

Regular Article

Antioxidant Activity of Novel Fused Heterocyclic Compounds Derived from Tetrahydropyrimidine Derivative

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Pyrimidines are of great importance in fundamental metabolism, being an integral part of DNA and RNA, found in the three bases uracil, thymine and cytosine of the six present in the nucleotides. They are found to possess diverse biological properties as bactericides, fungicides, viricides, insecticide, and mecticides Many derivatives of pyrimidines have been used as therapeutic agents. Several triazolo and pyrazolopyrimidine derivatives are found to possess antifungal and antileishmanial activity. Certain pyrimidine derivatives are known to display antimalarial antifilarial activities and also potent inhibitors of cancer cell proliferation. Many derivatives of pyrimidine have been utilized for synthesis of the fused heterocyclic compounds namely thiazolopyrimidines, tetrazolopyrimidine, pyrimidoquinazoline, pyrimidothiazolopyrimidine, pyrimidothiazolotriazine and pyrrolothiazolopyrimidine derivatives. The newly synthesized compounds were characterized by IR, 1H-NMR, 13C-NMR, and mass spectral data. Antioxidant activities of all synthesized compounds were investigated.

Key words arylidene; tetrahydropyrimidine; thiazolo[3,2-a]pyrimidine; antioxidant activity

Pyrimidines are of great importance in fundamental metabolism, being an integral part of DNA and RNA, found in the three bases uracil, thymine and cytosine of the six present in the nucleotides. They are found to possess diverse biological properties as bactericides, fungicides, viricides, insecticide, and mecticides Many derivatives of pyrimidines have been used as therapeutic agents. Several triazolo and pyrazolopyrimidine derivatives are found to possess antifungal and antileishmanial activity. Certain pyrimidine derivatives are known to display antimalarial antifilarial activities and also potent inhibitors of cancer cell proliferation. Many derivatives of pyrimidine have been utilized for synthesis of the fused heterocyclic compounds namely thiazolopyrimidines, tetrazolopyrimidine, pyrimidoquinazoline, pyrimidothiazolopyrimidine, pyrimidothiazolotriazine and pyrrolothiazolopyrimidine derivatives. The newly synthesized compounds were characterized by IR, 1H-NMR, 13C-NMR, and mass spectral data. Antioxidant activities of all synthesized compounds were investigated.

Key words arylidene; tetrahydropyrimidine; thiazolo[3,2-a]pyrimidine; antioxidant activity

 Results and Discussion

Chemistry When tetrahydropyrimidine 1 was submitted to react with bromomalononitrile in aqueous alcoholic potassium carbonate solution enaminonitrile 2 was obtained. The structural features of enaminonitrile 2 were identified on the basis of coupling band exhibited at \( \nu = 3391 \) and \( 3291 \text{ cm}^{-1} \) due to the amino \( \text{NH} \) functionality and disappearance of \( \nu_{\text{C-S}} \). 1H-NMR spectrum revealed D2O-exchangeable singlet at \( \delta = 8.48 \text{ ppm} \) due to amino group. Thiazolopyrimidine derivative 3 can be obtained via reaction of tetrahydropyrimidine 1 with chloroacetonitrile. The structural features of thiazolopyrimidine derivative 3 were established by elemental analysis as well as spectral data. The structure of compound 3 also confirmed chemically via condensation reaction with substituted aromatic aldehydes namely, 4-chlorobenzaldehyde and/or 4-methoxybenzaldehyde to afford the corresponding benzylidene derivatives 4a and b, respectively.

