

## Artigo

## Quinoxaline and Arylaminoalcohol Derivatives as Antiplasmodial and Leishmanicidal Agents: A Review of our First Ten Years in the Field

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### Derivados de Quinoxalina e Aril-Amino-Álcool como Agentes Antiplasmódicos e Leishmanicidas: Uma Revisão sobre os Nossos Primeiros Dez Anos nesta Área

**Resumo:** Doenças negligenciadas constituem um grande problema de saúde na atualidade. Contudo, estas doenças não são de interesse para a indústria farmacêutica, uma vez que elas geralmente afetam pessoas de baixo poder aquisitivo. Descrevemos aqui, o trabalho relacionado à malária e à leishmaniose que estamos desenvolvendo ao longo da última década. Nossa experiência neste campo é focada em duas famílias de compostos químicos: derivados de quinoxalina e aril-amino-álcool. Atualmente, esforços estão centralizados na pesquisa de novas entidades químicas, bem como na superação da resistência a compostos antimaláricos. Adicionalmente, entidades químicas relatadas por outros autores e derivados de quinoxalina relacionados são abordadas. Estas duas doenças são consideradas de extremo interesse científico e social, necessitando tanto de novos fármacos quanto do aperfeiçoamento dos tratamentos existentes.

**Palavras-chave:** Malária; Leishmaniose; Quinoxalina di-N-óxido; Aril-amino-álcool.

### Abstracts

Neglected diseases constitute a great health problem in today's world. However, these diseases are not of interest to the pharmaceutical industry as they generally affect populations of scarce economical resources. Here, we describe the work related to malaria and leishmaniasis that we have developed over the last ten years. Our experience in the field is focused on two families of chemical compounds: quinoxaline and arylamino alcohol derivatives. Current efforts are centered on researching new chemical entities as well as on overcoming drug resistance to antimalarial compounds. In addition, chemical entities reported by other authors and related quinoxaline derivatives are addressed. These two diseases are considered to be of great scientific and social interest, requiring new drugs so as to achieve improved treatments.

**Keywords:** Malaria; Leishmaniasis; Quinoxaline di-N-oxide; Arylaminoalcohols.

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## Quinoxaline and Arylaminoalcohol Derivatives as Antiplasmodial and Leishmanicidal Agents: A Review of our First Ten Years in the Field

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## 1. Introduction

Neglected diseases continue to cause important morbidity and mortality. The majority are tropical infectious diseases, which are medically diverse but share the feature of being diseases of poverty. From the 1,556 new drugs approved between 1975 and 2004, only 21 (1.3%) were specifically developed for tropical diseases and tuberculosis, even though, these diseases account for 11.4% of the global disease burden.<sup>1</sup> According to the WHO, neglected infectious diseases affect more than one billion human beings, mainly in tropical areas, in 149 underdeveloped or developing countries,<sup>2</sup> imposing a great economical burden to the already overloaded health

systems. Access to treatment for these diseases is problematic because the necessary medicines are unaffordable, currently ineffective, or are not adapted to local conditions of use. Due to globalized trade and travel, some diseases may emerge in the developing world or re-emerge where they were once controlled.<sup>3</sup>

The research group, led by professor Antonio Monge and integrated into the Drug Research and Development Unit of the University of Navarra, has dedicated a substantial amount of their work during the past 15 years to the search for therapeutic solutions to these types of diseases.<sup>4</sup> The first projects were related to tuberculosis, and then subsequent works were related to other significant diseases such as malaria and leishmaniasis. This review will focus on the

two latter groups of diseases. This earnest interest and dedication to provide possible solutions in the area of neglected infectious diseases (NIDs) is reflected in the fact that the University of Navarra has recently created the "Institute of Tropical Health". Its objective is to find solutions for the diagnosis, treatment, prevention and control of diseases frequently found in developing countries.

