Aula 14 – 26/08

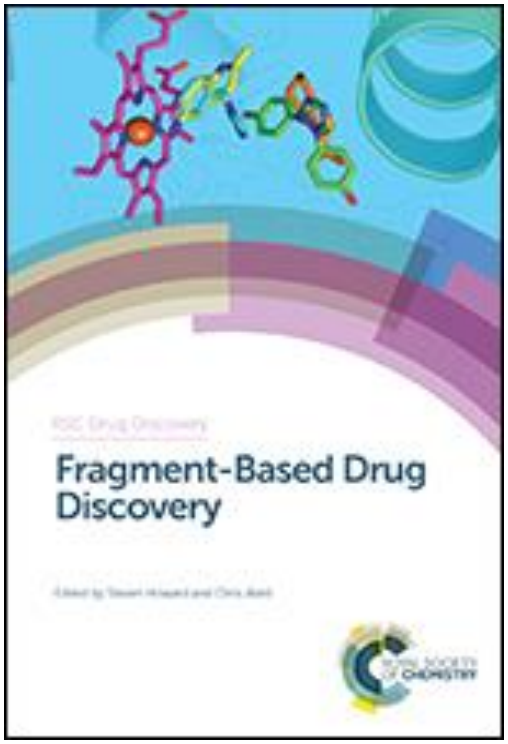
Tópicos Especiais em Química Medicinal

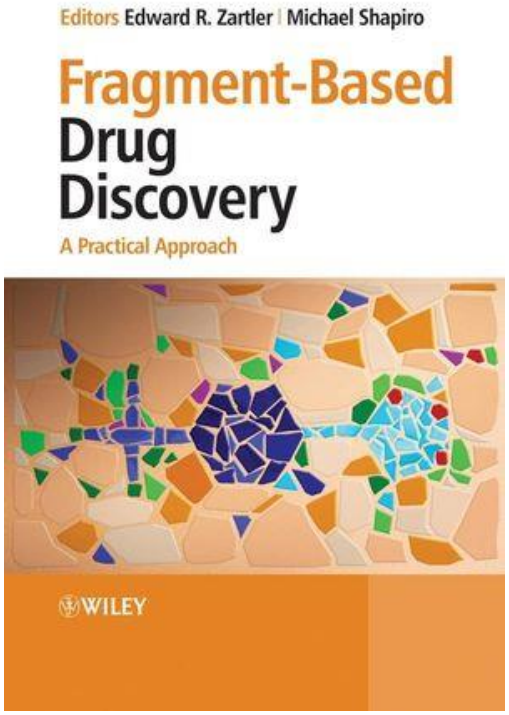
Tópicos Especiais
em Química Medicinal
Código: **BMF-777**
Carga Horária: 45 horas
Créditos: 3 créditos

Temas Livres

Composto,
Substância,
Derivado,
Estrutura,
Molécula,
Fórmula,
Radical.

FBDD





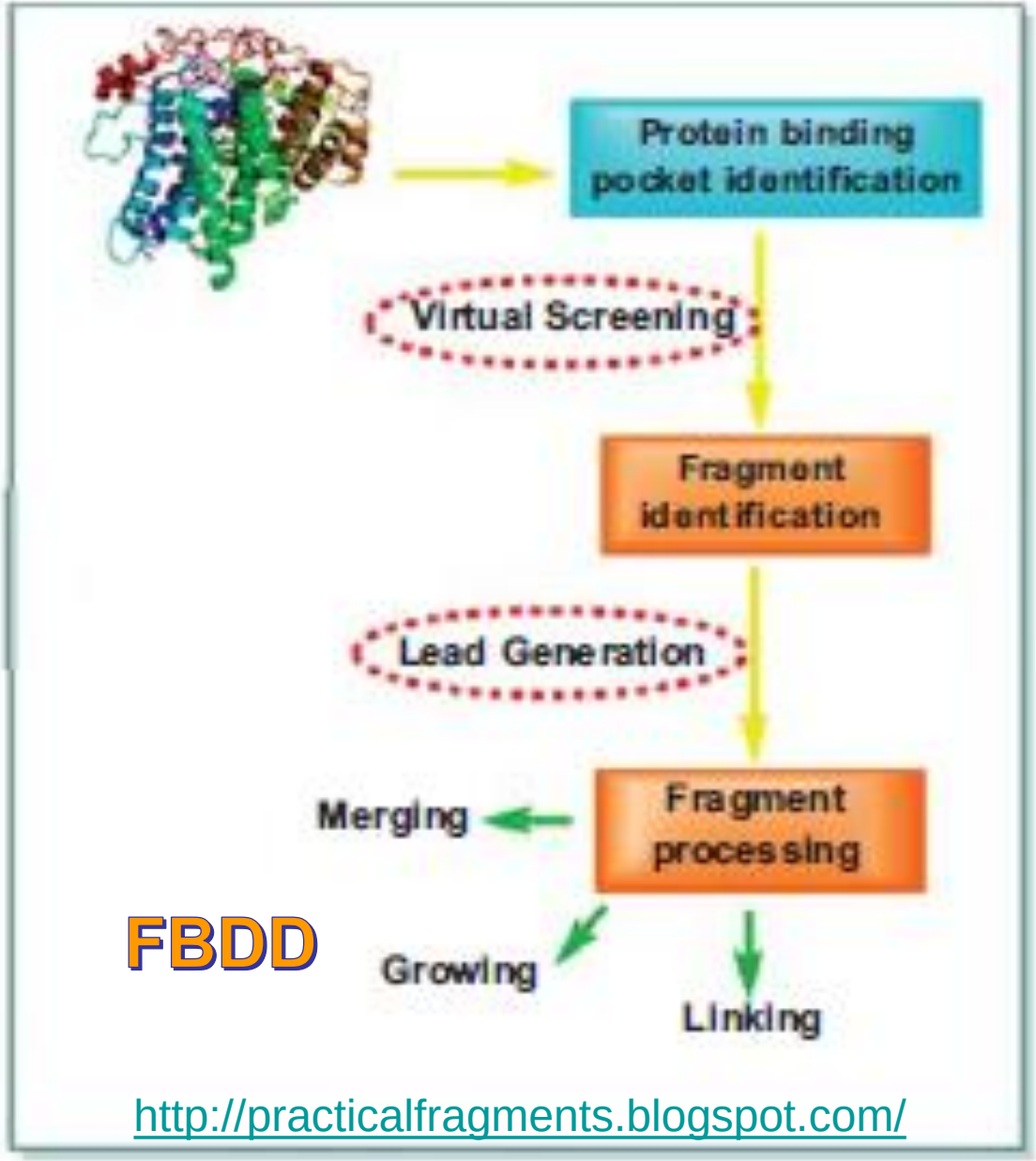
The Role of Fragment-based Discovery in Lead Finding

Roderick E. Hubbard

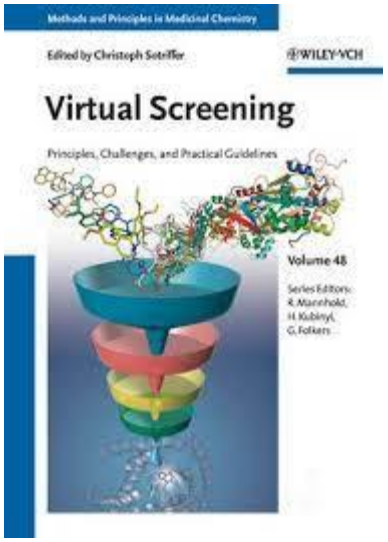
1.1 Introduction

Fragment-based lead discovery (FBLD) is now firmly established as a mature collection of methods and approaches for the discovery of small molecules that bind to protein or nucleic acid targets. The approach is being successfully applied in the search for new drugs, with many compounds now in clinical trials (see summary in [1]) and with the first fragment-derived compound now treating patients [2].

Screening virtual de fragmentos moleculares



http://practicalfragments.blogspot.com/



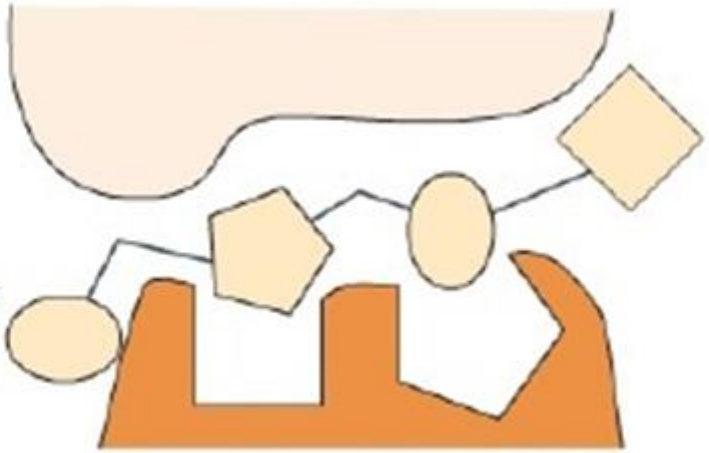
Screening virtual de fragmentos moleculares

