

Experimental and Theoretical Studies of 2-(naphthalen-1-yl(piperidin-1-yl)methyl)phenol Compound

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Summary: The 2-(naphthalen-1-yl(piperidin-1-yl)methyl)phenol compound is an alkylaminophenol compound and has been experimentally synthesized by the Petasis reaction. In this study Structural analysis was carried out by FT-IR, NMR, UV-Vis spectroscopy. The high antioxidant value of the compound showed that it could be a potential biologically active drug. Theoretical data support all experimental analysis of the new compound. Comparisons were made by double method. For this purpose, DFT (B3LYP) and HF methods have been used with 6-311G++(d,p) set. Also, the compound's electronic and structural properties (bond lengths, bond angles and dihedral angles), the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) energies, electrostatic potential (MEP), vibrational frequencies, Mulliken atomic charges, excitation energies, and oscillator strengths were calculated. As a result; the theoretical and experimental values were found to be compatible.

Keywords: Alkylaminophenol, B3LYP, HOMO-LUMO.

Introduction

Alkylaminophenol compounds are frequently used in chemotherapy due to its anticancer and antioxidant activities[1–3]. The variety of cancer types needs the presence of new drugs to be used in treatment. Alkylaminophenols, often used for the treatment of bone cancer, are synthesized by the Petasis reaction (Boronic Mannich Reaction) [4–6]. Nicos Petasis first used the Petasis reaction in 1993 as a practical method for the synthesis of naftifine, an antifungal agent[7,8]. The reaction takes place by the removal of boric acid from the boronate complex formed by the boronic acid added to the medium after the amine and carbonyl compounds form iminium ion[9,10]. Although there are many studies on the synthesis of alkylaminophenols in the literature[6,9–17], studies on quantum chemical calculations of these compounds are limited[18]. Therefore, the study; It was carried out in two separate sections. In the first part, a new alkylaminophenol was synthesized. In the second part; Quantum chemical calculations of the compound were carried out in DFT (B3LYP) and HF method in 6-311++G(d,p) set. TD-SCF method was used in the UV-Vis calculations.

Experimental

Materials and Measurement

The chemicals used for synthesis were used immediately without any extra purification. UV-1700 PharmaSpect UV/vis spectrophotometer; PerkinElmer 100 FT-IR spectrometry and Agilent

600MHz NMR spectrometers were applied to the analysis

Synthesis

The synthesis was carried out according to the methods in the literature[19].

2-(naphthalen-1-yl(piperidin-1-yl)methyl)phenol

Yield 0.238 g (75%), Orange solid, mp 123–124 °C. ¹H NMR (600 MHz, CDCl₃): δ(ppm) = 1.46–1.63 (m, 7H, piperidine); 2.48 (s, 3H, piperidine); 5.60 (s, 1H, methine); 6.66 (t, *J* = 7.2, 1H, Ar); 6.92 (t, *J* = 7.2, 2H, Ar); 7.14 (t, *J* = 7.2, 1H, Ar); 7.45 (t, *J* = 7.8, 1H, Ar); 7.52 (t, *J* = 7.2, 1H, Ar); 7.60 (s, 1H, Ar); 7.79 (d, *J* = 7.8, 2H, Ar); 7.89 (d, *J* = 7.8, 1H, Ar); 8.38 (d, *J* = 8.4, 1H, Ar); 12.84 (s, 1H, Ar-OH). ¹³C NMR (CDCl₃, 150 MHz): δ, ppm: 24.1 (piperidine); 26.2 (piperidine); 68.3 (piperidine); 117.1 (Aliphatic C); 119.0 (1-benzene); 125.5 (1-benzene); 125.9 (1-benzene); 126.2 (1-benzene); 128.2 (1-naphthalene); 129.0 (1-naphthalene) 129.2 (1-naphthalene); 132.2 (1-naphthalene); 133.9 (1-naphthalene); 135.8 (1-naphthalene); 157.6 (1-benzene). FT-IR: ν(cm⁻¹): 3752 (Ar-OH), 3200 (Ar-H in-plane), 2958, 2939, 2851 and 2809 (C-H, aliphatic), 1607, 1600, 1586 (C=C, aromatic), 1474, 1455, 1403 (C-H, aliphatic), 1356 (O-H, bending), 1250 (C-O, aromatic), 975, 873, 787 (C-H, aliphatic, out of plane bending).

Antioxidant Activity

The test process of the antioxidant activity was performed via 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging activity with small modifications in 96-well microplate [20]. DPPH was dissolved in methanol at 0.004% concentration. Test compounds were dissolved in Dimethyl Sulfoxide (DMSO). Concentrations were 1.25, 2.5, 5, and 10 mg/ml, respectively. Each well contained a solution of 200 μ l DPPH-methanol. 10 μ l of serial concentration of each test compound and controls were added separately into each well. Ascorbic acid (11.8 mM), Butylated hydroxytoluene (60 mM) and DMSO were also used as controls. Then, for 30 minutes, the microplates were incubated in the dark at room temperature. After incubation, the absorbance of test compounds' antioxidant activity was measured at 517 nm by the microplate reader. All tests were made in triplicate. The determination of the DPPH-free radical scavenging activity was performed by using the following equation:

$$\text{Inhibition of DPPH \%} = \frac{(\text{AbsControl} - \text{AbsSample})}{\text{AbsControl}} \times 100$$

where AbsControl refers to the absorbance of the DPPH-methanol solution and AbsSample refers to the absorbance of test compounds/controls blended with DPPH-methanol solution, separately.

Table-1: DPPH free radical scavenging activity.

