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ORIGINAL PAPER

Identification of new biologically active synthetic molecules: comparative experimental and theoretical studies on the structure-antioxidant activity relationship of cyclic 1,3-ketoamides

Riad Mustapha Kerbadou[1] · Ratiba Hadjadj Aoul[1] · Aouicha Benmaati[1,2] · Assya Taleb[1] · Salih Hacini[1] · Hadjira Habib Zahmani[1]

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Abstract

Antioxidant agent is a chemical that prevents the oxidation of other chemical substances. Its use is the most effective means of protecting the organism by neutralizing the harmful effects of free radicals caused by oxidative stress. In the present work, a series of β-ketoamides containing a variety of monosubstituted amide groups were synthesized and tested as antioxidant agents. In order to establish a possible structure-antioxidant activity relationship, we are presenting a systematic theoretical study of these molecules with the aim of clarifying the active sites. In particular, we discuss the selectivity resulting from the choice of a free radical/antioxidant system. The theoretical study of these molecules was carried out using density functional theory (DFT) calculations at the B3LYP/6-311G (d,p) level of theory. In order to shed light on the antioxidant properties of β-ketoamides, O–H bond dissociation enthalpies (BDEs), ionization potentials (IPs), electron affinities (EAs), proton affinities (PAs), and electron transfer enthalpies (ETEs) are performed in the gas phase and in ethanol. The results obtained show that the HAT mechanism is thermodynamically more favored in the gas phase, while the SPLET is preferred in the polar solvent.

Keywords β-Ketoamides · Antioxidant activity · Enolamide form · Ketoimidol form · DFT calculations · Mechanism

Introduction

Nowadays, the discovery of simple organic compounds with quantifiable impacts on living systems has consistently attracted the attention of chemists. In this line, antioxidants play an important role in preventing the onset and spread of oxidative diseases such as autoimmune diseases, cardiovascular diseases, neurovascular diseases, and neurodegenerative changes associated with aging [1–3]. In general, there are two basic categories of antioxidants, natural and synthetic ones. Natural antioxidants such as polyphenol-rich foods, fresh fruits, vegetables, or teas [4, 5] have protective effects against the abovementioned diseases and their protection has been partly attributed to the presence of several components such as vitamins [6–10], flavonoids [10], anthocyanins [11, 12], and other phenolic compounds. Several synthetic compounds have also been reported to exhibit a wide range of biological activities, including the antioxidant activity. Amide derivatives have been the focus of growing concern because they are an important class of therapeutic agents [13–15]. Different amides [16], N-(phenoxyalkyl) amides [17], and amides derived from cinnamic acid [18] or indole 2-carboxylic acid [19] or cinnamoyl amino ester or organotellurium compounds [20] possess important antioxidant properties. This makes amide an important lead structure in the creation of novel radical-scavenging compounds with specific functionality.

1,3-Ketoamide compounds are a prevalent structural motif in many natural products and bioactive molecules [21, 22]. In addition, β-ketoamides have been reported to be exceptional synthetic platforms with many adjacent reactive sites [23–26]. In this research, the in vitro antioxidant activity of these

✉ Hadjira Habib Zahmani
habibzahmanihadjira@gmail.com

[1] Laboratoire de Chimie Fine LCF, Université Oran 1 Ahmed Ben Bella, BP-1524-Menouar, 31000 Oran, Algeria

[2] Ecole Nationale Polytechnique d'Oran Maurice Audin, ENPO-MA, BP-1523-Menouar, 31000 Oran, Algeria

compounds was studied; we thought that molecules carrying both amide and ketone functions may be new molecular models likely to present biological properties besides their intriguing organic properties.

Results and discussion

Synthesis of β-ketoamide compounds

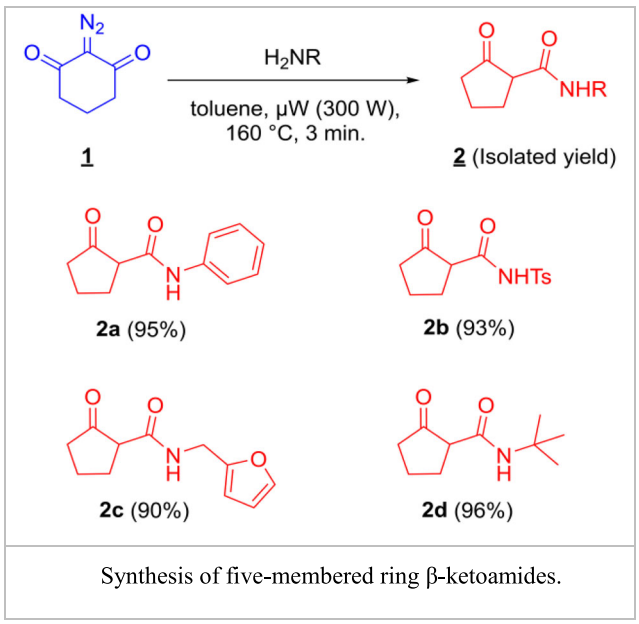
The selected β-ketoamides (**2a-2d**), (**3a-3d**) and (**4**) are prepared using two main methods that are characterized by a transamidation or re-arrangement reaction.

In the first place, the five 1,3-carbonylated cycloalkanones were prepared as follows. These compounds were synthesized by mixing a variety of primary amines and 2-diazodimethylcyclohexane-1,3-dione in toluene at 160 °C under microwave irradiation for 3 min [27] as shown in Scheme 1. These compounds (**2a-2d**) were produced in quantitative yields.

