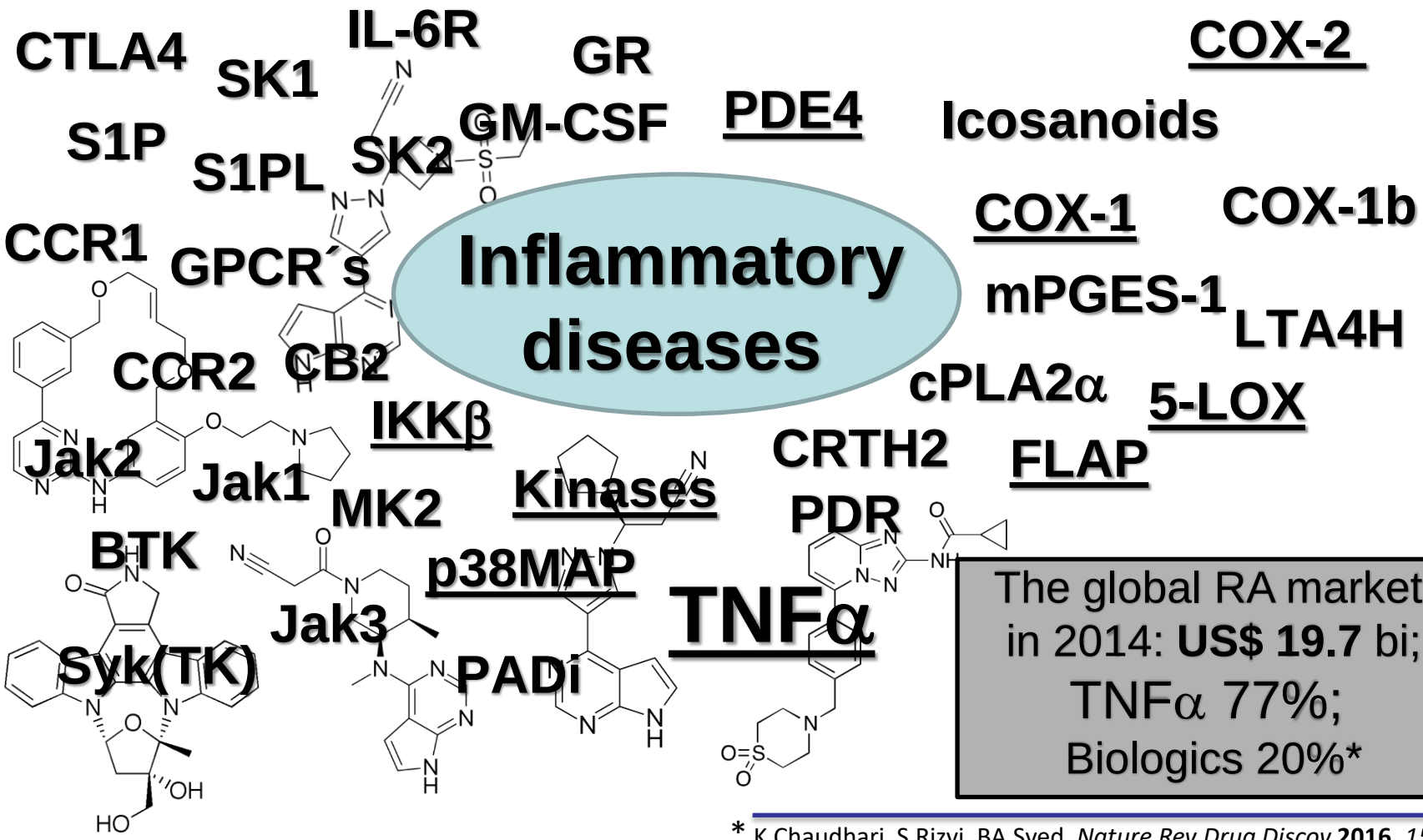
Aula 5 – 24/06

Tópicos Especiais em Química Medicinal

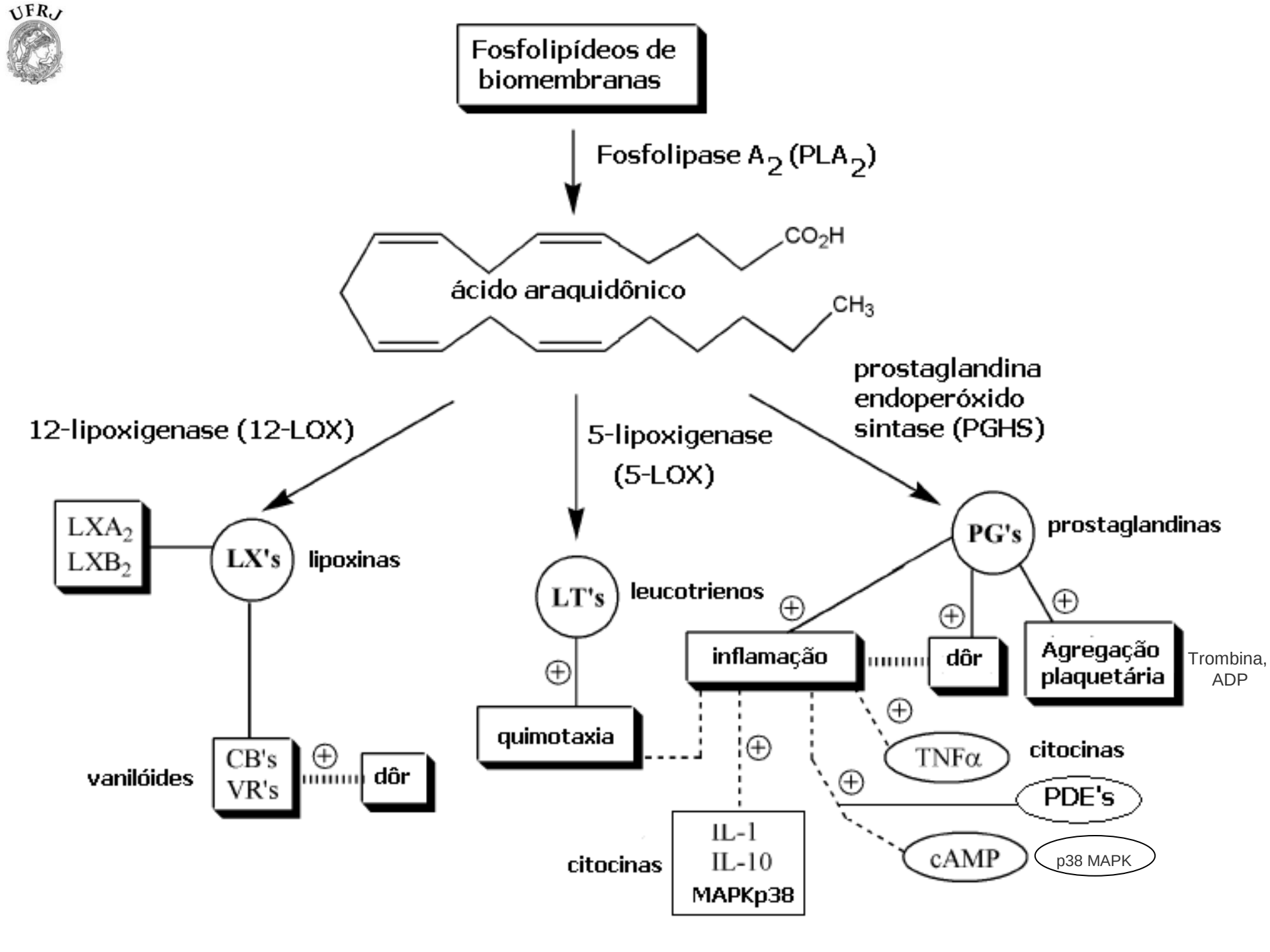
Tópicos Especiais
em Química Medicinal
Código: **BMF-777**
Carga Horária: 45 horas
Créditos: 3 créditos

