Fármacos:

O papel da Química Medicinal

XXII Semana Acadêmica de Química - UFF

Aula 2

UFRJ

Eliezer j. Barreiro

Professor Titular

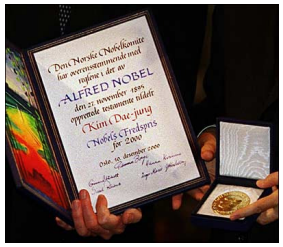
2011 ANO INTERNACIONAL DA QUÍMICA SBQ

Química Medicinal

Os fármacos e o Prêmio Nobel

Os fármacos e o Nobel !

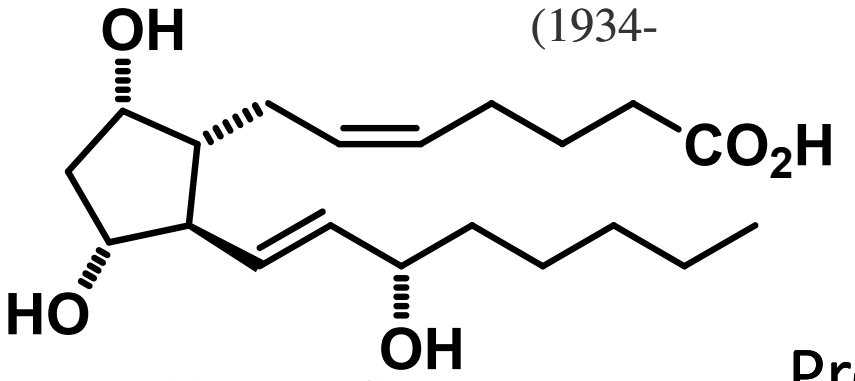
1982



John R. Vane
(1927-2004)

Sune K. Bergström
(1916-2004)

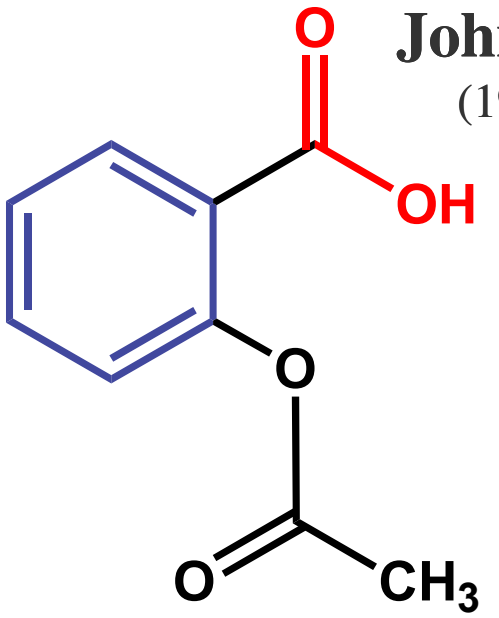
Bengt I. Samuelsson
(1934-



- **196 pesquisadores**

ganharam o Prêmio Nobel de Medicina

(1901-2010)



$C_9H_8O_4$

1982 – AAS

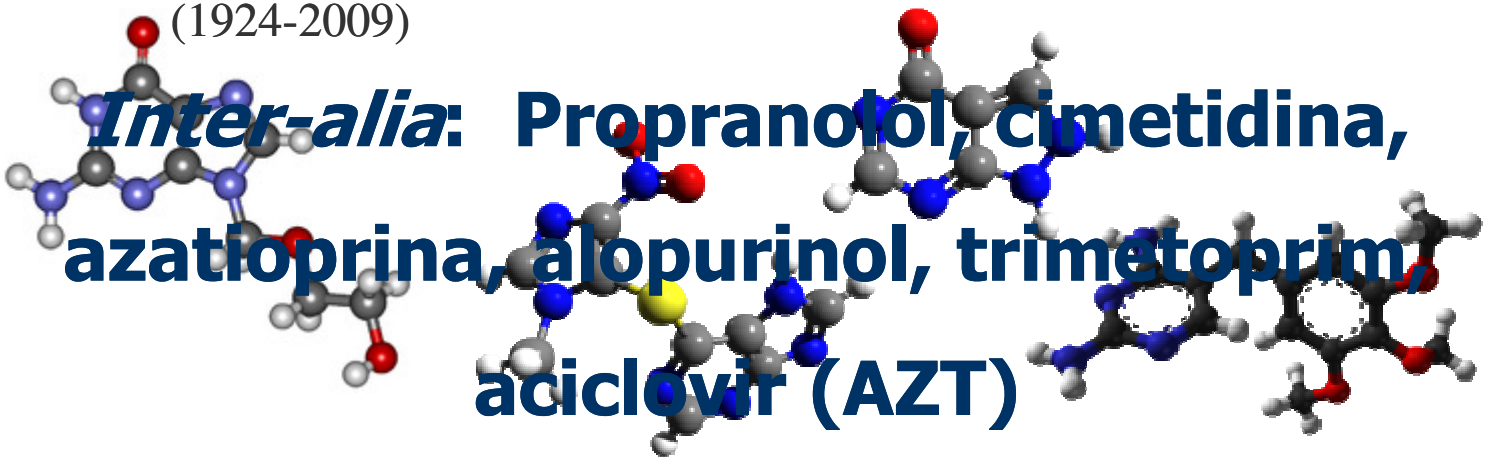
Prostaglandina $F_{2\alpha}$

“for their discoveries of important principles for drug treatment"

James W. Black
(1924-2009)

George Hitchings (1905-1998)

Gertrude B. Elion (1918-1999)



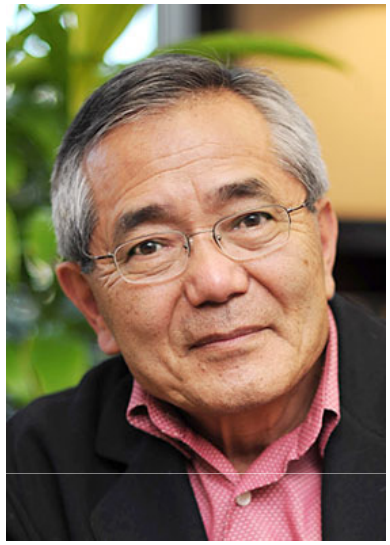
***Inter-alia*: Propranolol, cimetidina, azatioprina, alopurinol, trimetoprim, aciclovir (AZT)**

1988

Os fármacos e o Nobel !

