Schiff Base Complexes: A glimpse of Hope for Anti-onchocercal Drug Leads

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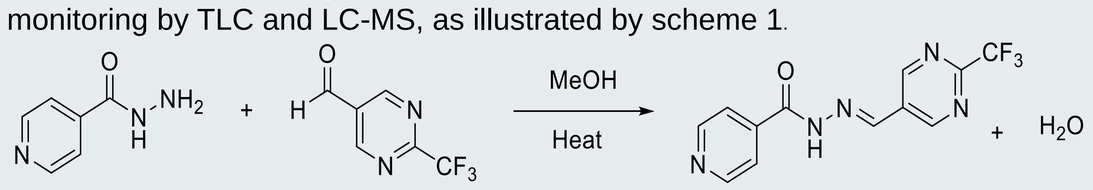
Introduction

- Onchocerciasis or "river blindness" is a parasitic disease caused by the filarial worm *Onchocerca volvulus* [1].
- Over 37 million people are affected, about 1.5 million with visual impairments and a risk population of over 120 million, with over 95% being in Africa.
- Ivermectin, the only drug of choice for mass drug administration programs is only microfilaricidal, requiring long treatment duration and has severe side effects in cases of *Loa loa* co-infection.
- The onchocerciasis burden is made worse by the absence of a drug effective against macrofilariae, thereby necessitating the search for safe and more effective drug leads.
- Our earlier studies suggested that Schiff base complexes could be potential anti-onchocercal agents [2]. This discovery was made by chance through a cross screening program at the University of Buea.

General Synthesis of the Schiff Bases

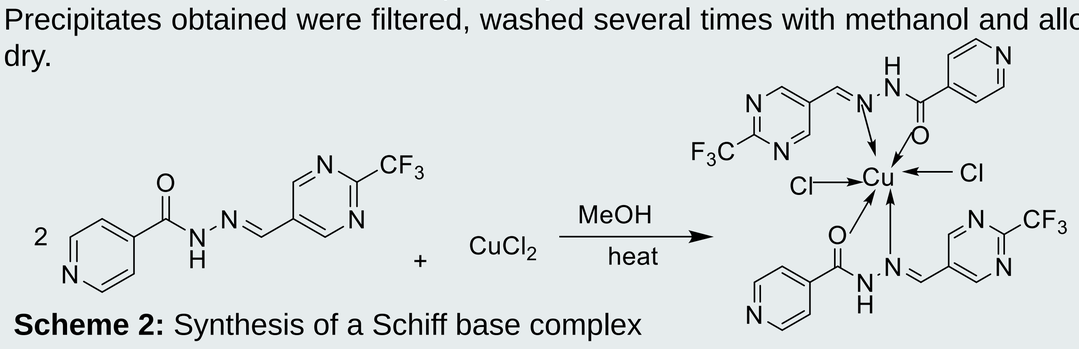
The Schiff bases were synthesised by reacting equimolar amounts of isoniazid and the selected aldehydes in methanol under reflux at 60°C for 4 hours while monitoring by TLC and LC-MS, as illustrated by scheme 1.



Scheme1: Synthesis of a Schiff base ligand

General Synthesis of the Schiff Base Complexes

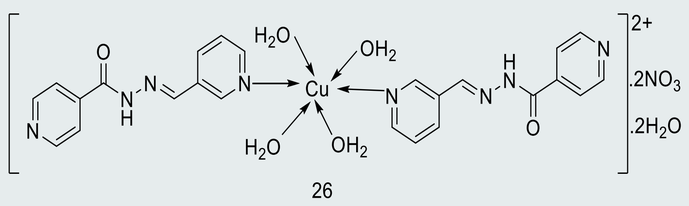
The complexes were synthesised by reacting the various metal (II) chlorides with the Schiff bases in the ratio 1:2 respectively in methanol as illustrated in scheme 2. The Precipitates obtained were filtered, washed several times with methanol and allowed to dry.



Scheme 2: Synthesis of a Schiff base complex

Results

In vitro anti onchocercal studies showed that some Schiff base complexes were active against *Onchocerca ochingi* microfilariae. Three complexes inhibited adult male motility by 100%. MTT/formazan assay was used to evaluate the potential activities against female worms and promising results obtained.



