

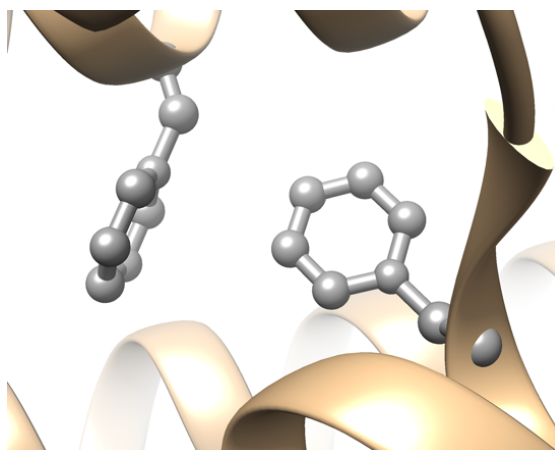
# Computer-Aided Drug Design

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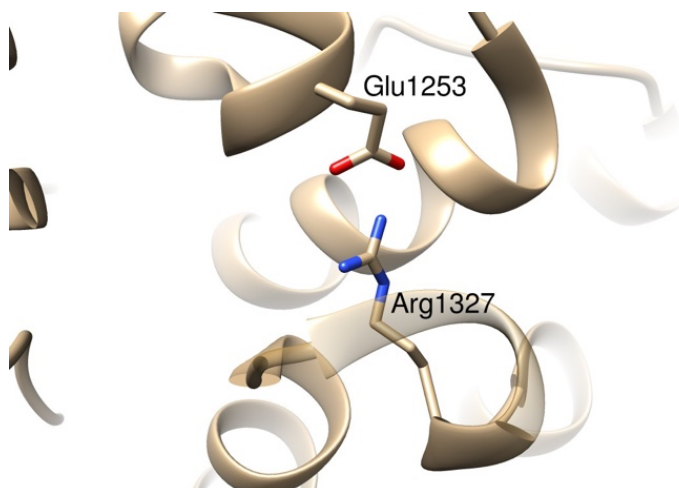
Your name:

Choose one answer or statement that matches best each of the 12 questions.  
There is no penalty for bad answers.



1. In the above structure, the side chains of the two amino acids displayed in ball-and-stick representation are making:

- a. a hydrogen bond
- b. a T-shaped  $\pi$ -stacking aromatic interaction
- c. an ionic interaction
- d. a disulfide bridge



2. In the structure displayed above the arginine (Arg1237) and glutamate (a.k.a. glutamic acid; Glu1253) residues are making:

- a. an aromatic interaction
- b. an ionic interaction (a.k.a. salt bridge in this case)
- c. a disulfide bridge
- d. a covalent bond

3. The quality report on the X-ray structure below indicates that :
- the overall quality of the experimental structure will enable a fine analysis of the position of a large proportion of the atoms
  - the overall quality of the experimental structure is limited and will, for example, only enable a qualitative analysis of the relative position of residues

