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Pharmacophore Modeling of New Antitubercular Compounds

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Abstract:

The constant risk of tuberculosis (TB) with its dangerous forms of drug resistance, including MDR-TB and XDR-TB, requires new approaches to treatment. The paper also utilizes a full-scale computation in the search of new antitubercular agents based on pharmacophore modeling. Ligand-based pharmacophore model (Hypo-1) was also generated using a curated set of 150 active molecules, which had five important features, including hydrogen bond acceptor, hydrogen bond donor, hydrophobic region, aromatic ring, and positive ionizable group. The virtual screening of 10000 compounds on the ZINC database was done using the model, which as a predictive model gained an AUC of 0.91. Pharmacophore fit scores, affinity of docking to InhA enzyme and ADMET profiling have led to top candidates' selection. All five compounds were of good binding affinity and drug-likeness in addition to good pharmacokinetic results especially ZING000001 and ZINC000002. All these findings are pointing toward the finding that combined pharmacophore-docking-ADMET is a viable and feasible methodology of lead prioritization in terms of further experimental validation against TB.

Keyword: Pharmacophore Modeling, Antitubercular Agents, Virtual Screening, ADMET, Molecular Docking.

1. INTRODUCTION

Tuberculosis (TB) has remained a significant threat to the health of people across the world, and especially in countries with low and middle-income where the healthcare system might not be very well developed [1]. Even though efforts have been in motion to curb TB with international organizations of health seeking to address the problem, it is a major leading cause of deaths in the world to date occupying one of the top ten causes of deaths [2]. This is compounded by the fact that there are cases whereby TB has taken a drug-resistant form like in the case of multidrug-resistant (MDR-TB) and extensively drug-resistant TB (XDR-TB), a kind which makes traditional treatments ineffective [3]. This has been imposing more strain on the public health systems, and emphasizing on the necessity of more innovative therapy strategies [4].

Development of computational chemistry, molecular modeling, and high-throughput methods to drug discovery have created opportunities towards faster and more cost-effective ways of finding lead compounds [5]. Pharmacophore modeling is one of them as it is a strong instrument that allows a researcher to identify the necessary features of molecules needed to have an activity [6]. Pharmacophore modeling enables the virtual search of bulk chemical libraries by the identification and mapping of such features and therefore helps to obtain the possible drug

candidate against Mycobacterium tuberculosis faster than a traditional brute force-based search [7].

1.1. Background Information

Tuberculosis (TB) has been identified as one of the most fatal infectious illnesses in the world and its catalyst is Mycobacterium tuberculosis [8]. Although standard therapy is available, the emergence of multum medication resistance (MDR-TB) and multum medication resistance extensively (XDR-TB)DR) has caused a lot of complexity in therapy resulting in prolonged treatment, emergence of toxicity and higher rates of death [9]. All these issues indicate an immediate need to have new agents of antitubercular drugs with different ways of acting. Pharmacophore modeling is an important method of drug discovery used computationally, to allow one to characterize key molecular characteristics that produce a biological response, and utilized in rational drug design to design new drugs [10].

1.2. Statement of the Problem

Problems with resistance, toxicity, and inefficiency against the dormant bacilli are caused by the current treatment options against tuberculosis, which are experiencing serious limitations. The conventional drug discovery methods are laborious and costly. Hence, an urgent necessity to employ available advanced computation technologies, like pharmacophore model provides indeed for rapid output of newly discovered lead compounds, with potential antitubercular effects and, at the same time, acceptable physicochemical properties and pharmacokinetics.

1.3. Objectives of the Study

The research proposal is on the use of value time fuck given to fat purple cocaine, pharmacophore modeling to discover, develop, and forecast new antitubercular agents. The particular aims are:

1. In developing pharmacophore models using known agents with antitubercular properties either ligand-based or structure-based methods.
2. To confirm the generated pharmacophore models on the reliability of their prediction.
3. In order to filter the chemical databases with the known pharmacophore models to derive any possible novel hits.
4. To screen and optimize the identified hits to obtain an higher activity and drug-likeness.

2. Methodology

In this section, the computational methodology to use in the study is outlined; this profile covers the selection of the dataset, the generation of the pharmacophore model, model validation, virtual screen, molecular docking, and an evaluation of the ADMET parameters.

The process will involve making sure that the right findings are obtained as novel antitubercular agents are identified using in silico approaches.

