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Structural determination of polyphenols by quantum mechanical calculations of ^{13}C NMR chemical shifts: development of a parameterized protocol using a set of chalcones

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Abstract: Polyphenols are one of the most important and certainly the most numerous among the groups of phytochemicals present in the plant kingdom, e.g., chalcones, curcumines, phenolic acids, stilbenoids etc [1]. Chalcone derivatives are found widespread in natural products [2]. This class of compounds is considered as key precursors for flavonoid and isoflavonoid syntheses [2]. They have several biological activities including anti-inflammatory, anti-leishmania, antimitotic and antiviral are some few examples of their broad range of action etc [2]. Herein, we present the development of a protocol for determination of polyphenols structures, using a set of 13 chalcones (totaling more than 200 chemical shifts, δ) with different substitution pattern, whose structures have been reliably elucidated in literature [3-5]. This protocol consists of GIAO-DFT calculations of δ (mPW1PW91/6-31G*//mPW1PW91/6-31G*) and application of a scaling factor based on a linear regression. The δ are obtained as $\delta_{calc} = \sigma_{TMS} - \sigma$, where σ_{TMS} is the isotropic shielding constant of the reference compound, tetramethysinale (TMS), calculate at the same level of theory. The scaling factor was generated by plotting calculated (δ_{calc}) against experimental chemical shifts of the set of chalcones. Thus, slope (a) and intercept (b) values obtained from this linear regression can be used to generate scaled chemical shifts (δ_{scal}), using the expression $\delta_{scal} = a.\delta_{calc} \pm b$ (1). Thus, sing a set of 13 chalcones the following equation was generated: $\delta_{scal} = 1.051.\delta_{calc} - 0.870$, $r^2 = 0.989$. Due to their great conformational flexibility, the set of 13 chalcones as well as 2',6'-dihydroxy-4',4-dimethoxy-dihydrochalcone [5] and 2-[3-(1,3-benzodioxol-5-yl)propyl]-5-methoxyphenol [6], i.e. the test molecules, were submitted to randomized conformational searches using Monte Carlo method and MMFF force field. For complete conformational analysis and the conformers selection protocol see Giacomello *et al.* [7]. All quantum mechanical calculations were performed in gas phase, using Gaussian 09 software package [8]. For the chalcone set, the Mean Absolute Deviation (MAD) and the Root Mean Square Deviation (RMSD), in ppm, before and after (in parenthesis) the application of the equation (1) are: MAD = 5.84 (2.71) and RMS = 6.61 (3.86). Finally, the robustness of the new protocol and its applicability to others

polyphenols class were evaluated by the calculation of the δ for 2 naturals compounds with synthesis, biological and therapeutic interest: 2',6'-dihydroxy-4,4'-dimethoxy-dihydrochalcone (dihydrochalcone) **(I)** and 2-[3-(1,3-benzodioxol-5-yl)propyl]-5-methoxyphenol (diarylpropane) **(II)**, figure 1. For these molecules the MAD and the RMSD, in ppm, before and after (in parenthesis) the application of the equation (1) are: **(I)** MAD = 4.66 (1.14); RMS = 5.21 (1.81) and **(II)** MAD = 4.94 (1.65); RMS = 5.44 (2.38). Considering a set of 13 chalcones with different substitution pattern, we developed a parameterized protocol for the calculation of ^{13}C NMR chemical shifts of polyphenols. This protocol, consisted of GIAO-DFT calculations and a linear scaling factor, was able to yield calculated chemical shifts with satisfactory accuracy. Therefore, the calculation protocol developed in this work is a very attractive tool as an alternative to more computationally demanding approaches for the calculation of polyphenols, such as dihydrochalcones and diarylpropanoids.

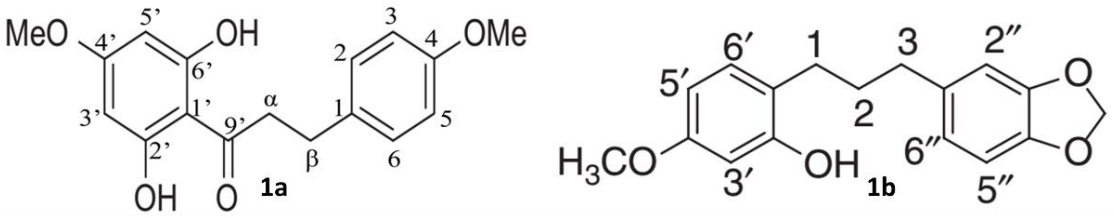

Figure 1. 2',6'-dihydroxy-4,4'-dimethoxy-dihydrochalcone (**1a**) and 2-[3-(1,3-benzodioxol-5-yl)propyl]-5-methoxyphenol (**1b**) molecules.

Key-words: GAIO-mPW1PW91/6-31G*//mPW1PW91/6-31G*, NMR, polyphenols, chalcones.
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