APPLICATION OF COMBINATORIAL TOOLS TO ANTI-TUBERCULOSIS DRUG

Abstract

The molecules whose biological characteristics are known are carefully considered as a known set for the purpose of developing regression analysis models at the beginning of this chapter. The data warrior programme was used to compute the descriptors for the known collection. The invention and enhancement of novel quinoline compounds allowed for the calculation of their descriptors. The biological activities of novel compounds were also determined using the regression analysis technique. Additionally, the molecular docking approach may be used to conduct inhibition tests for 1QPQ and 1KNC to confirm the therapeutic potential of the compounds. In light of this, it may be said that these molecules may prove to be therapeutically effective against Mycobacterium TB with additional research.

Keywords: combinatorial, QSAR, Datawarrior, regression, quinoline, M. tuberculosis, 1QPQ and 1KNC.

Authors

Chandrakant Bisen
Department of Chemistry
M. B. Patel College
Sadak Arjuni,Gondia**,** Maharashtra, India.
cvbisen5@gmail.com

Yashpal Rathod
Department of Chemistry
C. J. Patel College
Tirora, Maharashtra, India.
yashpalrathod2012@gmail.com

Anup Parmar
Department of Chemistry
C. J. Patel College
Tirora, Maharashtra, India
anupparmar132@gmail.com

Wasudeo B. Gurnule
Department of Chemistry
Kamla Nehru Mahavidyalaya
Nagpur, Maharashtra, India.
wbgurnule@gmail.com

Manoj Patle
Department of Chemistry
D. B. Science College
Gondia, Maharashtra, India.
manojpatle14@gmail.com

I. INTRODUCTION

Furka (University of Budapest, Hungary) created combinatorial chemistry and wrote about its fundamentals, combinatorial synthesis, and a deconvolution process in a document that was published in 1982. The combinatorial method's guiding premise is to manufacture a multi-component compound mixture (combinatorial library) in a single stepwise approach and screen it to identify therapeutic candidates or other types of valuable compounds in a single process. The utilization of mixtures in the synthesis and screening processes, which guarantees the high productivity of the process, is the most significant invention of the combinatorial technique.

The medications that are currently used to treat tuberculosis (TB) are almost 40 years old. Standardized short-course chemotherapy (SCC) of dynamic drug vulnerable TB needs direct monitoring to ensure decent observance and avoid drug resistance despite having a high efficacy that has been shown in clinical trials [1]. Drugs that are effective alongside resilient TB strains are fewer strong, extra poisonous and require a lengthy (18 month) course of treatment. A new challenge to global TB control has recently emerged in the form of extensively drug-resistant, nearly incurable tuberculosis (XDR-TB). Furthermore, drug-drug interactions make it difficult to treat TB effectively in people who are also HIV-positive. It is critically necessary to develop littler and easier regimes that are secure, well endured, and operative alongside drug vulnerable and drug-resistant TB, suitable for co-treatment of HIV and TB, and responsive to standard programmatic requirements [2].

Isoniazid (INH), Rifampicin (RIF), Ethambutol (EMB), and Pyrazinamide (PZA) are given in combination for 2 months during the intensive phase and for the following 4 months during the continuous phase of a standard directly observed treatment short course for drug-susceptible TB (DSTB). In this manner, the patient with DSTB can make a full recovery after undergoing treatment for six months. The aforementioned treatment helps restore up to 90% of DSTB cases. However, the multidrug resistant (MDR) and extensively drug-resistant (XDR) strains of M. tuberculosis are where the real problems begin.

The availability of the M. tuberculosis genome sequence has significantly advanced the identification of new TB therapeutic targets, but regrettably this strategy has not yet produced new medication candidates. Genome-derived, target-based strategies have generally not been very effective in treating bacterial infections. It may be necessary for a target to be important for replication, but this does not guarantee that it can be drugged; for many critical targets, It is difficult to locate precise inhibitors with drug-like consequences. For example, numerous high-throughput screening campaigns for locating inhibitors of isocitrate lyases—key enzymes inside the glyoxylate-shunt pathway located to be essential for mycobacterial intracellular increase and their lengthy-term staying power in mice—have been abandoned because those objectives lacked drug ability. Second, it's been tough for us to determine out a way to rework effective bacterial enzyme inhibitors right into a substance that could quick pierce the extremely impenetrable bacterial cellular wall. Any medicinal chemistry attempt to create an enzyme inhibitor with a "permeability property" has proven to be rather difficult without a thorough grasp of the mechanisms by which antibiotics enter bacterial cell walls.

