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FUJECE

Mesaj Aktarma Sinir Ağını Kullanarak Alzheimer Hastalığı için BACE-1 İnhibitörleri Verilerine İlişkin Etkileşim Tahmini

Suat TORAMAN[1]*, Bihter DAS[2]

[1]Hava Trafik Kontrol Bölümü, Sivil Havacılık Yüksekokulu, Fırat Üniversitesi, Elazığ, Türkiye.
[2]Yazılım Mühendisliği Bölümü, Teknoloji Fakültesi, Fırat Üniversitesi, Elazığ, Türkiye.
[1]storaman@firat.edu.tr, [2]bihterdas@firat.edu.tr

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Öz

Beyin hücrelerinin zamanla ölmesine bağlı olarak hafıza kaybı, demans ve bilişsel işlevlerde genel bir azalma şeklinde gelişen tıbbi duruma Alzheimer hastalığı denir. Bu hastalık, bilişsel işlevlerde kademeli bir düşüşe ve sonuçta kişinin günlük yaşamını etkileyen ciddi hafıza kayıplarına yol açabilmektedir. Alzheimer hastalığına neden olan mekanizma tam olarak anlaşılmamasına rağmen beyindeki plaklar ve nörofibriler demetler gibi bazı yapısal değişikliklerle ilişkilendirilmiştir. Bu çalışma, Alzheimer hastalığının tedavisinde ümit verici olan BACE-1 inhibitörlerinin keşfi için geometrik derin öğrenme yönteminin kullanımını araştırmaktadır. Eğitim sürecinde İletişim Geçiş Sinir Ağı ve Tamamen Bağlantılı Ağ kullanılarak özelleştirilmiş bir model geliştirilmiştir. Bu model, moleküler yapıların karmaşık özelliklerini yakalamak için grafik yerleştirmelerin ve tamamen bağlantılı ağların birleşimi yoluyla molekül etkileşimlerini tahmin etmektedir. Sonuçlar, geliştirilen modelin BACE-1 inhibitörlerinin etkileşimlerini başarılı bir şekilde tahmin edebildiğini göstermektedir. Modelin performans oranı %87,7 olarak belirlenmiştir. Bu çalışma, Alzheimer hastalığına yönelik yeni BACE-1 inhibitörlerinin keşfedilmesi ve geliştirilmesi için umut verici bir yol haritası sunmaktadır.

Anahtar kelimeler: BACE-1 ilaç etkileşimi, Alzheimer hastalığı, Geometrik derin öğrenme, Grafik ağı, BACE-1 inhibitörleri

*Yazışılan Yazar

İntihal Kontrol: Evet – Turnitin
Şikayet: fujece@firat.edu.tr

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Interaction Prediction on BACE-1 Inhibitors Data for Alzheimer Disease using Message Passing Neural Network

Suat TORAMAN[1]*, Bihter DAS[2]

[1]Air Traffic Control, Civil Aviation High School, Firat University, Elazig, Türkiye.
[2]Department of Software Engineering, Technology Faculty, Firat University, Elazig, Türkiye.
[1]storaman@firat.edu.tr, [2]bihterdas@firat.edu.tr

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Abstract

The medical condition that develops as memory loss, dementia, and a general decrease in cognitive functions due to the death of brain cells over time is called Alzheimer's disease. This disease can lead to a gradual decline in cognitive functions and eventually severe memory losses that affect a person's daily life. Although the exact mechanism that causes Alzheimer's disease is not fully understood, it has been associated with certain structural changes in the brain, such as plaques and neurofibrillary bundles. This study investigates the use of geometric deep learning methods for the discovery of BACE-1 inhibitors that are promising in addressing Alzheimer's disease. Our study builds on these advancements by integrating GDL with pharmacological criteria, such as the QED criterion and Lipinski's rule, to predict BACE-1 inhibitors with enhanced accuracy and drug-like properties. Our model, which combines message-passing neural networks (MPNNs) and fully connected network (FCN) architectures, achieved a success rate of 87.7%. This performance not only surpasses that of previous studies but also ensures the practical applicability of our findings in drug discovery for Alzheimer's disease. The dual focus on prediction accuracy and drug likeness sets our work apart, providing a more comprehensive approach to identifying effective therapeutic agents.

Keywords: BACE-1 drug interaction, Alzheimer's disease, Geometric deep learning, Graph network, BACE-1 inhibitors.

