European Journal of Medicinal Chemistry xxx (2014) 1–9

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Mini-review

Manzamine alkaloids as antileishmanial agents: A review

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ARTICLE INFO

Article history:
Received 9 April 2014
Received in revised form
30 June 2014
Accepted 3 July 2014
Available online xxx

Keywords:
Alkaloids
Cytotoxicity
Chemotherapy
Neglected diseases

ABSTRACT

Leishmaniasis is considered as one of the most Neglected Tropical Diseases (NTDs) in the world, caused by protozoan parasites of the genus *Leishmania*. Leishmaniasis control profoundly depends upon chemotherapy which includes pentavalent antimonials, paromomycin, pentamidine, amphotericin B and miltefosine. Miltefosine is the only oral drug used for the treatment of Visceral Leishmaniasis with high cure rate but decrease in susceptibility is observed in countries like India where it is extensively used. Hence, there is an urgent need to develop novel antileishmanial agents with good potency and better therapeutic profile. Manzamines are unique group of β-carboline alkaloids isolated from marine sponges and exhibited potent antileishmanial activity. In the present study, we described antileishmanial activity, cytotoxicity and structure activity relationship of natural manzamine alkaloids.

1. Introduction

Leishmaniasis is a group of diseases caused by protozoan parasites of the genus *Leishmania*. It is considered as one of the most neglected diseases and is endemic in 90 countries throughout the world. Leishmaniasis is the most prevalent vector born infectious disease after malaria in terms of fatality and total number of patients. It is estimated that, currently 350 millions are living at risk places and 1.3 millions affected with annual mortality of 30,000 [1–3]. Leishmaniasis traditionally has been classified in three different clinical forms (i. e.) Cutaneous Leishmaniasis (CL), Mucocutaneous Leishmaniasis (MCL) and Visceral Leishmaniasis (VL) [4,5]. CL is the most common form of the infection, 90% of cases occur in Afghanistan, Algeria, Brazil, Pakistan, Peru, Saudi Arabia, and Syria. It produces skin lesions on the exposed parts of the body, such as face, arms and legs [6]. Nearly about 20 species of *Leishmania* are responsible for CL which includes *Leishmania major*, *Leishmania braziliensis* (in Brazil), *Leishmania mexicana*, *Leishmania infantum* (in southern France) and *Leishmania panamensi*. Although CL is often self-healing, it can create serious permanent disfiguring scars [7]. Mucocutaneous Leishmaniasis (also called Espundia in South America) produces lesion on mucous membranes of the nose, mouth, throat cavities and surrounding tissues. These lesions can lead to partial or total destruction of the affected organs [8]. Around 90% of the cases occur in Brazil, Bolivia and Peru and 20% of the infections caused by *Leishmania braziliensis* develop as MCL [9]. Pathogenesis of MCL is still not clear but genetic factor of infected person plays an important role in progression of the disease [10]. Visceral Leishmaniasis also known as kala azar (Black Fever in Hindi) is the most severe form of Leishmaniasis, is caused by *Leishmania donovani* and *Leishmania infantum*. More than 90% of the cases occur in five countries: India, Bangladesh, Nepal, Sudan, Ethiopia and Brazil. Symptoms of VL are irregular fever, weight loss, mucosal ulcers, swelling of the liver, spleen and anaemia. Unlike cutaneous forms of Leishmaniasis, VL affects the internal organs such as liver, spleen, bone marrow and is usually fatal if left untreated [11,12]. After treatment and recovery of VL, generally patients develop chronic cutaneous Leishmaniasis, known as Post-kala-azar dermal leishmaniasis (PKDL). PKDL is prevalent after recovery of *L. donovani* infection but not from *L. infantum*. PKDL first appears as small, measle-like skin lesions on the face, which gradually increase in size and subsequently affect other parts of the body including conjunctival, nasal, oral and genital mucosa [13].

2. Leishmaniasis chemotherapy

Leishmaniasis control mainly depends upon chemotherapy using decade old drugs due to lack of availability to effective vaccine [14]. Pentavalent antimonials (sodium stibogluconate and meglumine antimoniate) are being used in treatment of leishmaniasis over more than five decades and still they are the first line drugs of choice where resistance is not reported [15]. In spite of its adverse effects, polyene antifungal drug, amphotericin B is the drug of choice where resistance to antimonials is reported [16]. Usefulness of second line

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http://dx.doi.org/10.1016/j.ejmech.2014.07.006
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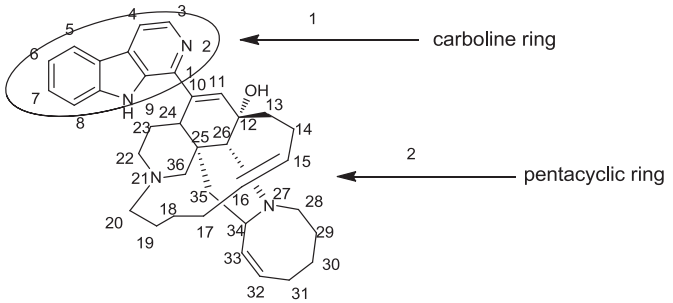

Fig. 1. Basic skeleton of manzamine alkaloids.

drugs like diamidine, pentamidine and aminoglycoside antibiotic paromomycin has been limited due to their toxicity [17,18]. Miltefosine is the first oral drug used for the treatment of VL, originally developed as anticancer agent [19,20]. Parasite can easily develop resistance to miltefosine because of its long half-life (150 h) and its use during pregnancy is restricted [21]. Low efficacy of Miltefosine is observed in countries like India where it is extensively used [22]. Hence, there is an urgent need to develop novel antileishmanial agents with good potency and better therapeutic profiles against both wild as well as resistant strains of *Leishmania*.

