Bioorganic & Medicinal Chemistry Letters 26 (2016) 5149–5159

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Digest paper

Recent progress on the discovery of antiamoebic agents

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ARTICLE INFO

Article history:
Received 2 August 2016
Revised 13 September 2016
Accepted 14 September 2016
Available online 15 September 2016

Keywords:
Antiamoebic
Entamoeba histolytica
Amoebiasis
Inhibitor
Protozoan

ABSTRACT

A large number of protozoans infect humans but *Entamoeba histolytica* is the only organism responsible for causing amoebiasis, a deadly disease after malaria. Numerous heterocycle-based antiamoebic agents have been previously synthesized as *E. histolytica* inhibitors and while some of these agents have shown moderate activity, the search for a novel and ideal antiamoebic compound is still ongoing. In this digest Letter, we present the latest data on antiamoebic agents from 2011 to 2016 based on the different classes of heterocyclic agents.

Parasitic infections constitute one of the most widespread human health problems, and most of them occur through the consumption of contaminated food or water. The human intestine is the major target of these ingested pathogenic microorganisms, and their effects result in severe infections including amoebiasis (dysentery). Amoebiasis is caused by *Entamoeba histolytica*, a protozoan parasite that can penetrate the intestinal mucosa to cause amoebic colitis, and then spreads via the portal circulation to other organs, typically the liver and brain. In the liver, this parasite induces amoebic liver abscess, which is the most common extraintestinal manifestation of invasive amoebiasis.[1–3] Furthermore, amoebiasis is well known to be transmitted by the ingestion of food or water containing the cyst of *E. histolytica*, which is prevalent in travelers and immigrants from endemic areas[4] and causes significant morbidity and mortality.[5] Infection by this parasite is responsible for 50 million cases of amoebiasis and 100,000 deaths annually.[1,6] Sexually transmitted *Entamoeba histolytica* infection has also been increasingly recognized among men who have sex with men, especially those are infected with human immunodeficiency virus (HIV), and their infection rate is higher in developed countries.[7–16] According to latest data information, the prevalence of HIV diagnosis increased from 32% to 45% (from 2006–2009 to 2010–2013) while the incidence of HIV diagnosis increased from 5.4% to 11.3% per 100 persons in a year among males, infected with *Entamoeba histolytica*.[17]

E. histolytica, a unicellular organism responsible for parasitic animal infections, is a pathogenic protozoan of the family *Entamoebidae*. This organism was identified and first described in the literature by Dr. F. Aleksandrovich Lösch from St. Petersburg in 1875.[18] It is important to note that the term amoebiasis is reserved only for diseases caused by *E. histolytica* and is not to be used in cases of infections by other amoeba species of the family *Entamoebidae*. Furthermore, *Entamoeba* protozoa consist of two species, which are the pathogenic *E. histolytica* and the nonpathogenic *E. dispar*. The pathogenic *E. histolytica* has a simple life cycle and exists either as the infectious cyst form or in the pathogenic amoeboid trophozoite stage. Infections usually begin with the ingestion of the cysts in contaminated food or water. *E. histolytica* cysts are round, quadrinucleated, and surrounded by chitin. They survive easily in the acidic environment of the stomach from where they are transported to the small intestine and the colon as excyst to form the trophozoite stage. Unlike the inert cysts, *E. histolytica* trophozoites are highly motile with a pleomorphic shape. Trophozoites ingest bacteria and food particles, reproduce by binary fission, encyst within the colon, and are then excreted into the environment in the stool. Trophozoites may be excreted in the stool as well, but they cannot survive outside the human host.[19–21]

E. histolytica produces considerable amounts of cysteine proteinases (CPs), and this class of enzymes is responsible for its pathogenicity. The highest prevalence of *E. histolytica* infections is observed in countries with poor sanitary conditions, and occurs particularly in Mexico, India, Central and South America as well as the tropical regions of Asia and Africa.[22–25] Numerous structurally diverse compounds have been investigated as potent antiamoebic

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http://dx.doi.org/10.1016/j.bmcl.2016.09.040
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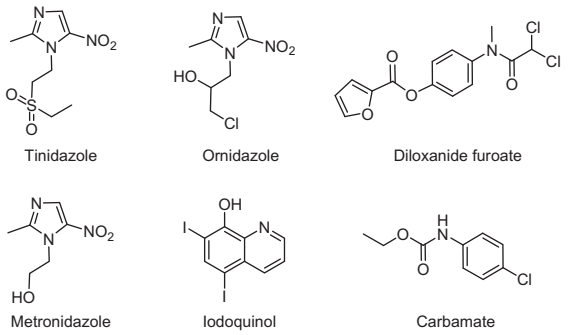