*Corresponding author

1. Introduction

Alzheimer's disease is a form of dementia that progresses slowly and increases with age, leading to cognitive impairment, memory loss, and eventually difficulty in activities of daily living. The disease is characterized by nerve cells in the brain becoming damaged and dying over time [1,2]. It is the most prevalent form of dementia and usually has a progressive course. The pathophysiology of Alzheimer's disease revolves around two key features, namely the accumulation of beta amyloid plaques and the formation of neuronal fibrillary tangles. These plaques and tangles block communication between nerve cells and lead to neuronal death. Alzheimer's disease is a health problem that is common in the elderly population and still has no cure. The pathophysiology of this disease is complex and is affected by factors such as the accumulation of beta amyloid (Aβ) plaques and abnormal accumulation of tau protein leading to neuronal toxicity. In the beginning of these pathological processes, the BACE-1 enzyme, also known as beta-secretase, plays a critical role [3,4]. Beta-secretase 1 (BACE-1), which plays a critical role in the production of beta amyloid (Aβ) peptides, is an enzyme associated with Alzheimer's disease [5]. BACE-1 initially produces the Aβ42 peptide by cleaving the amyloid precursor protein (APP). Aβ42 is one of the main components of toxic amyloid beta plaques that accumulate in the pathological process of Alzheimer's disease and cause the death of nerve cells. Therefore, the inhibition or diminishment of BACE-1 activity is being explored as a strategy to treat or prevent AZ. Inhibitors targeting the BACE-1 enzyme have garnered significant attention in research and development as potential therapeutic avenues for addressing AZ. Understanding the role of this enzyme's function is crucial in elucidating the pathophysiology of AZ and devising potential treatment modalities [6].

The geometric deep learning (GDL) approach is the application of advanced geometry techniques to drug data used to predict drug interactions by providing precise representations of molecular structures. Numerous studies in the literature delve into drug interactions using geometric deep learning. For instance, the work by Shen et al. [7] showcases the efficacy and promise of geometric deep learning in molecular data analysis. Specifically, research shows that molecular graphs composed solely of non-covalent bonds can yield comparable or superior results compared to those based on covalent bonds, which are conventionally accepted as the standard for representing molecular topology at the atomic level. In the context of geometric deep learning (GDL), molecules are typically modeled as molecular graphs, density functions, or molecular surfaces, and these representations are analyzed using various deep learning models such as (3D) convolutional neural networks (CNNs), graph neural networks (GNNs), recurrent neural networks (RNNs), and others [8-10]. In another investigation, researchers applied geometric deep learning techniques to drug discovery and the design processes of bioorganic and medicinal chemistry. Authors investigated the potential of geometric deep learning in tasks such as molecular property prediction, ligand binding site and location prediction, and structure-based new molecule design [11]. Additional studies [12-15] delve into the integration of symmetry information into 3D molecular representations and its incorporation into neural network architectures. These studies assess the efficacy of these methods, particularly in structured learning processes, and their utilization in structure-based drug design. Furthermore, a comprehensive review [16] offers insights into recent literature on GDL studies for drug discovery and symmetry learning. The review highlights GDL's applications in drug discovery, including tasks like molecular property prediction, interactions, design, conformation prediction, and 3D pretraining, while also addressing associated challenges. Nugroho et al. developed and optimized a fingerprint-based artificial neural network (ANN) model using three different Bat Algorithm strategies to predict Beta-secretase 1 (BACE-1) inhibitors as therapeutic agents for Alzheimer's disease [17]. More recently, Feinberg et al. [18] applied 3D convolutional neural networks (3D-CNNs) to molecular surfaces, achieving high accuracy in predicting protein-ligand binding affinities. Their study highlighted the importance of three-dimensional molecular representations in capturing interaction nuances. Ragoza et al. [19] developed a deep learning model that incorporates both 2D and 3D information of molecules for drug-target interaction predictions. Their model achieved state-of-the-art performance, showcasing the advantages of integrating multiple molecular representations.

In our study, we leverage both GDL and pharmacological criteria to predict interactions of BACE-1 inhibitors. Unlike previous studies, our model integrates MPNN and fully connected network (FCN) architectures, achieving a success rate of 87.7%. This study also advances the literature by providing a quantifiable success rate, which is often missing in previous studies. By incorporating pharmacological

criteria such as the QED criterion and Lipinski's rule, our model ensures not only effective interaction predictions but also favorable drug-like properties of the inhibitors. This dual focus enhances the practical applicability of our findings, offering a more comprehensive approach to drug discovery for Alzheimer's disease.

