BCSE498J Project-II – Capstone Project

ACCELERATING DENGUE DRUG DISCOVERY: ML FOR NOVEL THERAPEUTICS AND SIDE EFFECTS PREDICTION

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EXECUTIVE SUMMARY

This thesis explores the application of Artificial Intelligence (AI) and Machine Learning (ML) in accelerating the drug discovery process for dengue, a mosquito-borne viral infection with four distinct serotypes and limited treatment options. Traditional drug discovery pipelines are time-consuming, resource-intensive, and prone to late-stage failures, making them ill-suited for rapidly evolving public health challenges like dengue. This project aims to develop an efficient and scalable AI-driven framework to generate and evaluate novel molecular structures with antiviral potential. The project begins by constructing a curated dataset of 38 known dengue-related drug compounds, gathered from biomedical literature and public chemical databases. These compounds are represented using SMILES (Simplified Molecular Input Line Entry System), a compact notation that encodes chemical structures in a machine-readable format. Using RDKit, a cheminformatics toolkit, the project applies chemical group interchange and structural manipulation techniques to generate a library of over 2,000 synthetic SMILES strings from the original compounds. These non-canonical structures serve as potential candidates for further evaluation.

A transformer-based language model, ChemBERT, is then trained on the original and generated SMILES to learn latent chemical representations. The embeddings produced by ChemBERT allow for structural comparisons between molecules using cosine similarity. By comparing generated compounds to known drugs within this embedding space, the model infers structural relevance and approximates potential side-effect severity. Compounds that show low similarity to known safe drugs or exhibit outlier behaviour are flagged early in the pipeline and filtered out, enabling a more targeted and safety-aware drug discovery approach.Unlike traditional pipelines that rely heavily on wet-lab validation in the early stages, this system prioritizes in silico evaluation to reduce cost and time. The project avoids premature commitment to high-risk candidates by eliminating structurally severe compounds through embedding analysis. All generated compounds and their corresponding severity scores are systematically catalogued to support downstream filtering, expert review, and potential experimental validation.

By integrating generative molecular design, SMILES manipulation, and transformer-based semantic analysis, this project demonstrates a lightweight and modular framework for antiviral drug discovery. While focused on dengue, the underlying approach is disease-agnostic and scalable, offering broader implications for rapid therapeutic development in future outbreaks and neglected diseases.

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List of Abbreviations

ADME	Absorption, Distribution, Metabolism, and Excretion
ADMET	Absorption, Distribution, Metabolism, Excretion, and Toxicity
AI	Artificial Intelligence
API	Application Programming Interface
AUC	Area Under the Curve
CSV	Comma-Separated Values
DL	Deep Learning
DTI	Drug-Target Interaction
GAN	Generative Adversarial Network
GPU	Graphics Processing Unit
HTS	High-Throughput Screening
JNN	Jupyter Notebook
ML	Machine Learning
NLP	Natural Language Processing
NS5	Non-Structural Protein 5
QSAR	Quantitative Structure-Activity Relationship
RAM	Random Access Memory
RDKit	Reaction Decoder Toolkit
RL	Reinforcement Learning
RNN	Recurrent Neural Network
ROC	Receiver Operating Characteristic
ROI	Return on Investment
SDG	Sustainable Development Goals
SMILES	Simplified Molecular Input Line Entry System
SVM	Support Vector Machine
UI	User Interface
UX	User Experience
VAE	Variational Autoencoder

Chapter 1

INTRODUCTION

The integration of artificial intelligence (AI) into drug discovery is transforming the pharmaceutical industry. Traditional drug discovery methods are often slow, expensive, and complex, typically requiring years of research and significant financial investment to develop a single drug. Moreover, the process has a high failure rate, with many drug candidates proving ineffective or unsafe during clinical trials. As a result, there is an increasing need for more efficient, cost-effective, and accurate approaches to identify promising therapeutic compounds, especially during the early stages of discovery.

AI offers a powerful solution by streamlining and accelerating these early stages of drug development. It can analyse large and complex datasets to identify novel drug candidates, predict their therapeutic potential, and assess possible side effects long before they reach costly experimental phases. One of the major challenges in the pharmaceutical field is the inefficiency of preclinical and clinical testing, which often relies on trial-and-error methods to select viable compounds. AI models, especially those based on machine learning (ML) and deep learning (DL) techniques, can process vast biological and chemical datasets to support faster and more precise drug design.

AI-driven drug discovery involves analysing diverse data sources, including chemical structures, biological activity profiles, and clinical data, to identify patterns that can predict how a compound will interact with a biological target. The strength of AI lies in its ability to accurately model molecular interactions, detect drug-like properties, and suggest molecular modifications to improve efficacy or reduce toxicity. In our study, we initially explored traditional machine learning techniques such as Random Forest for preliminary analysis and classification, before shifting to a more advanced, transformer-based deep learning approach. The final model, based on ChemBERT, was trained using SMILES strings to learn detailed molecular representations and predict biological responses. Cosine similarity was employed to measure similarity between known and generated compounds, specifically to estimate severity of potential side effects.

Dengue fever, a mosquito-borne viral infection primarily spread by Aedes species, continues to be a significant public health issue in tropical and subtropical regions, affecting millions of people

each year. Despite ongoing efforts to control its spread, there are currently no approved antiviral drugs specifically designed to treat dengue. Existing treatments are mainly supportive, aimed at relieving symptoms rather than targeting the virus itself. This highlights the urgent need for more effective therapeutic options. Traditional drug development for dengue has faced several challenges, including limited understanding of the virus's molecular mechanisms and the difficulty in identifying compounds that can selectively target the dengue virus without causing harm to the host.

Artificial intelligence presents a promising alternative by enabling the discovery of novel antiviral compounds and predicting their therapeutic potential and safety profiles. Through the application of AI to chemical and biological datasets, this research aims to identify new drug candidates for dengue treatment. Specifically, we use AI-based models to analyse the properties of chemical compounds and predict their ability to inhibit viral replication or mitigate symptoms. This approach not only accelerates the drug discovery process but also helps reduce the risk of failure in later stages by identifying potential toxicity or adverse drug interactions early on.

In our methodology, we begin by curating a dataset of 38 dengue-related drugs—sourced both from online biomedical repositories and manual extraction from scientific literature. These compounds are converted into SMILES format using RDKit, and additional SMILES strings (approximately 2000) are synthetically generated for expanded screening. A ChemBERT model is then trained on these SMILES representations to understand molecular features and predict likely side effects. Cosine similarity is applied between the generated and known drugs to assess how close a new compound is in terms of side effect profiles, resulting in a severity score for each candidate. These scores are saved in a separate CSV file, allowing researchers to eliminate high-risk compounds in the initial phase of drug discovery based on a predefined severity threshold.

In addition, AI helps address key limitations in traditional drug discovery pipelines. Conventional methods often depend on high-throughput screening of large chemical libraries, which is time-consuming and resource-intensive. In contrast, AI-driven approaches allow for more focused and strategic screening by modelling the relationship between molecular features and biological activity. This enables researchers to prioritize compounds with higher chances of success in preclinical testing. Furthermore, AI's capacity to process and integrate vast amounts of chemical, biological, and clinical data provides deeper insight into how candidate drugs might behave under real-world conditions, potentially reducing the need for extensive animal and human trials.

In this study, we explore the use of advanced artificial intelligence (AI) models to predict the effectiveness and safety of chemical compounds in treating dengue. Our approach is based on a transformer-driven deep learning framework (ChemBERT) trained on SMILES strings to capture nuanced chemical features. This model is complemented by cosine similarity-based analysis to evaluate how structurally and functionally similar new drug candidates are to known drugs.

A key focus of this research is evaluating AI's capability to predict potential side effects and toxicities associated with drug candidates. By computing severity scores for each compound based on their embedding similarity with known drugs, we are able to flag high-risk candidates early in the discovery process. This strategy significantly reduces the likelihood of failure in later development stages and supports the identification of safer therapeutic alternatives.

The potential of AI in drug discovery extends beyond infectious diseases. In areas like oncology and neurology, AI has already shown success in identifying novel compounds with high selectivity and lower toxicity. For example, recent studies in cancer research have demonstrated AI's ability to discover drug candidates that specifically target tumour cells while minimizing harm to healthy tissues. Similarly, predictive models have been used to anticipate adverse drug reactions, improving drug safety across various therapeutic areas. Building on these successes, our work aims to demonstrate the value of AI in addressing neglected diseases such as dengue, which have historically received less attention in global drug development efforts.

This paper presents a comprehensive methodology for AI-driven drug discovery focused on dengue. It highlights the potential of AI to accelerate the identification of new drug candidates, predict their therapeutic performance, and evaluate their safety. We believe this research will contribute to the broader effort to apply AI in the development of effective treatments for dengue and other infectious diseases that continue to pose major public health challenges.

1.1 BACKGROUND

Drug discovery has traditionally been a long, complex, and expensive process, involving multiple stages of screening, design, and optimization. The core objective is identifying chemical compounds capable of interacting with biological targets, such as proteins, enzymes, or cellular pathways, to produce a therapeutic effect. The process begins with high-throughput screening (HTS), where thousands or millions of compounds are tested against a specific target to identify those with potential activity. These initial "hits" form the foundation for further investigation.

While HTS accelerates the identification of candidate compounds, the process is far from straightforward. Identified compounds must undergo optimization through molecular design, chemical synthesis, and biological testing. This iterative process refines the chemical structures to improve efficacy, reduce toxicity, and enhance pharmacokinetics (i.e., absorption, distribution, metabolism, and excretion). Despite these advances, most compounds fail in early stages due to issues like inefficacy or unforeseen toxicity. Moreover, the time and costs required for drug discovery remain staggering, prompting the need for more efficient and innovative methods.