Potência

µM -> nM

Propriedades

ADMET

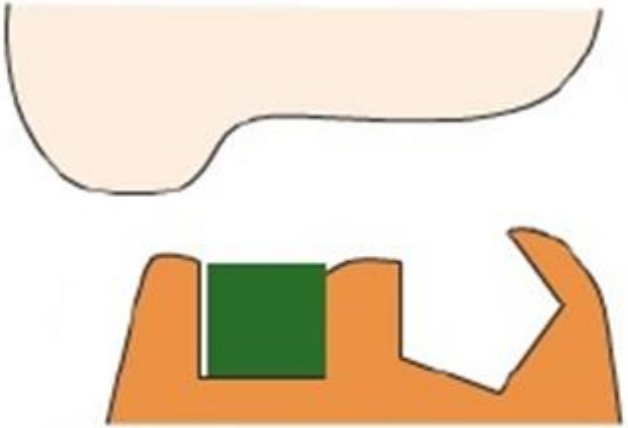


Baixa afinidade

>>Espaço química

Baixa potência intrínseca

mM -> µM

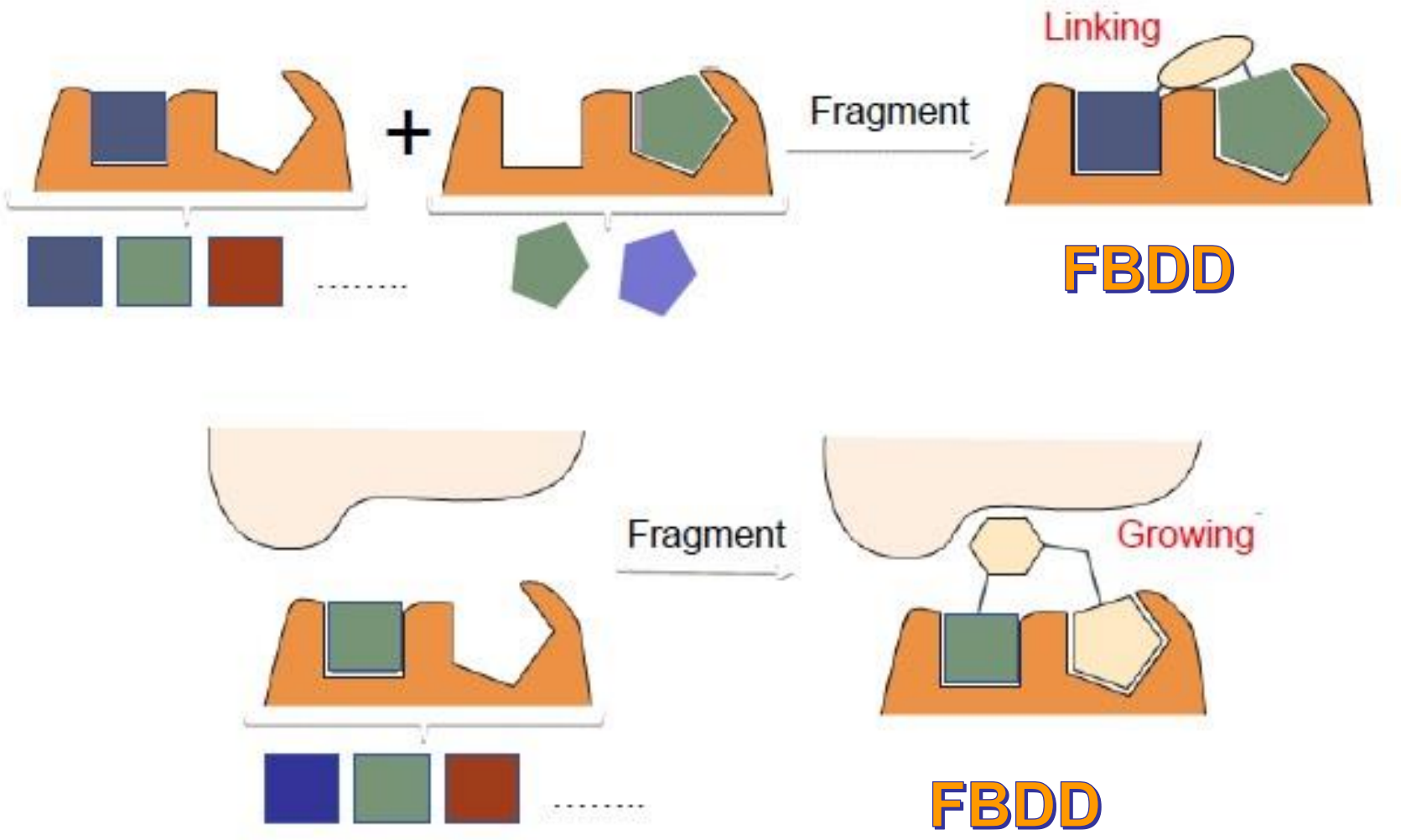


Propriedades

ADMET

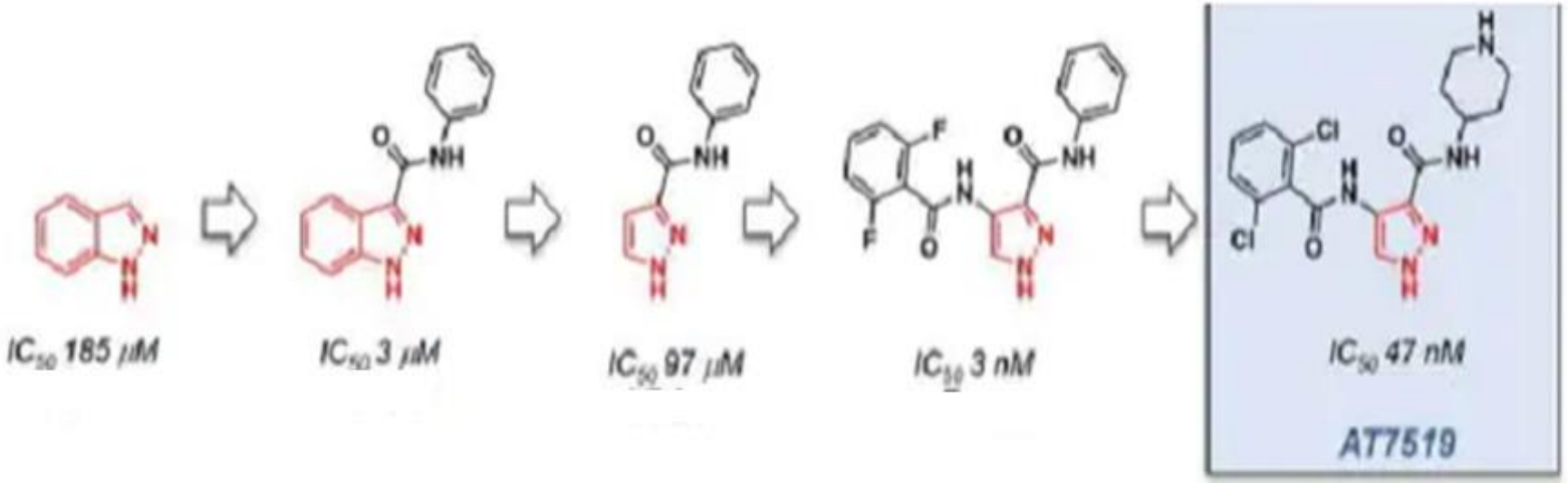
Rees, D.; Congreve, M.; Murray, C.; Carr, R. Fragment-based lead discovery. Nature reviews. Drug discovery (2004), 3, 660–72.

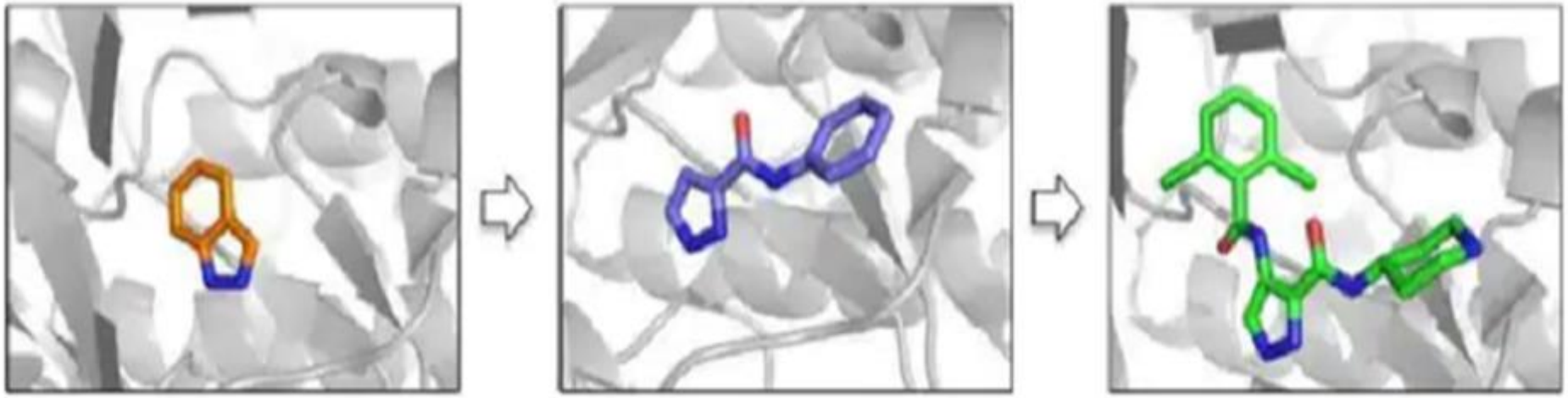
Screening virtual de fragmentos moleculares



Rees, D.; Congreve, M.; Murray, C.; Carr, R. Fragment-based lead discovery. Nature reviews. Drug discovery (2004), 3, 660–72.

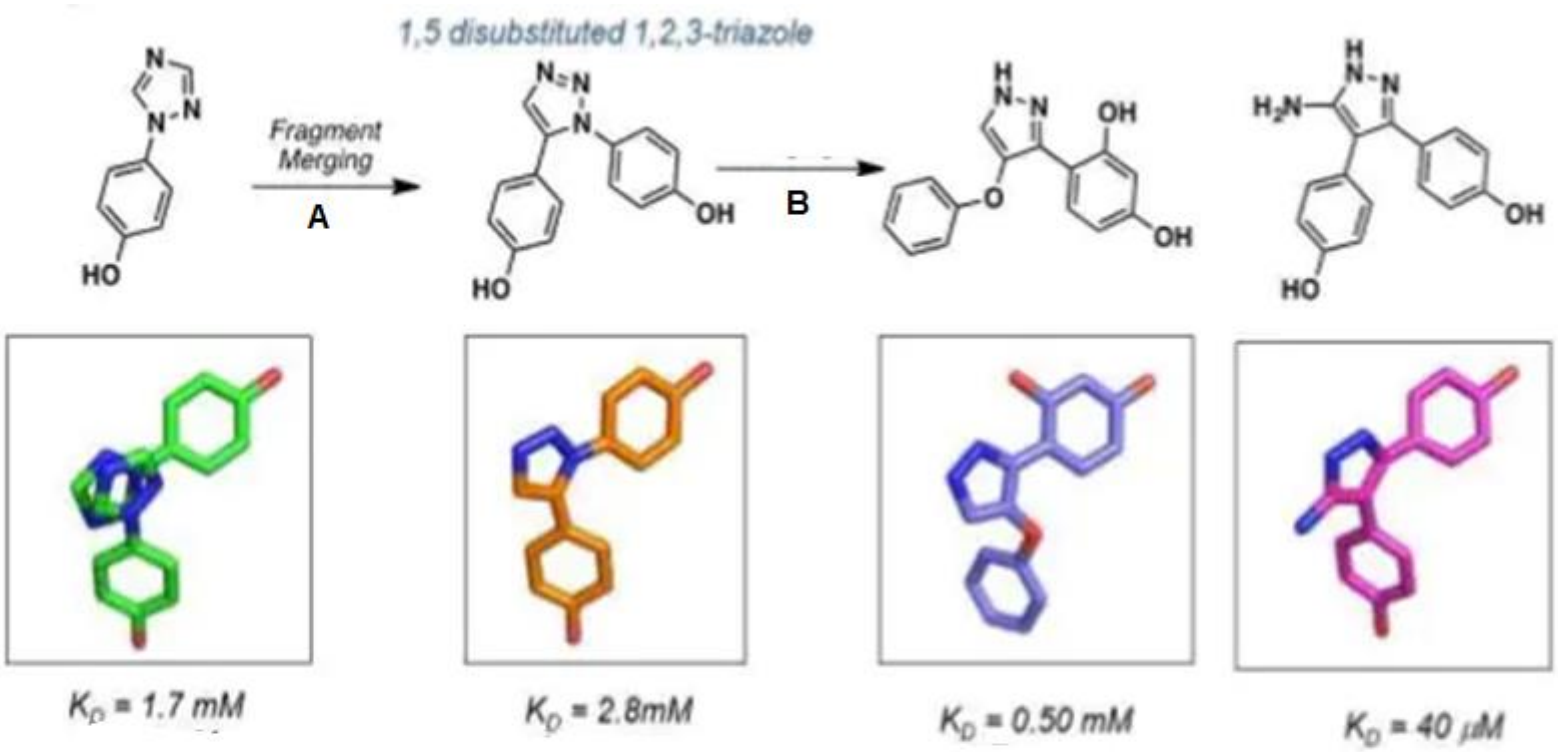
From FBDD to ligand: an example





Fragment growing of the initial indazole hit led to a compound with a 50 fold increase in potency. Removal of the phenyl ring of the indazole offered a new startpoint and this was subsequently elaborated to a compound with a IC_{50} of 47 nM

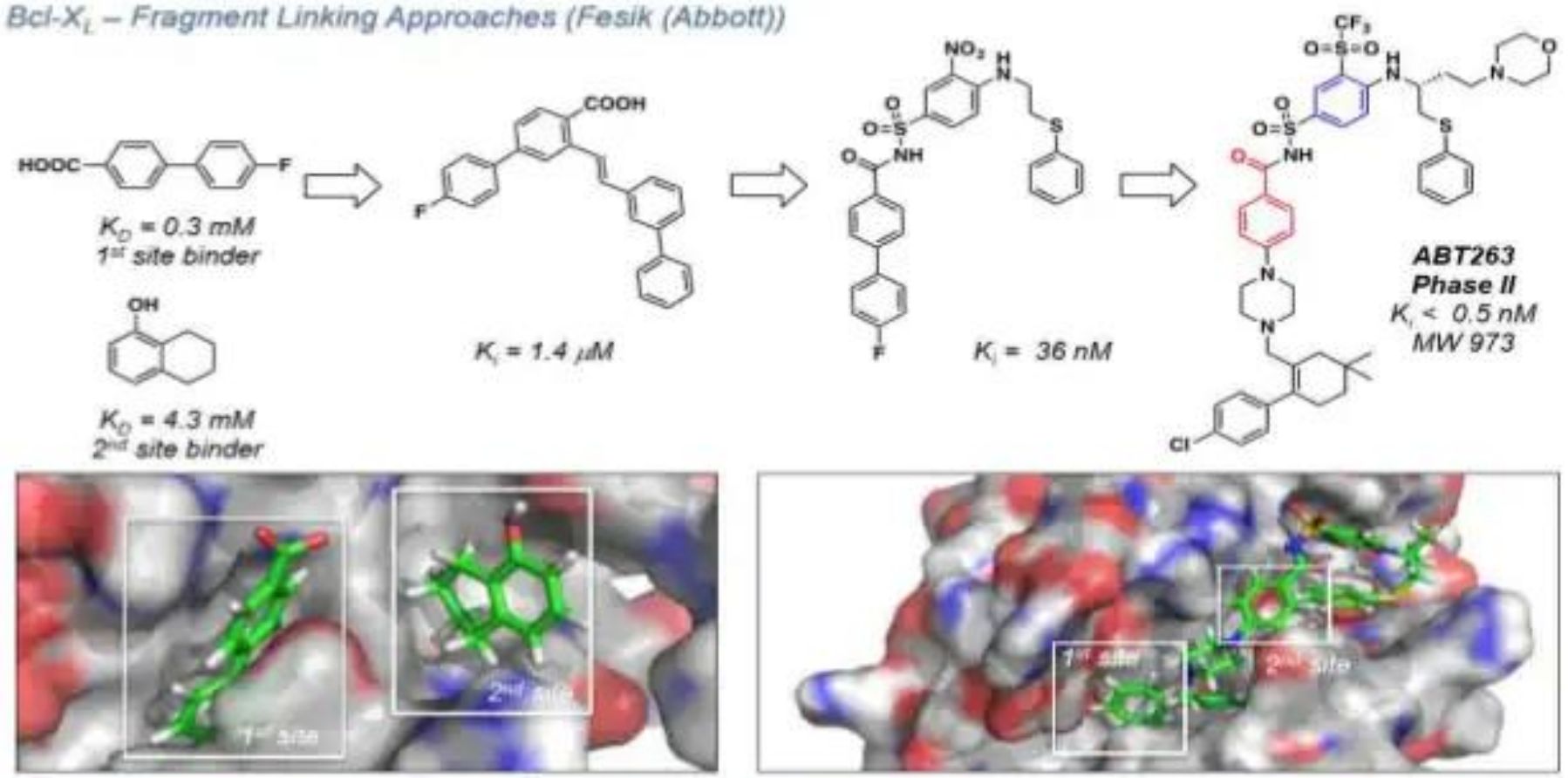
From FBDD to ligand: another example



A) *Merging of the two poses of the 1,2,4-triazole into a 1,5 disubstituted 1,2,3-triazole gave a compound which bound in a similar pose as the initial fragment hit however the potency was much poorer*

B) *Further elaboration of the triazole ring to a pyrazole and subsequently an aminopyrazole had a significant effect on the potency where this increased to 40 μM with a slight drop in ligand efficiency.*

