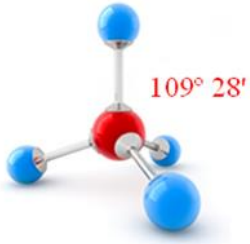
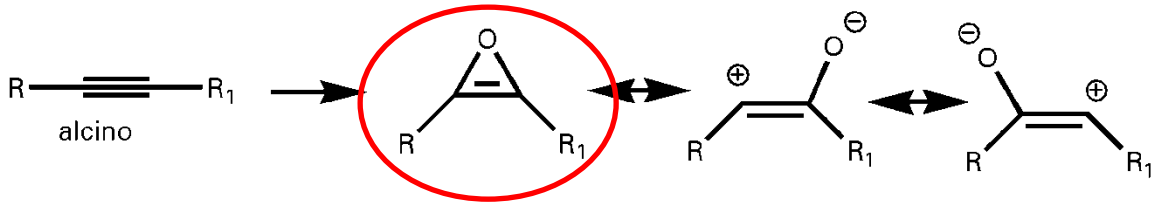
Aula 9 – 22/07

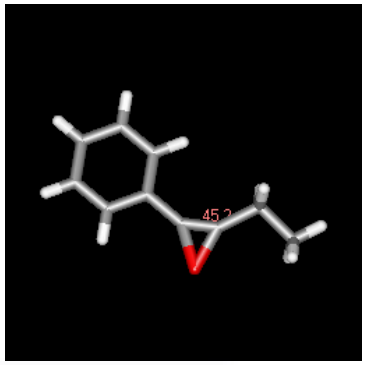
Tópicos Especiais em Química Medicinal

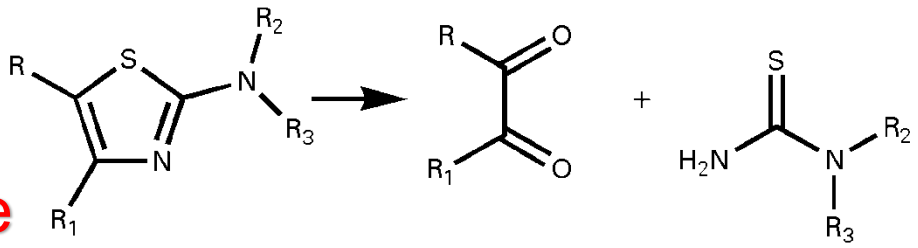
Tópicos Especiais
em Química Medicinal
Código: **BMF-777**
Carga Horária: 45 horas
Créditos: 3 créditos

