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EXPERIMENTAL AND THEORETICAL STUDY ON LINEAROL ISOLATED FROM *SIDERITIS* SPECIES[**]

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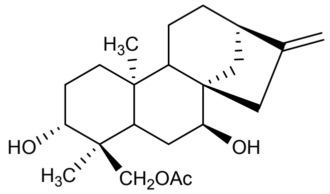
The molecular geometry, vibrational frequencies and gauge independent atomic orbital (GIAO) ^{1}H- and ^{13}C-NMR chemical shifts values of linearol (*ent*–3,7-dihidroksi,18-asetoksi-kaur–16-ene) in the ground state have been investigated using the Hartree–Fock (HF) and Density Functional Theory (DFT) employing the 6-31G and 6-31G(d) basis sets. The fundamental vibrational wavenumbers as well as their intensities were calculated and a good agreement between observed and calculated wavenumbers has been achieved. The optimized geometrical parameters obtained by theoretical calculations are in good conformity with single crystal X-ray data. The ^{1}H- and ^{13}C-nuclear magnetic resonance (NMR) chemical shifts of the molecule were compared with experimental values, which yield good agreement between the observed and calculated values.



INTRODUCTION

The genus *Sideritis* belongs to the Labiateae family. This genus comprises more than 150 perennial and annual vegetal species widely distributed in the Mediterranean area.[1,2] The name of the genus *Sideritis,* given by Dioscorides, seems to be derived from the Greek word “sideron” (iron) on account of an alleged efficacy in curing wounds produced with iron swords.[2] *Sideritis* species are commonly used as a herbal tea in folk medicine in Turkey. They are widespread used against gastrointestinal disorders, such as stomache ache, indigestion and flatulence, to alleviate the symptoms of common colds including fever, flu, sore throat, and bronchitis as well as a tonic and diuretic remedy.[3,4]

The chemical components found in *Sideritis* genus include terpenes, flavonoids, essential oil, iridoids, coumarins, lignanes and sterols, among others. Diterpenes, flavonoids and essential oil occur in almost every species and are the main compounds responsible for the observed in vivo and in vitro pharmacological activities. Linearol (Fig. 1) is a kaurene diterpene, the most frequently found in *Sideritis* species.[2] It is an important compound that has many derivatives with a wide range of interesting properties, such as antioxidant,[5] anti-inflammatory,[6] anti-apoptosis,[7] antimicrobial,[8] antibacterial, antifeedant, insecticidal,[9] hypotensive[10] and anti-HIV [11] activities.

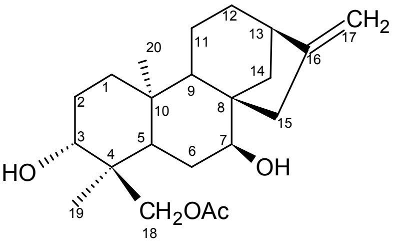


Fig. 1 – Structure of Linearol.

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[**] Supplementary material on http: //web.icf.ro/rrch/ or http: //revroum.lew.ro/

Semiempirical methods like AMI, PM3, MNDO can give great insight into structure and reactivity of even moderately large molecules. The theoretical ab-initio and DFT analyses also give information regarding the nature of the electronic structure, the functional groups, and orbital interactions and mixing of vibrational frequencies.[12] Literature survey reveals that to the best of our knowledge the structural characteristics and vibrational spectroscopic analyses of linearol by the quantum mechanical ab-initio and DFT methods have not been examined so far. Thus, considering the biological importance of natural compounds and their derivatives, an extensive experimental and theoretical ab-initio and DFT studies have been carried out on linearol to obtain accurate vibrational assignments and structural characteristics of the compound.

