Antiviral Libraries

Viruses are among the most demanded targets due to the diversity of diseases they cause and the absence of the common treatment. The variety of serovars is the first complexity faced by drug development. The second problem is the fact that this type of infection is tightly related to certain features of invasion process. It is absolutely different from bacterial or protozoa infection pathways. Viruses are characterized as organisms which have no functioning system of their own, just elements which incorporate in a host cell reproduction system and possess a protected capsid shell. Thus, these subunits can be inactivated only inside infected organisms and the most universal way to achieve this is by improvement of immune response and elimination of either subunits or infected cells. Another way (more selective and safe) is to inhibit elements responsible for reproduction (on stages of transcription or translation) or capsid assembling.

Antiviral Library by Combined Ligand-Based and Structure-Based Approaches

Life Chemicals prepared its Antiviral Library containing screening compounds potentially active against several most interesting and widely spread representative targets by combined ligand-based and structure- based approaches:

- *SARS coronavirus 3C-like proteinase*
- *Human herpesvirus 5 DNA polymerase*
- *Human herpesvirus 6 DNA polymerase*
- *Human herpesvirus 5 capsid protein P40*
- *Human herpesvirus 1 DNA polymerase*
- *Dengue virus type 2 NS3 protein*
- *Hepatitis C virus NS3 protease*
- *Hepatitis C virus NS5B RNA-dependent RNA polymerase*
- *Human rhinovirus A protease*
- *Human immunodeficiency virus type 1 reverse transcriptase*
- *Human immunodeficiency virus type 1 integrase*

A combination of ligand-based and structure-based approaches provided cross-validation and a higher degree of accuracy. To identify key features of the protein-ligand binding mechanism we used the RCSB database for protein crystal structures and ChEMBL DB for reference compounds. All of the most active compounds (with IC_{50} less than 1–1.5 uM) against each target were clustered and top compounds from each group were docked into the corresponding target's crystal structure to obtain bioactive conformation. For targets with unresolved structures such bioactive conformations of inhibitors were predicted with rigid alignment of generated conformers and statistical analysis. These aligned structures were further used for pharmacophore modeling. We used both Glide docking and UNITY pharmacophore search methods to select the most promising compounds (Figure 1).

About **3,500** potential antiviral agents were identified within the Life Chemicals HTS Compound Collection.

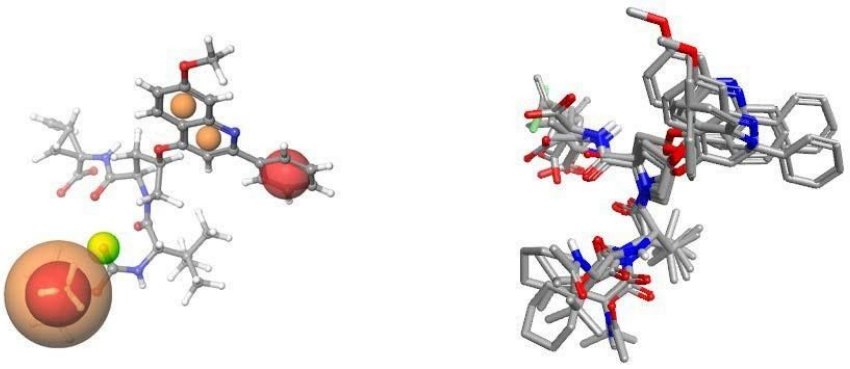

Figure 1. CHEMBL93512 inhibitor of NS3 protease/helicase

Antiviral Library by 2D Similarity

The Antiviral Screening Compound Library was designed with 2D fingerprint similarity search against the reference set of 6,937 biologically active compounds from 33 therapeutically relevant viral assays representing the following species of viruses:

- *Avian sarcoma virus*
- *Bluetongue virus*
- *Dengue virus*
- *Human herpes virus 4 type 2*
- *Human immunodeficiency virus 1*
- *Human immunodeficiency virus 2*
- *Influenza A virus (-Puerto Rico-8-34(H1N1))*
- *Influenza A virus (A-Puerto Rico-8-34-Mount Sinai(H1N1))*
- *Influenza A virus (A-Shangdong-9-1993(H3N2))*
- *Influenza A virus (A-Singapore-1-1957(H2N2))*
- *Influenza A virus (A-tern-Australia-G70C-1975(H11N9))*
- *Influenza A virus (A-Tokyo-3-1967(H2N2))*
- *Influenza B virus (B-Lee-40)*
- *Influenza B virus (B-Memphis-3-93)*
- *Influenza B virus (B-Nashville-6-89)*
- *Influenza B virus (STRAIN B-VICTORIA-3-85)*
- *Influenza B virus*
- *Measles virus*
- *Rous sarcoma virus (strain Schmidt-Ruppin A)*
- *West Nile virus*

The Life Chemicals collection was searched for compounds similar to the downloaded dataset using MDL public keys and the Tanimoto similarity cut-off of 90 %.

Over 18,000 potentially antiviral agents were selected for the Life Chemicals Antiviral Library.