


GHENT UNIVERSITY

Furan Modified DNA Building Blocks: A Toolbox for Crosslinking, Ligation and Secondary Structure Analysis

Laboratory for Organic and Biomimetic Chemistry

anneemieke.madder@ugent.be

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Ischia
September 28th 2010

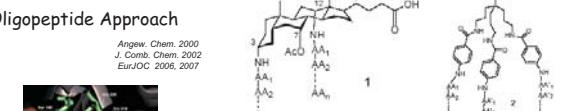

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Design and synthesis of serine-protease mimics

Oligopeptide Approach

Angew. Chem. 2000
J. Comb. Chem. 2002
EurJOC 2006, 2007

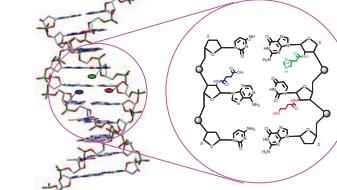
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Chymotrypsin active site

Oligonucleotide Approach

Molecules 2007, 2009



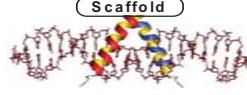
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Conformationally defined multipodal peptides as functional miniproteins

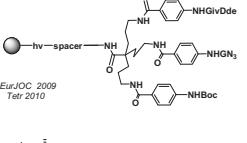
Estrogen receptor mimics
for solid phase extraction and
preconcentration of endocrine
disrupting chemicals

Scaffold



EurJOC 2009
Tetrahedron 2010

Epitope mimics as
Peptide vaccines



EurJOC 2009
Tetrahedron 2010

Transcription factor mimics
as DNA binding ligands



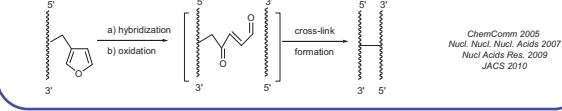
EurJOC 2007, Arkivoc 2007 (Alain Krief Issue)
Drug Discovery Today: Technol. 2010

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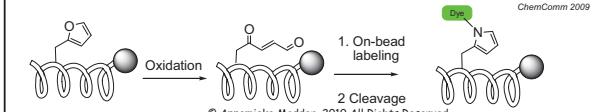
Novel techniques for crosslinking, labeling and conjugation of biomacromolecules

I. Crosslinking of oligonucleotides: Antisense, antigenic, crosslink repair, decoy DNA



ChemComm 2005
Nucl. Acids Res. 2007
Nucl. Acids Res. 2009
JACS 2010

II. Labeling of peptides: Imaging, conjugation

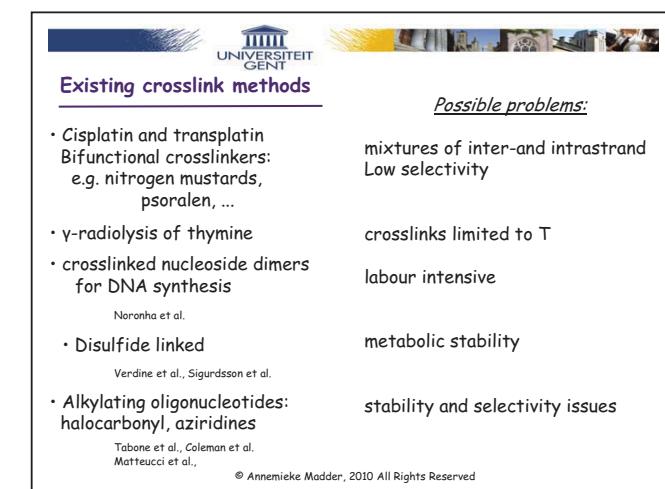
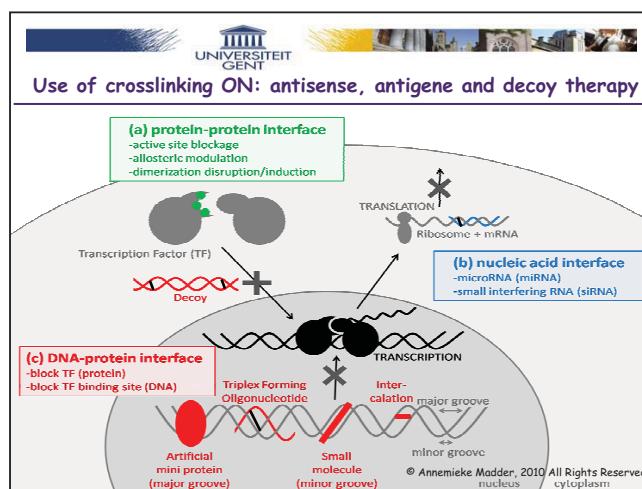
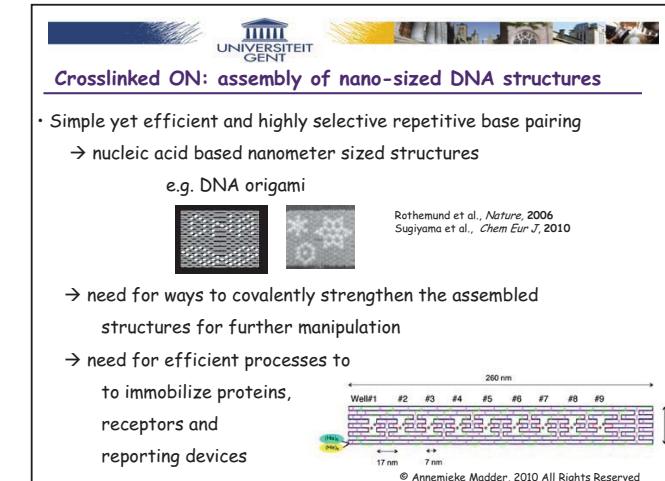
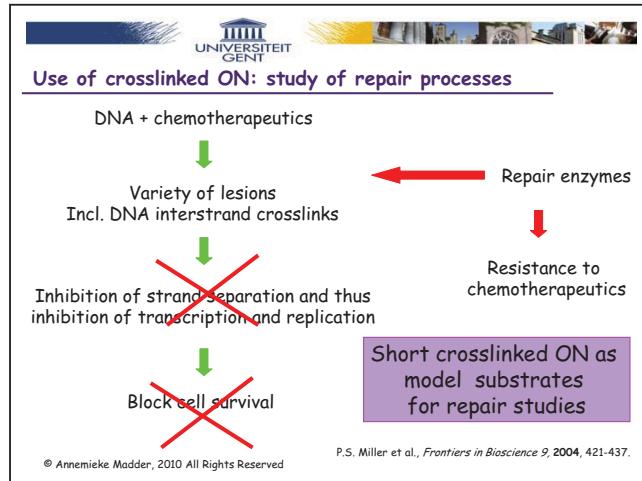


