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Synthesis and evaluation of antioxidant activity of some novel hydroxypyridinone derivatives: a DFT approach for explanation of their radical scavenging activity

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Abstract

Background and purpose: Reactive oxygen species (ROSs) are continuously produced as byproducts of cell metabolism. Free radicals are an unstable form of ROSs with the tendency to react readily with biomolecules such as amino acids, lipids and DNA. These reactions lead to oxidative damages to the cell. Oxidative stress occurs when the concentration of the ROSs exceeds the capacity of antioxidative protection systems of the body. 5-Hydroxypyridin-4-one derivatives can chelate Fe²⁺ and Fe³⁺ due to their α -hydroxyketone moiety. Also, tautomerism in hydroxypyridinone ring leads to enough level of aromaticity resulting in a catechol-like behavior that provides them with good chelating and radical scavenging properties.

Experimental approach: Different compounds were synthesized with 5-hydroxypyridine-4-one moiety as the core. The antioxidant properties of molecules were evaluated experimentally by DPPH scavenging method and theoretically using DFT/B3LYP with a 6-31++G (d,p) basis set. Electronic properties were investigated using frontier molecular orbital theory calculations. Furthermore, global descriptive parameters were obtained to find the chemical reactivity of molecules. The natural bond orbital analysis was performed to investigate charge distribution and hydrogen bonding.

Findings/Results: Structures of the synthesized compounds were confirmed using IR, ¹H-NMR, and ¹³C-NMR spectral analyses. Among all the synthesized compounds, Va and Vb showed the best antioxidant effect experimentally and computationally.

Conclusion and implications: Results of this study were valuable in terms of synthesis, *in silico*, and *in vitro* antioxidant evaluations and can be useful for future investigations about the design of novel 5-hydroxypyridin-4-one derivatives possessing iron-chelating and radical scavenging abilities.

Keywords: Antioxidant; DFT; Hydroxypyridinone; Radical scavenging.

INTRODUCTION

Reactive oxygen species (ROSs) are continuously produced as natural byproducts of normal cell metabolism and participate in cellular signaling. They include hydrogen peroxide (H₂O₂), alkoxy (RO[•]), hydroxyl (HO[•]), peroxy (ROO[•]), and nitric oxide (NO[•]) radicals, and superoxide radical anion (O₂^{•-}). Increase of ROS levels has harmful effects on

cell homeostasis, structure, and functions and leads to oxidative stress (1). Oxidative stress is a state that occurs when the concentration of the reactive free radical species exceeds the capacity of the endogenous and exogenous anti-oxidative protection systems of the body (2).

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Generated free radicals are unstable and tend to damage and react readily with biomolecules such as amino acids, lipids, carbohydrates, and DNA to achieve more stability (3). They include chemical and biological processes that are believed to be of the major causes of many diseases such as atherosclerosis, inflammation, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), Parkinson's disease, and cancer (4).

Antioxidants are compounds that inhibit oxidative reactions. When one electron is transferred from an antioxidant to a free radical to block its reactivity, the electron donor is also called a 'scavenger'. This one-electron transfer produces the radical form of the antioxidant. The reactivity of antioxidant radical has to be much lower than the original free radical for obtaining beneficial antioxidant effects (5).

Iron has a fundamental role in oxidative stress by the formation of hydroxyl radical through Fenton and Haber-Weiss reactions. Fe^{2+} is oxidized to Fe^{3+} by oxygen molecule and O_2^{\bullet} is formed which reacts with H^+ to produce H_2O_2 . This peroxide is then broken to hydroxyl anion and hydroxyl radical by Fe^{2+} in the Fenton reaction. Hydroxyl radicals can also be produced by the reaction of H_2O_2 in the presence of $\text{Fe}^{3+}/\text{Fe}^{2+}$ and O_2^{\bullet} through the Haber-Weiss reaction. Chemicals with iron-chelating ability can potentially suppress oxidative stress by preventing Fenton and Haber-Weiss reactions (6).

The design of compounds with the dual ability of iron chelation and also radical scavenging ability could be a prospective strategy to provide novel antioxidant agents. Prevention of post-ischemic cardiac injury using a combination of an iron-chelating agent, deferiprone, and a flavonoid antioxidant, cyanidanol; and more recently, combined treatment with deferiprone and the antioxidant idebenone in individuals with Friedreich's ataxia are some reported cases of this combination therapy (7).

The antioxidant properties of different natural and synthetic phenolic compounds are based on their ability to donate hydrogen to a free-radical which leads to a scavenging effect. Polyphenols, *e.g.* catecholes, can remove Fe^{2+} out of reach by chelation and inhibition of Fenton or Haber-Weiss reactions as well as free radical scavenging (8,9).

Hydroxypyridinone derivatives (*e.g.* deferiprone) can chelate Fe^{2+} and Fe^{3+} cations due to the similar behavior of their α -hydroxyketone moiety as catechols. The tautomerism phenomenon in these compounds leads to catechol-like behavior and also enough level of aromaticity of their rings. The result is an increase in the acidity of the OH group leading to phenolic properties, providing these compounds with good chelating and radical scavenging properties (10,11).

Density functional theory (DFT) calculations allow the researchers to make qualitative predictions about the reactivity of a given system. The chemical behavior and mechanism of action of the antioxidant molecules may be studied by investigating the relevant electronic properties and thermal enthalpies of them using DFT computations (12).

