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An efficient algorithm to find matched pairs of a peptide

Noel O'Boyle, Chris de Graaf
noel.oboyle@soseiheptares.com

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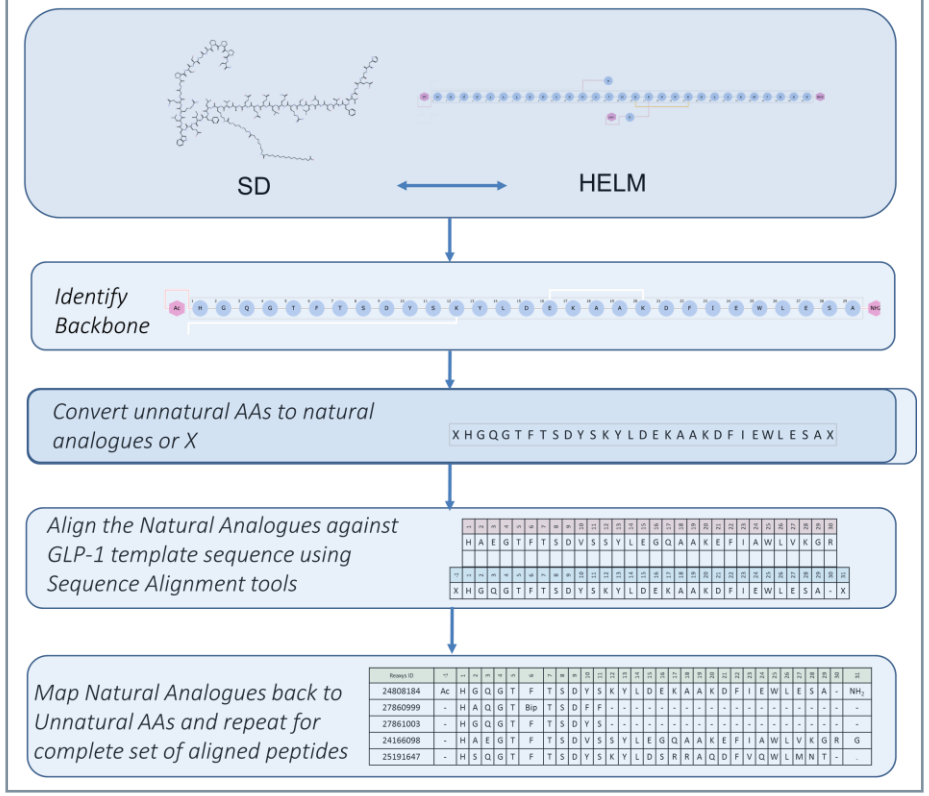
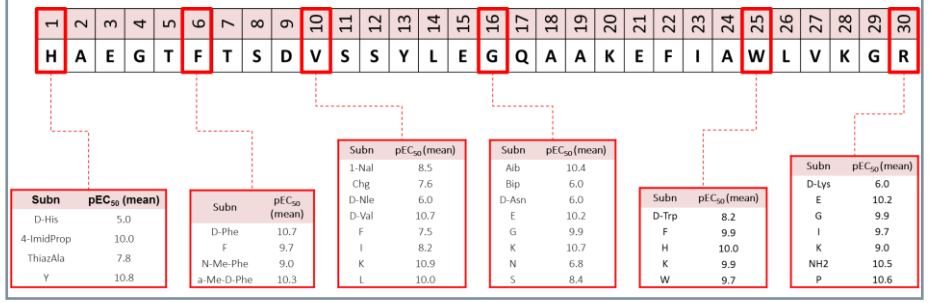
Structural Cheminformatics based GPCR Peptide Ligand Design

