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In vitro anti-*Giardia lamblia* activity of 2-aryl-3-hydroxymethyl imidazo[1,2-a]pyridines and -pyrimidines, individually and in combination with albendazole

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ABSTRACT

Giardiasis is a major diarrheal disease found throughout the world, the causative agent being the flagellate protozoan *Giardia intestinalis*. Infection is more common in children than in adults. The appearance of drug resistance has complicated the treatment of several parasitic diseases, including giardiasis. Thus, the aim of this investigation was to make an *in vitro* evaluation of the antigiardia response of synthetic derivatives 2-aryl-3-hydroxymethylimidazo[1,2-*a*]pyridines **1** and -pyrimidines **2** against trophozoites of *Giardia lamblia* WB, in comparison with the reference drug, albendazole. Additionally, the synergistic action of albendazole in combination with each of the most active 2-aryl-3-hydroxymethyl imidazo[1,2-*a*]pyridines and pyrimidines was also assessed. Based on the IC_{50} values obtained, the best anti-*Giardia* activity was provided by the 3-hydroxymethyl-4-fluorophenylimidazo[1,2-*a*]pyrimidine derivative **2c** and the corresponding imidazo[1,2-*a*]pyrimidine with the *p*-tolyl substituent **2d**, followed by **2a** and **2b**. These four compounds showed effectiveness at a concentration similar to that of albendazole. Regarding synergism, the IC_{50} of the combination of albendazole with **2a**, **2b** or **2c** gave the best anti-*Giardia* action, showing greater efficacy than albendazole alone. Hence, *G. lamblia WB* showed high susceptibility to some 2-aryl-3-hydroxymethyl imidazo[1,2-*a*] pyrimidines, which acted synergistically when used in combination with albendazole.

1. Introduction

Giardia duodenalis (also known as *G. lamblia* or *G. intestinalis*) is a single cell parasite that inhabits the small intestine, and is one of the most common and best known parasitic organisms. Giardiasis, is considered as a re-emerging infectious disease caused by this etiologic agent (Thompson, 2000). The main manifestations of the disease are chronic diarrhea and poor nutritional absorption. Fecal-oral transmission of infection is easier in places with such poor hygienic conditions as a clean water shortage or inappropriate sewage disposal. Other risk factors include overcrowding, close contact with farm animals, and a low educational level (O'Ryan et al., 2005..

The frequency of giardiasis in Mexico is variable, fluctuating between 2 and 39% depending on the region (Martínez, 1982; Sotelo, 1998). The statistical report of the CENAVECE (National Center for Alertness and Disease Control) in 2010 estimated that 9 million individuals were infected with *Giardia lamblia*. In that same year a total of 20,678 new cases of nursing and pre-school children aged 1–4 years were reported in three states of the Mexican republic (Centro Nacional de Programas Preventivos y Control de Enfermedades, 2013).

For many years metronidazole has been the drug of choice for the treatment of giardiasis. Other nitro-azole based drugs used are tinidazole, secnidazole and nitazoxanide. Currently, pharmacological treatment of giardiasis involves benzimidazoles (albendazole,

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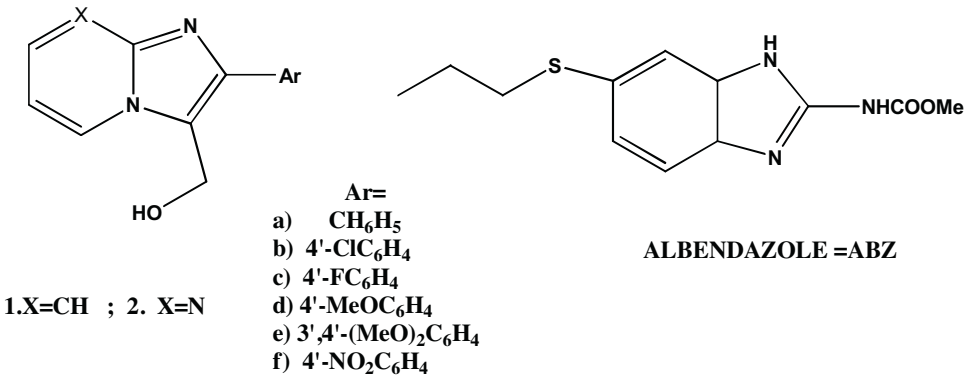

Fig. 1. Structures of 2-aryl-3-hydroxymethy imidazo[1,2-*a*]pyridines and -pyrimidines, and albendazole.

mebendazole and triclabendazole), nitrofuranes (furazolidone), quinacrine and macrocyclic lactones (El Sayad et al., 2002; Rosemblatt, 1999; Vanelle et al., 1991). Benzimidazoles and nitazoxanide are well tolerated and also have the advantage of being active against infection with helminths, which are endemic in developing countries (Davila-Gutierrez et al., 2002; Juan et al., 2002). However, therapeutic failure is now occurring more frequently in cases of giardiasis due to low compliance with drug therapy, re-infestation, or drug resistance to metronidazole and/or nitroimidazole-related compounds (Gardnern and Hill, 2001; Lindquist, 1996; Upcroft, 2001). Hence, there is an urgent need to search for new active agents against *G. lamblia* (Nash et al., 2001).

