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QSAR-Guided Design of Ferulic-Acid Derivatives as Acetylcholinesterase Inhibitors

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INTRODUCTION & AIM

Acetylcholinesterase (AChE) remains a validated symptomatic target in Alzheimer's disease (AD); disturbances in cholinergic signaling correlate with cognitive decline and are exploited by current AChE inhibitors [1]. Ferulic acid (FA)—a phenylpropanoid with antioxidant/neuroprotective properties—offers a safe, natural starting point, yet its potency and CNS exposure require optimisation [2]. This study aimed to build a predictive QSAR model for FA derivatives to guide structure prioritisation for AChE inhibition and early drug-design decisions.

METHOD

Compounds & bioactivity

We modelled ferulic-acid derivatives with in-vitro AChE IC_{50} measured by a (modified) Ellman assay; the set, including reference FA and donepezil, was taken from literature [3]. The series was split into training, validation, and external test subsets.

Descriptors & selection

Geometries were optimized (HyperChem), then 4,885 Dragon7 descriptors were computed; after quality filters, a reduced pool was retained, and four descriptors were selected by stepwise procedures in STATISTICA [2]. Descriptor families and their interpretability followed standard chemoinformatics principles [4–5].

Modelling and validation

Multilayer perceptrons (MLPs) were screened; the final network was an MLP 4-8-1 chosen by learning/testing/validation quality and error metrics [2]. Model performance was summarized by internal/external R^2, Q^2, and MAE according to QSAR good practice [4].

RESULTS & DISCUSSION

Model performance

The selected ANN reproduced IC_{50} values with high goodness-of-fit and predictive power; the parity plot (Figure 1) shows tight alignment of predictions with experiments, supporting low bias and robust generalization.

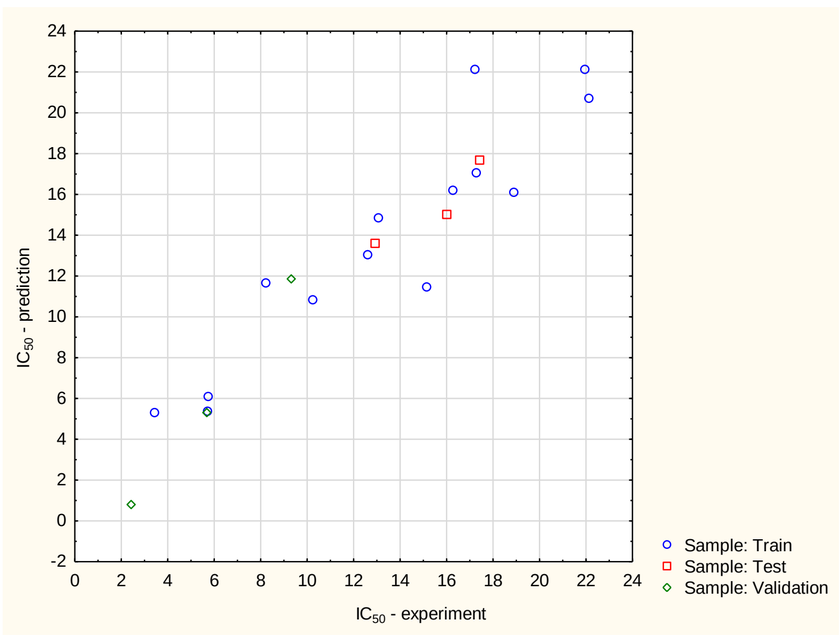

Figure 1. Predicted vs experimental IC_{50} (μM) for 20 studied analogues.

Key variables

Sensitivity analysis (Figure 2) ranked four descriptors (dataset-specific symbols): SpMax2_Bh(p), nCL, Mor16s, SpMax7_Bh(s). Their definitions connect chemical changes to potency: Burden eigenvalues (SpMax2_Bh(p), SpMax7_Bh(s)) capture polarizability/I-state-weighted electronic distribution; nCL counts chlorine atoms; Mor16s encodes 3D-MoRSE/I-state geometry [5]. These classes are widely used to relate shape/electron-distribution to bioactivity in QSAR [4–5].

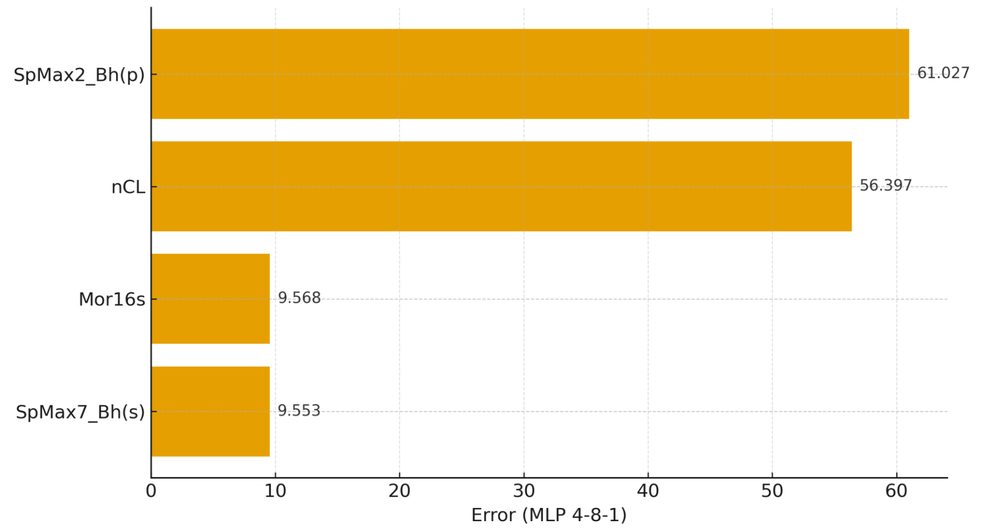

Figure 2. Descriptor importance derived from ANN sensitivity analysis.

Medicinal chemistry read-outs

The dominance of polarizability-weighted Burden terms suggests that extending π-systems and tuning substituent electronics (including judicious halogenation reflected by nCL) are productive levers—consistent with design practices and empirical AChE campaigns [6].

Design guidance synthesized from the model:

- Prioritise aryl/alkoxy patterns that increase polarizability without overshooting lipophilicity (to support BBB exposure) [2].
- Explore selective chloro-substitution (nCL) to reinforce noncovalent recognition, while monitoring CNS-relevant ADMET [6].
- Use the ANN-QSAR to triage virtual analogues before synthesis; such QSAR-guided loops have proven value across AChE discovery [6].

CONCLUSION

A compact, interpretable ANN-QSAR for ferulic-acid derivatives shows strong internal and external predictivity and highlights chemically actionable features (polarizability-rich scaffolds, selective halogenation). The model is suitable for early design and virtual screening of next FA-based AChE inhibitors.

FUTURE WORK / REFERENCES

Expand the chemical space, integrate BBB/ADMET filters upfront, and prospectively test top designs in enzyme/cellular assays to tighten the modelling loop [2].

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