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QSAR Study on Potent Derivatives with Anti-TB Activity: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Tuberculosis (TB), caused by Mycobacterium tuberculosis, continues to pose significant global health challenges, exacerbated by the rise of drug-resistant strains. The development of new anti-TB agents is crucial, and Quantitative Structure-Activity Relationship (QSAR) modelling has emerged as a powerful tool in this endeavour. This review summarizes recent advances in QSAR studies focused on potent derivatives with anti-TB activity. It discusses key molecular descriptors that correlate with biological efficacy, including topological, electronic, and steric properties. The paper also highlights successful predictive models that have facilitated the identification and optimization of novel compounds. Additionally, challenges such as data quality, model validation, and the complexity of biological systems are addressed. Future directions include the integration of machine learning techniques and omit data to

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enhance predictive accuracy and the discovery of new anti-TB agents. Overall, QSAR methodologies represent a vital approach to accelerating drug discovery and combating tuberculosis effectively.

Keywords: Anti-TB agents; QSAR modelling; drug discovery; drug development; biological efficacy.

1. INTRODUCTION

"Tuberculosis (TB), caused by Mycobacterium tuberculosis, remains a global health challenge. The emergence of drug-resistant strains necessitates the discovery of new anti-TB agents. Quantitative Structure-Activity Relationship (QSAR) studies play a crucial role in drug design, helping to predict the biological activity of compounds based on their chemical structure (Natarajan et al., 2020, WHO, 2013)".

- **Importance of QSAR in Anti-TB Research:**

1. Predictive Modeling: QSAR models enable the prediction of anti-TB activity of new compounds before synthesis.
2. Resource Efficiency: Reduces the need for extensive laboratory testing, saving time and resources.
3. Lead Optimization: Helps in modifying existing compounds to enhance efficacy and reduce toxicity (Cole et al., 1998).

- **Key Components of QSAR Studies:**

1. **Molecular Descriptors:** These are quantitative representations of molecular characteristics. Common descriptors include:
- **Topological:** Measures connectivity and shape.
- **Geometrical:** Relates to 3D structures.
- **Electronic:** Involves charge distribution and dipole moments.

2. **Data Sets:** A reliable data set is crucial for developing a robust QSAR model. Active compounds must be well characterized, often sourced from literature or databases like ChEMBL.

3. **Model Development:**
- **Regression Analysis:** Linear regression, multiple linear regression (MLR), or nonlinear models.
- **Machine Learning:** Techniques such as Random Forest, Support Vector Machines, and Neural Networks for more complex relationships.

4. **Validation:** Cross-validation and external validation are necessary to ensure model robustness and predictive capability (Lamichhane et al., 2011, DSP-1181, 2021).

- **Notable Findings in Anti-TB QSAR Studies:**

1. **Structure-Activity Correlations:** Many studies have highlighted key structural features that enhance anti-TB activity, such as:
- Presence of specific functional groups (e.g., nitro, thiophene).
- Ring systems that contribute to cell wall permeability.

2. **Predictive Models:** Successful QSAR models have identified critical molecular descriptors correlating with potency. For example, studies have shown that lipophilicity (LogP) and electronic properties (e.g., HOMO-LUMO gap) are often significant predictors.
3. **Drug Repurposing:** QSAR approaches have facilitated the repurposing of existing drugs by predicting their potential anti-TB activity based on structural similarities to known anti-TB agents (Madkour, 2004, OECD, 2021).

- **Challenges in QSAR Studies:**

1. **Data Quality and Availability:** Inconsistent or incomplete datasets can lead to inaccurate models.
2. **Over fitting:** Complexity in models can result in over fitting, where the model performs well on training data but poorly on new data.
3. **Biological Variability:** Biological systems are complex, and the interplay of various factors can complicate predictions (Cai et al., 2022).

- **Future Directions:**

1. **Integration of Omics Data:** Combining QSAR with genomics and proteomics data

may enhance the understanding of TB mechanisms and lead to better predictive models.

