

# Princípios de Química Medicinal

MedChem

24ª Semana da Química do Instituto de Química da UFRJ  
09-13 de maio de 2016



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Instituto de Ciências Biomédicas

Universidade Federal do Rio de Janeiro



Parte 1

Sumário

Introdução; O processo de inovação de fármacos; O paradigma de Ehrlich & Fischer; Os alfabetos bioquímicos; As fases da ação dos fármacos; Aspectos moleculares da ação dos fármacos; Breve noção sobre o papel dos produtos naturais na descoberta de fármacos; Aspectos da química computacional: modelagem molecular; Estratégias para o desenho de novos candidatos a fármacos; Exemplos selecionados: LASSBio-UFRJ.



ELIEZER J.  
BARREIRO  
CARLOS ALBERTO MANSSOUR  
FRAGA

# QUÍMICA MEDICINAL

AS BASES MOLECULARES DA AÇÃO DOS FÁRMACOS

3<sup>a</sup>  
EDIÇÃO

NOVA  
EDIÇÃO



artmed  
EDITORIA



# Antes de mais nada...

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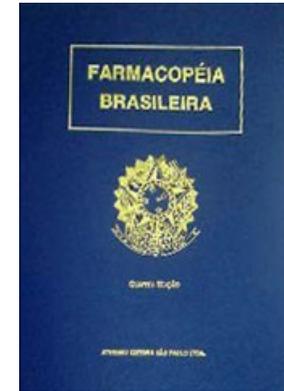




# Fármaco...

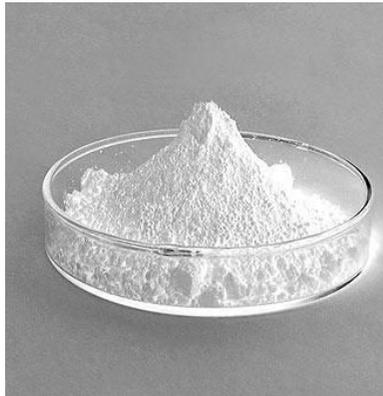


Formas  
Farmacêuticas

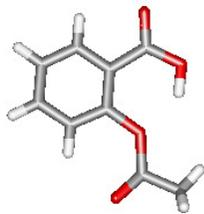
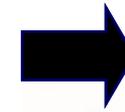
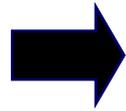


Farmoquímico

IFA



Pureza farmacopêica



Princípio ativo

IFA = insumo  
farmacêutico ativo

Tecnologia  
Farmacêutica



ácido acetilsalicílico

# .... & medicamento.



WILEY-VCH

Os fármacos são...

**MOLECULES  
THAT CHANGED THE  
WORLD**

Uma das maiores invenções do século XX

K. C. NICOLAOU • T. MONTAGNON



**A** *Química*  
*Medicinal*  
**é** *simplesmente*  
*fascinante!*

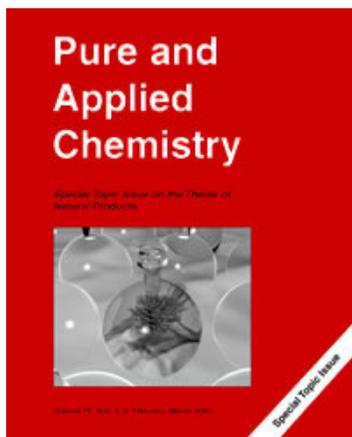




# IUPAC - Subcommittee Medicinal Chemistry & Drug Development

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Definição: **Química Medicinal** é a *disciplina* que estuda os aspectos relacionados à descoberta ou invenção dos fármacos, OS aspectos moleculares envolvidos em seu mecanismo de ação e aqueles que governam a *absorção, distribuição, metabolismo, eliminação toxicidade* (ADMET), incluindo a compreensão da relação entre a estrutura química e a atividade terapêutica (REA ou SAR).



**Química**  
m e d  
**Medicinal**  
c h e m

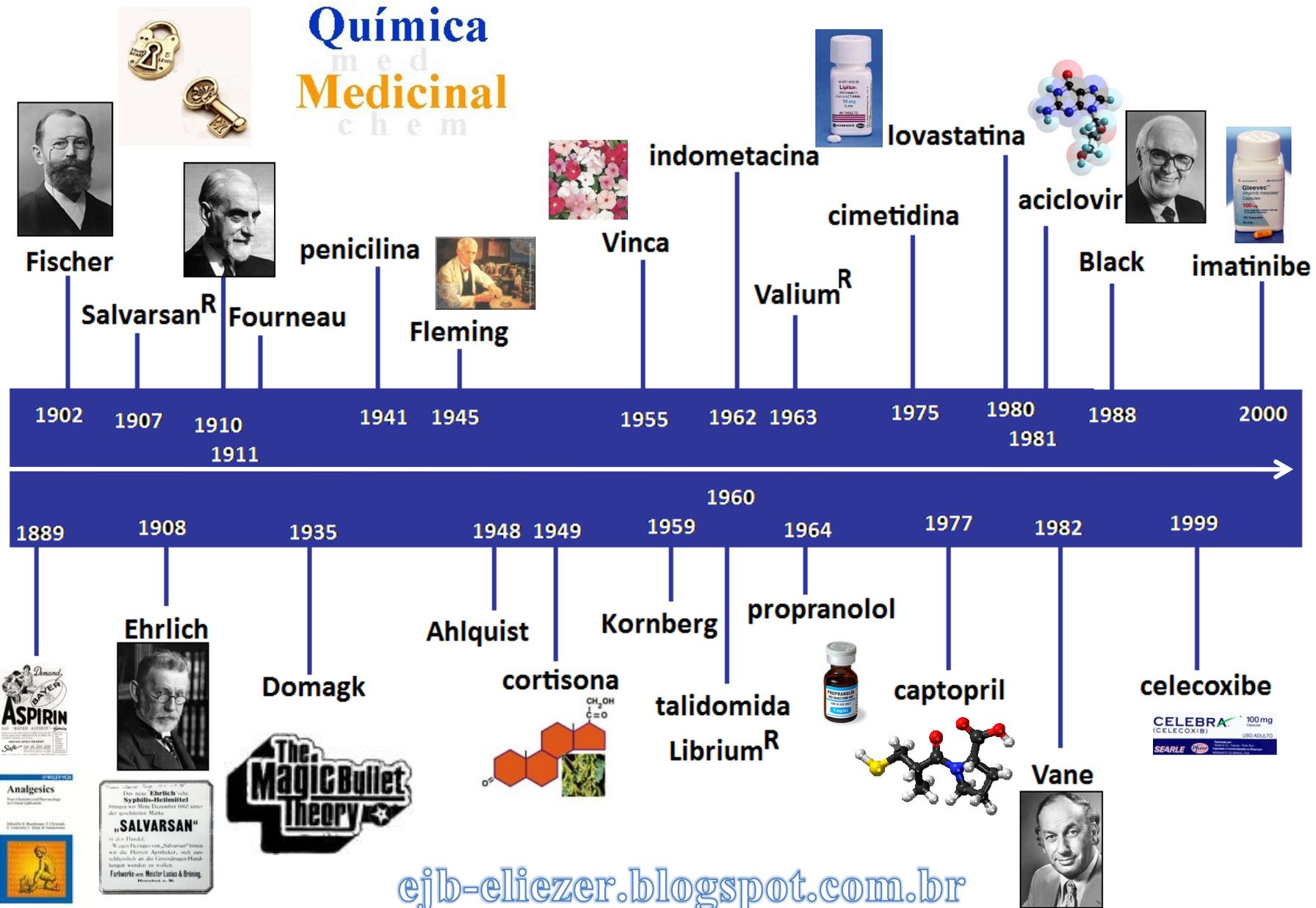
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IUPAC

*Pure & Appl. Chem.*, Vol. 70, No. 5, pp. 1129–1143, 1998.  
Printed in Great Britain.  
© 1998 IUPAC  
*Eur. J. Med. Chem.*, 31, 747 (1996)

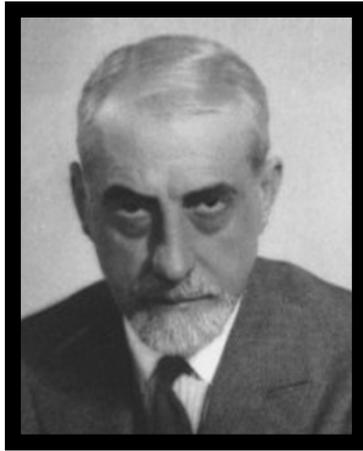


# Cronologia histórica da Química Medicinal





# O berço da Química Medicinal

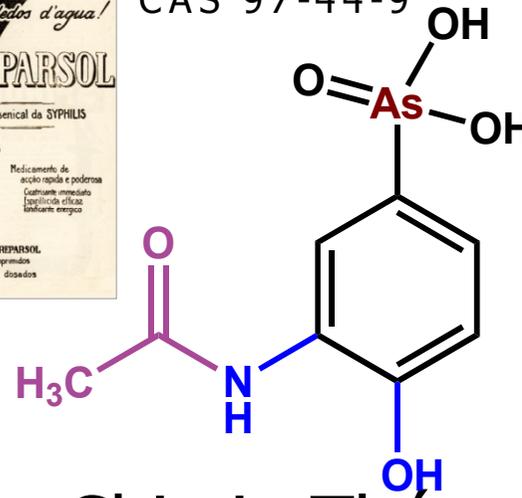


Ernest Fourneau  
1872-1949



Stovarsol

CAS 97-44-9



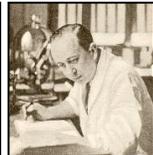
Institut Pasteur (1887)

## 1911- Laboratoire de Chimie Thérapeutique



Diretor: Emile Roux

1911-1944 – Jacques Tréfouël (1897-1977)  
 Thérèse Tréfouël (1892-1978)  
 Germaine Benoit (1901-1983)  
 Federico Nitti (1903-1947)



Daniel Bovet  
1907-1992 \*

\* Farmacêutico suíço  
Doutor *h.c.* UFRJ

Prêmio Nobel de  
Fisiologia/Medicina  
1957

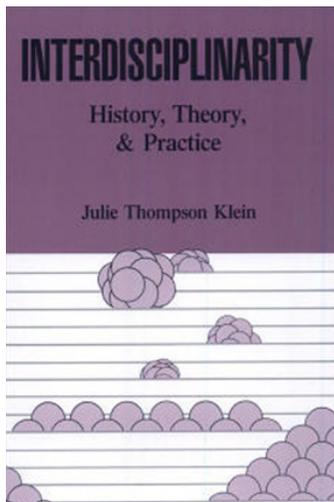
*Sulfonamidas,*  
anti-histamínicos.

