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Conformational study of galphimines A and B

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Abstract

A conformational study has been performed for galphimines A and B, which differ from each other only in an acetate moiety on ring B of galphimine A. Mechanical molecular calculations showed that the predominant conformers in a Boltzman distribution are those which establish an intramolecular hydrogen bond between the hydroxyls on rings A and B, keeping a similar conformation on the rest of the molecule. The existence of these conformers was confirmed by NMR spectroscopy in (D_6) DMSO solution. Furthermore, an unbound hydrogen conformation was found. These types of conformations very probably coexist in solution, for both types of galphimines A and B. Additional experiments suggest that the acetate group on galphimine A does not distort rings B and A, neither does it disturb the intramolecular hydrogen bond formation that also shows galphimine B. Finally, it does not present a steric effect on ring A to avoid any type of interaction of the functional groups on this ring with the biological receptor. The acetate group, which is responsible for the lost of activity of galphimine A very probably prevent that the hydroxyls OH(4) and OH(7) from interacting, either in a hydrogen bounded or free form, with the receptor, indicating the importance that these hydroxyls play in the biological activity of the molecule.

Keywords: *Galphimia glauca*; Galphimine; Hydrogen bond; Density functional method

1. Introduction

Galphimia glauca (Malphiaceae) is a Mexican plant used in folk medicine (indigenous), to treat psychiatric-like or neurological disorders [1]. Methanolic extracts of the aerial parts of the plant show sedative and anticonvulsive activities in animal models [2]. Two major nor-seco-triterpenoids were isolated, galphimines A and B (Fig. 1), having found that galphimine B is responsible for most of the biological activity as antispasmodic and central nervous system sedative [3].

Considering that the three-dimensional structure of a molecule play a fundamental role in understanding its chemical and biological behavior, we initiated a conformational study on galphimines A and B in order to sustain their different activity. It is convenient to highlight that the only structural difference among these two molecules (see Fig. 1) is the presence of an acetate group on C(6) of ring B, which should be responsible for the lose of activity of galphimine A. Thus, our main concern in this study was focused in analyzing this part of the molecule.

2. Experimental

The NMR ^{1}H and ^{13}C spectra were recorded using a Varian Inova 500 spectrometer operating at an observation frequency of 500.0 MHz for ^{1}H and 125.0 MHz for ^{13}C. Saturation transfer experiments and temperature dependence of the hydroxyl proton ^{1}H NMR chemical shifts were performed using an Eclipse 300 Jeol spectrometer operating at an observation frequency of 300.0 MHz for ^{1}H. The ^{1}H chemical shifts (δ) are given in ppm using the solvent as internal reference (2.49 ppm ^{1}H NMR).

Assignment of the hydroxyl protons was carried out by ^{1}H NMR, interchange with deuterated water and COSY experiments. The remaining signals of the ^{1}H and ^{13}C spectra in (D_6) DMSO were assigned using 2D NMR spectroscopy

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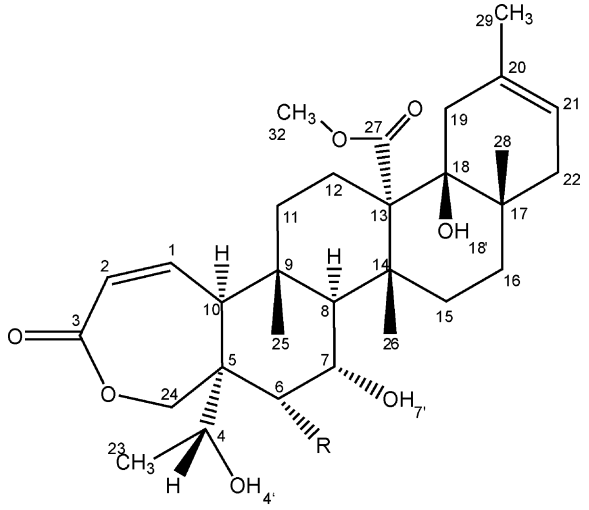

Fig. 1.

