SCIENCES & BIOENGINEERING SCIENCES

The Research Group of

Organic Chemistry

has the honor to invite you to the public defense of the PhD thesis of

Thomas BARLOW

to obtain the degree of Doctor of Sciences

Title of the PhD thesis:

Synthesis of triazole-fused N-heterocycles using catalyzed and uncatalyzed azide-alkyne cycloaddition reactions

Promotor:

Prof. Steven Ballet

The defense will take place on

Wednesday August 30 2017 at 17:00 h

in Auditorium D.0.03 at the Campus Humanities, Sciences and Engineering of the Vrije Universiteit Brussel, Pleinlaan 2 - 1050 Elsene, and will be followed by a reception.

Members of the jury:

Prof. Jan Steyaert (chairman)
Prof. Frank De Proft (secretary)
Prof. Vicky Caveliers (co-promotor)
Prof. Dr. em. Dirk Tourwé
Prof. Guido Verniest
Dr. Florine Cavelier (Univ. de Montpellier, F.)
Prof. Annemieke Madder (Univ. Gent)

Curriculum vitae

2008-2012
(University of Nottingham, UK)
MSci (Hons) Medicinal Chemistry

2011-2012
(University of Nottingham, UK)
Research project with GSK; "*Design and Development of integrin-$\alpha_V\beta_3$ antagonists for the treatment of idiopathic pulmonary fibrosis*"

2012
Recipient of IWT Bursary for Strategic Research

2013-2016
Doctoral Research in the Ballet Group (ORGC)

Abstract of the PhD research

Heterocyclic rings are widely used by researchers in the development of new drug candidates. There are many ways to synthesise such structures, and herein, we fully exploit a given reaction sequence – comprised of a multicomponent condensation (Ugi-4CR) and thermal Huisgen cycloaddition – to generate diverse *N*-heterocycles featuring a fused triazole.

The original discovery of the thermal Huisgen cycloaddition 50 years ago has been largely supplanted by the catalysed variants CuAAC and RuAAC. By using the uncatalysed Huisgen reaction, we have nevertheless been able to produce whole series of cyclic molecules, of which the smallest belongs to a category of "*privileged structures*".

We improved on the existing convergent syntheses of Ata-Xaa-dipeptides that involved tandem RuAAC and lactamisation. Using this methodology the Ata-dipeptides were synthesised in several steps with a maximum overall yield of 21%. By employing an Ugi four-component reaction followed by thermal Huisgen cycloaddition, we were able to generate a library of Ata-bearing di- and tripeptides in up to 94% in a one-pot-two-step process. Our improved methodology also provides two additional points of diversification compared to the products of the original conditions.

Our new conditions were improved further: a diethyl zinc-mediated cyclisation allowed the reduction of cyclisation time from 18-24 hours to just 2 hours. We also succeeded in installing a third point of diversification at the triazole 4'-position.

The Ugi-Huisgen methodology was also applied to the synthesis of benzo-fused *N*-heterocycles featuring a larger ring: this time of 8 atoms. Here, using a series of *ortho*-azidoanilines, we were able to generate a library of analogues with up to six points of diversification. These analogues were prepared in up to 82% yield and required similar reaction times as the 7-membered rings. From NMR studies, we also determined that these systems form Type IV ß-turns with an intramolecular hydrogen bond.

Finally, our Ugi-Huisgen methodology was applied to the synthesis of rings of 10-15 atoms. Starting from 12-atoms, however, the uncatalysed methodology was insufficient and RuAAC conditions were required for the successful cyclisation of these ring systems.