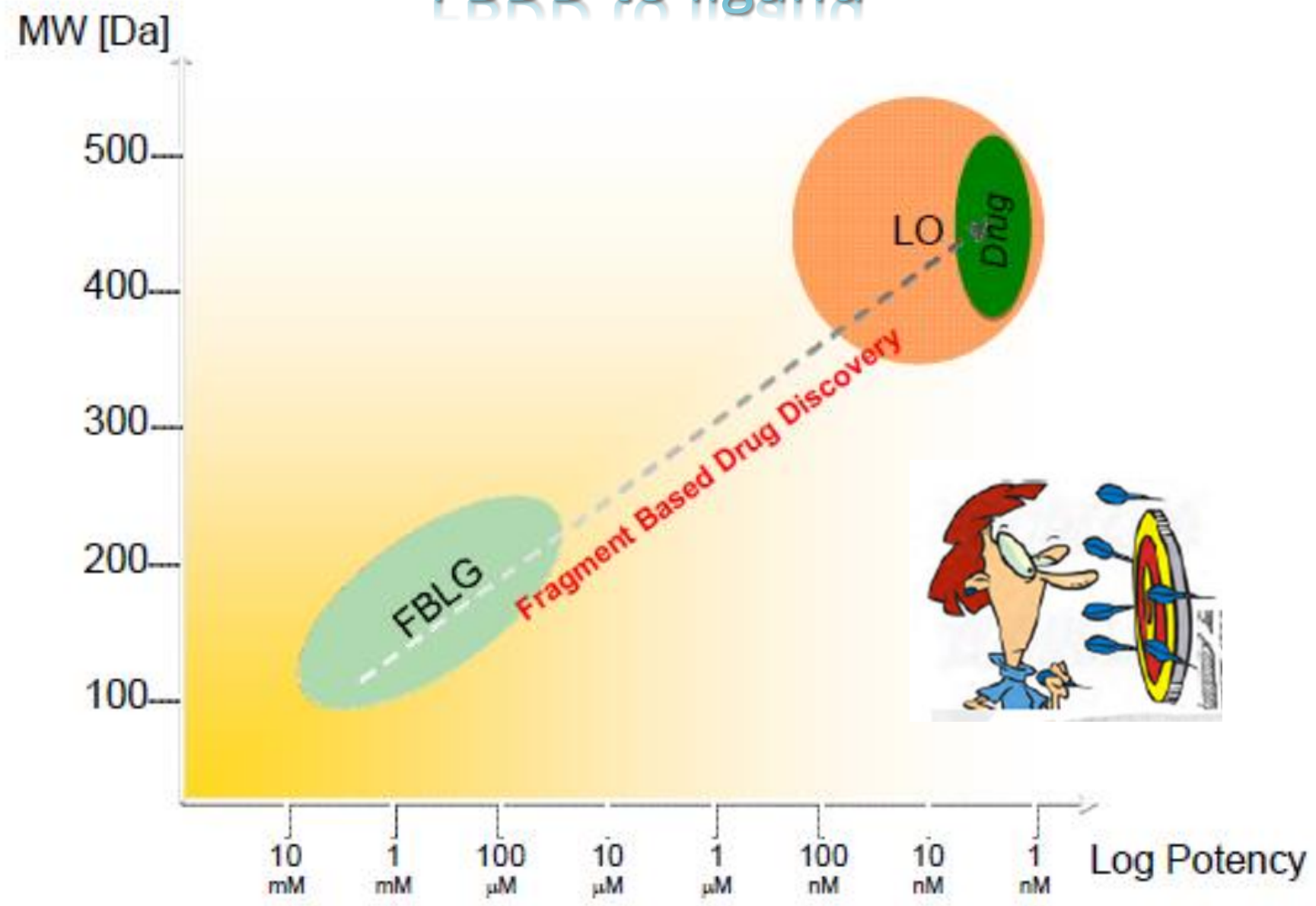
From FBDD to ligand: final example



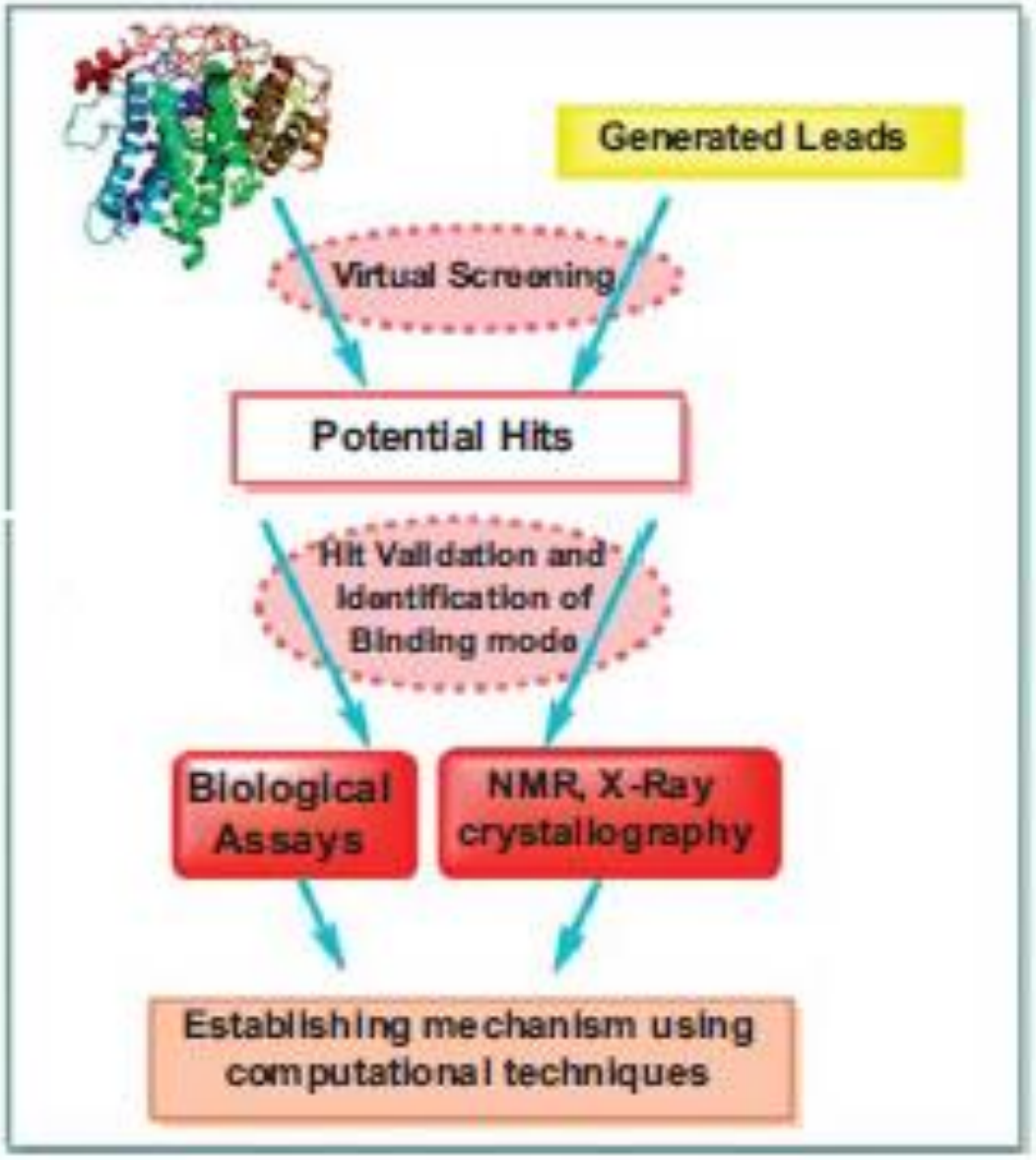
One of the first successful examples of fragment linking against Bcl-XL where the initial fragment linking with an alkene gave a significant drop in potency. Second site binder discovered through 'SAR by NMR'

Subsequent elaboration led to the development of ABT273 which has a Ki <0.5 nM although the molecular weight of this compound is large (MW 973). Looking at this structure there are still some components of the initial fragment hits present.

FBDD to ligand



Identificação de um Composto-hit



Química Medicinal

Quimioteca

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

MPRO
SARS-CoV-2

Fragmentos moleculares

FBDD

Virtual screen

Fragmentos

Hit

Indíce similaridade

Tanimoto

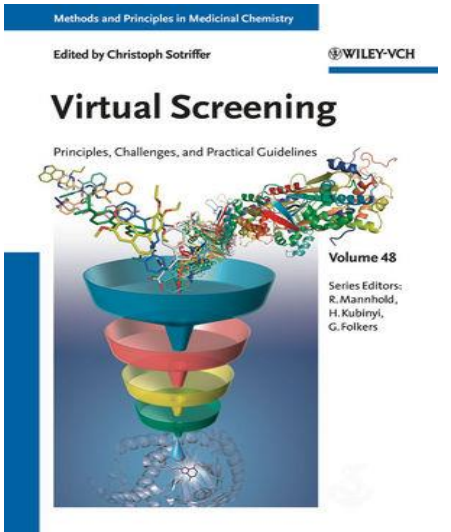
Cocrystals & Docking

Modelo Farmacofórico

Binding

H_2L

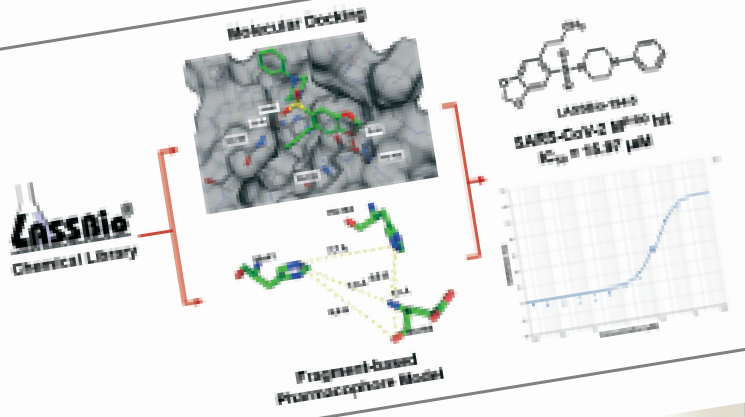
Ligante



Novo ligante para M^{PRO} de SARS-CoV-2

Quimioteca do LASSBio

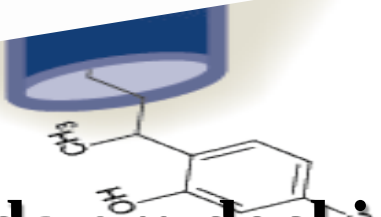
RSC Medicinal Chemistry



Identification of LASSBio-1945 as an inhibitor of SARS-CoV-2 main protease (M^{PRO}) through *in silico* screening supported by molecular docking and a fragment-based pharmacophore model

Lucas S. Franco, Rodolfo C. Maia and Eliezer J. Barreiro*

A SARS-CoV-2 main protease (M^{PRO}) inhibitor was discovered employing molecular docking and a fragment-based pharmacophore model as virtual screening strategies.



Triagem virtual baseada em docking molecular da Quimioteca do LASSBio sobre SARS-CoV-2 M^{Pro}

3D M^{Pro} 1,39A

Diamond Light Source Lab, Oxfordshire

Co-cristais fragmentos moleculares

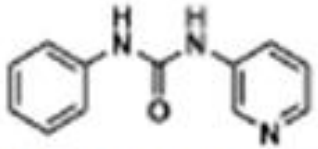
Main Protease Structure & XChem Fragment Screen.

Modêlo Farmacofórico 3D

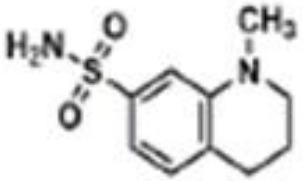
Quimioteca

LASSBio Laboratório de Avaliação e Síntese de Substâncias Bioativas

Índice de Similaridade Molecular

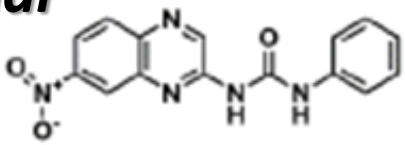


Mpro-x0434



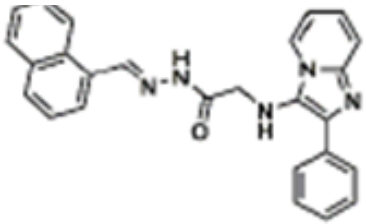
Mpro-x0195

0.52



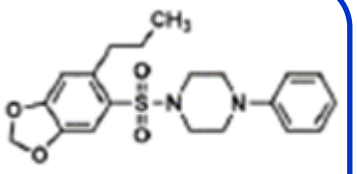
LASSBio-1962

0.42



LASSBio-1615

Atividade Inibitória sobre M^{Pro} SARS-CoV-2



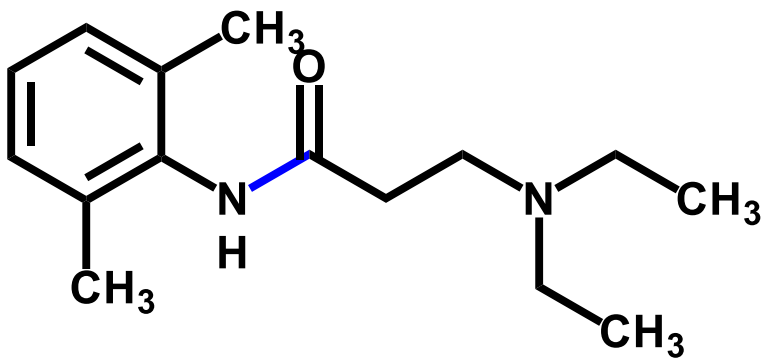
LASSBio-1945

IC_{50} = 15,9 µM

inct inofar

L. S. Franco, R. C. Maia, E. J. Barreiro, Discovery of LASSBio-1945 an Inhibitor of SARS CoV-2 Main Protease (M^{PRO}) through In Silico Screening supported by Molecular Docking and Fragment-Based Pharmacophore Model. *RSC Med Chem* **2021**,*12*,110-119 DOI: doi.org/10.1039/D0MD00282H

