

# Antioxidant activity of some khellin derivatives: a density functional theory study

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Received 25 July 2018

Accepted 16 August 2018

Egyptian Pharmaceutical Journal 2018, 17:212–217

## Background

The antioxidant activity of some benzofuran and 2*H*-pyran-2-one derivatives of naturally occurring khellin and visnagin was theoretically investigated using a quantum chemical method, density functional theory. These molecules possess a variety of biological and pharmacological activities including antioxidant activity.

## Materials and methods

The calculations were carried out using Gaussian 03 computational package in gas phase with the purpose of obtaining the intrinsic properties of the molecules studied, free of any interaction. The geometries of neutral species and their respective radicals and radical cations were optimized using PM3 and density functional theory/B3LYP calculations with cc-pVDZ basis set.

## Results

As they possess O-H, N-H, or both O-H and N-H bonds, we chose to investigate theoretically their antioxidant activity via H-atom transfer or single electron transfer pathway. In the gas phase, the ionization potential, the highest occupied molecular orbital (HOMO), bond dissociation energies of hydroxyl group O-H and N-H [bond-dissociation enthalpy (BDE)<sub>O-H</sub>–BDE<sub>N-H</sub>], and spin density distribution are carried out. Molecule 14 showed potential antioxidant activity as BDE for the N-H bond was found to be 84.71 and for the O-H bond was 85.32, whereas the ionization potential was 6.26 and the E<sub>HOMO</sub> was 5.39.

## Conclusion

Based on the antioxidant activities of 15 derivatives of naturally occurring khellin and visnagin, they were found to be potent antioxidant compounds comparable to quercetin or vitamin C.

## Keywords:

antioxidant, bond dissociation energy and ionization potential, density functional theory, free radicals, khellin derivatives

Egypt Pharmaceut J 17:212–217

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1687-4315

## Introduction

Antioxidants are chemical compounds that can quench the reactive radical intermediates formed during the oxidative reactions. The primary antioxidants comprise essentially sterically hindered phenols and secondary aromatic amines [1–3]. These antioxidants usually act through both chain transfer and chain termination.

In this study, the antioxidant activity of some benzofuran and 2*H*-pyran-2-one derivatives of naturally occurring khellin and visnagin was theoretically calculated using a quantum chemical method, density functional theory (DFT). The aforementioned molecules possess a variety of biological and pharmacological activities. Benzofuran derivatives possess antimicrobial [4–6], bacteriostatic, bacterial, fungi static, and fungicidal activities [7–10], whereas 2*H*-pyran-2-one derivatives represent a new class of HIV protease inhibitors [11,12]. As these molecules possess O-H, N-H, or both O-H and N-H bonds, we choose to investigate theoretically their antioxidant activities to have a new insight about their antioxidant activity.

Similar studies have been carried out earlier through using different classes of compounds [13,14]. To our knowledge, the antioxidant properties of khellin derivatives have never been investigated. The selection of these compounds was based on their chemical structure characteristics.

Benzofuran derivatives are synthesized and tested by Hassaneen *et al.* [15]. The 2*H*-pyran-2-one derivatives are synthesized and tested by Keshk [16]. Their antioxidant activities are discussed in the connection with the ionization potential (IP), highest occupied molecular orbital (HOMO), bond dissociation energies of hydroxyl group O-H or N-H (BDE<sub>O-H</sub> or BDE<sub>N-H</sub>), and spin density distribution.

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There are mainly two pathways through which antioxidants can scavenge the free radicals:

In the first one, the free radical gains a hydrogen atom from the radical scavenger, which becomes a radical:



The occurrence of such a hydrogen transfer is determined by the bond-dissociation enthalpy (BDE).

In the second mechanism, the radical scavenger gives an electron to the radical:



In that case, the IP is the significant energy factor of the reaction [17].

