MD Simulations – day 2
Part 2b - docking

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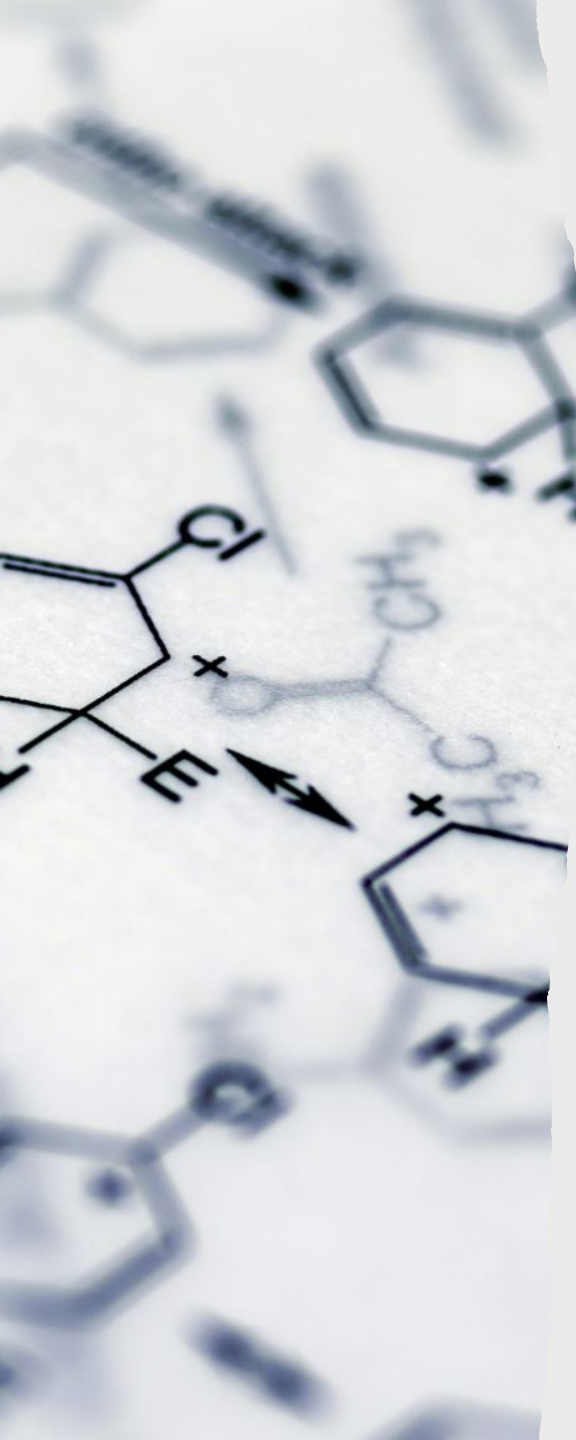www.giorginolab.it

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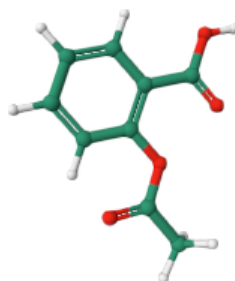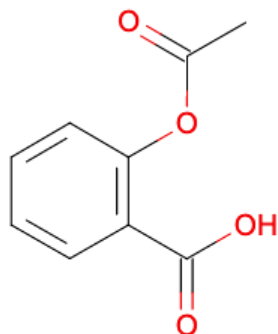for Prof. Fuxreiter's course @ University of Padova

May 2024

https://github.com/giorginolab/MD-Tutorial-Data

PTGS1* and **PTGS2** are the targets of nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin and ibuprofen.

Aspirin is able to produce an irreversible inactivation of the enzyme through a serine acetylation.

Inhibition of the PGHSs with NSAIDs acutely reduces inflammation, pain, and fever, and long-term use of these drugs reduces fatal thrombotic events, as well as the development of colon cancer and Alzheimer's disease.

PTGS2 is the principal isozyme responsible for production of inflammatory prostaglandins. New generation PTGSs inhibitors strive to be selective for PTGS2, to avoid side effects such as gastrointestinal complications and ulceration.

