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Support Vector Machine Screening for Dual Adenosine A2A Receptor Antagonists and Monoamine Oxidase B Inhibitors

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Abstract

Background: Adenosine A2A receptor antagonism and monoamine oxidase B (MAO-B) inhibition offer complementary approaches to motor fluctuations in Parkinson disease. This historical study examined ligand-based classifiers for prioritizing compounds predicted to have both activities.

Methods: The 2011 analysis used separate support vector machine (SVM) models with 98 molecular descriptors. Training sets contained 2,169 reported A2A receptor antagonists and 63,118 presumed inactive compounds, and 187 MAO-B inhibitors and 66,366 presumed inactive compounds. The reported activity threshold was a half-maximal inhibitory concentration (IC50) or inhibition constant (Ki) below 10 micromolar. Five-fold cross-validation was used for parameter selection. Evaluation included later-reported active-compound sets and a separate 14-compound dual-target benchmark. Screening involved approximately 13.56 million PubChem entries and 168,000 Molecular Design Limited Drug Data Report (MDDR) entries. This revision reports surviving aggregate results; no new screen was performed.

Results: The A2A receptor model retrieved 210 of 315 later-reported antagonists (66.7%), and the MAO-B model retrieved 84 of 88 inhibitors (95.5%). The receptor classifier retrieved nine of 14 dual-target benchmark compounds (64.3%); both classifiers jointly retrieved five (35.7%). Reported single-target positive counts were 8,285 and 1,307 in PubChem and 1,507 and 69 in MDDR for the receptor and enzyme models, respectively. The historical intersection count was 58. Candidate identities and individual outputs are unavailable, preventing independent verification and confirmation of uniqueness. Training/evaluation structural overlap could not be audited, and unreconciled MAO-B internal metrics were excluded from quantitative comparison.

Conclusions: Models trained on pre-2010 data retrieved most compounds in the selected later-reported single-target active sets, while joint retrieval was lower in the separate dual-target benchmark. These findings describe a historical screening approach but do not establish prospective accuracy or useful dual pharmacology. Missing candidate identities and computational records prevent independent verification of the 58-entry screening intersection and limit its use for experimental follow-up.

Categories: Family/General Practice, Neurology, Pharmacology
Keywords: adenosine a2a receptor, monoamine oxidase b, multitarget drug discovery, parkinson disease, support vector machine, virtual screening

Introduction

Parkinson disease causes progressive impairment of movement as nigrostriatal dopaminergic neurons are lost. Levodopa remains the most effective symptomatic treatment, but disease progression and chronic treatment can be accompanied by motor fluctuations and dyskinesia. OFF periods are times when medication provides insufficient benefit and motor symptoms return or worsen. ON periods are times when medication provides better control of motor symptoms. An important treatment goal is to increase ON time without troublesome dyskinesia while limiting other adverse effects [1,2].

Monoamine oxidase B (MAO-B) inhibitors reduce dopamine metabolism. Some agents are used for early motor symptoms, while adjunctive MAO-B inhibition can reduce OFF time in patients taking levodopa. Trials of safinamide demonstrate benefit as an adjunct to levodopa, and its United States indication is adjunctive treatment to levodopa/carbidopa in patients experiencing OFF episodes [3-5]. These symptomatic benefits do not establish neuroprotection or disease modification.

Adenosine A2A receptors are highly expressed in the striatum and modulate the indirect basal ganglia pathway. Their antagonism offers a nondopaminergic adjunctive mechanism for treating motor fluctuations. Istradefylline was approved in Japan in 2013 and in the United States in 2019; its United States indication is

adjunctive treatment to levodopa/carbidopa in adults experiencing OFF episodes [6,7]. Randomized trial evidence supports a reduction in OFF time [8]. Results across the drug class have varied: preladenant failed to demonstrate efficacy in phase 3 trials, and tozadenant development was stopped because of hematologic toxicity, including agranulocytosis [9].

Combining A2A receptor antagonism with MAO-B inhibition in one molecule is a plausible strategy for addressing motor fluctuations through complementary mechanisms. Medicinal-chemistry studies established that both activities can occur in the same compound [10,11]. Whether such a molecule would improve symptoms, tolerability, or treatment convenience beyond existing combination therapy remains a separate experimental question.

