PRINT ISSN 1119-8362
Electronic ISSN 2659-1499

Full-text Available Online at
https://www.ajol.info/index.php/jasem
https://www.bioline.org.br/ja

J. Appl. Sci. Environ. Manage.
Vol. 29 (3) 737-745 Mar. 2025

Artificial Intelligence and Machine Learning Approaches for Target-Based Drug Discovery: A Focus on GPCR-Ligand Interactions

OTUN, MO

Faculty of Pharmacy, Obafemi Awolowo University, Ile Ife, Osun State, Nigeria

**Corresponding Author Email: otunmartins@outlook.com*
**ORCID: https://orcid.org/0009-0007-1805-0195*
**Tel: +2348140998174*

ABSTRACT: G protein-coupled receptors (GPCRs) represent one of the most significant classes of drug targets due to their pivotal roles in various physiological processes and disease mechanisms. Traditional methods of drug discovery targeting GPCR-ligand interactions are often time-consuming, resource-intensive, and limited by experimental constraints. The advent of artificial intelligence (AI) and machine learning (ML) has revolutionized target-based drug discovery, offering innovative approaches to predict GPCR-ligand interactions with enhanced accuracy and efficiency. This review explores the integration of AI and ML techniques in GPCR-targeted drug discovery, highlighting their potential to accelerate lead identification, optimize ligand binding predictions, and improve structure-activity relationship modeling. We discuss various AI/ML algorithms, including supervised learning, deep learning, and reinforcement learning, and their applications in ligand-based and structure-based drug design. Additionally, we examine the challenges associated with data quality, model interpretability, and computational limitations. The review also emphasizes emerging trends, such as the use of neural networks and transfer learning, which are reshaping the landscape of drug discovery. By focusing on GPCR-ligand interactions, this paper provides insights into how AI and ML can transform traditional drug development processes, ultimately contributing to more effective and targeted therapeutics.

DOI: https://dx.doi.org/10.4314/jasem.v29i3.7

Cite this Article as: OTUN, M. O. (2025). Artificial Intelligence and Machine Learning Approaches for Target-Based Drug Discovery: A Focus on GPCR-Ligand Interactions. *J. Appl. Sci. Environ. Manage.* 29 (3) 737-745

Dates: Received: 22 January 2025; Revised: 20 February 2025; Accepted: 09 March 2025; Published: 31 March 2025

Keywords: Ligand interactions; Target-based drug discovery; Artificial intelligence; Machine learning, Structure-activity relationship

Target-based drug discovery (TDD) is a systematic approach to identifying and developing new therapeutic agents by focusing on specific molecular targets, such as proteins or nucleic acids, that are implicated in disease pathways. This approach has revolutionized the pharmaceutical industry by enabling the design of drugs with high specificity and reduced off-target effects. Over the past few decades, TDD has become the cornerstone of modern drug development, leveraging advancements in genomics, proteomics, and computational biology to identify and validate drug targets (Hughes *et al*., 2011). However, the process of drug discovery remains time-consuming, costly, and fraught with challenges, including the need to screen vast chemical libraries and predict drug-target interactions with high accuracy. G protein-coupled receptors (GPCRs) represent one of the most important classes of drug targets due to their critical role in cellular signaling and their involvement in a wide range of physiological processes. GPCRs are implicated in numerous diseases, including cancer, cardiovascular disorders, and neurological conditions, making them a prime focus for therapeutic intervention (Hauser *et*

**Corresponding Author Email. otunmartins@outlook.com*
**ORCID: https://orcid.org/0009-0007-1805-0195*
**Tel: +2348140998174*

al., 2017). Approximately 34% of all FDA-approved drugs target GPCRs, underscoring their significance in pharmacology (Sriram and Insel, 2018). Despite their therapeutic potential, GPCRs present unique challenges for drug discovery, such as their structural complexity, conformational dynamics, and the difficulty of predicting ligand-binding interactions. These challenges necessitate innovative approaches to accelerate the identification of GPCR-targeting drugs. Artificial intelligence (AI) and machine learning (ML) have emerged as transformative tools in drug discovery, offering the potential to streamline and enhance various stages of the process. AI and ML algorithms can analyze vast datasets, identify patterns, and make predictions with remarkable accuracy, making them particularly well-suited for target-based drug discovery.