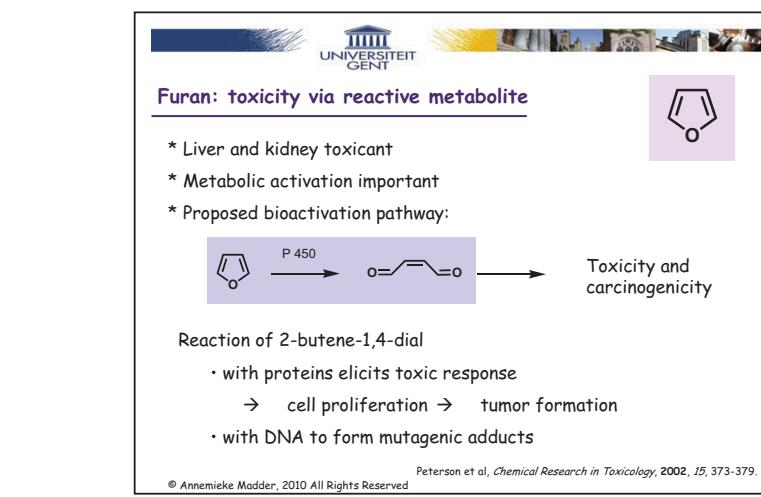
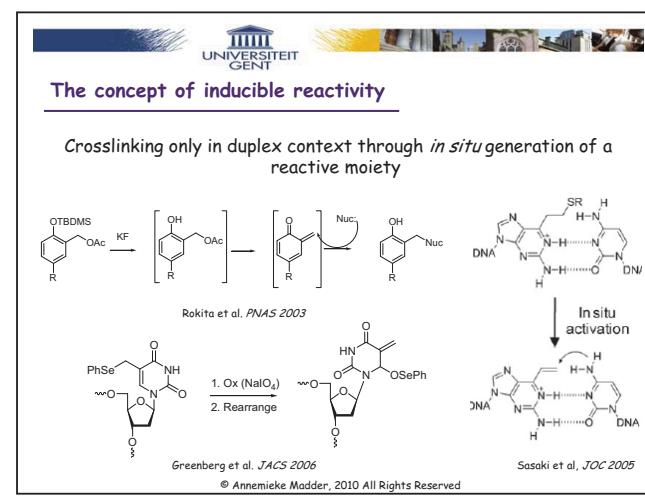
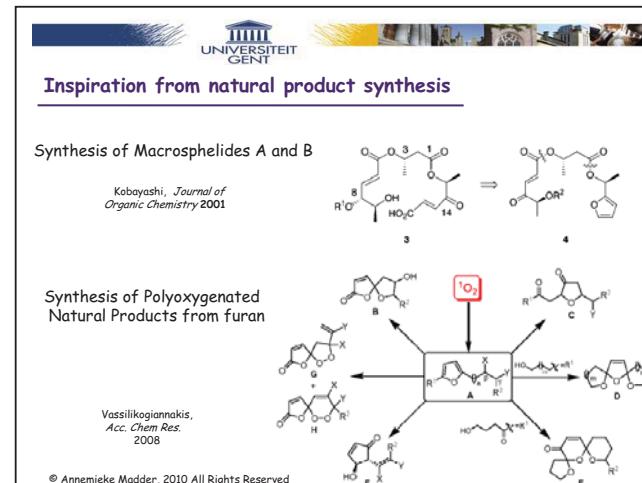
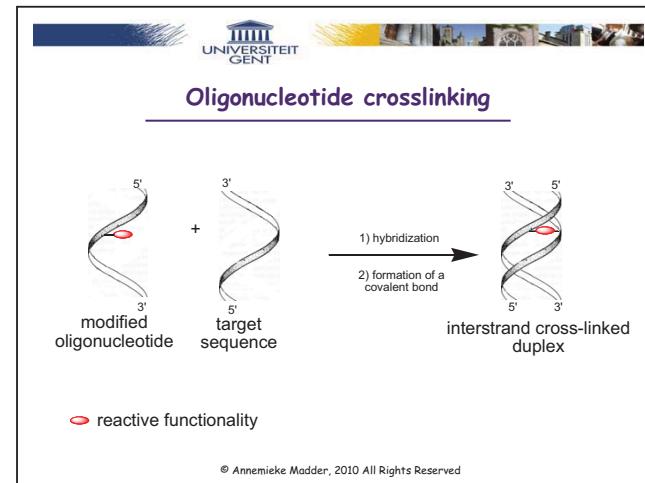
ChemComm 2009