Grupamentos toxicofóricos





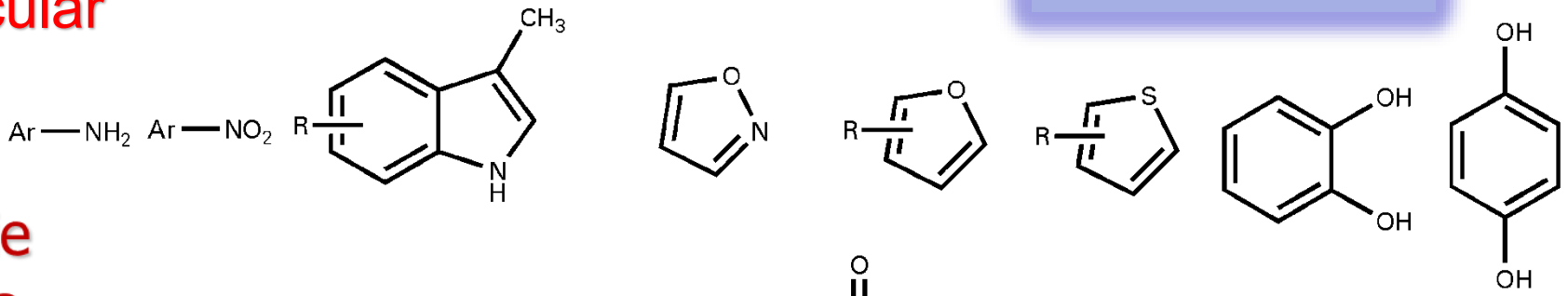


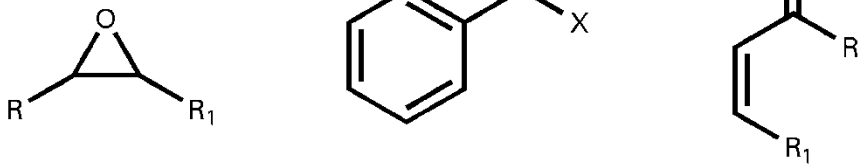


Toxicidade molecular

Toxicóforo

Espécie reativa



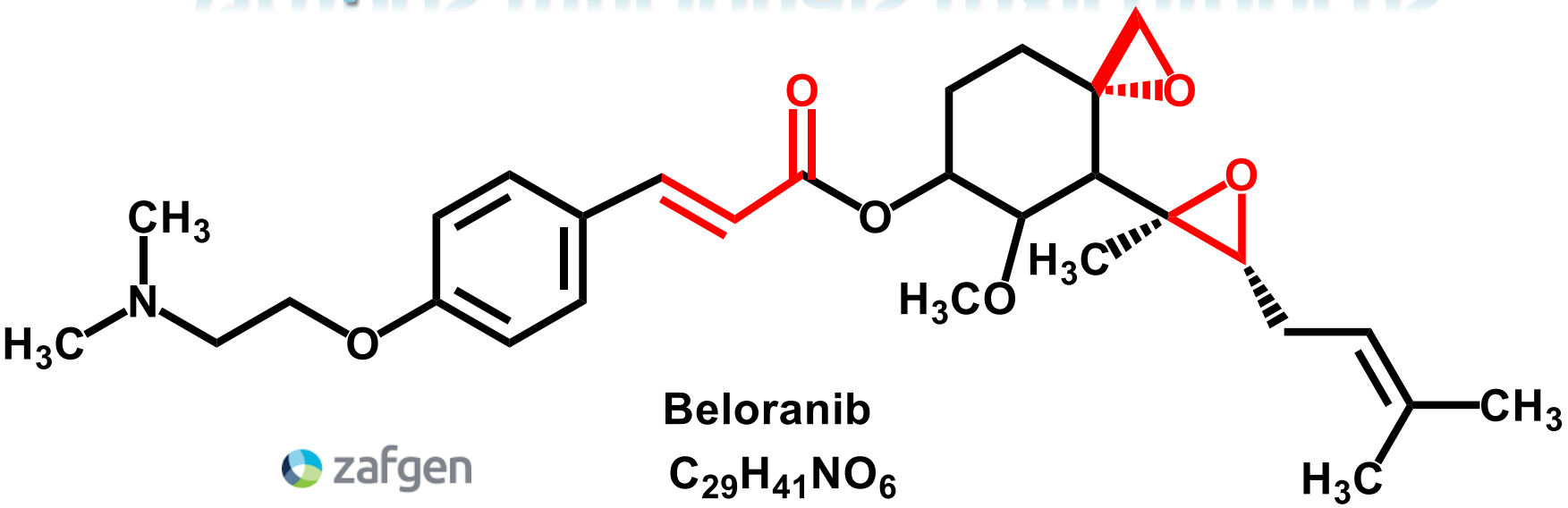


R, R_1, R_2, R_3= H, alquila, cicloalquila, arila, heteroarila
X= grupo abandonador

Um toxicóforo é a subunidade estrutural capaz de promover respostas tóxicas, diretamente ou via ativação metabólica.

AC Macherey, PM Dansette, Biotransformations Leading to Toxic Metabolites: Chemical Aspect, The Practice of Medicinal Chemistry, Academic Press, NY, 2015, pp 675−696 [Link]

Grupos funcionais toxicofóricos

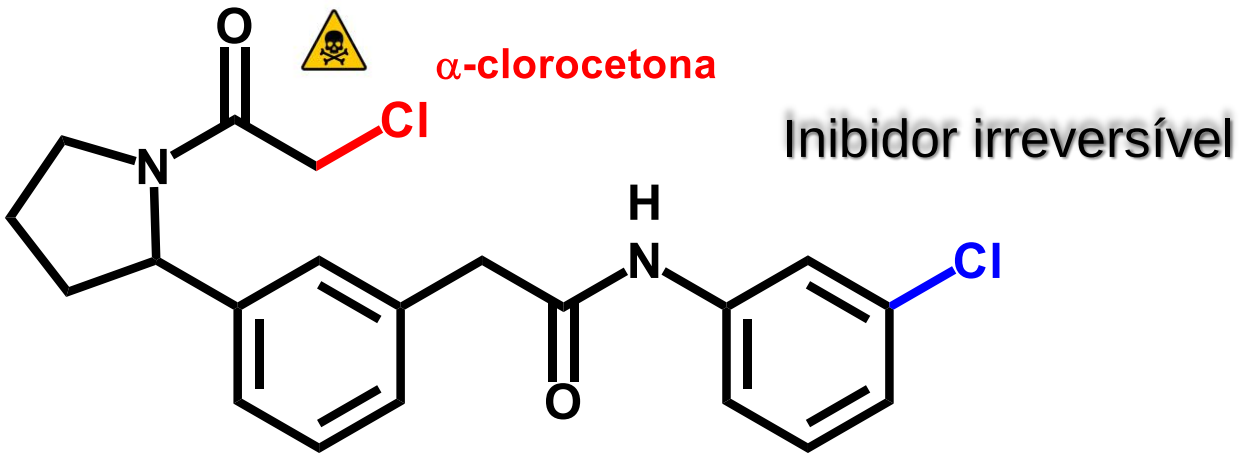


Beloranib

$C_{29}H_{41}NO_6$

zafgen

biopharmaceutical **company**



$C_{20}H_{20}Cl_2N_2O_2$

Grupos funcionais toxicofóricos

2-metil-tiazola

epóxido

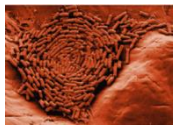
C_{16}-macrolactona

esterase

Epotilona-B

1993

Mixobacteria



Inibidor de microtúbulo

BMS, 2007

Análogo semi-sintético

epóxido

esterase

C_{16}-macrolactama

Química Medicinal

Ixabepilona

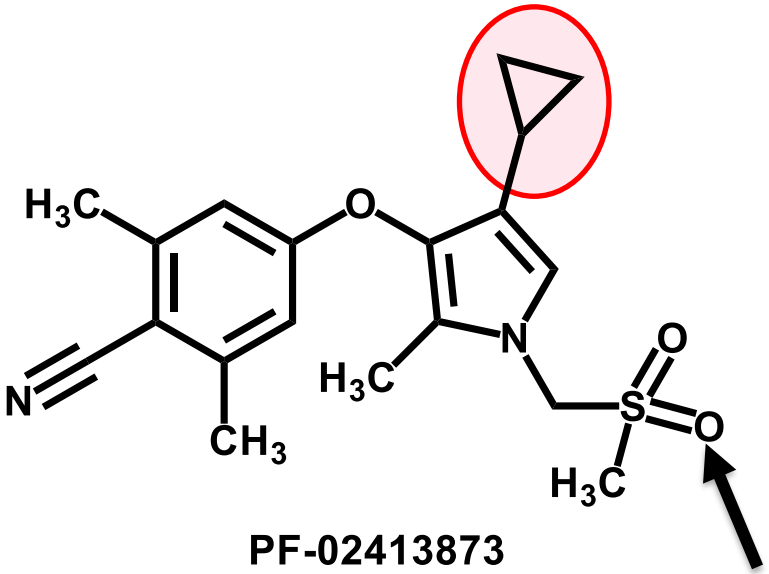
Ixempra^{R}

$T_{1/2}$ 17-52h (iv)

A Conlin, M Fornier, C Hudiis, S Kar, P. Kirkpatrick, *Nat. Rev. Drug Discov.* **2007**, *6*, 953

