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Ab initio ^{1}H- and ^{13}C-NMR Computational Study of Vorinostat: A Biologically Active Compound Against Cancer

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ABSTRACT

The[1]H- and [13]C-NMR isotropic chemical shifts of vorinostat, a recent anti-cancer agent approved by the U.S. Food and Drug Administration (FDA)were calculated using Density Functional Theory (DFT) by employing Becke's three-parameter hybrid functional (B3LYP) and 6-31G(d) basis set. The calculations yielded reliable results that were in good correlation with experimental data. This is a good foundation for alliance between experimentalists and quantum chemists.

Keywords: NMR spectra; Spartan 10 software; vorinostat; HDACs, FDA

INTRODUCTION

Vorinostat also known as suberanilohydroxamic acid (SAHA) is a member of a larger class of compounds that inhibits Histonedeacetylases (HDACs), a group of enzymes that regulate expression of tumor suppressor genes making them a promising therapeutic target for treatment of cancer. SAHA was the first HDAC inhibitor [1] approved by U.S. Food and Drug Administration (FDA). It has been shown to bind the active site of HDACs and acts as chelator of Zn ions also found in the active site of HDACs [2]. Its inhibition of HDACs results in the accumulation of acetylated histones and proteins including transcription factors crucial for the expression of genes needed to induce cell differentiation [2]. SAHA is also an interesting target for scientists interested in eradicating HIV from infected persons. It has recently shown to have both invivo and invitro effects against latently HIV infected T-cells [3;4]. The chemical structure of SAHA is shown in Fig.1

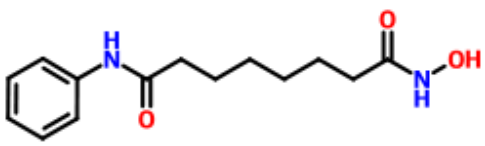

Fig. 1: Molecular structure of Vorinostat

Nuclear magnetic resonance (NMR) spectroscopy [5;6] is a widely used technique for obtaining physical, chemical and structural information about molecules in gaseous, liquid, solid and liquid crystal states of matter. It has find wide application in structure elucidation as well as investigations of the reactivity and reaction mechanisms involving organic molecules. NMR also has immense recognition in biochemistry, biology and pharmacy for structure determination and in studies of biomolecular dynamics [4].

The use of Quantum Chemical calculations to compute NMR chemical shifts for some structure and comparing them to existing NMR data avail the experimentalists the opportunity of accessing additional informations. If a good agreement exists between the two sets of NMR data. If the two sets of NMR data, all the molecular properties that were obtained by the calculations can be assigned to the new compound and accordingly[7]. It can thus be inferred that the calculation of NMR chemical shifts in this way provides an ideal basis for collaboration between experimentalists and quantum chemists. Summarily, modelling NMR parameters quantum chemically from first-principles is vital to complement the experiments, to obtain experimentally unavailable information and to makenew predictions.

2. Theoretical Background

In NMR spectroscopy, the chemical shift is the resonant frequency of a nucleus relative to a standard in a magnetic field. Often the position and number of chemical shifts are diagnostic of the structure of a molecule. It is usually expressed in parts per million (ppm) by frequency relative to a zero chemical shift reference compound known as TMS (tetramethylsilane) or DSS (4,4-dimethyl-4-silapentane-1-sulphonic acid) [8].

The energy, E of a magnetic momentum, μ, in a magnetic field, B, is expressed as follow:

$E = - \mu . (1 - \sigma) B$ ……eqn 1

where σ refers to the differential resonance shift due to the induced motion of the electrons. The chemical shielding is characterized by a real three-by-three Cartesian matrix, which can be divided into a single scalar term, three anti symmetric pseudo vector components, and five components corresponding to a symmetric tensor [9].

3.0 Computational Methods

Molecular structure of Vorinostat was optimized using Density Functional Theory (DFT) method by employing Becke's three-parameter hybrid functional (B3LYP) and 6-31G(d) basis set.Calculations were performed to study thermodynamic parameters extracted from NMR chemical shift data. All calculations were carried out using the ***Spartan 14 program*** package. The optimized geometric structure of Vorinostat based on theoretical methods is shown in Figure 2.