Sequence Alignment and Annotation workflow



Residue level analysis of Peptide properties

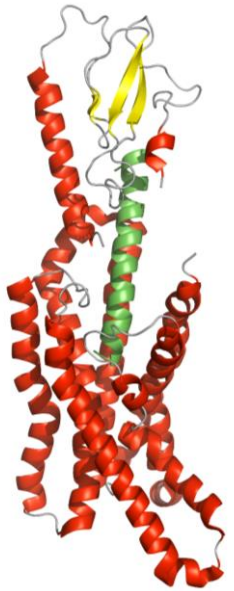


HELM

Chemaxon Biomolecular Toolkit

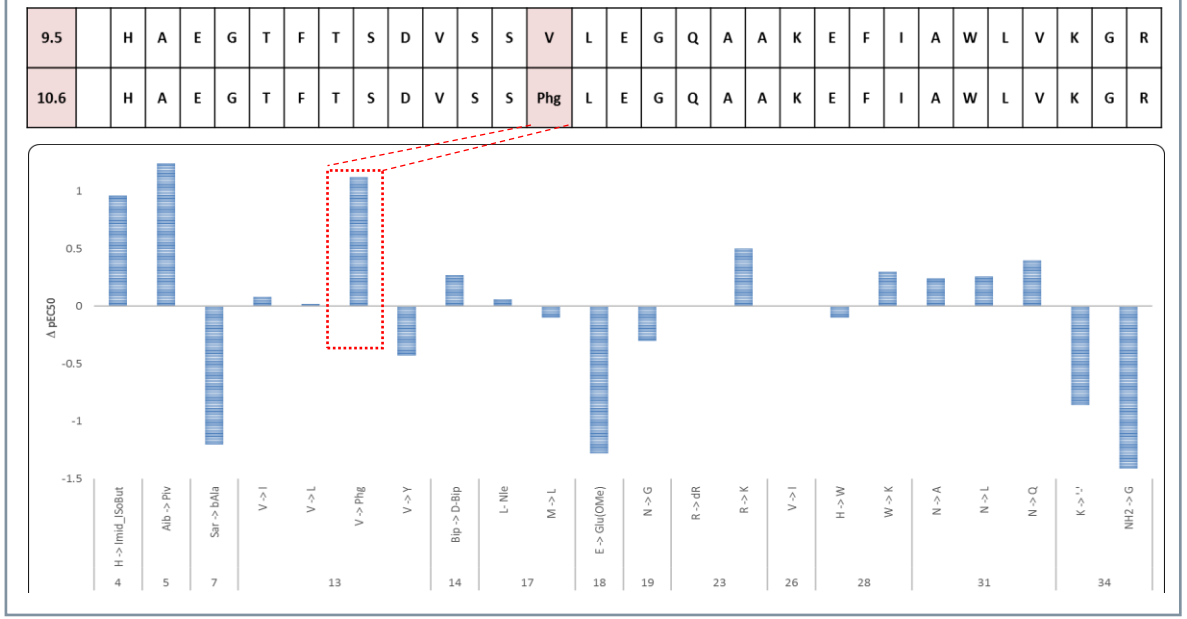
RDKit

sosei HEPTARES

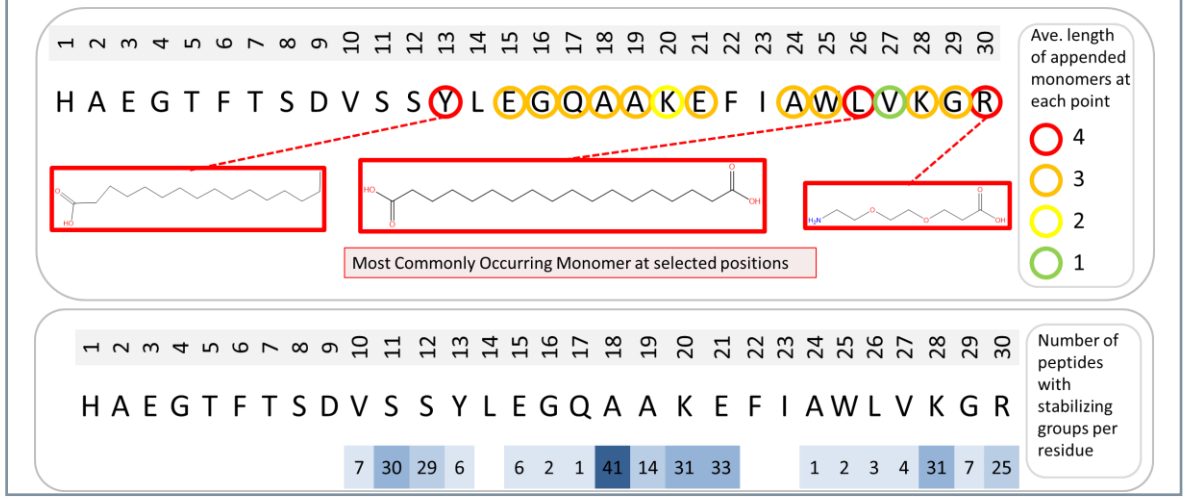


Structure-Based Peptide Ligand design

Property Modulation within Matched Peptide Pairs



Property Modulation within Matched Peptide Pairs



Davenport, Scully, De Graaf, Brown, Maguire (2020) Nature Rev Drug Discov 19: 389

Introduction

- "Making a hash of it: The advantage of selectively leaving out structural information"
  - https://www.nextmovesoftware.com/talks.html - 258th ACS National Meeting, Aug 2019
- Describes 'molhash'
  - Generate molecular hashes useful for finding pairs of tautomers, mesomers, regioisomers, etc.
  - https://nextmovesoftware.github.io/molhash/introduction.html
  - Using hashes can be an efficient alternative to brute-force algorithms
- Incorporated into RDKit (since 2019.09)
  - Example of use by Takayuki Serizawa: https://iwatobipen.wordpress.com/2019/10/27/a-new-function-of-rdkit201909-rdkit-chemoinformatics/
- The problem: finding all matched pairs (in terms of sequence) within a dataset of peptides
  - Singly-substituted peptides
  - Shout-out to related work: "Matched Peptides: Tuning Matched Molecular Pair Analysis for Biopharmaceutical Applications" – Julian Fuchs, Bernd Wellenzohn, Nils Weskamp, Klaus Liedl – *JCIM*. **2015**, *55*, 2315.

