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Research Done:

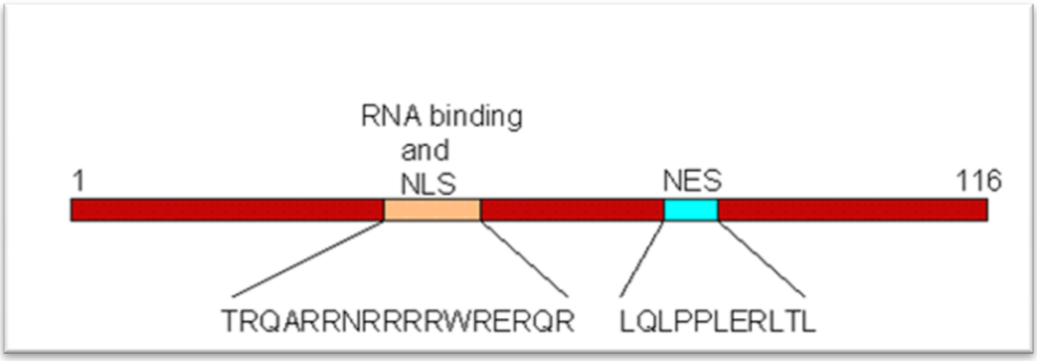
Synthesis of Conformationally Restricted alfa-Helix Mimics as Rev Multimerization Inhibitors and Synthesis of Functionalised 1-Hydroxypyrazin-2(1H)-one Scaffolds as Potential Integrase Inhibitors.

In this work, I worked on two different stages in the viral replication cycle in collaboration with Rega Institute, KULeuven. In the first part I focused on the inhibition of the Rev multimerization. Up to now, the Rev protein has received little attention as a therapeutical target. In order to perform the nuclear export function, Rev has to multimerize. The region responsible for this multimerization was known and is composed of two α;-helices. The truncated Rev fragment corresponding to of one of these two α-

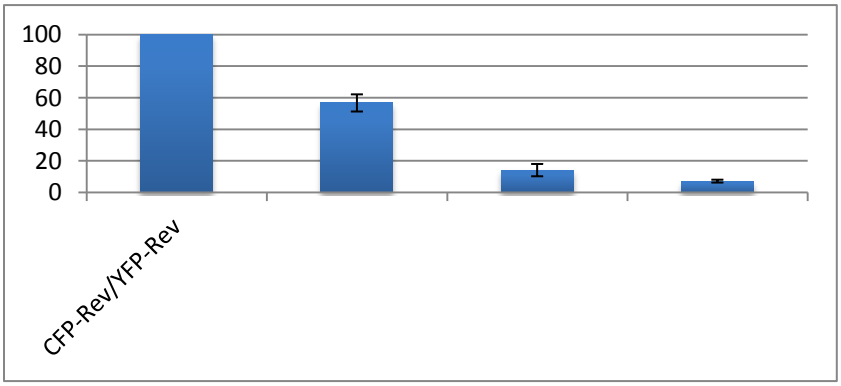
helices has been studied in a Rev multimerization assay developed by the group of Daelemans (Rega institute, KULeuven) but didn't show any inhibition.

We have modified this sequence in order to stabilize the helicity of the peptide by incorporation of a lactam bridge. This modified peptide 1 was synthesized by SPPS using Fmoc strategy. This peptide did show inhibition of Rev multimerization to some extent. Further scrambling experiments shed a light on the specificity of the inhibition.Following up on these results, two further approaches were worked out in the further design of potential Rev multimerization inhibitors.

In a first approach, peptides based on screening an independent α-helical peptide library were designed and synthesized. Secondly, a small molecule α-helix mimic based on a biphenyl molecule was synthesized. However, neither of these approaches delivered compounds that were able to inhibit the Rev multimerization.From this study we could conclude that to inhibit Rev multimerization, along with the α-helical nature of the synthesized peptide, the amino acid residue specificity is important too. We hope this work will help to further understand how to inhibit multimerization.



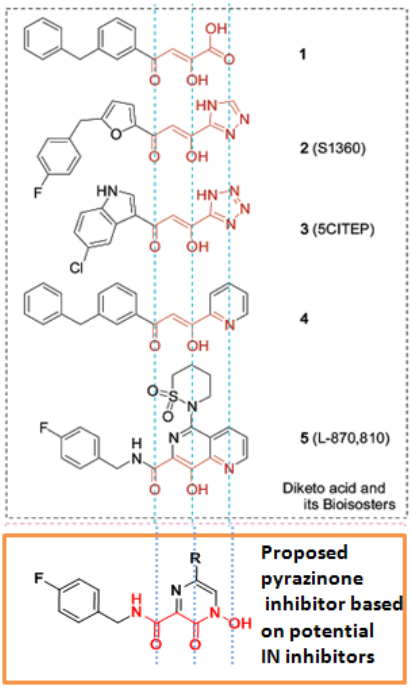
Rev protein structure



From this study we could conclude that to inhibit Rev multimerization, along with the α-helical nature of this synthesized peptide, the amino acid residue's specificity is important too. We hope this work would

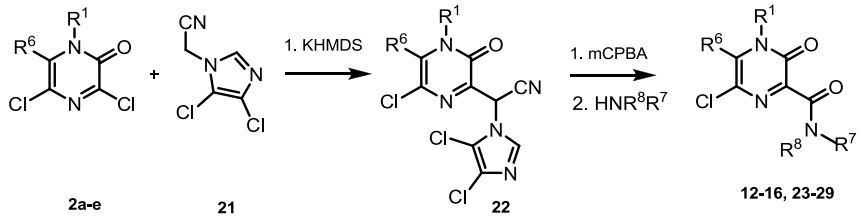
help to understand how to inhibit multimerization.