1. On-bead labeling
2. Cleavage

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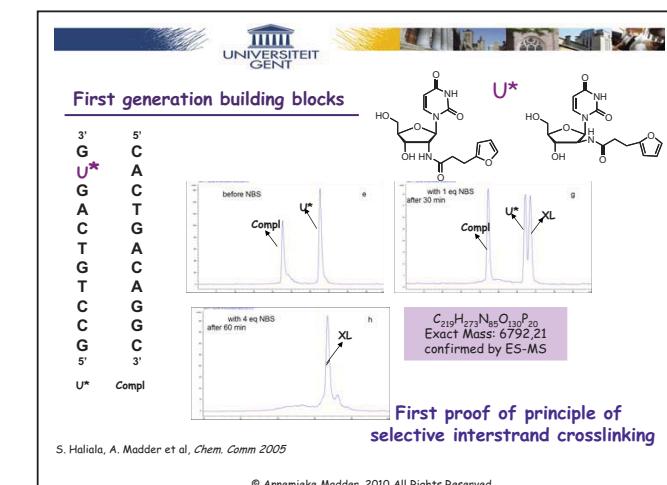
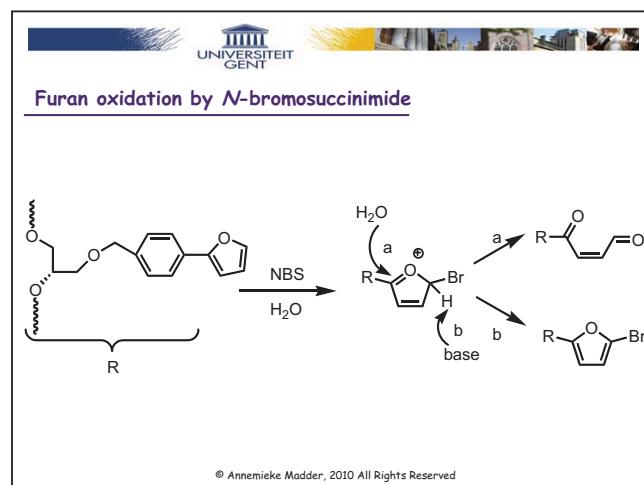
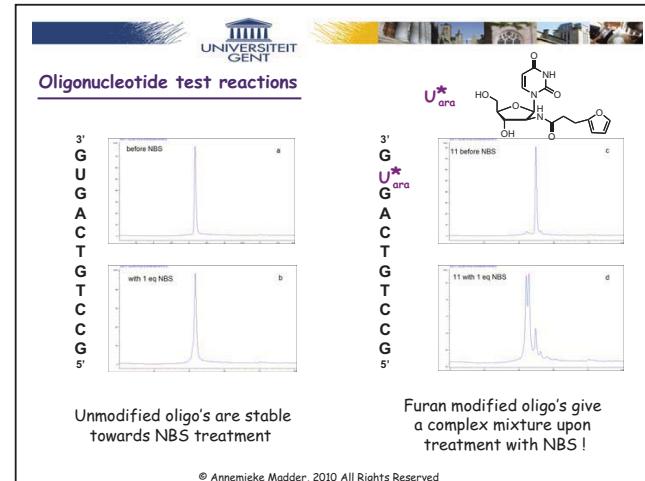


