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Applications of Bis-peptide nanostructures

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CANDO

- Large software package (180,00 lines of C++)
- Designing precise organic nanostructures (called bis-peptides) with programmable three-dimensional structures these nanostructures in software before synthesizing and testing them.
- Ported to Kraken and implemented OpenMPI message passing and a scripting language based on LISP to design bis-peptides to solve specific problems.

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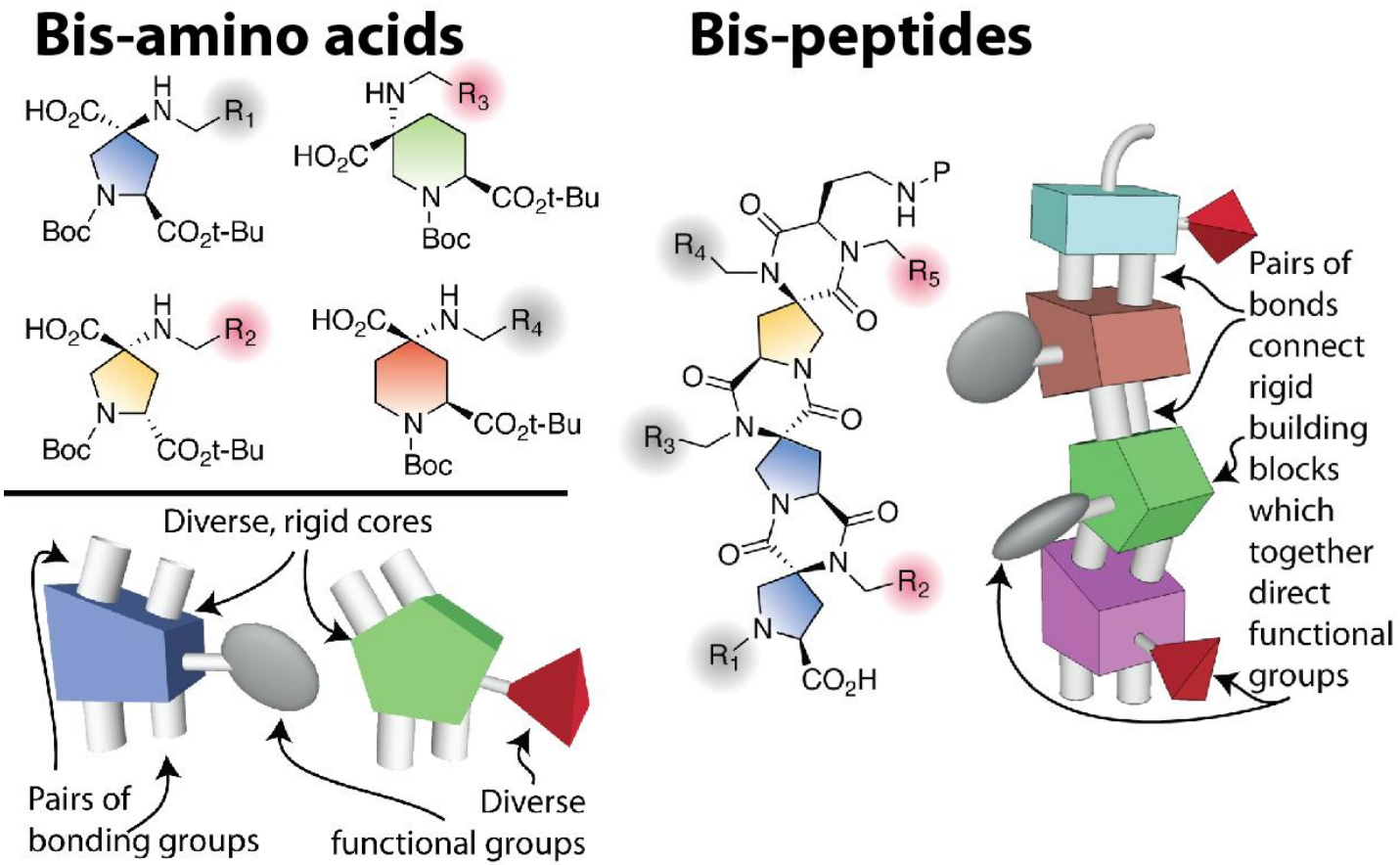
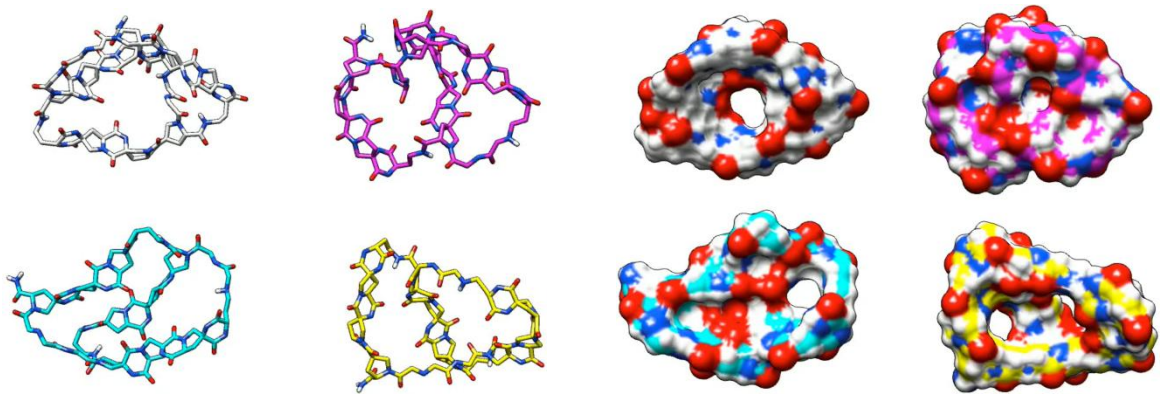


