



UFOP

Universidade Federal
de Ouro Preto

Universidade Federal de Ouro Preto
Instituto de Ciências Exatas e Biológicas
Departamento de Química

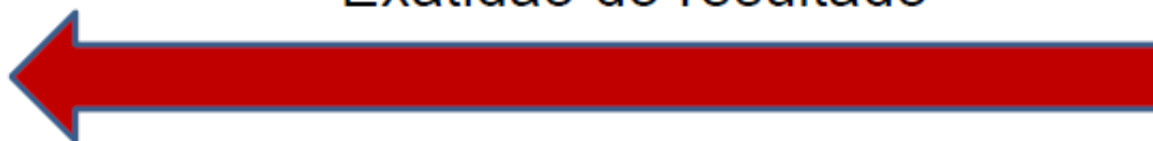


Métodos de Química Computacional

Professora: Melissa Soares Caetano

Mecânica Molecular

Exatidão do resultado



Primeiros princípios

Tentam se aproximar
da equação de
Schrodinger

Semi empíricos

Método que usa
aproximações
empíricas

Mecânica Molecular

Método puramente
empírico, não trata
os elétrons



Número de átomos do sistema

Mecânica Molecular

**Refere-se ao uso da mecânica Newtoniana
para modelar sistemas**

**Trata a molécula como um conjunto de esferas
ligadas por molas**



Vantagens:

- 1) Investiga grandes sistemas que são impossíveis por MQ;
- 2) Fácil entender

Desvantagens:

- 1) Pode ser difícil definir os potenciais de interação;
- 2) Nenhuma informação sobre as propriedades eletrônicas



Energia total

$$E = \underbrace{E_{\text{lig}} + E_{\text{ang}} + E_{\text{torsão}}}_{\text{Termos ligados}} + \underbrace{E_{\text{vanderwaals}} + E_{\text{eletrostática}}}_{\text{Termos não ligados}}$$

Diagram illustrating the components of total energy (E) in a molecular system, categorized into bonded terms (Termos ligados) and non-bonded terms (Termos não ligados).

Termos ligados (Bonded Terms):

- E_{lig} : Bond energy, represented by a diagram of two atoms connected by a single bond.
- E_{ang} : Angle energy, represented by a diagram of three atoms forming a bent angle.
- $E_{\text{torsão}}$: Torsion energy, represented by a diagram of four atoms in a chain showing a torsional angle around a central bond.

Termos não ligados (Non-bonded Terms):

- $E_{\text{vanderwaals}}$: van der Waals energy, represented by a diagram of several atoms with dashed lines indicating weak attractive forces.
- $E_{\text{eletrostática}}$: Electrostatic energy, represented by a diagram of several atoms with arrows indicating strong attractive or repulsive forces between charged groups.

Mecânica Molecular

Cálculo da energia molecular depende da existência de parâmetros no campo de força

$$E = E_{\text{ESTIRAMENTO}} + E_{\text{DEFORMAÇÃO}} \\ + E_{\text{TORSIONAL}} + E_{\text{NÃO-LIGADA}}$$

"CAMPO DE FORÇA"

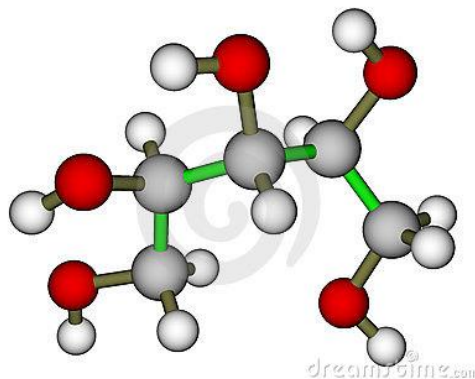
**SOMATÓRIO DE TERMOS INDIVIDUAIS
DE ENERGIA POTENCIAL**



E = ENERGIA CONFORMACIONAL

Modelagem molecular

Uso de diferentes teorias e programas de computador



Criar modelos de estrutura molecular e prever propriedades = energia

Docking - Planejamento Racional de novos fármacos

Até década de 80, novos compostos bioativos eram descobertos por testes aleatórios sem conhecimento de interação da molécula ligante



Mecanismo de reconhecimento molecular receptor-ligante = aspecto central para descoberta e planejamento de novos compostos!

Uso de metodologias computacionais motivado :

- 1) Redução do tempo;
- 2) Custos menores.

Indústrias Farmacêuticas



Docking ➡ **Universidades**



Empresas de biotecnologia



- Depósito de 10 patentes
- 6 capítulos de livro e 2 livros
- Teses e dissertações ultrapassando a marca de centenas

Docking = Ancoramento Molecular

- ➡ predição do modo de ligação de uma molécula ligante na região de ligação de um alvo molecular
- ➡ quantificação da afinidade de ligação receptor-ligante

Alvo molecular
Ou Receptor

Região de ligação
ou Sítio ativo



Ligante

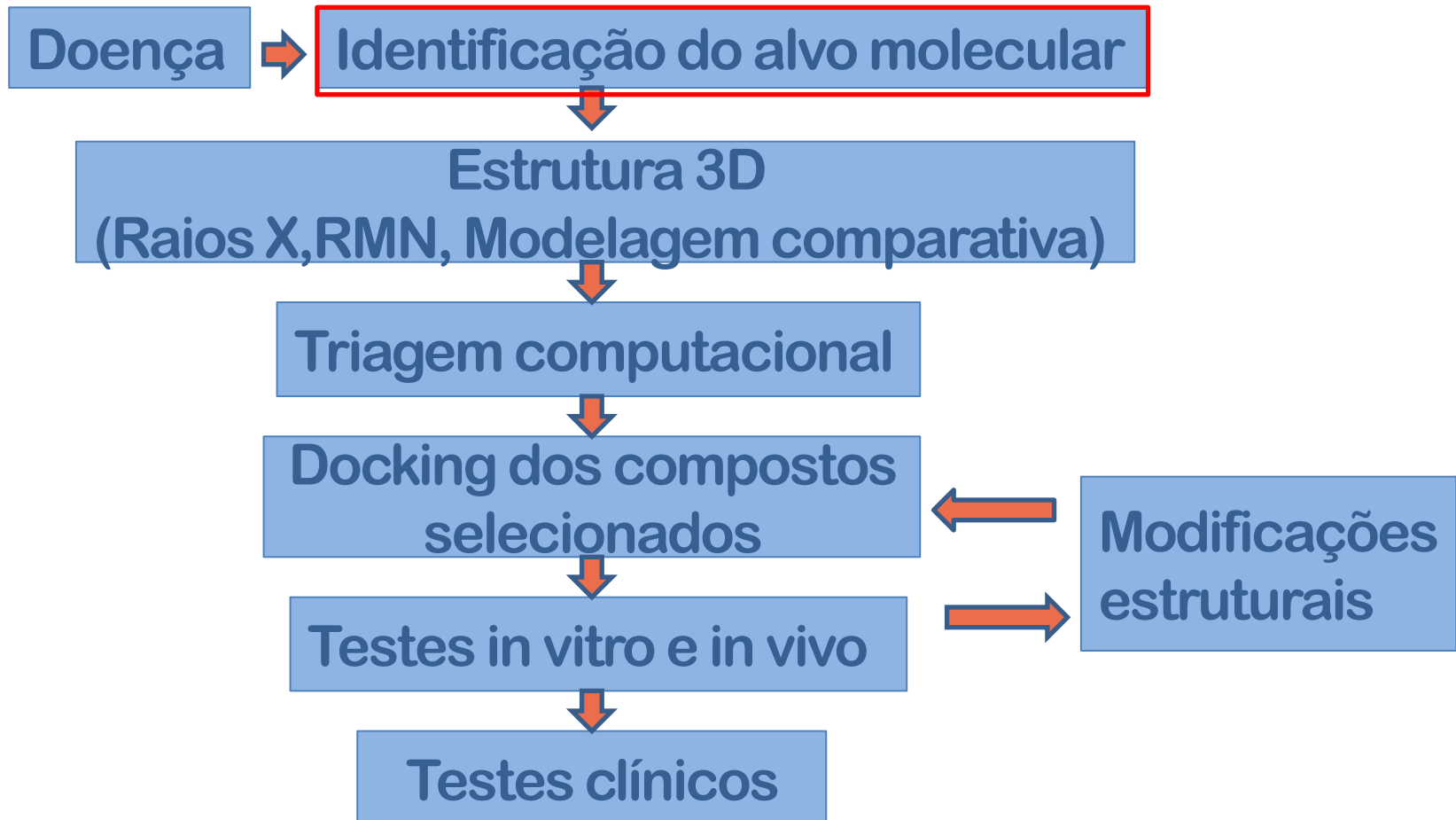
Tipos de ligantes



- ✓ Agonista natural = Chave original
- ✓ Agonista modificado = Chave modificada
- ✓ Antagonista = Chave falsa
 - ➔ Apesar de ter acesso não abre a porta