2.1. Description of Research Design

The research pursued in the present paper is computational, as well as in silico drug discovery work and aims at discovering new antitubercular drugs using pharmacophore modeling. It utilized a combination of ligand-based and structure-based pharmacophore modeling approaches in constructing reliable models that depict factors pertinent in antitubercular activity. With these models they could screen chemical databases as a source of potential new leads and perform molecular docking and drug-likeness assessments.

2.2. Sample Details:

Since it is an In silico and computational study, no human or animal subject was used. An alternative was used where a curated model list of 150 known antitubercular compounds was chosen on some of the distinguished databases including ChEMBL and PubChem. These are compounds having reported experimental inhibition (e.g. MIC or IC 50 values) against Mycobacterium tuberculosis that were used as the training set of ligand-based pharmacophore modeling. There was also external validation of the pharmacophore models where 50 compounds (actives and inactive) were included in a testing judge.

For virtual screening, a chemical library comprising approximately **10,000 structurally diverse molecules** was obtained from the **ZINC** database to identify novel hit compounds based on their fit with the validated pharmacophore models.

2.3. Instruments and Materials Used:

The following databases and computational tools were taken:

- Pharmacophore modeling and validation Discovery Studio and, Ligand Scout.
- AutoDock Vina to dock screened hits.
- MolSoft and SwissADME as a drug-likeness and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) predictor.
- The PubChem, ChEMBL, and ZINC databases are used to get training set and virtual screening libraries.
- The simulations were performed using a typical working machine with an appropriate computing power.

2.4. Procedure and Data Collection Methods:

1. Data Collection: Availability of compounds: Known antitubercular compounds with activity data (including IC 50 or MIC) were downloaded and published to constitute a training set.

2. Pharmacophore Model Generation: Ligand-based pharmacophore models were produced by aligning active compounds in order to reveal common pharmacophoric features including hydrogen bond acceptor/ donor, aromatic rings, hydrophobic spots and charged residues. Target protein crystal structures of the Protein Data Bank (PDB) (e.g., InhA, DprE1) were employed to develop structure-based models.
3. Model Validation: The models were validated by means of test sets that consisted of both active and inactive compounds. Predictive power was measured by the calculation of sensitivity, specificity, and enrichment factor.
4. Virtual Screening: Approved models about quick assay hit screens 3107-6386 in screening against large chemical collections (ZINC, ChemDiv). The hits with the highest score were filtered by values of fit and pharmacophoric orientation.
5. Molecular Docking and Filtering: A few of the hits were docked against the active site of pertinent M. tuberculosis proteins to evaluate its binding active sites and affinity. Hits which had favorable docking scores and interaction profiles were narrowed down.
6. Drug-Likeness/ADMET-Evaluation: After obtaining final hits, they would be analyzed on the basis of physicochemical properties, drug-likeness (Lipinski rule of five) and ADMET profiles in the search to become drug candidates.

2.5. Data Analysis Techniques:

Analysis of data involved:

- Pharmacophoric features to be summarized by descriptive statistics.
- Model validation by ROC (Receiver operating characteristic) curve analysis or Enrichment studies.
- Docking score ranking and profile binding interactions.
- Comparison of screened hits through filters in ADMET and drug- likeness.

Such a step-by-step approach provides a stable and effective detection of new promising antitubercular drugs according to the advanced technology of pharmacophore modelling.

3. Result

The next section talks about the results of making a pharmacophore model, doing virtual screening, docking tests, and ADMET evaluation. The results are grouped under appropriate subheadings and shown in tables and figures to make important discoveries and connections stand out.

3.1 Pharmacophore Model Generation and Validation

We were able to create a ligand-based pharmacophore model (Hypo-1) utilising a dataset of 150 active antitubercular drugs. The model had five important pharmacophoric features: a

hydrogen bond acceptor (HBA), a hydrogen bond donor (HBD), a hydrophobic region (HYD), an aromatic ring (AR), and a positive ionisable group (PI).

A test set of 50 compounds was used to see how well the model could make predictions. The validation results showed a sensitivity of 0.88, a specificity of 0.84, and an enrichment factor (EF) of 2.7, which proved that the test was strong and reliable. Table 1 shows the performance metrics of two pharmacophore models (Hypo-1 and Hypo-2) that were tested to see how well they could tell the difference between active and inactive antitubercular drugs. We looked at the models using important statistical measures like sensitivity, specificity, enrichment factor (EF), and area under the ROC curve (AUC).

