Tetracyclic fused glycomimetics by [4+2] ihDA reaction: a computational study

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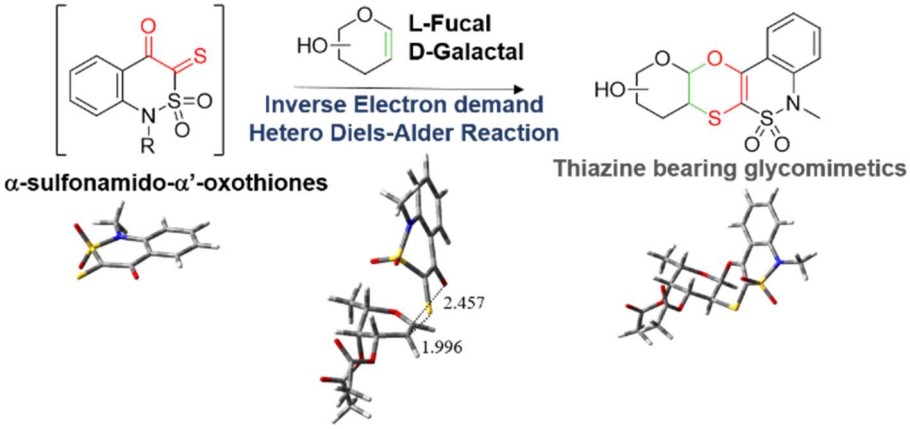
Abstract: Glycomimetics are useful tools in order to face up to fundamental questions in glycobiology and provide cutting-edge therapeutic strategies to address different disease settings. An interesting synthetic approach, to obtain them, is the [4+2] inverse electron demand hetero Diels-Alder (ihDA) reaction with structurally different electron-poor heterodienes and protected glycals as electron-rich dienophiles.



Here is described the [4+2] ihDA involving α-sulfonamido-α'-oxothiones as electron-poor heterodienes and differently protected silylated and acetylated glycals, derived from L-fucal and D-galactal, as dienophiles. These highly reactive electrophiles allow easily accessing to benzo-thiazine fused derivatives in a remarkable selective way, even using the acetylated glycals, unexplored within this version of ihDA. A computational mechanistic study was performed, in order to support and rationalize the experimental data. DFT calculations confirm the low energy barriers for these cycloaddiction reactions, showing that acetylated dienophiles can easily react, making cycloadditions feasible. Further studies are ongoing to extend the investigation of this ihDA to other acetylated glycals and to structurally different heterodienes, making available a new generation of glycomimetic drug.