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3. S. Tabet, S.F. Douglas, **K.D. Daze**, G.A.E. Garnett, K.J.H. Allen, E.M.M. Abrioux, J.E. Wulff, F. Hof, Synthetic trimethyllysine receptors that bind histone 3, trimethyllysine 27 (H3K27me3) and disrupt its interaction with the epigenetic reader protein CBX7. *Bioorg. Med. Chem,* **2013**, 21, 7004-7010
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5. **K.D. Daze**, F. Hof, The cation-□ interaction at protein-protein interaction interfaces: developing and learning from synthetic mimics of proteins that bind methylated lysines. *Acc. Chem. Res.* **2013**, 46, 937-945.
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11. C.S. Beshara, C.E. Jones, **K.D. Daze**, B.J. Lilgert, F. Hof, A Simple Calixarene Recognizes Post-translationally Methylated Lysine. *ChemBioChem*. **2010**, 11, 63-66.

[1]These authors contributed equally.

University of Victoria | Graduate Studies

PROGRAMME

The Final Oral Examination for the Degree of

DOCTOR OF PHILOSOPHY
(Department of Chemistry)

Kevin Daze

2009 Simon Fraser University BSc (Biology)

"Synthesis and Evaluation of Supramolecular Chemical Tools to Study and Disrupt Epigenetic Pathways"

Thursday, April 17, 2014
1:00pm, Engineering/Computer Science Building, room 128

Supervisory Committee:
Dr. Fraser Hof, Department of Chemistry, UVic (Supervisor)
Dr. Tom Fyles, Department of Chemistry, UVic (Member)
Dr. Irina Paci, Department of Chemistry, UVic (Member)
Dr. Chris Nelson, Department of Biochemistry and Microbiology, UVic (Outside Member)

External Examiner:
Dr. David Vocadlo, Department of Chemistry, Simon Fraser University

Chair of Oral Examination:
Dr. Christopher Douglas, Department of English, UVic

Abstract

Weak, non-covalent interactions play an important role in supramolecular and biological sciences. In the biological sciences numerous weak interactions combine to create the powerful ability of proteins to recognize and bind with specific guests. In supramolecular chemistry we attempt to recreate this ability in a much smaller, defined way to achieve the same feats of recognition and selection we see in proteins.

Epigenetics is a relatively new field, but has seen a sharp rise in interest over the past decade due to its role in numerous human diseases. Post-translational modifications to amino acids, in particular methylation of lysine and arginine residues, are a hallmark of epigenetics. This is a very small covalent change and yet acts as an anchor point for new protein-protein interactions that have large effects on gene expression. While these changes are structurally small, their implications on solvation, hydrogen bonding, electrostatics and cation-□ interactions are familiar to the supramolecular chemical community.

The aromatic cage is a protein recognition motif that recognizes methylated lysine residues through a combination of non-covalent interactions, like those mentioned above. In this thesis, we report on the study of a chemical mimic of the aromatic cage — a functionalized calix[4]arene macrocycle — that can bind methylated amino acids and peptides in buffered water with high affinities and moderate selectivities. We expand on this initial result by synthesizing new analogs in a variety of ways, which yielded a small, diverse library of aromatic cage mimics. Each of these compound classes displays unique and tunable affinities and selectivities for different methylated amino acid, peptide, and protein targets. We report on our efforts to use these mimics as chemical tools in two new applications: as fluorescent molecular sensors of post-translationally methylated analytes, and as disruptors of protein-protein interactions that depend on methylated lysine.

Awards, Scholarships, Fellowships

2013 Canadian Cancer Society – Travel Award (National)
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2013 Sachi Nakashima Keystone Travel Award – Cancer Epigenetics (International)
2013 WestCoast Ride-to-Live Prostate Cancer Studentship (Regional)
2013 Prostate Cancer Foundation of British Columbia Grant-in-Aide (Provincial)
2012 CIHR – Travel Award – Institute Community Support: Cancer Research (National)
2012 Yvonne Allen Cancer Research Fellowship (UVic)
2012 Lewis J. Clark Memorial Scholarship (UVic Chemistry)
2012 WestCoast Ride-to-Live Prostate Cancer Studentship (Regional)
2012 Prostate Cancer Foundation of British Columbia Grant-in-Aide (Provincial)
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2011 WestCoast Ride-to-Live Prostate Cancer Research Grant (Regional – co-applicant with F. Hof)
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2010 Dr. Julius Schleicher Graduate Fellowship Award (UVic)

Presentations

1. **K.D. Daze,** *et al.*, Discovery, optimization and chemical biology of the first chromodomain antagonists. **Poster Presentation**, *Keystone Symposia: Cancer Epigenetics*, Santa Fe, NM, USA, February 5, 2014.
2. **K.D. Daze**, *et al.*, Small molecular inhibitors and chemical tools to study protein-protein interactions invoked by trimethylated lysine. **Poster Presentation**, *Gordon Research Conference: Bioogranic Chemistry*, Andover, NH, USA. June 9, 2013.
3. **K.D. Daze**, F. Hof, Small molecule inhibitors and chemical probes to study protein-protein interactions triggered by trimethylated lysine, **Oral Presentation**, *Franco-Canadian Supramolecular Chemistry Workshop*, Victoria-Montreal-Paris (teleconference). May 24, 2013
4. **K.D. Daze**, F. Hof, Complex interplay of electrostatics and hydration effects in protein-ligand binding, **Oral Presentation**, *American Chemical Society National Meeting*, New Orleans, LA, USA. April 7, 2013
5. **K.D. Daze**, F. Hof, Design, synthesis and evaluation of small molecule inhibitors of H3K27me3-recognition proteins. **Poster Presentation**, *Playing Ball: The Scripps Research Institute Poster Session*, San Diego, CA, USA. March 26, 2012
6. **K.D. Daze**, F. Hof, Design, Synthesis and evaluation of small molecule inhibitors of H3K27me3-recognition proteins. **Oral Presentation**, *American Chemical Society National Meeting*, San Diego, CA, USA. March 26, 2012
7. **K.D. Daze,** F. Hof, Design, synthesis and testing of small molecule inhibitors of the H3K27me3 mark. **Poster Presentation**, *Volcano Conference on Chemical Biology*, Pack Forest, WA, USA. February 25, 2012.
8. **K.D. Daze**, F. Hof, Inhibitors and probes of epigenetic pathways. **Oral Presentation**, *SuMo Supramolecular Chemistry Symposium*, University of Oregon. Sept. 3, 2011.
9. **K.D. Daze**, F. Hof, Design, synthesis and testing of small molecule inhibitors of the EZH2 trimethylation mark. **Oral Presentation**, *Canadian Society of Chemistry National Conference*, Montreal, QC, Canada. June 9, 2011
10. **K.D. Daze,** F. Hof, Design, synthesis and testing of small molecule inhibitors of the EZH2 H3K27me3 mark. **Poster Presentation**, *Volcano Conference on Chemical Biology*, Pack Forest, WA, USA. February 26, 2011.