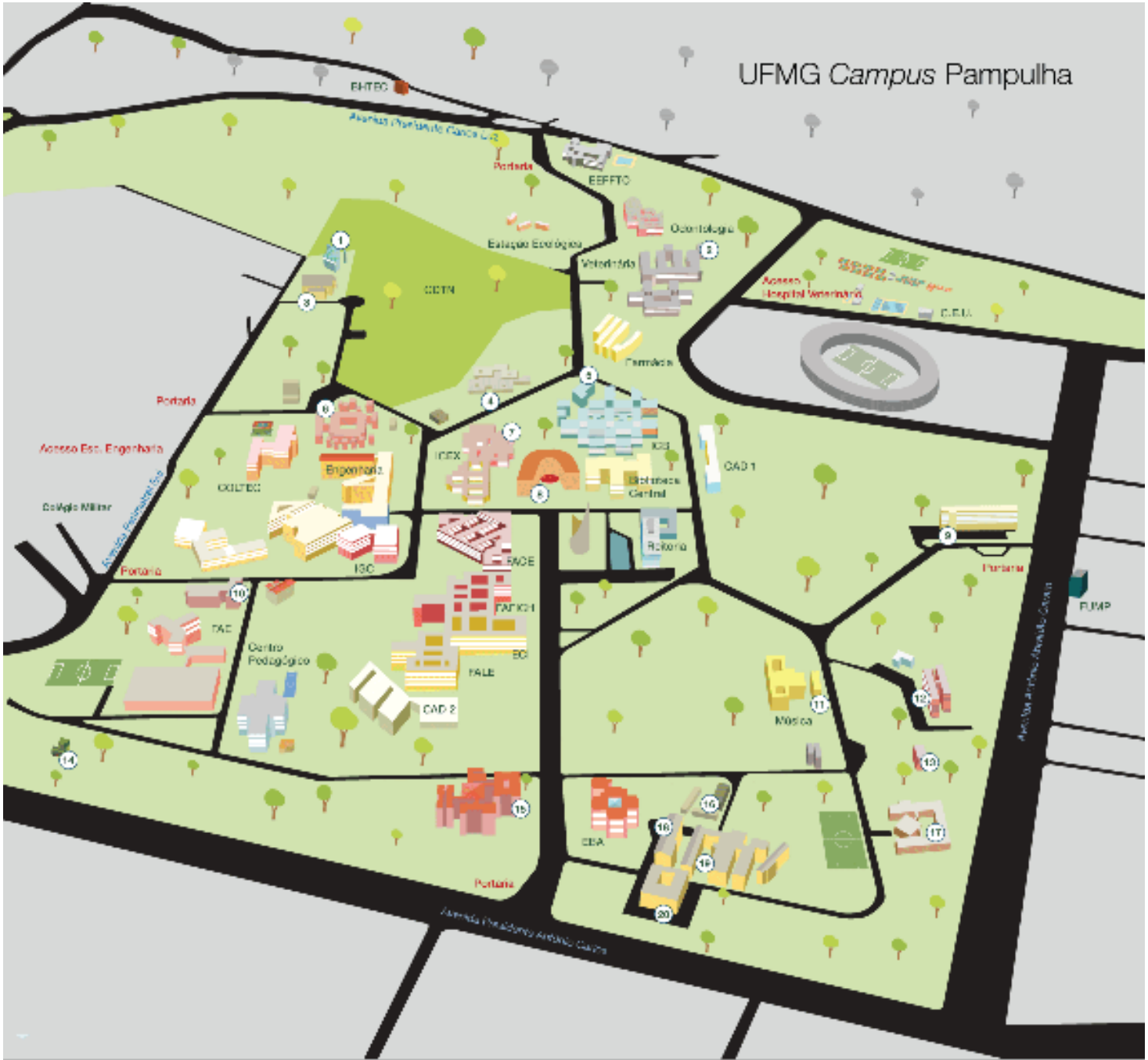
UNIVERSIDADE FEDERAL DE MINAS GERAIS
INSTITUTO DE CIÊNCIAS EXATAS – ICEx
DEPARTAMENTO DE QUÍMICA

Short, Regio- and Stereoselective Synthesis of *ent*-Isoquercetin and its Derivative with Potential Pharmacologic Activities

Prof. Dr. Gaspar Diaz Muñoz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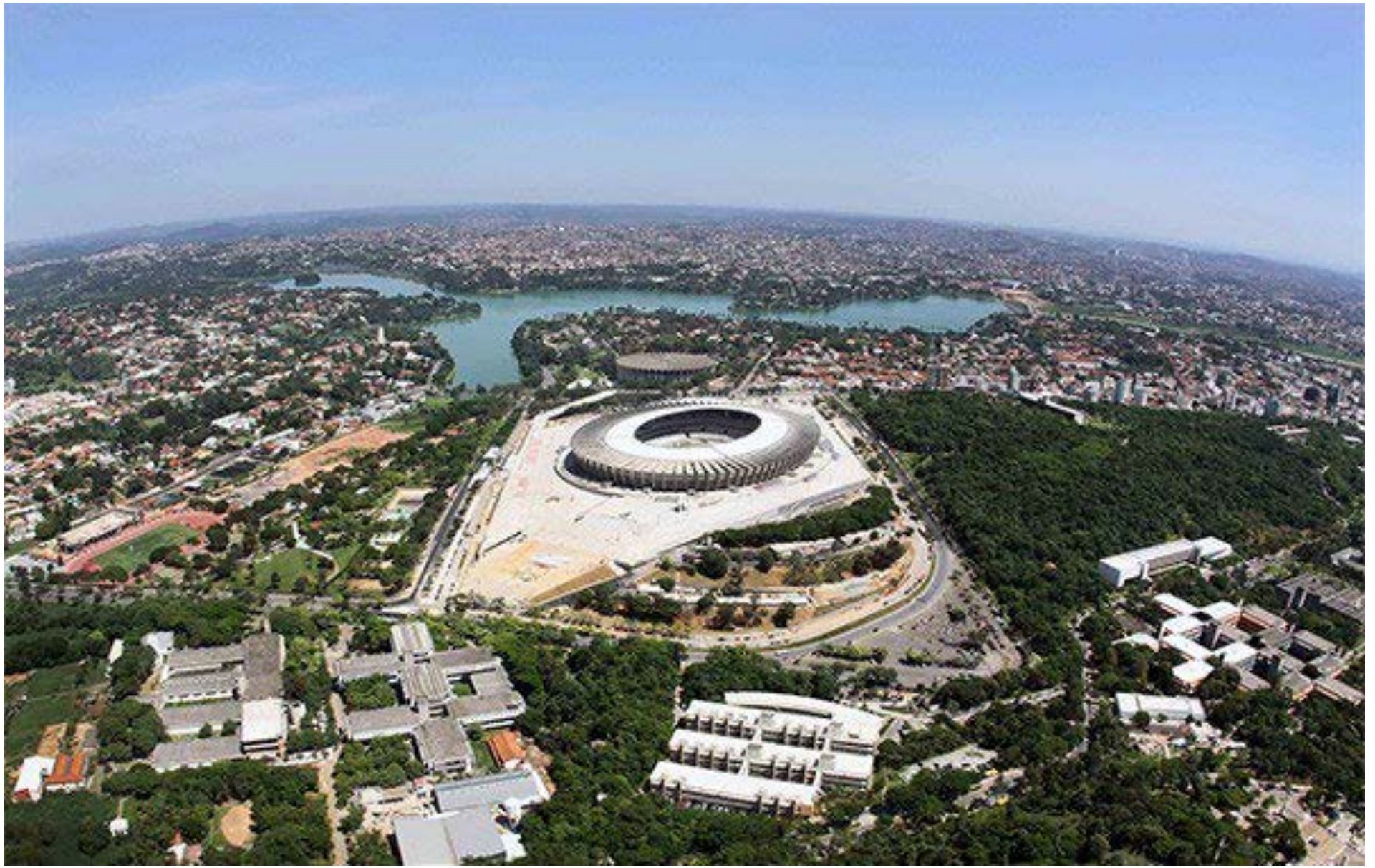
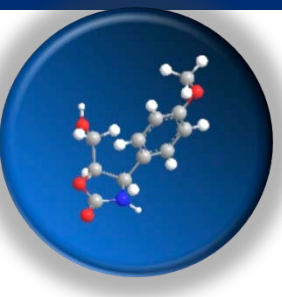
CARREIRA
OS TÉCNICO-ADMINISTRATIVOS EM EDUCAÇÃO DA UFMG ESTÃO EM GREVE
POR MELHORES CONDIÇÕES DE TRABALHO E GARANTIA DE DIREITOS SALARIAIS