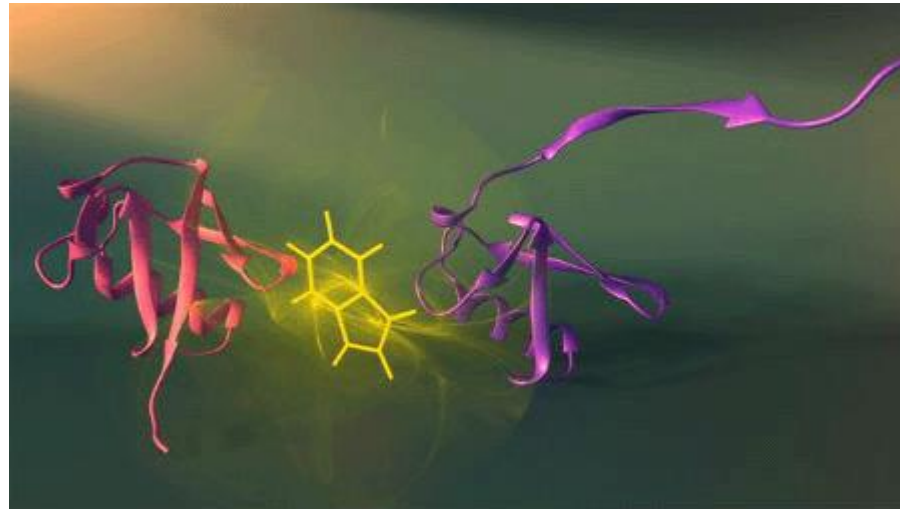
Tanto “chave” quanto “fechadura” são flexíveis

Etapas do desenho racional de novos compostos usando docking



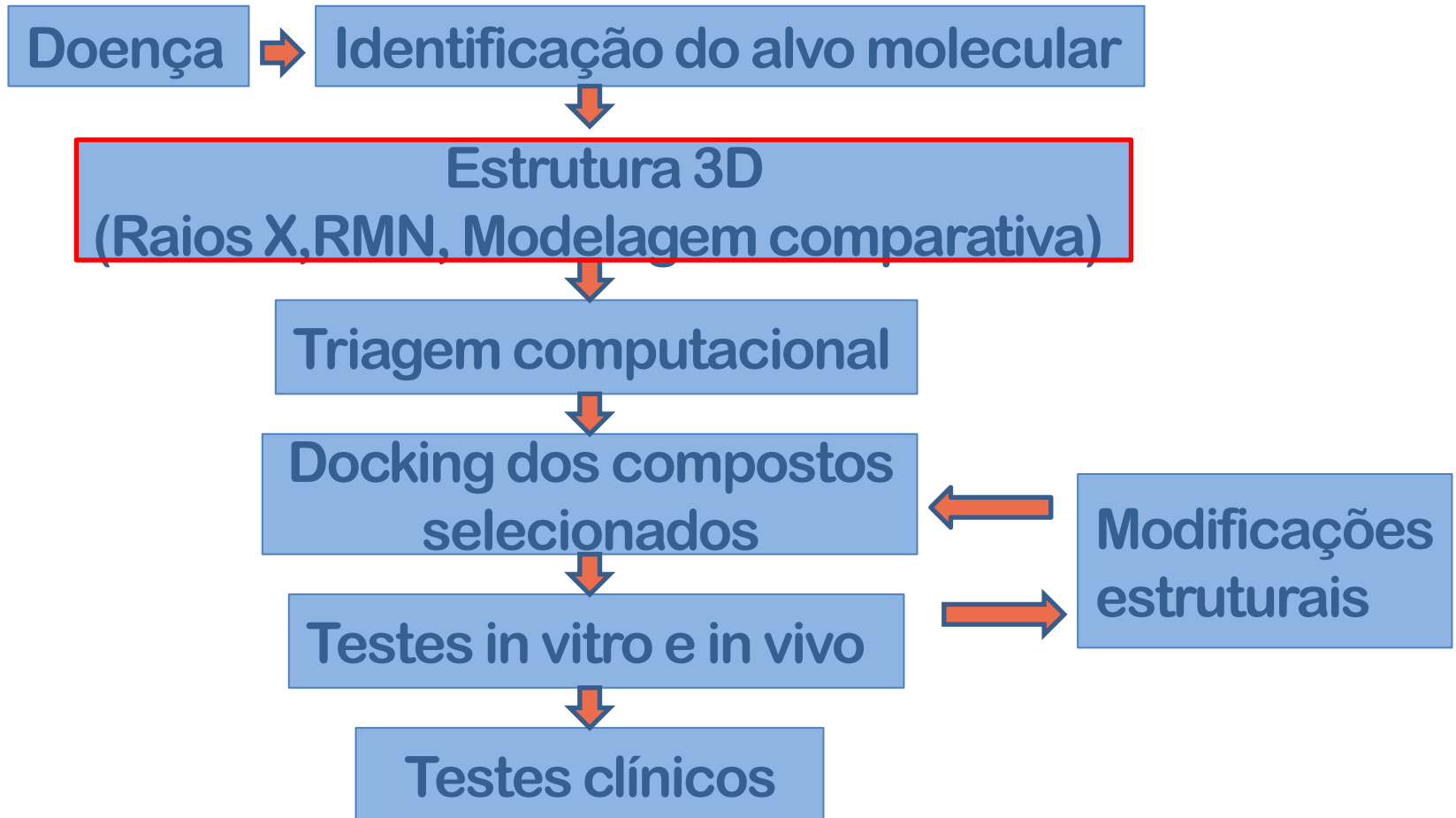
Identificação do alvo molecular

Proteína relacionada a doença para qual se deseja tratamento



Função pode ser ativada ou bloqueada

Etapas do desenho racional de novos compostos



Estrutura 3D

Bancos de acesso público



PROTEIN DATA BANK

MyPDB Login

A MEMBER OF THE  PDB

An Information Portal to Biological Macromolecular Structures

As of Tuesday Feb 09, 2010 at 4 PM PST there are 63271 Structures  | PDB Statistics 

WHAT'S NEW | HELP | PRINT

PDB ID or keyword

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Deposition

All Deposit Services

Electron Microscopy

NMR

Validation Server

BioSync Beamline

Related Tools

Search

Advanced Search

Latest Release

Latest Publications

Sequence Search

Ligand Search

Unreleased Entries

Browse Database

Histograms

Tools

File Downloads

FTP Services

File Formats

Services: RESTful | SOAP

Widgets

Compare Structures

Education

Looking at Structures

Molecule of the Month

Educational Resources

A Resource for Studying Biological Macromolecules

The PDB archive contains information about experimentally-determined structures of proteins, nucleic acids, and complex assemblies. As a member of the [wwPDB](#), the RCSB PDB curates and annotates PDB data according to agreed upon standards.

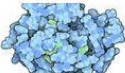
The RCSB PDB also provides a variety of tools and resources. Users can perform simple and advanced searches based on annotations relating to sequence, structure and function. These molecules are visualized, downloaded, and analyzed by users who range from students to specialized scientists.

