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Design and synthesis of novel *alfa*-mangostin-nitroimidazole hybrids with toxic effects on amastigotes of *Trypanosoma cruzi*

By

Douglas Pinto[1], Afonso Velez[1], Gabriella Magalhães[1], Paulo Santos[1], Marco Edilson Lima[1] Debora Ricardo[2] .

[1] *Instituto de Química, Orgânica - IQ, Universidade Federal Rural do Rio de Janeiro (UFRuralRJ);*

[2]*Instituto de Microbiologia e Imonologia Veterinária - IV, Universidade Federal Rural do Rio de Janeiro (UFRRJ).*

* Corresponding email: douglasdoti@hotmail.com

Design and synthesis of novel *alfa*-mangostin-nitroimidazole hybrids with toxic effects on amastigotes of *Trypanosoma cruzi*

G. Mangostana (mangosteen)

Crude extract

Flash Chromatography System

α-mangostin

Molecular modification

alfa-Mangostin (MGT) is the main product isolated from the the fruit pericarp of *Garcinia mangostana*. This xanthone exhibits important toxic effects on *T. cruzi* forms amastigotes. We describe herein the synthesis of new hybrid derivatives of MGT and nitroimidazoles using click reaction as the key-step. Toxic effects on intracellular amastigotes of *T. cruzi* (Tulahuen C2C4 LacZ).

Keywords: Chagas disease, Molecular hybridization, Click reaction, Antiparasitic chemotherapy, *Garcinia mangostana*.

Introduction

Natural products constitute inexhaustible sources of both raw materials and inspiration for obtaining and planning new molecules with potential biological activity.

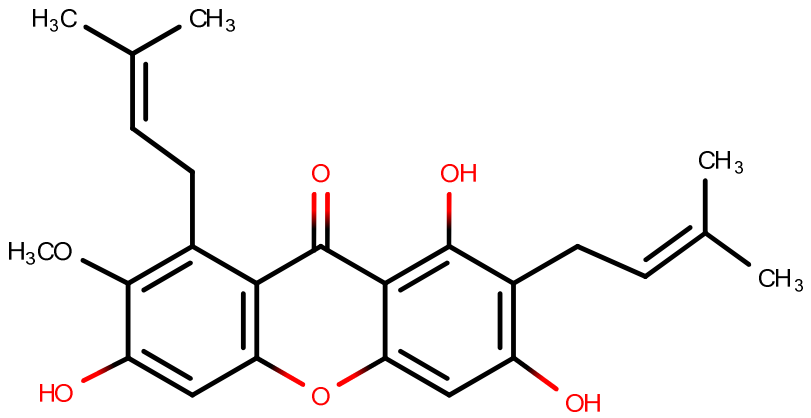
Mangosteen is a type of fruit tree that grows in the Asian region such as Malaysia, Myanmar, Thailand, Philippines, Sri Lanka and India.

In 1855, α-mangostin was found as the major xanthones taken from the pericarps of the mangosteen fruit.

Garcinia mangostana L.
(Clusiaceae)

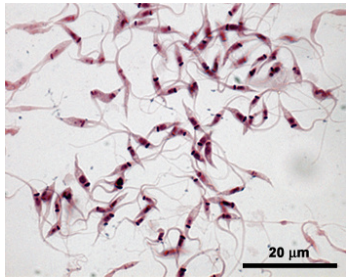
Mangosteen fruit

Excellent biological properties

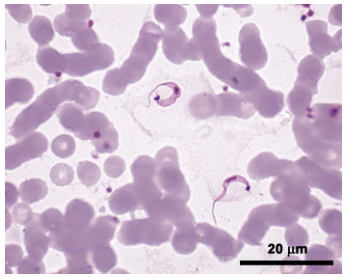


α-mangostin

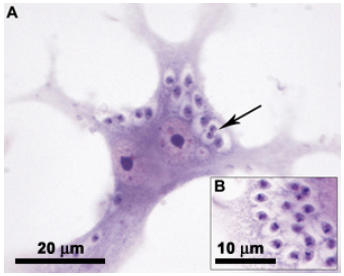
LIFE CYCLE OF *T. CRUZI* - *ETIOLOGIC AGENT OF CHAGAS DISEASE*