In this paper, we aim to use a geometric deep learning approach to perform interaction predictions for Alzheimer's disease on BACE-1 data. GDL has indeed emerged as a powerful method in molecular interaction prediction because it allows more precise representation of molecular structures and more accurate modeling of interaction mechanisms. This study also targets to make valuable contributions to the discovery of new therapeutic targets and drug development for the treatment and prevention of Alzheimer's disease. Application of geometric deep learning methods to interaction predictions on BACE-1 data may lead to the discovery of potential BACE-1 inhibitors and the development of innovative approaches to the treatment of Alzheimer's disease. This study aims to offer a new perspective in the fight against Alzheimer's disease and shed light on advancing treatment strategies. The main contributions of this study are outlined below:

- It offers a new approach to drug interaction prediction for Alzheimer's disease by investigating the use of geometric deep learning methods on BACE-1 data.
- Interaction predictions obtained through the use of MPNN based method can guide the design and optimization of BACE-1 inhibitors.
- The study contributes to a better understanding of the molecular interactions between the BACE-1 enzyme and potential inhibitors. This allows for the development of more effective strategies during the drug design process.

The structure of this paper as follows: Section 2 presents an in-depth exploration of the materials and methods employed. Section 3 delves into the experimental findings and discussions. Following that, Section 4 outlines the limitations encountered and suggests future avenues of research. Finally, Section 5 concludes the study of the paper.

2. Materials and Method

This section outlines the materials and methodologies employed in the study for the prediction of interactions with BACE-1 inhibitors. It encompasses the dataset description, model architecture, training procedure, and evaluation metrics utilized in the experiment. The proposed algorithm encompasses three key steps: dataset collection, training, and prediction. Additionally, Figure 1 shows the block diagram of the proposed model, providing a visual representation of the methodology employed in the study.

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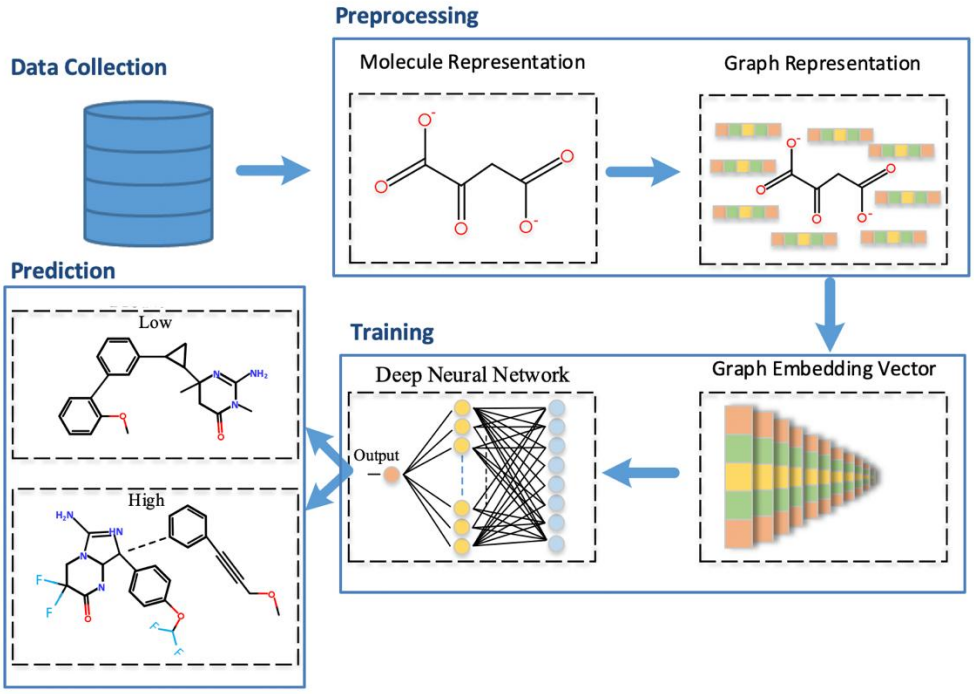