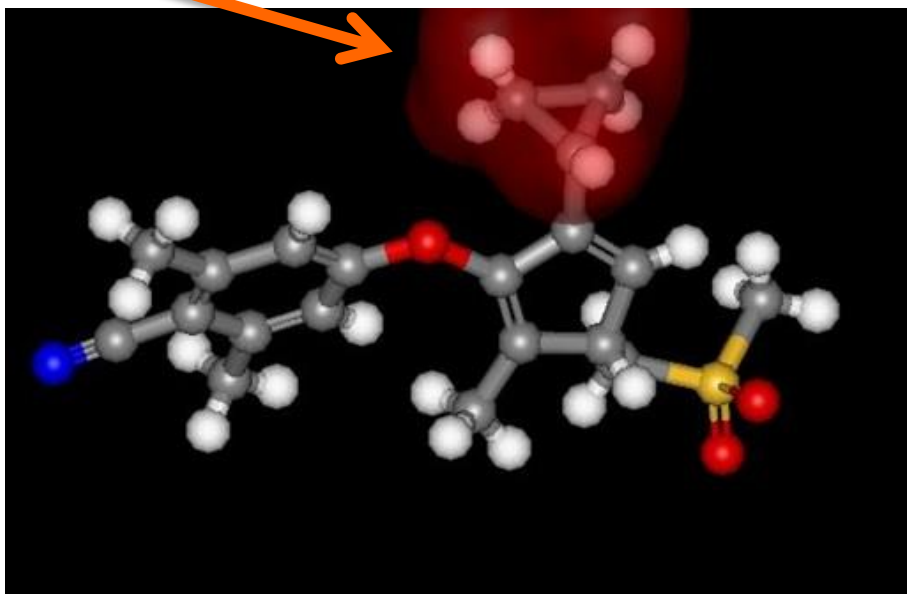
Ciclopropila

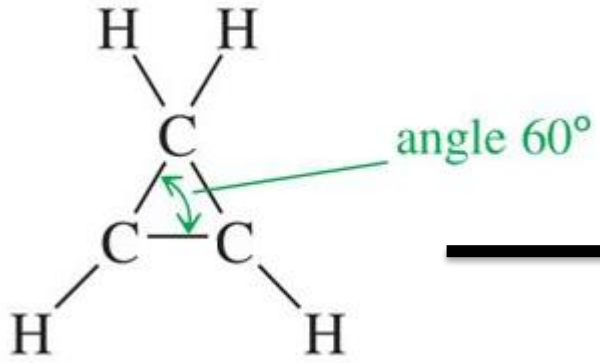
ciclopropila



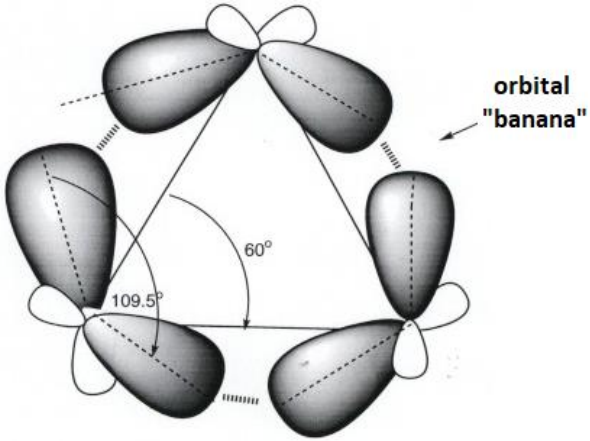
PF-02413873
PR-blocker

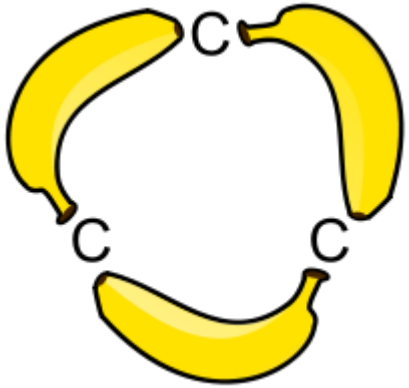
metilsulfona





Tensão angular

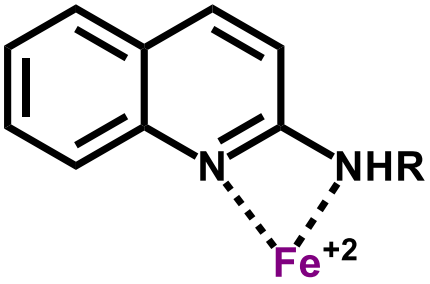


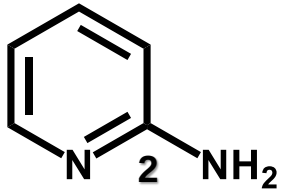


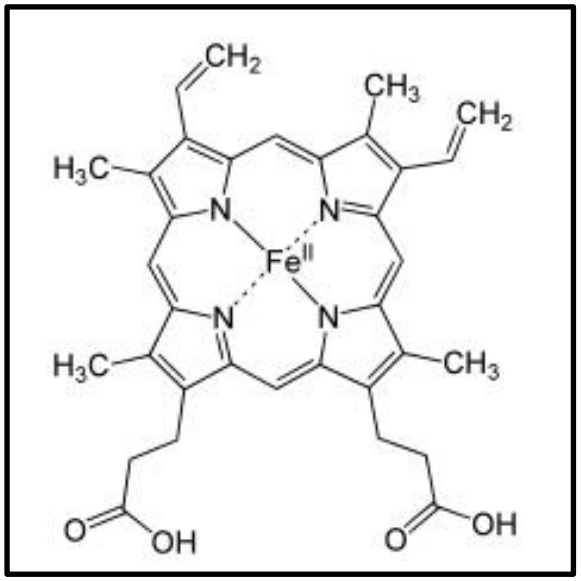
PJ Bungay et al., Preclinical and clinical pharmacokinetics of PF-02413873, a nonsteroidal progesterone receptor antagonist, *Drug Metab Dispos*. **2011**, *9*, 1396.