**Curare:**  
**SAR**

J-P Fourneau, « Ernest Fourneau fondateur de la Chimie Pharmaceutique française », *Revue de l'Histoire de la Pharmacie*, t.XXXIV, n° 275, 335-355



A interdisciplinaridade é indispensável



para a solução de problemas  
ou desafios complexos !



**Química**  
m e d  
**Medicinal**  
c h e m





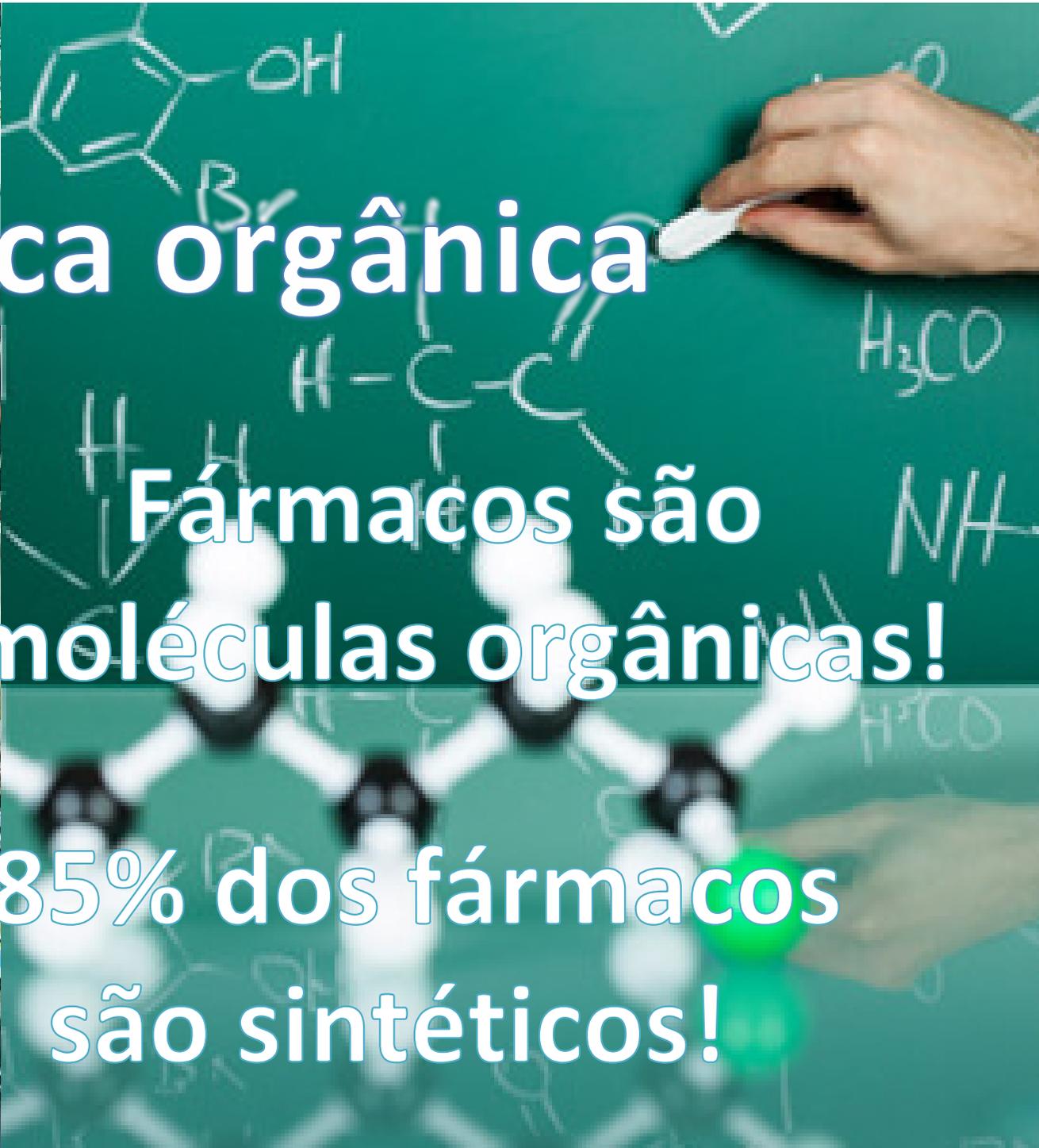


# Química orgânica

Fármacos são  
moléculas orgânicas!

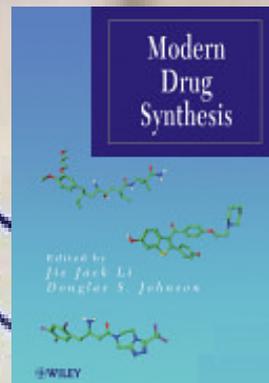
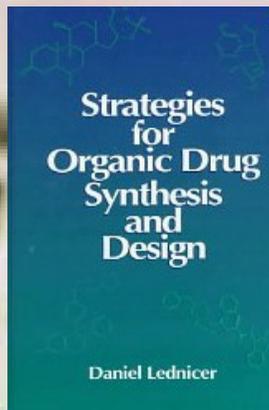
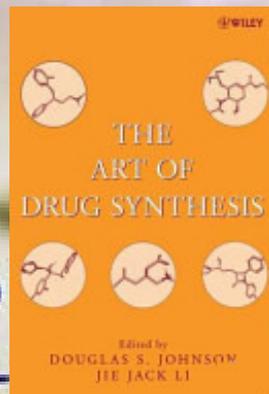


>85% dos fármacos  
são sintéticos!



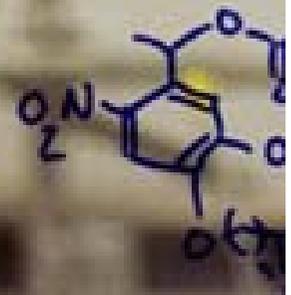
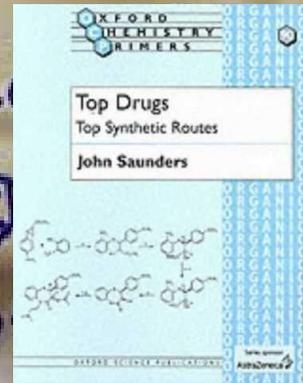
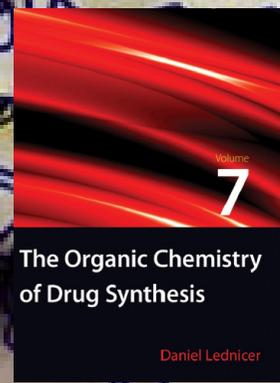
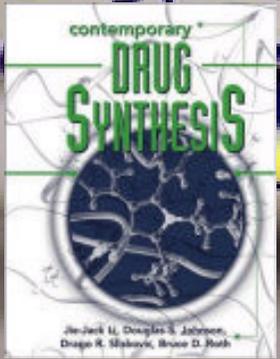


PEGA



# O mercado mundial em 2015:

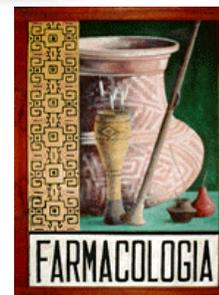
ca. US\$ 921 bi

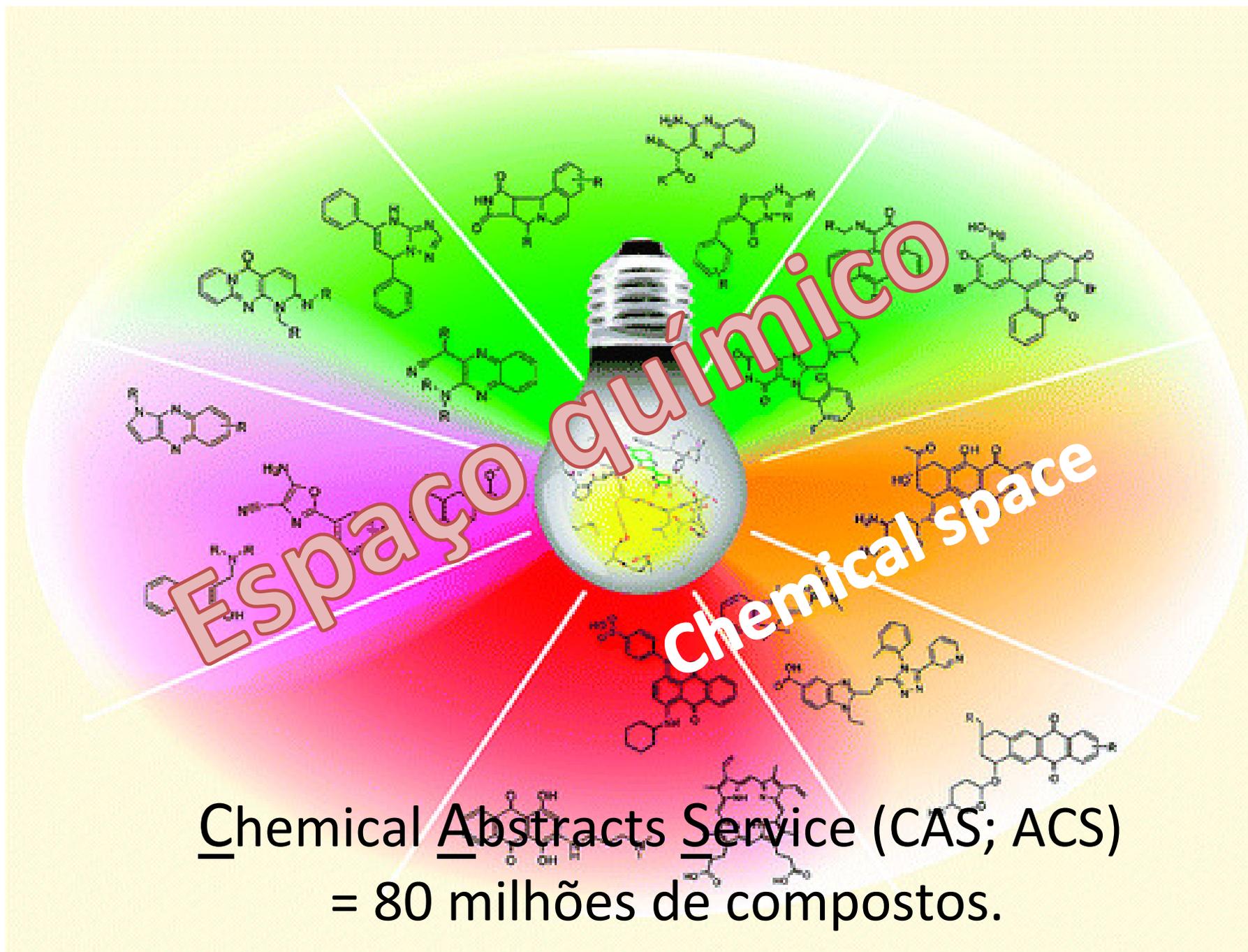






# E daí...?







Agulha no palheiro...?