Inflammation = Non-transmissible Multifactorial Chronical Diseases

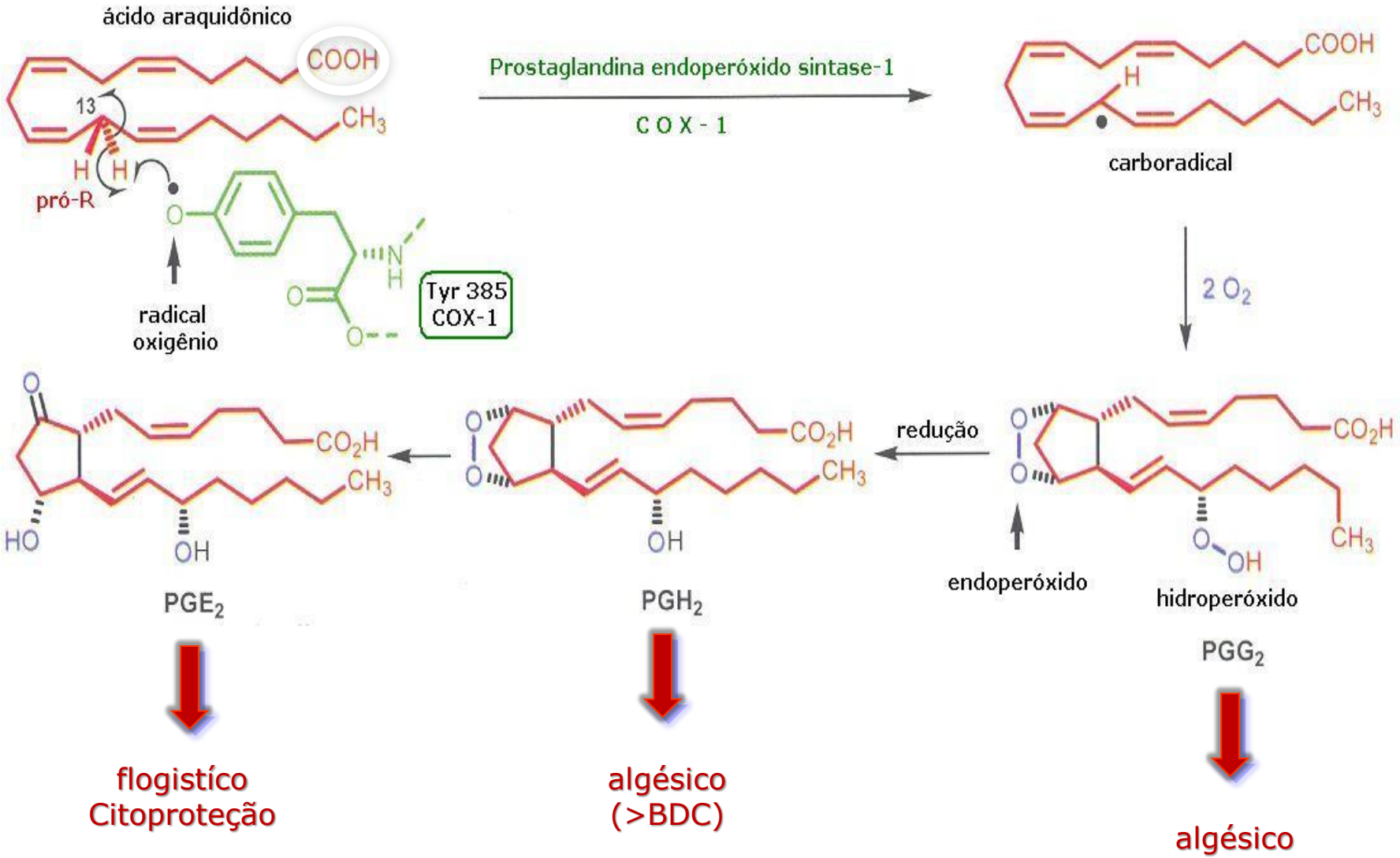


The global RA market in 2014: **US$ 19.7** bi; TNFα 77%; Biologics 20%*

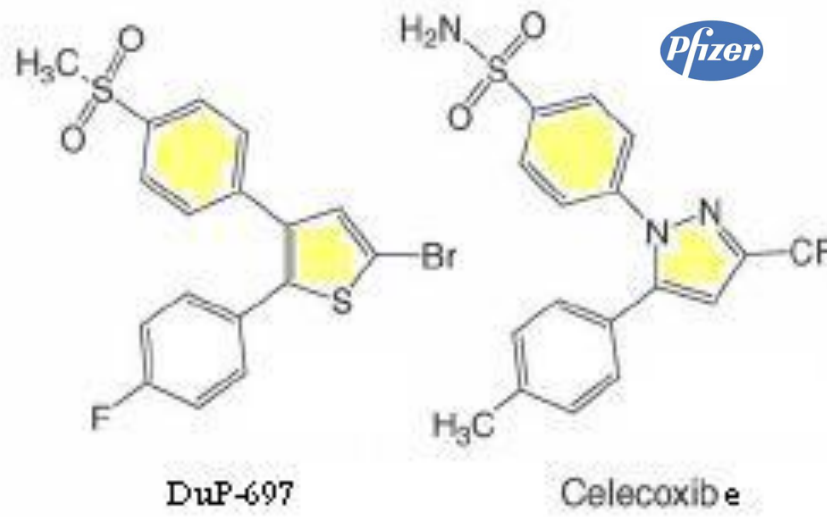
* K Chaudhari, S Rizvi, BA Syed, *Nature Rev Drug Discov* **2016**, *15*, 305

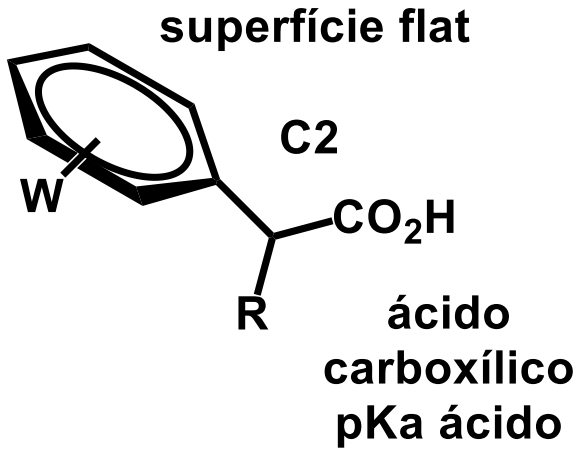

Fosfolipídeos de biomembranas
Fosfolipase A_2 (PLA_2)
CO_2H
ácido araquidônico
CH_3
12-lipoxigenase (12-LOX)
5-lipoxigenase (5-LOX)
prostaglandina endoperóxido sintase (PGHS)
LXA_2
LXB_2
LX's
lipoxinas
LT's
leucotrienos
PG's
prostaglandinas
inflamação
dôr
Agregação plaquetária
Trombina, ADP
quimotaxia
TNFα
citocinas
PDE's
cAMP
p38 MAPK
vanilóides
CB's
VR's
dôr
citocinas
IL-1
IL-10
MAPKp38

Cascata do Ácido Araquidônico

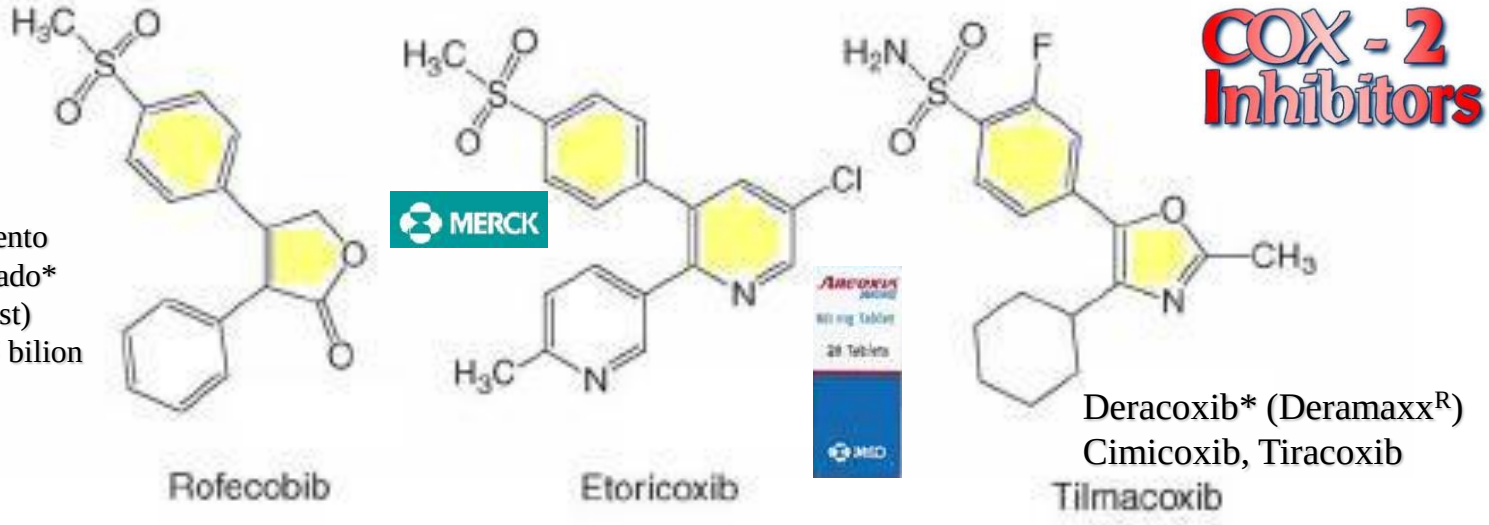


Coxibes





1999 – lançamento
09/2004 – retirado*
(APPROVe test)
2004 - US$ 2.5 bilion



Deracoxib* (Deramaxx^{R})
Cimicoxib, Tiracoxib

* P. Juni *et al*., "Risk of cardiovascular events and rofecoxib:cumulative meta-analysis", *Lancet* 2004, **364**, 2021

