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Evaluation of novel N^2-alkyl and N^2,N^4-dialkyl Nitrofurazones derivatives as a possible antituberculosis agents

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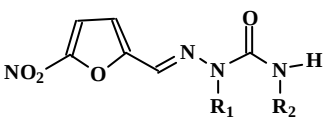
Introduction

A key problem in tuberculosis control is the persistence of *Mycobacterium tuberculosis*, despite prolonged chemotherapy. The emergence of difficult to cure multi drug-resistant tuberculosis is of great concern[1]. Mycobacteria are obligate aerobes, however, tubercle bacilli encounter hypoxic environments *in vivo*. Nitrocompounds are important class of antimicrobial agent, and the nitro group acts as an electron acceptor (reduction), interrupting the normal electron flow, with consequent DNA damage[2]. The nitrofurans are exceptional compounds for their range of activity, the relative lack of resistance, and their interesting chemistry[3]. Besides, Nitrofurazone presents weak solubility in watery way, being its total solubility gotten in DMF or DMSO and that compound with low or negative C log *P* (bioavailability) values cross the cell membranes very poorly[4]. Here, we report the *in vitro* antimycobacterium activity, for Nitrofurazone and novel N^2-alkyl and N^2,N^4-dialkyl derivatives, planned as more lipophylic agents.

Results and Discussion

Nitrofurazone (**NF**) and derivatives (**2a-d**) are showed in figure below, and dissolved in 30% of DMSO. For



NF - $R_1 = R_2 = H$
2a - R_1 = Butyl, $R_2 = H$
2b - R_1 = Pentyl, $R_2 = H$
2c - $R_1 = R_2$ = Butyl
2d - $R_1 = R_2$ = Pentyl

figure

the minimum inhibitory concentration (MIC) tests, the drugs was first diluted to the highest concentration (32 µg/mL) and then serial twofold dilutions were performed in a concentration range from 32µg/mL to 0,125 µg/mL in plates containing Müeller Hinton-Agar. The results of antimicrobial susceptibility testing against *Mycobacterium tuberculosis* and *Mycobacterium smegmatis* are showed in table 1. Nitrofurazone, also compound **2a** and **2b** had shown a moderate activity, strengthening the importance of the nitrofurans for the treatment against tubercle bacilli.

Table 1 Bactericidal activity of Nitrofurazone (**NF**) and derivatives against mycobacterium strains (spot test).

Microorganisms *	Inhibition zone in diameter (mm) at 300µg/mL				
	NF	**2a**	**2b**	**2c**	**2d**
M. tuberculosis	27	40	40	23	25
M. smegmatis	30	27	21	15	10

*From collection Dept. of Antibiotics of UFPE.

N^2,N^4-dialkyl-substituition (**2c-d**), more lipophylic of them all, do not showed any improvement of activity. Although, our results showed that, both N^2-alkyl derivatives have structurally requirements in order to retain activity against mycobacterium. Looking for these appreciative results**,** the bacteriostatic activity for *M. tuberculosis* was determinate *in vitro* for compound **2a** and the MIC values was equal to 10µg/mL, showing a highest potency against this strain, and more active than Nitrofurazone (the literature related that Nitrofurazone show MIC of 10-25mg/mL for mycobacterium strains)[1]. As well, all compounds showed potentially as good reducers (0.593 to 0.651V vs Ag|AgCl, Cl^- 0.1 mol.L^{-1}), favourable range to be reduced *in vivo*. As previously suggested, the redox potential can play an important role for the bactericidal activity of nitrofurans[1].

Conclusions

In summary, we can affirms that derivative **2a** is more potent than Nitrofurazone, considering its good values for the MIC and also it has a superior molecular weight, what results in a final lesser molar concentration in this assay. The gotten results had disclosed that the increase of liposolubility for Nitrofurazone is an important molecular modification for optimisation of this drug.

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