## Materials and methods

All calculations were carried out using Gaussian 03 computational package [18] in gas phase with the purpose of obtaining the intrinsic properties of the molecules studied, free of any interaction. The geometries of neutral species and their respective radicals and radical cations were optimized using PM3 and DFT/B3LYP calculations with cc-pVDZ basis set. Each stationary point was characterized as a minimum by analytical frequency calculations. Unrestricted open-shell calculations were used for radical species.  $BDE_{O-H}$  or  $BDE_{N-H}$  was calculated using the following formula:

$$BDE = E(ArOH^{\bullet}) + E(H^{\bullet}) - E(ArOH) \quad (3)$$

IP values in the gas phase were calculated using the following formula:

$$IP = E(ArOH^{\bullet+}) - E(ArOH) \quad (4)$$

## Results and discussion

The studied compounds are divided into two series: set 1, regrouped compounds with 4,6,7 trimethoxybenzofuran, whereas in set 2, the compounds have in common 4,7 dimethoxybenzofuran fragment (Figs 1 and 2).

### Highest occupied molecular orbital

The frontier orbital energy is an important parameter of molecular electron structure; the molecule that has the higher HOMO is the good electron donor [19]. The HOMO disposition of the molecule indicates its site scavenging free radicals. The HOMO values are showed in Table 1.

For the set 1, molecule 1 has the higher HOMO energy (-5.60 eV). In comparison, this value is

higher than the HOMO of vitamin C (-5.64 eV), quercetin (-5.70 eV), morin (-5.65 eV), and galangin (-5.87 eV) but lower than the HOMO energy of trolox and  $\alpha$ -tocopherol (-5.23 eV).

These results show that molecule 1 possesses very high radical trapping potential, similar to flavonoids. When the phenyl group in molecule 1 is replaced by methyl group in molecule 2, the HOMO energy decreases by 0.37 eV and also its electron donating ability decreases.

Molecule 3 is obtained by replacing the oxo 2*H*-pyran ring fragment by oxo pyridine fragments and the methyl amide fragment by nitrile fragment. From molecule 3 to molecule 4, the HOMO energy increased by 0.22 eV; this demonstrates that the presence of malononitrile instead of oxygen atom makes the molecule more electron donating.

In the case of molecule 5 (benzofuran 1*H*-pyrazole), its HOMO energy is -5.73 eV, comparable to the quercetin HOMO energy (-5.70 eV), which indicates that molecule 5 exhibit a good nucleophilic property.

In molecules 9, 6, 7 and 8, the benzofuran ring is attached to a fragment 4-nitrophenyl with different ramifications as shown in Fig. 1. These molecules have HOMO energy higher than molecule 1, so they possess more nucleophilic characteristics than molecule 1.

The second set of molecules represents the fragment 4,7 dimethoxybenzofuranol rings attached to different substituent as shown in Fig. 2. The HOMO energy of these molecules is higher than that of the molecule of set 1 and flavonoids. The HOMO is attributed to molecule 14 (-5.39 eV), so this type of molecules is a good donor of electrons.

