Available online www.ejaet.com

European Journal of Advances in Engineering and Technology, 2017, 4(12):955-958

Research Article ISSN: 2394 - 658X

In Silico Pharmacokinetic and Toxicity Studies of Some Reported Antitubercular Drugs

Mukesh Kumar Meena*

Department of Pharmaceutical Sciences, Mohanlal Sukhadia University, Udaipur (Raj.) 313001
**Correspondence to author: Mr. Mukesh Kumar Meena, Assistant Professor, Department of Pharmaceutical Sciences, Mohanlal Sukhadia University, Udaipur (Raj.) 313001*
Email: mukesh_meena27@rediffmail.com

ABSTRACT

The main objectives of tuberculosis therapy are to cure the patients and to minimize the possibility of transmission of the bacillus to healthy subjects. Adverse effects of anti-tubercular drugs or drug interactions (among anti-tuberculosis drugs or between anti-tubercular drugs and other drugs) can make it necessary to modify or discontinue treatment. This study aims in silico screening of the drugs available for adjunctive therapy of tuberculosis disease. The pharmacokinetic parameters, potential adverse effects, toxicity studies, and biological activity of the drugs were analyzed and summarized. The drugs chosen as adjunctive therapy in the treatment of tuberculosis disease have reported high chances of adverse drug events and require precautions before administration.

Keywords: Antitubercular drugs, toxicity profile, bioactivity score, drug likeness, drug score

INTRODUCTION

Tuberculosis (TB) is the leading cause of mortality worldwide, infecting about 9.2 million people and kills approximately 2.0 million people annually [1]. The organisms responsible for the disease are the tubercle bacilli, *Mycobacterium tuberculosis*, *Mycobacterium tuberculosis* complex including *Mycobacterium bovis* and *Mycobacterium africanum* [2]. Due to discovery of effective antimycobacterial agents, ethambutol, isoniazid, pyrazinamide, rifampicin and streptomycin, and reduction in poverty, there was drastic decrease in the number of TB cases, especially in developed countries. However, since 1980s, the number of TB cases throughout the world has been increasing rapidly due to the emergence of multi-drug resistant Mycobacterium tuberculosis (MDR-TB) [3]. The MDR forms of the disease are more often fatal and are difficult and expensive to treat [4]. The current WHO and CDC recommended treatment of active pulmonary TB patients infected with drug-susceptible *Mycobacterium tuberculosis* requires four drugs to be delivered concurrently for at least 6 months in a staged therapeutic regimen: isoniazid, rifampicin, ethambutol and pyrazinamide are given daily for 2 months (intensive phase), and isoniazid and rifampicin are continued, usually daily, for an additional 4–7 months (continuation phase). Failure to provide adequate drugs to patients, or failure of patients to complete the long-term therapy with all four drugs, results in the emergence of drug-resistant *M. tuberculosis [5]*. Adverse reactions to antituberculosis drugs are related to various factors, and the principal determinants of such reactions are the dose and time of day at which the medication is administered, as well as patient age and nutritional status, together with the presence of preexisting diseases or dysfunctions, such as alcoholism, impaired liver function, impaired kidney function, and HIV coinfection [6]. In this research work, we performed computational investigation of different pharmacokinetic, bioactivity and toxicity parameters for the design of new agents to overcome the existing side-effects of current antitubercular drugs for better potency.

MATERIALS AND METHODS

Pharmacokinetic parameters calculations

There are various physicochemical descriptors and pharmacokinetic properties of the antitubercular drugs were evaluated by using the tool Molinspiration Cheminformatics server (http://www.molinspiration.com). Molinspiration Cheminformatics offers broad range of tools supporting molecule manipulation and processing, including

SMILES and SDfile conversion, normalization of molecules, generation of tautomers, molecule fragmentation, calculation of various molecular properties needed in QSAR, molecular modelling and drug design, high quality molecule depiction, molecular database tools supporting substructure and similarity searches. This software also supports fragment-based virtual screening, bioactivity prediction and data visualization. Molinspiration tools are written in Java, therefore can be used practically on any computer platform [7-8]. Drug-likeness is qualitative concept used for drug like property that described as a complex balance of various molecular properties and structural features which determine whether particular molecule is similar to the known drugs. These properties are mainly hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size and flexibility and of course presence of various pharmacophoric features that influence the behaviour of molecule in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability and many others. The Lipinski rule of five deals four simple physicochemical parameters ranges (MWT ≤ 500, log P ≤ 5, Hbond donor's ≤ 5, H-bond acceptors ≤ 10) associated with 90% of orally active drugs that have passed phase II clinical status [9]. There are several scoring methods such as ligand efficiency and lipophilic efficiency can be used to express drug likeness as measure of potency. These physicochemical descriptors are associated with aqueous solubility and intestinal permeability within acceptable range.