This project originated in 2011, when support vector machine (SVM) methods were being explored for single-target and multi-target virtual screening [12-14]. Broader work on multi-target drug discovery and drug combinations provided a rationale for evaluating complementary target activities [15,16]. Ligand-based classifiers use molecular descriptors to distinguish reported active compounds from presumed inactive compounds, then apply that classification to untested structures [17]. Classification alone does not establish binding, functional antagonism, or the probability of clinical benefit.

The primary objective was to prioritize compounds predicted to have both A2A receptor antagonist and MAO-B inhibitory activity. Secondary objectives were to describe single-target retrieval of later-reported active compounds, joint retrieval in a known dual-target benchmark, and aggregate screening output. This report presents the surviving results of that historical analysis. Because the final candidate identities are unavailable, the objective of delivering an actionable compound list for experimental testing was only partially fulfilled.

The primary objective was to assess a ligand-based screening approach for identifying compounds with predicted activity at both targets. Secondary objectives were to evaluate retrieval of known actives by each classifier and examine how requiring agreement between classifiers affected retrieval of known dual-target compounds. Although conducted in 2011, the study illustrates a continuing challenge in multi-target screening: retrieval by individual classifiers does not necessarily translate into comparable retrieval when both predictions are required. Recent references provide clinical and methodological context; they were not used to develop or validate the original models.

Materials And Methods

Study design and compound population

This was an in silico, ligand-based screening study conducted in 2011 using compound-level bioactivity data. No human participants, animals, tissues, or patient records were involved. This report is based on the author's 2011 unpublished project report (Aisin I. *Discovery of Novel Dual Adenosine A2A Receptor and Monoamine Oxidase B Antagonists Using Machine Learning Methods*. National University of Singapore, 2011). The available report documents parts of the original workflow and preserves summary counts, but not the compound-level data. No models were retrained, and no new library screen was performed for this report. Later clinical literature is cited to place the original question in context.

Training compounds were reported before 2010, and the single-target evaluation sets comprised compounds reported in 2010 or later. Publication date alone does not establish structural independence. Duplicate structures, close analogues, and overlap between training and evaluation data could not be audited from the available records.

Compound-level bioactivity data were obtained from ChEMBL version 10: https://www.ebi.ac.uk/chembl, released on June 9, 2011. The data were retrieved on June 28, 2011. No new experimental bioactivity measurements were generated in this study. These existing data were used to develop and evaluate the support vector machine classifiers, which were subsequently applied to screen the PubChem and Molecular Design Limited Drug Data Report libraries.

Eligibility criteria and dataset size

Reported adenosine A2A receptor antagonists and MAO-B inhibitors were obtained from ChEMBL. The reported active-set threshold was a half-maximal inhibitory concentration (IC50) or inhibition constant (Ki) below 10 micromolar. Compounds without a qualifying value or outside the relevant reporting interval were excluded from that active set. Receptor antagonist labels were taken from the source annotations. Binding affinity alone cannot establish functional antagonism, and the original assay annotations could not be independently re-audited.

Putative inactive compounds were selected from chemical families without known activity at the corresponding target, following the general approach described by Han et al. [12]. This strategy broadens presumed-negative chemical-space coverage, but an absence of reported activity does not establish inactivity. Unrecognized active compounds may therefore have been included among the training negatives.

No formal sample-size calculation is documented. Dataset sizes reflect the compound collections available to the original analysis. Table *1* summarizes the reported active and presumed inactive sets.

Dataset	Reported actives (n)	Putative inactives (n)	Scope
Adenosine A2A receptor training	2,169	63,118	Reported before 2010; IC50 or Ki below 10 micromolar
Monoamine oxidase B training	187	66,366	Reported before 2010; IC50 or Ki below 10 micromolar
Adenosine A2A receptor later-active set	315	None evaluated	First reported in 2010 or later
Monoamine oxidase B later-active set	88	None evaluated	First reported in 2010 or later
Dual-target benchmark	14	None evaluated	Compounds from references [10,11]; independence from training not established

TABLE 1: Reported compound datasets

A2A denotes the adenosine A2A receptor subtype. MAO-B: monoamine oxidase B; IC50: half-maximal inhibitory concentration; Ki: inhibition constant. Counts are taken from the 2011 project report. Active training entries met the reported potency threshold and pre-2010 reporting cutoff. Later-reported active sets were defined by the publication-date cutoff; their structural independence from training could not be verified. Putative inactive compounds are presumed negatives, not confirmed assay negatives. All evaluation sets contain reported positives only. The 14-compound dual-target benchmark was attributed to references [10,11], but its independence from training is unconfirmed.