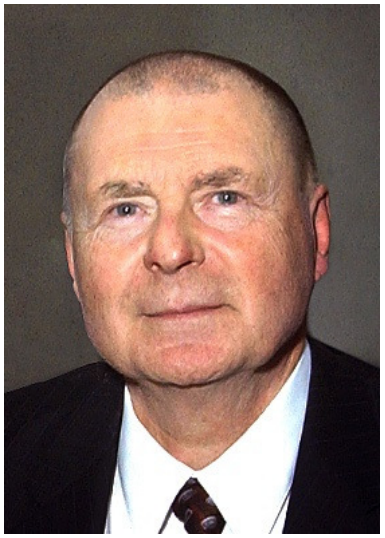
"for palladium-catalyzed cross couplings in organic synthesis".

2010



Ei-ichi Negishi

(1935-)



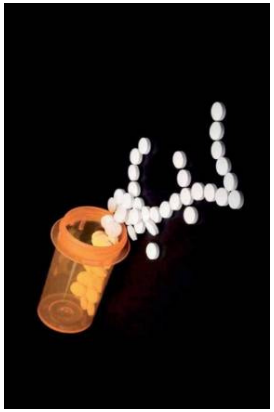
Richard F. Heck

(1931-)

Akira Suzuki

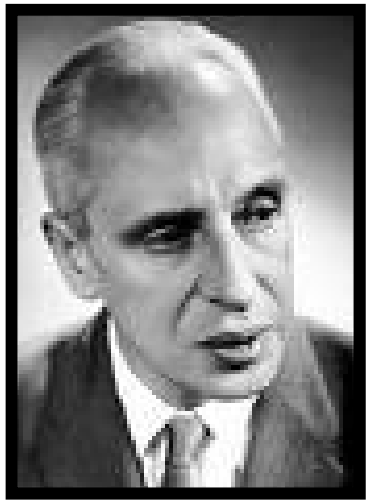
(1930-)

the essence of synthetic organic chemistry and the gateway to myriad compounds of value to medicine, agriculture and electronics



http://nobelprize.org/nobel_prizes/chemistry/laureates/20

Os fármacos e o Nobel !



Severo Ochoa
(1905-1993)

Arthur Kornberg
(1918-2007)

Prêmio Nobel de Fisiologia/Medicina 1959

"for their discovery of the mechanisms in the biological synthesis of RNA and DNA"

ARTHUR KORNBERG

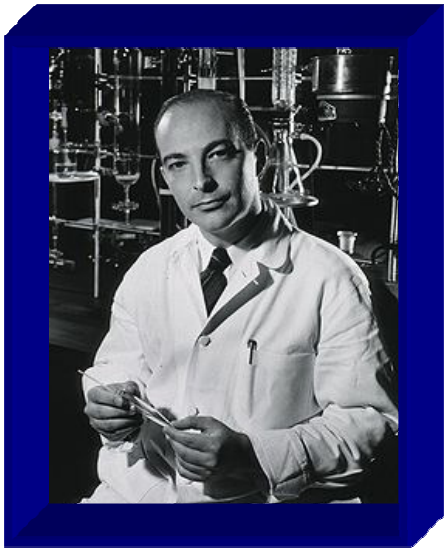
The biologic synthesis of deoxyribonucleic acid

Nobel Lecture, December 11, 1959

Interdisciplinaridade

EJB3

UFRJ



Arthur Kornberg
1918-2007

Prêmio Nobel, 1959

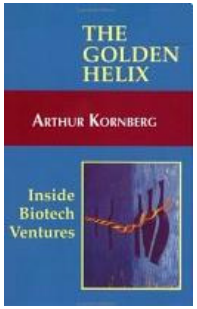
1987

The Two Cultures: Chemistry and Biology[1]

Arthur Kornberg

Department of Biochemistry, Stanford University, Stanford, California 94305

Received July 14, 1987

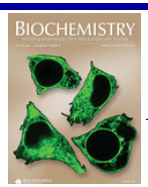


"Much of life can be understood in rational terms if expressed in the language of chemistry... the historical roots of ***chemistry*** *and* ***biology*** *are intertwined in many places…*

Pharmaceutical chemistry *was until recently the bastion of organic chemistry… in the search for alternative or superior drugs for the treatment of various diseases..."*

University of Stanford

Química Medicinal



Biochemistry **1987,** *26,* 6888-6891

Slide 7

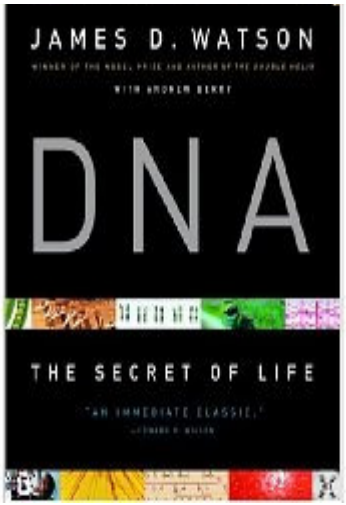
EJB3

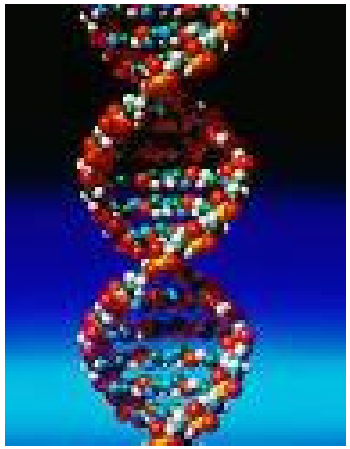
Kornberg definiu as bases da interdisciplinaridade das ciências dos fármacos quando antecipou a necessidade de aproximar-se a Química e a Biologia.

