ECMC-P 2025 Conference

The 1st International Electronic Conference on Medicinal Chemistry and Pharmaceutics

01–30 November 2025 | Online

MDPI

QSAR-Guided Optimisation of 5,6-Dimethoxyindanone-Piperazine Derivatives as Acetylcholinesterase Inhibitors

Marcin Gackowski[1,*], Weronika Długosz[1], Katarzyna Mądra-Gackowska[2], Łukasz Szeleszczuk[3]

[1] Department of Toxicology and Bromatology, Faculty of Pharmacy, L. Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, A. Jurasza 2 Street, PL–85089 Bydgoszcz, Poland
[2] Department of Geriatrics, Faculty of Health Sciences, L. Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Skłodowskiej Curie 9 Street, PL–85094 Bydgoszcz, Poland;
[3] Department of Organic and Physical Chemistry, Faculty of Pharmacy, Medical University of Warsaw, Banacha 1 Street, PL–02093 Warsaw, Poland;
* correspondence: marcin.gackowski@cm.umk.pl

INTRODUCTION & AIM

Alzheimer's disease (AD) is characterised by a progressive cholinergic deficit. Although current acetylcholinesterase (AChE) inhibitors alleviate cognitive symptoms, their brain penetration and tolerability remain sub-optimal [1]. 5,6-Dimethoxyindanone represents the pharmacophore of donepezil; substitution with a piperazine ring generates analogues with promising activity. The aim of this study was to develop a quantitative structure–activity relationship (QSAR) model able to predict the AChE-inhibitory potency (IC_{50}) of 5,6-dimethoxyindanone-piperazine derivatives, thereby guiding the design of improved inhibitors.

METHOD

A set of **15 literature analogues** with experimental IC_{50} (Ellman assay) was compiled from Mishra *et al.* (donepezil-based MTDLs) and used as the response source for modelling [2]. Conformers were energy-minimised (HyperChem $MM^+ \rightarrow$ PM3). **4,885** Dragon 7 descriptors were computed and reduced to **843** by low-variance and multicollinearity filtering ($r \geq 0.95$). Feature selection (Statistica 14) returned **four** variables (Mor22v, HATS8p, VE1_B(p), C-006); an artificial neural network (ANN) **MLP 4-3-1 (BFGS)** was trained on nine compounds and checked by LOO, a 3-compound external test, and a 3-compound validation set.

RESULTS & DISCUSSION

The final model achieved **R^2 = 0.961**, **Q^2 = 0.999**, and **MAE = 0.001 µM**; external prediction yielded **R^2_test = 0.928** with a near-unity regression slope (**≈ 0.98**) on the parity plot (**Figure 1**).

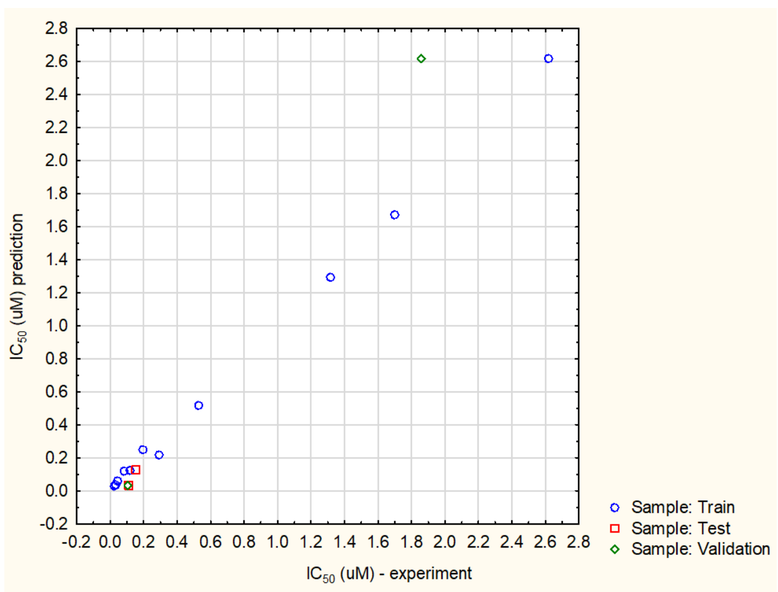

Figure 1. Predicted vs experimental IC_{50} (µM) for 15 studied analogues.