The reported training sets contained 65,287 entries for the A2A receptor model and 66,553 for the MAO-B model. The separate dual-target benchmark contained 14 compounds attributed to two earlier studies [10,11]. Both studies predate the training cutoff. Because the compound-level training records are unavailable, exclusion of these benchmark compounds and close analogues from training cannot be verified. This benchmark is therefore reported separately from the later-reported active-compound sets.

Molecular descriptors and model development

Each compound was represented by 98 one-dimensional and two-dimensional molecular descriptors, organized into four categories. Table *2* summarizes the reported categories and representative descriptor types, using established descriptor terminology [17]. These summaries do not constitute a complete, executable feature specification; the original calculation settings and ordered descriptor matrix are unavailable.

Descriptor class	Number	Representative descriptors
Simple molecular properties	18	Counts of carbon, nitrogen, oxygen, phosphorus, and sulfur atoms; total atom count; numbers of rings, bonds, and non-hydrogen bonds; molecular weight; rotatable bonds; hydrogen-bond donors and acceptors; aromatic and heterocyclic ring counts
Chemical properties	3	Sanderson electronegativity; molecular polarizability; aLogP
Molecular connectivity and shape	35	Schultz and Gutman topological indices; Wiener index; Harary index; Balaban J index; path counts; valence connectivity (chi) indices; Kier shape indices; Kappa alpha; molecular flexibility index
Electrotopological state	42	Electrotopological state (E-state) sums for individual atom types and for all heavy atoms, heteroatoms, and hydrogen-bond donors and acceptors

TABLE 2: Reported molecular descriptor categories

aLogP: an atom-based estimate of the logarithm of the octanol-water partition coefficient; E-state: electro-topological state. Counts sum to 98. Representative types describe the reported categories and established descriptor terminology [17]; the exact ordered feature list, implementation, and calculation settings are unavailable. This summary does not permit reconstruction of the original descriptor matrix.

Separate support vector machine (SVM) classifiers used a radial basis function kernel. The reported regularization parameter C was 100,000 for each model, with kernel-width parameter sigma values of 0.41 for the A2A receptor model and 0.81 for the MAO-B model. A large C imposes a high penalty for training misclassification, but its value alone does not establish overfitting. The original kernel implementation and its parameter convention could not be verified.

Because the original project records were incomplete, the ChEMBL release, extraction date, compound-standardization workflow, duplicate-handling rules, feature-scaling procedure, software version, cross-validation fold assignments, and random seeds could not be recovered. These limitations restrict exact reproduction of the original analysis. The analysis used software developed in-house by the Bioinformatics and Drug Design Group. Molecular descriptors were calculated using Molecular Descriptor Lab (MODEL) [18]. The specific software version used in the 2011 study was not recorded.

Validation and statistical analysis

Sigma was selected using five-fold cross-validation. Each model was trained on four folds and evaluated on the remaining fold, repeating the process until every fold had been evaluated. Values between 0.1 and 6 were considered. The exact selection criterion and aggregation of the reported performance metrics could not be verified. Parameter selection and internal performance estimation used the same cross-validation process; a separate nested evaluation is not documented. Fold-level predictions and confusion matrices are unavailable. Internal metrics that could not be reconciled were excluded from quantitative comparison rather than assigned an assumed correction.

Sensitivity is the fraction of reference-positive compounds retrieved. Specificity and accuracy additionally require reference-negative observations. The Matthews correlation coefficient summarizes the full binary confusion matrix and can help interpret performance when classes are imbalanced. Without the original predictions, the internal performance measures could not be recalculated.

The later-reported active-compound sets and the dual-target benchmark contain positives only. Their retrieval proportions describe sensitivity within the selected sets; specificity, precision, enrichment, and prospective experimental hit rate cannot be estimated from these evaluations. Two-sided 95% Wilson score intervals were calculated from the reported retrieval counts during manuscript revision. These descriptive intervals assume independent observations and may understate uncertainty when compounds belong to related chemical series.

Library screening

The historical screen applied both classifiers to approximately 13.56 million PubChem entries and 168,000 Molecular Design Limited Drug Data Report (MDDR) entries. Entries classified as positive by both models formed the reported intersection. These are classification outputs, not calibrated probabilities. Exact library snapshots, candidate identifiers, individual descriptor values, and compound-level outputs are unavailable, so the original intersection cannot be independently reconstructed.

