

Influence of anthraquinone scaffold on *E/Z* isomer distribution of two thiosemicarbazone derivatives. 2D NMR and DFT studies



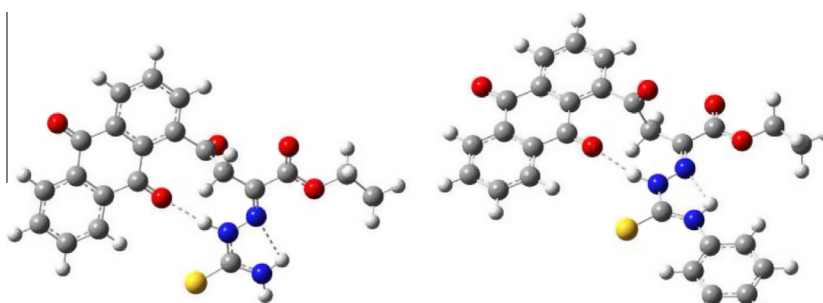
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HIGHLIGHTS

- 2D NMR: two anthraquinone-thiosemicarbazones exist as the *E*-isomers.
- The most stable conformers of the *E*- and *Z*-isomers of both compounds were revealed.
- DFT: *E*-isomers are thermodynamically more stable than *Z*-isomers.
- Perfect agreement between the experimental and calculated ^{13}C NMR spectra.
- The *E*-isomers dominate due to the ten-membered $\text{N}-\text{H}\cdots\text{O}$ hydrogen bonds.

GRAPHICAL ABSTRACT



Strong H-bond is engaged in a ten-membered ring

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ABSTRACT

A distribution of possible isomeric and tautomeric forms of two tautomerizable anthraquinone-thiosemicarbazones with pronounced cytotoxic potential was investigated using 2D NMR and DFT studies. Conformational analysis of the *E* and *Z* isomers of both thiosemicarbazones was performed to find out the most stable conformation for each molecule. It was found that superior stability of *E*-isomers results from ten-membered intramolecular hydrogen bond between thiosemicarbazone N2H and anthraquinone carbonyl group. This hydrogen bond is stronger than that between thiosemicarbazone N2H and ester oxygen, owing to the large partial negative charge on the anthraquinone oxygen.

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1. Introduction

Thiosemicarbazones are an important class of organic imine compounds with a wide range of potential pharmacological application, especially as antitumoral agents [1–3]. Their antitumor activity was revealed in ability to inhibit iron-containing ribonucleotide reductase by metal chelation [4] and topoisomerase

II by stabilization of the cleavable complex between this enzyme and DNA through a thiol alkylation [5]. Currently, triapine, the most attractive thiosemicarbazone derived from 3-aminopyridine-2-carboxaldehyde is undergoing human phase II trials as a cancer chemotherapeutic agent [6].

A characteristic issue in imine chemistry is the possibility of *E/Z* isomerism around $\text{C}=\text{N}$ double bond and the effect of isomerization on their behavior in biologically relevant conditions. Therefore, the implication of *E/Z* isomerism occurring in compounds with $\text{C}=\text{N}$ double bond appears of significant interest from not only synthetic but also biological aspects. For example,

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