Session 1: Natural Products-based Drug Discovery

In silico interaction of organic propolis molecules with targets related to oral mucositis.

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Abstract: Oral mucositis (OM) is a multifactorial disease which affects oncologic patients with severe pain, affecting nutrition and treatment, implicating in the mortality rate. This study aims to in silico analyze the interaction of seven biomolecules with targets related to OM. All selected targets showed RMSD < 2. In the docking of Single ligand, all ligands interacted in a promising way with all targets related to OM, especially TNF-a. Some ligands showed better results compared to the drug benzydamine, demonstrating a possible site-specific or multi-target action. In the docking of Multiple ligands, the target that presented the best interaction was TNF-a. Possible combined interactions of ligands were also detected, demonstrating inhibitory interactions with residues characteristic of protease enzymes. These results are validated by the previous publication, demonstrating that the biomolecules source has the therapeutic effects probably produced by the mechanisms of action here demonstrated, becoming strongly drug candidates for clinical trials.

Session 2: Computer-aided Drug Design (CADD)

Maximization of SARS-CoV-2 neutralization by antibodies through Monte Carlo optimization

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Abstract: One of the great challenges of science is to develop vaccines even before a possible new coronavirus comes into existence. We sought to predict which amino acid changes in the antigen could maximize the interaction with neutralizing antibodies. Therefore, using the "Affinity Maturation" functionality integrated into the "Residue Scanning" module implemented in the Schrödinger Maestro 2021-2 software, we were able to perform a Monte Carlo optimization to find the mutations that maximize the binding affinity between the antibody-antigen complex for IgG B38 (PDB ID: 7BZ5) and IgA1 (PDB ID: 10W0). Thus, we had mutations A352M, S477F in the antigen for the IgG B38 antibody resulting in a maximized affinity of -9.155 kcal/mol. As for the IgA-Fc1 antibody, we found mutations T345Q, N450L, A522V that maximize the value of antigen affinity to -9.975 kcal/mol. Therefore, we hope that these results can help in the development of vaccines against pancoronavirus.

Session 3: MedChem for Drug Addiction

Pharmacophore mapping combined with dbCICA reveals new insights on α4β2 and α7 nicotinic acetylcholine receptors ligand design

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Abstract: The α4β2 and α7 nicotinic acetylcholine receptors (nAChRs) have been studied for the development of novel drug candidates targeting Alzheimer's disease and nicotine dependence. Therefore, the aim of this study was to construct and validate pharmacophore maps for α4β2 (PDB 5KXI) and α7 (PDB 5AFH) nAChRs orthosteric sites. Ligands were constructed with BIOVIA-DSV software and optimized through PM7 semiempirical method (MOPAC2016). Molecular docking for the nAChRs was performed with all CSD-GOLD scoring functions and results were post-processed through docking-based comparative intermolecular contacts analysis (dbCICA). Pharmacophoric maps were built with CSD-CrossMiner and validated through ROC curve. In this sense, important features for the ligands were observed, such as hydrophobic regions, a planar ring, as well as hydrogen bond donor and acceptor atoms for α4β2 nAChRs. Additionally, a non-planar ring for α7 nAChRs. These results bring new insights for fragment-based drug design.

Session 4: Pre-clinical Development

Antitrypanosomal Benzoxazinone Series: Hit-to-Lead Campaign and Multiparametric Optimization

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Abstract: Lead Optimization Latin America (LOLA) is an ongoing project focused on the development of new chemical entities that target Chagas disease, a tropical neglected disease that affects 6 million people worldwide and is endemic in our region. In this context, we present the hit-to-lead campaign of a Benzoxazinone series based on initial phenotypic screening of commercial libraries. After hit assessment, we started the SAR expansion obtaining 79 compounds that were designed, synthesized, and tested against intracellular T. cruzi amastigotes. Furthermore, we also performed cytotoxicity, permeability, microsomal clearance, solubility and metabolite identification assays. As a result, LOLA779 was identified as an early lead showing submicromolar potency and balanced properties that merited the progression for a single dose in vivo PK study in mice. Finally, representative compounds were tested in T. cruzi-cidal assay and against a panel of discrete type units (DTUs) to shed light on the Benzoxazinones possible mode of action.

Session 5: MedChem for Neglected Diseases

Cheminformatics-driven identification of new antiplasmodial hits effective against asexual and sexual stages

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Abstract: Due to the emergence of resistance from artemisinin in Africa1, it is urgent the search for new antimalarials with new mechanisms of action, including transmission-blocking activity. This study aims to discover new antiplasmodial compounds for asexual and sexual stages. Initially, were generated and validated shape-based models for aurora kinase-2 from P. falciparum (PfArk-2) and QSAR models for ookinete formation inhibition. These models were employed in a virtual screening to find putative inhibitors of PfArk-2, with activity in 3D7 and W2 strains (in house models) and ookinete formation inhibition. Using these models, we prioritized ten compounds for experimental validation against asexual (3D7, Dd2) and transmission-blocking stages. Among them, four compounds showed antiplasmodial activity against 3D7 and Dd2 at low micromolar concentrations with selectivity indexes

between 17-66. In addition, three compounds inhibited ookinete formation at 10 μM. In conclusion, these compounds represent new chemical scaffolds for prospective hit-to-lead optimization.

Session 6: MedChem for Neurodegenerative Diseases

Triazole grandisin analog prevents memory deficit by antioxidant effects in an Alzheimer's Disease model.