Figure 1. The block diagrams of the GDL based model

2.1. Data collection

This section provides an overview of the dataset employed in the study. It includes quantitative (IC50) measurements and qualitative (binary label) binding outcomes, obtained from experiments conducted on a range of compounds targeting human β-secretase 1 (BACE-1). BACE-1 is an enzyme involved in the production of beta-amyloid peptides, which accumulate in the brains of Alzheimer's patients, contributing to the disease's progression. The BACE dataset includes a variety of columns and parameters that are crucial for developing and evaluating potential BACE-1 inhibitors. These features are broadly categorized into molecular descriptors, activity measurements, and annotations related to Alzheimer's disease. The dataset originates from the BACE data, specifically curated for research on Alzheimer's disease therapeutics. The dataset utilized in this study was sourced from https://moleculenet.org/datasets-1 database [20]. It comprises 1513 compounds represented in the SMILES format. The dataset is partitioned into training of 80%, validation of 10%, and test of 10% subsets. Additionally, the dataset's scaffold and rec-split methods were employed to ensure diverse representation and robust evaluation. 1D and 2D descriptive features were used to represent the compounds in the study. Basic molecular feature information such as molecular weight, number of hydrogen bond donors and acceptors, and LogP (partition coefficient) were selected as 1D descriptors. These descriptors are necessary to evaluate the drug-likeness of compounds based on Lipinski's rule of five. 2D descriptors, on the other hand, capture the molecular topology and include features such as the number of rings, the number of rotatable bonds, and the presence of specific functional groups. They provide a more detailed representation of the structure of the molecule. Table 1 shows the dataset used in the experiment.

Table 1. The detailed features of the dataset

Mol	CID	Class	pIC50	MW	AlogP	HBA	HBD	RB	Heavy Atom Count	Chiral Center Count	Chiral Center CountAll	Ring Count	PSA	Estate	MR	Polar
O1CC[C@@H](NC(=O)[C@@H](Cc2cc3cc(ccc3nc2N)-c2ccccc2C)C)CC1(C)C	BACE_1	1	9.1549015	431.56979	4.4014001	3	2	5	32	2	2	4	77.239998	67.251999	129.9039	58.397999
Fc1cc(cc(F)c1)C[C@H](NC(=O)[C@@H](N1CC[C@](NC(=O)C)(CC(C)C)C1=O)CCc1ccccc1)[C@H](O)[C@@H]1[NH2+]C[C@H](OCCC)C1	BACE_2	1	8.8538723	657.81073	2.6412001	5	4	16	47	6	6	4	124.58	115.417	173.6176	76.254997
S1(=O)(=O)N(c2cc(cc3c2n(cc3CC)CC1)C(=O)N[C@H]([C@H](O)C[NH2+]Cc1cc(OC)ccc1)Cc1ccccc1)C	BACE_3	1	8.6989698	591.74091	2.5499001	4	3	11	42	2	3	5	125.86	96.585999	160.12421	75.639
O=C(NCC1CCCCC1)[C@@H](Cc1cc2cc(ccc2nc1N)-c1ccccc1C)CCC	BACE_4	1	7.9586072	443.6236	7.0788999	2	2	8	33	1	1	4	68.010002	66.001999	137.3194	61.431
S1(=O)(=O)C[C@@H](Cc2cc3c([nH]cc3CC(F)F)cc2)[C@H](O)[C@@H]([NH2+]Cc2cc(ccc2)C(C)(C)C)C1	BACE_5	1	7.2596374	505.6402	2.7595999	2	3	8	35	3	4	4	95.150002	87.500999	132.3071	60.943001
O1[C@@H]2COCC[C@@]2(N=C1N)c1cc(ccc1)-c1cncnc1	BACE_6	0	4.0030508	296.32379	0.87709999	5	0	2	22	2	2	4	82.620003	47.750999	80.689301	37.137001
[NH+]=1[C@](N=C(c2ccccc2)C=1N)(C)c1cc(ccc1)-c1cccnc1	BACE_7	0	4	327.4024	1.4339	2	0	3	25	1	1	4	65.239998	49.251999	97.589897	48.525002
n1cccc(NCc2cc(ccc2)-c2cccnc2)c1N	BACE_8	0	4	276.33569	2.2346001	2	2	4	21	0	0	3	63.830002	44.334999	86.700699	41.577
O1CCC(OC(=O)[C@@H]2[NH2+]C[C@]3(C2)c2c(NC3=O)cccc2)CC1	BACE_9	0	3.9430952	317.35959	-1.0807	4	2	3	23	2	2	4	81.239998	53.084	80.653801	36.096001
O=C1NC(=NC(=C1)CCc1cc2[nH]ccc2cc1)N	BACE_10	0	3.8860567	254.2872	1.7381001	2	3	3	19	0	0	3	87.559998	44.001999	75.263802	34.915001

