Identification of potential trypanothione reductase inhibitors among commercially available beta-carboline derivatives using chemical space, lead-like and drug-like filters, pharmacophore models and molecular docking

Rodríguez-Becerra, J., Cáceres-Jensen, L., Hernández-Ramos, J., & Barrientos, L. (2017). Identification of potential trypanothione reductase inhibitors among commercially available $$\upbeta $$-carboline derivatives using chemical space, lead-like and drug-like filters, pharmacophore models and molecular docking. Molecular Diversity, 21(3), 697-711. <10.1007/s11030-017-9747-6> Accessed 05 Nov 2020.

Abstract

American trypanosomiasis or Chagas disease caused by the protozoan Trypanosoma cruzi (T. cruzi) is an important endemic trypanosomiasis in Central and South America. This disease was considered to be a priority in the global plan to combat neglected tropical diseases, 2008–2015, which indicates that there is an urgent need to develop more effective drugs. The development of new chemotherapeutic agents against Chagas disease can be related to an important biochemical feature of T. cruzi: its redox defense system. This system is based on trypanothione (N1,N8-bis(glutathyonil)spermidine) and trypanothione reductase (TR), which are rather unique to trypanosomes and completely absent in mammalian cells. In this regard, tricyclic compounds have been studied extensively due to their ability to inhibit the T. cruzi TR. However, synthetic derivatives of natural products, such as β-carboline derivatives (β-CDs), as potential TR inhibitors, has received little attention. This study presents an analysis of the structural and physicochemical properties of commercially available β-CDs in relation to compounds tested against T. cruzi in previously reported enzymatic assays and shows that β-CDs cover chemical space that has not been considered for the design of TR inhibitors. Moreover, this study presents a ligand-based approach to discover potential TR inhibitors among commercially available β-CDs, which could lead to the generation of promising β-CD candidates..

Keywords

Trypanothione reductase, Trypanosoma cruzi, β-Carboline, Chemical space, Pharmacophore modeling and docking.