The calculation of molecular structural parameters, vibrational frequencies, and energies of molecule by DFT method with the hybrid exchange–correlation functional B3LYP and HF methods were proved to be very effective for vibrational studies and considered to be especially important in systems containing extensive electron conjugation and electron lone pairs.[13]

EXPERIMENTAL

Plant material

Linearol (*ent*–3,7-dihidroksi,18-asetoksi-kaur–16-ene) having the *ent*-kaurene skeleton can be isolated from different species of *Sideritis* such as *S, athoa, S, argyrea, S, lycia, S, leptoclada, S, akmanii, S, niveotomentosa, S, brevidens, S, rubiflora, S, gulendami, S, huber-morathii, S, congesta, S, ozturkii, S, stricta, S, Condensata*.[14] In this study, linearol was isolated from *Sideritis stricta* Boiss. & Heldr, and *Sideritis brevidens* P.H.Davis, collected in July 2011 from Termesos National Park (Antalya Province, Turkey). The plants were identified by Assoc. Prof. Dr. Tuncay Dirmenci from University of Balikesir, Turkey.

Extraction and isolation

The powdered whole plant (1.5 kg) was extracted successively with acetone at room temperature. The combined acetone extracts were dried in vacuo at 40 ^{0}C. The total extract (55 g) was initially fractionated by chromatography on silica gel. Elution was started with hexane and continued with gradients of dichloromethane, acetone and methanol. From the acetone extract, linearol was isolated. In the previous study nine known and one new *ent*-kaurene diterpenoids were isolated from the acetone extract of *Sideritis stricta* Boiss & Heldr. They were identified as *ent*-1β-hydroxy-7α-acetyl-15β,16β-epoxykaurane, sideroxol, 7-acetylsideroxol, 7-epicandicandiol, linearol, *ent*-7α,15β,18-trihydroxy-kaur-16-ene, *ent*-7α-acetyl,15,18-dihydroxy-kaur-16-ene, foliol, sideridiol and siderol.[15] They were purified by preparative TLC. All the compounds were identified based on IR, ^{1}H- and ^{13}C-NMR and mass spectroscopic techniques. The structures of known compounds were confirmed by comparison to literature data. Silica gel 60 was used for column chromatography and Kieselgel 60F$_{254}$ pre-coated plates (E. Merck) for prep. TLC. All the solvents were purchased from Merck Co.

COMPUTATIONAL

The molecular structure of the title molecule in the ground state (in vacuo) was optimized using Hartree–Fock (HF) and DFT (B1LYP, B3LYP, B1B95, B3PW91, and MPW1PW91) with the 6-31G and 6–31G(d) basis sets.[16] All theoretical calculations were achieved by using GAUSSIAN 03W program package.[17] The calculations employed the B3LYP exchange-correlation functional, which combines the hybrid exchange functional of Becke with the gradient-correlation functional and the split valence polarized 6-31G and 6-31G(d) basis sets.

Molecular structure of linearol was initially obtained from the X-ray coordinates, and then optimized separately with the theoretical methods mentioned before. After that, vibrational frequencies for the optimized molecular structures of the title compound were calculated using these methods. The geometry of the title compound, together with that of tetramethylsilane (TMS), is fully optimized. ^{1}H and ^{13}C-NMR chemical shifts were calculated within the GIAO approach applying the same methods and basis set as used for geometry optimization. The ^{1}H- and ^{13}C-NMR chemical shifts were converted to the TMS scale by subtracting the calculated absolute chemical shielding of TMS. Experimental fundamentals are in better agreement with scaled fundamentals and are found to have a better correlation for B3LYP than HF. The frequency calculations were carried out at the same levels as the respective optimization process.

RESULTS AND DISCUSSION

Crystal structure and optimized geometry

It is well known that XRD data provide information on bond distances and angles, interand/or intra-molecular contacts and crystal packing pattern.[18] Therefore, starting geometries of compound were taken from X-ray refinement data. The molecular structure of the compound in the ground state is optimized by Density Functional Theory (DFT) and Hartree–Fock (HF) methods with 6-31G and 6-31G(d) basis sets. The experimental X-ray data[19] on the geometric structure of linearol were compared with DFT and HF methods. The crystal structure parameters of the compound are a = 7.785(1) A, b = 11.670(1) Å, c = 11.799(2) Å and V = 1023.2(2) Å^3.[19] Various calculated bond angles and dihedral angles are found to be in satisfactory agreement with the reported standard values. The geometrical parameters obtained from DFT methods are seen in good agreement with the experimental values of linearol. Calculated geometric parameters are listed in Table 1 (also see Supplementary Material) along with the experimental data. It is well known that HF-optimized bond lengths are usually longer and more accurate than other methods.[20] However it yields bond angles in excellent agreement with each other and also with the experimental values.

