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Structural Characterization of Two Novel, Biological Active Chalcone Derivatives, Using Density Functional Theory Studies

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Abstract: Xanthohumol is a prenylated chalcone derived from hops and very well known for its biological activity as an anticancer agent. We have previously reported a complete computational evaluation of two novel chalcone derivatives, substituted with diethanolamine on the second ring with increased biological activity. Herein, using density functional theory studies, we are representing a complete structural evaluation of these two molecules. It seems that the significant alterations on their spectroscopic data are responsible for their higher biological activity.

Keywords: xanthohumol; DFT; spectroscopy; biological activity.

1. Introduction

The xanthohumol molecule and some of the xanthohumol analog molecules such as Isoxanthohumol, 6-Prenylnaringenin, and 8-Prenylnaringenin, have been studied extensively by the researchers as potential drugs, especially because of their anticancer [1, 2, 3], antimicrobial [4-7], and antioxidant activities [8-12]. Moreover, several studies indicated apoptotic activity against different cancer cell lines [13-15, 16]. XN's antimicrobial and antioxidant activity was revealed because of the antimicrobial and antioxidant capacity of beer that has been discussed earlier [17, 18]. XN is a prenylated chalcone that can be found extensively in high amounts in hops and eventually into the beer as one of the main flavonoids [19].

Hops are responsible for the beer's bitter taste and contribute significantly to its quality and nutritional value [20]. In medicinal chemistry, XN is playing a serious role with many researchers from chemical and biological backgrounds trying to test the chalcone against obesity [21], menopause [22], cholesterol levels [23], infections [24], and cancer [25-29, 30, 31].

2. Materials and Methods

Density functional theory studies performed using the B3LYP/6 311++G(d,p) level of theory. The use of a one-dimensional potential energy surface is used to predict the reactivity of the design molecules [32-35]. The molecules were developed with Avogadro software [36],

the computational chemistry performed with ORCA 4.2 software [37] and the spectrum representation was done using the Gabedit software [38].

3. Results and Discussion

Xanthohumol molecules can be found in beer hops and are very well know for the anti-inflammatory, antibacterial and anticancer activity. In recent work, we have studied the activity of these molecules against several colon cancer-related proteins [39] theoretically. We found that the results were in correlation with other *in vitro* studies so, we decided if we could increase the biological binding affinity on that proteins by altering the structures of the molecules. By doing that, we have created two novels substituted on their second phenolic ring derivatives of Xanthohumol and 8-Prenylnaringenin. The interesting fact here is that the substituted molecules increased the studied proteins' binding affinity. So, we decided that further structural elucidation of that molecules to be done to correlate their structure to action activity is necessary. As we can see from Figure 1, Xanthohumol and Xanthohumol-Dea substituted molecules have slightly different IR spectra. The two strong absorptions located at 1225 and 1750 cm^{-1}, belong to C-O-C and C=O major functional group, respectively [40, 41]. The discrimination here is that the strong absorption at 3650-3590 cm^{-1}, which belongs to the -OH group is stronger for the substituted molecule as it has 5 -OH groups in comparison with Xanthohumol which has three. The 8-Prenylnaringenin IR spectrum is very similar to its correspondence 8-Prenylnaringenin-Dea substitute, differentiated only at 3650-3590 cm-^{1} again because of the increase of the hydroxyl groups of the substitute analog.