Molecule of the Month: Enhanceosome



Take a moment to ponder the form of your body: the shape of your face, the color of your eyes, the length of your fingers, the perfect articulation of your bones and muscles, the way your hair grows curly or straight. Now let your imagination travel inward, and think of the complex shapes and functions of your different cells, and the teeming molecular world inside each one. Remarkably, this amazing structure and form and function is specified by information in the genome, which encodes a mere 20,000-25,000 protein-coding genes. One of the great puzzles being pieced together by scientists is the mechanism by which these genes, and the methods used to control their expression, specify all of these different aspects of life. [Read more ...](#) [Previous Features](#)

PSI Featured Molecule: Sugarcoating the surface: yeast Alg13



Many proteins in our cells are decorated with carbohydrate chains, which make the proteins more stable and assist with their function. Using NMR, PSI researchers now understand how this enzyme builds these essential carbohydrates. [Read more from the Structural Genomics Knowledgebase](#) [Previous Features](#)

New user? Try the browser [compatibility check](#) and information on [Getting Started](#).

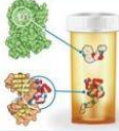
News

- Complete News
- Newsletter
- Discussion Forum
- Job Listings

wwPDB Statement on Retraction of PDB Entries

09-February-2010

Poster Download: How Do Drugs Work?



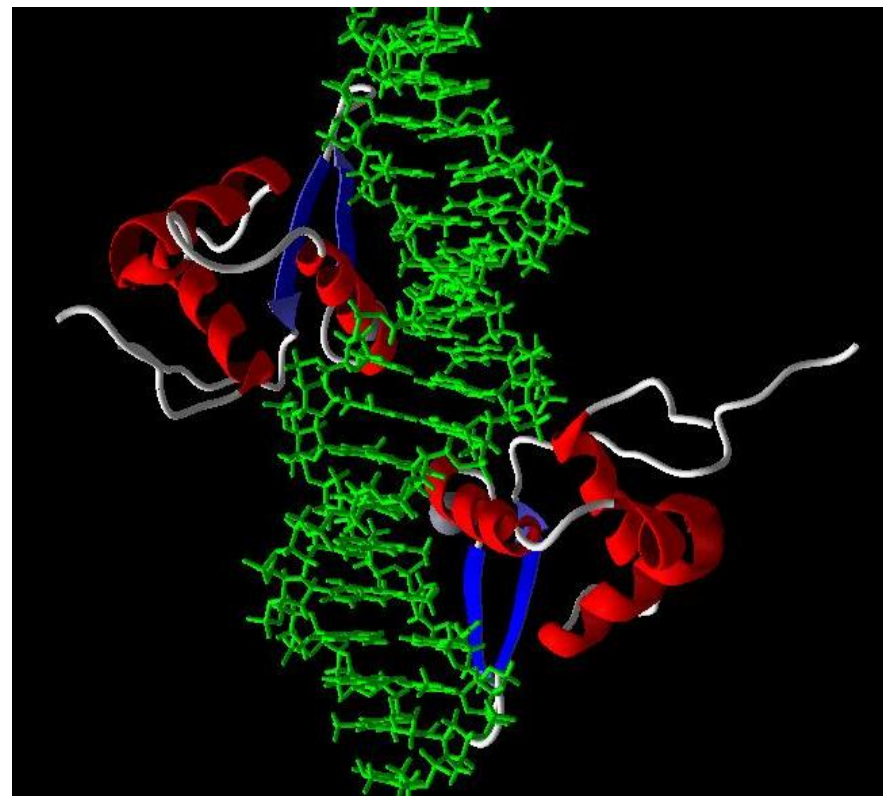
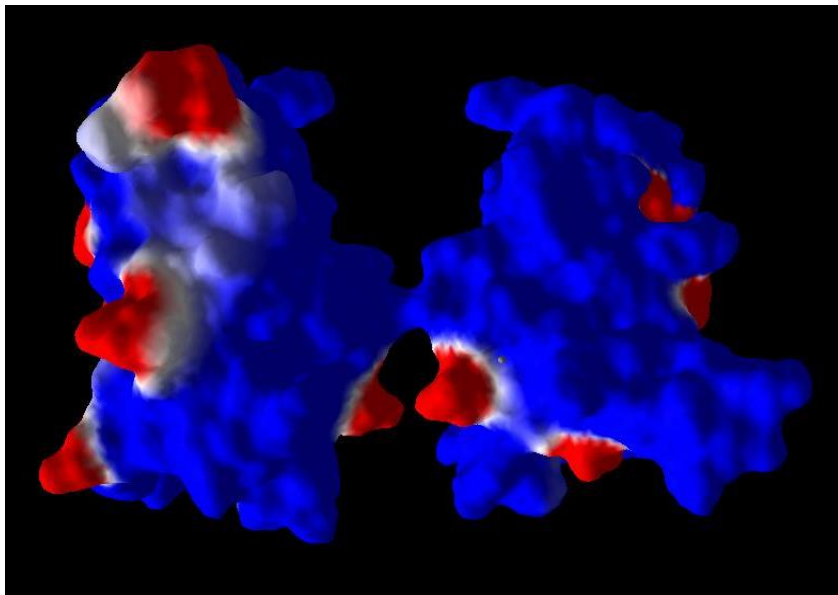
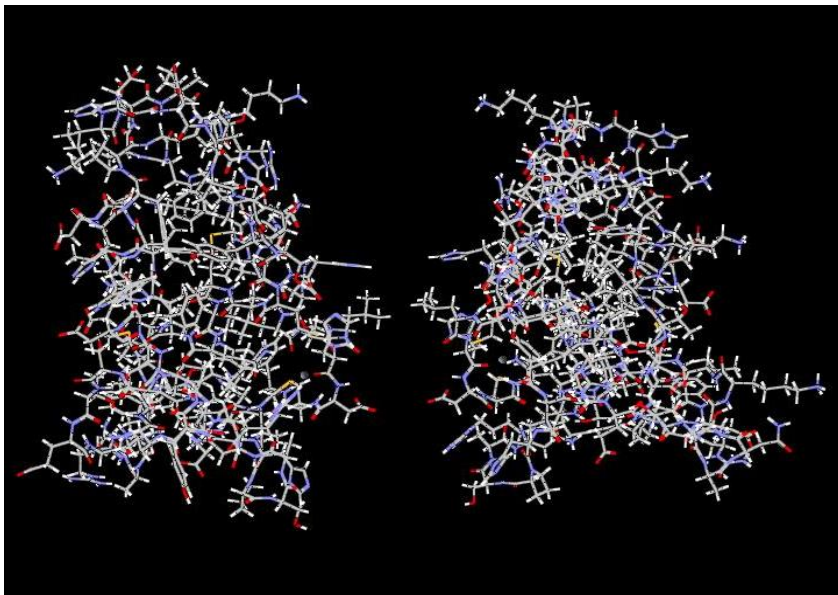
A new poster that explores different kinds of protein-drug structures found in the PDB archive is available for download. [More >>](#)

