INSTITUTO DE LA QUÍMICA Y METABOLISMO DEL FÁRMACO

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CONSEJO NACIONAL DE INVESTIGACIONES CIENTÍFICAS Y TÉCNICAS
FACULTAD DE FARMACIA Y BIOQUÍMICA – UNIVERSIDAD DE BUENOS AIRES

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4th Scientific Meeting of the Research Network Natural Products against Neglected Diseases

DDNDIC 2018

ResNet NPND

Book of abstracts

4th – 6th December 2018

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Charge density as a molecular descriptor to reveal differences on high active cruzain inhibitors

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Available chemotherapy for Chagas disease (CD) involves severe side effects and drug- resistance has been observed in some trypanosome strains. Thus, the discovery of new, safer and more effective drugs to treat CD is required [1].
Cruzain (Cz), a cysteine protease of the papain-like family, plays a vital role at every stage of the parasite's life cycle. The active-site region of enzyme is similar to those of other members of the papain superfamily with seven substrate-binding subsites, four (S4, S3, S2, S1) on the acyl side and three (S1', S2', S3') on the amino side of the cleaved substrate bond [2].
Currently, 25 inputs associated to this molecular target are registered in the Protein Data Bank (rcsb.org), where Cz has been co-crystallized with reversible and irreversible inhibitors. Thereby, Cz presents itself as an interesting target for development of potential therapeutics for the treatment of the disease by employing a structure-based approach. Among Cz inhibitors, those containing a vinyl sulfone warhead can exhibit good selectivity and a favorable in vivo safety profile despite the irreversible nature of inhibition [1].
Jaishankar et al. synthesized and determined the inhibition constant (and binding energies, ΔG) of a series of vinyl sulfone analogs. However, the analysis of key interactions among sub-pockets, that might explain the activity differences between the ligands, is not available yet [3].
The quantum theory of atoms in molecules (QTAIM) provides an important insight into the molecular interactions in ligand-receptor (L-R) complexes [4]. Through the mapping of the gradient vector field onto the complex charge density, a series of topological elements arise. Among these topological elements, the bond critical point (BCP) and, in particular, the charge density value (ρ_b) at an interaction BCP is considered as a measure of that interaction strength.
Unlike ΔG that is a global property of the entire system, ρ_b is a local property measured at each interaction BCP. This means that ρ_b can be used to decompose the binding energy in contributions by groups of atoms [5].
Accordingly, the aim of this work was to exploit charge density to decompose total binding energy in contributions by sub-pockets of Cz. In other words, we want to know how strong is the anchoring of known inhibitors to each Cz sub-pocket. This analysis allowed us to identify easily the anchoring points that could be improved (by optimizing inhibitors structure) in order to increase inhibitor affinity to Cz.

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Abstract

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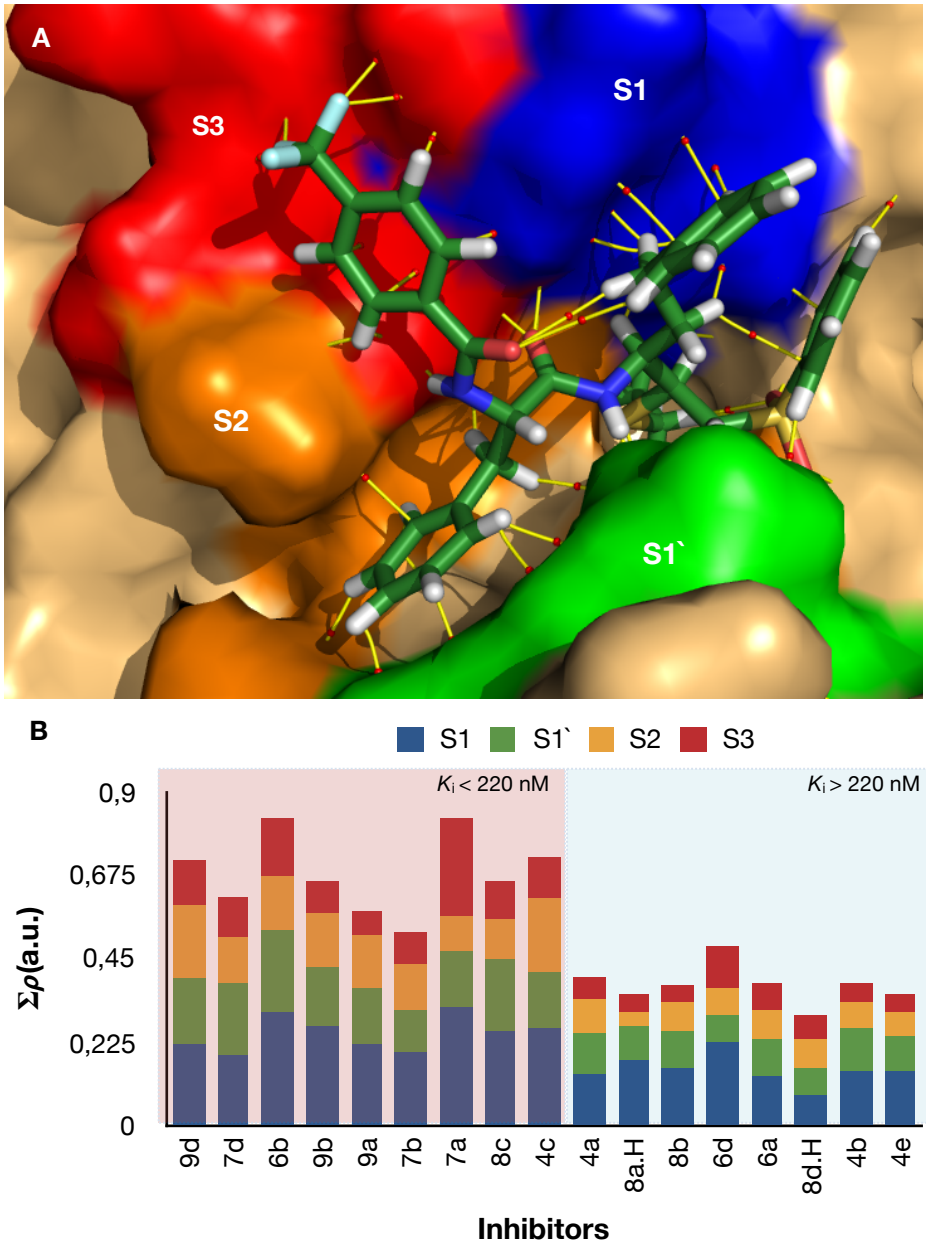

Figure1. A) Interactions of Cz inhibitor at the binding pocket. **B)** Charge density values at the BCPs in Cz-inhibitor complexes. Inhibitors naming taken from Ref 3. Sub-pockets S1 (blue stacked bars), S1` (green staked bars), S2 (orange stacked bars) and S3 (red stacked bars).

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