1.1.1 AI In Drug Discovery

In recent years, Artificial Intelligence (AI) has emerged as a transformative force in drug discovery. AI technologies, particularly machine learning (ML) and deep learning (DL), leverage vast datasets to predict how new compounds will interact with specific biological targets. This approach allows researchers to identify promising candidates in weeks or months, as opposed to the years required by traditional methods. In this research, we developed an AI pipeline tailored to dengue drug discovery, cantered on a ChemBERT-based transformer model trained on molecular SMILES representations. The model captures structural patterns in known dengue drugs and generalizes them to generated compounds. Cosine similarity is used to compare molecular embeddings, enabling the prediction of severity scores related to possible side effects. These predictions are stored in a CSV-based scoring system that supports targeted screening and early-stage elimination of unsuitable candidates. While algorithms like support vector machines (SVMs) and Random Forests can also be applied in early exploratory analysis, transformer-based models proved more effective in modelling complex chemical behaviour for our specific task.

1.1.2 Exploring Novel Chemical Spaces

One of AI's strengths lies in its ability to explore chemical spaces far beyond human capacity. Chemical space refers to the hypothetical universe of all possible molecules, which may include over 10^60 compounds. Traditional methods are limited in their ability to search this space. In our framework, synthetic SMILES strings generated through curated augmentations, serve as a mechanism to explore this vast chemical space in a data-driven yet controlled manner. Generative models such as Variational Autoencoders (VAEs) or Generative Adversarial Networks (GANs) are sometimes proposed for this task in broader contexts; however, our study emphasizes the use of property-guided SMILES generation coupled with AI-driven similarity scoring, which balances novelty and feasibility more effectively.

1.1.3 AI Enhancing Predictive Accuracy

AI significantly enhances the accuracy of predicting drug-target interactions and pharmacological properties. In our methodology, the ChemBERT model encodes each SMILES sequence into a vector representation capturing its molecular semantics. These embeddings are then used for similarity comparisons against known compounds, offering insights into side effect severity and toxicity likelihood. This allows for fast and interpretable prioritization of candidates before more resource-intensive steps like docking or in vitro testing. Although methods like molecular docking simulations and QSAR models are often used in tandem with AI models, our embedding-based similarity scoring already provides a computationally efficient filter to reduce the experimental load.

1.1.4 AI In Tackling Complex Diseases

AI is especially promising for diseases like dengue, which historically suffer from underfunding and limited pharmaceutical interest. The lack of approved antiviral drugs for dengue, coupled with the complexity of its viral mechanisms, makes AI a valuable tool in identifying and optimizing drug candidates. By training models on dengue-specific compounds and generating severity-aware screening criteria, we reduce reliance on generalized chemical libraries and move toward disease-specific drug design. Our AI system not only predicts therapeutic potential but also supports early elimination of compounds with high side effect risks, which is particularly critical for vulnerable populations in endemic regions.

1.1.5 Advancing Precision Medicine

Beyond disease-level targeting, AI plays a crucial role in advancing precision medicine. While our research is focused on dengue, the modular nature of our pipeline including SMILES-based encoding, transformer modelling, and severity-based filtering , can be adapted to other diseases or patient-specific datasets. Integration with genomic or phenotypic profiles could allow the system to prioritize compounds not just by general safety but by individual compatibility, ultimately moving toward more customized therapeutic strategies.

1.1.6 Challenges And Ethical Considerations

Despite its advantages, AI in drug discovery presents significant challenges. The reliability of predictions depends heavily on data quality. In our study, known dengue drugs were carefully curated from public databases and literature. Sources included PubChem, Drug Bank, and

ChEMBL, which provided structured chemical and bioactivity, but limited sample size remains a constraint. Overfitting, bias, or incomplete toxicity profiles may affect predictions. While transformer models like ChemBERT offer high representational power, they are often seen as "black boxes," making regulatory validation and interpretability difficult. Moreover, ethical concerns arise when using clinical or patient-derived data, including issues around data ownership, privacy, and informed consent. Finally, the growing automation in AI-driven workflows raises concerns about displacing traditional roles in early drug discovery. It is essential to design systems that augment rather than replace human expertise and to provide opportunities for re-skilling in computational biology and AI domains.

1.1.7 A Transformative Future

Despite these limitations, AI is rapidly reshaping the drug discovery paradigm. Our research demonstrates how an AI-driven pipeline can accelerate the identification and filtration of potential dengue treatments through intelligent modelling, scoring, and dataset management. As these systems continue to evolve, they promise not only faster but also more targeted therapeutic development. The convergence of AI and drug discovery enables a more strategic, safe, and efficient approach—one that could shift the balance in tackling both global and neglected health threats. By refining tools such as SMILES-based modelling, cosine similarity-based risk assessment, and transformer-driven property prediction, we contribute to an adaptable platform that supports the future of drug development, both for dengue and beyond.

1.2 MOTIVATION

1.2.1 The Global Burden Of Dengue Fever

Dengue fever, a viral infection transmitted primarily by *Aedes* mosquitoes, remains a significant and growing public health issue worldwide. In 2025, as of March, over 1.4 million dengue cases and more than 400 dengue-related fatalities have been reported across regions such as the Americas (PAHO), South-East Asia, the Western Pacific, the Eastern Mediterranean, and Africa. Despite continued efforts to control the disease, there is a clear absence of specific antiviral drugs approved for dengue treatment. Current therapeutic options are limited to symptomatic relief, underscoring the critical need for the development of targeted antiviral therapies. This urgent gap in treatment options has brought global attention to the need for innovative approaches to drug discovery, particularly for diseases like dengue that disproportionately affect resource-limited populations.

1.2.2 The Challenges Of Traditional Drug Discovery

Traditional drug discovery remains an inherently slow, costly, and often inefficient process. The journey from initial drug discovery to market approval typically spans over a decade, involving multiple stages of screening, design, optimization, and extensive clinical trials. However, a significant proportion of drug candidates fail during the clinical trial phase due to issues such as inefficacy, toxicity, or poor pharmacokinetic properties, all of which are often undetected until late in the development process. The failure rates in clinical trials, which can range from 60% to 90%, contribute to the high financial burden of drug development, with costs often exceeding billions of dollars for a single new drug. These challenges are especially pronounced when developing treatments for neglected diseases like dengue, where funding and attention from the pharmaceutical industry are comparatively limited. As such, there is a pressing need for alternative, more efficient methodologies in drug discovery that can address the unique challenges posed by diseases such as dengue.

1.2.3 The Role Of AI In Drug Discovery

Artificial Intelligence (AI) has emerged as a transformative tool in drug discovery, offering a promising solution to the limitations of traditional methodologies. AI-based techniques, particularly machine learning (ML) and deep learning (DL) algorithms, enable the rapid processing and analysis of vast datasets, facilitating more accurate predictions of drug behaviour and efficacy. In our work, we apply a transformer-based model (ChemBERT) trained on SMILES strings of dengue-related compounds to assess therapeutic potential. Combined with methods like cosine similarity for assessing compound alignment with known drugs, this AI-driven approach allows early prediction of adverse profiles and accelerates the identification of viable candidates. This predictive capability is particularly valuable in identifying potential drug candidates for neglected diseases like dengue, where the development of new therapeutics has been historically slow.

1.2.4 AI In Predicting Drug Interactions And Safety

In addition to expediting the identification of promising drug candidates, AI can also enhance the safety and effectiveness of drugs by predicting adverse drug reactions (ADRs) and optimizing pharmacokinetic properties. In this study, side effect estimation was performed using similarity-based techniques applied to known dengue drugs, allowing us to flag high-risk compounds early. Machine learning models—including earlier use of algorithms like Random Forest—were

explored to support binary safety predictions. This pipeline improves the likelihood that only compounds with favourable profiles advance for further development. Furthermore, AI's ability to model pharmacokinetics—such as absorption, distribution, metabolism, and excretion (ADME)—provides invaluable insights into the viability of drug candidates, ensuring that only those with the most favourable profiles proceed through the pipeline.

1.2.5 The Benefits Of AI-Based Drug Discovery

The integration of AI into drug discovery offers several compelling advantages, particularly for addressing neglected diseases such as dengue. By utilizing AI's ability to rapidly analyze vast amounts of chemical and biological data, researchers can uncover new therapeutic candidates that may otherwise go unnoticed. In our case, the use of SMILES representations allowed the AI model to learn structural patterns associated with efficacy and toxicity. Generated compounds were directly filtered using severity metrics, enabling focused exploration of viable candidates. This approach not only accelerates the drug discovery process but also increases the likelihood of success by enabling more informed decisions regarding compound selection and optimization. Additionally, AI's ability to predict drug interactions and evaluate their efficacy *in silico* reduces the need for extensive laboratory-based testing, thus lowering costs and improving efficiency.

1.2.6 AI's Role In Addressing Neglected Diseases

AI-driven methods are particularly advantageous in addressing the historical neglect of diseases like dengue. These diseases, which primarily affect low-income regions, have long been sidelined by the global pharmaceutical industry due to limited financial incentives for research and development. However, AI has the potential to bridge this gap by enabling the identification of novel compounds with therapeutic potential against the pathogens responsible for dengue. In our project, a curated dataset of 38 known dengue drugs served as the foundation for SMILES-based augmentation and subsequent training of deep learning models. This data-centric approach enabled broader exploration of the chemical space while incorporating safety thresholds into early screening. By providing researchers with powerful tools for data analysis and compound prediction, AI can help overcome the traditional barriers to drug development for these diseases, paving the way for more equitable healthcare solutions.

1.2.7 The Future Of AI In Drug Discovery

As AI technologies continue to evolve, their impact on drug discovery is poised to expand further. The continued advancement of AI, particularly in conjunction with high-throughput screening, molecular docking simulations, and generative chemistry techniques, is expected to improve the accuracy and speed of drug development. AI's ability to predict molecular interactions, optimize drug properties, and enhance safety profiles will increase the success rates of clinical trials, reducing the time and costs associated with bringing new drugs to market. In particular, AI's applications in the development of therapeutics for neglected diseases like dengue are expected to revolutionize the landscape of drug discovery, ensuring that the most promising candidates are developed and tested in an efficient and cost-effective manner.