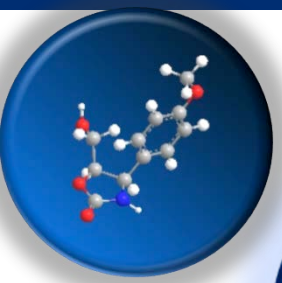
Introduction

Natural polyphenol compounds known as flavonoids (4000 chemically different) are plant secondary metabolite found in many foods, especially in fruits and vegetables.

In plants and most plant-derived food flavonoids are widely present in their conjugate form between the flavonoid aglycone and a sugar moiety linked by a β-glycosidic bond.

They are ingested by man and animals in varying amounts in their daily diets.

The daily consumption of flavonoids ranges from 6 mg in Finland to 70 mg in Japan.



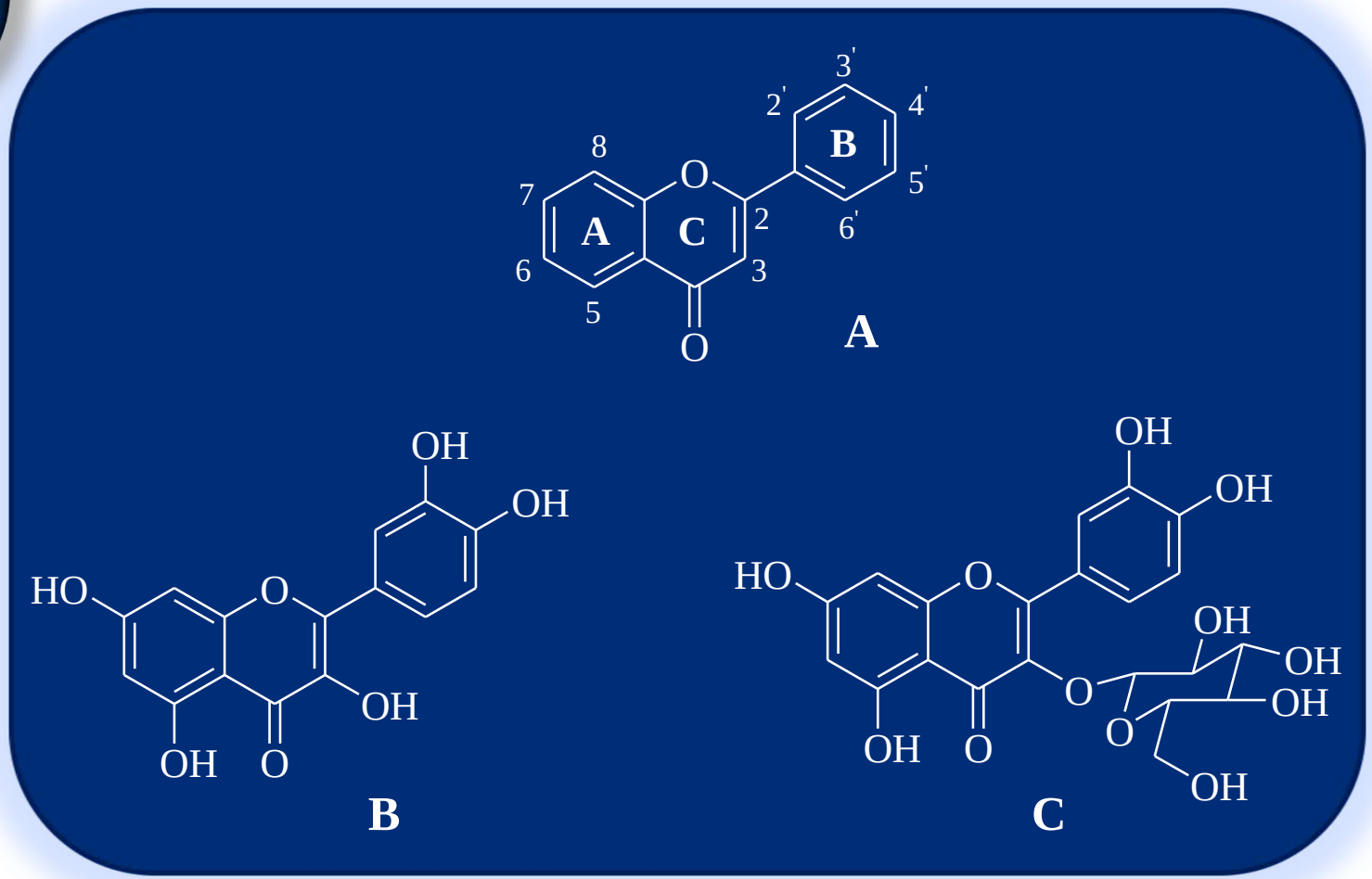


Figura 1. (A) Basic structure of flavonoids. (B) Quercetin structure. (C) Quercetin-3-*O*-D-glucopyranosíde.

Jeffrey B. Harborne:

He was born in Bristol.
1st September 1928 – 21st July 2002.
He has been the author or co-author of some 270 articles and author or editor of 40 books.

Tom J. Mabry

He was born in Austin-Texas .
June 6, 1932 - November 29, 2015.
Supervising more than 70 Ph.D. and M.S. students, whose research led to more than 700 publications including 15 books.