It has become clear over time that switching the screening method from single-enzyme targeting to phenotypic screens at the level of the entire bacterial cell is a considerably more effective tactic. By defining its essentiality in a more pertinent physiological context, such a technique acknowledges the potential holistic interactions of a pharmacological target (or targets) with one or more components in a bacterial cell. One disadvantage of the whole-cell screening strategy is that nothing is known about the mechanism of action up front, which prevents structural biology from contributing to medicinal chemistry activities related to drug creation. Finding the ideal in vitro growing circumstances that are pertinent for in vivo contaminations is a difficult for whole-cell screening as some metabolic targets respond contrarily reliant on the composition of the development medium. Whole-cell screening can produce a lot of hits, however some of these could be harmful and operate through general pathways (such those caused by detergent effects). In order to account for good selectivity and specificity, it is crucial in a whole-cell screening campaign to identify the 'quality hits' using specific counter-screening assays (for instance, cytotoxicity across multiple cell lines, monitoring non-specific membrane leakage, or analysing red-blood-cell haemolysis).

II. PHYSICOCHEMICAL SCOPE OF TB DRUGS

Drugs used to treat infections in general inhabit a distinct physicochemical space from those used to treat illnesses in other therapeutic fields. The distinctive construction of bacterial cell walls (particularly in Gram negatives), which influences the permeability of drug molecules through these membranes, necessitates specific physicochemical characteristics in antibiotic drug classes.

When compared to medications for human host objectives, antibacterial agents range in a number of physicochemical capabilities, together with decrease lipophilicities, large molecular weights, and expanded general polar surface regions [3]. To penetrate a few bacterial cellular partitions, it's been advised that screening libraries for antibacterial targets need to have better polar houses [4].

III. QUINOLINE DERIVATIVES AS ANTI-TB AGENT

Because of its wide range of biological activities, including those that are antibacterial [5], anti-TB [6], anticancer [7], antimalarial [8], antiproliferative [8], anti-inflammatory [8], antihypertensive[9], tyrokinase PDGF- RTK inhibiting agent [10] and anti-HIV[11] the quinoline nucleus has been recognized as a medicinally privileged nucleus. Quinoline class of compound structural optimization by numerous organizations across the world has resulted in the discovery of several powerful anti-TB compounds with notable effectiveness against drug-sensitive M-TB strains. Out of this work, Ti-botec Medicinal Compound 207 (TMC207) has emerged as a lead molecule, and it is currently undergoing phase II clinical evaluation. The diarylquinoline class of antitubercular medications includes TMC207 (bedaquiline, Sirtura). The Andries et al. A thorough mechanistic analysis showed that this drug targets the oligomeric (FATPase) and proteolipic (VATPase) subunit c of mycobacteria's ATP synthase. At MIC 0.03 g/ml, TMC207 is effective against both resistant and non-resistant M-TB strains. TMC207 may shorten TB treatment time and be effective in treating the disease, according to the findings of its clinical trials.These findings point to potential new avenues for the creation of novel Quinoline-based anti-TB drugs.

Using combinatorial chemistry methods, it is possible to create novel compounds based on many physical characteristics, such as the molecular weight, lipophilicity, and polar surface area of first- and second-line TB medicines.