* COX1 = Prostaglandin G/H synthase 1
    = PGH1_HUMAN = P23219

Display Files ▾   Download Files ▾   ⚙ Data API

AIN

2-(ACETYLOXY)BENZOIC ACID

Find entries where: AIN

☑ is present as a standalone ligand in 8 entries

search

Find related ligands:

Similar Ligands (Stereospecific)
Similar Ligands (including Stereoisomers)
Similar Ligands (Quick Screen)
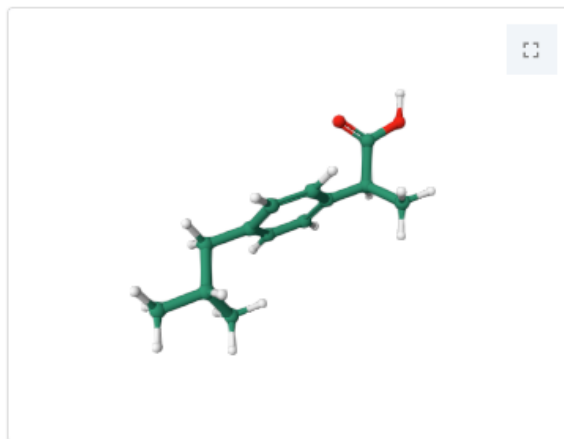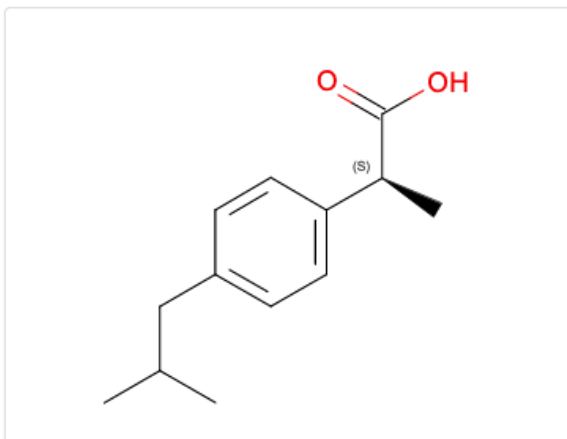Similar Ligands (Substructure Stereospecific)
Similar Ligands (Substructure including Stereoisomers)

Chemical Component Summary

Name	2-(ACETYLOXY)BENZOIC ACID
Synonyms	ACETYLSALICYLIC ACID; ASPIRIN
Identifiers	2-acetyloxybenzoic acid
Formula	$C_9 H_8 O_4$
Molecular Weight	180.157
Type	NON-POLYMER
Isomeric SMILES	CC(=O)Oc1ccccc1C(=O)O
InChI	InChI=1S/C9H8O4/c1-6(10)13-8-5-3-2-4-7(8)9(11)12/h2-5H,1H3,(H,11,12)
InChIKey	BSYNRYMUTXBXSQ-UHFFFAOYSA-N

Chemical Details

Formal Charge	0
Atom Count	21
Chiral Atom Count	0
Bond Count	21
Aromatic Bond Count	6

Toggle Hydrogen   Toggle Labels

Display Files ▾   ⊕ Download Files ▾   ⚙ Data API

IBP

IBUPROFEN

Find entries where: IBP

☑ is present as a standalone ligand in 14 entries

search

Find related ligands:

Similar Ligands (Stereospecific)
Similar Ligands (including Stereoisomers)
Similar Ligands (Quick Screen)
Similar Ligands (Substructure Stereospecific)
Similar Ligands (Substructure including Stereoisomers)

Chemical Component Summary

| Name	IBUPROFEN
Synonyms	2-(4-ISOBUTYLPHENYL)PROPIONIC ACID
Identifiers	(2S)-2-[4-(2-methylpropyl)phenyl]propanoic acid
Formula	$C_{13} H_{18} O_2$
Molecular Weight	206.281
Type	NON-POLYMER
Isomeric SMILES	CC(C)Cc1ccc(cc1)[C@H](C)C(=O)O
InChI	InChI=1S/C13H18O2/ c1-9(2)8-11-4-6-12(7-5-11)10(3)13(14)15/h4-7,9-10H, 8H2,1-3H3,(H,14,15)/t10-/m0/s1

Chemical Details

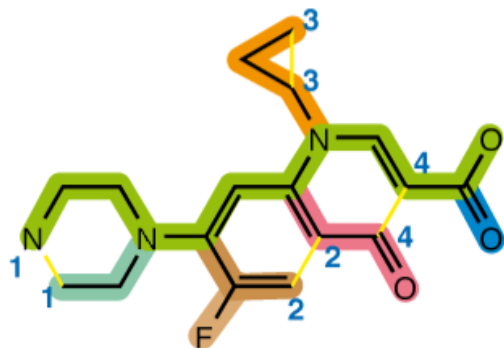| Formal Charge	0
Atom Count	33
Chiral Atom Count	1
Bond Count	33
Aromatic Bond Count	6

