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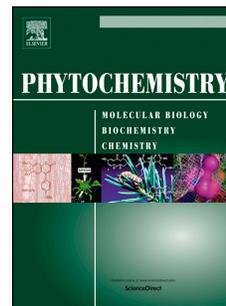
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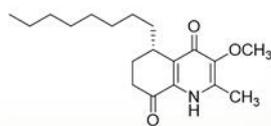
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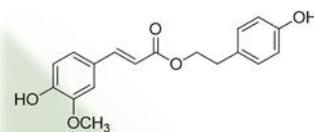
Inhibition of pentosidine-like *advanced glycation endproducts* (AGEs) formation



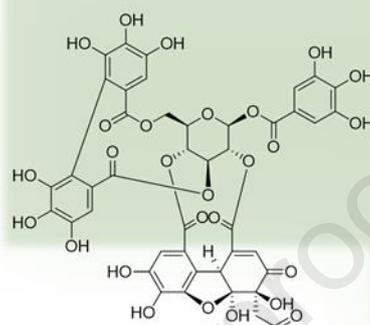
Antidesma bunius (L.) Spreng



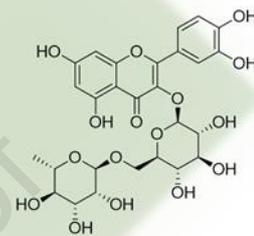
9 | $IC_{50} = 0.7 \text{ mM}$



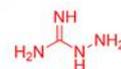
15 | $IC_{50} = 0.15 \text{ mM}$



23 | $IC_{50} = 0.2 \text{ mM}$



31 | $IC_{50} = 0.1 \text{ mM}$



control | $IC_{50} = 1.4 \text{ mM}$

1 **Chemical constituents of *Antidesma bunius* aerial parts and the anti-AGEs activity of**
2 **selected compounds**

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20

21

22 **Abstract**

23 Thirty-three natural products were isolated from the aerial parts of *Antidesma buni*,
24 Euphorbiaceae, a plant used in Vietnamese traditional medicine against rheumatoid arthritis.
25 All compounds were reported the first time for this species, and nine constituents resembled
26 undescribed natural products, noticeably three coumarinolignans with 2,2-dimethyl-1,3-
27 dioxolane moiety, two cyclopeptides, and two furofuran-type lignans connected with a
28 phenylpropanoid moiety. The individual structures were elucidated by combining NMR and
29 MS data, and their configuration was established by NOESY and ECD experiments and NMR
30 calculations. Compounds with sufficient amount were analyzed for their inhibition of advanced
31 glycation endproducts (AGEs) formation, metabolites involved in many diseases like
32 Alzheimer, joint diseases or diabetes. With IC₅₀ values below 0.2 mM rutin and *p*-
33 hydroxyphenethyl *trans*-ferulate showed to be moderately active, both still being 10-times more
34 active than the positive control aminoguanidine.

35

36 *Keywords:* *Antidesma buni*, Euphorbiaceae, Cyclopeptide, Coumarinolignan, Advanced
37 glycation endproducts

38

39 1. Introduction

40 *Antidesma bunius* (L.) Spreng. (Euphorbiaceae) is an up to 30 m tall tree, cultivated in
41 high-precipitation areas of China and some Southeast Asian countries like Indonesia, Laos,
42 Myanmar, Thailand, and Vietnam. In Java and the Philippines, its fruits are used as food, for
43 preparing syrups, jams, jellies, and wine and liqueur production. The leaves are consumed as a
44 vegetable and utilized in traditional medicine for the treatment of traumatic injury (eFloras,
45 2008). In Vietnam, the Dao ethnic community uses all plant parts to cure rheumatoid arthritis
46 (Asia Foundation, 2012).

