


Cite this: *RSC Adv.*, 2022, 12, 24579

# Synthesis and evaluation of the antioxidant activity of 3-pyrroline-2-ones: experimental and theoretical insights†

Nguyen Tran Nguyen,<sup>✉</sup> Vo Viet Dai,<sup>✉</sup> Adam Mechler,<sup>✉</sup> Nguyen Thi Hoa<sup>c</sup> and Quan V. Vo<sup>✉</sup>\*

The heterocyclic  $\gamma$ -lactam ring 2-pyrrolidinone has four carbon atoms and one nitrogen atom. Among the group of derivatives of 2-pyrrolidinones, 1,5-dihydro-2H-pyrrol-2-ones, also known as 3-pyrroline-2-ones, play a significant structural role in a variety of bioactive natural compounds. In this study, three-component reactions were used to successfully synthesize six polysubstituted 3-hydroxy-3-pyrroline-2-one derivatives. The antioxidant activity of the compounds was tested by the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay, identifying 4-ethoxycarbonyl-3-hydroxy-5-(4-methylphenyl)-1-phenyl-3-pyrroline-2-one (**4b**) as the most promising radical scavenger. Quantum chemistry calculations of the thermodynamics and kinetics of the radical scavenging activity also suggest that **4b** is an effective HO<sup>•</sup> radical scavenger, with  $k_{\text{overall}}$  values of  $2.05 \times 10^9$  and  $1.54 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$  in pentyl ethanoate and water, respectively. On the other hand, **4b** could not scavenge hydroperoxyl radicals in either media. The ability of **4b** to scavenge hydroxyl radicals in polar and non-polar environments is comparable to that of conventional antioxidants such as melatonin, gallic acid, indole-3-carbinol, ramalin, or Trolox. Thus **4b** may be classed as a promising HO<sup>•</sup> radical scavenger in the physiological environment.

Received 25th July 2022  
Accepted 22nd August 2022

DOI: 10.1039/d2ra04640g

rsc.li/rsc-advances

## 1. Introduction

2-Pyrrolidinone is a  $\gamma$ -lactam heterocyclic ring containing four carbon atoms and one nitrogen atom. Among the family of 2-pyrrolidinone derivatives, 1,5-dihydro-2H-pyrrol-2-ones (also named as 3-pyrroline-2-ones) are important structural subunits of numerous bioactive natural products (Fig. 1). For example, oteromycin that was isolated from fungus strains MF5810 and MF5811 is a HIV-1 integrase inhibitor,<sup>1</sup> while the *Fusarium pallidroseum*-originating equisetin is a natural antibiotic active against *Staphylococcus aureus* and *Bacillus subtilis*<sup>2</sup> while it is also a potent inhibitor against HIV-integrase with IC<sub>50</sub> values between 7 and 20  $\mu\text{M}$ .<sup>1</sup> In addition to natural products, more and more non-natural polysubstituted 1,5-dihydro-2H-pyrrol-2-ones have also been proven to possess a broad spectrum of pharmacological activities as e.g., anticancer,<sup>3–7</sup> antibacterial,<sup>8–10</sup> anti-HIV-1,<sup>11</sup> as well as anti-inflammatory<sup>12,13</sup> and antioxidant<sup>2,14–18</sup> agents. Based on the promising data it was

suggested that 1,5-dihydro-2H-pyrrol-2-one skeleton-containing heterocyclic compounds are potential drug candidates. Therefore, increasing attention has been directed at the synthesis of 1,5-dihydro-2H-pyrrol-2-ones, and especially 3-hydroxy-1,5-dihydro-2H-pyrrol-2-ones.<sup>19</sup>

Multi-component reactions (MCRs) offer an efficient synthetic pathway in organic chemistry to obtain complicated molecular structures.<sup>20</sup> Recently, the synthesis of polysubstituted 3-hydroxy-1,5-dihydro-2H-pyrrol-2-ones has been established based on three-component reactions of aromatic aldehydes, arylamines and dialkyl acetylenedicarboxylate.<sup>21–27</sup> The use of sodium diethyl oxalacetate instead of dialkyl acetylenedicarboxylate in the synthesis of polysubstituted 3-hydroxy-1,5-dihydro-2H-pyrrol-2-ones via three-component reactions has also been reported; however, there are still some disadvantages regarding to the use of sodium diethyl oxalacetate that need to be improved.<sup>28–30</sup> Therefore, optimizing reaction conditions to synthesize polysubstituted 3-hydroxy-3-pyrroline-2-ones via MCRs involving sodium diethyl oxalacetate is still in demand to the synthetic organic chemist community.

A key bioactivity described above is the potential antioxidant activity of this family of compounds.<sup>2,14–18,31</sup> The imbalance between the production and consumption of oxidants in biological systems leads to oxidative stress, that is, chemical breakdown/damage of various biologically important molecules.<sup>32</sup> Although there are natural oxidants of various chemical characteristics, free radicals are the main cause of oxidative

<sup>a</sup>The University of Danang – University of Science and Education, Danang 550000, Vietnam. E-mail: ntnguyen@ued.udn.vn

<sup>b</sup>Department of Biochemistry and Chemistry, La Trobe University, Victoria 3086, Australia

<sup>c</sup>The University of Danang – University of Technology and Education, Danang 550000, Vietnam. E-mail: vvquan@ute.udn.vn

† Electronic supplementary information (ESI) available. See <https://doi.org/10.1039/d2ra04640g>



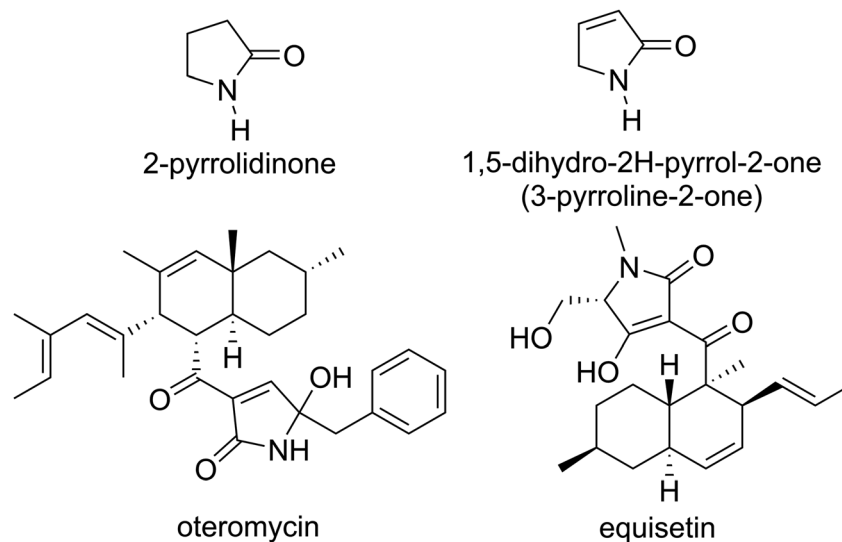


Fig. 1 Natural products containing 3-pyrroline-2-one subunit.

stress. They are highly reactive and capable of initiating chain reactions, hence propagating molecular damage. A representative reactive oxygen species is the hydroxyl radical.<sup>33</sup> It is so reactive that it would effectively assault nearly every organic molecule around the place of its production. This radical is held accountable for the majority of ionizing radiation-induced tissue damage<sup>34</sup> and is the most significant cause of oxidative DNA damage.<sup>35–37</sup> Inhibiting OH<sup>•</sup> generation would therefore be an effective means of reducing oxidative stress. However, studies of antioxidant activity of 3-hydroxy-3-pyrroline-2-ones are thus far limited: there is no information on the mechanism and kinetics of the antiradical activity, particularly in physiological environments.

The use of computational approaches to investigate the structure–activity relationship and to direct the design of novel medications with enhanced activity is well established,<sup>38–42</sup> making it possible to perform the evaluation of the radical (*i.e.*, HO<sup>•</sup> and HOO<sup>•</sup>) scavenging activity *in silico*, benchmarked against experimental data.

