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Insights into the Electronic Properties of Coumarins: A Comparative Study Synthesis, Characterization, and Theoretical Study of New Peptides Obtained by Opening Reactions of Sulfahydantoins

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Sulfhydantoin from glycine or *L*-valine is used as a precursor via heterocyclic opening reactions. The operating conditions used during electrophilicity tests influence the reactivity of heterocycles, the best control of the electrophilicity of our molecules, and consider as well as their use as enzyme inhibitors. The regioselectivity of the reactions carried out in various nucleophilic media leads to three new linear products derived from acetamide and butanamide and which are analogous to the peptide structures. The structures of the synthesized products 3-5 have been elucidated and confirmed by the usual spectroscopic methods. A theoretical study based on the DFT/PW6B95 method combined with the basic set 6-311G (2d,p) was carried out to determine the structural and electronic parameters such as the energy parameters, the molecular electrostatic potential (MEP), the natural bonding of orbitals (NBO), non-covalent interactions (NCI) and ^{1}H NMR.

Keywords: Sulfahydantoin, Nucleophiles, Opening reaction, DFT, NBO, NCI

INTRODUCTION

The five-membered nitrogenous heterocycles of the sulfahydantoin type are pharmacologically and chemically described as compounds potentially inhibiting viral proteases [1-2], as well as their wide bioavailability used for the synthesis of peptide analogues [3], they can also be used in various reactions such as aldolization [4], ring opening under reduction operating conditions [5].

In the literature, many opening reactions of heterocyclics have been widely studied, which have led to structural modifications allowing easy access to highly functionalized compounds in the case of oxazolidinones [6]. As well as widely explored small heterocycles such as *N*-alkylated and *N*-acetylated aziridines [7-9] which are used as precursors in ring-opening reactions, which are processed by nitrogen and oxygen nucleophiles.

Many heterocycle cleavage reactions have resulted in a departure from the SO_2 group. This type of reaction is encountered in reducing phenol [10,11], moreover, the reaction of the same type under various oxidation conditions leads to sulfonated bis amino alcohols analogous to dipeptides [6,12].

The synthetic methodology adopted and the realization of a process for opening sulfhydantoins which are derived from glycine and *L*-valine [5], which are used as generators for new derivatives which have mimetic structures at peptides under different nucleophilic conditions [13,14], these heterocycles have also been investigated in peptide chemistry. The objective of these syntheses was to use them as generators of functionalized peptide analogues for potential enzyme inhibition [15].

The three new derivatives obtained by this type of reaction are *N*-benzyl-2-(methylamino) acetamide 3, (*S*)-*N*-

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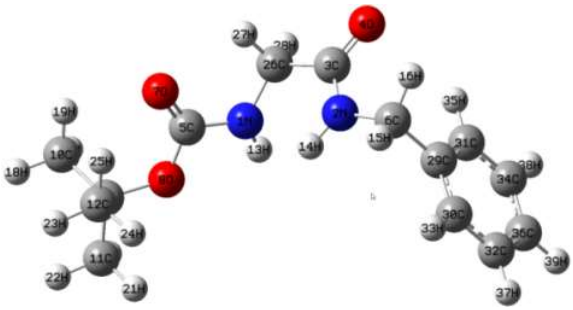
benzyl-3-methyl-2-(methylamino) butanamide 4, and *N*-benzyl-*N*-sulfodioxidepiperidinyl-2-(methylamino) acetamide 5 have linear structures carrying the amide function and possess electrophilic sites and nucleophilic sites can be used in several types of chemical reactions. Structurally they are analogous to peptide structures, these tri or dipeptides can also be deprotected and coupled with amino acids in order to access higher oligopeptides [16] as well as for the formation of glycosylated peptides which have an important role in many biological processes [17].

After the optimization of the molecules by the DFT/PW6B95 method combined with the 6-311G(2d,p) basis set, an in-depth theoretical study was carried out, the calculations were carried out using the visualization programs molecular Gauss View [18] and Gaussian16 [19] in the gaseous state. The determination of the different structural, electronic, reaction characteristics, and molecular interactions have been studied thanks to energy parameters evaluated by an exchange of enthalpy ΔH°, free enthalpy ΔG°, entropy magnitude ΔS°, E_{HOMO}, E_{LUMO}, ΔE_{gap}, absolute hardness (η), absolute electronegativity (χ), chemical potential (μ), structures optimized by spectral studies with ^{1}H NMR Based on B3LYP/6-311+G(2d,p), analysis of the GIAO theory, NCI-RDG analysis, MEP and NBO.

