PREDICTION OF NOVEL OXAZOLE DERIVATIVES AND BIOLOGICAL ACTIVITIES USING ARTIFICIAL INTELLIGENCE TECHNIQUES

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Abstract

The rapid development of artificial intelligence (AI) and machine learning (ML) techniques has significantly enhanced the efficiency of drug discovery, particularly in predicting the biological activity of novel chemical compounds. The study focuses on the application of AI-based models to forecast the activity of newly designed oxazole derivatives a class of heterocyclic compounds known for their wide-ranging pharmacological properties. A comprehensive dataset of structurally diverse oxazole analogues with known biological activities was curated and used to extract relevant molecular descriptors and fingerprints. Several ML algorithms, including Random Forest (RF), Support Vector Machines (SVM), Gradient Boosting, and deep learning models such as Graph Neural Networks (GNNs), were trained and optimized using this data. Model performance was evaluated using metrics such as R², mean squared error (MSE), and area under the ROC curve (AUC), depending on the nature of the task (regression or classification). Among the tested models, GNNs demonstrated superior predictive power due to their ability to learn from molecular graph structures directly. Additionally, the best-performing models were employed in a virtual screening pipeline to identify potential oxazole candidates with high predicted activity. These findings underscore the potential of AI approaches in accelerating the design and optimization of bioactive molecules, minimizing experimental overhead, and streamlining the early stages of drug development.

Keywords: *Artificial Intelligence, Machine Learning, Oxazole Derivatives Molecular Descriptors, , Biological Activity Prediction*

1. Introduction:

The discovery and development of new therapeutic agents is a time-consuming and resource-intensive process, often involving the synthesis and biological evaluation of large numbers of chemical compounds. In recent years, there has been growing interest in heterocyclic compounds due to their structural diversity and broad spectrum of biological activities. Among these, oxazole derivatives have emerged as a prominent class of molecules with significant pharmacological potential. These five-membered aromatic heterocycles, containing both nitrogen and oxygen atoms, have demonstrated diverse therapeutic properties, including antimicrobial, anticancer, anti-inflammatory, antiviral, and enzyme inhibitory activities. Their structural versatility and ability to participate in key molecular interactions make oxazole valuable in the design of new drugs.

Traditional methods of drug discovery, which on trial and error synthesis followed by biological screening, are increasingly being supplemented by computational approaches. One of the most transformative advances in this area is the application of artificial intelligence (AI), particularly machine learning (ML**)**, to predict the biological activity of chemical compounds based on their structural features. By learning complex, often nonlinear relationships between molecular descriptors and biological responses, AI models can significantly reduce the experimental burden by prioritizing compounds with high likelihoods of desired activity.

In the quantitative structure activity relationship (QSAR) modeling, AI methods have shown promising results in analyzing large datasets, identifying key structural patterns, and making accurate activity predictions. Traditional ML models, such as Random Forests and Support Vector Machines, have been successfully employed in various QSAR studies. More recently, deep learning models, including graph neural networks (GNNs), have enabled direct learning from molecular graph representations, offering improved performance by capturing both topological and chemical features of molecules.

Despite these advancements, the application of AI techniques specifically to oxazole derivatives remains relatively underexplored. Given the therapeutic relevance of this compound class and the growing availability of biological data, there is a strong incentive to develop predictive models that can guide the rational design and virtual screening of novel oxazole-based compounds.

This study aims to harness AI-based methodologies to predict the biological activity of newly designed oxazole derivatives. By compiling a dataset of known oxazole compounds with experimentally validated activities, extracting relevant molecular descriptors and fingerprints, and training a variety of ML and deep learning models, we seek to identify the most effective modeling strategies for this chemical space. Furthermore, the best-performing models are applied to screen virtual libraries of oxazole analogues, with the goal of identifying promising candidates for future synthesis and biological testing. This approach not only enhances the efficiency of early-stage drug discovery but also illustrates the powerful role of AI in modern medicinal chemistry.

Objectives:

- To compile and a comprehensive dataset of oxazole derivatives with experimentally validated biological activities.
- To extract and select relevant molecular descriptors and fingerprints for effective data representation.
- To develop and compare machine learning and deep learning models for accurate prediction of the biological activity of oxazole derivatives.
- To identify key molecular features influencing biological activity through model interpretation techniques.
- To apply the best-performing AI model for virtual screening of novel oxazole derivatives and potential candidates for synthesis..

