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Research Article

Computational Evaluation of Quinoline and Imidazopyridine Derivatives as Monoamine Oxidase-B and Monoamine Oxidase-A Inhibitors: Molecular Docking and Qsar Studies

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ABSTRACT

Monoamine oxidase (MAO) enzymes are important targets in neurological and psychiatric drug discovery. MAO-B inhibition is an established therapeutic strategy in Parkinson's disease, whereas MAO-A inhibition is relevant to the metabolism of monoamine neurotransmitters and the pharmacology of depression. This study used computer-aided drug-design methods to investigate quinoline derivatives against MAO-B and imidazopyridine derivatives against MAO-A. The MAO-B structure was selected using Protein Data Bank entry 2V5Z and the MAO-A structure using entry 2Z5X. Ligands were designed around selected pharmacophoric features, prepared for docking, and evaluated using AutoDockTools/AutoDock workflows. Predicted binding energies were used to rank the compounds. For the MAO-B series, the most favourable reported docking score was -7.86 kcal/mol (compound 5), while selected compounds 6 and 15 were highlighted for interaction visualization. For the MAO-A series, the most favourable reported docking score was -9.85 kcal/mol (compound 14); selected interaction snapshots were also presented for ligands 30 and 23. Multiple linear regression quantitative structure–activity relationship (QSAR) models were developed in ChemMaster using molecular descriptors and a Kennard–Stone training/test split. The MAO-B model used five descriptors and gave training/test R^2 values of 0.726/0.610, RMSE values of 0.224/0.214, MAE values of 0.170/0.167 and Q^2 of 0.610. The MAO-A model used seven descriptors and gave training/test R^2 values of 0.660/0.690, RMSE values of 0.960/0.598, MAE values of 0.676/0.471 and Q^2 of 0.547. These findings support computational prioritization, but experimental enzyme assays are required to confirm activity, selectivity and safety.

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INTRODUCTION

Parkinson's disease is a progressive neurodegenerative disorder associated with degeneration of dopaminergic neurons and reduced dopaminergic signalling. Monoamine oxidase-B (MAO-B) contributes to dopamine metabolism and is a validated pharmacological target in Parkinson's disease. MAO-B inhibitors are used clinically as part of symptomatic management, although the selection and optimization of inhibitors remain important because efficacy, tolerability and selectivity vary across compounds ¹⁻⁴.

Depression is a multifactorial psychiatric disorder involving biological, psychological and environmental contributors. Monoamine oxidase-A (MAO-A) metabolizes monoamine neurotransmitters, including serotonin and noradrenaline, and has consequently been investigated as a target in antidepressant drug discovery. The therapeutic relevance of MAO inhibition is well established, but inhibitor design must consider selectivity and potential safety liabilities ⁵⁻⁷.

Quinoline and imidazopyridine are nitrogen-containing heterocyclic scaffolds with broad medicinal-chemistry utility. Structure-based molecular docking estimates plausible ligand poses and ranks predicted protein–ligand interactions, while quantitative structure–activity relationship (QSAR) modelling relates numerical molecular descriptors to measured biological activity. These methods can support virtual screening and lead prioritization, but docking scores and QSAR predictions remain computational estimates and require suitable validation ⁸⁻¹¹.

The objective of the present study was to investigate designed quinoline derivatives against MAO-B and imidazopyridine derivatives against MAO-A using molecular docking, and to develop and evaluate multiple linear regression QSAR models for the corresponding activity datasets. Applicability-domain analysis was included to assess whether proposed compounds fell within the descriptor space represented by the models.

MATERIALS AND METHODS

Study design and computational tools

The project used a computational workflow comprising ligand drawing and preparation, target structure selection, molecular docking, descriptor calculation, QSAR model development, applicability-domain assessment, and in-silico drug-likeness/toxicity screening. The software reported in the project included ACD/ChemSketch, AutoDockTools 1.5.7/AutoDock, UCSF Chimera, BIOVIA Discovery Studio Visualizer, Molegro Molecular Viewer, PaDEL-Descriptor, ChemMaster, Microsoft Excel, SwissADME and OSIRIS Property Explorer.

Target selection and ligand design

MAO-B was selected as the target for the Parkinson's disease-related series using PDB entry 2V5Z. MAO-A was selected for the depression-related series using PDB entry 2Z5X. Quinoline derivatives were designed for the MAO-B series and imidazopyridine derivatives for the MAO-A series. Pharmacophoric considerations included aromatic rings, hydrophobic groups, hydrogen-bond donor/acceptor features and their spatial arrangement. The project reports novelty checking through PubChem; database non-retrieval was treated as a preliminary novelty check rather than proof of absolute novelty.

Protein and ligand preparation

Protein structures were imported into AutoDockTools. Unnecessary water molecules and unwanted heteroatoms were removed, polar hydrogens were added, and Kollman charges were assigned as described in the project. Ligands were constructed as three-dimensional structures, energy-minimized, assigned hydrogen atoms and Gasteiger partial charges, and had rotatable bonds defined. Prepared structures were saved in PDBQT format.