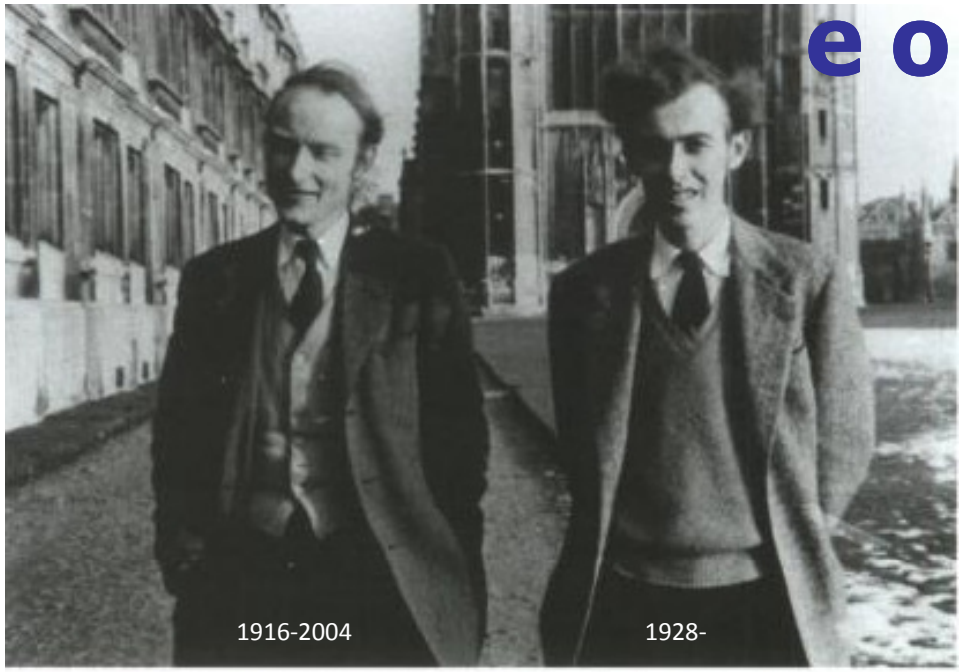
Eliezer J. Barreiro; 04/03/2010

EJB4

Os fármacos e o Nobel !







Francis Crick and James Watson in Cambridge, England, 1953
(Courtesy of the James D. Watson Special Collection. Cold Spring Harbor Laboratory Archives. From Watson J.D. 1968, *The Double Helix*. Atheneum Press, New York.)

1962

Maurice H. F. Wilkins

O físico Crick & biólogo Watson

J. D. Watson & F. H. C. Crick, Nature *1953,* **171**, 737–738

Interdisciplinaridade

Slide 8

EJB4

Exemplos de extraordinárias conquistas do conhecimento humano deveram-se às associações de capacidades e competências complementares, essenciais à sua consecução: e.g. DNA em publicação de apenas 2 páginas em prestigioso periódico científico que resultou, décadas depois, na era ômica.

JD Watson & FHC Crick, Nature, 1953, 171, 737-738

Eliezer J. Barreiro; 04/03/2010

O processo ...

(O Paradigma de Ehrlich & Fischer)