The aggregate results and reported methods describe the historical analysis but do not permit exact reproduction. Table *2* summarizes descriptor categories rather than a complete feature specification. Missing database snapshots, processing records, model files, and compound-level outputs prevent reconstruction of the models and screening intersection. Figure *1* summarizes the documented workflow.

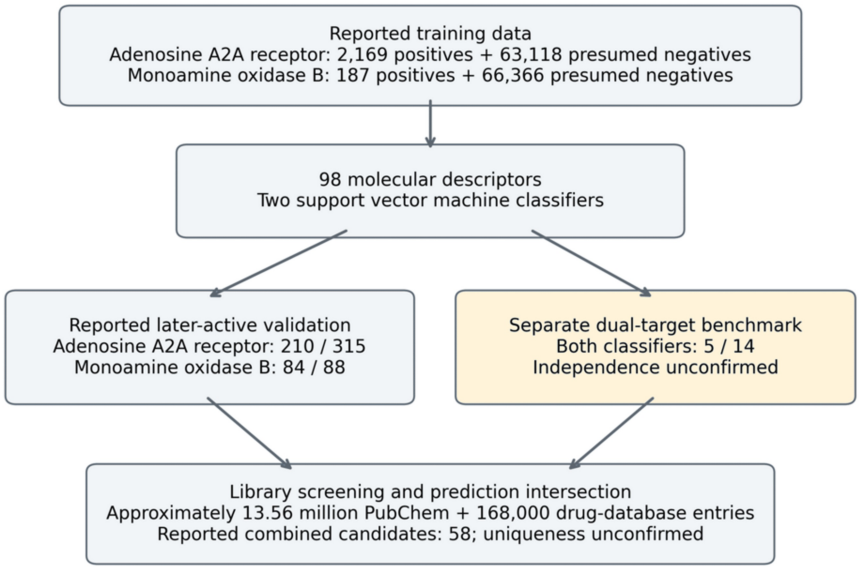


FIGURE 1: Ligand-based modeling and screening workflow

Schematic of the reported 2011 ligand-based workflow, redrawn for this manuscript. Separate support vector machine classifiers used 98 molecular descriptors. Later-reported active-compound retrieval is shown separately from the 14-compound dual-target benchmark, whose independence from training is unconfirmed. The final box gives the historical aggregate count of dual-positive entries; their identities, individual outputs, and uniqueness cannot be verified. The diagram is a summary of the reported workflow, not an executable reconstruction.

Results

Internal performance and retrieval of later-reported actives

The historical A2A receptor summary reported perfect internal classification at sigma 0.41. Retrieval was lower in the later-reported active-compound set: 210 of 315 compounds were identified, and 105 were missed, corresponding to 66.7% sensitivity. The available records do not distinguish the contributions of model-selection optimism, chemical similarity across folds, or differences between the training and later-reported compounds. Table *3* summarizes the historical internal results and their verification status.

Model	Reported sigma	Historical internal summary	Verification status
Adenosine A2A receptor classifier	0.41	Sensitivity, specificity, and accuracy reported as 100%; Matthews correlation coefficient reported as 1.000	Original fold predictions unavailable; not independently recalculated
Monoamine oxidase B classifier	0.81	Performance metrics withheld from quantitative comparison	Historical metrics could not be reconciled; no corrected value inferred

TABLE 3: Historical internal cross-validation results and verification status

Sigma is the reported radial basis function kernel-width parameter. Internal results were used for model selection and are not independent test estimates. Original fold-level predictions, confusion matrices, and metric-aggregation records are unavailable. The monoamine oxidase B summary could not be reconciled, so its sensitivity, specificity, accuracy, and Matthews correlation coefficient are not presented as verified estimates. No corrected value has been inferred.

Source: The 2011 project report.

The MAO-B model retrieved 84 of 88 later-reported inhibitors and missed four, corresponding to 95.5% sensitivity. Its historical internal metrics could not be reconciled without the original fold predictions and confusion matrices; they are therefore withheld from quantitative comparison. Table *3* distinguishes the historical internal summaries from their verification status. The two models were evaluated on different compound populations, so their retrieval percentages do not establish comparative screening performance.