### Ionization potential

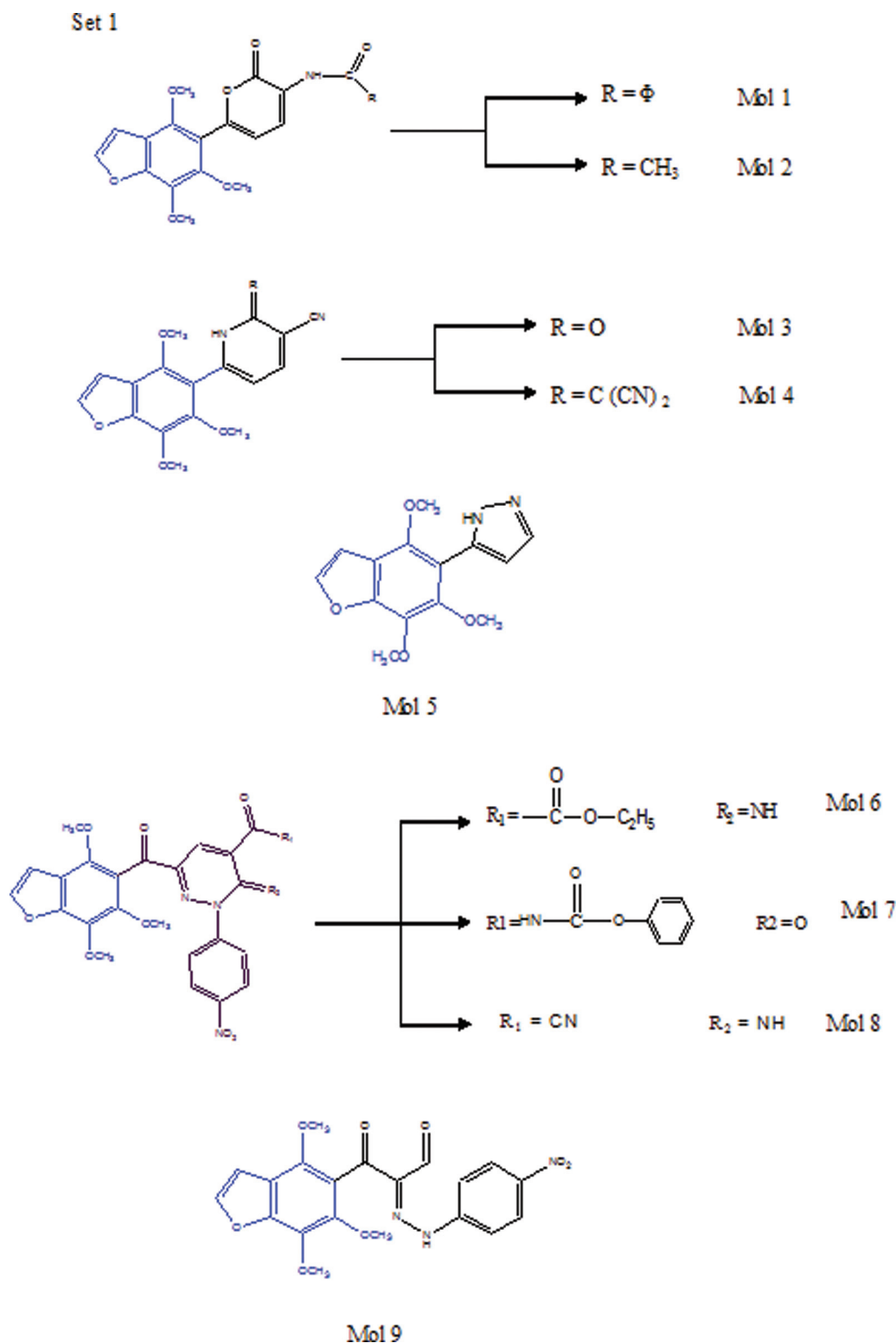
The IP represents the ease of electron donation, which provides hint toward the possible single electron transfer mechanism of these compounds; low IP values are favorable to raise the electron transfer reactivity [19].

Our results showed that the lowest IP of 6.26 eV is attributed to molecule 14, which has both O-H and N-H bonds. The resonance effect is mainly responsible for the cation free radical stabilization generated after electron abstraction. Therefore, this molecule exhibits excellent antioxidant activities.

### Bond-dissociation enthalpy and spin density

The bond dissociation energy (enthalpy) is the ease of hydrogen donation. The antioxidant potency is

Figure 1



Chemical structure of the compounds of set 1.