#### Experimental Data Snapshot

**Method:** X-RAY DIFFRACTION

**Resolution:** 4.20 Å

**R-Value Free:** 0.444

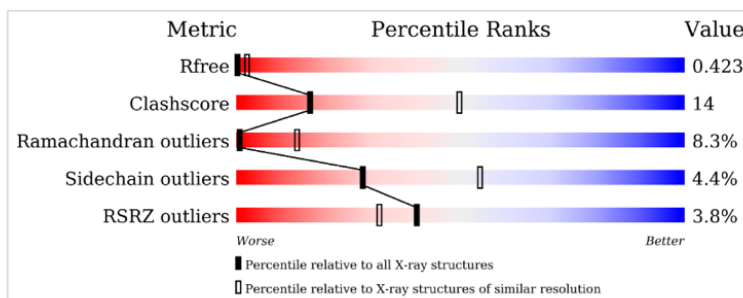
**R-Value Work:** 0.381

**R-Value Observed:** 0.388

#### wwPDB Validation

 3D Report

Full Report



4. Using a consensus approach to dock a small molecule on a protein could consist in:
- docking several similar ligands and check that their binding mode is alike
  - performing the docking using several different software, retaining the binding mode predicted by most of these programs as the most likely
  - using a protein 3D structure modelled with AlphaFold
5. Results of several docking runs performed using the same software, with the same ligand and the same protein prepared the same way, can be slightly different because:
- docking algorithms are often stochastic (=non-deterministic, i.e. based on random numbers) and can thus follow different optimization paths leading to different results
  - results depend on the quality of the processor of the computer
  - binding modes are inverted in the southern hemisphere
6. Virtual screening
- replaces experimental screening using in silico methods to identify all the actives and only the actives from a large library of small molecules.
  - applies structure-based or ligand-based approaches to a large collection of molecules, to establish a short list enriched in compounds likely to be active against the target and that could be tested in priority.
  - filters out all inactive and toxic molecules.
7. Target prediction consists in
- predicting all the small molecules that can bind to a given protein target, and is performed by molecular docking
  - identifying the protein at the origin of a disease using bioinformatics tools
  - predicting on which protein target a bioactive small molecule could bind, and can be performed by ligand-based reverse screening or docking
8. A molecule is considered druglike
- if it shows high similarity of molecular structure with known bioactive molecules
  - if its physicochemical properties are within optimal ranges for oral bioavailability
  - if it satisfies all criteria to enter clinical development

10. What is the most probable human protein targeted by molecule\_1, whose SMILES is given below?

C1=CC(Br)=C(CN2CCN(C3C=CC(C(=O)NS(=O)(C4C=CC=C([N+](=O)[O-])C=4)=O)=C(OC4C=CC=NC=4)C=3)CC2)C=C1

- SwissTargetPrediction predicts 20% of kinases at Top-15.
- SwissTargetPrediction predicts the Apoptosis regulator Bcl-2 with a probability of 1, thus it is not a prediction.
- SwissTargetPrediction predicts the Apoptosis regulator Bcl-2 with a probability of ~0.35.
- SwissADME displays many violations in druglikeness filters, thus it is not a bioactive molecule.

11. Which drug molecule in DrugBank is most similar to molecule\_1 for 3D-shape ?

- Ligand-based screening with SwissSimilarity returned compound CHEMBL4640212 with an Electroshape score of 0.913
- Ligand-based screening with SwissSimilarity returned Sonrotoclax with a FP2 score of 0.653
- Ligand-based screening with SwissSimilarity returned ligand CZT with an Electroshape score of 0.880
- Ligand-based screening with SwissSimilarity returned Cloxacepride with an Electroshape score of 0.859

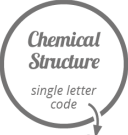
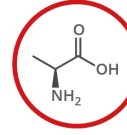
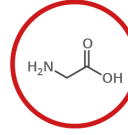
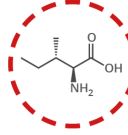
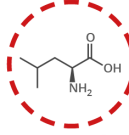
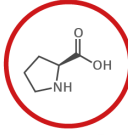
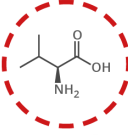
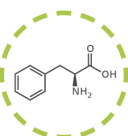
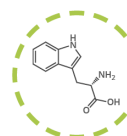
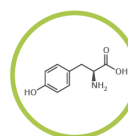
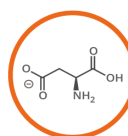
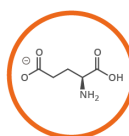
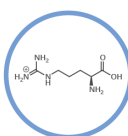
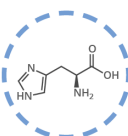
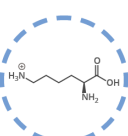
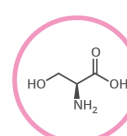
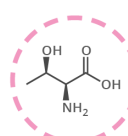
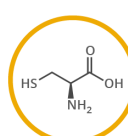
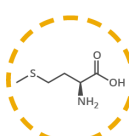
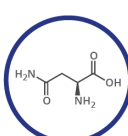
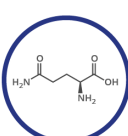
12. What prediction about the absorption and distribution of molecule\_1 given by the BOILED-Egg? This compound:

- displays properties to be well absorbed by the gastrointestinal tract but it can't permeate through the blood-brain barrier.
- displays properties to be well absorbed by the gastrointestinal tract but will be probably effluxed back to the lumen.
- cannot be well absorbed by the gastrointestinal tract, because it is a too lipophilic
- cannot be well absorbed by the gastrointestinal tract, because it has a too high apparent polarity

# A GUIDE TO THE TWENTY COMMON AMINO ACIDS

AMINO ACIDS ARE THE BUILDING BLOCKS OF PROTEINS IN LIVING ORGANISMS. THERE ARE OVER 500 AMINO ACIDS FOUND IN NATURE - HOWEVER, THE HUMAN GENETIC CODE ONLY DIRECTLY ENCODES 20. 'ESSENTIAL' AMINO ACIDS MUST BE OBTAINED FROM THE DIET, WHILST NON-ESSENTIAL AMINO ACIDS CAN BE SYNTHESISED IN THE BODY.