FTP Archive

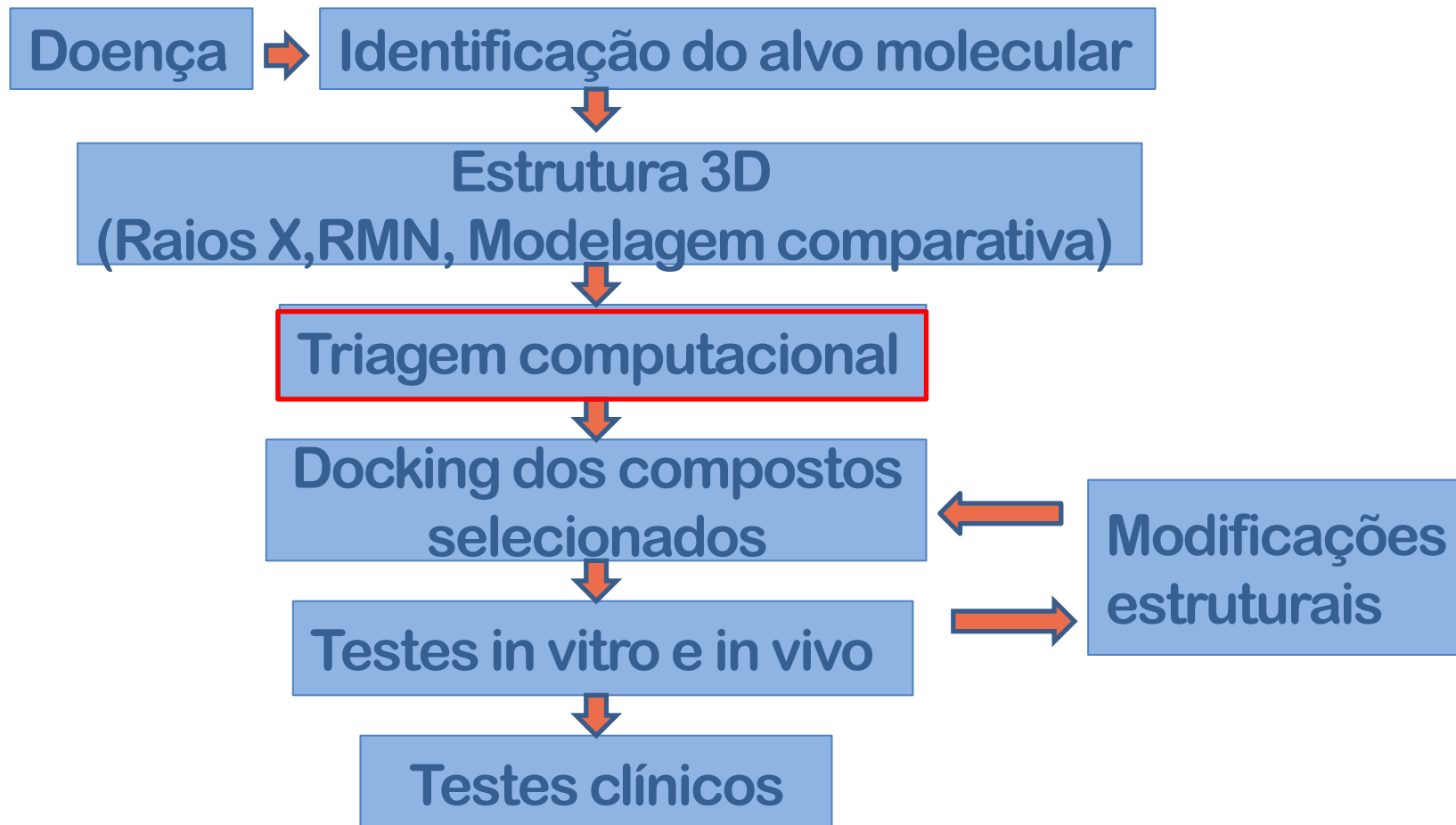
The up-to-date PDB archive is available at: <ftp://ftp.wwpdb.org>

Time-stamped yearly snapshots are available at: <ftp://snapshots.wwpdb.org>

Visualização do alvo molecular



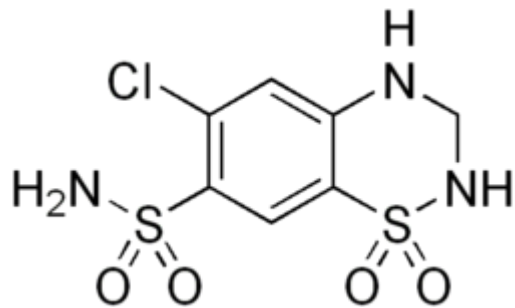
Etapas do desenho racional de novos compostos



Triagem computacional

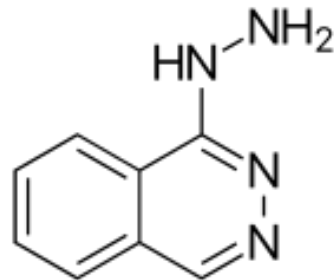
Possíveis tratamentos anti-hipertensivos

