Journal of Organometallic Chemistry 770 (2014) 51–60

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

Review

Importance of metal complexes for development of potential leishmanicidal agents

Azar Tahghighi*

Malaria and Vector Research Group (MVRG), Biotechnology Research Center (BRC), Pasteur Institute of Iran, P.O. Box: 1316943551, Tehran, Iran

ARTICLE INFO

Article history:
Received 3 May 2014
Received in revised form
5 August 2014
Accepted 11 August 2014
Available online 20 August 2014

Keywords:
Leishmaniasis
Anti-leishmania
Metal complexes
Metallointercalators
Antiprotozoal

ABSTRACT

The occurrence of adverse effects and the development of resistance associated with the administration of conventional anti-leishmanial drugs explicate the urgent need for development of new leishmanicidal agents. The potential use of metal complexes as drugs against parasitic diseases has so far been very little explored. Leishmaniasis affects millions of people around the world with very limited therapeutic options for their treatment. This review focuses on the recent advances in the development of complex anti-leishmania agents.

Contents

Introduction

The leishmaniasis are a composite of parasitic diseases caused by different species of the protozoan parasite Leishmania and are a major public health problem in many developing countries in the form of three clinical expressions: cutaneous leishmaniasis, mucocutaneous leishmaniasis and visceral leishmaniasis, which is fatal in the absence of treatment. It is estimated 350 million people will be at the risk of infection in the future [1]. There is no approved vaccine for clinical use. Despite a few research achievements, first-

Abbreviations: Pz, piperazine; SI, selectivity index; TI(IC50V79/IC50pro), therapeutic Index (concentration corresponding to 50% inhibition on mammalian V79 cells/ corresponds to the concentration with 50% antiproliferative activity against promastigotes, after incubation); ImN, imidazole coordinated by nitrogen; Cymene, 1-methyl-4-(1-methylethyl)benzene.

* Tel.: +98 2166480780; fax: +98 2166480749.
E-mail address: atahghighi2009@gmail.com.

http://dx.doi.org/10.1016/j.jorganchem.2014.08.007
0022-328X/

line chemotherapy is still based on pentavalent antimonials (Pentostam and glucantime) which are toxic and prone to drug resistance-developed more than 50 years ago [2]. Second-line drugs, such as pentamidine (PTM) and amphotericin B (Am B), are important in combined therapy or in cases of antimony treatment failures. Amphotericin B and pentamidine, the parenteral alternatives to antimony, cause serious and irreversible toxic effects which preclude their use [2]. A liposomal AmB formulation (AmBisome), less toxic than Amphotericin B deoxycholate, is gradually becoming the first-line therapy [3]. Experimental studies have identified the anticancer drug miltefosine as an effective antileishmanial agent. Miltefosine was the first drug registered against visceral leishmaniasis in the last decade; wherever, its toxicity and the appearance of drug resistance justify the search for new chemical series in order to find a safe and active drug [3].

Unfortunately, in the apparent absence of commercial profit, pharmaceutical companies are generally unwilling to address the critical need to develop new drugs against neglected vector-borne tropical diseases. Due to the rampant increase of this disease and the special focus of the WHO in the recent years on the issue, it is imperative to achieve novel, efficient, affordable and safe compounds for the treatment of leishmaniasis.

Today advancements in the rational design of metal-based therapeutic agents showcase increasingly significant research attempts towards the development of new compounds with fewer toxic side effects [4–9]. There exist a wide range of metal complexes; some of them used as pharmaceutical drugs. Anticancer complexes of platinum like *cis*-platin [*cis*-$Pt^{II}(NH_3)_2Cl_2$] which was discovered in the 1960s and used as antitumor, for instance, are the best known metal drugs [4].

This conclusion and the fact that many antiprotozoal drugs bind to DNA, have led some authors to propose that in general every DNA interacting compound could be active against parasites [10]. Thus, *cis*-Diammine Dichloro Platinum^{II} (*cis*-platin, *cis*-DDP) and other metal-containing antitumoral compounds were tested against kinetoplastid parasites and they displayed biological activity against protozoa [11]. Tumors resistant to *cis*-platin and other clinically used platinum compounds were caused other DNA metallointercalators as chemotherapeutic designed and prepared by researchers group and tested against Tumors resistant to platin complexes. It has been suggested that metallointercalating ligands can act like a carrier and interaction between DNA and complex increase by minimizing the disposal of the metal to inactivating cellular nucleophiles such as thiols [12,13].