2.2. Pre processing

This section describes the preprocessing steps applied to prepare the dataset for training the geometric deep learning-based model. In the experimental study, raw data represented in SMILES (Simplified Molecular Line Entry System) format was first converted into molecular graphs. The choice to use the SMILES format is to represent the structure of chemical compounds efficiently and concisely. The preprocessing steps began with parsing each compound's SMILES string to generate its corresponding molecular graph, identifying atoms and bonds, and constructing a graph where atoms are nodes and bonds are edges. These molecular graphs were then processed to extract node features such as atom types, hybridization states, and aromaticity, along with edge features like bond types and bond orders, which are crucial for accurately representing the molecules' chemical properties. Next, these molecule representations were used to construct graph structures suitable for input into the Message Passing Neural Network (MPNN), where each node (atom) was represented by a feature vector and each edge (bond) by an attribute vector. Feature normalization was applied to ensure that all input features were on a similar scale, enhancing the stability and performance of the neural network.

2.3. Training

This section elucidates the training protocol for our proposed model, which integrates a Message Passing Neural Network (MPNN) to forecast interactions with BACE-1 inhibitors. The training unfolds in two pivotal stages: MPNN and FCN. MPNN, a specialized neural network architecture tailored for processing molecular data depicted as graphs [21], plays a central role. It facilitates the conversion of graph data structure into a vector termed as a graph embedding. This embedding vector undergoes iterative updates grounded on messages exchanged among nodes within the graph. Leveraging MPNN, node feature vectors are transmuted into a distinct space, thereby enabling the generation of graph embedding [22-24]. Originally introduced by Gilmer et al., this approach reshapes spatial and spectral architectures within graph networks through two discernible phases: message passing and readout. Moreover, MPNN serves as a supervised learning framework for graphs, empowering the redefinition of spatial and spectral architectures within graph networks. MPNN's message passing and readout stages contribute to the model's ability to capture intricate structural and functional characteristics of molecules. By incorporating MPNN into our training pipeline, we aim to exploit the rich information present in molecular structures to accurately predict interactions with BACE-1 inhibitors.

In the GDL-based model used, the metric space is created by excluding the reading function. Since the entire graph is examined to predict molecule interactions with BACE inhibitors for results, simply placing node proximity information in the embedding field will not be sufficient. Within the proposed GDL framework, embedding values undergo processing through a fully connected layer to facilitate prediction. This layer comprises four dense layers, with a dropout rate of 20% implemented in the first three layers to counter overfitting. The initial dense layer encompasses 92 neurons, succeeded by 46 neurons in the second layer, 23 neurons in the third layer, and a solitary neuron in the output layer. Activation functions encompass ReLu for the first three layers and sigmoid for the final layer. The architecture of the methodology employed in the experimental application is delineated in Figure 2.