Molecular docking

A grid box was positioned around the selected binding region and the corresponding grid maps were generated using AutoGrid. Docking parameters were prepared in AutoDockTools, with the Lamarckian Genetic Algorithm used as the conformational search method. Docking poses were ranked by predicted binding energy (kcal/mol). Selected poses were inspected using molecular visualization software to examine potential



hydrogen-bonding, hydrophobic, π - π and π -alkyl interactions. The manuscript reports the docking energies explicitly tabulated in the project; residue-level distances were not added where numerical values were not reported.

QSAR dataset and descriptor calculation

Biological activity values were converted to pIC_{50} using $\text{pIC}_{50} = -\log_{10}[\text{IC}_{50} \text{ (M)}]$. Molecular descriptors were generated with PaDEL-Descriptor and associated with activity values. Separate multiple linear regression (MLR) models were developed for MAO-B and MAO-A in ChemMaster. The project reports use of the Kennard-Stone algorithm to divide compounds into training and test sets, with the test set withheld from model fitting.

QSAR modelling and validation

The MAO-B model used minHBint6, SHBint9, SHtCH, MDEO-11 and MDEC-11. The MAO-A model used WTPT-5, nHBint8, nHssNH, ATSm5, minHBa, MDEC-14 and LipinskiFailures. Model performance was summarized using training and test R^2 , root mean square error (RMSE), mean absolute error (MAE), and cross-validated Q^2 . Applicability domain was examined using leverage and standardized residuals in Williams plots. The warning leverage values reported were 0.600 for MAO-B and 0.5333 for MAO-A.

In-silico drug-likeness and toxicity screening

SwissADME was used in the project to estimate physicochemical and pharmacokinetic properties and drug-likeness. OSIRIS Property Explorer was used to screen predicted toxicity alerts, including mutagenicity, tumorigenicity, irritant effects and reproductive effects. These are prediction tools and do not substitute for experimental ADME or toxicology studies.

RESULTS AND DISCUSSION

Molecular docking of quinoline derivatives against MAO-B

Eleven quinoline-related compounds were tabulated in the project's MAO-B docking results. Predicted binding energies ranged from -6.00 to -7.86 kcal/mol. Compound 5 gave the most favourable reported score (-7.86 kcal/mol), followed by compound 2 (-7.29 kcal/mol) and compound 11 (-6.84 kcal/mol). Compounds 6 and 15 were separately highlighted in the project for visualization of their protein-ligand interaction poses. These scores suggest relative docking preference within the screened set only; they do not establish enzyme inhibition or selectivity.

Table 1: Reported Docking Energies for the MAO-B Series. Lower (More Negative) Scores Indicate More Favourable Predicted Binding Under the Scoring Function Used.

Compound number	Reported binding energy (kcal/mol)
1	-6.62
2	-7.29
3	-6.13
4	-6.32
5	-7.86
6	-6.47
7	-6.10
8	-6.18
9	-6.00
10	-6.53
11	-6.84

Molecular docking of imidazopyridine derivatives against MAO-A

Fifteen compounds were tabulated in the MAO-A docking results. Predicted binding energies ranged from -7.98 to -9.85 kcal/mol. Compound 14 showed the most favourable reported score (-9.85 kcal/mol), followed by compound 8 (-9.36 kcal/mol) and compounds 3 and 9 (each -8.97 kcal/mol). The project also presents interaction snapshots labelled ligand 30 and ligand 23; because the relationship between these labels and the numbered docking table is not explicitly reconciled in the source, they are not assumed to be the same compounds as the highest-scoring entries.



Table 2: Reported Docking Energies for the MAO-A Series. the Results Identify Compounds for Further Evaluation, but Comparisons Between MAO-A and MAO-B Scores Should Be Interpreted Cautiously Because the Proteins, Binding Sites and Ligand Series Differ.

Compound number	Reported binding energy (kcal/mol)
1	-8.36
2	-8.12
3	-8.97
4	-8.00
5	-8.54
6	-8.89
7	-8.54
8	-9.36
9	-8.97
10	-8.16
11	-7.98
12	-8.43
13	-8.40
14	-9.85
15	-8.65

QSAR model for MAO-B

The MAO-B MLR equation reported in the project was:

$$\text{pIC}_{50} = 0.0894 (\text{minHBint6}) - 0.0682 (\text{SHBint9}) - 0.2401 (\text{SHtCH}) + 0.1249 (\text{MDEO-11}) + 0.0558 (\text{MDEC-11}) + 5.6575$$

The model contained five molecular descriptors. The positive coefficients for minHBint6, MDEO-11 and MDEC-11 indicate positive model-associated contributions when other descriptors are held constant, whereas SHBint9 and SHtCH have negative coefficients. Coefficients describe the fitted model and should not be interpreted as causal mechanisms.

Table 3: Reported Statistical Performance of the MAO-B QSAR Model.