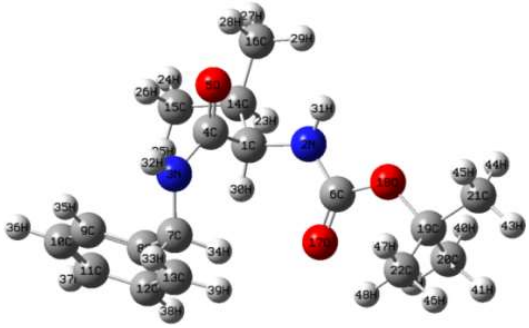
COMPUTATIONAL DETAILS

The calculations were performed using the density functional theory by optimizing the three compounds which are obtained by the sulfhydantoin-like five-membered heterocyclic opening reactions. All calculations for this work were performed using Gaussian16, Inc., Wallingford, CT software.

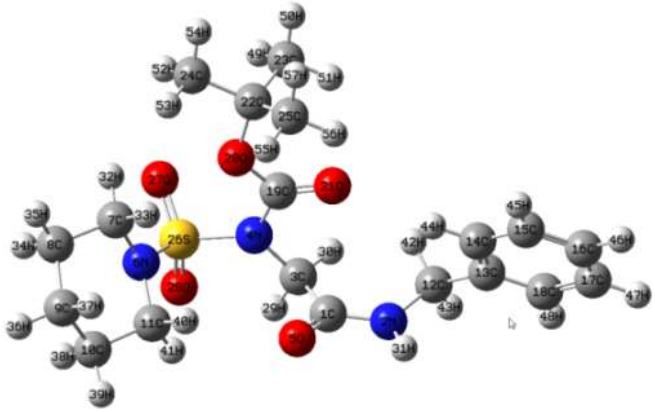
The visualization of the theoretical data was carried out using Gauss View [18], the DFT was chosen because of an excellent compromise between a computation time and an electronic correlation description. The PW6B95 method is used in this study to allow us to determine the different structural and electronic interactions of the three amides obtained such as the energy parameters, MEP, NCI, and chemical shifts. Figure 1 shows the molecular structures of derivatives 3-5 from the opening reactions of heterocyclic 1,



Compound 3



Compound 4



Compound 5

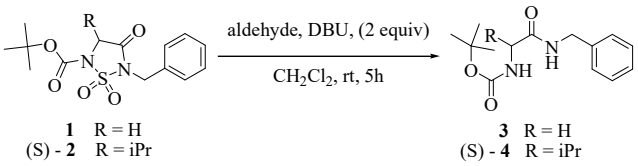
Fig. 1. Optimized molecular structure of compounds 3-5.

2 are optimized by the DFT/PW6B95 method with 6-311G(2d,p) in the gas phase. Carbon atoms are represented by gray spheres, oxygen by red, nitrogen by blue, sulfur by yellow, hydrogen by white spheres.

RESULTS AND DISCUSSIONS

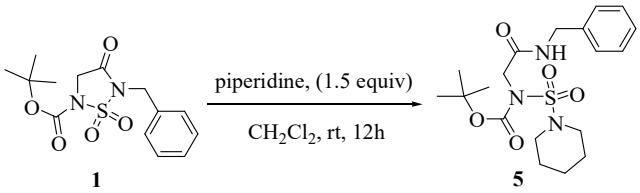
Synthesis

The opening of rings from glycine and *L*-valine *N*-protected by *tert*-butyloxycarbonyl (Boc) is carried out in a nucleophilic medium in the presence of an aldehyde and a DBU base in anhydrous dichloromethane and under stirring at room temperature, which causes the departure of the disulfoxide from two heterocycles. Linear derivatives 3, 4 were obtained with acceptable yields, a general procedure of this reaction is shown in Scheme 1.



Scheme 1. Synthetic Route of acetamide 3 and butanamide 4

The sulfahydontoin to be tested for a cleavage procedure is dissolved in a few mLl of anhydrous chloromethane. The piperidine, which acts as a nucleophile, is then added to the reaction medium which is placed under argon and with stirring at room temperature. The cleavage product 5 is obtained with a yield of 20%, according to Scheme 2.



Scheme 2. Synthetic Route of acetamide 5

The first way of synthesis consists in carrying out the reactions of the opening of the heterocycles by loss of units (SO_2). The cleavage is carried out from the precursor 1,1-dioxide-3-oxo-1,2,3-thiadiazolidines 1, 2 from glycine and *L*-valine, in the presence of benzaldehyde and *DL*-phenylpropionaldehyde in the second reaction and under the action of 1,8-diazabicyclo [5.4.0] undec-7-ene, DBU at room temperature. This type of reaction led to the linear products *N*-benzyl-2-(methylamino) acetamide 3 with a yield of 49% and *N*-benzyl-3-methyl-2-(methylamino) butanamide 4 with a yield of 47%.

In a second methodology, the evaluation of the electrophilicity of the synthesized sulfhydantoins is tested by a ring opening process in the presence of different nucleophiles. This type of reaction does not take place with ethyl alcohol and sulfuric acid. Only in the case of the piperidine at room temperature, the cleavage product *N*-benzyl-*N*-sulfodioxidepiperidinyl-2-(methylamino) acetamide 5 is recovered with a yield of 20%.