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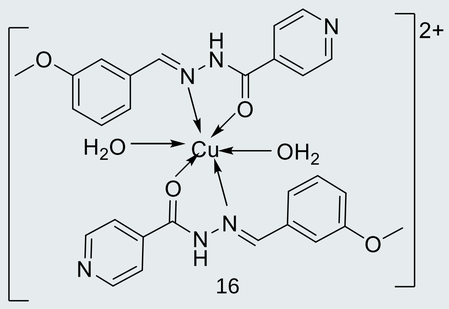

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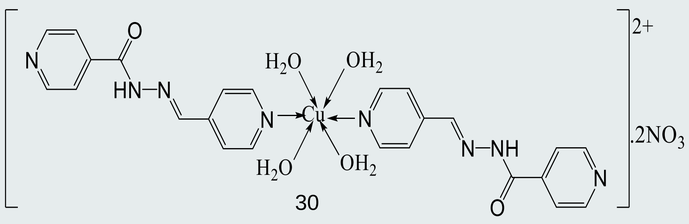

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MTT/Formazan assay

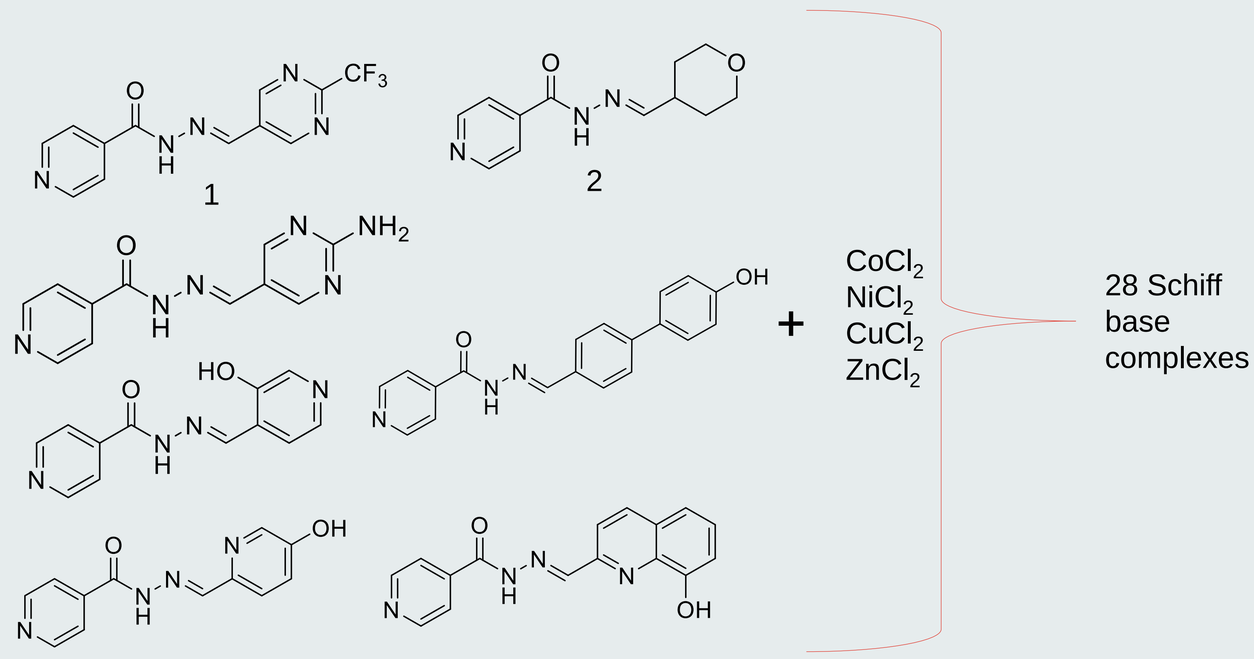
Activity on adult worms *in vitro*

Compound ID	Conc. (µg/mL)	% inhibition of male motility (5 days)			Mean activity	Activity on males (5 days)	% killing of adult females			Mean activity	Activity on female
16	10	/	/	/	ND	ND	100	100	100	100	100
26	10	100	100	100	100	100	90	100	90	90.3	90.3
30	10	/	/	100	100	100	50	50	0	33.3	33.3
Negative	0	/	/	/	ND	ND	0	0	0	0	0
Positive	10	/	100, 100	100	100	100	100	100	100	100	100