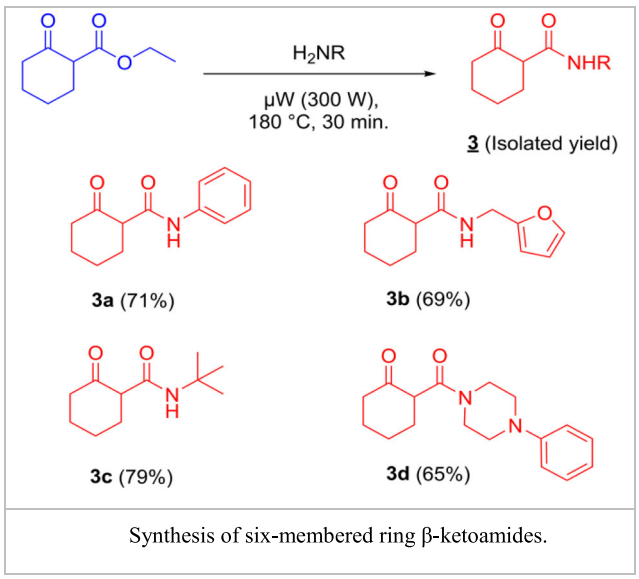
In our laboratory, we have also developed a very practical and economical new method of 1,3-ketoester amidation. The reaction is performed under dry conditions, activated by microwave radiation and does not require a catalyst [28]. Our sequence has a major advantage over other classical reactions: it gives access to β-ketoamides with a relatively short reaction time. The six-membered ring monosubstitued β-ketoamides (**3a-3c**) were obtained by reacting a variety of primary amines with ethyl 2-oxocyclohexane-1- carboxylate in toluene at 180 °C under microwave irradiation for 30 min. We also synthesized a disubstituted β-ketoamide (**3d**) by reacting ethyl 2-oxocyclohexane-1-carboxylate and 1-phenylpiperazine under the same reaction conditions (Schemes 2 and 3). All compounds in this study were purified using column chromatography and characterized by nuclear magnetic resonance (NMR) spectroscopy .

Antioxidant assays

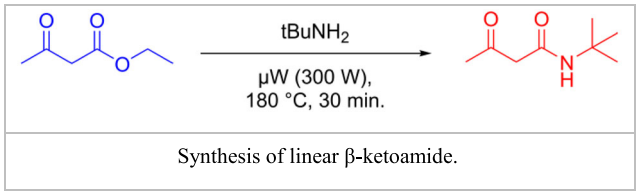
Antioxidants are substances that inhibit or slow down the oxidation of a substrate. They are present in many forms and can intervene to prevent the formation of free radicals, as well as to participate in their elimination. Several approaches are used to test antioxidants in food and biological systems consist of oxidizing the substrate under standard conditions and evaluating the activity using various methods to determine how much oxidation is inhibited. A variety of in vitro chemical methods are therefore used to determine the antioxidant activity of products and ingredients [29]. In the present study, the antioxidant activity of the synthesized compounds was evaluated in vitro by the 1,1-diphenyl-2-picrylhydrazile (DPPH) radical scavenging assay. DPPH is a common reagent used to determine the antioxidant potential as it is characterized as a stable free radical. The electron transfer produces a dark purple color, characterized by an absorption band in a concentrated methanol solution of approximately 517 nm. When a DPPH solution is mixed with an antioxidant compound that can give a hydrogen atom, this results in a reduced form. As a result, the color changes from purple to yellow. Color fading is shown indirectly by the radical-scavenging capacity of the antioxidant.



Scheme 1 Synthesis of five-membered ring β-ketoamides



Scheme 2 Synthesis of six-membered ring β-ketoamides



Synthesis of linear β-ketoamide.

Scheme 3 Synthesis of linear β-ketoamide

DPPH radical scavenging assay

The DPPH radical scavenging test was used to assess the antioxidant activity of our synthesized β-ketoamides. The tests were carried out in ethanol, a low toxic solvent and it is the most common solvent with the highest frequency for the study of antioxidants [30]. In addition, our compounds have shown high solubility in ethanol. A fresh solution of DPPH (4.10–4 M) in ethanol was prepared according to the method of Blois [31]. Ketoamide test samples (10–800 μg/mL) were dissolved in ethanol, and 1 mL of this solution was mixed with 1 mL of DPPH ethanol solutions in a quartz cuvette (2 mL). After a 30-min incubation period at room temperature in the dark, the absorbance of the mixture was measured at 517 nm, ascorbic acid (AA) was used as a reference compound. The tests were performed in duplicate. Percentage radical inhibition of DPPH was calculated using the following equation:

$$\%\text{inhibition of DPPH radical} = ([A_0 - A_1]/A_0) \times 100$$

where A_0 is the control absorbance (DPPH solution without the compound to be tested) and A_1 is the absorbance of the sample.

The half-maximum inhibitory concentration IC_{50} was calculated from the plot graph of the percent inhibition of the DPPH radical to the sample concentration (μg/mL).

Figures 1, 2, to 3 depict the antioxidant activity percentage at various concentrations and IC_{50} of the synthesized compounds. All β-ketoamides showed moderate-to-good antioxidant activity. These values suggested that six-membered ring 1,3-ketoamides compounds showed better antioxidant activity than their five-membered ring counterpart (Fig. 4). In the case of six-membered cyclic compounds, as shown in Fig. 2, the secondary aromatic cyclic β-ketoamides with phenyl or furyl group on the nitrogen (**3a** and **3b**) exhibited potent radical scavenging activity, with IC_{50} values 24.58 ± 1.12 and 45.71 ± 1.67 μg/mL respectively as given in the Table 1 and also represented graphically in Fig. 2. The introduction of aliphatic secondary amide (**3c**) makes the compound slightly less active 85.36 ± 1.82 μg/mL (Table 1). Replacement of secondary amide function by tertiary amide leads to a very sharp decrease in anti-radical power (**3d**) 172.64 ± 2.36 μg/mL. Five-membered ring 1,3-ketoamide showed moderate antioxidant activity; their IC_{50} values are in the range of 96.74 ± 2.15 to 146.02 ± 3.52 μg/mL. The most active substances were those containing tosyl or phenyl groups present on nitrogen (**2a** and **2b**) 100.08 ± 2.82 and 96.74 ± 2.15 μg/mL, respectively. It can also be concluded from the results that