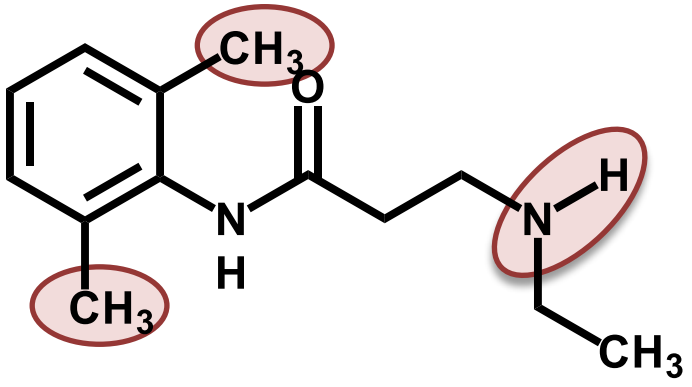
Efeito *orto*- em Química Medicinal



lidocaína

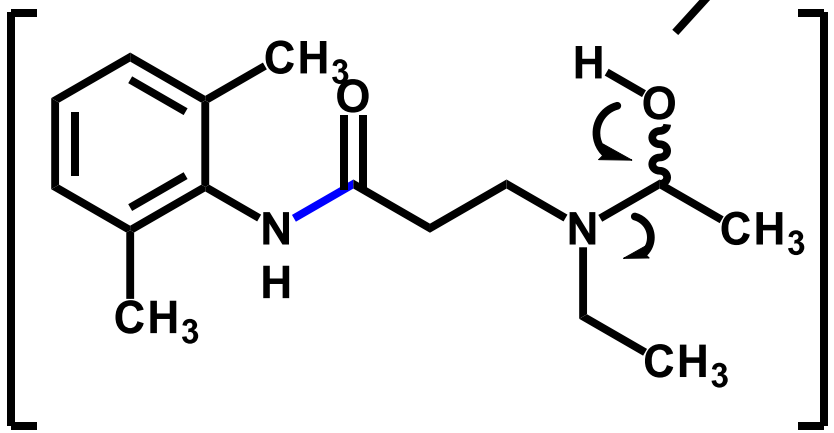
$C_{15}H_{24}N_2O$

[O]

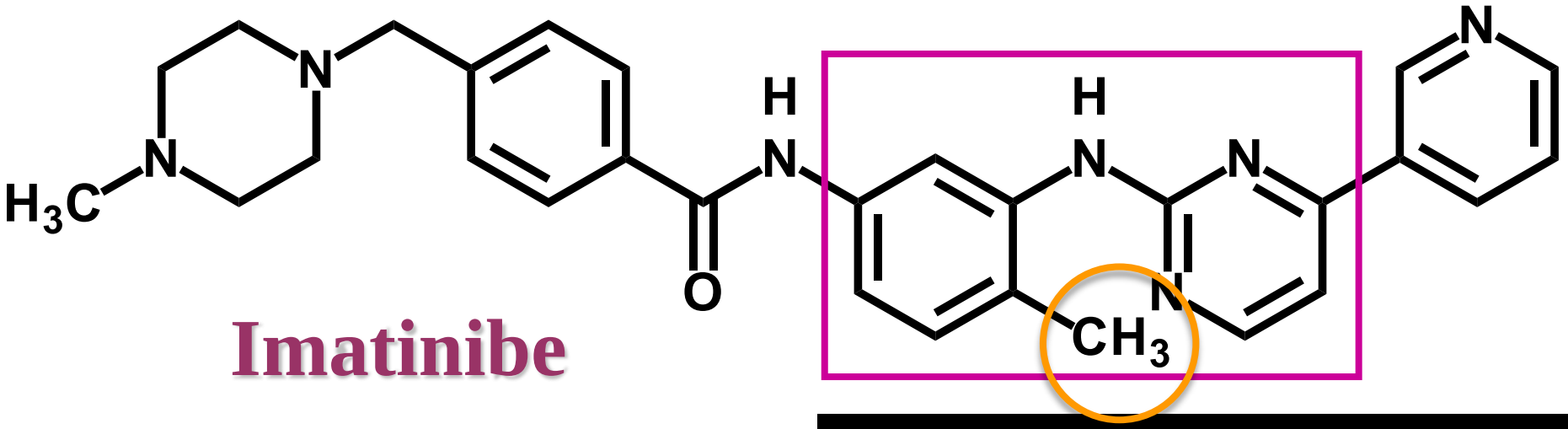


principal metabólito

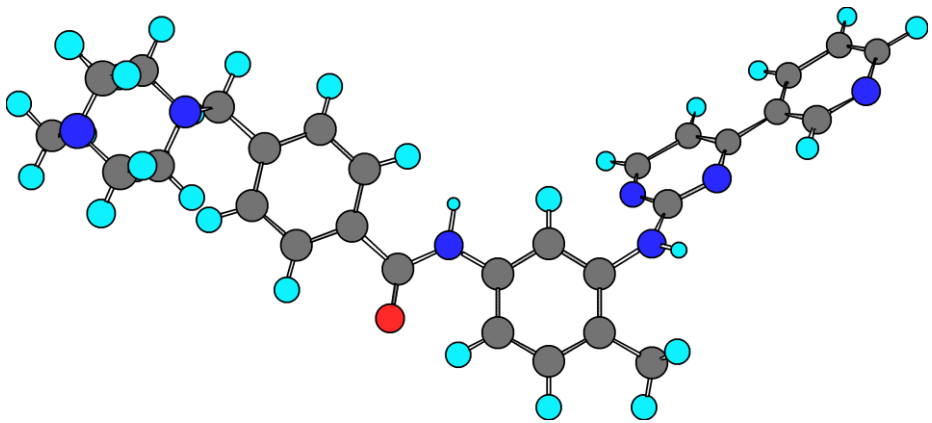
$C_{13}H_{20}N_2O$

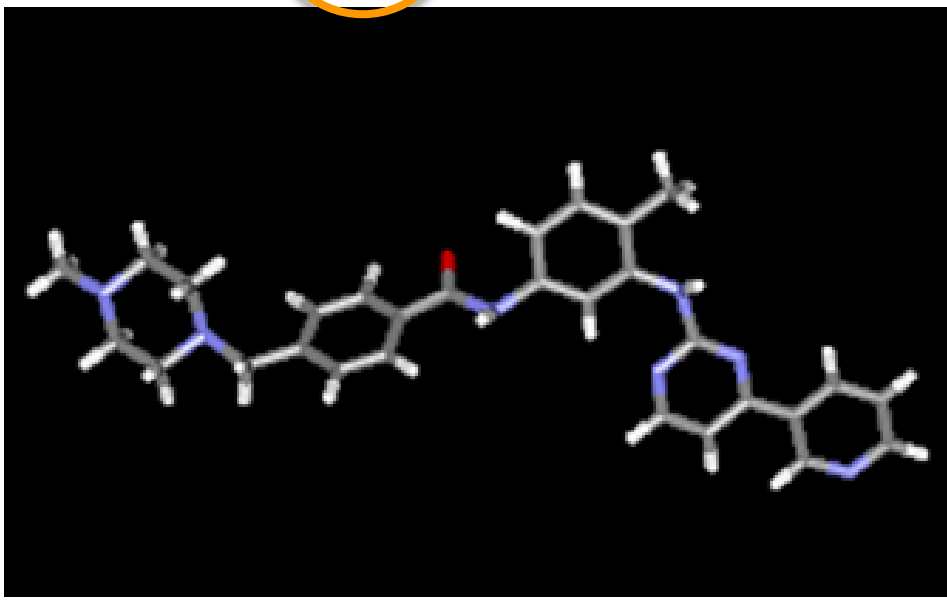


Efeito *orto-*



Imatinibe





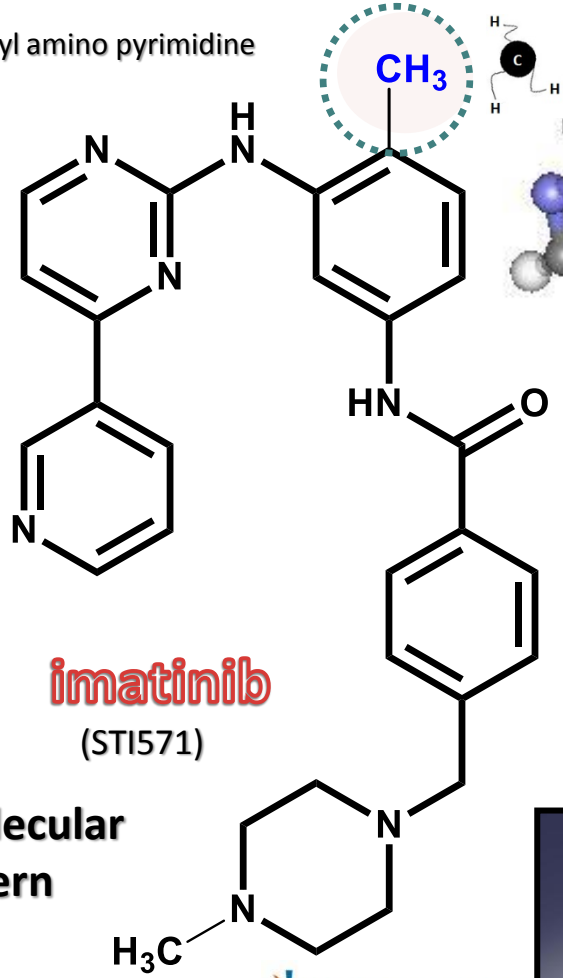
Gênese do Imatinibe

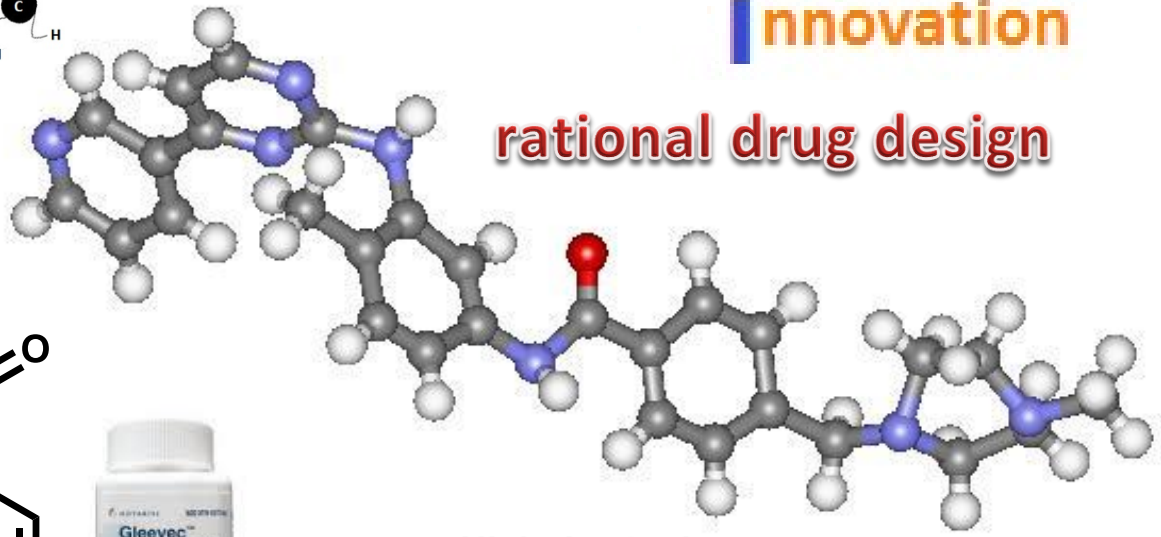
Efeito orto-

therapeutic innovation

rational drug design

2-phenyl amino pyrimidine





imatinib

(STI571)

New molecular pattern

1988 – **Nicholas Lydon, Brian J. Druker & Charles L Sawyers** &

1995 - **Compound STI571 ++**

2001 – Imatinibe (Gleevec[R], Novartis)[link]

2012 – US$ 92.000 / y; sales (2012): US$4,7 bi

chronic myelogenous leukemia (CML)

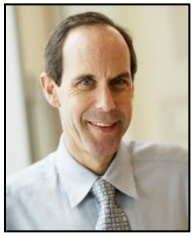
NOVARTIS

imatinibe

Nicholas B. Lydon
Blueprint Medicines Inc

Química Medicinal

OREGON HEALTH & SCIENCE UNIVERSITY



Brian J. Druker*
Blueprint Medicines Inc

HHMI HOWARD HUGHES MEDICAL INSTITUTE

Charles L. Sawyers**

& 2009 - Lasker Foundation Clinical Award (*J. Clin. Invest*. **2009**, *119*, 2863; DOI:10.1172/JCI41141); 2012 – Japon Prize

* Brian J. Druker has been awarded with the 2012 Japan Prize in Healthcare and Medical Technology;

** Charles L. Sawyers was named in 2011, Thomson Reuters Citation Laureate in Medicine;

Efeito-*orto* & Química Medicinal

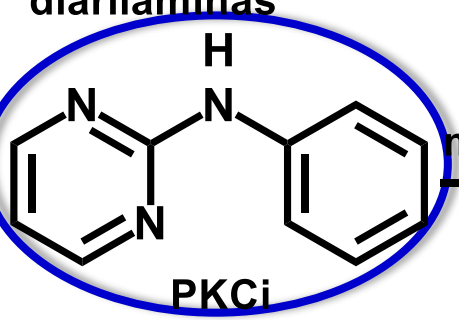
Imatinibe (Glivec^{R}, STI571)