**Chart Key:** ● ALIPHATIC ● AROMATIC ● ACIDIC ● BASIC ● HYDROXYLIC ● SULFUR-CONTAINING ● AMIDIC ○ NON-ESSENTIAL ○ ESSENTIAL

|                                                                                                                                                                                                           |                                                                                                                                                                   |                                                                                                                                                            |                                                                                                                                                        |                                                                                                                                                                     |                                                                                                                                                                       |                                                                                                                                                           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
|  <p><b>CHEMICAL STRUCTURE</b><br/>single letter code<br/><b>NAME</b> <b>A</b><br/>three letter code<br/>DNA codons</p> |  <p><b>ALANINE</b> <b>A</b><br/><i>Ala</i><br/>GCT, GCC, GCA, GCG</p>          |  <p><b>GLYCINE</b> <b>G</b><br/><i>Gly</i><br/>GGT, GGC, GGA, GGG</p>   |  <p><b>ISOLEUCINE</b> <b>I</b><br/><i>Ile</i><br/>ATT, ATC, ATA</p> |  <p><b>LEUCINE</b> <b>L</b><br/><i>Leu</i><br/>CTT, CTC, CTA, CTG, TTA, TTG</p> |  <p><b>PROLINE</b> <b>P</b><br/><i>Pro</i><br/>CCT, CCC, CCA, CCG</p>            |  <p><b>VALINE</b> <b>V</b><br/><i>Val</i><br/>GTT, GTC, GTA, GTG</p> |
|  <p><b>PHENYLALANINE</b> <b>F</b><br/><i>Phe</i><br/>TTT, TTC</p>                                                      |  <p><b>TRYPTOPHAN</b> <b>W</b><br/><i>Trp</i><br/>TGG</p>                      |  <p><b>TYROSINE</b> <b>Y</b><br/><i>Tyr</i><br/>TAT, TAC</p>            |  <p><b>ASPARTIC ACID</b> <b>D</b><br/><i>Asp</i><br/>GAT, GAC</p>   |  <p><b>GLUTAMIC ACID</b> <b>E</b><br/><i>Glu</i><br/>GAA, GAG</p>               |  <p><b>ARGININE</b> <b>R</b><br/><i>Arg</i><br/>CGT, CGC, CGA, CGG, AGA, AGG</p> |  <p><b>HISTIDINE</b> <b>H</b><br/><i>His</i><br/>CAT, CAC</p>        |
|  <p><b>LYSINE</b> <b>K</b><br/><i>Lys</i><br/>AAA, AAG</p>                                                             |  <p><b>SERINE</b> <b>S</b><br/><i>Ser</i><br/>TCT, TCC, TCA, TCG, AGT, AGC</p> |  <p><b>THREONINE</b> <b>T</b><br/><i>Thr</i><br/>ACT, ACC, ACA, ACG</p> |  <p><b>CYSTEINE</b> <b>C</b><br/><i>Cys</i><br/>TGT, TGC</p>        |  <p><b>METHIONINE</b> <b>M</b><br/><i>Met</i><br/>ATG</p>                       |  <p><b>ASPARAGINE</b> <b>N</b><br/><i>Asn</i><br/>AAT, AAC</p>                   |  <p><b>GLUTAMINE</b> <b>Q</b><br/><i>Gln</i><br/>CAA, CAG</p>        |

**Note:** This chart only shows those amino acids for which the human genetic code directly codes for. Selenocysteine is often referred to as the 21st amino acid, but is encoded in a special manner. In some cases, distinguishing between asparagine/aspartic acid and glutamine/glutamic acid is difficult. In these cases, the codes asx (B) and glx (Z) are respectively used.