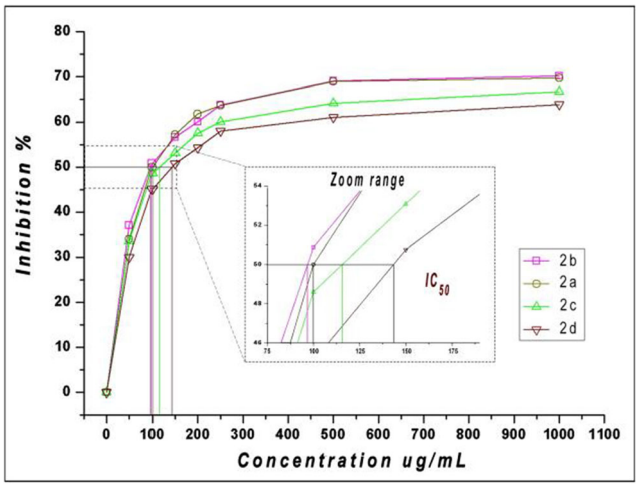


Fig. 1 Graphical representation of scavenging activity of five-membered ring β-ketoamides (**2a-2d**) in DPPH assay

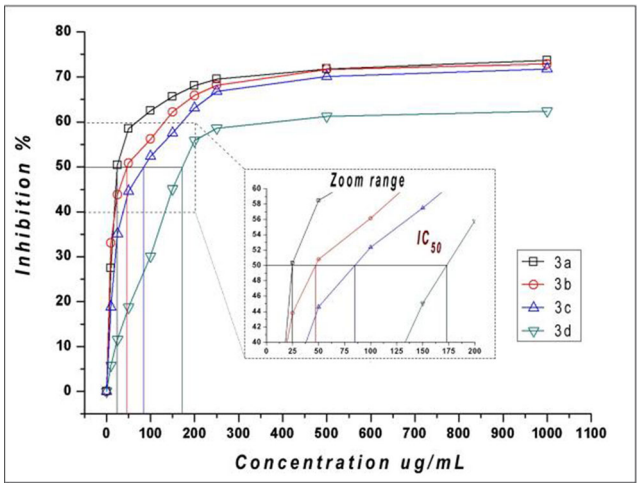


Fig. 2 Graphical representation of scavenging activity of six-membered ring β- ketoamides (**3a-3d**) in DPPH assay

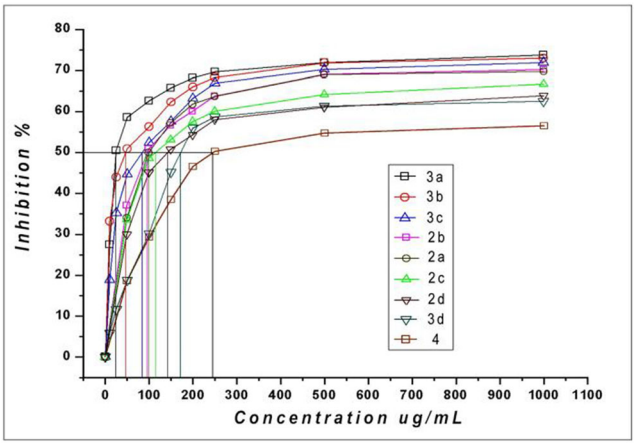


Fig. 3 Scavenging activity of β-ketoamides in DPPH assay

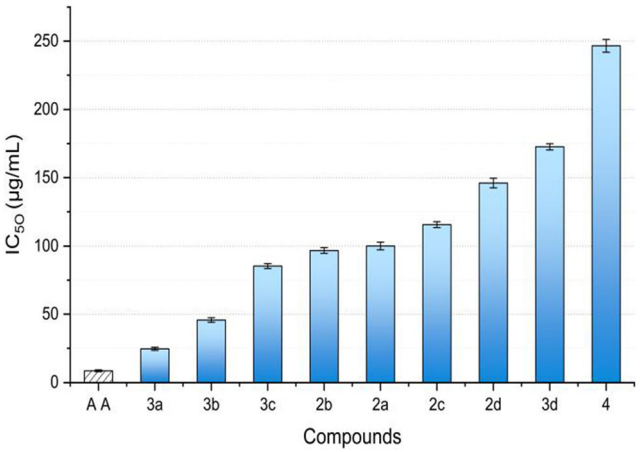


Fig. 4 IC_{50} values (μg/mL) of β-ketoamides and reference antioxidants in the DPPH assay

N-(tert-butyl)-2-oxocyclopentane-1-carboxamide (**2d**) is the only compound showing low activity 146.02 ± 3.52 μg/mL but slightly higher than its cyclohexane counterpart (**3c**). We also thought of testing a secondary linear ketoamide, the N-(tert-butyl)-3-oxobutanamide (**4**) showed very low activity with IC_{50} value 246.57 ± 4.68 μg/mL, 30 times higher compared to the IC_{50} value of ascorbic acid 8.43 ± 0.66 μg/mL (Table 1).

In order to evaluate the biological activity of our cyclic 1,3 ketoamides, we compared the antioxidant power (IC_{50}) of compound **3a** with different synthesized compounds (amides, urea, and amido-carbonyl oxime) described in the literature [32–34]. Obviously, the free radical scavenging properties of β-ketoamides are better compared to published data for similar compounds (Table 2).

In view of the prospect of this type of antioxidants, we then attempted to complete the study with a detailed computational investigation in order to identify the exact mechanism for the radical scavenging activity of β-ketoamide. The importance of elucidating the relationship between activity and structure will allow to answer the following questions: (i) Which structure is most important for ketoamide to retain antioxidant activity? (ii) Does the hydrogen of amide function take a role on increasing antioxidant activity? (iii) Why did six-membered ring β-ketoamide gave better antioxidant activity than its five-membered ring counterpart?