***In silico* toxicity evaluation**

The toxicity of the some selected antitubercular agents was evaluated by computational method using OSIRIS® Property Explorer program. This program is made accessible via cheminformatics.ch and chemistry. The tool enables one to analyse the mutagenicity, tumorigenicity, reproductive effects and irritant effects of a particular drug. The effects are indicated in green, yellow and red colours that represent drug confirm behaviour, medium risk and high risk for mutagenicity or low absorption in intestine respectively. The method is highly useful in eliminating harmful drugs in advance during the discovery of drugs and in their development. The tool also provides access to the drug score, T. P. S. A and drug likeness.

a. T. P. S. A- The penetration across blood- brain barrier and the absorption of drugs in intestine are properties associated with bioavailability of the drugs. The properties are correlated with T. P. S. A and is calculated as the sum of the fragment contribution mainly, O- and N- fragments.

b. Drug likeness- The drug likeness was also generated using OSIRIS program. Positive value as a result for drug likeness indicates that the compounds involved in the study are the fragments that are found in formulations that are commercially available.

iii. Overall drug score- A drug is considered favorable if the score is >0.5 and if the drug has minimal toxicity.

RESULTS AND DISCUSSIONS

Pharmacokinetic parameters calculations

There were some antitubercular drugs were selected and analyzed to ADME properties and drug-likeness (Lipinski's rule of five) which are given in Table 1. All antitubercular drugs have molecular weight in the range (MWT ≤ 500) except streptomycin and rifampicin. Low molecular weight containing molecules are easily absorbed, diffused and transported as compared to high molecular weight compounds. As molecular weight increases except certain limit, the bulkiness of the molecules are also increases comparably [10].

The MLogP value is used to calculate the lipophilic efficiency that measures the potency of drug. Therefore Octanol-water partition coefficient logP value is essential in rational drug design and QSAR studies. In the pharmacokinetic study, hydrophobicity of the molecule is assessed by evaluating logP value because hydrophobicity plays a vital role in the distribution of the drug in the body after absorption [11]. TPSA (Topological Polar Surface Area) is a very useful physiochemical parameter of molecule that gives the information about polarity of compounds. This parameter was evaluated for analyzing drug transport properties. Polar surface area is the sum of all polar atoms mainly oxygen and nitrogen including attached hydrogen [12]. Molecular volume assesses the transport properties of the molecule such as blood-brain barrier penetration. The number of rotatable bond was calculated and have found relevant. A molecule which have more number of rotatable bond become more flexible and have good binding affinity with binding pocket.

Table -1 Pharmacokinetic profiles of selected antitubercular drugs

Name	Molecular weight	LogP	TPSA	nON	nOHNH	Volume
Isoniazid	137.14	-0.97	68.01	4	3	122.56
Rifampicin	822.95	2.62	220.16	16	6	755.91
Ethambutol	204.31	0.35	64.51	4	4	221.06
Pyrazinamide	123.11	-0.71	68.88	4	2	106.00
Streptomycin	581.58	-5.35	336.45	19	16	497.25
Ethionamide	166.25	1.46	38.91	2	2	152.40

Table -2 Bioactivity profiles of selected antitubercular drugs

Name	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Isoniazid	-1.39	-1.45	-1.05	-2.33	-1.23	-0.66
Rifampicin	-2.10	-3.27	-3.04	-2.89	-1.61	-2.42
Ethambutol	-0.30	-0.16	-0.44	-0.68	-0.23	-0.08
Pyrazinamide	-1.97	-1.45	-1.71	-2.87	-1.84	-1.43
Streptomycin	0.09	-0.16	-0.17	-0.18	0.65	0.38
Ethionamide	-0.97	-1.11	-1.63	-1.55	-1.68	-0.53

Bioactivity of all selected antitubercular drugs was evaluated against six different protein structures. Biological activity is predicted by bioactivity score that are categorized under three different ranges

1. If bioactivity score is more than 0.00, having considerable biological activity.
2. If bioactivity score is 0.5 to 0.00, having moderately activity.
3. If bioactivity score is less than -0.50, having inactivity [13].

The result of this investigation was found that the selected antitubercular drugs are biologically active and have physiological effect. The bioactivity score profile of the all selected agents is given in Table 2.