O processo de DD...

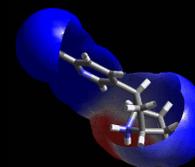
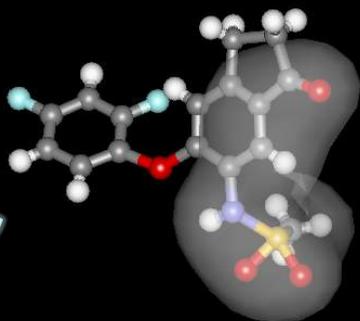


*...é brain-driven!*



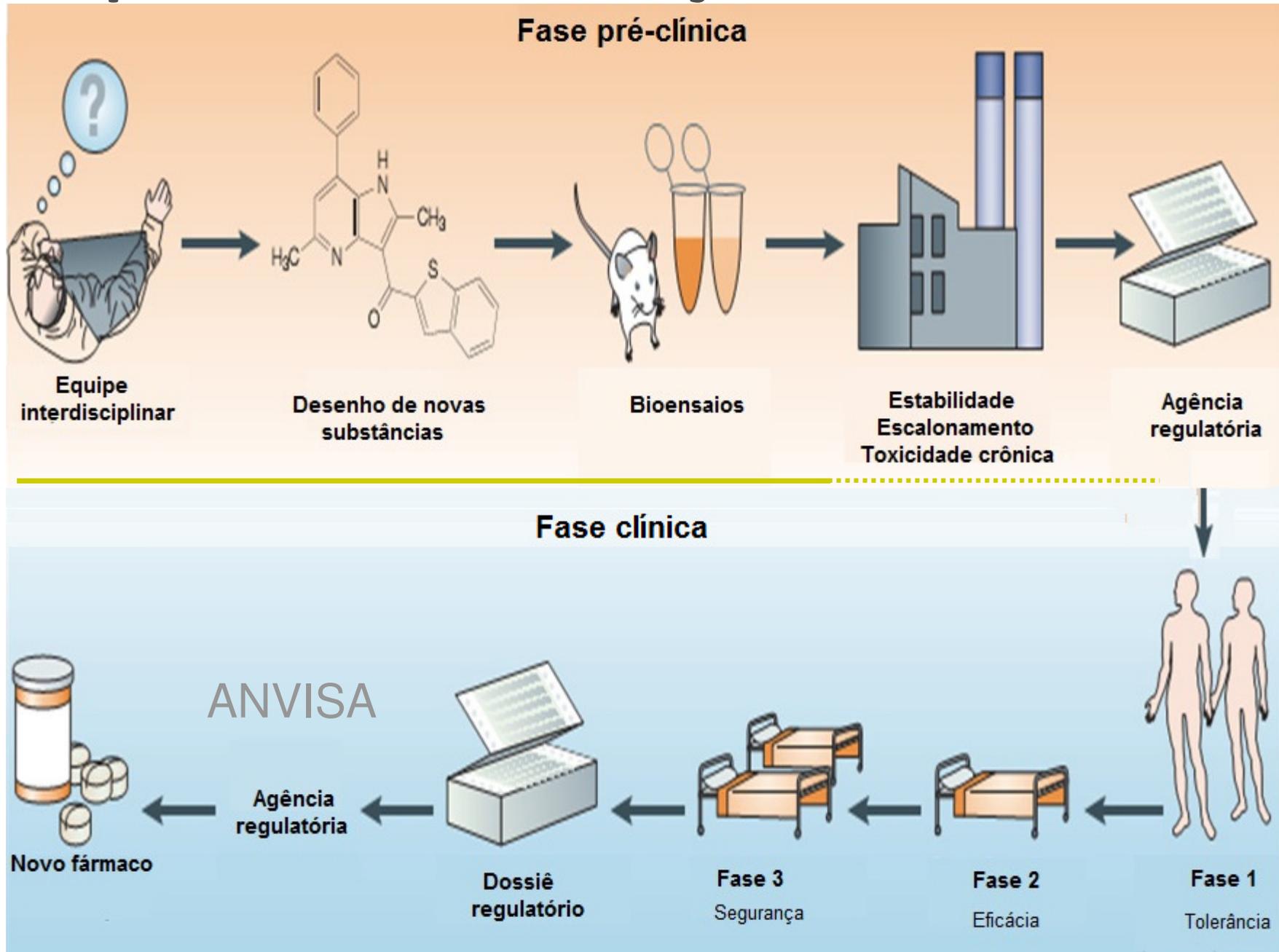
# Química medicinal

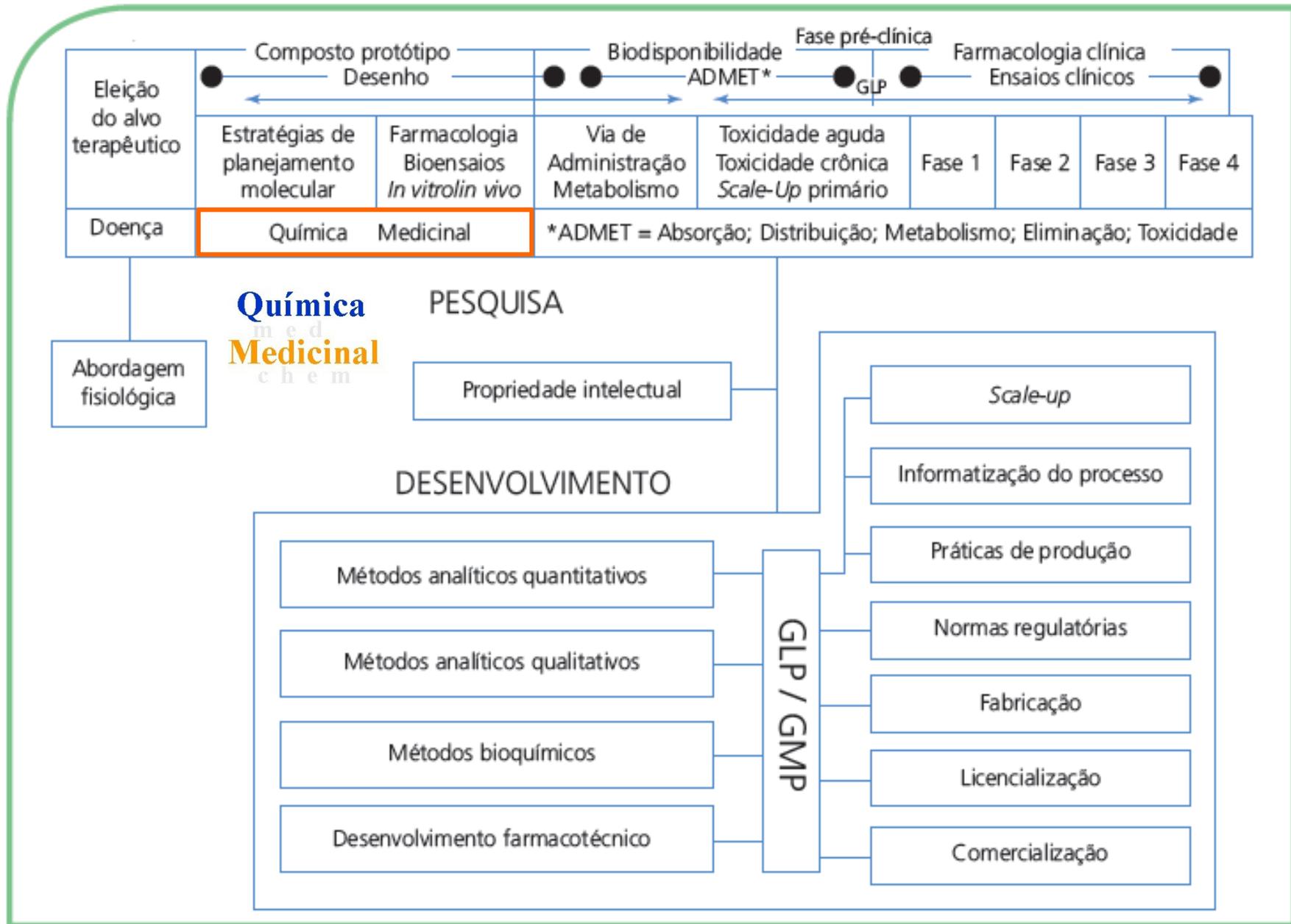
O processo de descoberta/  
invenção de fármacos,  
compreende identificar  
racionalmente um  
composto inédito, capaz de  
modular terapêuticamente  
um processo biológico.