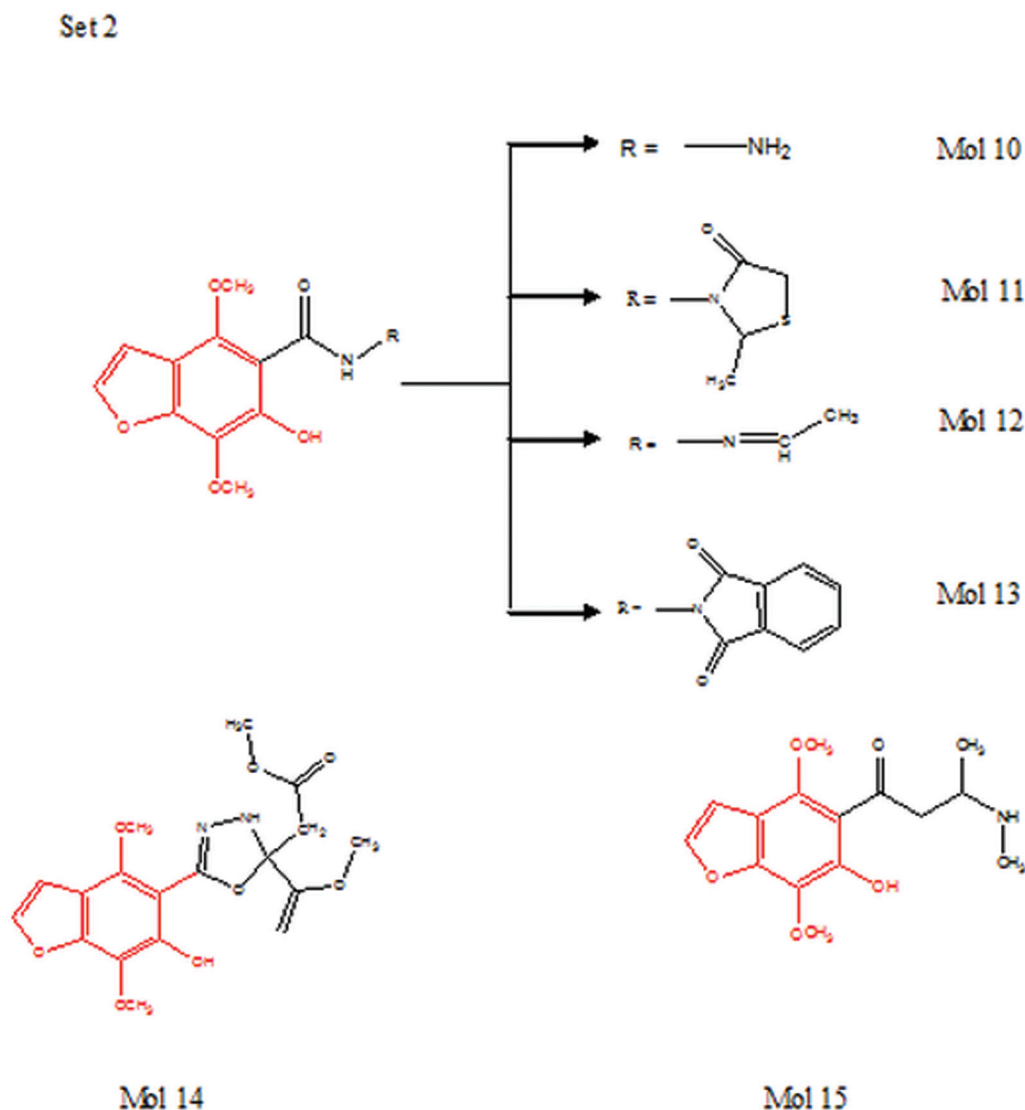
enhanced by relatively low BDE of relevant O-H and N-H bonds in phenol and amines, respectively [20].

In this work, BDEs of studied compounds were approximated from the calculated electronic energies [21]. Klein *et al.* [22] confirmed the plausibility of the assumption that contribution stemming from

transformation of electronic energies to enthalpies and the contribution of solvent will be cancelled at least to a great extent.

The  $BDE_{O-H}$  and the  $BDE_{N-H}$  are listed in Table 1. As can be seen from this table, for the set 1, the order of reactivity of BDEs of N-H groups is

Figure 2



Chemical structure of the compounds of set 2.

9>4>1>2>7>6>8>3>5. The abstraction of the hydrogen in molecule 1 is easy than in molecule 2 because the radical obtained in molecule 1 is more stable by resonance than in molecule 2 (presence of phenyl group). For the molecules 3 and 4, we can conclude that the presence of the two cyano groups makes the hydrogen atom more acidic in nature.