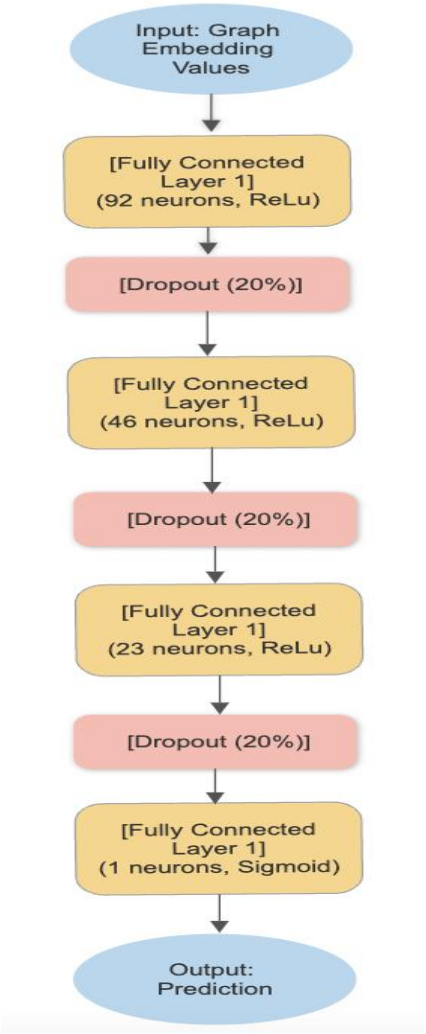


Figure 2. The Architecture of the FC Network Component

2.4. Prediction of interaction

In estimating the interaction of BACE-1 inhibitors, the Quantitative Estimates of Drug-likeness (QED) criterion is utilized [25,26]. This criterion allows quantitative evaluation of a combination of a compound's biological effect, drug properties, and pharmacological properties. This measure is calculated by evaluating molecular properties through a series of mathematical and statistical analyses. A compound with a higher QED score is considered to be more likely to succeed in the drug development process. Therefore, QED is used as an important tool in drug design and discovery processes. Figure 3 shows the interaction rates of QED on the BACE-1 inhibitors.

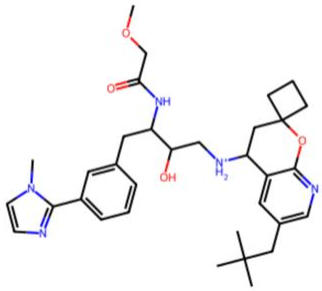
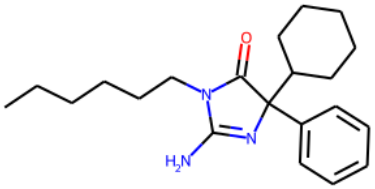
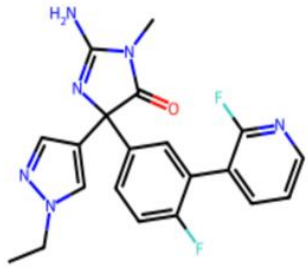
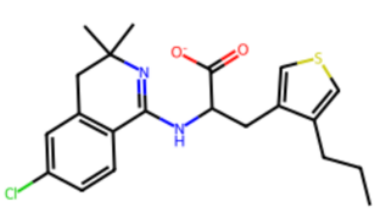
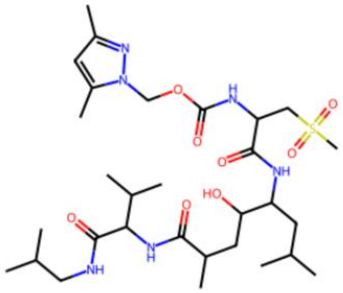
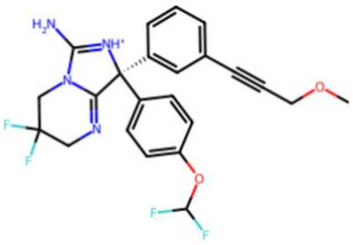
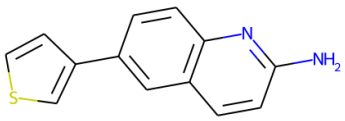
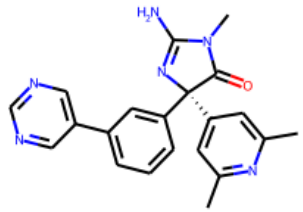
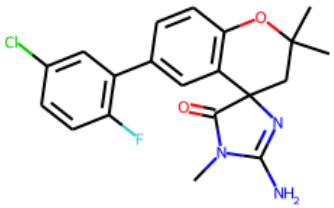
		
O1c2ncc(cc2C([NH2+]CC(O)C(NC(=O)COC)Cc2cc(ccc2)-c2nccn2C)CC12CCC2) CC(C)(C)C	O=C1N(CCCCCC)c(=NC1(C1CCCCC1)c1ccccc1)N	Fc1ccc(cc1-c1cccnc1F)C1(N=C(N)N(C)C1=O)c1cn(nc1)CC
y_true/ y_pred = 1/0.87	y_true/ y_pred = 0/0.21	y_true/ y_pred = 1/0.80
		