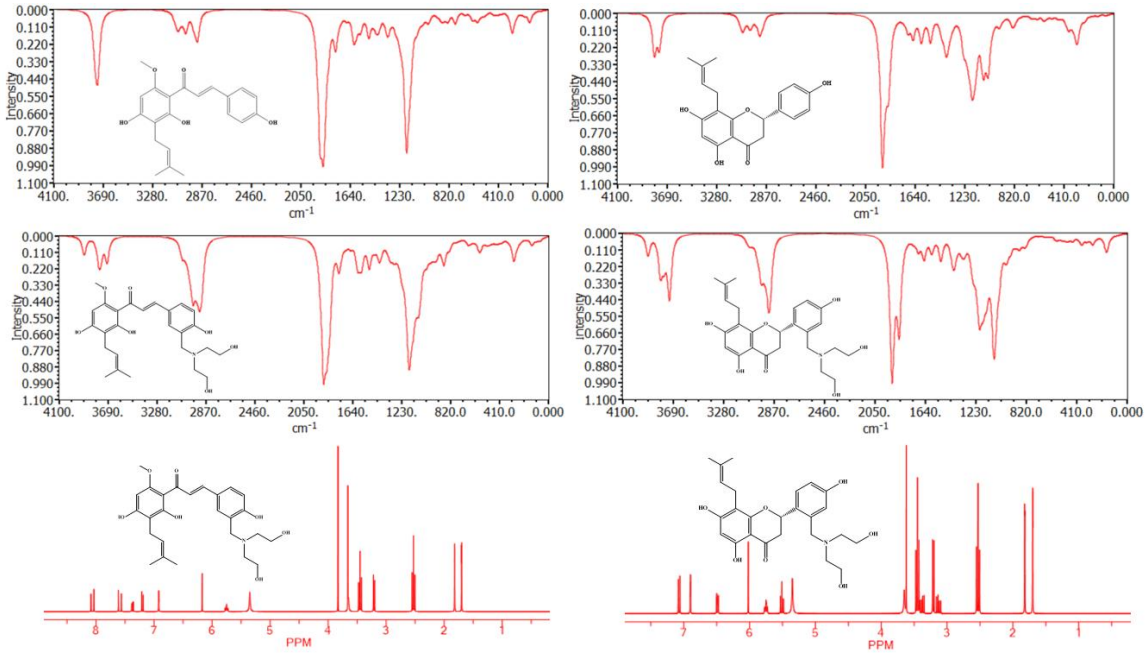

Figure 1. IR and NMR spectrum of the two novel chalcone derivatives.

Regarding the ^{1}HNMR spectrum, at 2.5 and 3.65 ppm, we can see the protons belonging to the diethanolamine molecule moiety. The calculated bond lengths and angles of Xanthohumol-Dea and 8-Prenylnaringenin-Dea can be found in Table 1. The full geometry of the molecules can be found in supplementary tables, S1 Table and S2 Table.