Energy Parameters

Are based on vibrational values, which are used to predict an assessment of standard thermodynamic parameters of systems [20], such as enthalpy change (ΔH°), free enthalpy or Gibbs thermal energy (ΔG°), and the influence of the amplitude of entropy (ΔS°) at the level of molecular systems. The thermodynamic quantities calculated by PW6B95/6-311G(2d,p) in the gas phase at p = 1 atm, T = 298.15 k for the three derivatives 3-5 are gathered in Table 1. An analysis of these thermodynamic parameters shows that the negative values obtained for ΔH° and ΔG° indicate that a chemical process is exothermic and also make it possible to quantify the spontaneity of a molecular system, the positive values for ΔS° characterize an increase in the disorder of 3 to 5 molecular systems and the negative values obtained for the electronic energies mean that these systems are structurally stable.

The chemical reactivity of molecular systems has been described by conceptual density functional theory (DFT) and Koopman's theorem [21]. The values of quantum chemical descriptors clearly describe the electronic structures of compounds, a mechanism and predict the formation of covalent bonds by different chemical reactions carried out by action of nucleophilic, and electrophilic species which are directly related to the relative energies of the HOMO and LUMO orbitals. To understand the global reactivity of chemical systems requires the determination of the values of quantum descriptors such as the energy difference ΔE_{gap} [22], the chemical hardness which is directly related to the stability, and the reactivity of a system in its initial state [23,

24], electronegativity (χ) [25], electronic chemical potential (μ) generally linked to the charge transfer capacity [26], electrophilicity index (ω) which provides information on both the transfer of electrons and on the stability of molecules [27]. These values are calculated with method PW6B95 and Base 6-311(2d,p) for derivatives 3-5 (Table 1).

The calculations of the thermodynamic parameters reveal that the entropy variation ΔS° of derivative 5 is the highest, which indicates large freedom of rotation at the structural scale, the negative values of free enthalpy ΔG° are the sign of reactions thermodynamically favourable and spontaneous. Values of enthalpy changes that are negative indicate that these 3-5 structural systems are exothermic. The low value of ΔE_{gap} of derivative 4 indicates the ease of electron movements between HOMO towards LUMO.

The chemical hardness of compound 4 is the lowest (η = 3.95 eV), while its electronegativity value is the highest (χ = 3.14 eV), so it is considered the best acceptor among the three derivatives, it also has a higher value of electrophilicity (ω = 1.24 eV) this reveals that this compound is the most electrophilic with a high chemical reactivity, it is also considered as a soft molecule, on the other hand, compound 3 has a low value (ω = 1.00 eV) which indicates that this nucleophilic characteristic is very remarkable.

All of these results show that compound 4 has a high chemical reactivity with its electrophilic characteristic, while compound 3 is stable and the most nucleophilic.

Molecular Electrostatic Potential (MEP)

A molecular electrostatic potential is very useful, it allows us to visualize an electrophilic and nucleophilic site as well as the overall size, shape, and polarity of molecules [28]. To facilitate an interpretation of the electrostatic potential energy data, a spectrum composed of colours indicates the different values of the calculated intensities of the MEP. The relationship between the increase in potential and the colours is as follows: (most negative) < orange < yellow < green < blue (most positive) (Fig. 2).

