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Synthesis and biological evaluation of quinoxaline di-*N*-oxide derivatives with in vitro trypanocidal activity

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ABSTRACT

We report the synthesis and in vitro activity against *Trypanosoma cruzi* epimastigotes of 15 novel quinoxaline derivatives. Ten of the derivatives presented IC_{50} values lower than the reference drugs Nfx and Bzn; four of them standed out with IC_{50} values lower than 1.5 μM. Moreover, unspecific cytotoxicity and genotoxicity studies are also reported. Compound **14** showed a SI higher than 24, whereas compound **10** was the only one that was negative in the genotoxicity screening.

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Chagas disease (CD) is classified as one of the 17 Neglected Tropical Diseases (NTD) as defined by WHO.[1] The 17 NTD account for a disease burden of at least 26 million disability-adjusted life years (DALYs) according to the Third WHO Report on Neglected Tropical Diseases[2] and are under the Sustainable Development Goals SDG3. However, only the 0.6% of the new therapeutic products registered from 2000 to 2011 were indicated for NTD and none of them were a NCE.[3] These facts highlight the urgent need of new effective and safe drugs for fighting NTDs.

CD, also known as American trypanosomiasis, is caused by the protozoan parasite *Trypanosoma cruzi*. It used to be considered as a zoonotic disease affecting rural areas in low-middle income countries in Latin America. Nevertheless, human migration has spread out the disease worldwide and, according to WHO, 8 million people are currently infected.[4] It is estimated that over 10000 people die every year from CD, and more than 25 million people are at risk of infection.

CD is curable if treatment is initiated soon after infection; therefore, access to diagnosis is essential. If not treated, 30% of the affected people develop heart damage and 10% suffer from digestive and/or neurological alterations. Nifurtimox (Lampit®) and Benznidazol (Rochagan®) are the only available drugs for CD and they were developed more than 40 years ago. Neither of them is approved by the FDA.[5] The major limitation of currently available drugs is their lower antiparasitic activity in the established chronic form of the disease, which is the most prevalent presentation. On the other hand, both drugs have undesired side effects that can lead to treatment discontinuation, which for Nfx include anorexia, nausea and vomiting causing severe weight loss, insomnia and irritability, while for Bnz the most common adverse effect is urticarial dermatitis.[6,7]

Three clinical trials have recently been conducted. A phase II proof-of-activity study of oral posaconazole in the treatment of asymptomatic chronic CD was completed in January 2015 and no conclusions have been reported.[8] The phase II clinical trial for the treatment of chronic CD with posaconazole and benznidazole (CHAGASAZOL) and a higher treatment failure was observed in patients in the posaconazole groups than in the Bnz group.[9,10]

Abbreviations: BFX, benzofuroxan; CD, chagas disease; Nfx, Nifurtimox; Bnz, Benznidazol; NCE, new chemical entity; N.T., not tested; NTD, Neglected Tropical Diseases; PGI, percentage of growth inhibition; SI, selectivity index; TPP, Target Product Profile.

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Finally, a proof-of-concept study of the promising NCE E1224 was recently completed but the development of E1224 as monotherapy has been stopped and it will be considered for new combinatory regimens.[5,11,12]

This background justifies the urgent need for novel and better drugs to treat both acute and chronic phases. Quinoxaline derivatives are a chemical scaffold that has showed a wide spectrum of biological activities.[13] Our group has vast experience in the synthesis and biological evaluation of quinoxaline derivatives with anticancer, anti-mycobacterium and anti-inflammatory activities among others.[14–26] One of the projects has been focused on the study of novel quinoxaline derivatives as anti *T. cruzi* agents. In this field, over 200 derivatives have been prepared and evaluated as anti-trypanosomatid agents and some structural requirements have been established for their anti-chagasic in vitro activity.[20,25,27,28] Therefore, it can be considered that the main structural requirements for the trypanocidal activity of quinoxaline derivatives are: the presence of the *N*-oxide moiety and the insertion of electro withdrawing substituents on the quinoxaline ring (e.g. fluoro, chloro, trifluoromethyl...). Despite the general opinion about the toxicity associated with *N*-oxides, it has been reported that quinoxaline derivatives mutagenicity seems to be associated with the substituents on the heterocycle.[29] With this background and with the aim of identifying a new lead with higher potency and selectivity and a better drug target profile a series of 15 novel quinoxaline derivatives were designed considering the structural requirements previously established by our group and the insertion of alicyclic amines of biological interest. Piperazine derivatives have been explored for their interest as anti-trypanosomatid agents and their activity as inhibitors of different targets of interest to fight against CD has been reported.[30–32] Structural similarity can be observed between the proposed compounds and fluoroquinolones (Fig. 1), a family of well-known antibacterial agents that have shown interesting activity data against trypanosomatids.[33–35]

