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SYNTHESIS AND ANTI-LEISHMANIAL EVALUATION OF NEW 2-AMINOSELENOPHENE DERIVATIVES AS ISOSTERES OF THE PROMISING DRUGS 2-AMINOTHIOPHENES

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ABSTRACT

Background: Leishmaniasis is one of the main neglected tropical diseases, according to the WHO. Its causative agents are protozoan of the genus *Leishmania sp.*, which are transmitted by the bite of a female phlebotomine vector. This infection has an incidence in more than 100 countries, with an estimated 12 million new cases a year. According to its clinical manifestations, it can be classified as mucocutaneous, cutaneous or visceral, the latter being the most serious form. Treatment remains limited to chemotherapy, based on old drugs, which are highly toxic, cause side effects and have led to the emergence of parasite resistance. There is therefore a clear need to develop new, more effective and safer drugs against *Leishmania sp*. In this sense, thiophenic derivatives have stood out as anti-*Leishmania* agents, and have even been the subject of studies by our research group, which has achieved excellent results for 2-aminothiophene-indole derivatives. The optimization of known prototypes involves the use of medicinal chemistry tools, such as bioisosterism. Thus, the potential of 2-aminothiophene-indole leads and the use of bioisosterism have stimulated the development of new promising series of 2-aminoselenophenes for their anti-*Leishmania* evaluations. **Objectives:** The aim of this study was the design and synthesis of new 2-aminoselenophenic derivatives, based on a proposal for bioisosterism from 2-aminothiophenic leads, to evaluate their anti-*Leishmania* potential. **Methods:** 2-Aminoselenophen adducts were synthesized using the Gewald reaction and then used as a starting point for condensation reactions with different substituted aromatic aldehydes. The reactions were monitored by thin-layer chromatography and the products purified by filtration. The physicochemical properties of the final derivatives were determined, and their chemical structures confirmed by infrared (IR) and nuclear magnetic resonance (NMR) spectroscopy. The compounds obtained were evaluated against promastigote forms of four strains of *Leishmania sp*. by MTT assay to determine their IC_{50} values. Cytotoxicity tests were carried out on RAW 264.7 macrophages, also by MTT method, allowing their CC_{50} values and selectivity indices to be determined. **Results and Discussion:** The final compounds planned were successfully obtained, with all their chemical structures confirmed by IR and NMR spectroscopy. Characteristic signals of the expected chemical structures could therefore be identified, such as absorption bands close to 1,600 cm^{-1} and a ^1H NMR chemical shift, in the form of singlet, between 8.5 and 9.0 ppm, both consistent with the imine group. For the biological evaluations, derivatives with $IC_{50} < 10$ µM were considered active. In general, series **2** derivatives were more active against *Leishmania sp*. strains than series **1** derivatives. The increased size of the cycloalkyl ring fused to the selenophene heterocycle may be the reason for this improvement, in line with what was observed for known 2-aminothiophene-indole derivatives. Among the most active derivatives, there was outstanding anti-*Leishmania* activity against the four strains tested, for representatives of series **2** (IC_{50} of 2.67-4.93 µM) with electron withdrawing substituents on the indolic portion or, in the case of the most potent compound, the substitution of this portion by an indazole ring, showing the positive effect of the increase in nitrogen heteroatoms in the aromatic system. None of the derivatives showed cytotoxicity against RAW 264.7 macrophages. **Conclusion:** The structural evidence of the expected final compounds clearly shows the success of the synthetic strategies used and the purification procedures adopted. The biological results confirmed that the bioisosterism strategy maintained the non-cytotoxic and anti-*Leishmania* profile of the 2-aminothiophene prototypes, highlighting the potential of 2-aminoselenophenes.