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Comparative Study of the Experimental and Theoretical Proton and Carbon-13 NMR of Belinostat: An Anti-Cancer Agent

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ABSTRACT

The experimental 1H- and 13C-NMR isotropic chemical shifts of Belinostat were obtained from literature. The theoretical values of these data were computed with the aid of Chem 3D pro 12.0/ChemDraw ultra 12.0 software. The theoretical values were compared with the experimental values through statistical analysis. Sound agreement exists between experimental and theoretical 1H- and 13C-NMR data of the molecule (Belinostat) as the R2 values of 0.9263 and 0.9886 were obtained for 1H- and 13C-NMR, respectively. The result of the study shows that experimental inaccessible information about Belinostat may be obtained from this theoretical calculations and new predictions made with reliability.

Keywords: NMR; Chem 3D pro 12.0; Belinostat; HDACs, Anti-cancer

INTRODUCTION

Cancer is a disease characterized by uncontrolled growth as a result of changes in a group of normal cells within the body causing a lump called a tumor [1]. The rising incidence of cancer among the human populace as well as the ever-rising prevalence of morbidity and mortality rate [2-6] orchestrated by this sickness has necessitated the need for rigorous research on any potential drug candidate against this deadly sickness.

Belinostat (E-N-Hydroxy-3-[N-phenylsulfamoyl] phenyl] acrylamide) is the generic name for the trade name drug Beleodaq®. It is a novel histonedeacetylase (HDAC) inhibitor with IC50 of 27 nM in a cell -free assay, with activity demonstrated in Cisplatin-resistant tumor [7,8]. Belinostat was reported to also possess the tendency of inducing apoptosis through PARP cleavage and acetylation of histones [9]. This drug candidate has also demonstrated immense inhibitory activity against bladder cancer [10] cell growth in addition to exhibiting enhanced tubulin acetylation in ovarian cancer cell lines [11]. Just recently, studies have shown that it activates protein kinase A in a TGF-β signaling -dependent mechanism and decrease surviving mRNA [7]. Its Structure is shown in Figure 1.

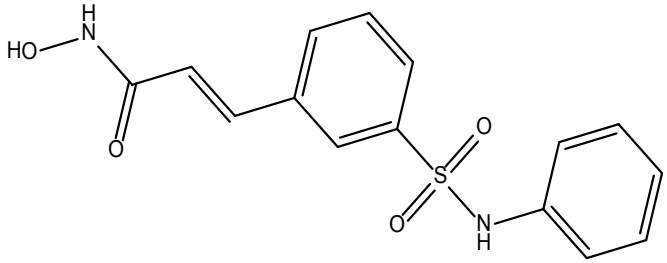

Figure 1: Molecular structure of Belinostat

Nuclear magnetic resonance spectroscopy, most commonly known as NMR spectroscopy, is a research technique that exploits the magnetic properties of certain atomic nuclei. It has found wide application in investigation of molecular structures [12].

Comparison of experimental NMR data with theoretically computed values provides a good basis to experimentalist for obtaining more vital information about the molecule under investigation through less expensive and less time consuming theoretical calculations, especially where excellent agreement exists between the two approaches [12,13].

The aim of this research is to ascertain the concord between experimental and theoretical 1H- and 13C-NMR data of the anti-cancer agent, Belinostat.

MATERIALS AND THEORETICAL METHODS

The energy of the structure of the compound was minimized with the aid of Chem 3D pro 12.0 program and saved as Chem 3D XML. The theoretical NMR data of the structure was then computed with the aid of ChemDraw ultra 12.0. The minimized geometry of the molecule as it appears on ChemDraw ultra's interface is depicted in Figure 2.

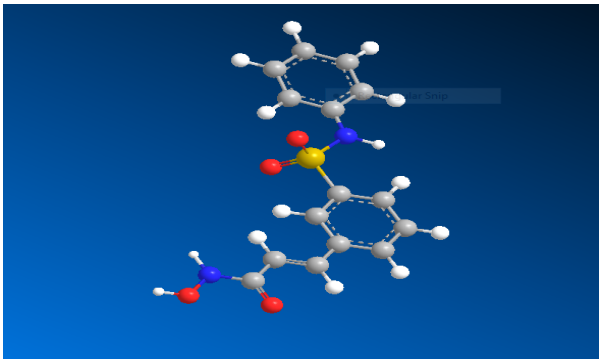

Figure 2: The optimized geometry of Belinostat

RESULTS

Assessment of the laboratory and theoretically computed proton and carbon-13 data

The theoretically computed 1H- and 13C- NMR data are depicted in Figure 3 and Figure 4, respectively.

