Design and Synthesis of the Candesartan Key Intermediate

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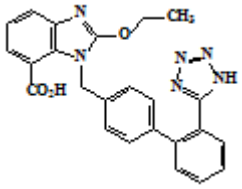
*This paper presents experimental data regarding the synthesis and structural characterization by: ^{1}H-NMR, ^{13}C-NMR, IR spectral analysis, melting point and thin layer chromatography of the candesartan key intermediate: methyl 2-[(tert-butoxycarbonyl)amino]-3-nitrobenzoate. In addition, a computational study of predicted molecular parameters, vibrational wavenumbers, frontier molecular orbitals energy diagram, molecular electrostatic potential map and other electronic distributions maps using restricted hybrid HF-DFT SCF calculation has been performed for obtaining the most stable conformer. For the most Stable conformer has been made a series of DFT calculations using the B3LYP levels using the 6-31G * basis set.*

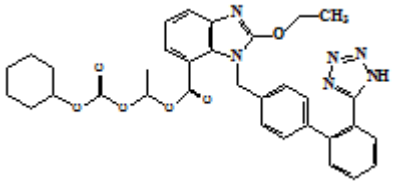
Keywords: sartans, candesartan, frontier molecular orbitals, electrostatic potential map

Cardiovascular disease or heart disease is a category of diseases involving the heart or blood vessels. From a technical point of view, the term cardiovascular disease refers to any disease that affects the cardiovascular system, commonly referred to as diseases related to atherosclerosis and/or hypertension. Cardiovascular disease remains the leading cause of death worldwide. Over the past two decades, the mortality rate caused by these diseases has evolved differently, while have been falling in many high-income countries, in low-income countries, deaths and cardiovascular disease have been rapidly growing. Every year, heart disease kills more people than cancer. In recent years, cardiovascular risk in women has been rising and killed more women than breast cancer. Emotional studies among young people showed that early atherosclerosis can occur in adolescence and primary prevention efforts have been made since childhood.

The development of angiotensin receptor blockers (*ARBs*) is a major advance for the treatment of hypertension and potentially for other cardiovascular disorders[1]. One of the angiotensin receptor blockers is the candesartan. Candesartan is administered as candesartan cilexetil, which has better bioavailability than candesartan. The prodrug is rapidly and completely hydrolyzed to candesartan during absorption by the gastrointestinal tract[2,3]. Candesartan cilexetil is indicated for the treatment of hypertension and also for the management of chronic heart failure[4].



1. Candesartan



2. Candesartan Cilexetil

One of the ways of the synthesis of Candesartan cilexetil is described in scheme 1. [5-8]. The synthesis pathway consists in the condensation of the alkyl 2-tert-butoxycarbonylamino-3-nitrobenzoate compound (1) (R = methyl or ethyl) with the 4-(2-cyanobiphenyl)-benzyl bromide (2). After the acid hydrolysis of the compound (3) and the reduction of the derivative (4), compound (5) (alkyl 3-amino-2 - [[(2'-cyanobiphenyl-4- yl) methyl] amino] benzoate) have been generated. By the cyclocondensation of the compound (5) with tetraethyl orthocarbonate and acetic acid or with triethyl orthoformate have been obtained alkyl ester of 1-[(2'-cyanobiphenyl)-4-yl-methyl]-2-ethoxybenzimidazole-7-carboxilyc acid (6). Compound (6) is further treated with trimethyl tin azide in toluene at the reflux generating compound (7) which after hydrolysis in the basic medium leads to the formation of candesartan (2-ethoxy-1-[[2'tetrazol-5-yl)biphenyl-4-yl]methyl] benzimidazole-7-carboxylic acid). The (8) Compound (2-ethoxy-1-[[2'-(N-triphenylmethyltetrazol-5-yl)biphenyl]-4-yl]methyl]benzimidazole-7-carboxylic acid) has been prepared by the reaction of (7) compound with the trityl and the triethyl amine in the appropriate solvent. After the esterification of the (9) compound with 1-haloethyl cyclohexyl carbonate has been obtained candesartan cilexetil trityl (9), compound which, following the hydrolysis reaction (in the acidic condition), leads to the formation of candesartan cilexetil.