In the separate dual-target benchmark, the A2A receptor classifier retrieved nine of 14 compounds. Requiring both classifiers to predict activity retained five of 14 and missed nine. Four compounds retrieved by the receptor classifier were excluded at the intersection step. The MAO-B classifier result for all 14 benchmark compounds was not recorded separately and cannot be inferred from the intersection. Table 4 presents the reported retrieval counts and descriptive intervals, separating the later-reported active sets from the benchmark. The later-reported active sets were assembled using the publication-date cutoff; their structural independence from training could not be verified.

Evaluation set	Retrieved	Sensitivity	95% Wilson score interval
Adenosine A2A receptor later-active set	210/315	66.7%	61.3% to 71.6%
Monoamine oxidase B later-active set	84/88	95.5%	88.9% to 98.2%
Adenosine A2A receptor classifier on dual-target benchmark	9/14	64.3%	38.8% to 83.7%
Both classifiers on dual-target benchmark	5/14	35.7%	16.3% to 61.2%

TABLE 4: Retrieval sensitivity in positive-only evaluation sets

Every set in Table 4 contains reported positives only. The interval for the benchmark is wide because the set is small, and the benchmark compounds may not be independent of the training data. Figure 2 presents the four retrieval proportions calculated from the aggregate counts recorded in the 2011 project report. The accompanying 95% Wilson score intervals were calculated during preparation of the present manuscript and were not part of the original analysis. These intervals are descriptive and do not account for possible dependence among structurally related compounds. They are shown because they make the uncertainty in a small count visible, above all in the 14-compound benchmark.

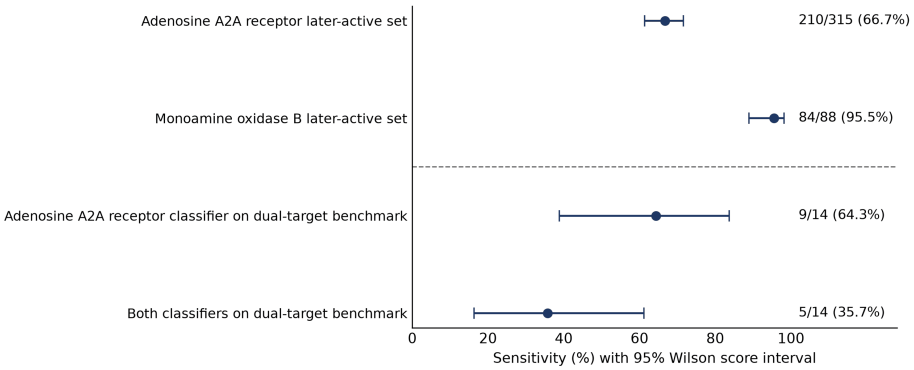


FIGURE 2: Retrieval sensitivity with descriptive uncertainty

Points show reported retrieval proportions, with two-sided 95% Wilson score intervals calculated from the aggregate counts during manuscript revision. The adenosine A2A receptor and monoamine oxidase B later-reported active sets contain 315 and 88 compounds, respectively. The separate dual-target benchmark contains 14 compounds and has unconfirmed independence from training. These are different positive-only populations; the figure does not compare prospective accuracy or experimental hit rate. Intervals assume independent observations and do not account for chemical-series clustering. The benchmark contributes two rows: the A2A classifier alone and both classifiers together.

The A2A receptor model produced more positive predictions than the MAO-B model in both libraries. Relative to the stated library sizes, both models classified a larger fraction of MDDR entries as positive than PubChem entries. Differences in library composition may contribute to this pattern, but its cause was not evaluated. Table 5 reports the aggregate counts and calculated positive-prediction fractions, which should not be interpreted as experimental hit rates.

Library	Entries screened (approximate)	Adenosine A2A receptor positive	Monoamine oxidase B positive
PubChem	13,560,000	8,285 (0.0611%)	1,307 (0.00964%)
Molecular Design Limited Drug Data Report	168,000	1,507 (0.897%)	69 (0.0411%)

TABLE 5: Reported single-target screening output

The screening summary in the 2011 project report recorded 58 entries predicted positive by both classifiers across the two libraries. The stated library sizes total approximately 13,728,000 entries before cross-library deduplication. Because the compound identifiers and the breakdown by library are unavailable, the number of distinct molecules among these 58 entries cannot be established. The 58 entries positive on both models are the overlap of the two single-target outputs across both libraries: 13,560,000 PubChem entries and 168,000 MDDR entries, for a total of 13,728,000 entries. The surviving summary does not divide the 58 between the libraries.