Química Medicinal

2011 ANO INTERNACIONAL DA QUÍMICA

SBQ

O paradigma de Ehrlich & Fischer

Emil Fischer

1852-1919

1902

E. Fischer, Ber. Dtsch. Chem. Ges. 1890, 23, 799

Paul Ehrlich

1854-1915

1908

Biorreceptor

macrobiomolécula

baseado no sítio de reconhecimento

Planejamento racional

BSRM

BL-AA

Fármaco

micromolécula

baseado no ligante / análogo-ativo

Physiologic

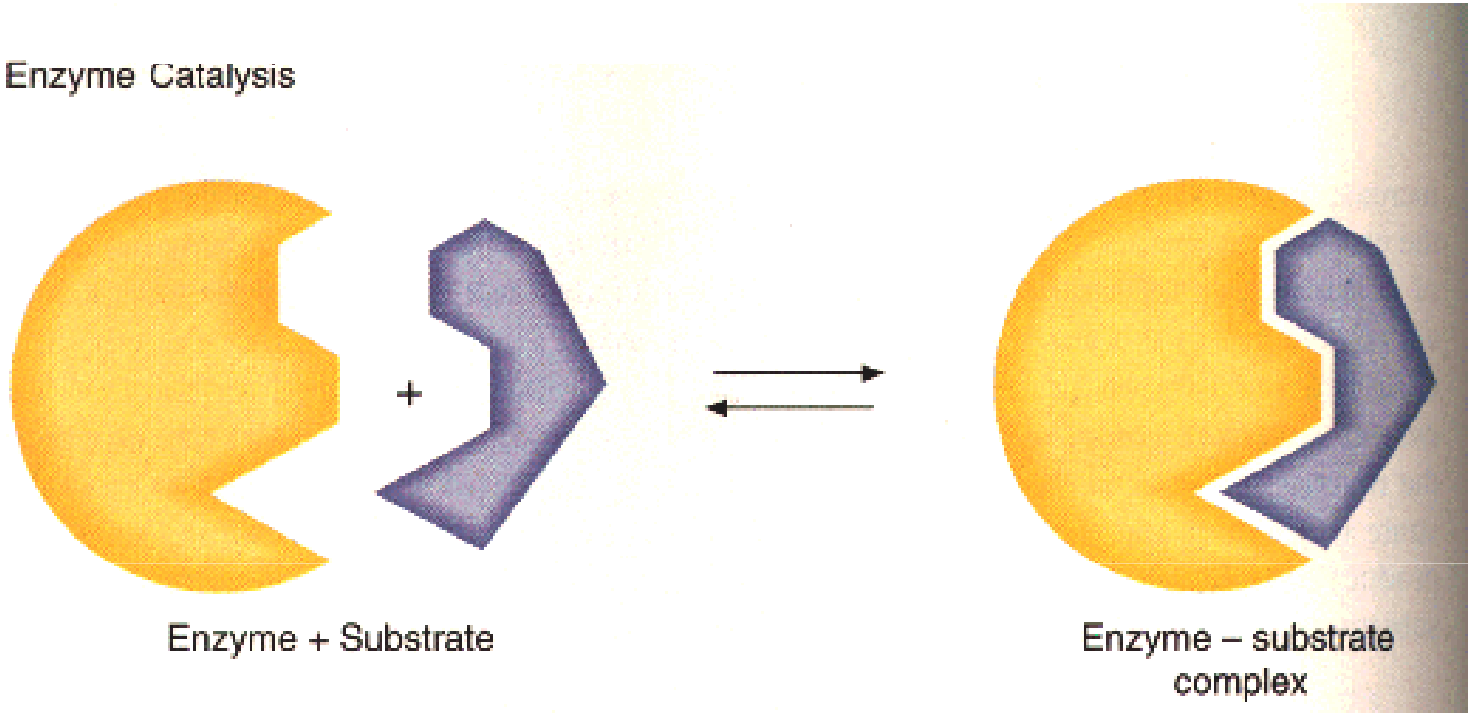
A abordagem

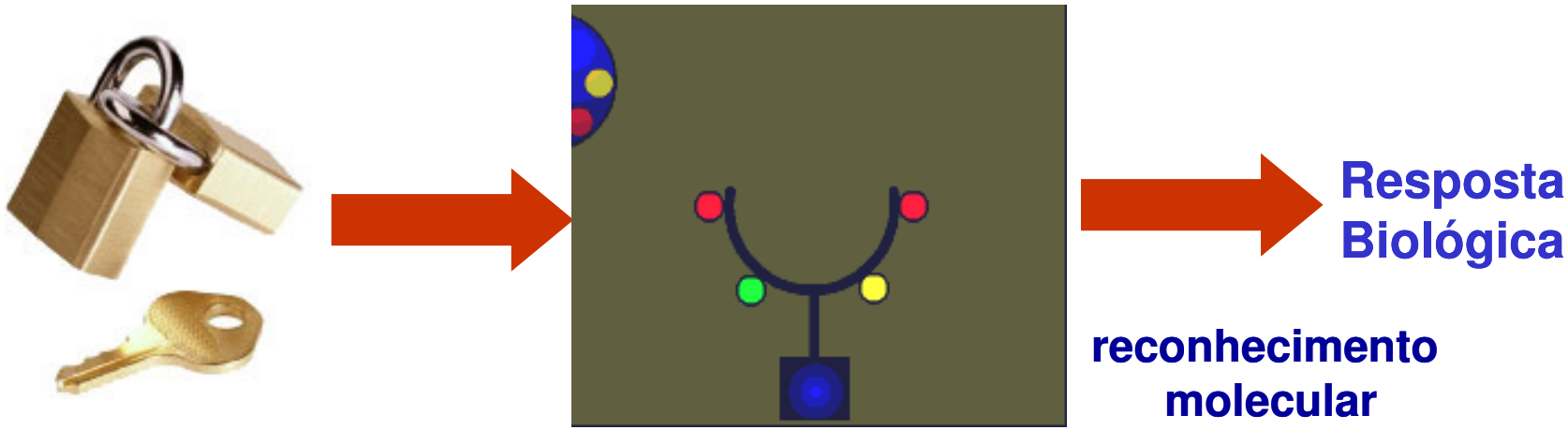
approach

fisiológica

P. Ehrlich, *Chemotherapeutics: scientific principles, methods and results*. *Lancet* 1913, **2**, 445

Modelo Chave-Fechadura

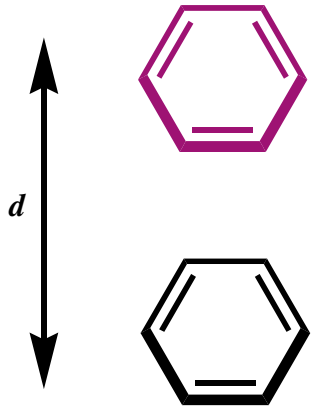




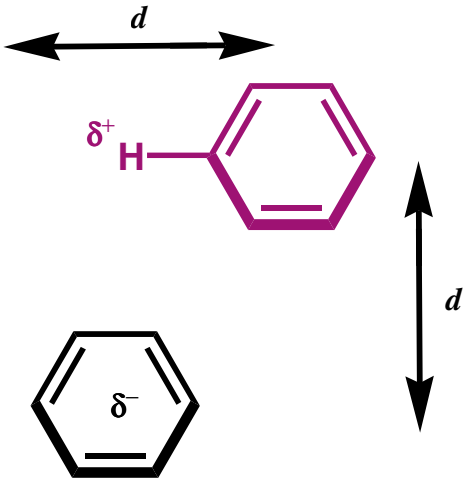
Resposta Biológica

reconhecimento molecular

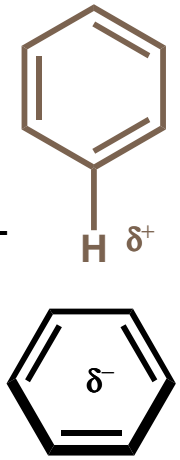
Interações π-π



Interação sanduíche
π-staking



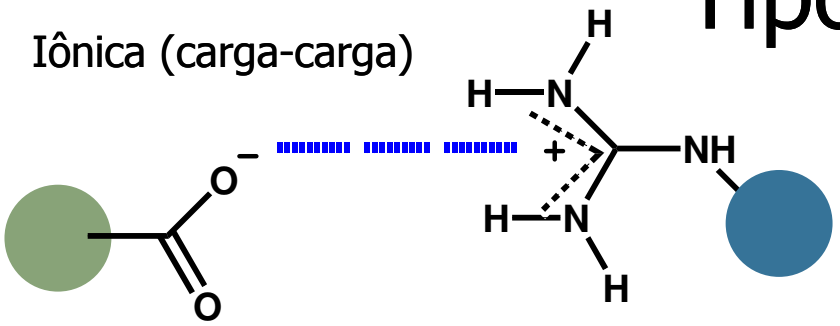
Interação paralela



Interação tipo-T
π-polar

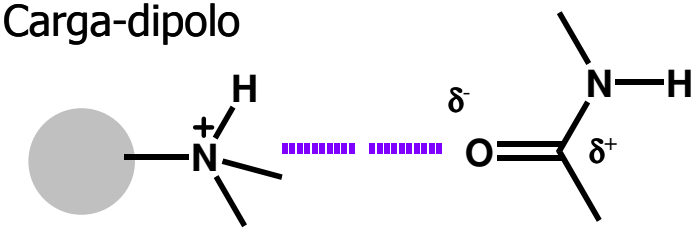
Tipos de interações F-Br

Iônica (carga-carga)