## 2. Malaria

Malaria is a devastating disease and the leading parasitic cause of morbidity and mortality worldwide, especially in developing countries where it has serious economic and social costs. Malaria is thought to slow annual economic growth by 1.3% in endemic areas with high prevalence. The economic cost of malaria in Africa is estimated at US\$12 billion every year. A total of 219 million new cases and 660,000 deaths were reported in 2010, showing the seriousness of the situation.<sup>5</sup>

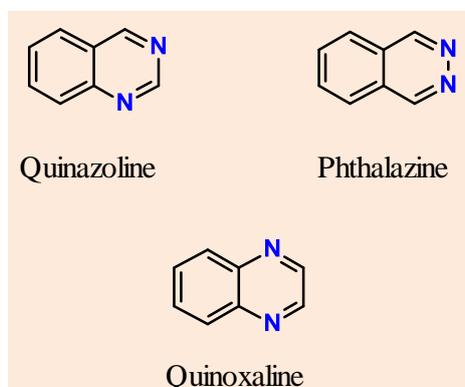
Although recent vaccine trials are giving promising results,<sup>6</sup> chemotherapy remains the mainstay of antimalarial treatment. Since chloroquine has lost its efficacy in most endemic areas due to the rapid development of drug resistance,<sup>7</sup> artemisinin-based combination therapies serve as the current gold standard.<sup>8</sup> Recently, signs of emerging

resistance to artemisinins have led to renewed efforts to develop novel antimalarial agents.<sup>9</sup>

Given our interest in obtaining active molecules against malaria and our knowledge of the quinoxaline system previously tested for our TB projects<sup>4</sup>, we decided to begin our work using quinoxaline di-*N*-oxide derivatives as a first step of introduction into this therapeutic area.

### 2.1 Quinoxaline derivatives

The first report on antimalarial activity related with quinoxaline and phthalazine systems was published in 1948.<sup>10</sup> Robert Haworth and Stanley Robinson synthesized and tested quinazoline analog compounds discussed by Curd *et al.* (Figure 1).<sup>11,12</sup> Their research basically involved the preparation of 1,4-dichlorophthalazine and 2,3-dichloroquinoxaline. In addition, amino groups, substituted anilines or dialkylamino groups successively replaced the halogen groups. The tests against *Plasmodium gallinaceum* indicated that the chlorine atom was vital for the activity. Following this same line, Crowther *et al.*<sup>13</sup> prepared a new series of dialkylaminoquinoxalines; the results demonstrated and supported the results previously obtained by Curd.<sup>11,12</sup>



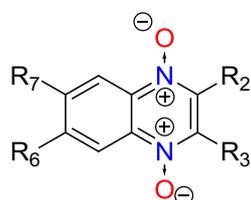
**Figure 1.** Core structures of quinazolines, phthalazines and quinoxalines

In the 1960s and 1970s, due to the similarities between quinoline and quinoxaline, as well as the presence of the quinoxaline moiety in some broad spectrum (yet toxic) antibiotics,<sup>14</sup> there was hope that quinoxaline analogs of quinoline antimalarials would exhibit antimalarial activity.

In 1974, Fisher and Moreno published two new series of substituted 5,8-dimethoxyquinoxaline,<sup>15</sup> but unfortunately, all the final compounds were inactive. Since then, reports of antimalarial activity with

quinoxaline derivatives have appeared from time to time in the reference literature.<sup>16-18</sup>

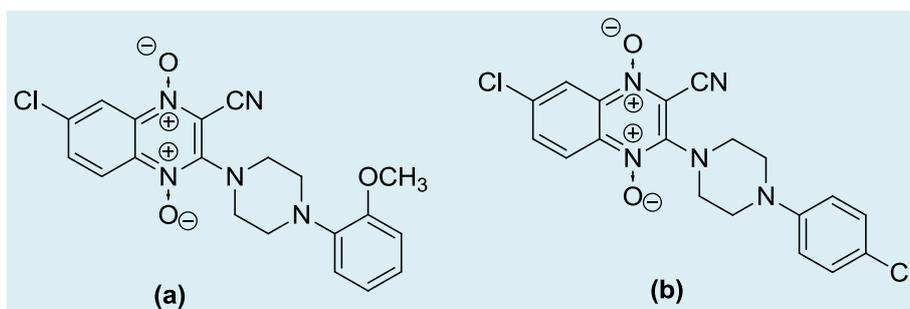
During this time, all the research was focused on reduced quinoxalines. In 2003, based on the good activities against *Mycobacterium tuberculosis* reported by some 1,4-di-*N*-oxides quinoxaline derivatives,<sup>19-21</sup> our group opened a new line of research, testing the 1,4-di-*N*-oxides quinoxaline derivatives as antimalarials (Figure 2).