Samples	DPPH%	Samples	DPPH%
Control	0	1,25	17.05 \pm 0.03
Ascorbic acid	70.68 \pm 0.03	2,5	19.35 \pm 0.03
BHT	68.64 \pm 0.01	5	34.26 \pm 0.03
DMSO	5.56 \pm 0.03	10	40.70 \pm 0.02

Antioxidants neutralise radicals in diseases such as cancer, which form free radicals in the body. Antioxidant capacity of the alkylaminophenol compound was seen increased by concentration (Table-1). This study is consist of two-part.

In the first part of the study, a synthesis and structural analysis of the compound was completed experimentally. In the second part of the study, experimental results were compared to theoretical data.

Computational method

All calculations of the new compound were carried out with the Gaussian 09W package program,

which has many methods and basic set options. In the visualisation of the molecule, GaussView 5.0.9 package program was used. All calculations include the B3LYP function at the DFT level and Hartree Fock method. 6-311++G (d, p) set is used in calculations[21–25]. Geometric, electronic and spectroscopic parameters of the molecule were calculated. Regression analyses were performed with using ^{13}C -NMR and ^1H -NMR chemical shift values. IR harmonic vibration frequency values were determined and scaled values were reached by multiplying the scale factors. Theoretical IR spectra were created using vibration frequency values and compared with experimental spectra. The geometric properties of the molecule (bond length, angle), electronegativity (χ), total energy, atomic charges, dipole moment (μ), chemical hardness (η) and softness (S), ionisation potential (I), energy difference (ΔE) properties were calculated. In addition, surface shapes such as molecular electron potential (MEP), surface maps (electron potential and electron density potential), total density have been determined. UV-vis calculations for the compound were performed using theory TD-DFT.

Results and Discussion

Molecular geometry

B3LYP, HF theories are calculated at 6-311++ G (d, p) basis set. The optimised Fig is shown in Fig 1. The bond length, bond angles and dihedral angles of the compound are compared in Table-2.

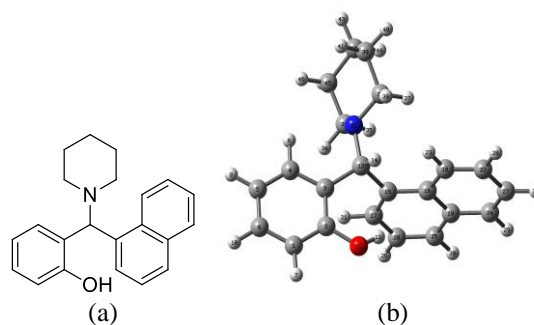


Fig. 1: (a) Molecular structure of alkylaminophenol compound.
(b) Optimized molecular structure of 2-(naphthalen-1-yl(piperidin-1-yl)methyl)phenol by DFT/B3LYP/6-311++G(d,p)

Table-2: Selected geometric parameters of 2-(naphthalen-1-yl(piperidin-1-yl)methyl)phenol.

Bond length (Å ^o)	Experimental Bond length	B3LYP	HF	Bond angles(°)	Experimental Bond Angles	B3LYP	HF
C13-C3	1.54	1.537	1.535	N32-C13-C3		112.0	111.9
C13-H14	1.10	1.093	1.080	N32-C13-C15		113.5	114.3
C3-C2	1.37	1.409	1.397	C3-C13-H14	109.5	104.7	104.1
C3-C4		1.398	1.388	C15-C13-H14		107.7	107.3
C4-C5		1.393	1.386	C3-C4-C5		122.0	121.8
C5-C6		1.393	1.383	C4-C5-C6		119.6	119.6
C6-C1		1.390	1.382	C6-C1-C2		120.4	120.2
C4-H8		1.082	1.071	C1-C2-C3		120.9	121.0
C5-H9		1.084	1.075	C2-O11-H12	104.5	110.1	111.4
C6-H10		1.084	1.075	C15-C16-C19		118.9	119.0
C1-H7		1.084	1.075	C16-C19-C25		119.7	119.9
C2-O11	1.43	1.372	1.358	C25-C20-C17		120.5	120.0
O11-H12	0.96	0.966	0.942	C17-C15-C16		118.6	118.3
C13-C15		1.545	1.544	C19-C16-C18		117.3	117.2
C15-C16		1.440	1.439	C16-C19-C24		119.6	119.8
C16-C19		1.438	1.414	C19-C24-C27		121.2	121.1
C16-C18		1.424	1.424	C24-C27-C22		119.6	119.5
C19-C24		1.420	1.420	C27-C22-C18		120.6	120.6
C24-C27		1.372	1.356	C22-C18-C16		121.6	121.5
C27-C22		1.412	1.413	N32-C36-C39		110.9	110.8
C22-C18		1.375	1.412	C36-C39-C42		111.1	110.9
C18-H23		1.081	1.070	C39-C42-C45		110.1	109.9
C22-H28		1.084	1.075	C42-C45-C33		111.0	111.2
C27-H31		1.084	1.075	C33-N32-C36		112.0	112.1
C25-H30		1.084	1.075	C4-C3-C13		121.8	122.5
C20-H26		1.084	1.075	C2-C3-C13		120.5	119.8
C17-H21		1.084	1.074	C13-C15-C17		119.3	119.7
N32-C13	1.47	1.477	1.464	C13-C15-C16		122.1	121.8
N32-C36		1.465	1.454	C15-C17-H21		119.0	119.4
N32-C33		1.466	1.455	C15-C16-C18		123.8	123.6
C33-C45		1.532	1.527	C16-C18-H23		119.9	120.1
C45-C42		1.532	1.527	N32-C33-H34		108.9	109.2
C42-C39		1.532	1.527	N32-C36-H38		108.3	108.6
C39-C36		1.532	1.526	Dihedral Angles			
C33-H34		1.092	1.082	N32-C13-C3-C2		-176.5	-168.3
C33-H35		1.104	1.094	N32-C13-C15-C17		-87.4	-90.9
C36-H37		1.105	1.094	C4-C3-C2-O11		-176.6	-176.6
C36-H38		1.094	1.084	C1-C2-O11-H12		158.3	144.1
C39-H40		1.095	1.087	C15-C16-C18-C22		179.3	179.2
C39-H41		1.095	1.087	C19-C16-C18-H23		-178.8	-178.9
C42-H43		1.094	1.086	C25-C19-C24-C27		-178.6	-178.5
C42-H44		1.098	1.089	C16-C15-C17-H21		-179.9	-178.0
C45-H46		1.096	1.087	N32-C33-C45-H47		178.2	177.8
C45-H47		1.095	1.087	N32-C36-C39-H40		-178.2	-178.3

