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QSAR Study and External Validation

Practical 23 - Molecular modelling practical

Aim

To construct and externally evaluate a small, interpretable two-dimensional QSAR model.

Principle

QSAR relates a precisely defined measured endpoint to molecular descriptors. Endpoint consistency, data curation, split design and an applicability domain are necessary; a high training R-squared is insufficient.

Materials and Requirements

- Benign reference structures with verified stereochemistry and protonation basis
- Institution-approved software with version, parameters and model documentation
- Independent reference or validation dataset
- Approved method or teaching-data pack and a dated record sheet

Procedure

1. Define the preparation or dataset, study question and method version. Record identities, units and the criteria to be used before examining the outcome.
2. Define the endpoint and retain unmodified input structures and identifiers. Standardise salts, tautomers and stereochemistry using a documented rule.
3. Curate duplicate structures, assay units, censored values and activity conditions; transform only by a documented rule.
4. Separate training and external test sets before descriptor selection and preprocessing; consider scaffold grouping to reduce leakage.
5. Fit a parsimonious model with internal validation and response randomisation where appropriate, then evaluate the untouched external set and domain.
6. Save input/output files, failures, parameter choices and independent validation results so the analysis can be reproduced.
7. Retain the original observations and calculations. State deviations, missing information and the limits of the conclusion; do not replace measured values with expected results.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Molecule / model	Input / settings	Output / diagnostic	Interpretation / limitation
Reference	Document	Record	Evaluate
Test molecules	Document	Record	Evaluate
Independent check	Document	Record	Evaluate

Calculations

- pIC50 = -log10(IC50 in mol/L)
- RMSE = sqrt[sum(observed - predicted)^2 / number of predictions]

Worked Example

Illustrative IC50 = 10 micromol/L = 10^-5 mol/L gives pIC50 = 5.0. A teaching model pIC50 = 3.0 + 0.5 log P predicts 4.0 at log P = 2.0.

The illustrative equation is not a validated medicinal-chemistry relationship; fit and test an actual curated dataset.

Result and Interpretation

- Report endpoint, split, descriptors, equation, validation metrics and domain, including failures.
- Predictions are not measured biological activity, clinical safety or regulatory approval.

Precautions

- Avoid training/test leakage and unsupported extrapolation.
- State software and model version and applicable domain.
- Do not select the best-looking model using the final test set.

Viva Questions and Answers

Why convert IC50 to mol/L?

The logarithmic endpoint requires a defined concentration unit.

What is leakage?

Information from evaluation data influences model development.

Why test externally?

Training fit does not establish predictive performance.

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