Chlorination of tetrahydropyrimidine 1 with a mixture of phosphorus pentachloride and phosphorus oxychloride as a chlorinating reagent gave the chloropyrimidine derivative 5. The structure of compound 5 was assigned from its spectroscopic data, a qualitative and quantitative elemental analysis which indicates the presence of chlorine. A chemical evidence for the structure assignment of compound 5 is the reaction with glycine, sodium azide and/or anthranilic acid to afford dihydroxypyrimidine 6, tetrazolopyrimidine 7 and pyrimidoquinazolinone 8, respectively. The IR spectrum of the dihydroxypyrimidine 6 showed a broad peak centered at 3206 cm\(^{-1}\) due to \( \nu_{\text{NH}} \) and \( \nu_{\text{OH}} \) and the carbonyl band of a carboxylic acid at 1700 cm\(^{-1}\). This spectrum pattern reveals the possibility of two interconvertible forms for the product 6 via 1,3-proton shift. Alkylation of tetrahydropyrimidine 1 with ethyl iodide in the presence of sodium ethoxide furnished 7-alkylated product 9, which has been chlorinated via reaction with phosphorus pentachloride in the presence of phosphorus oxychloride to afford the chlorinated product 10. Pyrimidine derivative 10 underwent thiation under the effect of thiourea to give thioxodihydroxypyrimidine 11. The IR spectrum of thioxodihydroxypyrimidine 11 displayed the appearance of \( \nu_{\text{NH}} \) and \( \nu_{\text{C-S}} \) at 3194 and 1240, respectively. 1H-NMR of compound 11 showed a broad peak centered at 3194 and 1240, respectively. 1H-NMR spectrum revealed D2O-exchangeable signal at 13.02 ppm due to NH proton. Alkaline hydrolysis of tetrahydropyrimidine 1 using 10% alcoholic sodium hydroxide solution gave dioxotetrahydropyrimidine derivative 12 (cf. Chart 1).

Enaminonitrile 2 is the key starting material for design and synthesis of fused novel heterocyclic systems such as pyrimidothiazolopyrimidine derivatives 13 and 14 and pyrimidothiazolotriazine 15. Thus, when enaminonitrile 2 was allowed to react with formamide, formic acid and/or sodium nitrite, it afforded pyrimidothiazolopyrimidine derivatives 13 and 14 and
pyrimidothiazolotriazine 15 respectively. Treatment of enamino-
nitrile 2 with ethyl chloroacetate and/or carbon disulfide in
pyridine furnished ethyl-2-(7-(benzo[d][1,3]dioxol-5-yl)-2,6-
dicyano-5-oxo-5\(H\)-thiazolo[3,2-a]pyrimidin-3-ylamino) acetate
(16) and/or (7-(benzo[d][1,3]dioxol-5-yl)-2,6-dicyano-5-oxo-
5\(H\)-thiazolo[3,2-a]pyrimidin-3-yl) carbamodithioic acid (17),
respectively (cf. Chart 2).

In one of our previous publications, \(^{12}\) it has been reported
that, the effect of boiling triethyl orthoformate on enaminoni-
trile resulted in ethyl formamidate derivative such as 18. In
the present work, reaction of neat triethyl orthoformate with
enaminonitrile 2 under reflux gave pyrrolothiazolopyrimidine
derivative 19 indicating that cyclization on the cyano func-
tionality takes place after the nucleophilic attack of the amino

Treatment of enamino-nitrile 2 with diethyl malonate
in ethanolic solution of sodium ethoxide afforded N-(7-
(benzo[d][1,3]dioxol-5-yl)-2,6-dicyano-5-oxo-5\(H\)-thiazolo[3,2-
a]pyrimidin-3-yl)acetamide (20). As \(\text{–NH}\) is more acidic than
\(\text{C–H}\) bond, the basic ethoxide ion abstracts a proton from \(\text{NH}_2\)
groups to generate \(\text{N}^+\) which attacks the carbonyl carbon of

Chart 1

(i) Br\(\text{CN}\)_\text{3}, \(\text{K}_2\text{CO}_3\), \(\text{EtOH}\); (ii) \(\text{CICH}_2\text{CONH}_2\), fused \(\text{AcONa}\), \(\text{EtOH}\); (iii) \(\text{Ar}_2\text{CHO}\), fused \(\text{AcONa}\), \(\text{EtOH}\); (iv) \(\text{POCl}_3\), \(\text{PCl}_5\); (v) \(\text{NH}_2\text{CH}_2\text{COOH}\), \(\text{Ac}_2\text{O}\); (vi) \(\text{NaN}_3\), gla-
cial \(\text{AcOH}\); (vii) anthranilic acid, \(\text{EtOH}\); (viii) \(\text{Et}, \text{EtONa}\); (ix) \(\text{NH}_2\text{CSNH}_2\), \(\text{EtOH}\); (x) \(\text{NaOH} 10\%\).