**Figure 2.** General structure of quinoxaline 1,4-di-*N*-oxide derivatives

The new activity of 6-chloro-3-carbonitrile-1,4-di-*N*-oxide derivatives against *P. falciparum* that we reported,<sup>22</sup> showed IC<sub>50</sub> values around 0.05 μM and 12.6 μM, being the most active 6-chloro-2-[4-(2-methoxyphenyl)-piperazin-1-yl]-quinoxaline-3-carbonitrile 1,4-di-*N*-oxide derivative (IC<sub>50</sub> 0.05 μM) (Figure 3a). Further studies reported the antimalarial activity of two novel series: 3-aryl-2-carbonitrile-1,4-di-*N*-oxide quinoxaline and 3-aryl-2-carbonitrile quinoxaline derivatives.<sup>23</sup> This work

concluded that quinoxaline 1,4-di-*N*-oxide derivatives have superior antimalarial activity than reduced quinoxaline. In addition, the best activity was observed with non-substituted 1,4-di-*N*-oxides in position 6 and 7 of the heterocyclic ring and with a hydrogen or chlorine substituent in *para* position of the phenyl group (Figure 3b). The evaluation was performed on chloroquine-resistant *P. falciparum* strains and the reported IC<sub>50</sub> value was 0.1 μg/mL.

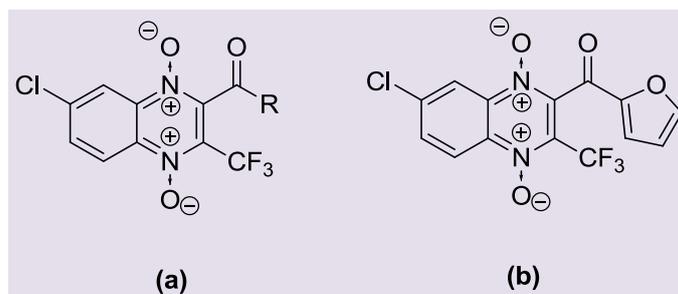


**Figure 3.** Chemical structures: (a) 6-chloro-2-[4-(2-methoxyphenyl)-piperazin-1-yl]-quinoxaline-3-carbonitrile 1,4-di-*N*-oxide derivative (b) 6-chloro-2-(4-chlorophenyl)-3-carbonitrile 1,4-di-*N*-oxide quinoxaline derivative

In 2006, based on a hypothesis regarding the bioisosteric relationship between the quinoline and pyrrolo-quinoxaline rings reported by Guillon et al.,<sup>24</sup> the *in vitro* antimalarial activity of certain 3-trifluoromethyl-2-carbonyl-1,4-di-*N*-oxide quinoxaline derivatives was reported by Zarranz *et al.*<sup>25</sup> (the best IC<sub>50</sub> value was 1.2 μM) (Figure 4a). The work described a novel structure pattern including a trifluoromethyl group in the antimalarial field, because these structures were previously only tested against tuberculosis and cancer.<sup>26,27</sup>

In 2008, after continued efforts made by the research group, 3-trifluoromethyl-2-arylcarbonyl 1,4-di-*N*-oxide quinoxaline

derivatives were synthesized and evaluated for their ability to inhibit the growth of chloroquine-resistant *P. falciparum*.<sup>28</sup> The conclusion drawn was that the optimization of the antiplasmodial profile of 3-trifluoromethyl-2-carbonyl 1,4-di-*N*-oxide quinoxaline derivatives depends on some structural characteristics, such as: (a) the presence of a trifluoromethyl group; (b) monosubstitution on the quinoxaline ring by an electron-withdrawing group or total absence of substitution; (c) a small aromatic ring linked to ketone moiety. The most active and less cytotoxic compound was 6-Chloro-3-(2-furylcarbonyl)-2-trifluoromethyl-1,4-di-*N*-oxide quinoxaline (IC<sub>50</sub> 0.1 μM) (Figure 4b).



