ECMC-P 2025 Conference

The 1st International Electronic Conference on Medicinal Chemistry and Pharmaceutics

01–30 November 2025 | Online

MDPI

QSAR Analysis of Curcumin Analogues as Potent LSD1 Inhibitors with Anticancer Potential

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INTRODUCTION & AIM

Lysine-specific demethylase-1 (LSD1/KDM1A) removes mono- and dimethyl marks from H3K4/H3K9 and is frequently over-expressed across tumor types, making it an attractive epigenetic target in oncology. Curcumin, while only a weak LSD1 inhibitor, provides a modular, low-toxicity scaffold that can be optimized by rational design. This study aimed to build a compact, predictive QSAR model for curcumin analogues that explains potency drivers and supports early-stage inhibitor design [1].

METHOD

Compounds and bioactivity

Nineteen curcumin analogues with recombinant LSD1 inhibitory potency (IC_{50}) were compiled from the literature source and used to derive pIC_{50} for modelling; the set was split into training (n=13), validation (n=3), and external test (n=3) subsets [2,3].

Geometry and descriptors

3-D structures were energy-minimized in HyperChem (MM+ → AM1). Dragon 7 computed 4,885 molecular descriptors; low-variance, missing-value, and high-collinearity ($r \geq 0.95$) filters yielded 763 variables. Stepwise selection in Statistica 13 retained four informative descriptors: P_VSA_s_5, JGI8, H2s, SpPosA_A [4,5].

Modelling and validation

A radial-basis-function artificial neural network (RBF-ANN; 4-6-1) was trained on the learning set and internally validated by leave-one-out (Q^2); predictivity was assessed on the external test set; error was summarized by MAE [4].

RESULTS & DISCUSSION

Model performance

The final RBF-ANN reproduced experimental potency with excellent fit and internal consistency ($R^2 = 0.999$; $Q^2 = 0.9996$; MAE = 0.11 log units) and showed strong external predictivity ($R^2\_test = 0.928$). The parity plot (Figure 1) illustrates tight agreement between predicted and experimental pIC_{50} across training, validation, and test subsets.

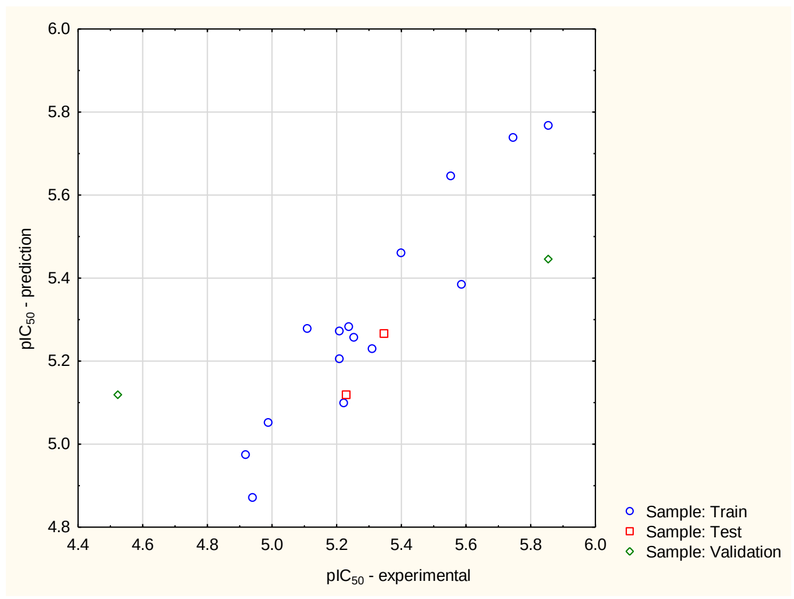

Figure 1. Predicted vs experimental pIC_{50} (μM) for 19 studied analogues.

Descriptor importance

Sensitivity analysis (Figure 2) ranked the four variables as follows: P_VSA_s_5 > JGI8 > H2s ≈ SpPosA_A. P_VSA_s_5 (polar van-der-Waals surface area in specific atomic states) dominated the response, indicating that enlarging and appropriately positioning polar surface enhances LSD1 engagement. JGI8 (8th-order mean topological charge) captured long-range charge-distribution patterns consistent with electrostatic complementarity. H2s (hydrogen-attached atom Sanderson electronegativity) and SpPosA_A (sum of atomic positive fragment surface areas) added finer-grained electronic/fragment-surface detail [5].

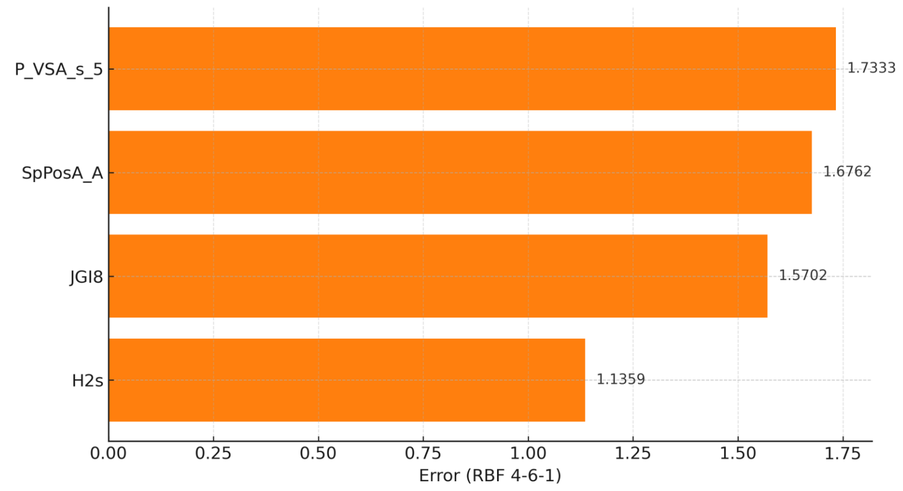

Figure 2. Descriptor importance derived from ANN sensitivity analysis.

Medicinal chemistry read-outs

The model supports three practical levers:

- tune polar surface via hydroxyl/alkoxy substitutions within the curcuminoid framework to increase P_VSA_s_5 without overshooting lipophilicity;
- modulate charge topology (JGI8) through electron-withdrawing/-donating patterns and strategic halogenation reported in the source series;
- preserve conjugation and H-bond capacity to maintain favourable H2s/SpPosA_A balance.

These trends are consistent with LSD1-ligand recognition principles and general QSAR guidance [2,4,5].

CONCLUSION

A concise, interpretable RBF-ANN QSAR model for curcumin analogues accurately reproduces LSD1 inhibition and yields actionable design rules centred on polar surface control and charge topology. The model is suitable for rapid triage of virtual analogues prior to synthesis.

FUTURE WORK / REFERENCES

Expand the chemical series, integrate CNS-relevant ADMET filters and permeability models, and prospectively validate top QSAR-prioritised analogues in enzyme and cellular assays [4].

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