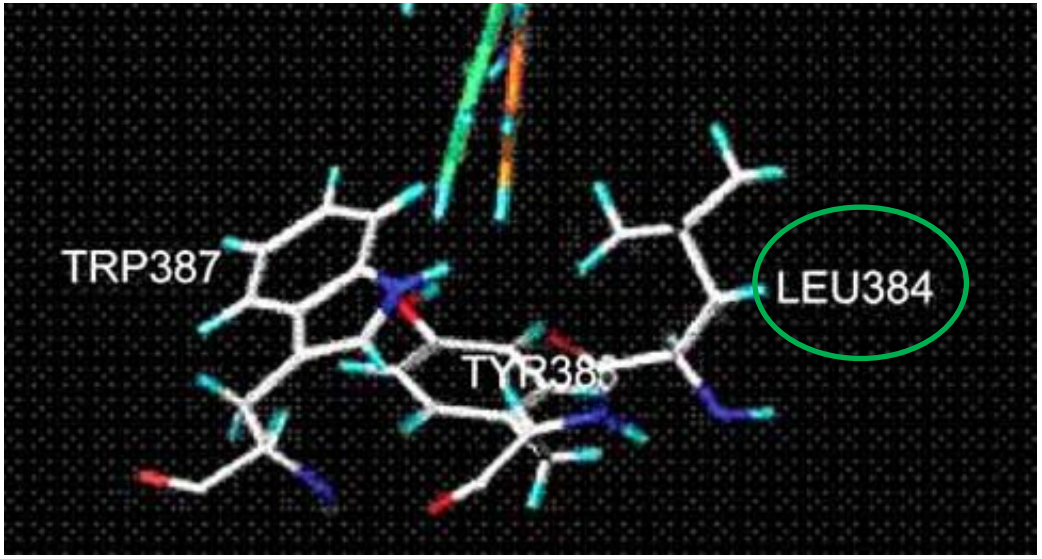
The Molecular Basis of COX-2 *Versus* COX-1 Selectivity of Lumiracoxib by Molecular Docking Studies

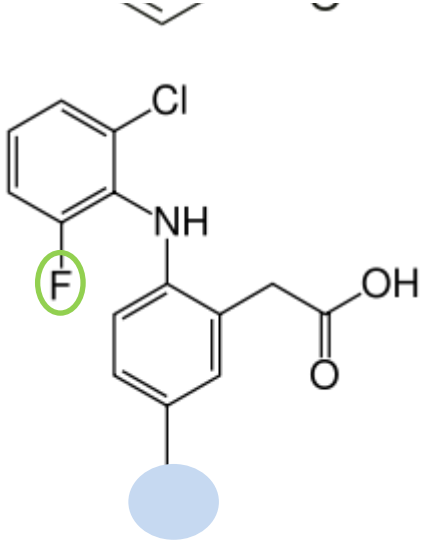
Célia M. Corrêa[a,b], André F. de Paula[a,c], Gilberto M.S. da Silva[a], Carlos M.R. Sant'Anna[a,d], Carlos A. M. Fraga[a] and Eliezer J. Barreiro*[,a]

[a]*Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, P.O. Box 68006, Rio de Janeiro, RJ, ZIP 21944-971, Brazil;* [b]*Departamento de Farmácia, Escola de Farmácia, Universidade Federal de Ouro Preto, Ouro Preto, MG, Brazil;* [c]*Departamento de Química Orgânica, Instituto de Química, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil;* [d]*Departamento de Química, ICE, Universidade Federal Rural do Rio de Janeiro, Seropédica, RJ, Brazil*

Received March 05, 2007: Revised May 10, 2007: Accepted May 15, 2007

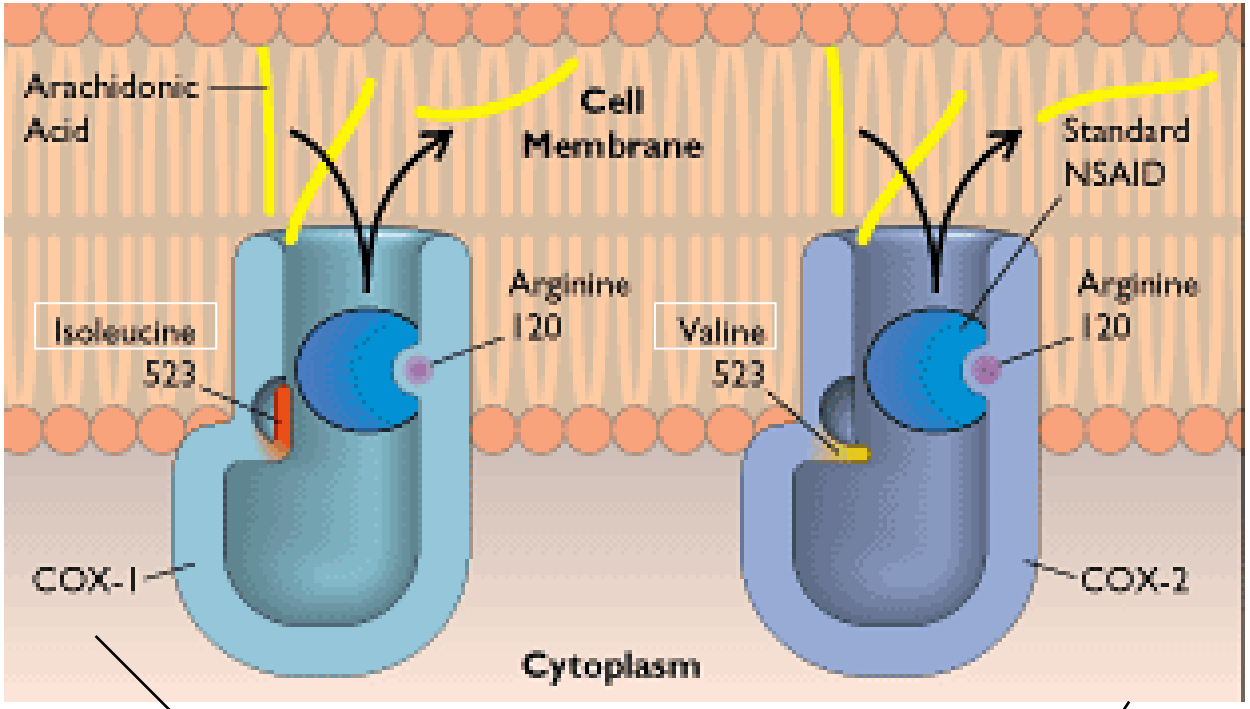
Abstract: A molecular rational basis for the COX-2/COX-1 selectivity of lumiracoxib using molecular docking approach is described. The COX-2 docking analysis for lumiracoxib and the diclofenac analogue revealed a similar binding mode, in contrast with the COX-1 docking analysis which revealed a different binding orientation for both inhibitors.

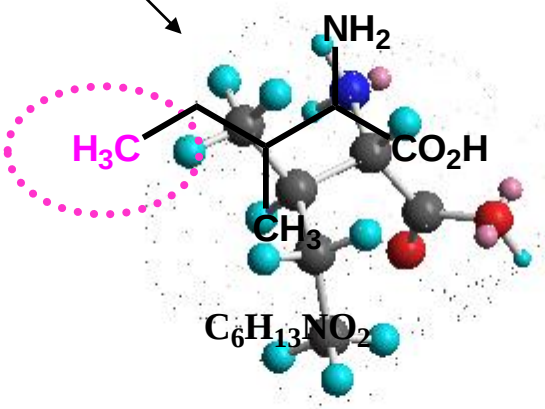




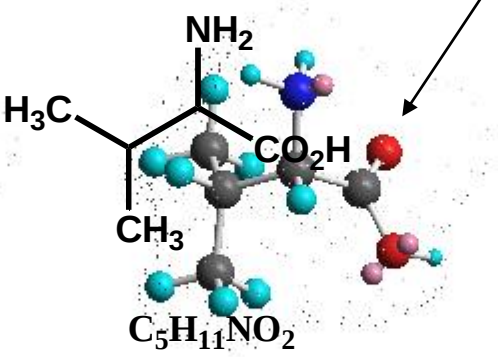
C. M. Corrêa, A.F. de Paula, G. M.S. da Silva, C. M.R. Sant'Annaa,C.A. M. Fraga, E.J. Barreiro, Letters in Drug Design & Discovery, 2007, 4, 422

