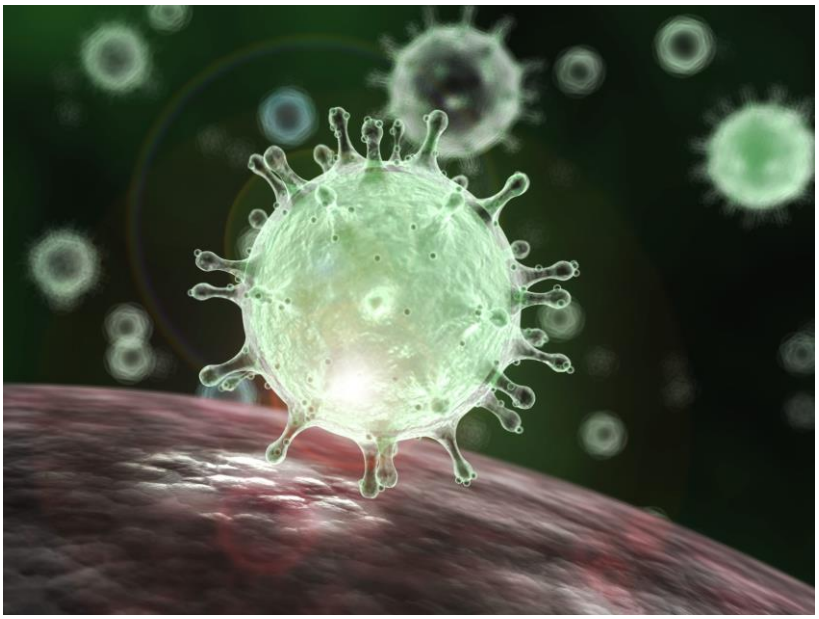
Coronavirus Screening Libraries

Coronaviruses are a large family of viruses that can cause diseases, ranging from the common cold to more serious respiratory infections like bronchitis, pneumonia, or severe acute respiratory syndrome (SARS). Rarely, animal coronaviruses can infect people, and even more rarely, these can then spread from person to person through close contact, for example, in a household, workplace, or health care center.

The 2019 novel coronavirus (COVID-19) causes a respiratory infection that originated in Wuhan, China. It has been determined that 2019-nCoV is most closely related to bat SARS-like coronaviruses (exhibiting more than 99 % sequence identity), from which SARS-CoV (about 79 % identity) evolved, and more distantly related to MERS coronaviruses (about 50 % identity).

Life Chemicals offers a dedicated **Collection of Screening Compound Libraries** for anti-coronavirus drug discovery research:

- 2019-nCoV Main Protease Targeted Library
- eEF1A Targeted Library
- 2019-nCoV Papain-Like Protease Targeted Library
- SARS Coronavirus Focused Library



2019-nCoV Main Protease Targeted Library

Deposited in Protein Data Bank in 2020 shortly after the current outbreak of coronavirus disease (COVID-19), the main protease of 2019-nCoV in complex with an inhibitor N3 has been used by Life Chemicals to design the focused library of compounds targeting this crucial virus enzyme. Docking-based virtual screening protocol (Glide by Schrödinger, SP mode) has been employed to search through the Life Chemicals HTS Compound Collection for potential 2019-

nCoV protease active site binders (Fig. 1). No docking constraints have been used to allow the docking algorithm to explore as many ligands' positions and orientations as possible.

More than **2,300** drug-like screening compounds resulting from the screening and filtering by toxicophore/reactive groups comprised the 2019-nCoV library. The Library has not been made Ro5 compliant as it would have filtered out many peptide-mimicking compounds.