QUIMIOTECA

diarilaminas → *N*-pirimidilanilina → **hit**

hit → lead

diarilaminas

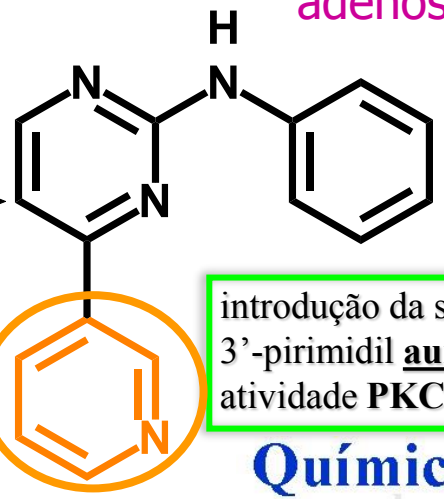


screening para inibidores de **PKC**

S. Teague, 1999

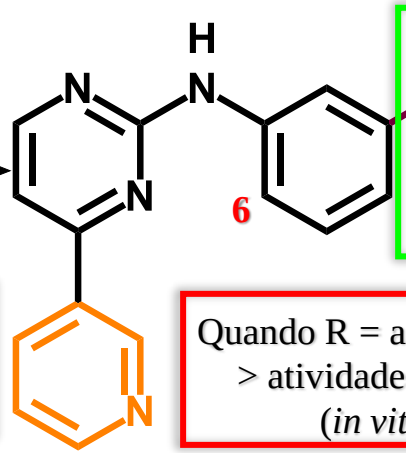
melhora da atividade

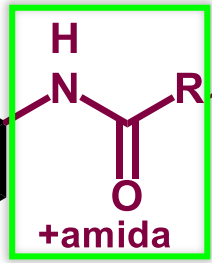
adenosina



introdução da subunidade 3'-pirimidil **aumentava** a atividade **PKC-i** (*in vitro*)

Bcr-Abl

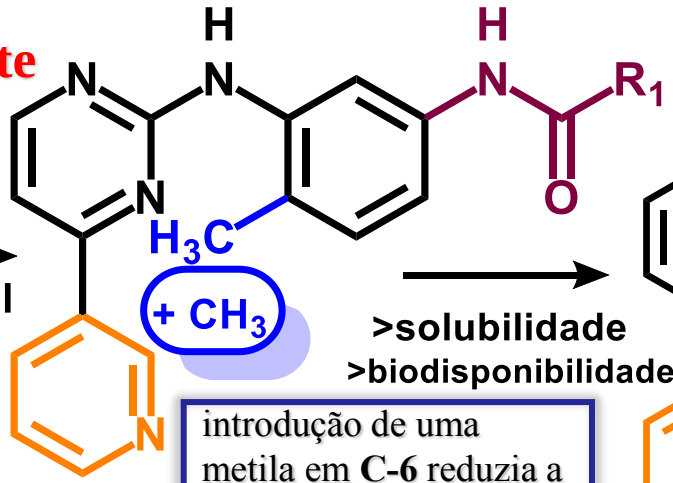




Quando R = alquilamida > atividade Bcr-Abl (*in vitro*)

Química Medicinal

Ligante



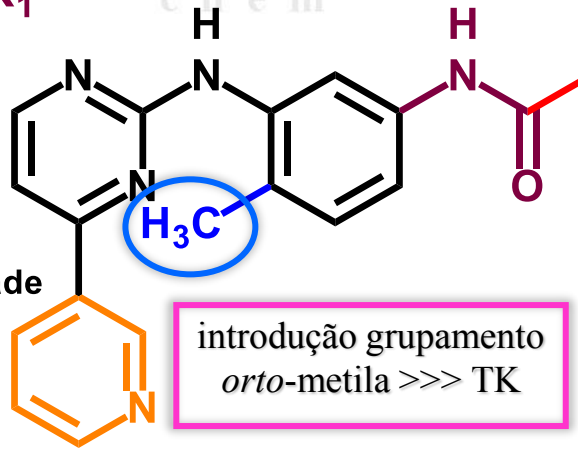
<<PKC

>Bcr-Abl

introdução de uma metila em **C-6** reduzia a atividade PKC-i (*in vitro*)

>solubilidade

>biodisponibilidade



introdução grupamento *orto*-metila >>> TK

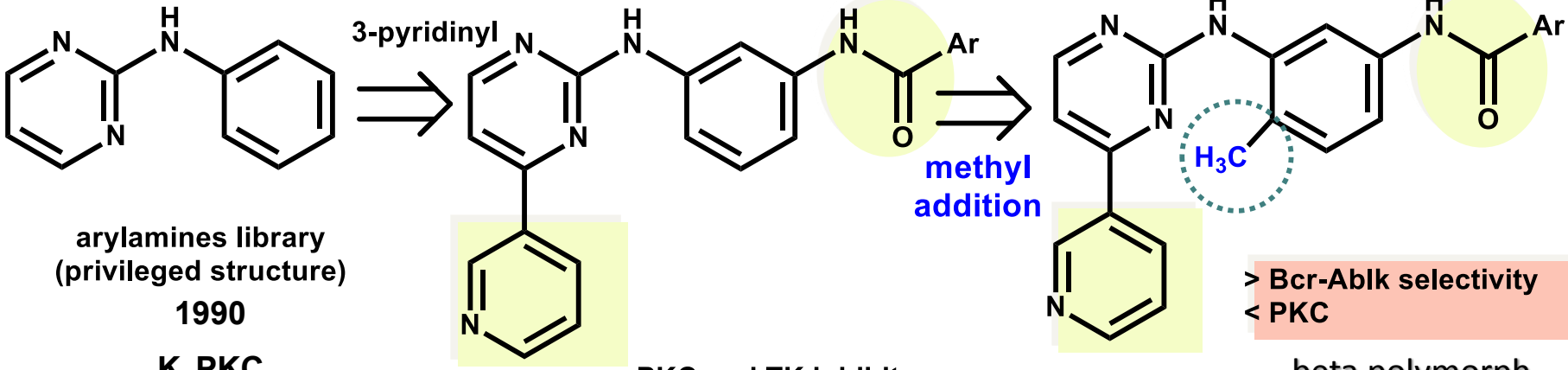
+*N*-metil-fenilpiperazina

introdução da *N*-metilfenil piperazina >> solubilidade aquosa >> PK (Bcr-Abl)

Química Medicinal

NOVARTIS

HTS



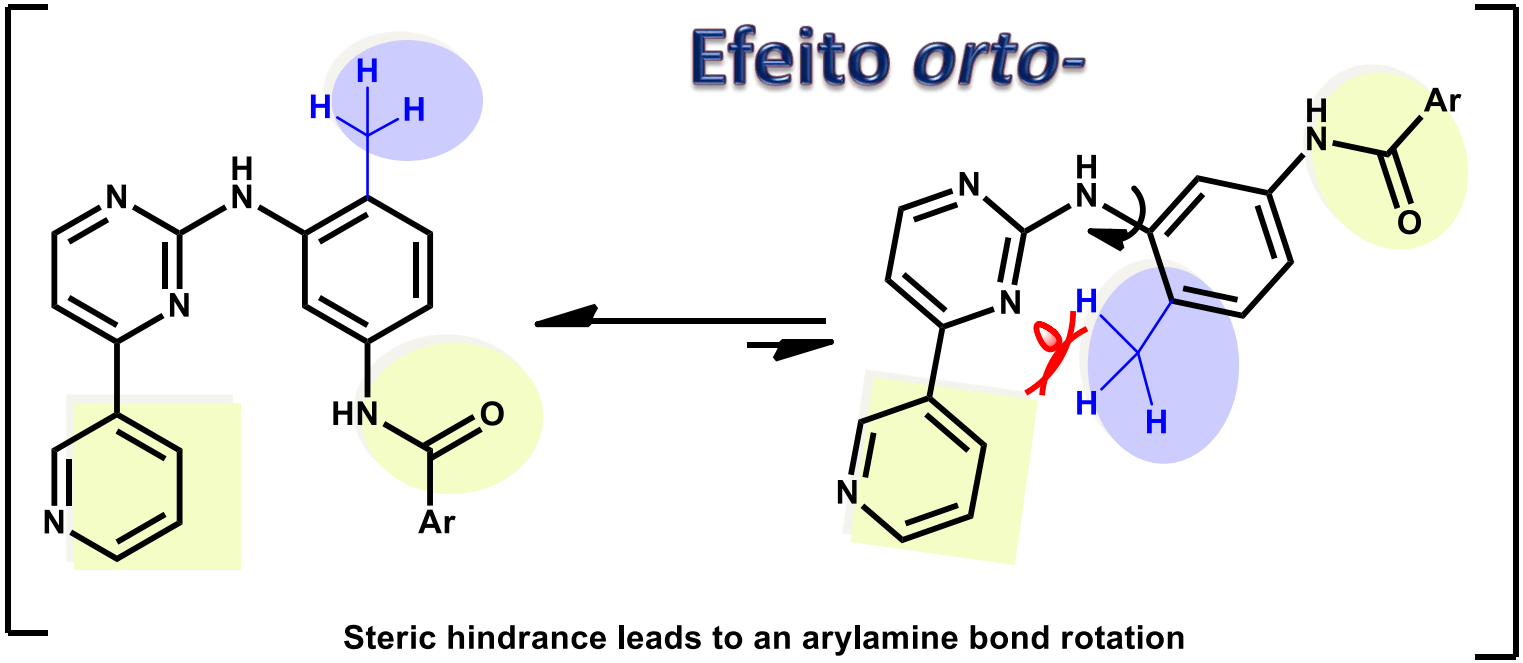
arylamines library
(privileged structure)
1990
K_i PKC

PKC and TK inhibitor
(Bcr-Ablk inhibitor)

> Bcr-Ablk selectivity
< PKC

beta polymorph

Efeito *orto*-



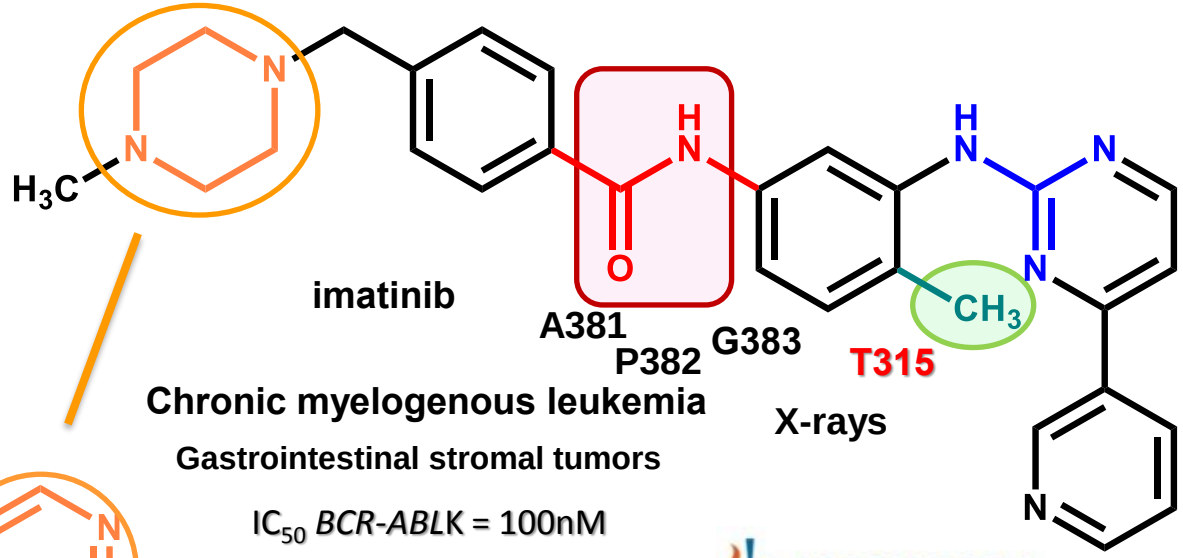
Steric hindrance leads to an arylamine bond rotation

PW Manley, J Zimmermann in Case Studies in Modern Drug Discovery and Development, X Huang & RG Aslanian, Eds.,Wiley, **2012**, pp.88-102

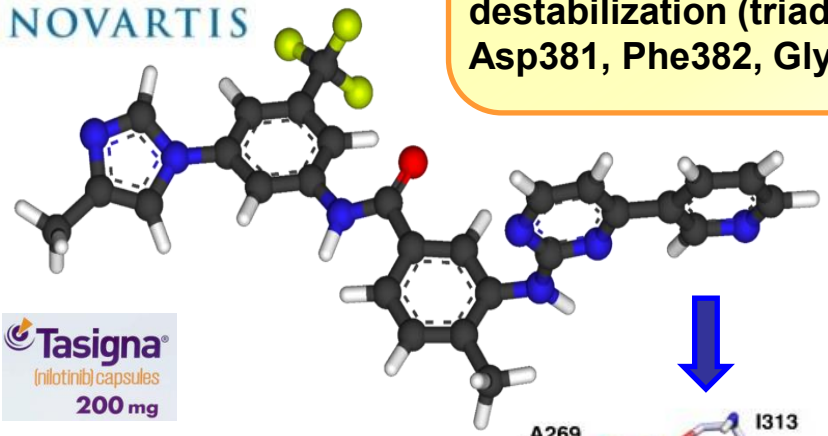
Combination with other drugs (*e.g.* taxoids) is useful to CML imatinib-resistant cells (20 times more potent than imatinib)

therapeutic innovation

BCR-ABL1 imatinib resistence due Thr315 point (T315) mutation, promote conformation destabilization (triade Asp381, Phe382, Gly383)