Epimastigote form
Non-infective and replicative form

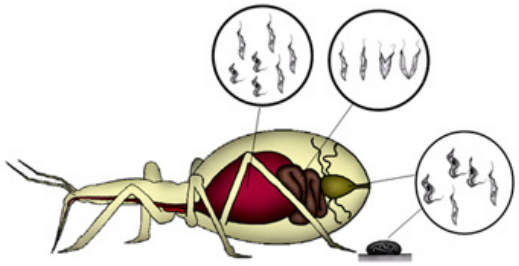


Blood trypomastigote form
- Vertebrate blood
- Extremely mobile
- Infective form



Intracellular amastigote form
- Vertebrate tissues
- Infective and replicative form

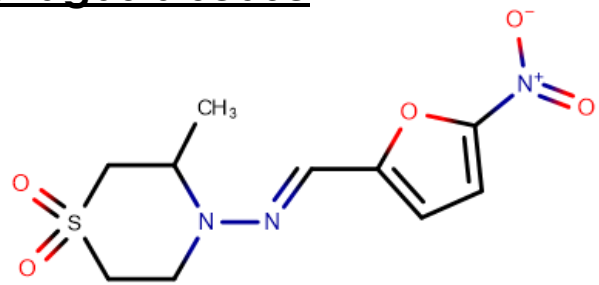
Epimastigote form



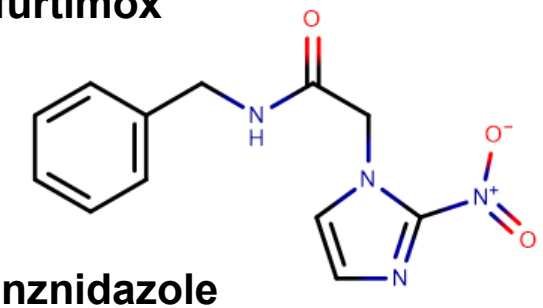
Triatoma infestans

In the digestive tract it differentiates into trypomastigotes

Drugs used for treatment chagas disease



Nifurtimox



Benznidazole

OUR GOALS

In this work we describe our efforts in the incorporation of natural xanthone α–mangostin to the set of natural molecules potentially useful to obtain new antichagasic molecules with improved activity and high selectivity against *T. cruzi.*

ISOLATION OF NATURAL PRODUCT

G. Mangostana (mangosteen)

Kiln drying
45ºC / 36h

Pericarp residue

10g dehydrated plant material

Ethyl acetate

Residue (extract)

2ª) Drying

Crude extract 1.14g

400mg

Purification

Vacuum rotary evaporator

Flash Chromatography System

α-mangostin

High yield and purity

MOLECULAR PLANNING

Molecular hybridization as structural planning tool

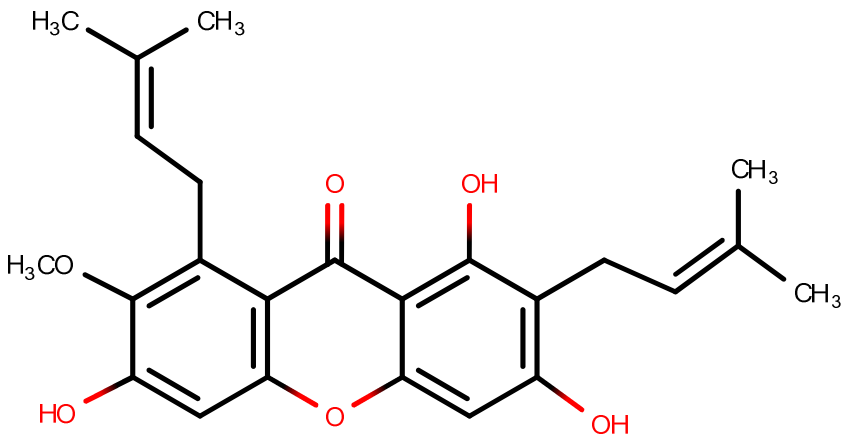
Exploring synthetic and reactional versatility of α-mangostin