Table 1

Selected geometrical structural parameters of linearol (see Supplementary material)

		HF	**HF**	**B3LYP**	**B3LYP**	**MPW1PW91**	**MPW1PW91**
Bond lengths	**Exp**,	**6-31G**	**6-31G(d)**	**6-31G**	**6-31G(d)**	**6-31G**	**6-31G(d)**
C3-O3	1.434	1.443	1.412	1.469	1.435	1.457	1.423
O3-H	-	0.951	0.947	0.978	0.969	0.973	0.956
C4-C18	1.536	1.550	1.551	1.558	1.556	1.548	1.546
O18’-C18	1.45	1.446	1.419	1.472	1.440	1.459	1.428
O18’-C21	1.312	1.344	1.324	1.377	1.353	1.368	1.345
C21-O21’	1.181	1.215	1.189	1.236	1.212	1.232	1.208
C21-C22’	1.48	1.491	1.503	1.500	1.509	1.492	1.501
O7’-C7	1.444	1.444	1.413	1.471	1.435	1.457	1.423
O7’-H	-	0.951	0.947	0.978	0.970	0.973	0.965
C8-C15	1.534	1.558	1.554	1.567	1.561	1.556	1.551
C8-C14	1.542	1.550	1.546	1.559	1.553	1.549	1.543
C13-C14	1.527	1.535	1.531	1.545	1.539	1.537	1.531
C16=C17	1.363	1.322	1.318	1.337	1.333	1.335	1.330
C15-C16	1.484	1.519	1.520	1.527	1.523	1.518	1.515
Bond angles							
C15-C16-C17	127.7	126.415	126.373	126.493	126.5	126.569	126.569
O21-C21-O18	121.5	123.091	124.460	123.600	124.57	123.525	124.542
C22-C21-O18	113.5	111.608	110.858	110.625	110.268	110.699	110.288
O21-C21-C22	124.9	125.293	124.676	125.773	125.155	125.773	125.167
C18-O18-C21	118.1	122.167	119.931	118.611	117.772	118.469	117.477
H22’-C22-C21	-	110.010	109.779	109.913	110.948	109.938	109.777
C3-O3-H3’	-	112.143	108.494	108.732	106.599	108.958	106.621
O18’-C18-H18’	-	108.856	109.175	108.486	108.742	108.617	108.856
C3-C4-C18	108.9	108.292	108.391	108.357	108.303	108.209	108.193
H7’-O7-C7	-	113.524	109.569	109.990	107.693	110.275	107.740
C3-C4-C5	107.5	103.377	107.551	107.473	107.697	107.521	107.753
C13-C16-C15	106.9	107.551	107.370	107.535	107.440	107.514	107.418

Vibrational analysis

For the compound, vibrational frequencies were calculated by using DFT and HF theories with 6-31G and 6-31G(d) basis sets. The theoretical vibrational frequencies and the assignments of linearol with the experimental data have been compared and the results have been given in Table 2. The calculated vibrational spectra of the title molecule belonging to C1 point group have no imaginary frequencies which helped to confirm that the structure of the compound deduced following geometry optimization corresponds to energy minimum.[20] The theoretical calculations predict 174 vibrations from 39-4105 cm^{-1}, the exact limits being dependent on the method of calculation. The vibrational analysis of linearol is performed on the basis of the characteristic vibrations of acetate group, methyl group, alcohol and C=C group. If the vibrational assignments are investigated one-by-one, the obtained assignments with related molecules are consistent with the determined DFT calculations. There is also a good agreement between the experimental and the computed vibrational frequencies. The symmetric C=C stretching frequencies observed at 1656 cm^{-1} are theoretically predicted at between 1750 cm^{-1} and 1886 cm^{-1}. Normal esters are characterized by the strong IR absorptions due to the C=O stretching vibration in the range 1750-1735 cm^{-1} and the other due to C-O stretching vibration near 1200 cm^{-1}. Moreover, the C=O stretching frequencies observed at 1714 cm^{-1} is theoretically predicted at between 1728 cm^{-1} and 2003 cm^{-1} in the title compound. The free OH group absorbs strongly in the region 3700-3580 cm^{-1}, whereas the existence of intermolecular hydrogen bond formation can lower the O-H stretching frequency to the 3550-3200 cm^{-1} region with increase in intensity and breath.[21] As seen from Table 2, the calculated values of OH group vibrations show no good agreement with the experimental results.

