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Drug Repurposing

Drug Discovery and Development(Prediction of Drug Type)

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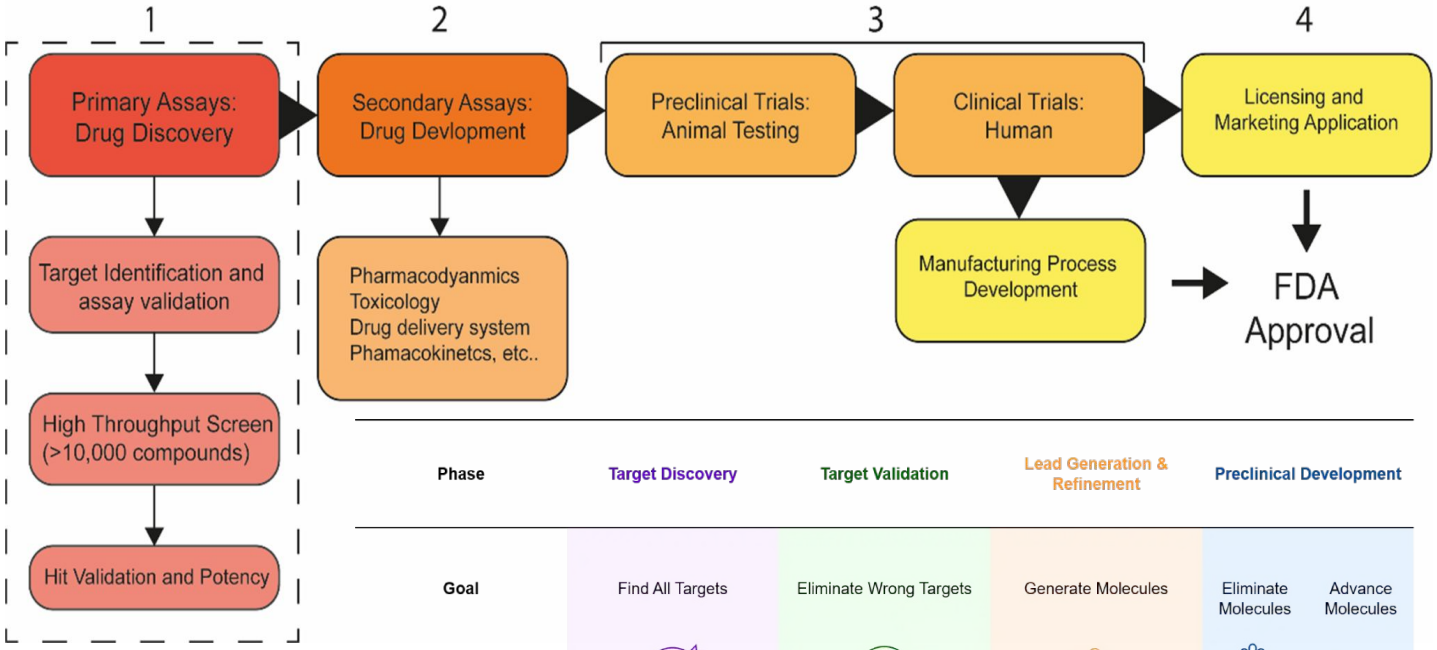
A Deep Dive into Drug Discovery:



Phase	Target Discovery	Target Validation	Lead Generation & Refinement	Preclinical Development	
Goal	Find All Targets	Eliminate Wrong Targets	Generate Molecules	Eliminate Molecules	Advance Molecules

Drug Repurposing:

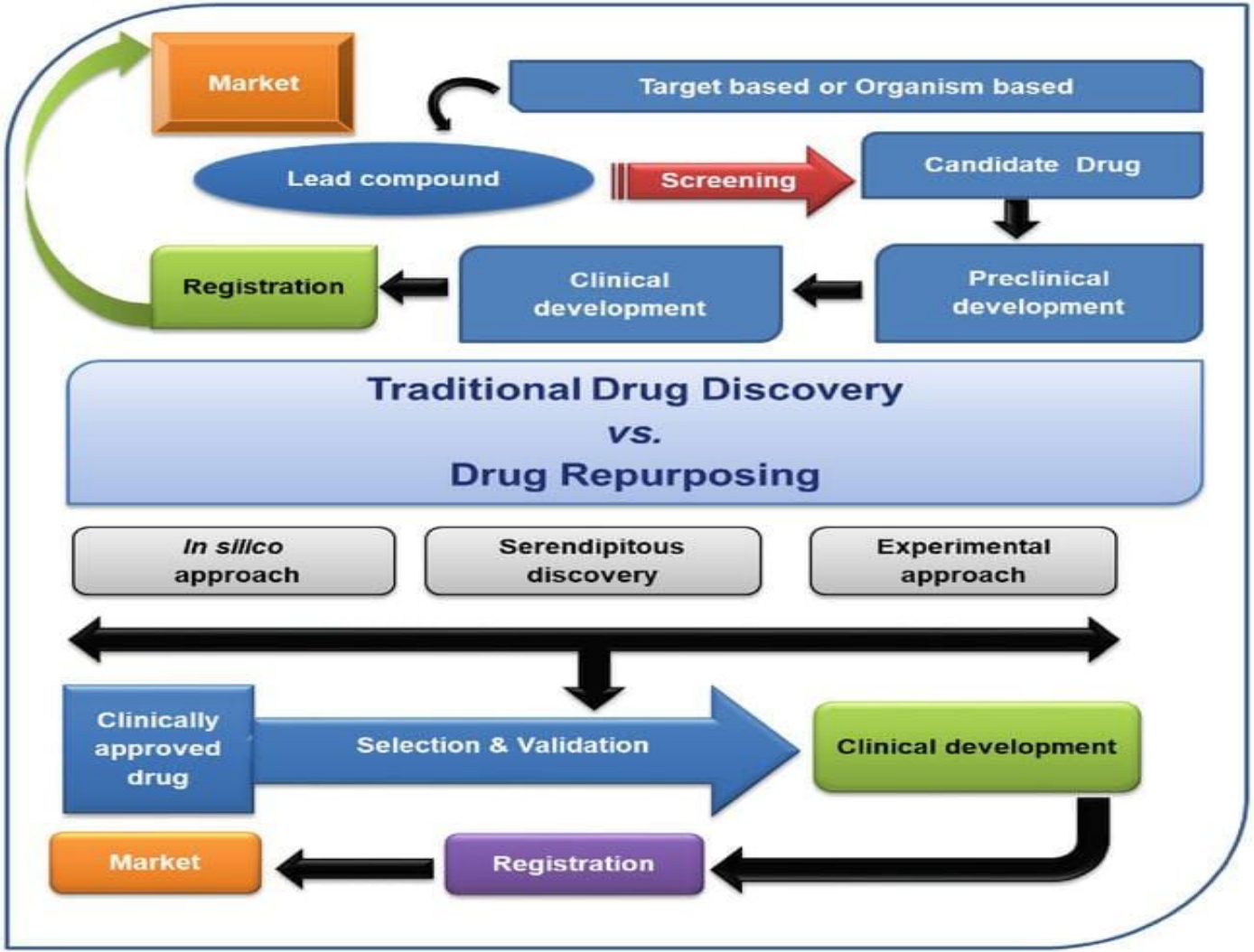
1. Drug repurposing is the technique of using an existing drug or drug candidate for a new treatment or medical condition.
2. Additionally, repurposed drugs have the advantage of a known safety profile, which reduces the risk of adverse effects and drug toxicity.
3. Drug repurposing can be done in various ways.
4. One approach involves identifying the off-target effects of a drug
5. Another strategy involves repurposing drugs based on their pharmacological properties and mechanisms of action.
6. This process brings the drugs directly to clinical trials, skipping the drug development process.
7. Thus It reduces time, cost in drug repurposing.