Experimental part

Melting points have been determined in opened capillary on Melting point apparatus OptiMelt and are uncorrected. Elemental analysis have been performed on a Perkin Elmer CHNS/O Analyzer 2400 Series II. UV-Vis have been recorded on an instrument UV-Vis LAMBDA 12. FT IR have been recorded on an instrument Bruker Vertex 70 with diamond optic. ^{1}H- and ^{13}C-NMR spectra have been recorded in DMSO-d_6, on two instruments Varian, Varian Gemini 300 BB (operating at 300 MHz for proton and 75 MHz for carbon) and UNITY 400 Plus(operating at 400 MHz for proton and 100 MHz for carbon). Tetramerthylsilane as internal standard have been the reference for the chemical shifts. All chemical shifts are given in the delta scale (ppm *vs* internal TMS).

Synthesis of 3- nitrophthalic acid

A mixture of phthalic anhydride (148g, 1 mol), nitric acid (247 mL), sulfuric acid (202 mL) was stirred at 75^{0}C, then slowly at 80^{0}C and then 2 h at 100^{0}C. At the end of the reaction, the mixture was cooled and was poured over 500 g ice and 100 mL of water. The precipitate formed (a mixture of 3- nitrophthalic acid and 4- nitrophthalic acid) was filtered off, washed with cold water, and after drying, was recrystallized from water to yield 3-nitrophtalic acid.

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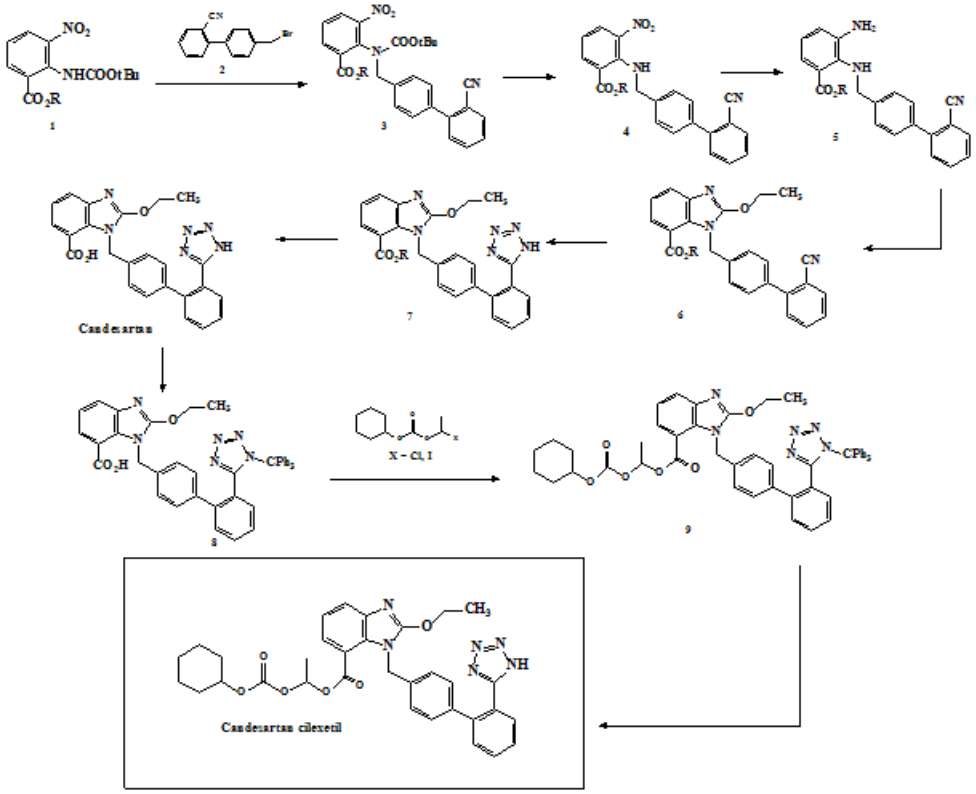