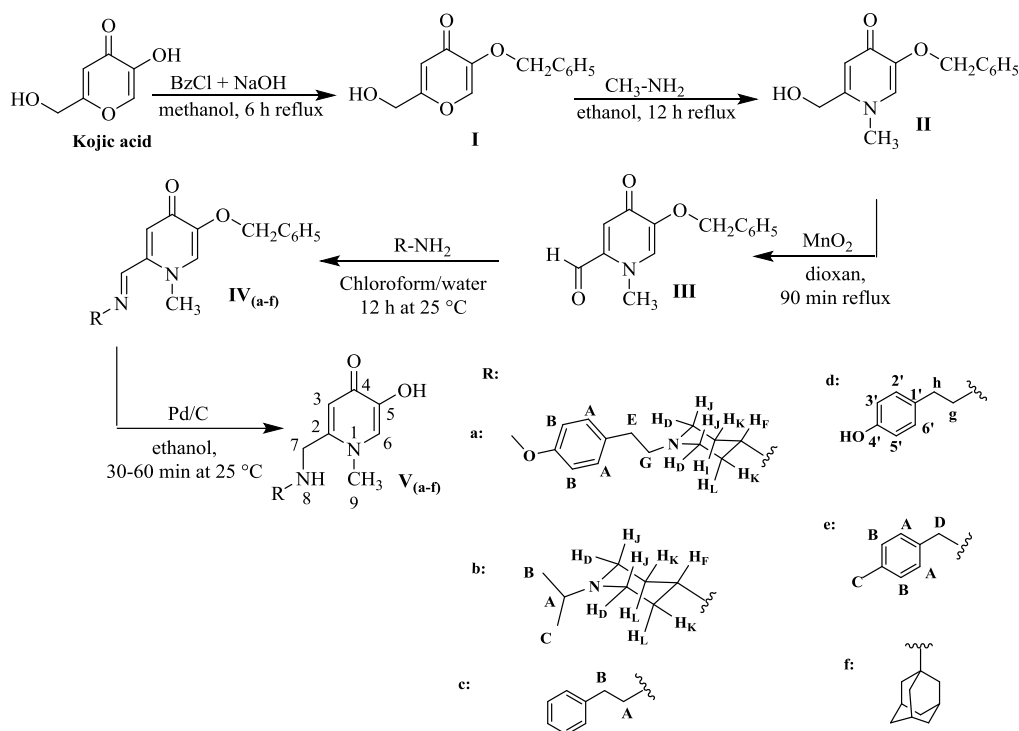
Here, we report the synthesis of some novel 5-hydroxypyridin-4-one derivatives possessing iron-chelating ability as well as their radical scavenging property. Our previous computational studies have proven that hydroxypyridinones have more aromatic character than hydroxypyranones (13). Thus, it can be expected that the designed derivatives may possess stronger antioxidant activity than kojic acid. The free radical scavenging activities of the compounds were experimentally determined using 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay and rationalized further using DFT-based computational studies.

MATERIALS AND METHODS

Experimental methodology

Materials

All chemicals used for the synthesis of the compounds were supplied by Merck or Sigma. The infrared (IR) spectra were recorded with a Perkin WQF-510 Ratio Recording IR spectrometer (USA) as a KBr disc (γ , cm^{-1}). The proton nuclear magnetic resonance (^1H NMR) and carbon-13 (^{13}C) NMR spectra (deuterated dimethyl sulfoxide, $\text{DMSO-}d_6$; or deuterated chloroform, CDCl_3) were recorded on a Bruker 400 MHz spectrometer (Germany). The general procedure for the synthesis of the desired compounds is depicted in Scheme 1.



Scheme 1. General procedure for the synthesis of 5-hydroxypyridine-4-one derivatives.

Synthesis of compounds I-II

These compounds were prepared according to the instructions reported previously (14-16).

General procedure for the synthesis of IV_{a-f} derivatives

Aqueous solutions (2.5-5.0 mL, 0.1-0.5 M) of the desired amines (**a-f**) were prepared using 5.0 moles of each amine and the pH of this solution was adjusted to 10 by adding NaOH or HCl, if necessary. One mole of appropriate aldehyde **III** was added to this aqueous solution and shaken vigorously for 5 min. Then an equal volume of chloroform was added and the reaction mixture was stirred at 25 °C until the aqueous layer became clear (12-24 h). Then the two layers were separated in a separator funnel and the chloroform layer was removed under vacuum until the volume of the remaining oil became constant or the solid product of the reaction appeared. Finally, further purification was made by crystallization from a 1:1 ethanol:ether solution. Crystals or amorphous solids of the products were dried in a vacuum at 40 °C for 12 h (17).

General procedure for the synthesis of V_{a-f} derivatives

Each of **IV_{a-f}** (0.5 mol) was dissolved in 50 mL of absolute ethanol. Then 5.0 mol of 10% of palladium/charcoal was added. Hydrogen gas was bubbled into the reaction mixture using a balloon connected to the reaction vessel. The mixture was shaken vigorously at room temperature for 30-60 min. When the reaction was completed, palladium/charcoal was filtrated off and washed three times by ethanol. The product was crystallized from the filtrate and dried under reduced pressure (18).

DPPH free radical scavenging assay

This assay was performed according to the method described by Blois (19). Briefly, 4.0 mL of different concentrations of methanolic solution of the standard or test compounds (10 to 2000 μM) were added to 2.0 mL of DPPH methanolic solution (60 μM). The mixture was shaken vigorously and allowed to stand for 30 min in a dark place, and then the absorbance of the resulting solution was measured at 517 nm using a Perkin-Elmer 1420 Ratio Recording

UV-Visible spectrophotometer (USA). The scavenging percentage of DPPH free radicals was calculated according to the equation (1):

$$\% \text{ of DPPH Scavenging} = \left(\frac{A_c - A_t}{A_c} \right) \times 100 \quad (1)$$

where, A_c is the absorbance of the control tube (containing all reagents except the test compound), and A_t is the absorbance of the test tube. Ascorbic acid was used as the standard.

Theoretical methodology

Molecular structures of the studied compounds and their corresponding free radicals, anions, and radical cations were drawn using Hyperchem v7.0 software and initially optimized using the semi-empirical PM₃ method. Then geometry optimization of the structures was carried out with standard conditions using the DFT methodology in the approach of the Becke's three parameters exact exchange functional (B3) combined with the non-local gradient corrected correlation functional of Lee-Yang-Parr (LYP), denoted as B3LYP, and the 6-311⁺⁺G** basis set as implemented in the Gaussian'03, revision C.02 package (20). Solvent effects of water were imitated by the self-consistent reaction field polarizable continuum model, CPCM method. The calculated structures representing minima at the potential energy surface were confirmed by frequency calculations (no imaginary frequency). Also zero-point energies and vibrational contributions to enthalpy were estimated using frequency calculations.

Electronic properties of the structures such as highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energies, single OMO (SOMO), and energy gaps (E_{gap}) between HOMO and LUMO of the studied compounds was studied using frontier molecular orbital theory calculations (21). Furthermore, global descriptive parameters were obtained to find a relationship between the chemical reactivity of the molecules and sensitivity to structural perturbation.

Natural bond orbital analysis was performed to investigate the atomic charge distribution, population analysis, and hydrogen bonding.

RESULTS

Chemistry

The structures of all compounds were confirmed by IR, ¹HNMR, and ¹³CNMR. Carbon atoms are numbered sequentially to facilitate the assignment of protons in ¹H-NMR and ¹³C-NMR (Scheme 1).