The main difference between Traditional Drug Discovery and Drug repurposing:

Drug Discovery: Include 5 stages:	**Drug Repurposing:** Include 4 stages:
• Discovery and preclinical • Safety review • Clinical research • FDA review • FDA post-market safety monitoring	• Compound identification • Compound acquisition • Development • FDA post-market safety monitoring

Note: Based on the research Drug discovery process will take 12 years, whereas drug repurposing process will take 5-8 years

Drug Discovery	Drug Repurposing
• Generally, more time consuming • High investment or cost • More risk of failure • Clinical efficacy and safety profile should be evaluated	• Less time consuming • Lesser investment compared to traditional drug discovery • Less risk of failure • Clinical efficacy and safety profiles already exist


Market
Target based or Organism based
Lead compound
Screening
Candidate Drug
Registration
Clinical development
Preclinical development
Traditional Drug Discovery
vs.
Drug Repurposing
In silico approach
Serendipitous discovery
Experimental approach
Clinically approved drug
Selection & Validation
Clinical development
Market
Registration

Drug properties:

Chemical Structure: The arrangement of atoms in a drug molecule.

Pharmacodynamics: The study of how drugs exert their effects on the body and their dose-response relationships. pharmacodynamic properties of a drug helps predict its therapeutic effects and potential side effects.

Pharmacokinetics: The study of drug absorption, distribution, metabolism, and excretion within the body.

Therapeutic Index: The ratio between the dose of a drug that produces therapeutic effects and the dose that produces toxic effects.

Drug-Drug Interactions: The potential for drugs to interact with each other, altering their effects.

Toxicity: Toxicity are evaluated during preclinical and clinical development to assess the safety profile of a drug.

Formulation and Delivery: Factors related to drug formulation including dosage form, stability, solubility. These properties influence the drug's pharmacokinetic profile.

Regulatory Considerations: Evaluation of drug properties by regulatory agencies to ensure safety and efficacy.

Disadvantage:

- Some drugs that have gone through several stages of clinical development and have been unsuccessful for the reason.
- In this process,the undesired side effects of Drug molecules can be a pointer to exploring the possibility of effectiveness.

Example: Thalidomide indicated for vomiting, was used to treat nausea in pregnant women and resulted in several disabilities. This tragic side effect on fetal development, its use was banned and restricted in several countries.

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- However, this type of repurposing has met objections from the scientific community, The benefit–to-risk ratio can be considered during repurposing cases. A rational decision from the regulatory authorities is essential to address the concern “Is it worth the risk? Or can an existing therapy perform better than the repurposed drug?”.

Benefit-to-risk ratio:

Benefits:

- Time and cost savings
- Known safety profile
- Diversification of Treatment options
- Potential for Faster clinical translation.

Risk:

- Limited Intellectual property protection
- Off-Label use concerns
- Unforeseen Adverse Effects
- Lack of Market Incentives

Application of Drug Repurposing:

Repurposing existing drugs offers a strategy for finding new treatments for diseases like COVID-19, where time is of the essence.

Metformin, an antidiabetic drug, is repurposed for anticancer effects, demonstrating its versatility in treating different conditions.

Repurposing addresses challenges like antibiotic resistance by finding new uses for existing drugs, such as pyridomycin(1950) for treating tuberculosis.

Challenges:

- The advantage of drug repurposing is that the early stages of clinical development are complete
- Drug repurposing leverages existing clinical trial data, reducing the cost and time required for development.
- However, skipping preclinical studies poses risks.
- Identifying a new therapeutic indication for an existing drug is a significant challenge and meeting regulatory requirements.
- Patent issues and IPR can hinder market entry for repurposed drugs, affecting investment and research efforts.

Conclusion:

- There are numerous diseases for which good therapeutic options have not been developed. The concept of repurposing a drug enables exploring the hidden potential of many molecules and better utilization of therapeutic agents. For better drug repositioning, more in-depth understanding along with integrated approaches between computational and experimental methods may be required to ensure high success rates of repositioned drugs.