(COSY [4], HMQC [5], NOESY [6] and HMBC [7] experiments).

Galphimines A and B were isolated from the aerial parts of *Galphimia glauca*. Methanolic extracts of this plant were evaporated to dryness. After flash column chromatography (silica gel, Kieselgel 60, 230–400 mesh, Merck), using mixtures of dichloromethane/acetone, galphimines A and B were obtained [8]. Further crystallization of galphimine A in ethyl acetate/hexane gave colorless needles of mp 219–221 °C. Galphimines B were used without any additional purification method and used together as the exo and endo forms of the double bond moiety in ring E.

Quantum chemical calculations were performed using Spartan'04 Win [9] to determine the minimal energy conformation of galphimines A and B. The MMFF94 [10] molecular mechanics method was used to determine the conformer distribution. Furthermore, the BP/6-31G* density functional method was selected to determine the energies and electronic properties of each selected conformer [11,12]. Initial coordinates were taken from the X-ray data reported for galphimine B [13], and optimizing distances and angles initial coordinates of the substituent acetate to simulate galphimine A were obtained.

3. Results

The theoretical conformer distribution search for galphimine A using the MMFF94 molecular mechanic method

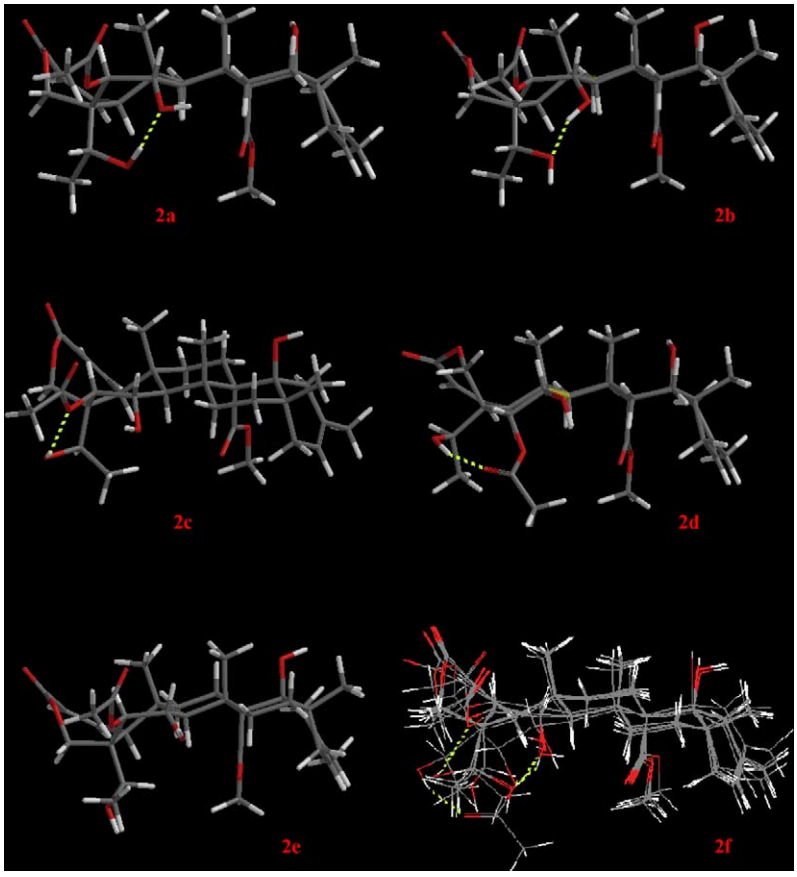

Fig. 2. Galphimine A. Minimal energy conformers. **2a** and **2b** show the intramolecular hydrogen bonds between hydroxyl groups O(4)─H(4′)...O(7), and O(7)─H(7′)...O(4), respectively. **2c** and **2d**, represent the intramolecular hydrogen bonds between hydroxyl group O(4)─H(4′) with the oxygens of the ester group bounded in C(6). **2e** shows the free conformer, and **2f** shows the superposition of the **2a**–**2e** conformers.