5-(Benzyloxy)-1-methyl-4-oxo-1,4-dihydropyridine-2-carbaldehyde (III)

Milky crystals; yield 75%; mp: 220-223 °C; IR (KBr) cm⁻¹: 3047 (C-H, aromatic), 2893 (C-H, aliphatic), 1716 (C=O, aldehyde), 1618 (C=O ketone), 1583 (C=C alkene), 1437 (C=C, aromatic); ¹HNMR (DMSO-*d*₆): δ 9.68 (s, 1H, CHO), 7.44 (s, 1H, C₆-H), 7.16-7.33 (m, 5H, CH₂-C₆H₅), 6.75 (s, 1H, C₃-H), 5.07 (s, 2H, O-CH₂ C₆H₅), 3.85 (s, 3H, NCH₃).

2-((1-(4-Methoxyphenethyl) piperidin-4-ylamino)methyl)-5-hydroxy-1-methylpyridin-4(1H) one (Va)

White crystals; yield 85%; mp: 199-201 °C; IR (KBr) cm⁻¹: 3550 (N-H), 3189 (O-H), 2850 (C-H aliphatic), 1618 (C=C, alkene), 1578 (C=O, ketone), 1515 (C=C, aromatic), 1301 (C-N), 1220 (C-O); ¹HNMR (DMSO-*d*₆): δ 7.39 (s, 1H, C₆-H), 7.11 (d, *J* = 6 Hz, 2H, B), 6.82 (d, *J* = 6 Hz, 2H, A), 6.20 (s, 1H, C₃-H), 3.71 (s, 3H, -O-CH₃), 3.66 (s, 3H, N-CH₃), 3.60 (s, 2H, -NH-CH₂), 2.99 (bs, 2H, -NH-, -OH), 2.85 (d, *J* = 9, 2H, H_D), 2.61-2.68 (m, 2H, H_G), 2.47-2.40 (m, 2H, H_E), 2.33-2.37 (m, 1H, H_F), 2.05 (t, *J* = 9 Hz, 2H, H_J), 1.81 (d, 2H, H_K), 1.20-1.30 (m, 2H, H_L). ¹³CNMR (DMSO-*d*₆): δ 170.39, 157.38, 146.98, 146.64, 132.39, 129.48, 124.22, 113.57, 112.98, 60.20, 54.90, 53.57, 51.97, 36.00, 32.06, 18.05.

5-(Hydroxy) -2-((1-isopropylpiperidin-4-ylamino)methyl)-1-methylpyridin-4(1H)-one (Vb)

Milky crystals; yield 81%; mp: 178-179 °C; IR (KBr) cm⁻¹: 3531 (N-H), 3100-3600 (O-H), 2941 (C-H, aliphatic), 1640 (C=C, alkene), 1581 (C=O, ketone); ¹HNMR (DMSO-*d*₆): δ 7.39 (s, 1H, C₆-H), 6.19 (s, 1H, C₃-H), 3.65 (s, 3H, N-CH₃), 3.59 (s, 2H, -NH-CH₂), 2.70 (d, 2H, H_D), 2.60-2.67 (m, 1H, H_F), 2.27-2.34 (m, 1H, H_A), 2.03-2.08 (m, 2H, H_J), 1.80 (d, 2H, H_K), 1.16-1.62 (m, 3H, H_L, -NH-CH₂).

^{13}C NMR (DMSO- d_6): δ 170.38, 146.99, 146.65, 124.26, 113.00, 54.44, 53.58, 46.88, 46.65, 32.47, 18.02.

5-Hydroxy- 1- methyl-2- ((phenethylamino) methyl) pyridin-4(1H)-one (V_c)

White crystals; yield 74%; mp: 223-224 °C; IR (KBr) cm^{-1} : 3241 (O-H), 2920 (C-H, C-H, aliphatic), 1637 (C=C, alkene), 1562 (C=O, ketone), 1491 (C=C, aromatic), 1243 (C-O); ^1H NMR (DMSO- d_6): δ 7.48 (s, 1H, C₆-H), 7.22-7.22 (m, 5H, -C₆H₅), 6.17 (s, 1H, C₃-H), 4.26 (s, 2H, -NH-CH₂), 4.09 (t, 2H, H_A), 3.54 (bs, 2H, -NH-CH₂-, -OH), 3.00 (t, 2H, H_B), 2.50 (s, 3H, -N-CH₃). ^{13}C NMR (DMSO- d_6): δ 170.62, 147.00, 146.95, 137.75, 128.92, 128.42, 126.60, 122.98, 112.35, 59.52, 52.63, 36.47.

2- ((4-Hydroxyphenethylamino)methyl) -5-hydroxy-1-methylpyridin-4(1H)-one (V_d)

Milky crystals; yield 87%; mp: 219-221 °C; IR (KBr) cm^{-1} : 3606 (N-H), 3150 (O-H), 1664 (shouldered, C=C, alkene), 1622 (C=O ketone), 1560, 1446 (C=C aromatic), 1313 (C-N), 1243 (C-O); ^1H NMR (DMSO- d_6): δ 7.51 (s, 1H, C₆-H), 7.10 (d, 2H, 2'H, 6'H), 6.78 (d, 2H, 3'H, 5'H), 6.30 (s, 1H, C₃-H), 3.73 (s, 3H, -N-CH₃), 3.71 (s, 2H, -NH-CH₂-), 2.80 (t, 2H, H_g), 2.71 (t, 2H, H_h). ^{13}C NMR (DMSO- d_6): δ 170.34, 155.39, 146.65, 146.47, 130.23, 129.35, 124.26, 114.96, 113.00, 50.71, 49.40, 34.82.

2-((4-Methylbenzylamino)methyl)-5-hydroxy-1-methylpyridin-4(1H)-one (V_e)

White crystals; yield 79%; mp: 195-196 °C; IR (KBr) cm^{-1} : 3539 (N-H), 3100-2700 (O-H), 1638 (1716, C=C alkene), 1569 (C=O ketone), 1321 (C-N), 1243 (C-O); ^1H NMR (DMSO- d_6): δ 7.40 (s, 1H, C₆-H), 7.22 (d, 2H, H_A), 7.12 (d, 2H, H_B), 6.18 (s, 1H, C₃-H), 3.64 (s, 2H, H_E), 3.62 (s, 3H, H_C), 3.52 (s, 2H, -NH-CH₂-), 2.27 (s, 3H, -N-CH₃). ^{13}C NMR (DMSO- d_6): δ 170.34, 146.67, 146.31, 137.23, 135.61, 128.71, 127.87, 124.30, 113.13, 51.89, 48.69, 20.67.