Discussion

This historical analysis examined whether separate ligand-based classifiers could retrieve compounds reported to act at both targets. Single-target retrieval was higher for MAO-B than for the A2A receptor in the respective later-reported active sets, while joint retrieval was five of 14 in the dual-target benchmark. These findings describe classifier behavior in selected positive sets. The reported 58 dual-positive screening entries remain an aggregate historical result because the identities and individual outputs are unavailable. The original goal of providing compounds that could be taken forward for experimental testing was therefore only partially fulfilled.

The target combination has a clinical rationale: adjunctive A2A receptor antagonism and MAO-B inhibition can improve motor fluctuations in levodopa-treated patients [3-8]. This does not establish an advantage for a single molecule with both activities. Such a molecule would couple exposure to the two mechanisms and limit independent dose adjustment. Both safinamide and istradefylline can worsen dyskinesia [5,6]. Balanced target potency, selectivity, brain exposure, and tolerability would need to be established before comparison with existing combination therapy. Figure *3* summarizes this rationale and the evidence required to evaluate it.

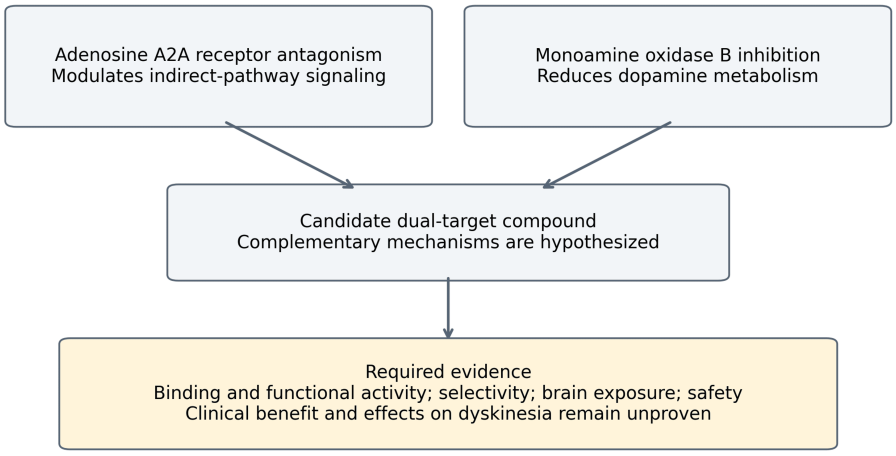


FIGURE 3: Pharmacologic rationale and required validation

Conceptual rationale for combining adenosine A2A receptor antagonism with monoamine oxidase B inhibition. The two mechanisms are complementary in principle; synergy, neuroprotection, and reduced dyskinesia were not demonstrated by this study. Binding, functional activity, target selectivity, brain exposure, safety, and clinical outcomes would require direct testing. Both approved comparator drugs can cause or worsen dyskinesia [5,6].

Earlier studies support the use of SVM methods for exploring large compound collections. Han et al.

evaluated broader presumed-inactive chemical-space coverage, while Ma et al. examined combinatorial classifiers and the effect of sparse active training sets [12-14]. Their enrichment and hit-rate estimates cannot be transferred to this study, which lacks comparable reference-negative evaluation data. More directly related structure-based studies also illustrate what additional evidence is needed. Jaiteh et al. screened approximately 5.4 million compounds and advanced 24 for experimental testing [19]. Perez-Castillo et al. combined docking scores to improve retrospective enrichment of known dual-target ligands [20]. The present analysis did not include experimental testing or a comparable ranking benchmark. Differences in datasets, endpoints, and validation prevent claims of superior performance. Clinical evidence supports MAO-B inhibitors for motor fluctuations, but does not validate these computational predictions [21]. The same approach was later applied to dopamine receptor subtype selective ligands, with similar retrieval behaviour on later reported compounds [22].

The reported decline from perfect internal A2A receptor classification to 66.7% retrieval of later-reported antagonists warrants caution. Selection of hyperparameters on the evaluation folds can produce optimistic estimates, and related chemical series may occur on both sides of a date cutoff. Later publication does not by itself establish structural independence. The high MAO-B retrieval proportion also leaves specificity and precision unresolved. In a library with a low prevalence of true actives, even a small false-positive rate can produce a large number of false-positive predictions. Prospective testing with appropriate controls would be needed to assess practical screening performance.