Grupos funcionais quelantes

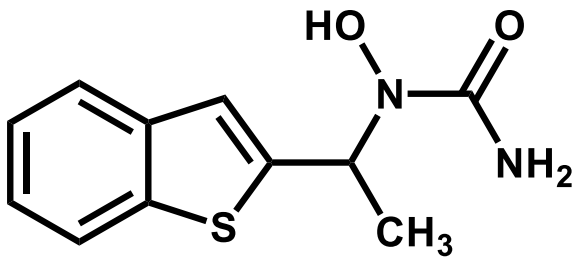
2-aminoquinolina ➡ 2-aminopiridina

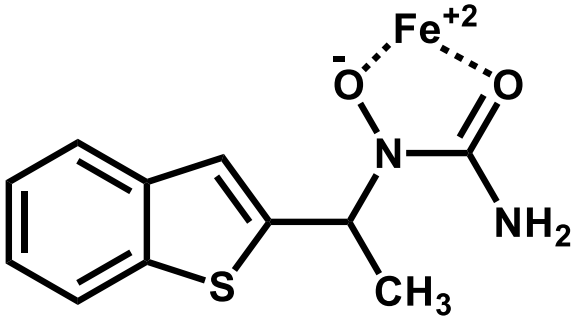




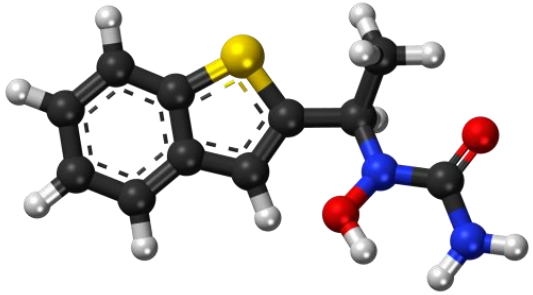


Ácido hidroxâmico





Zileuton

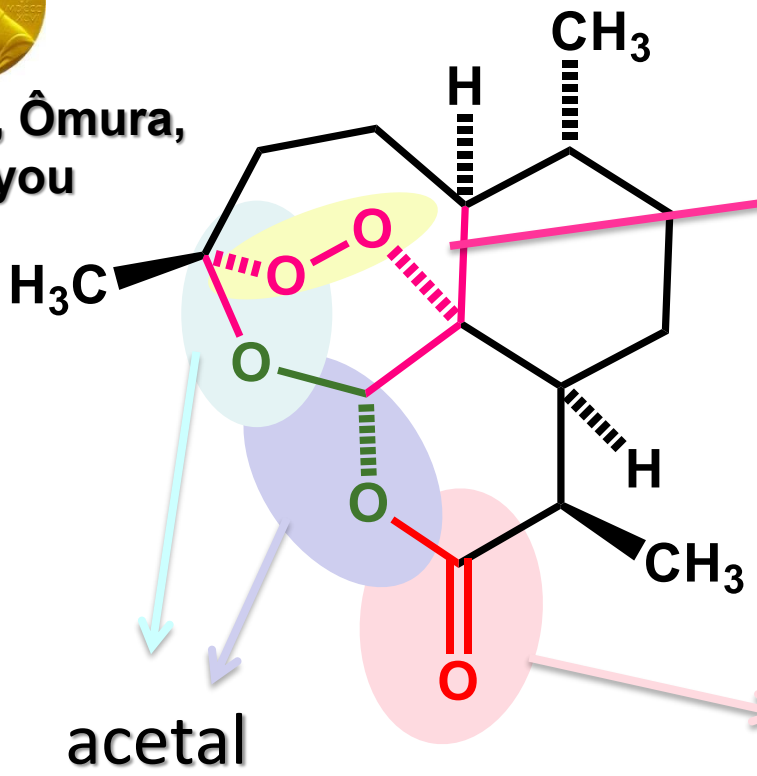


Vorinostat
Panobinostat
Tosedostat

Grupos funcionais *exóticos*

2015

Campbell, Ômura, Youyou



endoperóxido

Artemisinina

$T_{1/2}$ 0,6-2,6h

Log P = 2,27

PSA 54,0 A^2

acetal

Éster ciclíco = lactona

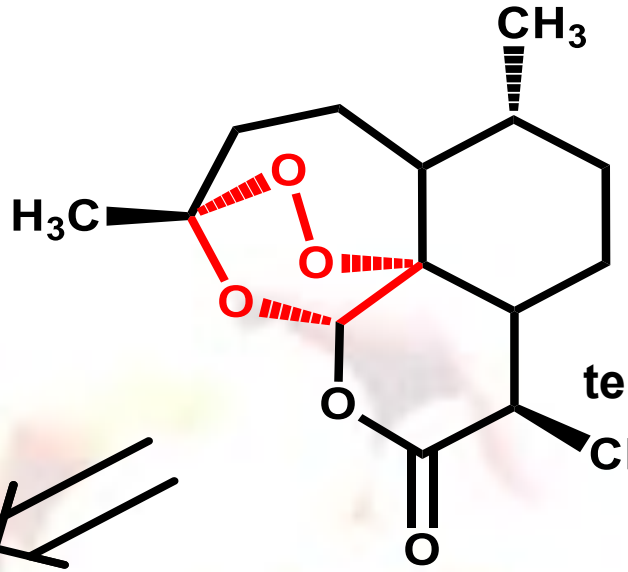
Sem o modêlo da natureza, nunca se teria *inventado* este padrão molecular!