Diuréticos



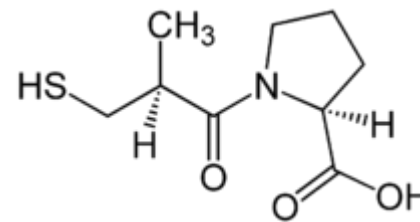
Tiazidas

Vasodilatadores

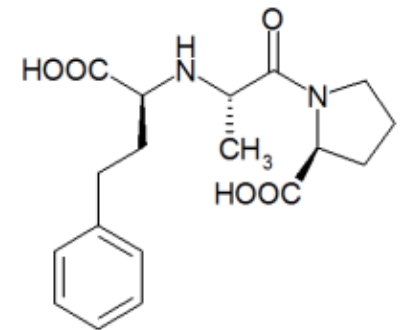


Hidralazina

Inibidores da enzima conversora de angiotensina

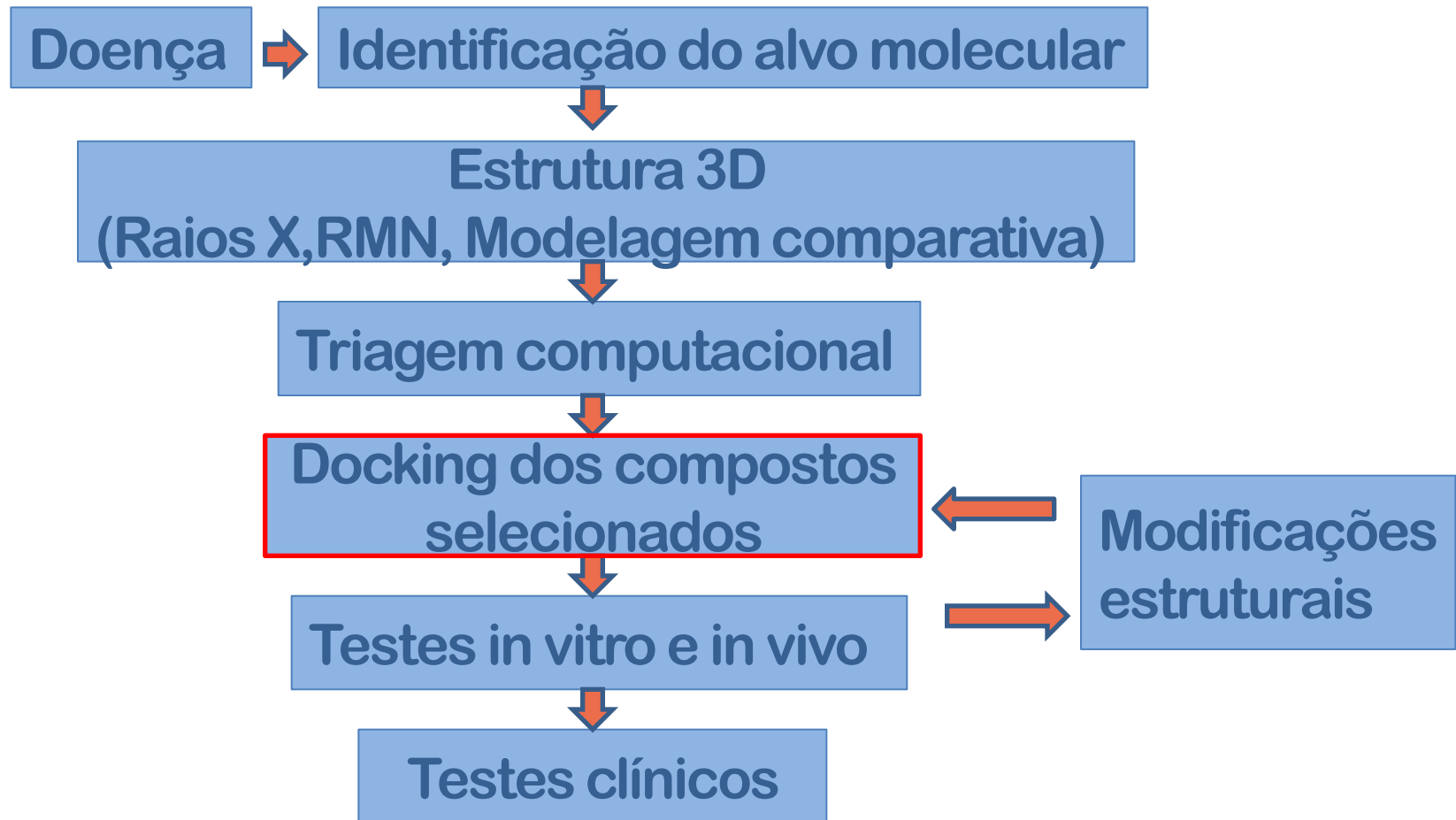


Captopril



Enalapril

Etapas do desenho racional de novos compostos



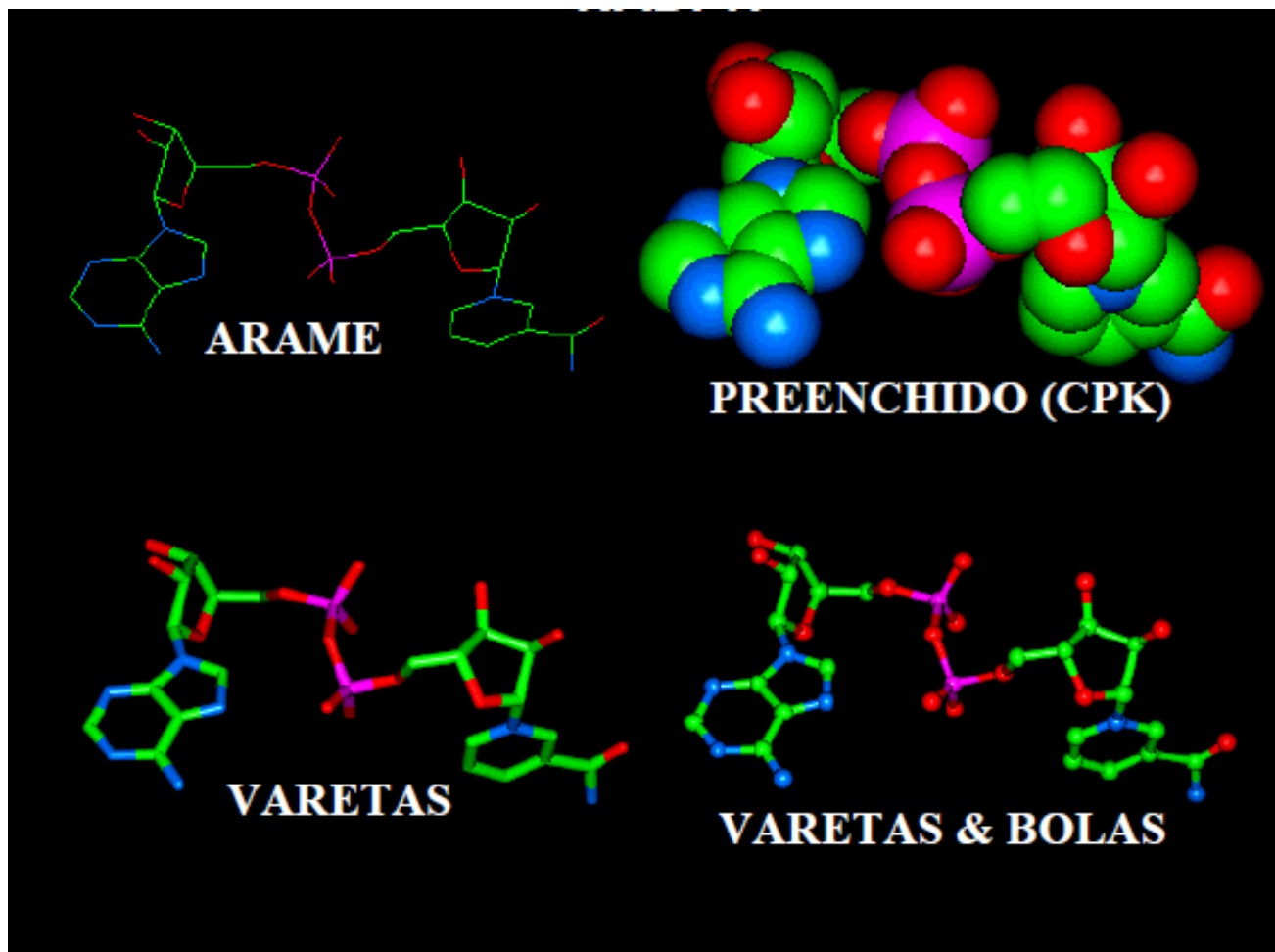
Docking

Identificar :

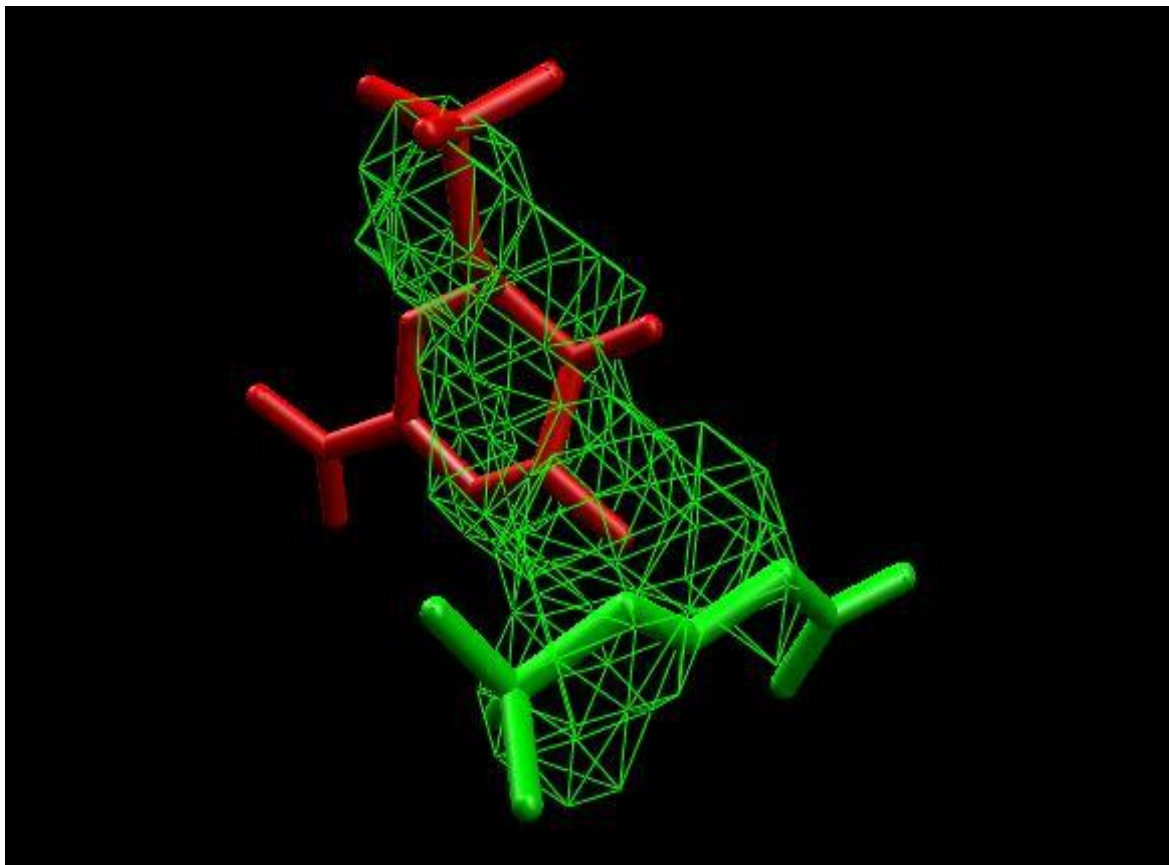
- 1) conformação do ligante
- 2) afinidade de ligação receptor-ligante