Experimental and calculated structural properties are given in Table-2. While the O-H bond length for the hydroxyl group was experimentally 0.96 Å, it was calculated as 0.966 Å by the B3LYP method and 0.942 by the HF method. While N32-C13 bond lengths were found 1.47 experimentally, it was calculated as 1.477 Å by B3LYP method and 1.464 by HF method. Similarly, while C = C bond length was experimentally 1.37 Å, theoretically C24 = C27 1,372 Å (B3LYP) and 1.356 Å (HF) were calculated. C3-C13-H14; C2-O11-H12 angles are experimental as 109.5 and 104.5, and used theoretically, calculated as 104.7 °, 110.1 ° (B3LYP) and 104.1, 111.4 (HF). As a result; It can be said that there is a good agreement between experimental bond length and bond angle and calculated values.

IR spectra

Vibration spectroscopy (FT-IR) is one of the most common methods used for functional groups and bond structures of compounds. While obtaining IR spectra, there are various differences between

experimental and theoretical calculations. This difference can be corrected by a scaling factor. 6- 311 ++ G (d, p) 4000-1700 cm⁻¹ region 0.958[26] and 1700-0 cm⁻¹ region 0.978[27] multiplier of the molecule can be scaled. The IR spectra given in Fig 2 were obtained using experimental and quantum mechanical calculations. The frequencies and vibration bands calculated for the compound are given in Table-3.

The vibration band experimentally observed at 3752 cm⁻¹ was theoretically calculated as 3824 cm⁻¹ (B3LYP) and 3974 cm⁻¹ (HF). Similarly, the aromatic vibration of = C-H was observed at 3200 cm⁻¹ was theoretically calculated as 3080 cm⁻¹ (B3LYP) and 3216 cm⁻¹ (HF). Experimentally, C = C aromatic vibration bands were observed in 1607, 1600, 1586 cm⁻¹, These values was theoretically calculated as 1619, 1611, 1594 cm⁻¹ (B3LYP) and 1778, 1751, 1742 cm⁻¹ (HF). The assignments of all other stress, torsion, and vibration bands are given in Table-3.

Table-3: Significant vibrational frequencies (cm^{-1}) in the FT-IR spectrum.

Vibrational modes (ν)	Exp*	B3LYP		HF	
		unscaled	scaled	unscaled	scaled
Ar-OH	3752	3749	3824	4150	3974
=C-H (aromatic)	3200	3213	3080	3359	3216
CH (aliphatic)	2958	3081	2950	3239	3103
	2939	3064	2935	3206	3078
	2851	3057	2927	3201	3069
	2809	3052	2919	3193	3060
C=C (aromatic)	1607	1658	1619	1814	1741
	1600	1648	1611	1795	1715
	1586	1634	1594	1782	1707
	1474	1514	1478	1644	1610
CH ₂ (aliphatic)	1455	1497	1463	1639	1601
	1403	1494	1455	1629	1593
	1356	1486	1447	1436	1399
OH bending	1250	1359	1330	1372	1346
C-O (aromatic)	975	1333	1306	1269	1241
C-H (aliphatic, out-of-plane bending)	873	979	954	996	977
	787	930	907	888	871

Scaled factor: 0,958 for 4000-1700 cm^{-1} ; 0,978 for 1700-400 cm^{-1}
Exp*= Experimental

NMR spectra

In this study, ¹H-NMR and ¹³C-NMR of the 2-(naphthalen-1-yl (piperidin-1-yl) methyl) phenol compound was first optimized to calculate the chemical shift values. The chemical shift values were created in CHCl₃ using the GIAO NMR approach in the HF and in the B3LYP methods by using the 6-311G++(d,p) basic set...” (Table-4.) [28–30]. Chemical shifts of ¹³C-NMR and ¹H-NMR were compared experimentally and theoretically. It was found that there is a match between the experimentally obtained and theoretically calculated

values of the molecule examined in CHCl₃ solvent medium.

Table-4: Selected Experimental and calculated ¹H and ¹³C NMR chemical shifts (ppm).

Atoms	Experimental	B3LYP	HF
		CHCl ₃	CHCl ₃
C13H	5.60	5.92	5.72
O11H	12.84	3.84	2.81
C4H	7.14	8.20	8.57
C5H	6.92	7.38	7.64
C7H	6.66	6.95	7.45
C17H	7.45	7.49	7.66
C20H	7.52	7.69	7.88
C25H	7.60	8.12	8.57
C22H	7.89	7.77	8.25
C18H	8.38	8.74	8.99
C13	117.1	67.4	61.6
C3	119.0	135.7	143.2
C2	157.2	160.8	163.8
C1	125.9	121.0	128.0
C16	129.2	139.3	145.8
C33	26.2	49.8	48.8

The C13H peak, which is one of the characteristic peaks of the compound, has been experimentally seen at 5.60 ppm, while it was found to be 5.92 in the calculations with the B3LYP method and 5.72 ppm in the calculations with the HF method. Another specific peak, the O11H peak, had a shift value at 12.84 experimentally, and this value was calculated as 3.84 and 2.81 theoretically. In alkylaminopheol compounds, the OH peak is normally not within the expected slip range. Intramolecular hydrogen bonds and chemical structure cause OH peak to be observed in a range of 12.00-13.00 ppm.