Thus, in this study, three-component reactions of aromatic aldehydes, amines and sodium diethyl oxalacetate will be optimized in order to shorten reaction time, increase the yields and eliminate the need for elevated temperature. Consecutively, the 1,1-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging capacity of six polysubstituted 3-hydroxy-3-pyrroline-2-ones will be measured. Finally, the interaction of the best performing 3-hydroxy-3-pyrroline-2-one with HO<sup>•</sup> and HOO<sup>•</sup> radicals will be evaluated using well-established model chemistry based on the quantum mechanics-based test for the overall free radical scavenging activity (QM-ORSA) protocol.<sup>40,43</sup>

## 2. Experimental and computational methods

### 2.1. Experimental

**2.1.1. Chemicals and experimental methods.** All chemicals were purchased from the main chemical suppliers: Merck,

Acros, or Sigma Aldrich. For column chromatography, 70–230 mesh silica 60 (E. M. Merck) was used as the stationary phase. Melting points (not corrected) were determined using a Büchi Melting Point B-545 apparatus. NMR spectra were acquired on Bruker Avance II+ 500 MHz or Bruker Avance II+ 600 MHz instruments and chemical shifts ( $\delta$ ) are reported in parts per million (ppm) referenced to tetramethylsilane (TMS) or the internal (NMR) solvent signals. Exact mass measurements were acquired on a quadrupole orthogonal acceleration time-of-flight mass spectrometer (Synapt G2 HDMS, Waters, Milford, MA). Samples were infused at 3  $\mu\text{L min}^{-1}$  and spectra were obtained in positive (or negative) ionization mode with a resolution of 15 000 (FWHM) using leucine enkephalin as lock mass. High-resolution mass measurements were recorded on a SCIEX X500 QTOF with an electrospray ionization source in a positive ion mode. The temperatures of the source were set at 300 °C. Curtain gas chambers were filled with high-purity nitrogen (25 psi). The capillary voltage was constantly kept at 5500 V. The collision energy was set at 10 V and zero collision energy spread. IDA mode was used to find mass in the range (100 to 1000).

**2.1.2. General procedure for the synthesis of 1,5-disubstituted-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-one.** Aromatic aldehyde (1 equiv.), amine (1 equiv.), citric acid (2 equiv.) and absolute ethanol (1.0 mL) were mixed in a round bottom flask. The mixture was magnetically stirred at room temperature under an argon atmosphere for 1 hour. Subsequently, sodium diethyl oxalacetate (2 equiv.) was added and the mixture was stirred vigorously at room temperature under Ar atmosphere for 8 hours and the formation of 1,5-disubstituted-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-one was followed by TLC (hexane/EtOAc = 5 : 1 and hexane/EtOAc = 5 : 3.5). Then, CH<sub>2</sub>Cl<sub>2</sub> and HCl (5%) were added and the resulting mixture was stirred vigorously for 15 minutes. The organic layer was separated, then washed three times with distilled water and dried over MgSO<sub>4</sub>. The crude product was purified *via* recrystallization in the solvent mixture of CH<sub>2</sub>Cl<sub>2</sub> and absolute ethanol or CH<sub>2</sub>Cl<sub>2</sub> and ethylacetate to obtain a pure product.



### 2.1.3. Spectra data of products

**2.1.3.1. 1,5-Diphenyl-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-one (4a).** M.p. 171–173 °C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.14 (s<sub>br</sub>, 1H; –OH), 7.49 (d, <sup>3</sup>J(H,H) = 7.80 Hz, 2H; Ar–H), 7.29–7.23 (m, 7H; Ar–H), 7.10 (t, <sup>3</sup>J(H,H) = 7.47 Hz, 1H; Ar–H), 5.75 (s, 1H), 4.20 (m, 2H; OCH<sub>2</sub>), 1.18 ppm (t, <sup>3</sup>J(H,H) = 7.13 Hz, 3H; CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 165.21, 162.99, 156.55, 136.36, 135.18, 129.05, 128.68, 128.61, 127.63, 125.93, 122.38, 113.29, 61.68, 61.35, 14.03 ppm. HRMS (ESI-TOF MS/MS) *m/z* [M + H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>17</sub>NO<sub>4</sub>: 324.1236; found: 324.1223.

**2.1.3.2. 4-Ethoxycarbonyl-3-hydroxy-5-(4-methylphenyl)-1-phenyl-3-pyrroline-2-one (4b).** M.p. 206–207 °C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.09 (s<sub>br</sub>, 1H; –OH), 7.49 (dd, <sup>3</sup>J(H,H) = 8.64 Hz, <sup>4</sup>J(H,H) = 1.08 Hz, 2H; Ar–H), 7.27 (m, 2H; Ar–H), 7.11 (m, 3H; Ar–H), 7.05 (d, <sup>3</sup>J(H,H) = 7.86 Hz, 2H; Ar–H), 5.72 (s, 1H), 4.19 (m, 2H; –OCH<sub>2</sub>–), 2.26 (s, 3H; CH<sub>3</sub>), 1.20 ppm (t, <sup>3</sup>J(H,H) = 7.14 Hz, 3H; CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 165.21, 193.01, 156.37, 138.36, 136.45, 132.04, 129.39, 129.03, 127.48, 125.85, 122.37, 113.37, 61.45, 61.34, 21.24, 14.07 ppm. HRMS (ESI-TOF MS/MS) *m/z* [M + H]<sup>+</sup> calcd for C<sub>20</sub>H<sub>19</sub>NO<sub>4</sub>: 338.1392; found: 338.1383.

**2.1.3.3. 4-Ethoxycarbonyl-3-hydroxy-5-(4-nitrophenyl)-1-phenyl-3-pyrroline-2-one (4c).** M.p. 173–175 °C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.05 (s<sub>br</sub>, 1H; –OH), 8.12 (d, <sup>3</sup>J(H,H) = 8.40 Hz, 2H; Ar–H), 7.43 (m, 4H; Ar–H), 7.28 (t, <sup>3</sup>J(H,H) = 7.71 Hz, 2H; Ar–H), 7.13 (t, <sup>3</sup>J(H,H) = 7.43 Hz, 1H; Ar–H), 5.85 (s, 1H), 4.21 (m, 2H; OCH<sub>2</sub>), 1.21 ppm (t, <sup>3</sup>J(H,H) = 7.15 Hz, 3H; CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 164.66, 162.65, 156.98, 148.16, 142.94, 135.84, 129.44, 128.69, 126.53, 125.07, 122.27, 112.33, 61.78, 60.79, 14.17 ppm. HRMS (ESI-TOF MS/MS) *m/z* [M + H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>16</sub>N<sub>2</sub>O<sub>6</sub>: 369.1087; found: 369.1081.

**2.1.3.4. 1-Benzyl-4-ethoxycarbonyl-3-hydroxy-5-(4-methylphenyl)-3-pyrroline-2-one (4d).** M.p. 184–186 °C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.05 (s<sub>br</sub>, 1H; –OH), 7.30 (m, 3H; Ar–H), 7.16 (d, <sup>3</sup>J(H,H) = 7.80 Hz, 2H; Ar–H), 7.12 (dd, <sup>3</sup>J(H,H) = 7.94 Hz, <sup>4</sup>J(H,H) = 2.02 Hz, 2H; Ar–H), 6.98 (d, <sup>3</sup>J(H,H) = 8.09 Hz, 2H; Ar–H), 5.18 (d, <sup>2</sup>J(H,H) = 14.79 Hz, 1H; –CH<sub>2</sub>N), 4.84 (s, 1H), 4.08 (m, 2H; OCH<sub>2</sub>), 3.54 (d, <sup>2</sup>J(H,H) = 14.83 Hz, 1H; –CH<sub>2</sub>N), 2.36 (s, 3H; CH<sub>3</sub>), 1.08 ppm (t, <sup>3</sup>J(H,H) = 7.16 Hz, 3H; CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 165.58, 163.59, 157.75, 138.79, 136.55, 131.53, 129.67, 128.94, 128.69, 127.97, 127.86, 113.43, 61.13, 59.54, 44.01, 21.37, 14.02 ppm. HRMS (ESI-quadrupole) *m/z* [M + H]<sup>+</sup> calcd for C<sub>21</sub>H<sub>21</sub>NO<sub>4</sub>: 352.1549; found: 352.1535.