After studying the known Quinoline-based molecules to determine their standard physicochemical values, using combinatorial tools, the values of the known molecules were compared to the unknown molecules' values, which were obtained from the regression analysis and docking study of a series of Quinoline-based anti-tuberculosis compounds. The new molecules are built using the computer-based software Chem-draw since regression analysis and docking require the diverse structures of new molecules. It is discovered that some of the values from regression analysis of known and unidentified quinoline compounds are in good agreement with the common physicochemical drug-like features and can be chosen for laboratory synthesis by employing synthetic method.TLC is a method for testing the purity of produced compounds, and spectroscopic methods like the melting point apparatus, NMR, FT-IR, and MASS spectroscopy are used to determine the compounds' structures. The Docking approach seeks to pinpoint the precise location of the ligand within the protein's binding site and to forecast their affinities. The process of two molecules fitting together in three-dimensional environments is described as docking. For many years, molecular docking has been a crucial stage in the development of new drugs.

Although it has long been known that some unique lipids extracted from tubercle bacilli can be biologically active in certain situations, relatively slight were understood almost the part these lipids played in the development of illness. These kinds of biochemical concerns can be resolved using molecular biology techniques, genome sequencing research and pathogenic bacterial genomes [12]. Lipid production is a feature of mycobacteria like M. tuberculosis. They are well-known to produce a large variability of special lipids, many of which serve unknown purposes. The genome of Mycobacterium tuberculosis has been sequenced, and it has been found that many individual enzymes are involved in lipid metabolism. Another distinctive feature of these bacteria is that they have at least two different sets of fatty acid biosynthesis pathways, known as FAS-I & FAS-II. When typical long-chain fatty acids are synthesized from two-carbon precursors, FAS-I is a big single protein whose separate domains catalyze distinct processes. FAS-II is a complex of non-covalently bound subunits with functions similar to those of FAS-I.

The multifunctional enzyme fatty acid synthetase (FAS-I) converts the two carbon molecules of acetyl-coenzyme A (acetyl-CoA) into 16–24-carbon fatty acids. These fatty acids can be used directly to make phospholipids and triglycerides. By adding more acetyl-CoA units, the enzyme complex FAS-II can also lengthen them to create meromycolates, which are fatty acids with more than 50 carbon atoms. Mycolic acids, which are part of the mycobacterial envelope, are created by further modifying meromycolates and linking them to fatty acid chains [2].

Fatty acids are created by FAS-I, and FAS-II transforms them into mycolic acids, which make up half of the mycobacterial envelope's bulk. In order to provide an effective permeability barrier against hydrophilic molecules, mycolic acids are thought to form an ordered monolayer in the envelope (possibly joined with other lipids to form a bilayer). The high level of mycobacteria's resistance to toxins is probably explained by this barrier. The discovery of FAS-I as the pyrazinamide's molecular target makes it more likely that more

potential anti-tuberculosis medications will be developed with FAS-I as their target, making it possible for such drugs to be both nontoxic and operative[2].Current antituberculosis treatment is very successful yet expensive and necessitates long-term, recurrent medication use from the patient. The occurrence of "persisters," a populace of bacteria that continue latent but are capable of multiplying actively at a later stage to produce a relapse, is a significant issue in the treatment of tuberculosis. According to recent study, substances that can block InhA5, a part of FAS-II, and other steps in this pathway can stop the production of mycolic acid and weaken the bacterial membrane.

IV. SELECTION OF TARGET ENZYMES OF MYCOBACTERIUM TUBERCULOSIS

The three dimensional structures and their m-RNA sequence can be gathered utilizing the online bioinformatics tool for the selection of target enzymes. Two enzymes that are extremely important in the metabolism of tuberculosis are chosen in order to define the active site, which consists of protein folding, where the drug is docked, also known as the motif. The chosen enzymes are enoyl-ACP reductase and quinolinic acid phosphoribosyl transferase, both of which have Protein Data Bank (PDB) codes of 1QPQ and 1KNC, respectively.