Table 1 IC_{50} values of the antiradical activities of β-ketoamides and ascorbic acid by DPPH assay

Compounds	IC_{50}±SD (μg/mL)
AA	8.43 ± 0.66
3a	24.58 ± 1.12
3b	45.71 ± 1.67
3c	85.36 ± 1.82
2b	96.74 ± 2.15
2a	100.08 ± 2.82
2c	115.51 ± 2.21
2d	146.02 ± 3.52
3d	172.64 ± 2.36
4	246.57 ± 4.68

The IC_{50} values represent means ± SD of two parallel experiments

Prediction of the antioxidant power by theoretical calculations

Most of the time, antioxidative compounds can be classified into two types: phenolics and β-diketones [35, 36]. Some results prove that the antioxidant activity of phenolic compounds is strongly dependent on their structural features and intrinsically related to the presence of hydroxyl function(s) in the aromatic structure [37, 38]. This type of phenolic compound often acts through its radical-scavenging activity, which is linked to their hydrogen- or electron-donating ability and to the stability of the resulting phenoxyl radicals. β-diketone exhibits keto-enol tautomerism in solution giving the enolate which acts mainly as an electron donor, a mechanism that is more typical for the scavenging activity of phenolic antioxidants [39]. Regarding our β-ketoamide derivatives, including those containing a secondary amide, literature studies on proton exchanges indicated that β-ketoamides containing N-H bond can be in equilibrium with their ketoimidol and enolamide forms [40–42] (Scheme 4).

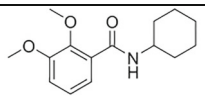
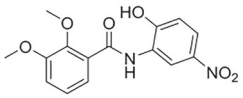
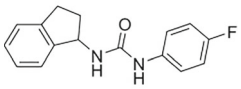
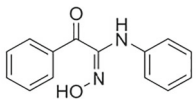
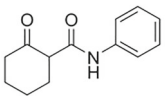
It is believed that one of the two forms of β-ketoamide: enolamide or ketoimidol can play a significant role in scavenging potential. This study was focused on describing the structure–activity relationship of 1,3-ketoamides, with computational chemistry methods. Appropriate assessment of the five-membered ring β-ketoamides (**2a–2d**) and the six-membered ring β-ketoamides (**3a–3c**) were performed using the density functional theory DFT with the restricted Becke's three-parameter hybrid functional (B3) for the exchange part and the Lee–Yang–Parr (LYP) correlation functional in conjunction with 6-311G(d,p) basis set implemented in Gamess-US packages [43]. All optimized structures are confirmed to be real minima by calculating the vibrational frequency at the same theoretical level (no imaginary frequency). Atomic charge and bond order analysis were performed by natural bond orbital (NBO) in order to explain stability of radicals.

Computational methods

Tautomeric equilibrium

Theoretical calculations on the substrates have shown that among the two proposed tautomeric forms, the enolic structure is the lowest in energy. The energy difference (ΔE) between the enolamide and ketoimidol forms is of the order of

Table 2 Comparison of IC_{50} between **3a** and other synthesized compounds

Compounds	Concentration of DPPH solution (μM)	$IC_{50} \pm SD$ (μg/mL)	Ref.
	400	76.50 ± 3.00	[33]
	400	79.30 ± 0.80	[33]
	100	58	[34]
	400	170.47 ± 5.14	[35]
	400	24.58 ± 1.12	This work

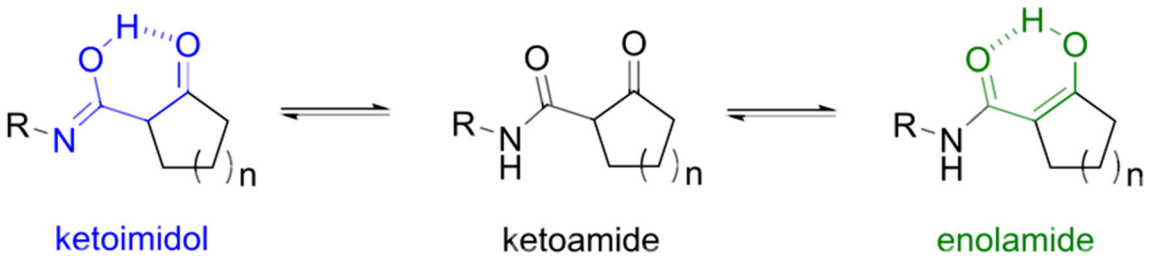
11 to 18 kcal.mol^{-1}, depending on the size of the ring and the substitution of the nitrogen atom (Table 3). Their relative populations were estimated using the Maxwell-Boltzmann distribution ($\exp(-\Delta E/k_BT)$) and it was found that the energy difference between the two forms is very large in favor of the enolamide form with a population of 100%. This result confirms the well-known assertion of the Boltzmann relationship "from a value of ΔE greater than 2 kcal.mol^{-1} the ratio between populations is equal to 100/1." Both forms enolamide and ketoimidol have an intramolecular H-bond, but the observed relative higher stability of the enolamide structure can be attributed to the extension of the conjugation along the enol chain. Consequently, it is the enolamide form that is considered in the remainder of this work.

Calculation of bond dissociation energy (BDE)

The correlation between IC_{50} and the calculated O-H BDE values has shown that the primary BDE values are a good predictor of radical scavenging activity with reasonable accuracy. In this study, the theoretical (BDE) and experimental (IC_{50}) trends in antioxidant activity of the studied structures are compared. The free radical scavenging activity of our β-ketoamides is generally determined by the strength of the O-H bond or the N-H bond, since the hydrogen of these groups is the most labile in the structure of our derivatives.