Simplificação molecular

Gary H. Posner

1943-2018

JI Seeman, *Tet* **2016**, *72*, 5950



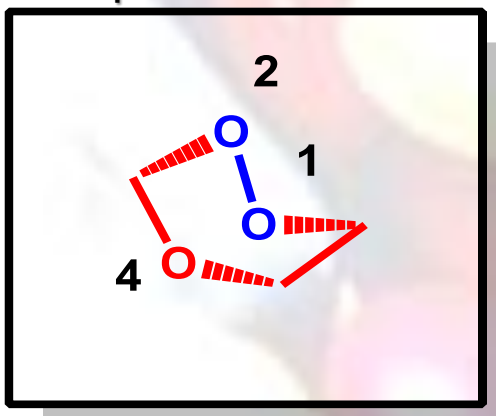
terpeno

Produto natural

Artemisia annua

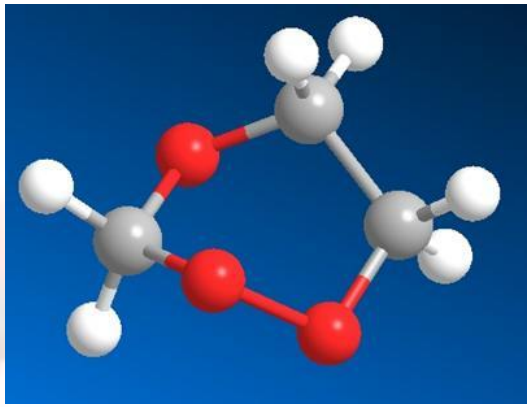
artemisina

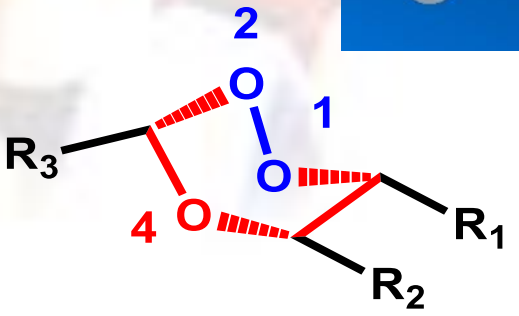
peróxido-éter



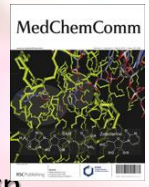
1,2,4-trioxana

Grupamento farmacofórico





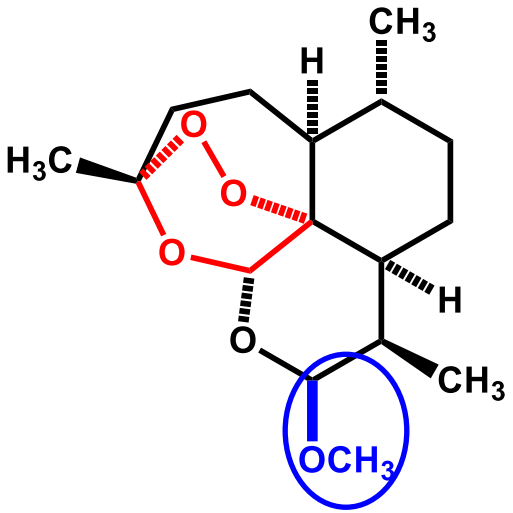
Johns Hopkins University



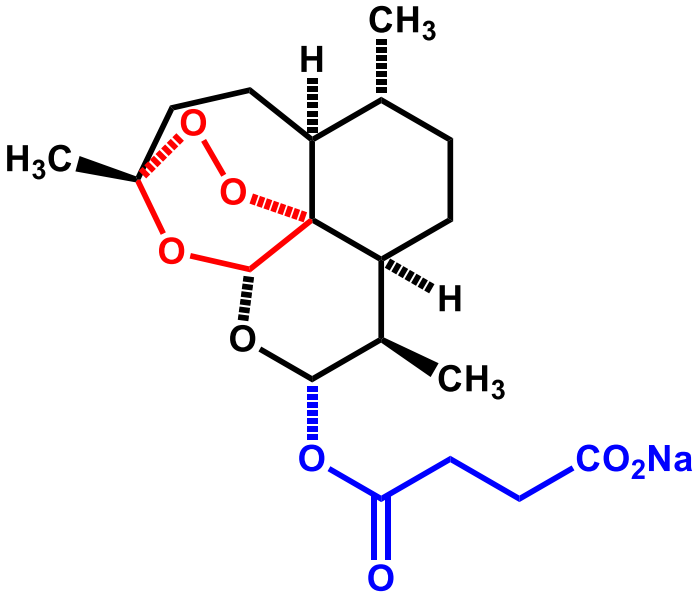
RD Slack, AM Jacobine, GH Posner, Antimalarial Peroxides: Advances in Drug Discovery and Design, *Med. Chem. Commun.*, **2012**, 3, 281.

derivados 1,2,4-trioxana

Quím Química Med Medicinal

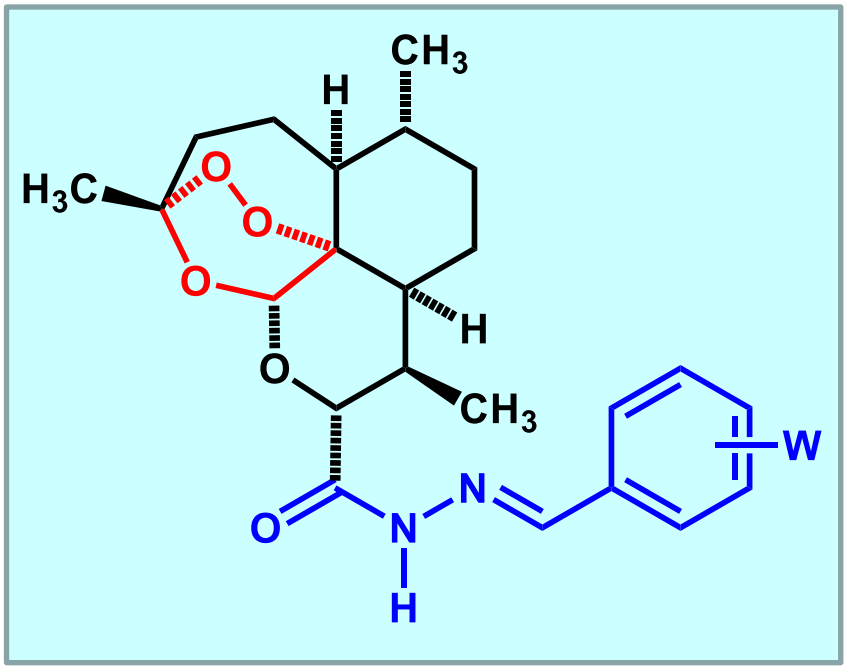


arteméter



artesunato de sódio

Quím
Química
Med
Medicinal



N-acylhydrazone analogue

M A Avery, M Alvim-Gaston[&] et al., Structure– activity relationships of the antimalarial agent artemisinin, *J Med Chem* **2002**, *45*, 292.