**2.1.3.5. 1-Benzyl-4-ethoxycarbonyl-3-hydroxy-5-(4-nitrophenyl)-3-pyrroline-2-one (4e).** M.p. 224–227 °C. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 12.01 (s<sub>br</sub>, 1H; –OH), 8.14 (d, <sup>3</sup>J(H,H) = 8.65 Hz, 2H; Ar–H), 7.40 (d, <sup>3</sup>J(H,H) = 8.57 Hz, 2H; Ar–H), 7.25 (m, 3H; Ar–H), 7.05 (dd, <sup>3</sup>J(H,H) = 7.72 Hz, <sup>4</sup>J(H,H) = 1.88 Hz, 2H; Ar–H), 5.16 (s, 1H), 4.78 (d, <sup>2</sup>J(H,H) = 15.35 Hz, 1H; –CH<sub>2</sub>N), 3.98 (dq, <sup>3</sup>J(H,H) = 7.03 Hz, <sup>2</sup>J(H,H) = 14.09 Hz, 1H; –OCH<sub>2</sub>–), 3.92 (dq, <sup>3</sup>J(H,H) = 6.96 Hz, <sup>2</sup>J(H,H) = 14.00 Hz, 1H; –OCH<sub>2</sub>–), 3.80 (d, <sup>2</sup>J(H,H) = 15.37 Hz, 1H; –CH<sub>2</sub>N), 1.01 ppm (t, <sup>3</sup>J(H,H) = 7.10 Hz, 3H; CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 164.88, 161.69, 154.09, 147.32, 144.04, 136.20, 129.29, 128.54, 127.77, 127.41, 123.61, 110.97, 59.64, 59.57, 44.18, 13.92 ppm. HRMS (ESI-

quadrupole) *m/z* [M + H]<sup>+</sup> calcd for C<sub>20</sub>H<sub>18</sub>N<sub>2</sub>O<sub>6</sub>: 383.1243; found: 383.1231.

**2.1.3.6. 4-Ethoxycarbonyl-3-hydroxy-5-(4-methylphenyl)-1-(3-nitrophenyl)-3-pyrroline-2-one (4f).** M.p. 179–181 °C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.08 (s<sub>br</sub>, 1H; –OH), 8.30 (t, <sup>4</sup>J(H,H) = 2.17 Hz, 1H; Ar–H), 8.09 (dd, <sup>3</sup>J(H,H) = 8.35 Hz, <sup>4</sup>J(H,H) = 2.29 Hz, 1H; Ar–H), 7.93 (dd, <sup>3</sup>J(H,H) = 8.25 Hz, <sup>4</sup>J(H,H) = 2.14 Hz, 1H; Ar–H), 7.45 (t, <sup>3</sup>J(H,H) = 8.22 Hz, 1H; Ar–H), 7.13 (d, <sup>3</sup>J(H,H) = 8.18 Hz, 2H; Ar–H), 7.08 (d, <sup>3</sup>J(H,H) = 7.93 Hz, 2H; Ar–H), 5.76 (s, 1H), 4.20 (m, 2H; –OCH<sub>2</sub>–), 2.67 (s, 3H; CH<sub>3</sub>), 1.20 ppm (t, <sup>3</sup>J(H,H) = 7.11 Hz, 3H; CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 165.24, 163.12, 156.11, 148.55, 139.05, 137.75, 131.16, 130.00, 129.81, 127.43, 127.34, 120.08, 116.06, 114.01, 61.70, 61.21, 21.29, 14.07 ppm. HRMS (ESI-quadrupole) *m/z* [M + H]<sup>+</sup> calcd for C<sub>20</sub>H<sub>18</sub>N<sub>2</sub>O<sub>6</sub>: 383.1243; found: 383.1232.

**2.1.4. DPPH assay.** Radical-scavenging properties of poly-substituted 3-hydroxy-3-pyrroline-2-ones were evaluated against 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical.<sup>44–48</sup> DPPH solution (1 mM) was prepared in methanol and solutions of each polysubstituted 3-hydroxy-3-pyrroline-2-one were prepared in DMSO at various concentrations (128, 32 and 8 μg mL<sup>–1</sup>). Then, 200 μL DPPH solution was added to 1.28 μL samples at each tested concentration and the free radical scavenging reactions were carried out on a 96-well plate at 37 °C for 30 minutes. The absorbance was measured at 517 nm wavelength by a BioTek Epoch 2 Microplate Spectrophotometer. The percentage of free radical scavenging was calculated as SP(%) = [(OD<sub>0</sub> – OD<sub>1</sub>)/OD<sub>0</sub>] × 100, where OD<sub>0</sub> was defined as the final absorbance of the control reaction with quercetin as the reference antioxidant, and OD<sub>1</sub> stands for the absorbance in the presence of the sample. Each experiment was repeated three times and quercetin was used as the positive control.

## 2.2. Computational details

All DFT calculations were carried out with the Gaussian 09 suite of programs.<sup>49</sup> M06-2X functional<sup>50</sup> and 6-311++G(d,p) basis set were used for all calculations. The M06-2X functional offers one of the most reliable methods to study the thermodynamics and kinetics of radical reactions.<sup>40,50–55</sup> The kinetic calculations were performed following the QM-ORSA protocol,<sup>40,43</sup> following the literature.<sup>54–61</sup> This method has been repeatedly benchmarked against experimental data, delivering results with low errors (*k*<sub>calc</sub>/*k*<sub>exp</sub> ratio = 1–2.9), particularly in lipid and aqueous solutions.<sup>40,43,52,62</sup> As a reference all details of the calculations are shown in Table S1, ESI.†

## 3. Results and discussion

### 3.1. Synthesis of polysubstituted 3-pyrroline-2-ones

The reaction between benzaldehyde (1a), aniline (2a) and sodium diethyl oxalacetate (3) in the presence of citric acid (2 equiv.) as the catalyst was used as the starting point to optimize the reaction conditions. Equimolar amounts of 1a, 2a and 3 at 0.5 M concentrations in absolute ethanol at room temperature turned over to 1,5-diphenyl-4-ethoxycarbonyl-3-hydroxy-3-



Table 1 Starting materials **1a** : **2a** : **3** optimization for the synthesis of **4a**

Entry	Solvent volume (mL)	Ratio <b>1a</b> : <b>2a</b> : <b>3</b> (equiv.)	Concentration <b>1a</b> : <b>2a</b> : <b>3</b> (mmol mL <sup>-1</sup> )	Yield (%)
1	1.0	1 : 1 : 1	0.5 : 0.5 : 0.5	42
2	1.5	1 : 1 : 1	0.34 : 0.34 : 0.34	35
3	1.0	1.5 : 1 : 1	0.75 : 0.5 : 0.5	37
4	1.0	1 : 1.5 : 1	0.5 : 0.75 : 0.5	38
5	1.0	1 : 1 : 1.5	0.5 : 0.5 : 0.75	68
6	1.0	1 : 1 : 2	0.5 : 0.5 : 1.0	86

Table 2 Synthesis of polysubstituted 3-hydroxy-1,5-dihydro-2H-pyrrol-2-ones

Entry	R <sup>1</sup>	R <sup>2</sup>	Product	Yield (%)
1	H	C <sub>6</sub> H <sub>5</sub>	<b>4a</b>	86
2	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	<b>4b</b>	72
3	NO <sub>2</sub>	C <sub>6</sub> H <sub>5</sub>	<b>4c</b>	91
4	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	<b>4d</b>	55
5	NO <sub>2</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	<b>4e</b>	79
6	CH <sub>3</sub>	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<b>4f</b>	70

pyrroline-2-one (**4a**) with 42% yield. This result is consistent with prior reports.<sup>29,30</sup>

There was a slight decrease in the yield of **4a** (35%) when the concentration of starting materials in solvent was reduced to 0.34 M. The yield was only 37–38% when the concentration of **1a** or **2a** was increased to 0.75 M in absolute ethanol. However, there was a dramatic increase in the yield of **4a** to 86% when 2 equiv of sodium diethyl oxalacetate (**3**) was used (Table 1). Therefore, the ratio 1 : 1 : 2 of reactants aromatic aldehyde, amine and sodium diethyl oxalacetate, respectively, was used to synthesize other polysubstituted 3-hydroxy-1,5-dihydro-2H-pyrrol-2-ones in absolute ethanol (1 mL) (Table 2).