Search for new therapeutic alternatives

➢ **Molecular modification Strategy**

Molecular hybridization

Changes in physico-chemical properties
Conformational changes
Chemical stability
Interaction with multiple targets



Molecule A (α-mangostin)

+ Molecule B

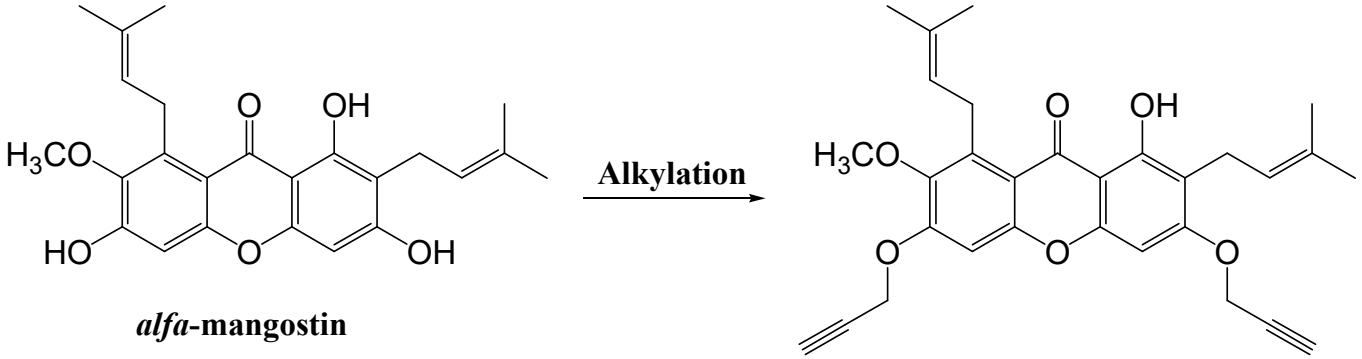
Intrinsic characteristics

Molecular hybridization

New potentially active hybrid

NEW HYBRID SYNTHESIS

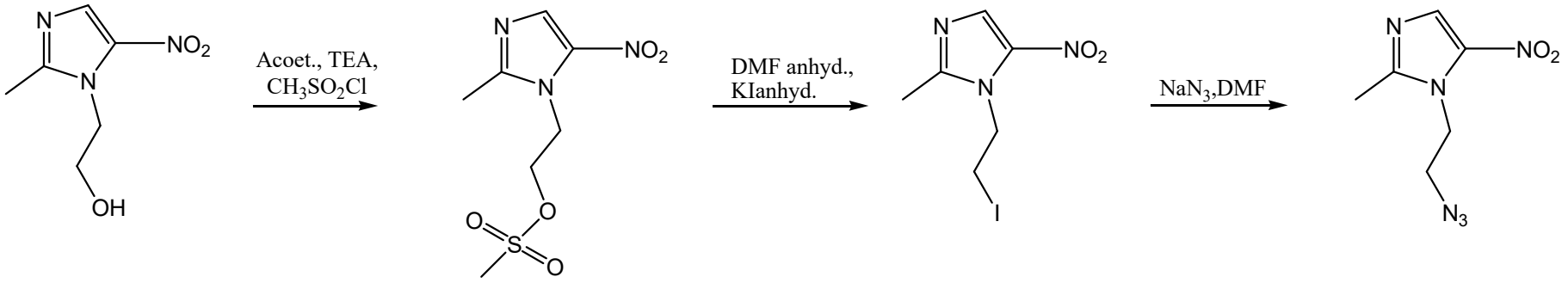
- ***Alfa*-mangostin *O*-alkylation reaction**



***alfa*-mangostin** **Alkylation** ***O*-alquil-*alfa*-mangostin**

Scheme 1. Propargyl bromide 80% (0.814 mmol, 2.2 eq.), Anhydrous DMF (51.7 mmol), Anhydrous K_2CO_3 (0.814 mmol), 60 ^{0}C, 2h, 74%.