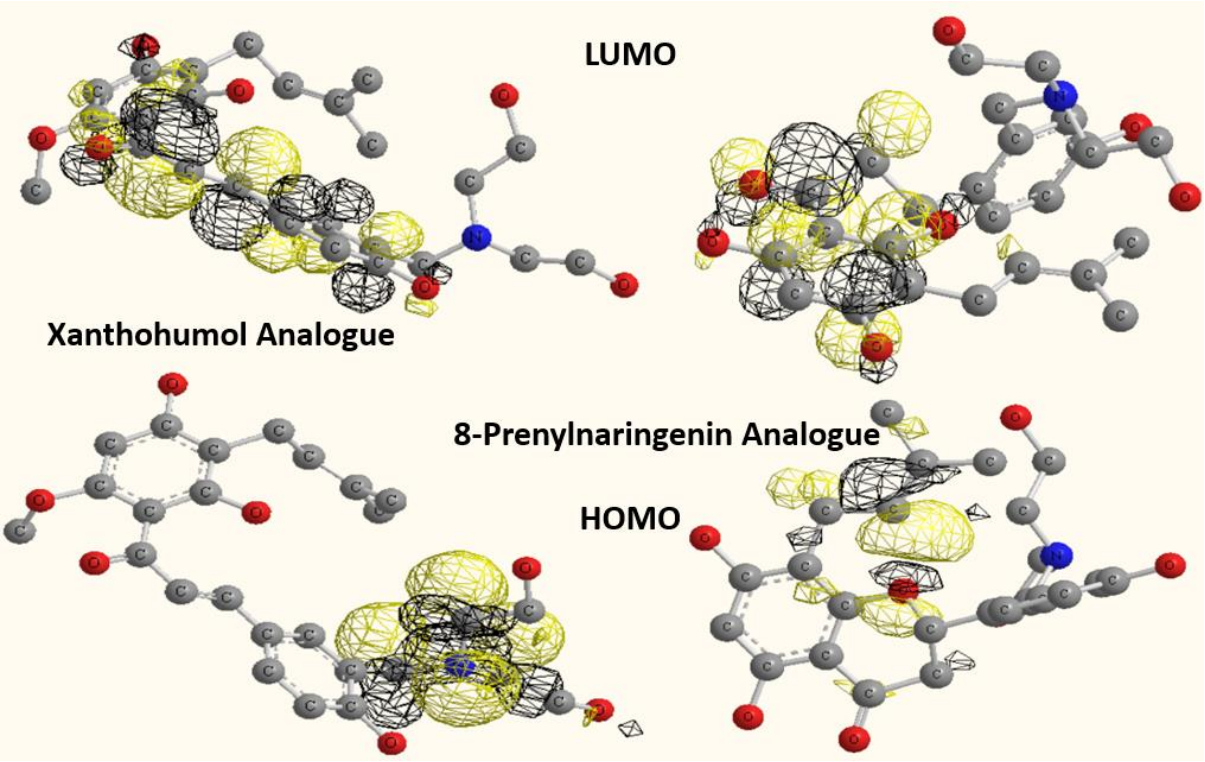

Figure 2. LUMO-HOMO orbitals of Xanthohumol and 8-Prenylnaringenin derivatives.

Using TDDFT studies, we were able to calculate the molecular orbitals of the two molecules as well. The value of the energy difference between HOMO and LUMO as well as the highest occupied molecular orbital (E_{HOMO}) and lowest unoccupied molecular orbital (E_{LUMO}) energies plays a very important role in the stability and reactivity of molecules. The E_{HOMO} energies of molecules show the molecule's ability to give electrons. On the other hand, E_{LUMO} characterizes the ability of the compound to accept electrons. Electronegativity (χ) is a measure of an atom's power to attract a bonding pair of electrons.

Based on equation $\chi = -(E_{HOMO} + E_{LUMO})$ 2 larger Δ_{gap} always indicates lower chemical reactivity and higher kinetic stability of the investigated species. The chemical reactivity of molecules is caused by the simultaneous effect of different parameters. The distribution and energy of HOMO is an important parameter to explain the antioxidant potential of phenolic antioxidants. The electron-donating capacity of the molecule can be predicted by looking at the energy values of HOMO. The value of the energy difference between HOMO and LUMO as well as the highest occupied molecular orbital (E_{HOMO}) and lowest unoccupied molecular orbital (E_{LUMO}) energies plays a very important role in stability and reactivity [42, 43]. In Figure 2, we can observe the HOMO-LUMO orbitals of the studied molecules. In particular, in the Xanthohumol derivative, the LUMO orbital equals -5.530 eV while the HOMO orbital equals -9.070 eV. On the other hand, regarding the 8-Prenylnaringenin derivative, the LUMO orbital equals -2.672 eV, and the HOMO orbital equals -5.173 eV. Based on that, the Xanthohumol derivative is more electronegative than the 8-Prenylnaringenin derivative (larger Δ_{gap}), which means that 8-Prenylnaringenin is a more reactive molecule than Xanthohumol. The full atomic charges profile of the molecules can be found in S1 and S2 Table.

Based on the above, we can see why these two molecules exhibit good anticancer potential activity, and we believe that the next step is the *in vitro* investigation of the synthesized molecules.

Table 1. Selected bond lengths and angles of the two chalcone derivatives.