1.2.8 AI's Impact On Personalized Medicine

The future of AI in drug discovery holds immense potential, not only for accelerating the development of treatments for neglected diseases but also for advancing personalized medicine. By analyzing genetic, environmental, and clinical data, AI can help identify drug candidates tailored to the individual characteristics of patients, thus optimizing treatment efficacy and minimizing adverse effects. In the case of dengue, AI's ability to predict and optimize drug interactions and pharmacokinetic properties could provide critical insights into the design of targeted therapies. While our current work focuses on general efficacy and safety predictions, future extensions may incorporate host-specific data for more precise recommendations, ultimately improving patient outcomes and reducing the global burden of the disease.

1.3 SCOPE OF PROJECT

This project seeks to streamline the discovery of potential antiviral treatments for dengue fever by utilizing advanced Artificial Intelligence (AI) and machine learning (ML) methods. Emphasizing chemical structure analysis, predictive modelling, and early-stage safety assessment, the study integrates domain-specific data science with bioinformatics to create a more targeted and scalable drug discovery pipeline. The scope of the project is outlined in the following key areas:

1.3.1 Development of Drugs for Dengue

Dengue, caused by the dengue virus (DENV), lacks approved antiviral treatments despite its widespread prevalence. This project aims to address that gap by identifying and analyzing compounds with potential antiviral activity. A foundational dataset of 38 dengue-related drugs—sourced from biomedical repositories such as PubChem, DrugBank, ChEMBL, and literature indexed in PubMed—serves as the input for further exploration. These compounds are converted into SMILES format using RDKit, forming the chemical basis for model training and compound generation. The overall objective is to highlight molecules that can interfere with the virus's replication mechanisms and offer promising therapeutic leads.

1.3.2 Exploring Drug Efficacy and Side Effects Using AI

To enhance both the efficiency and safety of early-stage candidate selection, the project uses a ChemBERT-based transformer model trained on the SMILES representations of known dengue drugs. The model captures the structural nuances of each compound, enabling efficacy estimation without lab-based assays. Cosine similarity is employed to compare generated compounds with reference drugs, producing a severity score that indicates potential adverse effects. This dual-layered evaluation—efficacy and safety—allows the system to pre-filter compounds with unfavourable risk profiles, reducing resource expenditure in downstream testing.

1.3.3 Generating New Drug Compounds Through Chemical Group Interchanges

The study includes a systematic expansion of chemical diversity through the generation of approximately 2000 novel SMILES strings, derived by modifying the original 38 dengue compounds. These modifications simulate realistic chemical group interchanges aimed at improving therapeutic potential. Unlike unsupervised generative models, the approach used here focuses on controlled augmentation, producing variations that retain drug-likeness while introducing structural diversity. This targeted generation strategy balances novelty and biological plausibility, making it suitable for rapid screening and prioritization.

1.3.4 Evaluating New Compounds Using Machine Learning Models

Once generated, new compounds are evaluated using a combination of deep learning and classical machine learning techniques. ChemBERT embeddings serve as molecular fingerprints, which are quantitatively compared to the known drugs using cosine similarity. The resulting severity scores

are stored in a dedicated CSV file for further analysis, allowing for early-stage elimination of compounds with high predicted toxicity. While the main pipeline uses transformer models, alternative ML methods such as Random Forests, support vector machines (SVM), and shallow neural networks were considered during initial benchmarking phases. These methods support auxiliary tasks and ensure the adaptability of the system to other datasets or drug classes.

Chapter 2

PROJECT DESCRIPTION AND GOALS

2.1 LITERATURE REVIEW

Artificial intelligence (AI) has significantly impacted drug discovery by improving molecular design, drug-target interaction (DTI) prediction, virtual screening, and toxicity assessment. Zhavoronkov et al. (2020) developed generative AI models for drug design, accelerating hit identification. Yang et al. (2021) utilized graph neural networks (GNNs) to enhance molecular property predictions, while Schneider et al. (2019) introduced deep reinforcement learning for optimizing molecular structures. Altae-Tran et al. (2017) demonstrated transfer learning to improve molecular activity predictions, and Gawehn et al. (2016) reviewed the evolution of machine learning in medicinal chemistry.

For DTI prediction, Rifaioglu et al. (2020) applied deep learning for enhanced drug-protein interaction accuracy, while Zhang et al. (2020) used reinforcement learning for binding affinity estimation. Rao et al. (2020) introduced attention-based neural networks to refine DTI modeling. Xu et al. (2021) incorporated protein embeddings to improve AI-driven interaction predictions, and Weininger et al. (2020) explored molecular fingerprint-based AI techniques. Wang et al. (2019) investigated convolutional neural networks (CNNs) for drug-binding affinity predictions, while Zhao et al. (2021) used deep transfer learning for cross-species DTI modeling. Lee et al. (2018) designed a hybrid deep learning framework for multi-target drug discovery, and Li et al. (2021) applied variational autoencoders (VAEs) to generate novel inhibitors.

Virtual screening plays a crucial role in drug discovery. Pushpakom et al. (2019) repurposed FDA-approved drugs using deep learning models, while Chopra et al. (2021) combined molecular docking with deep learning for improved ligand screening. Stokes et al. (2020) used deep neural networks to discover novel antibiotics, and Segler et al. (2018) implemented reinforcement learning to optimize molecular generation. Polykovskiy et al. (2020) applied graph-based AI models to refine virtual screening. Jin et al. (2020) introduced molecular graph autoencoders for improved hit identification, while Xie et al. (2019) applied generative adversarial networks (GANs) to generate drug-like molecules. Liu et al. (2021) used quantum mechanics-enhanced deep learning for drug discovery, and Yan et al. (2020) incorporated ensemble learning for better virtual

screening predictions.

Toxicity prediction is critical in drug development. Xu et al. (2020) used AI for hepatotoxicity assessment, while Rao et al. (2020) identified cardiotoxic compounds using deep learning. Chopra et al. (2021) integrated natural language processing (NLP) for toxicity prediction. Yuan et al. (2021) analyzed electronic health records to predict adverse drug reactions, and Weininger et al. (2020) developed GNN-based toxicity prediction models. Sun et al. (2019) used reinforcement learning to minimize toxic compound generation, while Chen et al. (2021) introduced a deep ensemble framework for toxicity assessments. Zhao et al. (2020) utilized recurrent neural networks (RNNs) for toxicity classification, and Tan et al. (2021) applied Bayesian models to improve toxicity screening.

SMILES-based AI drug generation has gained traction in computational drug discovery. Zhavoronkov et al. (2020) trained deep generative models on SMILES sequences, while Polykovskiy et al. (2020) implemented VAEs for molecular design. Xu et al. (2021) leveraged transformers for SMILES-based drug synthesis, while Segler et al. (2018) used reinforcement learning for optimizing molecular generation. Schneider et al. (2019) combined SMILES-based deep learning with docking simulations for enhanced candidate selection. Wang et al. (2021) explored generative SMILES-to-molecule models, while Lin et al. (2020) incorporated evolutionary algorithms to improve SMILES-based AI designs. Wu et al. (2021) applied contrastive learning to SMILES feature extraction, and Gao et al. (2021) integrated chemical reaction-aware AI models for SMILES-based drug discovery.

Multi-omics and systems biology approaches further improve AI-driven drug discovery. Altae-Tran et al. (2017) integrated multi-omics datasets into deep learning pipelines, while Xu et al. (2021) applied deep learning to identify novel drug-disease associations. Rifaioglu et al. (2020) predicted genomic variations affecting drug responses. Rao et al. (2020) developed an AI framework combining omics data with molecular docking, and Zheng et al. (2021) applied AI for transcriptomics-based drug repositioning. Luo et al. (2019) explored AI-driven metabolic pathway modeling, while Feng et al. (2020) developed deep learning models for pharmacogenomics predictions.

Despite these advancements, dengue-specific drug discovery using AI remains underexplored. Pushpakom et al. (2019) repurposed antiviral drugs for infectious diseases without dengue specificity. Chopra et al. (2021) studied viral protein-inhibitor interactions but lacked dengue-

focused modeling. Zhang et al. (2020) used high-throughput screening for viral drugs but did not incorporate dengue-specific datasets. Rao et al. (2020) explored AI-assisted repurposing but required further optimization for targeting dengue.

2.2 RESEARCH GAPS

2.2.1 Limited AI-Driven Drug Discovery Specifically for Dengue

Although AI has made significant strides in drug discovery across various domains, its targeted application to dengue remains largely unexplored. Most existing AI models do not incorporate dengue-specific datasets, viral proteins, or molecular targets, resulting in a lack of precision in identifying effective antiviral candidates for this disease.

2.2.2 Underutilization of SMILES-Based Deep Learning in Neglected Diseases

SMILES-based modelling has shown promise in various AI-driven studies; however, there is limited work applying transformer-based architectures such as ChemBERT specifically to dengue-related compounds. The potential of such models to capture fine-grained molecular features for neglected diseases remains largely untapped.

2.2.3 Absence of Early-Stage Safety Evaluation in AI Pipelines

Many AI systems focus predominantly on drug efficacy while overlooking early prediction of side effects or toxicity. There is a lack of integrated frameworks that allow for pre-screening and prioritization of low-risk candidates using molecular similarity or other computational scoring strategies during the initial stages of discovery.

2.2.4 Lack of Efficient Filtering Strategies for High-Risk Compounds

Existing pipelines often rely on downstream validation or trial-and-error elimination of compounds. There is a gap in methods that proactively score and deprioritize potentially harmful candidates early, particularly through approaches grounded in structural similarity to known high-risk drugs.

2.2.5 Overreliance on Generalized Virtual Screening and DTI Models

While virtual screening and DTI prediction are core components of AI-based drug discovery, most models are developed using broad-spectrum datasets not specific to dengue. This generalization

limits their relevance and effectiveness when applied to diseases with unique viral mechanisms and structural targets.

2.2.6 Underexplored Use of Controlled Compound Augmentation Techniques

Generative models such as GANs or VAEs have been proposed for novel molecule generation but often lack controllability and contextual specificity. There is limited research on guided augmentation techniques such as structurally informed chemical modifications that are better suited to generating viable dengue-focused candidates.