Scheme 1. Preparation of candesartan cilexetil

(mp 217-218^{0}C; yield 41%). ^{1}H-NMR (dmso-d6, δppm, *J* Hz): 8.29(dd, 1H, H-4, 0.8, 8.0); 8.21(dd, 1H, H-6, 0.8, 8.0); 7.78(t, 1H, H-5, 8.0). ^{13}C-NMR (dmso-d6, δ ppm): 166.08(C-8); 165.86(C-7); 146.51(C-3); 135.07(C-5); 131.33(C-6); 130.78(C-1); 130.63(C-4); 127.68(C-2). Elemental Analyses: Calculated for: $C_8H_5NO_6$: C: 45.51%; H: 2.39%; N: 6.63%. Found: C: 45.46%; H: 1.67%; N: 6.65%.

Synthesis of methyl 2-carboxy-3-nitro-benzoate

17.21 mL Trimethyl ortoformiate (16.98 g; 0.16 mol) and 2.2 mL sulfuric acid 98 % was added to a solution of 3-nitrophtalic acid (25 g; 0.118 mol) in 60 mL methanol, and the mixture was stirred at reflux temperature for 24 h, and then was evaporated to dryness. The crude compound was recrystallized from water to yield methyl 2-carboxy-3-nitro-benzoate (mp 162.5-165°C; yield 87%). ^{1}H-NMR (dmso-d6, δ ppm, *J* Hz): 8.33(dd, 1H, H-5, 1.4, 8.0); 8.21(dd, 1H, H-3, 1.4, 8.0); 7.82(t, 1H, H-4, 8.0), 3.86(s, 3H, H-9, CH_3). ^{13}C-NMR (dmso-d6, δ ppm): 165.75 (C-7); 164.78(C-8); 146.54(C-6); 134.88(C-4); 130.87(C-3); 130.61(C-2); 129.94(C-5); 128.05(C-1); 53.07(C-9).). Elemental Analyses: Calculated for: $C_9H_7NO_6$: C: 48.0%; H: 3.14%; N: 6.22%. Found: C: 47.78%; H: 2.77%; N: 6.48%.

Synthesis of methyl-2- (chlorocarbonyl) -3-nitrobenzoate

2.7 mL SO_2Cl_2 was added to a solution of methyl 2-carboxy-3-nitro-benzoate (4.5 g; 0.02 mol), N,N-dimethylformamide (1 mL), in chloroform (25 mL), and the mixture was stirred at the room temperature 30 min. and then 4 hours at the refux temperature. The mixture was washed with water and sodium carbonate 20%. The organic layer was dried over Na_2SO_4, and will be used in the next step of the synthesis without isolation of the compound from the reaction mixture.

Synthesis of methyl 2- (azidocarbonyl) -3-nitrobenzoate

The chloroformic solution containing methyl 2-(chlorocarbonyl) -3-nitrobenzoate was added to a mixture of sodium azide (1.82 g; 0.028mL) in N, N-dimethyl-formamide (10 mL), and the mixture was stirred at the 5^0 C for 1 h. The mixture was washed with 40 mL water. The organic layer was dried over Na_2SO_4, and will be used in the next step of the synthesis without isolation of the compound from the reaction mixture.