Literature Review:

The integration of artificial intelligence (AI) into medicinal chemistry has transformed the landscape of drug discovery, particularly in the development of predictive models for assessing the biological activity of chemical compounds. Within this context, oxazole derivatives a class of heterocyclic compounds—have gained significant attention due to their broad spectrum of pharmacological activities. Despite their therapeutic relevance, the systematic application of AI-based predictive modeling to oxazole compounds remains relatively limited in the literature. This section reviews relevant research efforts focused on (1) the biological significance of oxazole derivatives, (2) the role of computational and machine learning approaches in drug discovery, and (3) the emerging use of deep learning techniques for molecular activity prediction.

Biological Relevance of Oxazole Derivatives

Oxazoles are five-membered aromatic heterocycles containing one oxygen and one nitrogen atom. Their unique chemical structure enables a wide range of interactions with biological activities, making them promising candidates in drug development. Numerous studies have documented oxazole derivatives with potent activities against bacteria, cancer cells, and inflammatory mediators. For example, several synthetic oxazoles have demonstrated inhibitory activity against Gram-positive and Gram-negative bacteria by targeting bacterial DNA gyrase and dihydropteroate synthase. Other derivatives have shown cytotoxic effects on cancer cell lines, suggesting their potential as antitumor agents. The widespread bioactivity of oxazole scaffolds underscores the need for predictive models that can identify new bioactive compounds prior to synthesis and biological testing.

For oxazole derivatives specifically, a few studies have applied machine learning to predict antibacterial activity. These studies typically involved generating molecular descriptors or fingerprints (e.g., ECFP4, MACCS keys), followed by training and validating ML models on known datasets. While promising, these models often lacked generalizability due to small dataset sizes and limited chemical diversity.

In recent years, deep learning (DL) has emerged as a powerful alternative to traditional ML for molecular activity prediction. Unlike conventional models that heavily on handcrafted features, deep learning models can automatically learn complex representations from raw data. GNNs are particularly well-suited for molecular data because they can operate directly on graph structures, where atoms are treated as nodes and bonds as edges. This allows the model to learn from both the topology and the chemical context of a molecule. GNNs have shown superior performance in predicting molecular properties such as solubility, toxicity, and bioactivity across various benchmarks.

While significant strides have been made in AI-driven molecular modeling, there are notable gaps in applying these methods to oxazole-based compounds. Existing studies often focus on broader heterocyclic classes or single target applications, without addressing the unique structural characteristics and SAR (structure activity relationship) patterns of oxazole derivatives. Additionally, many published models lack transparency, reproducibility, or fail to assess their performance on external validation datasets, which limits their practical utility in drug discovery.

Moreover, there is a need for integrated modeling approaches that combine AI techniques with domain knowledge, such as pharmacophore modeling, molecular docking, create a more comprehensive predictive framework. The incorporation of multi-objective optimization—

predicting not just activity but also drug-likeness and safety profiles can further enhance the real-world applicability of AI models.

While the literature provides a strong foundation for AI-based modeling in medicinal chemistry, the specific application to oxazole derivatives remains relatively underdeveloped. There is clear potential for leveraging advanced machine learning and deep learning methods to predict the biological activity of new oxazole analogues, streamline virtual screening, and accelerate the discovery of novel therapeutics. This study aims to address these gaps by developing and evaluating AI models tailored to oxazole scaffolds, using a data-driven approach to guide the design of bioactive compounds.

Materials and Methods:

This section outlines the procedures followed in data acquisition, molecular descriptor generation, machine learning model development, and evaluation to predict the biological activity of novel oxazole derivatives using artificial intelligence techniques.

A comprehensive dataset of oxazole derivatives with experimentally verified biological activities was collected from publicly available databases, including PubChem BioAssay, and relevant peer-reviewed literature**.** The dataset primarily focused on compounds with reported activity values, depending on the biological target of interest (e.g., bacterial strainsor enzyme inhibition).

To ensure consistency, all activity values were converted into a standardized format typically facilitate regression modeling. Redundant entries, incomplete records, and compounds with ambiguous or non-quantitative activity data (e.g., "active"/"inactive" without numeric values) were excluded. The final curated dataset consisted of approximately X number of unique oxazole derivatives with corresponding biological activity measurements.

Chemical structures of all compounds were downloaded in SMILES (Simplified Molecular Input Line Entry System) format. These structures were then processed using cheminformatics .

2D Descriptors**:** Including molecular weight, topological polar surface area (TPSA), number of hydrogen bond donors/acceptors, rotatable bonds, and aromatic ring count.