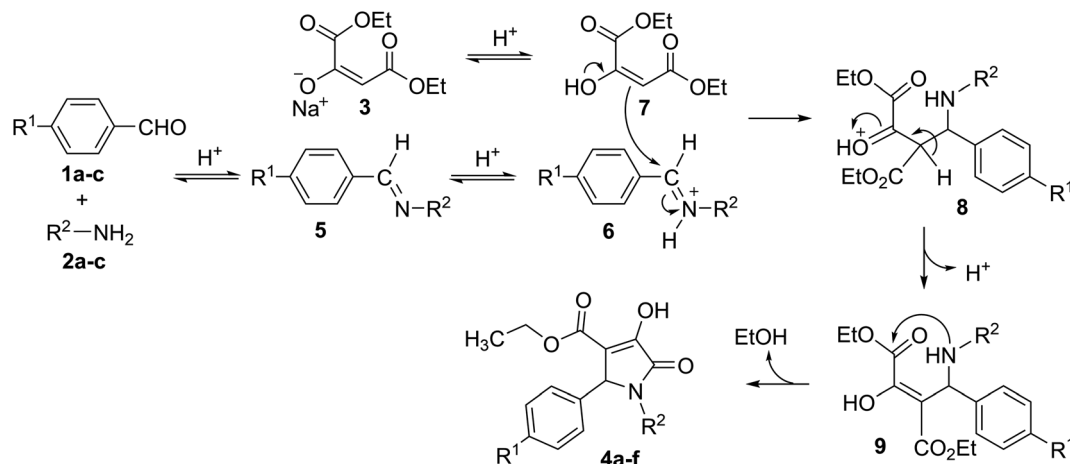
The initial step in the multi-component reaction to synthesize polysubstituted 3-hydroxy-1,5-dihydro-2H-pyrrol-2-ones proceeds *via* acid-catalyzed condensation of aromatic aldehyde (**1a–c**) and amine (**2a–c**) in the presence of citric acid as the catalyst to yield imine (**5**) which will be then protonated to iminium (**6**).<sup>21,24</sup> In the next step, sodium diethyl oxalacetate (**3**) affords the enol derivative (**7**) in an acidic environment, and subsequently, enol (**7**) will react with iminium species **6** to obtain intermediate **8** containing protonated ketone functional group. Then, the deprotonation of **8** will result in intermediate **9** containing enol moiety. The intramolecular nucleophilic attack of the secondary amino group present in intermediate **9** to the carbonyl carbon of a carboxylate moiety results in the formation

of polysubstituted 3-hydroxy-1,5-dihydro-2H-pyrrol-2-ones (**4a–f**) (Scheme 1).<sup>19,21,24</sup>

The presence of methyl group in 4-methylbenzaldehyde (**1b**) will reduce the electrophilicity of carbonyl carbon *via* a positive inductive effect as compared to benzaldehyde. In contrast, the electron-withdrawing property of the nitro group in 4-nitrobenzaldehyde (**1c**) results in an increase in the electrophilicity of the carbonyl carbon.<sup>63</sup> Consequently, the rate of imine formation reaction between 4-nitrobenzaldehyde (**1c**) and aniline (**2a**) is faster than that between 4-methylbenzaldehyde (**1b**) and aniline (**2a**).<sup>64</sup> The easier the imine formation, the higher the yield of desired product polysubstituted 3-hydroxy-1,5-dihydro-2H-pyrrol-2-one. Moreover, the formation of the –CH=N– double bond will decrease when using aliphatic amines as compared to aromatic amines.<sup>65,66</sup> Therefore, the yields of polysubstituted 3-hydroxy-1,5-dihydro-2H-pyrrol-2-ones **4b**, **4c** are higher than that of **4d**, **4e**, respectively.

In the structure of polysubstituted 3-hydroxy-1,5-dihydro-2H-pyrrol-2-ones, the –C(O)OCH<sub>2</sub>CH<sub>3</sub> group is almost coplanar with the plane of the 3-pyrroline-2-one.<sup>21,22</sup> As a consequence, two protons of methylene group are diastereotopic and they will show geminal coupling in <sup>1</sup>H NMR. In addition, methylene protons (CH<sub>2</sub>) will also couple with protons of methyl group (CH<sub>3</sub>) separated by three sigma bonds. Therefore, two protons of methylene group should be represented by two doublet of quartet (dq) instead of a simple quartet. For instance, <sup>1</sup>H NMR



Scheme 1 Mechanism for the synthesis of polysubstituted 3-hydroxy-1,5-dihydro-2H-pyrrol-2-ones.<sup>19</sup>

of 1-benzyl-4-ethoxycarbonyl-3-hydroxy-5-(4-nitrophenyl)-3-pyrroline-2-one (**4e**) showed two doublet of quartet at the chemical shift of 3.92 and 3.98 ppm representing for two methylene protons of  $-\text{C}(\text{O})\text{OCH}_2\text{CH}_3$  group. In addition, two protons of methylene group attached to nitrogen at 1-position are also diastereotopic and thus, represented by two doublets at the chemical shifts of 4.78 and 3.80 ppm.

### 3.2. Radical scavenging activity of 3-pyrroline-2-ones

**3.2.1. DPPH antioxidant assay.** In the initial evaluation of the antioxidant activity of the synthetic 3-pyrroline-2-ones, the DPPH assay was used following the literature<sup>44,47,48</sup> using quercetin as the reference antioxidant (Table 3). Under the tested conditions, the studied compound exhibited lower DPPH scavenging activity ( $\text{EC}_{50} > 128 \mu\text{g mL}^{-1}$ , 0.33–0.39 mM) than quercetin ( $9.97 \pm 0.25 \mu\text{g mL}^{-1}$ , 0.033 mM). Among the synthetic compounds, the best DPPH antiradical activity was observed for **4b** (40% DPPH at  $128 \mu\text{g mL}^{-1}$ ), which was more than five times higher than that of **4d** (7% DPPH) or **4f** (6% DPPH). Activities of **4a**, **4c** and **4e** were intermediate at 14, 32 and 26% DPPH, respectively. However, previous studies showed that the 3-pyrroline-2-one derivatives could exhibit potent radical scavenging activity in more biologically relevant settings (*i.e.*, against  $\text{HO}^\bullet$  or lipid peroxidation)<sup>2,15–18</sup> thus the  $\text{HO}^\bullet$  and

$\text{HOO}^\bullet$  radical scavenging activity of the most active compound (*i.e.*, **4b**) in physiological environments has been investigated further using computational chemistry.

#### 3.2.2. Calculations of the $\text{HOO}^\bullet$ and $\text{HO}^\bullet$ radical scavenging activity of the most active compound (**4b**)

**3.2.2.1 The antiradical activity in the gas phase.** The antioxidant properties of **4b** were initially tested in the gas phase in order to identify the predominant antioxidant mechanism(s) for the more complex calculations in physiological environments. As previously demonstrated, this approach decreases computation time while giving accurate and reliable data.<sup>55</sup> In the first step, the principal thermodynamic properties (proton affinity (PA), ionization energy (IE) and bond dissociation enthalpy (BDE)) that define the radical scavenging activity mechanisms (sequential proton loss electron transfer (SPLET), single electron transfer proton transfer (SETPT) and formal hydrogen transfer (FHT)),<sup>67,68</sup> of **4b** were computed (Table 4).

The lowest calculated BDE was observed at the C5–H bond at  $76.0 \text{ kcal mol}^{-1}$ , whereas those of the other C(O)–H bonds were higher by about  $13.7\text{--}25.5 \text{ kcal mol}^{-1}$ . Thus, data implies that the C5–H bond dominates the antioxidant activity of **4b** following the FHT pathway. On the other hand, the radical scavenging activity of **4b** according to either the SPLET or SETPT would be challenging due to the high PA and IE values ( $\text{PA} = 326.6 \text{ kcal mol}^{-1}$  and  $\text{IE} = 186.4 \text{ kcal mol}^{-1}$ ) in comparison to the BDEs.