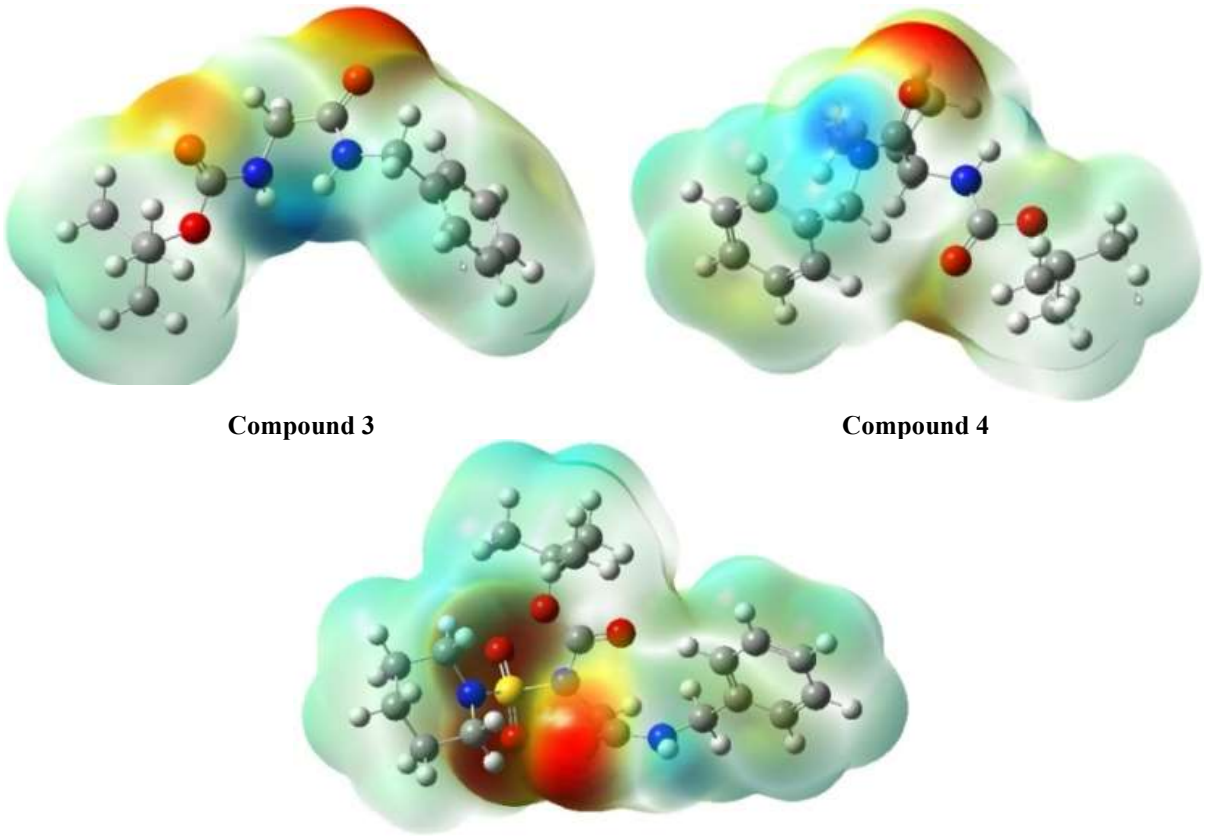
From its surfaces, an electrostatic potential of the molecules 3-5, indicates that the regions with negative electrostatic potential are located on the carbonyl group, while the regions that exhibit positive potential are located on the rest of the molecules that represent the hydrogen atom alkyl groups and on the benzene ring.

Natural Bonding Orbital Analysis (NBO)

A study by the (NBO) method is carried out to understand the nature of the bonds of natural intra and intermolecular orbitals as well as the delocalization of the electron density by charge transfer between a donor and an acceptor in the molecular systems to present the classical structure of molecules [29]. NBO theory also helps identify

Table 1. Calculations of Thermodynamic Parameters (kcal mol^{-1}) by Method PW6B95/6-311G(2d,p) in the Gas Phase of Derivatives 3-5 at 1 atm and 298.15 K

Energies	Compound 3	Compound 4	Compound 5
ΔE° (kcal mol^{-1})	-553519.63	-627641.18	-1055667.72
ΔH° (kcal mol^{-1})	-553298.75	-627364.46	-1055347.07
ΔG° (kcal mol^{-1})	-553343.93	-627414.03	-1055403.55
ΔS° (cal mol^{-1} K^{-1})	150.36	166.10	190.42
E_{HOMO} (eV)	-6.96	-7.10	-7.07
E_{LUMO} (eV)	1.22	0.81	1.14
ΔE_{gap} (eV)	8.19	7.91	8.21
μ (eV)	-2.87	-3.14	-2.96
χ (eV)	2.87	3,14	2.96
η (eV)	4.09	3,95	4.10
ω (eV)	1.00	1.24	1.07



Compound 3 **Compound 4**

Compound 5

Fig. 2. The molecular electrostatic potential surface of derivatives 3-5.

hybridization, covalence, and Van der Waals interactions. Additionally, it explains the individual bonds and energies associated with lone-pair electrons that play an essential role in chemical processes [30-32]. Some orbitals are electron donors and some are acceptors, a difference in energy between these bonding and antibonding orbitals makes a molecule susceptible to interactions [33,34]. Moreover, low occupancy of anti-valence bonds signals an irreducible shrinkage of the localized Lewis structure, indicating true delocalization effects [35].

The binding-anti-binding interaction can be quantitatively described in terms of the NBO approach which is expressed by means of a second-order perturbation interaction energy E2 [36,37]. A second-order Fock matrix was performed to evaluate the donor (i) and acceptor (j) interaction in the NBO database [38]. The stabilization energy E2 associated with electronic delocalization between a donor (i) and an acceptor (j) [39,40], is expressed by:

$$E2 = \Delta E_{i\,j} = q_i [F\,(i, j)^2/(\varepsilon_j - \varepsilon_i)]$$

Where qi is the donor orbital occupancy, i and j are diagonal elements, and fij is the Fock matrix element. The larger the E2 value, the stronger the interaction between electron donors and acceptors, which means a greater degree of conjugation of the whole system [41].

A transfer of charge between the occupied orbitals and the vacant orbitals is described by the analysis of the NBO theory to have more information on the nature of the bonds and their interactions of derivatives 3-5 using the method PW6B95/6-311G(2d,p). The results of the NBO calculations are shown in Table 2.

