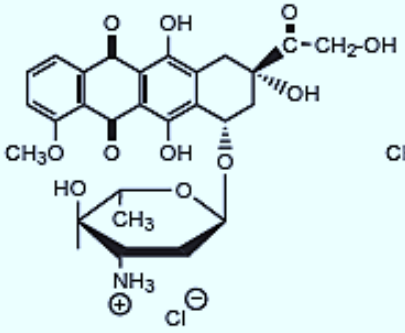
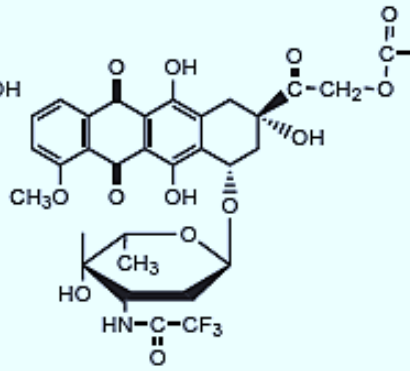


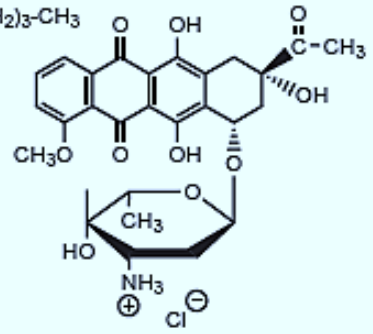
Doxorubicin hydrochloride
(Adriamycin)



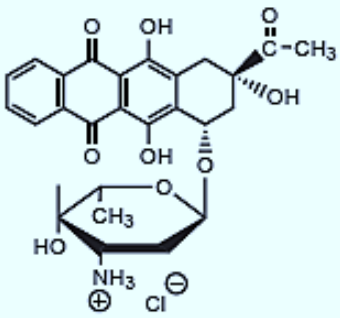
Epirubicin hydrochloride
(Ellence)



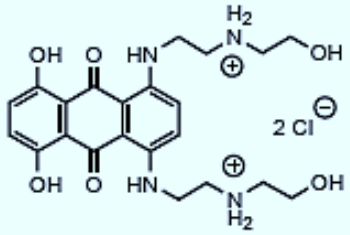
Valrubicin
(Valstar)
Entrada na célula



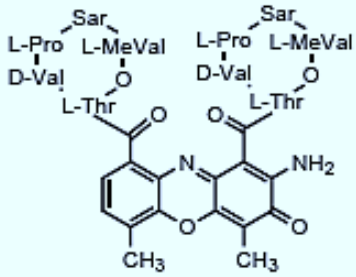
Daunorubicin hydrochloride
(Cerubidine)



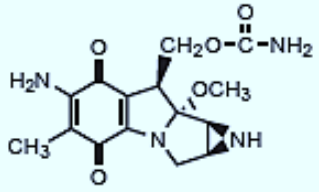
Idarubicin hydrochloride
(Idamycin PFS)



Mitoxantrone hydrochloride
(Novantrone)

