SYNTHESIS OF METHYLIDENE-1-TETRALONE DERIVATIVES WITH POTENTIAL ANTI-CHAGASIC ACTIVITY

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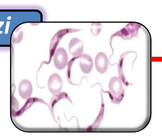
Introduction

Tripanosomiasis Americana (Enfermedad de Chagas)[1-2]

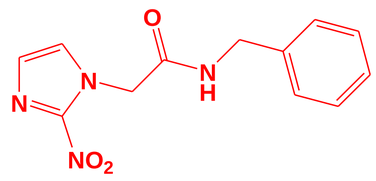
Enfermedad infecciosa parasitaria causada por *T. cruzi*



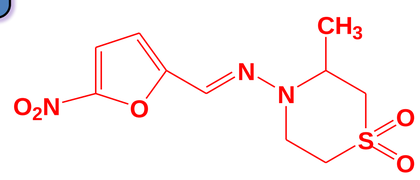
Afecta 6 millones de personas en el mundo, 30.000 nuevos casos anuales y 12.000 defunciones anuales.

Tratamiento basado

- Benznidazol (Bnz)



- Nifurtimox (Nfx)

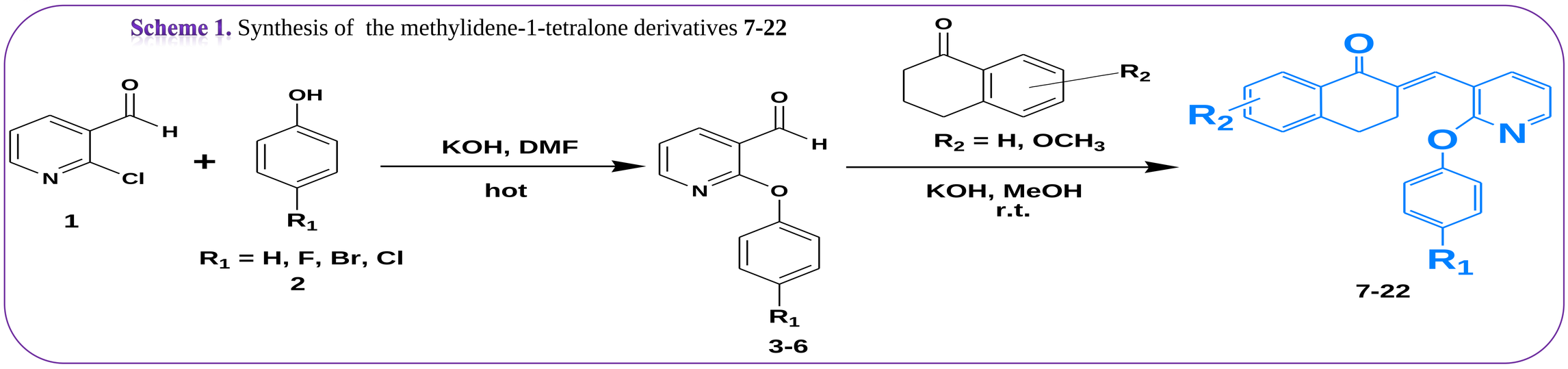


T. Cruzi Ha creado RESISTENCIA

Synthesis of methylidene-1-tetralone derivatives

Intermediates **3-6** were generated through simple nucleophilic substitution of **1** with **2**. Final compounds **7-22** were generated through a Claisen-Schmidt cross aldol condensation between **3-6** and the 1-tetralone respective (scheme 1), the final products were obtained between 41-96% yield. The synthesized compounds **7-22** were characterized using modern spectroscopic techniques of ^{1}H NMR, ^{13}C NMR and IR taken in a Perkin Elmer with Fourier transform.

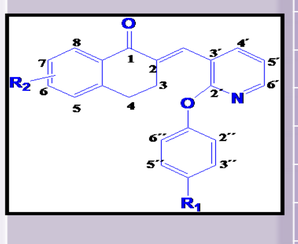
Scheme 1. Synthesis of the methylidene-1-tetralone derivatives **7-22**



Biological Results

Compounds **19** and **20** exhibited moderate trypanocidal activity, while compounds **21** and **22** showed a marked inhibitory effect on the growth of the epimasigotes of *T. cruzi* (table I).

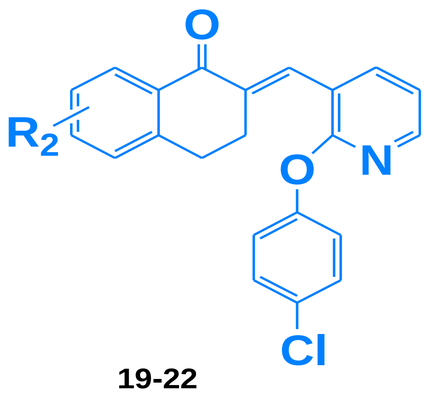
Table I. Evaluation of the anti-chagasic activity of the derivatives methylidene-1-tetralone **7-22** on *T. cruzi* epimastigotes, VERO cells and BMDM cells, by the MTT method.

COMPOUND		R_1	R_2	IC_{50} (µM) 72 h *T. cruzi* (YBM)	VERO	BMDM
	7	H	H	> 60	> 100	> 1000
	8	H	5-OCH_3	> 60	< 100	> 1000
	9	H	6-OCH_3	> 60	89 ± 15	< 1000
	10	H	7-OCH_3	> 60	< 100	< 1000
	11	F	H	> 100	–	–
	12	F	5-OCH_3	> 100	–	–
	13	F	6-OCH_3	> 100	–	–
	14	F	7-OCH_3	> 100	–	–
	15	Br	H	> 100	–	–
	16	Br	5-OCH_3	> 100	–	–
	17	Br	6-OCH_3	> 100	–	–
	18	Br	7-OCH_3	> 100	–	–
	19	Cl	H	57.38 ± 3.60	> 1000	> 1000
	20	Cl	5-OCH_3	35.5 ± 10	103 ± 15	> 1000
	21	Cl	6-OCH_3	5.03 ± 0.49	> 100	468
	22	Cl	7-OCH_3	4.91 ± 0.98	100 ± 16	> 1000

VERO = African green monkey kidney epithelial cells **BMDM** = mouse bone marrow derived macrophage cells
Positive control = benznidazole (Bnz) (IC_{50} = 20 µM) on *T. cruzi* , benznidazole (Bnz) (IC_{50} = 120 µM) on VERO and BMDM cells

Conclusions

- These compounds **19-22** showed higher trypanocidal activity than the reference drug Bnz, they were selective and cytotoxic, which could be considered as promising future compounds as trypanocidal agents to treat CD in America.



19-22

- It can be inferred with this limited number of compounds, that the type of halogen in position 4´´ (R_1) of the aromatic ring and a methoxy substituent in position 6 or 7 of tetralone play an important role in favoring the activity and selectivity of this type of chalcones as trypanocides.

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