2. **Artificial Intelligence:** Leveraging AI and deep learning techniques can improve the accuracy of QSAR models by identifying non-linear relationships in large datasets.
3. **Collaborative Databases:** Development of comprehensive databases that compile structural and biological data for anti-TB compounds to facilitate future research.

2. REVIEW OF LITERATURE

Nidhi et al. stated – "The increasing global incidence of tuberculosis (TB), coupled with the emergence of multi-drug resistant (MDR) and extensively drug-resistant (XDR) strains, and highlights the urgent need for new therapeutic options. To accelerate drug development, QSAR-based rational approaches offer a rapid and cost-effective method for designing and optimizing new drug candidates. This review provides a comprehensive overview of QSAR studies focused on novel anti-tubercular agents, including nitroimidazoles, fluoroquinolones, quinoxalines, carboxamides, and other molecular classes. It also discusses both 2D and 3D-QSAR methodologies, emphasizing the recent trend of integrating these techniques with virtual screening, utilizing 3D pharmacophore modelling and molecular docking to identify and design innovative anti-tubercular compounds (Nidhi and Siddiqi, 2014, Lill and Danielson, 2011)".

Emmy Yunita et al. stated – "Based on the experimental results and discussions, the optimal QSAR equation identified is: Log MIC = 3.113 + 11.627 qC1 + 15.955 qC4 + 11.702 qC9. Derivatives of 3,6-dihydroxy and 1,3,6-trihydroxy xanthones are recognized for their promising anti-tuberculosis activity, especially when combined with amide, sulfoxide, and carboxylate groups. Docking analysis further revealed that these compounds function as KasA inhibitors, targeting the mechanisms within the cell wall of Mycobacterium tuberculosis (Yuanita et al., 2020)".

Marcelo N Gomes et al. *stated*- "There is an urgent need for new anti-tuberculosis (anti-TB) drugs to combat drug-resistant strains of Mycobacterium tuberculosis and to shorten the current treatment duration of 6 to 12 months. To address this, we first established structure-activity relationship (SAR) rules and developed binary QSAR models using data from the literature. These models guided the targeted design of new heteroaryl chalcone compounds with potential anti-TB activity. We prioritized 33 compounds for synthesis and biological evaluation, ultimately identifying 10 heteroaryl chalcone compounds that demonstrated nanomolar activity against replicating mycobacteria (Gomes et al., 2017)".

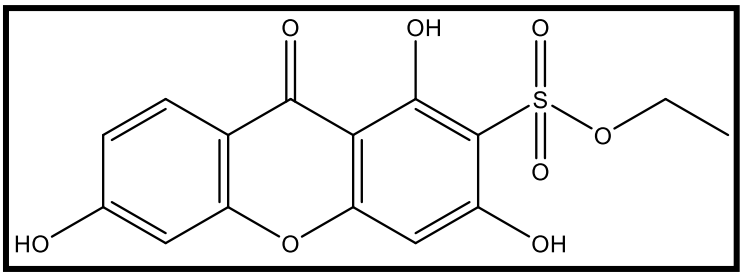

Fig. 1. ethyl 1,3,6-trihydroxy-9-oxo-9H-xanthene-2-sulfonate (Yuanita et al., 2020)

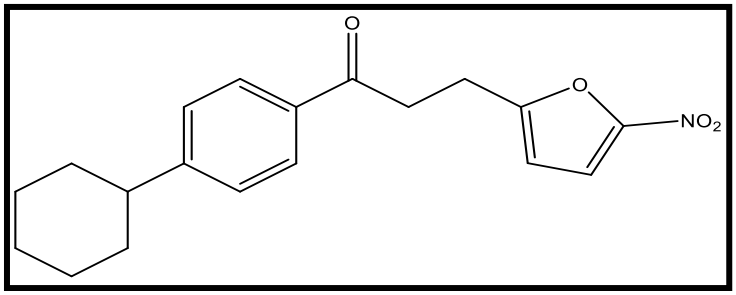

Fig. 2. 1-(4-cyclohexylphenyl)-3-(5-nitrofuran-2-yl)propan-1-one (Gomes et al., 2017)