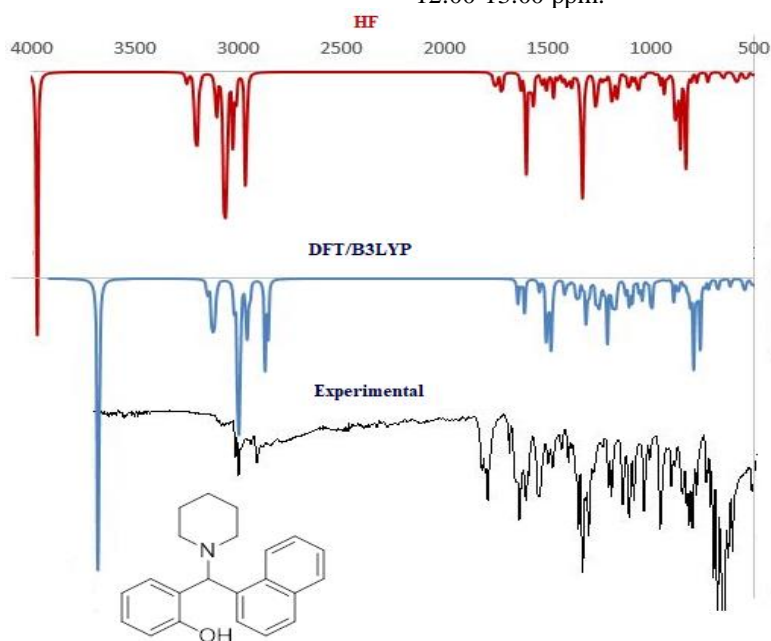


Fig. 2: Theoretical (HF red, B3LYP blue) and experimental (black) and IR spectra of 2-(naphthalen-1-yl(piperidin-1-yl)methyl)phenol.

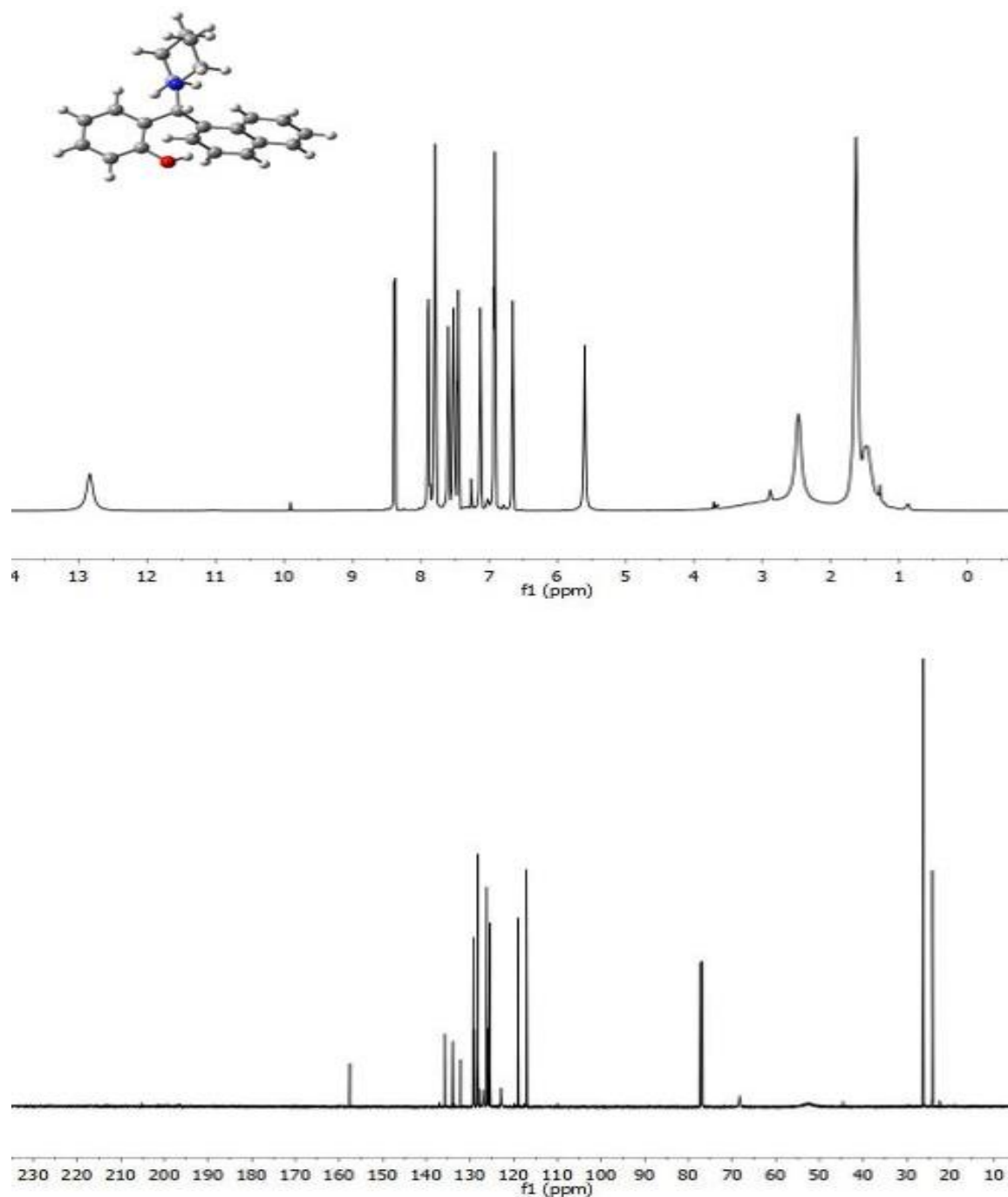


Fig. 3: Experimental ^1H -NMR and ^{13}C -NMR spectra of 2-(naphthalen-1-yl(piperidin-1-yl)methyl)phenol.

