university of groningen 2014 | 400 years

NUCLEO.QUERY

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

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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

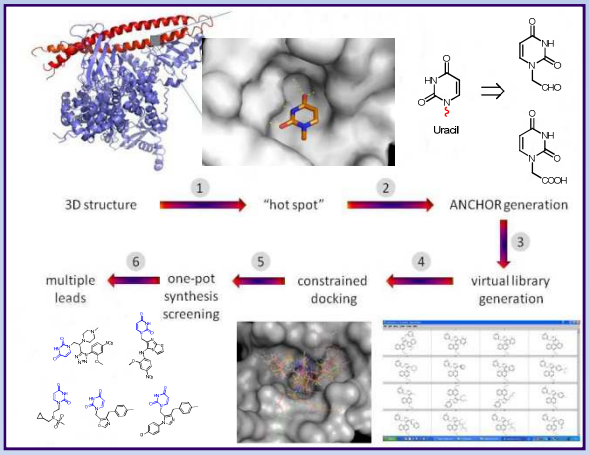
leading to..

- ✓ 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

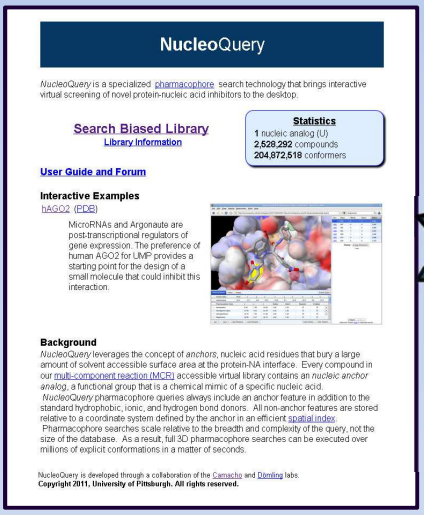
Therefore drug discovery urgently needs a novel "out of the box" approach

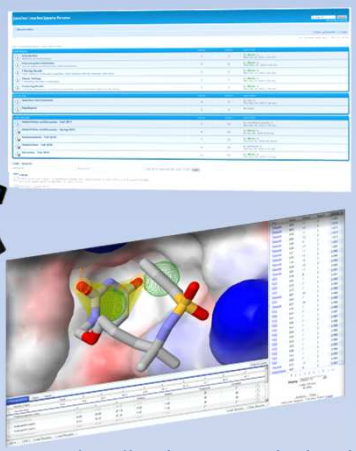
Results and discussion

1 Concept



2 Implementation



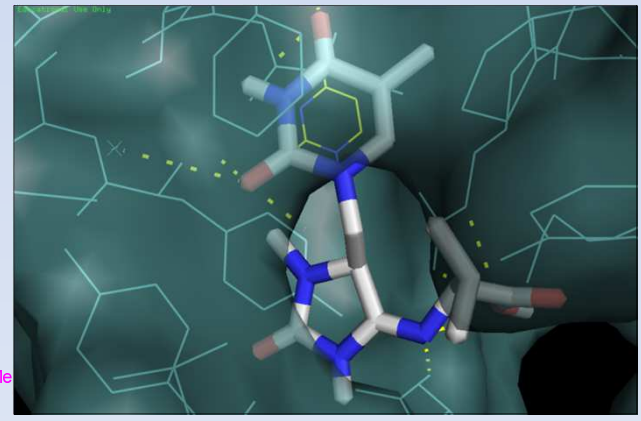


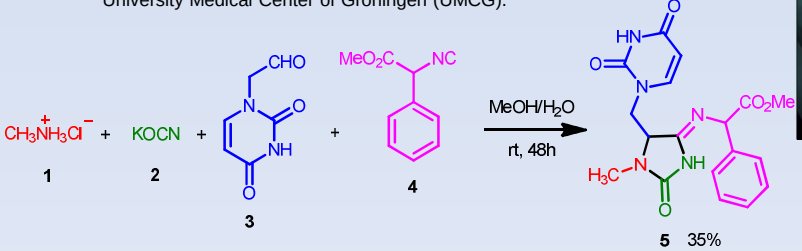
***Freeware* :** http://nucleoquery.csb.pitt.edu/

- ✓ 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