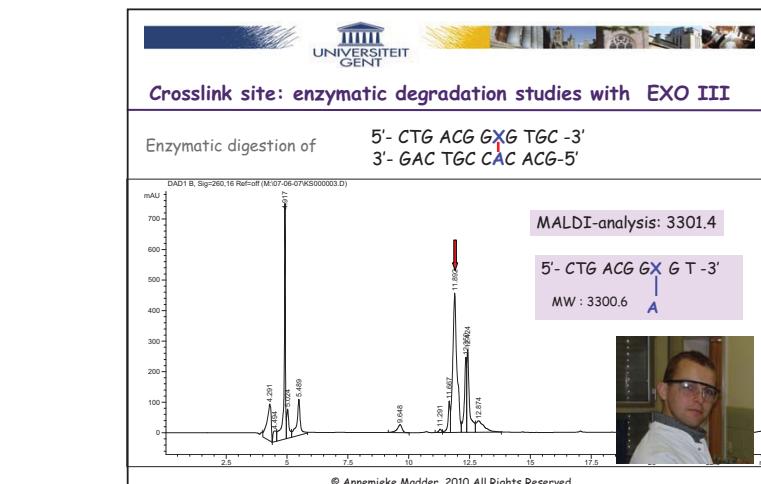
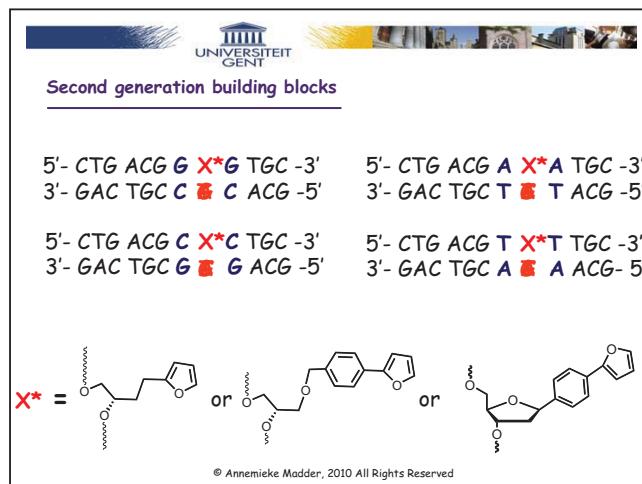
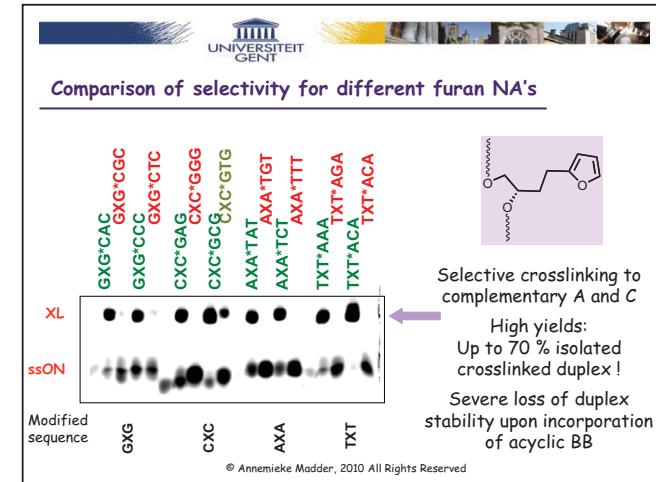
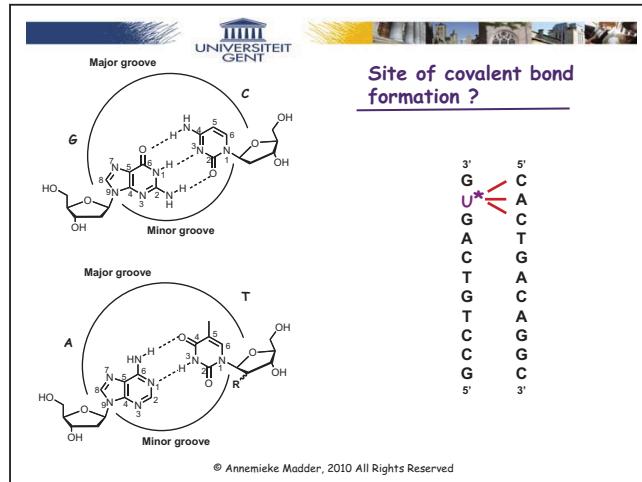