Clc1cc2CC(N=C(NC(Cc3cscc3CCC)C(=O)[O-])c2cc1)(C)C	S(=O)(=O))CC(NC(OCn1nc(cc1C)C)=O)C(=O)NC(C(O)CC(C=O)NC(C(C)C)C(=O)NCC(C)C)C)CC(C)C)C	FC1(F)CN2C(=NC1)[C@](NH+]=C2N)(c1cc(ccc1)C#CCOC)c1ccc(OC(F)F)cc1
y_true/ y_pred = 0/0.15	y_true/ y_pred = 1/0.50	y_true/ y_pred = 1/0.87
		
s1cc(cc1)-c1cc2c(nc(N)cc2)cc1	O=C1N(C)C(=N[C@]1(c1cc(nc(c1)C)C) c1cc(ccc1)-c1cncnc1)N	Clc1cc(-c2cc3c(OC(CC34N=C(N)N(C)C4=O)(C)C)cc2)c(F)cc1
y_true/ y_pred = 1/0.16	y_true/ y_pred = 0/0.64	y_true/ y_pred = 1/0.50

Figure 3. The QED results for interaction on BACE-1 inhibitors

3. Experimental Results and Discussion

In this study, Lipinski's rule was also taken into account for the prediction of drug interactions of BACE-1 inhibitors. The Lipinski rule consists of a set of rules used to evaluate whether oral bioavailability of a compound is likely [27]. This rule is important for determining the pharmacokinetic properties of a compound and is widely used in the development of drug candidates. Lipinski's rules are [28]:

- The molecular weight of the molecule has not been more than 500.
- The total number of hydrogen bonds (sum of N and O atoms) has not been more than 5.
- The number of donor hydrogen bonds has not been more than 5.
- To determine the lipophilicity of the molecule, the distribution coefficient (LogP) value should not be more than 5.

The BACE-1 drug interaction prediction performance value obtained by using the GDL model was determined as 0.877. To assess the effectiveness of the GDL model, the area under the curve (AUC) was calculated, indicating the accuracy of the proposed model. The ROC curve was used to provide a clearer

visual interpretation of the drug prediction of BACE-1 inhibitors. Figure 4 shows the results of the AUC, F1 score and negative predictive value performance values of the proposed model. Figure 4 shows that the AUC value approaches 90. In the ROC curve, the under the curve is defined as AUC. The desired situation is for the ROC curve to be close to 1. This shows that the discrimination of the system is high. In Figure 4a, the high AUC value shows that the discrimination of the system is high.

Accuracy is a performance criterion that is frequently used to measure the success of a model, but is not sufficient to measure system performance. F1 score is used to avoid making a wrong choice, especially when there is an imbalance in data between classes. Figure 4b shows the F1 score values for the training and validation data sets. As seen in Figure 4b, the F1 score reached approximately 80% at the end of 60 epochs.

When a test result is negative, the value that indicates the probability of the result actually being negative is called Negative Predictive Value. As can be seen in Figure 4c, it was actually negative, but the percentage defined as negative in the system was approximately 78%.