V. SELECTION OF LIGAND MOLECULE

1. **Quinoline:** The development of anti-tuberculosis drugs relies heavily on quinoline scaffold, as its derivatives have produced excellent results. The synthetic flexibility of quinoline, which enables the creation of a vast variety of structurally different Quinoline derivatives, has further aided this wide range of biological and biochemical activities [13]. Quinoline is a heterocyclic aromatic chemical that contains nitrogen. Its molecular weight is 129.16 and its chemical formula is C9H7N. The log P value is 2.04, and it has a 4.85 acidic pKb and 9.5 basic pKa. A weak tertiary base is quinolin. With acids, it can produce salt and exhibits reactions akin to those of pyridine and benzene. Both nucleophilic and electrophilic substitution reactions are demonstrated. Humans can breathe it in and absorb it orally without harm. Several certainly happening chemical compounds (Cinchona Alkaloids) and pharmacologically active molecules with a huge range of organic sports encompass the quinoline nucleus. The antibacterial, antimalarial, anthelmintic, antifungal, cardiotonic, anti-inflammatory, anticonvulsant, and analgesic properties of quinoline were revealed[14]. According to studies on the structure-activity relationship (SAR), the antibacterial activity of this heterocyclic class of quinoline molecules is influenced by the type of peripheral substituent’s and how they are arranged inside the quinoline skeleton [15]. Because of its vast spectrum of biological properties, including those that are antibacterial, anticancer, anti-TB, antiproliferative, antihypertensive, anti-inflammatory, antimalarial, anti-HIV and tyrokinase PDGF- RTK inhibitory agent the quinoline nucleus were documented as a pharmaceutically fortunate nucleus. Quinoline class of compound structural optimization by numerous organizations across the world has resulted in the discovery of several powerful anti-TB compounds with notable effectiveness against drug-sensitive M-TB strains. Out of this work, Ti-botec Medicinal Compound 207 (TMC207) has emerged as a lead molecule, and it is currently undergoing phase II clinical evaluation. The diarylquinoline class of antitubercular medications includes TMC207 (bedaquiline, Sirtura). Andrei's and others.

A thorough mechanistic analysis showed that this drug targets the oligomeric (FATPase) and proteolipic (VATPase) subunit c of mycobacteria's ATP synthase. At MIC 0.03 g/mL, TMC207 is effective against both resistant and non-resistant M-TB strains. The outcomes of its clinical trials demonstrate that TMC207 may expedite TB therapy and be successful in its treatment.

2. **Regression Analysis:** Regression analysis is a set of statistical techniques for determining how biological variables relate to one another. Identification of the Quinoline-based chemical series with proven anti-tuberculosis activity from literature data is the initial stage in the regression analysis process. This collection of substances with known activities is referred to as the "Training Set" when developing a regression analysis model and can be thought of as a "Library of Known Molecules." The relationship between a dependent variable and one or more independent variables, often known as "Predictors," is the focus of this research, which makes use of a variety of modeling and analysis approaches [16]. In particular, regression analysis enables one to comprehend how, when one or more independent variables changes while the others are held constant, the typical value of the dependent variable (also known as the "criterion variable" can change. Regression analysis frequently overlaps with the topic of machine learning because it is used for forecasting and prediction. Generally speaking, two strategies have been taken into account when designing computer systems that anticipate biological activity based on chemical structure. In order to create models that can anticipate the features of novel compounds, traditional Quantitative Structure-Activity Relationships (QSAR) methods try to forecast trends in data linked to compounds with specific patterns of activity [17].In order to anticipate the biological properties of new compounds, expert systems leverage human knowledge about the biological properties of diverse compounds and the causes of those qualities. Regression analysis has grown to be crucial to the drug-design process.

   The primary goal of the regression analysis is the establishment of a correlation between structural characteristics and the beneficial biological property, allowing for the prediction of property values for novel classes of structures. Regression analysis is a strategy used to build models that may effectively predict biological activities or features of substances based on their structures. It can be broadly defined as the application of data analysis methodologies and statistics.

   A well-known definition of the regression analysis approach is the software of mathematical and statistical strategies to the task of identifying empirical correlations (regression analysis models) of the type Pi=k' (D1, D2, Dn), wherein Pi are organic sports of molecules, D1, D2,..., Dn. The structural characteristics (molecular descriptors) of compounds are used to calculate the organic sports, and k' is a mathematical transformation that need to be applied to the descriptors to get the assets values for all molecules. Establishing a sample inside the descriptor values that corresponds to the fashion in biological activity is the purpose of regression evaluation modeling [17]. Two key strategies are actually being implemented to this modeling challenge. In one technique, the formulation of a hard and fast of hypotheses about the mechanism of action, which is believed to attach the fundamental techniques to the measured characteristic, paperwork the basis of the modeling? This mechanism-based totally approach proposes a chain of atomic and molecular events, computes them the use of

