

MOLECULAR DOCKING ANALYSIS OF SELECTED COMPONENTS OF THE COMBINED ENTERIC-SOLUBLE DOSAGE FORM “BIOMAYRIN” AGAINST KEY MYCOBACTERIUM TUBERCULOSIS TARGETS

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Annotatsiya: Ushbu ishda kombinatsiyalangan ichakda eruvchan “Biomayrin” dori shaklining ayrim faol komponentlari rifampitsin, izoniazid va etambutolning *Mycobacterium tuberculosis* ning muhim oqsil nishonlari bilan o‘zaro ta’siri molekulyar docking usuli yordamida o‘rganildi. Rifampitsin 5UHB, izoniazid 2NV6, etambutol esa 7BVF strukturasi bilan docking qilindi. Natijalarga ko‘ra, rifampitsin eng qulay bog‘lanish natijasini ko‘rsatdi, izoniazid va etambutol esa o‘rtacha darajadagi bog‘lanish moyilligini namoyon qildi. SwissADME tahlili izoniazid va etambutol uchun maqbul fizik-kimyoviy hamda farmakokinetik ko‘rsatkichlarni ko‘rsatdi, rifampitsin esa tuzilishining murakkabligi sababli qoidaviy drug-likeness mezonlariga kamroq mos kelishini namoyon etdi. Olingan ma’lumotlar “Biomayrin” tarkibidagi ayrim moddalarning molekulyar darajadagi xatti-harakatini izohlashga va ularning biologik nishonlar bilan o‘zaro ta’sirini tushuntirishga xizmat qiladi.

Kalit so‘zlar: Biomayrin, molekulyar docking, rifampitsin, izoniazid, etambutol, *Mycobacterium tuberculosis*, SwissADME.

Аннотация: В данной работе методом молекулярного докинга исследованы отдельные активные компоненты комбинированной кишечнорастворимой лекарственной формы «Биомайрин» — рифампицин, изониазид и этамбутол в отношении ключевых белковых мишеней *Mycobacterium tuberculosis*. Докинг проводили для систем 5UHB (рифампицин), 2NV6 (изониазид) и 7BVF (этамбутол). Рифампицин показал наиболее благоприятный результат связывания, тогда как изониазид и этамбутол продемонстрировали умеренную склонность к связыванию в выбранных моделях. Анализ SwissADME выявил приемлемые физико-химические и фармакокинетические характеристики для изониазида и этамбутола, тогда как рифампицин из-за структурной сложности показал меньшее соответствие стандартным критериям drug-likeness. Полученные данные могут служить молекулярным обоснованием для дальнейшего изучения отдельных компонентов препарата «Биомайрин» и их взаимодействия с биологически значимыми мишенями.

Ключевые слова: Биомайрин, молекулярный докинг, рифампицин, изониазид, этамбутол, *Mycobacterium tuberculosis*, SwissADME.

Abstract: This study investigated selected active components of the combined enteric-soluble dosage form **Biomayrin rifampicin, isoniazid, and ethambutol** — by molecular docking against key protein targets of *Mycobacterium tuberculosis*. Rifampicin was docked with **5UHB**, isoniazid with **2NV6**, and ethambutol with **7BVF**. Among the three ligands, rifampicin showed the most favorable predicted binding, whereas isoniazid and ethambutol demonstrated moderate docking affinities in the selected systems. **SwissADME** analysis revealed acceptable physicochemical and pharmacokinetic properties for isoniazid and ethambutol, while rifampicin showed lower compliance with conventional drug-likeness criteria due to its structural complexity. The obtained results provide molecular-level support for further investigation of selected Biomayrin components and their interactions with biologically relevant anti-tuberculosis targets.

Keywords: Biomayrin, molecular docking, rifampicin, isoniazid, ethambutol, *Mycobacterium tuberculosis*, SwissADME.

Introduction

The combined enteric-soluble anti-tuberculosis dosage form “Biomayrin” (containing rifampicin, isoniazid, and ethambutol) has shown favourable results in preclinical and clinical studies [1, 2]. Pharmacokinetic evaluation revealed that the polysaccharide matrix of Biomayrin significantly prolongs the half-life of its active components – isoniazid by 4 times, and rifampicin and ethambutol by 3 times compared to conventional formulations [2]. These findings confirm the therapeutic potential of the combined formulation but also raise questions about the molecular interactions of each component with key *Mycobacterium tuberculosis* targets.

To better understand the mechanistic basis of the observed effects, computational approaches such as molecular docking and *in silico* ADME prediction are useful [3–5]. The SwissDrugDesign platform (SwissDock, SwissADME) provides free, web-based tools for evaluating ligand–protein binding modes and pharmacokinetic properties [5, 6]. Therefore, the present study focuses on the molecular docking behaviour of rifampicin, isoniazid, and ethambutol against essential *M. tuberculosis* proteins, complemented by SwissADME analysis.