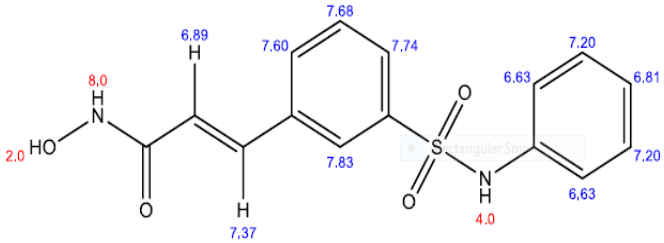

Figure 3: Theoretical 1H-NMR chemical shift values of Belinostat

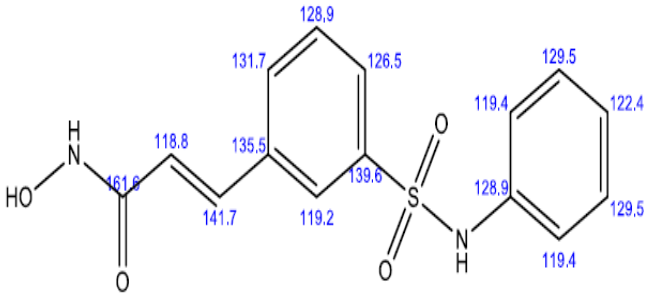

Figure 4: Theoretical 13C -NMR chemical shift values of Belinostat

DISCUSSION

The theoretical and experimental 1H- and 13C NMR data and assignments for Belinostat are presented in Table 1 and Table 2, respectively. The experimental 1H- and 13C NMR data of the compound were obtained from past work [6]. A good agreement exists between the two set of values in each case, an indication that theoretical calculations could

be a sound complement to experimental measurement of 1H- and 13C NMR. Thus, theoretical calculations of this nature could be a vital source of other additional information about Belinostat.

Table 1: Assignment of theoretical 1H-NMR values

Calculated Shift	Experimental Shift
—	12-9
8.0	7.90
7.83	7.76
7.74	7.70
7.68	—
7.60	7.56
7.37	7.44
7.20	7.22
6.89	7.08
6.81	7.01
6.63	6.50
4.0	—
2.0	—

Table 2: Assignment of theoretical 13C-NMR values

Theoretical shift	Experimental shift
161.6	162.1
141.7	140.6
139.6	138
135.5	136.5
135.5	135.9
131.7	131.8
129.5	130
128.9	129.2
128.5	127.1
122.4	124.8
122.4	124.1
122.4	121.3
119.4	120.4
119.2	—
118	—

Figure 5 and Figure 6 give the statistical fit of the concord between the experimentally measured and theoretically computed 1H and 13C NMR data respectively, for Belinostat. The high coefficient of correlations (R2 values) of 0.93 and 0.99 for 1H and 13C, respectively is a strong indication that excellent correlation exists between these sets of values.

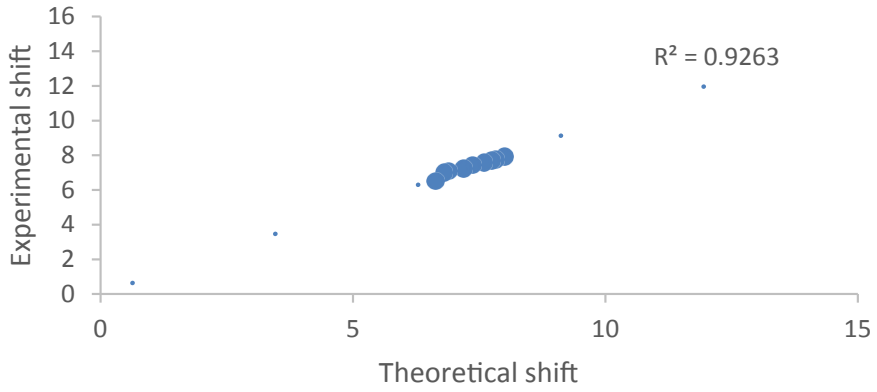

Figure 5: Graph of experimental verses theoretical 1H NMR data for Belinostat

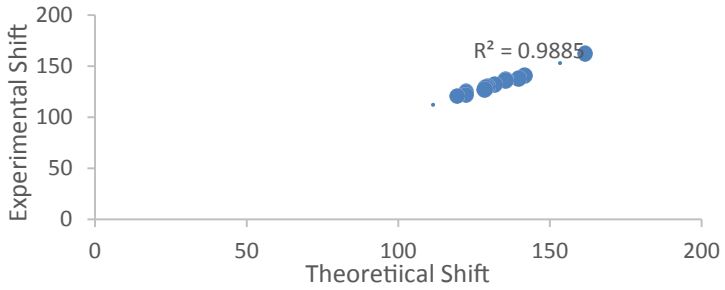

Figure 6: Graph of experimental verses theoretical 13C-NMR data for Belinostat

CONCLUSION

The 1H- and 13C-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. It can thus be inferred that experimentally unavailable information about Belinostat may be obtained from this theoretical calculations and new predictions made with reliability.

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