A
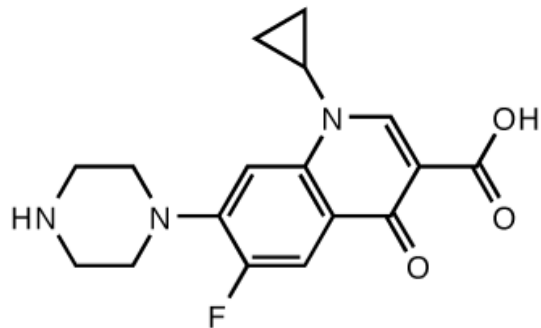
B
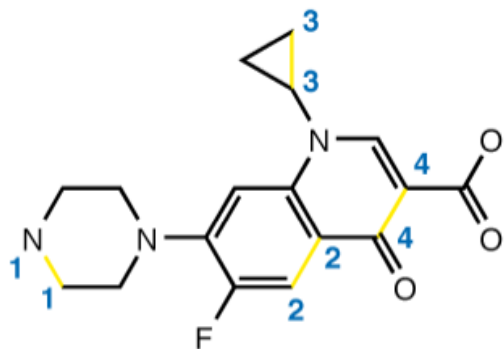
C

D

N1CCN(CC1)C(C(F)=C2)=CC(=C2C4=O)N(C3CC3)C=C4C(=O)O

- SMILES is a "1D" representation of the molecular graph.

- However, it **can** encode stereochemistry and cis/trans isomerism.

- It does **not** encode precise 2D or 3D coordinates, which must be generated.

- It is very compact and often molecular databases are distributed as such.

General principle

- Search a $\mathbb{R}^3 \times \mathbb{R}^3 \times \mathbb{R}^m$ space to max. score