On the other hand, the similarity between metabolic pathway of leishmania parasites and tumor cells [14], was caused to use some of these ligands in the design of metallointercalatores with antileishmania activity. The ultimate goal was, these compounds were evaluated against some parasites and their interaction with DNA supplied maximum antiprotozoal activity. On the other hand, by reducing the therapeutic dose and/or confuse the development of drug resistance diminished toxic effect for host [15].

Several transition metal complexes have been designed and studied to be DNA intercalating agents with potential antileishmania activity. Iridium, ruthenium, gold, copper, platinum and rhodium complexes with different organic drugs such as PTM, clotrimazole (CTZ), chloroquine (CHQ), and ketoconazole (KTZ) [17–20], are examples of these. Also, some of synthetic metal complexes with different ligands have been introduced, especially those that have leishmainicidal activity which could be associated with their interaction with the parasitic DNA [20]. Here, we present some of metal complexes with leishmanicidal activity based on the type of their metals.

In the design of other complexes, the use of metals of known clinical application and low toxicity to humans, with ligands typically employed in the synthesis of metallointercalatores, such as the planar organic compounds Dipyrido[3,2-*a*:2′,3′-*c*]phenazine (Dppz, **1**), Dipyrido[3,2-*a*:2′,3′-*h*]quinoxoline (Dpq, **2**), 4,7-dihydro-5-methyl-7-oxo[1,2,4]-triazolo-[1,5-*a*]pyrimidine(HmtpO, **3**), 4,5-dihydro-5-oxo-[1,2,4]triazolo-[1,5-*a*]pyrimidine (5HtpO, **4**) and 4,7-dihydro-7-oxo-[1,2,4]-triazolo-[1,5-*a*]pyrimidine (7HtpO, **5**) whose structures are shown in Fig. 1 [21].

Our research group has been synthesized thiadiazole compounds with good and excellent leishmanicidal activity [22–25]. Recently, we have focused our attention on synthesis of inorganic antileishmanial compounds. Thus, we searched synthetic complexes in literature and review here some of these complexes with antiprotozoal activity.

The metal complexes as potential anti-leishmanial agents

Coordination of different ligands to metal is a strategy for finding new leishmanicidal drugs which combine low toxicity and high activity. Usually, with this combination is displayed an attractive biological activity because of the possible ability of the new metal complexes to inhibit DNA replication through single or simultaneous interactions such as intercalation and/or covalent coordination to DNA [11]. Of course, other mechanisms may also contribute to this biological activity. In this review article, we will explore some of these complexes that researchers have synthesized and evaluated as antileishmanial agents.

Pt complexes

Authors have published the important biological activity that *cis*-platin and other metallic antitumoral compounds have against kinetoplastid parasites (*Trypanosoma* and *Leishmania*), which is probably a consequence of the similitude between the metabolisms of tumor cells and kinetoplastid parasites [14]. Furthermore, studies conducted on Leishmania cultures with DNA interacting compounds have allowed researchers to recommend that every DNA interacting compound could have antiprotozoal activity [11,26].

Some platinum complexes such as (2,2′:6′,2″-terpyridine) platinum^{II} and their analogs were reported to bind to double stranded DNA by intercalation [27]. These complexes showed remarkable growth inhibition of the intracellular amastigote forms of Leishmania donovani (*L. donovani*) [28]. The best compounds (**6** and **7**)

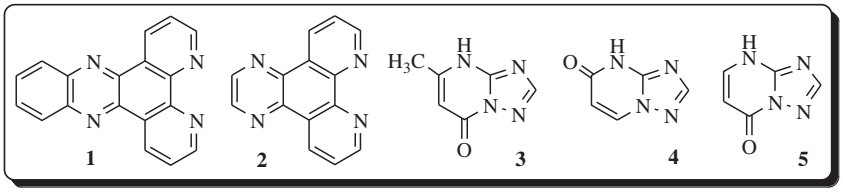

Fig. 1. Structure of ligands (**1**–**5**).