Table-5: Experimental and calculated electronic transitions, oscillator strengths and their assignments for 2-(naphthalen-1-yl(piperidin-1-yl)methyl)phenol.

Experimental values		B3LYP calculated values		$f_{\text{(oscillator strength)}}$	Transitions
$\lambda_{\text{max}}(\text{nm})$	absorbans	$\lambda_{\text{max}}(\text{nm})$	Excitation energy(eV)		
224	1.672	302.4	4.100	0.0168	HOMO-1 - LUMO ($\pi-\pi^*$)
285	0.234	339.4	3.653	0.0692	HOMO - LUMO ($n-\pi^*$)

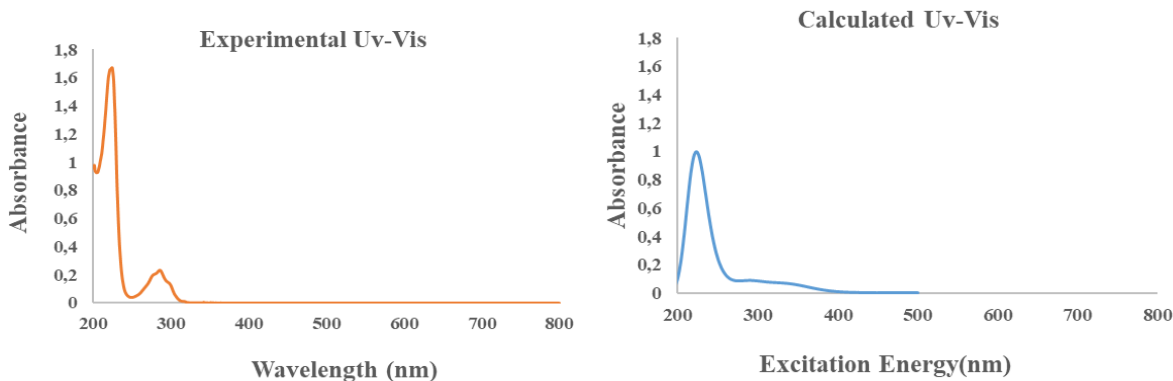


Fig. 4: a) Experimental UV-vis absorption spectra of 2-(naphthalen-1-yl(piperidin-1-yl)methyl)phenol
b) Uv-Vis spectrum drawn by TD-DFT- B3LYP / 6-311 ++ G (d, p) method.

UV-Vis spectra

UV-Vis spectra of the alkylaminophenol compound were taken in ethanol. Experimental absorption wavelengths were observed at 285 and 224 nm. The excitation energies of the absorption spectroscopy of the molecule, the wavelengths (λ) to which they absorb the maximum absorption, oscillator strength (f) were calculated using the TD-SCF method in ethanol solvent medium. In saturated compounds with heteroatom (C = C) π - π * (224); The n - π * (285 nm) transitions that are effective in unsaturated systems with heteroatoms carrying non-bonding electrons are significant in our alkylaminophenol compound. In this case; From HOMO-1 to LUMO π - π *; corresponding n - π * transitions are seen in HOMO-LUMO.

Mulliken charge

Mulliken charge distribution is the most common of population analysis methods. It is based on obtaining molecular orbitals with linear combination of atomic orbitals. However, this distribution does not fully reflect the electronegativity of each element. Therefore, it is used to make some qualitative estimates rather than quantitatively estimate experimental results. Mulliken density analysis was performed with B3LYP and HF / 6-311G ++ (d, p) methods

B3LYP and HF methods, which are given in Table-6. Mulliken charge in the B3LYP method is between -0.701 and 0.701, The atomic charge analysis of alkylaminophenol showed the C₁, O₁₁, C₁₃, C₁₅ atoms a maximum negative charges, The N₁ and C₃ atoms have positive charges of 0.335 and 0.701 a.u., respectively. Mulliken charge in the HF method is between -0.620 ve 0.620. The atomic charge analysis of alkylaminophenol showed the C₁, O₁₁, C₁₃, C₁₅ atoms a maximum negative charges, The N₁ and C₃ atoms have positive charges of 0.502 and 0.568 a.u., respectively.

Table-6: Mulliken and natural population charges of 2-(naphthalen-1-yl(piperidin-1-yl)methyl)phenol.

Atoms	Mulliken(B3LYP)	Mulliken(HF)
C1	-0.230	-0.359
C2	-0.656	-0.509
C3	0.701	0.568
C4	0.238	0.143
C5	-0.509	-0.490
C6	-0.262	-0.445
O11	-0.251	-0.340
C13	-0.029	-0.140
C15	-0.079	-0.011
C16	0.0	-0.021
C17	-0.233	-0.276
C18	-0.103	-0.278
C19	0.202	0.322
C20	-0.330	-0.351
C22	-0.304	-0.354
C27	-0.519	-0.520
C24	-0.005	-0.062
N32	0.335	0.520
C33	-0.356	-0.293
C36	-0.205	-0.170
C39	-0.369	-0.455
C45	-0.405	-0.575
C42	-0.345	-0.377

The data obtained has an important role in the quantum mechanical studies of the molecule, such as dipole moment, chemical reactivity, and electronic properties.