Computational methods:

Machine learning methods- Machine learning methods for drug discovery include random forests, support vector machines, neural networks, decision trees, and KNN etc.

Molecular docking simulations-Molecular docking simulations involve computational modeling to predict and analyze the interactions between a small molecule (ligand) and a target biomolecule (often a protein), aiming to identify potential binding modes and binding affinities.

Quantitative structure-activity relationship (QSAR) models- QSAR models predict the biological activity or properties of molecules based on their chemical structure and physicochemical properties.

Graph Neural Network:

- Graph Neural Networks (GNN) are a computational method increasingly used in drug repurposing efforts.
- GNN are well-suited for analyzing molecular structures, which can be represented as graphs, with atoms or molecules as nodes and chemical bonds as edges.
- By leveraging the graph structure, GNN can capture important relationships between atoms, substructures, and molecular properties, making them effective for tasks such as predicting molecular properties, identifying drug-target interactions, and suggesting potential therapeutic indications for existing drugs.
- Therefore, GNN play a significant role in the computational exploration of drug repurposing by analyzing molecular graphs and uncovering hidden patterns within them.
- I have used GCN model to treat prediction of drug type.

Problem statement:

- The problem statement describes a binary classification task. Specifically, the goal is to predict whether a type is drug or non-drug for repurposing based on its molecular structure and chemical properties.

In the context:

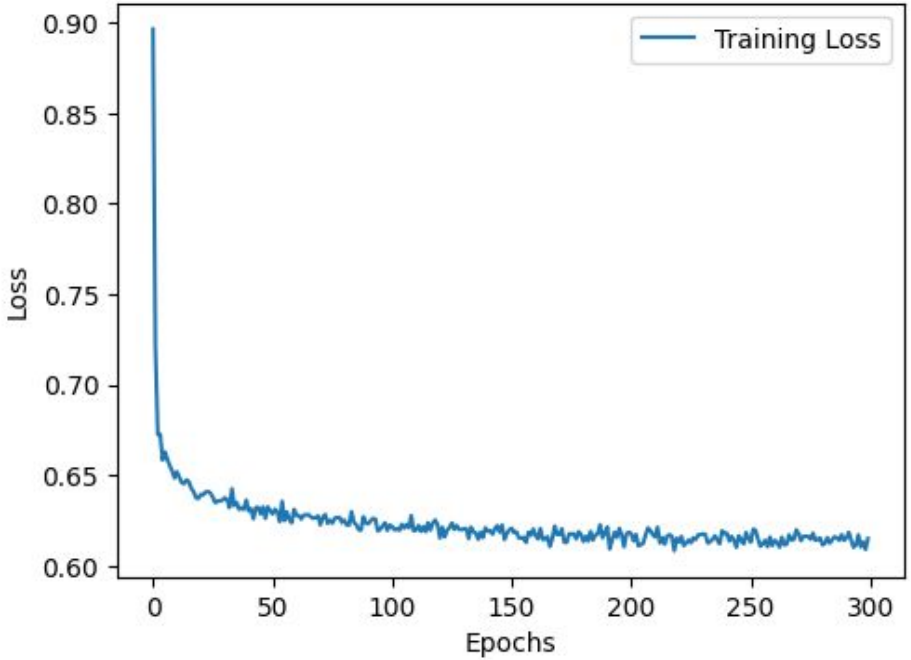
Positive Class (1): Drug

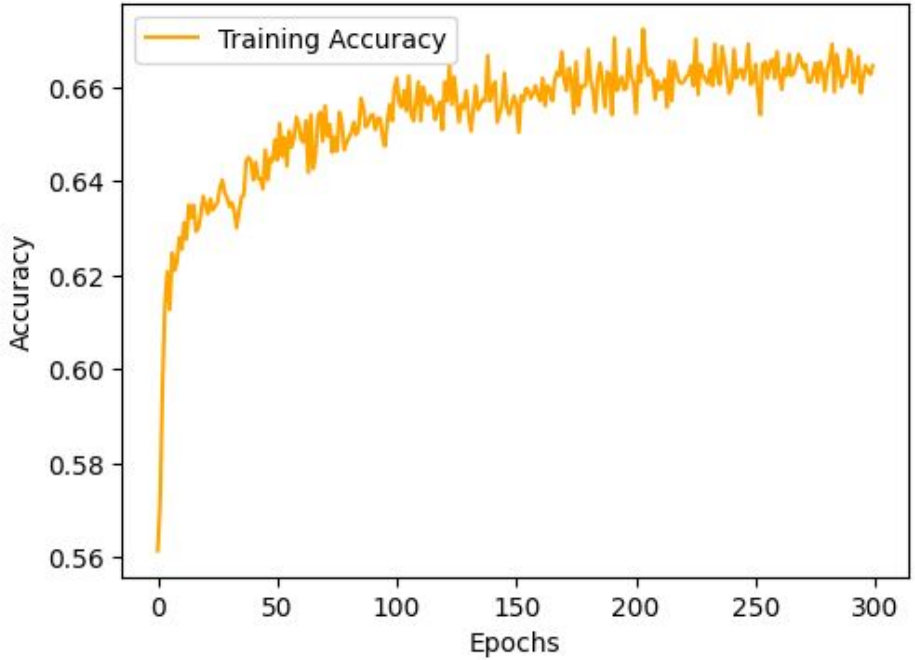
Negative Class (0): Non-Drug

Results:

Epoch 300/300, Loss: 0.6151278512691384, F1 Score: 0.5003984063745021,

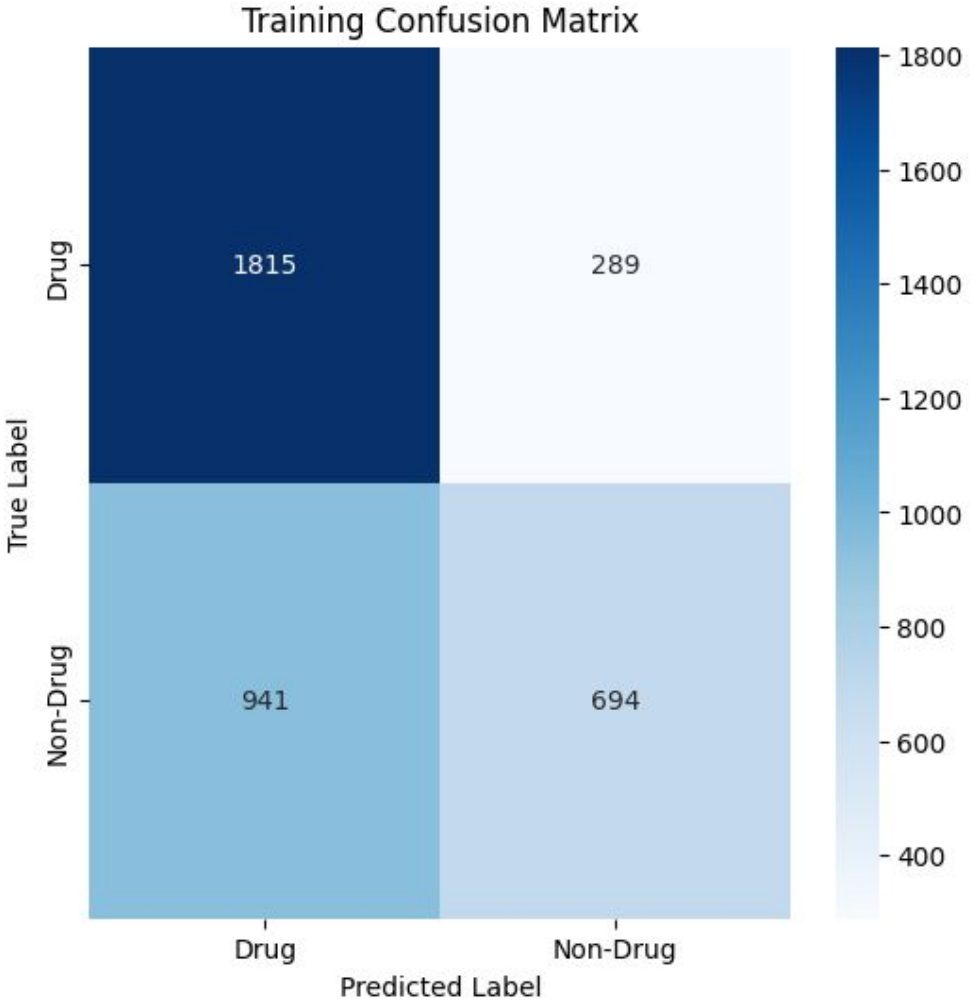
Training Accuracy: 0.6646162075421236,Test Accuracy: 0.6491978609625668

