Synthetic indol and melatonin derivatives exhibit antimalarial activity on the cell cycle of the human malaria parasite Plasmodium falciparum

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Keywords: melatonin, indol derivatives, *Plasmodium falciparum*, *malaria.*

Introduction

Annually, more than 300 million people are infected by the Plasmodium protozoan the ethiological agent of malaria and approximately one million people are expected to die each year acccording to the World Health Organization (WHO). Whereas chemotherapy has previously been quite successful in the treatment of malaria, the *Plasmodium* parasite currently exhibits an increased resistance to classical antimalarials, hastening the search for new compounds[1].

Discovering the mechanisms by which cell signaling controls the cell cycle of the human malaria parasite *Plasmodium falciparum* is fundamental to designing more effective antimalarials. To better understand the impacts of melatonin structure and function on the cell cycle of *P. falciparum*, we have synthesized two families of structurally-related melatonin compounds. All synthesized melatonin analogs were assayed in *P. falciparum* culture and their antimalarial activities were measured by flow cytometry.

Results and Discussion

Melatonin has a central role in the control of parasite replication and establishment of parasitemia, so targeting and blocking this hormone pathway can contribute to the discovery of new antimalarial drugs. Our interest in the development of new melatonin antagonists prompted us to synthesize and test the ability of new melatonin-related compounds 7-11 and 12-16 to modulate the human malaria parasite cell cycle and block parasite's development acting as antimalarials. Among the melatonin derivatives, only the compounds 12, 13 and 14 were capable of inhibiting the *P. falciparum* growth in low micromolar IC50. These results open good perspectives for the development of new drugs with novel mechanisms of action.

Conclusions

We tested the ability of these two series of 2-(indol-3-yl)ethylamine derivatives 7-11 and (2-(5-methoxy-1H-indol-3-yl)ethyl)amine derivatives 12-16 to modulate the cycle of the parasite, similarly to melatonin, as well assessed the ability of these compounds to block the effect of the hormone on cell cycle of *P. falciparum*, acting as inhibitors. Compounds 9 and 10 shown promising results, not being able to modulate cycle of the parasite but being able to block the effect of melatonin in *Plasmodium*.

Compounds 12-14 are promising lead structures for the development of new derivatives with antimalarial activity. We are currently working with these compounds to increase their activities, in particular by introducing structural changes at position N-1 of the indole ring.

Acknowledgments

We thank FAPESP, Malaria CNPq-FAPESP Pronex, and INCT-INBqMed for funding C.R.S. Garcia and V. Ferreira are CNPQ fellows. D.S. received a CAPES Fellowship.

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