New synthetic approaches to rigid indole-imidazole frameworks and their study as antileishmanial agents

Keywords: Palladium, leishmania, topoisomerase, green chemistry, electrochemistry, mechanochemistry, cross-coupling.

PE5_18 Medicinal Chemistry

LS6_6 Infectious Disease

PE5_17 Organic Chemistry

3. General presentation of the project and state of the art

Leishmaniasis is a neglected parasitic disease, which is endemic in almost 100 countries. It exists in almost 20 different forms, the most severe of which (kala-azar) infects 300,000 patients per year, out of which 40,000 die. Current treatments [1] are very limited and is based on only a few drugs, which often exhibit important side effects, high production costs and, with the exception of oral miltefosine and topical paromomycin, require parenteral administration and therefore hospitalization of the patient. Furthermore, drug resistance is frequent and threatens the effectiveness of chemotherapy. Thus, there is an urgent need to discover new antileishmanial drugs.

Recently, the antileishmanial activity of a family of polycyclic nitrogen heterocycles derived from the imidazo[1',2':1,2]pyrido[3,4-b]indole skeleton (**1**) has been discovered by the Urbino group, although the number of examples studied is limited. Some of these compounds are promising, having shown sub-micromolar activities in *Leishmania infantum* amastigotes and excellent selectivity indexes, in the 250-300 range. The synthesis of **1** was based on a palladium-catalyzed double C-H activation process from indole-based alkyl-linked biheterocycles.[2]

4. Objectives

The main objectives of this project (figure 1) are:

Extension of the initial library in order to obtain reliable struture-activity relationships by variation in the R^1-R^4 substituents. Isosteric replacements of the imidazole ring (oxazole, thiazole) as well as its extension to benzimidazole will be studied. The introduction of substituents bearing ionizable groups to increase aqueous solubility will also be considered.

Study of green methodologies for the C-H/C-H activation process for the formation of the desired C-C bond.

Determination of biological activities and establishment of structure-activity relationships in order to aid additional optimization cycles. This part of the project will be performed in collaboration with the groups of Prof. Anabela Cordeiro Silva at the University of Porto (Portugal) and Prof. Luca Galluzzi at the University of Urbino. Mechanistic studies will also be performed and will be in principle aimed at leishmanial topoisomerase enzymes in collaboration with the group of Prof. Rafael Balaña Fouce at the University of Leon (Spain). This work, if successful, will be supported by molecular modeling studies in collaboration with Prof. Alessio Lodola at the University of Parma.

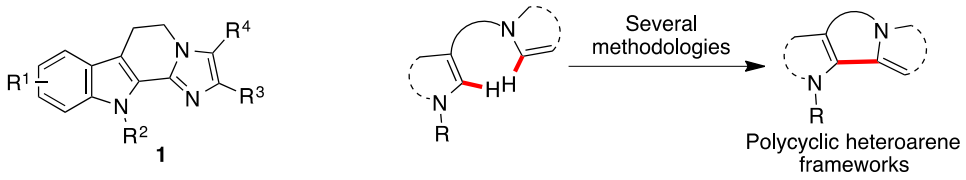

Figure 1

5. Methodology

Nowadays green chemistry should be one of the methodologies objectives of synthesis. Therefore, green chemistry methodologies are included in this project, in particular the use of Pd catalysis, electrochemical and mechanochemical methods.

The use of 3d metals for catalysis is already a greener methodology than conventional cross-coupling reactions because these base metals appear in many biological processes and are less toxic than their 4d and 5d counterparts. Moreover, the use of electrochemistry for the functionalization of C-H bonds uses those 3d metals and uses electricity as oxidant which leads to more economical and environmentally friendly reactions. Another methodology that exhibits green characteristics is mechanochemistry, which takes place in the absence of solvents or external heating[3].

The biological study of the libraries will be performed in collaborative work. Computational studies will involve docking and molecular dynamics studies.

6. Expected Results

Novel, efficient and green methods of C-H activation for the formation of C-C bonds are expected to be discovered, as well as obtaining relevant information about between structure-activity relationships of a several libraries of polycyclic nitrogen heterocycles, in order to reach a good candidate molecule for development as an antileishmanial.

7. References

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(2) Mantenuto, S.; Ciccolini, C.; Lucarini, S.; Piersanti, G.; Favi, G.; Mantellini, F. *Organic Letters* **2017**, *19* (3), 608–611. https://doi.org/10.1021/acs.orglett.6b03775.

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8. Description of the research in the three-year period (feasibility)

The initial structure-activity relationship studies will be carried out during the first half of the research at Urbino University, initially employing Pd-catalyzed double C-H reactions in solution. The experience of the Urbino group in this chemistry guarantees the feasibility of this part of the project. Mechanochemical reactions will take place at Universidad Complutense during the second half of the research work, and again the experience of the Madrid group in this area will be an important asset in project feasibility. The electrochemical and molecular modeling work will be performed at both sites.