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Abstract: Alzheimer's disease (AD) is a chronic neurodegenerative disease caused by the accumulation of amyloid-beta protein (Aβ), leading to inflammatory and oxidative damage. Pharmacotherapy exhibits unpleasant side effects and limited efficacy over time. Studies showed in vitro and in vivo efficacy of the tetrahydrofuran neolignan, grandisin, regarding its anti-inflammatory and antioxidant properties[1–2]. Herein, considering the neuroprotective effects of tetrahydrofuran neolignans[3], a triazole grandisin-derivative analog (TGA) was designed by bioisosterism. Hence, we evaluated its possible protective effects on memory in an AD model. Male C57/Bl6 mice received intracerebroventricular (ICV) injections of Aβ or vehicle. Intraperitoneal (IP) injections with TGA (1mg/Kg) or vehicle for 14 days was perfromed (n=7-8 animals/group). Object recognition memory, oxidative stress, and inflammatory biomarkers were measured. TGA treatment prevented memory impairment, also decreasing cortical/hippocampal Aβ lipoperoxidation, without alteration of myeloperoxidase, in this animal model. Therefore, TGA shows potential for AD therapy in further studies.

Session 7: Multi-target Directed Ligands

Heterocyclic multitargeting ligands of cholinesterases, histamine and dopamine receptor subtypes: promising agents for cognitive dysfunctions

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Abstract: The role of histamine, dopamine and acetylcholine in cognitive processes make their receptors and regulating proteins attractive targets for designing procognitive compounds [1,2]. Thus, we designed multitargeting ligands of histamine H3 (H3R)/dopamine D3 (D3R) receptors, acetyl- and butyrylcholinesterases (AChE/BChE, respectively) considering modifications on aromatic, linker and basic moieties. 21 compounds were assessed, and the results showed that several compounds were ligands at H3R (10), D3R (6), AChE (3) and BChE (9). We obtained

three H3R/D3R, three H3R/ChE and one D3R/ChE ligands. Hopefully, three compounds showed H3R/D3R/ChE profile. Compound LINS05015 is highlighted for its ability to bind at all targets in comparable concentration ranges (Ki H3R 1.1 μM; D3R 3.1 μM; IC50 AChE 97.8 μM; BChE 43.7 μM). The results suggest that longer linkers increased the affinity for ChEs, while phenyl-piperazine and 4-pyridyl-piperazine moieties played important roles in D3R/H3R affinities, respectively. The obtained SAR information is valuable for further compound design.

Session 8: MedChem for infectious diseases

COMPUTATIONAL APPROACH FOR THE RATIONAL DEVELOPMENT OF INHIBITORS OF NS5 METHYLTRANSFERASE SEROTYPE 2-DENGUE

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Abstract: We proposed the implementation of a series of tools to develop a rational approach in drug discovery. So, we plan to perform organic synthesis, computational modeling supported by NMR experiments to measure protein-ligand interactions, and in vitro activity assays of new compounds. The line of research on the synthesis of metabolites that we were developing has led us to methyltransferases as a biological target. In our particular case, dengue virus type 2 methyltransferase NS5. This methyltransferase has S-adenosylmethionine (SAM) as a methyl donor cofactor. We started with the optimization of the computational docking with the crystal structure 1L9K of the pdb. Employing the docking program MOE-GOLD we achieved the conditions to obtain a re-docking pose and a cross-docking pose (using 5ZQK) with an RMSD lower than 2A. Currently, we are testing the predicting power of the docking system. For that, we are employing other technics as dynamics simulation and MMPBSA.

Session 9: MedChem for Orphan Diseases

In Silico Study of the Free Energy of Binding of Kallikrein Inhibitors

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Abstract: The serine proteases KLK5, KLK7, and KLK6 play a crucial role in the pathogenesis of Netherton Syndrome (KLK5 and KLK7)1,2 and have been linked to neurodegenerative diseases (KLK6).3 Therefore, these enzymes may represent attractive targets for therapeutic interventions.4 Here we evaluated the accuracy of several computational methods in predicting the free energy of binding (ΔGbind) of inhibitors of KLK5, KLK6 and KLK7. The results of these calculations showed that sometimes, a good qualitative agreement with experiment can be obtained using just docking. However, in some cases where all the other methods fail, the free energy

perturbation (FEP) method yield significantly superior results. In conclusion, the application of FEP can considerably enhance the success rate of structure-based drug design of KLK inhibitors.

Session 10: MedChem for Cancer

Development of Dihydrodiazepinones as Inhibitors of the human Vaccinia-related Kinase 2 (VRK2)

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Abstract: Kinases are known drug targets especially for cancer therapy but only 49 of them are primary drug targets among FDA approved small molecules1. Vaccinia-related kinases 1/2 (VRK1/VRK2) are understudied kinases linked to abnormal cellular division and neurological disorders.2,3 A better understanding of the cellular roles of VRK1 and VRK2 has been hampered by a lack of potent and selective chemical tools that can be used to investigate the functions of these protein kinases in normal and disease biology.2,3 Here, we describe the synthesis and evaluation of 45 new compounds designed to provide a SAR study specifically for VRK2. The most potent dihydrodiazepinone has a Ki = 15 nM, is 8 times more selective for VRK2 inhibition over VRK1 and it is fairly selective in a panel of 28 human kinases. We will further evaluate our compounds in a larger selectivity panel and in cellular models.