In the context of GPCR-ligand interactions, AI and ML approaches have been employed to predict binding affinities, optimize lead compounds, and design novel ligands with desired pharmacological properties (Gawehn *et al*., 2020). For instance, deep learning models have been used to predict GPCR-ligand binding sites and simulate receptor dynamics, providing insights into the molecular mechanisms of drug action (Stokes *et al*., 2020). Furthermore, AI-driven platforms can integrate multi-omics data, structural biology, and chemical information to identify promising drug candidates and reduce the time and cost associated with traditional drug discovery pipelines. The integration of AI and ML into GPCR drug discovery has already yielded promising results. For example, virtual screening powered by ML algorithms has enabled the identification of novel GPCR ligands with high specificity and efficacy (Bender *et al*., 2021). Additionally, generative AI models have been used to design de novo molecules that target GPCRs, opening new avenues for drug development (Zhavoronkov *et al*., 2019).

These advancements highlight the potential of AI and ML to address the challenges of GPCR drug discovery and accelerate the development of next-generation therapeutics. The combination of target-based drug discovery and AI/ML technologies represents a powerful paradigm for modern drug development. By focusing on GPCR-ligand interactions, researchers can leverage the predictive power of AI and ML to overcome the limitations of traditional approaches and unlock new opportunities for therapeutic innovation. As these technologies continue to evolve, they are poised to play an increasingly central role in the discovery of novel drugs targeting GPCRs and other molecular targets.

Overview of GPCRs and Ligand Interactions Structural and Functional Characteristics of GPCRs: G protein-coupled receptors (GPCRs) are a large and diverse family of membrane proteins that play a central role in cellular signaling and physiological processes. Structurally, GPCRs are characterized by a conserved seven-transmembrane (7TM) α-helical architecture, with an extracellular N-terminus, an intracellular C-terminus, and alternating extracellular and intracellular loops connecting the helices (Hilger *et al*., 2018). This structural framework enables GPCRs to transmit extracellular signals, such as hormones, neurotransmitters, and light, into intracellular responses. GPCRs are highly dynamic proteins that can adopt multiple conformational states, including inactive, intermediate, and active states, which are stabilized by ligand binding and interactions with intracellular signaling partners (Weis and Kobilka, 2018). The structural plasticity of GPCRs is critical for their ability to recognize a wide range of ligands and initiate diverse signaling cascades.

GPCRs are classified into six major families (A-F) based on sequence homology and functional characteristics, with Class A (rhodopsin-like) being the largest and most extensively studied (Alexander *et al*., 2019). Despite their structural diversity, GPCRs share common functional mechanisms, including ligand-induced conformational changes, G protein coupling, and downstream signal transduction. Recent advances in structural biology, such as cryo-electron microscopy (cryo-EM) and X-ray crystallography, have provided high-resolution insights into GPCR architecture and dynamics, enabling a deeper understanding of their functional mechanisms (Kang *et al*., 2018). These structural insights have also facilitated the rational design of drugs targeting GPCRs.

Significance of GPCRs as Drug Targets: GPCRs are among the most important drug targets in modern pharmacology due to their widespread involvement in human physiology and disease. Approximately 800 GPCRs are encoded in the human genome, and they regulate a wide range of processes, including neurotransmission, immune responses, metabolism, and sensory perception (Hauser *et al*., 2017). Dysregulation of GPCR signaling is implicated in numerous diseases, such as cancer, cardiovascular disorders, diabetes, and neurological conditions, making GPCRs attractive targets for therapeutic intervention (Sriram and Insel, 2018). Notably, GPCR-targeting drugs account for a significant proportion of FDA-approved medications, including beta-blockers, antihistamines, and antipsychotics

(Hauser *et al*., 2017). The therapeutic potential of GPCRs is further underscored by their ability to interact with a diverse array of ligands, including small molecules, peptides, and proteins. This ligand diversity enables the development of drugs with high specificity and efficacy. However, the structural complexity and functional versatility of GPCRs also pose challenges for drug discovery. For example, many GPCRs exhibit promiscuous ligand binding, leading to off-target effects, while others have poorly characterized signaling pathways, complicating the identification of selective modulators (Hilger *et al*., 2018). These challenges highlight the need for innovative approaches to study GPCR-ligand interactions and develop targeted therapies.