NBO analysis indicates the main allowed intermolecular interactions between donor-acceptor electrons are only LP-σ* type at high E2 stabilization energies, while σ-σ* type interactions are present at low E2 values, on the other hand, the absence of interactions between the π-π* orbitals in the three derivatives 3-5.

Table 2. Stabilization Energy E2 (kcal mol^{-1}) of the Most Important Donor-acceptor Interactions in Three Molecules

Orbital donor	Orbital acceptor	E_2 (Kcal mol^{-1})	E(j)-E(i) a.u	F (i, j) a.u
Compound 3				
LP (1) N2	σ*(2) C3-O4	45.87	0.39	0.121
LP (2) O7	σ*(1) C5-O8	33.44	0.64	0.136
LP (2) O4	σ*(1) N2-C3	25.87	0.77	0.128
LP (2) O7	σ*(1) N1-C5	25.15	0.74	0.124
σ (2) C31-C34	σ*(2) C29-C30	23.46	0.31	0.124
σ (2) C29-C30	σ*(2) C32-C36	22.73	0.30	0.076
LP (2) O4	σ*(1) C3-C26	21.97	0.65	0.108
LP (1) N1	σ*(1) C5-O7	15.98	0.64	0.091
Compound 4				
LP (1) N3	σ*(2) C4-O5	69.64	0.30	0.130
LP (2) O17	σ*(1) C6-O18	32.32	0.68	0.134
LP (2) O5	σ*(1) N3-C4	25.53	0.77	0.127
σ (2) C9-C10	σ*(2) C8-C13	23.32	0.31	0.076
LP (2) O17	σ*(1) N2-C6	23.11	0.76	0.121
σ (2) C8-C13	σ*(2) C11-C12	22.58	0.30	0.074
LP (1) N2	σ*(2) C6-O17	22.25	0.51	0.095
LP (2) O5	σ*(1) C1-C4	21.14	0.65	0.106
Compound 5				
LP (2) O20	σ*(2) C19-O21	46.93	0.39	0.126
LP (1) N4	σ*(2) C19-O21	45.55	0.34	0.113
LP (2) O21	σ*(1) C19-O20	30.48	0.70	0.133
LP (1) N2	σ*(2) C1-O5	28.75	0.46	0.104
LP (2) O21	σ*(1) N4-C19	25.33	0.72	0.123
LP (2) O5	σ*(1) C1-N2	25.02	0.78	0.126
σ (2) C14-C15	σ*(2) C13-C18	23.45	0.30	0.076
σ (2) C14-C15	σ*(2) C16-C17	22.69	0.30	0.074

Analysis of Non-covalent Interactions (NCI)

Graphical visualization of our molecules 3 to 5 is performed by NCI-RDG analysis to locate the spaces of the most nucleophilic and electrophilic sites in molecular systems. On the other hand, thanks to a code made up of simple colours [42], which makes it possible to determine the different types of interactions, to distinguish between hydrogen bonds and the existence of weak bonds of the Van der Waals (VdW) type which are responsible for the stability of molecular structures as well as the interactions that generate the destabilizing steric effects of molecules [43].

The existence of weak type interactions (VdW) is indicated by the majority presence of green colour within three molecules 3-5, the absence of blue colour indicates that hydrogen bond type interactions no longer exist in all derivatives. The red areas observed indicate that the steric interactions are located in the middle of the benzene rings and the piperidine ring in derivative 5, close to the nitrogen atoms

and the germ located at the level of the carbonyl groups, Fig. 3.

According to the results, the NCI analysis shows that the Van der Waals interactions are predominant and participate in the stability of the molecular structures for derivatives 3-5.