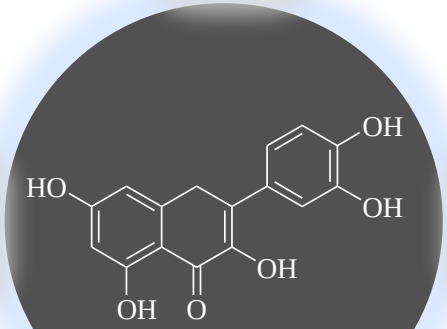
Biological activities presented by quercetin

Anticancer

Choi, J. A. et al. *Int. J. Oncol*. **2001**, *19*, 837.

Antioxidant

Pietta, P. G. *J. Nat. Prod*. **2000**, *63*, 1035.



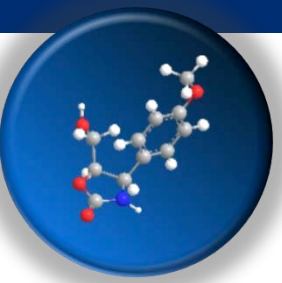
quercetin (**1**)

Yoshizumi, M.. et al. *Mol. Pharmacol*. **2001**, *60*, 656.

Cardiovascular disease

Neurodegenerative disease

Schroeter, H. et al. *Biochem. J*. **2001**, *358*, 547.



Introduction

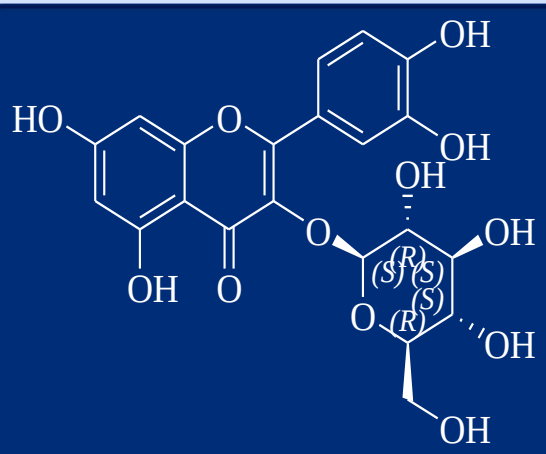
However, most of the *in vitro* biological studies for assessing the properties of quercetin are performed on quercetin and not on their glucuronide metabolites. They are not readily available from commercial sources.

For example, quercetin-3-*O*-β-D-glucuronide must be isolated from green beans which contains in the most suitable variety 15 mg per kg of fresh beans or prepared in low yield by direct glucuronidation of quercetin and separated by tedious preparative HPLC procedures.

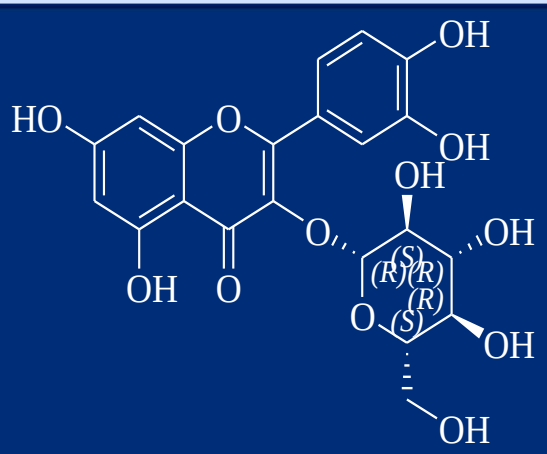
Introduction

All studies have focused on isoquercetin [D-glucose binding at the 3-OH position (**2**)]. However, up to now, the enantiomer of isoquercetin, [quercetin-3-*O*-β-L-glucoside (**3**)], were not described as natural products, nor reported in synthesis and bioactivity studies.

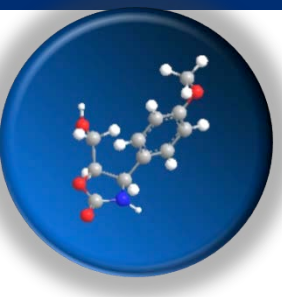
Therefore, the biological activities and synthetic methodologies for the preparation of this compound remain unknown.



quercetin-3-*O*-β-D-glucoside (**2**)
(isoquercetin from D-glucose)



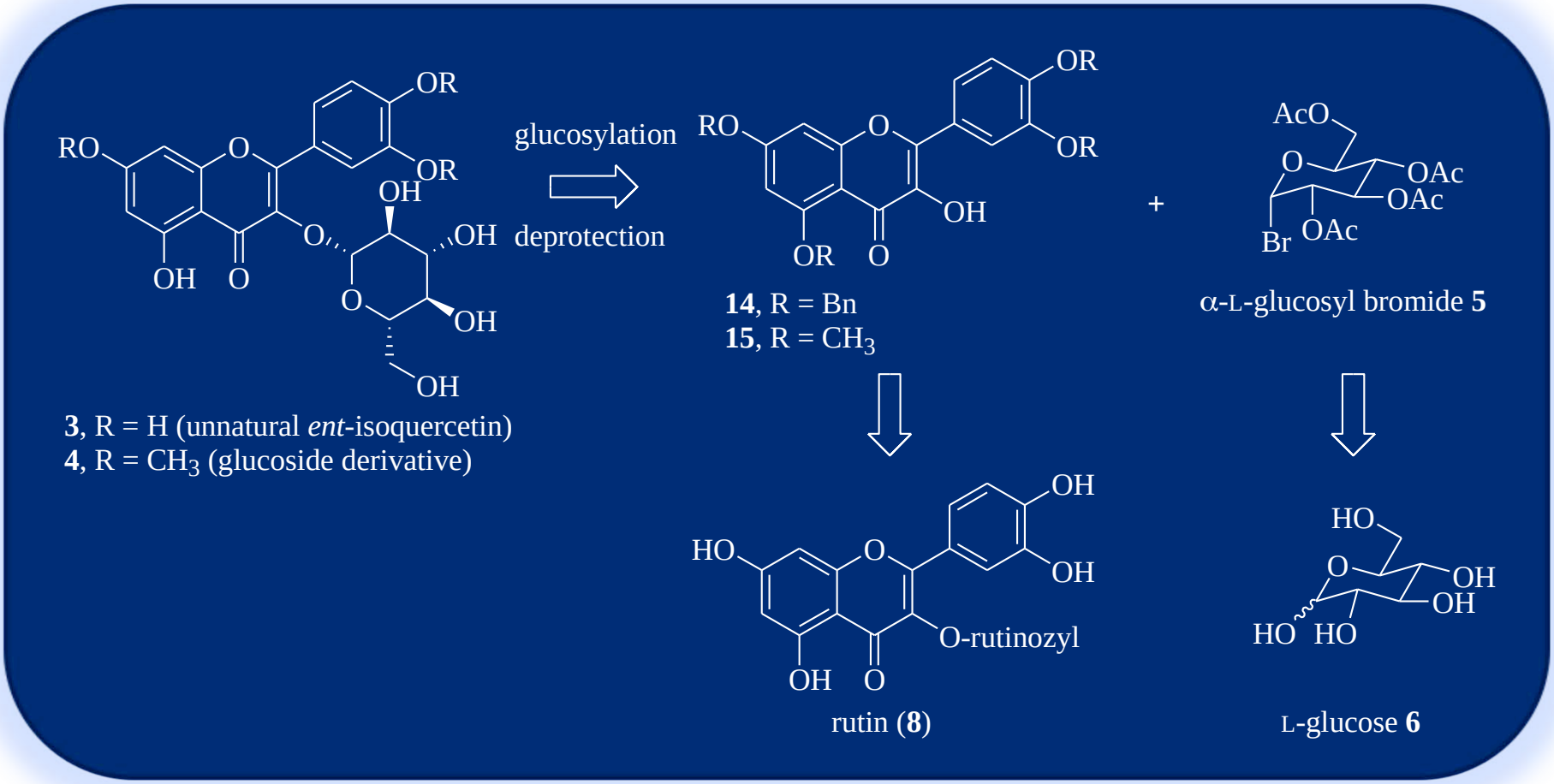
quercetin-3-*O*-β-D-glucoside (**3**)
(unnatural *ent*-isoquercetin from L-glucose)