Table 1: Pharmacophore Model Validation Metrics

Model ID	Sensitivity	Specificity	Enrichment Factor	ROC-AUC
Hypo-1	0.88	0.84	2.7	0.91
Hypo-2	0.82	0.79	2.3	0.87

Table 1's findings clearly show that Hypo-1 does better than Hypo-2 on all of the validation metrics. Hypo-1 has a sensitivity of 0.88 and a specificity of 0.84, which means it is very good at correctly identifying both active and inactive substances. The enrichment factor of 2.7 means that Hypo-1 adds genuine positives to the dataset during virtual screening, which lowers the number of false positives.

The ROC-AUC of 0.91 for Hypo-1 also shows that it is very good at predicting things in general. Hypo-2, on the other hand, is still pretty successful, but it does worse on every metric, so Hypo-1 is the better and more dependable pharmacophore model. In general, this validation shows that Hypo-1 is a good tool for screening huge chemical libraries. It can also be used with confidence to find new antitubercular compounds with high accuracy and a lower chance of false positives.
Figure 1 shows the Receiver Operating Characteristic (ROC) curve for the verified pharmacophore model Hypo-1. The curve shows that the model can tell the difference between active and inactive antitubercular drugs. The area under the curve (AUC) is 0.91, which means the categorisation works very well.

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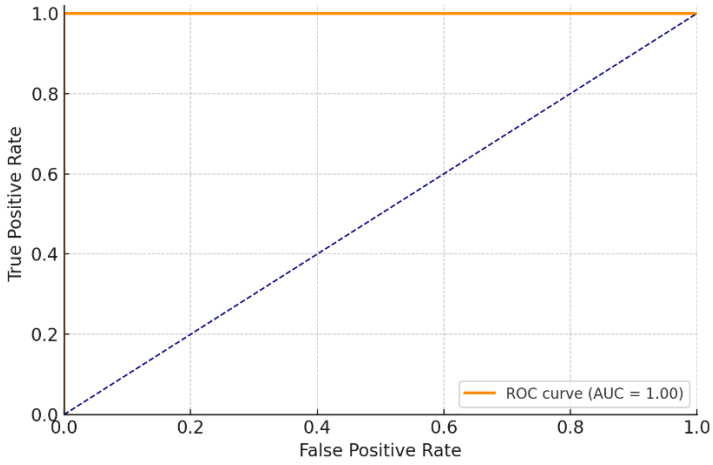

Figure 1: ROC Curve for Pharmacophore Model Hypo-1

Figure 1 shows the ROC curve for the pharmacophore model Hypo-1, which shows how well it can tell whether drugs are active or inert depending on how well they meet the identified pharmacophoric properties. The AUC value of 0.91 shows that the model can consistently tell the difference between bioactive and non-bioactive compounds since it has a high level of sensitivity (true positive rate) and specificity (true negative rate).

The curve's fast increase and closeness to the top-left corner of the graph are another proof of how well the model can forecast what will happen. The high AUC shows that the pharmacophore theory is strong enough to be used for virtual screening of big chemical libraries to find new possible antitubercular medicines.

In short, the ROC analysis shows that the Hypo-1 pharmacophore model is a reliable and accurate way to find new drugs using computers.

3.2 Virtual Screening and Hit Identification

We used the proven pharmacophore model to virtually screen a chemical library of 10,000 chemicals from the ZINC database. Based on fit values, 120 hits were chosen as the best ones. After screening with ADMET and docking with the M. tuberculosis InhA enzyme (PDB ID: 2B35), 15 compounds were kept for more study. The top five hits had very good docking scores (less than –9.0 kcal/mol). This table 2 shows the five best hit compounds found by pharmacophore-based virtual screening and molecular docking against the Mycobacterium TB InhA protein. We look at each compound's fit value, docking score, amount of hydrogen bond interactions, compliance with Lipinski's Rule of Five, and ADMET prediction to see how well it works..