Frontier molecular orbitals (FMOs)

The molecular reactivity (FMO) of a molecule is important in defining its optical and electrical properties, and in defining the absorption of light. According to the molecular orbital theory; all molecules have HOMO (Highest occupied molecular orbital) and LUMO (Lowest Unoccupied molecular orbital). The frontier molecular orbital (HOMO and LUMO) shapes of 2-(naphthalen-1-yl(piperidin-1-yl)methyl)phenol were determined using DFT/B3LYP and HF methods with 6-311++G(d,p) basis sets. The HOMO and LUMO orbitals for this molecule are given in Fig 4. The calculated HOMO and LUMO energies of 2-

(naphthalen-1-yl (piperidin-1-yl) methyl) phenol were -5.939 and -1.689 eV, respectively, so the energy difference was 4.25 eV. Some physicochemical parameters were calculated by these equations: hardness, $\eta = (I - A) / 2 = 2.125$, electronegativity, $\chi = (I + A) / 2 = 3.814$, softness $S = 1.0625$ and electrophilicity index $\omega = \chi^2 / 2\eta = 3.422$ where A (-ELUMO) and I (-EHOMO) are electron affinity and ionization potential. The same procedures were applied in the HF method. All data were shown in Table-7. These parameters were used to understand toxicity in terms of reactivity. In terms of reaction, theoretical toxicity is determined using the electrophilicity index.

Molecular electrostatic potential (MEP)

MEP surface describes the charge distribution in the molecule. Molecular electrostatic potential (MEP) is used to investigate the chemical reactivity of a molecule. Surfaces of the optimized electronic structures were drawn using the B3LYP and HF / 6 - 311 ++ G (d, p) sets in Fig 5. The colour code of this map ranges from -4.310 e^{-2} and $+4.310 \text{ e}^{-2}$ a.u. and -

4.785 e^{-2} and $+4.785 \text{ e}^{-2}$ a.u. Where blue shows the strongest attraction and red indicates repulsion. From MEP surface, the negative potential area is on the oxygen atom of the hydroxyl group while positive potential areas are on the phenyl hydrogen atoms. These results provide information about the region where the compounds may have inter-molecular interactions, especially with biological molecules.

Table-7: HOMO and LUMO energies, the energy gap (ΔE), absolute electronegativity (χ) chemical hardness (η), softness (S) and electrophilicity index (ω) of 2-(naphthalen-1-yl(piperidin-1-yl)methyl)phenol using B3LYP/6-311++G(d,p) and HF/6-311++G(d,p) levels

Global reactivity descriptors	B3LYP/6-311++G(d,p)	HF/6-311++G(d,p)
E(HOMO, eV)	-5.939	-8.094
E(LUMO, eV)	-1.689	0.010
ΔE (eV)	4.250	8.104
χ	3.814	4.042
η	2.125	4.052
s	1.063	2.026
ω	3.423	4.032

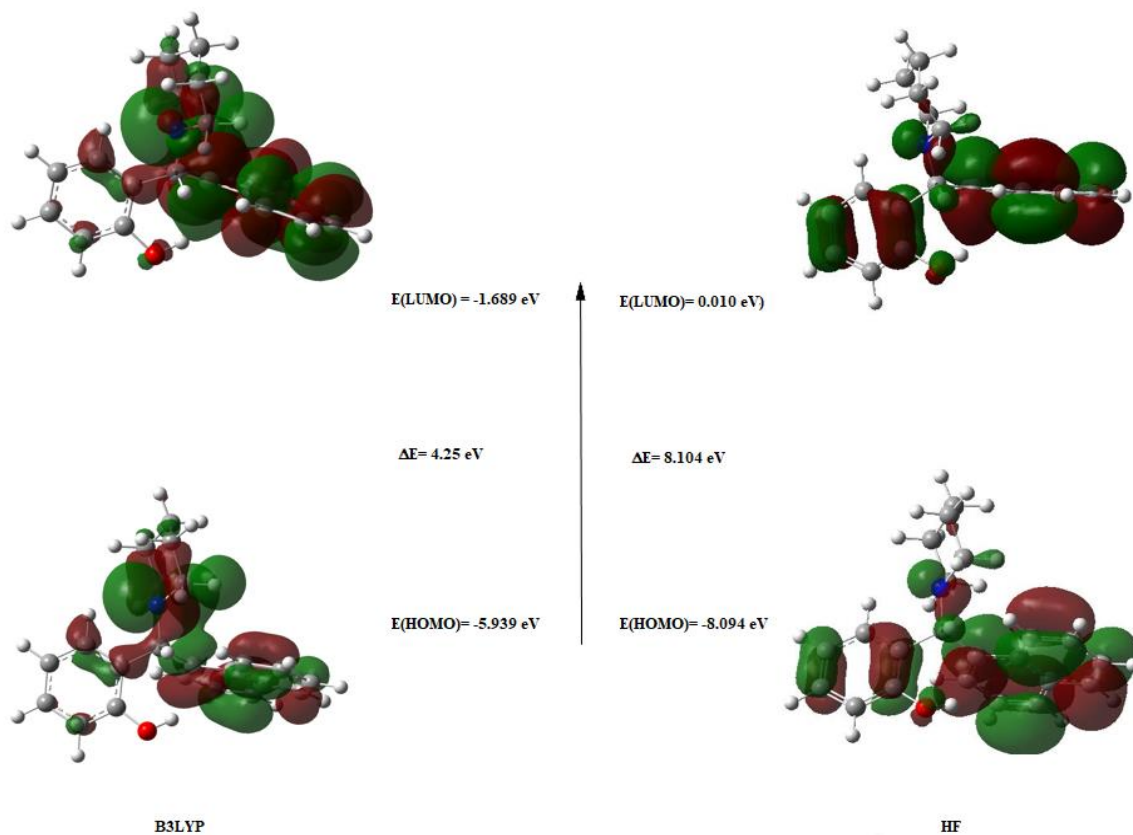


Fig. 5: HOMO and LUMO orbitals of 2-(naphthalen-1-yl(piperidin-1-yl)methyl)phenol with the energy gap.