Objectives

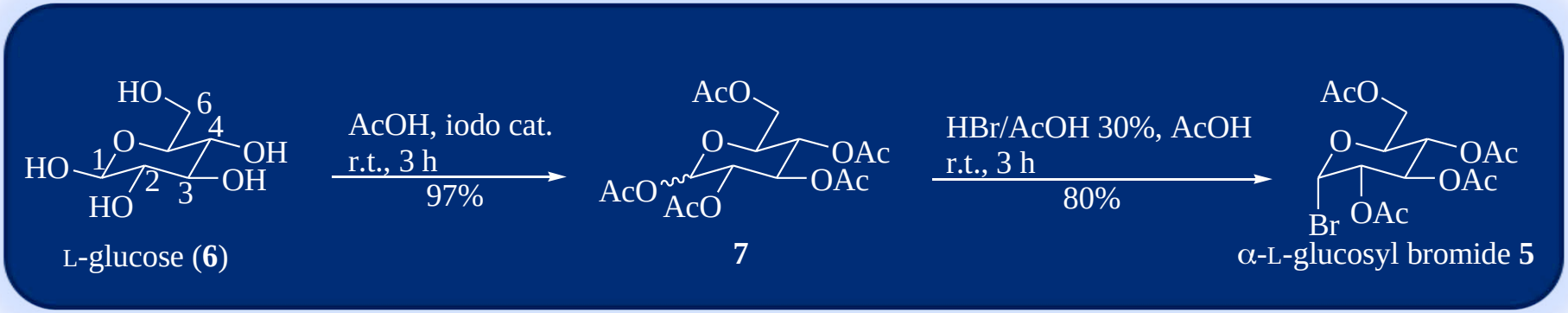
Based on the possibility of its use in the bioprospecting of new drugs, the present study proposed a new approach of stereoselective synthesis of unnatural products: quercetin-3-*O*-β-L-glycoside (**3**) and its glycosidic derivatives.

Bioassay against neglected diseases: Leishmania, Chagas' disease and schistosomiasis.



Scheme 1. Retrosynthetic analysis of quercetin-3-*O*-β-L-glucoside (**3**) and 5,7,4’,5’-tetramethoxylated glucoside derivative (**4**)

Results and Discussion

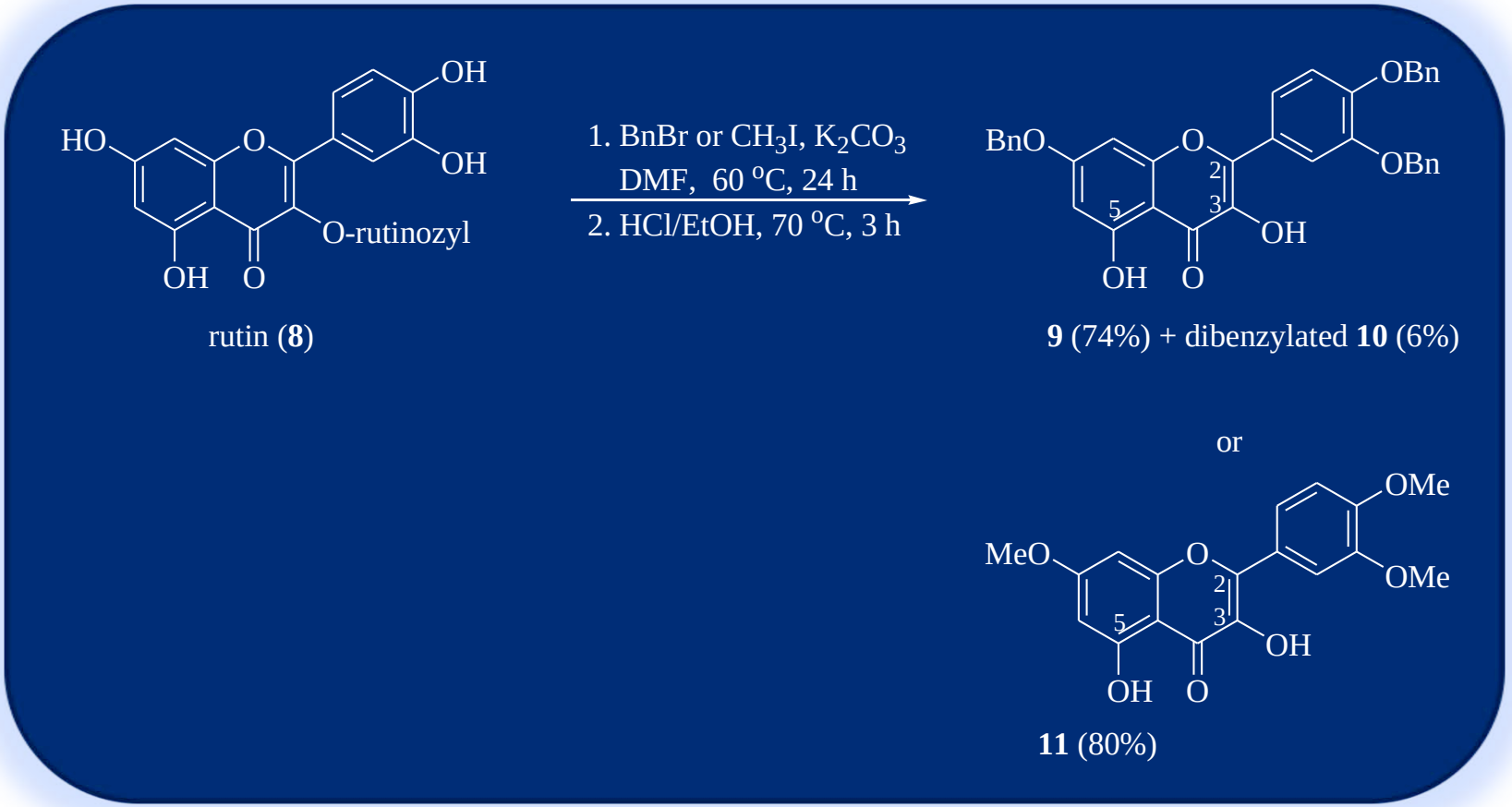


Lemieux, R. U.; Lineback, R.; *Annu. Rev. Biochem.* **1963**, *32*, 155.

