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
✓ 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

3 Application

✓ 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

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