To make a comparison with the experimental observations, we present correlation graphs based on the theoretical calculations in Supplementary material part (Fig. S1). The correlation values are found to be 0.984, 0.9847, 0.9854, 0.9883, 0.9883, 0.989 and 0.989 for HF, B1LYP, B1B95, B3LYP, B3P86, B3PW91, and MPW1PWP1 with the 6-31G basis set and 0.979, 0.9874, 0.9852, 0.9852, 0.9852, 0.986, 0.9855 for HF, B1LYP, B1B95, B3LYP, B3P86, B3PW91 and MPW1PWP1 with 6-31G(d) respectively. It can be easily understood that B3PW91, and MPW1PW91 calculations are better than B1LYP, B1B95, B3P86, B3LYP, and HF calculations.

Table 2

Selected experimental and theoretical vibrational wavenumbers of linearol (see Supplementary material)

Exp,	**HF/ 6-31G**	**HF/ 6-31G(d)**	**B3LYP/ 6-31G**	**B3LYP/ 6-31G (d)**	**MPW1PW91/ 6-31G**	**MPW1PW91/ 6-31G (d)**	***Approximate description***
	287.1293	284.1300	273.1445	292.1236	281.1139	293.1223	O-H rocking (C7)
	297.1267	299.1276	289.1277	278.1285	292.1187	310.1213	O-H rocking (C3)
	910	994.1005	945	956.971	993	941.963	C=CH_2 rocking
	652	661	652	597	573	603	O=C-CH_3 twisting
871.4	790	786	730	725	732	726	C=CH_2 twisting
	1009	1023.1048	1142	901.905	976	907.910	C=CH_2 wagging
	1182	1089.1178	1068	1004	1095	1077	O=C-CH_3 wagging
	1433	1419.1425	1314	1377	1301	1298	H_2C=C-CH_2 wagging
	1243	1322	1185	1339	1100	1094.1174	H_2C=C-CH_2 twisting
1045.7	1474	1494	1327	1353	1320	1342.1368	O=C-O-CH_2 twisting
1262	1549	1550	1418	1435	1420	1414.1441	O=C-O-CH_2 wagging
	1607	1591	1493	1474	1482	1476	C=CH_2 scissoring

Table 2 (continued)

	1626	1622	1517	1503.1506	1520	1504.1509	$\mathrm{O{=}C{-}C}\mathbf{H_3}$ scissoring
	1659	1665	1530	1526	1532	1516	$\mathrm{O{=}C{-}O{-}C}\mathbf{H_2}$ scissoring
1714	1883	2003	1728	1825	1766	1861	C=O symmetrical stretching
1656	1886	1893	1742	1744	1762	1766	C=C symmetrical stretching
2879.6	3169	3170	2992	2975	3017	3001	H-O-C-H symmetrical stretching (C7)
2928	3199	3184	3017	3003	3037	3025	H-O-C-H symmetrical stretching (C3)
	3223	3232	3071	3073	3099	3101	$\mathrm{O{=}C{-}C}\mathbf{H_3}$ symmetrical stretching
	3300	3276	3111	3101	3170	3135	$\mathrm{H_2C{=}C{-}C}\mathbf{H_2}$ asymmetrical stretching
	3233	3222	3048	3047	3073	3073	$\mathrm{H_2C{=}C{-}C}\mathbf{H_2}$ symmetrical stretching
	3310	3316	3153	3149	3183	3179	$\mathrm{C{=}C}\mathbf{H_2}$ symmetrical stretching
	3332	3299.3335	3146	3140	3185	3178.3216	$\mathrm{O{=}C{-}C}\mathbf{H_3}$ asymmetrical stretching
	3355	3350	3169	3150	3195	3175	$\mathrm{O{=}C{-}O{-}C}\mathbf{H_2}$ asymmetrical stretching
	3280	3295	3089	3097	3107	3110	$\mathrm{O{=}C{-}O{-}C}\mathbf{H_2}$ symmetrical stretching
	3387	3389	3233	3223	3270	3259	$\mathrm{C{=}C}\mathbf{H_2}$ asymmetrical stretching
3393	4018	4104	3632	3738	3704	3811	O-H symmetrical stretching (C7)
3493	4021	4105	3638	3742	3710	3815	O-H symmetrical stretching (C3)