Interestingly, the lowest BDE value is observed with molecule 9 with N-H bond, which is 16.08 kcal/mol lower than that observed with aniline (92.25 kcal/mol) [23]. Thus, explain the high acidity of molecule 9 compared with aniline. The following  $BDE_{N-H}$  reactivity order is observed: 14>10>15>11>12>13.

The highest  $BDE_{N-H}$  value is of molecule 14 which is favored by 8.54 kcal/mol than that obtained for molecule 9. This can be explained by the

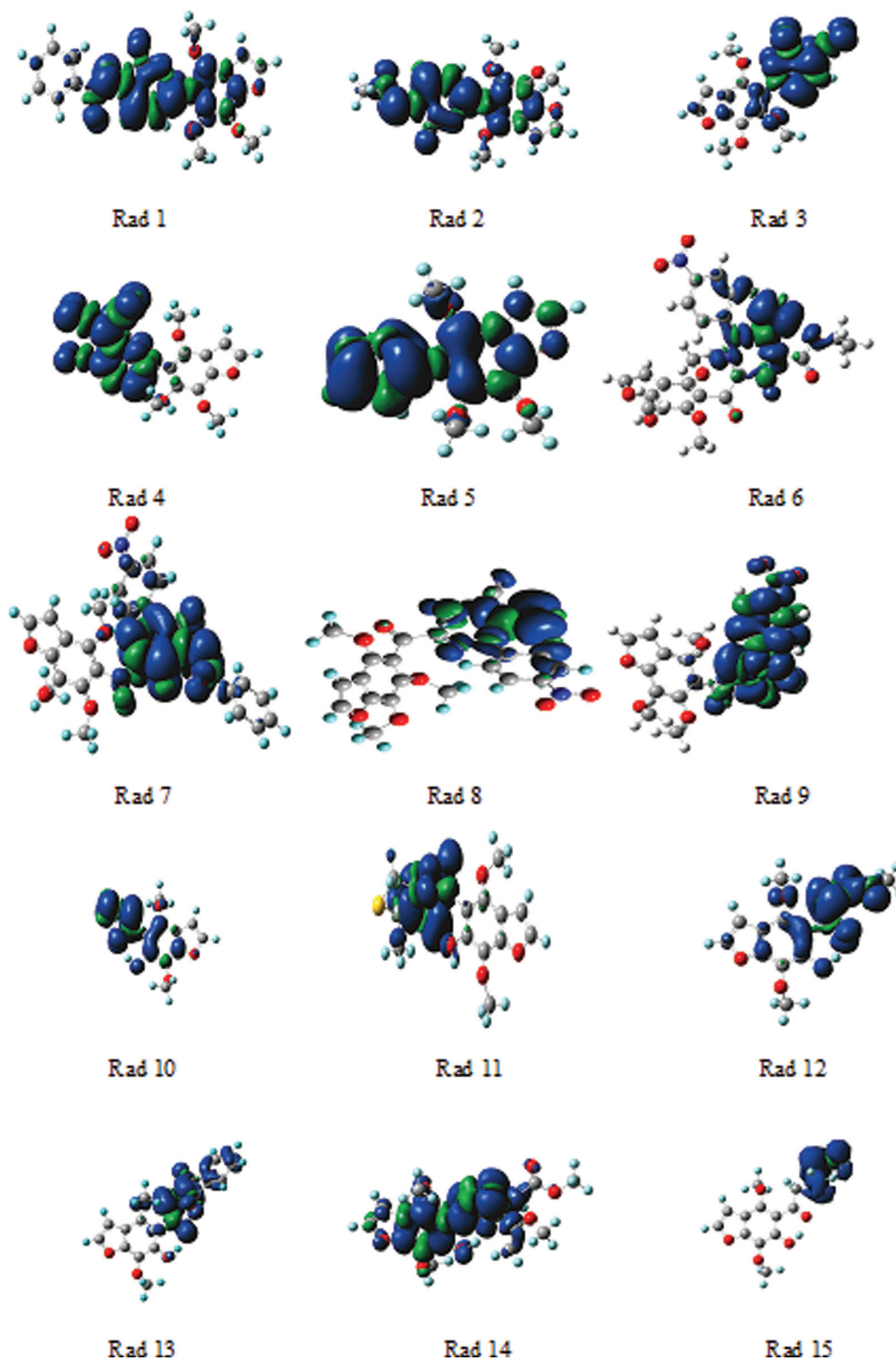
establishment of hydrogen bond between acidic proton and oxygen of carbonyl function.