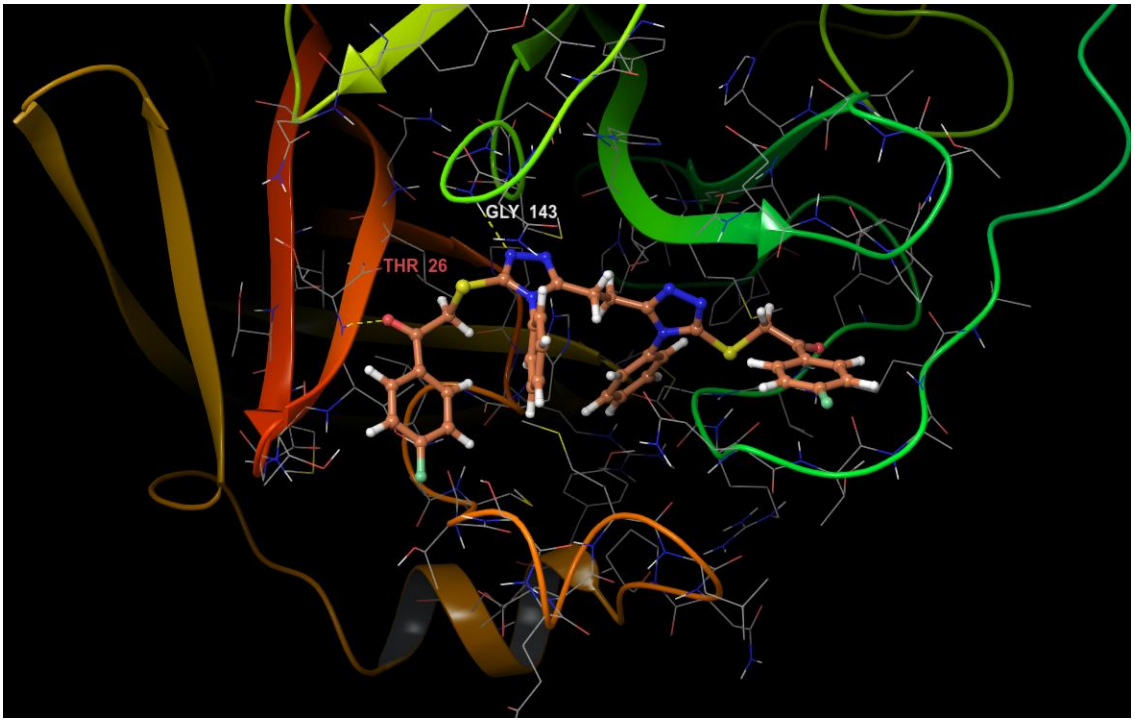


Fig. 1. Binding mode of compound F1259-0053 in the active site of 2019-nCoV main protease. Molecular complex obtained by docking.

eEF1A Targeted Library

According to the recent news related to the COVID-19 potential treatment, it has been proposed that human elongation factor 1-alpha (eEF1A) could be a promising anti-coronavirus drug target. Indeed, a number of publications highlight an important role of eEF1A in virus replication[1,2]. There is no X-ray data for eEF1A available. However, using the high-quality structural model obtained earlier[3], Life Chemicals has designed the eEF1A Targeted Library with docking-based virtual screening. Two distinct binding sites on the surface eEF1A have been used for the docking: GTP-binding site and eEF1Bα-binding site. No docking constraints have been used since the detailed mechanisms of the binding remain unclear. Results of two separate virtual screens allowed us to select almost **3,000** promising ligands with a high predicted affinity to eEF1A (Fig. 2). These ligands are Ro5-compliant and do not comprise PAINS, toxic or reactive groups. Within this targeted library, separate compound subsets for each binding site are available with docking scores indicated.

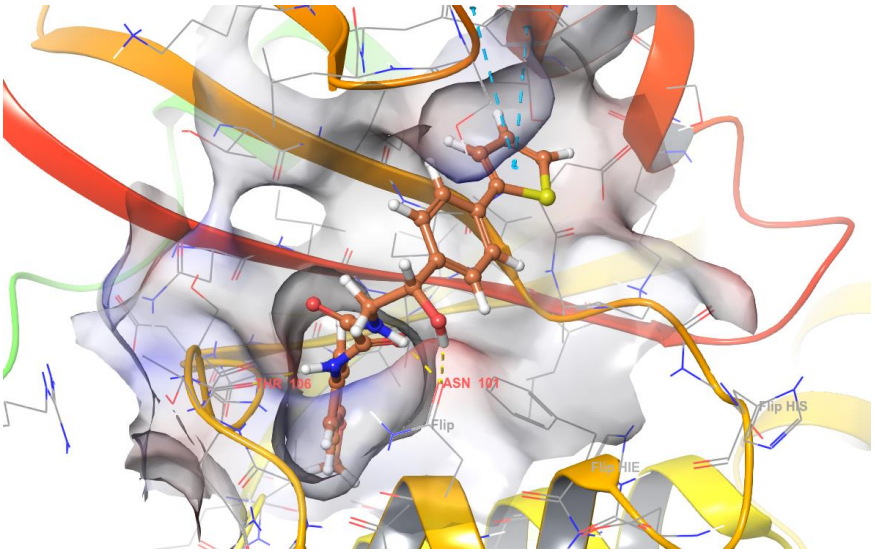


Fig. 2. Binding mode of compound F6517-4533 in the eEF1Bα-binding site of eEF1A. Molecular complex obtained by docking.

2019-nCoV Papain-Like Protease Targeted Library

Another recently resolved X-ray protein structure from the SARS CoV-2 is a papain-like protease (PLpro). PLpro is a key enzyme in the life cycle of coronaviruses (and RNA viruses in general). It is a cysteine protease with multiple functions that processes both viral polyprotein and host cell proteins and facilitates virus replication by hydrolyzing peptide bonds in viral and cellular substrates. PLpro is utilized as a drug target in different coronaviruses, including SARS, MERS, and HCV.

