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

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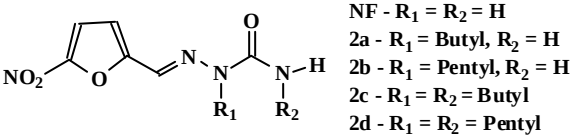
Introduction

Nitrofurazone is a potent antichagasic agent, that present weak solubility in watery way, being its total solubility gotten in DMF or DMSO[1]. The molecular modifications in Nitrofurazone structure so far are limited alkylation / arylation in the NH of amide or then in reduction of hydrazone group. Both modifications do not reveal improvement in the pharmacological optimisation of these compounds, since the hydrazone group is important for the complexing abilities with metals and that the free amide is a structural requisite for the antimicrobial action of compounds containing semicarbazones or thiosemicarbazones moiety[2]. Thus we have planed the introduction of a flexible alkyl side chain selectively in the N^2-hydrazine position and unselectively N^2,N^4-semicarbazide position (figure 1). Nitrofurazone (**NF**) and derivatives (**2a-d**) were characterised for their activity against epimastigote form of *T. cruzi* (IC_{50} in nM), as well the first cathodic potentials (*E*pc) measured by cyclic voltammetry and frontier molecular orbital LUMO values (at AM1 semiempirical level, with geometry optimised).

Results and Discussion



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 1

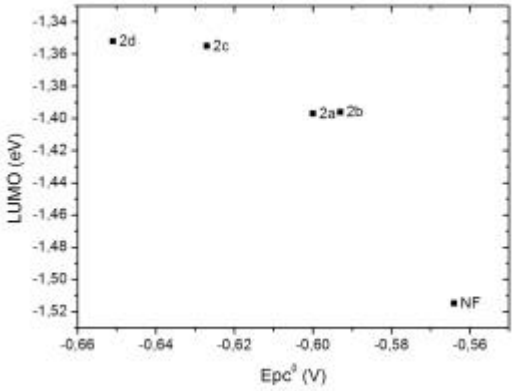
As shown in **Table 1**, compound N^2,N^4-dipentyl-Nitrofurazone (**2d**) was the most potent antitrypanosomal agent. The simple extension of the *n*-butyl of **2a** to *n*-pentyl **2b** reduce the potency in this agents, however, the extension of *n*-butyl (compound **2c**) to *n*-pentyl (compound **2d**) gives three times improvement of activity, with potency equivalent to Benznidazole and more potent than prototype, Nitrofurazone. These results could show that the Nitrofurazone is a potent antitrypanosomal agent, but, presumably, present limitation in transport for cross cell membranes.

Table 1: Biological and chemical properties of developed 5-nitrofuryl derivatives.

Drug	Y strain		C log*P*
	IC_{50} (nM)	$rPGI_{NF}$*	
NF	2.20	PGI = 40%	0.23
2a	4.63	0.7	1.57
2b	6.64	0.4	2.07
2c	4.71	0.7	2.76
2d	1.05	1.8	2.85
Benznidazol	1.82		1.2

*PGI_{NF} is ratio of percentage of growth inhibition at 1,5 nM for Nitroturazone (PGI is percentage of growth inhibition at 1,5 nM).

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. Analysis of E_{pc} versus the LUMO energy (eV), calculated at AM1 level, were performed and finding that how more negative are the reduction potentials, less negative are the LUMO energies, or smaller are the electron affinities (graphic 1).



Conclusions

These finding to indicate that the improvement of C log *P* and with maintenance or increase of reduction potential (E_{pc}) are important parameters for optimisation of antichagasic agents.

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[1] Chung M.C, Guido R.V.C, Martinelli T.F, Ferreira E. I. *Bioorg. Med. Chem.* **2003**, *11*, 4779-4783.

[2] Cerecetto H, F. *Bioorg. Med. Chem.* **2004**, *12*, 4885-4893.