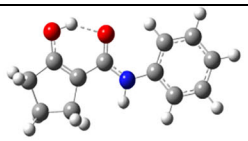
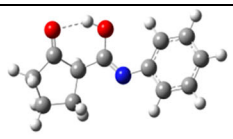
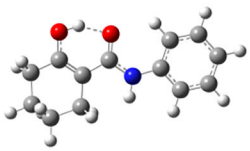
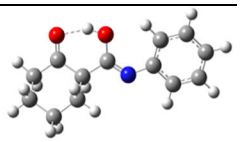
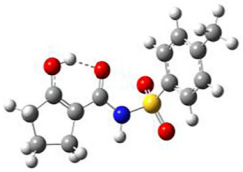
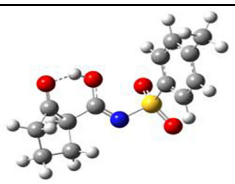
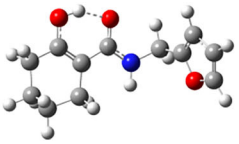
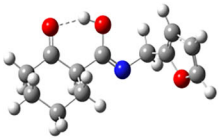
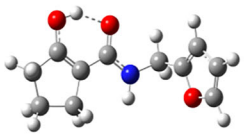
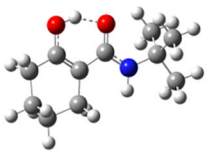
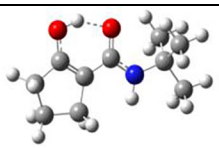
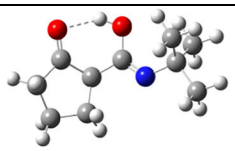
For this purpose, we have calculated the accurate BDE (X-H) values for a series of five and six-membered ring β-ketoamides, by using the same B3LYP/6-311G (d,p) level of theory. The optimized structure was ascertained to conform to a real minimum utilizing frequency calculation (no imaginary frequency). The homolytic bond dissociation enthalpies (BDEs), for O–H and N–H bond of different β-ketoamides, were calculated in ethanol at 298.15 K and 1.0 atm pressure. The solvent contribution to the total enthalpies was computed by using the integral equation formalism variant (IEF-PCM) of PCM model [44], as this method presents good accuracy, reliability, adaptability, and a reduced computational effort in describing solvent effects. Unrestricted formulation is used for radical species. Calculated BDEs of O–H and N–H of different cyclic β-ketoamides are shown in Table 4, together with experimental antioxidant activity.

From the results reported in Table 4, the theoretical results of the calculation are consistent with the results of the experimental in vitro antioxidant test. The lower BDE value



Scheme 4 Different forms of β-ketoamide

Table 3 Optimized structures and relatives energies (kcal.mol^{-1}) of the possible forms of β-ketoamide, obtained at B3lyp/6-311G (d,p) level of theory

Compounds	ΔE (kcal.mol^{-1}) Enolamide	Ketoimidol	Compounds	ΔE (kcal.mol^{-1}) Enolamide	Ketoimidol
2a	 0.00	 14.08	**3a**	 0.00	 16.20
2b	 0.00	 16.13	**3b**	 0.00	 18.26
2c	 0.00	 11.43	**3c**	 0.00	 18.30
2d	 0.00	 16.06			

Atom color code: oxygen (red), carbon (gray), nitrogen (blue), sulfur (yellow), and hydrogen (white)

indicates that the corresponding X−H bond is weaker and can be easily broken. The lower BDE parameter therefore points to a better antioxidant property of the molecule under investigation. All BDEs (N-H) of this series of compounds are higher than 90 kcal.mol^{-1} (Table 4), excepted in the case of compound **2b** in which there is not a great difference between BDE of OH and NH (0.7 kcal.mol^{-1}). As a result, the enolamide form is more susceptible to the transfer of H atoms by the function of alcohol than to the N–H of the ketoimidol form. On the other hand, BDE values show that OH radicalization processes of different substituted β-ketoamides require almost the same amount of energy in the two series of five and six-membered cyclic compounds. The BDE ranges from 85 to 86 kcal.mol^{-1} for five-membered cycle and from 80 to 82 kcal.mol^{-1} for six-membered cycle. These values suggested that six-membered cyclic 1,3-ketoamides compounds showed better antioxidant activity than their five-membered counterpart. This result is attributed, in the case of six-

Table 4 BDEs (kcal.mol^{-1}) of cyclic β-ketoamide, as calculated with IEF-PCM-B3lyp/6-311G(d,p) level of theory

Compounds	BDE_{OH} (kcal.mol^{-1})	BDE_{NH} (kcal.mol^{-1})	IC_{50}±SD (μg/mL)
3a	80.36	92.27	24.58 ± 1.12
3b	81.66	93.54	45.71 ± 1.67
3c	82.00	93.98	85.36 ± 1.82
2b	85.39	86.09	96.74 ± 2.15
2a	85.20	92.92	100.08 ± 2.82
2c	85.90	91.45	115.51 ± 2.21
2d	86.00	103.73	146.02 ± 3.52

membered ring, to the stabilization of the corresponding radicals by the formation of intramolecular hydrogen bonds (IHBs), in this form (Table 4, Fig. 5). In fact, two possible conformers of these radicals have been identified. They vary in the dihedral rotation angle of the carbonyl group (amide function) relative to the other carbonyl group. The 180° angle corresponds to the six-membered ring angle and the 24° for the five-membered ring counterpart (Fig. 5).

The natural bond orbital (NBO) analysis of investigated radicals reveals that the oxygen lone pair-antibonding orbital interactions between the carbonyl oxygen and amide proton (N-H bond) are responsible for the IHB formation, namely the charge transfer from the lone pair on carbonyl oxygen (2p orbital) to the σ* anti-bonding N-H orbital is a favorable donor-acceptor interaction. The conformations of the radical without IHBs are less stable. We have also confirmed this result by atomic charge analysis (Scheme 5) and bond order analysis from NBO.