Pharmacology

Antioxidant Evaluation
The antioxidant activities of the synthesized compounds
were determined and listed in Table 1 and Fig. 1. The results
revealed that all compounds were found to be potent. More-
over, the results showed that nearly three compounds 1, 6 and
9 were found to be the most potent levels of activity. Addi-
tionally, compounds 2, 4b, 8, 11, 14, 17 and 20 were found
to have moderate activity.

The following points were noticed. On comparison between
the compounds 1, 6 and 9, it was noticed that compound 6
indicating that the presence of COOH group was more effec-
tive than the tetrahydropyrimidine 1, while conversion of the
\(\text{C} = \text{S}\) group in tertrahydropyrimidine 1 to -C-S-Et group in
compound 9, resulted in low activity of 9.

On the other hand when C=O in compound 9 convert into
C=S in compound 11 antioxidant activity decrease. Chloropy-
rimidine 5 is less active than tetrahydropryrimidine 1 but more
active than pyrimidioquinazoline 8. Compound 19 is more
potent antioxidant than compounds 14, 17 and 20 that is due
to the presence of \(-\text{NH}\) group.

**Experimental**

All melting points were measured on a Gallenkamp electric melting point apparatus and are uncorrected. The infrared spectra were recorded using potassium bromide disks on a Pye Unicam SP-3-300 infrared spectrophotometer. $^1$H- and

$^{13}$C-NMR experiments were run at 300 MHz on a Varian Mercury VX-300 NMR spectrometer using tetramethylsilane (TMS) as internal standard in deuterated chloroform or dimethylsulphoxide. Chemical shifts are quoted as $\delta$. The mass spectra were recorded on Shimadzu GCMS-QP-1000EX mass spectrometers at 70 eV. All the spectral measurements as well as the elemental analyses were carried out at the Micro analytical Center of Cairo University. All the newly synthesized compounds gave satisfactory elemental analyses. The reactions and the purity of all new compounds were monitored by TLC.

**Synthesis**

3-Amino-7-(benzo[\(d\)]1,3]dioxol-5-yl)-5-oxo-5H-thiazolo[3,2-a]pyrimidine-2,6-dicarbonitrile (2)

A mixture of tetrahydropyrimidine 1\textsuperscript{11} (2.73 g, 0.01 mol), bromomalononitrile (1.44 g, 0.01 mol) and potassium carbonate (1.38 g, 0.01 mol/25 mL H$_2$O) in ethanol (25 mL) was heated under reflux for 2h, cooled and then poured onto ice with stirring. The resulted solid product was filtered, dried and recrystallized from ethanol to give enaminonitrile 2 as orange crystals. mp 260–262°C, yield 60%. FT-IR (KBr, cm$^{-1}$): 3391, 3291 $\nu$$_{\text{NH}_2}$, 3081 $\nu$$_\text{CH}$ aromatic, 2909 $\nu$$_{\text{CH}}$ aliphatic,

![Diagram](chart2)

(i) HCONH$_2$; (ii) HCOOH; (iii) NaNO$_2$, AcOH, HCl; (iv) CICH$_2$COOEt, pyridine; (v) CS$_2$, pyridine; (vi) CH$_2$(COOEt)$_2$, EtONa.

**Chart 2**

![Diagram](chart3)

(iii) HCONH$_2$; (iv) HCOOH; (v) CICH$_2$COOEt, pyridine; (vi) CICH$_2$COOEt, pyridine; (vii) CICH$_2$COOEt, pyridine.

**Table 1. Total Antioxidant Capacity of the Synthesized Compounds**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Total antioxidant capacity (mg AAE/g compound)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>308.33±1.25</td>
</tr>
<tr>
<td>2</td>
<td>132.54±1.65</td>
</tr>
<tr>
<td>3</td>
<td>69.01±2.55</td>
</tr>
<tr>
<td>4a</td>
<td>20.38±1.85</td>
</tr>
<tr>
<td>4b</td>
<td>102.74±1.35</td>
</tr>
<tr>
<td>5</td>
<td>112.15±2.40</td>
</tr>
<tr>
<td>6</td>
<td>436.85±2.25</td>
</tr>
<tr>
<td>7</td>
<td>97.25±2.75</td>
</tr>
<tr>
<td>8</td>
<td>109.01±1.15</td>
</tr>
<tr>
<td>9</td>
<td>225.87±1.50</td>
</tr>
<tr>
<td>10</td>
<td>82.34±2.45</td>
</tr>
<tr>
<td>11</td>
<td>176.46±1.60</td>
</tr>
<tr>
<td>12</td>
<td>56.46±1.30</td>
</tr>
<tr>
<td>13</td>
<td>76.07±1.95</td>
</tr>
<tr>
<td>14</td>
<td>163.91±2.80</td>
</tr>
<tr>
<td>15</td>
<td>95.68±1.20</td>
</tr>
<tr>
<td>16</td>
<td>81.56±2.45</td>
</tr>
<tr>
<td>17</td>
<td>123.91±2.45</td>
</tr>
<tr>
<td>19</td>
<td>176.46±1.75</td>
</tr>
<tr>
<td>20</td>
<td>145.88±3.30</td>
</tr>
</tbody>
</table>

