CONFORMATIONAL PROPERTIES AND BIOLOGICAL TARGETS OF THIOCARBOHYDRAZONE AND CHALCONE-DERIVED 3,4-DIHYDROPYRIMIDINE THIONE

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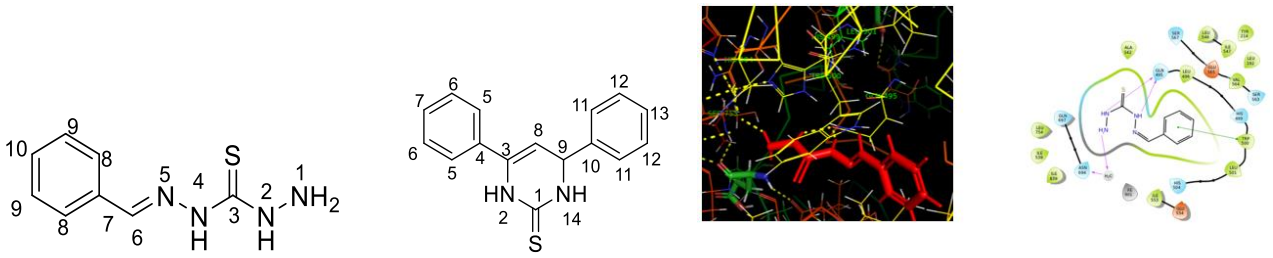
The potential of the 4,6-diphenyl-3,4-dihydropyrimidine-2(1H)-thione (abbreviated as **KKII5**) and (E)-N'-benzylidenehydrazinecarbothiohydrazide (abbreviated as **DKI5**) compounds as possible drug leads is investigated. The **KKII5** and **DKI5** are synthesized here in high yield up to 97%. Their structure, binging in the active site of LOX-1 enzyme, and their toxicity are studied via joint experimental and computational methodologies. Specifically, the structure assignment and conformational analysis were performed through homonuclear and heteronuclear 2D Nuclear Magnetic Resonance (NMR) spectroscopy (2D-COSY, 2D-NOESY, 2D-HSQC, and 2D-HMBC) and via Density Functional Theory (DFT). The DFT lowest energy conformers were compatible with the spatial correlations observed in the 2D-NOESY spectra. Additionally, docking and molecular dynamics simulations were performed to discover their ability to bind and stability to remain in the active site of the LOX-1 enzyme. These *in silico* experiments and DFT calculations indicated favorable binding for the enzyme under study. The strongest binding energy, -9.60 kcal/mol, was observed for dihydropyrimidine-thione **KKII5** in the active site of LOX-1. ADMET calculations showed that the two molecules lack of major toxicities and could serve as possible drug leads. The redox potential of the active center of LOX-1 with the binding molecules were calculated via DFT methodology. The results showed a significantly smaller energy attachment of 2.8 eV when **KKII5** is binding in comparison to **DKI5**. Thus, **KKII5** enhanced importantly the ability of the active center to receive electrons compared to **DKI5** This is related to the stronger binding interaction of **KKII5** relatively to **DK15** to LOX-1. The two very potent LOX-1 inhibitors exerted IC_{50} 19 μM (**KKII5)** and 22.5 μM (**DKI5).** Furthermore, they both strongly inhibit lipid peroxidation, namely 98% for **KKII5** and 94% for **DKI5**.



Scheme 1: Structures of (left) **DKI5** and (right) **KKII5** compounds and interactions of DKI5 with LOX-1.

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