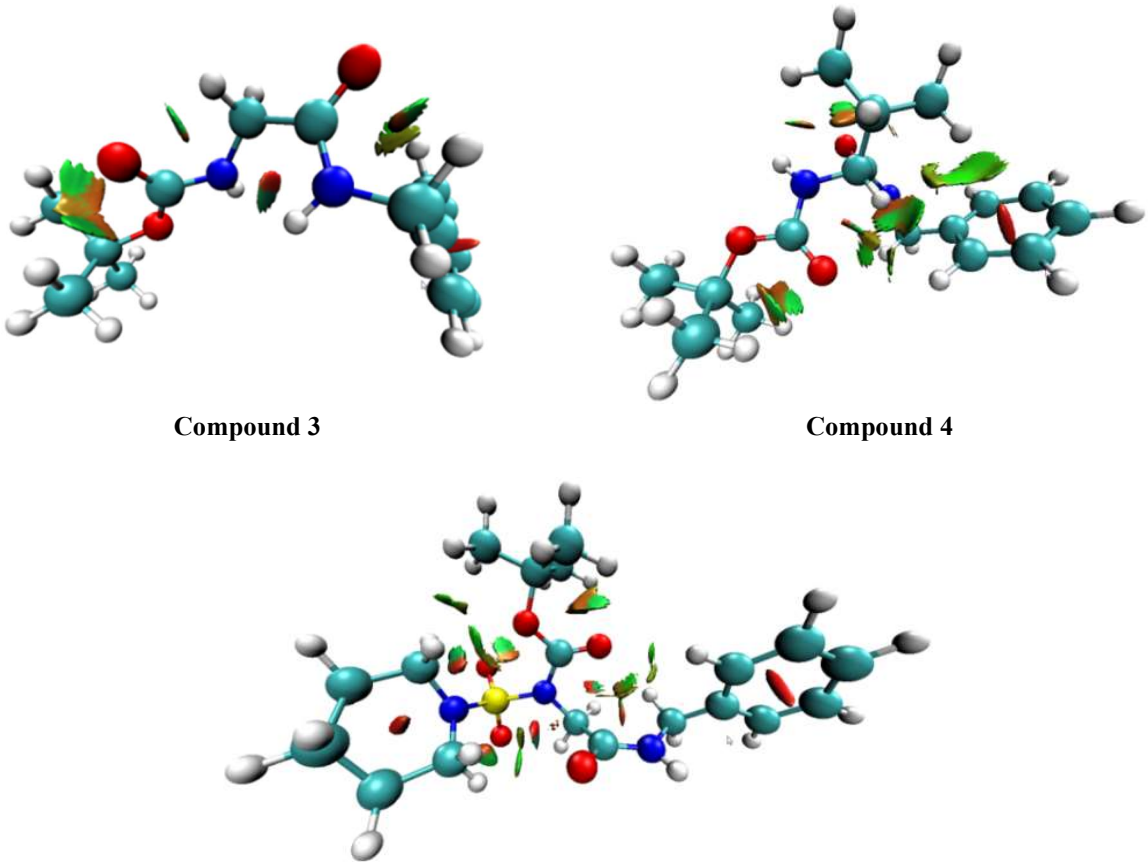
^{1}H NMR Analysis

Based on this analysis optimized by the density functional theory B3LYP/6-311+G(2d,p), a calculation of the chemical shifts (δ) of the protons (^{1}H NMR) and the chemical shift values which are obtained from the independent atomic orbital method, GIAO concerning TMS [44] used as a reference. A study carried out by the analysis of the GIAO theory for the 3-5 derivatives, reveals that there is a resemblance between the calculated chemical shift values and the experimental values, which confirms the results obtained by spectroscopic analysis of the three derivatives, Table 3.

The observable changes between the estimated theoretical chemical shifts and the experimental data (Δδ) are of relatively modest magnitude of the three derivatives 3-5, the largest changes in chemical shifts have generally been observed for the proton N-H13 and a low value for the signal of derivative 3 of N-H14.On the other hand, a large value of Δδ was observed in derivative 5 for the signal of N-H31.

A difference in the theoretical values for the benzylic protons C-H15 and C-H16 of derivative 3 is very large, the H16 proton being strongly shielded compared to the H15 proton, which is influenced by an adjacent nitrogen atom.

The different values of the chemical shifts of the aromatic protons are very low for the three derivatives 3-5, as well as for the nine protons of the Boc group and six protons of the two isopropyl methyl which present a rapprochement between the calculated values and that of the experimental. The experimental shift of the signal for the proton carried by the nitrogen N-H31 of derivative 4 was not observed, this



Compound 3 **Compound 4**

Compound 5

Fig. 3. Visualization of different types of bonds by RDG as a function of multiple electron density for derivatives 3-5.

Table 3. Theoretical and Experimental Chemical Shifts (ppm) of ^{1}H NMR of Derivatives 3-5, Optimized and Calculated by B3LYP/6-311+G(2d,p), and GIAO Method