Xanthohumol Derivative	Bond Length (Å)	Bond Angle	Bond Angle °
O(34)-H(67)	0.9610	H(67)-O(34)-C(33)	109.2515
C(33)-H(66)	1.1110	H(66)-C(33)-H(65)	109.4346
C(33)-H(65)	1.1110	H(66)-C(33)-O(34)	107.1432
C(33)-O(34)	1.4080	H(66)-C(33)-C(32)	111.2957
C(32)-H(64)	1.1130	H(65)-C(33)-O(34)	106.4787
C(32)-H(63)	1.1130	H(65)-C(33)-C(32)	112.8275
C(32)-C(33)	1.5140	O(34)-C(33)-C(32)	109.3932
O(31)-H(62)	0.9610	H(64)-C(32)-H(63)	107.1842
C(30)-H(61)	1.1110	H(64)-C(32)-C(33)	108.6036
C(30)-H(60)	1.1110	C(33)-C(32)-N(28)	113.8698
C(30)-O(31)	1.4080	H(62)-O(31)-C(30)	109.3392
C(29)-H(59)	1.1130	H(61)-C(30)-H(60)	109.5652
C(29)-H(58)	1.1130	H(61)-C(30)-O(31)	107.1315
C(29)-C(30)	1.5140	H(61)-C(30)-C(29)	111.3585
N(28)-C(32)	1.4380	H(60)-C(30)-O(31)	106.3492
N(28)-C(29)	1.4380	H(60)-C(30)-C(29)	112.7064
C(27)-H(57)	1.1130	O(31)-C(30)-C(29)	109.4585
C(27)-H(56)	1.1130	H(59)-C(29)-H(58)	107.0890
C(27)-N(28)	1.4380	H(59)-C(29)-C(30)	109.1427
O(26)-H(55)	0.9720	C(33)-C(32)-N(28)	113.8698
C(25)-C(27)	1.4970	H(62)-O(31)-C(30)	109.3392
8-Prenylnaringenin Derivative	**Bond Length (Å)**	**Bond Angle**	**Bond Angle °**
O(33)-H(64)	0.9610	H(64)-O(33)-C(32)	109.3757
C(32)-H(63)	1.1110	H(63)-C(32)-H(62)	109.4744
C(32)-H(62)	1.1110	H(63)-C(32)-O(33)	107.2782
C(31)-H(61)	1.1130	H(63)-C(32)-C(31)	111.3428
C(31)-H(60)	1.1130	H(62)-C(32)-O(33)	106.5672
O(30)-H(59)	0.9610	H(62)-C(32)-C(31)	112.6167
C(29)-H(58)	1.1110	O(33)-C(32)-C(31)	109.3117
C(29)-H(57)	1.1110	H(61)-C(31)-H(60)	106.4268
C(28)-H(56)	1.1130	H(61)-C(31)-C(32)	109.4620
C(28)-H(55)	1.1130	H(59)-O(30)-C(29)	109.4713
C(26)-H(54)	1.1130	H(58)-C(29)-H(57)	109.0734
C(26)-H(53)	1.1130	H(58)-C(29)-O(30)	106.6903
C(25)-H(52)	1.1130	H(58)-C(29)-C(28)	112.5453
C(25)-H(51)	1.1130	H(57)-C(29)-O(30)	106.5982
C(25)-H(50)	1.1130	H(57)-C(29)-C(28)	112.5316
O(24)-H(49)	0.9720	O(30)-C(29)-C(28)	109.0664
O(23)-H(48)	0.9720	H(56)-C(28)-H(55)	103.8769
O(22)-H(47)	0.9720	H(56)-C(28)-C(29)	108.9133
C(20)-H(46)	1.1000	H(59)-O(30)-C(29)	109.4713
C(18)-H(45)	1.1000	C(31)-N(27)-C(28)	113.6412
C(17)-H(44)	1.1000	C(31)-N(27)-C(26)	110.6734

4. Conclusions

In this short communication, we have evaluated the structural characteristics of two novel chalcone derivatives with potential biological activity. We have compared the structures with ones of Xanthohumol and 8-Prenylnaringenin (parental molecules) and gave a possible explanation about their increased binding affinities in colon cancer-related properties. Future applications were also discussed.

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None.

Conflicts of Interest

None.

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