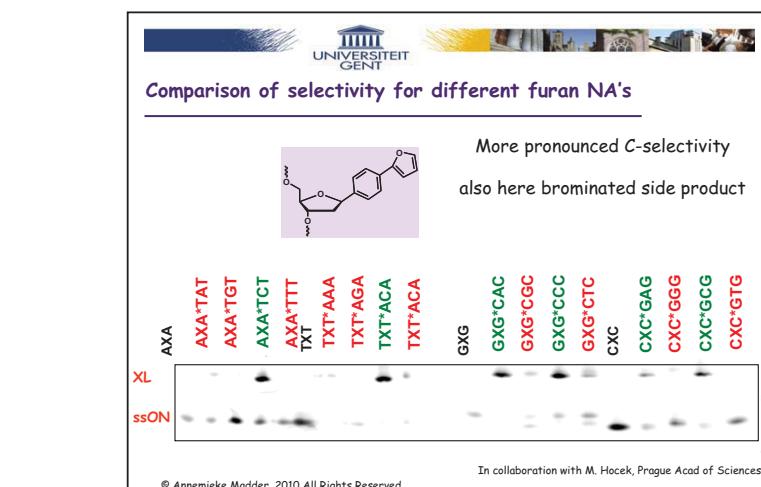
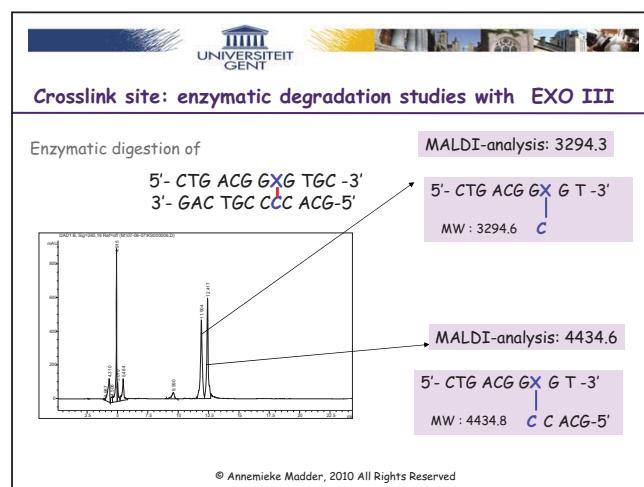
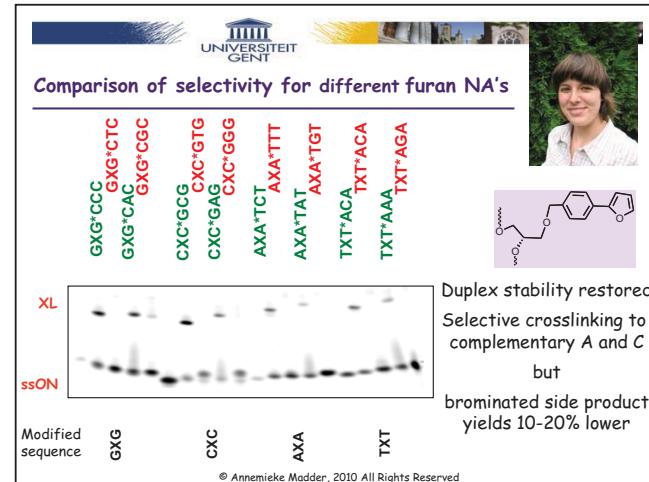
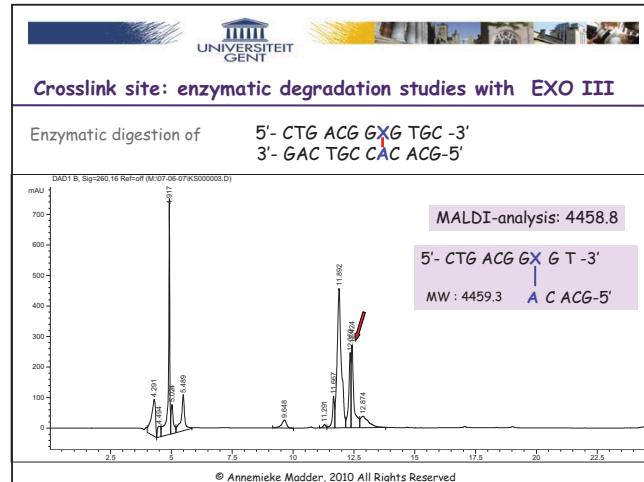
A possible furan-oxidation crosslink strategy ?