Moulishankar A. et al. stated - “In the QSAR model, the molecular descriptors MATS8s, Chi4, bcutv8, Petitjeant, and for_aniline had a significant impact on antitubercular activity. This developed QSAR model is useful for predicting the antitubercular activity of tetrahydronaphthalene derivatives” (Moulishankarand Thirugnana Sambandam, 2023, Taghour et al., 2022, Eldehna et al., 2015).

Moulishankar A. et al. stated – “The quantitative structure-activity relationship (QSAR) approach successfully predicted the antitubercular activity of thiazolidine-4-one derivatives. For this study, we gathered data on 53 molecules with antitubercular activity against H37Rv from the literature. The most effective model, featuring an R^2 of 0.9092, an adjusted R^2 of 0.8950, and a LOF parameter of 0.0289, demonstrated a strong fit. In this QSAR equation, the molecular descriptors MLFER_S, GATSe2, Shal, and EstateVSA 6 showed a positive correlation with antitubercular activity, while SpMAD_Dzs 6 displayed a negative correlation” (Moulishankar and Sundarrajan, 2023, Abdel-Aziz et al., 2014, Jiang et al., 2018, Karalı et al., 2007, Shahlaei et al., 2009).

Adeniji SE et al. stated – “The model incorporating both 2D and 3D descriptors demonstrates superior performance, showing a strong correlation with anti-Mycobacterium tuberculosis activity. This combination enhances the predictive capability for the anti-Mycobacterium tuberculosis activities of the compounds. The generated QSAR model meets the minimum recommended validation parameters for an acceptable QSAR model. Molecular docking analysis revealed that nearly all 1,2,4-triazole derivatives can potentially inhibit Mtb CYP121. Notably, four compounds exhibited higher binding scores ranging from −10.03 to −11.02 kcal/mol. These four compounds were able to dock deeply within the binding pocket of Mtb CYP121, forming hydrogen bonds and hydrophobic interactions with the target amino acids. The QSAR model provides a valuable framework for ligand-based design, while the molecular docking studies offer insights for structure-based design” (Adeniji et al., 2018, Sarkar et al., 2016, Hansch and Leo, 1979).

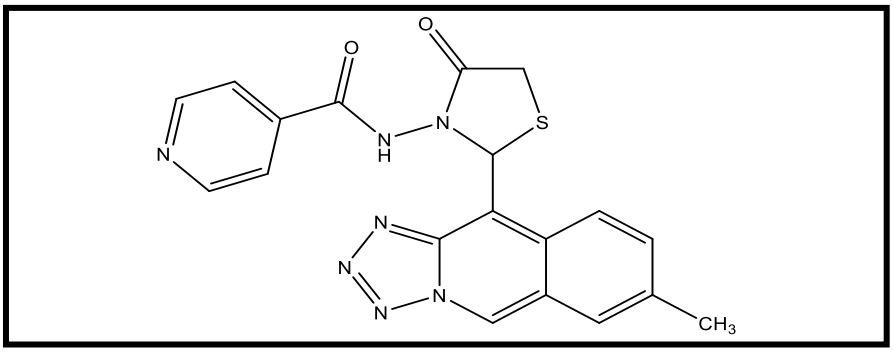

Fig. 3. N-(2-(7-methyltetrazolo[1,5-b]isoquinolin-10-yl)-4-oxothiazolidin-3-yl)isonicotinamide (Moulishankar and Sundarrajan, 2023)