2.2.7 Minimal Emphasis on Severity-Aware Prioritization for Neglected Diseases

Current literature rarely addresses compound ranking based on predicted adverse outcomes alongside efficacy. Especially in the context of neglected tropical diseases, severity-aware filtering remains an underdeveloped area. There is a need for AI frameworks that incorporate side effect predictions to balance safety and therapeutic potential from the outset.

2.3 OBJECTIVES

2.3.1 Generation of Novel Dengue Drug Candidates from Known Compounds

Develop a data-driven method to generate novel drug-like compounds for dengue by modifying existing dengue-related molecules. This process uses SMILES representations and RDKit-based augmentation to simulate chemical group interchanges while preserving structural relevance.

2.3.2 Transformer-Based Modeling for Efficacy and Severity Prediction

Utilize a ChemBERT transformer model trained on SMILES strings to predict potential efficacy and estimate side effect severity of generated compounds. The model captures molecular-level features to support informed screening decisions.

2.3.3 Similarity-Driven Severity Scoring for Early Filtering

Apply cosine similarity between known and generated compound embeddings to compute severity scores. This allows early elimination of compounds with high predicted toxicity or undesirable similarity to risky molecules, improving the safety profile of selected candidates.

2.3.4 Acceleration of Drug Discovery Through Automation

Demonstrate how automation of compound generation, prediction, and filtering using AI significantly reduces the time and effort involved in early-phase drug discovery for dengue, replacing manual trial-and-error approaches with efficient, scalable computation.

2.3.5 Compilation of Structured Compound Output for Future Research

Compile the generated compounds along with their severity scores and model outputs into a structured dataset. This output supports downstream analysis, reproducibility, and future extensions in dengue-focused drug development.

2.4 PROBLEM STATEMENT

Traditional drug discovery is slow, expensive, and often inefficient, typically requiring over a decade and billions of dollars to develop a single drug. For rapidly spreading diseases like dengue, which involves four distinct and evolving serotypes, such delays are especially critical. Existing drug development pipelines struggle to adapt to the virus's complexity and high mutation rate, leaving a gap in timely therapeutic intervention.

AI and machine learning (ML)-based approaches offer a faster, more cost-effective alternative by enabling in silico predictions of drug efficacy and safety. These methods can analyze molecular structures, simulate interactions, and identify promising candidates before physical testing, reducing the risk of late-stage failure. In this project, transformer-based deep learning models (ChemBERT) trained on SMILES strings are used to generate and evaluate novel compounds. Cosine similarity-based scoring further helps identify structurally high-risk molecules early. Together, these techniques support a faster, safer, and more targeted approach to discovering antiviral leads for dengue.

2.5 PROJECT PLAN

2.5.1 Data Collection and Preprocessing

The project begins with collecting a dataset of dengue-related drug compounds from public databases such as PubChem, ChEMBL, and DrugBank, as well as manually curated entries from scientific literature. The dataset includes SMILES strings and side effect annotations.

Preprocessing steps include the removal of incomplete entries, normalization of SMILES representations, and binary labelling of compounds based on side effect severity. Compounds are labelled as severe or not severe depending on the presence of severity-indicating keywords. The processed dataset is split into training and testing sets for model development.

2.5.2 Model Training with ChemBERT

The ChemBERTa transformer model, pretrained on large-scale chemical data, is fine-tuned on the SMILES dataset using binary classification to predict side effect severity. The SMILES strings are tokenized and converted into embeddings using a tokenizer compatible with ChemBERT. PyTorch-based dataset objects are created to facilitate training and evaluation through the HuggingFace Trainer API. Model performance is evaluated using accuracy metrics on the test set.

2.5.3 Similarity-Based Severity Prediction and Ranking

After training, the model is used to predict the severity of newly generated SMILES compounds. For each compound, the predicted probability is interpreted as a severity score. Cosine similarity is computed between embeddings of generated and known compounds to identify the most structurally similar entries. The associated side effects from the top similar compounds are aggregated and ranked to produce an interpretable list of likely adverse effects. This dual approach ensures both statistical scoring and contextual relevance.

2.5.4 Generation and Evaluation of Novel Compounds

A set of approximately 2000 novel SMILES compounds is generated by applying modifications to the original dengue-related drugs. These generated compounds are passed through the trained ChemBERT model to obtain severity scores and predicted side effects. Compounds are filtered based on score thresholds, allowing the early removal of high-risk candidates from the pool. Visual tools such as histograms and heatmaps are used to analyze and interpret severity distribution and frequent adverse reactions.

2.5.5 Final Analysis and Dataset Compilation

The final stage involves compiling all evaluated compounds along with their predicted severity, associated side effects, and similarity rankings into a structured dataset. This compilation serves as a foundation for future exploration and optimization in dengue drug discovery. The approach demonstrates how AI and transformer-based models can assist in filtering and prioritizing antiviral drug candidates efficiently and systematically.

Chapter 3

TECHNICAL SPECIFICATION

3.1 REQUIREMENTS

3.1.1 Functional requirements

3.1.1.1 Data collection and management

Data collection begins with identifying a list of known dengue-related drugs, partly from public databases (e.g., PubChem, DrugBank, ChEMBL) and partly through manual curation from scientific literature and bio-resources like PubMed. Data is either manually extracted or collected via scripts that scrape structured data (e.g., SMILES, names) from scientific databases. Each compound entry includes its name, molecular structure in SMILES format, and other identifiers. Focus is on collecting valid and unique SMILES representations for downstream processing. SMILES strings are normalized, and duplicates or invalid entries are automatically removed using RDKit. The datasets and generated outputs are stored in CSV format for portability, with the option to move to a scalable database system depending on future system requirements.

3.1.1.2 Drug compound generation

A compound generation pipeline uses RDKit to create approximately 2000 new SMILES strings by applying chemical transformations on the original 38 dengue-related compounds. Modifications introduce structural variability to increase chemical diversity and improve novelty potential. Newly generated SMILES are stored along with references to their parent compounds and generation metadata in a CSV file.

3.1.1.3 Machine learning model integration

A ChemBERT transformer model is used for analyzing SMILES strings. The model is fine-tuned to predict potential side effect severity. The generated compounds are tokenized and passed through the model to compute embeddings. Cosine similarity is used to compare generated compounds with known ones to infer potential side effects. The similarity and model outputs together generate a severity score per compound. While the current pipeline uses a transformer-based ChemBERT model, the system is adaptable to include other ML models like Random Forest or XGBoost for property prediction.

3.1.1.4 Validation of predictions

Cosine similarity to known drugs provides an approximate validation by referencing existing side effect profiles. Though the primary output is the severity score, future extensions may include precision, recall, F1 score, and ROC-AUC for model evaluation, especially if supervised labels are available. The current focus is on in silico methods; however, the architecture allows integration with experimental pipelines if

required.

3.1.1.5 Results visualization and reporting

Histograms and heatmaps are used to visualize the distribution of severity scores across the generated compound set. Thresholds can be applied to exclude high-severity compounds early in the discovery process. Outputs are compiled into structured CSV datasets. Future enhancements may include automated report generation with visualization snapshots and scoring summaries.

3.1.2 Non-Functional Requirements

Non-functional requirements ensure that the machine learning pipeline for dengue drug discovery performs efficiently, securely, and with the robustness needed for reliable and scalable scientific research. These requirements support performance, maintainability, and usability across various computational scenarios.

3.1.2.1 Performance

The system must be capable of handling thousands of chemical compounds efficiently. For the current project, nearly 2000 SMILES were processed using RDKit for compound manipulation and ChemBERT for model prediction. The processing time should scale appropriately with the dataset size. Embedding and cosine similarity operations should be optimized for quick turnaround, preferably completing small datasets within minutes and larger batches (10K+) within a few hours.

3.1.2.2 Reliability

The code pipeline must exhibit high fault tolerance, especially during batch processing and model inference. Failures such as data corruption or interrupted similarity analysis should trigger fallback mechanisms or save points for safe resumption. Logging and consistent intermediate storage help support error recovery.

3.1.2.3 Security

Although the prototype runs locally and uses flat files (CSV), future deployments should include data encryption (e.g., AES-256) for sensitive biological data and implement role-based access. Logging mechanisms can record experiment metadata and access trails to ensure audit readiness.

3.1.2.4 Usability

The code is structured with clarity to aid users in understanding each module's functionality. Although no UI is present, the scripts are modular and documented to allow researchers to run or modify parts as needed. Jupyter Notebooks are used for clarity and educational value.

3.1.2.5 Interoperability

The pipeline is designed around open tools like RDKit and ChemBERT, ensuring compatibility with other cheminformatics libraries. Input/output formats such as CSV and SMILES are supported to maximize flexibility for downstream tasks, including molecular docking and further analysis.

3.1.2.6 Extensibility

The architecture supports adding more drug types, predictive endpoints (like efficacy or toxicity), or advanced algorithms. With modular components for SMILES generation, modeling, and scoring, new datasets and ML models can be integrated with minimal refactoring. APIs or notebook modules may be developed for external calls or pipeline extension.

3.1.2.7 Maintainability

Each notebook and module are commented and modular. The separation of dataset preparation, model training, similarity computation, and output generation ensures that any part can be updated independently. Future maintainability will benefit from transition into class-based Python scripts or packages.

3.1.2.8 Energy Efficiency

Given ChemBERT's transformer architecture, training is resource-intensive, but inference on generated compounds remains efficient. Minimal resource use is achieved by running only essential computations. Future versions can implement batch predictions and cloud resource throttling for better energy management.

3.1.2.9 Robust Data Handling

Data is cleaned and standardized early using RDKit, ensuring structural uniformity. Intermediate and final outputs are saved as versioned CSV files, and processes are designed to be repeatable and transparent. Adding automated backups or Git-based versioning can further improve reliability.