Bis-peptides are constructed by connecting cyclic building blocks (bis-amino acids) through pairs of bonds to create shape-programmable ladder oligomers. Time on Kraken is used to construct a database of three-dimensional structures bis-amino acid building blocks and to assemble these building blocks into bis-peptides. The bis-peptide models are then scored based on how well they are able to present functional groups to carry out protein binding or catalytic function.

Four breakthroughs using Kraken

1) **Designed, synthesized and demonstrated a bis-peptide that binds the protein HDM2 and causes the levels of a key cancer related protein called p53 to drop.**
   - **Built millions of bis-peptides and identify those that could present three functional groups in a 3D arrangement that is consistent with binding HDM2.**

2) **Demonstrated the ability to connect several bis-peptides together and covalently tie them into bundles the size and complexity of small proteins.**
   - **These nanostructures will be used to construct enzyme-like catalysts, new drugs and molecular devices. The computer aided design of these nanostructures is much easier than solving the protein folding problem because they are chemically constrained.**



Four bis-peptide bundle structures that display different pockets (left: stick model, right: solvent accessible surface). These molecules are about two nanometers across and display pockets the size of small protein active sites.

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Breakthroughs using Kraken

3) Designed, synthesized and demonstrated bi-functional bis-peptides that hold a base close to an alcohol and enhance the reactivity of the alcohol by more than 150-fold.

- **Activation of water and alcohols is one of the most common catalytic operations of enzymes and we are working to mimic this capability in bis-peptide nanostructures to incrementally build enzyme-like active sites that can carry out transesterification, ester hydrolysis and phosphate ester hydrolysis.**

4) Designed, synthesized and demonstrated bi-functional bis-peptides that hold a carboxylic acid and a phenol close to each other and simultaneously accelerate an aromatic Claisen rearrangement.

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Computation intensive with Kraken

- The most computationally intensive use of Kraken occurred when building a database of bis-peptide fragments that are needed to build larger structures.
  - The fragment database involves hundreds of thousands of molecular mechanics conformational searches of small molecules with non-linear energy minimization.
  - Number of cores : varying from 1000 to 4000 cores
  - Time : from 15 minutes to more than 60 minutes .
  - Each calculation is saved and incorporated into the database and no processing cycles are wasted.
- The other computationally intensive use of Kraken occurs when use it to design bis-peptide bundles. These involve conformational searches interleaved with non-linear energy optimization.

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