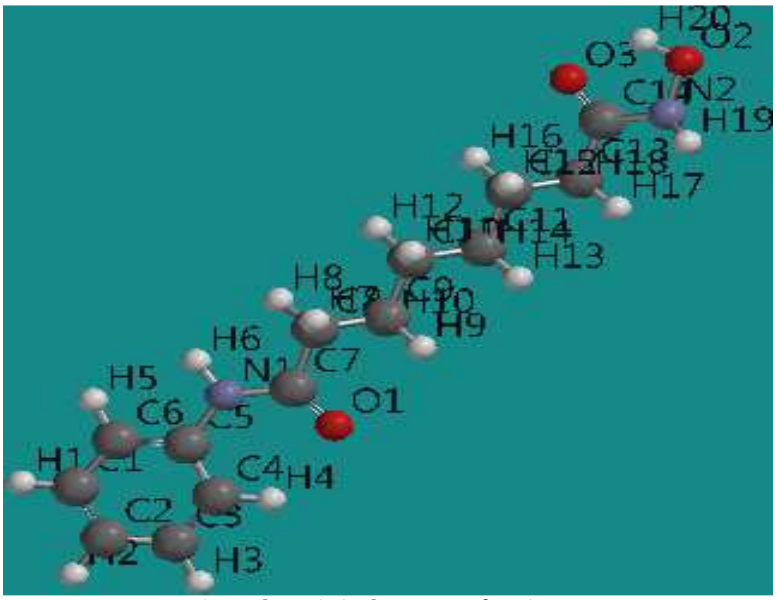

Fig. 2. The optimized geometry of Vorinostat

RESULTS AND DISCUSSION

4.1 Comparison of the experimentally measured and theoretically computed shifts

Chemical shifts calculated using the B3LYP level with the 6-31*G (d) basis sets can be utilized to eliminate the uncertainties in the fundamental assignments of the spectra. The ^{1}H- and ^{13}C- theoretical and experimental isotropic chemical shifts and assignments of Vorinostatare presented in Tables 1 and 2, respectively.

TABLE 1: The experimental and calculated ^{1}H-isotropic chemical shifts in ppm, with respect to DMSO-*d*6

Assignment	Calculated shift	Experimental shift
H_1	7.12	7.27
H_2	6.86	7.03
H_3	7.12	7.27
H_4	7.40	7.3
H_5	7.40	7.58
H_6	—	—
H_7	2.10	2.29
H_8	2.10	2.29
H_9	1.84	1.94
H_{10}	1.84	1.94
H_{11}	1.36	1.27
H_{12}	1.36	1.27
H_{13}	1.43	1.27
H_{14}	1.43	1.27
H_{15}	1.73	1.53
H_{16}	1.73	1.53
H_{17}	1.87	1.94
H_{18}	1.87	1.94
H_{19}	—	—
H_{20}	—	—

TABLE 2: The experimental and calculated ^{13}C-isotropic chemical shifts in ppm, with respect to DMSO-*d*6

Assignment	Calculated shift	Experimental shift
C_1	122.0	122.96
C_2	115.9	119.01
C_3	122.0	122.96
C_4	110.5	119.01
C_5	132.2	139.24
C_6	110.5	119.01
C_7	—	—
C_8	38.3	36.34
C_9	27.4	25.04
C_{10}	32.0	32.24
C_{11}	32.7	32.24
C_{12}	28.7	28.43
C_{13}	34.8	32.24
C_{14}	—	—

At the higher temperature, the hydrogen of the hydroxyl and amine groups (H_{19}, H_6 and H_{20})of vorinostat were not visible in the ^{1}H-NMR spectrum (Table 1), because of fast hydrogen/deuterium exchange. It is also interesting to note that this hydrogen was also not visible on the theoretical spectra obtained from the software. The software does not estimate shifts for hydrogen atoms attached to heteroatoms because it also takes into consideration the effects of the solvent[10].

The correlation factors of the linear regression used to compare the experimentally measured and theoretically computed ^{1}H – and ^{13}CNMR shifts for vorinostat are shown in Fig. 3 and Fig.4, respectively. The high coefficient of regressions depicted in the plots implies that a sound agreement exists between the experimentally measured and theoretically computed ^{1}H – and ^{13}C NMR shifts of the compound.