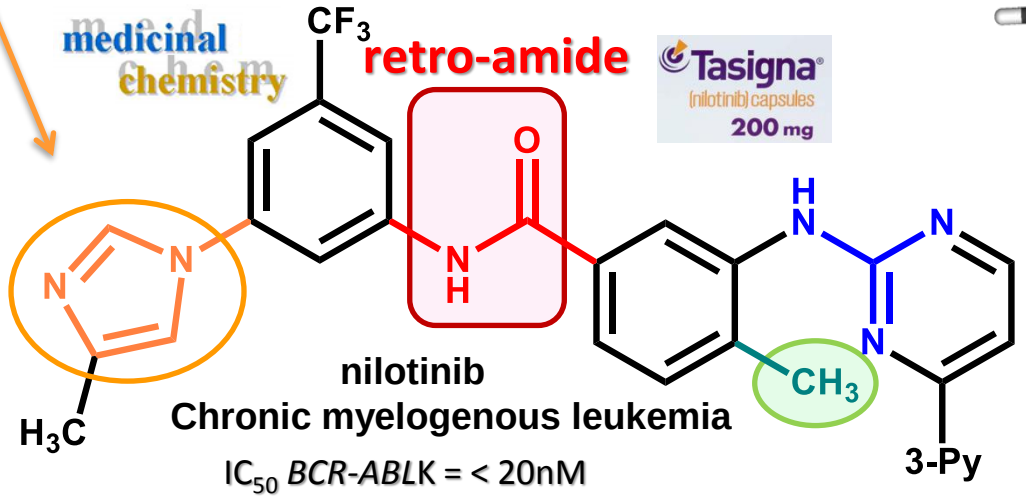
NOVARTIS

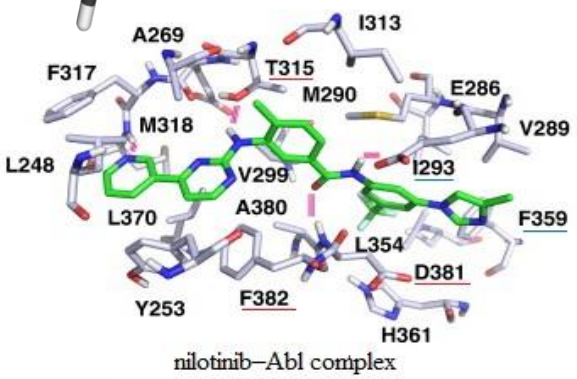


medicinal chemistry

retro-amide

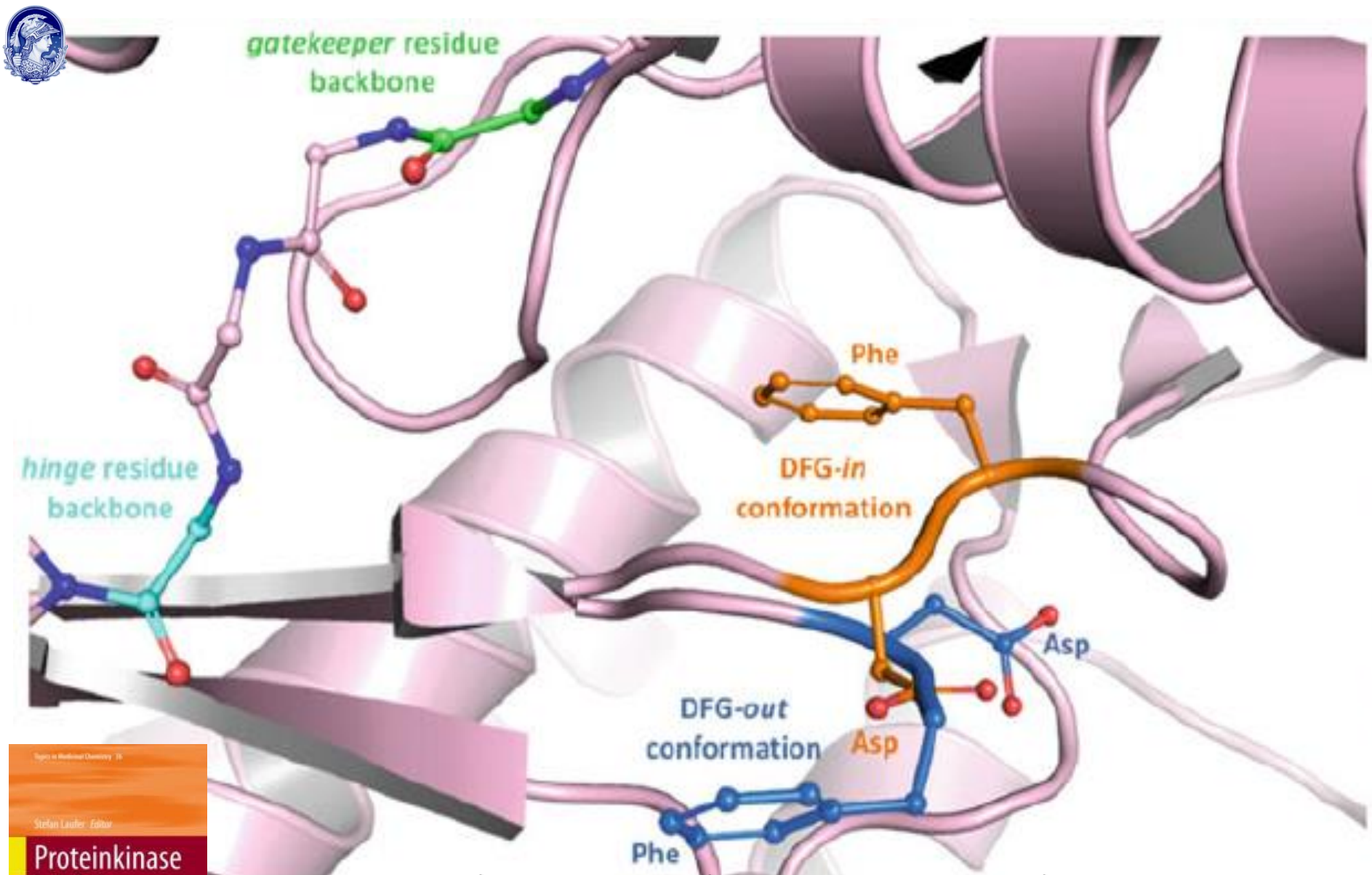
Tasigna (nilotinib) capsules 200 mg

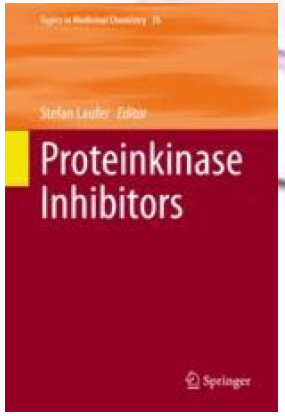




nilotinib–Abl complex

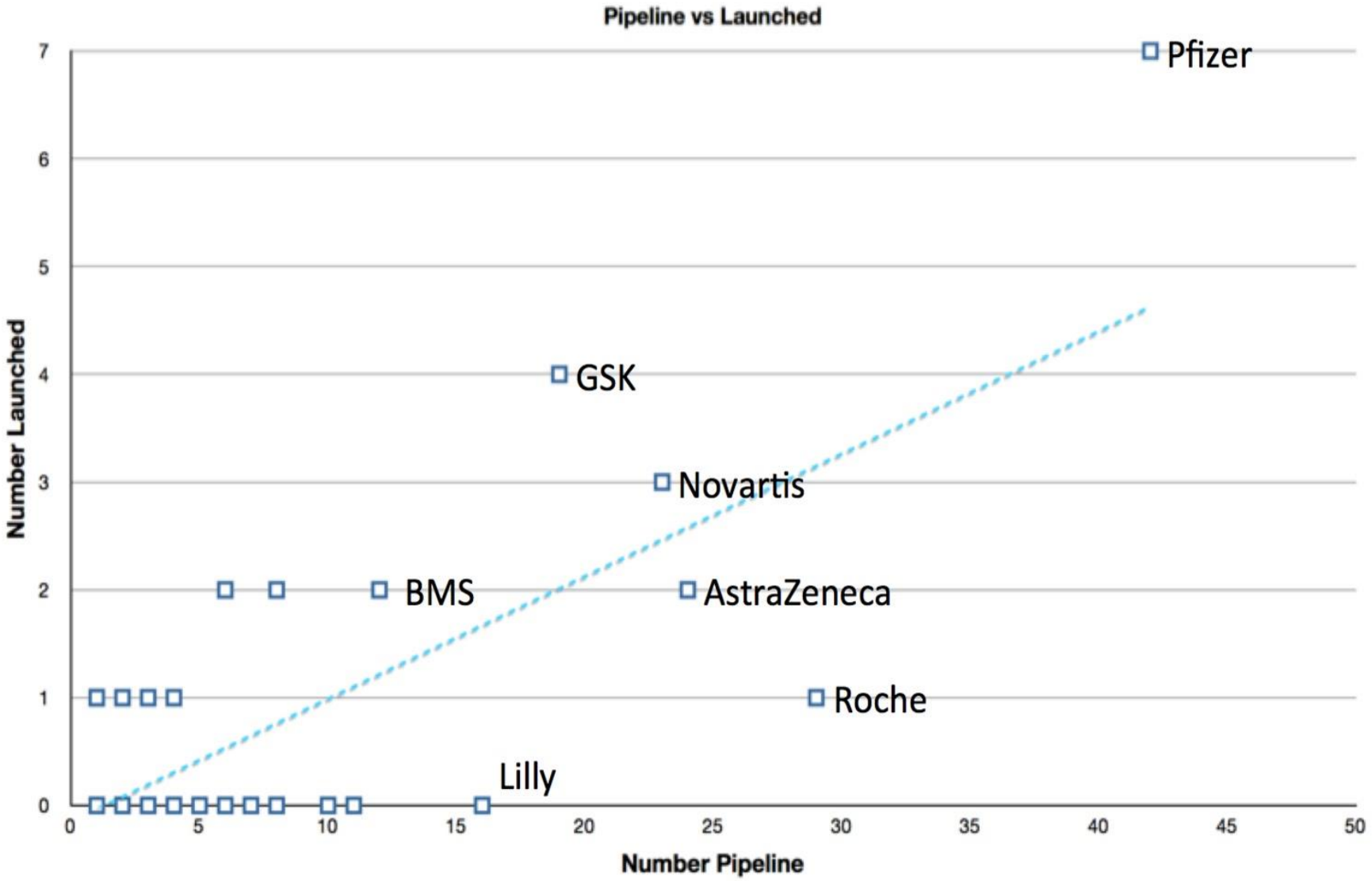
P.W. Manley, J. Zimmermann in *Case Studies in Modern Drug Discovery and Development*, X. Huang & R.G. Aslanian, Eds., Wiley, **2012**, p.88-102

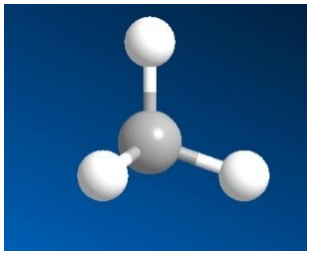


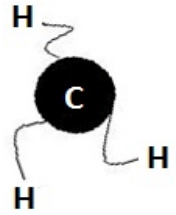


LM Lima, MLC Barbosa, DN Amaral, E J Barreiro, *Case Study on Receptor Tyrosine Kinases EGFR, VEGFR, and PDGFR,* In: S. Laufer (eds) Protein kinase Inhibitors. *Topics in Medicinal Chemistry*, **2021**, vol. *36*. 155-203. Springer, Cham. DOI:10.1007/7355_2020_95

Kinase Inhibitor Success in the Clinic

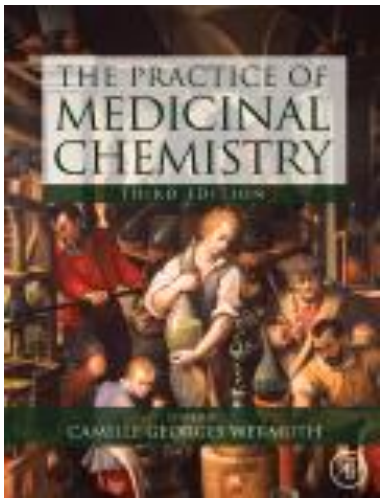






"The methyl group, so often considered as chemically inert, is able to alter deeply the pharmacological properties of a molecule."