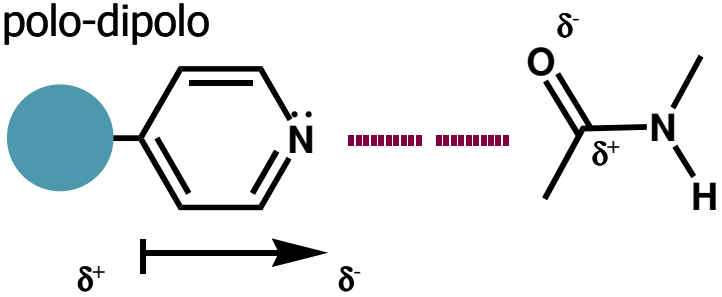
ΔG = 20-40kJ/mol

Carga-dipolo



ΔG = 12-20kJ/mol

Dipolo-dipolo

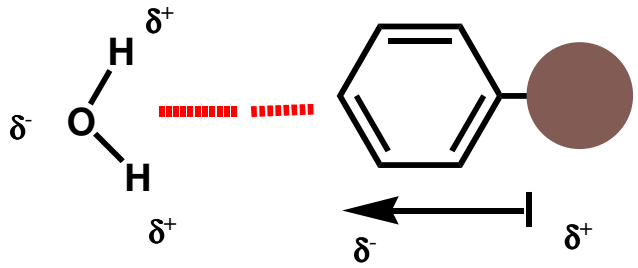


ΔG = 4-12 kJ/mol

Carga-dipolo induzido

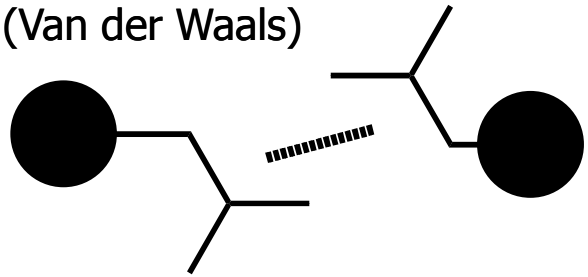
ΔG = 2-10 kJ/mol

Dipolo induzido-dipolo



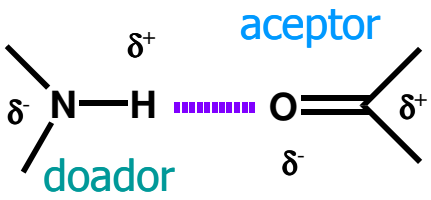
ΔG = 2 kJ/mol

Dispersão (Van der Waals)



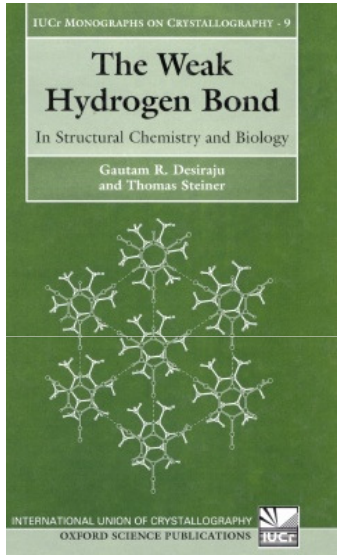
ΔG = 2-4 kJ/mol

Ligação-H



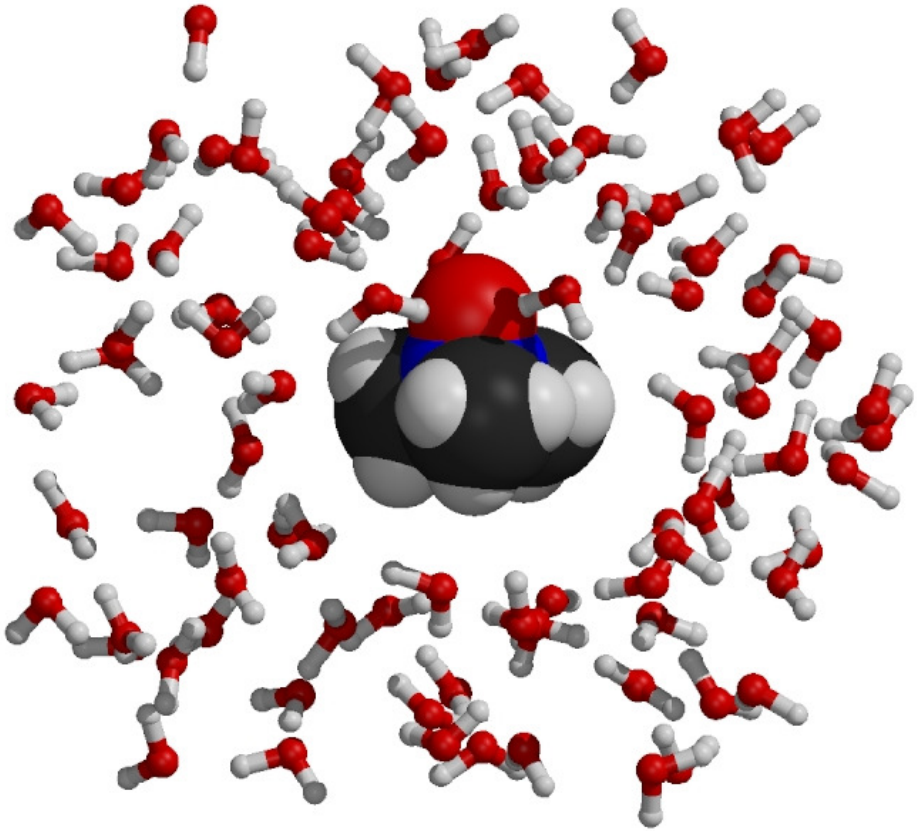
ΔG = 4-30 kJ/mol

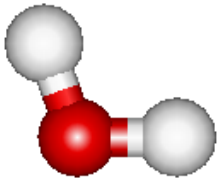
A importância das "*ligações*" frágeis...