The models were developed from compounds reported before 2010, so their performance on current libraries or unfamiliar scaffolds is unknown. Neither the later-reported active sets nor the dual-target benchmark represents the prevalence of activity in a screening library. Because specificity was not measured on independently tested screening compounds, the number of false-positive predictions among the 58 reported entries cannot be estimated. A new screen with documented compound identities and appropriate validation would be needed to support experimental follow-up.

The group's related studies describe the development and application of SVM screening methods [12,14,22]. The present report documents the 2011 project using the records that remain. It preserves aggregate retrieval results but cannot provide the compound lists or complete prediction files needed for independent verification. Its conclusions are therefore limited to the reported evaluation results and do not extend to an actionable candidate list.

Limitations

The training labels introduce uncertainty. Presumed inactive compounds may include unrecognized actives, and heterogeneous assay conditions can affect reported potency. Binding measurements alone do not distinguish receptor antagonists from agonists. The surviving records do not support an independent audit of target species, functional annotations, standardization, or duplicate handling.

Validation is limited by model selection and the composition of the evaluation sets. A separate nested evaluation is not documented, and structural separation between training and evaluation compounds cannot be established. All later-reported evaluation compounds and all 14 benchmark compounds are reference positives, so these results cannot establish specificity, precision, or experimental hit rate. Possible overlap with training further limits interpretation of the small dual-target benchmark. The Wilson intervals describe binomial uncertainty only and do not account for related chemical series or curation decisions.

The loss of primary computational records is a substantial limitation. Database snapshots, extraction dates, software versions, descriptor settings, feature scaling, fold assignments, and random seeds are unavailable. The historical MAO-B internal metrics could not be reconciled and were withheld from quantitative comparison. Most importantly, the 58 candidate identifiers, structures, descriptors, individual predictions, and source-library assignments cannot be supplied. Their novelty, uniqueness, and suitability for follow-up therefore cannot be assessed. Acknowledging these gaps improves transparency but does not restore reproducibility or independently verify the principal screening result.

No candidate underwent experimental testing for binding, receptor antagonism, enzyme inhibition, selectivity, pharmacokinetics, or safety. Activity against other adenosine receptor subtypes and monoamine oxidase A was not modeled. Consequently, the study provides no evidence that the predicted entries have clinically useful dual activity, protect neurons, reduce dyskinesia, or offer therapeutic benefit.

Subsequent work has expanded molecular discovery through deep learning [23], protein-structure prediction [24], graph-based molecular representations [25], and prospective computational workflows coupled to laboratory testing [26]. These developments offer ways to revisit the target combination. A new analysis should document its data sources and processing, use chemically separated evaluation sets, compare models on the same benchmark, and publish compound-level predictions with code. Any reconstructed analysis would constitute new work and should be distinguished from the 2011 results.

Future studies should publish the training compounds, analysis code, and complete screening output.

Evaluation should include structurally independent active and inactive compounds, with model selection separated from performance estimation. Experimental testing would then be needed to determine whether predicted compounds have the intended activity at both targets.

Conclusions

The 2011 support vector machine models retrieved 210 of 315 later-reported adenosine A2A receptor antagonists and 84 of 88 monoamine oxidase B inhibitors. Requiring positive predictions from both classifiers retrieved five of the 14 known dual-target compounds. This result illustrates the loss of retrieval associated with the intersection approach in this benchmark, although the small sample and uncertain independence from the training data limit broader conclusions. These positive-only evaluations do not establish specificity or prospective screening performance, and overlap with training chemistry could not be excluded.

The original screening summary recorded 58 dual-positive entries across approximately 13.728 million library entries before cross-library deduplication. Their identities and individual predictions are unavailable, so this count cannot be independently verified or used to select compounds for testing. The report documents the historical results and their limits. Further investigation of this target combination will require reproducible compound-level predictions, independent evaluation, and experimental confirmation before any pharmacologic or clinical advantage can be assessed.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Ikken Aisin

Acquisition, analysis, or interpretation of data: Ikken Aisin

Drafting of the manuscript: Ikken Aisin

Critical review of the manuscript for important intellectual content: Ikken Aisin

Disclosures

Human subjects: All authors have confirmed that this study did not involve human participants or tissue. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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