2- ((Tricyclo[3.3.1.1^{3,7}] decane-3-ylamino) methyl)-5-hydroxy-1-methylpyridin-4(1H)-one (V_f)

White crystals; yield 75%; mp: 260-261 °C; IR (KBr) cm^{-1} : 3121 (O-H), 2880 (C-H, aliphatic), 1636 (C=C, alkene), 1552 (C=O,

ketone), 1314 (C-N), 1241 (C-O); ^1H NMR (DMSO- d_6): δ 7.37 (s, 1H, C₆-H), 6.22 (s, 1H, C₃-H), 3.5 (bs, 2H, -NH-CH₂-), 3.67 (s, 3H, -N-CH₃), 3.54 (s, 2H, -NH-CH₂), 1.55-1.61 (m, 15H, adamantane). ^{13}C NMR (DMSO- d_6): δ 170.41, 147.86, 146.63, 124.14, 113.18, 50.30, 41.86, 41.37, 36.25, 28.91.

Experimental DPPH radical scavenging activity assay

DPPH scavenging evaluation is a common and rapid antioxidant assay which determines the ability of the compound to react with a DPPH as a stable free radical to scavenge it.

The freshly prepared methanolic solution of the DPPH has a deep purple color with an absorption maximum at 517 nm. This color generally disappears when an antioxidant is present in the medium. Thus, antioxidant molecules can react with DPPH and convert them to colorless or bleached product (18).

Methanolic solutions of the synthesized derivatives V_{a-f} were examined against DPPH at different concentrations (10 to 2000 μM) and the results were compared with ascorbic acid as a standard natural antioxidant. All results are presented as IC₅₀ values in Fig. 1.

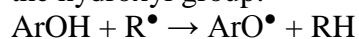
The highest scavenging activity was observed for compound V_a whose IC₅₀ value was 708.623 μM . The compounds' DPPH scavenging activities were in the following order:

Ascorbic acid > V_a > V_b > V_d > V_e > V_c > V_f > kojic acid.

Theoretical radical scavenging investigation

In this study, two concepts were considered for computing the parameters related to the antioxidant activity. The first one was the energy-vertical method, which is based on the difference in the sum of the electronic and thermal enthalpies when an electron is added to or removed from the neutral molecule. The second was based on the E_{gap} of the HOMO and the LUMO of the neutral molecule and is known as the orbital-vertical method.

Three mechanisms are commonly proposed to explain the radical scavenging processes for phenolic antioxidants. The first mechanism involves hydrogen atom transfer (HAT) from the hydroxyl group:



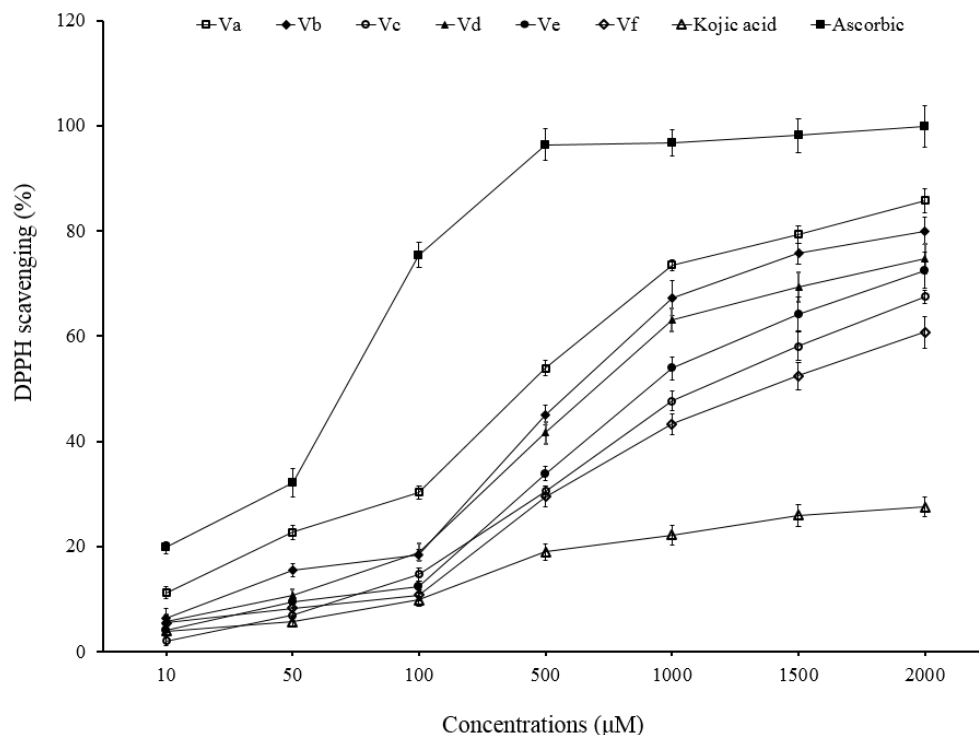
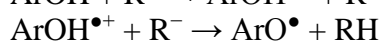
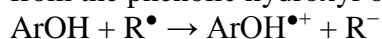
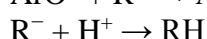
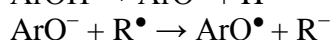
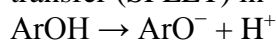


Fig. 1. The percentage of DPPH scavenging activity of the studied compounds in different concentrations (10-2000 μM). DPPH, 2,2-diphenyl-1-picrylhydrazyl.

Stepwise electron transfer-proton transfer (SETPT) is the other prominent antioxidant mechanism for the phenolic antioxidants in which an electron and then a proton transfer from the phenolic hydroxyl oxygen:



And finally, sequential proton loss electron transfer (SPLET) in which:



In the HAT mechanism, the antioxidant (Ar-OH) reacts with the free radical (R^\bullet) by transferring a hydrogen atom through the homolytic cleavage of the O-H bond. The reactivity of an Ar-OH can be estimated by calculating the bond dissociation energy (BDE) of OH group. Lower BDE value corresponds to higher radical scavenging activity. BDE is calculated using the electronic and thermal enthalpies summation as follows:

$$\text{BDE} = H_r + H_h - H_n \quad (2)$$

where, H_r is the enthalpy of the radicals generated through H-atom abstraction, H_h is the enthalpy of the hydrogen atom, which is -4.0

kJ/mol and H_n is the enthalpy of related neutral compound (22).

Ionization potential (IP) and proton dissociation enthalpy (PDE) are quantities related to the SETPT mechanism and are calculated using electronic and thermal enthalpies of the related compounds as follows:

$$\text{IP} = H_{\text{rad.cat}} - H_n + H_e \quad (3)$$

$$\text{PDE} = H_r + H_{\text{pro}} - H_{\text{rad.cat}} \quad (4)$$

where, H_r is the enthalpy of the radical; $H_{\text{rad.cat}}$, the enthalpy of the radical cation; H_{pro} , the proton enthalpy, which is -1152.6 kJ/mol; and H_e , the enthalpy of the electron which is -105.2 kJ/mol (22). Molecules with low IP and PDE values are expected to have high scavenging activity.

