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Computational Pharmacokinetic Profiling via Hybrid Multimodal Using Deep Learning Architectures

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Abstract: Accurate Prediction of Pharmacokinetic behavior Plays a critical role in early drug discovery, where rapid screening of Molecular candidates can significantly reduce Laboratory workload and development cost. Traditional ADME Modeling Approaches rely heavily on handcrafted descriptors or Rule-Based filters, making them limited in Generalization and often Unsuitable for structurally diverse compounds. Recent Advances in Deep Learning have introduced architectures capable of learning directly from molecular structure, yet single-Modality Models still struggle to capture the full spectrum of chemical information. This paper presents a Hybrid Multimodal Deep Learning framework that integrates three complementary molecular Representations: Engineered chemical descriptors, Atom-Bond Graph Structures processed through graph neural networks (GNNS) and smiles sequences encoded using Transformer architectures Such as chemberta. By combining these modalities through a unified fusion network the system capture Global physicochemical trends, local structural patterns, and contextual sequence information simultaneously. The Framework includes explain ability modules based on snap values and graph-Attribution Techniques to Assist chemists in understanding model decisions. A Stream Lit-Based Interface and API enable practical development for Real-time ADME prediction. Experimental Evaluation on Publicly Available datasets demonstrates that the Multimodal Architecture consistently outperforms descriptors-only,GNN-only, and transformer only baselines across multiple ADME endpoints . The Results Highlight the potential of Multimodal Learning as a Robust, Interpretable, and User-Friendly Computational toll for early Pharmacokinetic Profiling.
Keywords: Adme Prediction, Multimodal Deep Learning, Graph Neutral Networks, Chenberta, Explainable AI, Machine Learning, Pharmacokinetics, Drug Discovery.

I. INTRODUCTION

Pharmacokinetic evaluation determines how a compound behaves in the body, influencing its absorption, distribution, metabolism, and excretion (ADME). These properties dictate whether a molecule can progress through drug development. Although experimental methods provide accurate measurements, they require specialised laboratory infrastructure, extensive time, and considerable resources. As drug development pipelines continue to expand, the need for computational tools that can pre-screen large chemical libraries has become increasingly pressing. Computational ADME models have evolved from simple rule-based filters and descriptor-driven QSAR techniques to more advanced machine learning architectures. While classical models remain useful for interpreting global molecular trends, they lack the capacity to capture rich structural information. Deep learning approaches such as Graph Neural Networks that treat molecules as graphs and transformer-based models that process SMILES sequences have significantly advanced predictive accuracy. However, relying on a single representation modality limits the model's ability to generalise across diverse chemotypes. To address this challenge, we propose a hybrid multimodal ADME prediction framework that integrates descriptor features, graph-based embeddings, and SMILES transformer representations into a unified system. This approach allows the model to leverage complementary chemical signals and produce more robust predictions.

Additionally, explainability techniques are incorporated to ensure transparency and support scientific reasoning. This work aims to deliver a practical, high-performance, and interpretable computational ADME solution suitable for early-stage screening.

II. LITERATURE SURVEY

Efforts to model ADME properties computationally have historically relied on QSAR approaches that employ physicochemical descriptors, fingerprints, and statistical learning algorithms. These models provide valuable insights but struggle with non-linear structure–property relationships and often do not generalise well to novel chemical scaffolds. The advent of deep learning introduced more expressive models. Graph Neural Networks treat molecules as graphs of atoms and bonds, using message-passing mechanisms to encode local neighbourhood information. GNNs have shown strong performance on molecular property prediction tasks due to their ability to learn structural patterns without requiring predefined features. In parallel, SMILES-based transformers such as ChemBERTa and MolFormer leverage self-attention mechanisms to extract contextual and sequential information from chemical strings, capturing long-range dependencies and stereochemical cues. These models excel at representing global structural context but may overlook fine-grained atomic interactions that GNNs capture well. Recent studies highlight the promise of multimodal architectures, which combine descriptors, graphs, and sequences to create enriched representations. Such hybrid systems tend to outperform single-modality approaches by merging global physicochemical features, local graph topology, and sequential context. Explainable AI methods such as SHAP, attention visualisations, and subgraph attribution have additionally become important for validating model decisions and guiding medicinal chemistry. Overall, existing literature suggests that integrating multiple molecular modalities leads to improved accuracy and interpretability, motivating the multimodal approach developed in this work.