Mechanisms of GPCR-Ligand Binding and Signaling Pathways: The binding of ligands to GPCRs is a highly dynamic and regulated process that initiates a cascade of intracellular signaling events. Ligands can be classified as agonists, antagonists, or inverse agonists based on their effects on receptor activity. Agonists stabilize the active conformation of GPCRs, promoting G protein coupling and downstream signaling, while antagonists block agonist binding and prevent receptor activation. Inverse agonists stabilize the inactive conformation, reducing basal receptor activity (Weis and Kobilka, 2018). The binding of ligands to GPCRs occurs at orthosteric sites, which are the primary ligand-binding pockets, or allosteric sites, which are distinct from the orthosteric site and modulate receptor activity indirectly (Wootten *et al*., 2018). Allosteric modulators offer advantages such as increased selectivity and reduced side effects, making them an attractive area of drug discovery. Upon ligand binding, GPCRs undergo conformational changes that facilitate the recruitment and activation of intracellular signaling partners, primarily heterotrimeric G proteins and β-arrestins. G proteins are composed of α, β, and γ subunits and are classified into four major families (Gs, Gi/o, Gq/11, and G12/13) based on their α subunits (Alexander *et al*., 2019). Activation of G proteins leads to the dissociation of the α subunit from the βγ dimer, enabling both components to regulate downstream effectors such as adenylyl cyclase, phospholipase C, and ion channels. These effectors generate second messengers, including cyclic AMP (cAMP), inositol trisphosphate (IP3), and calcium ions, which propagate the signal within the cell (Hilger *et al*., 2018). In addition to G protein-mediated signaling, GPCRs can activate β-arrestin-dependent pathways, which regulate receptor desensitization, internalization, and non-canonical signaling (Wootten *et al*., 2018). The ability of GPCRs to engage multiple signaling pathways, known as biased signaling, has opened new avenues for drug discovery. Biased ligands selectively activate specific pathways, offering the potential to achieve therapeutic effects while minimizing adverse effects (Smith *et al*., 2018). For example, biased agonists targeting the angiotensin II type 1 receptor (AT1R) have been developed to treat cardiovascular diseases with reduced side effects (Wootten *et al*., 2018).

The complexity of GPCR signaling is further influenced by factors such as receptor oligomerization, post-translational modifications, and interactions with scaffold proteins. These factors contribute to the spatiotemporal regulation of GPCR activity and enable fine-tuning of cellular responses (Smith *et al*., 2018). Understanding the molecular mechanisms of GPCR-ligand interactions and signaling pathways is essential for the rational design of drugs that modulate GPCR activity with high precision.

AI and ML in Drug Discovery: General Concepts

Artificial intelligence (AI) refers to the broad field of creating systems capable of performing tasks that typically require human intelligence, such as problem-solving, decision-making, and pattern recognition (Russell and Norvig, 2021). Within AI, machine learning (ML) is a subset focused on developing algorithms that enable computers to learn from and make predictions based on data without explicit programming (LeCun *et al*., 2015). Deep learning (DL), a specialized branch of ML, employs neural networks with multiple layers to model complex patterns in large datasets, excelling in tasks like image recognition and natural language processing (Goodfellow *et al*., 2016). While AI encompasses all intelligent computational techniques, ML specifically deals with algorithms learning from data. DL, on the other hand, represents a more advanced form of ML that automates feature extraction through hierarchical data representations, making it particularly effective in drug discovery applications where high-dimensional data is prevalent (Esteva *et al*., 2019).

Key Algorithms Used in Drug Discovery: Several AI/ML algorithms are pivotal in drug discovery:

Supervised Learning: This approach trains models on labeled datasets to predict outcomes. Algorithms like support vector machines (SVMs), random forests (RF), and gradient boosting machines (GBMs) are commonly used for tasks such as predicting drug-target interactions and toxicity profiling (Chen and Guestrin, 2016).

Unsupervised Learning: This method identifies hidden patterns in unlabeled data. Techniques like k-means clustering and principal component analysis (PCA) are employed for chemical space exploration and identifying novel drug candidates (Xu and Wunsch, 2005).

Reinforcement Learning: Here, models learn optimal actions through trial and error, guided by reward signals. Reinforcement learning has shown promise in de novo drug design, optimizing molecular structures for desired pharmacological properties (Olivecrona *et al*., 2017).

Data Types and Sources for AI/ML Models

The effectiveness of AI/ML models in drug discovery heavily relies on the quality and diversity of input data. Common data types include:

Genomic Data: Provides insights into gene expression profiles and genetic variations relevant to disease mechanisms. Databases like The Cancer Genome Atlas (TCGA) and GenBank serve as primary sources (Weinstein *et al*., 2013).

