Ciclo de charlas

Computer Simulation Predictions of Binding Free Energies of compounds with trypanocidal activity

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Chagas disease, also known as American trypanosomiasis, is a potentially life-threatening illness caused by the protozoan parasite Trypanosoma cruzi. In 2010, the World Health Organization (WHO) estimated that around 7 to 8 million people worldwide were infected with T. cruzi, resulting in more than 50,000 deaths every year (WHO 2013). Most cases are found in Latin American countries where the disease is endemic. However, the past decades have seen a substantial spread of this illness in the United States, Canada, and many European and some Western Pacific countries.

Trypanosomiasis is the name given to a group of diseases in vertebrates caused by parasitic protozoan trypanosomes of the genus Trypanosoma. The diseases include Chagas disease, caused by Trypanosoma cruzi, and African trypanosomiasis or sleeping sickness, caused by Trypanosoma brucei.

Trypanosoma is a group of unicellular parasitic flagellate protozoa. Most trypanosomes are vector-driven and require more than one obligatory host to fulfil their life cycle. Usually, the propagation of a Trypanosoma species is done by blood-feeding invertebrates plus a second phase that happens in the bloodstream or an intracellular environment in the mammalian host.

Here, we investigate the dynamic and energy behaviour of a set of noncovalent inhibitors of the enzymes cruzain and rhodesain. Different protonation states of the enzymes' catalytic residues (His 162 and Cys 25) and the ligand were tested by molecular dynamics simulations, to elucidate a possible binding mode of the noncovalent inhibitor B95 and a series of analogues of this ligand. The molecular dynamic analysis indicated that the protonation of both catalytic residues, known as ion pair, together with the protonation of the ligand was the most favourable in a possible binding mode. For the analogues compounds, free energy calculations were done, and the cruzain systems showed good agreement between the calculated relative free energy of binding and experimental relative free energy of binding.

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