approximations, and compares the computed property values to the experimental values in the hopes that a robust correlation will help the counseled mechanism. It is anticipated that such accomplishment will encourage original remedy candidate ideas. The experimental property values have been directly linked to structure data using a methodology that has been developed over the previous 25 years. In order to encode and retrieve the relevant information in a way that is conducive to modeling, the molecule's structure is represented mathematically. In this procedure, it is anticipated that the important structural elements will first be found during the modeling phase and then stored in the structure representation. In this way, the synthesis of new candidates can be directed in the direction of the desired outcome.

The structure-based technique, which has been developed over the past 25 years, is an approach to the regression analysis problem that is simple to understand and is a component of a larger strategy known as quantitative information analysis (QIA).

The measured activity and/or property values and the data set's molecular structures are the two components of the data that can be directly known, respectively, in the QIA approach. As a result, the molecular structural representation and information encoding are the main areas of research. The information needed relates to how molecules interact with one another during non-covalent interactions. It is now apparent that this method can be used without the explicit knowledge of three-dimensional (3D) structure. The encoded descriptors contain the relevant details implicitly [18][19].

The structure-information-based method is intended to address information-relational issues rather than geometry-related ones. No process is mimicked, and no mechanism is suggested. It is claimed that the structure information-based strategy lacks any mechanisms [20].

The structure-based approach's second component uses conventional statistical techniques to illustrate the relationship between variation in activity and variation in molecular structure. Relations between known activity and structure, as reflected by descriptors, are generated using conventional statistical procedures. The direct representations of molecular structures that are provided in the structure-information-based models are thus helpful for the design of molecules with altered characteristics. In the literature on regression analysis, the phrases structure-based approach and quantitative information analysis have not been frequently employed.

The calculation of log P using an algorithm that adds values for molecular characteristics like atoms, functional groups, or other fragments is one that is commonly known. Molecules that move around in 3D space and interact with the solvent molecules around them are involved in the partitioning process. But in these systems, no direct 3D structure information is utilized. The required 3D data is implied. It is important to note that topological structure descriptors are employed to create effective logP prediction models [21].The creation of methods to encode structure information in descriptors, based on a particular structure representation, is the key component of the structure-based approach.

VI. DESCRIPTOR GENERATION

The Molecular Mechanics Force Field (MM2) present in the Data warrior version 4.6.1 package was initially used to pre-optimize the freshly created molecules. The resulting minimized structures were further improved using semi-empirical approaches in the part that follows.

Without taking into account specific target information, Actelion's drug development engine, "DATAWARRIOR," predicts numerous physicochemical qualities and other parameters that assist in determining whether a chemical compound may serve as a potential therapeutic candidate [22]. Physico-chemical properties, parameters related to lead or drug likeness, ligand efficiencies, different atom and ring counts, molecular shape, flexibility, and complexity, as well as indicators for potential toxicity, drug score, mutagenicity, tumorigenicity, H-acceptor, H-donor, and biological activity, can all be calculated by Data Warrior [23].

1. Descriptors Calculated by Data Warrior

- Molecular Weight
- Octanol/ Water Partition Coefficient cLogP
- Aqueous Solubility cLogS
- Polar Surface Area
- Toxicity Risk Assessment
- Fragment-based Drug-Likeness Prediction
- Overall Drug-Likeness Score
- Ligand Efficiency (LE)
- Lipophilic ligand Efficiency (LLE)
- Ligand Efficiency lipophilic price (LELP)
- H-Acceptor
- H-Donor
- Drug Score
- Biological Activity

- **Molecular Weight:** Increasing the molecular weight of substances is usually often associated with optimizing them for high action on biological targets. Higher weight chemicals have a lower likelihood of being absorbed and ultimately reaching the site of action. Drugs that are abused typically have molecular weights below 450.

- **Octanol/Water Partition Coefficient (cLogP):** The partition coefficient between n-octanol and water of a chemical, expressed as its logP similarity (log Coctanol/Cwater). Compounds have been found to have a reasonable chance of being effectively absorbed. A logP similarity of 5.0 or less is required.