NMR analysis

NMR is a sensitive and versatile probe of molecular-scale structure and dynamics in solids and liquids. It has been widely used in chemistry, materials and geochemistry and it enables to get faster and easier structural information. The standard 1D and 2D hetero and homonuclear NMR experiments are sufficient to afford complete assignment of organic compounds, and effective to afford molecular structure information.[22] ^{1}H-NMR spectrum provides information about the number of different types of protons and also the nature immediate environment to each of them. ^{13}C-NMR spectrum also provides the structural information with regard to different carbon atoms present in the molecule. Theoretically computed ^{13}C chemical shifts can be obtained at a level of accuracy sufficient to allow application to configurational and conformational determination of organic molecules.[23]

After the optimization of the title compound, ^{1}H- and ^{13}C-NMR chemical shifts were calculated. More detailed information about the structure of compounds was provided by the ^{13}C-NMR spectra.[24] Linearol shows 22 different carbon atoms, which is consistent with the structure of the molecule. Owing to a lacking molecular symmetry, 22 carbon peaks are observed in ^{13}C-NMR spectrum of linearol. The peak which appears at 171.82 ppm belongs to the (C=O) carbonyl group. Its computed values are in the range of 161.16 and 189.06 ppm. The CH_3 groups C(19) and (C20) resonance at 11.91 and 17.93 ppm, respectively. Their computed values are at between 11.97 and 19.90 ppm with various theoretical methods (Table 3).

The ^{1}H-NMR chemical shift values (with respect to TMS) have been calculated to be -0.4–5.56 ppm with HF level, -0.31–5.22 ppm with B1LYP level, -0.29–5.20 ppm with B3LYP level, -0.22–5.30 ppm with B3P86 level, -0.16–5.57 ppm with B3PW91 level, -0.32–5.34 ppm with MPW1PW91 level. Meanwhile, the O-H signal was obtained as -0.43–0.51 (C3) and -0.43–0.33 (C7) ppm theoretically. The H17 signals was observed as 4.81 ppm, this signal was computed as 5.11–5.56 ppm by HF and DFT theories with the 6-31G basis set, and 4.82–5.89 ppm with the 6-31G(d) basis set. We have also reported the theoretical and the experimental chemical shifts of linearol (see Supplementary material, Fig. S2) in detail, and the obtained results are shown in Tables 3 and 4. It can be deduced that the MPW1PW91 level with 6-31G(d) basis set is the best method for ^{13}C-NMR and the B3PW91 level with 6-31G(d) basis set is the best method for ^{1}H-NMR. The correlation values for proton and carbon chemical shifts are 0.9285 and 0.9984.

Table 3

Experimental and theoretical ^{13}C-NMR chemical shifts of linearol (in ppm, and see Supplementary material)

	Exp,	**HF/ 6-31G**	**HF/ 6-31G(d)**	**B3LYP/ 6-31G**	**B3LYP/ 6-31G(d)**	**MPW1PW91/ 6-31G**	**MPW1PW91/ 6-31G(d)**
C1	38.37	28.28	32.23	39.27	38.22	38.50	35.25
C2	27.28	26.04	27.03	30.55	30.91	29.63	27.78
C3	72.21	69.01	64.86	79.96	75.12	77.69	71.10
C4	38.76	38.60	35.53	47.70	44.22	44.51	39.05
C5	38.73	36.07	34.09	45.25	42.82	43.11	38.60
C6	26.44	27.12	27.06	32.03	31.65	31.11	28.53
C7	76.84	71.28	67.07	81.51	77.04	79.18	72.98
C8	47.93	43.38	39.68	53.03	49.27	50.10	44.34
C9	50.22	45.75	42.91	54.99	52.37	52.39	47.70
C10	38.27	35.25	32.47	45.07	41.67	41.80	36.38
C11	17.81	16.71	16.23	21.68	20.65	20.62	17.35
C12	33.51	29.59	28.97	36.44	35.69	35.45	32.55
C13	43.62	40.06	37.44	48.04	45.70	46.60	42.17
C14	38.14	35.26	33.54	42.04	40.55	41.02	37.37
C15	44.01	43.42	39.63	48.39	45.85	48.09	43.32
C16	154.95	158.69	149.69	152.67	148.07	153.14	146.53
C17	103.55	108.40	103.57	102.65	100.97	105.05	101.18
C18	66.01	67.80	63.24	74.85	70.70	73.53	67.46
C19	11.91	12.90	12.71	14.28	14.09	14.39	11.90
C20	17.93	17.40	17.12	19.33	19.03	19.90	17.22
C21	171.82	189.06	164.54	176.97	162.32	177.91	161.16
C22	21.15	24.10	22.37	22.47	21.44	23.37	19.93