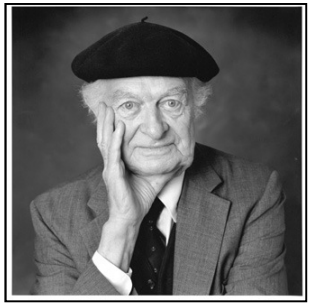
D—H.....A

Pauling, 1939



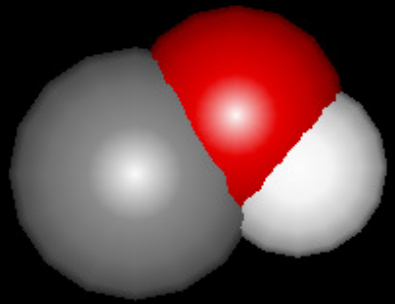


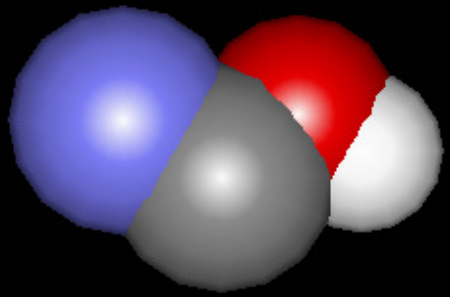
"*ligações*"
de hidrogênio ...



