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Original article

Design, synthesis and biological evaluation of quinazoline derivatives as anti-trypanosomatid and anti-plasmodial agents

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ABSTRACT

In this paper, the design, synthesis and biological evaluation of a set of quinazoline-2,4,6-triamine derivatives (**1**–**9**) as trypanocidal, antileishmanial and antiplasmodial agents are explained. The compounds were rationalized basing on docking studies of the dihydrofolate reductase (DHFR from *Trypanosoma cruzi*, *Leishmania major* and *Plasmodium vivax*) and pteridin reductase (PTR from *T. cruzi* and *L. major*) structures. All compounds were in vitro screened against both bloodstream trypomastigotes of *T. cruzi* (NINOA and INC-5 strains) and promatigotes of *Leishmania mexicana* (MHOM/BZ/61/M379 strain), and also for cytotoxicity using Vero cell line. Against *T. cruzi*, three compounds (**5**, **6** and **8**) were the most effective showing a better activity profile than nifurtimox and benznidazole (reference drugs). Against *L. mexicana*, four compounds (**5**, **6**, **8**, and **9**) exhibited the highest activity, even than glucantime (reference drug). In the cytotoxicity assay, protozoa were more susceptible than Vero cells. In vivo *Plasmodium berghei* assay (ANKA strain), the compounds **1**, **5**, **6** and **8** showed a more comparable activity than chloroquine and pyrimethamine (reference drugs) when they were administrated by the oral route. The antiprotozoal activity of these substances, endowed with redox properties, represented a good starting point for a medicinal chemistry program aiming for chemotherapy of Chagas' disease, leishmaniosis and malaria.

1. Introduction

Parasitic infectious diseases due to pathogenic protozoan still constitute a major health problem world wide and mainly occur in underdeveloped countries [1]. Chagas' disease (CD), caused by *Trypanosoma cruzi* [2], leishmaniosis, caused by *Leishmania* spp. [3], and malaria, caused by *Plasmodium vivax* and *Plasmodium falciparum* [4], are among the most serious infections in the tropical regions. CD is broadly disperse in Latin America and the Caribbean region, affecting approximately 8 million people, of whom 30–40% either have or will develop cardiomyopathy, digestive megasyndromes, or both [2]. Leishmaniosis are endemic in 98 countries or territories with an estimated incidence of 0.2–0.4 million cases of visceral leishmaniosis (VL) and 0.7–1.2 million cases of cutaneous leishmaniasis (CL) each year [5]. The clinical manifestations may vary from single cutaneous lesions to fatal VL [3,5]. Meanwhile, malaria remains in large areas of the developing world, with 40% of the earth's population living in malaria-endangered areas. As a direct consequence, over 1 million humans per year die of this disease, with the estimate of 550 million clinical cases [4]. These public health problems are accentuated by multiple factors including the AIDS epidemic, the increase of international travel and difficulties controlling vectors.

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In the absence of effective vaccines, chemotherapy plays a critical role controlling these diseases [1,6]. The treatment of CD relies on two available drugs; nifurtimox (**Nfx**, Lampit™) and benznidazole (**Bnz**, Rochagan™), introduced into the clinical therapy over four decades ago. Although in most cases these drugs are efficient in the acute phase of the disease, they are almost ineffective in the chronic phase [7]. For the treatment of leishmaniosis, glucantime, miltefosine and amphotericine B, are in use to date; however, these compounds have common drawbacks such as high toxicity, high cost or emerging resistance [8]. Regarding malaria, sulfadoxine–pyrimethamine, quinine, chloroquine and their derivatives, are still in use today; new therapies based on artemisinin were recently introduced into the clinic [9]. Moreover, the emergences of drug-resistant strains of the causative organisms have seriously impaired their therapeutic value. This has frustrated attempts to eradicate these diseases by means of chemotherapy, and the currently used drugs have an increased risk of becoming obsolete. In this context, intensive efforts have been devoted to find novel prototype compounds among natural and synthetic sources to develop new drugs to treat these infectious diseases.