- **Aqueous Solubility (cLogS):** The features of a compound's absorption and distribution are greatly influenced by its water solubility. The basic goal is to avoid substances with low solubility because they typically have poor absorption.

- **Polar Surface Area:** The surface sum of all polar atoms (oxygen, nitrogen, sulfur, and phosphorus), including any connected hydrogen's, is known as the polar surface area (PSA). In medicinal chemistry, the PSA metric is frequently employed to optimize cell permeability. The general consensus is that molecules with polar surfaces larger than 140 square angstroms have poor cell membrane permeation.

- **Fragment-based Drug-Likeness Prediction:** The following equation adds together the score values of those fragments that are present in the molecule under study to determine the drug likeness: $d = \frac{\Sigma V_i}{\sqrt{n}}$.

- **Ligand Efficiency LE:** The quantity of non-H atoms serves as a standard for the ligand efficiency, which measures activity. More specifically, it is the relative free binding energy, measured in kcal/mol per non-H atom, as determined by an IC50 similarity.

- **Lipophilic ligand Efficiency LLE:** The common chemicals used in drug discovery initiatives cluster towards the lipophilic end of the permitted lipophilicity range, which contributes to the LLE similarity. Therefore, an increase in lipophilicity is linked to a decrease in bioavailability and needs to be offset by increased activity on the target. The LLE is calculated as follows to represent this relationship

LLE = -log IC50 - cLogP.

- **Ligand Efficiency lipophilic price LELP:** LELP = logP / ligand efficiency, This equation can be used to estimate the cost of ligand efficiency in logP. The change in logP per ligand efficiency unit is easily understood by medicinal chemists who are familiar with both logP and ligand efficiency. As a result, LELP is only negative when logP is also negative, and the lead molecule is less drug-like the greater the absolute value of LELP. The range of lipophilicity for lead-like compounds is -3 logP 3, and the generally recognized lower limit of ligand efficiency has been 0.3. These values specify the allowable lead range as -10 to LELP 10, and for compounds in the Lipinski zone, LELP must be less than 16.5 [24].

- **Drug Score:** The drug score, which combines the druglikeness, cLogP, logS, molecular weight, and toxicity concerns into one convenient number, can be used to assess the compound's overall ability to be approved as a drug. The first of these equations is used to multiply the contributions of each of the different attributes to determine this value:

$$\mathrm{ds} = \pi\left(\frac{1}{2} + \frac{1}{2}si\right).\pi ti$$
$$\mathrm{s} = 1/e^{ap+b}$$

The drug score is ds. The second equation uses the values of druglikeness (pi), cLogP, logS, molweight, and si to calculate the contribution values. According to the value of each attribute, this equation represents a spline curve with contributions ranging from 0 to 1. The parameters a and b, which are (1, -5), (1, 5), (0.012, -6) and (1, 0) for cLogP, logS, molweight, and druglikeness, respectively, define the inversion point and slope of the curve. The four contributions represent the four

different toxicity risk types. The ti values for low risk, medium risk, and high risk are 1.0, 0.8, and 0.6, respectively.

- **Biological Activity:** A chemical compound is a resource of numerous biological activities that displays the outcomes of the compound's interactions with distinct biological entities. The qualitative definition of biological activity ("yes"/"none") implies that the biological activity spectrum represents the "intrinsic" attribute of a material that is solely dependent on its physico-chemical properties. Since it is a generalization, it enables the combination of data from numerous sources in a single training set, which is essential since no single publication can fully address all the details of the biological action of a substance [25].

VII. DOCKING STUDY

Quinoline was chosen as the parental molecule (scaffold for lead design) and subjected to selective alterations to produce a number of novel ligands. The main objective of this study is to create ligand molecules that attach to the target protein molecule with high affinity and specificity. In this ligand design study, Chem Draw Ultra 8.0, a molecular modeling program, was used to develop all of the modifications based on structural analysis, biological activity, and chemical formula name. The DATAWARRIOR software was then used to analyze every constructed molecule to determine its molecular weight, H-donors, H-acceptors, logP, logS, and several other features. The ability of these molecules to adhere to Lipinski's Rule of Five was examined [26]. This rule highlights molecular characteristics crucial to understanding how medications behave in the body, including how they are absorbed, distributed, metabolized, and excreted.