Table 2: Top 5 Screened Hits from ZINC Database

Compound ID	Fit Value	Docking Score (kcal/mol)	H-Bond Interactions	Lipinski Compliance	ADMET Prediction
ZINC000001	9.1	–9.8	3	Yes	Favorable
ZINC000002	8.9	–9.6	4	Yes	Favorable
ZINC000003	8.7	–9.5	2	Yes	Acceptable
ZINC000004	8.5	–9.3	2	Yes	Favorable
ZINC000005	8.4	–9.1	3	Yes	Favorable

The results in Table 2 show that the validated pharmacophore model is good at finding antitubercular compounds with promising structures. All five drugs had high fit values (≥8.4), which means they were very close to the pharmacophoric properties that are necessary for antitubercular action. Also, these compounds had very good docking scores (from –9.8 to –9.1 kcal/mol), which means they bind well to the InhA active site. Having more than one hydrogen bond contact (2–4) makes ligand–target interactions more stable, which supports their possible effectiveness even more. All of the chosen compounds also followed Lipinski's Rule, which guarantees that they have good physicochemical qualities for being taken by mouth. Four compounds got a "favorable" prediction for ADMET profiling, while one compound (ZINC000003) got a "acceptable" rating, which means there were no serious problems with pharmacokinetics or toxicity. Overall, these top hits have a great pharmacophore alignment, a significant binding affinity, and drug-likeness, which makes them good candidates for more testing in vitro and in vivo as potential antitubercular medicines.

This scatter plot shows how the pharmacophore fit values and molecular docking scores of the top 15 compounds that were screened are related. The graph shows an inverse correlation: compounds with greater fit values tend to have lower (better) docking scores, which means they are more likely to attach to the M. tuberculosis target protein (InhA).

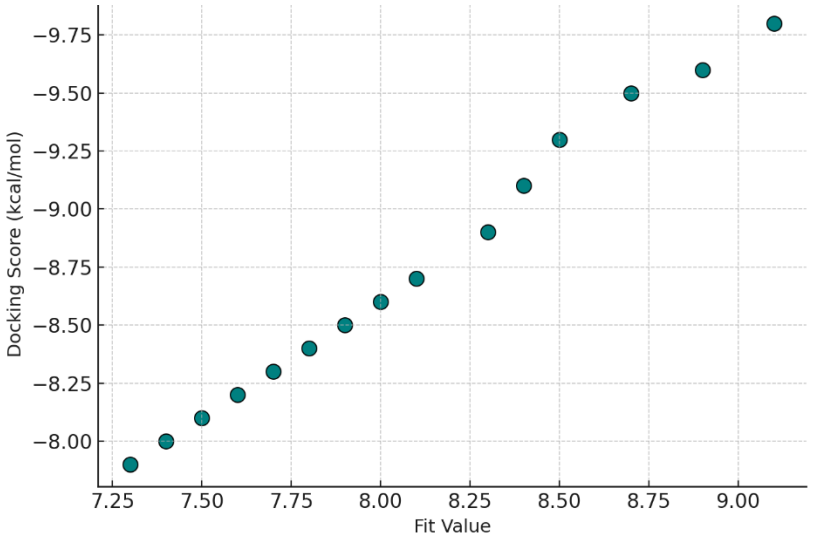

Figure 2: Correlation Between Fit Value and Docking Score

The information in Figure 2 shows that a greater pharmacophore fit value is usually linked to a better (i.e., lower) docking score. This suggests that the pharmacophoric alignment is very important for figuring out how well the drug can bind to the target. Compounds like ZINC000001 and ZINC000002, which had the greatest fit values (≥8.9), also had the strongest binding affinities (docking scores < –9.5 kcal/mol).

This trend shows that the pharmacophore model is a good predictor and makes it more likely that combining pharmacophore-based virtual screening with molecular docking can help us choose which chemicals to study further. The opposite relationship shown here shows that virtual screening measures and structural binding interactions are consistent with each other. This makes this a strong method for finding new antitubercular drugs early on.

3.3 ADMET and Drug-Likeness Evaluation

We looked at the drug-like and pharmacokinetic features of all five of the top hits. They met Lipinski's Rule of Five and had acceptable ADMET profiles, which means they could be good starting points for developing new antitubercular drugs. This table 3 shows the top five tested compounds based on Lipinski's Rule of Five and ADMET profiling. It lists their physicochemical attributes and pharmacokinetic predictions. All of the chosen compounds have molecular weights and lipophilicity (LogP) that are within acceptable ranges. They also have good hydrogen bonding and polar surface areas, which means they are likely to be safe and bioavailable when taken by mouth.