3.2 FEASIBILITY STUDY

3.2.1 Technical Feasibility

3.2.1.1 Technology Readiness

The technologies used in this project, such as ChemBERT transformer models and cheminformatics tools like RDKit, are mature and suitable for molecular structure analysis and drug discovery. ChemBERT has been pretrained on chemical data and is fine-tuned for SMILES-based tasks, enabling side effect prediction. RDKit facilitates SMILES manipulation and molecule generation. Data was collected from reliable resources such as PubMed and structured in CSV format for compatibility.

3.2.1.2 Development Environment

The development environment is based on Python and Jupyter Notebooks, leveraging packages like HuggingFace Transformers, RDKit, and Scikit-learn. These tools run effectively on standard computational resources, and training can be performed locally or on cloud services when scalability is needed. The modularity of the code enables easy updates and repeatability of experiments.

3.2.1.3 Expertise Requirements

The project primarily requires expertise in cheminformatics, molecular data processing, and AI model development using transformers. While no UI is developed, scripting knowledge is essential. Understanding of dengue biology also supports effective compound selection and relevance of the prediction models. The modular structure ensures that contributions from specialists in different areas can be integrated smoothly.

3.2.1.4 Challenges and Mitigation Strategies

Key challenges include the quality and completeness of biological data, which may impact model performance. This is addressed by applying rigorous preprocessing steps such as normalization and deduplication. Computational load during similarity calculations is managed by precomputing embeddings and batch processing the SMILES inputs. Using cosine similarity also reduces the need for heavy docking simulations at early stages.

3.2.2 Economic Feasibility

3.2.2.1 Cost Breakdown

Since the implementation uses open-source tools like RDKit and HuggingFace Transformers, software costs are minimized. Hardware requirements are also modest due to local processing. A minimal setup includes a workstation with GPU support, but scalability can be achieved using cloud resources. No commercial software or high-cost servers are required in the current phase, reducing upfront expenses.

3.2.2.2 Potential Savings and Benefits

The early-stage filtering of toxic drug candidates based on severity scoring reduces the burden on later experimental stages. By eliminating unsuitable compounds computationally, researchers can save both time and cost. Compared to traditional drug screening, which is expensive and time-consuming, this ML-based pipeline significantly accelerates discovery and reduces wastage.

3.2.2.3 Return on Investment (ROI)

The framework can be extended to other diseases beyond dengue, increasing its utility and cost-effectiveness. Since most of the investment lies in computational research and minimal hardware, the ROI improves over time with each successful use case or expansion. The system offers long-term financial value in both academic and commercial biomedical research environments.

3.2.3 Social Feasibility

3.2.3.1 Addressing Public Health Challenges

The system contributes directly to addressing dengue, a widespread and high-impact viral disease. By accelerating the identification of promising drug candidates, the project supports efforts to reduce infection severity and global disease burden. This aligns with the need for rapid, accessible healthcare innovation in vulnerable regions.

3.2.3.2 Social Acceptance of AI in Healthcare

AI adoption in healthcare is increasing due to its success in diagnostics and treatment prediction. The project's reliance on interpretable scores, cosine similarity for validation, and known reference compounds makes it more explainable and acceptable. Educating stakeholders about the system's workings can further build trust.

3.2.3.3 Ethical Considerations

Ethical use of AI is central to the project. While the current dataset is research-oriented, care is taken to ensure fair representation and transparency. The approach avoids opaque black-box predictions by using similarity measures with known drugs. Any future real-world deployment will comply with data protection policies like GDPR and HIPAA.

3.2.3.4 Societal Benefits

This project promotes skill development in AI and biomedical fields, especially for students and researchers. It opens opportunities in interdisciplinary collaboration and supports open science practices. Ultimately, it helps advance public health while offering technical and educational growth.

3.2.3.5 Sustainability

The workflow is resource-efficient and avoids redundant computation. By reducing the number of compounds needing experimental testing, it contributes to energy-saving and cost-effective practices in early-stage drug development.

3.2.3.6 Alignment with Sustainable Development Goals (SDGs)

The project aligns with SDG 3 (Good Health and Well-being) by supporting the development of treatments for infectious diseases like dengue. It also promotes SDG 9 (Industry, Innovation, and Infrastructure) through its AI-driven approach. By focusing on open science and accessible AI, it advances SDG 10 (Reduced Inequality) and SDG 13 (Climate Action) by enabling sustainable drug discovery practices.

3.3 SYSTEM SPECIFICATION

3.3.1 Hardware Specification

3.3.1.1 Processing Power

The system was developed on a workstation with a multi-core Intel or AMD processor, enabling efficient batch processing and SMILES-based transformation using RDKit. For ML tasks using ChemBERT, GPU acceleration such as NVIDIA RTX 3090 or equivalent is recommended, particularly for training or inference on large chemical datasets.

3.3.1.2 Memory Requirements

64 GB of RAM is sufficient for working with datasets of up to several thousand compounds. Storage includes 1–2 TB SSD for working directories and result caching, and an optional external HDD (4 TB or more) for backing up datasets, CSV outputs, and temporary model checkpoints.

3.3.1.3 Networking Components

A standard broadband internet connection is used for downloading datasets and accessing code repositories. Higher-speed connections (>100 Mbps) are preferred when working with remote GPU resources or for syncing large files to cloud platforms.

3.3.1.4 Power Supply and Cooling

A stable power supply and UPS are advisable when training or running batch experiments to prevent interruption. Mid-range cooling solutions (like cabinet fans or AIO coolers) are sufficient for long-running RDKit and transformer inference tasks.

3.3.1.5 Peripherals

Basic peripherals such as HD monitors, standard keyboards, and mice are sufficient. Dual monitors can help manage Jupyter notebooks, logs, and datasets during experimentation.

3.3.1.6 Cloud-Based Alternatives

For scaling to larger datasets or running parallelized experiments, platforms like Google Collab Pro+, AWS EC2 with GPU instances, or Azure ML can be used. These services allow the use of high-performance virtual environments without maintaining physical hardware.

3.3.2 Software Specification

3.3.2.1 Operating Systems

Windows 11 was used for model development, document creation, plotting, and running Jupyter-based notebooks due to its compatibility with RDKit, PyTorch, and HuggingFace Transformers.

3.3.2.2 Programming Languages

Python was the primary programming language due to its mature ML and cheminformatics libraries. No R or SQL was used, as data handling was primarily done using Pandas and CSV formats.

3.3.2.3 Machine Learning Frameworks

PyTorch was used via HuggingFace Transformers for implementing the ChemBERT model. Additional ML tasks like cosine similarity were computed using Scikit-learn and NumPy. TensorFlow was not part of this implementation.

3.3.2.4 Cheminformatics Tools

RDKit was central to molecular SMILES generation and validation. No docking tools like AutoDock or Open Babel were used in the current workflow.

3.3.2.5 Database Management Systems (DBMS)

No formal DBMS was used. All drug and SMILES data were handled using structured CSV files. If scaling is required, integration with SQLite or PostgreSQL is recommended.

3.3.2.6 Data Visualization Tools

Matplotlib and Seaborn were used for generating histograms and heatmaps to analyze severity score distributions and similarity metrics.

3.3.2.7 Integrated Development Environments (IDEs)

Jupyter Notebooks were the main development environment, allowing code explanation, result visualization, and testing in one interface. PyCharm was used occasionally for script debugging.

3.3.2.8 Version Control and Collaboration

Git was used locally for versioning. Public or collaborative repositories (e.g., GitHub) were not required but are suggested for future expansion.

3.3.2.9 Cloud and Containerization Tools

The current implementation is local. However, future scalability could include containerization with Docker and cloud orchestration using platforms like AWS SageMaker or Collab.

3.3.2.10 Validation and Testing Tools

The primary evaluation involved cosine similarity and severity score comparison. No formal test suite or bioinformatics tools were used. Further validation modules may be integrated for broader ADMET checks.

3.3.2.11 Security Tools

Since the application is local and for research use, no advanced security layers were applied. For institutional or public deployment, encryption, access controls, and audit logging should be implemented.

3.3.2.12 User Interface Development

No graphical user interface was created. All operations were executed through Python scripts and Jupyter notebooks. The system can be extended to integrate a lightweight web UI if needed.

3.3.2.13 Deployment and Monitoring Tools

As this was a local research project, deployment was not required. For production-level deployment, CI/CD tools like GitHub Actions and monitoring via Grafana or Prometheus could be considered.

Chapter 4

DESIGN APPROACH AND DETAILS

4.1 SYSTEM ARCHITECTURE

4.1.1 Overview and components

The system follows a modular architecture optimized for research-oriented compound generation and analysis in AI-driven drug discovery. It comprises five conceptual layers—data, processing, ML modeling, result interpretation, and reporting. Each layer is loosely coupled to enable modular upgrades and targeted troubleshooting.

4.1.2 Data layer

4.1.2.1 Data sources

Data is manually curated from scientific publications and bio-databases like PubMed, PubChem, and ChEMBL. The curated drug list comprises 38 known compounds related to dengue treatment.

4.1.2.2 Data storage

No SQL/NoSQL databases were used in the current workflow. All compound data including SMILES, generated molecules, and severity scores are stored as CSV files to ensure portability and simplicity.

4.1.2.3 ETL pipeline

A preprocessing pipeline normalizes SMILES using RDKit, handles missing or invalid entries, and generates new compounds algorithmically through structural modifications. The data is structured into training-ready format and saved as CSV.

4.1.3 Processing layer

4.1.3.1 Feature engineering

RDKit is used to convert input molecules to SMILES format and perform structural transformations. ChemBERT handles SMILES tokenization and embedding generation.

4.1.3.2 Dataset preparation

The curated dataset and generated SMILES (approx. 2000) are compiled, filtered, and converted to embedding form. These embeddings are used as model input for side effect severity estimation.

4.1.4 Machine learning layer

4.1.4.1 Model types

The primary model used is a transformer-based ChemBERT architecture. Cosine similarity is employed to assess the relationship between generated and known drugs based on embedding distance, which supports severity scoring.