In the second part of the research, I focused on another important target namely the integrase. Integrase enzymes play a very important role in the HIV replication cycle. Integration is required for viral replication, because transcription of the viral genome and the production of viral protein require that the viral cDNA is fully integrated into a chromosome. The approval of Raltegravir as a first drug targeting the integration step in the HIV life cycle, has paved the way for a new class of drugs disturbing HIV replication.



Design of new potent integrase inhibitor based on 2 (1*H*)-pyrazinone

We designed a new potential integrase inhibitor based on structural analogy withknown inhibitors andproposed N-hydroxy-2(1H)-pyrazinone-3-carboxamides as candidates for synthesis. To synthesize this proposed scaffold, we first optimized functionalizing 3,5-dichloro-2(1H)-pyrazinones at the 3 position with a carboxamide functional group. Application of this method to the desired N-hydroxy final compounds however was not possible. Alternatively we have tried to synthesize the proposed molecules starting from diethyl aminomalonate. Using this method we succeeded in making a number of analogues of the designed scaffold. However upon testing them for antiviral activity we found none of them to be active.



2a, $R^1 = CH_2Ph$, $R^6 = H$
2b, $R^1 = CH_2CH_2Ph$, $R^6 = H$
2c, $R^1 = Ph$, $R^6 = H$
2d, $R^1 = CH_2Ph$, $R^6 = CH_3$
2e, $R^1 = CH_2Ph$, $R^6 = Ph(p\text{-}OMe)$

Compound	R^1	R^6	R^7	R^8	Yield[a] (%)
12	CH_2Ph	H	Me	Me	60[b], 24[c], 33[d]
13	CH_2CH_2Ph	H	Me	Me	63[b]
14	Ph	CH_3	Me	Me	74[b]
15	CH_2Ph	CH_3	Me	Me	67[b]
16	CH_2Ph	Ph (*p*-OMe)	Me	Me	83[b]
23	CH_2Ph	Ph (*p*-OMe)	H	$(CH_2)_2CH(CH_3)_2$	73[b]
24	CH_2Ph	Ph (*p*-OMe)	Pyrrolidine		88[b]
25	CH_2Ph	Ph (*p*-OMe)	Et	Et	72[b]
26	CH_2Ph	Ph (*p*-OMe)	H	$(CH_2)_5CH_3$	81[b]
27	CH_2Ph	Ph (*p*-OMe)	H	allyl	49[b]
28	CH_2Ph	Ph (*p*-OMe)	H	CH_2Ph(p-OMe)	79[b]
29	CH_2Ph	Ph (*p*-OMe)	H	$CH_2CH_2OCH_3$	76[b]

a Isolated yield using oxidant. *b* *m*CPBA. *c* Na_2O_2. *d* CH_3CO_3H.

One pot synthesis: affording secondary and tertiary carboxamides.

In second part of the research, we focused on another important target, integrase inhibitor. Integrase enzymes play a very important role in HIV replication cycle. Integration is required for viral replication, because transcription of the viral genome and the production of viral protein require that the viral cDNA is fully integrated into a chromosome.

Area of Interest in Research:

Peptide Chemistry,
Medicinal Chemistry,
Heterocyclic chemistry

Books Published:

Name of Book	Author(s)	ISBN No.	Year	Edition	Publisher

Research publications:

Vercruysse, T.; **Pawar, S**.; De Borggraeve, W.; Pardon, E.; Pavlakis, G. N.; Pannecouque, C.; Steyaert, J.; Balzarini, J.; Daelemans, D., Measuring cooperative Rev protein-protein interactions on Rev responsive RNA by fluorescence resonance energy transfer. *RNA Biology* **2011,** *8* (2), 316-324.
Pawar, S., Vercruysse, T., Dehaen, W., Daelemans, D., De Borggraeve, W. Synthesis of Conformationally Restricted alpha-Helix Mimics ss Rev Multimerization Inhibitors. *Biopolymers: vol. 92* (4). 21st American Peptide Symposium. Bloomington, **7-12 june 2009**, 331-331.
Pawar, S. V.; Pawar, V. G.; Dehaen, W; De Borggraeve, W. M.; Synthesis of Highly Functionalized 2(1*H*)-Pyrazinone 3-Carboxamide Scaffolds. *Organic Letters*, **2008**. 10(20): p. 4473-4476.
Anh Hung Mai, Sonalika Pawar, Wim M. De Borggaeve, Synthesis of 1-benzyloxypyrazin-2(1*H*)-one derivatives. *Tetrahedron Letters*, **2014**, 55(33): p. 4664-4666

Seminars and Workshops Attended:-

12th Sigma Aldrich Symposium, Spa, Belgium 2008
13th Sigma Aldrich Symposium, Leuven la naue, Belgium 2009
American Peptide Symposium, Indianapolis, Indiana, USA, 2009

Seminars and Workshops Organized:-

Other Accomplishments:-

Travel Award, American Peptide Society, USA, 2009
Doctoral Scholarship of the interfacaulty Council for Development Co-operation (IRO), 2007-2011, KULeuven, Belgium