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Research paper

Synthesis and leishmanicidal activity of eugenol derivatives bearing 1,2,3-triazole functionalities

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ABSTRACT

In this paper, it is described the synthesis and the evaluation of the leishmanicidal activity of twenty-six eugenol derivatives bearing 1,2,3-triazole functionalities. The evaluation of the compounds on promastigotes of *Leishmania amazonensis* (WHOM/BR/75/Josefa) showed that eugenol derivatives present leishmanicidal activities with varying degrees of effectiveness. The most active compound, namely 4-(3-(4-allyl-2-methoxyphenoxy)propyl)-1-(4-methylbenzyl)-1*H*-1,2,3-triazole (**7k**) ($IC_{50} = 7.4 \pm 0.8\ \mu mol\ L^{-1}$), also targeted *Leishmania* parasites inside peritoneal macrophages ($IC_{50} = 1.6\ \mu mol\ L^{-1}$) without interfering with cell viability. The cytotoxicity of **7k** against macrophage cells presented IC_{50} of 211.9 $\mu mol\ L^{-1}$ and the selective index was equal to 132.5. Under similar conditions, compound **7k** was more effective than glucantime and pentamidine, two drugs currently in the clinic. In addition, theoretical calculations showed that this compound also presents most physicochemical and pharmacokinetic properties within the ranges expected for orally available drugs. It is believed that eugenol bearing 1,2,3-triazole functionalities may represent a scaffold to be explored toward the development of new agents to treat leishmaniasis.

1. Introduction

Parasitic diseases affect millions of hundreds of people annually and constitute an important global health problem. These diseases affect mainly the poorest population around the world and represent a significant issue in terms of human health and well-being. Malaria, River blindness (Onchocerciasis), Lymphatic Filasis, Schistosomiasis, Trypanosomiasis, and Leishmaniasis are some examples of parasitic diseases.

Leishmaniasis is a complex of diseases caused by the protozoan *Leishmania* and classified as one of the most important neglected tropical diseases (NTDs) that affect 350 million people in 98 countries, with a global incidence of 0.9–1.6 million cases per year [1]. *Leishmania* parasites are transmitted *via* the bites of infected female phlebotomine sandflies. Three main clinical manifestations of leishmaniasis, depending on the parasite species and the host-parasite relationship, are known: visceral (often known as Kalazar and the most serious form of the disease), cutaneous (the most common), and mucocutaneous [2]. Visceral leishmaniasis is responsible for 20,000–40,000 deaths annually [1].

Currently, several investigations have been conducted to find alternative treatments for leishmaniasis [3] due to the small number of available drugs and the development of resistance or decreased the sensitivity of parasite strains to existing treatments that have been utilized for human therapy [3]. These studies have sought new methods and targets for diagnosis, new vaccine candidates and new rationally designed drugs that can be applied not

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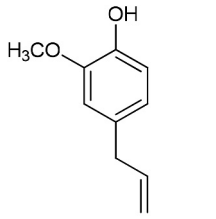
only in humans but also in dogs because canines are considered the major reservoirs of several species of *Leishmania* [4,5].

Historically, chemotherapy for leishmaniasis has relied on the use of pentavalent antimonial drugs, such as *N*-methylglucamine antimoniate (Fig. 1), which is one of the most widely used drugs [6]. However, this drug has limited clinical potential due to the occurrence of serious side effects and high incidence of disease recurrence [7]. Pentamidine (Fig. 1) is another antileishmanial agent, but it is inadequate as a first-line treatment because of its high toxicity [8]. Amphotericin B has been used as a second-choice drug in the treatment of leishmaniasis since the 1960s, but the rate of resistance against this drug is high [8]. Two other examples of antileishmanial compounds are miltefosine and paromomycin (Fig. 1). The major limitation of miltefosine is teratogenicity, excluding its use in women of child-bearing age [9,10]. The most common side effect associated with the paromomycin is the ototoxicity, as well as problems in liver function. In patients treated with the ointment formulation, skin rashes, local pruritus and burs have been encountered [11]. Additionally, the drugs used in therapy have some limitations in common: (i) they are toxic and their long-time administration causes various undesirable side effects; (ii) they are costly; (iii) they show low efficacy in endemic areas due to the observed resistance of various parasite species [12]. The aforementioned problems illustrate the need to develop new antileishmanial drugs.

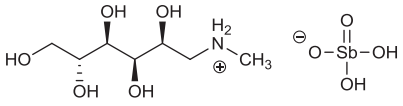
In the search for new drugs for the treatment of diseases, the exploitation of natural products is a viable approach [13–18]. In this regard, compounds obtained from nature can be used directly as a pharmaceutical or can be chemically modified to afford derivatives with improved pharmacological activity.

Eugenol (**1**) (Fig. 2) is a natural compound which has been identified in several aromatic plants such as *Myristica fragrans* Houtt. (nutmeg), *Cinnamomum verum* J.Presl (true cinnamon), *C. loureirii* Nees. (Saigon cinnamon), *Ocimum gratissimum* Forssk. (basil) and *Ocimum basilicum* L. (sweet basil). However, *Eugenia caryophyllata* (=*Syzygium aromaticum*) can be considered the principal natural source of this compound as it represents between 45% and 90% of the composition of the essential oil derived from this species. Several biological activities have been reported for eugenol (**1**) including antibacterial, antifungal, antiplasmodial,

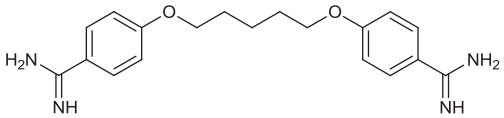


Eugenol (1)

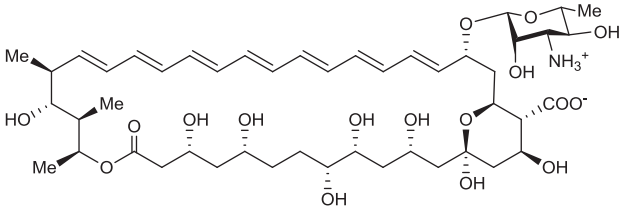
Fig. 2. The structure of eugenol (**1**).



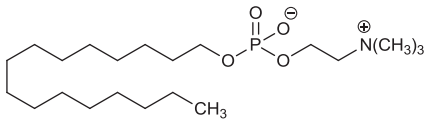
***N*-methylglucamine antimoniate**



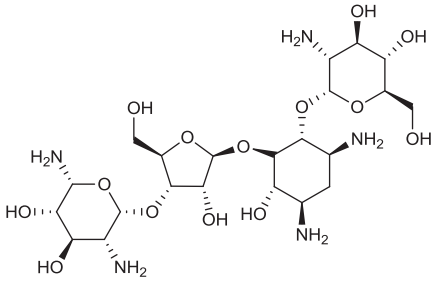
pentamidine



amphotericin B



miltefosine



paromomycin

Fig. 1. Structures of drugs used for the treatment of leishmaniasis.