Electron transfer enthalpy (ETE) and proton affinity (PA) of anion form are parameters related to the SPLET mechanism and are calculated using the electronic and thermal enthalpy of the related compounds as follows:

$$\text{PA} = H_{\text{an}} + H_{\text{pro}} - H_n \quad (5)$$

$$\text{ETE} = H_r + H_e - H_{\text{an}} \quad (6)$$

where H_{an} is the enthalpy of the anion species (22).

Table 1. Calculated enthalpies for the different steps of possible mechanisms of scavenging activity. kJ/mol, at 298.15 K, CPCM, B3LYP/6-311++G** level of theory.

| Compounds | BDE | IP | PDE | PA | ETE |
|--------------------------------|----------|---------|---------|---------|---------|
| V _a | 1638.648 | 406.584 | 113.064 | 213.539 | 304.108 |
| V _b | 1640.296 | 397.420 | 119.874 | 213.510 | 306.785 |
| V _c | 1642.837 | 463.523 | 56.313 | 215.697 | 307.139 |
| V _d (5-OH radical) | 1642.672 | 463.363 | 56.308 | 213.266 | 316.405 |
| V _d (4'-OH radical) | 1648.671 | 463.363 | 62.307 | 204.150 | 321.520 |
| V _e | 1642.380 | 463.334 | 56.048 | 210.496 | 318.886 |
| V _f | 1642.698 | 461.099 | 58.598 | 215.298 | 314.399 |
| Kojic acid | 1675.020 | 726.703 | 174.608 | 403.421 | 348.594 |

BDE, bond dissociation energy; IP, Ionization potential; PDE, proton dissociation enthalpy; PA, proton affinity; ETE, Electron transfer enthalpy.

Table 2. Global parameters were calculated at B3LYP/6-311++G** level of theory [eV]. * V_d (5-OH/4'-OH).

| Parameters | Compounds | | | | | | |
|-------------------|----------------|----------------|----------------|-----------------|----------------|----------------|------------|
| | V _a | V _b | V _c | V _d | V _e | V _f | Kojic acid |
| E _{HOMO} | -6.020 | -5.998 | -6.144 | -6.143 | -6.143 | -6.129 | -6.870 |
| E _{SOMO} | -6.013 | -6.013 | -6.040 | -6.068/-6.149 * | -6.084 | -6.040 | -6.960 |
| E _{LUMO} | -1.142 | -1.141 | -1.149 | -1.148 | -1.172 | -1.069 | -1.750 |
| ΔE _{gap} | 4.877 | 4.857 | 4.994 | 4.994 | 4.971 | 5.060 | 5.120 |
| IP | 6.020 | 5.998 | 6.144 | 6.143 | 6.143 | 6.129 | 6.870 |
| EA | 1.142 | 1.141 | 1.149 | 1.148 | 1.172 | 1.069 | 1.750 |
| η | 2.438 | 2.428 | 2.497 | 2.497 | 2.485 | 2.530 | 2.560 |
| μ | -3.581 | -3.569 | -3.647 | -3.645 | -3.657 | -3.599 | -4.310 |
| S | 0.205 | 0.199 | 0.200 | 0.200 | 0.201 | 0.197 | 0.190 |
| ω | 2.630 | 2.623 | 2.663 | 2.661 | 2.691 | 2.560 | 2.872 |
| ω ⁺ | 0.133 | 0.134 | 0.132 | 0.132 | 0.138 | 0.113 | 0.173 |
| ω ⁻ | 3.715 | 3.703 | 3.779 | 3.777 | 3.795 | 3.712 | 3.921 |
| χ | 3.581 | 3.569 | 3.647 | 3.645 | 3.657 | 3.599 | 4.310 |

HOMO, highest occupied molecular orbital; SOMO, single occupied molecular orbital; LUMO, lowest unoccupied molecular orbital, IP, Ionization potential, EA, electron affinity; η, chemical hardness; μ, chemical potential; s, softness; ω, electrophilicity; ω⁺, electron acceptor power; ω⁻, electron donor power.

The enthalpy calculation results of the reactions for the studied compounds are presented in Table 1.

The frontier orbital energies, E_{HOMO}, E_{LUMO}, and E_{SOMO} are other important parameters of the molecular and radical electronic structures. HOMO and LUMO as the main orbitals within the molecules take part in the chemical reactions. These orbitals and electron transfer between them correspond to chemical reactivity, bioactivity, and stability of the compounds (23). In this study, important electronic descriptors, i.e. the HOMO and LUMO energies, ΔE_{gap}, IP, and electron affinity (EA), were calculated (equations 6-8) (24). Global reactivity indices including chemical hardness (η), chemical potential (μ), softness (s), electrophilicity (ω), electron acceptor power (ω⁺), electron donor power (ω⁻) of the

molecular systems were also computed by equations 10-16 (25). The results of these calculations are provided in Table 2.

$$\Delta E_{\text{gap}} = E_{\text{HOMO}} - E_{\text{LUMO}} \quad (7)$$

$$\text{IP} = -E_{\text{HOMO}} \quad (8)$$

$$\text{EA} = -E_{\text{LUMO}} \quad (9)$$

$$\eta = (\text{IP} - \text{EA}) / 2 \quad (10)$$

$$\mu = -(\text{IP} + \text{EA}) / 2 \quad (11)$$

$$S = 1 / (2\eta) \quad (12)$$

$$\omega = \mu^2 / 2\eta \quad (13)$$

$$\omega^+ = \text{EA}^2 / 2(\text{IP} - \text{EA}) \quad (14)$$

$$\omega^- = \text{IP}^2 / 2(\text{IP} - \text{EA}) \quad (15)$$

$$\chi = -\mu = (\text{IP} - \text{EA}) / 2 \quad (16)$$

In all three mechanisms, PCET, SPLET, and ETPT, the formation of ArO[•] must take place. Therefore, irrespective of which mechanism is operating, the radical scavenging activity, or the antioxidant activity of the studied compounds can also be related to the stability of the radicals formed.