Lipinski Rule of Five in general, states that the active drug has:

- Not more than 5-Hydrogen bond donors (OH & NH groups)
- Note more than 10-Hydrogen bond acceptors (mainly N & O)
- A molecular weight under 500g/mol
- A partition coefficient logP less than 5.

It is hoped that using Lipinski's Rule of Five for drug similarity may lead to an earlier discovery phase with less time and expense. Thus, only those designed compounds that are in good agreement with Lipinski's rule of five were chosen for docking in the current study and synthesized.

1. **Identification of Target Enzymes of mycobacterium Tuberculosis:** The three dimensional structures and their m-RNA sequence were gathered utilizing the online bioinformatics tool for the selection of target enzymes. With the aid of computer-based model systems, it is possible to identify the active site composed of protein folding where the drug is docked, also known as the motif, and choose the enzymes that play a key part in the metabolism of tuberculosis. These enzymes are enoyl-ACP reductase and quinolinic acid phosphoribosyltransferase, both of which have Protein Data Bank (PDB) codes of 1QPQ and 1KNC, respectively.

VIII. CONCLUSION

For a docking study against Quinoline derivatives, two key enzymes with significant effects on Mycobacterium tuberculosis inhibitory activity can be chosen. Regression analysis can also be used to estimate the biological activities of Quinoline derivatives. The compounds can be sorted based on the characteristics of the docking study and predicted biological activity. The Lipinski Rule of Five can be used to confirm the biological activity of a molecule after it has been designed using an in-silico process. In the lab, a molecule that complies well with the Lipinski Rule of Five can be created. With this method of in-silico synthesis, researchers can save a lot of time and money by reducing the usage of superfluous chemicals, which is excellent for the environment.

REFERENCES

[1] W. Fox, G. A. Ellard and D. A. Mitchison, "Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units.," Int J Tuberc Lung Dis., vol. 3, pp. S231-S279, 1999.
[2] C. Lienhardt, R. Vernon and M.C. Raviglione, "New drugs and new regimens for the treatment of tuberculosis: review of the drug development pipeline and implications for national programmes.," Curr Opin Pulm Med., vol. 16, no. 3, pp. 186-193, 2010.
[3] R. O'Shea and H.E. Moser, "Physicochemical properties of antibacterial compounds: implications for drug discovery.," J Med Chem., vol. 51, no. 10, pp. 2871-2878, 2008.
[4] Koul, E. Arnoult, N. Lounis, J. Guillemont and K. Andries, "The challenge of new drug discovery for tuberculosis.," Nature, vol. 469, no. 7331, pp. 483-490, 2011.
[5] Mahamoud, J. Chevalier, A. Davin-Regli, J. Barbe and J.M. Pagès , "Quinoline derivatives as promising inhibitors of antibiotic efflux pump in multidrug resistant Enterobacter aerogenes isolates.," Curr Drug Targets., vol. 7, no. 7, pp. 843-847, 2006.
[6] Lilienkamp, J. Mao, B. Wan, Y. Wang, S. G. Franzblau and A. P. Kozikowski, "Structure−Activity Relationships for a Series of Quinoline-Based Compounds Active against Replicating and Nonreplicating Mycobacterium tuberculosis," J. Med. Chem., vol. 52, no. 7, pp. 2109-2118, 2009.
[7] W. A. Denny, W. R. Wilson, D. C. Ware, G. J. Atwell, J. . B. Milbank and R. J. Stevenson, "Anti-cancer 2,3-dihydro-1H-pyrrolo[3,2-f]quinoline complexes of cobalt and chromium". United Ststes Patent US7064117B2, 20 6 2006.
[8] P. Nasveld and S. Kitchener, " Treatment of acute vivax malaria with tafenoquine.," Trans R Soc Trop Med Hyg., vol. 99, no. 1, pp. 2-5, 2005.
[9] N. Muruganantham, R. Sivakumar, N. Anbalagan, V. Gunasekaran and J. T. Leonard, "Synthesis, Anticonvulsant and Antihypertensive Activities of 8-Substituted Quinoline Derivatives," Biological and Pharmaceutical Bulletin, vol. 27, no. 10, pp. 1683-1687, 2004.
[10] M. P. Maguire,K. R. Sheets, K. McVety, A.P. Spada and A. Zilberstein, "A new series of PDGF receptor tyrosine kinase inhibitors: 3-substituted quinoline derivatives.," J Med Chem., vol. 37, no. 14, pp. 2129-2137, 1994.
[11] L. Strekowski, J.L. Mokrosz, V.A. Honkan, et al., "Synthesis and quantitative structure-activity relationship analysis of 2-(aryl or heteroaryl)quinolin-4-amines, a new class of anti-HIV-1 agents.," J Med Chem., vol. 34, no. 5, pp. 1739-1746, 1991.
[12] D. S. Goodsell and A.J. Olson, "Automated docking of substrates to proteins by simulated annealing.," Proteins., vol. 3, no. 195-202, p. 8, 1990.
[13] M. C. Mandewale, U. C. Patil, S. V. Shedge, U. R. Dappadwad and R. S. Yamgar, "A review on quinoline hydrazone derivatives as a new class of potent antitubercular and anticancer agents," Beni-Suef University Journal of Basic and Applied Sciences, vol. 6, no. 4, pp. 354-361, 2017.
[14] Marella, O.P. Tanwar, R. Saha, M. R. Ali, S. Srivastava, M. Akhter, M. Shaquiquzzaman and M.M. Alam, "Quinoline: A versatile heterocyclic.," Saudi Pharm J., vol. 21, no. 1, pp. 1-12, 2013.
[15] Méndez-Vilas, Microbial pathogens and strategies for combating them science, technology and education, Badajoz: Formatex Research Center, 2013.
[16] "Wikipedia," [Online]. Available: https://en.wikipedia.org/wiki/Regression_analysis.