Aim of the Study

To investigate the molecular docking interactions of the three active components of *Biomayrin* with key *M. tuberculosis* targets and to evaluate their physicochemical and pharmacokinetic profiles using *SwissADME*.

Materials and Methods

Ligands

Three ligands – rifampicin, isoniazid, and ethambutol – were selected. Their three-dimensional structural data in CIF format were obtained from the Cambridge Structural Database (CSD) [7].

Protein Targets

Protein structures were retrieved from the Protein Data Bank (PDB) [8]:

Rifampicin → RNA polymerase / RpoB complex (PDB: 5UHB); Isoniazid → InhA (PDB: 2NV6); Ethambutol → EmbA–EmbB complex (PDB: 7BVF).

Docking Procedure

Molecular docking was performed using the CB-Dock2 web server [9]. Default preparation and blind docking protocols were applied. The best pose for each complex was selected based on the most favourable docking score and contact residues.

SwissADME Analysis

Physicochemical and pharmacokinetic properties were evaluated using SwissADME [10]. Outputs for isoniazid and ethambutol included molecular weight, TPSA, lipophilicity, solubility, GI absorption, BBB permeability, CYP inhibition, and drug-likeness.

Results and Discussion

Docking of Rifampicin with 5UHB

Docking analysis of rifampicin against the 5UHB receptor identified pocket F1 as the most favorable binding region, with a FitDock score of –9.5. The predicted interaction involved several residues of chain C, including ARG173, VAL176, SER434, GLN435, LEU436, SER437, GLN438, PHE439, ASP441, HIS451, ARG454, SER456, LEU458, GLY459, ARG465, PRO489, ASN493, ILE497, ARG613, and HIS680.

This result indicates a favorable accommodation of rifampicin within the selected receptor cavity. Since 5UHB represents an RNA polymerase-related anti-tuberculosis target, the obtained docking pose supports the relevance of this system for evaluating rifampicin binding. Among the studied compounds, rifampicin produced the most favorable docking score in the present dataset, suggesting a strong predicted interaction with the selected target under the applied docking conditions.

Docking of Isoniazid with 2NV6

For isoniazid, the best docking result was obtained in pocket C1, with a Vina score of –6.0. The ligand interacted with multiple residues of chain A, including SER13, GLY14, ILE15, ILE16, SER20, ILE21, ALA22, THR39, GLY40, PHE41, ILE47, LEU63, ASP64, VAL65, GLN66, ALA94, ILE95, GLY96, PHE97, LYS118, ILE122, MET147, ASP148, PHE149, ASP150, PRO151, SER152, ARG153, ALA154, MET155, TYR158, LYS165, VAL189, ALA191, GLY192, PRO193, ILE194, THR196, and MET199.

The obtained score suggests moderate predicted binding of free isoniazid toward the selected receptor pocket. However, this result should be interpreted cautiously. Isoniazid is a prodrug, and its biological anti-tuberculosis activity is associated with its activated inhibitory form rather than the free ligand alone. Therefore, the docking result obtained here reflects the interaction tendency of the free isoniazid molecule within the selected system, but it should not be considered a complete mechanistic representation of the active inhibitory state.

Docking of Ethambutol with 7BVF

Docking of ethambutol against the 7BVF receptor produced the best result in pocket 2, with a docking score of -5.3 . The predicted pose involved residues of chain A, including THR807, ASP808, SER809, THR812, PHE830, ILE916, GLY917, PRO918, ALA921, TRP922, ARG923, ASN924, LEU925, ARG926, LEU1008, PRO1009, ASP1010, HIS1011, THR1014, THR1041, ILE1042, ALA1043, THR1044, TYR1045, ASP1053, TRP1054, GLY1055, SER1056, and VAL1057.

This result indicates a possible but moderate binding tendency of ethambutol toward the selected receptor pocket. The obtained score was lower than that of rifampicin and slightly lower than that of free isoniazid in the present docking set. Nevertheless, this should not be interpreted as evidence of lower biological importance of ethambutol, because the ligands were docked against different protein targets, and cross-target docking scores are not strictly directly comparable in an absolute sense.

Comparative Docking Interpretation

Within the current docking setup, the studied ligands showed the following best docking scores:

- Rifampicin / 5UHB: -9.5
- Isoniazid / 2NV6: -6.0
- Ethambutol / 7BVF: -5.3

These data indicate that rifampicin showed the most favorable predicted binding within its selected target system. Free isoniazid and ethambutol demonstrated moderate binding tendencies in their respective receptors. At the same time, a direct numerical comparison between all three ligands must be made carefully because the receptors, pocket geometries, residue environments, and docking contexts differ substantially.