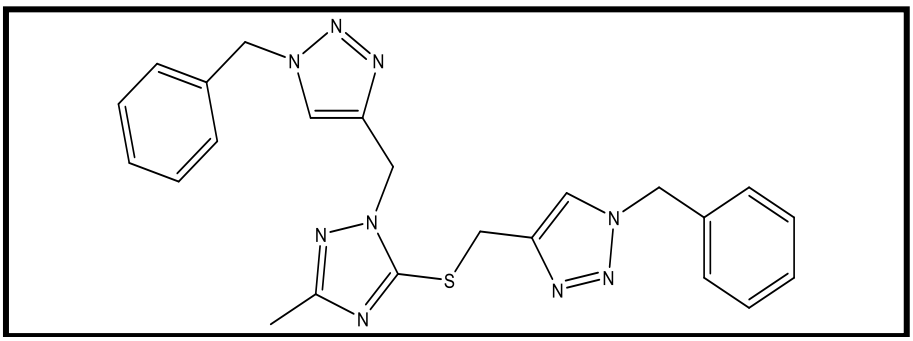

Fig. 4. 1-benzyl-4-(((1-((1-benzyl-1H-1.2.3-triazol-4-yl)methyl)-3-methyl-1H-1,2,4-triazole (Adeniji et al., 2018)

Ponnurengam Malliappan Sivakumar et al. stated- "Quantitative structure-activity relationships (QSAR) were developed for chalcones. Key molecular descriptors identified included Jurs descriptors (Jurs charged partial surface area), hydrogen bond donor counts, principal moment of inertia, molecular energy, dipole moment, molecular area, and various absorption, distribution, metabolism, and excretion (ADME) properties, as well as Chi indices (Kier & Hall connectivity indices). This approach resulted in excellent, statistically significant models for the four compound groups, with \(r^2\) values ranging from 0.80 to 0.97. The cross-validated \(r^2 \) (XV \(r^2 \)), which indicates the predictive capability of the models, was also strong, ranging from 0.79 to 0.94" (Sivakumar et al., 2007).

Teixeira C et al. stated- "As the cinnamoyl scaffold is a privileged and important pharmacophore in medicinal chemistry, some studies were conducted to find novel cinnamic acid derivatives (CAD) potentially active against tuberculosis. In this context, we have engaged in the setting up of a quantitative structure–activity relationships (QSAR) strategy to: (i) derive through multiple linear regression analysis a statistically significant model to describe the antitubercular activity of CAD towards wild-type *Mtb*; and (ii) identify the most relevant properties with an impact on the antitubercular behavior of those derivatives. The best-found model involved only geometrical and electronic CAD related properties and was successfully challenged through strict internal and external validation procedures. The physicochemical information encoded by the identified descriptors can be used to propose specific structural modifications to design better CAD antitubercular compounds" (Teixeira et al., 2020, Wong et al., 2014).

Trupti S et al. stated- "2D and 3D quantitative structure activity relationship (QSAR) studies were carried out on a series of thiazinan Isoniazid pharmacophore to design newer analogues. For 2D QSAR, the best statistical model was generated using SA-MLR method (r^2=0.958, q^2=0.922) while 3D QSAR model was derived using the SA KNN method (q2=0.8498). Furthermore, molecular docking was performed to gauze the binding affinity of the designed analogues for enoyl ACP reductase enzyme. Amongst all the designed analogues the binding energies of SKS 01 and SKS 05 were found to be 5.267kcal/mol and 5.237kcal/mol respectively which was comparable with the binding energy of the standard Isoniazid (6.254kcal/mol)" (Chitre et al., 2017).

Kharkar P. et al. (stated- "2D and 3D QSAR methods, specifically CoMFA and CoMSIA, were utilized to rationalize the antitubercular activity of a set of 33 molecules from the 1,4-dihydropyridine class. The inclusion of LUMO energies, which indicate donor-acceptor interactions, and ClogP, a parameter for lipophilicity, did not enhance the significance of the CoMFA and CoMSIA models. The results demonstrated strong correlations between steric and electrostatic fields and their corresponding anti-TB activity" (Kharkar et al., 2002, ChemBioDraw, 2020, O'Boyle et al., 2011, Online Chemical Database, 2020).