Table 4

Experimental and theoretical ^{1}H-NMR chemical shifts of linearol (in ppm, and see Supplementary material)

	Exp,	**HF/ 6-31G**	**HF/ 6-31G(d)**	**B3LYP/ 6-31G**	**B3LYP/ 6-31G(d)**	**MPW1PW91/ 6-31G**	**MPW1PW91/ 6-31G(d)**
H1a		0.84	0.77	1.17	1.09	1.16	1.07
H1b		1.56	1.41	1.85	1.74	1.88	1.75
H2a		1.04	1.05	1.08	1.08	1.09	1.08
H2b		1.74	1.53	2.02	1.81	2.03	1.80
H3	3.53	3.58	3.48	4.14	4.01	4.09	3.98
H5		1.51	1.27	2.23	2.01	2.24	2.01
H6a		0.87	0.81	1.13	1.09	1.16	1.12
H6b		1.53	1.32	2.06	1.87	2.05	1.84
H7	3.67	3.21	3.11	3.69	3.65	3.63	3.59
H9		1.46	1.20	1.99	1.79	1.97	1.76
H11a		1.19	1.16	1.53	1.47	1.53	1.46
H11b		1.53	1.30	1.87	1.68	1.88	1.67
H12a		1.40	1.31	1.58	1.50	1.59	1.49
H12b		1.44	1.34	1.76	1.68	1.78	1.68
H13	2.72	2.40	2.34	2.55	2.55	2.58	2.57
H14a		1.02	0.92	1.33	1.25	1.36	1.25
H14b		1.43	1.41	1.84	1.82	1.86	1.83
H15a		2.65	2.26	2.81	2.52	2.85	2.52
H15b		2.51	2.22	2.74	2.53	2.75	2.52
H17a	4.81	5.46	4.93	5.11	4.82	5.26	4.94
H17b	4.81	5.56	5.01	5.20	4.88	5.35	5.00
H18a	3.99	3.69	3.15	3.60	3.25	3.63	3.26
H18b	4.07	4.58	4.33	4.94	4.73	4.94	4.74
H19a		0.57	0.52	0.58	0.55	0.61	0.56
H19b	0.77	0.99	0.90	1.12	1.02	1.16	1.03
H19c		2.21	1.69	2.21	1.77	2.24	1.77
H20a	1.05	1.14	0.98	1.40	1.20	1.43	1.21
H20b	1.05	1.11	1.01	1.38	1.27	1.41	1.28
H20c	1.05	0.80	0.67	0.97	0.83	1.03	0.87

CONCLUSIONS

Linearol (**1**) characterized by using spectral methods has been isolated from *Sideritis stricta* Boiss. & Heldr. and *Sideritis brevidens* P.H.Davis, The structural parameters, vibrational frequencies, infrared intensities, ^{1}H- and ^{13}C-NMR chemical shifts of linearol in the ground state have been calculated by using DFT and HF methods with both 6-31G and 6-31G(d) basis sets. The experimental and theoretical vibrational analysis of linearol has also been performed for the first time. The calculated vibrational frequencies have been compared with that obtained from the experimental IR spectrum. Experimental fundamentals are found to have slightly a better correlation for DFT methods than HF methods. Moreover, ^{1}H- and ^{13}C-NMR chemical shifts have been compared with experimental values. The DFT results with 6-31G(d) basis set have shown better fit to experimental ones than HF methods in evaluating ^{1}H- and ^{13}C-NMR chemical shifts.