***In silico* toxicity evaluation**

The OSIRIS property explorer was used to determine the physicochemical properties of the selected drug compounds. Rifampicin and streptomycin show higher TPSA values. The absorption, transport and penetration are based on the TPSA value of the drugs. All of the drugs except ethionamide indicate mutagenicity, irritancy, tumorigenicity or reproductive effect considering the results obtained from OSIRIS property explorer. The drug likeness value is comparatively lower than the other compounds. A positive value indicates that the other four drugs contain fragments that are mostly present in the commercial drugs available in the market. The drug score is the summation of the cLogP, logs, molecular weight and toxicity risks. The purpose of drug score is to evaluate the potential of a chemical compound to meet the criteria of a possible drug candidate. The results obtained from OSIRIS are listed in Table 3.

Table -3 Toxicity profiles of selected antitubercular drugs

Name	Mutagenic	Tumorigenic	Irritant	Reproductive effect	Druglikeness	Drug score
Isoniazid	Red	Red	Red	Red	-5.06	0.06
Rifampicin	Red	Red	Green	Green	10.5	0.09
Ethambutol	Green	Green	Red	Green	2.38	0.56
Pyrazinamide	Red	Red	Green	Red	-0.68	0.14
Streptomycin	Green	Green	Red	Green	0.83	0.32
Ethionamide	Green	Green	Green	Green	-2.28	0.53

CONCLUSION

These research findings provide the lead for the design and development of new antitubercular agents. Currently, all existing antitubercular agents having serious toxicity profile. In an attempt to study the properties and the toxic effects of the drugs used in adjunct therapy, *in silico* screening was carried out in order to predict the interactions of the drugs. Therefore, it is essential that the development of new antitubercular agents molecules with lesser side effects and toxicity. Computational study of all selected antitubercular agents gives the information about the pharmacokinetics of the existing drugs that provide the lead for development of functional drug with more effectiveness and lesser toxicity.

REFERENCES

[1]. World Health Organization. (**2008**). Global tuberculosis control: surveillance, planning, financing: WHO report 2008 (Vol. 393). World Health Organization.

[2]. Selassie, C. D., & Abraham, D. J. (**2003**). Burger's medicinal chemistry and drug discovery. In Drug Discovery (Vol. 1). DJ Abraham, Hoboken, John Wiley & Sons New York.

[3]. Chan, E. D., & Iseman, M. D. (**2002**). Current medical treatment for tuberculosis. Bmj, 325(7375), 1282.

[4]. Bastian, I., & Colebunders, R. (**1999**). Treatment and prevention of multidrug-resistant tuberculosis. Drugs, 58(4), 633-661.

[5]. Tripathi, R. P., Tewari, N., Dwivedi, N., & Tiwari, V. K. (**2005**). Fighting tuberculosis: an old disease with new challenges. Medicinal Research Reviews, 25(1), 93-131.

[6]. Arbex, M. A., Varella, M. D. C. L., Siqueira, H. R. D., & Mello, F. A. F. D. (**2010**). Antituberculosis drugs: drug interactions, adverse effects, and use in special situations-part 1: first-line drugs. Jornal Brasileiro de Pneumologia, 36, 626-640.
[7]. Lipinski CA. Lead-and drug-like compounds: the rule-of-five revolution. Drug Discovery Today: Technologies. **2004**; 1(4):337-341.
[8]. Srimai V, Ramesh M, Parameshwar KS, Parthasarathy T. Computer-aided design of selective Cytochrome P450 inhibitors and docking studies of alkyl resorcinol derivatives. Medicinal Chemistry Research. **2013**; 22(11):5314-5323.
[9]. Palm K, Stenberg P, Luthman, K, Artursson P. Polar molecular surface properties predict the intestinal absorption of drugs in humans. Pharmaceutical research. **1997**; 14(5):568-571.
[10]. Sharma CS, Verma T, Singh HP, Kumar N. Synthesis, characterization and preliminary anticonvulsant evaluation of some flavanone incorporated semicarbazides. Medicinal Chemistry Research **2014**; 23(11):4814-4824.
[11]. Verma A. Lead finding from Phyllanthus debelis with hepatoprotective potentials. Asian Pacific Journal of Tropical Biomedicine. **2012**; 2(3): S1735-S1737.
[12]. Yamashita, F., & Hashida, M. (**2004**). In silico approaches for predicting ADME properties of drugs. Drug metabolism and pharmacokinetics, 19(5), 327-338.
[13]. Khan, T., Dixit, S., Ahmad, R., Raza, S., Azad, I., Joshi, S., & Khan, A. R. (**2017**). Molecular docking, PASS analysis, bioactivity score prediction, synthesis, characterization and biological activity evaluation of a functionalized 2-butanone thiosemicarbazone ligand and its complexes. Journal of chemical biology, 10(3), 91-104.