The radical adduct formation (RAF) process also plays a key role in the radical scavenging of compounds with double bonds,

Table 3 DPPH radical scavenging activity

Compound	DPPH (%)			
	128 ( $\mu\text{g mL}^{-1}$ )	32 ( $\mu\text{g mL}^{-1}$ )	8 ( $\mu\text{g mL}^{-1}$ )	$\text{EC}_{50}$ ( $\mu\text{g mL}^{-1}$ )
<b>4a</b>	14	0	0	>128
<b>4b</b>	40	12	0	>128
<b>4c</b>	32	11	0	>128
<b>4d</b>	7	0	0	>128
<b>4e</b>	26	5	0	>128
<b>4f</b>	6	1	0	>128
Quercetin	100	45.5	0	$9.97 \pm 0.25$

Table 4 The calculated BDEs, PAs and IEs (in  $\text{kcal mol}^{-1}$ )<sup>a</sup>

Positions	BDE	PA	IE
O3–H	93.2	326.6	186.4
C5–H	76.0		
O7–H	96.1		
C8–H	101.5		
O21–H	89.7		

<sup>a</sup> **4b** numbering is shown in Fig. 3.



**Table 5** The calculated  $\Delta G^\circ$  values (in kcal mol<sup>-1</sup>) of the reactions of **4b** with HO<sup>•</sup> and HOO<sup>•</sup> following the FHT, SET and RAF mechanisms

Mechanisms	Positions	$\Delta G^\circ$	
		HO <sup>•</sup>	HOO <sup>•</sup>
FHT	O3-H	-22.8	8.5
	C5-H	-41.5	-10.2
	C7-H	-21.0	10.2
	C8-H	-15.8	15.4
	C21-H	-25.8	5.4
RAF	C3	-24.8	6.3
	C4	-25.0	3.2
	C9	-6.7	
	C10	-11.5	
	C11	-4.5	
	C12	-7.4	
	C13	-4.4	
	C14	-8.4	
	C15	-8.6	
	C16	-6.2	
	C17	-6.3	
	C18	-9.3	
	C19	-7.1	
	C20	-5.1	
SET		158.8	163.5

particularly in the HO<sup>•</sup> antiradical action, as demonstrated by prior research<sup>62,69-71</sup> and hence this pathway should be also examined. Gibbs free energy changes ( $\Delta G^\circ$ ) for the HO<sup>•</sup> and HOO<sup>•</sup> radical scavenging reactions of **4b** via the FHT, SET and RAF mechanisms were calculated in the gas phase and is presented in Table 5. With the exception of the SET reaction ( $\Delta G^\circ = 158.8$  kcal mol<sup>-1</sup>), it was found that the HO<sup>•</sup> radical scavenging reactions are spontaneous ( $\Delta G^\circ < 0$ ) for all positions in **4b**;

however, the HOO<sup>•</sup> radical scavenging is spontaneous only at the C5-H bond ( $\Delta G^\circ = -10.2$  kcal mol<sup>-1</sup>) according to the FHT mechanism. Consistently all positions ( $\Delta G^\circ < 0$ , Table 5) were evaluated kinetically for the radical scavenging of **4b** against the HO<sup>•</sup> radical in a vacuum, while only the H-abstraction of the C5-H bond was estimated for the HOO<sup>•</sup> radical. The results are presented in Table 6 and Fig. 2.

The overall rate constant ( $k_{\text{overall}}$ ) for HO<sup>•</sup> radical scavenging in the gas phase was  $5.77 \times 10^{10}$  M<sup>-1</sup> s<sup>-1</sup>, however only  $5.48 \times 10^1$  M<sup>-1</sup> s<sup>-1</sup> for HOO<sup>•</sup> antiradical activity (Table 6). The hydroxyl antiradical activity was defined by a combination of the RAF mechanism (at the C3 ( $\Gamma = 3.3\%$ ) and C4 ( $\Gamma = 55.1\%$ )) and the FHT mechanism (at the C5-H ( $\Gamma = 37.9\%$ ) and C7-H ( $\Gamma = 2.4\%$ )). The H-abstraction of the C5-H bond determined the HOO<sup>•</sup> antiradical activity while contributing 37.9% to the total HO<sup>•</sup> radical scavenging. Thus these reactions should be used for further kinetic evaluation in the physiological environments.

### 3.2.2.2. The antiradical activity in the physiological environments

**3.2.2.2.1. Acid base equilibrium.** In order to account for the influence of physiological settings, the radical scavenging of **4b** against HO<sup>•</sup> and HOO<sup>•</sup> radicals was simulated in water at pH = 7.4 for the aqueous solution and in pentyl ethanoate for lipid medium.<sup>40,55</sup> Following the literature,<sup>72,73</sup> the acid-base equilibria of **4b** at the O3-H bond were computed to estimate the state of **4b** in aqueous solution at pH = 7.4 (Fig. 3). The pK<sub>a</sub> value was 5.40. Fig. 3 shows that **4b** consistently exists both in the neutral state (**HA**, 1.0%) and the monoanion state (**A<sup>-</sup>**, 99.0%) at physiological pH (7.40). These states are employed for further investigation in the polar medium.

The QM-ORSA protocol was used to evaluate the kinetics of the HO<sup>•</sup> and HOO<sup>•</sup> scavenging reactions in physiological

**Table 6** Calculated activation energies ( $\Delta G^\ddagger$  (kcal mol<sup>-1</sup>)), tunneling corrections ( $\kappa$ ) and  $k_{\text{Eck}}$ ,  $k_{\text{overall}}$  (M<sup>-1</sup> s<sup>-1</sup>) and branching ratios ( $\Gamma$ , %) at 298.15 K for the HO<sup>•</sup> and HOO<sup>•</sup> scavenging of **4b**

Mechanisms	Positions	HO <sup>•</sup>				HOO <sup>•</sup>		
		$\Delta G^\ddagger$	$\kappa$	$k_{\text{Eck}}$	$\Gamma$	$\Delta G^\ddagger$	$\kappa$	$k_{\text{Eck}}$
FHT	O3-H	10.7	21.3	$1.93 \times 10^6$	0.0			
	C5-H	3.4	1.1	$2.19 \times 10^{10}$	37.9	18.0	43.8	$5.48 \times 10^1$
	C7-H	5.0	1.0	$1.39 \times 10^9$	2.4			
	C8-H	9.4	2.7	$2.11 \times 10^6$	0.0			
	C21-H	6.8	1.1	$7.23 \times 10^7$	0.1			
RAF	C3	4.8	1.0	$1.93 \times 10^9$	3.3			
	C4	3.2	1.1	$3.18 \times 10^{10}$	55.1			
	C9	10.2	1.3	$2.89 \times 10^5$	0.0			
	C10	5.5	1.1	$6.43 \times 10^8$	1.1			
	C11	9.2	1.3	$1.51 \times 10^6$	0.0			
	C12	7.9	1.2	$1.26 \times 10^7$	0.0			
	C13	9.8	1.3	$5.36 \times 10^5$	0.0			
	C14	7.9	1.1	$1.20 \times 10^7$	0.0			
	C15	9.7	1.1	$5.06 \times 10^5$	0.0			
	C16	7.4	1.1	$5.06 \times 10^5$	0.0			
	C17	7.6	1.2	$5.06 \times 10^5$	0.0			
	C18	8.0	1.0	$5.06 \times 10^5$	0.0			
	C19	6.8	1.1	$5.06 \times 10^5$	0.0			
	C20	7.4	1.2	$5.06 \times 10^5$	0.0			
$k_{\text{overall}}$				$5.77 \times 10^{10}$				$5.48 \times 10^1$