Linus Pauling
1901-1994
1954 & 1962

Efeitos estruturais



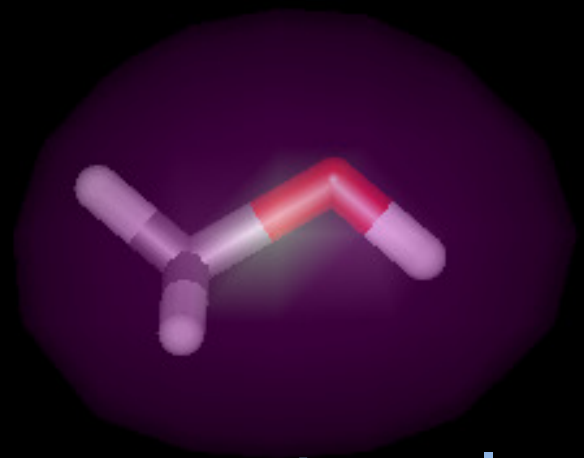


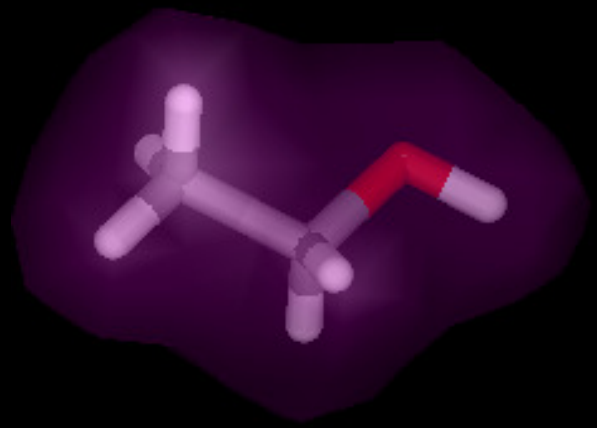
H-O-H

H_3C-O-H

H_3C-CH_2-O-H

CH_3





*m*etanol

etanol

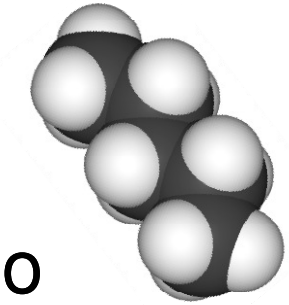
metano

etano

propano

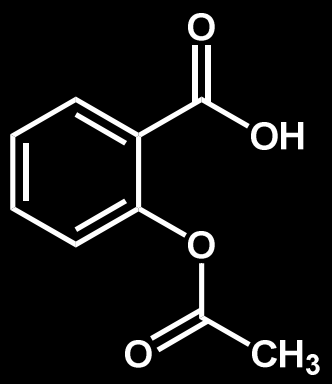
n-butano

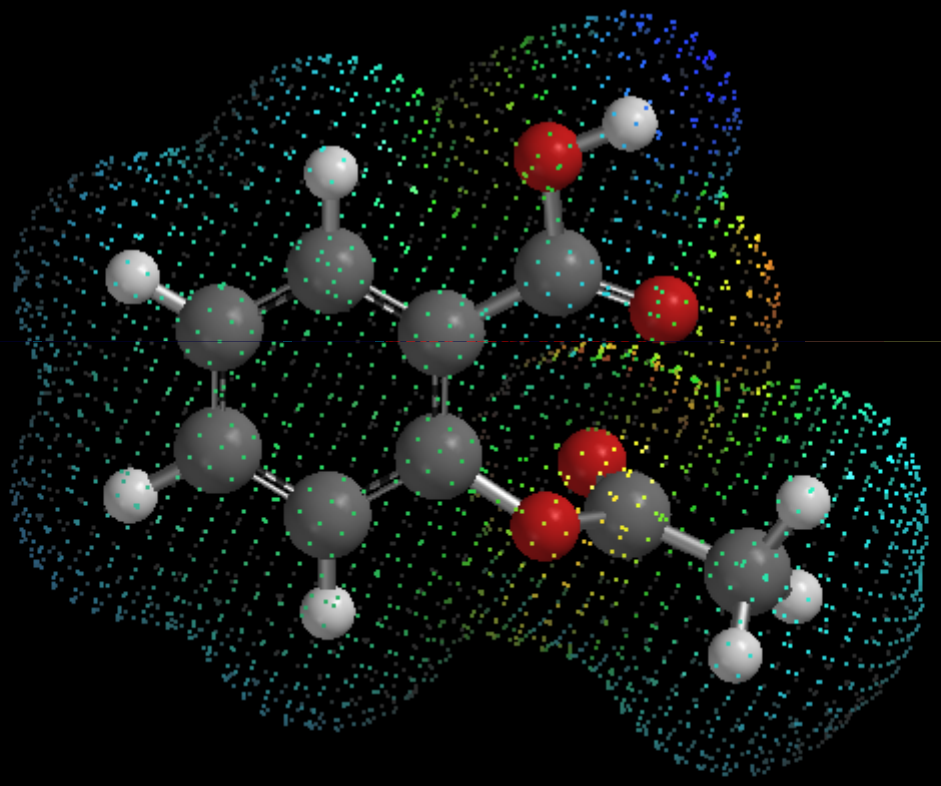
Homólogos

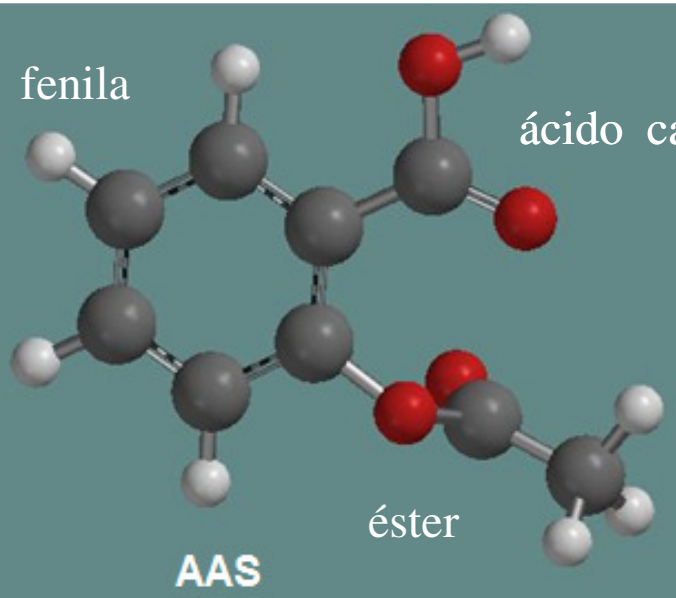


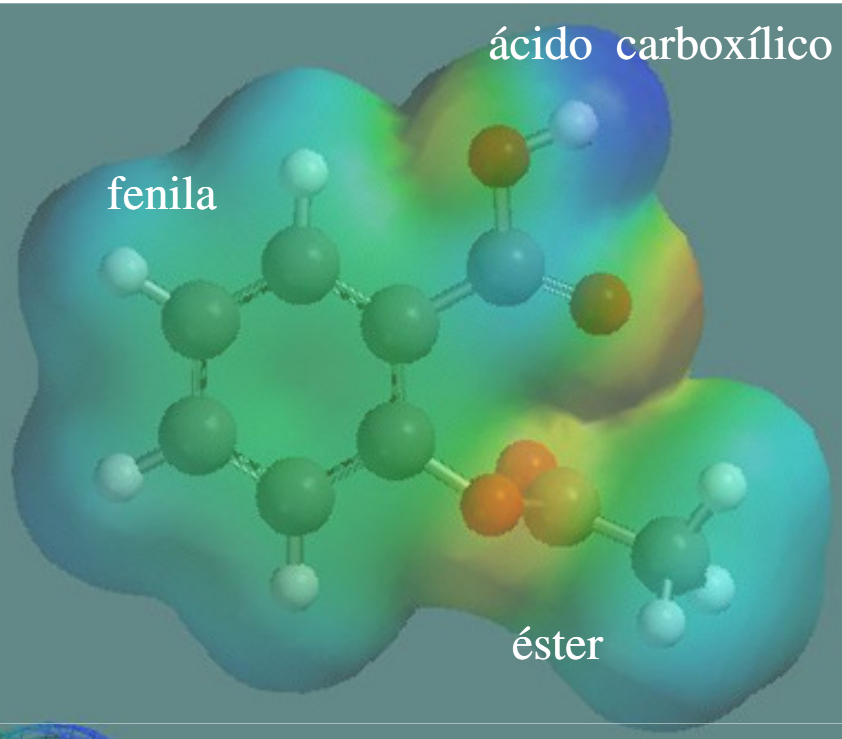
n-pentano