III. PROPOSED SYSTEM

The proposed system integrates three different types of molecular representations into a unified predictive framework:

1. Descriptor-Based Representation

Physicochemical descriptors and fingerprint vectors are computed using cheminformatics tools. These include ECFP fingerprints, MACCS keys, logP, TPSA, molecular weight, hydrogen bond features, and other shape- and charge-related properties. Descriptors provide global chemical information and are computationally efficient.

2. Graph Neural Network Representation

Molecules are converted into atom–bond graphs, where nodes represent atoms and edges represent chemical bonds. Features such as atomic number, aromaticity, hybridisation, and bond type are encoded. A GNN processes the graph using message-passing layers to learn structural and electronic interactions.

3. SMILES Transformer Representation

SMILES strings are tokenised and passed through a transformer encoder (e.g., ChemBERTa). Through multi-head attention, the transformer captures global sequence patterns, contextual relationships, and subtle stereo chemical cues. A fusion module aggregates embeddings from all three branches and outputs predictions for multiple ADME endpoints. The system includes an explain ability layer to provide insights into model reasoning and a deployment layer for real-time usage through a web interface and API.

A. System Architecture

The system architecture is designed as a modular, multimodal pipeline in which each molecular representation descriptors, graph structures, and SMILES sequences is processed independently before being merged through a fusion network. The architecture ensures scalability, interpretability, and high predictive performance through parallel processing and clearly separated functional components.

1 Architectural Overview

The overall system follows a four-layered design:

A. Data Processing Layer

This layer handles the ingestion and preparation of molecular data:

- SMILES validation, cleaning, and canonicalization
- Conversion into graph objects (atoms, bonds)
- Descriptor computation (ECFP, MACCS, physicochemical features)
- Tokenisation for SMILES transformers

All processing is performed using RDKit and custom preprocessing modules.

B. Representation Learning Layer

Three parallel submodules operate on the representations:

1. Descriptor Model

- Input: high-dimensional fingerprint vectors and physicochemical descriptors
- Model: MLP or XGBoost
- Output: Dense descriptor embedding capturing global molecular properties

2. Graph Neural Network Model

- Input: atom–bond graph
- Model: GNN architecture (GCN, GAT, or MPNN)
- Output: Graph embedding capturing atomic interactions and structural topology

3. SMILES Transformer Model

- Input: tokenised SMILES sequence
- Model: Transformer encoder (ChemBERTa)
- Output: Contextual sequence embedding representing long-range chemical patterns

Each model is trained separately before being aligned for fusion.

C. Fusion and Prediction Layer

All three embeddings are projected into a unified dimensional space and concatenated. A fusion network consisting of dense layers performs:

- Feature alignment
- Representation integration
- Multi-task prediction across ADME endpoints (solubility, permeability, BBB penetration, clearance, etc.)

This fusion layer is responsible for the performance gain observed over single-modality models.

D. Explain ability & Deployment Layer

To ensure transparency and real-world usability:

- SHAP values explain global and local descriptor contributions
- GNN Explainer highlights critical atoms and bonds
- Transformer attention maps visualise influential SMILES tokens

Deployment is handled through:

- A Streamlit web interface for interactive use
- A Fast API backend for programmatic access
- Docker containerization to ensure replicability and scalability

This modular architecture enables flexible updates, reproducibility, and seamless user experience.