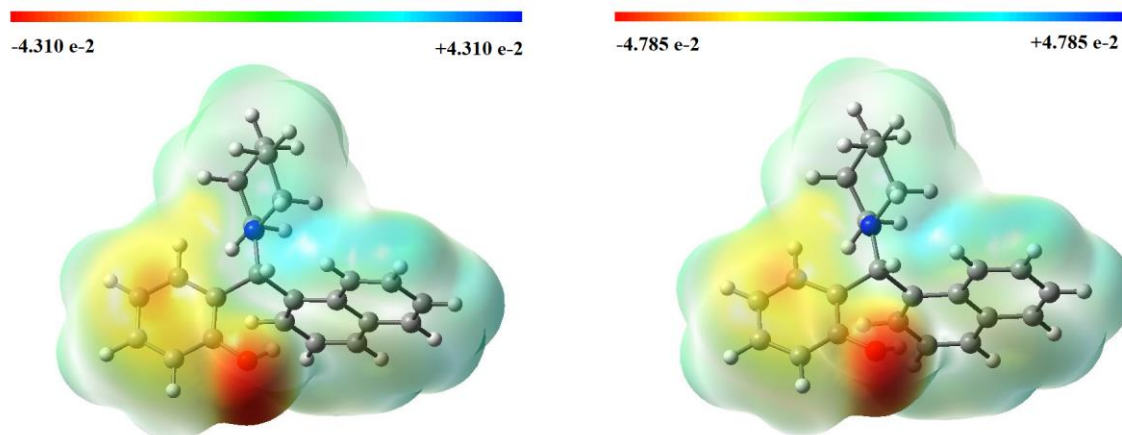


Fig. 6: The total electron density mapped with molecular electrostatic potential surface of 2-(naphthalen-1-yl)(piperidin-1-yl)methylphenol with B3LYP and HF methods.

Conclusions

In this study, for the first time, alkylaminophenol derivative 2-(azepan-1-yl (naphthalen-1-yl) methyl) phenol compound was synthesized with very high efficiency. Structural analysis of the compound was carried out experimentally with FT-IR, NMR, UV-vis. Because of quantum chemical calculations of alkylaminophenol are limited in the literature, the physicochemical parameters of the compound were examined in comparison with the DFT/B3LYP and HF methods using (6-311 ++ G (d, p) basis set. Electrical, magnetic and vibration properties of the molecule were obtained about information. It was observed that the theoretical and experimental data were compatible. The high electronegativity of some atomic group caused a slight deviation in the values. Because, when high electronegativity is combined with other factors, it has been observed that it affects the correlation between experimental and theoretical results. As a result; a potential drug active compound was synthesised, and all electronic properties of the compound were examined by quantum chemical calculations.

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References

1. N. Takahashi, T. Ohba, T. Yamauchi and K. Higashiyama, Antioxidant and anticancer activities of novel p-alkylaminophenols and p-

acylaminophenols (aminophenol analogues) *Bioorganic Med. Chem.*, **14**, 6089 (2006).

2. R. Wang and J. Xu, Selective alkylation of aminophenols, *Arkivoc*, **2010**, 293 (2010).
3. Y. Ulaş, A. İ. Özkan and V. Tolun, Synthesis of New p-Alkylaminophenol Compounds and Investigation of Their Antimicrobial and Antioxidant Activity, *Eur. J. Sci. Technol.*, **16**, 701 (2019).
4. P. Wu, M. Givskov and T. E. Nielsen, Reactivity and Synthetic Applications of Multicomponent Petasis Reactions, *Chem. Rev.*, **119**, 11245 (2019).
5. J. Zhang, F. Yun, R. Xie, C. Cheng, G. Chen, J. Li, P. Tang and Q. Yuan, Petasis three-component reaction accelerated by trifluoroacetic acid: synthesis of indoline-derived glycines, *Tetrahedron Lett.*, **57**, 3916 (2016).
6. N. R. Candeias, F. Montalbano, P. M. S. D. Cal and P. M. P. Gois, Boronic acids and esters in the petasis-borono mannich multicomponent reaction, *Chem. Rev.*, **110**, 6169 (2010).
7. N. A. Petasis and I. A. Zavialov, Highly stereocontrolled one-step synthesis of anti- β -amino alcohols from organoboronic acids, amines, and α -hydroxy aldehydes, *J. Am. Chem. Soc.*, **120**, 11798 (1998).
8. N. A. Petasis, A. Goodman and I. A. Zavialov, A new synthesis of α -arylglycines from aryl boronic acids, *Tetrahedron*, **53**, 16463 (1997).
9. Y. Ulaş, Akıllı Malzemelerin Hazırlanmasında Kullanılacak Amin Türevi Monomerlerin Sentez ve Karakterizasyonu, *Eur. J. Sci. Technol.*, **16**, 242 (2019).
10. Y. Liu, L. Wang, Y. Sui and J. Yu, Solvent-free synthesis of alkylaminophenols via petasis Boronic Mannich reaction in one pot without