In addition to N-H bond, O-H bond can also be found in molecules of set 2.  $BDE_{O-H}$  ranges between 74 and 88 kcal/mol compared with flavonoids according to the following order: 11>14>13>15>12≈10.

In molecule 10, the proton forms hydrogen bond with the oxygen of carbonyl function at distance of 1.565 Å. In molecule 14, this distance is 1.736 Å, in molecule 13 is 1.612 Å, in molecule 15 is 1.557 Å, and in molecules 12 and 10 is 1.554 and 1.564 Å, respectively.

In molecule 11, the proton is completely distain of the carbonyl function which explains the reactivity order in this set.

Figure 3



Spin density distribution for the radical of the studied molecules.

The spin density is an important parameter to characterize the stability of the free radicals. The higher the unpaired electron delocalizes, the lower the energy of the radical is, and the more stable the radical will be.

Figure 3 shows the spin density distribution for the radical forms of the studied molecules. We can see that

the global contribution of the near entourage of the abstraction of the hydrogen and the contribution of the trimethoxybenzofuran or dimethoxybenzofuran is small or absent. But the spin density of radical 14 distributes on the whole of molecule, therefore radical 14 is the most stable one, which is stabilized by resonance.



**Table 1** Density functional theory/cc-pVDZ calculated bond dissociation energies (kcal/mol), ionization potential (in eV), and highest occupied molecular orbital energies (eV) of the studied molecules

	BDE	IP	-E <sub>HOMO</sub>
Molecule 1	87.85	6.56	5.60
Molecule 2	93.49	6.66	5.71
Molecule 3	99.77	7.02	5.97
Molecule 4	84.08	7.05	5.75
Molecule 5	106.67	6.74	5.73
Molecule 6	95.38	6.83	6.04
Molecule 7	94.75	6.69	5.64
Molecule 8	98.52	6.91	6.04
Molecule 9	76.14	6.64	5.82
Molecule 10	86.59 <sup>a</sup> 87.22 <sup>b</sup>	6.50	5.51
Molecule 11	95.38 <sup>a</sup> 74.04 <sup>b</sup>	6.72	5.51
Molecule 12	97.89 <sup>a</sup> 87.22 <sup>b</sup>	6.50	5.51
Molecule 13	102.28 <sup>a</sup> 77.81 <sup>b</sup>	6.58	5.59
Molecule 14	84.71 <sup>a</sup> 80.32 <sup>b</sup>	6.26	5.39
Molecule 15	94.12 <sup>a</sup> 85.34 <sup>b</sup>	6.56	5.58
Trolox	77.18	6.67	5.23
Vitamin C	82.20	8.35	6.54
Quercetin	92.24104.7976.5577.1889.73	7.05	5.70
Morin	89.1067.7778.44111.69108.56	7.05	5.65
Galangin	77.81111.69108.56	7.32	5.87

BDE, bond-dissociation enthalpy; HOMO, highest occupied molecular orbital; IP, ionization potential. <sup>a</sup>BDE of the N-H bond. <sup>b</sup>BDE of the O-H bond.

## Conclusion

In this paper, we report B3LYP/cc-pVDZ investigation of 15 molecules of some benzofuran and 2H-pyran-2-one derivative of naturally occurring khellin and visnagin in gas phase.

From DFT investigation of the 15 studied compounds, including HOMO, IP and BDE calculations, the results indicated that molecule 14 exhibited potential antioxidant activity. Further studies will need to be carried out to improve on its antioxidant activity through molecular and structural modification.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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