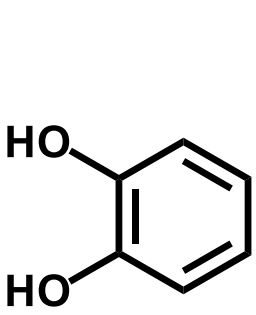
THE UNIVERSITY of MISSISSIPPI
SCHOOL OF PHARMACY

Oxford, Miss

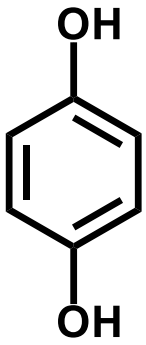
[&] Atual Innovation Director, Eli Lilly Co., IN, EUA

Lilly

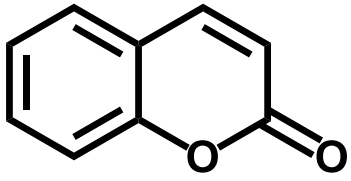
Grupos funcionais redox ativos



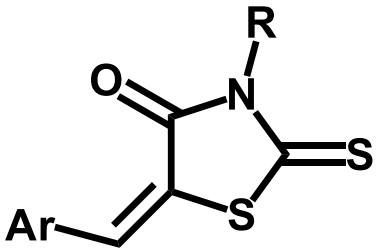
catecol



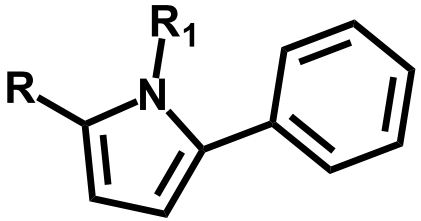
para-hidróxifenol



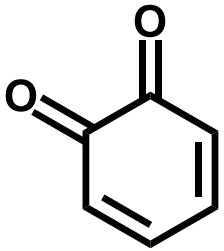
cumarina



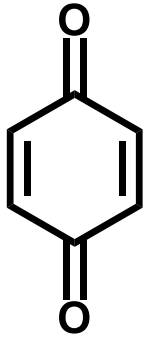
rhodanina



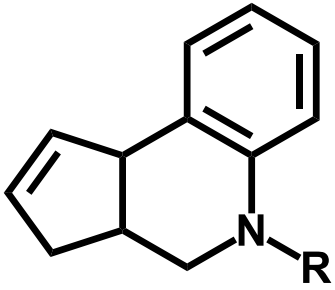
N-alquilarilpirrola



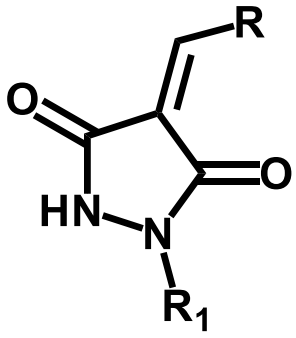
orto-quinona



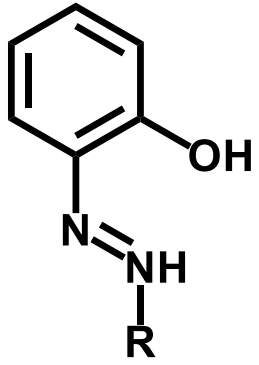
para-quinona



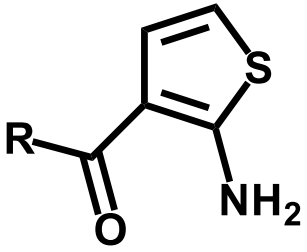
tetraidroquinolina



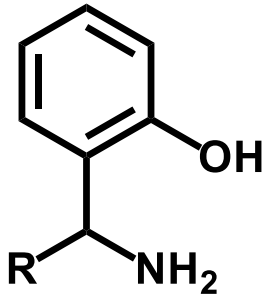
pirazolidinodiona



orto-hidróxifenil hidrazona



2-amino-3-cetotiofeno



Mannich basse fenólica

Carbamatos

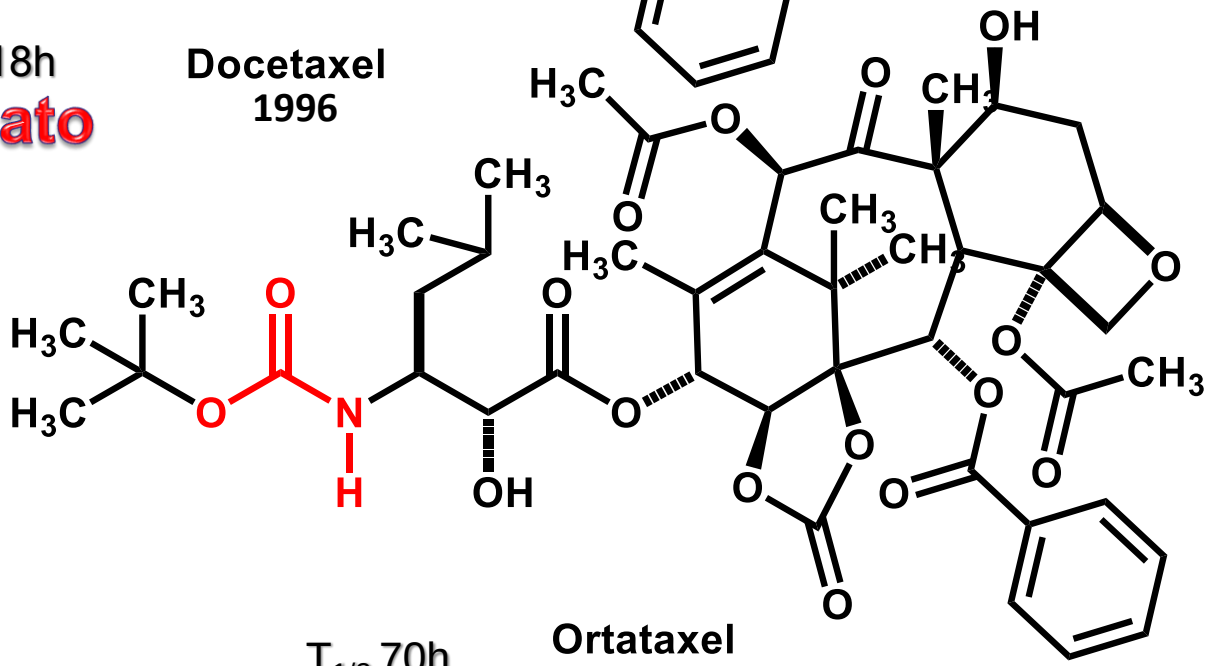
Pierre Potier
1934-2006

Andy E Greene
UJF-FR

$T_{1/2}$ 11-18h

carbamato

Docetaxel
1996



$T_{1/2}$ 70h

Ortataxel
2009

Química Medicinal

De fármacos e suas descobertas

http://ejb-eliezer.blogspot.com/

Pretende-se tratar de temas, opiniões, comentários sobre a Ciência dos Fármacos, seu uso seguro e benefícios. História da descoberta/invenção de fármacos e aspectos da formação qualificada de universitários e pós-graduandos nas Ciências dos Fármacos também são de interesse.