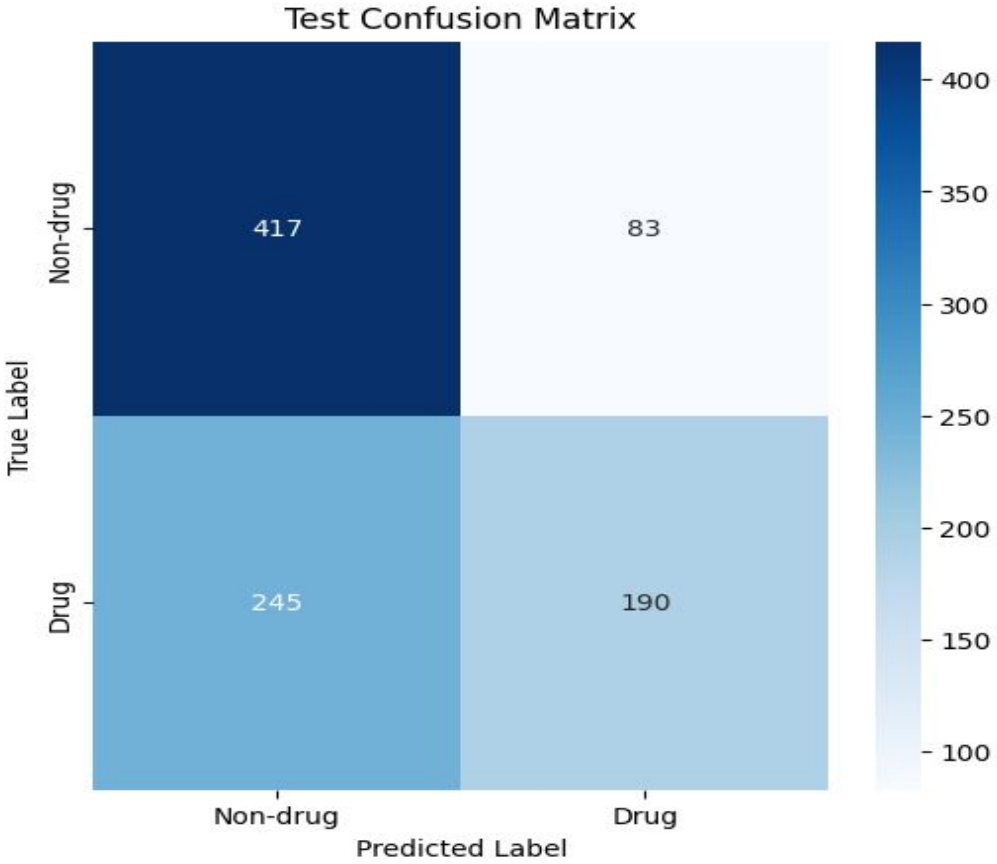




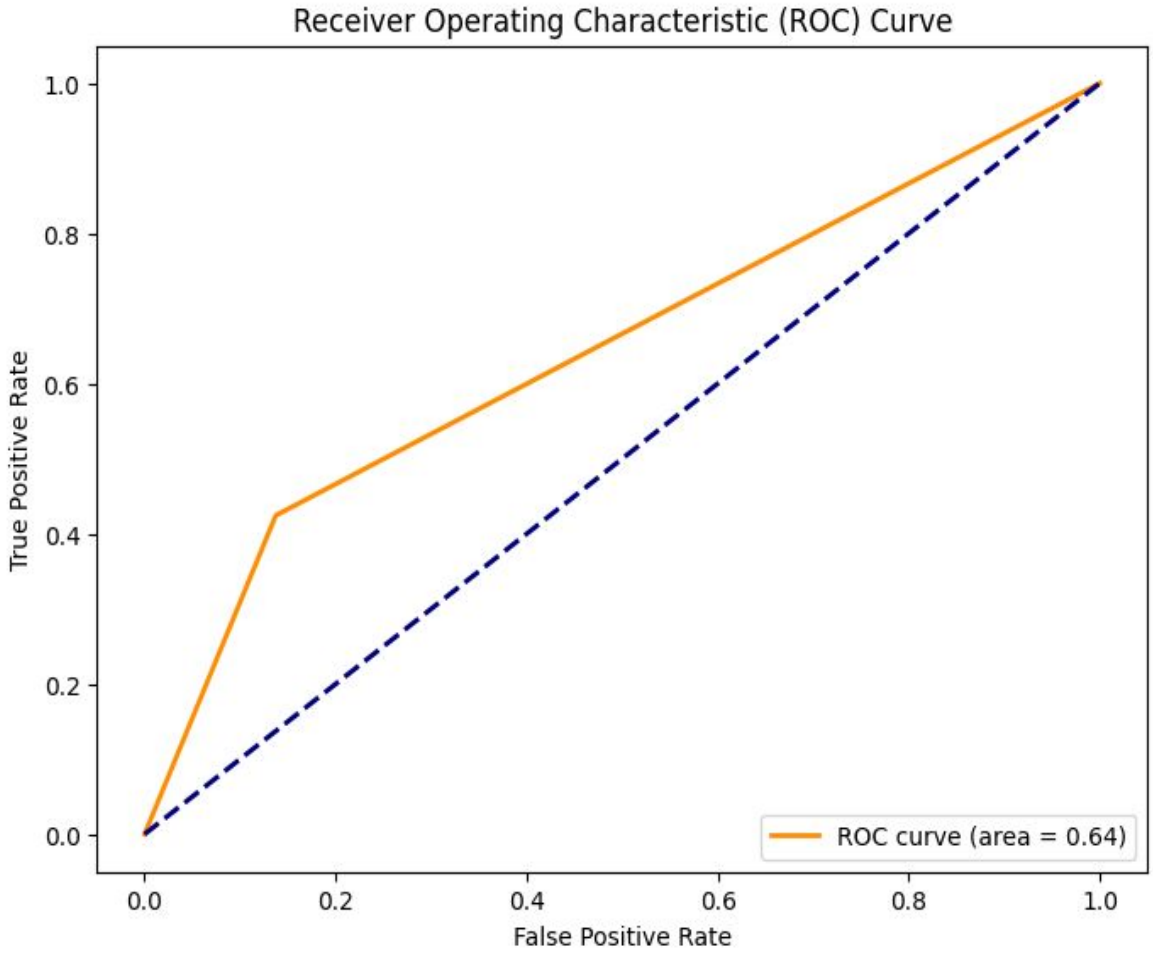
Results:

- It compares the predicted labels of the model with the actual labels across different classes.




Test Confusion Matrix
Non-drug
Drug
True Label
417
83
245
190
Non-drug
Drug
Predicted Label
400
350
300
250
200
150
100

The ROC (Receiver Operating Characteristic) graph is a graphical representation used to evaluate the performance of a binary classification model. It plots the true positive rate (TPR) against the false positive rate (FPR) .



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Thank you :)