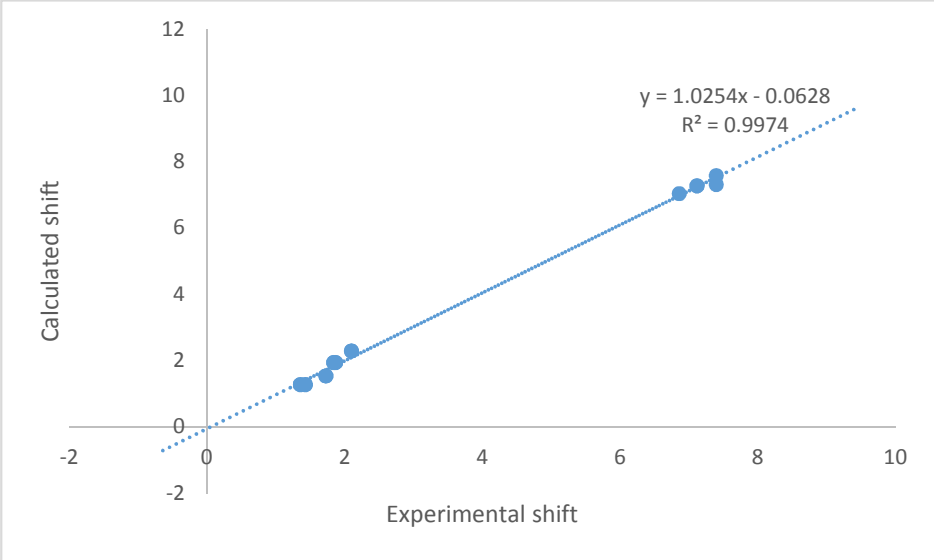

Fig. 3: Plot of calculated chemical shift against experimental ^{1}H NMR chemical shift values

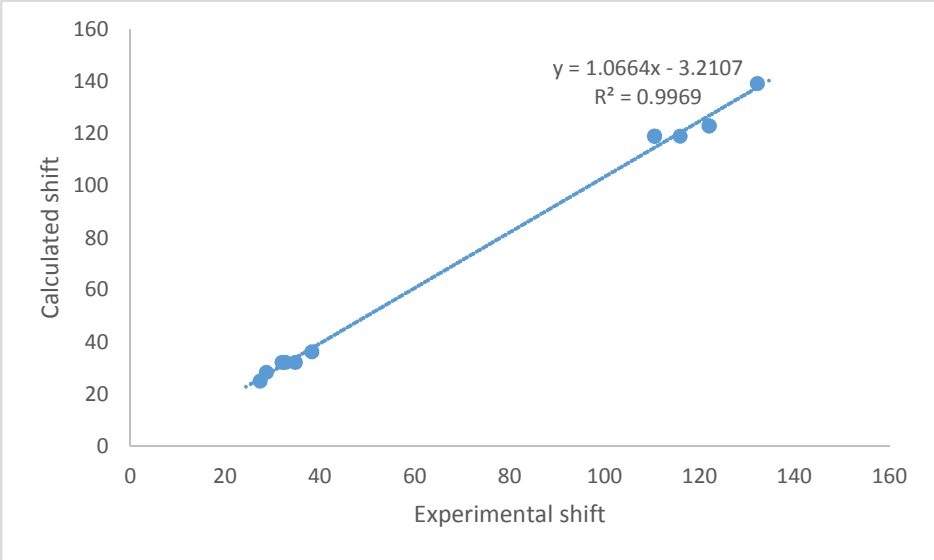

Fig. 4: Plot of calculated chemical shift against experimental ^{13}C NMR chemical shift values

CONCLUSION

Selected structural parameters of the optimized geometry of the vorinostat were obtained by DFT calculations. The ^{1}H and ^{13}C-NMR chemical shifts were calculated and the assignments were compared with the experimental values. Sound agreement was obtained between experimental and the theoretical chemical shifts. The conducted research provided complete NMR chemical shifts of these compounds.

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