A ROBUST VIRTUAL SCREENING PROTOCOL FOR FRAGMENT BASED DRUG DISCOVERY

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EXCELENCIA MARÍA DE MAEZTU

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Introduction: To facilitate the identification of potential drug candidates, we stablished a multistep virtual screening (VS) protocol combining the predictive power of ensemble Molecular Docking and Molecular Dynamics (MD) simulations as an alternative strategy in the field. Based on iterative steps of MD production and free-binding energy evaluations, only the best complexes will finally be selected for experimental in vitro testing. Several studies have demonstrated the effectiveness of the method [1-5], thus shedding light to new opportunities for drug development.

TARGETS:

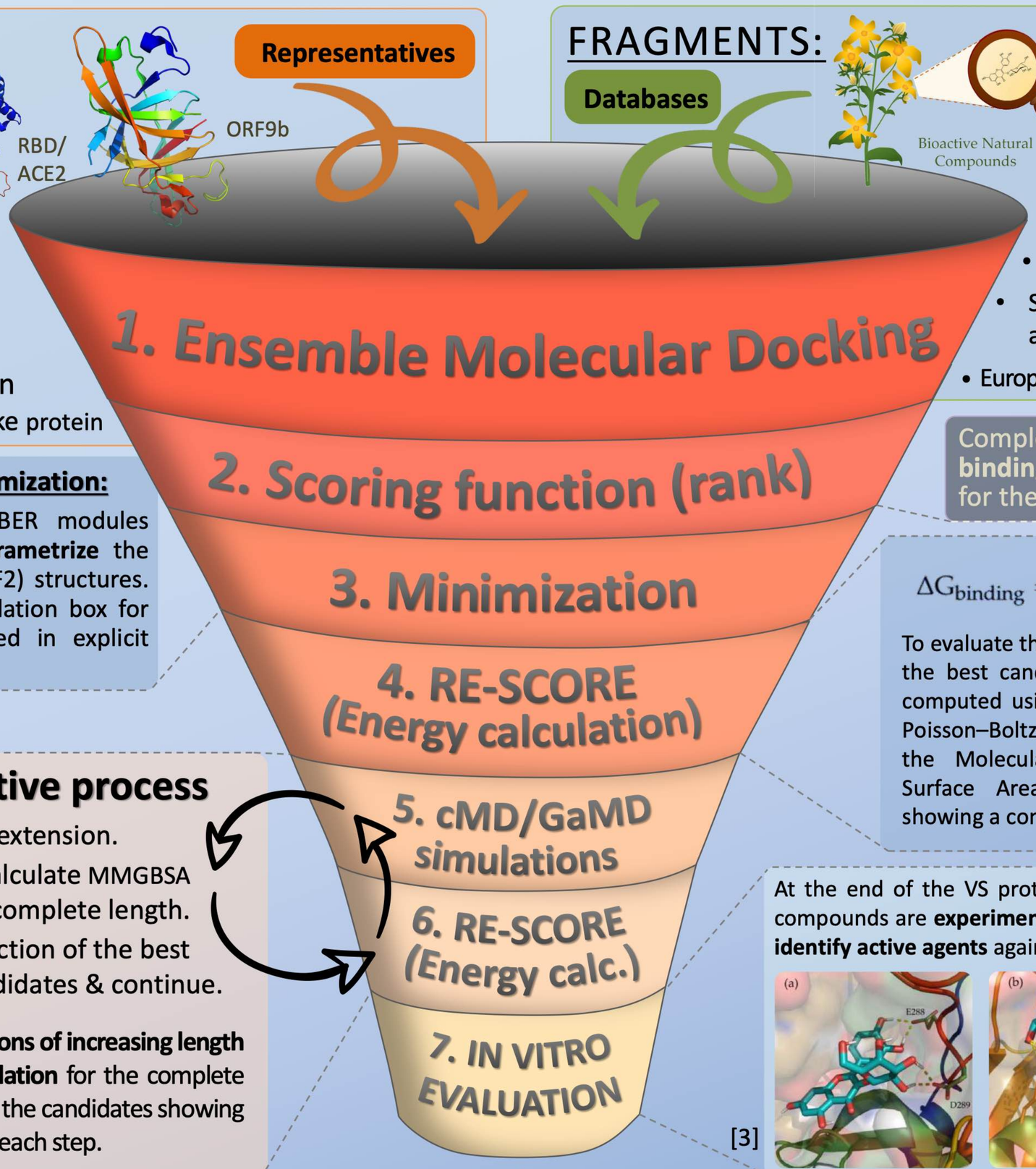
SARS-CoV-2 targets:

- Main Protease (Mpro)
- ORF9b accessory protein
- RBD/ACE2 complex of Spike protein

FRAGMENTS:

Databases:

- Dark Chemical Matter (DCM)
- Selleck FDA Approved Drugs and Natural Products database
- European Chemical Biology Library (ECBL)



System preparation and minimization:

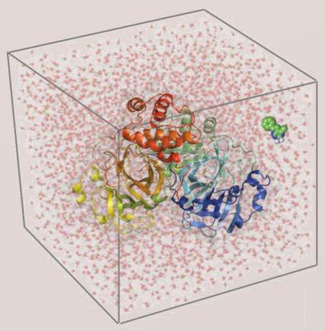
ANTECHAMBER and LeaP AMBER modules were used to prepare and **parametrize** the target (ff14SB) and ligand (GAFF2) structures. Next, **minimization** of the simulation box for the selected complexes solvated in explicit TIP3P water medium, was done.