Synthesis of methyl 2- (tert-butoxycarbonylamino)-3-nitrobenzoate

9 mL (0.095 mol) *tert*-butanol was added to a solution of methyl 2- (azidocarbonyl)-3-nitrobenzoate in chloroform and the mixture was stirred at 30^{0}C 15 min., and then at 95^0 C, 30 min. At the end of the reaction, the mixture was cooled and was diluted with water to precipitate the product. The precipitate formed was filtered off, washed with water, and after drying, was recrystallized from methanol to yield methyl 2- (tert-butoxycarbonylamino)-3-nitrobenzoate. (m.p. 104-105.5°C; yield 58 %). ^{1}H-NMR(dmso-d6, δ ppm, *J* Hz): 9.53(bs, 1H, NH, deuterable); 8.11(dd, 1H, H-4, 1.6, 8.3); 8.05(dd, 1H, H-6, 1.6, 8.3); 7.46(t, 1H, H-5, 8.3); 3.84(s, 3H, H-8); 1.42(s, 9H, H-11); ^{13}C-NMR(dmso-d6, δ ppm): 165.71(C-7); 152.70(C-9); 144.65(C-3); 134.47(C-4); 131.00(C-2); 128.52(CH-6); 126.67(Cq-1); 125.00(CH-5);80.62(C-10); 52.70(C-8); 27.85(C-11).FT-IR(ATR in solid, ν cm^{-1}): 3284m; 3089w; 3014w; 2987w; 1728m; 1697vs; 1606w; 1580w; 1534s; 1491m; 1443w; 1394s; 1359m; 1310sh; 1271s; 1210m; 1153s; 1132m; 1044w; 1012m; 981w; 911w; 839w; 770m; 747m; 713m. Elemental Analyses: Calculated for: $C_{13}H_{16}N_2O$: C: 52.7% ; H: 5.45%; N:9.45%. Found: C: 52.65%; H: 5.22%; N:9.52%.

Molecular mechanics calculations

The molecular modeling study of predicted molecular parameters, vibrational wavenumbers, frontier molecular orbitals energy diagram, molecular electrostatic potential map and other electronic distributions maps using restricted hybrid HF-DFT SCF calculation have been performed for obtaining the most stable conformer. For the most stable conformer have been made a series of DFT calculations using the B3LYP levels using the 6-31G * basis set [9]. The most important topological,

conformational characteristics and QSAR properties has been calculated: weight, no. of conformers and tautomers, area, volume, ovality, polarizability, log P, energy of solvation, dipole moment, energy of the HOMO and LUMO orbitals, angles and distances, dihedral angles. NMR, UV and IR spectra of the methyl 2-[(*tert*-butoxycarbonyl)amino]-3-nitrobenzoate compound have been calculated with Spartan 14 software.

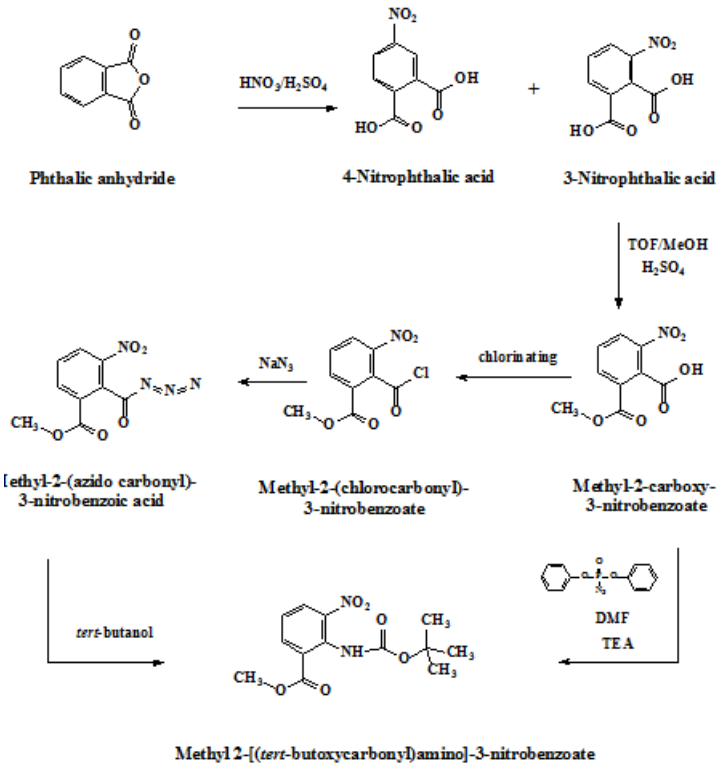
Results and discussions

The key intermediate 2-(N-tert-butoxycarbonylamino) -3-nitrobenzoate was obtained according to scheme 1.The synthesis starts from phthalic anhydride, by nitration reaction. Recrystallization from hot water afforded 3-nitrophthalic, which further by esterification with trimethyl orthoformate (TOF) in the presence of concentrated sulfuric acid in methanol, leads to obtaining the methyl 2-carboxy-3-nitrobenzoate. The methyl ester is subjected to chlorination reaction with thionyl chloride in the presence of N, N-dimethylfomamide. Methyl 2- (chlorocarbonyl)-3-nitrobenzoate is further treated with sodium azide, and the corresponding azide, methyl-2-(azidocarbonyl)-3-nitrobenzoate, by heating under reflux in tert-butanol leads to the formation of the key intermediate, methyl 2-(N-tert-butoxycarbonylamino)-3-nitrobenzoate.