# O processo da inovação em fármacos







Farmacologia

Fisiologia

Bioquímica

Química Medicinal

LASSBio

Laboratório de Avaliação e Síntese de Substâncias Bioativas

Biologia  
molecular

Síntese  
orgânica

Physiologic approach  
A abordagem fisiológica



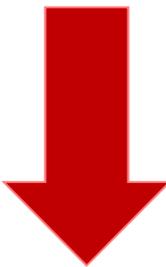
# Processo de invenção de fármacos





Physiologic  
**A abordagem**  
approach  
fisiológica

# A eleição do alvo-terapêutico



Química  
med  
Medicinal  
chem

# Conhecimento da fisiopatologia

Doenças multifatoriais

Quimioterapia  
**SNC**

Doença crônica



# O paradigma de Ehrlich & Fischer



**Emil Fischer**  
1852-1919  
**1902**

**LOCK & KEY**  
CONCEPT

Biorreceptor  
macromolécula  
baseado no sítio de  
reconhecimento



Manejaemento  
racional

**BSRM**

**BL-AA**

He postulated the existence of specific receptors, associated with cells or distributed in the blood

Strebhardt & A Ullrich, Paul Ehrlich magic bullet concept: 100 years of progress, *Nature Rev. Cancer* **2008**, 8, 473

**THE LANCET**

"In patients with locally advanced or high-risk local prostate cancer, addition of local radiotherapy to endocrine treatment halved 10-year prostate-cancer-specific mortality."

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

Fármaco  
micromolécula

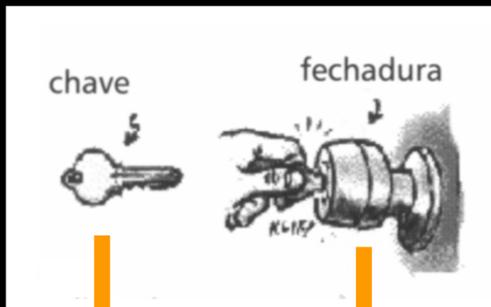
baseado no ligante  
/ análogo-ativo

Química  
med  
Medicinal  
chem

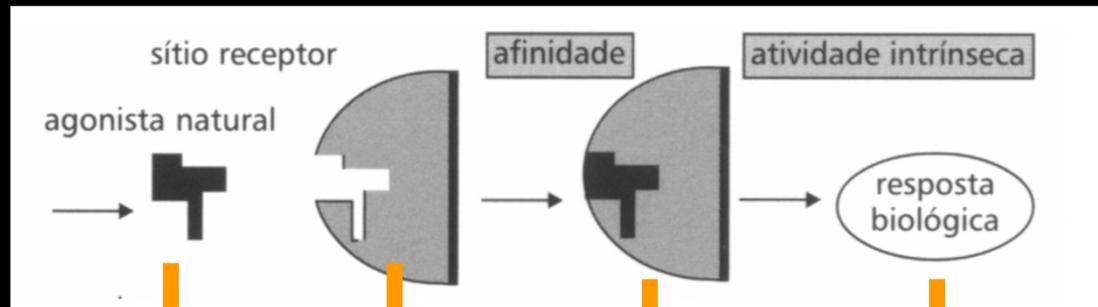
**O Modelo**  
**Paul Ehrlich**  
1854-1915  
**1908**



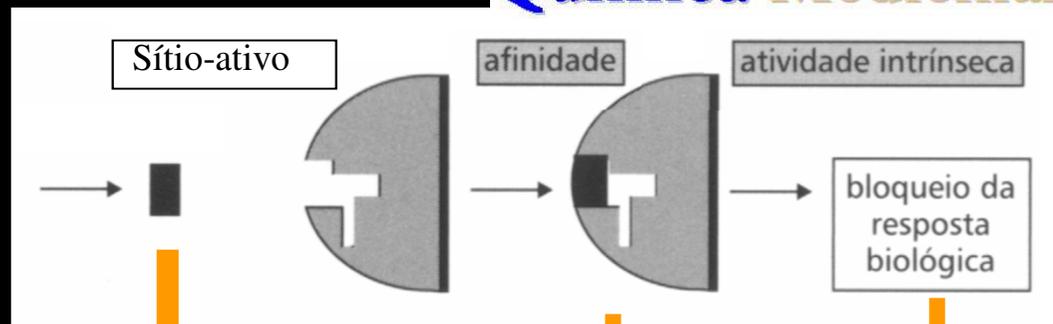
# O Centenário Modelo "Chave-Fechadura"



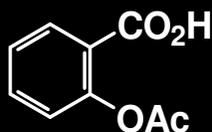
Fármaco Substrato natural = Alvo terapêutico



Ácido araquidônico PGHS-1 PGHS-2 PGE<sub>2</sub> inflamação icosanóide



Inibidor: AAS PGHS-2 PGHS-1 NSAI



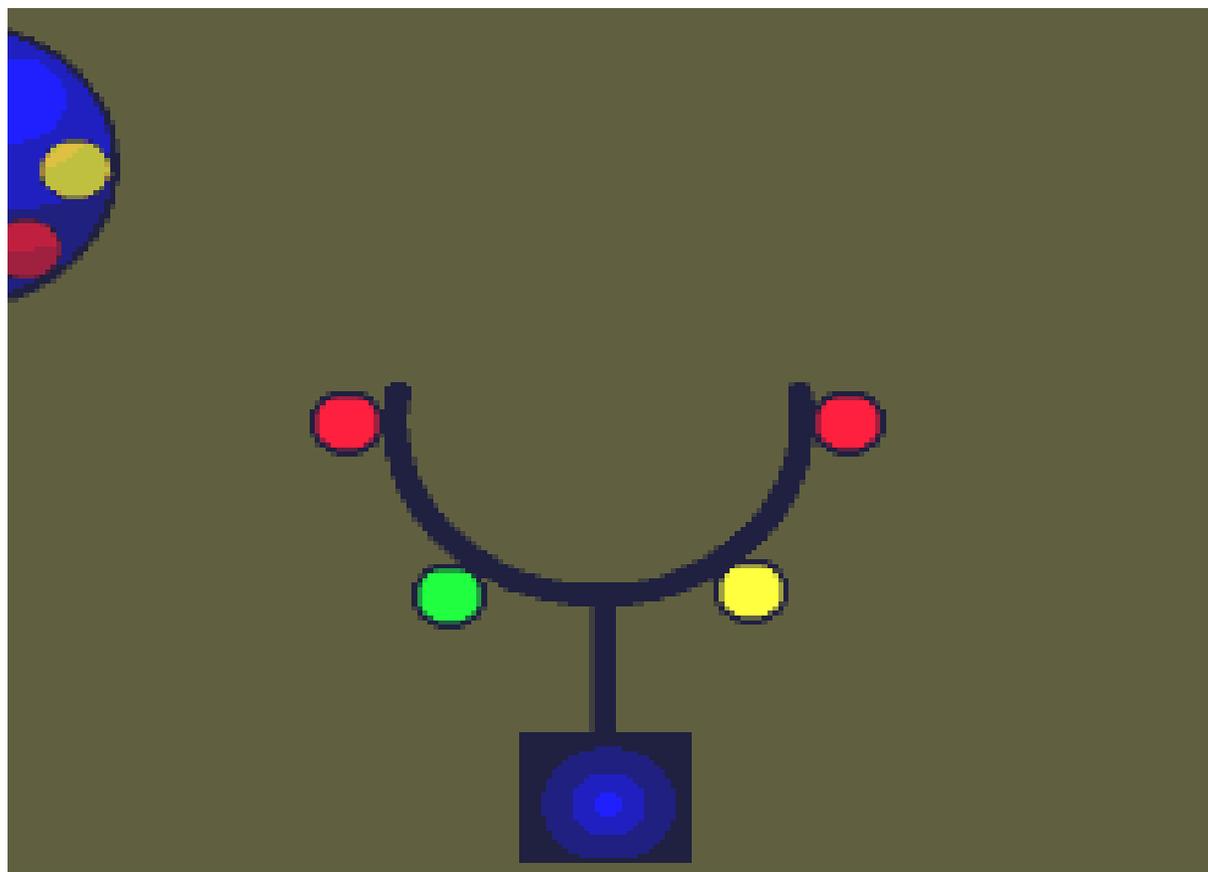
NSAI = antiinflamatórios não-esteróides

Química Medicinal



# Reconhecimento & complementaridade molecular

Química  
m e d  
Medicinal  
c h e m



## Potência & eficácia



Biorreceptor

Estrutura 3D do alvo terapêutico

Sítio de reconhecimento molecular

Fármaco

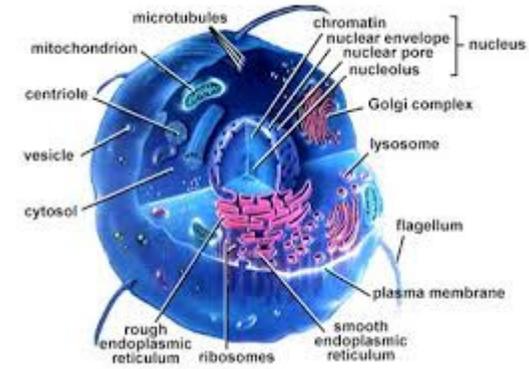
Alfabetos bioquímicos da vida....

**483** são os alvos-terapêuticos

dos fármacos contemporâneos!

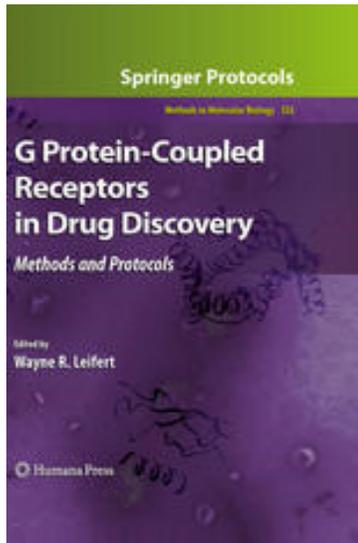
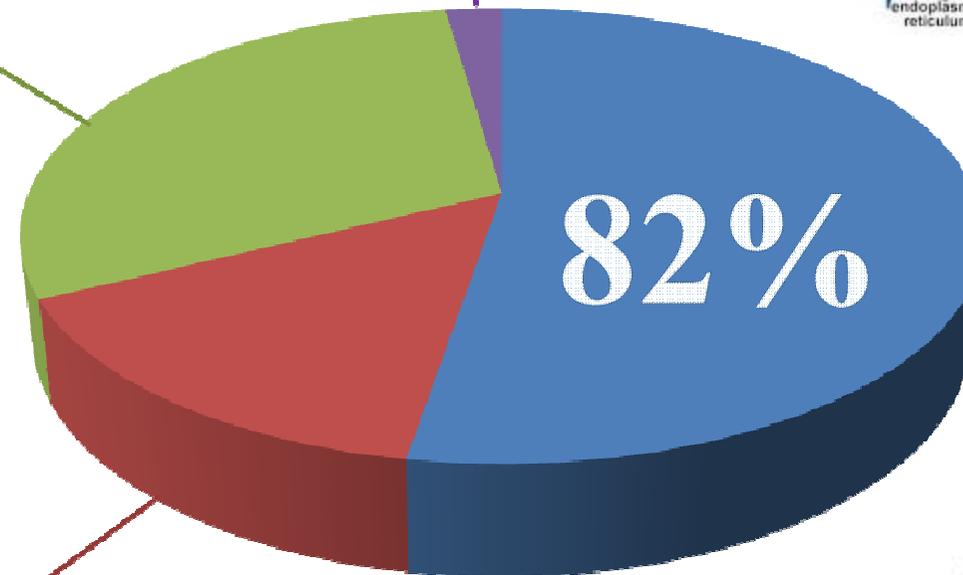