Compound 3			Compound 4			Compound 5		
Protons	(δ) cal (ppm)	(δ) exp (ppm)	Protons	(δ) cal (ppm)	(δ) exp (ppm)	Protons	(δ) cal (ppm)	(δ) exp (ppm)
H_{39}	7.81	7.30	H_{39}	7.94	7.30	H_{44}	7.93	7.45
H_{38}	7.32	7.30	H_{36}	7.41	7.30	H_{45}	7.43	7.45
H_{39}	7.23	7.30	H_{35}	7. 40	7.30	H_{46}	7.31	7.45
H_{37}	7.21	7.20	H_{38}	7.40	7.20	H_{47}	7.27	7.25
H_{33}	7.06	7.20	H_{37}	7.30	7.20	H_{48}	7.18	7.25
H_{14}	6.04	6.4	H_{34}	4.95	4.25	H_{42}	5.19	4.50
H_{16}	5.48	4.4	H_{32}	4.88	5.55	H_{29}	4.21	4.55
H_{27}	4.39	3.75	H_{30}	4.48	4.55	H_{30}	4.07	4.55
H_{13}	3.29	5.1	H_{31}	4.36	/	H_{31}	3.56	5.85
H_{28}	3.03	3.75	H_{33}	3.74	4.55	H_{32}	3.90	3.55
H_{15}	3.01	4.4	H_{48}	2.69	1.45	H_{43}	3.74	4.50
H_{25}	2.65	1.35	H_{42}	2.66	1.45	H_{41}	3.67	3.55
H_{19}	2.59	1.35	H_{28}	1.29	1.15	H_{40}	2.96	3.55
H_{20}	0.97	1.35	H_{23}	1.18	2.48	H_{33}	2.96	3.55
H_{21}	0.97	1.35	H_{45}	1.07	1.45	H_{56}	2.65	1.50
H_{24}	0.77	1.35	H_{44}	1.07	1.45	H_{51}	2.37	1.50
H_{17}	0.74	1.35	H_{47}	0.87	1.45	H_{36}	1.53	1.60
H_{23}	0.71	1.35	H_{40}	0.86	1.45	H_{52}	1.43	1.50
H_{22}	0.70	1.35	H_{46}	0.75	1.45	H_{39}	1.36	1.60
H_{18}	0.68	1.35	H_{41}	0.73	1.45	H_{35}	1.33	1.60
			H_{43}	0.71	1.45	H_{34}	1.22	1.60
			H_{29}	0.69	1.15	H_{38}	1.21	1.60
			H_{27}	0.21	1.15	H_{53}	1.18	1.50
			H_{24}	0.02	0.95	H_{55}	1.08	1.50
			H_{26}	-0.22	0.95	H_{49}	1.03	1.50
			H_{25}	-1.16	0.95	H_{37}	0.99	1.60
						H_{57}	0.83	1.50
						H_{54}	0.75	1.50
						H_{50}	0.68	1.50

does not mean that it does not exist, but may not be visible in the temperature window used or by the cause of the phenomenon of the anisochrony of the hydrogen carried by the nitrogen.

The protons C-H26 and C-H25 of derivative 4 have negative theoretical values lower than the value of TMS, which means that they are more highly shielded (Fig. 4).

EXPERIMENTAL

General

All solvents were dried by standard methods and all

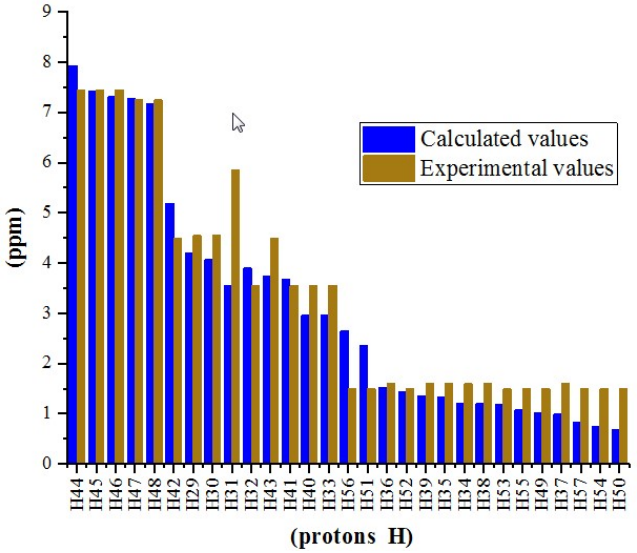


Fig. 4. Calculated and experimental chemical shifts in (ppm) of 1HNMR of the compound 5, optimized byB3LYP/6-311+G(2d,p), and GIAO method.

commercial reagents were used without purification. All reactions were realized under an inert atmosphere of nitrogen. The purification of the compound was performed by column chromatography using silica gel60 (35-70 µm) or Merck h60 (Art. 9385) and spots were visualized with UV light. All melting points were determined by open capillary tubes on an electrothermal apparatus (Barnstead/Electrothermal) and are uncorrected). High-Resolution Mass Spectra (HRMS) were obtained on JEOL JMS DX300-SX102 high-resolution magnetic sector mass spectrometer. ^{1}H NMR and ^{13}C were recorded with Bruker 400 MHz, respectively. The Mass spectra (MS) were recorded using the positive mode electrospray ionization method (ESI > 0) the data was reported in m/e (intensity to 100%). At a cone voltage of 30 V, with a Micronas model Platform instrument.

Synthesis of acetamide 3 and butanamide 4. DBU (2 eq, 0.6 ml, 4 mmol) was added to a stirred solution of sulfahydantoin 1 or 2 (1 eq, 2 mmol) and DL-2-phenyl propionaldehyde (67 mg, 0.5 ml) for sulfahydantoin 1 and benzaldehyde (2 ml, 20 mmol) for sulfahydantoin 2 in dichloromethane anhydrous (30 ml) under nitrogen.