Molecular mechanics calculations

The molecular modeling study of predicted molecular parameters have been performed for obtaining the most stable conformer [7]. In this paper, the DFT/B3LYP/6-31 G* level of basis set has been used for the computation of molecular structure, vibrational frequencies and energies of optimized structures (fig. 1). In order to perform structure–activity relationship (SAR) studies, some electronic properties (table 1), such as HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) energy values, HOMO and LUMO orbital coefficients distribution, molecular dipole moment, polar surface area (PSA), the ovality, polarizability, the octanol water partition coefficient (logP), the number of hydrogen-bond donors (HBDs) and ad acceptors (HBAs) and acceptor sites (HBAs) and positive and negative ionizable sites derive from CFD assignments. HBA/HBD and +/- Centers, Hydrophobe Centers including aromatic centers, can be viewed in figure 2. The polarizability is useful to predict the interactions between non-polar atoms or groups and other electrically charged species, such as ions and polar molecules having a strong dipole moment.

Molecular polar surface area (PSA), is a descriptor that has been shown to correlate well with passive molecular transport through membranes and therefore allows the prediction of transport properties of the drugs. LogP is



Scheme 2. Preparation of methyl 2- (tert-butoxycarbonylamino)-3-nitrobenzoate

Table 1

MOLECULAR PROPERTIES FOR CPK MODEL COMPUTATIONS FOR STUDIED COMPOUND USING SPARTAN'14 V1.1.4 SOFTWARE

Compound	Molecular properties									
	Dipole moment [Debye]	E HOMO [eV]	E LUMO [eV]	HOMO-LUMO GAP	Polarizability [10^{-30} m^3]	PSA[A^2]	Ovality	Log P	HBA count	HBD count
Methyl 2-[(*tert*-butoxycarbonyl) amino]-3-nitrobenzoate	3.20	-6.69	-2.64	4.05	63.29	81.063	1.48	0.51	6	1

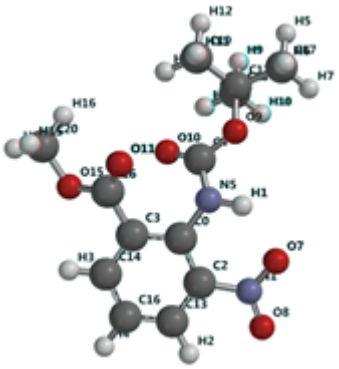


Fig. 1. The theoretical optimized geometric structure with atoms numbering according to the software

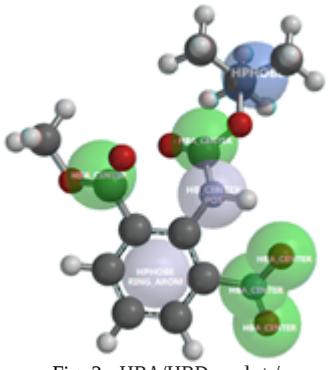


Fig. 2. HBA/HBD and +/- Centers, Hydrophobe Centers

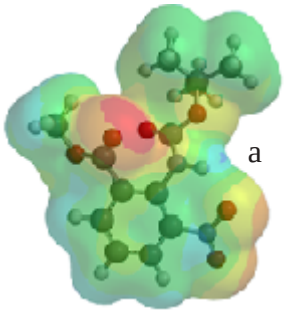


Fig. 3a. The optimized geometry and electrostatic potential patern of the surface (red- negative, high electron density, blue-positive area, low electron density)