The 2019-nCoV Papain-Like Protease Targeted Library designed by Life Chemicals comprises **1,700** screening compounds selected by docking-based virtual screening (Fig. 3). The molecular docking has been performed based on the crystal structure of the SARS CoV-2 papain-like protease in a complex with peptide inhibitor VIR250 (PDB ID: 6WUU). All compounds from the Life Chemicals HTS Compound Collection have been docked into the PLpro catalytic site with 6 intermolecular hydrogen bond constraints set (3 of them were essential). Rotated groups in the active site were allowed where necessary. The final Library has been selected based on docking score values and inspection of intermolecular contacts formed. PAINS compounds as well as compounds with toxic and reactive groups were removed from the Library with proprietary MedChem filters.

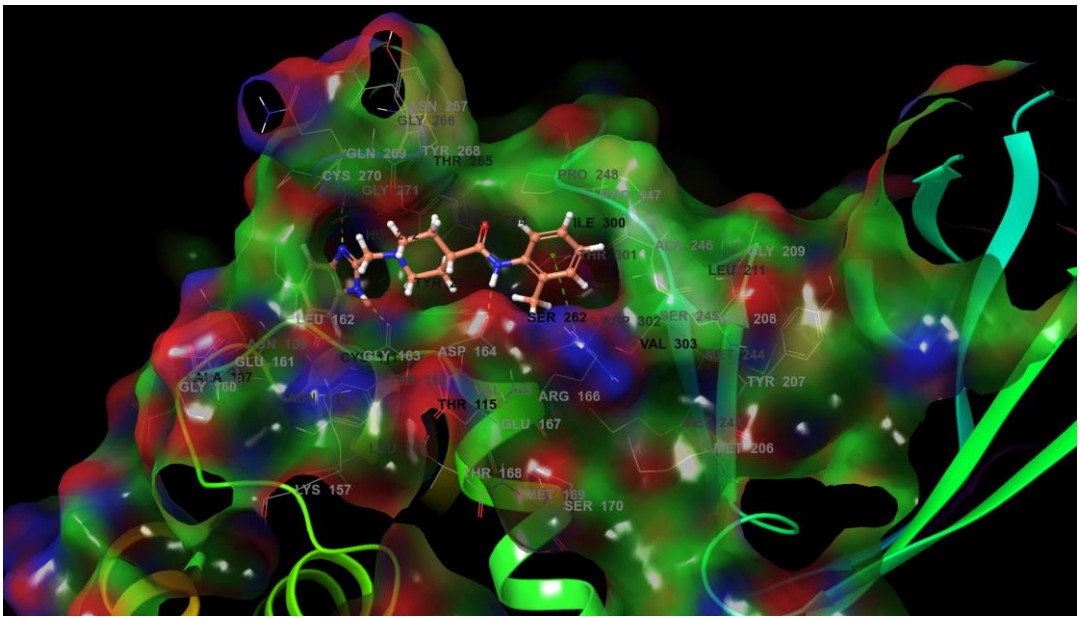


Fig. 3. Binding mode of compound F5824-0042 in the PLpro catalytic site. Molecular complex obtained by docking.

SARS Coronavirus Focused Library

Using the 2D fingerprints similarity search approach, the Tanimoto similarity cut-off of 75 % was applied for screening of a reference set of compounds known to be active against SARS coronavirus (data taken from ChEMBL database). The target activities included:

1. SARS coronavirus
2. SARS coronavirus 3C-like proteinase
3. Replicase polyprotein 1ab

All compounds in the reference set were chosen in accordance with accepted maximum activity value (IC_{50}, KI_{50} < 1000 nM, Inhibition >25 %). In total, almost 300 unique compounds were included in the reference set for subsequent similarity search.

As a result, **437** small-molecule analogues were identified in the Life Chemicals HTS Compound Collection and included in the Library.

References:

1. Zhou B, Liu J, Wang Q, Liu X, Li X, Li P, Ma Q, Cao C. The nucleocapsid protein of severe acute respiratory syndrome coronavirus inhibits cell cytokinesis and proliferation by interacting with translation elongation factor 1alpha. J Virol. **2008**, 82(14):6962-71.
2. Zhang X, Shi H, Chen J, Shi D, Li C, Feng L. EF1A interacting with nucleocapsid protein of transmissible gastroenteritis coronavirus and plays a role in virus replication. Vet Microbiol. **2014**, 172(3-4):443-8.
3. Soares DC, Barlow PN, Newbery HJ, Porteous DJ, Abbott CM. Structural models of human eEF1A1 and eEF1A2 reveal two distinct surface clusters of sequence variation and potential differences in phosphorylation. PLoS One. **2009**, 4(7):e6315.