The highest charge (−0.579) is on the carbonyl oxygen of radical of the compound **3a** which in turn is the site for the stable radical formation. Again, this is confirmed with the bond order values from NBO analysis, the lowest bond order value has been observed for the –OH group of parent molecules **3a and 2a** (0.6357 for **3a** and 0.6559 for **2a**) and it is the weakest bond.

Evaluating the most likely mechanism

According to the literature, it is difficult to envisage a single molecular mechanism for the antioxidant activity of all the natural and synthetic antioxidant compounds that exist [45, 46]. In this study, we evaluated the three most common antioxidant mechanisms used [36, 47–55].

First, a process involving the hydrogen atom transfer mechanism (HAT), which is a single electron transfer. Stable radicals can be obtained directly, via homolytic cleavage of hydroxyl O–H bond. A quantitative descriptor of this process can be assigned to the Bond Dissociation Enthalpy (BDE) Eq. (1).

$$ETEFE = \Delta G(RO^{\cdot}) + \Delta G(e^{-}) - \Delta G(RO^{-})$$

The second mechanism is a sequential electron transfer–proton transfer (SET-PT), proposed in two steps: a neutral antioxidant leaves an electron forming a cation radical, which in turn loses its proton giving a radical species.

$$\begin{array}{ll} Step\ 1 & ROH \rightarrow ROH^{\cdot +} + e^{-} \\ Step\ 2 & ROH^{\cdot +} \rightarrow RO^{\cdot} + H^{+} \end{array}$$

The enthalpy of this process (SET-PT) can be calculated from Eq. (5). It is the sum of Eq. (3) the adiabatic ionization potential (IP) and Eq. (4) proton dissociation enthalpy (PDE).

A third mechanism of primary antioxidant action has recently been identified. Sequential proton loss-electron transfer (SPLET), a neutral antioxidant, leaves a proton forming an anion that loses an electron giving rise to a radical in the second step.

$$\begin{array}{ll} Step1 & ROH \rightarrow RO^{-} + H^{+} \\ Step2 & RO^{-} \rightarrow RO^{\cdot} + e^{-} \end{array}$$

The enthalpy of sequential proton loss-electron transfer (SPLET) Eq. (8) is equal to the sum of the proton affinity enthalpy (PA) Eq. (6) and the electron transfer enthalpy (ETE) Eq. (7).

In this context, the following quantities have been determined in gas phase and polar media (ethanol) to predict the preferred thermodynamically dominant mechanism:

$$BDE = H(RO^{\cdot}) + H(H^{\cdot}) - H(ROH) \quad (1)$$

$$BDE = HAT \quad (2)$$

$$IP = H(ROH^{\cdot +}) + H(e^{-}) - H(ROH) \quad (3)$$

$$PDE = H(RO^{\cdot}) + H(H^{+}) - H(ROH^{\cdot +}) \quad (4)$$

$$SET\text{-}PT = IP + PDE \quad (5)$$

$$PA = H(RO^{-}) + H(H^{+}) - H(ROH) \quad (6)$$

$$ETE = H(RO^{\cdot}) + H(e^{-}) - H(RO^{-}) \quad (7)$$

$$SPLET = PA + ETE \quad (8)$$

where H(R–OH) refers to the enthalpy of the parent molecule, H(R–O$^{\cdot}$), H(R–OH$^{\bullet +}$), and H(R–O^{-}) refer to the enthalpy of the corresponding radical, cation radical and anion, respectively. In our case, R = (C(n = 5,6)-R(ONH)), so H(C(n = 5,6)-R(ONH)-OH) refers to the enthalpy of the

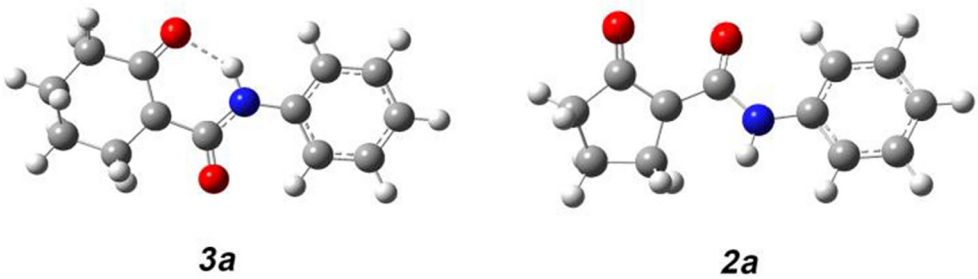
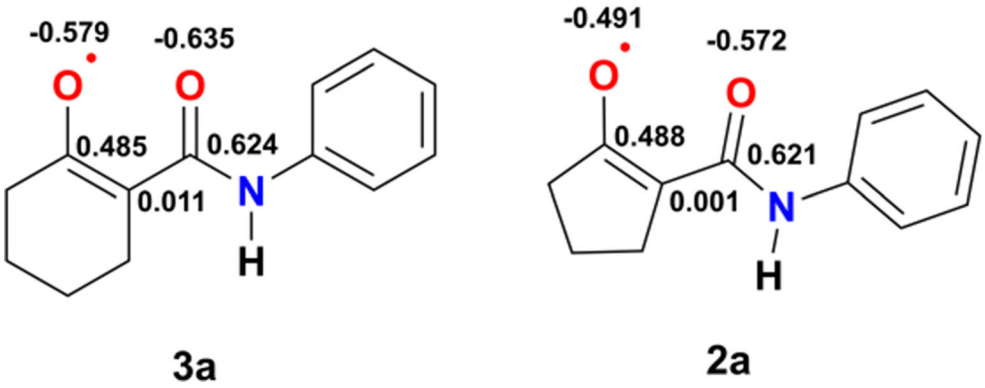


Fig. 5 Structure of radicals of **3a** and **2a** optimized at B3lyp/6-311G(d,p) level of theory

Scheme 5 NBO (u.e) charges of radicals obtained from **3a** and **2a**



parent molecule of different cyclic substituted β-ketoamides, H(C(n = 5,6)-R(ONH)-O$^{\bullet}$), H(C(n = 5,6)-R(ONH)-OH$^{\bullet+}$), and H(C(n = 5,6)-R(ONH)-O^{-}) to enthalpy of their corresponding radical, cation radical and anion, respectively.