4.1.4.2 Training environment

The model is fine-tuned using PyTorch and HuggingFace Transformers in a local Jupyter Notebook environment. The pipeline includes embedding generation, scoring, and similarity-based inference.

4.1.4.3 Functional modules

Severity estimation is the key function performed by the ML pipeline. Toxic compounds can be flagged early based on high severity scores, reducing further evaluation effort.

4.1.5 Application layer

4.1.5.1 User interface

The project is currently implemented via Jupyter notebooks. There is no frontend interface; however, the code structure supports easy extension to a future UI for researcher interaction.

4.1.5.2 Backend system

Backend processing, including SMILES generation, tokenization, embedding, and similarity comparison, is managed through Python scripts using RDKit, NumPy, and PyTorch libraries.

4.1.5.3 API integration

The current system is script-driven, with no API integrations implemented. However, the modular structure is ready for future RESTful API layers for web-based deployments.

4.1.6 Visualization and reporting layer

4.1.6.1 Visualization tools

Histograms and heatmaps are used to show severity score distribution and drug similarity clusters. These are generated using Seaborn and Matplotlib.

4.1.6.2 Reporting system

CSV outputs include the generated SMILES, predicted severity score, and top cosine similarity matches. These serve as foundational data for downstream documentation and reporting.

4.1.7 System workflow

The system workflow begins with SMILES ingestion and preprocessing. Embeddings are generated via ChemBERT, and similarity scoring is performed. Results are stored in CSV and visualized using plots, enabling researchers to filter candidates based on severity thresholds.

4.1.8 Scalability and flexibility

The modular design supports scalability through code reuse, component isolation, and easy upgrade paths. The architecture can be extended to other diseases or model types by swapping data sources or ML modules.

4.1.9 Security and reliability

Although currently deployed for local academic research, the codebase supports reproducibility and basic data safety. For future deployments, encryption and access control can be layered on top using available Python libraries or containerized environments.

4.2 DESIGN

4.2.1 Data Flow Diagram

Figure 4.1: Data Flow Diagram

4.2.2Class Diagram

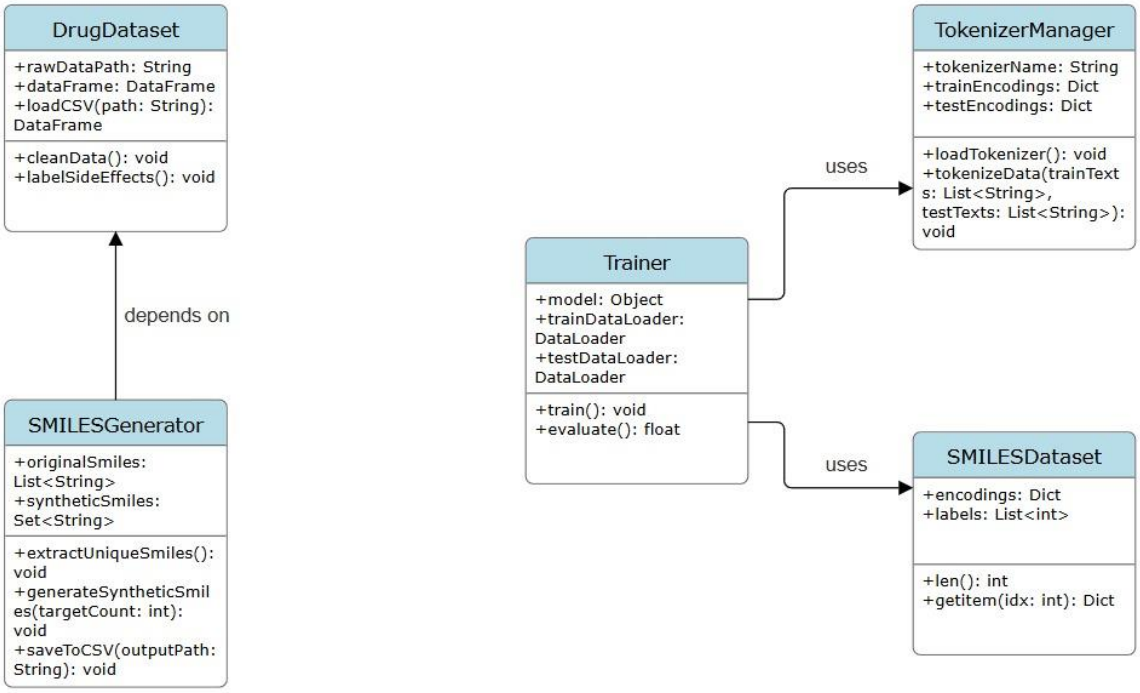

Figure 4.2: Class Diagram

Chapter 5

METHODOLOGY AND TESTING

5.1 MODULE DESCRIPTION

The system comprises several modular components organized in a sequential pipeline. Each module handles a specific step in the AI-based dengue drug discovery process, from data acquisition to output visualization. This modularity ensures that updates to one stage do not disrupt the functioning of others.

5.1.1 Data Collection and SMILES Conversion

The first module involves gathering an initial set of 38 dengue-related drugs from online biomedical repositories and literature sources like PubMed. These compounds are manually curated and converted into SMILES strings using RDKit. This conversion is crucial for representing molecular structures in a format suitable for further processing and model interpretation. The dataset is stored in CSV format for reproducibility and is verified for structural validity using RDKit's sanitization methods.

5.1.2 SMILES-Based Compound Generation

To expand the chemical space, the original SMILES dataset undergoes structural transformations using RDKit's molecule editing utilities. These transformations include functional group modifications, ring alterations, and substituent replacement. Approximately 2000 new compounds are generated. This synthetic expansion introduces variability while retaining structural similarity to known antiviral compounds.

5.1.3 ChemBERT Embedding and Severity Prediction

The generated SMILES strings are processed through a ChemBERT-based transformer model using the HuggingFace Transformers library. Tokenization converts each SMILES into an embedding vector. These embeddings are input to a fine-tuned model that outputs a severity score. This score acts as a proxy for adverse effect likelihood, guiding early-phase elimination of high-risk drug candidates.

5.1.4 Cosine Similarity Computation

To contextualize severity predictions, cosine similarity is computed between the embeddings of generated and known compounds. This similarity is used to infer possible side effects by mapping novel drugs to structurally close known drugs. It adds a layer of interpretability to the model's numerical predictions, enabling insight into compound behavior.

5.1.5 Severity Scoring and Filtering

Once all compounds are scored, a filtering mechanism removes high-severity compounds. A predefined threshold can be adjusted depending on the researcher's risk tolerance. This filtering narrows the scope of candidates for further investigation or simulation, ensuring only low-risk compounds are retained in the pipeline.

5.1.6 Visualization and Output Compilation

The final module generates histograms, similarity heatmaps, and summary tables. These visualizations provide an overview of the severity distribution across the generated dataset and highlight clusters of compounds with desirable characteristics. All processed data is compiled and saved into structured CSV files, ensuring ease of access and reusability for further study.

5.2 TESTING

Testing ensures that each component functions correctly and the outputs align with expectations. Since this is a research-grade pipeline built with Jupyter notebooks, testing is performed through inline validations, output inspection, and assertion checks at critical stages.

5.2.1 Data Integrity Testing

The initial SMILES dataset is validated for syntax and molecular feasibility using RDKit. Invalid entries are logged and excluded automatically to prevent error propagation. Generated molecules are also checked for structural validity before proceeding to modeling.

5.2.2 Model Functionality Testing

ChemBERT embeddings and severity scores are validated through dimensionality checks and sample inference outputs. Predictions are examined for consistency across batches and checked against known compounds for expected similarity behavior.

5.2.3 Similarity Score Validation

Randomly sampled compound pairs are manually verified to ensure that high cosine similarity corresponds with close chemical resemblance. This confirms that the embedding space preserves molecular structure representations effectively.

5.2.4 Filtering and Visualization Checks

5.2.4.1Severity threshold testing

Filtering modules are tested by adjusting severity thresholds and comparing resulting datasets. This allows the evaluation of how different severity cutoffs affect the compound pool. Researchers can dynamically control stringency and analyze how candidate selections change accordingly.

5.2.4.2Cross-checking of visual outputs

Visualization modules are validated by cross-checking plot outputs with raw data distributions to ensure consistency. These include checking histogram and heatmap outputs against severity score datasets to confirm their accuracy and graphical integrity.

5.2.4.3Structural data validation

Each SMILES string undergoes verification to ensure consistent representation. Duplicate and structurally invalid entries are removed, and canonicalization is applied. This prepares the dataset for downstream tasks with uniform formatting and removes ambiguity in structure-to-severity mapping.

5.2.4.4Transformation logging and traceability

Transformations are designed to preserve essential pharmacophores while exploring peripheral substitutions. This mimics medicinal chemistry workflows where new analogs are synthesized to probe activity landscapes. Multiple variations per parent compound are logged with metadata for traceability.

5.2.4.5Attention-based prediction capability

The model uses attention mechanisms to capture both local and global structural patterns in SMILES strings. This allows it to generalize from existing severity patterns and assign meaningful scores to unseen molecules based on latent features.

5.2.4.5Similarity clustering and explanation

Cosine similarity not only ranks closeness but also helps in cluster analysis. Generated compounds are visualized in embedding space and matched with their nearest neighbors. These mappings are later used to explain predictions and guide experimental prioritization.

5.2.4.6Output formatting for downstream use

CSV files include generated SMILES, severity scores, and their closest known counterparts. Alongside visualizations, these datasets are intended for collaboration with experimental teams and can be used to drive future in-vitro validation pipelines.

5.2.4.7Tokenizer and embedding consistency checks

Unit-level tests verify the consistency of tokenizer output and embedding shapes. Outliers in severity predictions are flagged for manual inspection, ensuring no systemic bias or malformed encoding influences the results.

5.2.4.8Similarity validation through controls

Control experiments are performed using known molecule pairs to benchmark the cosine similarity algorithm. Embeddings for identical or isomeric molecules are expected to produce near-perfect similarity, validating the embedding space's chemical fidelity.