Sensitivity ranked **C-006 (42.1) > Mor22v (16.4) > VE1_B(p) (8.3) > HATS8p (3.1)**, consistent with the variable-importance profile shown in the **descriptor importance bar chart (Figure 2)**.

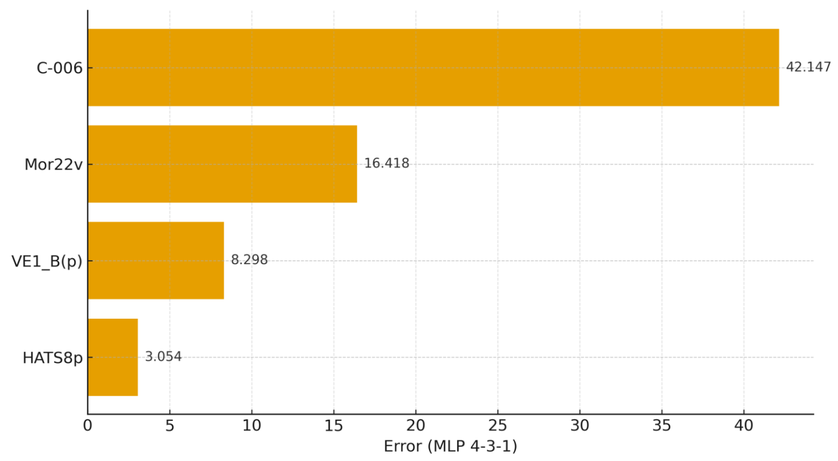

Figure 2. Descriptor importance derived from ANN sensitivity analysis.

Descriptor interpretation:

• **Mor22v (3D-MoRSE)** captures short-range atom-pair contributions and vdW-weighted shape; its prominence matches the geometric constraints of the AChE gorge and correlates with π-fragment placement;

• **HATS8p (GETAWAY)** encodes geometry-weighted **polarizability**, highlighting benefits of π-rich/heteroatom motifs and their spatial dispersion for non-covalent recognition

;

• **VE1_B(p)** (Burden eigenvalue, polarizability-weighted) reflects global electron-distribution patterns relevant to aromatic stacking/edge contacts within the catalytic and peripheral sites;

• **C-006 (ACF)** counts **CH_2–R–X** fragments, tying potency to substitution density near the indanone–piperazine junction and linker electronics.

Design takeaways:

• Maintain compact molecular volume while **increasing polarizability** (e.g., para-aryl, ether or judicious halo/CF_3) to lift Mor22v/HATS8p without overshooting lipophilicity; tune **CH_2–R–X** around the hinge to optimize **C-006**.

• These rules align with broader AChE-QSAR evidence that descriptor families blending **3D geometry + atom-weighting** (GETAWAY) and **electron-diffraction-like 3D codes** (3D-MoRSE) tend to dominate predictivity.

• Prioritizing analogues with **log P ≈ 2–4** should support BBB penetration while limiting non-specific binding.

CONCLUSION

An interpretable ANN-QSAR for 5,6-dimethoxyindanone-piperazine AChE inhibitors shows high internal and external performance and yields actionable rules (enhanced polarizability; targeted CH_2–R–X substitution) to streamline analogue selection for experimental follow-up.

FUTURE WORK / REFERENCES

Expand the chemical domain (≥ 40 analogues), couple training with **BBB/ADMET** in-silico filters, and prospectively validate top-ranked designs in enzyme/cellular assays.

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