



In vitro anti-onchocerca activity of 1-aryl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline analogs

Joelle, Ngo Hanna^{ab},

^a*Department of Chemistry, Faculty of Science, University of Buea, P.O.Box 63, South West Region, Cameroon;* ^b*Department of Chemistry, Faculty of Science, University of Douala, P.O. Box 24157, Littoral Region, Cameroon*

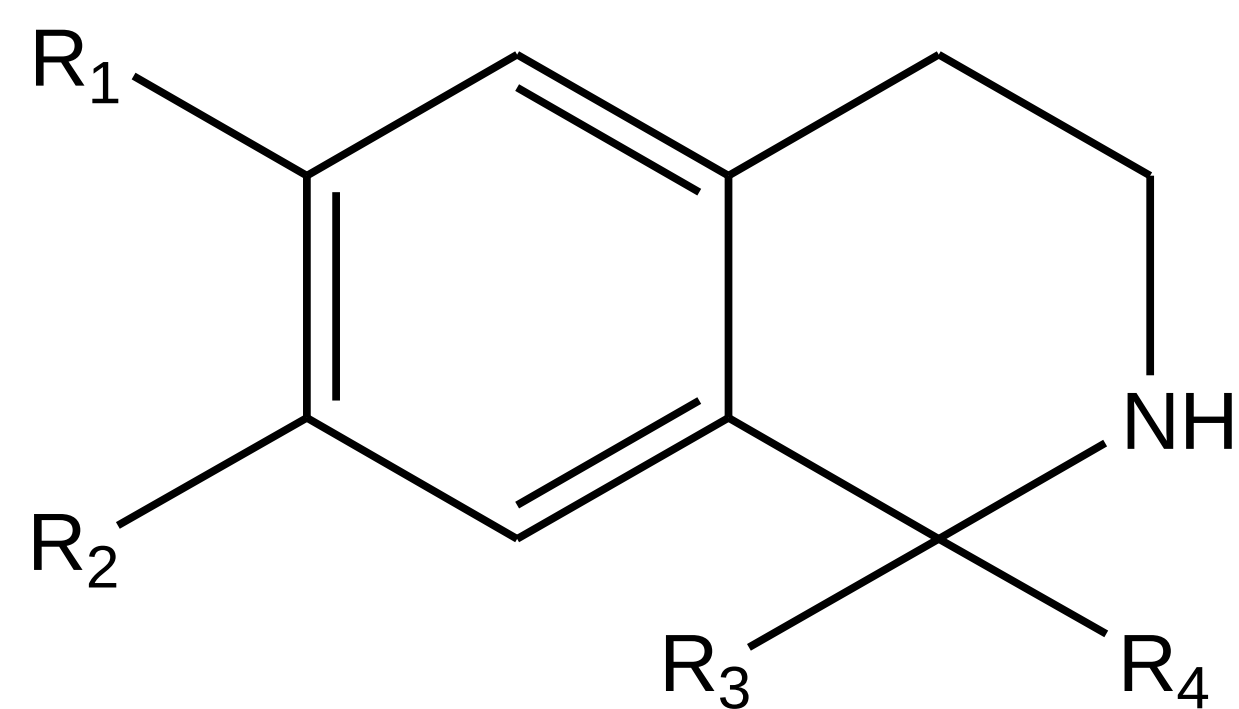
INTRODUCTION

Onchocerciasis (river blindness), a vector-borne parasitic disease caused by the filarial worm *Onchocerca volvulus*, constitutes a major public health and socio-economic problem in 37 million people in tropical Africa and 140,000 others in Central and South America and the Yemen.

So far no vaccine exists to protect against onchocerciasis and mass drug administration (MDA) of ivermectin as treatment for onchocerciasis is contraindicated in many foci of Central Africa where loiasis (eye-worm), another filarial infection, is co-endemic with onchocerciasis. As such, ivermectin is not suitable for the treatment of individuals with high *Loa loa* microfilaraemia (microfilariae in blood). Therefore, there is a need to develop new treatments for onchocerciasis.

In the search for substances with potential for the treatment of onchocerciasis, tetrahydroisoquinoline (THIQs) alkaloids have attracted much interest from chemists due to their important antiparasitic activities.

The synthesis of structurally simple tetrahydroisoquinolines (THIQs, **1**) and their evaluation as potential anti-onchocerca agents was our focus.

