European Journal of Medicinal Chemistry 135 (2017) 241–259

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Review article

An overview of azoles targeting sterol 14α-demethylase for antileishmanial therapy

Saeed Emami [a, *], Pegah Tavangar [a], Masoud Keighobadi [b]

[a] Department of Medicinal Chemistry and Pharmaceutical Sciences Research Center, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran

[b] Student Research Committee, Pharmaceutical Sciences Research Center, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran

ARTICLE INFO

Article history:
Received 26 January 2017
Received in revised form
11 April 2017
Accepted 18 April 2017
Available online 21 April 2017

Keywords:
Azole antifungals
Antileishmanial agents
Sterol 14α-demethylase
Leishmaniasis
Imidazole
Triazole

ABSTRACT

The azole antifungal drugs are an important class of chemotherapeutic agents with broad-spectrum of activity against yeasts and filamentous fungi, act in the ergosterol biosynthetic pathway through inhibition of the cytochrome P450-dependent enzyme sterol 14α-demethylase. Azole antifungals have also been repurposed for treatment of tropical protozoan infections including human leishmaniasis. Recent advances in molecular biology and computational chemistry areas have increased our knowledge about sterol biochemical pathway in *Leishmania* parasites. Based on the importance of sterol biosynthetic pathway in *Leishmania* parasites, we reviewed all studies reported on azoles for potential antileishmanial therapy along their structural and biological aspects. This review may help medicinal chemists for design of new azole-derived antileishmanial drugs.

Contents

1. Introduction

Leishmaniasis is a complex protozoan parasitic disease which is endemic in many parts of the world, threatening about 350 million people in more than 98 countries [1]. The disease is currently considered as a major public health problem, causing remarkable

* Corresponding author.
E-mail address: sd_emami@yahoo.com (S. Emami).

http://dx.doi.org/10.1016/j.ejmech.2017.04.044
0223-5234/

morbidity and mortality in Asia, Africa, Latin America and Mediterranean regions [2]. Moreover, several factors including the prevalence of AIDS, increased global travel, lack of vaccine, difficulties in controlling vectors, and the development of drug resistance can increase the prevalence of leishmaniasis worldwide [3]. Recent reports indicated that about 1.3 million new cases are reported every year, with an estimated 20,000 to 40,000 deaths every year [4].

Leishmaniasis is generated by infection of *Leishmania* parasites which are transmitted by the bite of phlebotomine sand flies, producing a spectrum of clinical manifestations. *Leishmania* parasites are trypanosomatid digenetic microorganisms which infect humans and other mammals [5]. Basically, *Leishmania* parasites are found in two forms namely amastigote and promastigote [6]. In the sandfly host, the parasites are in the extracellular motile promastigote forms, which are long and flagellate. *Leishmania* parasites multiply in the digestive tract of sandfly, and are transmitted to the mammalian host during blood feeding (Fig. 1). The amastigote form is an intracellular, spherical, and non-flagellated form of *Leishmania*, multiplying within mammalian macrophages [7–9].

It should be noted that about 30 pathogenic species including *L. major, L. tropica, L. mexicana, L. aethiopia, L. braziliensis, L. panamensis, L. donovani, L. infantum* and *L. chagasi* can cause different forms of the disease [10]. Thus, depending on *Leishmania* species, host genetic factors, and geographical distribution, numerous types of leishmaniasis are observed in human [11]. The most typical form is cutaneous leishmaniasis which produces skin sores on the exposed parts of the body. The second type of leishmaniasis is called visceral leishmaniasis, also known as kala-azar that disturbs several organs such as, liver, bone marrow and spleen. This form is the most severe type of the disease and has high mortality rate when not treated [12,13]. The last type which is the less common form is known as mucocutaneous leishmaniasis [14]. This type of leishmaniasis can be originated by infection with type of parasite that causes cutaneous leishmaniasis and the symptoms are sores in the mucous membranes of the nose, mouth and throat [15]. The best way to avoid mucosal leishmaniasis is treatment of the original cutaneous infection that affects skins [16].