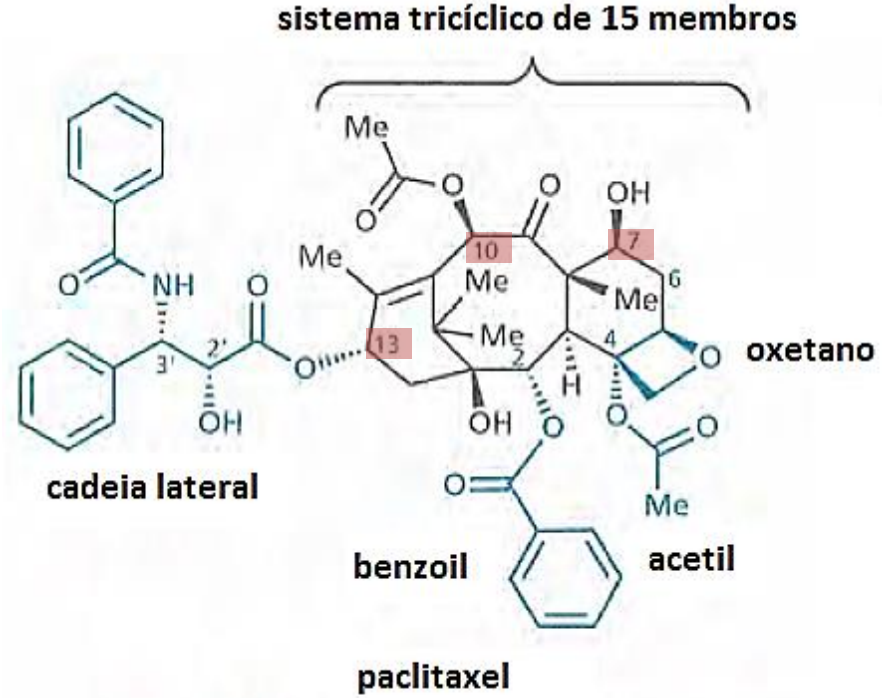


Dactinomycin
(Cosmegen)



Mitomycin
(Mutamycin)

2 Antineoplásicos
2.4 Inibidores da mitose



paclitaxel (taxol)

- ✓ Inibe despolimerização de tubulina
- ✓ Isolado de *Taxus ssp*
- ✓ Síntese completa em 1994, porém **inviável**
- ✓ Análogos: dodetaxel, ortataxel (administração por **via oral**)

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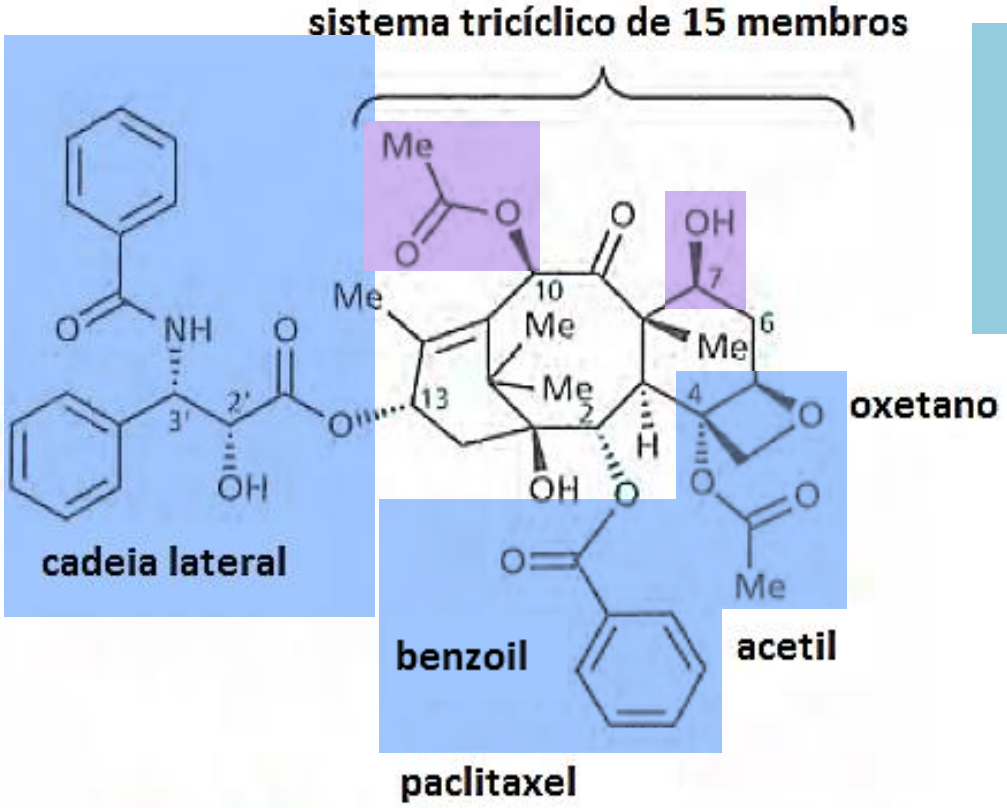
3 Antineoplásicos