Visualização do ligante



Sítio de ligação do ligante

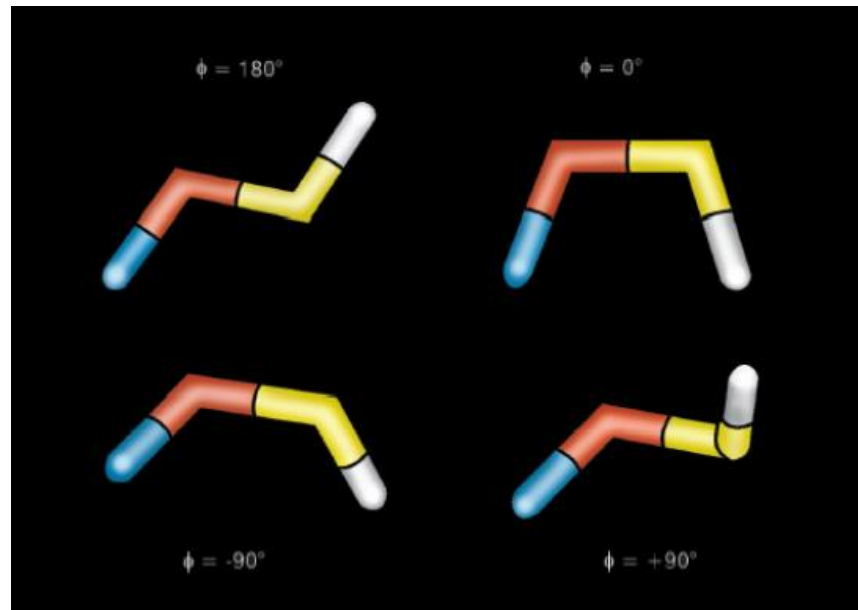


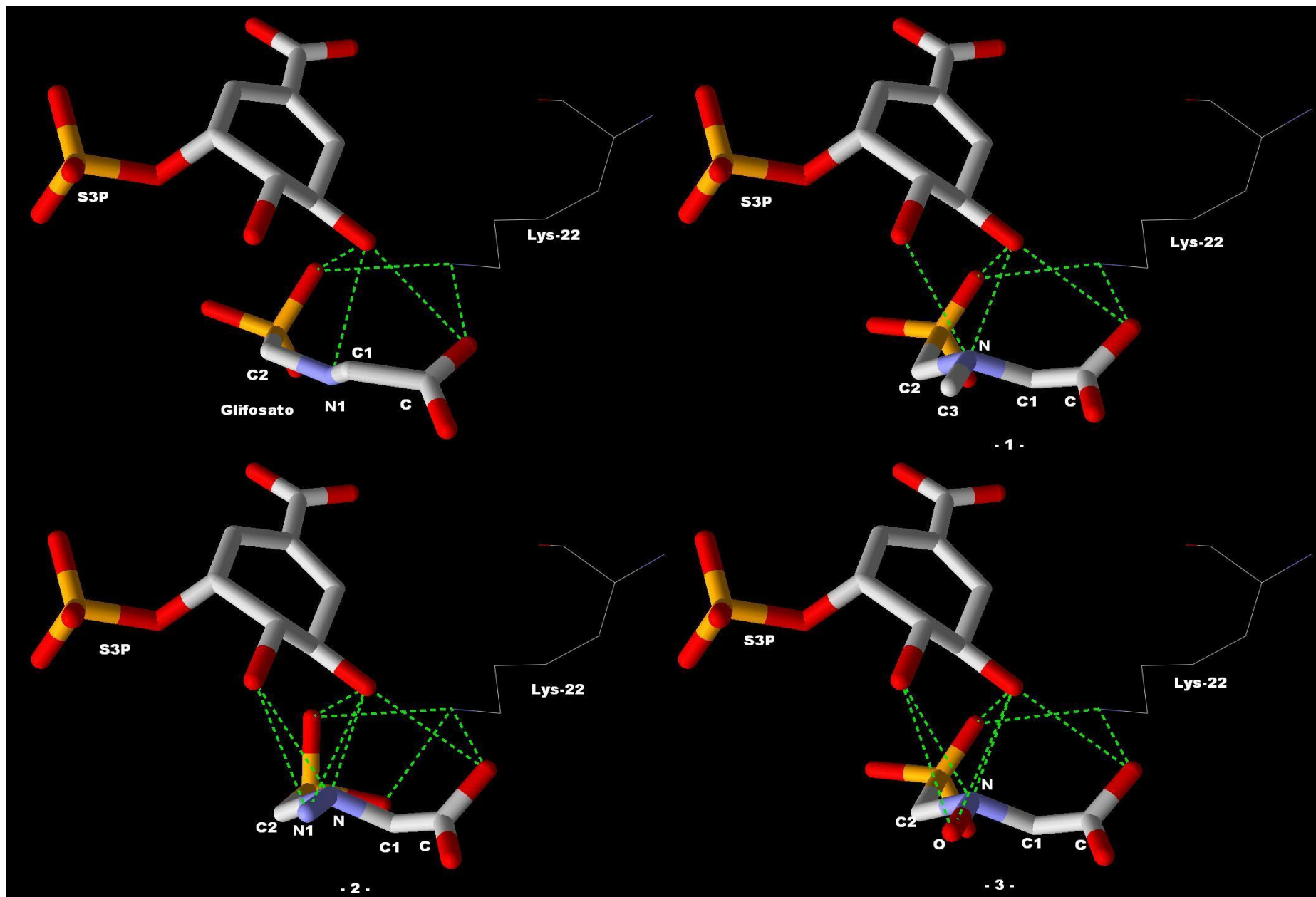
Análise conformacional

Nem sempre molécula desenhada inicialmente estará em sua conformação de menor energia