Results are (mean±S.D.) (n=3) and AAE.
To a solution of tetrahydropyrimidine 1 (2.73 g, 0.01 mol) in ethanol (20 mL), chloroacetamide (0.93 g, 0.01 mol) and sodium acetate (0.66 g, 0.0055 mol), in ethanol (20 mL), chloroacetamide (0.93 g, 0.01 mol) and sodium acetate (1.23 g, 0.015 mol), was added. The reaction mixture was cooled then poured onto crushed ice, collect the product by filtration, dried and recrystallized from ethanol to afford thioxodihydropyrimidine derivative 2 as yellow crystals, mp 195–197°C, yield 77%. FT-IR (KBr, cm⁻¹): 3033 νCH aromatic, 2919 νCH aliphatic, 2224 νC=O, 1654 νC=O acid, 1606 νC=S), 7.31–6.94 (m, 7H, Ar-H), 6.07 (s, 2H, O–CH₂–O) and 3.87 (s, 3H, –OCH₃). 13C-NMR (75 MHz, DMSO-d₆): 7.89 (OCH₃), 101.26 (O–CH₂–O), 107.42, 107.49, 108.33, 108.42, 120.15, 122.49, 122.51, 132.64, 146.72, 148.37, 158.55, 165.86 (2C=O, C=N), 170.90. MS m/z: 337 (M⁺). Anal. Calcd for C₂₃H₁₇N₃O₄S: C, 53.41; H, 2.09; N, 13.31; S, 10.15. Found: C, 53.46; H, 2.15; N, 13.41; S, 10.15.

6-(Benzo[d][1,3]dioxol-5-yl)-4-chloro-2-thioxo-1,2-dihydropyrimidin-5-carbonitrile (5)

A mixture of tetrahydropyrimidine 1 (2.73 g, 0.01 mol), and phosphorus pentachloride (2.5 g, 0.01 mol) in phosphorus oxychloride (7 mL), 0.01 mol) was heated on a water bath for 8 h. The reaction mixture was cooled then poured onto crushed ice, collect the product by filtration, dried and recrystallized from ethanol to afford thioxodihydropyrimidine derivative 5 as beige crystals, mp >300°C, yield 86%. FT-IR (KBr, cm⁻¹): 3202 νNH, 3151 νCH aromatic, 2987 νCH aliphatic, 2225 νC=S, 1652 νC=O, 1220 νC=O, 11:09. MS m/z: 330 (M⁺). Anal. Calcd for C₁₄H₁₀C₄N₂O₄S: 9.26. Found: C, 50.85; H, 2.99; N, 16.79; S, 9.73.

2-(4-Methoxybenzylidene)-7-(benzo[d][1,3]dioxol-5-yl)-3,5-dioxo-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carbonitrile (4b)

White crystals, mp >300°C, yield 72%, FT-IR (KBr, cm⁻¹): 3141 νCH aromatic, 2980 νCH aliphatic, 2205 νC=O, 1713 and 1662 νC=O. 1H-NMR (300 MHz, DMSO-d₆): 9.87 (s, 1H, –CH=C=S), 7.31–6.94 (m, 7H, Ar-H), 6.07 (s, 2H, O–CH₂–O) and 3.87 (s, 3H, –OCH₃). 13C-NMR (75 MHz, DMSO-d₆): 77.89 (OCH₃), 101.26 (O–CH₂–O), 107.42, 107.49, 108.33, 108.42, 120.15, 122.49, 122.51, 132.64, 146.72, 148.37, 158.55, 165.86 (2C=O, C=N), 170.90. MS m/z: 431 (M⁺). Anal. Calcd for C₁₄H₁₀N₂O₄S: 62.24. Found: C, 61.12; H, 3.00; N, 9.65; S, 7.34.
7-(Benzod[1,3]dioxol-5-yl)-5-thioxo-5,6-dihydrotetrazolo[1,5-f]pyrimidine-8-carbonitrile (7)