Diferenças entre COX-1 e COX-2

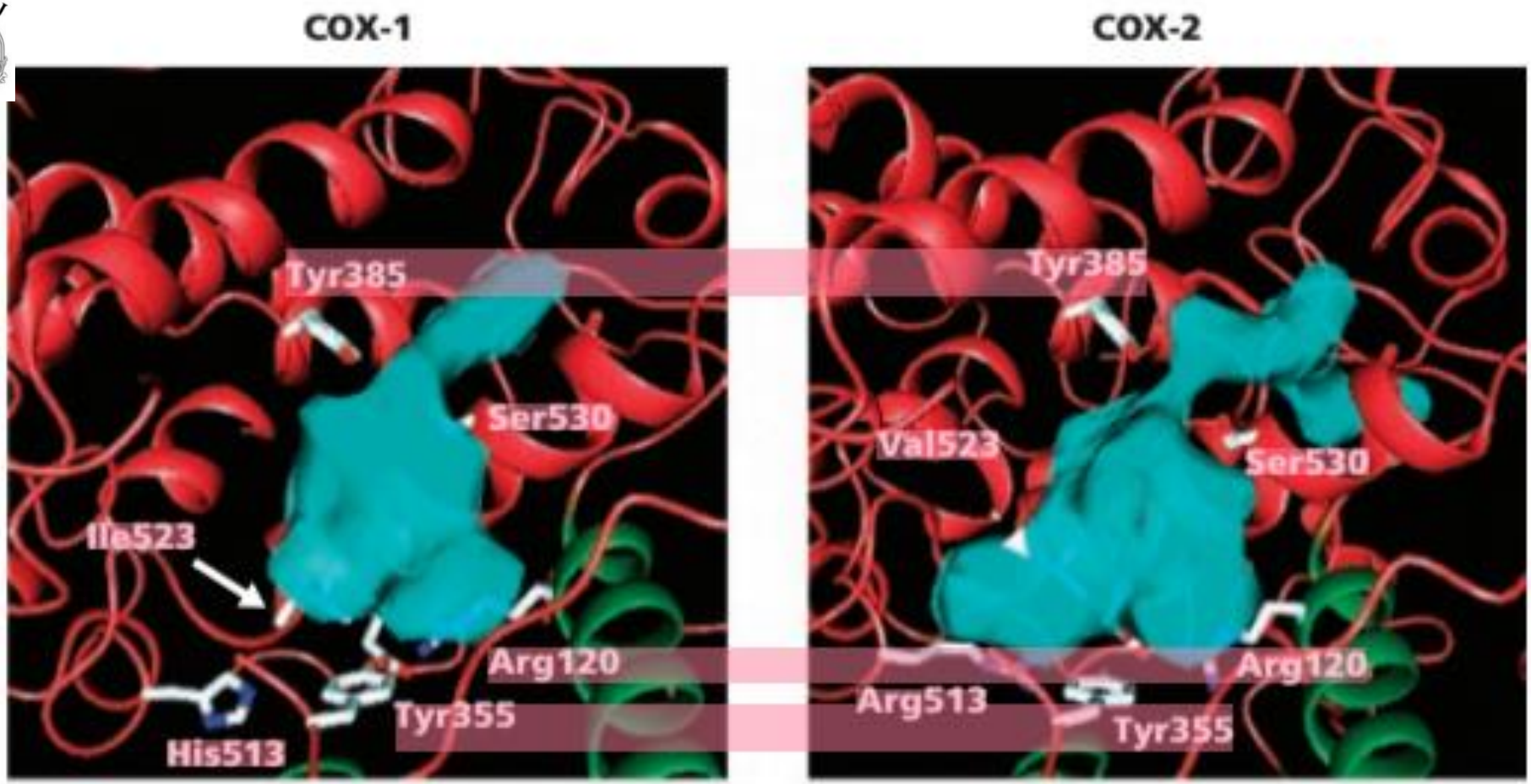




isoleucina

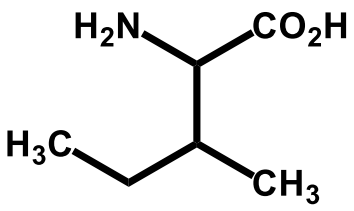


valina



SHOWING BINDING POCKETS OF COX-1 AND COX-2

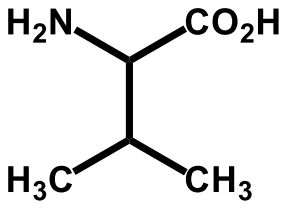
isoleucina



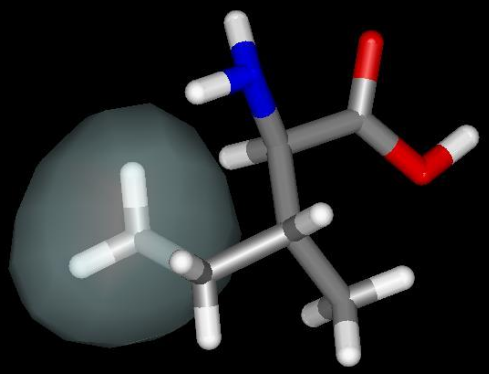
$C_6H_{13}NO_2$

homólogos

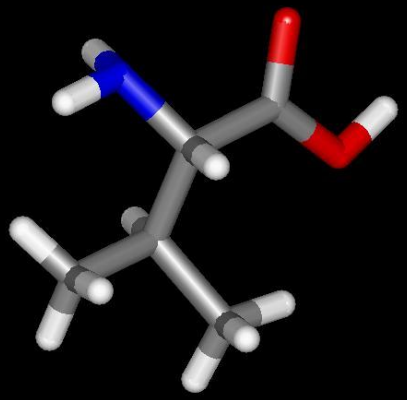
valina



$C_5H_{11}NO_2$

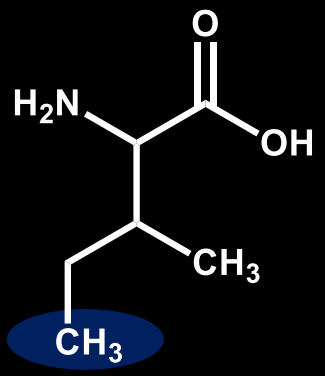


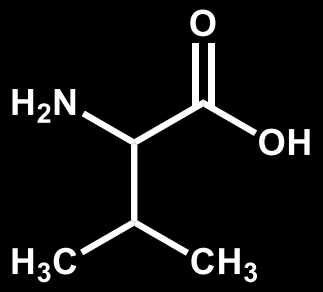
+ CH_3

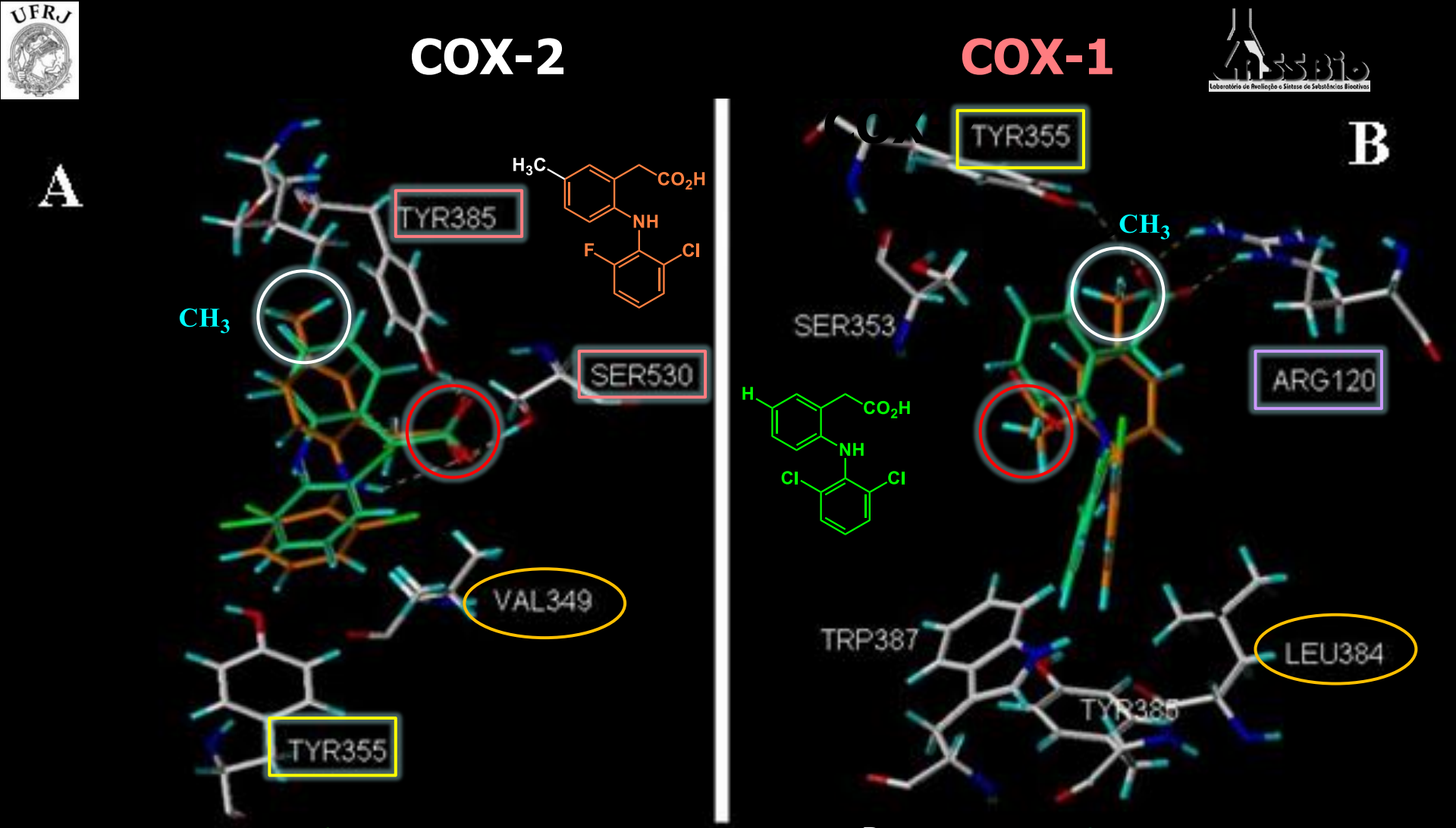


isoleucina

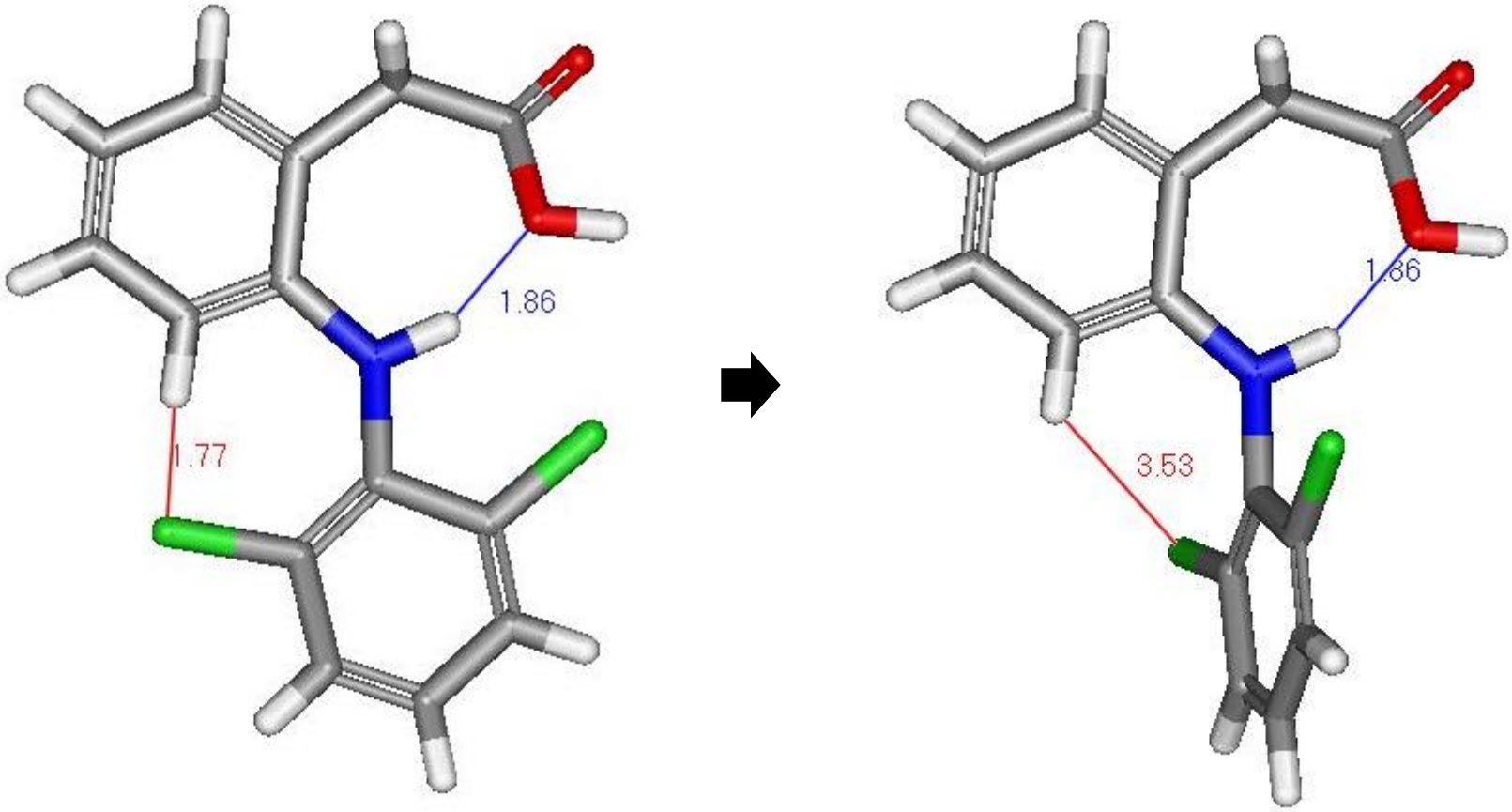
valina

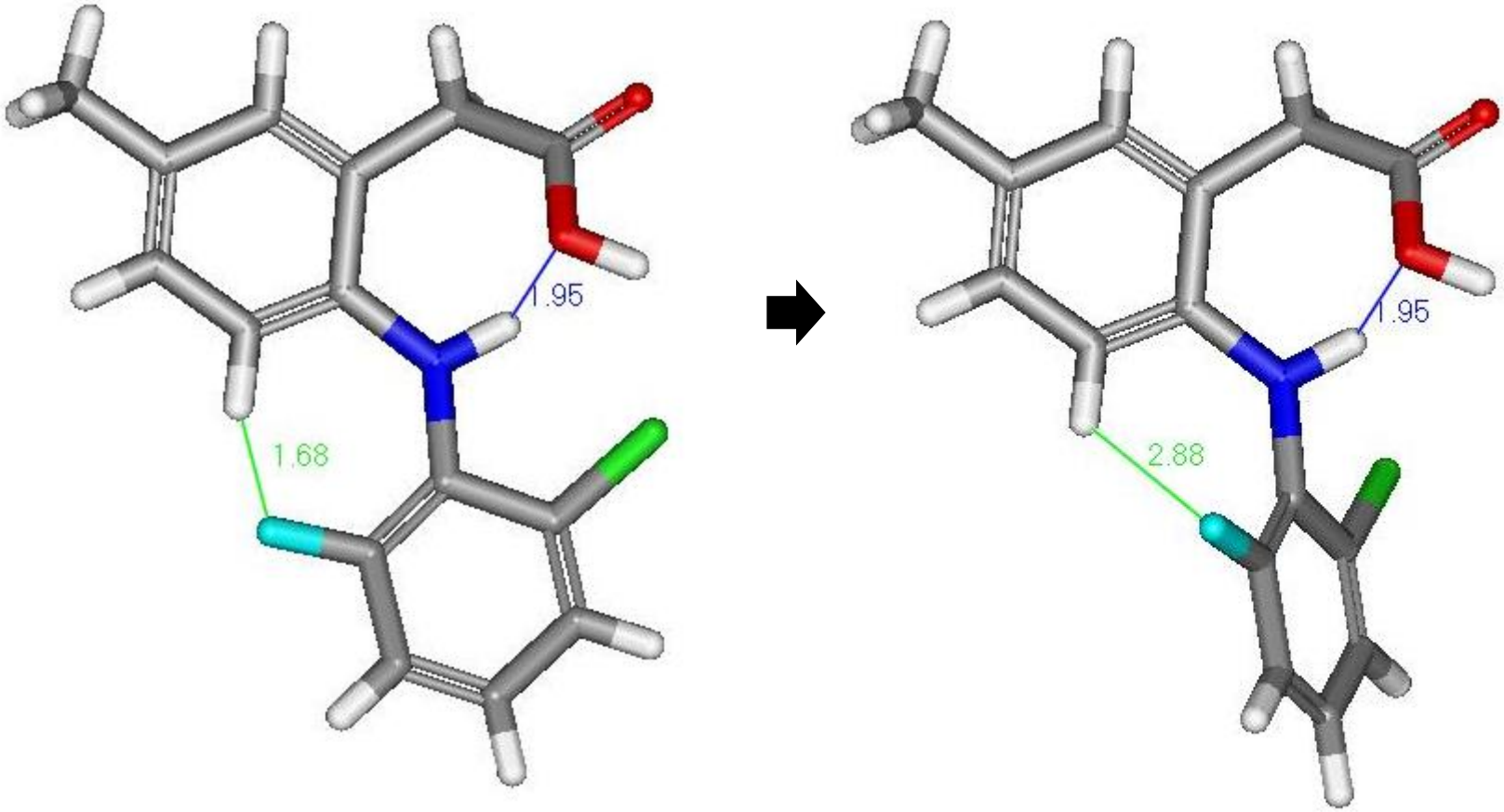