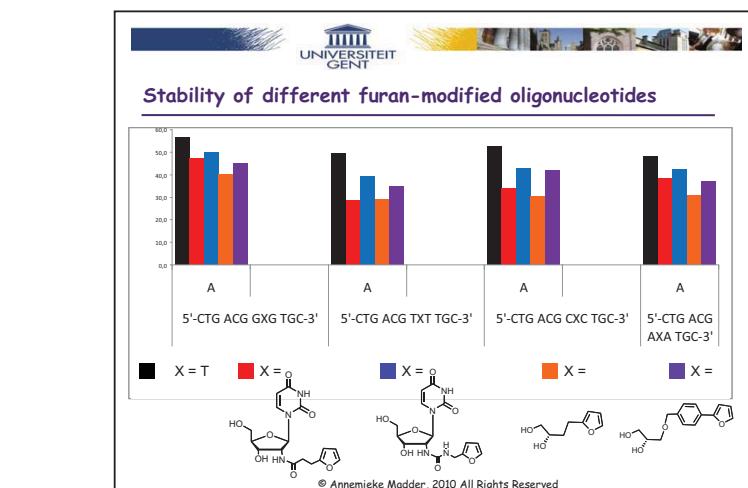
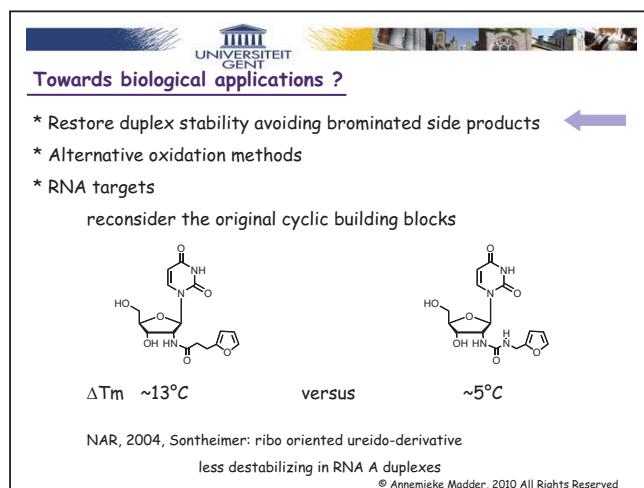
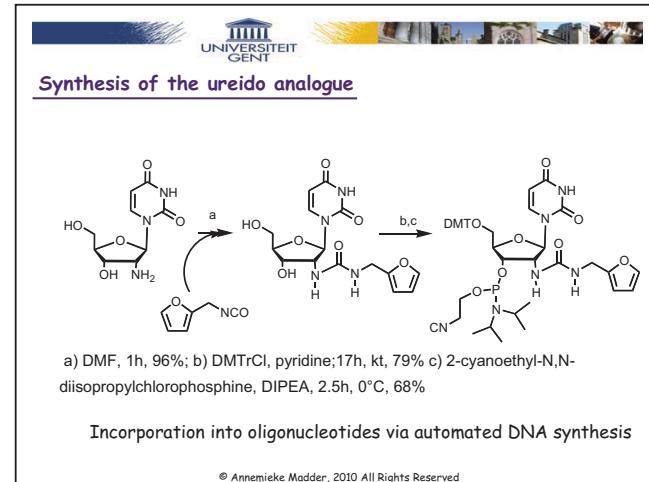
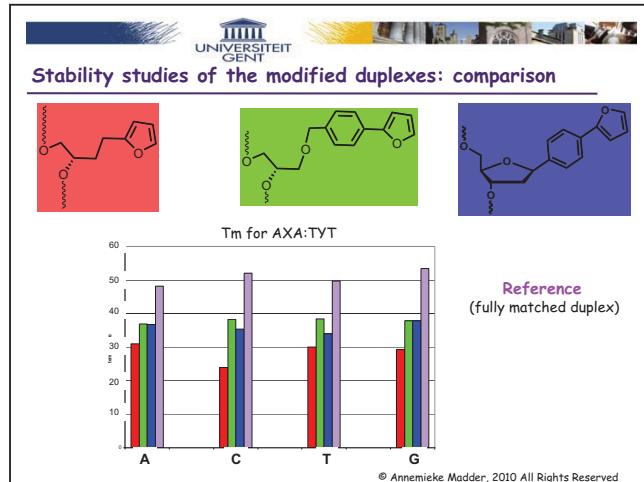
- Crosslinking only in duplex context
 - Use of furan as latent functionality for reactive aldehyde

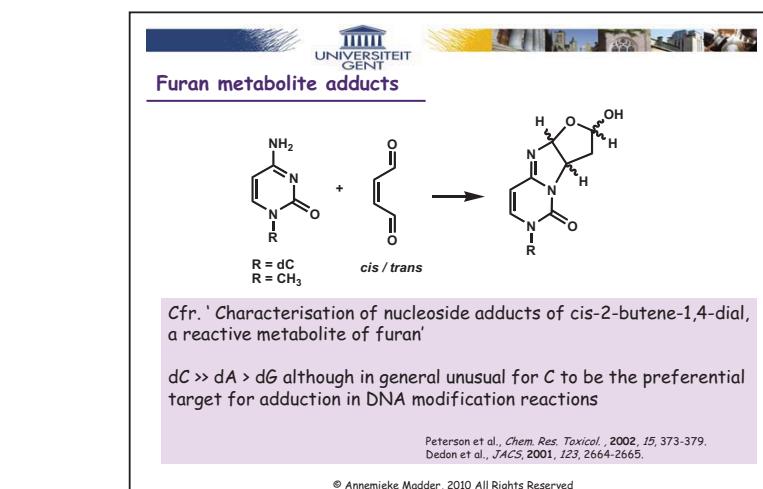
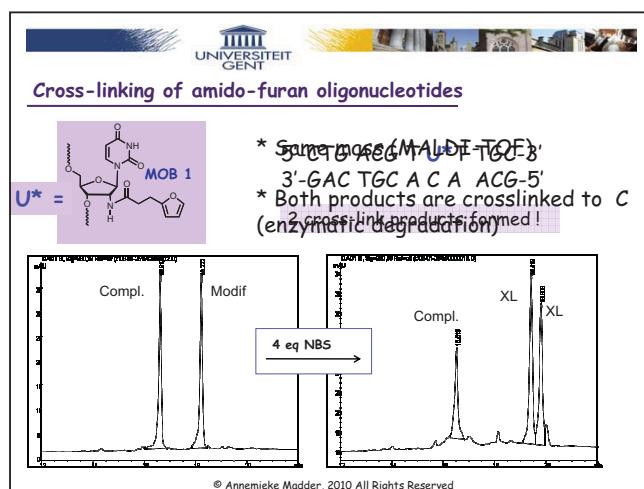
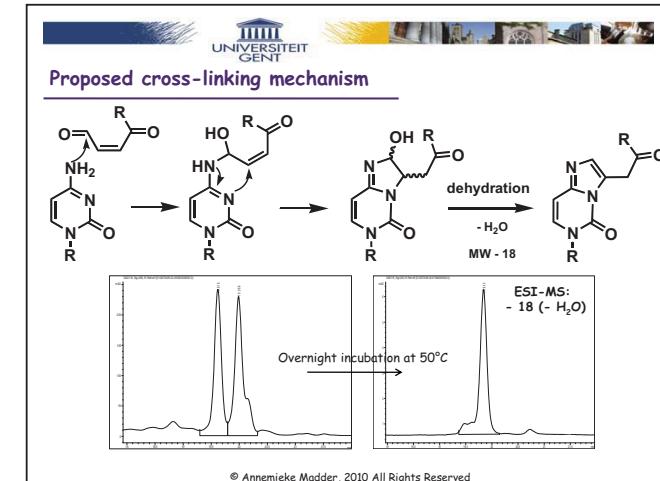
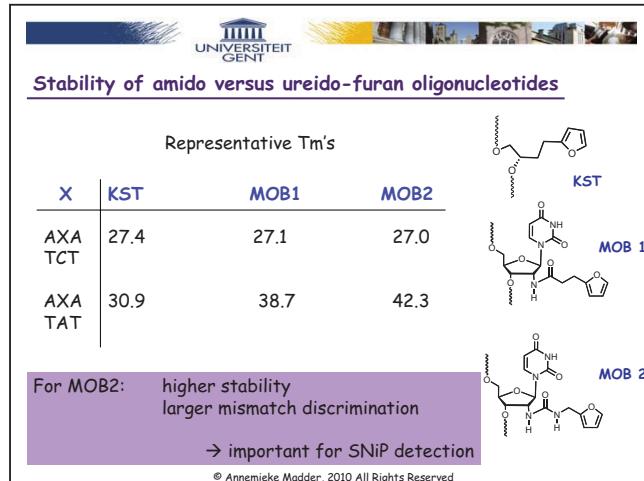
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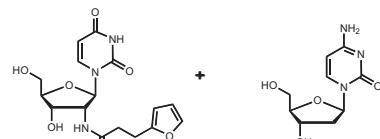