"The Bible"



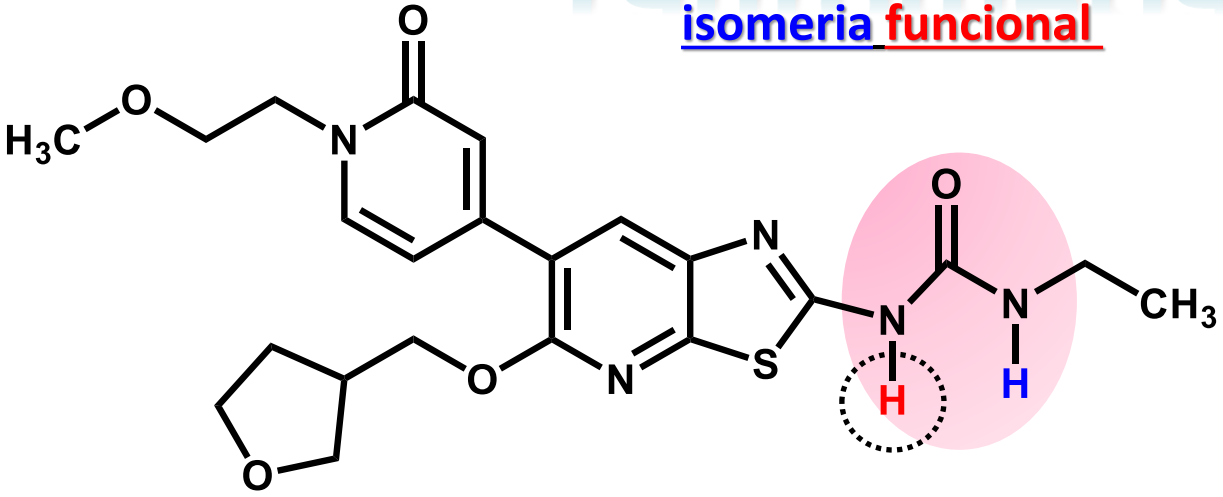
CG Wermuth & EJ Barreiro, Prestwick Co., Strasbourg, FR (2009)

Camille G. Wermuth

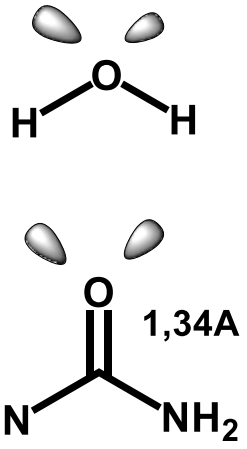
Memorial

Tautomeria

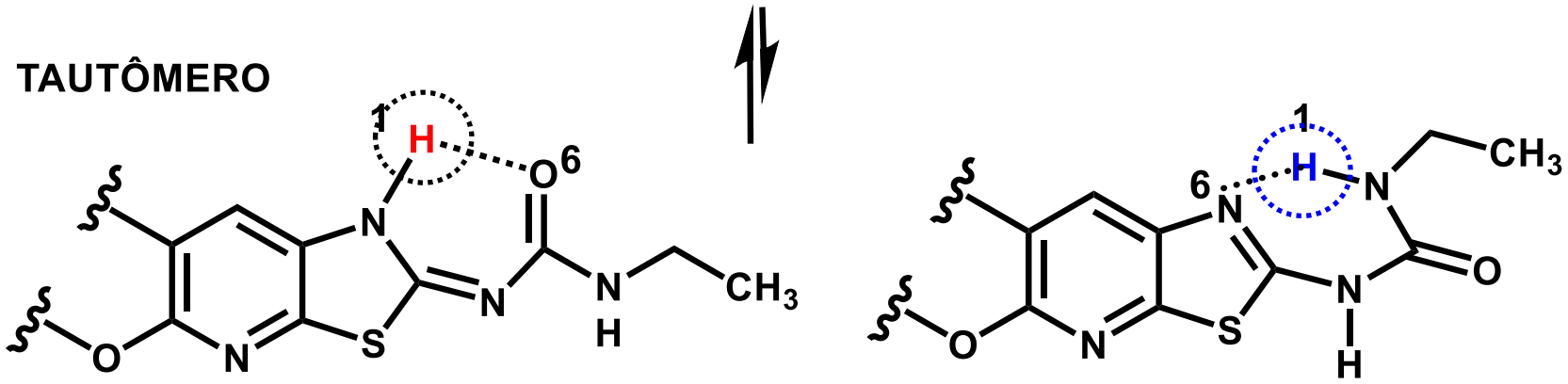
isomeria funcional



Tiazolopiridina-uréia



TAUTÔMERO

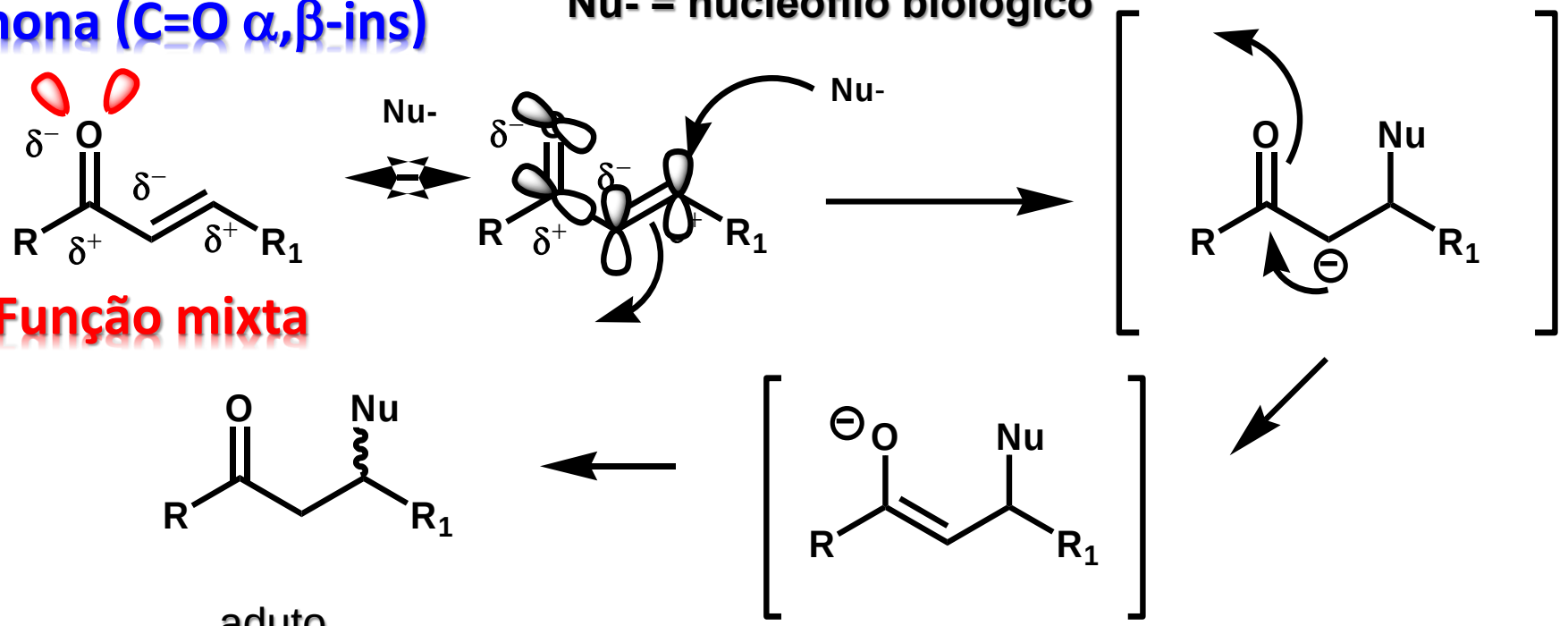


Interação-H intramolecular

Formação de aduto de Michael

Enona (C=O α,β-ins)

Nu- = nucleófilo biológico



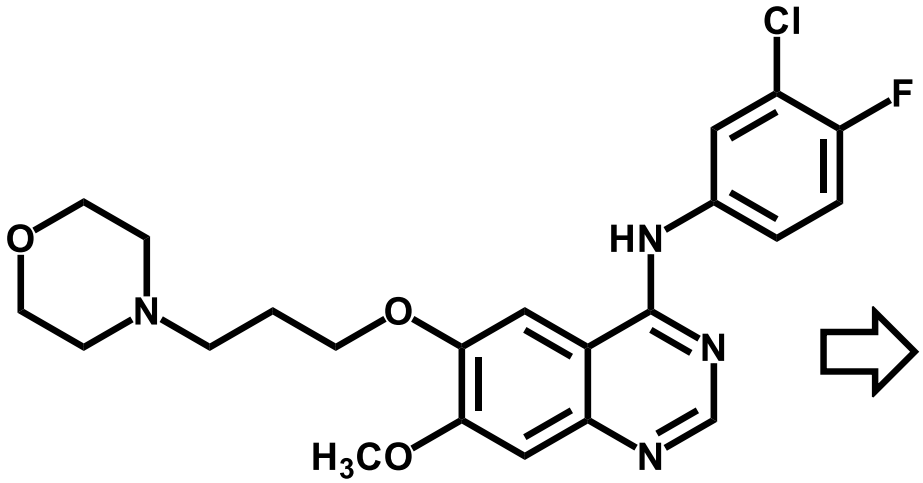
Função mixta

aduto

(irreversível)

Acrilamidas

Inibidores covalentes irreversíveis



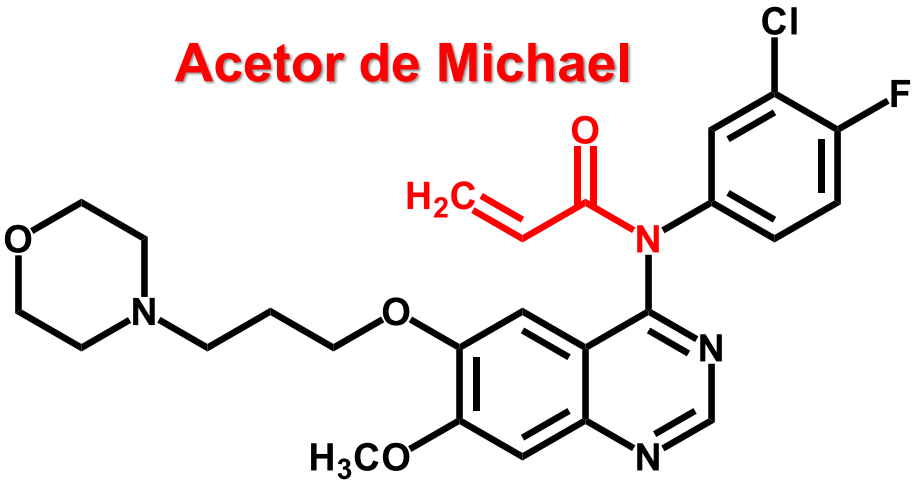
Gefitinibe

EGFR IC_{50} < 0,5 nM

A549 IC_{50} = 5,74 μM

Log $D_{7,4}$ = 2,41

Acetor de Michael



Análogo *N*-acrilamida

EGFR IC_{50} = 65,2 nM

A549 IC_{50} = 0,15 μM

Log $D_{7,4}$ = 2,01

K-D Wu et al., Acrylamide Functional Group Incorporation Improves Drug-like Properties: An Example with EGFR Inhibitors, *ACS Med. Chem. Lett*. **2019**, *10*, 22 [DOI:10.1021/acsmedchemlett.8b00548]

Acrilamidas

Grupos funcionais reativos

Química Medicinal

Função mixta

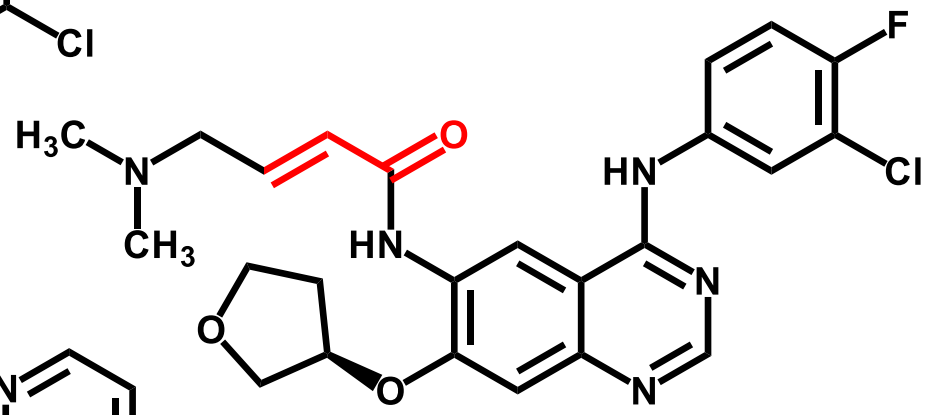
acrilamida

2015 - Pfizer
(Discontinued)