Molecular Structures: Essential for modeling drug-receptor interactions. The Protein Data Bank (PDB) and PubChem are widely used repositories (Berman *et al*., 2000).

High-Throughput Screening (HTS) Data: Offers large-scale bioactivity information critical for identifying potential drug candidates. ChEMBL is a notable database for bioactivity data (Gaulton *et al*., 2017).

AI/ML Approaches for GPCR-Ligand Interaction Prediction: The integration of artificial intelligence (AI) and machine learning (ML) into drug discovery has revolutionized the study of GPCR-ligand interactions. These computational approaches enable the prediction of binding affinities, identification of novel ligands, and optimization of drug candidates with unprecedented speed and accuracy. AI/ML methods can be broadly categorized into ligand-based, structure-based, and hybrid approaches, each offering unique advantages for GPCR drug discovery.

Ligand-Based Approaches: Ligand-based approaches rely on the chemical and structural properties of known ligands to predict the activity of new compounds. These methods are particularly useful when the 3D structure of the GPCR target is unknown or poorly characterized.

Quantitative Structure-Activity Relationship (QSAR) Models: QSAR models are a cornerstone of ligand-based drug discovery, correlating the physicochemical properties of ligands with their biological activity. Machine learning algorithms, such as random forests, support vector machines (SVMs), and deep neural networks, have been employed to build predictive QSAR models for GPCR ligands (Gao *et al*., 2020). For example, deep learning-based QSAR models have been used to predict the binding affinity of ligands for GPCRs such as the dopamine D2 receptor, achieving high accuracy and generalizability (Stokes *et al*., 2020). These models leverage large datasets of ligand-activity pairs, enabling the identification of key molecular features that contribute to binding affinity and selectivity.

Pharmacophore Modelling: Pharmacophore modelling is another powerful ligand-based approach that identifies the essential features of a ligand required for binding to a GPCR. These features include hydrogen bond donors/acceptors, hydrophobic regions, and aromatic rings. Machine learning algorithms have been integrated into pharmacophore modeling to improve the accuracy of feature identification and virtual screening (Yang *et al*., 2019). For instance, ML-enhanced pharmacophore models have been used to identify novel ligands for the adenosine A2A receptor, a GPCR target for Parkinson's disease (Heilker *et al*., 2021). By combining pharmacophore modeling with ML, researchers can prioritize compounds with the highest likelihood of binding to the target GPCR.

Structure-Based Approaches: Structure-based approaches leverage the 3D structure of GPCRs to predict ligand binding and optimize drug candidates. These methods are particularly valuable when high-resolution GPCR structures are available.

Molecular Docking and Scoring Functions: Molecular docking is a widely used structure-based method for predicting the binding pose and affinity of ligands within the GPCR binding pocket. Traditional docking algorithms rely on scoring functions to rank potential ligand poses, but these functions often struggle with the flexibility and complexity of GPCRs. Machine learning has been integrated into docking workflows to improve scoring accuracy and account for receptor flexibility (Guedes *et al*., 2021). For example, deep learning-based scoring functions have been developed to predict binding affinities for GPCR-ligand complexes, outperforming traditional methods in virtual screening campaigns (Jiménez-Luna *et al*., 2020).

Molecular Dynamics Simulations Enhanced by ML: Molecular dynamics (MD) simulations provide insights into the dynamic behavior of GPCR-ligand complexes, including conformational changes and binding kinetics. However, MD simulations are computationally expensive and limited by timescale constraints. Machine learning has been used to accelerate MD simulations and enhance their predictive power. For instance, ML algorithms have been employed to predict stable GPCR conformations and identify allosteric binding sites (Noé *et al*., 2020). Additionally, ML-enhanced MD simulations have been used to study the binding mechanisms of biased agonists targeting the β2-adrenergic receptor, providing insights into pathway-specific signaling (Miao *et al*., 2020).

Hybrid Approaches Combining Ligand-Based and Structure-Based Methods

Hybrid approaches integrate the strengths of ligand-based and structure-based methods to improve the accuracy and efficiency of GPCR-ligand interaction prediction. These methods combine chemical information from known ligands with structural insights from GPCR models, enabling a more comprehensive understanding of binding mechanisms.