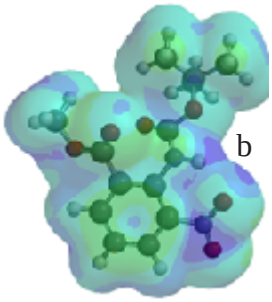


Fig. 3b. The optimized geometry and local ionization potential map

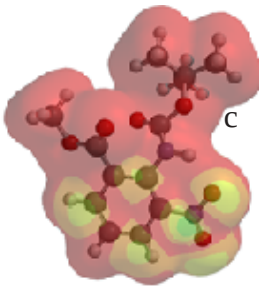


Fig. 3c. The optimized geometry and LUMO map

estimated according to the method of Ghose, Pritchett and Crippen [8]. A few important graphical quantities resulted from quantum chemical calculations were displayed, manipulated and interrogated. Another indicator of electrophilic addition local map is provided by the ionization potential, overlapping energy to remove electrons (ionization) the electron density. In addition, the *electrostatic potential map* (fig. 3a), an overlay of the electrostatic potential (the attraction or repulsion of a positive charge for a molecule) on the electron density, is valuable for describing the overall distribution of molecular charge, as well as to predict the sites of electrophilic addition. Another indicator of the electrophilic addition is supplied by the *local ionization potential map* (fig. 3b), an overlapping of the energy of electron removal (ionization) on the electron density. In the end, an indicator of nucleophilic addition is offered by the */LUMO/ map* (fig. 3c), an overlap of the absolute value of the lowest-unoccupied molecular (LUMO).

Atomic net charges

Three different atomic charges, Electrostatic, Mulliken and Natural, have been calculated (table 2) using DFT/ B3LYP/6-31G (d, p) level and have been given in units of

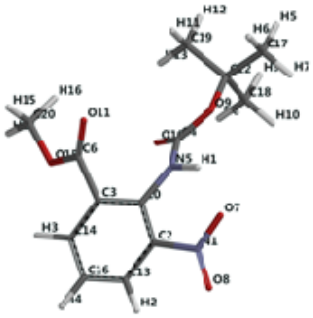


Table 2
ELECTROSTATIC, MULLIKEN AND NATURAL ATOMIC CHARGES

Atom	Atomic Charges			Atom	Atomic Charges		
	Electrostatic	Mulliken	Natural		Electrostatic	Mulliken	Natural
C0	+0.458	+0.331	+0.224	C19	-0.746	-0.467	-0.702
N1	+0.763	+0.369	+0.514	C20	-0.348	-0.219	-0.322
C2	-0.232	+0.243	+0.032	H1	+0.426	−0.386	+0.462
C3	-0.296	+0.058	-0.152	H2	+0.143	−0.189	+0.274
C4	+0.872	+0.824	+0.966	H3	+0.117	−0.169	+0.260
N5	-0.746	-0.749	-0.648	H4	+0.142	−0.152	+0.251
C6	+0.732	+0.593	+0.826	H5	+0.191	−0.148	+0.237
O7	-0.447	-0.425	-0.415	H6	+0.199	−0.159	+0.243
O8	-0.398	-0.384	-0.372	H7	+0.199	−0.157	+0.241
O9	-0.524	-0.516	-0.574	H8	+0.205	−0.187	+0.258
O10	-0.526	-0.511	-0.642	H9	+0.200	−0.146	+0.237
O11	0.489	0.486	0.589	H10	+0.195	−0.151	+0.237
C12	+1.001 *	+0.310	+0.284	H11	+0.184	−0.160	+0.242
C13	-0.056	-0.152	-0.190	H12	+0.172	−0.143	+0.236
C14	+0.000	-0.152	-0.161	H13	+0.195	−0.184	+0.257
O15	-0.288	-0.455	-0.543	H14	+0.177	−0.165	+0.223
C16	-0.181	-0.140	-0.250	H15	+0.158	−0.170	+0.219
C17	-0.792	-0.452	-0.685	H16	+0.169	−0.180	+0.225
C18	-0.828	-0.468	-0.702				