**Figure 4.** Chemical structures: (a) 3-alkylcarbonyl-6-chloro-2-trifluoromethyl 1,4-di-*N*-oxide quinoxaline derivatives; (b) 6-Chloro-3-(2-furylcarbonyl)-2-trifluoromethyl-1,4-di-*N*-oxide quinoxaline

Novel 3-phenylquinoxaline 1,4-di-*N*-oxide derivatives were synthesized and evaluated against *P. falciparum*, including sensitive and resistant strains.<sup>29</sup> The antimalarial lead compound, 3-(4-chloro)phenyl-2-carbonitrile 1,4-di-*N*-oxide quinoxaline, was taken into account for establishing structure-activity relationship studies. The importance of a cyano group and the variations in the electronic pattern in the 1,4-di-*N*-oxide quinoxaline core were studied. The results indicated that the replacement of the cyano group by either an ester or a carboxylic acid failed to improve the antiplasmodial activity, confirming its pharmacophoric character. In addition, 6-methyl or 6-methoxy-2-phenylquinoxaline-3-carbonitrile 1,4-di-*N*-oxide compounds with chlorine or fluorine

atom in *para*-position (W) of the phenyl substituent were shown to be more actives (IC<sub>50</sub> values of 0.48 and 0.88 μM) (Figure 5).

The synthesized 3-phenylquinoxaline-2-carbonitrile 1,4-di-*N*-oxide derivatives were studied once again.<sup>30</sup> The structural modification was the substitution of the phenyl subunit in position 3 by 2-furyl or 2-thienyl moieties, based on bioisosteric replacement, a tool commonly used in medicinal chemistry (Figure 6). The results showed that only 2-thienyl derivatives had an IC<sub>50</sub> of 1 μM, whereas all the 2-furyl derivatives had IC<sub>50</sub> values between 0.49 and 0.93 μM. The data indicated that 3-(2-furyl)-2-carbonitrile 1,4-di-*N*-oxide quinoxaline derivatives appear to be novel and promising antimalarial drug candidates.

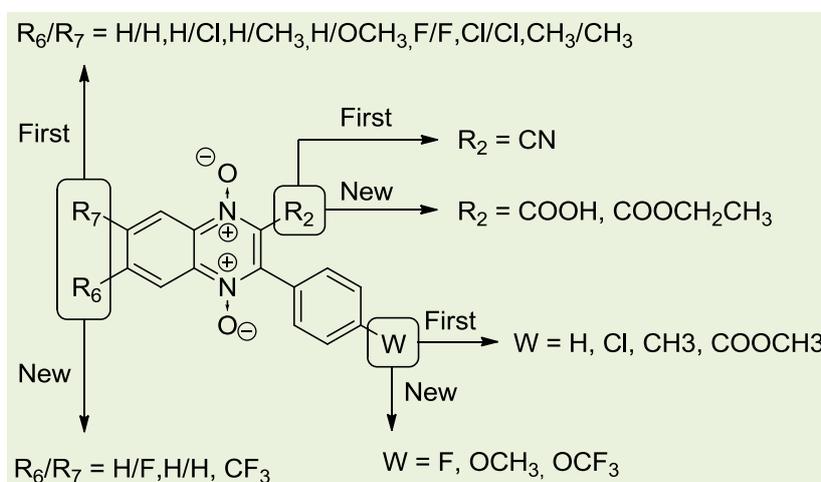


Figure 5. Scheme of the 3-phenylquinoxaline 1,4-di-*N*-oxide derivatives

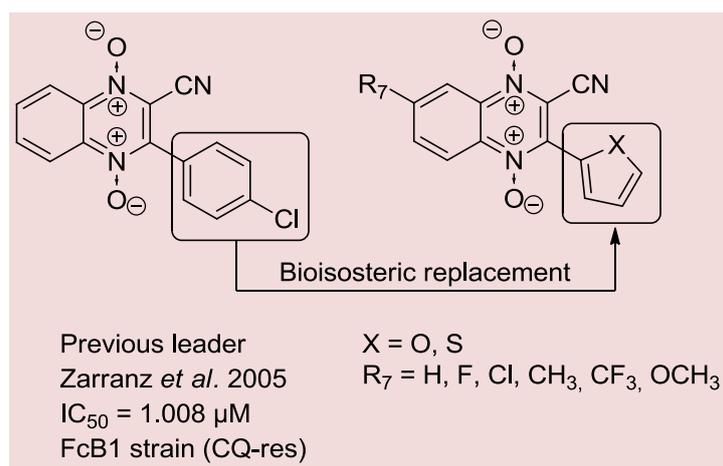


Figure 6. Design of 3-(2-furyl/thionyl)-2-carbonitrile 1,4-di-*N*-oxide quinoxaline derivatives