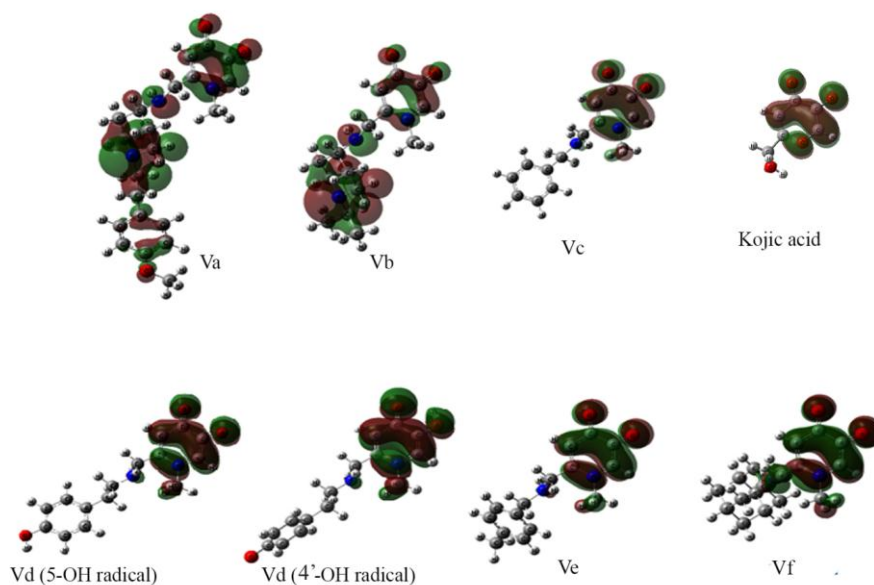


Fig. 2. Single occupied molecular orbital compositions of the radical species of the studied compounds.

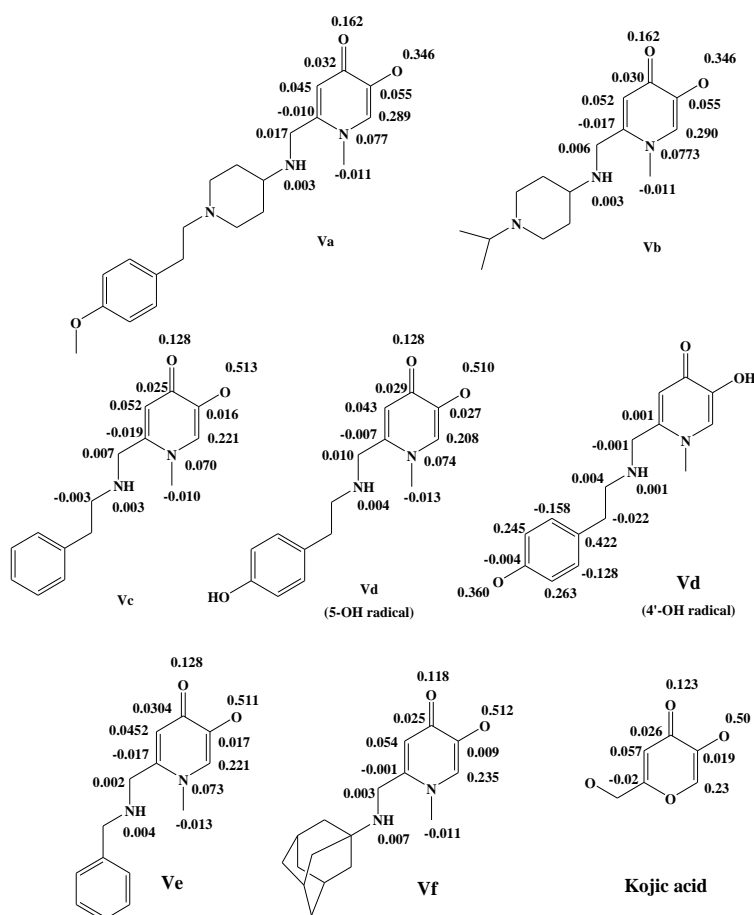


Fig. 3. Spin density distribution in radical species of the studied compounds.

To assess this, the delocalization of the unpaired electron in ArO^{\bullet} is analyzed based on SOMO distribution of radical and radical cation

species (26). Thus, SOMO compositions of the radical species of the studied compounds are presented in Fig. 2.

The spin density is a reliable parameter which provides a better representation of the stability of radical species (27). According to Parkinson, the more delocalized the spin density in the radical, the easier is the radical formed, and thus the lower is the BDE (26). The assessment of spin density distribution was undertaken on the radical and radical cation species of the studied compounds to rationalize the differences in the reactivity of the OH sites and consequently the differences in BDE. Total spin densities distribution of the radical and radical cation forms of the studied compounds are presented in Figs. 3 and 4, respectively.

Natural bond orbital analysis revealed that the lone pair anti-bonding orbital interaction between the ketone oxygen and the adjacent

O-H bonds are responsible for the intramolecular hydrogen bonding (IHB) in the studied structures. The IHB energies between 5-hydroxyl and 4-keto moieties in 5-hydroxypyridin-4-one system were obtained thanks to natural bond orbital analysis and provided in Table 3.

Table 3. Natural bond orbital calculated energies of intra-molecular hydrogen bonding (HB) between 5-hydroxy and 4-ketone moieties.

| Compounds | HB energy (kJ/mol) |
|-------------------------------|--------------------|
| V _a | 17.736 |
| V _b | 17.777 |
| V _c | 16.836 |
| V _d (5-OH radical) | 16.717 |
| V _e | 16.010 |
| V _f | 16.530 |
| Kojic acid | 16.401 |

