In silico ADME, Bioactivity and Toxicity Parameters Calculation of Some Selected Anti-Tubercular Drugs

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ABSTRACT

Tuberculosis, one of the most frequent infectious diseases, is caused by a mycobacterium tuberculosis bacteria and it infects several hundred million people each year, results in several million deaths annually. Because there is development of antibiotic resistance, the disease becomes incurable. So, in the absence of effective and potent drug with minimal resistance problems, the mortality rate increases annually. In this computational investigation, we performed *In-silico* ADME, bioactivity and toxicity parameters calculation of some selected anti-tuberculosis agents. To design a new molecule having good pharmacological profile, this study will provide the lead information.

Key Words: Tuberculosis (TB), Bacillus Calmette-Guerin vaccine, TPSA, *In Silico* toxicity

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INTRODUCTION

Tuberculosis (TB) remains the most frequent infectious diseases with high mortality rate, globally. The world health organization estimates that about 8 to 10 million new tuberculosis cases occur annually worldwide that increase the incidence of tuberculosis [1]. Among tuberculosis cases, pulmonary tuberculosis is found to be most common form of tuberculosis with highly contagious and life threatening infection. There are various preventive factors such as early detection, vaccination with Bacillus Calmette-Guerin vaccine. Development of antibiotic-resistance is the most common problem associated with tuberculosis diseases. So, there is essential requirement to develop new and potent anti-tuberculosis agents with lesser resistance problems. This research investigation involves the computational study of pharmacokinetic parameters, bioactivity score and toxicity parameters calculation of few selected anti-tuberculosis agents.

MATERIALS AND METHODS

In silico Pharmacokinetic study

There are several pharmacokinetic parameters and physicochemical descriptors were evaluated for antitubercular drugs through application of the tool Molinspiration Cheminformatics server (http://www.molinspiration.com).

The server Molinspiration Cheminformatics provides various 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 modeling and drug design, high quality molecule depiction, molecular database tools supporting substructure and similarity searches. This software also offers fragment-based virtual screening, bioactivity prediction and data visualization. Molinspiration tools are written in Java, therefore can be used practically on any computer platform [2].

Drug-likeness is described as a complex balance of various molecular properties and structural features which determine whether particular molecule is similar to the known drugs.

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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 parameter ranges (MWT ≤ 500, log P ≤ 5, H-bond donor's ≤ 5, Hbond acceptors ≤ 10) associated with 90% of orally active drugs that have passed phase II clinical status. [3] These physicochemical features are associated with acceptable aqueous solubility and intestinal permeability.

In silico Bioactivity study

The bioactivity score of selected agents were also evaluated using the tool Molinspiration Cheminformatics server (http://www.molinspiration.com). In this computational chemistry technique large chemical databases are analyzed in order to identify possible new drug candidates.

In the Molinspiration tool, the miscreen engine first analyze a training set of active structures (in extreme case even single active molecule is sufficient to built a usable model) and compares it with inactive molecules by using sophisticated Bayesian statistics. Only SMILES or SDfile structures of active molecules are sufficient for the training, no information about the active site or binding mode is necessary. This is particularly useful in projects where structure-based approach cannot be applied because information about 3D receptor structure is not available, for example in screens aiming to find ligands modulating G-protein coupled receptors.

In silico Toxicity study

The toxicity study of selected anti-tubercular drugs were evaluated by *In silico* model using Pallas version 3.1 ADMETox prediction software pentium IV processor. This software tool was started by double click on the icon. The molecule to be predicted was drawn by double click on new option, and then molecule was subjected for evaluation of toxicity by selecting ToxAlert options. Various types of toxicities including oncogenicity, neurotoxicity, teratogenicity, immunotoxicity, etc. were generated and toxicity profile of molecule noted.

RESULT AND DISCUSSION

There were some anti-tuberculosis agents selected and analyzed to pharmacokinetic properties and drug likeness (Lipinski's rule of five) which are given in Table 1. All selected agents have molecular weight in the acceptable range (MWT ≤ 500). 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 [4].

Among selected anti-tuberculosis agents, all are found to be within acceptable range. The MLogP (octanol / water partition co efficient) of all agents were calculated and found to be within acceptable range according to Lipinski's rule. 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 [5]. 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 [6]. Percent absorption were also evaluated for all selected antiepileptic agents by %ABS = 109- (0.345 * TPSA) [7]. 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.

Bioactivity of all selected antimalarial agents was evaluated against six different protein structures. Biological activity is measured 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 [8].

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

Table1. Pharmacokinetic Parameters of Anti-tuberculosis agents

Name	Molecular formula	Molecular weight	LogP	TPSA	nON	nOHNH	nrotb	volume	*In silico* % absorption
Isoniazid	$C_6H_7N_3O$	137.14	-0.97	68.01	4	3	1	122.56	85.53
Pyrazinamide	$C_5H_5N_3O$	123.11	-0.71	68.88	4	2	1	106.00	85.23
Ethambutol	$C_{10}H_{24}N_2O_2$	204.31	0.35	64.51	4	4	9	221.06	86.74
Para amino salicylic acid	$C_7H_7NO_3$	153.14	0.92	83.55	4	4	1	130.35	80.17
Ethionamide	$C_8H_{10}N_2S$	166.25	1.46	38.91	2	2	2	152.40	95.57
Ciprofloxacin	$C_{17}H_{18}FN_3O_3$	331.35	-0.70	74.57	6	2	3	285.46	83.27

Table 2. Bioactivity of Adrenergic agents

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
Pyrazinamide	-1.97	-1.45	-1.71	-2.87	-1.84	-1.43
Ethambutol	-0.30	-0.16	-0.44	-0.68	-0.23	-0.08
Para amino salicylic acid	-0.79	-0.23	-0.79	-0.87	-0.86	-0.16
Ethionamide	-0.97	-1.11	-1.63	-1.55	-1.68	-0.53
Ciprofloxacin	0.12	-0.04	-0.07	-0.19	-0.21	0.28

Table 3. Toxicity Profile of Adrenergic agents

Name	Toxicity	Overall toxicity	Oncogenicity	Mutagenicity	Teratogenicity	Irritation	Sensitivity	Immunotoxicity	Neurotoxicity
Isoniazid	Highly Probable	76	76	67	29	47	0	0	0
Pyrazinamide	Highly Probable	76	76	0	17	0	0	0	0
Ethambutol	Not Probable	19	0	0	19	0	0	0	0
Para amino salicylic acid	Highly Probable	76	76	51	19	53	29	0	29
Ethionamide	Not Probable	0	0	0	0	0	0	0	0
Ciprofloxacin	Highly Probable	76	76	0	34	0	0	0	0

The bioactivity score provide the information about the binding cascade of the drugs that is used for the development of a new functional drug with increased binding selectivity profile and less undesirable effects.

All selected anti-tuberculosis agents were evaluated to toxicity profile and given in Table 3. All of the drugs were found to be highly probable to toxicity except ethambutol and ethionamide.

These research findings provide the lead for the design and development of new potent anti-tuberculosis drugs. Computational study of all selected anti-tuberculosis drugs 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.

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