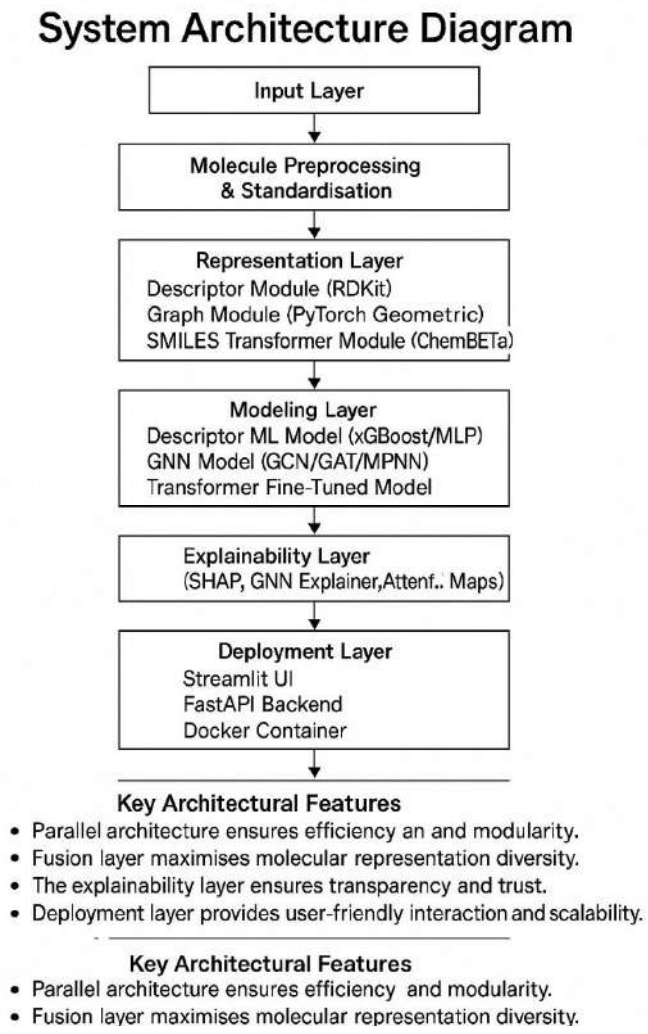

Fig 1. Simplified architecture system architecture

B. Methodology

The methodology consists of several stages, each contributing to the final multimodal prediction framework.

1 Data Preparation

Chemical datasets containing experimentally measured ADME properties were collected from public repositories such as ChEMBL, PubChem, and ADMETlab. SMILES strings were standardized by removing salts, correcting valence issues, and enforcing canonical formatting. Data was partitioned using scaffold-based splitting to prevent structural overlap between training and testing sets.

2 Representation Extraction

Three representation streams were created:

- Descriptor vectors using RDKit
- Graph objects for GNN processing
- Tokenised SMILES sequences for transformer models

Each representation captures different facets of molecular structure and behaviour.

3 Model Training

Separate models were trained for each modality:

- MLP and ensemble methods for descriptor vectors
- GCN, GAT, or MPNN models for graph structures
- ChemBERTa for sequence embeddings

4 Fusion Learning

Embeddings from each representation were projected into a common dimensional space and concatenated. A dense meta-learning module processed the combined vector to produce ADME predictions. This fusion approach enhances robustness by combining complementary molecular information.

5 Explain ability

SHAP was used to interpret the descriptor-based and fusion outputs, offering insight into which chemical features influenced predictions. Graph-based attribution and transformer attention visualisations provided localized explanations for structural and sequence features.

IV. IMPLEMENTATION

The system was implemented using a modular architecture designed for scalability and ease of deployment.

1 Frontend Interface

A Streamlit-based user interface allows users to:

- Input single SMILES strings
- Upload batch datasets
- Visualise predicted ADME properties
- View SHAP plots and graph attention maps
- Download results in CSV format

The interface is designed for researchers without programming expertise.

2 Backend Architecture

A FastAPI backend handles:

- Molecular preprocessing
- Model inference for each modality
- Multimodal fusion
- Explainability generation

The backend exposes REST endpoints enabling integration with external tools. Docker is used to containerise the system for portable deployment.

3 Model Pipeline

The complete inference pipeline includes:

1. Input validation and molecular standardisation
2. Descriptor, graph, and SMILES extraction
3. Independent predictions from each branch
4. Fusion and final ADME estimation
5. Generation of interpretability explanations

This pipeline ensures consistent, reproducible predictions.