Structural characterisation of crosslinked duplex

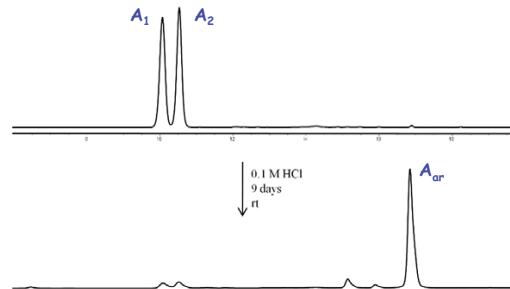
Confirmation of the proposed cross-link structure:

- * Cross-linking of individual nucleosides to the dinucleotide
- * Complete enzymatic degradation of the cross-linked duplex
- * Coinjection on RP-HPLC



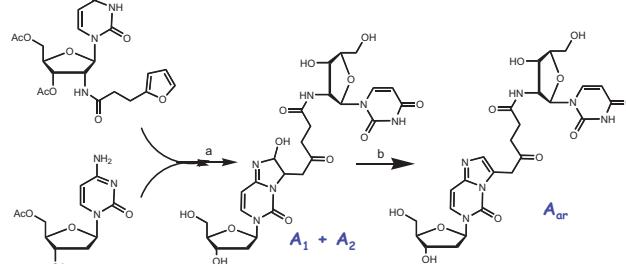
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Structural confirmation of crosslinked duplex



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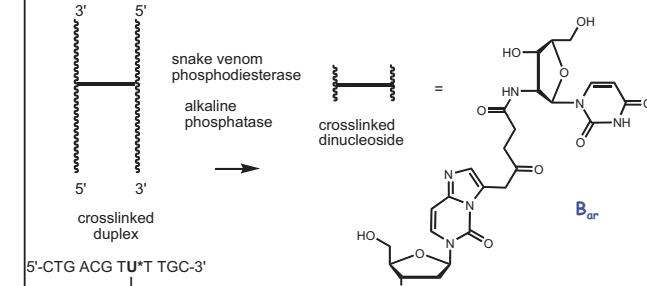
Structural characterisation of crosslinked duplex: starting from individual nucleosides