Thermodynamic descriptors BDE, IP, PA, PDE, and ETE which allow to hypothesize what is the mechanism followed by antioxidants are collected in Table 5. These descriptors are calculated according to Eqs. (1)–(8), in gas and in ethanol (dielectric constant is 24.5).

The calculated gas phase enthalpies of the hydrogen atom H($H^{\bullet}$), proton H(H^{+}), and electron H(e^{-}), are −312.03, 1.48, and 0.75 kcal.mol^{-1}, respectively [56]. Because the solvation enthalpy of the proton and the electron in ethanol is not available in the literature with IEF-PM-B3lyp/6-311G**, we have calculated it, using the Eqs. (9) and (10). The values of ΔH_{solv} (H^{+}) and ΔH_{solv} (e^{-}) are −245.40 and − 3.04 kcal.mol^{-1}, respectively.

$$solvent(1) + H^{+}(g) \rightarrow solvent^{+}(solv) \quad (9)$$

$$solvent(1) + e^{-}(g) \rightarrow solvent^{-}(solv) \quad (10)$$

The particle (H^{+} or e^{-}) is attached to one molecule of the same solvent.

For open-shell species, accuracy of the energy measurement is sensible to spin contamination. Here, spin contamination was found to be small ($<S^2> - 0.75–0.76$) after spin annihilation, regardless of phase. Therefore, spin contamination should not bias computed enthalpies.

The results of Table 5 show that:

In the gas phase, the lowest enthalpy of homolytic dissociation of the O-H bond (BDE) was mainly produced for the elimination of hydrogen atoms by homolytic cleavage of the O-H bond and the formation of the C(n = 5.6)-R(ONH)-O$^{\bullet}$ radical in a single step. As a result, the HAT process is expected to be more favored during the gas phase.

The comparison of the BDE and IP values is already sufficient to suggest that the HAT mechanism is much more thermodynamically favorable than SET-PT, in the gas phase.

SPLET is a stepwise mechanism. The amount of energy required for the whole process corresponds to the sum of PAs and ETEs. Again, by comparing the amount of energy required for HAT and that required for the first step of the SPLET mechanism, it is concluded that the HAT is thermodynamically favored in the gas phase.

On the other hand, the influence of the environment of the solution on the antioxidant mechanism has also been studied, with a significant decrease in PA (step 1 of the SPLET mechanism) and PDE (step 2 of the SET-PT mechanism) observed. Thus, the solvent effects are not significant for HAT mechanism, while they become meaningful for SET-PT and SPLET

Table 5 Thermochemical descriptors at B3lyp/6-311G(d,p) level

Compounds	In gas phase					In ethanol				
	BDE_{OH}	SPLET		SET-PT		BDE_{OH}	SPLET		SET-PT	
		PA	ETE	IP	PDE		PA	ETE	IP	PDE
2a	90.38	348.99	57.24	172.27	233.96	85.20	56.53	95.33	131.96	19.90
2b	90.34	340.64	65.55	184.43	221.76	85.39	50.05	102.00	141.30	10.26
2c	90.54	353.71	52.68	174.49	231.90	85.90	59.03	93.44	133.31	19.26
2d	90.50	356.09	50.26	171.92	234.43	86.00	60.78	91.89	127.79	24.87
3a	80.61	355.34	41.12	171.57	224.89	80.36	62.83	84.20	132.12	14.91
3b	82,78	343.33	55.30	173.56	225.07	81.66	65.48	83.19	131.11	17.22
3c	82.21	362.26	35.80	171.92	226.14	82.00	67.26	81.40	129.31	19.35

ones. As expected, PAs and PDEs are highly solvent-dependent, as the species, anion and proton are involved in this process [57].

Finally, the PA represents the difficulty for a hydroxyl of neutral β-ketoamide to lose the proton by generating the corresponding anion. The PAs in Table 5 indicate that SPLET is more favorable in polar media than the HAT and SET-PT mechanisms and will remain the dominant reaction mechanism in this system.

Test of basis set and solvent model

In our study of the antioxidant properties of cyclic ketoamides, we tested two ring sizes: six-membered rings and five-membered rings in which the amide carrying the phenyl group (**3a**, **2a**) has the best antioxidant power in each series. So, for this reason, it seems wise to only calculate the baseline test and the solvent model on these two substrates.

Test of basis set In order to test the influence of diffuse functions in the basis set on antioxidant mechanism of β-ketoamide, all thermochemical descriptors were reoptimized at the same level (B3lyp) by using the 6–31++G** basis set. In ethanol, the calculated solvation enthalpy of the hydrogen atom H($H^{\bullet}$) is Δ_{solv} H($H^{\bullet}$) = −245.40 kcal.mol^{-1}. The solvation enthalpies of electron H(e^-) and proton H(H^+) in ethanol were reported by Rimarcík and al [58]. The results are listed in Table 6.

The data in Table 6 show that adding the diffuse functions confirms that the radical scavenging of the investigated β-ketoamides takes place via SPLET mechanism in polar media. The IP values are high for all investigated compounds in both cases; this fact undoubtedly suggests that SET-PT is not a plausible mechanism. On the other hand, the PA values are notably lower than the BDE values. This means that the SPLET mechanism is more probable reaction path than the HAT mechanism. These results show the same trend as that obtained with our level of calculation. Consequently, the basis set. 6-311G(d,p) is well suitable for our calculations.