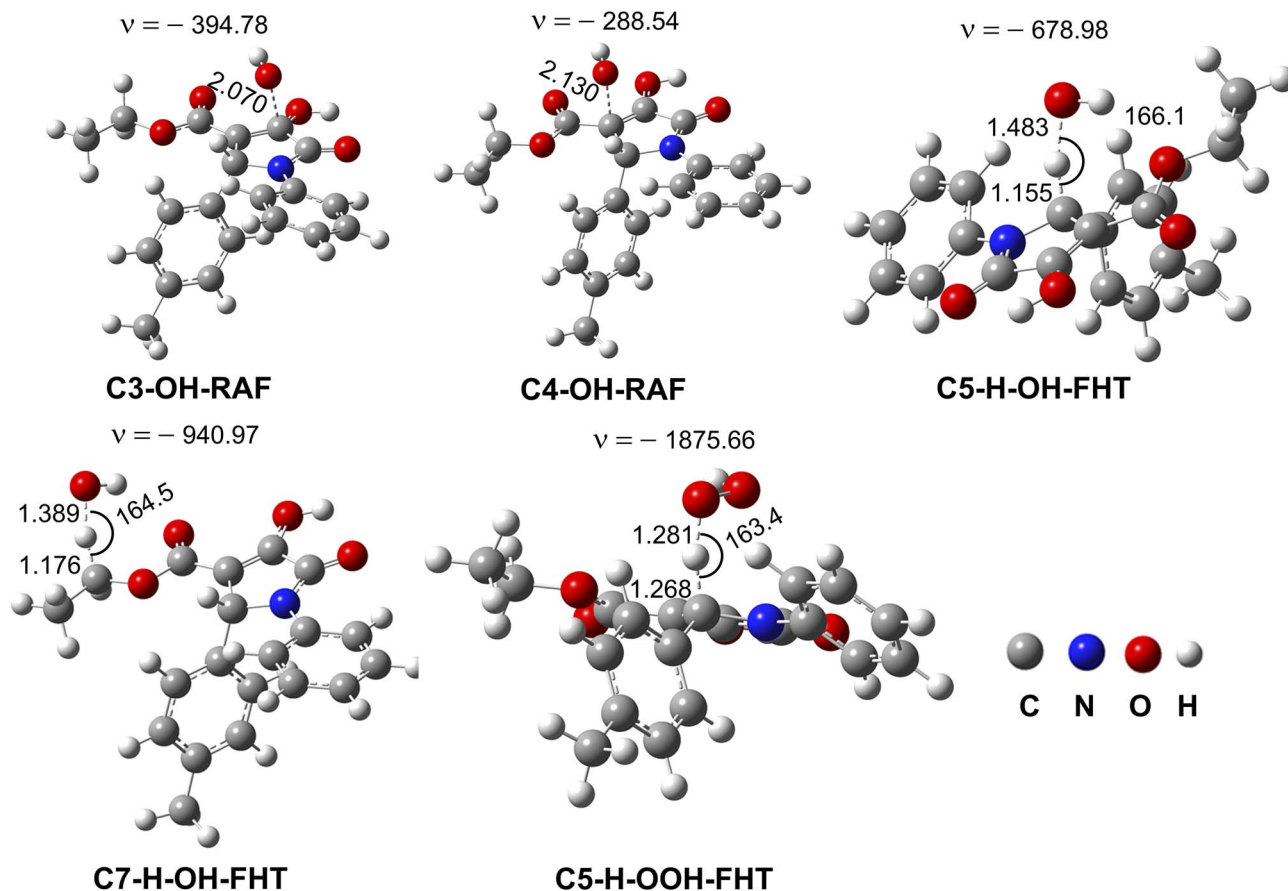


Fig. 2 Optimized geometries of the main transition states between **4b** and HO•/HOO• radicals according to FHT and RAF processes.

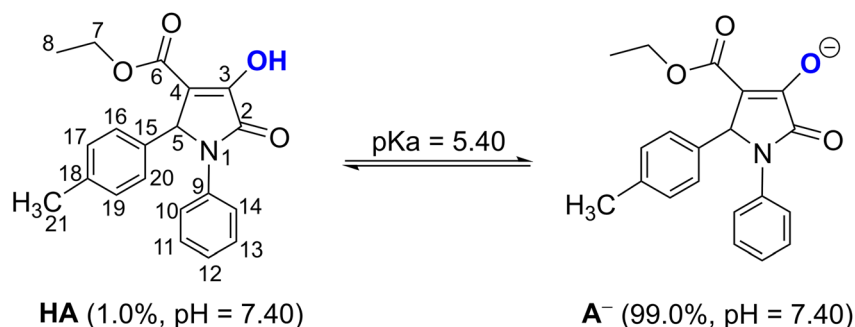


Fig. 3 The deprotonation of **4b** at pH = 7.40.

environments.<sup>40</sup> The results are shown in Table 7. The results showed that in pentyl ethanoate and water solvents, the  $k_{\text{overall}}$  values for the **4b** + HO• + reaction were  $2.05 \times 10^9$  and  $1.54 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ , respectively, while those were  $6.90 \times 10^{-1}$  and  $1.82 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$  for the **4b** + HOO• reaction. The HO• anti-radical activity in lipid medium was defined by the RAF mechanism at the C4 position ( $I = 57.1\%$ ) and the FHT pathway at C5-H bond ( $I = 30.6\%$ ), whereas that for the aqueous solution was characterized by the SET reaction of the anion state ( $I = 56.7\%$ ). The RAF and FHT reactions of the anion state contributed more than 40% in the hydroxyl antiradical activity

in water at pH = 7.40, however these reactions of the neutral state had no contribution to the activity. At the same time, the FHT (C5-H,  $I = 59.7\%$ ) and RAF (C4,  $I = 40.2\%$ ) reactions of the anion state played a decisive role in the HOO• antiradical activity of **4b** in water at pH = 7.40. The ability of **4b** to scavenge hydroxyl radical in polar and non-polar environments is comparable to that of common antioxidants such melatonin,<sup>74</sup> gallic acid,<sup>75</sup> indole-3-carbinol,<sup>71</sup> ramalin,<sup>70</sup> and Trolox.<sup>40</sup> However, **4b** exhibited low hydroperoxyl radical scavenging activity in both the lipid and polar media. Thus **4b** is a good but not exceptional hydroxyl radical scavenger in the physiological



**Table 7** Gibbs free energies of activation ( $\Delta G^\ddagger$ , kcal mol<sup>-1</sup>), rate constants ( $k_{\text{app}}$ ,  $k_f$ , M<sup>-1</sup> s<sup>-1</sup>) and branching ratios ( $\Gamma$ , %) at 298.15 K, in the NPY oxidation by HO<sup>•</sup>/HOO<sup>•</sup> radicals in the studied environments

States	Mechanisms	Pentyl ethanoate			Water				
		$\Delta G^\ddagger$	$k_{\text{app}}$	$\Gamma$	$\Delta G^\ddagger$	$k_{\text{app}}$	$f$	$k_f$	$\Gamma$
HO <sup>•</sup>	HA	SET			22.8	$1.20 \times 10^{-4}$	0.01	$1.20 \times 10^{-6}$	0.0
		FHT	C5-H	5.5	$6.27 \times 10^8$	30.6	5.6	$6.76 \times 10^8$	0.01
			C7-H	6.6	$1.19 \times 10^8$	5.8	8.2	$8.10 \times 10^6$	0.01
		RAF	C3	6.5	$1.32 \times 10^8$	6.4	6.3	$1.95 \times 10^8$	0.01
			C4	5.2	$1.17 \times 10^9$	57.1	4.7	$3.08 \times 10^9$	0.01
	A <sup>-</sup>	SET			0.7	$8.80 \times 10^9$	0.99	$8.71 \times 10^9$	56.7
		FHT	C5-H		3.8	$2.38 \times 10^9$	0.99	$2.35 \times 10^9$	15.3
			C7-H		6.1	$2.13 \times 10^8$	0.99	$2.11 \times 10^8$	1.4
		RAF	C3		~0	$2.10 \times 10^9$	0.99	$2.08 \times 10^9$	13.5
			C4		~0	$2.00 \times 10^9$	0.99	$1.98 \times 10^9$	12.9
HOO <sup>•</sup>	$k_{\text{overall}}$		$2.05 \times 10^9$					$1.54 \times 10^{10}$	
	HA	FHT	C5-H	20.6	$6.90 \times 10^{-1}$	100.0	19.9	3.10	0.01
	A <sup>-</sup>	SET					19.3	$4.80 \times 10^{-2}$	0.99
		FHT	C5-H				15.0	$1.10 \times 10^3$	0.99
		RAF	C3				17.5	1.10	0.99
			C4				13.6	$7.40 \times 10^2$	0.99
	$k_{\text{overall}}$		$6.90 \times 10^{-1}$					$7.33 \times 10^2$	40.2

environment with targeted activities that may invite further studies into its activity against specific compounds.