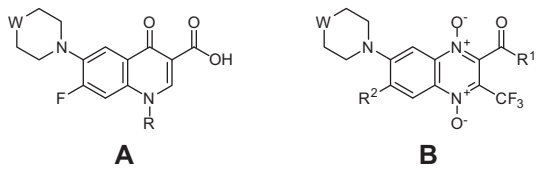


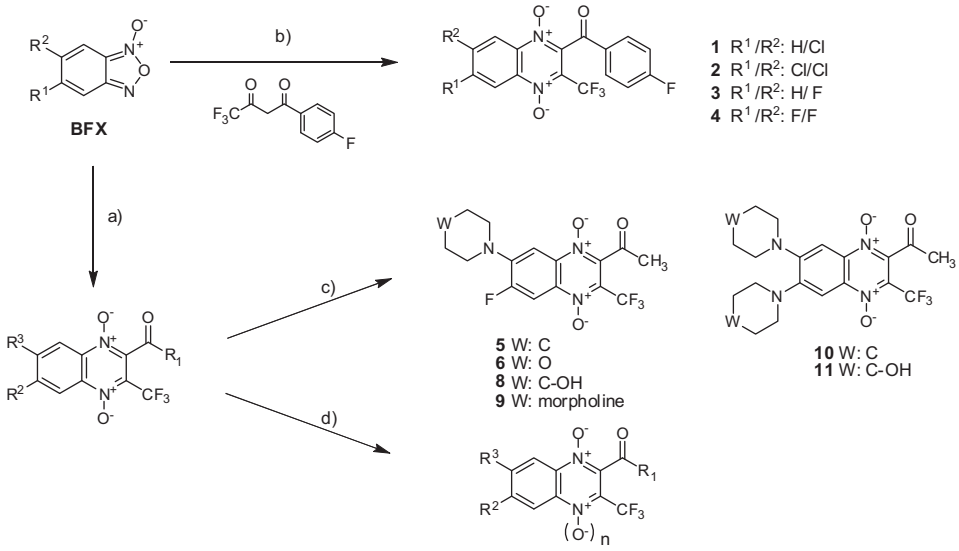
Figure 1. Structural similarity between fluoroquinolones (A) and proposed quinoxaline derivatives (B).

The design, synthesis and in vitro evaluation of new quinoxaline derivatives (**1**–**15**) as antitrypanosomal agents are described and SARs are discussed. The non-specific toxicity against mammalian cells was studied in order to evaluate the quinoxaline selectivity to the parasites and the SOS/umu test was included as a preliminary genotoxicity screening assay.

The designed compounds (**1**–**15**) were synthesized according to the sequence of reactions outlined in Scheme 1.

4 new quinoxaline 1,4-di-*N*-oxide derivatives (**1**–**4**) were prepared using a variation of the Beirut reaction using microwave irradiation in which the corresponding BFX reacted with the 1-(4-fluorophenyl)-4,4,4-trifluoro-1,3-butanedione using toluene as solvent and triethylamine as base. The use of microwave assisted organic synthesis reduced the reaction times and simplifies the purification of quinoxaline derivatives. This fact led to an increase in the yield mainly when quinoxalines are substituted by halogens in positions 6 and/or 7 of the ring.

Compounds substituted by a cyclic amine on positions 6 and/or 7 of the quinoxaline ring were prepared by nucleophilic aromatic substitution of the corresponding quinoxaline. All the quinoxalines presented a chloro or fluoro substituted on positions 6 and/or 7 of the ring as leaving group and different cyclic amines were used as nucleophiles. As expected, the fluoro acts as a better leaving group decreasing the reaction times in comparison with the chloro. The longer reaction times needed when a chloro was substituted on positions 6 and 7 of the heterocycle led to the generation of the mono-reduced quinoxaline (**14** and **15**) complicating the purification of the desired compounds.[37,38] Different synthetic



Scheme 1. Synthesis of quinoxaline derivatives **1**–**15**. (a) Previously reported in Refs. 27,36; (b) toluene, triethylamine, MW; (c) acetonitrile, triethylamine, rt; (d) *N*,*N*-DMF, reflux.

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