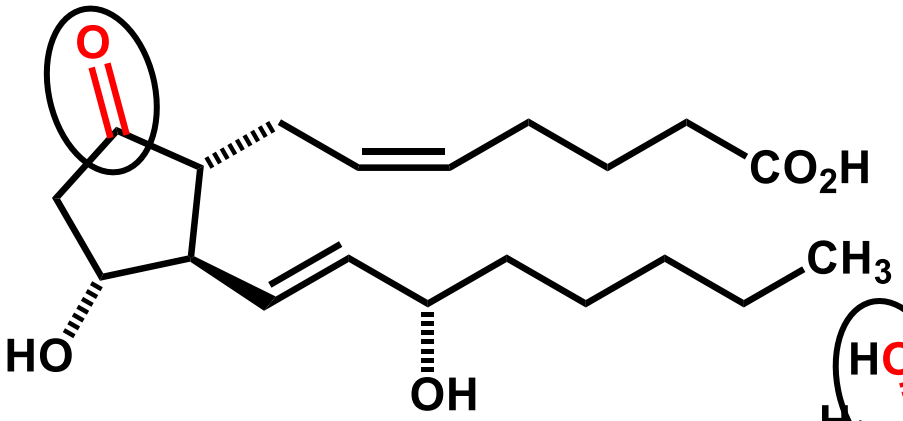


Em verde o diclofenaco e em laranja o lumiracoxibe; Em **B** observa-se as fortes interações do carboxilato com Arg-120 e ligação-H com Tyr-355 na COX-1; a presença da isoleucina-384, nesta isoforma, induz orientação distinta dos pontos farmacofóricos dos inibidores, permitindo que a metila do lumiracoxibe previna estas interações, possíveis na **COX-2**. Nesta isoforma, ambos inibidores tem interações-H com Tyr-385 enquanto que o lumiracoxibe interage também com a Ser-530. Em suma temos, neste caso, um duplo efeito-Me do ligante e do biorreceptor.