Total de visualizações de página

135,307

Seguidores

Próxima

domingo, 1 de julho de 2018

Os carbamatos & os fármacos

A função carbamato, representada pela "hidroxilação" do carbono de uma amida = HO-C=O-NH_2 (originando o ácido carbâmico), tem enorme importância em Química Medicinal, sendo parte da estrutura de várias moléculas de fármacos e de pró-fármacos. Denomina-se também uretanas, embora esta denominação não seja muito empregada. É uma função química presente em outros tipos de compostos bioativos como pesticidas e em determinados tipos de polímeros. Tem grande aplicação em síntese orgânica, empregado como grupo protetor de aminas (e.g N-BOC), o que evidencia a facilidade de sua síntese.

As fases da ação dos fármacos


PD / PK
Estrutura & Atividade
Propriedade & Atividade
Challenge
SAR
SPR
Química Medicinal

A fase farmacocinética (PK)

CAPÍTULO 2
FUNDAMENTOS DO METABOLISMO DE FÁRMACOS 43

1 Desintegração & Dissolução

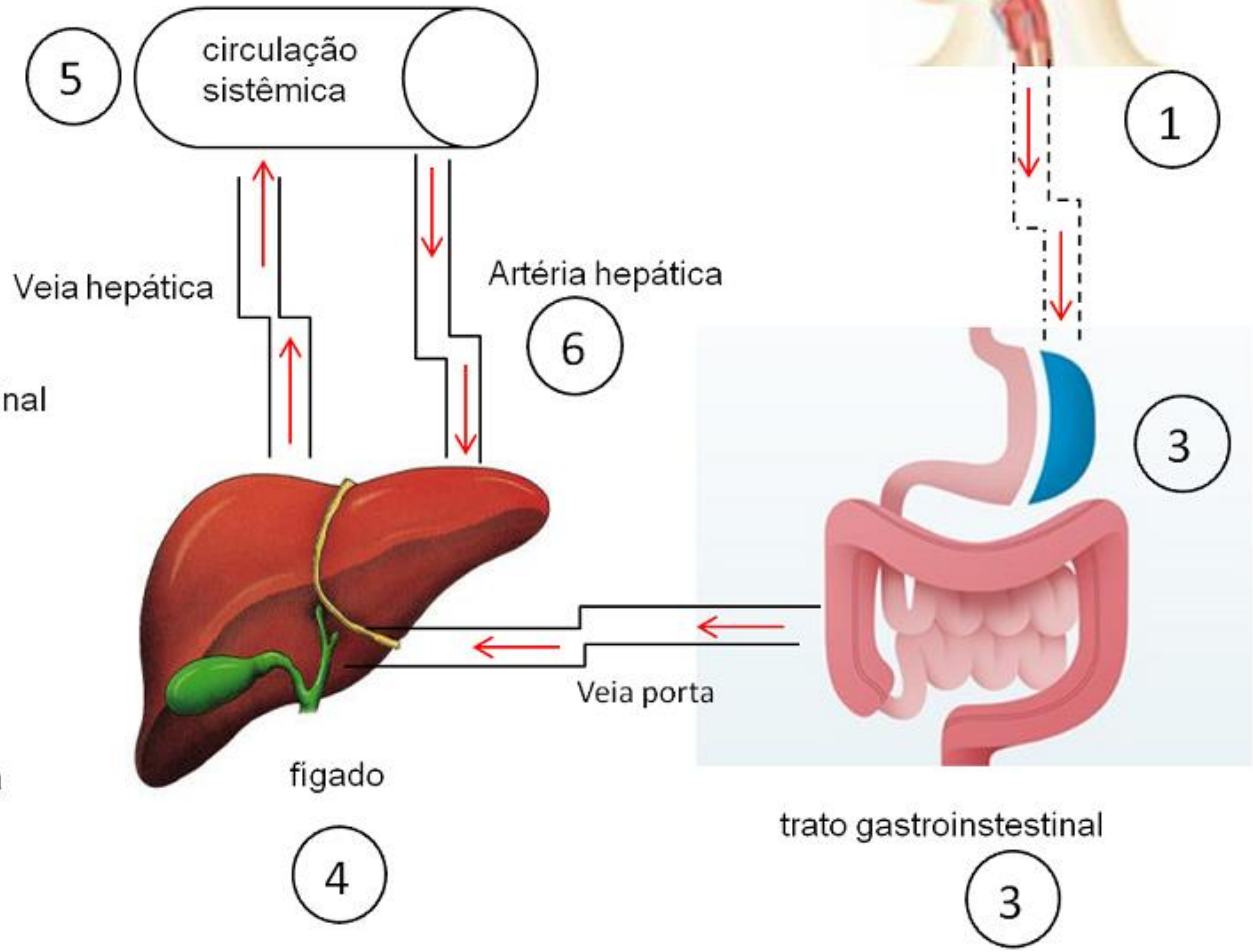
2 Absorção

3 Efeito de 1ª passagem intestinal

4 Efeito 1ª passagem hepático

5 Distribuição

6 Recirculação entero-hepática



Biodisponibilidade; posologia; efeitos adversos; interações medicamentosas;