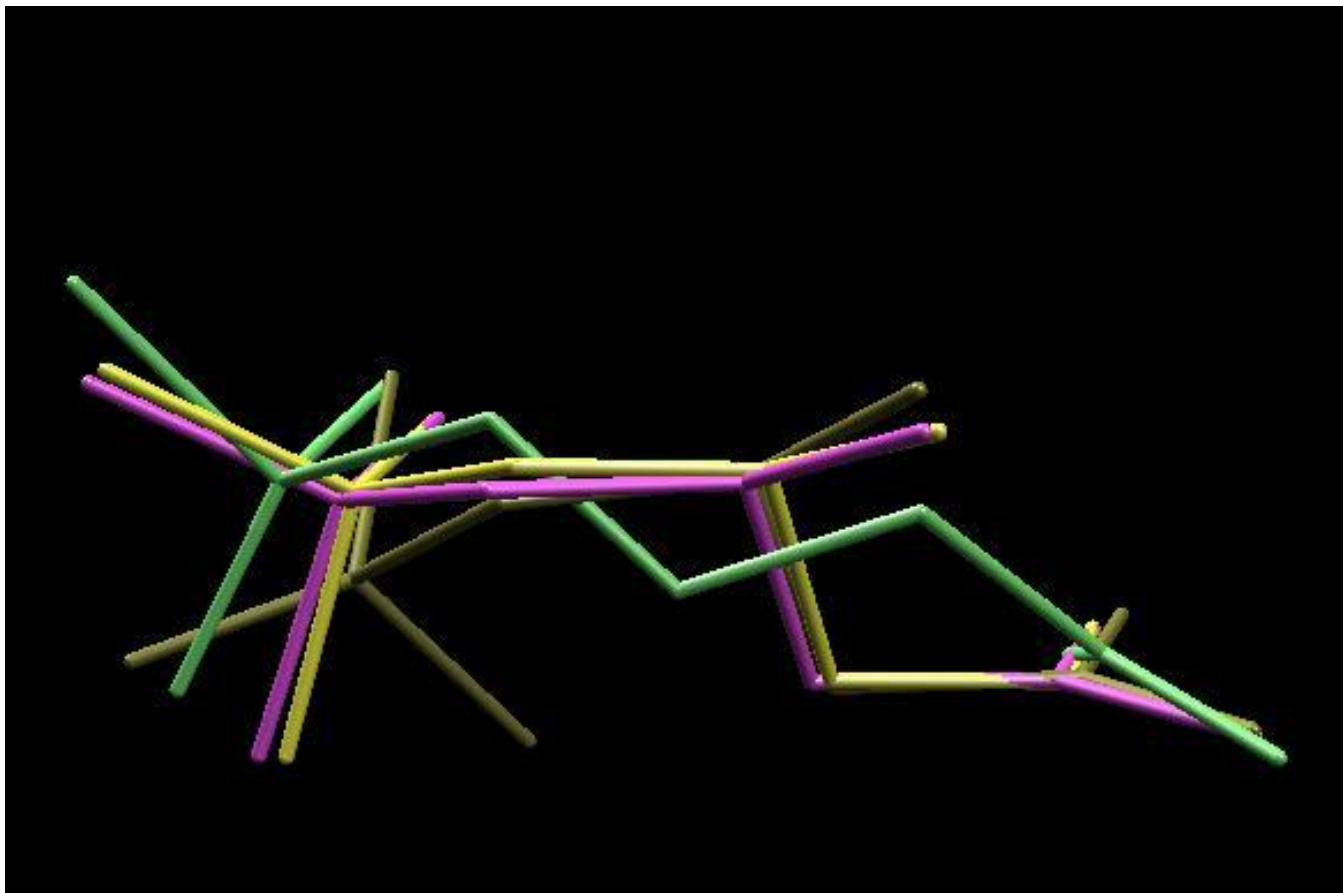


Pesquisa necessária para encontrar conformação bioativa

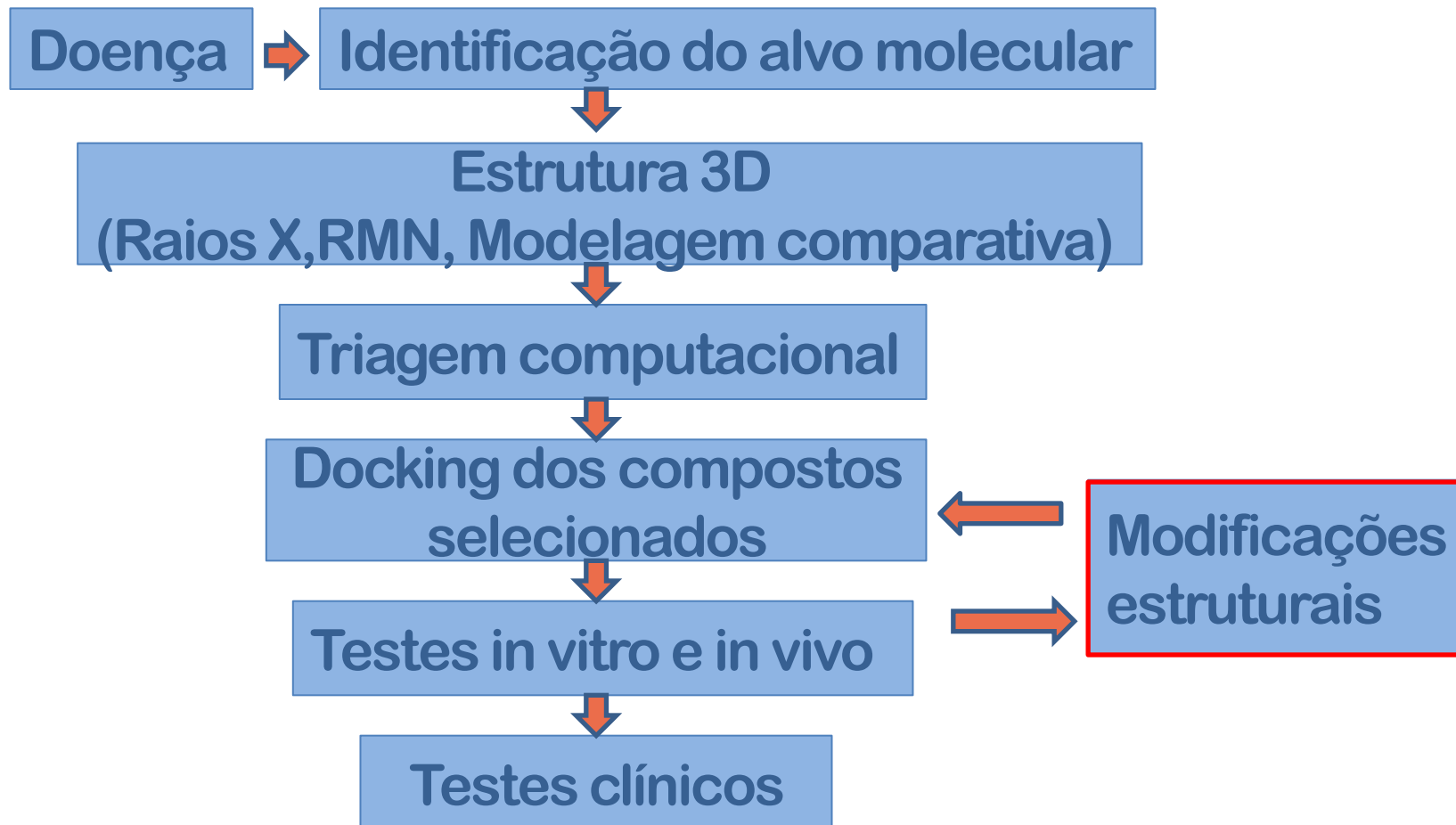




Diferença conformacional

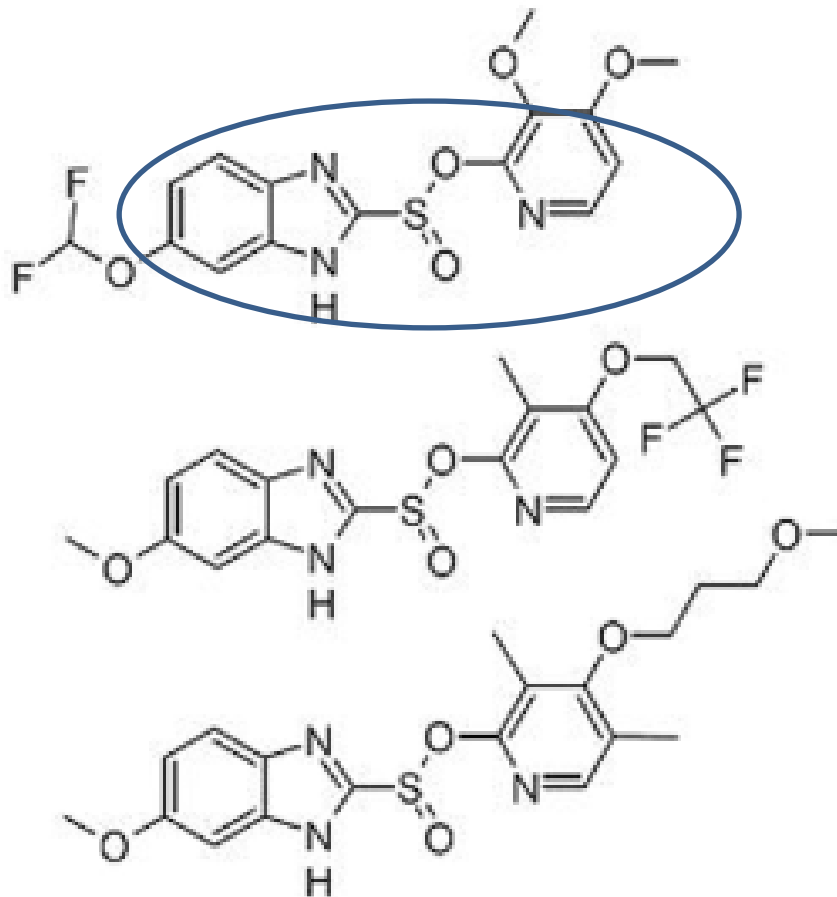


Etapas do desenho racional de novos compostos

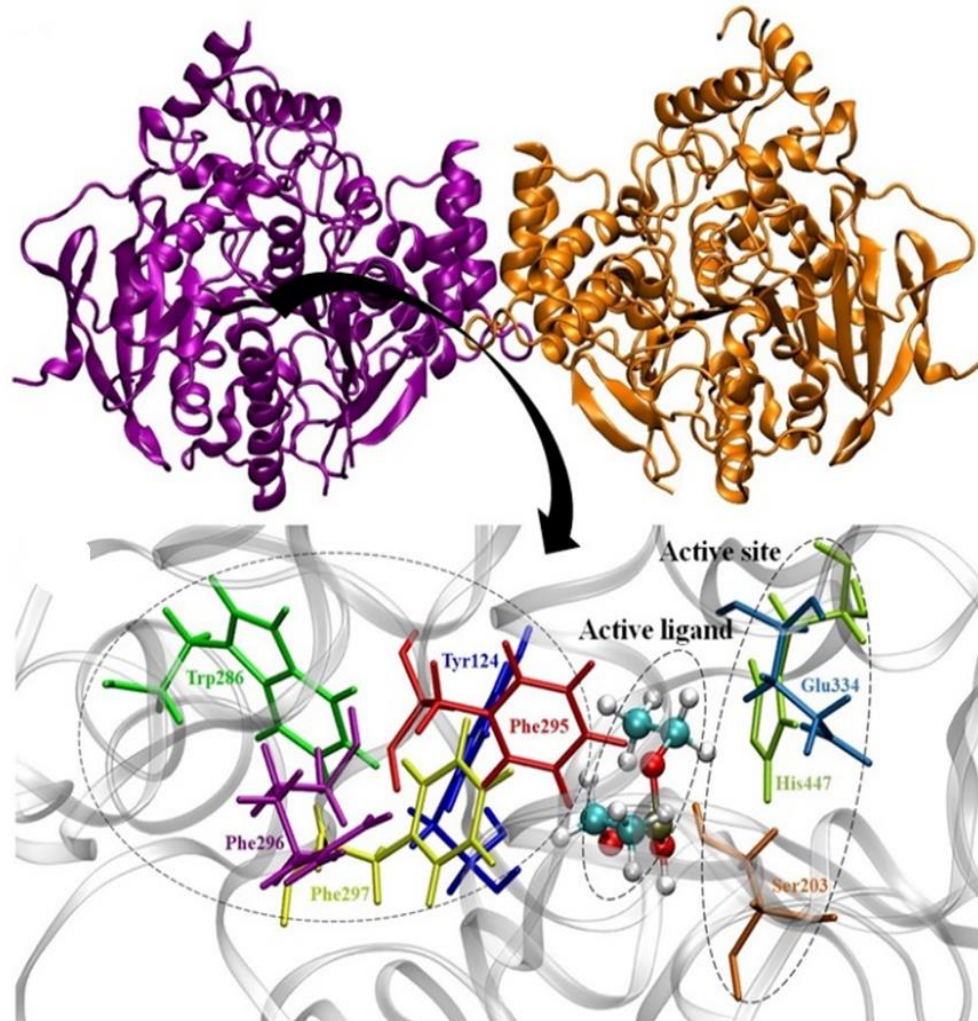