Currently, the control and therapy of leishmaniasis remains a serious problem in the field of neglected tropical diseases. There are no vaccines, and chemotherapy with limited drugs is the only option for management of leishmaniasis [17]. The main recommended drugs for the treatment of leishmaniasis include old drugs like pentavalent antimonials [sodium stibogluconate (**1**) and meglumine antimoniate (**2**)] [18], amphotericin B (**3**), paromomycin (**4**), pentamidine (**5**), and new drug miltefosine (**6**, Fig. 2) [19–21]. Also, an 8-aminoquinoline drug sitamaquine (**7**) is under development as orally administrated antileishmanial agent for treatment of visceral leishmaniasis [22]. In general, these drugs have some limitations such as long term of treatment, parenteral administration, toxic side effects, high cost and the emergence of resistant [23]. Therefore, the discovery and development of new antileishmanial agents with high potency, low cost, acceptable toxicity and pharmacokinetics properties is an urgent need [24,25].

Nowadays, the design and development of antileishmanial agents from both synthetic and natural origins have been considered extensively [26]. Furthermore, drug repositioning approach or identifying new indications for clinically useful drugs in the field of antileishmanial chemotherapy is an important strategy [27–29]. Indeed, most of the current antileishmanial drugs including amphotericin B (**3**) [30], paromomycin (**4**) [31] and miltefosine (**6**) [32,33] were repurposed from other indications (antifungal, antiamoebic, and anticancer, respectively). In particular, azole antifungals have also been repurposed for treatment of tropical protozoan infections including human leishmaniasis [26,27]. The azole antifungals are an important class of antifungal agents with broad-spectrum of activity against most yeasts and filamentous fungi and act in the ergosterol biosynthetic pathway through inhibition of the cytochrome P450-dependent enzyme sterol 14α-demethylase [34]. Recent advances in molecular biology and computational

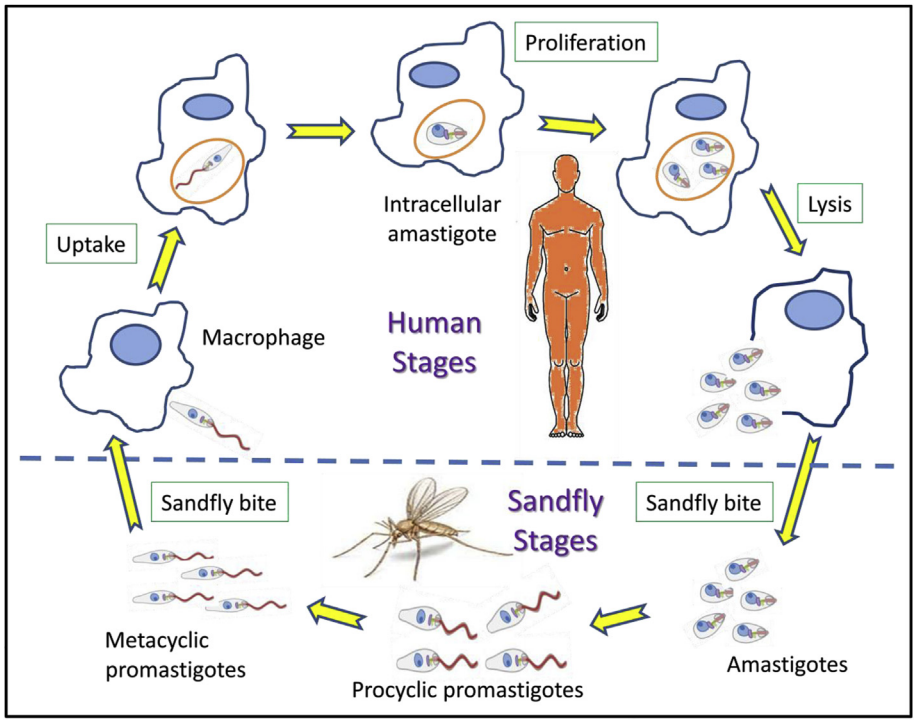

Fig. 1. The life cycle of *Leishmania* spp.