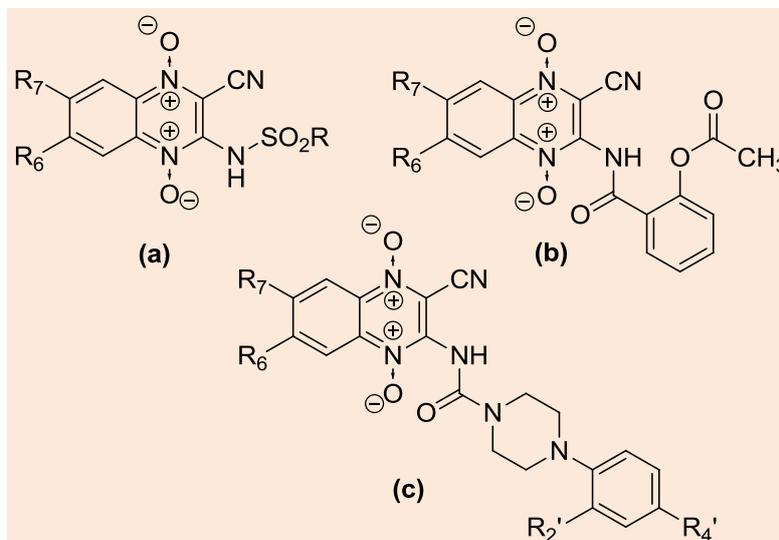
In 2010, based on the wide-ranging structure-activity relationship (SAR) data reported for 3-arylquinoxaline-2-carbonitrile 1,4-di-*N*-oxide derivatives,<sup>29,30</sup> a Quantitative Structure-Activity Relationship (QSAR) study was performed in an effort to continue identifying new active compounds against malaria.<sup>31</sup> The optimized molecular structures of 60 compounds were represented by 1497 DRAGON-type descriptors. The numerical descriptors for compounds include 1D, 2D and 3D aspects of their chemical structures. Statistical parameters showed that single lipophilicity values are unable to characterize

antiplasmodial activities ( $R=0.288$ ). The best equation was a linear model using four descriptors (MATS5e, HGM, H7vm and R1p+) ( $R=0.914$ ). Therefore, the QSAR equation was able to calculate biological activities. These results provided us insights into active and inactive structures for the following studies.

Recently, derivatives combining 3-amino-1,4-di-*N*-oxide quinoxaline-2-carbonitrile with *O*-acetyl salicyloyl chloride and aromatic sulfonyl chloride derivatives in order to synthesize sulfonamides were evaluated for their *in vitro* antimalarial activity against *P. falciparum*.<sup>32</sup> Finally, 2-cyano-3-(4-

phenylpiperazine-1-carboxamido) 1,4-di-*N*-oxide quinoxaline derivatives were evaluated for their *in vitro* antimalarial against

erythrocytic forms of *P. falciparum*.<sup>33</sup> None of these compounds showed remarkable activity (Figure 7).



**Figure 7.** General structures: (a) sulfonamide derivatives (b) salicylamide derivatives (c) phenylpiperazine-1-carboxamide derivatives

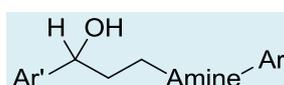
## 2.2 Arylamino alcohols derivatives

In another effort to discover new antimalarial leads, we decided to broaden the structural diversity and work with other types of molecular structures that were clearly differentiated from the quinoxaline derivatives. The arylamino alcohols were selected as a structural moiety of reference for opening a new field of work.

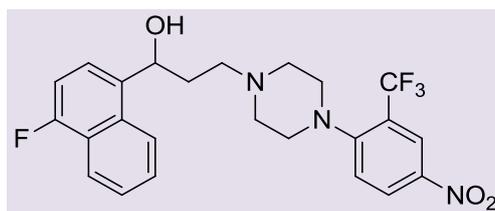
Arylamino alcohols are an important group of compounds with known antimalarial activity and they have been used as antimalarial agents since the 40's.<sup>34</sup> Hydroxypropyl-piperazines derivatives, belonging to this chemical family, have shown outstanding activity against *P. falciparum* chloroquine-resistant strains.<sup>35,36</sup> According to recent publications,<sup>37,38</sup> arylamino alcohol derivatives could target the *Plasmodium plasmepsin II* enzyme. This

enzyme, of recent interest, is involved in the initial steps of the hemoglobin degradation, which is a critical issue in the intra-erythrocytic cycle of the parasite, taking place inside the food vacuole.<sup>39</sup>

