Biomedicine & Pharmacotherapy 83 (2016) 141–152

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EM|consulte
www.em-consulte.com/en

Original article

High-throughput virtual screening and quantum mechanics approach to develop imipramine analogues as leads against trypanothione reductase of leishmania

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ARTICLE INFO

Article history:
Received 28 March 2016
Received in revised form 3 June 2016
Accepted 6 June 2016

Keywords:
Imipramine
Molecular dynamics
Trypanothione reductase
Visceral leishmaniasis
ADMET

ABSTRACT

Visceral leishmaniasis (VL) has been considered as one of the most fatal form of leishmaniasis which affects 70 countries worldwide. Increased drug resistance in Indian subcontinent urged the need of new antileishmanial compounds with high efficacy and negligible toxicity. Imipramine compounds have shown impressive antileishmanial activity. To find out most potent analogue from imipramine series and explore the inhibitory activity of imipramine, we docked imipramine analogues (n = 93,328) against trypanothione reductase in three sequential modes. Furthermore, 98 ligands having better docking score than reference ligand were subjected to ADME and toxicity, binding energy calculation and docking validation. Finally, Molecular dynamic and single point energy was estimated for best two ligands. This study uncovers the inhibitory activity of imipramine against Leishmania parasites.

1. Introduction

Leishmaniasis is a group of most neglected infectious diseases, caused by leishmania parasite and spread by the bite of infected female sandflies of genus *Phlebotomine*. The statistics of global infectious disease reveal the presence of leishmaniasis in 98 countries and targeting poorest to poor people worldwide [1]. However, the effort of the World Health Organization evidenced the risk of leishmaniasis among 350 million people and the occurrence of 2 million new cases yearly worldwide [2]. Among the four variants of leishmaniasis, the most lethal visceral form affects 58,200 individuals while its self-healing cutaneous form affects 220,000 individuals annually worldwide. The majority of visceral leishmaniasis (VL) cases is found in India, Bangladesh, Nepal, Brazil, Sudan and Ethiopia. In the Indian subcontinent, some district of Bihar state has challenged worst endemic since 1970s [3]. *Leishmania donovani* is the major species to cause visceral leishmaniasis (VL) in the Indian subcontinent while *Leishmania infantum* grant for the same in the new world [4]. However, the life cycle of *L. donovani* is digenetic; the extracellular flagellated promastigotes form is present in sandflies while intracellular aflagellated amastigotes form is present in mononuclear phagocytes of mammalian host.

In current scenario, due to the absence of an effective vaccine against VL; its treatment solely depends on chemotherapeutic. However, more than 60 years have evidenced the use of antimonial compounds as the first line treatment to cure visceral form of leishmaniasis. The commonly used antimonial drugs were sodium antimony gluconate and meglumine antimoniate [5]. But, the increasing clinical resistance by antimonials made it unsuitable for its further use [6,7]. The second-line drugs used as a treatment option against VL were pentamidine and amphotericin B. But their cost and side effects were the major hurdle of their use. The newly introduced antileishmanial drug miltefosine; was formerly developed as an anticancer agent, but now it has been used as first oral drug against VL. But its increasing resistance and 7–10% patient relapse at 6 months [8] and 20% relapse rate at about 12 months in clinical trial [9], demanding the search for a new drug molecule with good efficacy and negligible toxicity.

Imipramine is a tricyclic antidepressant drug used to treat depression. However, it is also used to prevent bedwetting in children [10]. The combination therapy of imipramine can protect

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http://dx.doi.org/10.1016/j.biopha.2016.06.010
0753-3322/

against the harmful effect of corticosterone on depression like behavior, granule neuron maturation and hippocampal reelin expression [11]. Imipramine nucleus containing tricyclic compounds had also shown an inhibitory effect towards trypanothione reductase of *Trypanosoma cruzi* [12]. Imipramine compound has shown good antileishmanial activity against *Leishmania donovani* parasites in the experiment conducted *in vitro* and *in vivo* [13,14]. But the imipramine group of compounds was never evaluated against *L. donovani* trypanothione reductase. Therefore, the current study represents the chemoinformatics evidences for the imipramine group of compounds to kill *L. donovani* protozoan parasites.