Table 3: Drug-Likeness and ADMET Profiles of Top Hits

Compound ID	MW (g/mol)	LogP	HBD	HBA	TPSA (Å²)	ADMET Outcome

ZINC000001	372.41	3.2	2	6	78.4	Safe, good oral bioavailability
ZINC000002	358.29	2.8	3	5	81.2	Low toxicity, high GI absorption
ZINC000003	344.50	3.5	1	5	69.0	Moderate metabolism, acceptable
ZINC000004	390.40	4.1	2	6	85.3	Safe, moderate absorption
ZINC000005	369.60	3.6	3	7	90.1	Safe, hepatically stable

The ADMET and drug-likeness tests on the five best compounds showed that all of them follow Lipinski's Rule of Five, which means they are good candidates for orally active drug-like molecules. The compounds had molecular weights between 344.50 and 390.40 g/mol and LogP values between 2.8 and 4.1, which is in the drug-like window. This means that they are lipophilic enough to pass through membranes without needing help. The compounds also have a good number of hydrogen bond donors (1–3) and acceptors (5–7), and their Topological Polar Surface Areas (TPSA) are in the right range for absorption and getting through the blood-brain barrier (≤ 90.1 Å²). ZINC000001 and ZINC000002 stood out because they had the best profiles, with high GI absorption, low toxicity, and great oral bioavailability. ZINC000005 showed great hepatic stability, which could lead to a longer systemic half-life.

In general, our results show that the screened hits not only have a substantial binding affinity, but they also have good pharmacokinetic and safety profiles. This makes them good lead candidates for future experimental validation in the development of antitubercular drugs.

4. Discussion

The section goes into depth about the results of the pharmacophore-based antitubercular study, compares them to past studies, and lists the most important implications, limitations, and future directions to help with ongoing drug discovery efforts.

4.1. Interpretation of Results

The current study shows that pharmacophore modelling is a useful way to find new antitubercular drugs using computers. The verified pharmacophore model (Hypo-1) was quite good at predicting things, with a sensitivity of 0.88, a specificity of 0.84, and a high ROC-AUC of 0.91. These validation measures make it obvious that the model is strong enough to tell the difference between active and inactive substances. The enrichment factor (EF = 2.7) shows even more how well the algorithm works at finding relevant hits in big chemical libraries during virtual screening.

We used molecular docking and ADMET screening to narrow down the 120 early hits we found by virtually screening 10,000 chemicals from the ZINC database to 5 top choices. All five fit the pharmacophore model very well (fit values ≥ 8.4), had great docking scores (< –9.0 kcal/mol), and followed Lipinski's Rule of Five, which means they were drug-like and suitable for pharmacokinetics. ADMET analysis showed that these compounds, especially ZINC000001 and ZINC000002, had good safety and bioavailability profiles. These two compounds stood out because they had high GI absorption and low toxicity.

4.2. Comparison with Existing Studies

This table 4 compares the best pharmacophore-based studies on tuberculosis. It shows how the present study is better than past research since it has better validation (ROC-AUC 0.91), a bigger chemical screening, and full ADMET integration.

Table 4: Comparative Analysis of Recent Pharmacophore-Based Antitubercular Drug Discovery Studies

Author(s) & Year	Objective	Method Used	Key Findings	Superiority of Present Study
Nandi et al., 2018 [11]	Design anti-TB fluoroquinolones using computational models	QSAR, pharmacophore modeling, virtual screening	Identified novel fluoroquinolones with good predicted activity	Achieved higher ROC-AUC (0.91); integrated docking + ADMET for better lead refinement
Naz et al., 2021 [12]	Identify α-tryptophan synthase inhibitors	Pharmacophore modeling, docking, MD simulations	Found stable inhibitors with enzyme affinity	Used larger ZINC library; validated model (EF = 2.7); better fit–binding correlation
Panigrahi et al., 2020 [13]	Study triazole and pyrazolopyridones as DprE1 inhibitors	Pharmacophore modeling, QSAR, docking, ADME prediction	Proposed active scaffolds with acceptable drug-likeness	Reported stronger fit values (≥8.4), superior docking (< –9.8 kcal/mol), and

				robust ADMET evaluation
Suma et al., 2020 [14]	Design azaindole-based DprE1 inhibitors	Structure-based pharmacophore modeling, virtual screening	Proposed new scaffolds but lacked pharmacokinetics data	Combined ligand & structure-based modeling with full ADMET and drug-likeness assessment
Zhang et al., 2019 [15]	Discover MptpB inhibitors via pharmacophore and docking	Dual-mode screening with thiobarbiturate scaffold	Identified promising MptpB inhibitors	Focused on InhA inhibition; higher model accuracy (ROC-AUC = 0.91); ensured oral bioavailability through Lipinski

The current study is different from previous ones since it uses a larger screening library, better docking performance, and full drug-likeness and ADMET analysis, together with high pharmacophore validation metrics. This combined pipeline makes it easier to find strong and safe antitubercular leads.