Besalú et al. stated – "A QSAR approach utilizing various topological indices as novel theoretical molecular descriptors was applied to a study of 64 anti-tuberculosis agents, specifically substituted benzoxazines and phenylquinazolines. To assess the reliability of the proposed linear QSAR model, several statistical tests were conducted. The resulting model was then applied to a larger virtual molecular library, which, in addition to the original set of 64 known active compounds, included another 512 molecules for which predictions were generated" (Besalú et al., 2003).

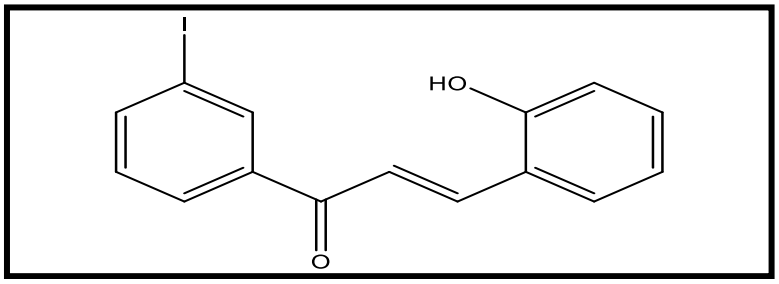

Fig. 5. (E)-3-(2-hydroxyphenyl)-1-(3-iodophenyl)prop-2-en-1-one (Sivakumar et al., 2007)

Adeniji et al. stated – “In this study, a validated QSAR model was developed to predict the biological activities of several anti-tubercular compounds and to design new hypothetical drugs based on molecular descriptors, including AATS7s, VR1_Dzi, VR1_Dzs, SpMin7_Bhe, and TDB8e. The model's reliability was confirmed through internal and external validation tests. Fig. 6, identified as a lead compound with high anti-tubercular activity, was used as a template for designing improved derivatives., with pBA values ranging from 8.8981 to 9.0377” (Adeniji and Adalumo, 2020).

Zhang et al. stated- “Tuberculosis (TB), caused by Mycobacterium tuberculosis (Mtb) infection, is a global infectious disease that poses significant public health challenges due to high incidence and mortality rates. This situation has created a substantial burden on global TB prevention and control efforts, highlighting the urgent need for novel anti-TB drugs. In this study, we employed QSAR modeling methods to systematically explore the relationship between the chemical structures of 36 aryl fluorosulfate derivatives and their inhibitory activity against Mtb. We developed robust and predictive Topomer CoMFA and HQSAR models, achieving parameters for the Topomer CoMFA model of $q^2 = 0.659$, $r^2 = 0.969$, F = 102.877, N = 6, and SEE = 0.138, while the HQSAR model parameters were $q^2 = 0.705$, $r^2 = 0.873$, SEE = 0.264, HL = 199, and N = 4. Using these models, we applied structural modifications to the compounds based on the ZINC15 database, resulting in the successful design and screening of three novel compounds with promising inhibitory activity. Molecular docking and ADMET predictions indicated that these new compounds demonstrate strong binding capabilities and significant pharmaceutical potential. This study offers valuable insights and directions for further research into aryl fluorosulfate derivatives as potential agents for tuberculosis treatment and as innovative drug candidates” (Zhang et al., 2024, Eldehna et al., 2018).