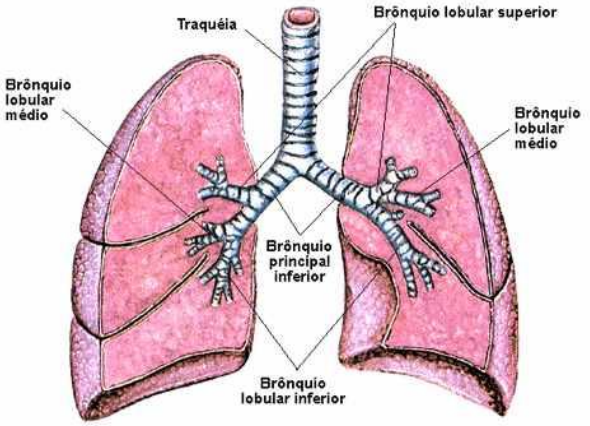

1.86
1.77
1.86
3.53

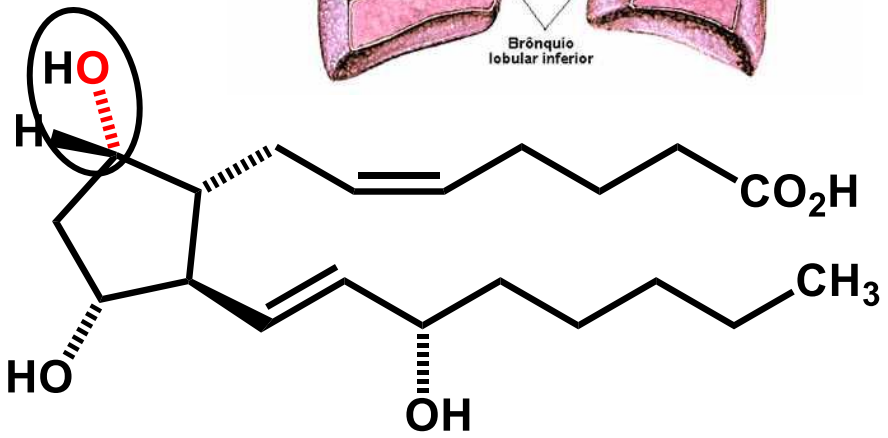

1.95
1.68
1.95
2.88

Reconhecimento Molecular



PGE_2



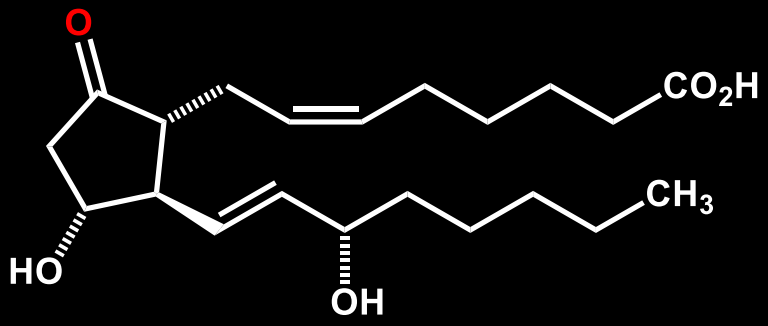


PGE_2 em cães provoca intensa <u>broncodilatação</u>

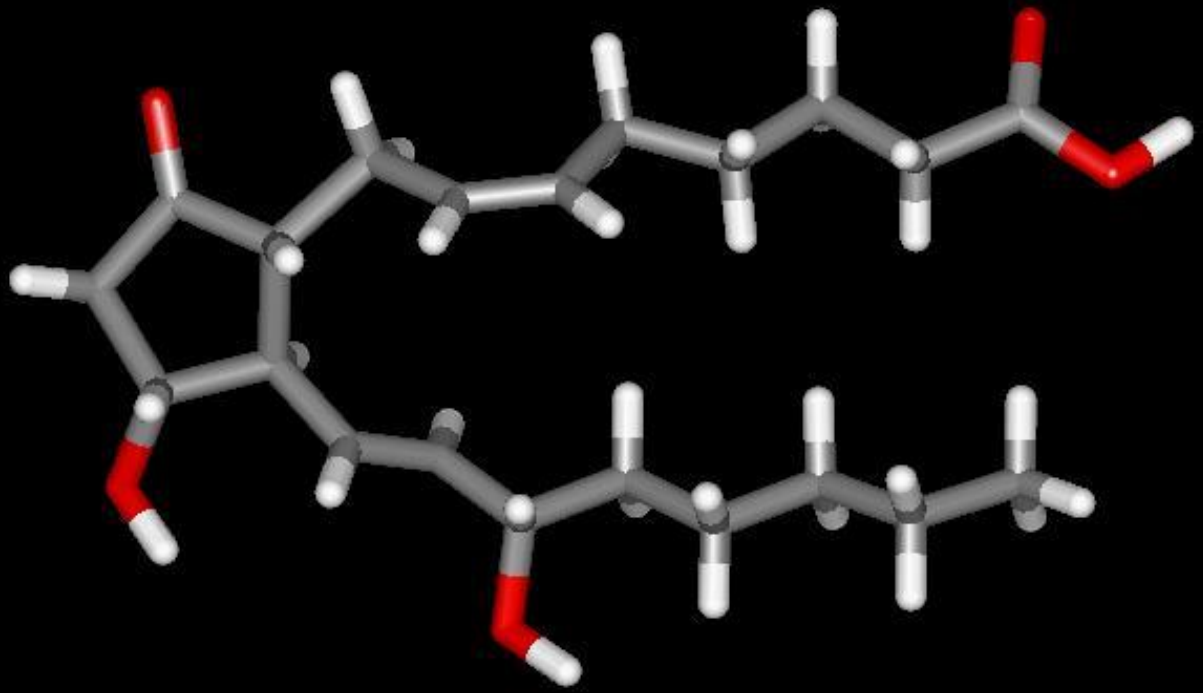
$PGF_{2\alpha}$

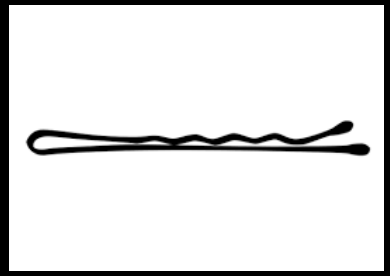
$PGF_{2\alpha}$ em cães provoca severa <u>broncoconstrição</u>