Scheme 2. Synthesis of 2,3,4,6-tetra-*O*-acetyl-α-L-glucopyranosyl bromide (**5**).

Synthesis of quercetin derivatives (**9**) and (**11**)

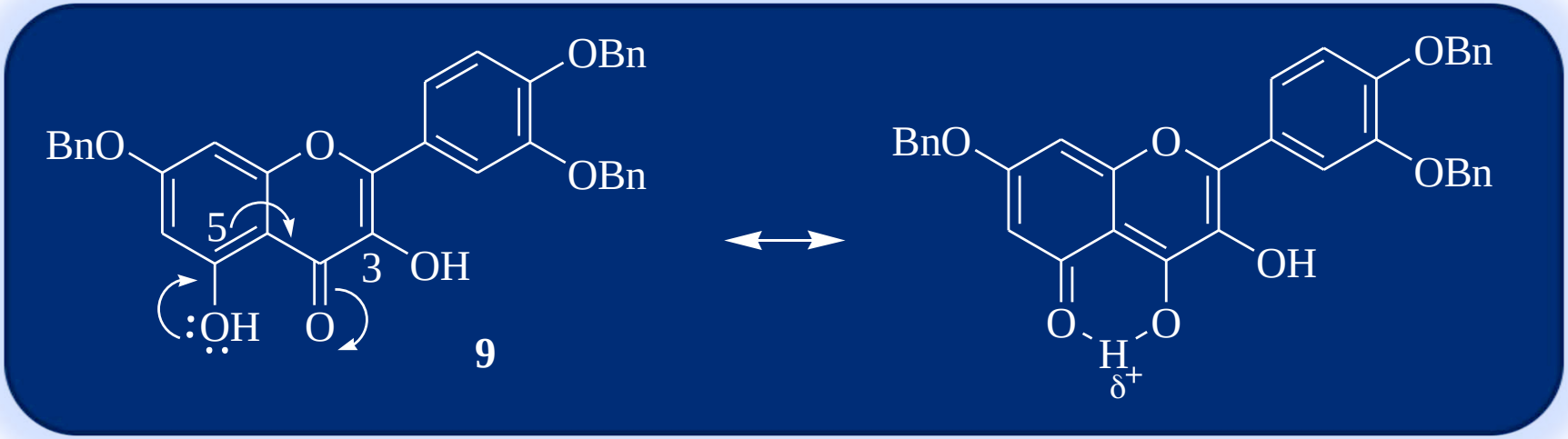
The commercially available rutin (**8**) was employed as starting material in this work.



Scheme 3. Synthesis of quercetin derivatives (**9**) and (**11**).

The 5-OH group is, in fact, less acidic than the other OH phenolic, by a weakening effect of the acid from the intramolecular hydrogen bond between the 5-hydroxyl group and the 4-keto group.

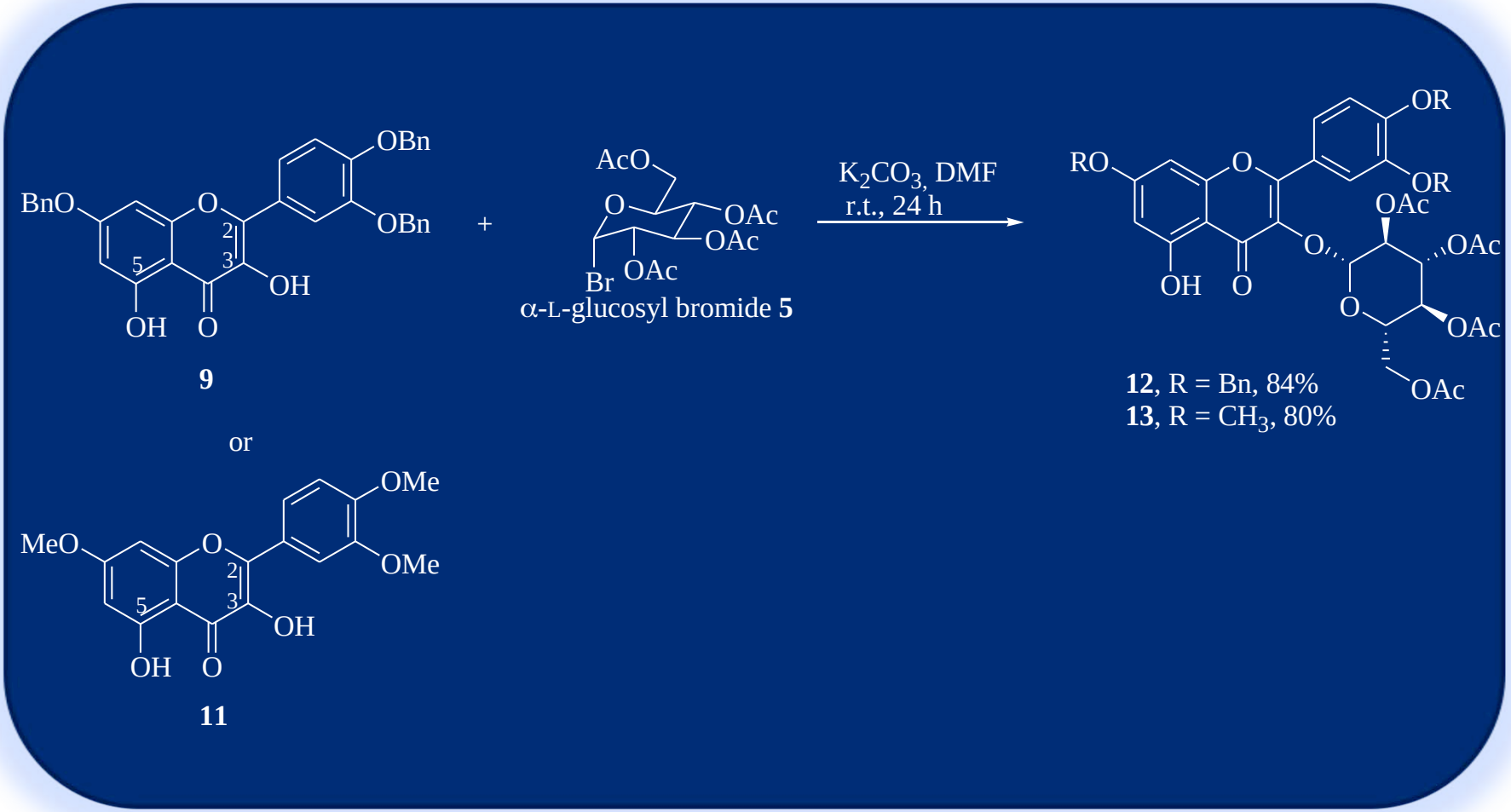
(a) Picq, M. et at. *Tetrahedron Lett.* **1984**, *25*, 2227. (b) Slabbert, N. P.; *Tetrahedron* **1977**, *33*, 821.