Albendazole and mebendazole have proven effective against many parasites, including *G. lamblia*, and elicit fewer side effects than metronidazole. In part, benzimidazoles exert their toxic action on *G. lamblia* by binding to the parasite β-tubulin microtubules (Morgan et al., 1993), resulting in the inhibition of microtubular polymerization and impaired glucose uptake (Kohler, 2001). Nevertheless, the use of these compounds is limited because of resistance to their pharmacological activity, which is caused by point mutations in the parasite's β-tubulin (Lindquist, 1996).

In the past few years, interest in the synthetic derivatives of imidazo[1,2-*a*]pyridines and -pyrimidines has been growing due to the extent of their pharmacological applications (see for instance: El Kazzouli et al., 2011; Enguehard-Gueiffier and Gueiffier, 2007). The structural and electronic similarity between the nucleus of benzimidazole and that of imidazo[1,2-*a*]pyridine (pyrimidine) led us to consider the possibility that adequately substituted derivatives of the imidazopyridine system may have anti-parasitic activity. Therefore, 2-aryl-3-hydroxymethyl imidazo[1,2-*a*]pyridines **1** and the corresponding analogues 2-aryl-3-hydroxymethyl imidazo[1,2-*a*]pyrimidines **2** (Fig. 1) were selected and synthesized.

The aim of the present investigation was to assess the *in vitro* effect against *G. lamblia* trophozoites of imidazo[1,2-*a*]pyridines **1** and -pyrimidines **2**, as well as that of albendazole alone or in combination with each of the most active compounds in both series.

2. Materials and methods

2.1. Drug assessment

Derivatives of 2-aryl-3-hydroxymethyl imidazo[1,2-a]pyridines (**1a–g**) and -pyrimidines (**2a–g**) were prepared in house by reduction of the corresponding 2-arylimidazo[1,2-*a*]pyridine or imidazo[1,2-*a*] pyrimidine-3-carbaldehyde. Synthesis details and the proper characterization of **1** and **2** has been previously reported (Velázquez-Olvera et al., 2012). Albendazole was kindly provided by Smith Kline Beechman Co., (Bedford, Middlesex, UK).

Albendazole was dissolved in analytical grade dimethyl sulfoxide (Baker, Mexico). The 2-aryl-3-hydroxymethyl imidazo[1,2-

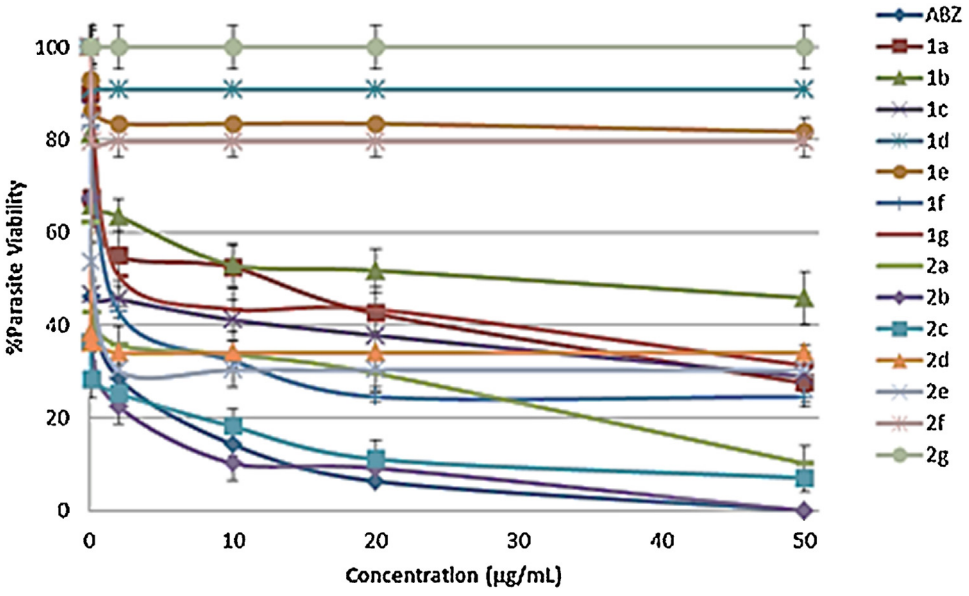

Fig. 2. Inhibitory response of 2-aryl-3-hydroxymethyl imidazo[1,2-a]azines and albendazole on the *Giardia lamblia* WB culture *in vitro*.