Abdelrahman et al. stated-, “Present the design and synthesis of two series of isatin-tethered quinolines as part of our research focused on developing novel isatin-based anti-tubercular candidates. In a previous study, we developed a series of small molecules featuring a quinoline-3-carbohydrazone moiety, with compound demonstrating the highest potency, exhibiting an MIC value of 6.24 µg/mL. In the current work, we employed a bioisosteric replacement strategy, substituting the 3,4,5-trimethoxy-benzylidene moiety in lead compound with the isatin motif—a privileged scaffold in TB drug discovery—resulting in the first series of target molecules. Subsequently, we introduced N-substituents, either methyl or benzyl groups, to the isatin motif, yielding the second series. All designed quinoline-isatin conjugates, were synthesized and biologically evaluated for their anti-tubercular activity against drug-susceptible, MDR, and XDR strains. Notably, the N-benzyl-bearing compound exhibited the best activity against the tested M. tuberculosis strains, with MICs of 0.06, 0.24, and 1.95 µg/mL, respectively” (Abdelrahman et al., 2022, Larif et al., 2013, Becke, 1993, OECD, 2014, Snedecor and Cochran, 1989, Cheke et al., 2022, Brandão et al., 2020, Chowdhary et al., 2022, Varun et al., 2019).

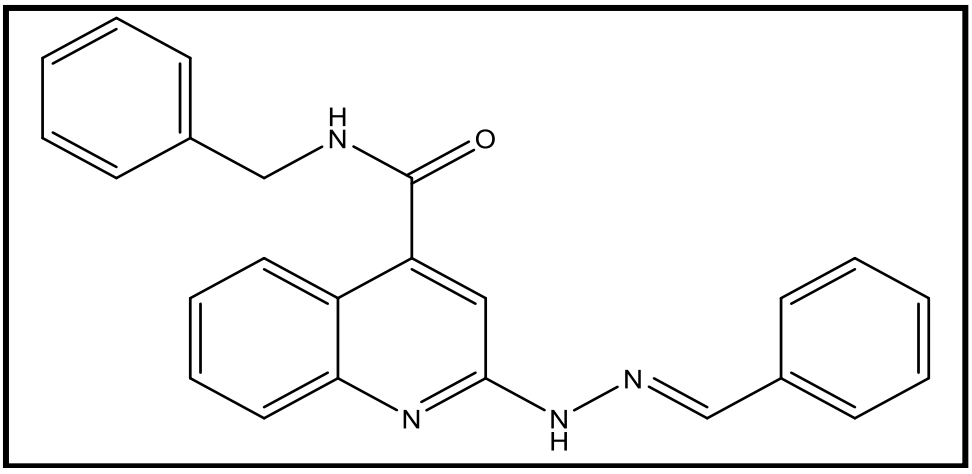

Fig. 6. (E)-N-benzyl-2-(2-benzylidenehydrazineyl)quinoline-4-carboxamide (Adeniji and Adalumo, 2020)

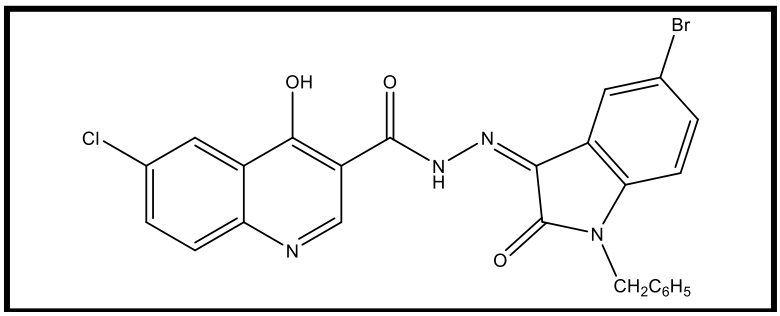

Fig. 7. (Z)-N-(1-benzyl-5-bromo-2-oxoindolin-3-ylidene)-6-chloro-4-hydroxyquinoline-3-carbohydrazide (Abdelrahman et al., 2022)