Therefore, we began studying the antiplasmodial activity and docking properties of new arylamino alcohol derivatives. As a result, a new possible pharmacophore was proposed (Figure 8), where Ar' is an optionally substituted aromatic group selected from the phenyl, naphthyl and benzo[b]thiophenyl groups. "Amine" is a cyclic amine attached to the aromatic system by a chain of propanol; a third fragment of the molecule is inserted as aromatic moiety, preferably with withdrawing groups (Ar). A representative compound is the fluoronaphthyl derivative (Figure 9) with an IC<sub>50</sub> of 0.5 μM similar to that of the control drug, chloroquine, against resistant strain.



**Figure 8.** Scheme of the proposed pharmacophore



**Figure 9.** Chemical structure of (1-(4-fluoronaphthalen-1-yl)-3-[4-(4-nitro-2-trifluoromethylphenyl) piperazin-1-yl] propan-1-ol) (I)

Moreover, the arylamino alcohol derivatives were active *in vivo* in murine model. As a result of the data obtained with this type of molecules, we discovered compounds with a promising profile as antiplasmodial agents.<sup>36</sup>

Parallely, important facts, such as the genome project and advancement of computer technology and techniques within the computer-assisted drug discovery and development (CADD) discipline, have revolutionized the manner in which public and private laboratories work. Novel techniques or approaches such as absorption, distribution, metabolism, excretion and toxicity (ADMET) prediction, molecular docking, homology modeling, and molecular dynamics, among others, are currently part of the routine procedures in several drug discovery groups. Our group who consciously takes these approaches as new opportunities, carried out research in which the *in silico* component reveals important findings and new evidence.

With regard to malaria, our group has performed molecular modeling studies in order to search and study mechanisms that would permit the obtainment of novel antimalarial compounds. Among these studies, routine geometric optimization is used to locate stable conformations of a molecule. Molecular electrostatic potential (MEP) is calculated to understand the electrostatic properties based on charge densities; docking procedures are used to predict how small molecules, such as substrates or drug candidates, bind to a receptor of known 3D structure.

Geometric optimization, MEP and computational molecular binding studies were carried out by our group in order to study the possible interactions of compound (I) with a potential target, responsible for the biological activity. MEP was generated for compound I after its geometry was energy-minimized. As was expected, computed potentials using *ab initio* method showed a net electronegative potential around the piperazine group and partial electronegative potentials around fluorine, hydroxyl and nitro groups. From this, it can be deduced that the most active compounds would share a similar distribution of electronegative potential and mode of action. Computational docking study was then performed between plasmepsin II and compound (I). We found that this compound made a hydrogen bond with one of the catalytic aspartates on the active site of the enzyme (Asp214 and Asp34). This interaction involves the unique hydroxyl group present in the compound and residue Asp214 (Figure 10). In addition, it provides a possible and rational explanation of the important role of hydroxyl group in modulating the activity of the compound. In fact, as previously reported, this interaction is mandatory in plasmepsin II inhibitors.<sup>40</sup> This mode of union is associated with a free Gibbs energy of -6.16 kcal/mol with a theoretical  $K_i$  of 30.6  $\mu$ M which is higher than other values of free energy of piperazine derivatives.<sup>37</sup> This fact is also reflected in the  $IC_{50}$  value reported for this compound from our *in vitro* results. Molecular docking studies also suggested subsites of union to compound (I), situated near the S1', S1 and S3 pockets of the protein.<sup>36</sup> The 4-nitro-2-trifluoromethyl

phenyl group of this conformation was set close to the S1 and S3 pockets and the 4-fluoro-1-naphtyl is located in the vicinity of the S2 pocket.

Further investigations are warranted in order to explore the properties of the arylamino alcohols as possible antimalarial

drugs. A study will be conducted in order to find new galenic forms so as to enhance its bioavailability. The separation of the enantiomeric forms of the most interesting compounds is also planned in order to identify the stereoisomer responsible for the activity.



