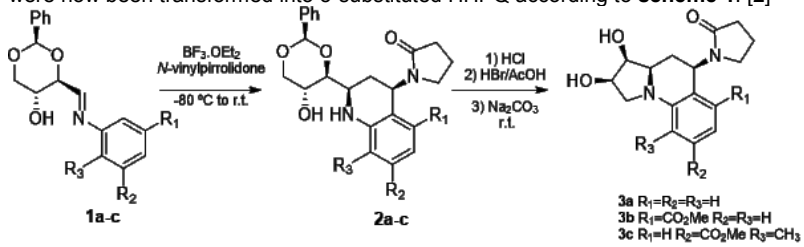
Stereoselective synthesis of 5-substituted hexahydropyrroquinolines-2,3-diol from functionalized tetrahydroquinolines.

Artem Drogalin[1,*], Maria José Alves[1], Tarsila G. Castro[2]
[1]Universidade do Minho, Departamento de Química, Braga, Portugal
[2]Universidade do Minho, Centro de Engenharia Biológica, Braga, Portugal
**e-mail del autor de contacto: pg33723@alunos.uminho.pt*

1,2,3,4-Tetrahydroquinolines (THQ) had shown diverse biological activities such as antiarrhythmic, cardiovascular, anticancer and immunosuppressor agents [1]. In this work tetrahydroquinolines **2** were synthesized by Povarov's reaction [3] from Schiff base **1**, being subsequently cyclized to hexahydropyrroquinolines-2,3-diol (HHPQ) **3a-c** using trivial reagents**.** Some new THQ bearing a trihydroxypropyl arm have already been synthetized. Those and others were now been transformed into 5-substituted HHPQ according to **scheme 1**. [2]



Scheme 1. Synthesis of tetrahydroquinolines of type **2**, and its further cyclization into hexahydropyrroquinolines

The synthetic process consists in: 1) *in situ* condensation of *m*-substituted anilines containing electron-withdrawing groups or aniline itself to D-erythrose; 2) cycloaddition of the obtained Schiff base **1**, with electron-rich *N*-vinylpyrrolidone in the presence of BF_3.etherate (0.3 eq.) giving **2a-c** compounds; 3) acetal cleavage, bromination of terminal hydroxyl, and amino-cyclization to give final products **3a-c**. A single cycloadduct was obtained when R_1=CO_2Me in yield 44%; two structural isomers were obtained in cases where larger alkyl groups are present in the ester function [4]. To guide the ester group into the position where R_2 is in **2c**, an *ortho-meta* substituted aniline was used.

Docking studies shed light on the interaction patterns of compounds of type **3** to Golgi α-mannosidase II and lysosomal α-mannosidases. These results represent a starting point in the rational design of type **3** based molecules towards selective Golgi α-mannosidase inhibition, assisted by molecular modelling techniques.

Acknowledgments: NMR Portuguese network (PTNMR, Bruker Avance III 400-Univ. Minho), and FCT and FEDER (European Fund for Regional Development)-COMPETE-QREN-EU for financial support to CQ/UM. Search-ON2: Revitalization of HPC infrastructure of UMinho, (NORTE-07-0162-FEDER-000086), co-funded by the North Portugal Regional Operational Programme (ON.2-O Novo Norte), under the National Strategic Reference Framework (NSRF), through the European Regional Development Fund (ERDF).

References:

[1] Vallaisamy S., Suryavanshi P. A., Mendez J. C., *Chem. Rev.* **2011**, 111, pg. 7160;
[2] Drogalin A., Alvés M. J., Fortes A. G., (November 2018) *Synthesis of functionalized tetrahydroquinolines, and its further transformation into hexahydropyrroloquinoline-2,3-diol by aminocyclization.* Poster session presented at the XXIV Encontro Luso-Galego de Química;
[3] Povarov L. S., Mikhailov B. M. *Izv. Akad. Nauk SSR, Ser. Khim.* **1963**, 953–956;
[4] Drogalin A., Alvés M. J., (May 2019) *Regio-selectivity studies of D-erythrosyl 4-substituted-phenylimines in Povarov's reaction with N-vinylpyrrolidone in the synthesis of Swainsonine precursors.* Poster session presented at the 4th Symposium on Medicinal Chemistry of the University of Minho