Scheme 4. Hydroxyl group 3-OH more reactive than 5-OH.

Synthesis of quercetin-3-*O*-β-L-glucoside derivatives (**12**) and (**13**)

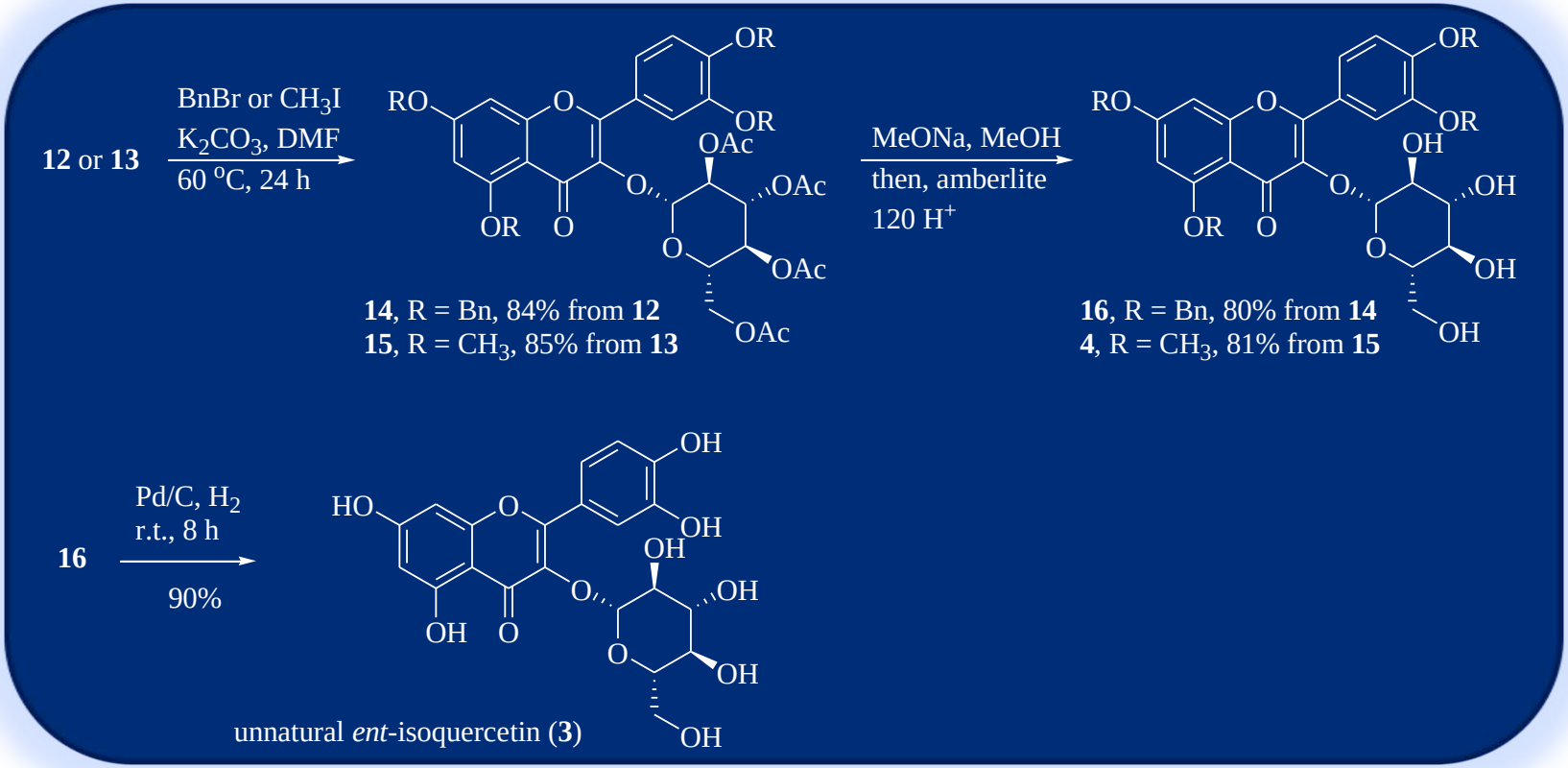
Approach regio- and stereoselective glycosylation (**12**) and (**13**).



Scheme 5. Synthesis of quercetin-3-*O*-β-L-glucoside derivatives (**12**) and (**13**).

Preparation of *ent*-isoquercetin (**3**) and 5,7,4',5'-tetramethyl-quercetin (**4**)

Additional protections of free OH at position 5 in precursors **12** and **13** were required. The direct debenzylation and deacetylation to produce the *ent*-isoquercetin (**3**) was not possible.



Scheme 6. Synthesis of 5,7,4',5'-tetramethoxylated glucoside derivative (**4**) and *ent*-isoquercetin (**3**).

Search for NTPDase-1 inhibitors – 2004, 2009 and 2014

OPEN ACCESS Freely available online

PLoS NEGLECTED TROPICAL DISEASES

Influence of Ecto-Nucleoside Triphosphate Diphosphohydrolase Activity on *Trypanosoma cruzi* Infectivity and Virulence

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1 Núcleo de Pesquisa em Ciências Biológicas Universidade Federal de Ouro Preto, Minas Gerais, Brazil, 2 Departamento de Bioquímica e Biologia Molecular, Universidade Federal de Viçosa, Minas Gerais, Brazil, 3 Departamento de Física e Informática, Instituto de Física de São Carlos, Universidade de São Paulo, São Paulo, Brazil, 4 Departamento de Bioquímica, Instituto de Química, Universidade de São Paulo, São Paulo, Brazil

Conclusions/Significance: The results suggest that Ecto-NTPDases act as facilitators of infection and virulence *in vitro* and *in vivo* of Chagas disease.

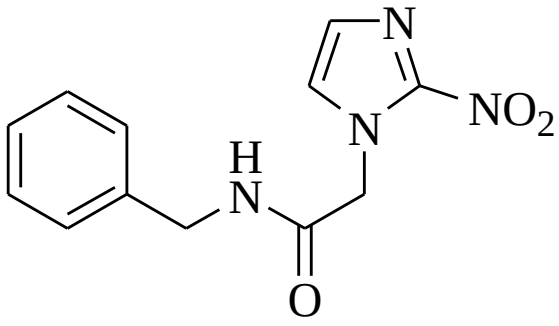
NTPDases emerge as target candidates in chemotherapy.

Anti-Chagasic Bioassays

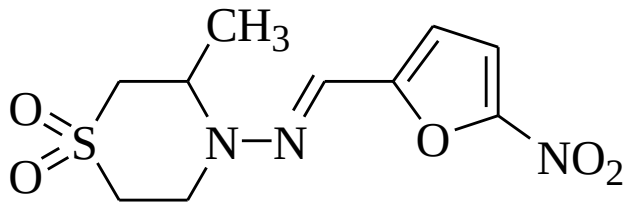
Chagas disease is one of the neglected tropical diseases with the greatest impact in Latin America.

