

NUCLEO.QUERY

A free web-based virtual screening platform targeting nucleotide cofactor proteins

Constantinos Neochoritis¹, Alexander Dömling¹, Tryfon Zarganes-Tzitzikas¹, Carlos Camacho², Dave Koes², Kareem Khoury³

¹ Dept. Drug Design, RUG, Netherlands, ² PITT, Pittsburgh, USA, ³ Carmolex BV, Groningen, Netherlands

Introduction

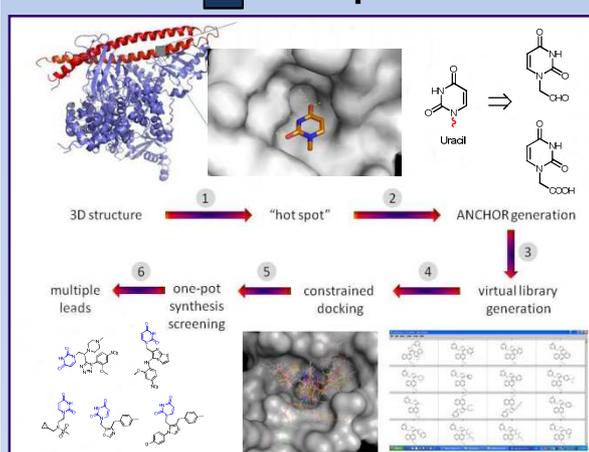
- ✓ Today's industrial screening paradigm is **high throughput screening** (HTS)
- ✓ Rather limited chemical libraries continue to be the mainstay
- ✓ Low numbers of drugs showing only incremental benefits for the patients enter the market every year
- ✓ Expensive, time consuming screening of millions of library compounds
- ✓ Industry largely fails to serve the vast number of genomics derived non-traditional targets (e.g. protein protein interactions)
- ✓ A general strategy-switch from small molecules to biotechnology drugs is observed in most big pharma companies

leading to..

Therefore drug discovery urgently needs a novel "out of the box" approach

Results and discussion

1 Concept



2 Implementation

NucleoQuery

NucleoQuery is a specialized pharmacophore search technology that brings interactive virtual screening of novel protein-nucleic acid inhibitors to the desktop.

Search Biased Library

Library Information

1 nucleic binding (L1)

2,528,292 compounds

204,972,518 conformers

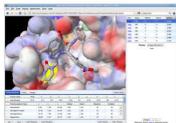
Statistics

[User Guide and Forum](#)

Interactive Examples

hAGO2 (E2E)

MicroRNAs and Argonaute are post-transcriptional regulators of gene expression. The presence of human AGO2 for LMP provides a starting point for the design of a small molecule that could inhibit this interaction.

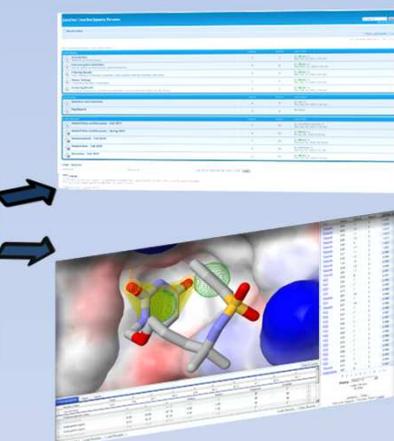


Background

NucleoQuery leverages the concept of anchors, nucleic acid residues that bury a large amount of solvent accessible surface area at the protein-NA interface. Every compound in our **multi-anchored search (MCS)** accessible virtual library contains an **nucleic anchor analog**, a functional group that is a chemical mimic of a specific nucleic acid.

NucleoQuery pharmacophore queries always include an anchor feature in addition to the standard hydrophobic, ionic, and hydrogen bond donors. All non-anchor features are stored relative to a coordinate system defined by the anchor in an efficient **spatial index**. Pharmacophore searches scale relative to the breadth and complexity of the query, not the size of the database. As a result, full 3D pharmacophore searches can be executed over millions of explicit conformations in a matter of seconds.

NucleoQuery is developed through a collaboration of the [Camacho and Dömling](#) labs. Copyright 2011, University of Pittsburgh. All rights reserved.

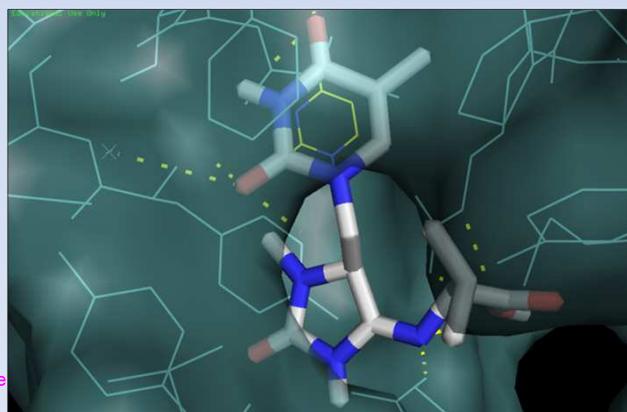
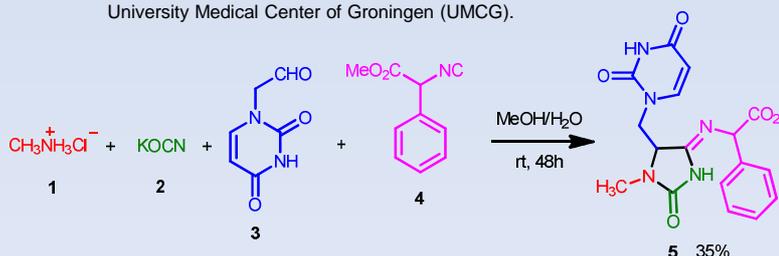


Freeware : <http://nucleoquery.csb.pitt.edu/>

- ✓ Nucleotide containing proteins are highly underrepresented drug target class (except kinases)
- ✓ With **NucleoQuery** we leverage >7.000 pharma-relevant nucleotide-protein targets in the Protein Data Bank (PDB)
- ✓ Efficient screening of a very large chemical space of instantaneously synthesizable virtual compounds

3 Application

- Here we demonstrate the powerful usage of NUCLEO.QUERY for the rapid discovery of potent cell active anti tuberculosis agents by targeting *Mycobacterium tuberculosis* thymidylate kinase (TMK).
- Thymidylate kinase (TMK) has emerged as an attractive therapeutic target because inhibiting TMK functions blocks DNA synthesis in replicating organisms, such as *Mycobacterium tuberculosis* and no shunt-pathway is known.
- Based on a multi-component reaction, **Ugi-hydantoin variation**, we were able to synthesize the first hit compound which is currently under evaluation in the University Medical Center of Groningen (UMCG).



References

1. Koes, D. et al. **Enabling large-scale design, synthesis and validation of small molecule protein-protein antagonists** *PLoS One* 2012, 7: e32839
2. Huang, Y. et al. **Discovery of highly potent p53-MDM2 antagonists and structural basis for anti-acute myeloid leukemia activities** *ACS Chem. Biol.* 2014, 9, 802