Antileishmanial screening of a library of *N*-acylhydrazones

Fernanda R. Andre[1] (PG), Carina R. Amorim[1] (PG), Patrícia B. Xander[1] (PQ), Daniela G. Rando[1] (PQ)*.
[1]Instituto de Ciências Ambientais, Químicas e Farmacêuticas da Universidade Federal de São Paulo

*UNIFESP- Campus Diadema – Rua São Nicolau, 210, 2º andar, Diadema, SP. *dgrando@unifesp.br*

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Introduction

Leishmaniasis is a neglected disease provoked by protozoa from *Leishmania* genus and which is responsible for 350 million cases in 88 countries[1]. Due to a limited and unappropriated therapeutics, it has become urgent the need for new antileishmanial drugs. Cysteine proteases are enzymes related with several parasite vital processes, such as host cell invasion. These proteases, therefore, have become potential targets to be explored. Nitro compounds, for instance, have their antiprotozoal activities recently associated with inhibition of parasites cysteine proteases, in addition to their well-known free radical production mechanism through nitro group reduction[2]. This work aims the search for new antileishmanial compounds by means of screening a library of nitro *N*-acylhydrazones and analogues, against cultures of *Leishmania amazonensis*.

Results and Discussions

A series of 24 compounds was synthesized by parallel synthesis methodologies and by applying two sets of building blocks.

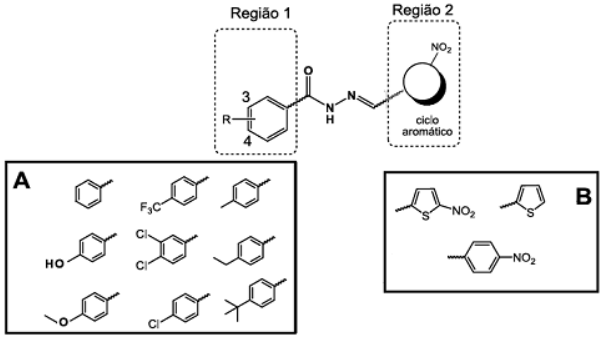
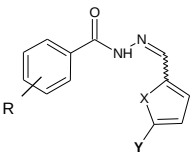


Figure 1. *N*-acylhydrazones synthesized library.

Molecular diversification was accomplished by varying the general hydrophobicity of compounds (set A), and the kind of ring system directly bounded to the nitro group (set B). Non-nitrated compounds were also proposed aiming to point out the importance of the nitro itself to the antileishmanial activity. Compounds were synthesized with variable yields, but in good purity. Promastigotes of *L. amazonensis* were exposed to compounds at five different concentrations (25 to 0,78 μg/mL) and IC_{50} values calculated and expressed in μM (Table 1).

Table 1. Antileishmanial activities (μM).



R	IC_{50} (μM)		
	X: S Y: NO_2	X: S Y: H	X: CH=CH Y: NO_2
H	5.16	354.09	ND
4-METHYL	2.75	116.35	93.72
4-ETHYL	4.68	225.26	Inactive
4-TERCBUTYL	ND	9.81	70.67
4-METHOXI	2.51	112.55	Inactive
4-CHLORO	9.88	207.1	Inactive
3,4-DICHLORO	3.90	ND	38.95
4-HYDROXI	ND	ND	354.09
PENTAMIDINE	2,29		
AMPHOTERICIN	26,77		

*ND – not determined

Conclusions

Substitution of thiophene by its isostere benzene decreased the antileishmanial action of the compounds, indicating the importance of sulfur heteroatom to this activity. Nitro group seems to be important but not essential to the activity since the non-nitrated *tert*-butyl derivative showed significant IC_{50} value (9.9 μM). The best derivatives, however, were those presenting the nitro group and thiophene system. Qualitative structure-activity relationship studies have already been started aiming to explain the behavior of the series.

Acknowledgments

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[1]WHO. World Health Organization. Accessed on September, **2014**, in Leishmaniasis: http://www.who.int/leishmaniasis/en/.
[2]Rojas, R.. Instituto de Ciências Biomédicas, Universidade de São Paulo, **2007**, p.14-20.