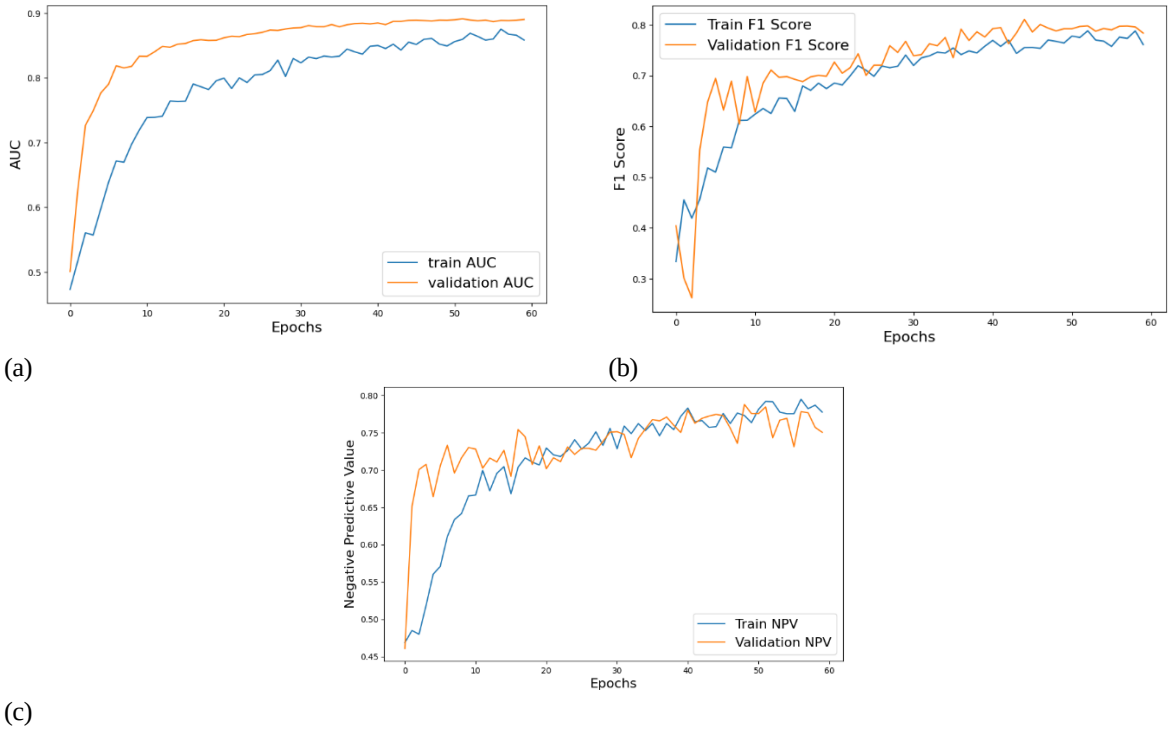


Figure 4. (a) The AUC (b) The F1 Score (c) The Negative Predictive Value performance of GDL based model

This study examined the potential role of BACE-1 inhibitors in the treatment of Alzheimer's. When we review other studies in the existing literature [29-32], there is sample evidence that BACE-1 inhibitors are an important therapeutic strategy targeting AD pathology. In particular, BACE-1 inhibitors have been shown to inhibit Aβ oligomerization and consequent amyloid plaque formation and thus may slow disease progression. Other studies in the literature reveal that BACE-1 inhibitors often face significant challenges in terms of their selectivity and drug-like properties. In this study, we showed that the GDL model we developed provides a high accuracy in predicting the efficacy of BACE-1 inhibitors. It is important to highlight the potential use of this model as a tool in the design and screening of BACE-1 inhibitors. However, the current study has some limitations. For example, the data set used was limited and only covered a specific chemical space. Additionally, further work is required on the generalizability and applicability of the GDL model to other molecular targets. Additionally, we think this study is an important step to further investigate the potential of BACE-1 in the treatment of AD. In the future, with further experimental studies and clinical trials, it will be possible to realize this potential and develop an effective therapeutic strategy in the treatment of AD.

Upon reviewing the literature, it is evident that many studies in the field do not explicitly report success rates in a manner that allows for direct comparison. For example, studies by Korolev et al. [33], Wang et al. [34], and Ghosh et al. [35] focus primarily on clinical and biochemical evaluations, providing valuable insights into binding mechanisms and pharmacokinetic properties, but do not offer quantifiable success rates for predictive modeling. This study makes significant contributions to the literature by leveraging geometric deep-learning techniques to predict interactions of BACE-1 inhibitors, an approach not widely explored in previous studies. Unlike traditional methods, our model utilizes the Message Passing Neural Network (MPNN) and Fully Connected Network (FCN) to effectively capture and represent complex molecular structures and their interactions. A key superiority of our study is the quantifiable success rate of 87.7%, which demonstrates the robustness and accuracy of our predictive model. This metric provides a clear benchmark for future research and offers a measurable improvement over previous studies that often lack explicit success rates.

4. Conclusion

This study assessed the applicability of geometric deep learning techniques in forecasting interactions of BACE-1 inhibitors for addressing Alzheimer's disease. During the training process, a customized model was developed using a Communication Transition Neural Network (MPNN) and Fully Connected Network (FCN). This model predicts molecule interactions through the combination of graph embedding and fully connected networks to capture complex structural and functional features in molecular structures. Our results show that the geometric deep learning model we developed can successfully predict the interactions of BACE-1 inhibitors. The performance rate of our model was evaluated based on the curve under area (AUC) value and was determined as 87.7%. By using pharmacological criteria such as the QED criterion and Lipinski's rule, the effectiveness of our model has further increased. These findings offer a novel approach for identifying and developing potential BACE-1 inhibitors aimed at treating Alzheimer's disease.

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6. Author Contribution Statement

S.T. contributed to the design, analysis of the data, interpretation of the results, spelling check and content, and B.D. contributed to the creation of the idea, literature review, analysis of the data, interpretation of the results, spelling check and checking the paper in terms of content.

7. Ethics Committee Approval and Conflict of Interest

There is no need for an ethics committee approval in the prepared paper. There is no conflict of interest with any person/institution in the prepared paper.

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