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Identification of potential inhibitor and enzyme-inhibitor complex on trypanothione reductase to control Chagas disease

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ABSTRACT

Chagas is a parasitic disease with major threat to public health due to its resistance against commonly available drugs. Trypanothione reductase (TryR) is the key enzyme to develop this disease. Though this enzyme is well thought-out as potential drug target, the accurate structure of enzyme-inhibitor complex is required to design a potential inhibitor which is less available for TryR. In this research, we aimed to investigate the advanced drug over the available existing drugs by designing inhibitors as well as to identify a new enzyme-inhibitor complex that may act as a template for drug design. A set of analogues were designed from a known inhibitor Quinacrine Mustard (QUM) to identify the effective inhibitor against this enzyme. Further, the pharmacoinformatics elucidation and structural properties of designed inhibitor proposed effective drug candidates against Chagas disease. Molecular docking study suggests that a designed inhibitor has higher binding affinity in both crystal and modeled TryR and also poses similar interacting residues as of crystal TryR-QUM complex structure. The comparative studies based on *in silico* prediction proposed an enzyme-inhibitor complex which could be effective to control the disease activity. So our *in silico* analysis based on TryR built model, Pharmacophore and docking analysis might play an important role for the development of novel therapy for Chagas disease. But both animal model experiments and clinical trials must be done to confirm the efficacy of the therapy.

1. Introduction

Trypanosomiasis is a parasitic disease that affects both humans and animals (Abimbola et al., 2013). It is called American Trypanosomiasis or Chagas disease when it develops in humans. Chagas disease is endemic in Latin America but it is much less explored. *Trypanosoma cruzi,* a protozoan parasite, is liable for Chagas disease. It is found all over the American continent in a range of wild mammalian reservoirs and spread out by the triatomine bug insect vector. Besides such transmission, humans can also be infected by *T. cruzi* through food ingestion, contaminated drinks with live parasites, contaminated blood transfusion, familial transmission during pregnancy and organ transplantation (Moraes et al., 2014). It is estimated that 10 million people of the world are infected with *T. cruzi*, mostly in the Latin America (World Health Organization, 2010) and about 100 million people are at high risk of the disease in the Americas, with a total estimated incidence of 800,000 new cases per year (Moncayo and Ortiz Yanine, 2006). In more recent years, huge migration of Latin Americans introduced a large number of infected persons to non-endemic areas like North America, Europe, Australia and Japan (Gascon et al., 2010; Bern and Montgomery, 2009). Chagas disease has passed around hundred years since its discovery but there are still no suitable therapies that might lead to reliable cure in the chronic phase of the disease. The importance of producing novel inhibitors against this disease is reinforced due to high death rate

Abbreviations: TryR, trypanothione reductase; *T. cruzi*, *Trypanosoma cruzi*; QUM, quinacrine mustard; ADMET, absorption, distribution, metabolism distribution and toxicity; BBB, blood brain barrier transport; LogBB, Blood Brain Distribution; LogPS, blood brain barrier permeability; DBP, Drug binding to plasma protein; Vd, volume of distribution; Pgp, P-glycoprotein; QSAR, quantititive structure–activity relationship; LogS, solubility; TPSA, the polar surface area; cLogP, logarithm of partition coefficient; Mw, molecular weight.