Propriedades moleculares

AMES

K_i / IC_{50} / ED_{50}

Tox

$T_{1/2}$

PD

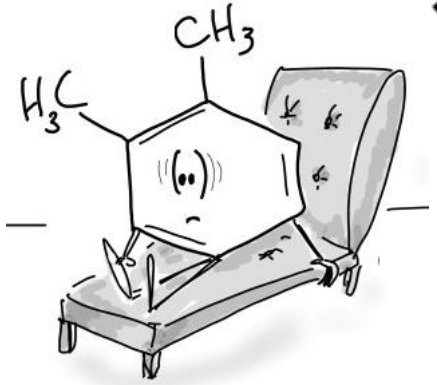
F

PK

PK

Biodisponibilidade

Permeabilidade



Caco-2

PK

PK

PAMPA

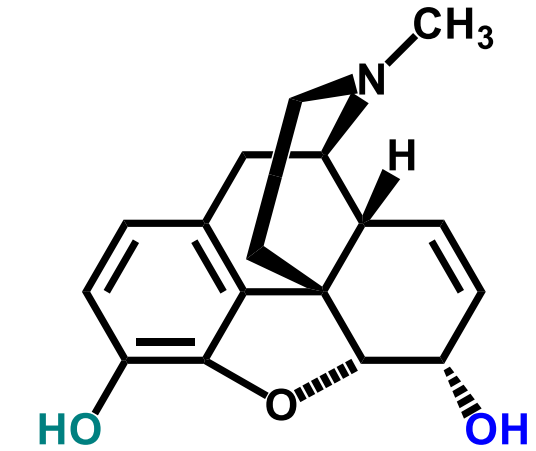
Química Medicinal

solubilidade

LogP

G. T. Balogh, Physicochemical characterization in drug discovery, *Drug Discov Today: Technologies* **2018**, *27*,

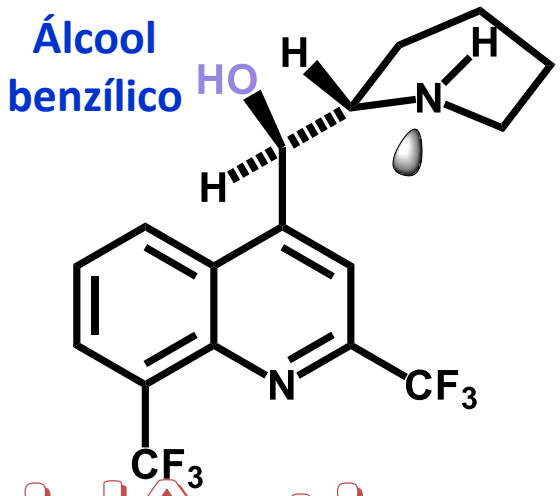
Fármacos hidroxilados

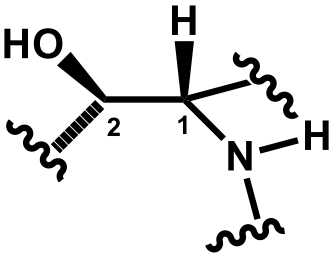


fenol

álcool alílico

Álcool benzílico



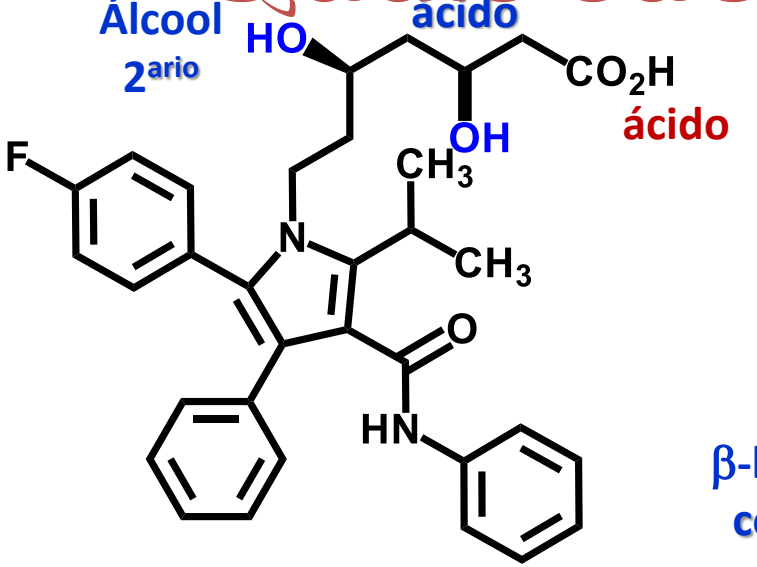


Etanol-amina

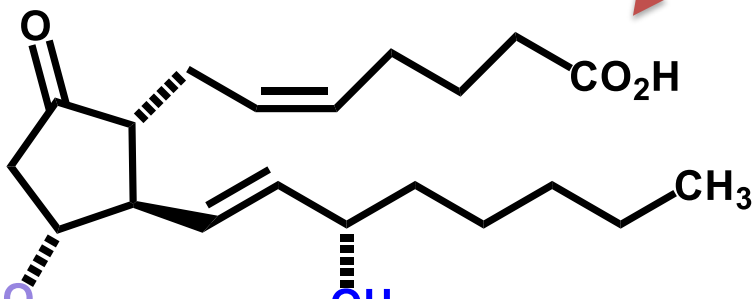
Quais são idênticos?

Álcool 2ario

ácido



ácido



HO

β-hidróxi cetona

OH

álcool alílico