## 4. Conclusion

Six polysubstituted 3-hydroxy-3-pyrroline-2-ones were successfully synthesized by using three-component reactions at room temperature. The DPPH assay indicated that **4b** exhibits the highest DPPH radical scavenging activity. The thermodynamic and kinetic calculations also showed that **4b** is a potent HO<sup>•</sup> radical scavenger with  $k_{\text{overall}} = 2.05 \times 10^9$  and  $1.54 \times 10^{10}$  M<sup>-1</sup> s<sup>-1</sup> in pentyl ethanoate and water, respectively. However, **4b** exhibited only low hydroperoxyl radical scavenging activity in either of the lipid and polar media. Compared to typical anti-oxidants such as melatonin, gallic acid, indole-3-carbinol, ramalin, and Trolox, the ability of **4b** to scavenge hydroxyl radicals in polar and non-polar environments is similar to that of these compounds. Thus **4b** is a promising HO<sup>•</sup> radical scavenger in physiological environments.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

This research is funded by the Vietnamese Ministry of Education and Training under project number B2021-DNA-17 (N.T.N.).

## References

- S. B. Singh, D. L. Zink, M. A. Goetz, A. W. Dombrowski, J. D. Polishook and D. J. Hazuda, *Tetrahedron Lett.*, 1998, **39**, 2243–2246.
- J. Whitt, S. M. Shipley, D. J. Newman and K. M. Zuck, *J. Nat. Prod.*, 2014, **77**, 173–177.
- X. Del Corte, A. López-Francés, A. Maestro, I. Villate-Beitia, M. Sainz-Ramos, E. Martínez de Marigorta, J. L. Pedraz, F. Palacios and J. Vicario, *Pharmaceuticals*, 2021, **14**, 782.
- E. Surmiak, A. Twarda-Clapa, K. M. Zak, B. Musielak, M. D. Tomala, K. Kubica, P. Grudnik, M. Madej, M. Jablonski and J. Potempa, *ACS Chem. Biol.*, 2016, **11**, 3310–3318.
- N. Joksimović, J. Petronijević, N. Janković, D. Baskić, S. Popović, D. Todorović, S. Matić, G. A. Bogdanović, M. Vraneš and A. Tot, *Bioorg. Chem.*, 2019, **88**, 102954.
- J. Kuznecovs, M. Vorona, I. Domracheva, I. Kanepe-Lapsa, M. Petrova, E. Liepins, S. Belyakov, A. Leonchiks and G. Veinberg, *Chem. Heterocycl. Compd.*, 2018, **54**, 514–519.
- J. Li, Y. Wu, Z. Guo, C. Zhuang, J. Yao, G. Dong, Z. Yu, X. Min, S. Wang and Y. Liu, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 2648–2650.
- V. Gein, V. Mihalev, N. Kasimova, E. Voronina, M. Vakhrin and E. Babushkina, *Pharm. Chem. J.*, 2007, **41**, 208–210.
- A. Q. Cusumano and J. G. Pierce, *Bioorg. Med. Chem. Lett.*, 2018, **28**, 2732–2735.
- A. López-Pérez, S. Freischem, I. Grimm, O. Weiergräber, A. J. Dingley, M. P. López-Alberca, H. Waldmann, W. Vollmer, K. Kumar and C. Vuong, *Antibiotics*, 2021, **10**, 529.
- K. Ma, P. Wang, W. Fu, X. Wan, L. Zhou, Y. Chu and D. Ye, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 6724–6727.
- V. Gein, V. Yushkov, N. Kasimova, N. Shuklina, M. Y. Vasil'eva and M. Gubanova, *Pharm. Chem. J.*, 2005, **39**, 484–487.
- N. V. Ortiz Zacarías, J. P. van Veldhoven, L. Portner, E. van Spronsen, S. Ullo, M. Veenhuizen, W. J. van der Velden,