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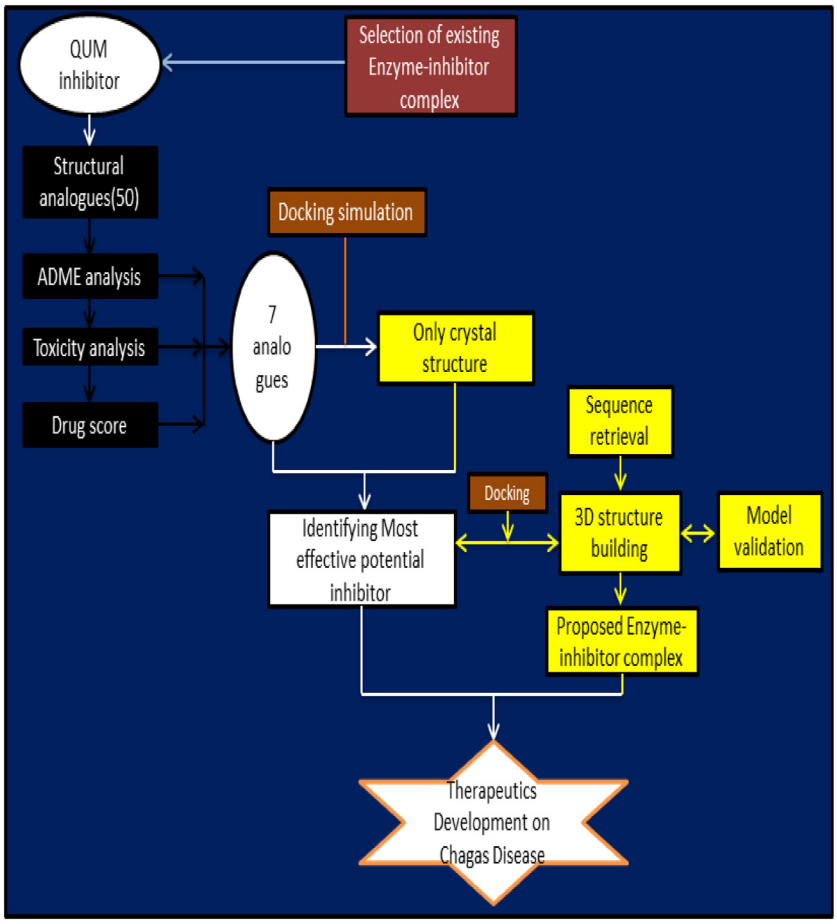

Fig. 1. Schematic representation of whole work.

and the development of drug resistance against existing drugs like nifurtimox and benznidazole. (Coura, 2007; Hamilton, 2002; Wilkinson et al., 2008).

Parasites contain different essential metabolic pathways which are not present in humans. Development of new drugs might target such essential metabolic pathways in the parasite by identifying novel inhibitors. Thiol metabolism could be a promising target of these prototozoa to design such inhibitors. A low molecular mass dithiol named Trypanothione ($T[SH]_2$ or N1,N8-bis-(glutathionyl)-spermidine) is responsible for the thiol metabolism and it plays crucial role to maintain the intracellular redox balance in kinetoplastids (Fairlamb et al., 1985). This dithiol molecule is the key machinery to counteract environmental stress in parasites, by taking part in different types of enzymatic and non-enzymatic reactions—commonly known as the protective reactions. There is also evidence showing that it has the capability to confer the resistance to the chemotherapeutic agents (Schmidt and Krauth-Siegel, 2002; Ouellette and Papadopoulou, 1993). The protective reactions are involved in oxidizing $T[SH]_2$ to trypanothione disulphide ($T[S]_2$), which is then recycled back to $T[SH]_2$ by TryR. Hence, TryR acts as the checkpoint on the sole path for the transfer of reducing equivalents from the $NADP^+$/NADPH couple to thiol-containing species (Fairlamb and Cerami, 1992). So, it is quite logical to think that, to inhibit the TryR activity would be a suitable target for the development of anti-trypanosomal drugs.

The current study demonstrates pharmacophore-based information to identify novel inhibitor and drug template against Chagas disease. Structural analogues were designed from QUM, a potent inhibitor of TryR, for the identification of the most potent novel inhibitor against Chagas disease. The analogues showing no toxic profile as well as having good ADMET (Absorption, Distribution, Metabolism and Excretion) properties were selected for this study. Furthermore, only one designed analogue was selected as the most potent inhibitor on TryR based on binding energy in the same position of QUM on TryR and ADMET properties. Moreover, an enzyme-inhibitor complex was also anticipated for better therapeutics against Chagas disease .

2. Materials and methods

2.1. Potential inhibitor identification

2.1.1. Crystal structure preparation

The crystal structure of Trypanothione Reductase, PDB ID: 1GXF was retrieved from RCSB Protein Data Bank (Hillisch et al., 2004). The ligands from PDB files were removed using Discovery Studio 4.0 client (http://accelrys.com/products/discovery-studio/). Only chain A of 1GXF was saved as PDB file format for further analysis.

2.1.2. Drug identification and preparation

To identify the effective drug against Chagas disease, fifty structural analogues from QUM were designed using ACD Chemsketch (Fan et al., 2002),http://www.click2drug.org/, http://www.zinc.docking.org/. Two dimensional structures of designed molecules were retrieved as SD file format. Before initiating the docking studies, the SD files of designed analogues