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TABLE OF CONTENTS

07

STRUCTURAL BIOINFORMATICS - BIOMOLECULAR SIMULATIONS

07

Network analysis in complex protein-inhibitor systems: a Cruzain case study

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Chagas disease is a neglected tropical disease caused by *Trypanosoma cruzi*. Cruzain (Cz), the parasite major cysteine-protease, is a viable target for developing new drugs. A survey on public databases with activity annotations revealed that several Cz inhibitors containing a halogen atom (LX, X = Cl, Br, I) were up to thousands of times more active than their non-halogenated analogs (LH) giving rise to an activity cliff in the Cz/inhibitor interaction landscape. On the other hand, structural evidence indicates that halogenated compounds form an X···S halogen bond (XB) with Methionine 68 (PDB ID 3KKU). These findings altogether suggest that XB formation could induce disruptive changes within the protein structure. Network analysis has been used extensively to study allosterism in proteins, but coupled with molecular dynamics (MD) becomes an invaluable tool to study conformational changes and flexibility regions in proteins. Four pairs of LX/LH inhibitors from the thiosemicarbazone family that met these “activity cliff” characteristics were compiled and subjected to Docking calculations followed by MD simulations. Non-local effects of XB over remote regions of the protein were also analyzed through the Dynamic Cross-Correlation Matrix and derived studies such asNetwork Analysis and Principal Component Analysis. Through the Network Analysis, it was found that the integrity of the network associated with the halogenated complexes is particularly affected by the loss of communication between two specific regions of Cz, which induces conformational changes that could enhance complex stability. The loss of communication was revealed by pathway analysis showing that XBs have longer paths along with the selected residues from S2 sub-pocket and other important sites of the protein. These results provide some clues about how XBs can be exploited to design more potent Cz inhibitors.

Keywords: Cruzain, proteins, network analysis, structure-based drug design.

Network analysis in complex Protein-Inhibitor systems: a Cruzain case study

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ABSTRACT

Chagas disease is a neglected tropical disease caused by *Trypanosoma cruzi*. Cruzain (Cz), the parasite major cysteine-protease, is a viable target for developing new drugs. A survey on public databases with activity annotations revealed that several Cz inhibitors containing a halogen atom (LX, X = Cl, Br, I) were up to thousands of times more active than their non-halogenated analogs (LH) giving rise to an activity cliff in the Cz/inhibitor interaction landscape. On the other hand, structural evidence indicates that halogenated compounds form an X···S halogen bond (XB) with Methionine 68 (PDB ID 3KKU). These findings altogether suggest that XB formation could induce disruptive changes within the protein structure.

INTRODUCTION

Halogen bonds have been found to occur in a multitude of inorganic, organic, and biological systems affecting materials science, crystal engineering and drug discovery and design. Particularly, in medicinal chemistry, their ability to form molecular interactions have also been studied to understand their contribution the binding affinity improvements (Shinada, 2019).

In protein−ligand environments, halogen bonds can be formed between a halogenated ligand and any accessible Lewis base in the binding pocket (Wilcken, 2013).

Network analysis has been used extensively to study allosterism in proteins, but coupled with molecular dynamics (MD) becomes an invaluable tool to study conformational changes and flexibility regions in proteins.

Fig 1. Cruzain with LX1 (green) and residues Gly-23 and Asp-60 highlighted in orange.

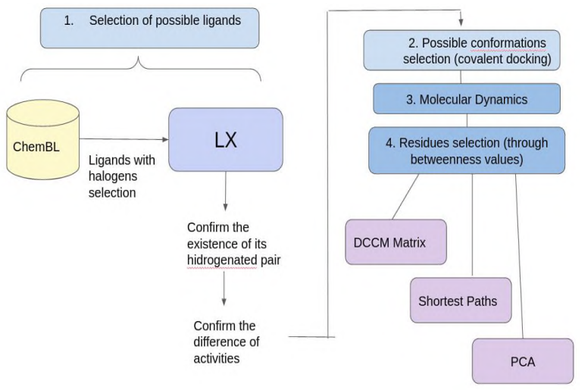


Fig 2. General schema of the work.

METHODS

Four pairs of LX/LH inhibitors from the thiosemicarbazone family that met these "activity cliff" characteristics (Table 1) were compiled and subjected to Docking calculations followed by MD simulations.

LX	LH
LX1 (Ligand 5)	LH1 (Ligand 7)
LX2 (Ligand 22)	LH2 (Ligand 26)
LX3 (Ligand 23)	LH3 (Ligand 27)
LX4 (Ligand 1)	LH4 (Ligand 2)

Table 1. Pairs of studied ligands. LX= halogenated pairs; LH= hidrogenated pairs

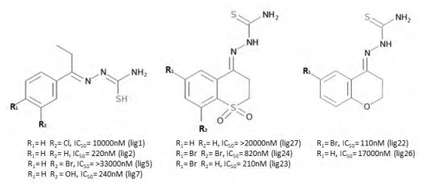


Fig 3. Chemical structures of thiosemicarbazones

MOLECULAR DYNAMICS: Halogenated ligands inhibitors of Cruzipain with affinity data were obtained from the CHEMBL database (ebi.ac.uk/chembl/). Subsequently, the LX / LH pairs were filtered from database using chemoinformatic tools; finally five LX / LH pairs were selected with a significant difference in activity. These inhibitors were then covalently linked to enzyme active site residue Cystein 25. Covalent docking was performed with rDock and two possible poses of each ligand were selected to perform the Molecular Dynamics simulations.