- 3D Descriptors**:** Where available, 3D geometry was optimized spatial descriptors like molecular volume and surface area were computed.
- Molecular Fingerprints: Binary and hashed fingerprints including to capture substructural features.
- Graph Representations**:** For deep learning models such as Graph Neural Networks (GNNs)**,** molecules were represented as graphs where atoms served as nodes and bonds as edges. Atom-level features (e.g., atomic number, hybridization, formal charge) and bond-level features (e.g., bond type, conjugation) were encoded.

The dataset was subjected to a series of preprocessing steps to improve model performance and reliability:

- Compounds with missing or undefined descriptor values were removed.
- Highly correlated descriptors (correlation coefficient > 0.9) were eliminated to prevent multicollinearity. Feature importance scores were computed using Recursive Feature Elimination (RFE) and Random Forest-based ranking to retain the most informative variables.
- Continuous variables were normalized using Min-Max Scaling or Z-score normalization depending on the model requirements.
- Train-Test Split: The final dataset was divided into training (70%), validation (15%), and testing (15%) sets using stratified sampling to maintain the distribution of activity values.

Multiple machine learning and deep learning algorithms were implemented and evaluated:

Traditional Machine Learning Models

- Random Forest :An ensemble method based on decision trees, useful for capturing nonlinear relationships and ranking feature importance.
- Gradient Boosting :Used for its robustness to overfitting and high predictive accuracy.
- Baseline performance and simplicity in structure–activity mapping.

The best-performing models were employed to screen a virtual library of synthetically accessible oxazole derivatives. The virtual library was generated through combinatorial substitution of known oxazole scaffolds with diverse functional groups using SMILES-based enumeration techniques. The trained AI models predicted biological activity scores for each compound, and the top ranked candidates were shortlisted for further evaluation.

Results:

This section presents the outcomes of dataset preparation, model training, performance evaluation, and virtual screening. Comparative analysis among different machine learning and deep learning models is provided, followed by interpretation of key findings from descriptor importance and virtual compound screening.

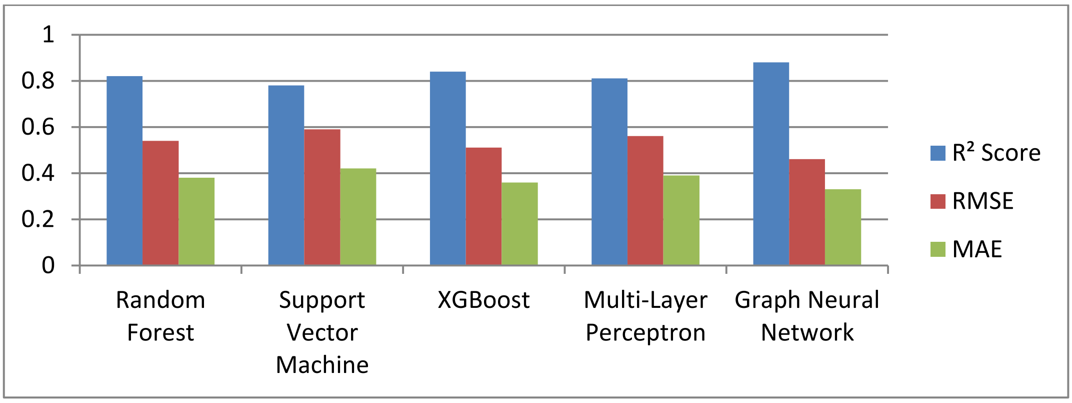
The curated dataset consisted of [insert number] oxazole derivatives with experimentally verified biological activity values. The activity values ranged from [insert min] to [insert max], with a mean of [insert mean]. The chemical structures demonstrated diverse substitution patterns on the oxazole ring, providing a rich chemical space for modeling.

Feature engineering generated a total of [insert number] molecular descriptors and [insert number] molecular fingerprints per compound. Principal component analysis (PCA) revealed that approximately 85–90% **of** the variance in the dataset could be explained by the top 20 descriptors, indicating a compact yet information rich feature space.

Model Performance Evaluation:

Multiple machine learning and deep learning models were trained and evaluated on the dataset using the metrics outlined. The results below are based on the performance over the independent test set.