Trypanothione reductase (TR) is a crucial drug target enzyme playing central role in thiol metabolism of *L. donovani*. It is an NADPH dependent flavoprotein oxidoreductase, maintains the intracellular redox balance of the parasite and its inhibition leads to parasite clearance [15–17]. Trypanothione reductase is a functional homodimer, analogous to human glutathione reductase but these two enzymes are mutually substrate specific [16]. There is a presence of two natural ligand viz. Flavin adenine Di nucleotide (FAD) and sulfate ion (SO_4^{-2}) in the catalytic center of TR. As it is a homodimer, consist of two chains viz. chain-A and chain-B; and the amino acid residues of these chains participating in hydrogen bond

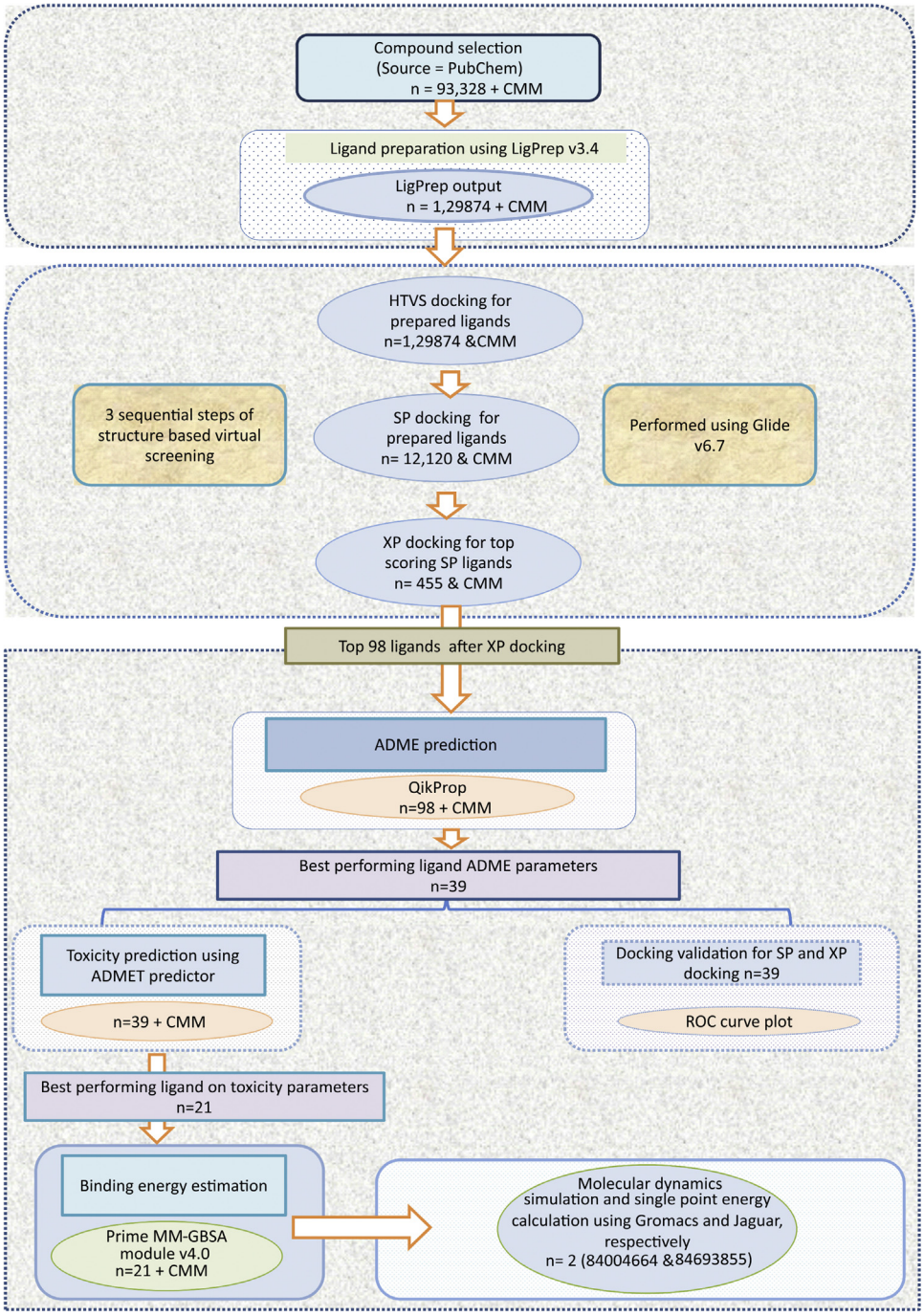

Fig. 1. Ray diagram representing flow of work performed during the screening of imipramine analogues against trypanothione reductase of *Leishmania donovani*.