# A maioria dos biorreceptores dos fármacos contemporâneos são enzimas ...

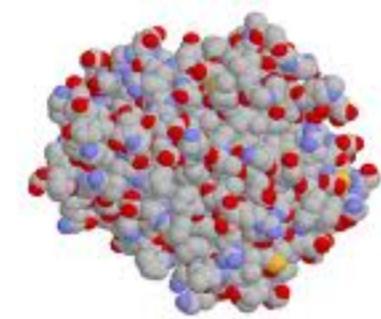
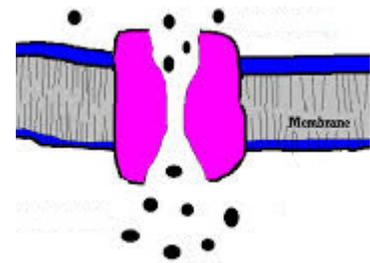


receptores nucleares  
150

receptores acoplados a proteína G (GPCR)  
2000



canais iônicos  
1000



[www.nature.com/reviews/drugdisc](http://www.nature.com/reviews/drugdisc)  
Hopkins, A. L. & Groom, C. R. The druggable genome. *Nature Rev. Drug Discov.* 1, 727-30 (2002).

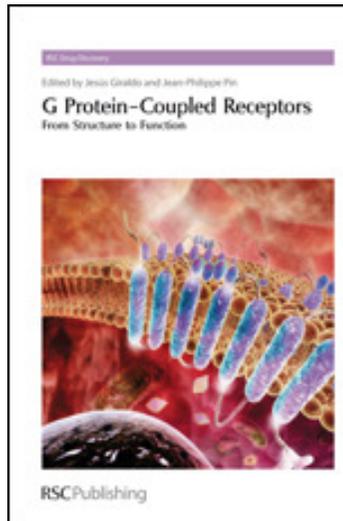


# Receptores acoplados a proteína-G



**Alfred Goodman Gilman**

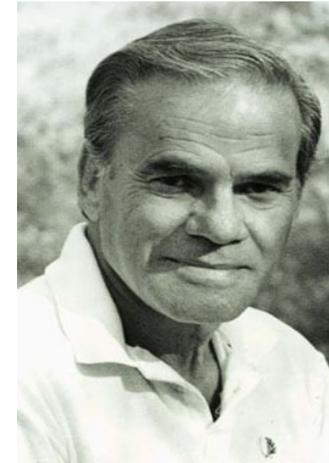
(1941-2015)



*G-protein*



**1994**



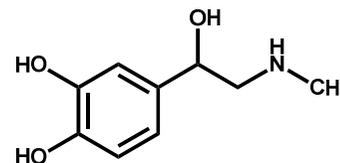
**Martin Rodbell**

(1925-1998)

*GPCR's*



**2012**



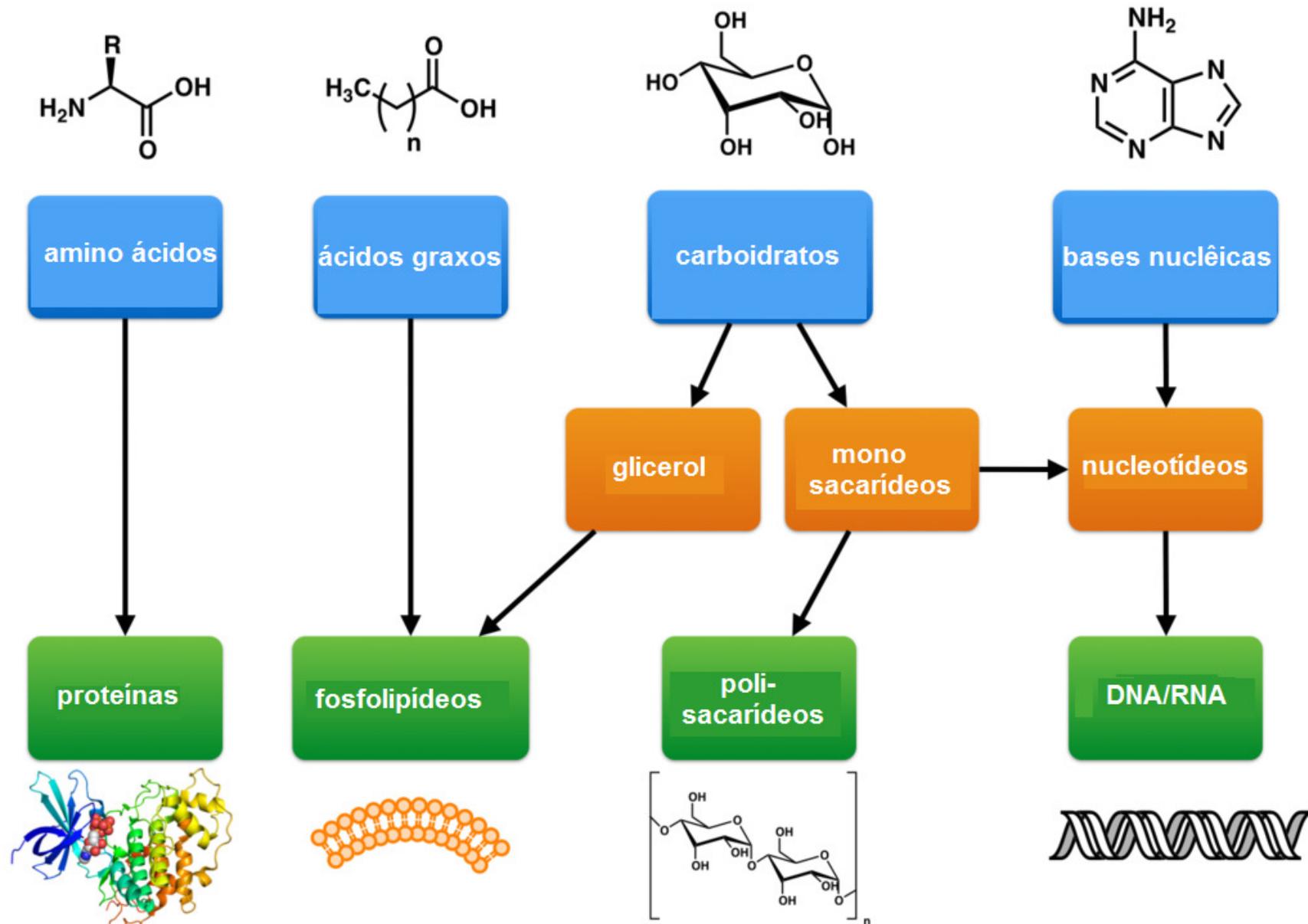
**Robert J. Lefkowitz**



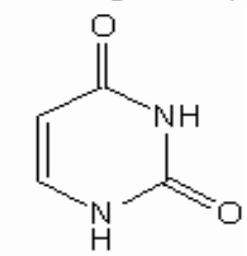
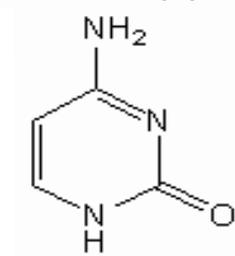
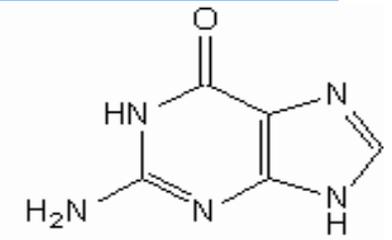
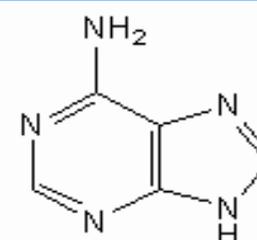
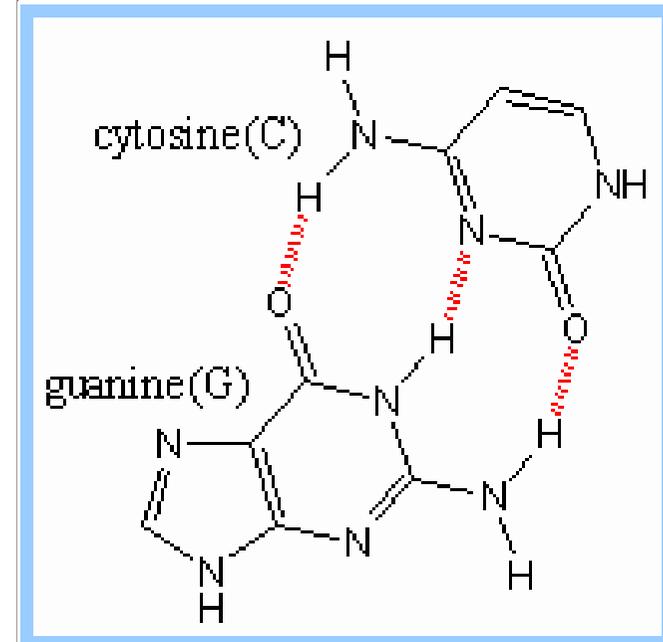
**Brian K. Kobilka**