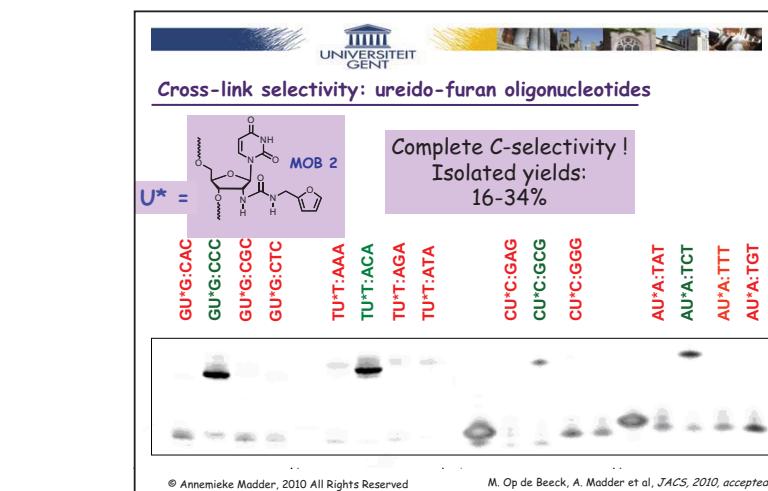
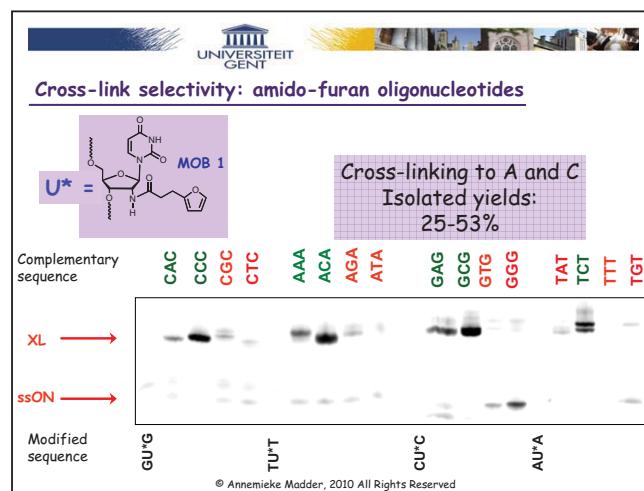
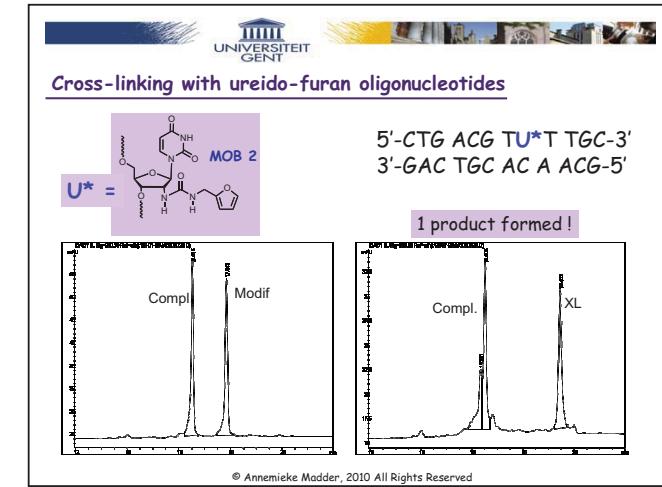
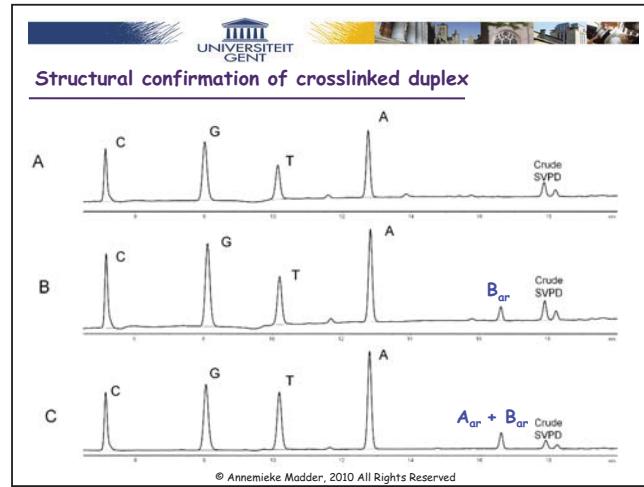
a) i. NBS, pyridine, THF/acetone/H₂O 5/4/2, overnight, rt; ii. NH₃/MeOH; overnight, rt, 80% (over 2 steps);
b) 0.1 M HCl, 9 days, rt, quantitative

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Structural confirmation of crosslinked duplex: starting from crosslinked duplex



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Furan-probes for Adenine detection

Cfr. Work of Akio Kobori et al., Kyoto Institute of Technology,
Dept of Biomolecular Engineering
→ Diagnosis of A related DNA mutations

5'-furan conjugated probes directed against the point mutation site in the JAK2gene, associated with chronic myeloproliferative disease

A clearly distinguished versus C through formation of fluorescent derivative

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A. Kobori et al., BMC Lett. 2009, 3567

Thanks to

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Annelies Deceuninck
Marieke Op De Beeck
Sara Figaroli

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Prof. Michal Hocek, Prague
Prof. Floris Van Delft, Nijmegen
Dr. Sami Halila
Dr. Trinidad Velasco

FWO-Vlaanderen
Ugent - BOF
EC (HPRN-CT-2000-00014)

Conclusions

Incorporation of a furan moiety as a masked reactive functionality into oligonucleotides:

- new, efficient and high yielding ON crosslink method using a proximity based reaction
- modular strategy: allows for stability and selectivity tuning