V. RESULT AND DISCUSSION

Results demonstrate that the multimodal fusion model consistently outperforms single-modality baselines across multiple ADME endpoints.

1 Performance Comparison

Compared with descriptor-only, GNN-only, and SMILES-transformer-only models:

- RMSE for solubility showed notable reduction
- ROC-AUC for BBB penetration improved significantly
- Permeability and clearance predictions gained higher accuracy

These improvements indicate that each representation contributes unique chemical information, and their combination yields richer predictive capability.

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2 Explain ability Insights

SHAP analysis revealed intuitive relationships between features and predicted ADME outcomes, such as the influence of molecular polarity on permeability. GNN attribution maps highlighted functional groups and bond environments relevant to metabolic stability. Transformer attention illustrated the importance of heteroatoms and branching tokens in sequence-based understanding.

3 Discussion

The multimodal architecture proved especially beneficial for structurally diverse datasets, where single-modality models struggled. The unified design also reduced prediction inconsistencies across ADME endpoints. Explainability features enhanced transparency, making the tool more suitable for medicinal chemistry workflows.

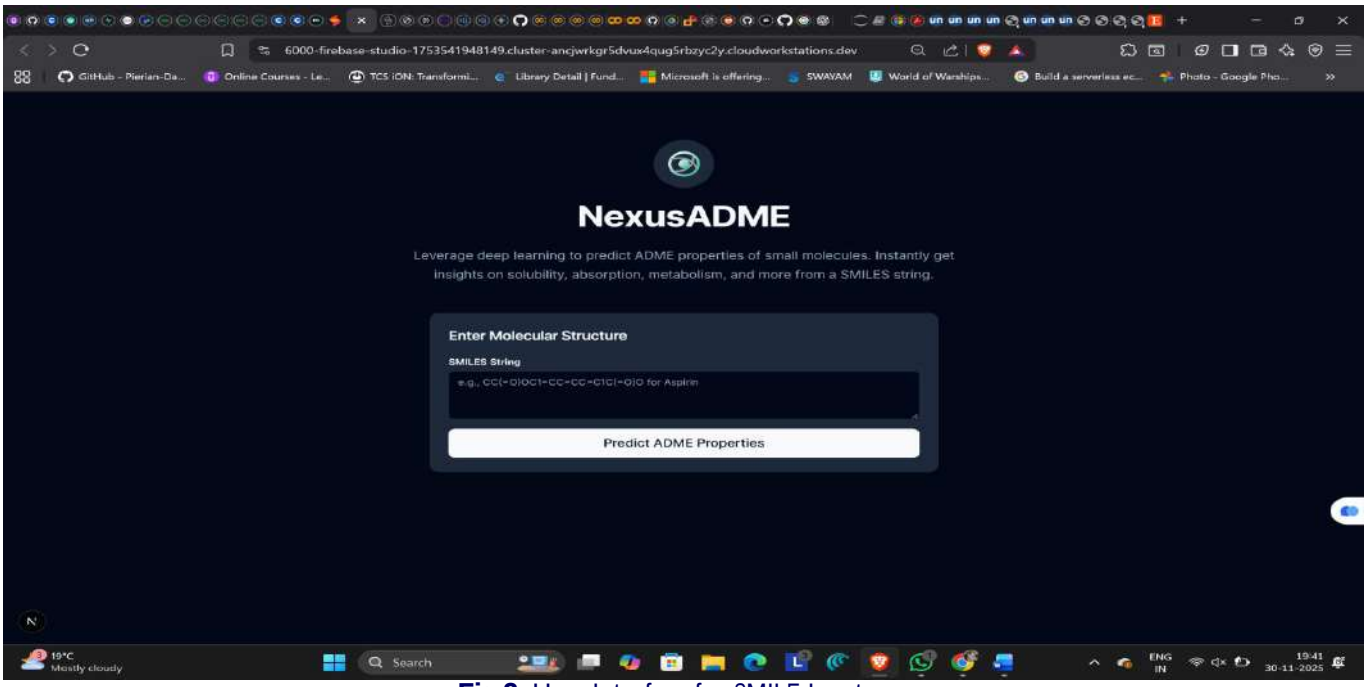

Fig 2: User Interface for SMILE Input

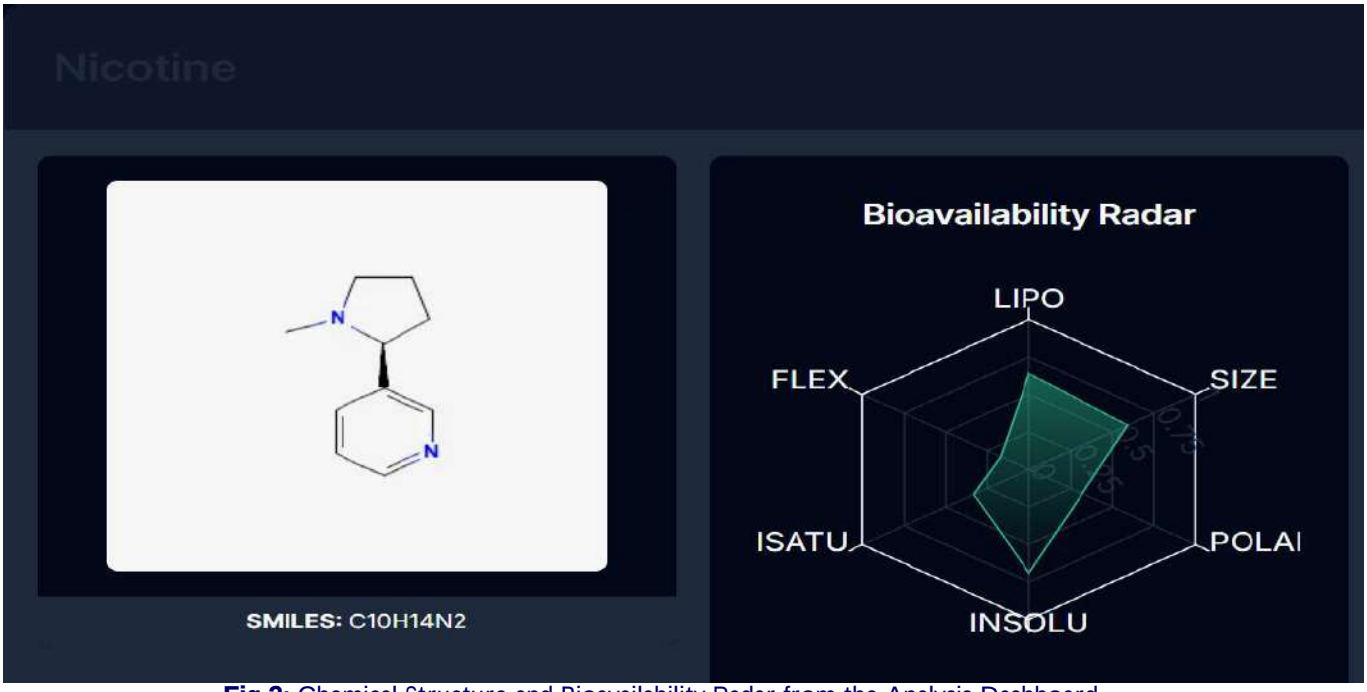

Fig 3: Chemical Structure and Bioavailability Radar from the Analysis Dashboard

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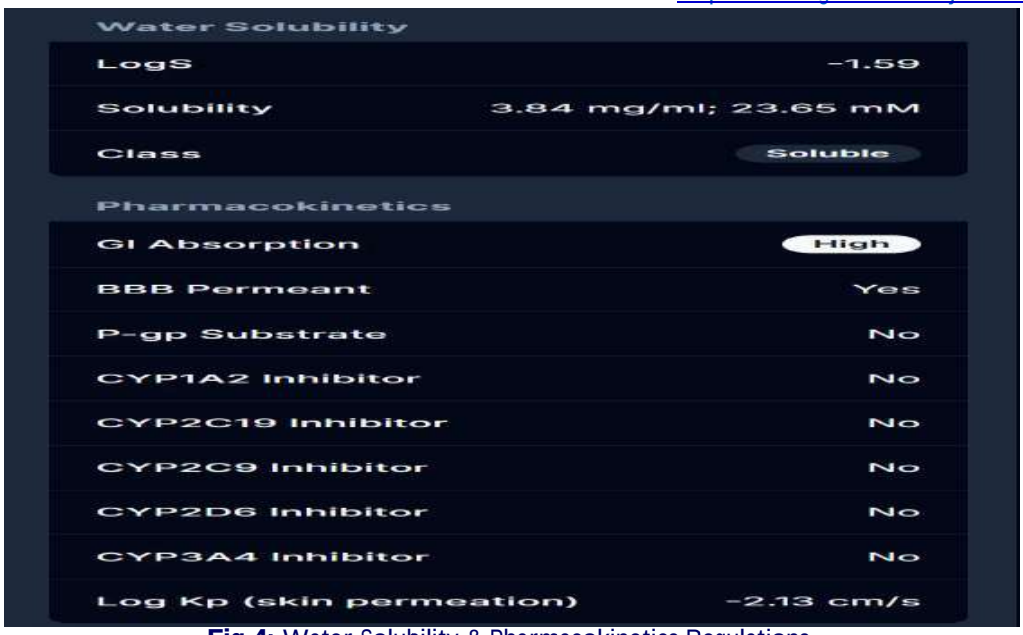