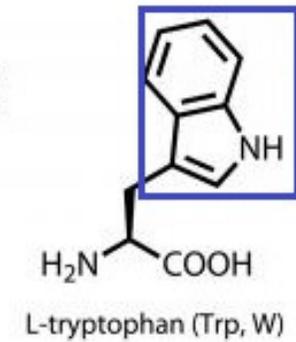
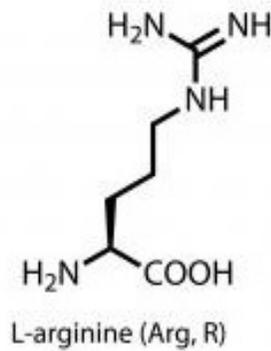
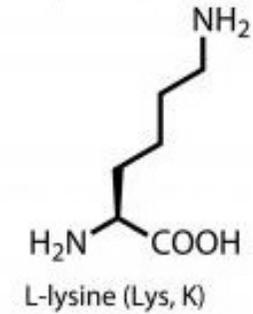
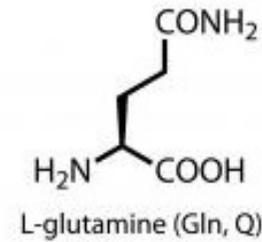
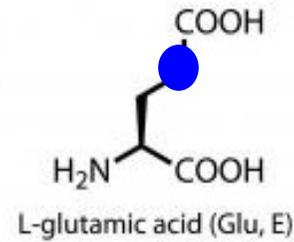
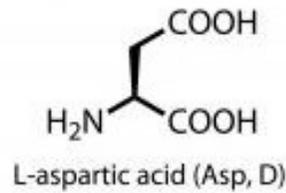
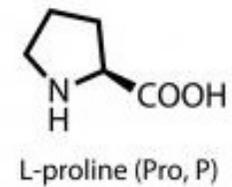
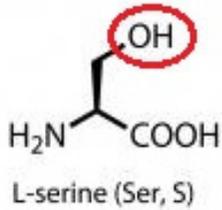
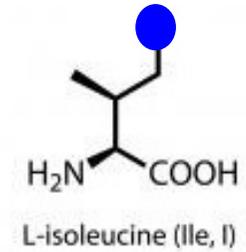
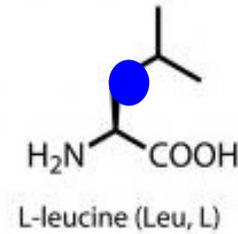
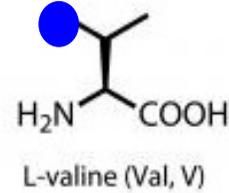
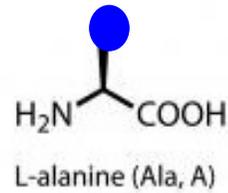
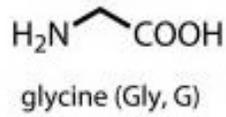
# Os biorreceptores: alfabetos bioquímicos



# Proteínas, carboidratos, DNA, lipídeos, canais iônicos

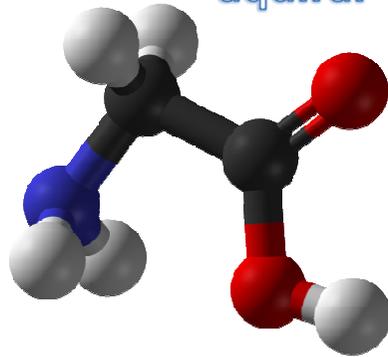




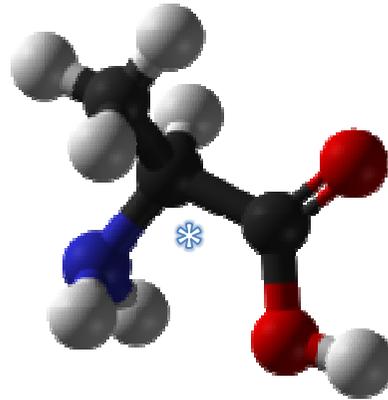




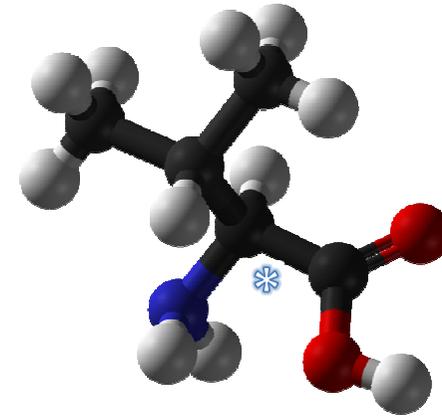
aquiral



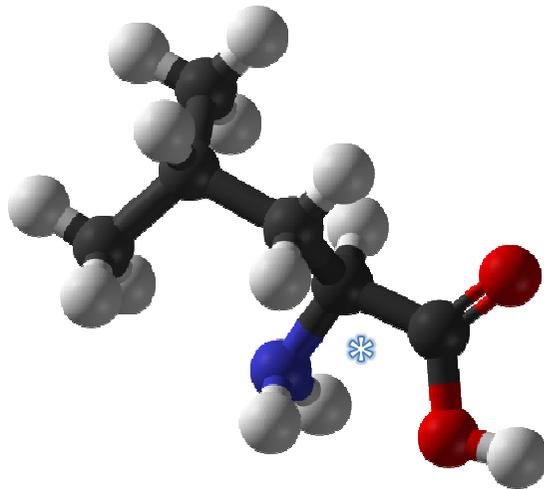
Glicina



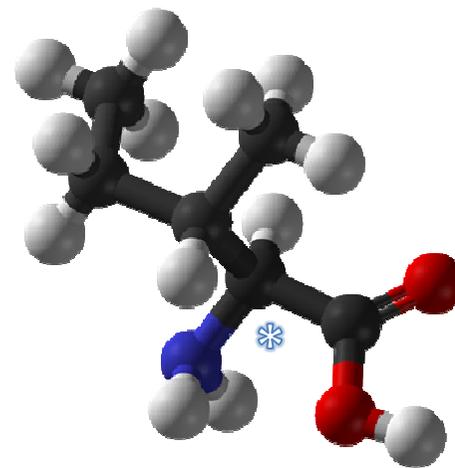
Alanina



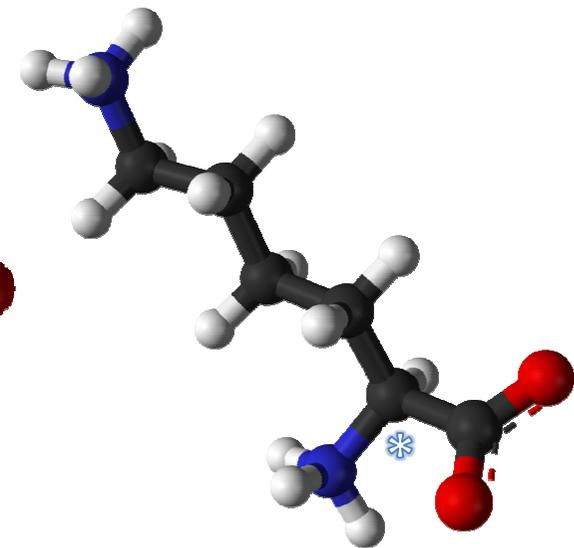
Valina



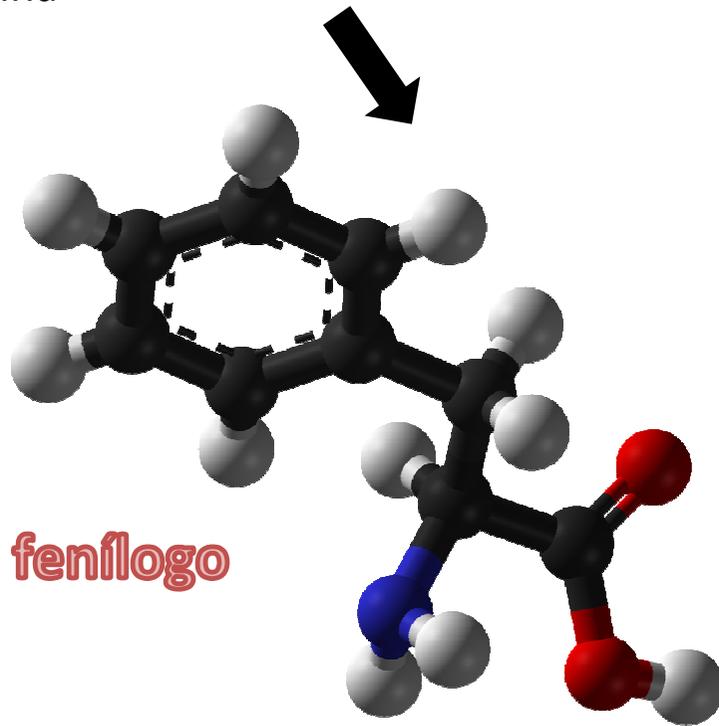
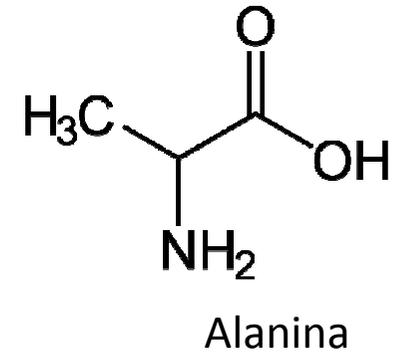
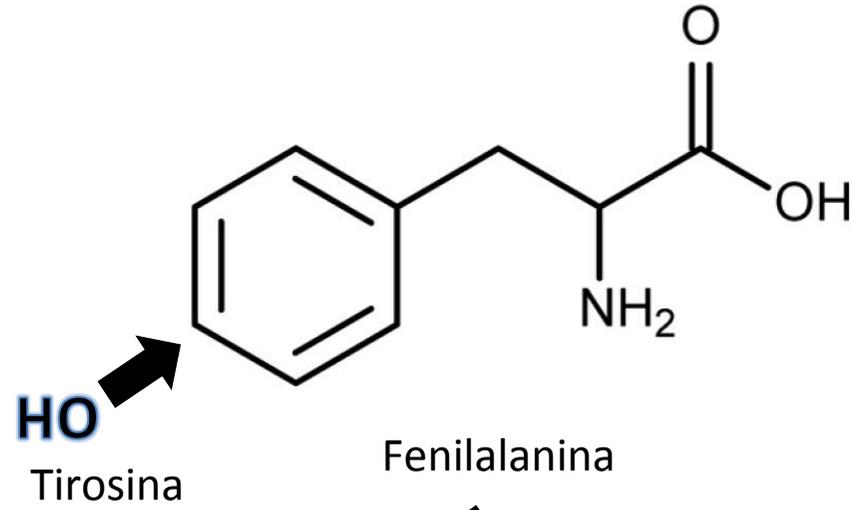
Leucina