**Figure 10.** Molecular binding study between compound (I) (green) and protein plasmepsin II (yellow). Representation of the best conformation found for compound (I) within the active site of plasmepsin II. Hydrogen bond interaction (involving the hydroxyl group and Asp214) is coded by yellow dashed lines. Active site residues Asp 214 and Asp34 are displayed by white sticks

### 3. Leishmaniasis

Although leishmaniasis is not comparable with malaria with regard to its lower morbidity and mortality rates, it can be said that the former surpasses the latter due to the lack of interest and lack of resources that the pharmaceutical industry dedicates in the study of this disease.

Leishmania parasites are named after W.B Leishman, who developed one of the earliest stains of leishmaniasis in 1901. Visceral leishmaniasis (VL), the most serious form, also known as kala-azar, is a disseminated intracellular protozoan infection.

Leishmaniasis occurs in 98 countries, with 350 million people living at risk of this disease. VL affects poor populations living in remote areas throughout more than 80 countries across Asia, East Africa, South America, and the Mediterranean region. The 7 most affected countries – Bangladesh, Brazil, India, Ethiopia, Kenya, Nepal, and Sudan – represent over 90% of new cases. Cutaneous Leishmaniasis (CL), the most common form of the disease, has a broader geographic range. The impact of the disease is 300,000 new cases of VL each year, 1 million new cases of CL each year, and 40,000 deaths due to VL. A lack of surveillance systems and the frequency of disease in remote areas and marginalized population

mean that it is difficult to estimate the true incidence of leishmaniasis and the case-fatality of VL.<sup>1</sup>

The drugs being used are antimonials, pentamidine and amphotericin B, all of which are toxic and must be administered via injection. In addition, this therapy is expensive and has a limited therapeutic range.<sup>41</sup> Although miltefosine has been found to be active when administered by oral route in the treatment of mucosal leishmaniasis in Bolivia,<sup>42</sup> it is not very active in the other forms of leishmaniasis.<sup>43</sup>

### 3.1 Leishmanicidal activity of quinoxaline 1,4-di-*N*-oxides

In the search for molecules that are active against leishmaniasis, our work began by using quinoxaline di-*N*-oxide derivatives.

Compared to other studied fields, the exploration of the quinoxaline nucleus is very recent. In 2003, Loriga *et al.* published the first report of anti-leishmanial activity related to quinoxaline.<sup>44</sup> They reported trifluoromethylquinoxalines as analogs of classical and non-classical antifolate methotrexate and trimetrexate. In 2006, a series of 29 new quinoxalines was synthesized and evaluated *in vitro* against *Leishmania donovani*. Several of these compounds displayed interesting activities, and four quinoxaline amides showed *in vitro* antileishmanial properties (IC<sub>50</sub> less than 20 μM).<sup>45</sup>

Finally, in 2007, an original series of 4-substituted pyrrolo[1,2-*a*]quinoxaline derivatives, new structural analogs of the

Galipea species of quinoline alkaloids, was synthesized from various substituted 2-nitroanilines via multistep heterocyclizations and tested for *in vitro* antiparasitic activity on *Leishmania amazonensis* and *Leishmania infantum* strains.<sup>46</sup>

As in the case of malaria, reduced quinoxalines alone had been previously studied. In 2008, our group thought to introduce the quinoxaline di-*N*-oxide moiety in a chalcone system in order to initiate a new line of research against leishmaniasis. Chalcones are ketones that are abundantly distributed throughout the plant kingdom, with a broad range of biological activities, among which antimalarial and leishmanicidal activities are included. In 2006, Boeck *et al.*<sup>47</sup> synthesized analogs of a natural chalcone using xanthoxyline and some derivatives, and they showed that some of them displayed selective activity against the parasites compared with the natural chalcone. Licochalcone A was isolated from Chinese liquorice and it showed interesting activity on visceral and cutaneous leishmaniasis when administered by oral route (Figure 11).<sup>48</sup> In this way, a series of ring-substituted 3-phenyl-1-(1,4-di-*N*-oxide quinoxalin-2-yl)-2-propen-1-one derivatives were synthesized and tested for *in vitro* leishmanicidal activity against amastigotes of *L. amazonensis* in axenic cultures and murine-infected macrophages (Figure 12). Structure-activity relationships demonstrated the importance of a methoxy radical at position R3', R4' and R5'. (2*E*)-3-(3,4,5-trimethoxy-phenyl)-1-(3,6,7-trimethyl-1,4-dioxy-quinoxalin-2-yl)-propenone was the most active. Cytotoxicity on macrophages revealed that this product was almost six times more active than it was toxic.<sup>49</sup>

