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In silico prediction of Pharmacokinetic, Bioactivity and Toxicity Parameters of Some Selected benzimidazoles as Anthelminthic Agents

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Abstract Anthelmintics are drugs that are used to treat infections with parasitic worms. This includes both flat worms, e.g., flukes and tapeworms and round worms, i.e., nematodes. Anthelmintic resistance in parasites is now widespread. It is a major threat to the sustainability of modern ruminant livestock production, resulting in reduced productivity, compromised animal health and welfare, and increased greenhouse gas emissions through increased parasitism and farm inputs. Treatment with an antihelminthic drug kills worms whose phenotype renders them susceptible to the drug, but resistant parasites survive and pass on their "resistance" genes. Resistant varieties accumulate, and treatment failure finally occurs. This research investigation finds the various pharmacokinetic, bioactivity and toxicity parameters for some selected Anthelminthic Agents for designing new agents.

Keywords QSAR, ADMETox, Teratogenicity, MLogP, Anthelminthic Agents

Introduction

The poorest and most neglected communities are mostly affected by helminth infections, which are transmitted through soil, and these infections are one of the most prevalent illnesses worldwide. They spread through eggs of helminths found in human feces, which pollute the soil in places where sanitation is poor. The three main types of worms that infect people are hookworms (Necator americanus and Ancylostoma duodenale), whipworms (Trichuris trichiura), and roundworms (Ascaris lumbricoides). Due to their shared diagnostic requirements and therapeutic responses, these STH species are typically addressed collectively as a group [1].

Anthelmintics that are routinely and widely used include benzimidazoles. All benzimidazoles are believed to function in a similar manner, and variations in the medications' effectiveness against particular parasite species are most likely caused by variations in their bioavailability in the host animal. Various factors, including sex, age, environmental conditions, and others, alter an anthelmintic's pharmacokinetic behavior [2]

These medications are known to hinder the transport and uptake of glucose, which ultimately results in cell death, in parasites and mammalian cells' microtubule networks. Albendazole was initially made available in 1975, and in 1982, it was given the go-ahead for usage in humans. Mebendazole was used on humans for the first time in 1971. In the human gut, oral albendazole and mebendazole are absorbed at a rate of 1–5%. A metabolite of albendazole, which is thought to be the primary metabolite responsible for anthelmintic activity, is albendazole sulfoxide.

Although these medications are often safe and have few side effects, extended use may occasionally result in liver damage, allergic responses, and other negative effects [3].

Materials and Methods

Pharmacokinetic Descriptor Calculation through Computational Approaches

There are various physicochemical descriptors and pharmacokinetic relevant properties of the anthelminthic agents, some of which 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 [4-5].

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 $\leq$ 500, log P $\leq$ 5, Hbond donor's $\leq$ 5, H-bond acceptors $\leq$ 10) associated with 90% of orally active drugs that have passed phase II clinical status [6]. 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 anthelminthic agents was evaluated by computational method 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

Some anthelminthic agents were selected and analyzed to ADME properties and drug-likeness (Lipinski's rule of five) which are given in Table 1. All anthelminthic agents have molecular weight in the range (MWT $\leq$ 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 [7].

Table 1: Pharmacokinetic Properties of Anthelmintic agents

Name	Molecular formula	Molecular weight	LogP	TPSA	nON	nOHNH	nrotb	volume	*In silico* % absorption
Albendazole	$C_{12}H_{15}N_3O_2S$	265.34	2.75	67.02	5	2	5	234.09	85.88
Mebendazole	$C_{16}H_{13}N_3O_3$	295.3	2.89	84.09	6	2	4	256.19	79.99
Thiabendazole	$C_{10}H_7N_3S$	201.25	2.35	41.58	3	1	1	166.83	94.65
Fenbendazole	$C_{15}H_{13}N_3O_2S$	299.36	3.40	67.02	5	2	4	255.33	85.88
Triclabendazole	$C_{14}H_9Cl_3N_2OS$	359.67	5.94	37.92	3	1	3	264.56	95.92
Flubendazole	$C_{16}H_{12}FN_3O_3$	313.29	3.05	84.09	6	2	4	261.12	79.99

All selected anthelminthic agents have number of H-bond acceptors and number of Hbond donors is within range according to Lipinski's rule of five, so selected anthelminthic agents have no violations. The MLogP (octanol / water partition co efficient) of all agents were calculated and were found to be within 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 [8-16]. 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 [17]. Percent absorption were also evaluated for all selected anthelminthic agents by %ABS = 109- (0.345 * TPSA) [18]. 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 has more number of rotatable bond become more flexible and have good binding affinity with binding pocket.

Bioactivity of all selected anthelminthic agents 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 [19-20].

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

Table 2: Bioactivity of Anthelmintic agents

Name	GPCR Ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Albendazole	-0.11	-0.10	-0.04	-0.62	-0.18	-0.02
Mebendazole	0.20	0.18	0.51	-0.15	0.02	0.18
Thiabendazole	-0.06	0.28	0.21	0.61	-0.17	0.31
Fenbendazole	0.17	0.00	0.39	-0.33	0.04	0.16
Triclabendazole	-0.14	-0.31	0.01	-0.39	-0.56	-0.05
Flubendazole	0.22	0.15	0.53	-0.10	0.01	0.15

Table 3: Toxicity Profile of Anthelmintic agents

Name	Toxicity	Overall toxicity	Oncogenicity	Mutagenicity	Teratogenicity	Irritation	Sensitivity	Immunotoxicity	Neurotoxicity
Albendazole	Highly Probable	76	76	53	29	0	0	0	57
Mebendazole	Highly Probable	91	77	91	29	0	0	0	57
Thiabendazole	Highly Probable	100	100	53	0	0	0	0	0
Fenbendazole	Highly Probable	76	76	53	29	0	0	0	57
Triclabendazole	Probable	53	53	53	29	0	0	29	0
Flubendazole	Highly Probable	91	77	91	29	0	0	0	57

The bioactivity score provides 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 anthelminthic agents were evaluated to toxicity profile and given in Table 3. All of the drugs were found to be highly probable to toxicity. The interesting fact about toxicity is all selected anthelminthic agents were found to be teratogenic and exhibits teratogenicity.

Conclusion

These research findings provide the lead for the design and development of new anthelminthic agents. Currently, all existing anthelminthic agents having serious toxicity profile. Therefore, it is essential that the development of new anthelminthic agents molecules with lesser side effects and toxicity.
Computational study of all selected anthelminthic 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.

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