*Structure contains interior atoms. Charges flagged with * may be meaningless*

Wavelength (nm)	Oscillator strength	MO Component	Contribution
263.68	0.0504	HOMO -> LUMO+1	57%
		HOMO-1 -> LUMO+1	14%
		HOMO-3 -> LUMO	12%
		HOMO-5 -> LUMO	11%
290.10	0.0230	HOMO-2 -> LUMO	58%
		HOMO-1 -> LUMO	22%
326.39	0.0027	HOMO-5 -> LUMO	46%
		HOMO-3 -> LUMO	33%
		HOMO-1 -> LUMO	11%
350.99	0.1022	HOMO -> LUMO	91%

Table 3
UV/Vis ALLOWED TRANSITIONS

electrons. A positive charge indicates a deficiency of electrons on an atom and a negative charge, an excess of electrons [10]. More charge density has been found at C4 (carbon atom) than the other carbon atoms. The high positive charge (+0.824e) are due to the O10 (oxygen atom) attached with C4. The high negative charge charge (-0.749e) has been found nitrogen atom N5.

UV spectral analysis

The methyl 2-(tert-butoxycarbonylamino)-3-nitrobenzoate allows strong π-π^* or σ- σ^* transition in the UV-Vis region with the high extinction coefficients (table 3).

The calculation of the molecular orbital geometry (calculated with Spartan software) shows that, the visible absorption maxima correspond from HOMO to LUMO (91 %). In the electronic absorption spectrum of the studied compound, there are four absorption Banda with a maximum 351, 326, 290 and 264 nm.

The UV-Vis experimental spectrum of the compound methyl 2- (tert-butoxycarbonylamino)-3-nitrobenzoate is shown in the figure 4.

Table 4
CHARACTERISTIC ABSORPTION BAND OF THE METHYL 2- (*TERT*-BUTOXYCARBONYLAMINO)-3-NITROBENZOATE IN METHANOL

Characteristic bands [nm]	Absorbance
206.98	0.803290
209.00	0792300
238.85	0.522530
304.86	0.069224
309.77	0.067271
321.03	0.069473
327.19	0.069937
329.95	0.067773

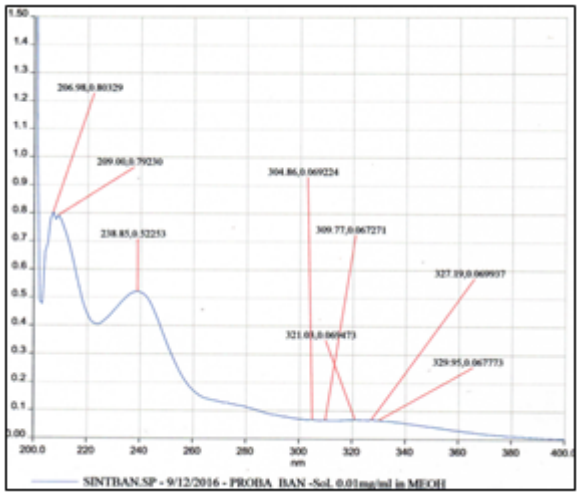


Fig. 4. UV-Vis experimental spectrum of methyl 2- (tert-butoxycarbonylamino)-3-nitrobenzoate

Frontier molecular orbital analysis

The molecular orbital analysis of the Frontier molecular orbital's (FMOs) play an essential role in the chemical stability of a molecule and in the interactions between atoms. They provide information that can be used to predict the characteristics of molecules such as optical properties and biological activities. Between them the most important are the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) (fig. 5) The HOMO represents the ability of a molecule to donate an electron, while the LUMO represents the ability to accept an electron [8,9,11,12].

