

Physicochemical Descriptors and Lipinski Rule of Five

Practical 15 | Medicinal Chemistry III

Aim

To study Physicochemical Descriptors and Lipinski Rule of Five, and interpret the recorded observations.

Principle

- Drug-design software estimates descriptors for a specific drawn structure. The rule of five is a screening heuristic for oral absorption/permeability tendencies, not proof of efficacy or bioavailability.
- Choose the calculation or statistical model appropriate to the data structure and assumptions.
- Units, paired or independent observations, and the direction of the measured effect must be explicit.
- LogP describes neutral-species partitioning; logD is pH-dependent total-species distribution.
- cLogP is a calculated prediction. State the model rather than reporting it as a measured value.
- Molar refractivity is an additional descriptor and is not one of the four rule-of-five thresholds.

Materials and Apparatus

- Assigned drug structures, descriptor software and a spreadsheet for consistent comparisons.
- Instructor-provided dataset and the stated study/model assumptions.
- Calculator or spreadsheet/statistical software and a record sheet.

Method

1. Choose a consistent structural convention for each assigned drug.
2. Check connectivity, charges, stereochemistry and whether counterions are included.
3. Record software/version and the descriptor model used.
4. Calculate molar mass, logP/cLogP, molar refractivity and donor/acceptor counts.
5. Compare the results with the stated rule-of-five thresholds.
6. Explain exceptions and distinguish a screening flag from an experimental conclusion.

Observation Record

Complete this record using actual laboratory findings or the provided teaching data.

Observation / parameter	Record / finding
Drug/form	_____
Molar mass	_____
LogP or cLogP	_____
Molar refractivity	_____
H-bond donors	_____
H-bond acceptors	_____
Rule violations	_____

Calculations and Interpretation

- Common screening thresholds: molar mass not above 500 g/mol; H-bond donors not above 5; acceptors not above 10; cLogP not above 5.
- Count violated thresholds consistently; values are screening descriptors rather than acceptance specifications.

Result

Record the actual finding, calculated value with units where relevant, and a conclusion supported by the observations.

Finding: _____

Conclusion: _____

Precautions

- Do not interchange paired and independent analyses.
- Keep unit conversions explicit and round at the final reporting stage.
- A model estimate or p-value does not by itself establish a causal or clinical conclusion.

Viva Questions

1. Can a compound outside the rule of five be a useful drug?

Yes. The rules are empirical screening guidance and have exceptions, including mechanisms or delivery routes outside their intended context.

2. Why state assumptions?

An equation or test can give a misleading answer when its underlying assumptions do not hold.

3. Why keep intermediate calculations?

They make the result reproducible and expose unit or transcription errors.

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