Joshi S et al. stated- "The enoyl-ACP reductase (ENR) enzyme catalyzes the nicotinamide adenine dinucleotide (NADH)-dependent reduction of trans-2-enoyl acyl carrier protein (ACP), resulting in the production of NAD+ and reduced enoyl thioester-ACP substrate. ENR plays a crucial role in type II fatty acid synthesis (FAS-II) (PubMed identifier 15139852) and serves as a valuable target for the discovery of antimicrobial drugs due to its essential role in metabolism. Thus, inhibiting ENR may offer a novel strategy for developing antitubercular (anti-TB) agents. Quinolines represent an important class of heterocycles found in a variety of natural and synthetic products. In this study, we conducted docking and three-dimensional quantitative structure–activity relationship (3D-QSAR) analyses, including comparative molecular field analysis (CoMFA), comparative molecular similarity indices analysis (CoMSIA), and Topomer CoMFA, on a series of quinoline hydrazones. Docking studies revealed that the active site of the enzyme, particularly the amino acid residue TYR158 and the co-factor NAD+, are critical for ligand binding. Among the compounds tested, compounds 45 and 46 exhibited the highest docking score of 6.22, while compound 26 scored 6.09. The CoMFA model demonstrated a q^2 of 0.617 and an r^2 of 0.81, the CoMSIA model yielded a q^2 of 0.631 and an r^2 of 0.755, and the Topomer CoMFA model provided a q^2 of 0.644 and an r^2 of 0.865, with a standard error of estimate (SEE) of 0.37. The docking results elucidated important structural features of the binding interactions between quinoline hydrazones and the ENR enzyme, providing valuable insights for designing compounds with enhanced inhibitory activity" (Joshi et al., 2014, Hawkins et al., 2007, Cheke et al., 2018, Elsayed et al., 2021).

Aher RB et al. stated- "Treating latent TB is crucial for reducing treatment duration and the incidence of drug resistance. In this context, we aimed to develop quantitative structure-activity relationship (QSAR) models—both regression and classification—specifically targeting the dormant form of MTB. We then utilized the developed classification models, including linear discriminant analysis (LDA) and random forest (RF), for two-fold classifications (Eldehna et al., 2016, Xu et al., 2016). This two-fold classification approach enhances the confidence in correct classifications. 2D-QSAR modeling identified several key factors contributing to the prediction of antitubercular activity against dormant MTB, including burden eigen, edge adjacency, van der Waals (vdW) surface area, topological charge, and pharmacophoric indices. The LDA model achieved classification accuracies of 85.14% for the training set and 87.10% for the test set, while the RF model demonstrated accuracies of 100.00% and 80.65% for the respective sets. Notably, the final models utilized only two-dimensional (2D) descriptors, which are easy to compute and eliminate the need for the computationally intensive processes of structure conversion, optimization, and energy minimization typically required for three-dimensional (3D) descriptors. These models can facilitate the identification and selection of more effective compounds against the dormant form of MTB" (Aher and Sarkar, 2022).

Ravichandran V et al. stated- The primary challenge facing many anti-tubercular agents is the resistance of Mycobacterium tuberculosis strains. Quinoline compounds have emerged as promising anti-mycobacterial agents, demonstrating significant anti-tubercular activity. This study aims to develop 2D QSAR models for a series of arylthioquinoline derivatives to predict their optimal characteristics as potential anti-tubercular agents. The primary challenge facing many anti-tubercular agents is the resistance of Mycobacterium tuberculosis strains. Quinoline

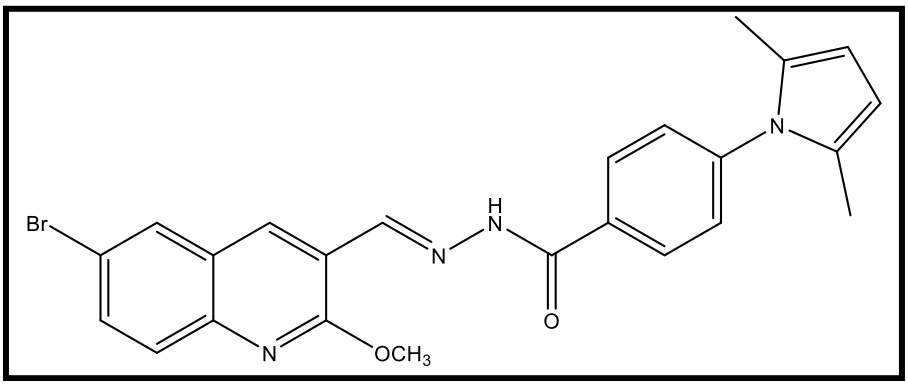

Fig. 8. (E)-N-((6-bromo-2-methoxyquinolin-3-yl)methylene)-4-(2,5-dimethyl-1H-pyrrol-1-yl)benzohydrazide (Joshi et al., 2014)