3. Manzamine alkaloids

Nature is an important source of discovery of medicinally importance compounds and the use of alkaloids for the treatment of parasitic infections is well known from the ages [23]. Hence

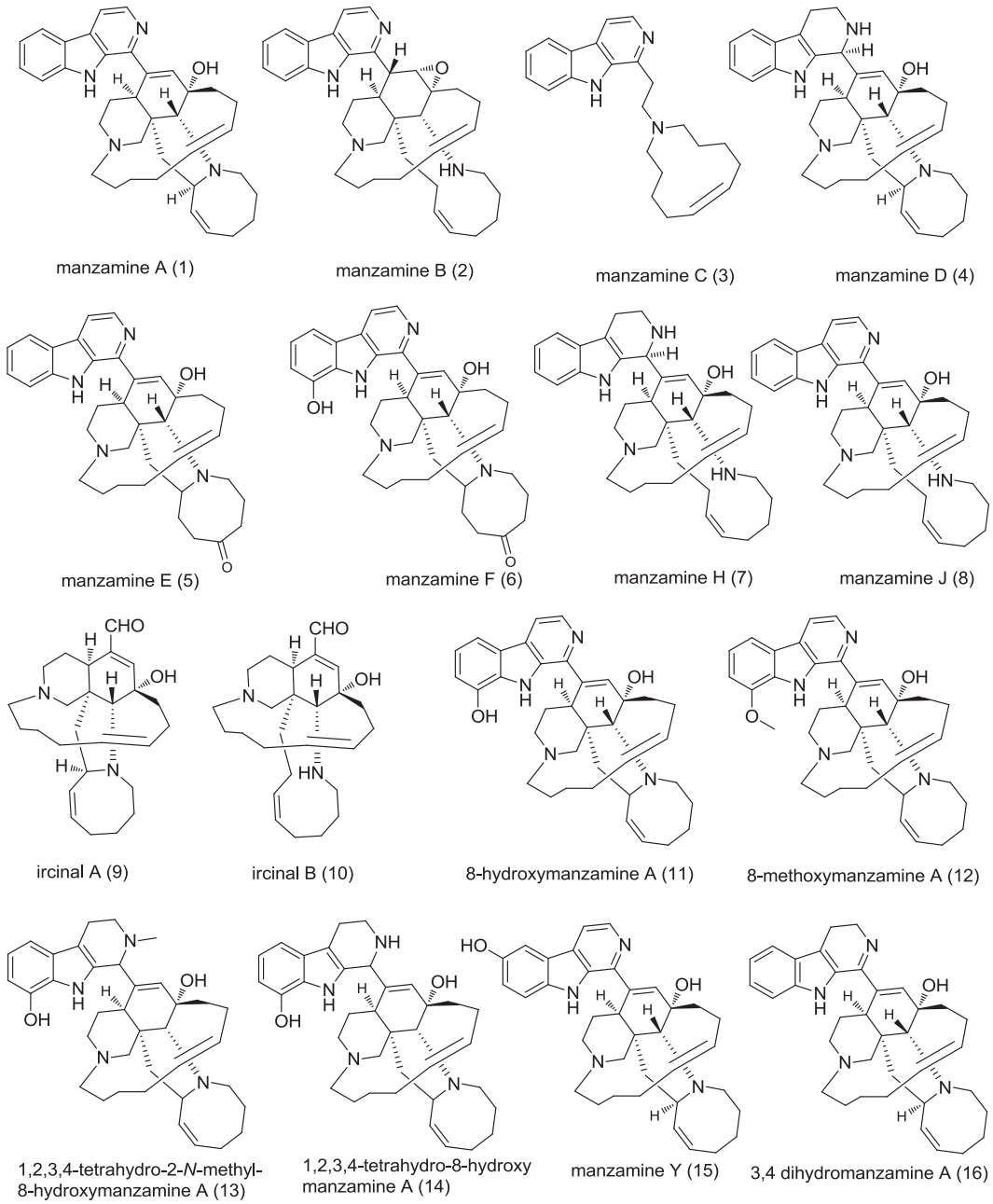

Fig. 2. Structures of natural manzamine alkaloids.

Please cite this article in press as: P. Ashok, et al., Manzamine alkaloids as antileishmanial agents: A review, European Journal of Medicinal Chemistry (2014), http://dx.doi.org/10.1016/j.ejmech.2014.07.006