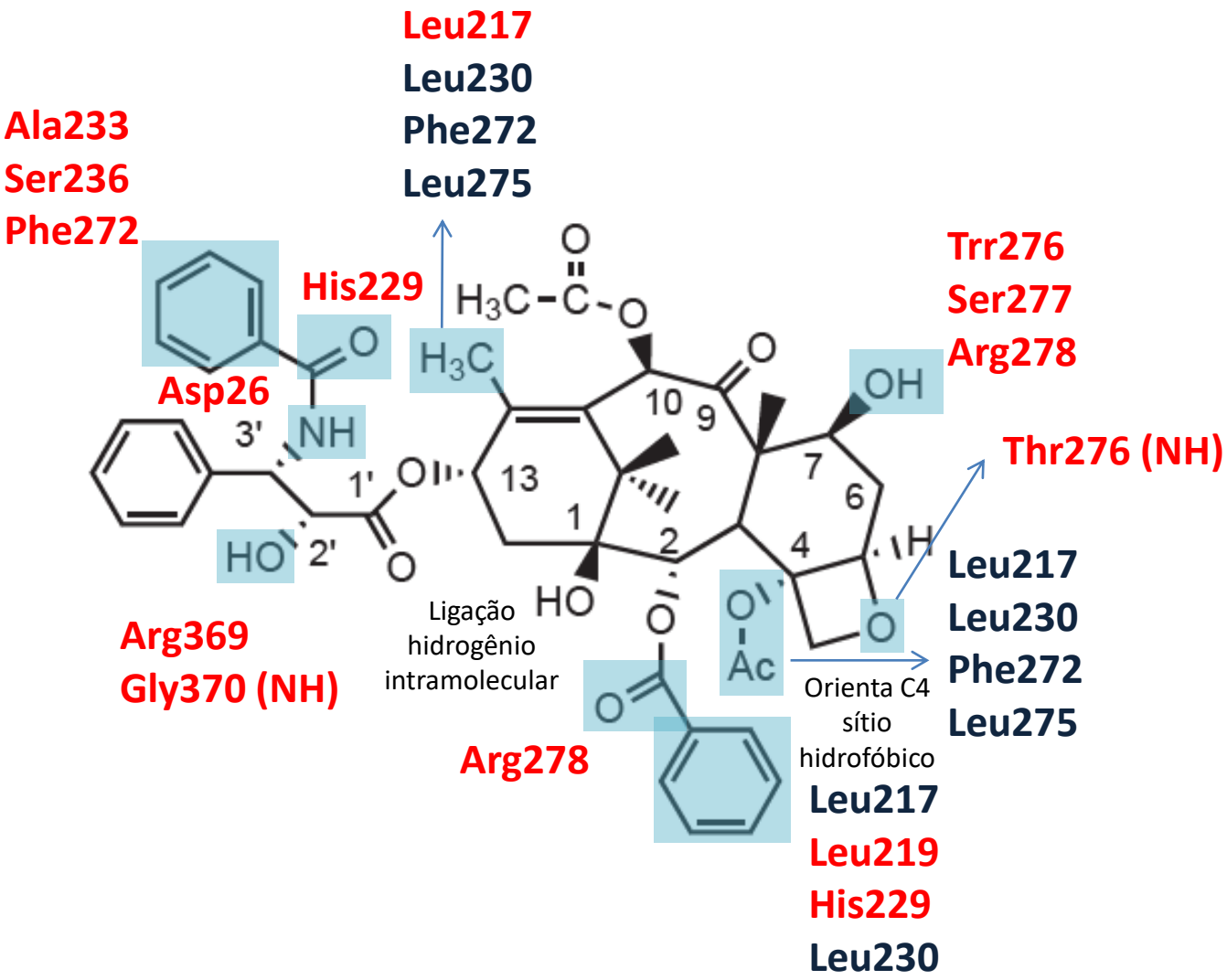
3.4 Inibidores da mitose

Relação estrutura-atividade

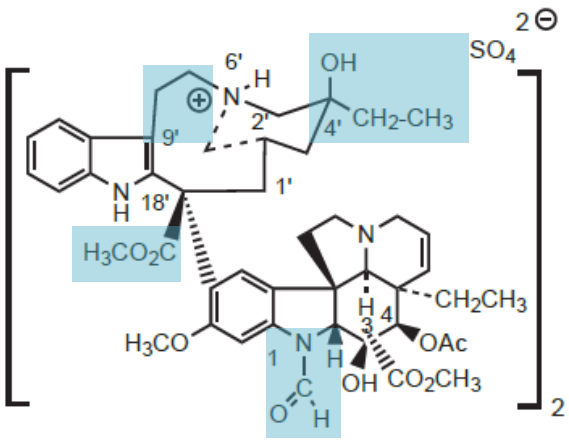
Ação em cepas resistentes



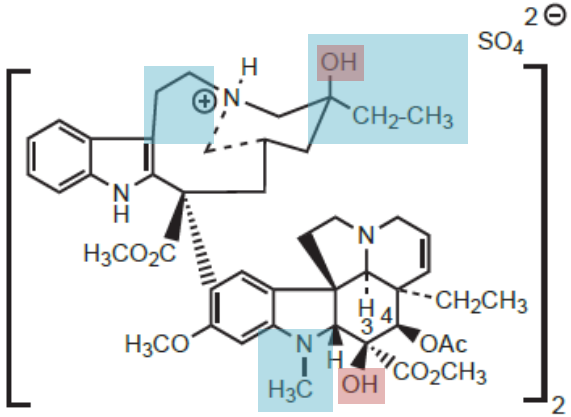
Importantes para adequada conformação de grupos funcionais essenciais


Leu217
Leu230
Phe272
Leu275
Ala233
Ser236
Phe272
His229
Asp26
Trr276
Ser277
Arg278
Thr276 (NH)
Leu217
Leu230
Phe272
Leu275
Arg369
Gly370 (NH)
Ligação hidrogênio intramolecular
Orienta C4 sítio hidrofóbico