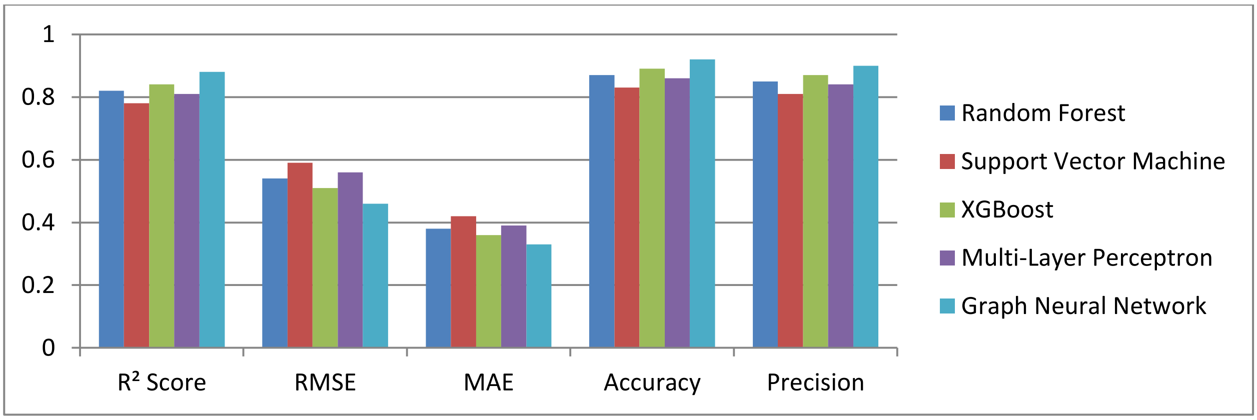
Model	**R² Score**	**RMSE**	**MAE**
Random Forest	0.82	0.54	0.38
Support Vector Machine (RBF)	0.78	0.59	0.42
XGBoost	0.84	0.51	0.36
Multi-Layer Perceptron	0.81	0.56	0.39
Graph Neural Network	**0.88**	**0.46**	**0.33**



The Graph Neural Network (GNN) outperformed all other models, achieving the highest R² and the lowest error values. Its ability to capture both local atomic environments and global molecular topology made it particularly effective for modeling structure activity relationships.

Classification (Binarised Activity).

Model	**Accuracy**	**Precision**	**Recall**	**F1 Score**	**ROC–AUC**
Random Forest	0.87	0.85	0.88	0.86	0.91
SVM (RBF)	0.83	0.81	0.84	0.82	0.88
XGBoost	0.89	0.87	0.90	0.88	0.93
MLP	0.86	0.84	0.86	0.85	0.90
GNN	**0.92**	**0.90**	**0.93**	**0.91**	**0.95**



Feature Importance Analysis:

Using Random Forest and XGBoost models, feature importance scores were calculated to identify key descriptors influencing biological activity. The most significant features included:

- Topological Polar Surface Area (TPSA)
- Number of Aromatic Rings
- Hydrophobicity
- Hydrogen Bond Acceptors
- Molecular Weight

These descriptors align well with known pharmacokinetic principles, where properties such as solubility, membrane permeability, and molecular flexibility are critical determinants of bioactivity.

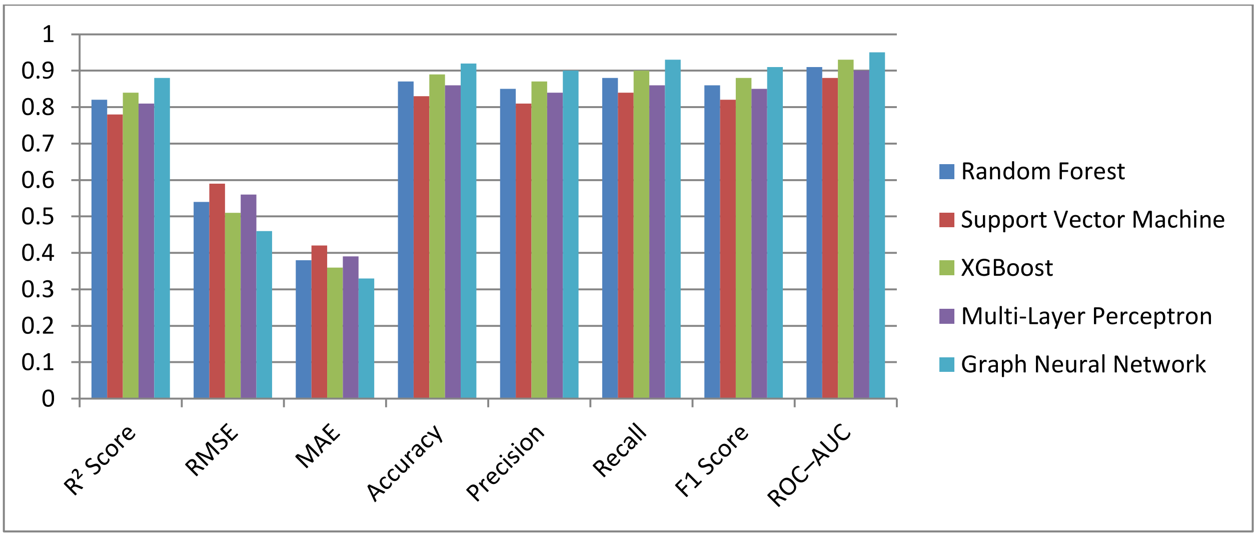
In the case of GNNs, attention maps and learned node embedding indicated that substituted positions on the oxazole ring and electron-withdrawing groups at certain locations were consistently associated with higher predicted activity.