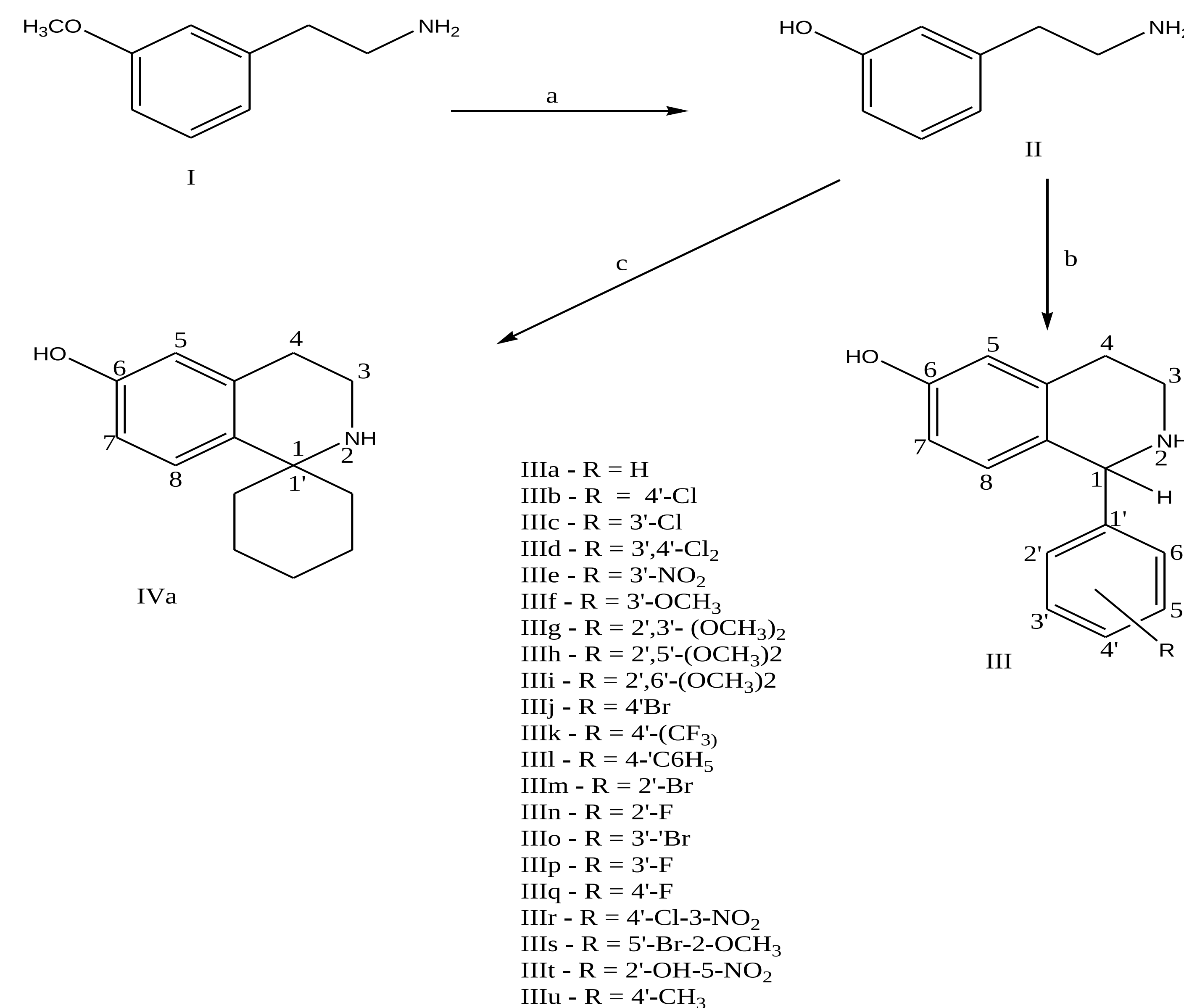


BIOLOGICAL SCREENING

- Anti-onchocercal activity: All the target compounds were tested in the form of their corresponding hydrochloride salts. *In vitro* screens of the target compounds against *O. ochengi* microfilariae (mfs) in a ten-day and five-day assay were carried out in the collaborating Biotechnology Unit Research Laboratories, Department of Biochemistry and Molecular Biology, Faculty of Science, University of Buea.

- For the cytotoxicity: *in vitro* sensitivity assays using Monkey kidney epithelial cells (LLC-MK2 from ATCC)

SYNTHESIS



BIOLOGICAL ACTIVITY

n°	Compounds code	% inhibition of <i>O.ochengi</i> microfilariae motility at 10µg/ml		Comment on cytotoxicity on monkey kidney epithelial cell (LLCMK2) on day 5
		Day 5	Day 10	
1	IIIa, H	75	100	Non-Cytotoxic
2	IIIb, 4-Cl	50		Moderately Cytotoxic
3	IIIc, 3,4-Cl ₂	75	100	Non-Cytotoxic
4	IIId, 3-Cl	50		
5	IIIe, 3-NO ₂	0		
6	IIIf, 2,3-OMe ₂	0		
7	IIIg, 2,5-OMe ₂	0		
8	IIIh, 2,6-OMe ₂	0		
9	IIIi, 4-Br	75	100	Non-Cytotoxic
10	IIIj, 4-CF ₃	0		
11	IIIk, 4-phenyl	100/100 at 5µg/ml	100	Non-Cytotoxic at 10 µg/ml
12	IIIl, 2-Br	0	100	Cytotoxic
13	IIIm, 2-F	0		
14	IIIn, 3-Br	0	100	Cytotoxic
15	IIIo, 3-F	75	100	Non-Cytotoxic
16	IIIp, 4-F	0		
17	IIIq, 4-Cl,3-NO ₂	0		
18	IIIr, 5-Br,2-OMe	75	100	Non-Cytotoxic
19	IIIs, 2-OH,5-NO ₂	0		
20	IIIu, 4-CH ₃	0		

CONCLUSION AND PRESPECTIVE

- 1-aryl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline analogues showed sufficient anti-onchocercal activity favourable to warrant further investigation

On the basis of our findings, we suggest that:

-The optimisation of the R substituent on the phenyl side chain of the isoquinoline scaffold should be the point of focus for future investigations.

-The target compounds should be screened *in vitro* against *Loa loa* worms in order to verify if they inhibit their motility.

		Activity on Macrofilariae	
		% Inhibition of Adult Male Worms Motility (120 h)	% Death of Adult Female Worm (168 h)
	IIIa, H	62.5	33.4
“	IIIc, 3,4-Cl ₂	62.5	6.25
“	IIIi, 4-Br	85	75
“	IIIk, 4-phenyl	100	100
“	IIIo, 3-F	58	25
“	IIIr, 5-Br,2-OMe	75	68
–	2% DMSO	0	0
–	Amocarzine	100	100