Fig 4: Water Solubility & Pharmacokinetics Regulations

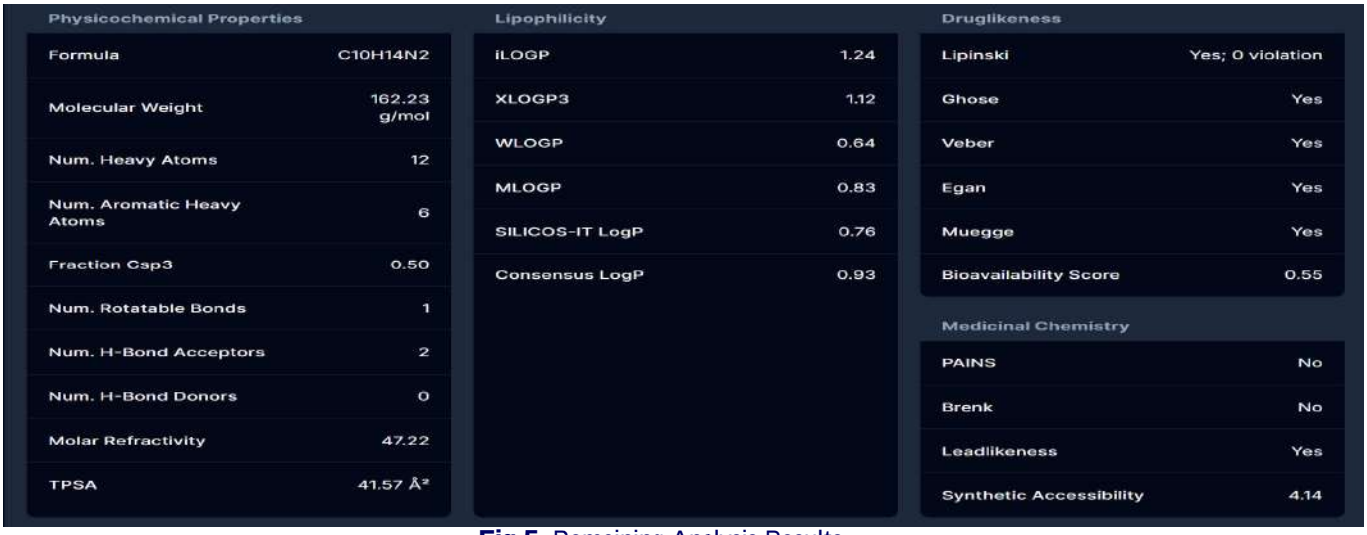

Fig 5: Remaining Analysis Results

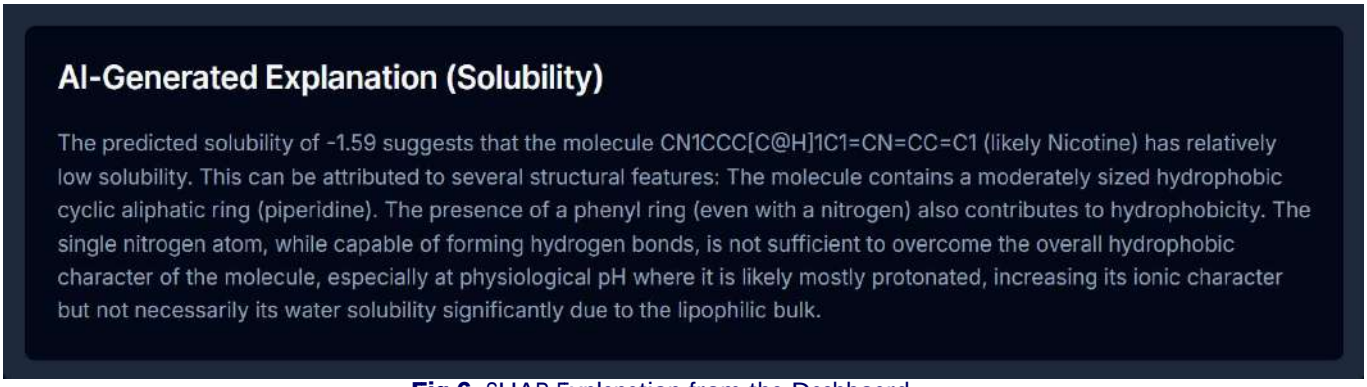

Fig 6: SHAP Explanation from the Dashboard

VI. FUTURESCOPE

While the hybrid multimodal framework presented here demonstrates strong performance, several directions remain open for further expansion and refinement.

1 Integration of 3D Structural Information

Future versions can incorporate 3D conformer-based models such as SchNet, DimeNet++, or EGNN to capture spatial geometry, which plays a key role in metabolism and binding.

2 Protein–Ligand Interaction Modelling

Current ADME predictions consider only small-molecule structures. Including protein context for transporters and metabolising enzymes (e.g., CYP450 family) could enhance prediction accuracy for clearance and distribution.

3 Expansion to Toxicity and DMPK Endpoints

The system can be extended to predict:

- hepatotoxicity
- cardiotoxicity (hERG inhibition)
- mutagenicity
- bioavailability
- plasma protein binding

This would enable end-to-end preclinical profiling.

4 Active Learning and Continual Model Updating

Incorporating active learning could help the model identify uncertain molecules and request new labels, making it adaptive and data-efficient.

5 Large-Scale Self-Supervised Pretraining

Training transformer or GNN models on billions of unlabeled molecules could enable richer chemical representations and generalisation to unexplored chemical space.

6 GPU-Accelerated Cloud Deployment

Deploying the framework on scalable cloud infrastructures would support:

- high-throughput virtual screening
- multi-user access
- API-based integration with existing drug discovery pipelines

7 Integration with Reinforcement Learning for Molecule Optimisation

The model could guide generative models (RL or diffusion-based) to propose new molecules with optimised ADME properties. Overall, the framework serves as a strong foundation for developing an advanced AI-driven drug discovery platform.

VII. CONCLUSION

This work presents a hybrid multimodal deep learning system for computational ADME prediction, integrating descriptors, GNN embeddings, and SMILES transformer representations into a unified architecture. The model delivers stronger performance than single-modality baselines and offers interpretability tools that support chemical insight. Through a practical deployment that includes both a user-friendly interface and an API, the framework serves as an accessible, scalable solution for early-stage pharmacokinetic profiling. Future work may explore integration of 3D structural representations, protein–ligand interaction modelling, and expanded endpoint coverage such as toxicity and metabolic pathways.

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