Chapter 6

PROJECT DEMONSTRATION

The first step of the process involved aggregating side effects from curated dengue-related compounds. The data was visualized to determine which symptoms occur most frequently among known drugs. This provides insight into what adverse effects need to be monitored when generating new candidate molecules.

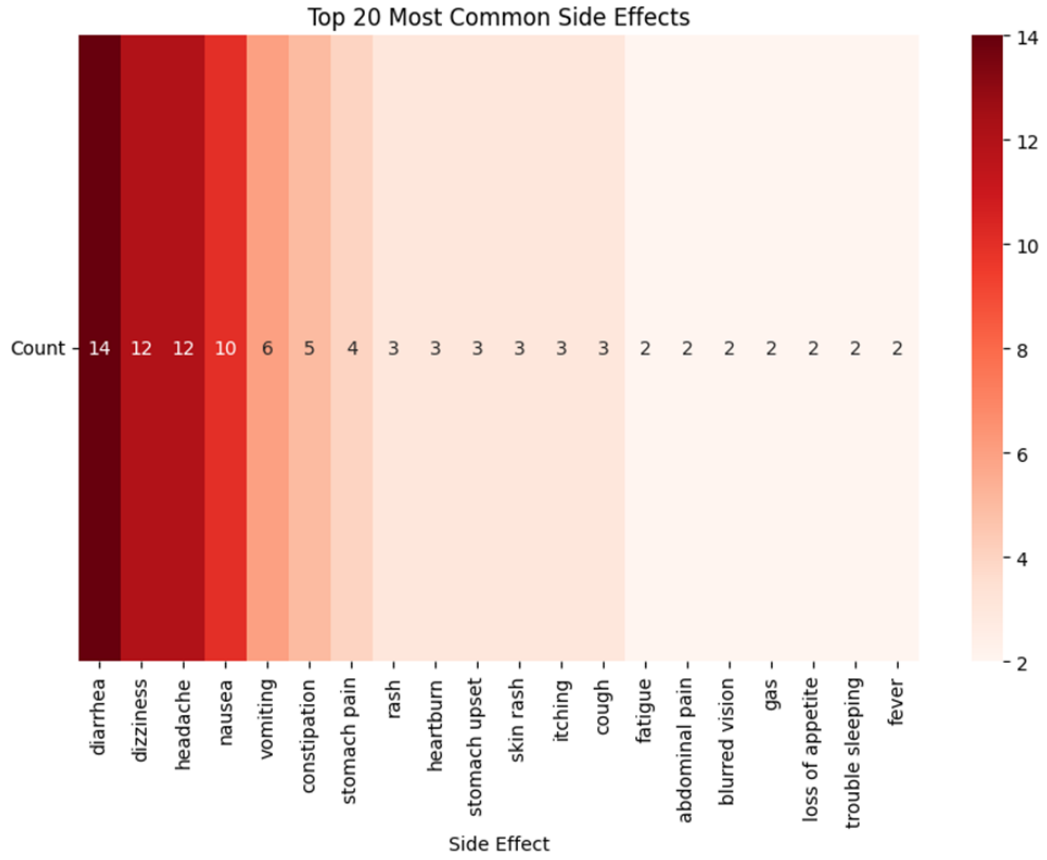

Figure 6.1: Top 20 Most Common Side Effects

To simplify severity estimation, a binary classification label was added based on manually defined thresholds using keyword indicators. The figure below shows a significant class imbalance, with most compounds labeled as 'not severe'. This influenced the choice of evaluation metrics during model validation.

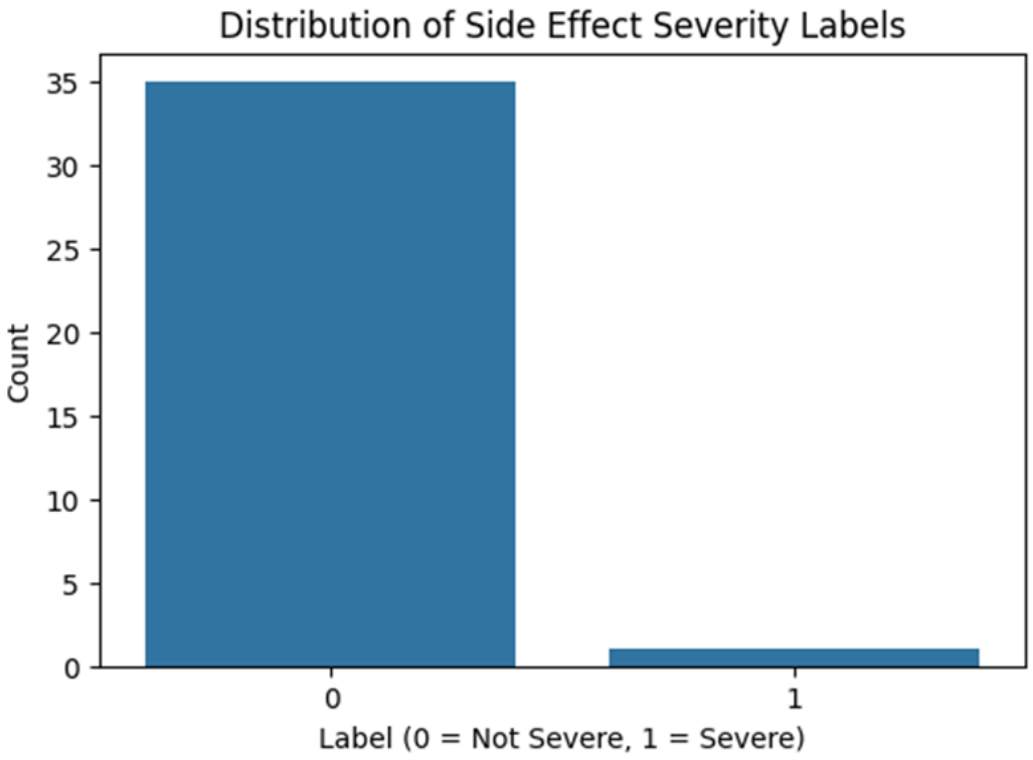

Figure 6.2: Distribution of Side Effect Severity Labels

Once new compounds were generated using SMILES transformations, they were processed through the ChemBERT model to infer severity scores. The distribution of scores, shown below, is slightly right-skewed with a peak between 0.1 and 0.15, suggesting that most candidates are low-risk.

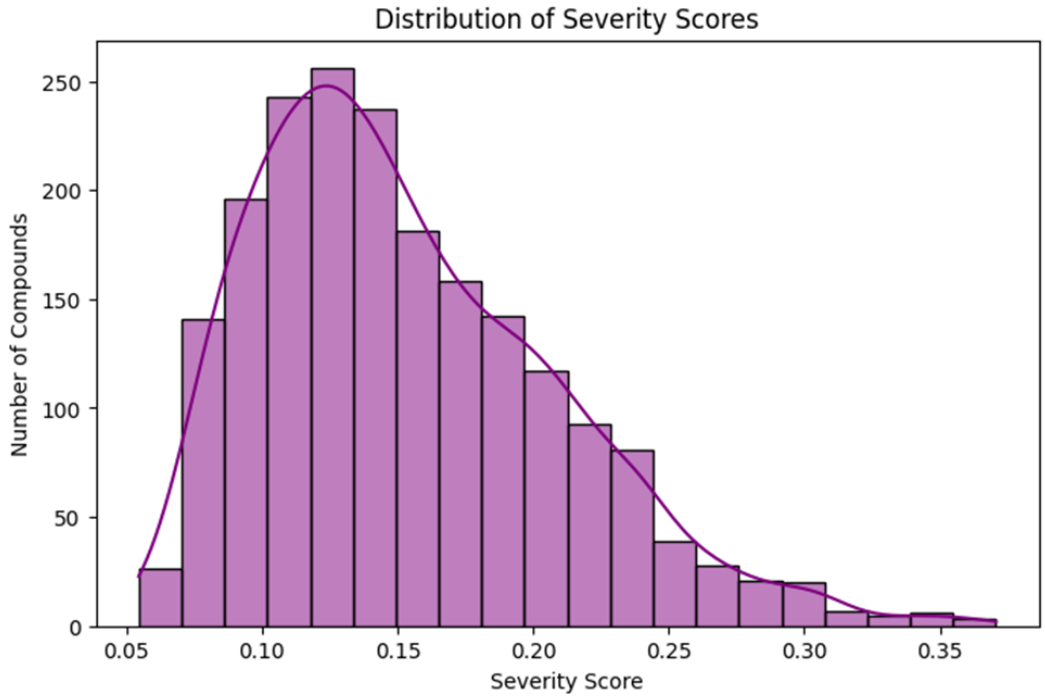

Figure 6.3: Distribution of Severity Scores for Generated Compounds

The ChemBERT model was trained over five epochs using a binary classification loss function. The training and validation losses steadily decreased, indicating that the model was learning effectively without significant overfitting. The validation loss stabilized by epoch 5, as shown below.

[10/10 00:08, Epoch 5/5]

Epoch	Training Loss	Validation Loss
1	No log	0.306146
2	No log	0.177636
3	No log	0.119358
4	No log	0.093995
5	0.290200	0.085502

```
TrainOutput(global_step=10, training_loss=0.29024405479431153, metrics={'train_runtime': 9.2163, 'train_samples_per_second':
15.191, 'train_steps_per_second': 1.085, 'total_flos': 12061777588560.0, 'train_loss': 0.29024405479431153, 'epoch': 5.0})
```

Figure 6.4: Training and Validation Loss Over Epochs

For every newly generated compound, the system predicts a severity score and corresponding label. The figure below shows a representative output, including SMILES notation, the predicted severity score, and likely side effects inferred through cosine similarity with known drugs.

```
SMILES: N([C@@H]1[C@@H](NC(C)=O)[C@@H](OC(C(=O)O)=C1)[C@H](O)[C@H](O)CO)=C(N)N
Severity Score: 0.0899
Prediction: Not Severe
Predicted Side Effects: dizziness, diarrhea, headache, nausea, vomiting
```

Figure 6.5: Severity Prediction Output Sample with Side Effects

After final validation on the test set, the model achieved a high accuracy of 97.81%. This performance metric confirms that the model is well-calibrated to distinguish between severe and non-severe compounds, especially in the imbalanced dataset setting.

```
Test Accuracy: 0.9781
```

Figure 6.6: Final Test Accuracy of Trained Model

Chapter 7

RESULT AND DISCUSSION

The proposed AI-based framework for dengue drug discovery leverages a multi-step pipeline to generate and evaluate novel drug candidates. The pipeline starts by curating dengue-specific compounds, generating structural analogs through RDKit-based SMILES transformations, and scoring them using a fine-tuned ChemBERT model for side effect severity. Cosine similarity is used for structural relevance and interpretability, linking new compounds to existing drugs and side effects.