To a solution of thioxodihydropyrimidine derivative 5 (2.92 g, 0.01 mol) in glacial acetic acid (30 mL), sodium azide (0.65 g, 0.01 mol), was added. The reaction mixture was refluxed for 5 h and allowed to cool. The solid formed was collected, dried and recrystallized from ethanol to give compound 7 as brown crystals, mp >300°C, yield 63%. FT-IR (KBr, cm⁻¹): 3217 νNH, 2216 νCN, 1612 νC=O. 1H-NMR (300 MHz, DMSO-d₆): δ 7.77–7.07 (m, 3H, Ar-H), 6.13 (s, 2H, O–CH₂–O) and 3.40 (br, 1H, −NH, D₂O-exchangeable). MS m/z: 298 (M⁺). Anal. Calcd for C₁₄H₁₁N₃O₂S₂ (317.3): C, 52.98; H, 3.36; N, 13.11; S, 20.03.

3-(Benzod[1,3]dioxol-5-yl)-10-oxo-1-thioxo-2,10-dihydro-1H-pyrrolo[1,6-b]quinazoline-4-carbonitrile (8)

A mixture of thioxodihydropyrimidine derivative 5 (2.92 g, 0.01 mol), and anhydric acid (1.37 g, 0.01 mol) in ethanol (50 mL) was refluxed for 6 h, cooled, filtered, dried and recrystallized from ethanol to afford compound 8 as pale brown crystals, mp 270–272°C, yield 68%. FT-IR (KBr, cm⁻¹): 3346, 3209 νNH, 2216 νCN, 1645 νC=O pyrimidine, 1605 νCN = 1247 νC=O, 1H-NMR (300 MHz, DMSO-d₆): 8.10 (br, 1H, −NH, D₂O-exchangeable), 7.50–7.13 (m, 7H, Ar-H), 6.17 (s, 2H, O–CH₂–O). MS m/z: 374 (M⁺). Anal. Calcd for C₁₄H₁₁N₃O₂S₂ (374.37): C, 60.96; H, 2.69; N, 14.97; S, 8.56. Found: C, 60.82; H, 2.58; N, 14.89; S, 8.47.

4-(Benzod[1,3]dioxol-5-yl)-2-(ethylthio)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (9)

A mixture of tetrahydropyrimidine 1 (2.73 g, 0.01 mol) in ethanol solution of sodium ethoxide (20 mL), ethyl iodide (1.82 g, 0.01 mol), was added and then refluxed for 6 h. Left to cool, the solid was filtered, dried and recrystallized from ethanol to give compound 9 as yellow crystals, mp 274–275°C, yield 55%. FT-IR (KBr, cm⁻¹): 3167 νNH, 3082 νCH₃ aromatic, 2969 νCO biphatic, 2234 νC=O pyrimidine, 1672 νC=O, 1H-NMR (300 MHz, DMSO-d₆): 13.10 (s, 1H, −NH, D₂O-exchangeable), 7.24–7.10 (m, 3H, Ar-H), 6.17 (s, 2H, O–CH₂–O), 3.45 (q, 2H, −CH₂CH₃, J=6.0 Hz) and 1.55 (t, 3H, −CH₂CH₃, J=6.0 Hz). 13C-NMR (75 MHz, DMSO-d₆): 14.30, 14.57, 62.78, 100.08, 102.54, 109.38, 126.21, 129.97, 154.42, 154.80, 178.65. MS m/z: 301 (M⁺). Anal. Calcd for C₁₄H₁₁N₃O₂S₂ (301.32): C, 55.80; H, 3.68; N, 13.95; S, 10.64. Found: C, 55.68; H, 3.75; N, 13.78; S, 10.60.