compounds have emerged as promising anti-mycobacterial agents, demonstrating significant anti-tubercular activity. This study aims to develop 2D QSAR models for a series of arylthioquinoline derivatives to predict their optimal characteristics as potential anti-tubercular agents. The significance and predictive capability of the developed QSAR model were confirmed by meeting the following criteria: \(r^2 = 0.817 > 0.6 \); \(CCC_{tr} = 0.899 > 0.85 \); \(q_{LOO} = 0.729 > 0.5 \); \($pred_{r^2}$ = 0.922 > 0.6 \); \($pred_{r^2}_{se}$ = 0.186 \); \(CCC_{pred} = 0.907 > 0.85 \); \(r^2m = 0.753 > 0.5 \); \(r'^2_m = 0.714 > 0.5 \); \(\Delta r^2_m = 0.039 < 0.2 \); \(k' = 0.966 \); \(k = 1.014 \) (with thresholds of \(0.85 \) and \(0.5 \)); and \(q^2_{LMO} = 0.650 > 0.5 (Ravichandran et al., 2015, Soliman et al., 2017, Güzel et al., 2008, Eldehna et al., 2021).

Martins F et al. stated- **"**The alarming rise of multidrug-resistant strains of Mycobacterium tuberculosis (Mtb) has prompted the scientific community to urgently seek new and effective antitubercular drugs. While several drugs are currently under investigation, isoniazid remains the cornerstone and most effective component in all WHO-recommended multi-therapeutic regimens. This paper presents a QSAR-oriented design, synthesis, and evaluation of the in vitro antitubercular activity of various potent isoniazid derivatives, including isonicotinoyl hydrazones and isonicotinoyl hydrazides, against H37Rv and two resistant Mtb strains.The QSAR studies involved the development of random forest (RF) and artificial neural network (ASNN) classification models, as well as multiple linear regression (MLR) models. Strict validation procedures were employed to ensure the robustness and predictive accuracy of the models" (Abdel-Aziz et al., 2015, Eric et al., 2016, Hussain et al., n.d.). Interestingly, lipophilicity was found to be irrelevant in explaining the activity of these derivatives, while shorter NeN distances and longer substituents correlated with increased potency.Among the compounds tested, compounds 1, 2, 4, 5, and 6 exhibited activities against H37Rv that surpassed that of isoniazid, with a minimum inhibitory concentration (MIC) of 0.28 mM. Notably, compound 9 demonstrated a six-fold improvement in MIC against the katG (S315T) mutated strain compared to isoniazid (6.9 mM vs. 43.8 mM). However, all compounds were ineffective against H37RvINH (DkatG), a strain with a complete deletion of the katG gene (Martins et al., 2014, Singh et al., 2011, Abo-Ashour et al., 2018).

3. CONCLUSION

QSAR studies are invaluable in the search for new anti-TB agents, providing insights into structure-activity relationships and guiding the optimization of lead compounds. Continued advancements in computational techniques and data integration will further enhance the potential of QSAR in combating tuberculosis.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that generative AI technologies such as Large Language Models, etc have been used during writing or editing of this manuscript. This explanation will include the name, version, model, and source of the generative AI technology and as well as all input prompts provided to the generative AI technology.

Details of the AI usage are given below:

OpenAI. (2024). *ChatGPT* (GPT-4) [Large language model]. OpenAI.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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