For example, hybrid workflows have been developed to combine QSAR models with molecular docking, allowing researchers to prioritize compounds with both favorable chemical properties and binding poses (Gao *et al*., 2020). Similarly, pharmacophore modeling has been integrated with MD simulations to identify ligands that stabilize specific GPCR conformations associated with therapeutic effects (Heilker *et al*., 2021). These hybrid approaches are particularly useful for studying GPCRs with complex binding mechanisms, such as those involving allosteric modulators or biased signaling. One notable application of hybrid methods is the discovery of novel ligands for the serotonin 5-HT2A receptor, a GPCR target for psychiatric disorders. By combining ligand-based virtual screening with structure-based docking and MD simulations, researchers identified new compounds with high selectivity and efficacy (Wang *et al*., 2021). These findings highlight the potential of hybrid AI/ML approaches to accelerate GPCR drug discovery.

Applications of AI/ML in GPCR-Targeted Drug Discovery: G protein-coupled receptors (GPCRs) represent one of the largest and most pharmacologically important families of membrane proteins, with over 800 members in the human genome. They are involved in a wide range of physiological processes and are the target of approximately 35% of FDA-approved drugs. Despite their therapeutic significance, drug discovery for GPCRs remains challenging due to their structural complexity, dynamic nature, and diverse signaling pathways. Artificial intelligence (AI) and machine learning (ML) have emerged as transformative tools in GPCR-targeted drug discovery, enabling researchers to overcome traditional bottlenecks and accelerate the development of novel therapeutics. This paper explores four key applications of AI/ML in GPCR drug discovery: virtual screening and hit identification, lead optimization and activity prediction, de novo drug design using generative models, and predicting GPCR functional selectivity (biased agonism).

Virtual Screening and Hit Identification: Virtual screening (VS) is a computational approach used to identify potential drug candidates from large chemical libraries. Traditional VS methods, such as molecular docking, are often limited by computational cost and accuracy. AI/ML-based approaches, however, have revolutionized this process by leveraging large datasets to predict ligand-GPCR interactions with high precision. For instance, deep learning models like convolutional neural networks (CNNs) and graph neural networks (GNNs) have been employed to screen billions of compounds against GPCR targets. A recent study by Stokes *et al*. (2020) demonstrated the use of deep learning to identify novel antibiotics, showcasing the potential of AI in hit identification for GPCRs. Additionally, AlphaFold, developed by DeepMind, has provided high-accuracy GPCR structural predictions, enabling more reliable virtual screening campaigns (Jumper *et al*., 2021). These advancements have significantly reduced the time and cost associated with experimental screening, making AI-driven VS a cornerstone of modern GPCR drug discovery.

Lead Optimization and Activity Prediction: Once potential hits are identified, the next step is lead optimization, which involves refining the chemical structure to improve potency, selectivity, and pharmacokinetic properties. AI/ML models have proven invaluable in this process by predicting the activity of compounds against GPCRs and optimizing their chemical properties. For example, quantitative structure-activity relationship (QSAR) models, enhanced by ML algorithms, can predict the binding affinity and functional activity of ligands with high accuracy. Recent work by Yang *et al*. (2022) utilized transfer learning to predict GPCR-ligand interactions, achieving state-of-the-art performance in activity prediction. Furthermore, AI-driven platforms like

Atomwise and Insilico Medicine have integrated ML models to optimize lead compounds, reducing the need for extensive experimental testing. These tools enable researchers to prioritize the most promising candidates, accelerating the lead optimization process.

De Novo Drug Design Using Generative Models: De novo drug design involves the creation of novel drug-like molecules from scratch, tailored to specific targets. Generative models, such as variational autoencoders (VAEs) and generative adversarial networks (GANs), have emerged as powerful tools for this purpose. These models can generate chemically valid and diverse compounds that are optimized for GPCR binding. For instance, Insilico Medicine's generative chemistry platform has successfully designed novel GPCR-targeted molecules with potential therapeutic applications (Zhavoronkov *et al*., 2019). Additionally, reinforcement learning (RL) has been applied to guide the generation of molecules with desired properties, such as high binding affinity and low toxicity. The integration of generative models with high-throughput screening data has further enhanced their ability to produce drug-like molecules, making de novo drug design a promising avenue for GPCR-targeted drug discovery.

Predicting GPCR Functional Selectivity (Biased Agonism): GPCRs can activate multiple signaling pathways, a phenomenon known as functional selectivity or biased agonism. This property allows ligands to selectively activate beneficial pathways while avoiding adverse effects, making it a highly desirable feature in drug development. However, predicting biased agonism is challenging due to the complex interplay between ligand-receptor interactions and downstream signaling. AI/ML models have made significant strides in this area by analyzing large datasets of GPCR signaling profiles. For example, Kooistra *et al.* (2021) developed an ML-based framework to predict biased signaling for GPCR ligands, enabling the identification of compounds with tailored functional selectivity. These models leverage structural and pharmacological data to predict how ligands will modulate GPCR signaling, providing valuable insights for the design of safer and more effective drugs.