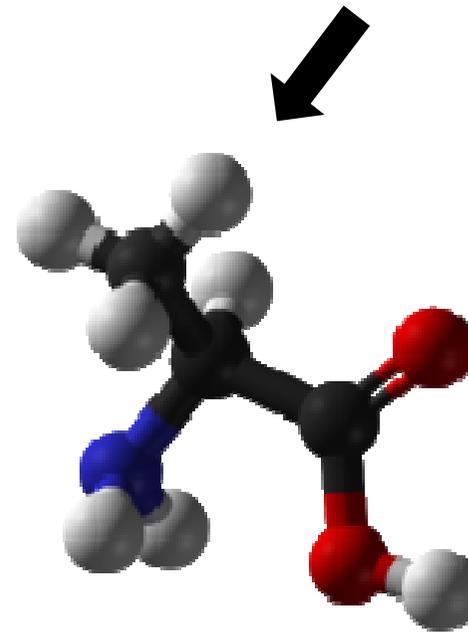
Isoleucina



Lisina



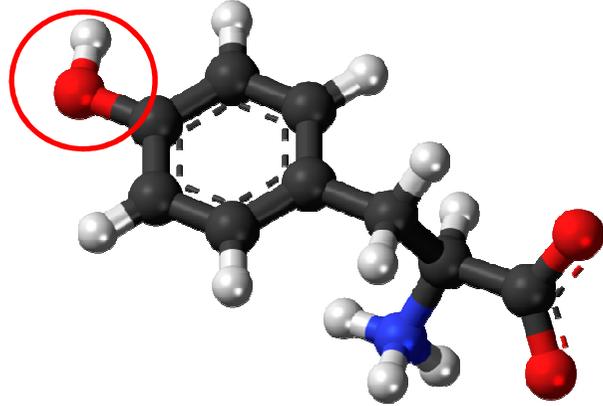
Fenilalanina



Alanina

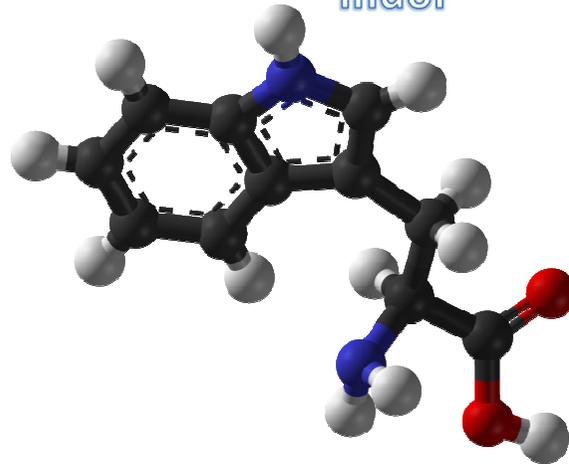


fenol



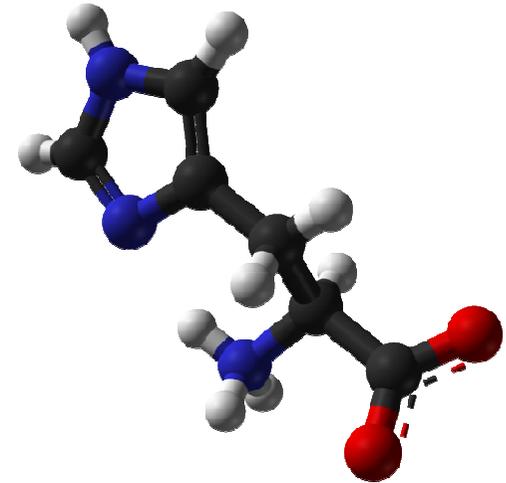
Tirosina

indol

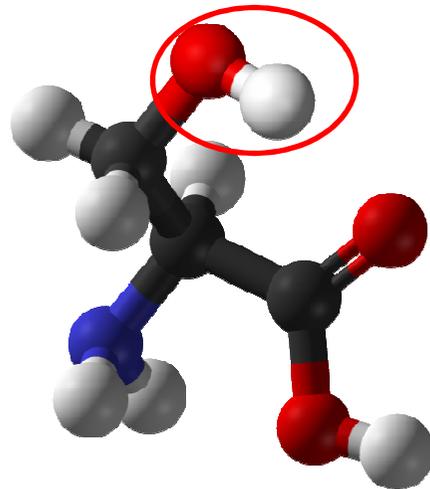


Triptofano

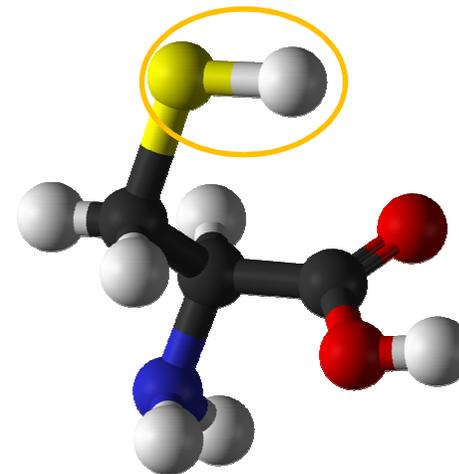
imidazol



Histidina



Serina



Cisteína



# Tabela Periódica

## The Periodic Table of the Elements

period 1

group 1

18

atomic mass or most stable mass number

1st ionization energy in kJ/mol

chemical symbol

name

electron configuration

atomic number

electronegativity

oxidation states most common are bold

alkali metals

alkaline metals

other metals

transition metals

lanthanoids

actinoids

metalloids

nonmetals

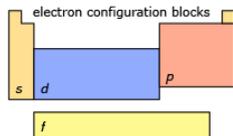
halogens

noble gases

unknown elements

radioactive elements have masses in parentheses

1.00794 1912.0 0.98 H Hydrogen 1s <sup>1</sup>																	4.002602 2372.3 He Helium 1s <sup>2</sup>
6.941 520.2 0.98 3 Li Lithium 1s <sup>2</sup> 2s <sup>1</sup>	9.012182 899.5 1.57 4 Be Beryllium 1s <sup>2</sup> 2s <sup>2</sup>											10.811 800.6 2.04 5 B Boron 1s <sup>2</sup> 2s <sup>2</sup> 2p <sup>1</sup>	12.0107 1096.5 2.65 6 C Carbon 1s <sup>2</sup> 2s <sup>2</sup> 2p <sup>2</sup>	14.0067 1400.3 3.04 7 N Nitrogen 1s <sup>2</sup> 2s <sup>2</sup> 2p <sup>3</sup>	15.9994 1313.9 3.44 8 O Oxygen 1s <sup>2</sup> 2s <sup>2</sup> 2p <sup>4</sup>	18.998403 1681.0 3.98 9 F Fluorine 1s <sup>2</sup> 2s <sup>2</sup> 2p <sup>5</sup>	20.1797 2080.7 Ne Neon 1s <sup>2</sup> 2s <sup>2</sup> 2p <sup>6</sup>
22.98976 495.8 0.93 11 Na Sodium [Ne] 3s <sup>1</sup>	24.3050 737.7 1.31 12 Mg Magnesium [Ne] 3s <sup>2</sup>											26.98153 577.5 1.61 13 Al Aluminium [Ne] 3s <sup>2</sup> 3p <sup>1</sup>	28.0855 786.5 1.90 14 Si Silicon [Ne] 3s <sup>2</sup> 3p <sup>2</sup>	30.97696 1011.8 2.19 15 P Phosphorus [Ne] 3s <sup>2</sup> 3p <sup>3</sup>	32.065 999.6 2.58 16 S Sulfur [Ne] 3s <sup>2</sup> 3p <sup>4</sup>	35.453 1251.2 3.16 17 Cl Chlorine [Ne] 3s <sup>2</sup> 3p <sup>5</sup>	39.948 1620.6 Ar Argon [Ne] 3s <sup>2</sup> 3p <sup>6</sup>
39.0983 418.8 0.82 19 K Potassium [Ar] 4s <sup>1</sup>	40.078 589.8 1.00 20 Ca Calcium [Ar] 4s <sup>2</sup>	44.95591 633.1 1.96 21 Sc Scandium [Ar] 3d <sup>1</sup> 4s <sup>2</sup>	47.867 658.8 1.54 22 Ti Titanium [Ar] 3d <sup>2</sup> 4s <sup>2</sup>	50.9415 650.9 1.63 23 V Vanadium [Ar] 3d <sup>3</sup> 4s <sup>2</sup>	51.9962 652.9 1.66 24 Cr Chromium [Ar] 3d <sup>5</sup> 4s <sup>1</sup>	54.93804 717.3 1.55 25 Mn Manganese [Ar] 3d <sup>5</sup> 4s <sup>2</sup>	55.845 762.5 1.83 26 Fe Iron [Ar] 3d <sup>6</sup> 4s <sup>2</sup>	58.93319 762.5 1.83 27 Co Cobalt [Ar] 3d <sup>7</sup> 4s <sup>2</sup>	58.933 786.4 1.91 28 Ni Nickel [Ar] 3d <sup>8</sup> 4s <sup>2</sup>	63.546 745.5 1.90 29 Cu Copper [Ar] 3d <sup>10</sup> 4s <sup>1</sup>	65.38 786.4 1.90 30 Zn Zinc [Ar] 3d <sup>10</sup> 4s <sup>2</sup>	69.723 578.8 1.81 31 Ga Gallium [Ar] 3d <sup>10</sup> 4s <sup>2</sup> 4p <sup>1</sup>	72.64 726.0 2.01 32 Ge Germanium [Ar] 3d <sup>10</sup> 4s <sup>2</sup> 4p <sup>2</sup>	74.92160 947.0 2.18 33 As Arsenic [Ar] 3d <sup>10</sup> 4s <sup>2</sup> 4p <sup>3</sup>	78.96 947.0 2.55 34 Se Selenium [Ar] 3d <sup>10</sup> 4s <sup>2</sup> 4p <sup>4</sup>	79.904 1159.9 3.00 35 Br Bromine [Ar] 3d <sup>10</sup> 4s <sup>2</sup> 4p <sup>5</sup>	83.798 1350.4 3.00 36 Kr Krypton [Ar] 3d <sup>10</sup> 4s <sup>2</sup> 4p <sup>6</sup>
85.4678 489.0 0.82 37 Rb Rubidium [Kr] 5s <sup>1</sup>	87.62 502.9 0.89 38 Sr Strontium [Kr] 5s <sup>2</sup>	88.90585 600.0 1.22 39 Y Yttrium [Kr] 4d <sup>1</sup> 5s <sup>2</sup>	91.224 640.1 1.33 40 Zr Zirconium [Kr] 4d <sup>2</sup> 5s <sup>2</sup>	92.90638 652.1 1.60 41 Nb Niobium [Kr] 4d <sup>4</sup> 5s <sup>1</sup>	95.96 684.3 2.16 42 Mo Molybdenum [Kr] 4d <sup>5</sup> 5s <sup>1</sup>	(98) 702.0 2.20 43 Tc Technetium [Kr] 4d <sup>5</sup> 5s <sup>2</sup>	101.07 710.2 2.20 44 Ru Ruthenium [Kr] 4d <sup>7</sup> 5s <sup>1</sup>	102.9055 719.7 2.28 45 Rh Rhodium [Kr] 4d <sup>8</sup> 5s <sup>1</sup>	106.42 804.4 2.20 46 Pd Palladium [Kr] 4d <sup>10</sup>	107.8682 791.0 1.93 47 Ag Silver [Kr] 4d <sup>10</sup> 5s <sup>1</sup>	112.441 897.8 1.89 48 Cd Cadmium [Kr] 4d <sup>10</sup> 5s <sup>2</sup>	114.818 588.4 1.78 49 In Indium [Kr] 4d <sup>10</sup> 5s <sup>2</sup> 5p <sup>1</sup>	118.710 703.0 1.96 50 Sn Tin [Kr] 4d <sup>10</sup> 5s <sup>2</sup> 5p <sup>2</sup>	121.760 854.0 2.06 51 Sb Antimony [Kr] 4d <sup>10</sup> 5s <sup>2</sup> 5p <sup>3</sup>	127.60 959.3 2.10 52 Te Tellurium [Kr] 4d <sup>10</sup> 5s <sup>2</sup> 5p <sup>4</sup>	126.9044 1090.0 2.06 53 I Iodine [Kr] 4d <sup>10</sup> 5s <sup>2</sup> 5p <sup>5</sup>	131.293 1170.4 2.60 54 Xe Xenon [Kr] 4d <sup>10</sup> 5s <sup>2</sup> 5p <sup>6</sup>