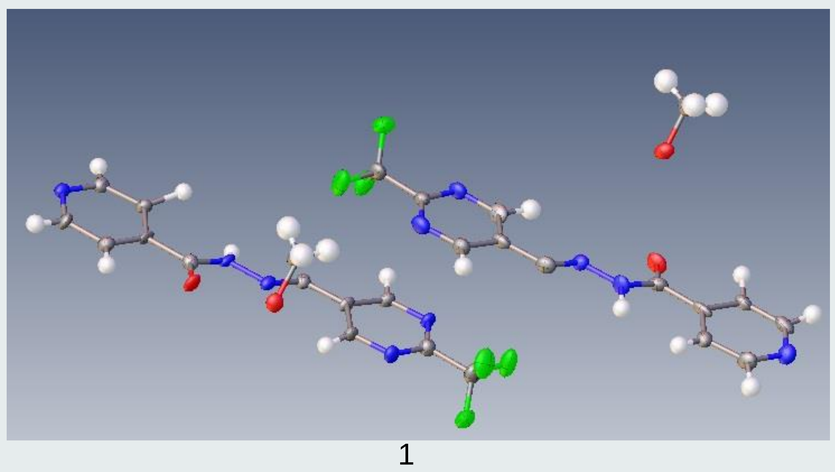
New library

Ongoing studies on this class of compounds are aimed at expanding the library of ligands and their metal complexes designed for superior solubility with the hope of finding more potential drug leads. The previous ligands have log P values from 1.11- 4.02, while the new ligands have log P values as low as -0.03.

Schiff Bases



Single Crystal Structures of 1 and 2



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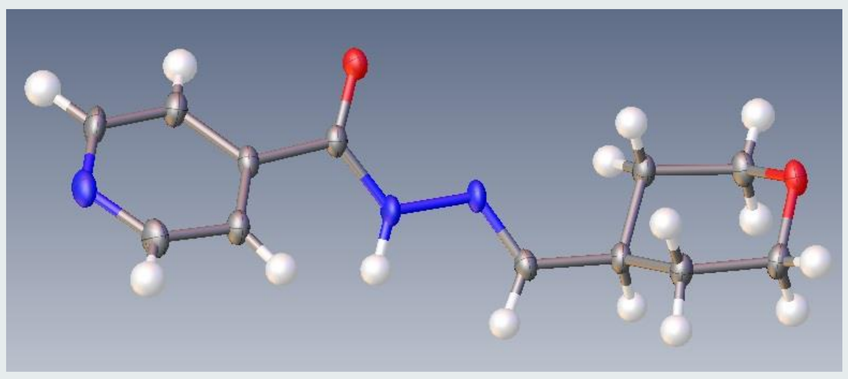

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Conclusion

Our group has reported for the first time the potential of Schiff base complexes as anti-onchocercal drug leads. The new library is made up of seven ligands and twenty-eight complexes. It is hoped that the new library will reveal compounds with greater activities against microfilariae as the compounds were designed for superior solubility.

ONGOING WORK

1. Work is ongoing on the biological study of the new library against *Brugia malayi in vitro* using inhibition of microfilariae motility assay.
2. Active compounds will be screened against both *Ochengi* microfilariae and macrofilariae
3. We are currently building an Open Source Oncho-1 (OSO-1) repository on GitHub.

Acknowledgments

We thank AREF RDF for funding.

GitHub: https://github.com/OpenSourceOncho/OSO1-Schiffbases

References: 1. https://www.who.int/onchocerciasis/en/ Accessed March 16, 2024 2. Evans N. Mainsah, Sally-Judith E. Ntum, Moses Samje, Fidelis Cho-Ngwa, Peter T. Ndifon and Joseph N. Yong (2016). *Anti-Infective Agents*, *14*, 47-52