Validation parameter	Training set	Test set
R ²	0.726	0.610
RMSE	0.224	0.214
MAE	0.170	0.167
Q ²	0.610	Not separately reported

The training R² of 0.726 indicates that the model explained a substantial proportion of the activity variance in the training set. The test R² of 0.610 suggests moderate external agreement. Training and test RMSE and MAE values were low and similar, suggesting that prediction errors were not markedly increased in the test set. The reported Q² of 0.610 supports internal cross-validated predictivity. These statistics should be interpreted alongside the dataset size, descriptor selection procedure, endpoint consistency and applicability domain.

QSAR model for MAO-A

The MAO-A MLR equation reported in the project was:

$$\text{pIC}_{50} = 0.3668 (\text{WTPT-5}) - 0.7007 (\text{nHBint8}) - 0.5599 (\text{nHssNH}) + 0.7184 (\text{ATSm5}) - 0.2918 (\text{minHBa}) - 0.4550 (\text{MDEC-14}) - 0.2969 (\text{LipinskiFailures}) + 5.8979$$

The model used seven descriptors representing path/connectivity, atom-type and autocorrelation characteristics, hydrogen-bond-acceptor environment, carbon-distance relationships and Lipinski-rule violations.



Table 4: Reported Statistical Performance of the MAO-A QSAR Model.

Validation parameter	Training set	Test set
R ²	0.660	0.690
RMSE	0.960	0.598
MAE	0.676	0.471
Q ²	0.547	Not separately reported

The MAO-A model showed similar training and test R² values (0.660 and 0.690), indicating comparable correlation in the two subsets. However, its RMSE and MAE were higher than those of the MAO-B model, indicating larger absolute prediction errors on the pIC₅₀ scale. The reported Q² of 0.547 suggests moderate internal predictive ability. Therefore, the MAO-A model may be useful for preliminary prioritization, but its predictions warrant greater caution and independent validation.

Novel compounds and applicability domain

For the MAO-B novel-compound table, the reported predicted pIC₅₀ values were approximately 5.467–5.781, with leverage values below the warning leverage of 0.600. The project marked the listed candidates as inside the applicability domain. For the MAO-A novel-compound table, predicted pIC₅₀ values for the displayed candidates ranged from 6.0406 to 8.4511, with leverage values below the warning leverage of 0.5333; the listed candidates were presented as inside the applicability domain. These classifications indicate that the compounds were not flagged by the project's leverage criterion, but they do not guarantee accurate prediction. A Williams plot should be interpreted using both leverage and standardized residuals; points with absolute standardized residuals greater than about 3 may be considered response outliers.

The MAO-B model performed more consistently in terms of prediction error, with lower RMSE and MAE and similar training/test errors. The MAO-A model had a slightly higher test R² than training R², but this does not offset its larger errors. Differences between the two models may reflect the datasets, endpoint distributions, descriptor sets and chemical diversity, and cannot be attributed to any single descriptor without additional analysis.

Drug-likeness and toxicity predictions

The project used SwissADME for physicochemical and pharmacokinetic prediction and OSIRIS Property Explorer for toxicity alerts. The project reports that selected displayed compounds did not show the listed OSIRIS alerts (tumorigenicity, mutagenicity, irritant and reproductive effects). Because the source does not provide a complete numerical ADME/toxicity table for all compounds in a form suitable for quantitative comparison, no additional numerical claims are made here. In-silico absence of an alert should not be interpreted as evidence of safety, and predicted blood–brain barrier penetration or drug-likeness should be confirmed experimentally.

Limitations

This work is entirely computational. Docking scores are approximate scoring-function outputs and may be affected by protein preparation, protonation, grid placement, receptor flexibility and scoring-function limitations. The project does not report experimental enzyme-inhibition measurements for the newly designed candidates. The MAO-A interaction snapshots use ligand labels that are not reconciled with the numbered docking table, and the complete underlying QSAR prediction/residual data are not reproduced here. Consequently, the findings should be regarded as a prioritization exercise rather than evidence of validated inhibitory activity, selectivity, efficacy or safety.

CONCLUSION

The study combined molecular docking and QSAR modelling to prioritize quinoline derivatives for MAO-B and imidazopyridine derivatives for MAO-A. In the reported docking tables, compound 5 was the most favourable MAO-B entry (–7.86 kcal/mol), while



compound 14 was the most favourable MAO-A entry (-9.85 kcal/mol). The MAO-B MLR model showed R^2 values of 0.726 and 0.610 for the training and test sets, Q^2 of 0.610, and low, closely matched RMSE/MAE values. The MAO-A model showed training/test R^2 values of 0.660/0.690 and Q^2 of 0.547, but larger prediction errors. The project's leverage-based analysis placed the displayed novel candidates within the stated applicability-domain thresholds. Overall, the results provide a computational basis for selecting compounds for further study; they do not prove biological activity or safety. Priority candidates should be evaluated in validated in-vitro MAO-A and MAO-B inhibition assays, followed by selectivity, ADME and toxicity studies before any therapeutic claims are considered.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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