Explicit solvent

Among the most intriguing aspects of studying solvation processes is the influence of solvent on the ongoing chemical reaction or on the structural stability of substrates. Thus, we have continued this study by measuring the effect of ethanol on the antioxidant properties of our β-ketoamide derivatives. Indeed, in polar solvents, like ethanol, solvation effects should be taken into account, particularly for the charged species like cation radical ($ROH^{\bullet+}$) and anions (RO^-). Herein, the discrete-continuum model has been applied to the calculations of the solvation free energies related to the three-antioxidant scavenging process. In this model, as suggested by Mo and al [59], the solvent was taken into account in a hybrid manner. The first solvation shell was modeled explicitly and the remaining solvents were represented by a continuum. So, we have determined the following quantities: bond dissociation free energy (BDFE), ionization potential free energy (IPFE), proton dissociation free energy (PDFE), proton affinity free energy (PAFE), and electron transfer free energy (ETFE), in Eqs. (11–15), for the compounds **2a** and **3a** when one molecule of ethanol is added.

$$BDFE = \Delta G(RO^{\cdot}) + \Delta G(H^{\cdot}) - \Delta G(ROH) \quad (11)$$

$$IPFE = \Delta G(ROH^{\cdot+}) + \Delta G(e^-) - \Delta G(ROH) \quad (12)$$

$$PDFE = \Delta G(RO^{\cdot}) + \Delta G(H^+) - \Delta G(ROH^{\cdot+}) \quad (13)$$

$$PAFE = \Delta G(RO^-) + \Delta G(H^+) - \Delta G(ROH) \quad (14)$$

$$ETEFE = \Delta G(RO^{\cdot}) + \Delta G(e^-) - \Delta G(RO^-) \quad (15)$$

Table 6 Thermochemical descriptors of the β-ketoamide **2a** and **3a**, obtained at B3lyp/6–311++G(d,p) level of theory, in the gas phase and in ethanol (kcal.mol-1). Comparison with Thermochemical descriptors at B3lyp/6-311G(d,p) level

Compounds	B3lyp/6-311G(d,p)					B3lyp/6–311++G(d,p)				
	BDE_{OH}	SPLET		SET-PT		BDE_{OH}	SPLET		SET-PT	
		PA	ETE	IP	PDE		PA	ETE	IP	PDE
	In gas phase									
2a	90.38	348.99	57.24	172.27	233.96	90.06	343.82	62.15	174.40	231.51
3a	80.61	355.34	41.12	171.57	224.89	80.87	350.41	46.32	173.67	223.06
	In ethanol									
2a	85.20	56.53	95.33	131.96	19.90	84.14	44.43	85.32	118.70	11.05
3a	80.36	62.83	84.20	132.12	14.90	80.52	50.92	75.13	118.84	7.21

Table 7 Thermochemical descriptors within the discrete-continuum model (kcal.mol^{-1}) in presence of one molecule of ethanol. The values of free energies calculated with IEF-PCM are also presented in this table for comparison

Compounds	PCM model					discrete continuum model				
	HAT	SPLET	SET-PT			HAT	SPLET		SET-PT	
	BDE	PA	ETE	IP	PDE	BDE	PA	ETE	IP	PDE
2a	76.14	55.91	96.10	133.46	18.55	74.86	60.23	87.28	119.30	28.21
3a	71.36	61.88	85.35	133.42	13.81	70.55	65.35	77.85	126.19	16.94

For the solvation free energy of hydrogen atom ($H^{\bullet}$), electron (e^{-}), and proton (H^{+}), we employed the values of −321.80, −244.54, and − 1.38 kcal.mol^{-1}, in IEF-PCM approach respectively. We are also interested to calculate the solvation free energy of electron and proton in explicit ethanol using a good model already used by other authors [60–62].

The results presented in this Table 7 point out a substantial improvement in the theoretical solvation free energy of charged species, with one ethanol molecule included in the discrete-part of the solvent. In the case of the HAT mechanism, a smaller difference (< than 2 kcal.mol^{-1}) in the values of BDFE is obtained by comparing the two models of solvation. Indeed, as this mechanism does not involve any charged species ($RO^{\bullet}$), solvation has little effect on the BDFE values. The solvent favors the deprotonation process, that is why the PA values obtained in solvents are far away lower than those in the gas phase, due to the large solvation free energy of proton. The solvent influences the IPs drastically comparatively to solvent effect upon BDFEs. This is not unexpected, because it is well-known that cation radicals are charged and they are quite sensitive to the solvent. This result is well represented in the two models of solvation. Consequently, the lower PA values in ethanol in both models indicate that the SPLET process is predicted to be more favored in polar media. Our results confirm that using the well-known polarizable continuum model (PCM) gives findings in very good agreement with the experimental results.

Conclusion

In conclusion, the idea of inculcating two functional groups into a single organic compound has made it possible to obtain new synthetic derivatives with a biological activity profile. Thus, we synthesized a series of functionalized cyclic β-ketoamides and evaluated them for antioxidant activity in vitro using the DPPH method. Results have shown that the nature of the amide function—secondary or tertiary—as well as the size of the ring are important factors that influence the antioxidant activity. Regarding the prediction of antioxidant power using theoretical calculations, a detailed mechanistic study has allowed us to demonstrate that the enol form of 1,3-ketoamides is more stable than the ketoimidol form. This is due to the intramolecular hydrogen bond formed in the enol with the extended conjugation of the ring chain. We calculated the BDEs for the two forms of our C_5 and C_6 ketoamides; in all cases, the O–H bond of the enolamide form is the weakest and most sensitive to the transfer of hydrogen atoms. The free radical scavenging capacity of these compounds is mainly produced by SPLET rather than by HAT or SET-PT in ethanol as a solvent. Therefore, the data from all our research confirms the importance of exploring cyclic β-ketoamide systems as models for the development of new antioxidant agents.

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Data availability All data and material cited in this study are available.

Declarations

Ethics approval All authors of this paper have read and approved the final version submitted.

Consent to participate All authors of this research paper have directly participated in the planning, execution, or analysis of this study.

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Conflict of interest The authors declare that they have no conflict of interest.

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