Thus, the present docking results are best viewed not as a strict ranking of drug potency, but as a molecular interpretation of the interaction potential of selected Biomayrin components with their relevant anti-tuberculosis protein targets.

SwissADME Analysis

SwissADME Analysis

SwissADME analysis was performed for rifampicin, ethambutol, and isoniazid.

For rifampicin, the calculated molecular weight was 822.94 g/mol, TPSA was 220.15 Å², and the consensus LogP was 2.95, indicating a relatively lipophilic but highly polar and structurally complex molecule. The compound was predicted to have low gastrointestinal absorption, no BBB permeation, and P-glycoprotein substrate properties. Rifampicin did not comply with several conventional drug-likeness rules, including Lipinski, Ghose, Veber, Egan, and Muegge criteria, mainly because of its high molecular weight, large polar surface area, and extensive hydrogen-bonding capacity. Solubility predictions ranged from poorly soluble to moderately soluble, depending on the applied model. Despite these unfavorable rule-based descriptors, rifampicin remains a clinically established anti-tuberculosis agent, indicating that standard drug-likeness filters should be interpreted cautiously for structurally complex antibiotics.

For ethambutol, the calculated molecular weight was 204.31 g/mol, TPSA was 64.52 Å², and the consensus LogP was 0.60, indicating relatively balanced lipophilicity. The compound showed high gastrointestinal absorption, no predicted BBB permeation, no predicted inhibition of the major analyzed CYP isoforms, and compliance with Lipinski's rule of five without violations. Ethambutol was predicted to be very soluble to soluble, depending on the applied model, which is favorable from the perspective of oral absorption.

For isoniazid, the molecular weight was 137.14 g/mol, TPSA was 68.01 Å², and the consensus LogP was -0.35, indicating a more hydrophilic profile. The compound also showed high gastrointestinal absorption, no predicted BBB permeation, and no predicted inhibition of the major tested CYP enzymes. It satisfied Lipinski's rule, while some alerts and rule-based limitations reflected its small size and hydrazine-related structural features.

Overall, the SwissADME results suggest that the analyzed ligands show different physicochemical and pharmacokinetic profiles. In particular, isoniazid and ethambutol displayed favorable oral absorption-related characteristics and acceptable drug-likeness descriptors, whereas rifampicin showed a less favorable rule-based ADME profile due to its structural complexity. Nevertheless, the inclusion of rifampicin remains highly relevant because its established clinical efficacy confirms that therapeutic value cannot always be predicted solely from general drug-likeness criteria.

The present study was motivated by the promising therapeutic profile of the combined enteric-soluble dosage form Biomayrin. Since this formulation has already shown favorable preclinical and clinical results, investigation of its selected components at the molecular level becomes a logical next step. The docking results presented here provide a mechanistic supplement to formulation-oriented and pharmacological observations.

The main value of this work lies in showing that the selected Biomayrin components are capable of forming plausible ligand-protein complexes with biologically relevant *M. tuberculosis* targets.

Rifampicin demonstrated the strongest predicted binding in the selected model system, while free isoniazid and ethambutol showed moderate but meaningful interaction patterns. These findings support the idea that the therapeutic effect of a combined formulation can be interpreted, at least in part, through the molecular behavior of its individual active ingredients.

At the same time, it is important to emphasize that molecular docking alone does not prove the full clinical efficacy of a dosage form. The overall behavior of Biomayrin is also influenced by formulation design, release characteristics, absorption, stability, tissue distribution, and possible synergistic effects among the components. Therefore, the present results should be interpreted as supportive molecular evidence, not as a substitute for pharmacological or clinical evaluation.

Conclusion

This study showed that molecular docking can serve as an informative **in silico** tool for exploring the interaction of selected active components of the combined enteric-soluble dosage form Biomayrin with key *Mycobacterium tuberculosis* protein targets. Rifampicin exhibited the most favorable predicted binding toward 5UHB, while free isoniazid and ethambutol showed moderate binding tendencies toward 2NV6 and 7BVF, respectively. SwissADME analysis indicated that isoniazid and ethambutol have favorable physicochemical and pharmacokinetic properties, whereas rifampicin showed lower compliance with conventional drug-likeness criteria because of its large size and structural complexity.

Overall, the obtained data provide supportive molecular evidence that complements the favorable pharmaceutical, preclinical, and clinical profile of Biomayrin. The results also justify further investigation of its active ingredients at the molecular level and may serve as a basis for future computational, biochemical, and pharmacological studies directed toward a more comprehensive understanding of the mechanisms underlying the therapeutic potential of this combined anti-tuberculosis dosage form.

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