132.9054 375.7 0.79 55 Cs Caesium [Xe] 6s <sup>1</sup>	137.327 502.9 0.89 56 Ba Barium [Xe] 6s <sup>2</sup>	174.9668 523.5 1.27 71 Lu Lutetium [Xe] 4f <sup>14</sup> 5d <sup>1</sup> 6s <sup>2</sup>	178.49 608.5 1.30 72 Hf Hafnium [Xe] 4f <sup>14</sup> 5d <sup>2</sup> 6s <sup>2</sup>	180.9478 761.0 1.50 73 Ta Tantalum [Xe] 4f <sup>14</sup> 5d <sup>3</sup> 6s <sup>2</sup>	183.84 770.0 2.36 74 W Tungsten [Xe] 4f <sup>14</sup> 5d <sup>4</sup> 6s <sup>2</sup>	186.207 760.0 1.90 75 Re Rhenium [Xe] 4f <sup>14</sup> 5d <sup>5</sup> 6s <sup>2</sup>	190.23 840.0 2.20 76 Os Osmium [Xe] 4f <sup>14</sup> 5d <sup>6</sup> 6s <sup>2</sup>	192.227 880.0 2.20 77 Ir Iridium [Xe] 4f <sup>14</sup> 5d <sup>7</sup> 6s <sup>2</sup>	195.084 870.0 2.28 78 Pt Platinum [Xe] 4f <sup>14</sup> 5d <sup>9</sup> 6s <sup>1</sup>	196.9665 890.1 2.54 79 Au Gold [Xe] 4f <sup>14</sup> 5d <sup>10</sup> 6s <sup>1</sup>	200.59 1007.1 2.00 80 Hg Mercury [Xe] 4f <sup>14</sup> 5d <sup>10</sup> 6s <sup>2</sup>	204.3833 589.4 1.62 81 Tl Thallium [Xe] 4f <sup>14</sup> 5d <sup>10</sup> 6s <sup>2</sup> 6p <sup>1</sup>	207.2 703.0 2.33 82 Pb Lead [Xe] 4f <sup>14</sup> 5d <sup>10</sup> 6s <sup>2</sup> 6p <sup>2</sup>	208.9804 703.0 2.02 83 Bi Bismuth [Xe] 4f <sup>14</sup> 5d <sup>10</sup> 6s <sup>2</sup> 6p <sup>3</sup>	(210) 812.1 2.00 84 Po Polonium [Xe] 4f <sup>14</sup> 5d <sup>10</sup> 6s <sup>2</sup> 6p <sup>4</sup>	(210) 890.0 2.20 85 At Astatine [Xe] 4f <sup>14</sup> 5d <sup>10</sup> 6s <sup>2</sup> 6p <sup>5</sup>	(220) 1097.0 Rn Radon [Xe] 4f <sup>14</sup> 5d <sup>10</sup> 6s <sup>2</sup> 6p <sup>6</sup>
(223) 380.0 0.70 87 Fr Francium [Rn] 7s <sup>1</sup>	(226) 509.3 0.90 88 Ra Radium [Rn] 7s <sup>2</sup>	(262) 470.0 103 Lr Lawrencium [Rn] 5f <sup>14</sup> 7s <sup>2</sup> 7p <sup>1</sup>	(261) 580.0 104 Rf Rutherfordium [Rn] 5f <sup>14</sup> 7s <sup>2</sup> 7p <sup>2</sup>	(262) 105 Db Dubnium	(266) 106 Sg Seaborgium	(264) 107 Bh Bohrium	(277) 108 Hs Hassium	(268) 109 Mt Meitnerium	(271) 110 Ds Darmstadtium	(272) 111 Rg Roentgenium	(285) 112 Cn Copernicium	(284) 113 Uut Ununtrium	(289) 114 Fl Flerovium	(288) 115 Uup Ununpentium	(292) 116 Lv Livermorium	117 Uus Ununseptium	(294) 118 Uuo Ununoctium



### notes

- as of yet, elements 113,115,117 and 118 have no official name designated by the IUPAC.
- 1 kJ/mol ≈ 96.485 eV.
- all elements are implied to have an oxidation state of zero.

138.9054 538.1 1.10 57 La Lanthanum [Xe] 5d <sup>1</sup> 6s <sup>2</sup>	140.116 584.4 1.12 58 Ce Cerium [Xe] 4f <sup>1</sup> 5d <sup>1</sup> 6s <sup>2</sup>	140.9076 527.0 1.13 59 Pr Praseodymium [Xe] 4f <sup>3</sup> 6s <sup>2</sup>	144.242 533.1 1.14 60 Nd Neodymium [Xe] 4f <sup>4</sup> 6s <sup>2</sup>	(145) 540.0 61 Pm Promethium [Xe] 4f <sup>5</sup> 6s <sup>2</sup>	150.36 544.5 1.17 62 Sm Samarium [Xe] 4f <sup>6</sup> 6s <sup>2</sup>	151.964 547.1 63 Eu Europium [Xe] 4f <sup>7</sup> 6s <sup>2</sup>	157.25 589.4 1.20 64 Gd Gadolinium [Xe] 4f <sup>7</sup> 5d <sup>1</sup> 6s <sup>2</sup>	158.9253 588.6 65 Tb Terbium [Xe] 4f <sup>9</sup> 6s <sup>2</sup>	162.500 579.0 1.22 66 Dy Dysprosium [Xe] 4f <sup>10</sup> 6s <sup>2</sup>	164.9303 581.0 1.23 67 Ho Holmium [Xe] 4f <sup>11</sup> 6s <sup>2</sup>	167.259 589.3 1.24 68 Er Erbium [Xe] 4f <sup>12</sup> 6s <sup>2</sup>	168.9342 589.7 1.25 69 Tm Thulium [Xe] 4f <sup>13</sup> 6s <sup>2</sup>	173.054 603.4 70 Yb Ytterbium [Xe] 4f <sup>14</sup> 6s <sup>2</sup>
(227) 489.0 1.10 89 Ac Actinium [Rn] 6d <sup>1</sup> 7s <sup>2</sup>	(232.0380 587.0 1.30 90 Th Thorium [Rn] 6d <sup>2</sup> 7s <sup>2</sup>	231.0358 563.0 1.50 91 Pa Protactinium [Rn] 5f <sup>2</sup> 6d <sup>1</sup> 7s <sup>2</sup>	238.0289 587.0 1.38 92 U Uranium [Rn] 5f <sup>3</sup> 6d <sup>1</sup> 7s <sup>2</sup>	(237) 604.5 1.36 93 Np Neptunium [Rn] 5f <sup>4</sup> 6d <sup>1</sup> 7s <sup>2</sup>	(244) 604.7 1.28 94 Pu Plutonium [Rn] 5f <sup>6</sup> 7s <sup>2</sup>	(243) 578.0 1.30 95 Am Americium [Rn] 5f <sup>7</sup> 7s <sup>2</sup>	(247) 581.0 1.30 96 Cm Curium [Rn] 5f <sup>7</sup> 6d <sup>1</sup> 7s <sup>2</sup>	(247) 601.0 1.30 97 Bk Berkelium [Rn] 5f <sup>9</sup> 7s <sup>2</sup>	(251) 608.0 1.30 98 Cf Californium [Rn] 5f <sup>10</sup> 7s <sup>2</sup>	(252) 618.0 1.30 99 Es Einsteinium [Rn] 5f <sup>11</sup> 6d <sup>1</sup> 7s <sup>2</sup>	(257) 627.0 1.30 100 Fm Fermium [Rn] 5f <sup>12</sup> 7s <sup>2</sup>	(258) 635.0 1.30 101 Md Mendelevium [Rn] 5f <sup>13</sup> 7s <sup>2</sup>	(259) 642.0 1.30 102 No Nobelium [Rn] 5f <sup>14</sup> 7s <sup>2</sup>