Find words that differ by a single letter – brute force

- For each word in a list of English words, convert each letter to each of the other letters of the alphabet in turn
  - Check whether there is a match in the list

- "isotropic": 225 substitutions tested
  - **asotropic**
  - **bsotropic**
  - **csotropic**
  - **dsotropic**
  - **esotropic** ⇦
  - **fsotropic**
  - **...**
  - **iaotropic**
  - **ibotropic**
  - **icotropic**

- Not an efficient approach
  - Consider the extension to two letters changed – 22500
- Does not handle letters or other characters not initially considered
  - diacritics (naïve, piñata, ångström), Greek characters, capital letters, hyphens

Find words that differ by a single letter – using a hash

- For each word in a list of English words, create hashes where each letter in turn is replaced by an asterisk
  - Collate words using the hashes: `collate = defaultdict(list); collate[myhash].append(word)`

- "isotropic":
  - ***sotropic**
  - **i*otropic**
  - **is*tropic**
  - **iso*ropic**
  - **isot*opic**
  - **isotr*pic**
  - **isotro*ic**
  - **isotrop*c**
  - **isotropi***
- "inotropic":
  - ***notropic**
  - **i*otropic**
  - **in*tropic**
  - **ino*ropic**
  - **inot*opic**
  - **inotr*pic**
  - **inotro*ic**
  - **inotrop*c**
  - **inotropi***
- "esotropic":
  - ***sotropic**
  - **e*otropic**
  - **es*tropic**
  - **eso*ropic**
  - **esot*opic**
  - **esotr*pic**
  - **esotro*ic**
  - **esotrop*c**
  - **esotropi***
- Collated by hash:
  - ***sotropic**: [isotropic, esotropic]
  - **i*otropic**: [isotropic, inotropic]
  - **is*tropic**: [isotropic]
  - **iso*ropic**: [isotropic]
  - …30 other hashes with a single entry
- For each word in a list of length ≥ 2, use that word to collate other words in the same list:
  - isotropic: [inotropic, esotropic]
  - inotropic: [isotropic]
  - esotropic: [isotropic]

Find sequences that differ by a single residue – using a hash

- For each sequence in a list of peptides, create hashes where each residue in turn is replaced by an asterisk
  - Collate sequences using the hashes: `collate = defaultdict(list); collate[myhash].append(seq)`

- "isotropic":
  - ***sotropic**
  - **i*otropic**
  - **is*tropic**
  - **iso*ropic**
  - **isot*opic**
  - **isotr*pic**
  - **isotro*ic**
  - **isotrop*c**
  - **isotropi***
- "inotropic":
  - ***notropic**
  - **i*otropic**
  - **in*tropic**
  - **ino*ropic**
  - **inot*opic**
  - **inotr*pic**
  - **inotro*ic**
  - **inotrop*c**
  - **inotropi***
- "esotropic":
  - ***sotropic**
  - **e*otropic**
  - **es*tropic**
  - **eso*ropic**
  - **esot*opic**
  - **esotr*pic**
  - **esotro*ic**
  - **esotrop*c**
  - **esotropi***
- Collated by hash:
  - ***sotropic**: [isotropic, esotropic]
  - **i*otropic**: [isotropic, inotropic]
  - **is*tropic**: [isotropic]
  - **iso*ropic**: [isotropic]
  - …30 other hashes with a single entry
- For each sequence in a list of length ≥ 2, use that sequence to collate other sequences in the same list:
  - isotropic: [inotropic, esotropic]
  - inotropic: [isotropic]
  - esotropic: [isotropic]

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Some tweaks

- Support doubly-substituted matched pairs
  - “isotropic”: `**otropic`, `*s*tropic`, etc.
- Consider one-residue extension/deletion as a matched pair:
  - As well as the nine “isotropic” hashes shown earlier, also include `*isotropic` and `isotropic*` (no other changes needed)
- Use a list, instead of representing the peptide sequence as a string
  - Residues can be represented by arbitrary strings, such as three-letter codes, modified residues, or internal names: e.g. [“Ile”, “N(Me)Ser(O-Ac)”, …]
  - Generate a hash by replacing one of the entries with a “*” (copy the list first), and convert to a string with “-”.join(mylist).