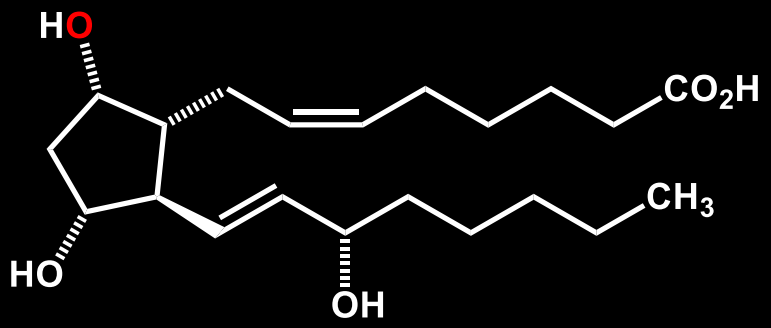
Similaridade molecular



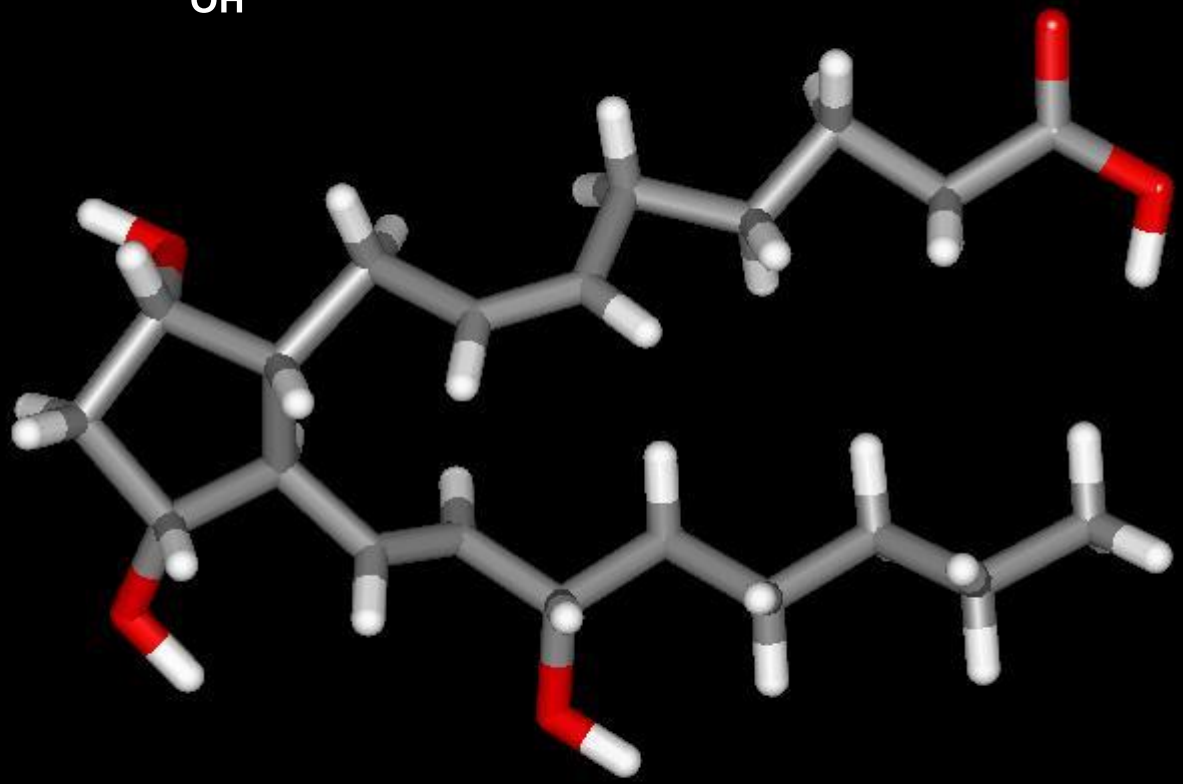
PGE_2

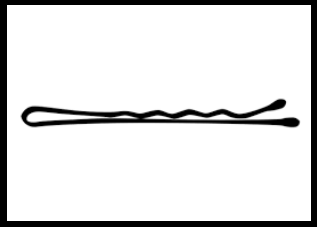




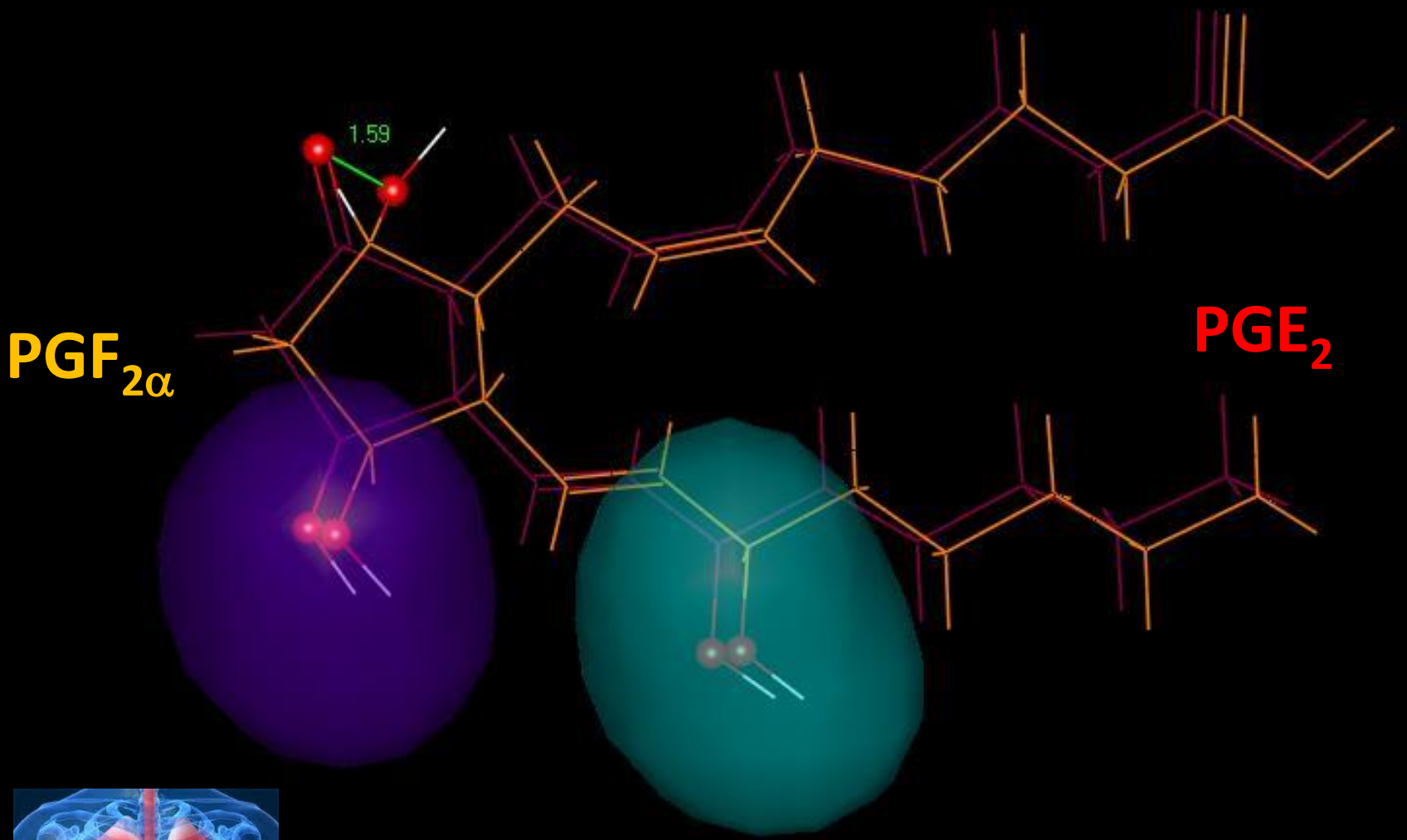


$PGF_{2\alpha}$





Sobreposição molecular

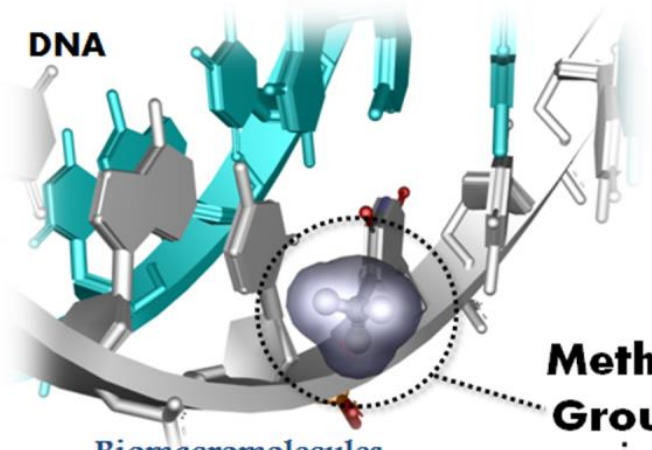


Pontos farmacofóricos

CHEMICAL REVIEWS
Chem. Rev. 2011, 111, 5215-5246
REVIEW
dx.doi.org/10.1021/cr200060g

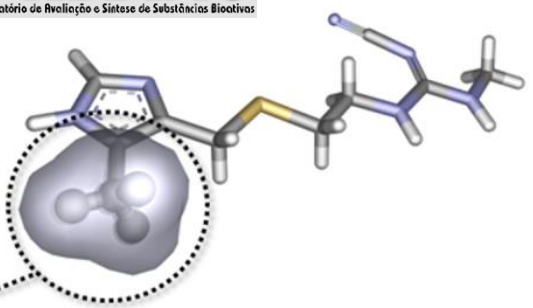
The Methylation Effect in Medicinal Chemistry

E. J. Barreiro, A. E. Kümmerle and C. A. M. Fraga



LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

Química Medicinal



Methyl Group

Biomacromolecules

CH/π interactions from the methyl group of timine. Conformational changes, wich could be involved on maintenance of life.

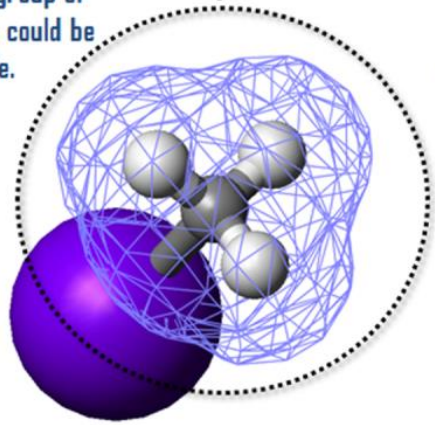
Micromolecules

The inductive eletronic effect of the methyl group is the responsible for the subtype receptors selectivity (H_2x H_1) on cimetidine

CH_3

15 Da

The stereoelectronic effects of the methyl group have great importance on biological events and are widely used by the Medicinal Chemistries in the development of new drugs.