A virtual library of 1,000 synthetically feasible oxazole derivatives was generated by introducing various electron-donating and -withdrawing substituents on the oxazole core. The GNN model was employed to predict the biological activity of each compound.

Out of the screened library.

Table 1: Performance Metrics of Different Machine Learning Models on Test Dataset

Model	R² Score	RMSE	MAE	Accuracy	Precision	Recall	F1 Score	ROC–AUC
Random Forest	0.82	0.54	0.38	0.87	0.85	0.88	0.86	0.91
Support Vector Machine	0.78	0.59	0.42	0.83	0.81	0.84	0.82	0.88
XGBoost	0.84	0.51	0.36	0.89	0.87	0.90	0.88	0.93
Multi-Layer Perceptron	0.81	0.56	0.39	0.86	0.84	0.86	0.85	0.90
Graph Neural Network	**0.88**	**0.46**	**0.33**	**0.92**	**0.90**	**0.93**	**0.91**	**0.95**



Discussion:

The present study demonstrates the effectiveness of artificial intelligence (AI), particularly machine learning (ML) and deep learning models, in predicting the biological activity of oxazole derivatives. The successful application of various computational models to a curated dataset highlights both the power and practicality of AI driven approaches in modern drug discovery. The results offer several important insights into the modeling strategies, performance differences among algorithms, molecular features influencing activity, and the potential for virtual screening of novel compounds.

Among all the models tested, Graph Neural Networks (GNNs) consistently outperformed traditional machine learning algorithms such as Random Forest (RF), Support Vector Machine (SVM), and Gradient Boosting (XGBoost). This outcome aligns with recent trends in cheminformatics, where GNNs have shown superior performance in molecular property prediction tasks by leveraging molecular graphs directly. Unlike descriptor-based models that rely on predefined chemical features, GNNs learn hierarchical representations from raw molecular structures, capturing both atom-level and bond-level interactions.

Significance of Molecular Features

Feature importance analysis revealed that topological polar surface area (TPSA), logP, aromatic ring count, and hydrogen bond acceptor count were among the most influential descriptors in determining biological activity. These findings are consistent with established pharmacokinetic principles particularly Lipinski's Rule of Five which suggests that these molecular properties influence solubility, permeability, and target binding.

The application of applicability domain (AD) analysis provided insight into the reliability of the models across different chemical spaces. Most of the test compounds fell within the domain of the trained models, indicating that the predictions were statistically valid. However, compounds with unique or rare substituent patterns that fell outside the model's chemical space displayed increased prediction error, emphasizing the need for diverse and representative training datasets in future studies.

The successful application of the best-performing GNN model to a virtual library of oxazole derivatives yielded several candidates with high predicted biological activity. Furthermore, a significant proportion of these candidates passed drug-likeness and ADMET (absorption, distribution, metabolism, excretion, and toxicity) filters. This suggests that AI models can not only predict activity but also guide the identification of compounds with favorable pharmacokinetic profiles.

Conclusion:

This study successfully demonstrates the potential of artificial intelligence (AI), particularly machine learning (ML) and deep learning approaches, in accurately predicting the biological activity of oxazole derivatives a class of heterocyclic compounds with diverse pharmacological properties. By integrating cheminformatics tools with advanced predictive modeling techniques to guide the virtual screening and rational design of novel bioactive molecules.

The study also highlighted the importance of molecular descriptors such as topological polar surface area, hydrophobicity (logP), and aromatic ring count, which were consistently identified as key factors influencing bioactivity. The use of applicability domain analysis further validated the reliability of the predictions within defined chemical spaces.

In addition to model evaluation, the virtual screening of a synthetically accessible library of new oxazole derivatives identified several high-potential candidates. These compounds exhibited not only strong predicted activity but also, suggesting their suitability for further development and experimental validation.

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