- A. J. Zweemer, R. M. Kreekel and K. Oenema, *J. Med. Chem.*, 2018, **61**, 9146–9161.
- 14 S. Zykova, M. Danchuk, V. Talismanov, N. Tokareva, N. Igidov, I. Rodin, A. Koshchaev, N. Gugushvili and O. Karmanova, *J. Pharm. Sci. Res.*, 2018, **10**, 164–166.
- 15 X. Liu, L. Zang, C. J. Van der Schyf, K. Igarashi, K. Castagnoli and N. Castagnoli, *Chem. Res. Toxicol.*, 1999, **12**, 508–512.
- 16 W.-H. Zhang, J. Liu, G. Xu, Q. Yuan and L. M. Sayre, *Chem. Res. Toxicol.*, 2003, **16**, 512–523.
- 17 K. Itakura, T. Osawa and K. Uchida, *J. Org. Chem.*, 1998, **63**, 185–187.
- 18 L. Tsai, P. A. Szweda, O. Vinogradova and L. I. Szweda, *Proc. Natl. Acad. Sci. U. S. A.*, 1998, **95**, 7975–7980.
- 19 E. M. de Marigorta, M. Jesús, A. M. O. de Retana, J. Vicario and F. Palacios, *Synthesis*, 2018, **50**, 4539–4554.
- 20 J. Zhu, Q. Wang and M. Wang, *Multicomponent reactions in organic synthesis*, John Wiley & Sons, 2014.
- 21 H. Ahankar, A. Ramazani, K. Ślepokura, T. Lis and S. W. Joo, *Green Chem.*, 2016, **18**, 3582–3593.
- 22 Z. Hosseinzadeh, A. Ramazani, H. Ahankar, K. Ślepokura and T. Lis, *Silicon*, 2019, **11**, 2933–2943.
- 23 R. Ghorbani-Vaghei, N. Sarmast and J. Mahmoodi, *Appl. Organomet. Chem.*, 2017, **31**, e3681.
- 24 M. Saha and A. R. Das, *ChemistrySelect*, 2017, **2**, 10249–10260.
- 25 R. Sarkar and C. Mukhopadhyay, *Tetrahedron Lett.*, 2013, **54**, 3706–3711.
- 26 S. Esmailzadeh and D. Setamdideh, *J. Serbian Chem. Soc.*, 2021, **59**.
- 27 A. Dutta, M. A. Rohman, R. Nongrum, A. Thongni, S. Mitra and R. Nongkhaw, *New J. Chem.*, 2021, **45**, 8136–8148.
- 28 B. Metten, M. Kostermans, G. Van Baelen, M. Smet and W. Dehaen, *Tetrahedron*, 2006, **62**, 6018–6028.
- 29 M. Mohammat, Z. Shaameri and A. Hamzah, *Molecules*, 2009, **14**, 250–256.
- 30 S. Manta, D.-N. Gkaragkouni, E. Kaffesaki, P. Gkizis, D. Hadjipavlou-Litina, E. Pontiki, J. Balzarini, W. Dehaen and D. Komiotis, *Tetrahedron Lett.*, 2014, **55**, 1873–1876.
- 31 A. V. Dolzhenko and A. V. Dolzhenko, in *Green synthetic approaches for biologically relevant heterocycles*, Elsevier, 2015, pp. 101–139.
- 32 L. M. Sayre, G. Perry and M. A. Smith, *Chem. Res. Toxicol.*, 2008, **21**, 172–188.
- 33 W. A. Pryor, *Free Radicals Biol. Med.*, 1988, **4**, 219–223.
- 34 R. J. Reiter, D.-X. Tan, T. S. Herman and C. R. Thomas Jr, *Int. J. Radiat. Oncol., Biol., Phys.*, 2004, **59**, 639–653.
- 35 L. P. Candeias and S. Steenken, *Chem. Eur. J.*, 2000, **6**, 475–484.
- 36 C. Chatgililoglu, M. D'Angelantonio, M. Guerra, P. Kaloudis and Q. G. Mulazzani, *Angew. Chem., Int. Ed. Engl.*, 2009, **48**, 2214–2217.
- 37 A. Galano and J. R. Alvarez-Idaboy, *Org. Lett.*, 2009, **11**, 5114–5117.
- 38 M. Leopoldini, N. Russo and M. Toscano, *Food Chem.*, 2011, **125**, 288–306.
- 39 J. S. Wright, E. R. Johnson and G. A. DiLabio, *J. Am. Chem. Soc.*, 2001, **123**, 1173–1183.
- 40 A. Galano and J. R. Alvarez-Idaboy, *J. Comput. Chem.*, 2013, **34**, 2430–2445.
- 41 A. Galano, G. Mazzone, R. Alvarez-Diduk, T. Marino, J. R. Alvarez-Idaboy and N. Russo, *Annu. Rev. Food Sci. Technol.*, 2016, **7**, 335–352.
- 42 M. Leopoldini, N. Russo, S. Chiodo and M. Toscano, *J. Agric. Food Chem.*, 2006, **54**, 6343–6351.
- 43 A. Galano and J. Raúl Alvarez-Idaboy, *Int. J. Quantum Chem.*, 2019, **119**, e25665.
- 44 M. Cuendet, K. Hostettmann, O. Potterat and W. Dyatmiko, *Helv. Chim. Acta*, 1997, **80**, 1144–1152.
- 45 A. I. Elshamy, T. Yoneyama, N. Van Trang, N. T. Son, Y. Okamoto, S. Ban, M. Noji and A. Umeyama, *J. Mol. Struct.*, 2020, **1200**, 127061.
- 46 L. T. T. Anh, N. Van Tuyen, P. T. Thuy, P. M. Quan, N. T. T. Ha and N. T. Tra, *Mol. Divers.*, 2022, **26**, 229–243.
- 47 K. Marxen, K. H. Vanselow, S. Lippemeier, R. Hintze, A. Ruser and U.-P. Hansen, *Sensors*, 2007, **7**, 2080–2095.
- 48 M. Burits and F. Bucar, *Phytother. Res.*, 2000, **14**, 323–328.
- 49 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, A. F. I. H. P. Hratchian, J. Bloino, G. Zheng, M. H. J. L. Sonnenberg, M. Ehara, K. Toyota, J. H. R. Fukuda, M. Ishida, T. Nakajima, Y. Honda, H. N. O. Kitao, T. Vreven, J. A. Montgomery Jr, F. O. J. E. Peralta, M. J. Bearpark, J. Heyd, K. N. K. E. N. Brothers, V. N. Staroverov, R. Kobayashi, K. R. J. Normand, A. P. Rendell, J. C. Burant, J. T. S. S. Iyengar, M. Cossi, N. Rega, N. J. Millam, J. E. K. M. Klene, J. B. Cross, V. Bakken, C. Adamo, R. G. J. Jaramillo, R. E. Stratmann, O. Yazyev, R. C. A. J. Austin, C. Pomelli, J. W. Ochterski, K. M. R. L. Martin, V. G. Zakrzewski, G. A. Voth, J. J. D. P. Salvador, S. Dapprich, A. D. Daniels, J. B. F. Ö. Farkas, J. V. Ortiz, J. Cioslowski, and D. J. Fox, *Gaussian 09*, Gaussian, Inc., Wallingford CT, 2009.
- 50 Y. Zhao and D. G. Truhlar, *J. Phys. Chem. A*, 2008, **112**, 1095–1099.
- 51 A. Galano and J. R. Alvarez-Idaboy, *J. Comput. Chem.*, 2014, **35**, 2019–2026.
- 52 J. R. I. Alvarez-Idaboy and A. Galano, *J. Phys. Chem. B*, 2012, **116**, 9316–9325.
- 53 M. E. Alberto, N. Russo, A. Grand and A. Galano, *Phys. Chem. Chem. Phys.*, 2013, **15**, 4642–4650.
- 54 E. Dzib, J. L. Cabellos, F. Ortíz-Chi, S. Pan, A. Galano and G. Merino, *Int. J. Quantum Chem.*, 2019, **119**, e25686.
- 55 Q. V. Vo, M. V. Bay, P. C. Nam, D. T. Quang, M. Flavel, N. T. Hoa and A. Mechler, *J. Org. Chem.*, 2020, **85**, 15514–15520.
- 56 M. G. Evans and M. Polanyi, *Trans. Faraday Soc.*, 1935, **31**, 875–894.
- 57 H. Eyring, *J. Chem. Phys.*, 1935, **3**, 107–115.
- 58 D. G. Truhlar, W. L. Hase and J. T. Hynes, *J. Phys. Chem.*, 1983, **87**, 2664–2682.
- 59 T. Furuncuoglu, I. Ugur, I. Degirmenci and V. Aviyente, *Macromolecules*, 2010, **43**, 1823–1835.



- 60 E. Vélez, J. Quijano, R. Notario, E. Pabón, J. Murillo, J. Leal, E. Zapata and G. Alarcón, *J. Phys. Org. Chem.*, 2009, **22**, 971–977.
- 61 E. Dzib, J. L. Cabellos, F. Ortiz-Chi, S. Pan, A. Galano and G. Merino, *Eyringpy 1.0.2*, Cinvestav Mérida, Yucatán, 2018.
- 62 Q. V. Vo, M. V. Bay, P. C. Nam and A. Mechler, *J. Phys. Chem. B*, 2019, **123**, 7777–7784.
- 63 A. K. Chakraborti, S. Bhagat and S. Rudrawar, *Tetrahedron Lett.*, 2004, **45**, 7641–7644.
- 64 B. Mostafa, S. M. Habibi-Khorassani and M. Shahraki, *J. Phys. Org. Chem.*, 2017, **30**, e3616.
- 65 A. Simion, C. Simion, T. Kanda, S. Nagashima, Y. Mitoma, T. Yamada, K. Mimura and M. Tashiro, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2071–2078.
- 66 J. Clayden, N. Greeves and S. Warren, *Organic chemistry*, Oxford university press, 2012.
- 67 A. Galano, *J. Mex. Chem. Soc.*, 2015, **59**, 231–262.
- 68 Y.-Z. Zheng, G. Deng, Q. Liang, D.-F. Chen, R. Guo and R.-C. Lai, *Sci. Rep.*, 2017, **7**, 1–11.
- 69 C. Iuga, J. R. Alvarez-Idaboy and A. Vivier-Bunge, *J. Phys. Chem. B*, 2011, **115**, 12234–12246.
- 70 Q. V. Vo, N. M. Tam, M. Van Bay and A. Mechler, *Chem. Phys. Lett.*, 2020, **739**, 137004.
- 71 Q. V. Vo, M. Van Bay, P. C. Nam and A. Mechler, *ACS Omega*, 2019, **4**, 19375–19381.
- 72 A. Galano, A. Pérez-González, R. Castañeda-Arriaga, L. Muñoz-Rugeles, G. Mendoza-Sarmiento, A. Romero-Silva, A. Ibarra-Escutia, A. M. Rebollar-Zepeda, J. R. León-Carmona and M. A. Hernández-Olivares, *J. Chem. Inf. Model.*, 2016, **56**, 1714–1724.
- 73 Q. V. Vo, N. M. Tam, M. Van Bay, N. M. Thong, T. Le Huyen, N. T. Hoa and A. Mechler, *RSC Adv.*, 2020, **10**, 14937–14943.
- 74 A. Galano, *Phys. Chem. Chem. Phys.*, 2011, **13**, 7178–7188.
- 75 T. Marino, A. Galano and N. Russo, *J. Phys. Chem. B*, 2014, **118**, 10380–10389.