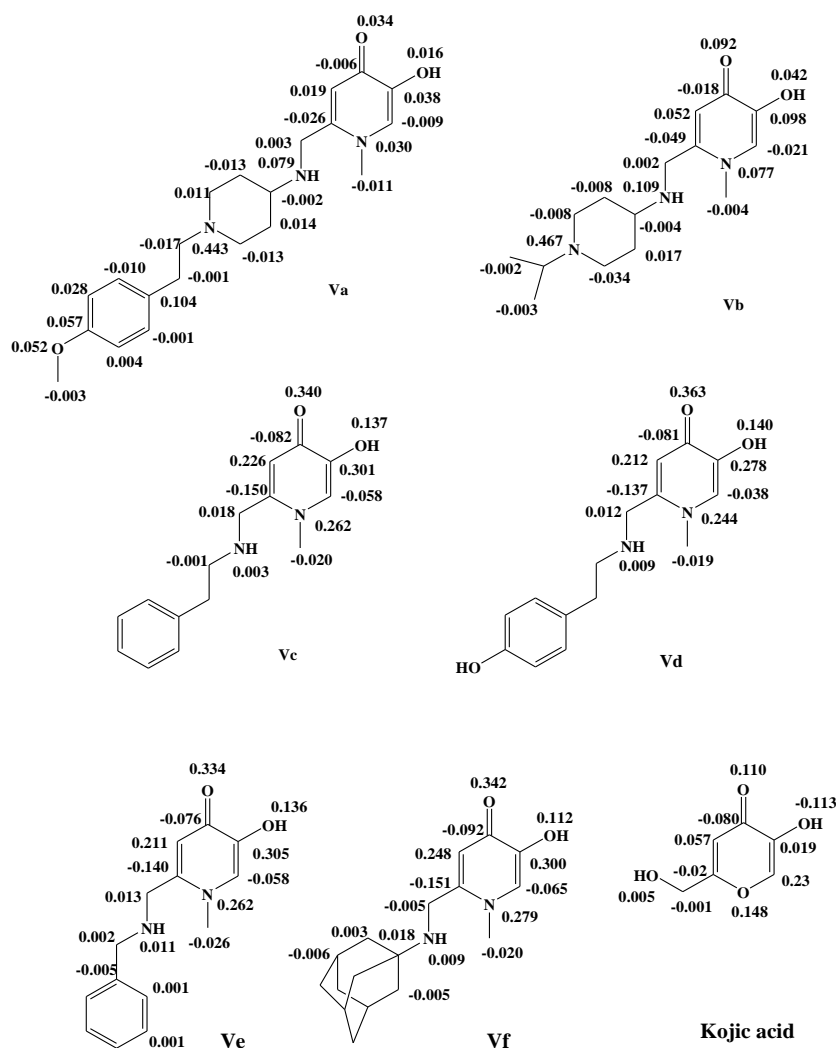


Fig. 4. Spin density distribution in radical cation species of the studied compounds.

DISCUSSION

Regarding the energy-vertical concept, parameters corresponding to the difference in the sum of the electronic and thermal enthalpies while transferring an electron during oxidation were calculated.

BDE value, as the homolytic O-H bond cleavage enthalpy, is a good parameter for analyzing the HAT mechanism. As specified from the calculated BDE values in Table 1, **V_a** and **V_b** showed the lowest BDE values of 1638.648 and 1640.296 kJ/mol, respectively. Kojic acid had the highest BDE value (1675.020 kJ/mol) compared to the BDE for the other studied compounds. Furthermore, there is a correlation between the BDE and the IC₅₀ values where the percentage of DPPH free radical scavenging activity increases almost exponentially with the increase in the BDE values. Thus, it can be concluded that **V_a** and **V_b** are better antioxidants than kojic acid and the other studied compounds if the HAT was regarded as the dominant mechanism for their antioxidant effects.

The IHB energies between 5-hydroxyl and 4-keto moieties on the 5-hydroxypyridin-4-one ring are provided in Table 3. Lower IHB energy was associated with higher BDE, as a consequence, higher antioxidant activity. In accordance with BDE, IHB energies for **V_a** and **V_b** were confirmed by experimental DPPH results as the best antioxidant compounds.

In the first step of SET-PT reactions, the neutral compound is converted to a radical cation form by electron donation to the free radicals. For antioxidants, this radical cation form should be more stable thus less reactive towards oxidative reactions. The IP parameter which describes the process of the electron donation by the antioxidant is related to the first step of SET-PT mechanism. Low IP values are favorable to promote the electron transfer reactivity while high IP values decrease the electron-transfer rate between the antioxidant and free radicals. Thus, molecules with lower IP values are more susceptible to ionization and have stronger antioxidant properties. **V_a** and **V_b** show the smallest values of IP and if SETPT is regarded as the dominant mechanism for antioxidant effects, these compounds can be

referred to as better antioxidants than kojic acid and the other studied compounds (Table 1).

In the second step of the possible SETPT antioxidant mechanism, the radical cation form converts to the common radical form following proton dissociation. PDE values which are presented in Table 1 characterize the second step of the SETPT mechanism. The lower PDE values confirm stronger antioxidant properties.

As shown in Table 1, the order of PDE values for heterolytic O-H bond cleavage of the radical cation species in the PCM phase is (decreasing to the right) as follow: kojic acid, **V_b**, **V_a**, **V_d** (4'-OH), **V_f**, **V_c**, **V_d** (5-OH), and **V_e**. This implies that a heterolytic cleavage of the 5-OH bond in the radical cation form of **V_e** is strongly favored. In contrast, the formation of radical in kojic acid, **V_a**, and **V_b** is very unlikely. The PDE results are not in accordance with the experimental data. The important thing to note here is that a radical cation may have a high tendency to lose a proton to be converted to a radical but, the formation of this radical cation form might be essentially impossible in the first step of the SETPT mechanism.

PA parameter is related to the first step of SPLET mechanism (Table 1). The lower PA value means that heterolytic cleavage of the O-H bond and proton release is powerfully preferential. The PA values for all the investigated compounds are almost similar. But **V_a**, **V_b**, and **V_d** show the smallest PA values corresponding to better antioxidant effects than the kojic acid and the other studied compounds (Table 1).

The second part of the possible SPLET antioxidant mechanism is the formation of the common radical species from the anion form. An important task for the explanation of the second part of the SPLET mechanism could be the study of ETE values (Table 1). **V_b** and **V_d** show the smallest ETE values, referring to the better antioxidant effects than kojic acid and the other studied compounds if SPLET is the dominant mechanism for antioxidant effects.

In the orbital-vertical concept, the E_{gap} of the HOMO and the LUMO (ΔE_{gap}) of the neutral molecule is applied to explain the antioxidant mechanism of compounds.

The HOMO values are used to characterize the donating ability of the molecule. A higher

value of HOMO energy indicates a predisposition of the molecular system to lose electrons. A higher value of HOMO energy is therefore an indication of the good electron donor and higher antioxidant activity. Due to the close values of E_{HOMO} among the studied compounds, ΔE_{gap} was also exploited to evaluate the affinity for losing an electron to form radical forms. ΔE_{gap} determines the chemical reactivity. The lower ΔE_{gap} , the easier electrons donation, and the more antioxidant effect (28). Data from Table 2 for the HOMO, LUMO energies and the ΔE_{gap} suggest that **V_a** and **V_b** have the highest antioxidant potential since they have the lowest ΔE_{gap} values.

The IP can give the idea about energy necessary to eject an electron from a molecule. From higher values of IP for a molecule, it can be concluded that the molecule does not lose electron easily. The estimated IP could provide an understanding of the initial energy required to release an electron from the compounds (3,21), which implied an inverse relation between the scavengers and IP. Therefore, the lower the energy required to remove an electron, the higher is the compound's antioxidant activity, or, in other words, the higher the E_{HOMO} , the smaller is the IP (29). Compounds **V_a** and **V_b** have the lower IP and higher E_{HOMO} among all the studied compounds.