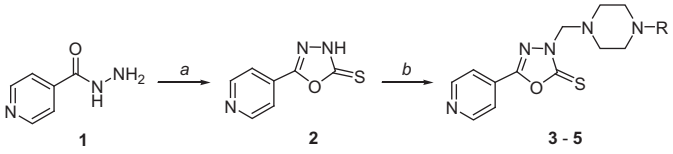
Figure 1. Different classes of antiamoebic agents.

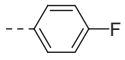
agents, and some have been used in medical practice (Fig. 1). Based on their structural features, these compounds can be classified into different groups including the azoles (e.g., metronidazole [MNZ], tinidazole, and ornidazole); quinolines (e.g., iodoquinol); dichloroacetamides (e.g., diloxanide furoate); and some carbamate derivatives.[26–29] Among these compounds, MNZ is known to be a highly effective antiamoebic agent, and is considered the drug of choice for treating amoebiasis.[30] However, this drug is potentially carcinogenic to humans because of its cellular genotoxicity. Furthermore, MNZ is associated with several serious side effects such as seizures, ataxia, peripheral neuropathy, transient myopia, gastric mucus irritation, spermatozoid damage, and hematuria.[27,31–35] Moreover, failures in the treatment of several intestinal protozoan parasites may result from drug resistant to parasites.[36,37]

Considering that MNZ is not safe for the human system, numerous research studies have synthesized several heterocyclic compounds as novel antiamoebic agents. In this article, we have compiled the recent (2011–2016) research data on the development of novel antiamoebic agents based on the investigation of different classes of heterocyclic compounds. Furthermore, the details of these research studies are summarized here.

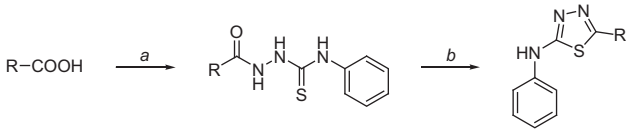
Azole-based antiamoebic agents: Azoles are an important class of biologically active compounds. Azole-based heterocyclic compounds such as imidazole, benzimidazole, pyrazole, and triazole have been frequently found to display a variety of biological activities such as antihelmintic,[38] antihistaminic,[39] anticancer,[40] antiviral,[41] anti-inflammatory,[42] antiproliferative,[43] antioxidant,[44] anticoagulant,[45] antitubercular,[46] and anticonvulsant.[47] In addition, these properties of azole heterocycles have attracted a large number of pharmaceutical companies to investigate their medicinal activities. From 2011 to 2016, a number of research studies have synthesized numerous azole-based heterocycles for evaluation as potentially superior antiamoebic agents to the currently existing options, and their findings are compiled here.

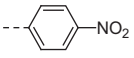
Siddiqui et al.[48] reported the synthesis of some azole derivatives and their in vitro antiamoebic activity, evaluated using a microdilution method against the HM1:IMMS strain of *E. histolytica*, and the biological activities were compared with those of MNZ (reference drug). All the compounds were prepared as shown in Schemes 1–4. According to Scheme 1, a series of 5-(pyridine-4-yl)-1,3,4-



No.	R	Antiamoebic activity IC_{50} (μM)	Cytotoxicity IC_{50} (μM)
3		0.245 ± 0.009	> 250
4		1.06 ± 0.015	> 250
5	Ethyl	0.327 ± 0.005	> 250

Scheme 1. Reagents and conditions: (a) CS_2, KOH; then H^+, reflux (b) *N*-substituted piperazine, HCHO, EtOH, rt.



No.	R	Antiamoebic activity IC_{50} (μM)	Cytotoxicity IC_{50} (μM)
8		0.670 ± 0.007	> 250
9		1.60 ± 0.009	> 250
10	Me	0.522 ± 0.008	> 250

Scheme 2. Reagents and conditions: (a) (i) H_2SO_4, CH_3OH, reflux; (ii) N_2H_4, H_2O/EtOH, reflux; (iii) C_6H_5NCS, EtOH, reflux; (b) concd H_2SO_4, rt.