Key outcomes include a refined list of over 2000 generated compounds with associated severity scores, side effect predictions, and similarity-based annotations. The majority of the predictions fell into the non-severe category, as shown in the histogram analysis, supporting the utility of the generation strategy. Cosine similarity further enriched each compound profile by identifying the closest known analogs, thus reinforcing trust in AI predictions.

Visualization tools such as histograms and heatmaps were used to interpret score distributions and identify compound clusters. The training loss and final model accuracy (97.81%) validate that the ChemBERT model is well-calibrated for binary classification of side effect severity. Since this score is central to eliminating high-risk candidates early in the pipeline, accuracy plays a crucial role in overall system effectiveness.

From a cost perspective, the entire pipeline is built using open-source tools, including RDKit, PyTorch, HuggingFace Transformers, and Jupyter Notebooks. All data handling is done through CSV files, removing the need for database overheads. The project was executed on a single GPU-enabled workstation, with no additional hardware or cloud expenses, making it highly cost-efficient.

The model architecture supports scalability and future deployment. As the system requires only basic computational resources, it is accessible for academic institutions and research teams with limited funding. The codebase is reusable and extendable for other infectious diseases, giving this research broader applicability beyond dengue.

Chapter 8

CONCLUSION AND FUTURE ENHANCEMENTS

8.1 CONCLUSION

This project introduces a practical and modular AI-driven drug discovery pipeline specifically applied to dengue, a neglected tropical disease with increasing global impact. By integrating cheminformatics tools like RDKit and leveraging transformer-based ChemBERT models, the system enables the generation, scoring, and filtering of synthetic compounds derived from a curated dengue drug dataset. Using cosine similarity between known and generated molecules, the model estimates severity scores that help prioritize low-risk candidates early in the drug development cycle.

Key achievements include the successful conversion of 38 known dengue-related compounds into a pool of over 2000 novel SMILES structures, model-based prediction of toxicity severity, and visualization-driven analysis of score distributions. The system's ability to operate locally on open-source infrastructure enhances accessibility and cost-efficiency, making it viable for low-resource research environments. The structured CSV outputs provide a foundation for reproducibility and downstream analysis.

8.2 FUTURE ENHANCEMENTS

8.2.1 Emphasis on High-Quality, Dengue-Specific Datasets

As identified in the literature review and research gaps, most current AI models in drug discovery are trained on generalized bioactivity datasets. Future work should aim to construct and utilize dengue-specific datasets incorporating experimentally validated compounds, serotype-specific viral proteins (e.g., NS5), and host-pathogen interaction data to improve model specificity and reliability.

8.2.2 Expansion to Efficacy and ADMET Predictions

The current system focuses on severity prediction as a safety filter. Extending the architecture to include efficacy scoring against dengue targets and ADMET (absorption, distribution, metabolism, excretion, toxicity) profiling will improve compound prioritization. Multi-task models could be employed to balance therapeutic potential and safety simultaneously.

8.2.3 Integration of Protein-Ligand Docking Modules

To complement similarity-based severity scoring, molecular docking simulations using platforms like AutoDock or PyRx can be incorporated to validate compound interactions with dengue virus proteins. This hybrid approach can confirm binding efficacy and propose candidates for wet-lab testing.

8.2.4 Advanced Compound Generation with Controlled Augmentation

Current SMILES generation is based on structural transformations using RDKit. Future pipelines may include controlled generative approaches, such as VAEs or reinforcement learning agents trained on dengue-specific structural features. These methods can be guided by desired pharmacophore patterns or scaffold constraints to optimize novelty and therapeutic relevance.

8.2.5 Reinforcement Learning for Lead Optimization

Integrating reinforcement learning (RL) can enable iterative optimization of lead candidates by balancing efficacy, safety, and drug-likeness. RL agents can be trained to reward molecules that meet severity thresholds and exhibit favorable docking interactions.

8.2.6 UI/UX Layer for Interdisciplinary Accessibility

To make the system accessible to researchers from biology or pharmacology domains, a user interface layer with visualization, filtering, and data export features can be developed. Integration with molecular editors and drag-and-drop input handling can enhance usability.

8.2.7 Multi-Omics and Systems-Level Modeling

As highlighted in the literature review, integrating multi-omics data (transcriptomics, proteomics) can enhance target specificity and drug repurposing predictions. Future frameworks may include omics-aware embeddings for compounds to capture functional and regulatory context, thereby increasing translational potential.

8.2.8 Severity-Aware Ranking and Dataset Expansion

Severity-aware ranking remains underexplored in most neglected disease pipelines. This framework sets the stage for combining severity, efficacy, and ADMET scores to derive composite compound rankings. Continuous expansion of the generated compound dataset and its use in benchmarking will allow wider adoption and collaborative development.

Chapter 9

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APPENDIX A – Sample Code

Smiles_generation.ipynb:

```
import pandas as pd
from rdkit import Chem

# Load the original dataset
df = pd.read_csv('drug_dataset.csv')

# Identify the SMILES column
smiles_col = None
for col in ['smiles', 'SMILES']:
    if col in df.columns:
        smiles_col = col
        break

if smiles_col is None:
    raise ValueError("No SMILES column found in the data. Expected a column named 'smiles' or 'SMILES'.")

# Extract unique non-null SMILES
original_smiles = df[smiles_col].dropna().unique()
print(f"Found {len(original_smiles)} unique original SMILES.")

# Generate at least 2000 unique non-canonical SMILES strings
synthetic_smiles_set = set()

while len(synthetic_smiles_set) < 2000:
    for s in original_smiles:
        mol = Chem.MolFromSmiles(s)
```

```
        if mol is not None:
            new_smile = Chem.MolToSmiles(mol, doRandom=True)
            synthetic_smiles_set.add(new_smile)
        if len(synthetic_smiles_set) >= 2000:
            break

print(f"Generated {len(synthetic_smiles_set)} unique synthetic SMILES.")

# Save to CSV
synthetic_df = pd.DataFrame({smiles_col: list(synthetic_smiles_set)})
synthetic_df.to_csv('new_gen_smiles1.csv', index=False)

print("Synthetic SMILES saved to 'synthetic_dengue_smiles1.csv'")
```

dengue_sideEffect_prediction.ipynb:

Data Preprocessing

```
import pandas as pd
from sklearn.model_selection import train_test_split

data = pd.read_csv('drug_dataset.csv')
data['label'] = data['Side Effects'].fillna("unknown").apply(lambda x: 1 if "severe" in str(x).lower()
else 0)
data = data.dropna(subset=["SMILES"])
train_texts, test_texts, train_labels, test_labels = train_test_split(
    data['SMILES'].tolist(), data['label'].tolist(), test_size=0.2, random_state=42)
```

Tokenization and Dataset Preparation

```
from transformers import AutoTokenizer
import torch

tokenizer = AutoTokenizer.from_pretrained("seyonec/ChemBERTa-zinc-base-v1")
train_encodings = tokenizer(train_texts, truncation=True, padding=True)
test_encodings = tokenizer(test_texts, truncation=True, padding=True)
```

```
class SMILESDataset(torch.utils.data.Dataset):
    def __init__(self, encodings, labels):
        self.encodings = encodings
        self.labels = labels
    def __len__(self):
        return len(self.labels)
    def __getitem__(self, idx):
        item = {key: torch.tensor(val[idx]) for key, val in self.encodings.items()}
        item["labels"] = torch.tensor(self.labels[idx])
        return item

train_dataset = SMILESDataset(train_encodings, train_labels)
test_dataset = SMILESDataset(test_encodings, test_labels)
```

Model Training with ChemBERTa

```
from transformers import AutoModelForSequenceClassification, Trainer, TrainingArguments

model = AutoModelForSequenceClassification.from_pretrained("seyonec/ChemBERTa-zinc-base-v1", num_labels=2)

training_args = TrainingArguments(
    output_dir="./results",
    evaluation_strategy="epoch",
    learning_rate=2e-5,
    per_device_train_batch_size=16,
    per_device_eval_batch_size=16,
    num_train_epochs=5,
    weight_decay=0.01,
    logging_dir="./logs",
    logging_steps=10,
)

trainer = Trainer(
    model=model,
```

```
    args=training_args,
    train_dataset=train_dataset,
    eval_dataset=test_dataset,
)
trainer.train()
```

Batch Prediction with Cosine Similarity

```
from sklearn.metrics.pairwise import cosine_similarity
from collections import Counter

def predict_batch_from_csv(input_csv, output_csv, model, tokenizer, dataset_df, top_k=5):
    ...
    for smiles_str in tqdm(df_input['SMILES'], desc="Processing SMILES"):
        ...
        logits = outputs.logits
        probs = torch.softmax(logits, dim=1).cpu().numpy().flatten()
        score = probs[1]
        label = "Severe" if score > 0.5 else "Not Severe"
        ...
        effect_counts = Counter(all_effects)
        most_common_effects = [effect for effect, _ in effect_counts.most_common(5)]
        predicted_effects = ", ".join(most_common_effects)
        results.append({
            "SMILES": smiles_str,
            "Predicted Side Effects": predicted_effects,
            "Severity": label,
            "Severity Score": round(score, 4)
        })
```