Université catholique de Louvain **UCL** SECTEUR DES SCIENCES ET TECHNOLOGIES

Institut de la Matière Condensée et des Nanosciences

# Invitation à la soutenance publique de thèse

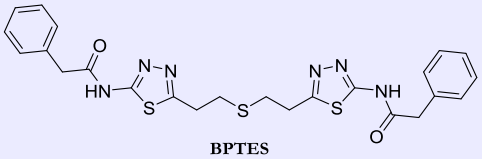
## Pour l'obtention du grade de Docteur en Sciences

## Monsieur Xavier DROZAK

**Master en sciences chimiques à finalité approfondie**

## Design, synthesis and biological evaluation of new glutaminase inhibitors

Tumor cells depend strongly on the consumption of glutamine to produce energy, metabolites and to mitigate the oxidative stress linked to their intensive proliferation. Mammalian tissues express two isoforms of glutaminase. The *kidney* type (KGA) is coded by the *GLS1* gene and the *liver* type is coded by *GLS2*. *GLS1* has been shown to be overexpressed in tumor cells by the oncogenic transcription factor *MYC*. This recently led to the development of therapeutic strategies aiming to inhibit the glutamine metabolism.
Bis-2-(5-phenylacetamido-1,2,4-thiadiazol-2-yl)ethyl sulfide (**BPTES**) is a potent and selective inhibitor of human kidney *glutaminase* (KGA). In an attempt to improve its potency and its pharmacological properties, **BPTES** analogs were synthesized and their cytotoxic activities were evaluated against the cancer cell line *SiHa* acclimated at low pH. Proceedings of those modifications, the new targets and their evaluation will be presented.



BPTES

First, a modification of the phenylacetamido moiety of **BPTES** was performed. Second, a modification of the linker moiety was performed. Finally, a modification of one of the heterocycles was carried out.

Chronologically, at this point of the project, several references containing an important number of newly synthesized **BPTES**-derivatives were published. In total, the number of new compounds synthesized and evaluated was close to 1,000. Strategically, the decision was made to redirect the research project. Since all these former compounds belong to the **BPTES** family, there was a necessity to look for molecules possessing a new chemotype capable of inhibiting GLS1.

The strategy chosen was to use the structural and biological data published to develop a docking model followed by a pharmacophore. The docking model was built, evaluated and used to determine the spatial orientation of known inhibitors of *GLS1*. This information allowed the development of a pharmacophore followed by a virtual screening of a large database composed of a large set of virtual compounds.

**Jeudi 15 juin 2017 à 15h00**

Auditoire LAVO 51
Bâtiment Lavoisier
Place Louis Pasteur, 1
1348 Louvain-la-Neuve

**Membres du jury :**

Prof. Olivier Riant (UCL), promoteur
Prof. Olivier Feron (UCL), promoteur
Prof. Yann Garcia (UCL), président
Prof. Raphaël Robiette (UCL), secrétaire
Prof. Raphaël Frederick (UCL)
Prof. Guido Verniest (VUB)
Prof. Séverine Ravez (Université de Lille 2, France)