translations

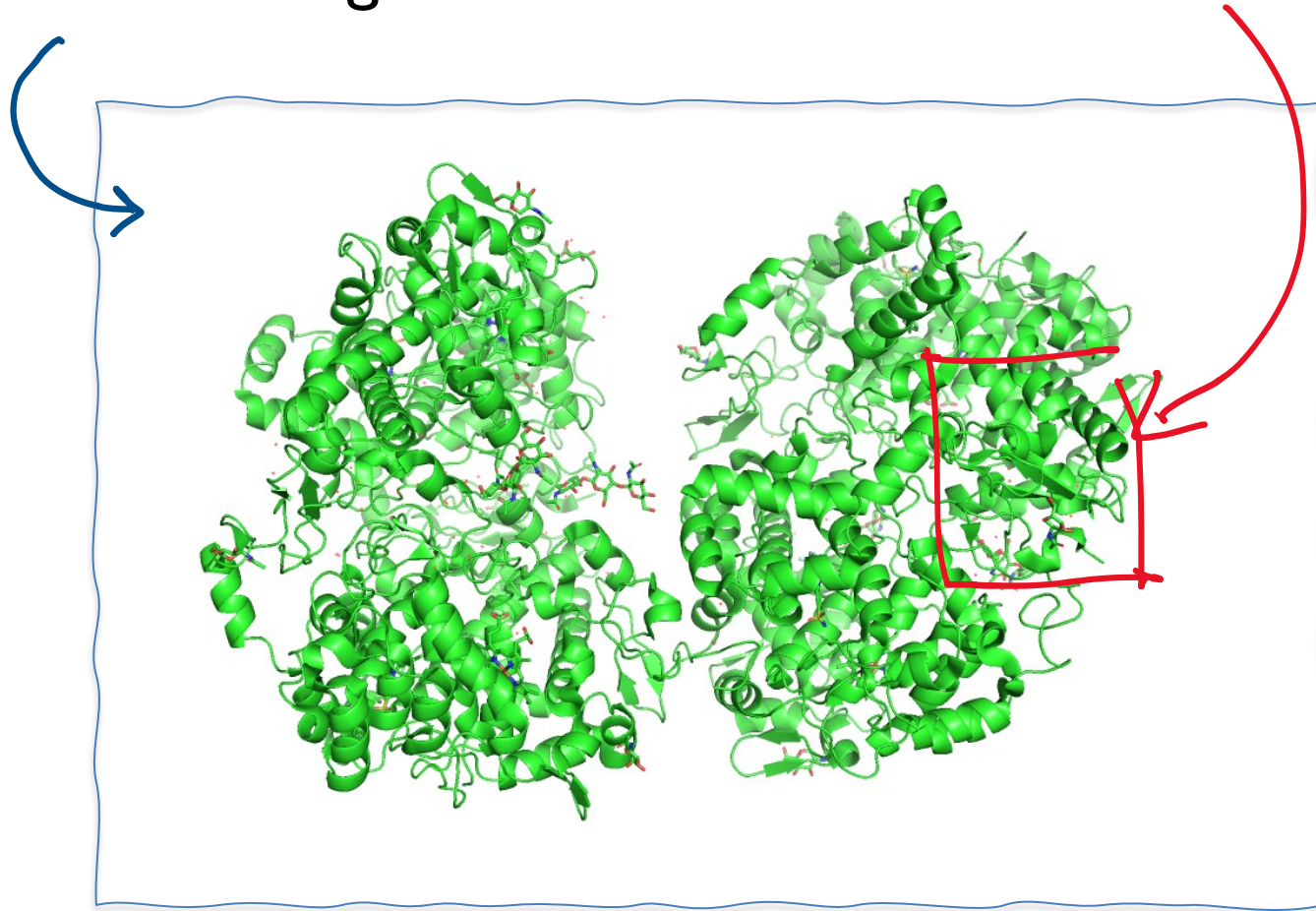rigid rotations

torsions
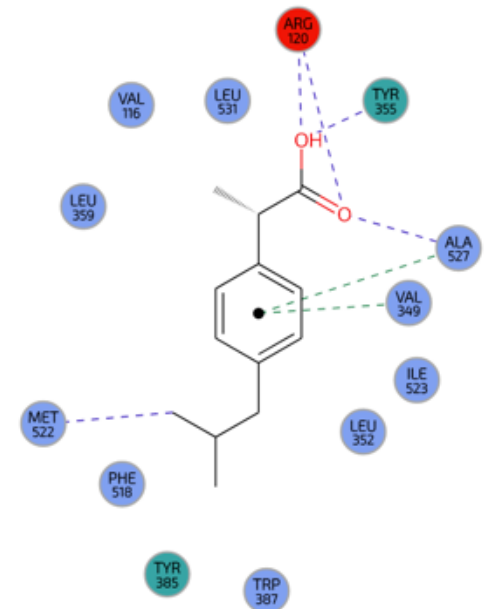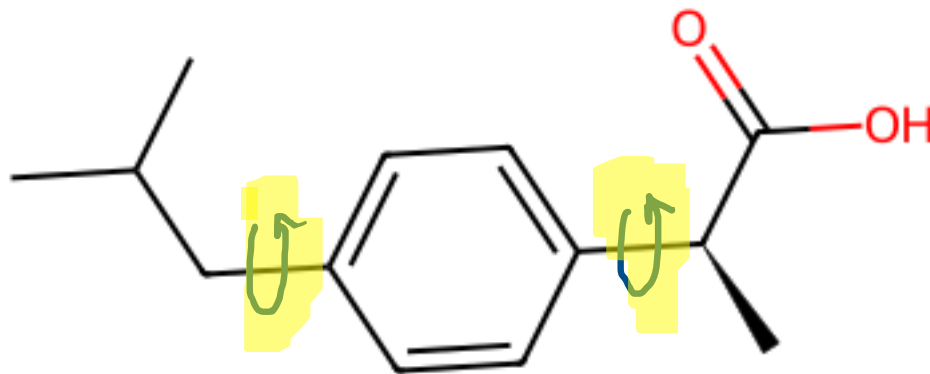
Docking types

- Blind docking

- Known-site

Pitfalls

- Protonation states

- Stereoisomerism

- Redocking optimism

- Receptor flexibility

- Receptor protonation states

- Thoroughness of the search

- Non-determinism

Advanced topics

- ML-based docking: diffusion models
  - DiffDock [1]
- Combine MD with docking
  - Ensemble docking [2]
- Enumeration of states
  - gypsum_dl [3]

<> **Code**   ⊙ Issues   ⑂ Pull requests   ⊙ Actions   ⊞ Projects   ⊡ Wiki   ⊘ **Security**   ⤢

⊡ **Files**

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> 📁 amber-build-run-with-ligand

∨ 📁 docking

     📄 Docking_2024.ipynb

> 📁 etc

2024-MolSim-UniPD / **docking** /   ⧉

🧑 **tonigi** Creato con Colab

Name
📁 ..
📄 Docking_2024.ipynb

References

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- Bender BJ, Gahbauer S, Luttens A, Lyu J, Webb CM, Stein RM, et al. A practical guide to large-scale docking. Nat Protoc. 2021 Sep 24;1–34.
- Basciu A, Malloci G, Pietrucci F, Bonvin AMJJ, Vargiu AV. Holo-like and Druggable Protein Conformations from Enhanced Sampling of Binding Pocket Volume and Shape. J Chem Inf Model. 2019 Apr 22;59(4):1515–28.
- McNutt AT, Francoeur P, Aggarwal R, Masuda T, Meli R, Ragoza M, et al. GNINA 1.0: molecular docking with deep learning. Journal of Cheminformatics. 2021 Jun 9;13(1):43.

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