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STRUCTURAL DETERMINATION OF OSELTAMIVIR BY CALCULATIONS OF ^{13}C NMR CHEMICAL SHIFT

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Abstract

One of the most widely used antiviral classes for the treatment of influenza is neuraminidase inhibitors (NAIs), and this includes Oseltamivir [1], one of the most important anti-influenza drugs [2]. The combination of experimental and calculated NMR chemical shift studies (δ) helps to confirm the structure of molecules [3]. In this work we intend to correlation ^{13}C NMR scaled chemical shift with experimental chemical shift of Osetalmivir based on the application of scale factor. In the Spartan '08 program, Molecular Mechanics conformational analyzes are performed using the Monte Carlo method, in order to select the most stable conformer of the Osetalmivir molecule. It is also calculated Single Point with the purpose of confirming the most stable conformer. After selecting these conformer, they are submitted, in the Gaussian '09 program, to optimization and vibrational frequency calculations to show the stationary points and also confirm the nature of the stationary points, respectively. After we know the lower relative energy confomer, the chemical shift of ^{13}C are calculated, taking into account the Boltzmann distribution. All of these chemical shift calculations were computed at the mPW1PW91/6-31G(d) level using the GIAO method. The chemical shift scaled data (δ_{scal}) is obtained according to the equation $\delta_{scal} = 1.05.\delta_{calc} - 1.22$ (1) [4]. In order to achieve a generalized application of a scaling factor to the GIAO-HDFT ^{13}C chemical shift, it is desirable to combine excellent MAD (absolute mean deviation) and RMSD (mean square error) precision. The comparison showed a strong agreement between experimental and calculated NMR chemical shift. For the osetalmivir molecule MAD and RMSD before (after) in ppm, the application of the scaling factor is: 4.90 (3.82) and 6.77 (5.41), respectively. In conclusion, the level of GIAO-mPW1PW91/6-31G(d) theory applied to calculate gas phase chemical displacement along with the use of a scaling factor is a very attractive tool as an alternative to the most demanding approaches in terms which are generally applied to reproduce ^{13}C chemical shift of SSRMN.

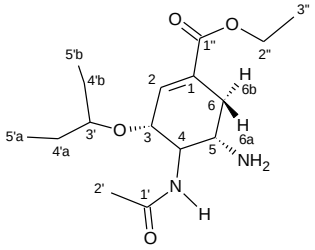

Figure 1: Oseltamivir molecule.

[1] José M. Fraile e Carlos J. Saavedra, "Application of Heterogeneous Catalysts in the First Steps of the Oseltamivir Synthesis".
[2] da Silva e Iha, "Polimorfismo: Caracterização e estudo das propriedades de uma fase cristalina".
[3] Lakshmi Prasanthi et al., "A Review on Polymorphism Perpetuates Pharmaceuticals".
[4] Giacomello et al., "Protocol for Calculating ^{13}C Nuclear Magnetic Resonance Chemical Shifts of Flexible Organic Molecules".