Complexes presenting the **best binding energy values** are **selected** for the next step of the VS protocol.

$$\Delta G_{binding} = \Delta H^{gas} + \Delta G^{solv} - T\Delta S^{gas}$$

To evaluate the affinity of the complex and select the best candidates, free binding energies are computed using both the Molecular Mechanics Poisson–Boltzmann Surface Area (MMPBSA) and the Molecular Mechanics Generalized—Born Surface Area (MMGBSA). Energetic profiles showing a converged behaviour are selected.

AMBER MD



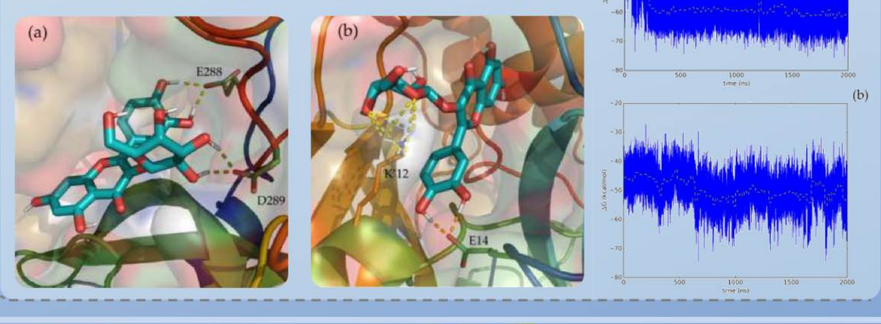
Iterative process

1) MD extension.
2) Recalculate MMGBSA for complete length.
3) Selection of the best candidates & continue.

Interatively, cMD/GaMD **simulations of increasing length** and **free-binding energy recalculation** for the complete trajectory are performed only for the candidates showing the **best energetic behaviours** at each step.

At the end of the VS protocol, the **best** compounds are **experimentally tested** to **identify active agents** against the target.

[3]



Success rate of 45% [1]

5/11 tested

TARGET: SARS-CoV-2 main protease (Mpro) monomer.

FRAGMENTS: From the Selleck database of Natural Compounds library.

Success rate of 33,3% [2]

1/3 tested

TARGET: SARS-CoV-2 main protease dimer (Mpro).

FRAGMENTS: From natural compounds present in the autochthonous Peruvian flora.

Success rate of 20% [3]

2/10 tested

TARGET: RBD/ACE2 complex of the SARS-CoV-2 Spike (S) protein.

FRAGMENTS: From Selleck FDA approved drugs and Natural Products database.

Success rate of 25% [4]

1/4 tested

TARGET: SARS-CoV-2 main protease (Mpro) dimer.

FRAGMENTS: From the Dark Chemical Matter (DCM) compound database.

NEW! Check out Natalia De Moya Poster! [5]

TARGET: The SARS-CoV-2 ORF9b accessory protein.

FRAGMENTS: From the European Chemical Biology Library (ECBL) database.

References:

[1] Abian, O.; Velázquez-Campoy, A.; Thomson, T.M.; et al. Discovery of Diverse Natural Products as Inhibitors of SARS-CoV-2 M pro Protease through Virtual Screening. *J. Chem. Inf. Model*. **2021**, 61, 6094–6106, doi:10.1021/acs.jcim.1c00951.

[2] Peralta-Moreno, M.N.; Anton-Muñoz, V.; Ortega-Alarcon, D.; Jimenez-Alesanco, A.; Vega, S.; Abian, O.; Velazquez-Campoy, A.; Thomson, T.M.; Granadino-Roldán, J.M.; Machicado, C.; et al. Autochthonous Peruvian Natural Plants as Potential SARS-CoV-2 Mpro Main Protease Inhibitors. *Pharmaceuticals*, **2023**, 16, 585, doi:10.3390/ph16040585.

[3] Avilés-Alía, A.I.; Zulaica, J.; Perez, J.J.; Rubio-Martínez, J.; Geller, R.; Granadino-Roldán, J.M. The Discovery of Inhibitors of the SARS-CoV-2 S Protein through Computational Drug Repurposing. *Computers in Biology and Medicine*, **2024**, 171, 108163, doi:10.1016/j.compbiomed.2024.108163

[4] Peralta-Moreno, M.N.; Mena, Y.; Ortega-Alarcon, D.; Jimenez-Alesanco, A.; Vega, S.; Abian, O.; Velazquez-Campoy, A.; Thomson, T.M.; Pinto, M.; Granadino-Roldán, J.M.; et al. Shedding Light on Dark Chemical Matter: The Discovery of a SARS-CoV-2 Mpro Main Protease Inhibitor through Intensive Virtual Screening and In Vitro Evaluation. *IJMS,* **2024**, 25, 6119, doi:10.3390/ijms25116119.

[5] Zodda, E.; Pons, M.; DeMoya-Valenzuela, N.; Calvo-González, C.; Benítez-Rodríguez, C.; Díes López-Ayllón, B.; Hibot, A.; Cascante, M.; Montoya, M.; Pujol, M.D.; Rubio-Martínez, J.; Thomson, T.M. Dominant induction of the inflammasome by the SARS-CoV-2 accessory protein ORF9b, abrogated by small-molecule ORF9b homodimerization inhibitors. *bioRxiv (Preprint)*, **2024**.