- **Formation of azides from nitroimidazoles**

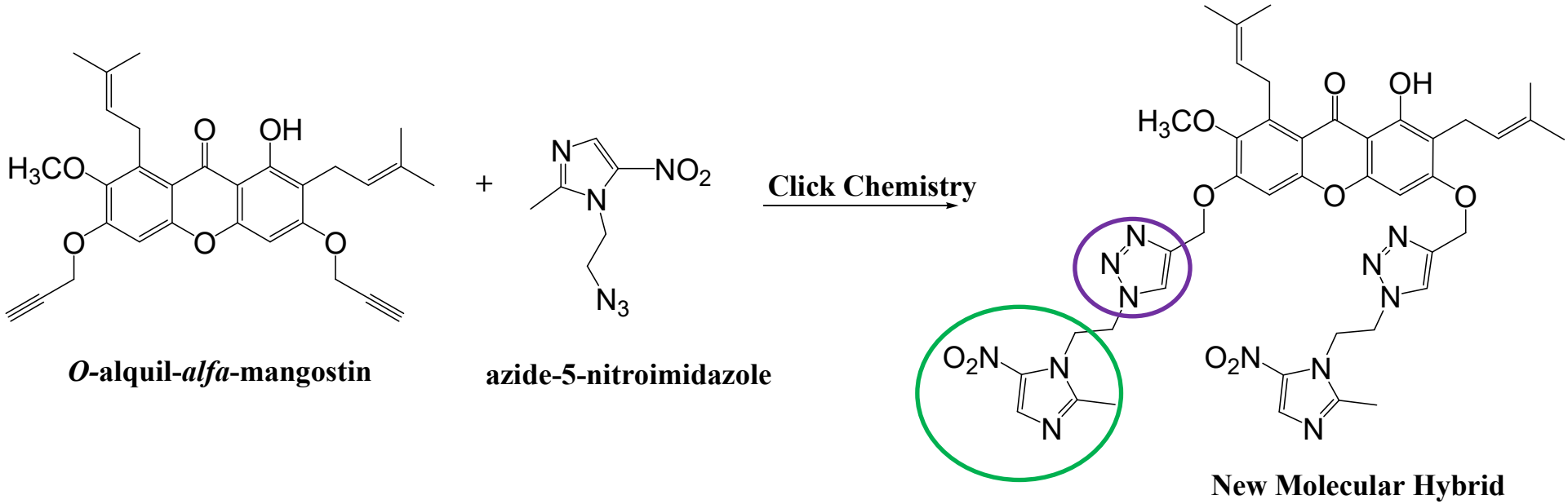


5-nitoimidazole **methylmethanesulfonate-5-nitoimidazole** **Iodo-5-nitoimidazole** **azide-5-nitroimidazole**

Scheme 2. Synthesis of azides from nitroimidazoles.

SYNTHESIS OF THE NEW MOLECULAR HYBRID

Using the molecular hybridization strategy and having the Cu(I)-catalysed azide-alkyne cycloaddition (CuAAC) "click" reaction.



***O*-alquil-*alfa*-mangostin** **azide-5-nitroimidazole** **New Molecular Hybrid**

Scheme 3. NaN_3 (0.048g, 0.247 mmol), ethanol/water (4.0 mL), $C_6H_7O_6Na$ (0.0097g, 0.049 mmol), $CuSO_4 \cdot 5H_2O$, (0.003g, 0.0123 mmol) 50 ^{0}C, 3,5h, 76.8%.

Conclusions

- The molecular design as well the synthetic strategy developed in this work led to the preparation of a new hybrid of natural α-mangostin and metronidazole.

- In preliminary evaluation (at a concentration of 100 μM) the new hybrid showed an inhibition of about 30% against intracellular amastigotes of *T. cruzi*.

- The biological results must be refined and repeated at lower concentrations due to that low solubility of the new hybrid under the test conditions.

- The preparation of other derivatives is underway as well as the *in vitro* evaluation of the anti-amastigote activity of the new hybrids obtained.

Acknowledgments