In previous research work using quinazoline-2,4,6-triamine (**TAQ**) as template, Davoll et al. [10] synthesized a series of derivatives bearing different substituents at the 6-position. Several compounds displayed strong antiparasitic activity against *Plasmodium berghei*, and modest activity against *T. cruzi* in cultures of chicken embryo cells and in mice, respectively. Subsequently, other studies showed the ability of **TAQ** to co-crystallize with pteridine reductase 1 of *Leishmania major* (lmPTR1) [11] and that several quinazoline-2,4-diamine derivatives had the ability to interact with dihydrofolate reductase (DHFR) isolated from *Leishmania mexicana* (lmxDHFR) and *T. cruzi* (tcDHFR) [12,13]. PTR1 and DHFR are implicated in the metabolism of folate parasitic protozoa, and they are treatable targets for antiparasitic leads [8]. In addition, it is known that the mechanism of antifolate resistance in *L. major* and *T. cruzi* is mediated by PTR and its isoforms [14,15].

The sum of these results encouraged the further search for other **TAQ** derivatives as trypanocidal, antileishmanial and antiplasmodial agents. In this context, this document presents the design and synthesis of nine quinazoline derivatives (**1**–**9**, Table 1) with their in vitro evaluation against bloodstream trypomastigotes of *T. cruzi* (NINOA and INC-5 strains) and promastigotes of *L. mexicana* (MHOM/BZ/61/M379 strain). Likewise, compounds were evaluated in *P. berghei* mouse model of infection.

The design was conducted searching the best ligand arrangement into tcDHFR, lmDHFR, pvDHFR, tcPTR2 and lmPTR1.

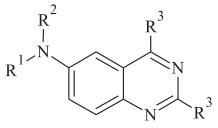
2. Results and discussion

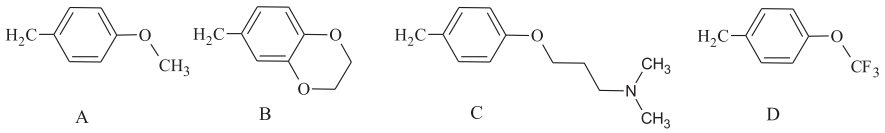
2.1. Design

The quinazoline derivative **1** showed a good profile against *T. cruzi* and *P. berghei* in previous studies [10]. In order to know the factors for this behavior, the theoretical interaction of this compound with tcDHFR and tcPTR2 (Fig. 1) was analyzed.

According to the molecular docking of **1** with both proteins, three regions with different characteristics were found in tcDHFR and two in tcPTR2. Similar findings were presented with lmDHFR, pvDHFR, hDHFR, and lmPTR1 (Table 2). Into DHFR, region I present a lipoid character because it is constituted by alkyl and aromatic side chains. Region II has got a hydrophilic character mainly formed by hydrophilic amino acids, CO and NH groups of the peptide bonds. Region III has got arginine capable of bridging hydrogen with the 4-methoxy substituent of **1**. The three regions are present in DHFR for both, human and parasite; however, they strongly differ in region I, where the parasite proteins have got an aromatic ring (Phe or Tyr) whereas the human protein is more hydrophilic (Asn64). Selective parasite protein compounds should be directed primarily towards region I. The best interaction of **1** with DHFR or PTR is with region I. On the other hand, **TAQ** moiety interacts with the previously reported aminoacids [11,13].

Table 1
Quinazoline derivatives.





Compound	R^1	R^2	R^3	MW	Mp (°C)	Clog P[a]	HBD[b]	HBA[c]	PSA (Å^2)[d]
1	A	H	NH_2	295	215–216	2.24	5	6	99.09
2	A	H	$NHCOCH_3$	371	187–188	2.13	3	8	105.24
3	B	H	NH_2	323	134–136	1.61	5	7	108.33
4	C	H	NH_2	366	198–200	2.54	5	7	102.33
5	D	H	NH_2	349	206–207	3.15	5	6	99.09
6	D	Ethyl	NH_2	377	177–178	3.77	4	6	90.30
7	A	A	NH_2	415	106–107	3.94	4	7	99.54
8	A	D	NH_2	469	121–122	4.85	4	7	99.54
9	D	D	NH_2	523	133–135	5.76	4	7	99.54

[a] Calculated from molinspiration (www.molinspiration.com).
[b] HBA: Hydrogen bond-acceptor group.
[c] HBD: Hydrogen bond-donor group.
[d] PSA: Polar surface area.