The mixture is left for 5 h with stirring at room temperature, and then the solvent is evaporated off under reduced pressure. A residue 3 or 4 is taken up in ethyl acetate, and then the organic phase is washed with 2 × 20 ml HCl and then 20 ml H_2O. After evaporation and drying over $MgSO_4$, a white residue is obtained which is then purified by chromatography on silica gel, eluting with dichloromethane.

N-benzyl-2-(methylamino)acetamide 3. Transparent oil, yield 49%, *Rf* = 0.6 (DCM/AcOEt, v/v, 8:2), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.3-7.2 (m, 5H, H-Ar), 6.4 (s-large, 1H, NH-Boc), 5.1 (s-large, 1H, NH-CO), 4.4 (d, 2H, *J* = 5.8 Hz, CH_2Ph), 3.75 (d, 2H, CH_2, *J* = 5.75 Hz), 1.35 (s, 9H, $3CH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) (δ ppm):169.60, 156.50, 128.13, 129.00, 127.96, 127.85, 80.20, 43.70, 28.52. SMHR: **[**M+H**]**$^{+}$ = 265.

(S)-N-benzyl-3-methy-2-(methylamino)butanamide 4. White solid, yield 47%, *Rf* = 0.57 (DCM/AcOEt, v/v, 7:3), M.p. = 138-140 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.3- 7.2 (m, 5H, Ar), 5.55 (t, *J* = 7.54 Hz, 1H, NH,), 4.55 (d, *J* = 9.0 Hz, 1H, CH_{α},), 4.25 (m, 2H, CH_2-C_6H_5), 2.48 (m. 1H. $CH(CH_3)_2$), 1.45(s, 9H, $3CH_3$), 1.15 (d, *J* = 6.47 Hz, 3H, CH_3CH), 0.95 (d, *J* = 7.0 Hz, 3H, CH_3CH).^{13}C NMR ($CDCl_3$, 100 MHz)(δ ppm) : 174.78, 151.10, 135.79, 128.83, 128.18, 128.09, 85.33, 65.55, 47.86, 27.06, 22.13, 19.70. MS ESI^{+} 30 evm/z: **[** M+H**]**$^{+}$ = 329.

Synthesis of N-benzyl-N-sulfodioxyde pipéridinyl-2-(methylamino) acetamide 5. The solution of sulfahydantoin (1eq, 200 mg, 0.61 mmol) and piperidine (1.5eq, 78.35 mg, 0.92 mmol) in anhydrous dichloromethane 10 ml. The reaction mixture medium is placed under argon and with stirring at room temperature for 12 h; the solvent was evaporated under vacuum. The residue was purified by column chromatography on silica gel with dichloromethane and ethyl acetate as the eluent to afford **5** in 20% yield.White solid, *Rf* = 0.57 (DCM/AcOEt , v/v , 9:1), M.p. = 94-96 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45-7.25 (m, 5H, H-Ar),5.85 (d, *J* = 6.0 Hz, 1H, NH), 4.55 (s, 2H, $(CH_2)_{\alpha}$), 4.5 (d, *J* = 6.0 Hz, 2H, CH_2-Ph), 3.55 (t, 2H, CH_2, pipé), 3.35 (t, 2H, CH_2, pipé), 1.55-1.7 (m, 6H, $3CH_2$, pipé), 1.5 (s, 9H, $3CH_3$, Boc). ^{13}C NMR ($CDCl_3$, 100 MHz) (δ ppm): 165.84, 151.69, 137.01, 128.64, 128.09, 127.76, 84.25, 48.71, 48.69, 45.85, 43.50, 28.0224.36, 25.53, 26.27. SMHR: **[**M+H**]** $^{+}$ = 412.

CONCLUSIONS

To control the electrophilicity of *tert*-butyloxycarbonyl-

activated sulfhydantoins derived from the amino acid glycine and *L*-valine under nucleophilic conditions, regioselective opening is affected by the loss of sulfur dioxide, on the one hand, and the attack of piperidine on the other hand. This reaction leads to new derivatives 3-5 analogous to the peptide structures; each sulfahydantoin used in this type of reaction seems to have its own chemistry.

A theoretical study based on the PW6B95/6-311G(2d,p) method was carried out in the gaseous state using Gaussian16. Calculations of thermodynamic parameters performed at 1atm and 298.15k reveal the structural and thermodynamic behaviours in terms of stability of our molecular systems 3-5.

The calculations of the chemical shifts of the protons (^{1}H NMR) are carried out by the B3LYP/6-311+G(2d,p) method, these values are obtained by GIAO method. The similarity of the theoretical and experimental chemical shift magnitudes clearly confirms the chemical structures of our derivatives. Also, the determination of the stabilization energy E2 *via* NBO analysis, the MEP and NCI analysis methods associated with this study of the different amide groups (3-5) have been discussed above. Finally, we hope that these derivatives will be useful in research in various fields, especially in obtaining bioactive molecules of therapeutic interest.

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