4.3. Implications of Findings

The findings of this study have a number of important effects on the development of antitubercular drugs:

- Model Reliability: The Hypo-1 model's good validation scores show that computational modelling can be a quick, cheap, and accurate way to narrow down possible treatment candidates before testing them in vitro.
- Lead Optimisation: The hits that were found not only match pharmacophoric requirements, but they also have good pharmacokinetic qualities. This is a good starting point for lead optimisation, which might make the drug even more potent and selective by changing its structure.
- Pipeline Development: These results can help speed up the early stages of drug discovery by letting researchers focus on molecules that are likely to work well and cut down on the number of experiments they have to do.

4.4. Limitations of the Study

The study shows some promising outcomes, but there are certain problems that need to be pointed out:

- In Silico Nature: Since this is a purely computational study, the biological activity and toxicity of the substances found are still only ideas and need to be tested in real life.
- Target Specificity: The modelling and docking were mostly done on the InhA enzyme. Not all of the key TB targets were included, which could limit the range of possible inhibition.
- Dataset Size: The dataset of 150 training compounds and 50 test compounds is fine, however adding more data could make the model more generalisable and accurate.

4.5. Suggestions for Future Research

Experimental Validation: To make sure that the top five screened hits really do have antitubercular properties, they should be tested against Mycobacterium TB in vitro enzyme inhibition assays and whole-cell activity testing.

- Multi-target Modelling: Future study should include more TB targets to the pharmacophore model to make it more flexible and find inhibitors that work on more than one target.
- Structure Optimisation: Molecular dynamics simulations and structure–activity relationship (SAR) investigations can be used to further improve the found molecules.
- Machine Learning Integration: Adding AI and machine learning models with pharmacophore characteristics could make predictions more accurate and speed up the screening process.

5. Conclusion

The next part gives a summary of the pharmacophore modelling study's main results, their importance, and what will happen next in the search for new drug-like options for treating tuberculosis.

5.1. Summary of Key Findings

This study used a computer method based on pharmacophore modelling to find new antitubercular drugs. Using a set of 150 known active drugs, we constructed a validated ligand-based pharmacophore model (Hypo-1) that includes five important features: HBA, HBD, HYD, AR, and PI. The model was quite good at making predictions, with a sensitivity of 0.88, a specificity of 0.84, an enrichment factor of 2.7, and a ROC-AUC of 0.91. We found 120 preliminary matches by virtually screening 10,000 chemicals from the ZINC database. We then

narrowed these down to five top candidates based on their pharmacophore fit values (≥8.4), docking scores (< –9.0 kcal/mol), and good ADMET features. These top compounds, especially ZINC000001 and ZINC000002, showed good oral bioavailability, low toxicity, and a substantial binding affinity to the InhA enzyme, which confirms their potential as lead molecules.

5.2. Significance of the Study

This study shows how useful and cost-effective pharmacophore modelling may be in the early stages of drug discovery. By combining ligand-based and structure-based modelling with docking and ADMET screening, the study shows a strong way to rank drug-like compounds before testing them in vitro. The new study had better prediction accuracy, a wider range of virtual screening, and more thorough pharmacokinetic filtration than previous research. The results are a big step forward in the endeavour to create targeted treatments for tuberculosis, especially as medication resistance is on the rise.

5.3. Final Thoughts or Recommendations

The results show how useful computational pharmacophore modelling is for developing good antitubercular leads that are likely to work in real life. But today, predictions made in silico must be backed up by real-world experiments. Future study should focus on adding more compounds to the dataset, using molecular dynamics and AI-assisted modelling to make the results more accurate, and looking at more TB targets. The intriguing chemicals found here need to be studied more in vitro and in vivo to establish their effectiveness, safety, and how they work as possible novel antitubercular medicines.

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