Modificações estruturais

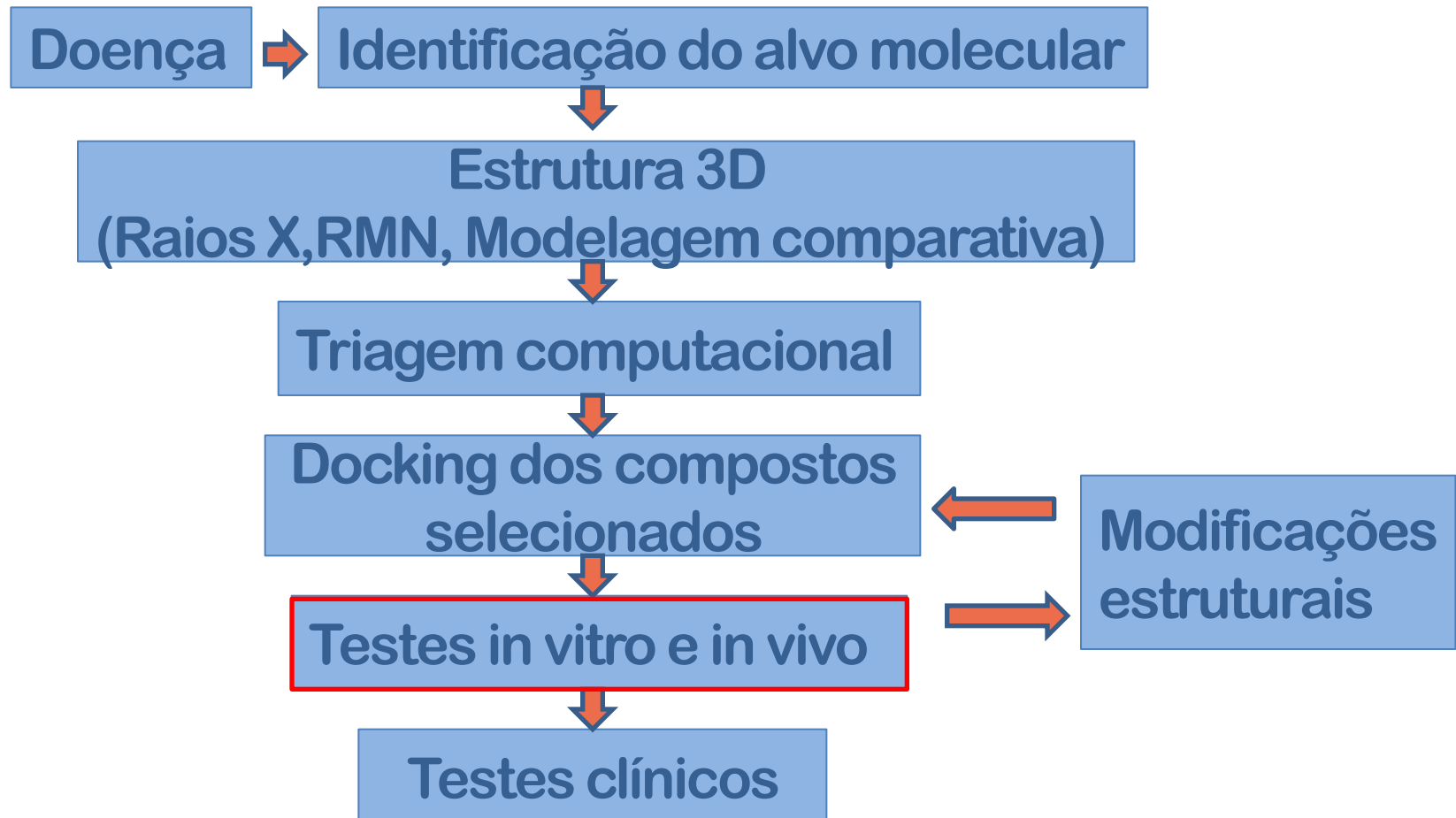
Identificação de grupos farmacofóricos



Interação fármaco-receptor



Etapas do desenho racional de novos compostos



Testes *in vitro* e *in vivo*

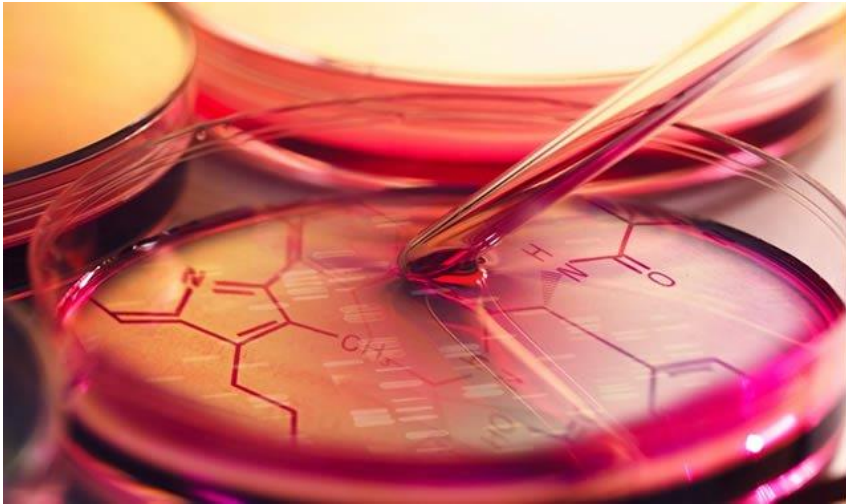


Foto Divulgação



Etapas do desenho racional de novos compostos