Canertinibe

$C_{24}H_{25}ClFN_5O_3$

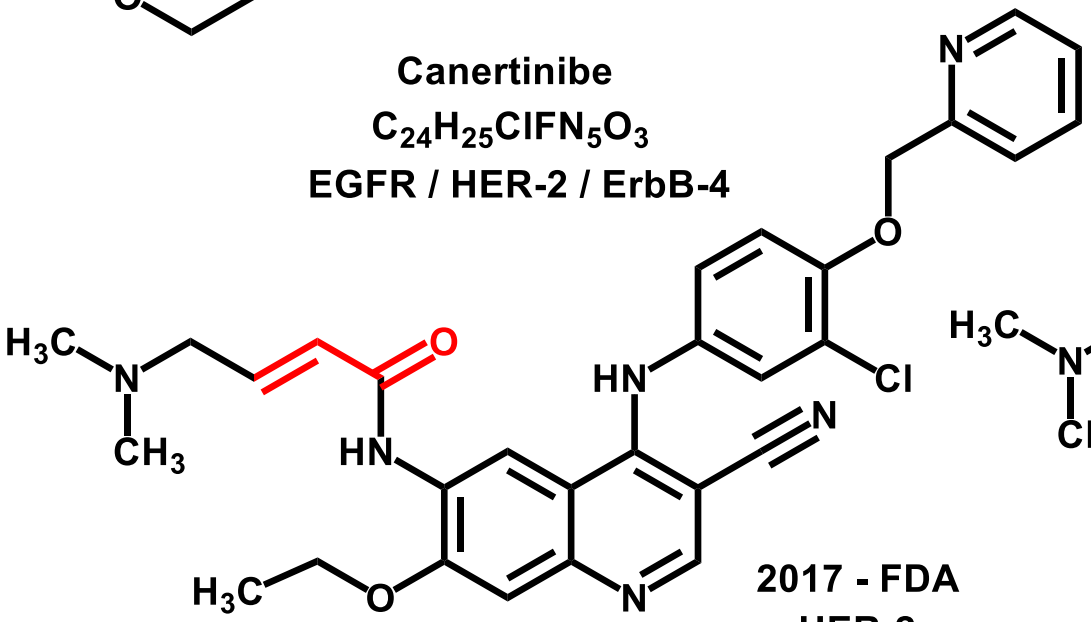
EGFR / HER-2 / ErbB-4



Afatinibe

$C_{24}H_{25}ClFN_5O_3$

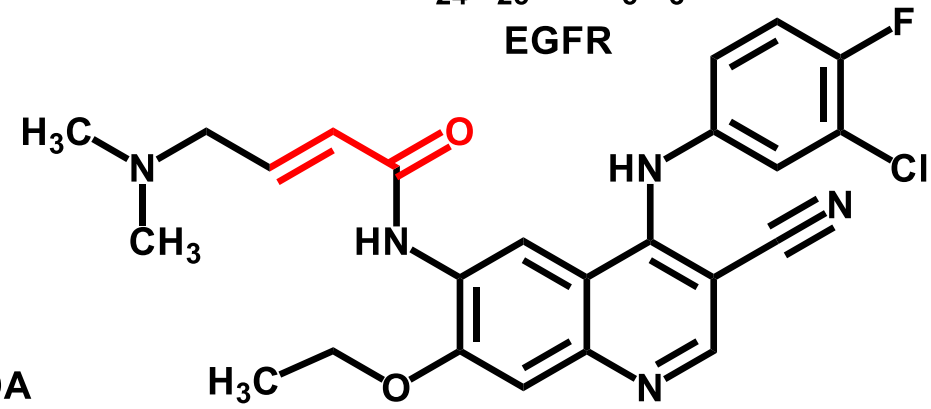
EGFR



Neratinibe

$C_{30}H_{29}ClN_6O_3$

2017 - FDA
HER-2

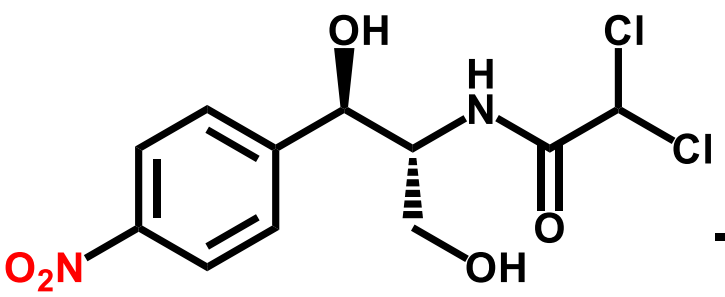


Pelitinibe

EGFR

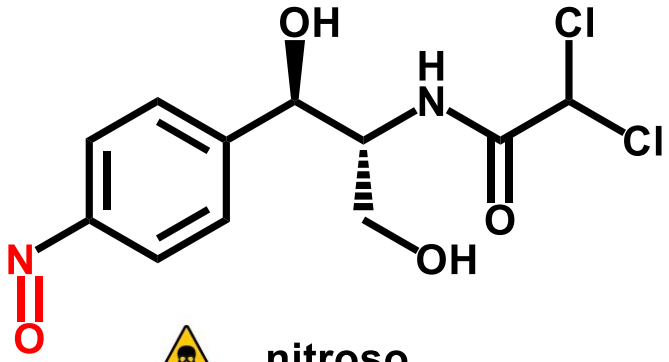
$C_{24}H_{23}ClFN_5O_2$

Grupos funcionais toxicofóricos



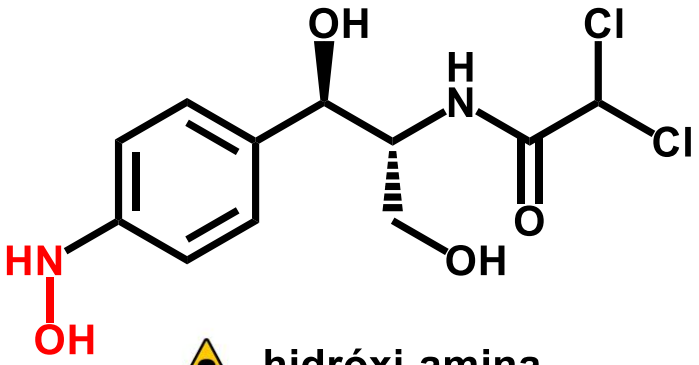
cloranfenicol

[Red]



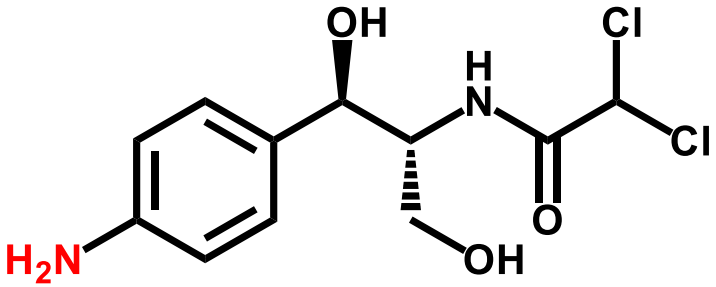
nitroso

[O]



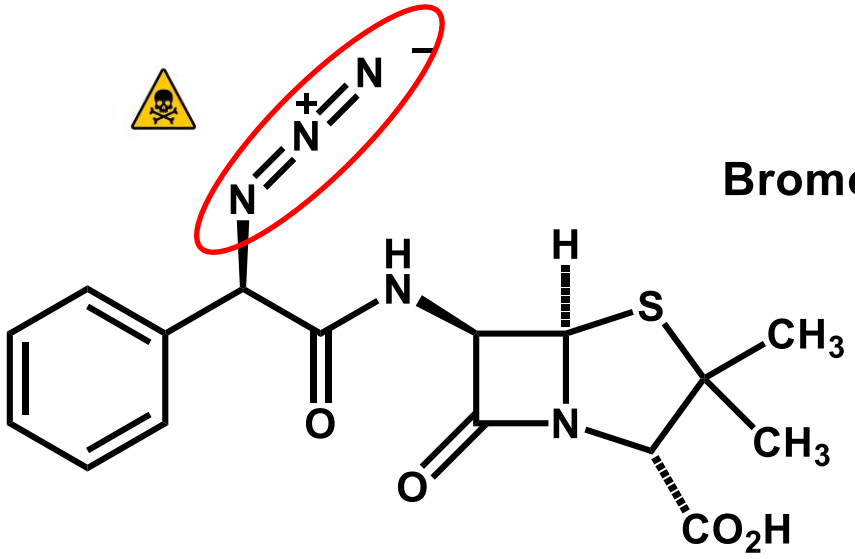
hidróxi-amina

[Red]



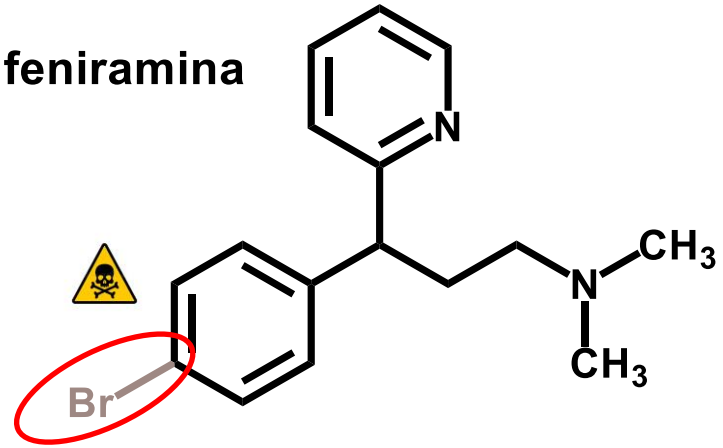
amina

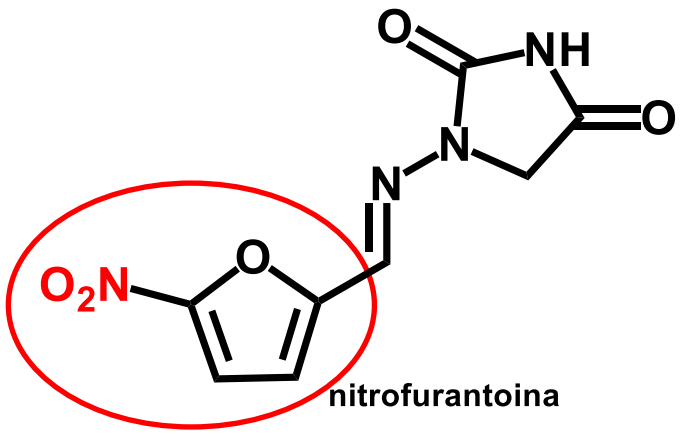
Grupos funcionais toxicofóricos



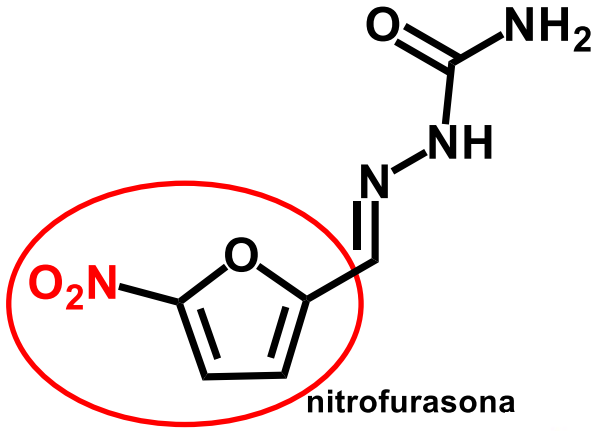
azidociclina

Bromo feniramina





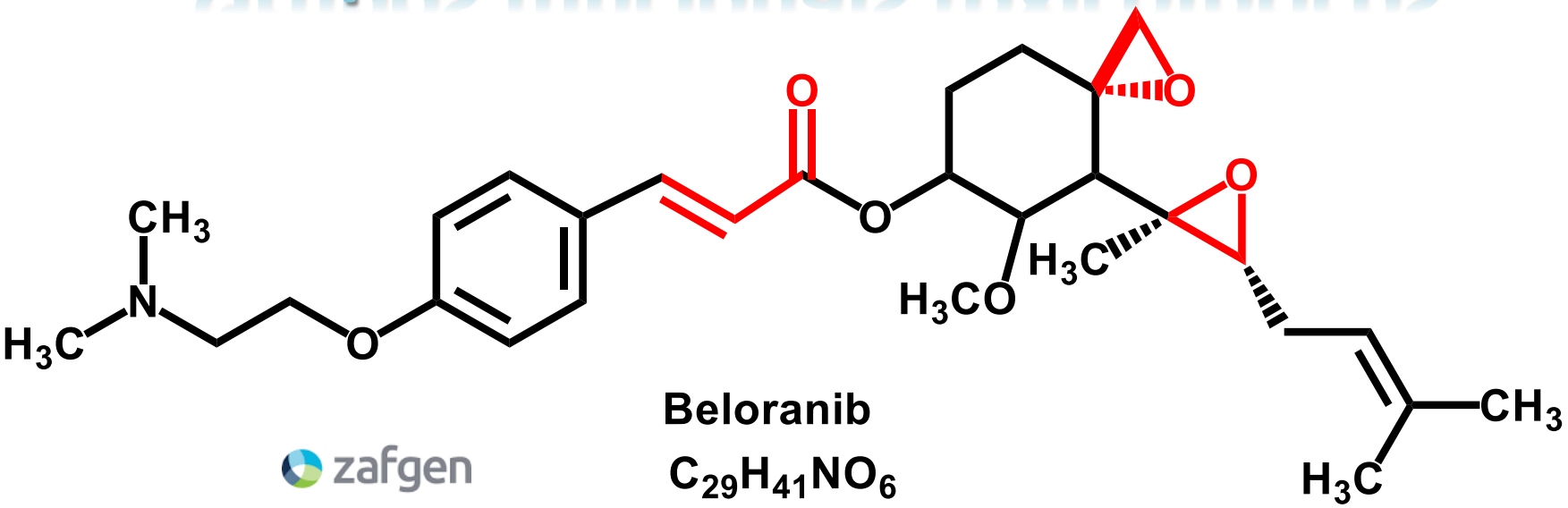
nitrofurantoina



nitrofurasona

K Nepali et al., Nitro-Group-Containing Drugs, *J Med Chem* **2019**, *62*, 000 [10.1021/acs.jmedchem.8b00147]

Grupos funcionais toxicofóricos

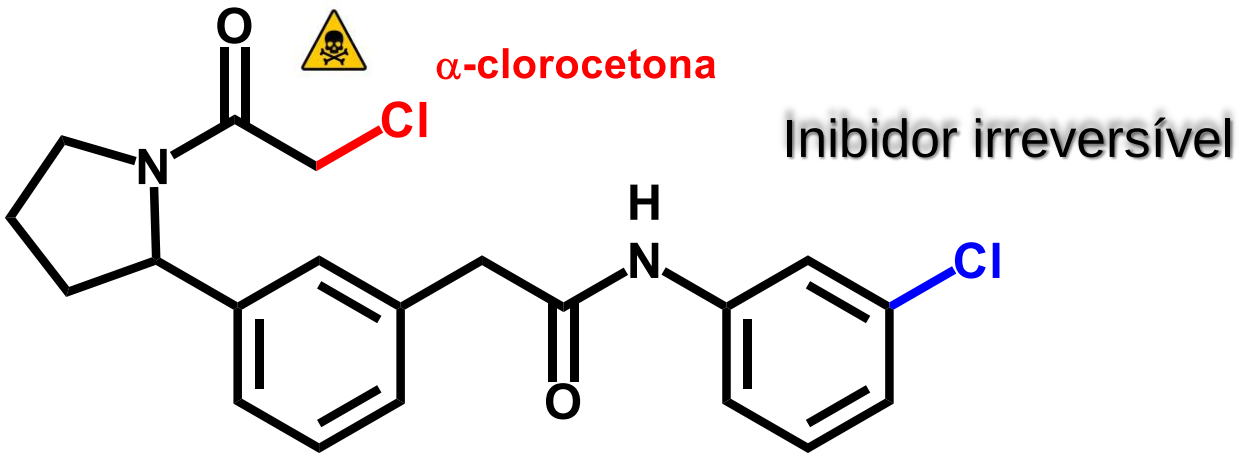


Beloranib

$C_{29}H_{41}NO_6$

zafgen

biopharmaceutical **company**



$C_{20}H_{20}Cl_2N_2O_2$

Grupos funcionais toxicofóricos

2-metil-tiazola

epóxido

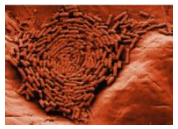
C_{16}-macrolactona

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