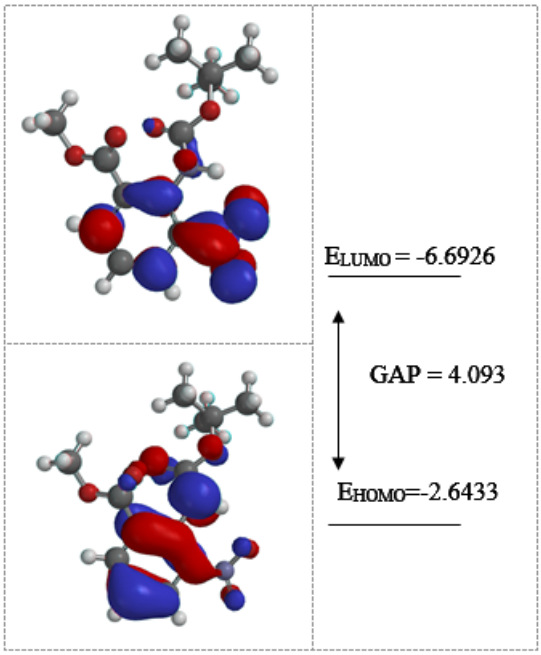


Fig. 5. HOMO, LUMO surfaces of methyl 2- (tert-butoxycarbonylamino)-3-nitrobenzoate

NMR spectral analysis

NMR spectra of the methyl 2- (tert-butoxycarbonyl-amino)-3-nitrobenzoate has been calculated with DFT/B3LYP/6-31G (d, p) level. After analyzing the experimental and calculated spectra (H-NMR, C-NMR) the correlation between experimental and calculated data has been observed.

*Experimental spectrum : ^{1}H-NMR(dmso-d6, δ ppm, **J Hz):*** 9.53(bs, 1H, NH, deuterable); 8.11(dd, 1H, H-4, 1.6, 8.3); 8.05(dd, 1H, H-6, 1.6, 8.3); 7.46(t, 1H, H-5, 8.3); 3.84(s, 3H, H-8); 1.42(s, 9H, H-11). (atoms numbering according to the fig. 6)

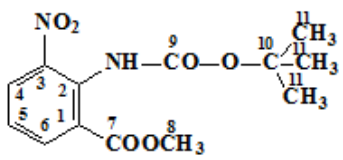


Fig. 6. 2D Structure of the methyl 2- (*tert*-butoxycarbonylamino)-3-nitrobenzoate

Experimental spectrum: *^{13}C-NMR(dmso-d6, δ ppm):* 165.71(C-7); 152.70(C-9); 144.65(C-3); 134.47(C-4); 131.00(C-2); 128.52(CH-6); 126.67(Cq-1); 125.00(CH-5);80.62(C-10); 52.70(C-8); 27.85(C-11). (atoms numbering according to the fig. 6)

Calculated spectrum:^{1}H-NMR corrected: 8.17 (H2); 7.69 (H3); 6.89 (H4); 3.78 (H14; H15; H16); 1.51 (H8, H 9, H10; H5, H6, H7; H11, H12, H13) (atoms numbering according to the software, fig. 1)

Experimental spectrum: ^{13}C-NMR corrected: 169.1 (C6); 155.8 (C4); 141.02 (C2); 137.37 (C14); 137.3 (C0); 130.80(C3); 129.22 (C13); 120.15 (C16); 81.2 (C12); 53.1 (C20); 27.0 (C17; C18; C19) (atoms numbering according to the software-fig. 1)

Conclusions

In the present study, we have reported the synthesis of the methyl 2-(tert-butoxycarbonylamino)-3-nitrobenzoate, an intermediate used in the synthesis of an angiotensin receptor blockers (ARBs), candesartan cilexetil [13]. Its structure has been determined and confirmed by the following methods: elemental analysis, IR spectral analysis, H-NMR, C-NMR, thin layer chromatography. The molecular modeling study of predicted molecular parameters, vibrational wavenumbers, frontier molecular orbitals energy diagram, molecular electrostatic potential map and other electronic distributions maps using restricted hybrid HF-DFT SCF calculation have been performed for obtaining the most stable conformer. For the most stable conformer have been made a series of DFT calculations using the B3LYP levels using the 6-31G * basis set. The most important topological, conformational characteristics and QSAR properties has been calculated: weight, no. of conformers and tautomers, area, volume, ovality, polarizability, log P, energy of solvation, dipole moment, energy of the HOMO and LUMO orbitals. NMR, UV and IR spectra of the methyl 2-[(*tert*-butoxycarbonyl) amino]-3-nitrobenzoate compound have been calculated with Spartan 14 software.

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