Arg278
Leu217
Leu219
His229
Leu230

3 Antineoplásicos
3.4 Inibidores da mitose
- Alcalóides da VINCA

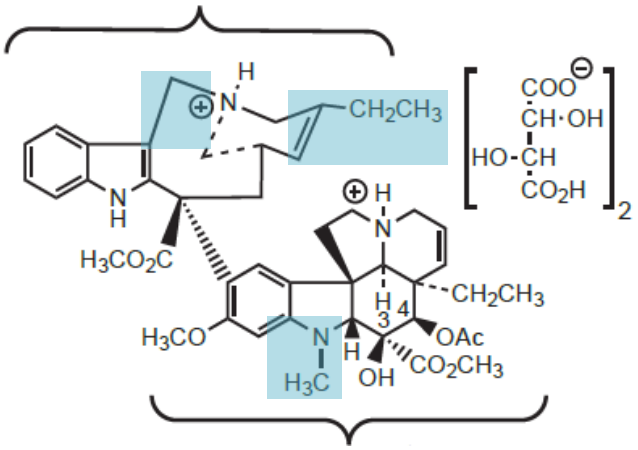


vincristina



vimblastina

Porção catarantina



Porção vindolina

vinorelbina

- ✓ Ligam-se à tubulina e previnem a polimerização de microtúbulos
- ✓ Diferença: ação, potência e toxicidade
- ✓ Porções (**cataramina e vindolina**) são essenciais para ação

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Obrigada por sua atenção