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REFERENCES

1. E. Kupeli, F.P. Sahin, İ. Çalıs, E. Yeşilada and N. Ezer, *J. Ethnopharmacology*, **2007**, *112*, 356-360.

2. F. Piozzi, M. Bruno, S. Rosselli and A. Maggio, *Nat. Prod. Chem.*, **2006,** *33*, 493-540.
3. E. Gonzalez-Burgos, M.E. Carretero and M.P. Gomez-Serranillos, *J. Ethnopharmacology*, **2011**, *135*, 209-225.
4. S. Çarıkçı, T. Kılıç, A. Azizoglu and G. Topçu, *Rec. Nat. Prod.*, **2012**, *6*, 101-109.
5. X. Liu, T. Berezniak, J. J. Panek and A. Jezierska-Mazzarello, *Chem. Phys. Lett.*, **2013**, *557*, 140-144.
6. B. de las Heras and S. Hortelano, *Inflammation & Allergy - Drug Targets*, **2009**, *8*, 28-39.
7. B. de las Heras, S. Hortelano, N. Girno, P. Bermejo, B. Rodríguez and L. Bosca, *British J. Pharmacology*, **2007**, *152*, 240-255.
8. H.I. Ugras, U. Cakir, A. Azizoglu, T. Kılıc and C. Erk, *J. Incl. Phenom. Macrocycl. Chem.*, **2006**, *55*, 159-165.
9. G. Topçu and A. C. Gören, *Rec. Nat. Prod.*, **2007**, *1*, 1-16.
10. L. N. Monsalve, S. Rosselli, and M. Bruno and A. Baldessari, *Eur. J. Org. Chem.*, **2005**, *10***,** 2106-2115.
11. M. Bruno, S. Rosselli, I. Pibiri, N. Kilgore and K.-H. Lee, *J. Nat. Prod.*, **2002**, *65*, 1594-1597.
12. C. Tablet, L. Dumitrache, L. Minea and Mihaela Hillebrand, *Rev. Roum. Chim.*, **2012**, *57*, 665-673.
13. J. Weinberg, D.A. Lerner and C. Bălăceanu-Stolnici, *Rev. Roum. Chim.*, **2007**, *52*, 759-764.
14. B. M. Fraga, *Phytochemistry*, **2012**, *76*, 7-24.
15. S. Çarıkçı, Ç. Çöl, T. Kılıç and A. Azizoglu, *Rec. Nat. Prod.*, **2007**, *1*, 44-50.
16. W.J. Hehre, L. Radom, P.v.R. Schleyer and J.A. Pople, "Ab initio molecular orbital theory", Wiley, New York, 1986, p. 548.
17. M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A.Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa,M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox,H.P. Hratchian, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E.Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y.Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S.Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K.Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J.Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L.Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M.Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez and J.A.Pople, Gaussian 03. Revision C02, Gaussian Inc., Pittsburgh, PA. 2003.
18. M. Wolniak, M. Tomczyk, J. Gudej and I. Wawer, *J. Mol. Struct.*, **2006**, *825*, 26-31.
19. T. Hökelek, E. Kilic and A. Öztemer, *Anal. Sci.*, **1999**, *15*,1167-1168.
20. A. Azizoglu, Z. Özer and T. Kilic, *Collect. Czech. Chem. Comm.*, **2011**, *76*, 95-114.
21. A. Ungurean, N. Leopold, L. David and V. Chis, *Spect. Chim. Acta A*, **2013**, *102*, 52-58.
22. T. Izgi, O. Alver, C. Parlak, M.T. Aytekin and M. Senyel, *Spect. Chim. Acta A*, **2007**, *68*, 55-62.
23. Z. Dega-Szafran, A. Katrusiak and M. Szafran, *J. Mol. Struct.*, **2008**, *891*, 258-265.
24. M. Balci, "Basic ^{1}H- and ^{13}C-NMR Spectroscopy", Elsevier, Amsterdam, 2005, p. 430.