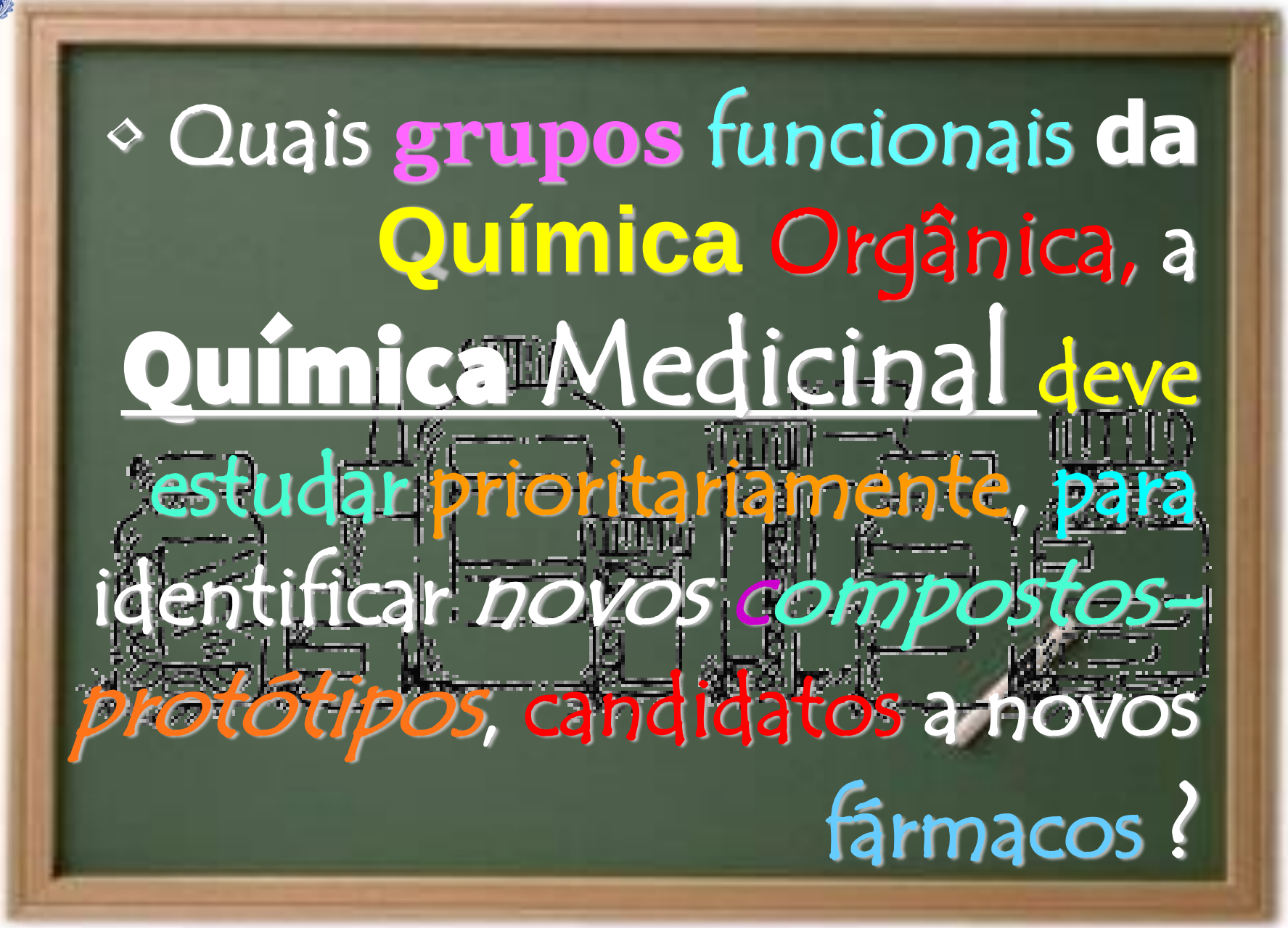


Stereoelectronic Properties

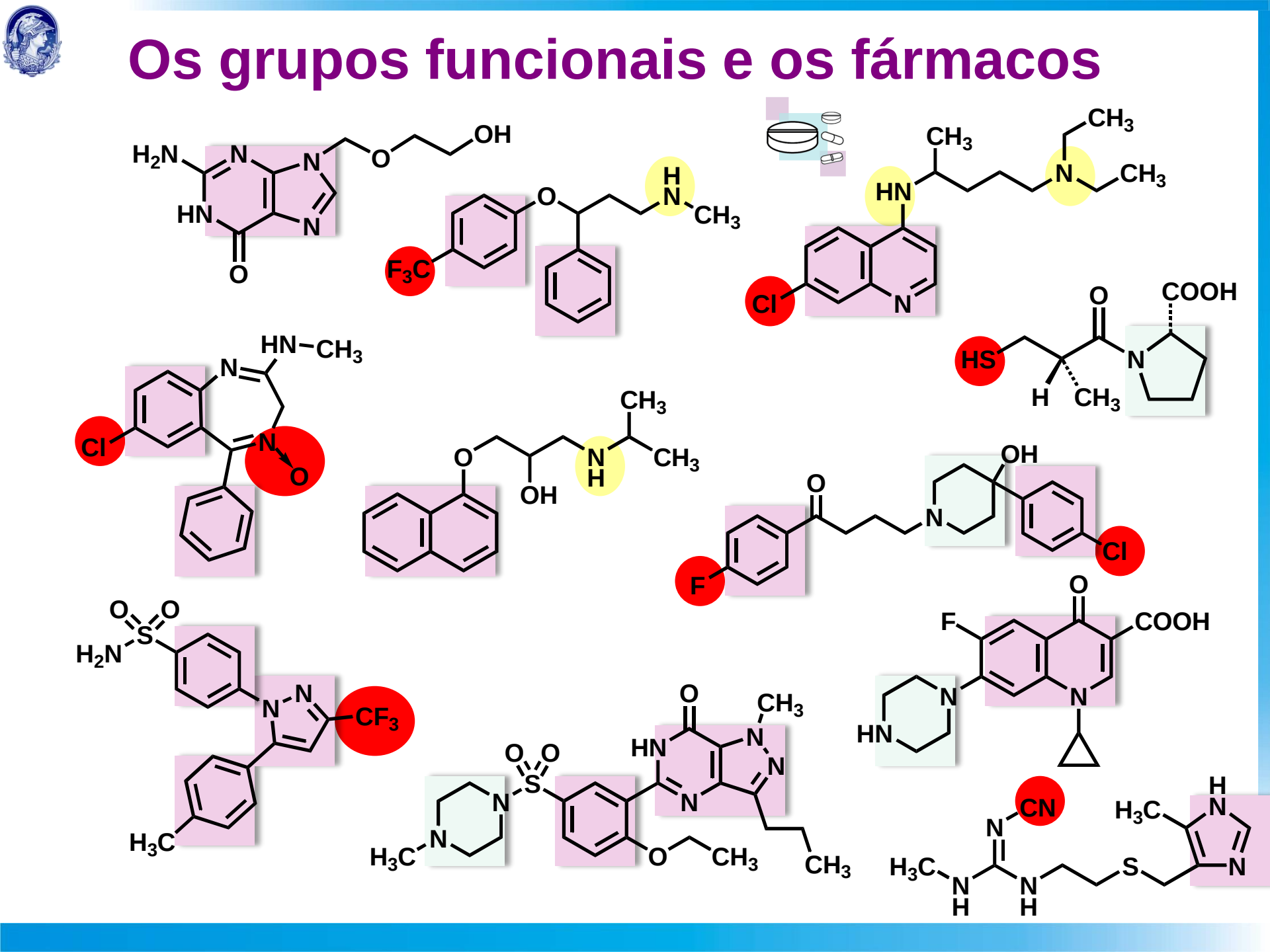
MW = 15,03
MR = 5,65 cm³/mol
π hansch = 0,56
σ hammett = -0,17

Os grupamentos funcionais

XXV Escola de Verão em Química Farmacêutica Medicinal
[Link]


◇ Quais grupos funcionais da Química Orgânica, a Química Medicinal deve estudar prioritariamente, para identificar novos compostos-protótipos, candidatos a novos fármacos ?

Os grupos funcionais e os fármacos



Características estruturais comuns aos onze fármacos :

- Representam inovações terapêuticas importantes: aciclovir, fluoxetina, cloroquina, clordiazepóxido, propranolol, captopril, haloperidol, celecoxibe, sildenafila, ciprofloxacina, cimetidina;
- pertencem a 08 classes terapêuticas distintas: > SNC;
- São substâncias com singela diversidade química;
- Possuem apenas 7 elementos químicos: C,H,O,N,S,F,Cl;
- 10/11 possuem heteroátomos, 10/11 têm heterocíclos;
- 11/11 são multicíclicos (< cinco anéis);
- 10/11 possuem sub-unidades aromáticas;

- Têm 15 funções químicas: alcano, areno, álcool, tiol, haleto, éter, tio-éter, amina, cetona, amida, ácido carboxílico, *N*-óxido, amidina, sulfonamida, nitrila;
- *11/11 são de origem sintética, como > 88% dos fármacos;*
- *são moléculas **pequenas, valiosas** & inteligentes !*