Currently, only two drugs are used to treatment, but both presents serious side effects and are not effective in the chronic phase of the disease.

Therefore, it is urgent to develop a less harmful and more efficient treatment.



Benznidazol



Nifurtimox

Side effects including: anorexia, vomiting, and allergic dermatites.

Common side effects include abdominal pain, headache, nausea, and weight loss.

In this work, a synthetized derivative flavonoid class was able to abolish the activity of the enzyme.

The binding of this compound to the active site of the enzyme, was evaluated by molecular modeling.

Anti-Chagasic Bioassays

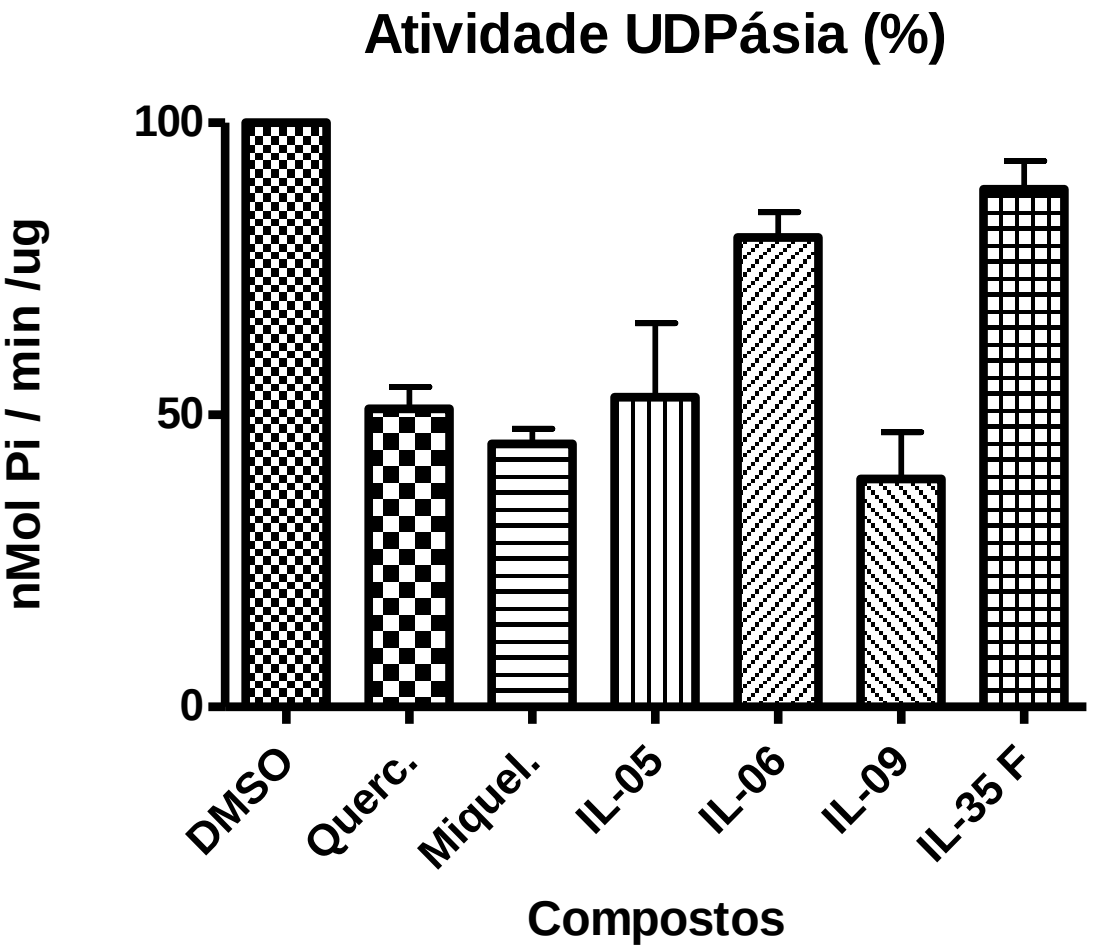


Figure 8. Inhibition assays of sPTPase-1 UDPase activity with quercetin derivatives. **2.5 mM UDP and 100 µM/µg of each of the compounds**. The control contained 1% of DMSO. **(High concentration of substrate)**