4-(Benzod[1,3]dioxol-5-yl)-6-chloro-2-(ethylthio)-pyrimidine-5-carbonitrile (10)

A mixture of S-alkylated pyrimidine 9 (3.01 g, 0.01 mol), was heated under reflux in phosphorus oxychloride (7 mL, 0.01 mol) and phosphorus pentoxide (2.5 g, 0.01 mol) for 8 h, cooled and poured onto ice. The precipitated solid was filtered off, dried and recrystallized from ethanol to give compound 10 as brown crystals, mp 220–222°C, yield 73%. FT-IR (KBr, cm⁻¹): 3205 νNH aromatic, 2914 νCH₃ aliphatic, 2222 νC=O, 1655 νC=O, 1H-NMR (300 MHz, DMSO-d₆): 7.30–6.95 (m, 3H, Ar-H), 6.17 (s, 2H, O–CH₂–O), 3.43 (q, 2H, −CH₂CH₃, J=7.5 Hz), 1.06 (t, 3H, −CH₂CH₃, J=7.5 Hz). MS m/z: 319 (M⁺). Anal. Calcd for C₁₄H₁₁ClN₃O₂S (319.77): C, 52.59; H, 3.15; Cl, 11.09; N, 13.14; S, 10.03. Found: C, 52.45; H, 3.03; Cl, 11.00; N, 13.02; S, 10.14.
acid (30 mL) and conc. HCl (15 mL). After completion of the addition the ice bath was removed and stirring continued for an additional 2 h. The crude product was filtered, dried, then recrystallized from ethanol to afford 15 as brown crystals, mp 92–94°C, yield 78%. FT-IR (KBr, cm⁻¹): 3389, 3211, 2215, 2192 (2 νCN), 1673 νC=O (pyrimidine) 1628 νC=O amide νH-NMR (300 MHz, DMSO-d₆): 8.48 (bs, 1H, –NH, D₂O-exchangeable), 7.62–7.11 (m, 3H, Ar-H), 6.17 (s, 2H, O–CH₂–O) and 1.26 (s, 3H, –CH₃). MS m/z: 381 (M+2)², 380 (M+1)², 379 (M⁺). Anal. Calcd for C₁₇H₉N₅O₄S (379.35): C, 53.82; H, 2.39; N, 18.46; S, 8.45. Found: C, 53.69; H, 2.24; N, 18.38; S, 8.31.

**Determination of Total Antioxidant Capacity (TAC)**

The antioxidant activity (AOA) of a compound was determined according to phosphomolybdenum method using ascorbic acid as standard. This assay is based on the reduction of Mo⁶⁺ to Mo⁵⁺ by the sample analytic and subsequent formation of a green colored [phosphate=Mo⁵⁺] complex at acidic pH. In this method, 0.5 mL of the compound (100 μg/mL) in methanol was combined in dried vial with 5 mL of reagent solution (0.6 m sulfuric acid, 28 mm sodium phosphate and 4 mm ammonium molybdate solutions). The vials containing the reaction mixture were capped and incubated in a thermal block at 95°C for 90 min. After the samples had cooled at room temperature, the absorbance was measured at 695 nm against a blank. The blank consisted of all reagents and solvents without the sample and it was incubated under the same conditions. All experiments were carried out in triplicate. The antioxidant activity of the sample was expressed as the number of ascorbic acid equivalent (AAE). The phosphomolybdenum assay is based on the reduction of Mo⁶⁺ to Mo⁵⁺ by antioxidant compounds and the formation of a green phosphate/Mo⁵⁺ complex with a maximal absorption at 695 nm.

**Statistical Analysis**

All data were presented as mean±standard deviation (S.D.) using SPSS 13.0 program.

**Conclusion**

A variety of fused and non fused heterocyclic systems containing pyrimidine nucleus have been synthesized from the reaction of tetrahydropyrimidine with different reagents. All the synthesized pyrimidines are potent antioxidants. In particular the tetrahydropyrimidine 6 and dihydropyrimidine 6 and S-alkylated product 9 showed the most antioxidant activity (AOA) expressed in 308.33±1.25, 436.85±2.25 and 225.87±1.50 mg AAE/g compound (AAE) using ascorbic acid as standard.

**Acknowledgment**

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**Conflict of Interest**

The authors declare no conflict of interest.

**References**