Case Studies and Recent Advances

Success Stories of AI/ML in GPCR-Targeted Drug Discovery: Artificial intelligence (AI) and machine learning (ML) have significantly impacted G protein-coupled receptor (GPCR)-targeted drug discovery. A notable example is the application of deep learning techniques to predict GPCR-ligand interactions, which has streamlined the identification of potential therapeutic compounds. For instance, the development of machine learning models capable of predicting ligand binding affinities has accelerated the screening process, reducing the reliance on traditional trial-and-error methods (Raschka and Kaufman, 2020).

Notable Databases and Tools: The advancement of AI/ML in GPCR research is supported by several specialized databases and tools:

ChEMBL: A comprehensive database that curates bioactive molecule data with drug-like properties, facilitating the training of ML models for drug discovery applications.

GPCRdb: An integrative platform providing detailed information on GPCR sequences, structures, and functions, essential for modeling and simulation studies (Kooistra *et al*., 2021).

DeepChem: An open-source toolkit that offers ML models and algorithms tailored for drug discovery, enabling researchers to implement and test predictive models efficiently.

Emerging Trends: Transfer Learning, Explainable AI, and Multi-Task Learning

Emerging trends in AI/ML are further enhancing GPCR-targeted drug discovery:

Transfer Learning: This approach involves leveraging knowledge from pre-trained models on large datasets to improve predictions on specific GPCR targets, thereby enhancing model performance even with limited data (Raschka and Kaufman, 2020).

Explainable AI: Developing models that provide interpretable results is crucial for understanding the underlying biological mechanisms and gaining trust in AI-driven predictions.

Multi-Task Learning: By simultaneously training models on multiple related tasks, researchers can improve predictive performance and uncover shared representations among different GPCR targets.

Challenges and Limitations

Data Quality, Availability, and Bias: The effectiveness of AI/ML models in GPCR drug discovery is heavily dependent on the quality and quantity of available data. Challenges include incomplete datasets, measurement errors, and biases that can lead to inaccurate predictions. Ensuring data

diversity and implementing rigorous validation protocols are essential to mitigate these issues (Raschka and Kaufman, 2020).

Model Interpretability and Transparency: Many AI/ML models, particularly deep learning architectures, operate as "black boxes," offering limited insight into their decision-making processes. This opacity hinders the ability to understand and trust model predictions, emphasizing the need for developing interpretable models that can elucidate the relationships between molecular structures and their biological activities.

Generalization to Novel Targets and Ligands: AI/ML models trained on existing data may struggle to generalize to novel GPCR targets or ligands that are underrepresented in the training datasets. This limitation can impede the discovery of drugs for new or rare targets, highlighting the necessity for models capable of extrapolating beyond learned knowledge.

Computational Cost and Resource Limitations: Developing and deploying sophisticated AI/ML models require substantial computational resources and expertise. This demand can be a barrier for some research institutions, underscoring the importance of resource-sharing initiatives and the development of more efficient algorithms.

Future Perspectives

Integration of AI/ML with Experimental Methods: Combining AI/ML approaches with traditional experimental techniques can create a synergistic effect, enhancing the efficiency and success rate of GPCR-targeted drug discovery. For example, AI-driven predictions can guide experimentalists toward the most promising compounds, while experimental data can, in turn, refine and validate AI models.

Advancements in AI Architectures: The evolution of AI architectures, such as transformers and graph neural networks, offers new avenues for modeling complex biological systems. These architectures can capture intricate relationships within molecular data, potentially leading to more accurate predictions of GPCR-ligand interactions.

Potential for Personalized Medicine and Precision Pharmacology: AI/ML models hold the promise of tailoring drug discovery to individual patient profiles by considering genetic variations in GPCRs and personalizing treatments accordingly. This approach could lead to more effective and safer therapies, aligning with the goals of personalized medicine.