- catalysts, *Chinese J. Chem.*, **28**, 2039 (2010).
11. F. Berrée, A. M. Debache, Y. Marsac, B. Collet, P. Girard-Le Bleiz and B., Carboni Stereoselective synthesis of 2-hydroxymorpholines and aminodiols via a three-component boro-Mannich reaction *Tetrahedron*, **62**, 4027 (2006).
 12. I. Althagafi and H. E. Gaffer, Synthesis, molecular modeling and antioxidant activity of new phenolic bis-azobenzene derivatives, *J. Mol. Struct.*, **1182**, 22 (2019).
 13. Í. Neto, J. Andrade, A. S. Fernandes, C. Pinto Reis, J. K. Salunke, A. Priimagi, N. R. Candeias and P. Rijo, Multicomponent Petasis-borono Mannich Preparation of Alkylaminophenols and Antimicrobial Activity Studies, *ChemMedChem*, **11**, 2015 (2016).
 14. X. Yang, Z. H. Cao, Y. Zhou, F. Cheng, Z. W. Lin, Z. Ou, Y. Yuan and Y. Y. Huang, Petasis-Type gem-Difluoroallylation Reactions Assisted by the Neighboring Hydroxyl Group in Amines, *Org. Lett.* **20**, 2585 (2018).
 15. C. Z. Tao, Z. T. Zhang, J. W. Wu, R. H. Li and Z. L. Cao, Synthesis of unnatural N-glycosyl α -amino acids via Petasis reaction, *Chinese Chem. Lett.* **25**, 532 (2014).
 16. D. Naskar, A. Roy, W. L. Seibel and D. E., Portlock Hydroxylamines and sulfinamide as amine components in the Petasis boronic acid-Mannich reaction: Synthesis of N-hydroxy or alkoxy- α -aminocarboxylicacids and N-(tert-butyl sulfinyl)- α -amino carboxylicacids, *Tetrahedron Lett.*, **44**, 8865 (2003).
 17. S. Noushini, M. Mahdavi, L. Firoozpour, S. Moghimi, A. Shafiee and A. Foroumadi, Efficient multi-component synthesis of 1,4-benzodiazepine-3,5-diones: a Petasis-based approach, *Tetrahedron*, **71**, 6272 (2015).
 18. D. Mahadevan, S. Periandy and S. Ramalingam, Comparative vibrational analysis of 1,2-Dinitro benzene and 1-Fluoro-3-nitro benzene: A combined experimental (FT-IR and FT-Raman) and theoretical study (DFT/B3LYP/B3PW91), *Spectrochim. Acta - Part A Mol. Biomol. Spectrosc.*, **84**, 86 (2011).
 19. B. Kaboudin, A. Zangoeei, F. Kazemi and T. Yokomatsu, Catalyst-free Petasis-type reaction: Three-component decarboxylative coupling of boronic acids with proline and salicylaldehyde for the synthesis of alkylaminophenols, *Tetrahedron Lett.*, **59**, 1046 (2018).
 20. O. P. Sharma and T. K. Bhat, DPPH antioxidant assay revisited, *Food Chem.*, **113**, 1202 (2009).
 21. G. Kotan and H. Yükses, Spektroskopik , Geometrik, Termodinamik ve Elektronik Analizi DFT (B3LYP / B3PW91)/ HF of 3-Phenyl-5- (4-pyridyl) -1, 2, 4-triazole Molecule, *Eur. J. Sci. Technol.*, 933 (2019).
 22. J. Kujawski, K. Czaja, K. Dettlaff, J. Żwawiak, T. Ratajczak and M. K. Bernard, Structural and spectroscopic properties of posaconazole – Experimental and theoretical studies, *J. Mol. Struct.*, **1181** 179 (2019).
 23. I. Kucuk, Y. Kaya and A. A. Kaya, Structural, spectroscopic (FT-IR, NMR, UV-visible), nonlinear optical (NLO), cytotoxic and molecular docking studies of 4-nitroisonitrosoacetophenone (ninapH) by DFT method, *J. Mol. Struct.*, **1139**, 308 (2017).
 24. E. Klein and V. Lukeš, DFT/B3LYP study of O-H bond dissociation enthalpies of para and meta substituted phenols: Correlation with the phenolic C-O bond length, *J. Mol. Struct., THEOCHEM*, **767**, 43 (2006).
 25. L. Wang, Y. Wang, Q. Zhang and J. Zhao, Theoretical exploration about the ES IPT mechanism and hydrogen bonding interaction for 2-(3,5-dichloro-2-hydroxy-phenyl)-benzoxazole-6-carboxylicacid, *J. Phys. Org. Chem.*, 1 (2019)
 26. N. Sundaraganesan, S. Ilakiamani, H. Saleem, P. M. Wojciechowski and D. Michalska, FT-Raman and FT-IR spectra, vibrational assignments and density functional studies of 5-bromo-2-nitropyridine, *Spectrochim. Acta - Part A Mol. Biomol. Spectrosc.*, **61**, 2995 (2005).
 27. A. J. L. Jesus, M. T. S. Rosado, I. Reva, R. Fausto, M. E. Eusebio and J. S. Redinha, Conformational study of monomeric 2,3-butanediols by matrix-isolation infrared spectroscopy and DFT calculations, *J. Phys. Chem. A*, **110**, 4169 (2006).
 28. M. Raja, R. R. Muhamed, S. Muthu and M. Suresh, Synthesis, spectroscopic (FT-IR, FT-Raman, NMR, UV-Visible), first order hyperpolarizability, NBO and molecular docking study of (E)-1-(4-bromobenzylidene)semicarbazide, *J. Mol. Struct.*, **1128**, 481 (2017).
 29. D. Mahadevan, S. Periandy, M. Karabacak and S. Ramalingam, FT-IR and FT-Raman, UV spectroscopic investigation of 1-bromo-3-fluorobenzene using DFT (B3LYP, B3PW91 and MPW91PW91) calculations, *Spectrochim. Acta - Part A Mol. Biomol. Spectrosc.*, **82**, 481 (2011).
 30. G. Nageswari, G. George, S. Ramalingam and M. Govindarajan, Molecular analyses using FT-IR, FT-Raman and UV spectral investigation; quantum chemical calculations of dimethyl phthalate, *J. Mol. Struct.*, **1195**, 331 (2019).