Anti-Chagasic Bioassays

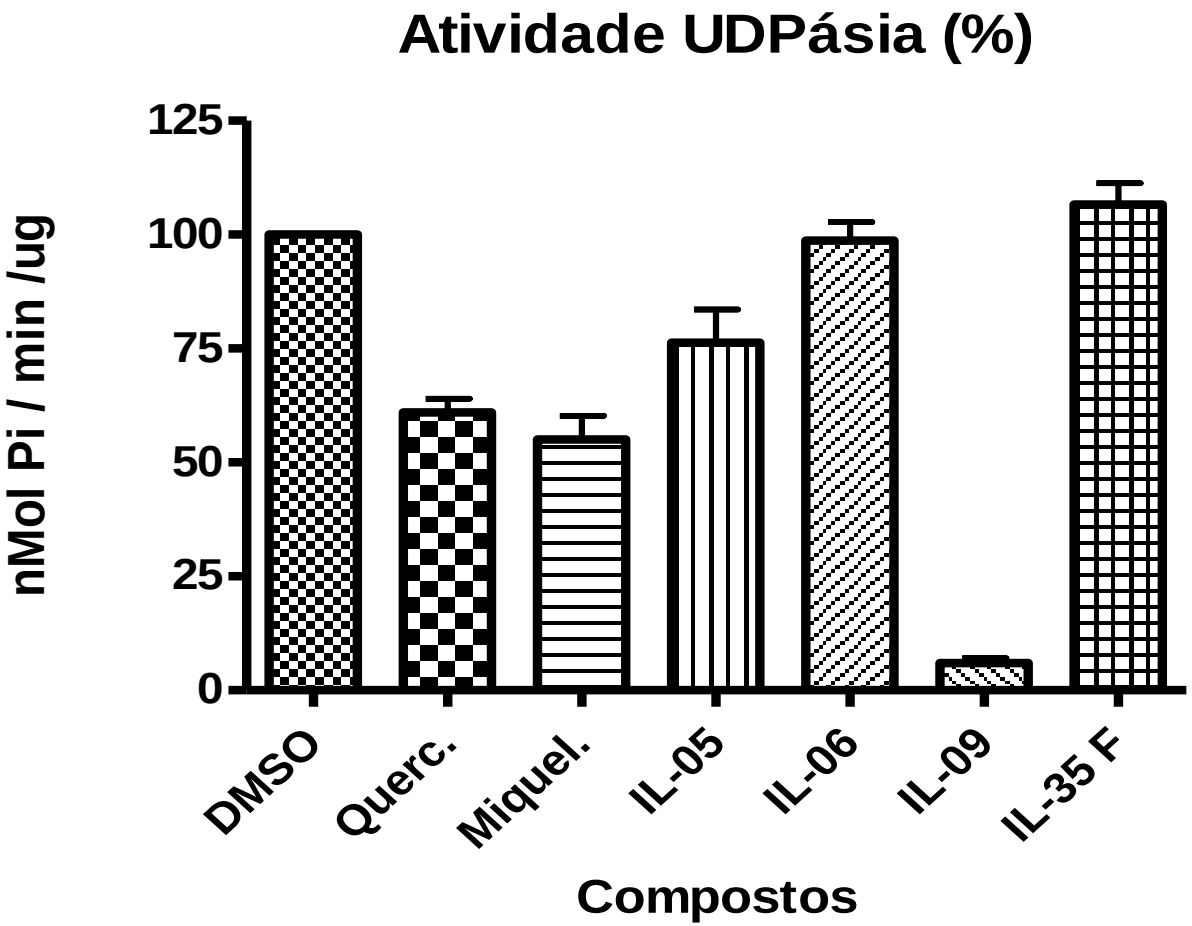


Figure 3. Inhibition assays of sPTPase-1 UDPase activity with quercetin derivatives. **100 µM UDP and 100 µM/µg of each of the compounds**. The control contained 1% DMSO. **(Low concentration of substrate)**

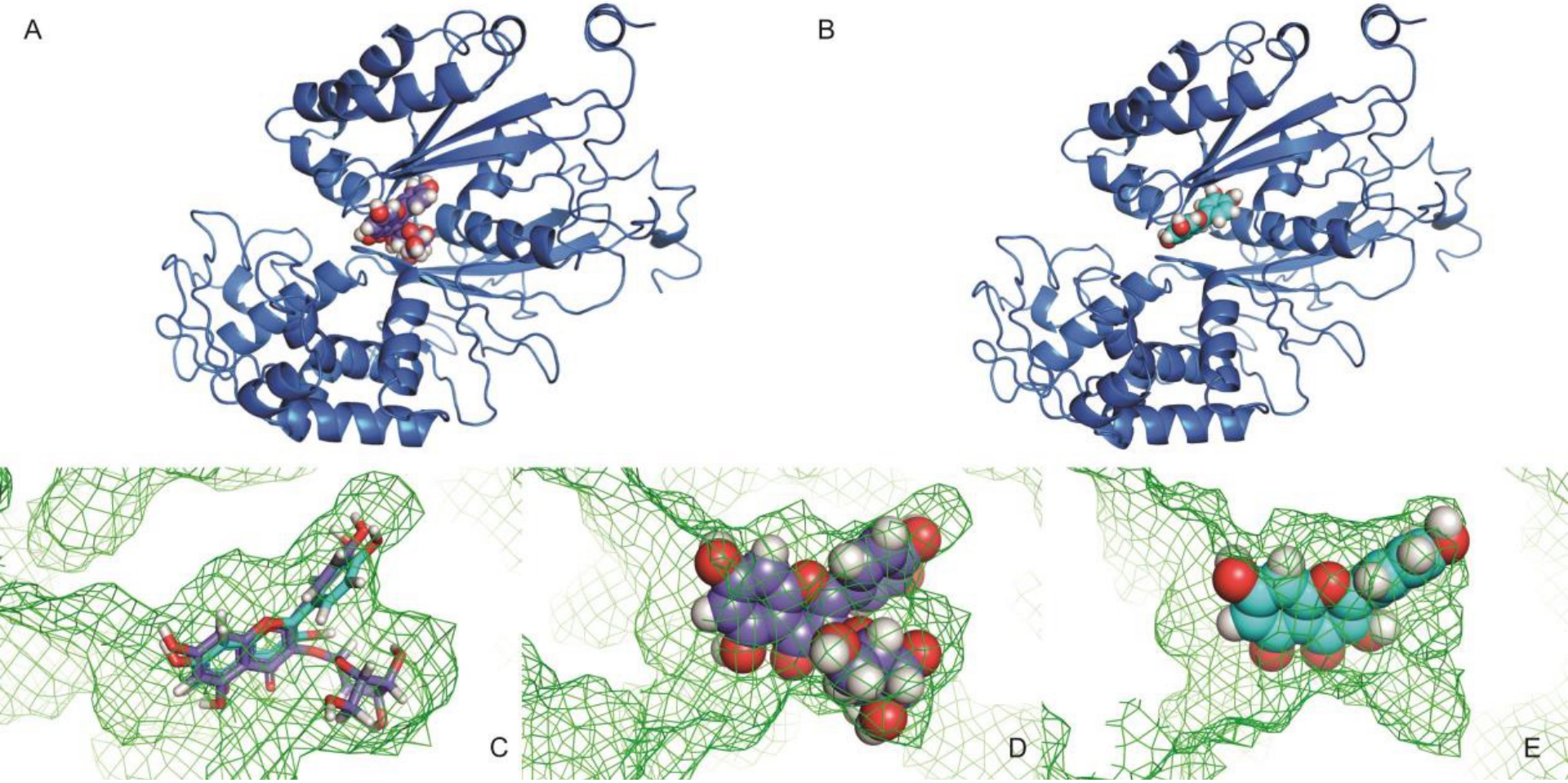
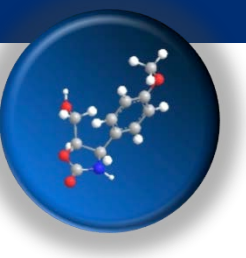


Figure 4 - Anchoring of quercetin and IL-09 on the sNTPDase-1 active site. (A) Anchoring of IL-09 on the sNTPDase-1. (B) Anchoring of quercetin on the sNTPDase-1. (C-E) Detail showing of the sNTPDase-1 active site with anchoring. (C) Quercetin, overlapped with IL-09. (D) only IL-09 e (E) only quercetin.

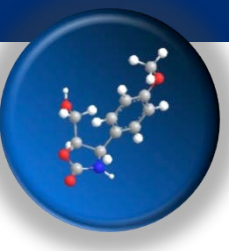


Conclusions

• The glycosidic derivative of quercetin was able to abolish the UDPase activity of sNTPDase-1;

• The optical isomerism of the quercetin derivative proved to be fundamental for its inhibitory activity;

• The L-glycosidic portion of flavonoid makes it more specific compared to quercetin;



Future perspectives

- Evaluate the biological effects of the selected inhibitors on "*in vitro*" and "*in vivo*" infection.

- Evaluate the cytotoxicity effects of the selected inhibitors.

- From these results propose the preparation of an anti-chagasic vaccine.

Acknowledgments

FAPEMIG, **CNPq** and **CAPES** for financial support.

Co-workers:

Juliana Lopes Rangel Fietto (DBB-UFV) - partner
Suélen Karine Sartori – PhD stuent (UFMG)
Daniele Cristina de Rezende - Master's Degree student (UFMG)
Marcela Lima dos Anjos Resende - student of scientific initiation (UFMG)