The EA can be expressed as the amount of energy released when an electron is absorbed by a neutral molecule. The greater electronic affinity of a molecule/atom means to absorb the electrons easily. The Higher EA values allow a compound to easily absorb the electrons. Thus the higher EA values are related to the better antioxidant activity (30). Compounds **V_a**, **V_f**, and **V_b** have the lowest EA respectively among all the studied compounds.

The χ is a measure of the tendency to attract electrons in a chemical bond and is defined as the negative of the μ in DFT. Thus, a compound with a lower χ is expected to have a higher antioxidant activity (31). Compounds **V_a**, **V_f**, and **V_b** have the lower χ respectively, among all the studied compounds.

The ω used to find the electrons affinity and measures the maximum electron flow between a donor and an acceptor. A good, reactive,

nucleophile is characterized by lower values of χ and also ω and conversely, a reactive electrophile is characterized by higher values of χ and ω (31). The presented results in Table 2 are indicating that **V_f** and **V_b** have the lowest ω values and they are part of the nucleophiles, whereas kojic acid and **V_e** have the highest ω value and they are strongly electrophil.

Lower ω^- means the good capacity to donate an electron, whereas higher ω^+ indicates a good capacity to accept an electron (32). **V_a** and **V_b** exhibited the lowest ω^- values and it means they have good capacity to donate an electron, whereas kojic acid and **V_e** show higher ω^+ and good capacity to accept an electron.

According to the frontier molecular orbital theory, The HOMO acts as an electron-donor and the LUMO acts as an electron-acceptor. Also, the η is electron or charge transfer resistance, and the S is the measure of the capacity of an atom to transferring an electron or charge (33,34). A molecule is considered as softer and has an excellent chemical reactivity when it has the smaller ΔE_{gap} and the higher E_{HOMO} . Meanwhile, a molecule is considered to have a higher η and is assumed to have good stability when it has a larger ΔE_{gap} value and lower E_{HOMO} (35,36). Also, the structure with the lower E_{HOMO} is a weak electron donor while the structure with the higher E_{HOMO} energy is a good electron donor and thus has the highest antioxidant activity (28). The HOMO and LUMO energy values as well as ΔE_{gap} values of the studied compounds are shown in Table 2. **V_a** and **V_b** have higher E_{HOMO} and also lower ΔE_{gap} values which resulted in good reactivity and antioxidant activity of **V_a** and **V_b** among all the studied compounds. On the other hand, it can be comprehended that **V_a** and **V_b** are softer and have good reactivity to electron transfer and scavenging of free radicals by electron donation behavior. Also, the E_{SOMO} of radical species can be used for estimation of stability of radical species. The lower E_{SOMO} values in **V_a** and **V_b** radical species indicated this fact that these radicals are more stable and formed easier after electron donation to free radicals.

Theoretically, it was conceivable that the HOMO, SOMO, and LUMO energies are a valid indicator of scavenging activity. Also, the HOMO and SOMO compositions could be

considered to understand the relation between the π -electrons delocalization and scavenging activity (37). The differences in the scavenging activities of the synthesized compounds essentially refer to the delocalization of π -electrons, leading to the stability of the radicals acquired after hydrogen abstraction. The SOMO compositions of V_a and V_b (Fig. 2) are delocalized over the entire structure than the other synthesized molecules or kojic acid. It leads to the delocalization of π -electrons and more stability of the radicals in V_a and V_b , which are highly compatible with the results of theoretical and experimental free radical scavenging activity investigations.

Analysis of spin density is useful to evaluate the delocalization of the unpaired electron in the radical species. In general, a radical system with more delocalized spin density is more active for free radical scavenging. Moreover, extended conjugation of the π -electrons to more than one aromatic ring enhances the stability of the radical systems as well as the radical scavenging activity. The spin densities of the radical and radical cation forms were compared (Figs. 3 and 4). Higher spin density delocalization indicates the easier formation of radical or radical cation species and lower value of the BDE (26). In general, a decrease in the spin density at the oxygen of $ArO\cdot$ shows an increase in the radical scavenging activity, in terms of its IC_{50} values. The spin densities seem to be slightly more delocalized for the radicals and radical cations created from V_a and V_b than for the other synthesized compounds and kojic acid. The spin density evaluation results are in accordance with the results of theoretical and experimental radical scavenging activity investigations.

CONCLUSION

In this paper free radical scavenging activity of synthesized 3-hydroxypyridine-4-one derivatives and kojic acid were evaluated experimentally using DPPH free radical scavenging method. Also, the HAT, SPLET, and SETPT mechanisms of antioxidant behavior were investigated based on the DFT computations. The preferred mechanism of the antioxidant activity can be estimated using the

energy-vertical method from values of the BDE (for HAT mechanism), IP (for the first step of the SETPT mechanism), and PA of anion form (for the first step of the SPLET mechanism) (38). Also, according to the Wright's rules for IP more than 151 kJ/mol and BDE of around 188 kJ/mol HAT is considered to be the dominant mechanism, whereas, for IP lower than 188 kJ/mol, the predominant mechanism is SETPT (39). Generally, for the synthesized compounds, the values of PA are lower than the corresponding values of BDE and IP. Therefore, SPLET represents the most probable reaction pathway from the thermodynamic point of view in the water environment. In contrast, the huge BDE values indicate that HAT is not the preferred antioxidant mechanism for these molecules. These results are in accordance with the results of Foti *et al* researching group who supported the SPLET mechanism for the reaction of DPPH with the flavonoids and quercetin in polar solvents. They concluded HAT is thermodynamically preferred in the gas phase (40). Comparison between the above properties related to electronic descriptors and reactivity indices and experimental DPPH scavenging results demonstrate that these compounds are capable of donating the electrons to free radicals instead of capturing them and it's an indication of their antioxidant behavior.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest in this study.

AUTHORS' CONTRIBUTION

The idea was developed by A. Fassihi, A. Movahedian Attar, and F. Hasanzadeh. A. Fassihi, A. Movahedian Attar, and F. Hasanzadeh supervised this work. Synthesizes was done by A. Fassihi,

F. Hasanzadeh, L. Saghaie, and M. Mohammadpour Dehkordi. *in vitro* and *in silico* investigations were done by A. Movahedian Attar, L. Saghaie, and M. Mohammadpour Dehkordi. Data collection and analysis was performed by A. Fassihi, A. Movahedian Attar, F. Hasanzadeh, and M. Mohammadpour Dehkordi. A. Fassihi and M. Mohammadpour Dehkordi contributed in manuscript preparation and revision.

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روش تحقیق کمی



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