MD simulations were performed using the AMBER software package (Case, 2005) at 300K of temperature and extended to 100 ns of global simulation time. To simulate the σ-hole on the halogen atom, a positively charged. Massless extra-point (EP) was introduced into the Amber force field (Ibrahim, 2011). The parameterization of the EP was carried out following the procedure of the same author. The angle C (ar) -X-EP was set at 180 ° and the distance X-EP was equal to the atomic radius of the halogen, that is, 2.22 Å for bromine and 1.95 Å for chlorine. Atomic partial charges (including EP) were assigned using the restricted electrostatic potential (RESP) method. Once the trajectories were obtained with the CPPTRAJ module, the RMSD was obtained and the distances of possible halogen bonds were analyzed. Finally, the structure of the minimum potential energy was obtained and the clustering of each trajectory was carried out.

NETWORK ANALYSIS (NA) : The network analysis was performed using R statistical software (v3.6.3) and Bio3d package (http://thegrantlab.org/bio3d/) was used for shortest paths calculation.

PRINCIPAL COMPONENT ANALYSIS (PCA): Analysis was performed using Protein Dynamics and Sequence Analysis (ProDy) package (http://prody.csb.pitt.edu/index.html).

RESULTS

In first place, we study the betweenness values of all the residues of the protein. Betweenness centrality of a node is the unique shortest paths crossing that node. The residues with higher values of betweenness centrality were selected (in this case, the residues 23 and 60) (Fig 1).

After that, a correlation analysis was performed. The output of this analysis is a matrix of residue-by-residue cross-correlations (DCCM Matrix). The DCCM Matrix then was the input for networks analysis.

The communication between distal regions in a protein can be investigated throughout suboptimal path analysis. In this search, multiple shortest paths are calculated between two sites (a "source" and a "sink", respectively). In this analysis, 200 paths were calculated between residues 23 and 60. The path length distribution can be used to measure the overall coupling strength of the network.

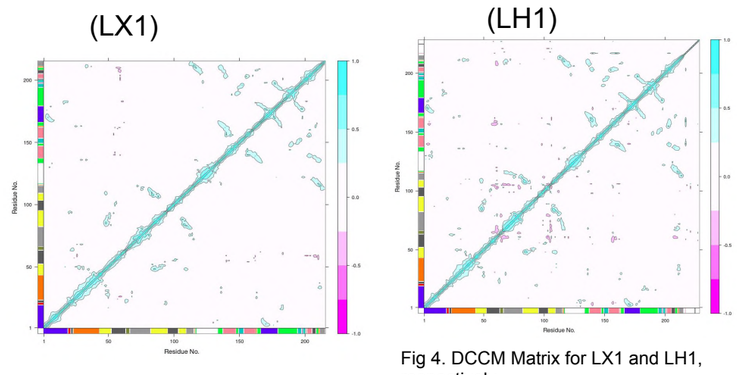
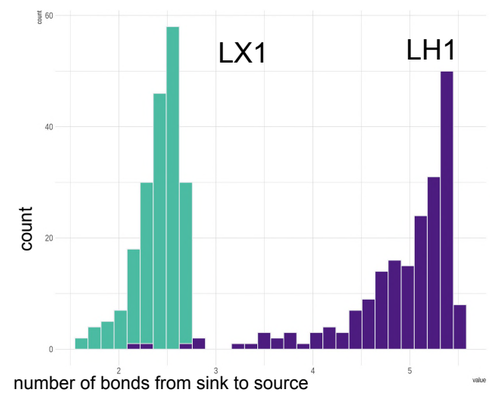


Fig 4. DCCM Matrix for LX1 and LH1, respectively



The histogram (Fig 5) shows that it takes more residues from sink to source in LH1 complex than in LX1 complex. The coupling strength in LX1 is higher than in LH1.

Fig 5. Distribution of shortest paths

MD trajectories of LX1 and LH1 separates well along the first principal component (Fig 6)

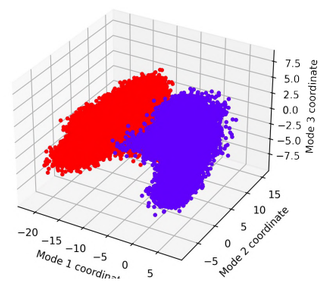


Fig 6. PCA for LX1 (red) and LH1 (blue)

CONCLUSIONS

Through the Network Analysis, it was found that the integrity of the network associated with the halogenated complexes is particularly affected by the loss of communication between two specific regions of Cz, which induces conformational changes that could enhance complex stability. The loss of communication was revealed by pathway analysis showing that XBs have longer paths along with the selected residues from S2 sub-pocket and other important sites of the protein. These results provide some clues about how XBs can be exploited to design more potent Cz inhibitors.

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