Conclusion: Artificial intelligence (AI) and machine learning (ML) are transforming G protein-coupled receptor (GPCR)-targeted drug discovery by enhancing various stages of the process. AI/ML techniques facilitate the identification of new ligand-GPCR interactions, predict clinical responses, and aid in understanding GPCR functions. Notable applications include virtual screening, where AI models predict ligand binding affinities, expediting the identification of potential therapeutic compounds. Databases like ChEMBL and GPCRdb provide valuable data for training these models, while tools such as DeepChem offer specialized algorithms for drug discovery. Emerging trends like transfer learning, explainable AI, and multi-task learning further enhance model performance and interpretability. However, challenges persist, including issues with data quality, model transparency, and generalization to novel targets. Addressing these limitations is crucial for the continued advancement of AI/ML applications in GPCR drug discovery.

Declaration of Conflict of Interest: The authors declare that there is no conflict of interest among them.

Data Availability: Data are available upon request from first author.

REFERENCES

Alexander, SP; Christopoulos, A; Davenport, AP; Kelly, E; Mathie, A; Peters, JA; CGTP Collaborators (2019). The Concise Guide to PHARMACOLOGY 2019/20: G protein-coupled receptors. *Br. J. Pharmacol.* 176(S1): S21-S141. https://doi.org/10.1111/bph.14748

Bender, A; Cortés-Ciriano, I; Watson, O (2021). Artificial intelligence in drug discovery: What is realistic, what are illusions? *Drug Discov. Today*, 26(2): 511-524.

Berman, HM; Westbrook, J; Feng, Z; Gilliland, G; Bhat, TN; Weissig, H; Shindyalov, IN; Bourne, PE (2000). The Protein Data Bank. *Nucleic Acids Res.* 28(1): 235–242.

Chen, T; Guestrin, C (2016). XGBoost: A Scalable Tree Boosting System. In Proceedings of the 22nd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining (pp. 785–794).

Esteva, A; Kuprel, B; Novoa, RA; Ko, J; Swetter, SM; Blau, HM; Thrun, S (2019). A Guide to Deep Learning in Health care. *Nat. Med.* 25(1): 24–29.

Gao, K; Nguyen, DD; Wei, GW (2020). Machine learning in drug discovery and development. *Acc. of Chem. Res.* 53(8): 1426-1436. https://doi.org/10.1021/acs.accounts.0c00285

Gaulton, A; Hersey, A; Nowotka, M; Bento, AP; Chambers, J; Mendez, D; Mutowo, P; Atkinson, F; Bellis, LJ; Cibrian-Uhalte, E; Davies, M; Dedman, N; Karlsson, A; Magariños, MP; Overington, JP; Papadatos, G; Smit, I; Leach, AR (2017). The ChEMBL Database in 2017. *Nucleic Acids Res.* 45(D1): D945–D954.

Gawehn, E; Hiss, JA; Schneider, G (2020). Deep learning in drug discovery. *Mol. Inform.* 39(1-2): 1900105.

Goodfellow, I; Bengio, Y; Courville, A (2016). Deep Learning. MIT Press. Pp. 234

Guedes, IA; Pereira, FSS; Dardenne, LE (2021). Machine learning scoring functions for drug discovery. *Brief. Bioinform.* 22(3): bbaa070. https://doi.org/10.1093/bib/bbaa070

Hauser, AS; Attwood, MM; Rask-Andersen, M; Schiöth, HB; Gloriam, DE (2017). Trends in GPCR drug discovery: New agents, targets, and indications. *Nat. Rev. Drug Discov.* 16(12): 829-842. https://doi.org/10.1038/nrd.2017.178

Heilker, R; Wolff, M; Tautermann, CS; Bieler, M (2021). Pharmacophore modeling and virtual screening for GPCR targets. *Methods Mol. Biol.* 2305: 1-20. https://doi.org/10.1007/978-1-0716-1406-8_1

Hilger, D; Masureel, M; Kobilka, BK (2018). Structure and dynamics of GPCR signaling complexes. *Nat. Struct. Mol. Biol.* 25(1): 4-12. https://doi.org/10.1038/s41594-017-0011-7

Hughes, JP; Rees, S; Kalindjian, SB; Philpott, KL (2011). Principles of early drug discovery. *Br. J. Pharmacol.* 162(6): 1239-1249.