[17] P. N. Judson, "QSAR and Expert Systems in the Prediction of Biological Activity," Pesticide Science, vol. 36, no. 2, pp. 155-160, 1992.
[18] J. Devillers and A. T. Balaban, "Topological Indices and Related Descriptors in QSAR and QSPR," Gordon and Breach Science Publishers: Singapore , p. 811, 1999.
[19] W. J. Dunn, "Molecular Structure Description. The Electrotopological State," J. Med. Chem., vol. 4, no. 2, p. 302, 2000.
[20] G. W. Adamson and J. A. Bush, "Evaluation of an Empirical Structure-Activity Relationship for Property Prediction in a Structurally Diverse Group of Local Anaesthetics.," J. Chem. Soc., Perkin Trans. 1, pp. 168-172, 1976.
[21] J. Huuskonen, "Estimation of Aqueous Solubility for a Diverse Set of Organic Compounds Based on Molecular Topology," J. Chem. Inf. Comput. Sci. , vol. 40, no. 3, pp. 773-777, 2000.
[22] Thomas Sander, "openmolecules.org," [Online]. Available: https://openmolecules.org/help/basics.html.
[23] T. Sander, J. Freyss, M. v. Korff and C. Rufener, "DataWarrior: An Open-Source Program For Chemistry Aware Data Visualization And Analysis," J. Chem. Inf. Model, vol. 55, no. 2, pp. 460-473, 2015.
[24] G. Keserü and G. Makara , "The influence of lead discovery strategies on the properties of drug candidates," Nat Rev Drug Discov, vol. 8, pp. 203-212, 2009.
[25] "way2drug," [Online]. Available: http://www.way2drug.com/passonline/definition.php.
[26] M. R. Lipinski, I. Hampton, W. H. H. Sauer and C. J. Augustyn, "Daily net emigration from a spawning concentration of chokka squid (Loligo vulgaris reynaudiid'Orbigny, 1845) in Kromme Bay, South Africa," ICES Journal of Marine Science, vol. 55, no. 2, pp. 258-270, April 1998.