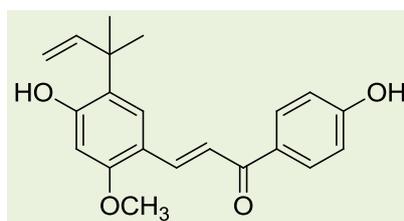
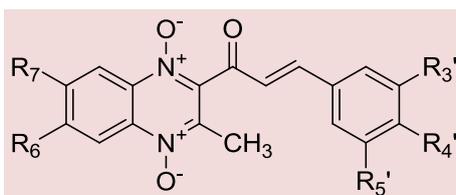


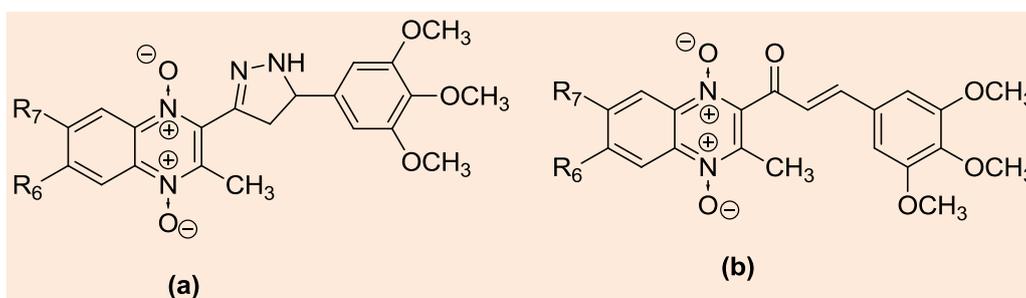
Figure 11. Licochalcone A



**Figure 12.** General structure of 3-phenyl-1-(1,4-di-*N*-oxide quinoxalin-2-yl)-2-propen-1-one derivatives

In 2011, 4,5-dihydro-1-*H*-pyrazole and propenone quinoxaline derivatives were tested against intracellular forms of *L. peruviana* (Figure 13). Both series were tested for toxicity against proliferative and nonproliferative cells. The compound (2*E*)-3-

(3,4,5-trimethoxyphenyl)-1-(3,(6),7-dimethyl-1,4-quinoxalin-2-yl)-propenone was found to inhibit 50% of *Leishmania* growth at 8.9  $\mu$ M, with no impact against proliferative kidney cells and with low toxicity against THP-1 cells and murine macrophages.<sup>50</sup>



**Figure 13.** General structures: (a) trimethoxyphenyl-4,5-dihydro-1-*H*-pyrazole 1,4-di-*N*-oxide quinoxaline derivatives; (b) trimethoxy-phenyl propenone quinoxaline derivatives

As previously reported in the malaria section, in 2011, Barea *et al.* synthesized and evaluated 3-amino-2-carbonitrile 1,4-di-*N*-oxide quinoxaline derivatives.<sup>32</sup> These compounds were also evaluated against *L. amazonensis*. Unfortunately, relevant activities were not reported. A similar case was observed for thirteen new 2-cyano-3-(4-phenylpiperazine-1-carboxamido) 1,4-di-*N*-oxide quinoxaline derivatives synthesized and evaluated against *L. infantum*. However, two of them showed good activity.<sup>33</sup> Our future plans with regard to leishmania include defining a reference target on which to base the design of new molecules that improve the activities obtained up to now and which can be interpreted as an advancement in the fight against this disease.

#### 4. Conclusions and Outlook

The research based on the quinoxaline nucleus has led to the obtainment of compounds with good activity, thereby permitting us to take the next step in our work, which involves compound optimization. The arylamino alcohol system appears to be very interesting with regard to carrying out further in depth studies. Therefore, our intention is to continue using classic and modern approaches in this field, such as *in silico* ADMET prediction and docking studies, carried out by our group in this field. In the following months, the metabolism predictions and the optimizations of the drug-likeness behavior will be our new goals for obtaining better

molecules as drug candidates. Our objective is to be able to contribute to the discovery of drugs for “neglected diseases”, providing products that alleviate suffering and serve as valid treatments for these illnesses.

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