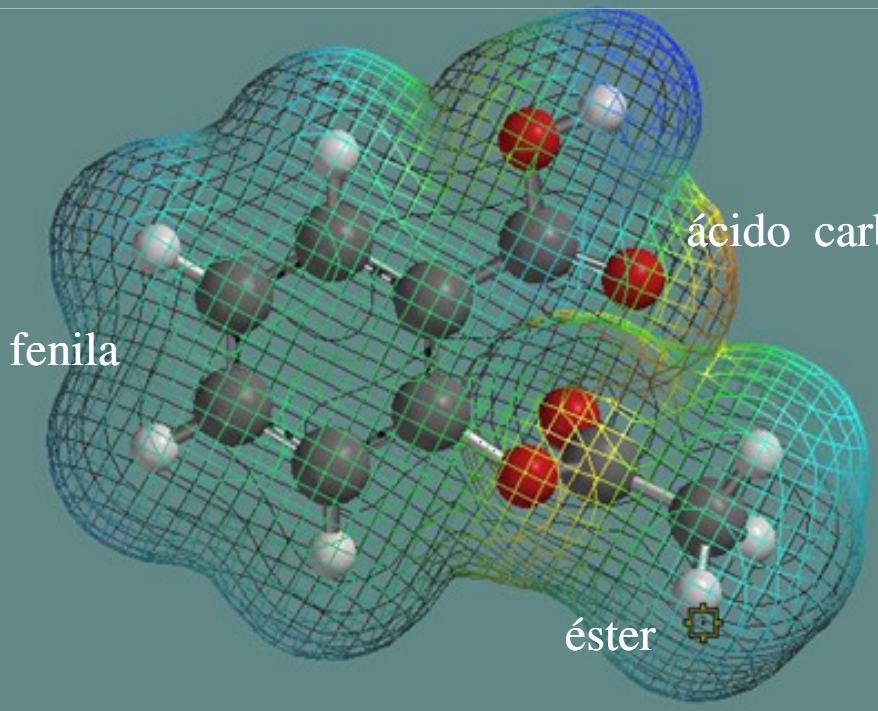
O Centenário Modelo *"Chave-Fechadura"*






fenila
ácido carboxílico
éster
AAS


ácido carboxílico
fenila
éster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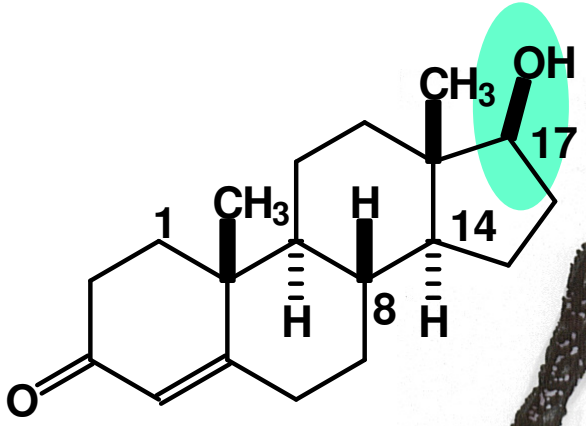
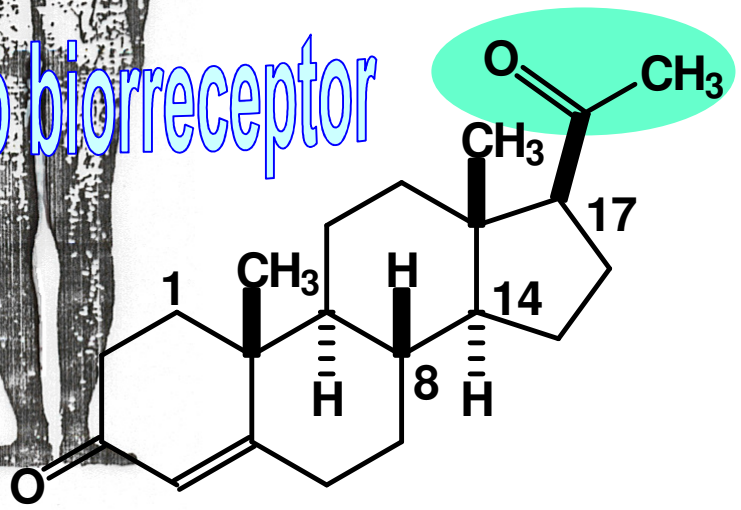
fenila
éster

Similaridade & Dissimilaridade Molecular

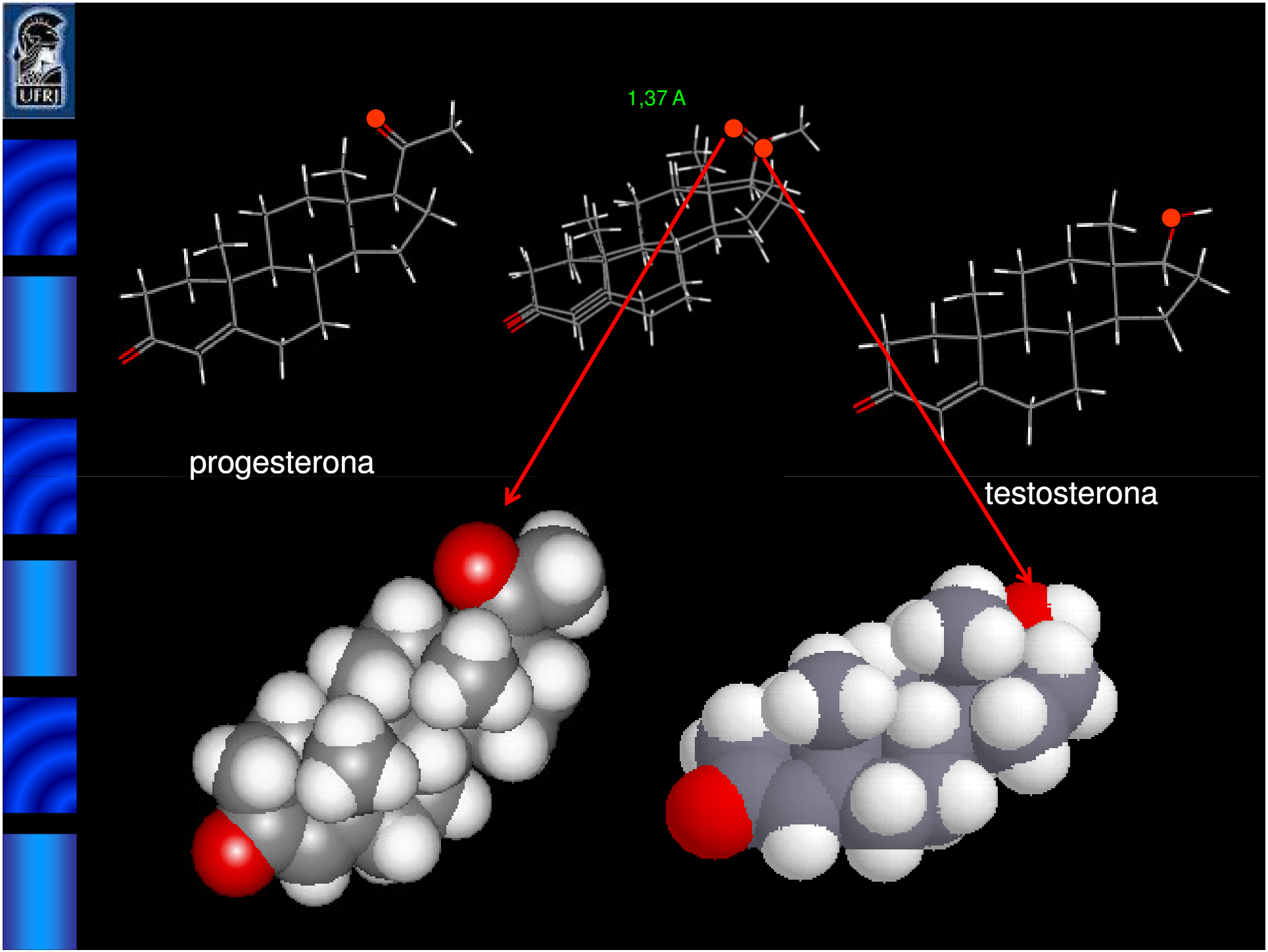


testosterona

no reconhecimento molecular do biorreceptor



progesterona


1,37 A
progesterona
testosterona