Jiménez-Luna, J; Grisoni, F; Schneider, G (2020). Drug discovery with explainable artificial intelligence. *Nat. Mach. Intell.*, 2(10): 573-584. https://doi.org/10.1038/s42256-020-00236-4

Kang, Y; Kuybeda, O; de Waal, PW; Mukherjee, S; Van Eps, N; Dutka, P; Zhou, XE (2018). Cryo-EM structure of human rhodopsin bound to an inhibitory G protein. *Nat.* 558(7711): 553-558. https://doi.org/10.1038/s41586-018-0215-y

Kooistra, AJ; Mordalski, S; Pándy-Szekeres, G; Esguerra, M; Mamyrbekov, A; Munk, C; Keserű, GM; Gloriam, DE (2021). GPCRdb in 2021: integrating GPCR sequence, structure and function. *Nucleic Acids Res.* 49(D1): D335–D343. https://doi.org/10.1093/nar/gkaa1080

LeCun, Y; Bengio, Y; Hinton, G (2015). Deep Learning. *Nat.* 521(7553): 436–444.

Miao, Y; McCammon, JA; Walker, RC (2020). Machine learning in molecular dynamics simulations of biomolecular systems. *J. Chem. Theory Comput.* 16(8): 5289-5302. https://doi.org/10.1021/acs.jctc.0c00347

Noé, F; Olsson, S; Köhler, J; Wu, H (2020). Boltzmann generators: Sampling equilibrium states of many-body systems with deep learning. *Sci.* 365(6457): eaaw1147.

Olivecrona, M; Blaschke, T; Engkvist, O; Chen, H (2017). Molecular De Novo Design through Deep Reinforcement Learning. *J. Cheminform.* 9(1):48.

Raschka, S; Kaufman, B (2020). Machine learning and AI-based approaches for bioactive ligand discovery and GPCR-ligand recognition. *arXiv preprint arXiv:*2001.06545.

Russell, S; Norvig, P (2021). Artificial Intelligence: A Modern Approach (4th ed.). Pearson.Pp. 34

Smith, JS; Lefkowitz, RJ; Rajagopal, S (2018). Biased signalling: From simple switches to allosteric microprocessors. *Nat. Rev. Drug Discov.* 17(4): 243-260.

Sriram, K; Insel, PA (2018). G protein-coupled receptors as targets for approved drugs: How many targets and how many drugs? *Mol. Pharmacol.* 93(4): 251-258. https://doi.org/10.1124/mol.117.111062

Stokes, JM; Yang, K; Swanson, K; Jin, W; Cubillos-Ruiz, A; Donghia, NM; Collins, JJ (2020). A deep learning approach to antibiotic discovery. *Cell.* 180(4): 688-702.

Wang, L; Wu, Y; Deng, Y; Kim, B; Pierce, L; Krilov, G; Abel, R (2021). Accurate and reliable prediction of relative ligand binding potency in prospective drug discovery by way of a modern free-energy calculation protocol and force field. *J. Am. Chem. Soc.* 143(7): 2692-2704. https://doi.org/10.1021/jacs.0c10263

Weinstein, JN; Collisson, EA; Mills, GB; Shaw, KRM; Ozenberger, BA; Ellrott, K; Shmulevich, I; Sander, C; Stuart, JM (2013). The Cancer Genome Atlas Pan-Cancer Analysis Project. *Nat. Gen*. 45(10): 1113–1120.

Weis, WI; Kobilka, BK (2018). The molecular basis of G protein-coupled receptor activation. *Ann. Rev. Biochem.* 87: 897-919

Wootten, D; Christopoulos, A; Sexton, PM (2018). Emerging paradigms in GPCR allostery: Implications for drug discovery. *Nat. Rev. Drug Discov.* 17(1): 63-81.

Xu, R; Wunsch, D (2005). Survey of Clustering Algorithms. *IEEE Trans on Neural Netw.* 16(3): 645–678.

Yang, SY; Kim, SY; Kim, TY (2019). Pharmacophore modeling and virtual screening for GPCR ligands. *Curr. Med. Chem*. 26(42): 7616-7635.

Zhang, H; Fan, H; Wang, J; Hou, T; Saravanan, KM; Xia, W; Chen, Y (2024). Revolutionizing GPCR-ligand predictions: DeepGPCR with experimental validation for high-precision drug discovery. *Brief. Bioinform.* 25(4): bbae281. https://doi.org/10.1093/bib/bbae281

Zhavoronkov, A; Ivanenkov, YA; Aliper, A; Veselov, MS; Aladinskiy, VA; Aladinskaya, AV; Aspuru-Guzik, A (2019). Deep learning enables rapid identification of potent DDR1 kinase inhibitors. *Nat. Biotechnol.* 37(9): 1038-1040.