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Pseudopeptides for Transfection:

Chemical synthesis, biopysical investigations of supramolecular complexes and biological assays

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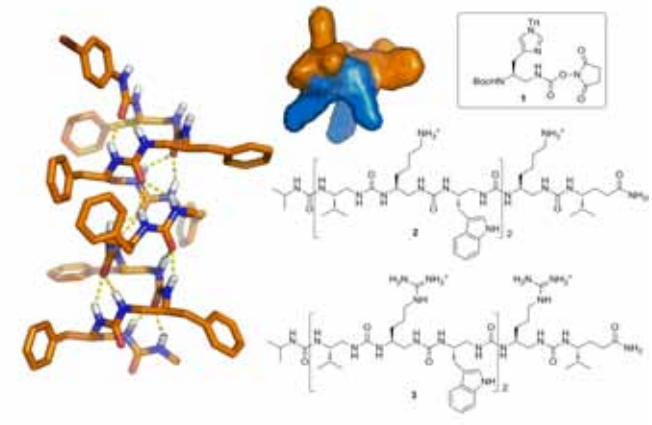
Context

Histidine-rich peptides designed in our laboratories exhibit potent transfection activities for DNA and siRNA, and therefore considerable potential for gene therapy and future therapeutic gene silencing approaches. At neutral pH these peptides condense nucleic acids into transfection complexes. Biochemical and biophysical investigations indicate that the complexes enter the cell interior via an endocytotic pathway. Upon acidification of the organelle the histidines change protonation state and as a consequence about half of the peptides are released from the complexes. These lyse the endosomal membrane and ensure very efficient delivery into the cell interior. In order to further ameliorate their utility e.g. in the presence of serum and proteases we explore urea-peptide analogues for this type of applications.

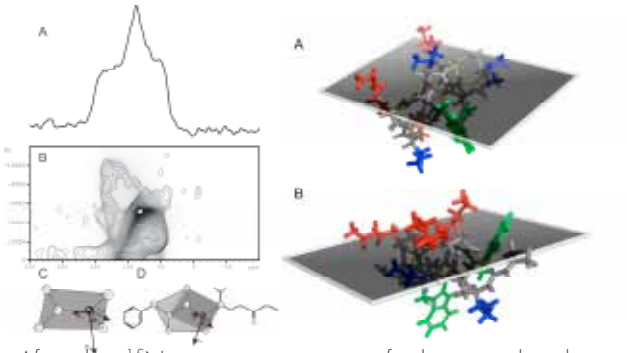
Results

Chemical synthesis of new urea-peptide foldamers (8-11 units) incl. the development of protocols for and first-time preparation of the 'histidine' building block 1:



Goals

The design and preparation of urea-peptide analogues, that are potentially active in nucleic acid transfection. The development of novel building blocks for the chemical synthesis of these compounds. Understanding of the functional mechanisms through structural and biophysical investigations in combination with biological assays. This in turn requires determination of a number of parameters such as the ^{15}N chemical shift tensor and the transition dipole moment before the membrane interactions could be investigated by solid-state NMR and FTIR.



After the ^{15}N interaction tensor of oligourea bonds was determined with a model compound (left panel) the topology of oligoureas was analyzed by oriented solid-state NMR (2, right). FTIR data confirm the membrane alignment.

Conclusions and Impact

A first series of oligourea analogues has been designed, prepared and tested. In particular those carrying arginine analogues (e.g. 3) exhibit good transfection activities. Compounds rich in imidazole side chains (1) are currently investigated. Furthermore, biophysical investigations indicate how these pseudopeptides interact with the membrane and knowing key interaction parameters will allow a more routine analysis and design of improved compounds in the future.

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