47 In 2016, Do et al. reported the isolation of two biflavones and three terpenoid glycosides
48 from the methanolic extract of *A. bunius* leaves. The compounds displayed moderate inhibitory
49 effects on NO production in BV2 cells and LPS-induced RAW264.7 macrophages (Trang et
50 al., 2016). Mauldina and colleagues (2017) published a study on the bioactivity-guided isolation
51 of natural products from *A. bunius* stem bark, which identified friedelin, β -sitosterol, and
52 betulinic acid as potent α -glucosidase inhibitors (Mauldina et al., 2017). Other studies focused
53 on pharmacological properties of *A. bunius* berries, indicating inhibition of the adipogenesis
54 process and differentiation of adipocytes (Krongyut and Sutthanut, 2019), stimulation of fat
55 metabolism in the liver (Ngamlerst et al., 2019), and a reduced formation of plaques in arteries
56 (Tawali S et al., 2019). Besides, to the best of our knowledge, nothing else is known about the
57 phytochemical composition of *A. bunius* aerial parts. Thus, in order to enable better insights
58 into the constituents and pharmacological activity of this relevant medicinal plant, we have
59 conducted the current investigation utilizing plant material collected in the Dao ethnic
60 community of Ba Vi, Hanoi, Vietnam. Our efforts resulted in the isolation and identification of
61 nine previously undescribed (**1-5**, **8**, **16**, **17**, and **20**) and 24 known (**6**, **7**, **9-15**, **18**, **19**, **21-33**)
62 compounds. Some of the isolated compounds were then examined for their potential to inhibit
63 the formation of advanced glycation endproducts (AGEs).

64 In the organism, AGEs result from the non-enzymatic reaction between simple sugars or
65 their oxidized derivatives (i.e., 1,2-dicarbonyl compounds) with the primary amino group of
66 certain amino acids to form a Schiff base as intermediate. It is irreversibly converted to a
67 ketoamine, the so-called Amadori product, which can undergo further reactions involving
68 dicarbonyl intermediates to finally give stable AGEs (Nagaraj et al., 1996; Ueno et al., 2003).
69 The latter are inflammatory mediators involved in vascular complications of diabetes, as well
70 as many chronic inflammatory diseases such as rheumatoid arthritis (Dariya and Nagaraju,
71 2020; De Groot et al., 2010). Preventing AGEs formation using natural products, herbal drugs

72 or food could help avoiding such disorders by stopping oxidation and/or trapping dicarbonyl
73 species (Khan et al., 2020).

74

75 2. Results and discussion

76 2.1. Isolation and structural elucidation of compounds

77 Nine previously not reported (**1-5**, **8**, **16**, **17**, and **20**), along with 24 known (**6**, **7**, **9-15**,
78 **18**, **19**, **21-33**) compounds, could be isolated from *A. bunius* leaves, and the corresponding
79 structures were elucidated through extensive analysis of 1D and 2D NMR spectroscopic, and
80 HRESIMS data. The absolute configuration of previously undescribed compounds was
81 established by characteristic NMR shift values, electronic circular dichroism (ECD)
82 calculations (**1-5**, and **8**), and other techniques, including GC-MS analysis for sugar
83 identification (**20**) as well as Rh₂(OCOCF₃)₄-induced CD spectra (**16** and **17**) (Fig. 1).

84 Compound **1** was isolated as colorless oil. Its molecular formula C₃₂H₃₈O₉ was established
85 by a HRESIMS ion peak at *m/z* 565.2424 ([M-H]⁻, calcd for C₃₂H₃₇O₉, 565.2443),
86 corresponding to 14 indices of hydrogen deficiency. The ¹H NMR spectrum showed the
87 presence of an ABX-spin system [δ_{H} 6.94 (1H, dd, *J* = 1.8, 8.4 Hz), 6.91 (1H, d, *J* = 1.8 Hz), and
88 6.89 (1H, d, *J* = 8.4 Hz)], two aromatic singlet protons [δ_{H} 7.46 (1H, s) and 6.45 (1H, s)], two
89 methoxy groups [δ_{H} 3.87 (3H, s) and 3.84 (3H, s)], and six methyl groups [δ_{H} 1.48 (6H, s), 1.38
90 (3H, s), 1.35 (3H, s), 0.97 (3H, s), and 0.72 (3H, s)]. The ¹³C NMR revealed one esteric (δ_{C}
91 159.9), 14 aromatic and olefinic (in the range of 100-150 ppm), and four oxygenated signals
92 (δ_{C} 65.4, 76.4, 79.5, and 80.3). The upfield-shifted esteric carbon at δ_{C} 159.9 suggested a
93 coumarin scaffold. This prediction was supported by HMBC correlations of H-4 (δ_{H} 7.46)/ C-
94 2 (δ_{C} 159.9), C-5 (δ_{C} 100.0), C-9 (δ_{C} 137.9); H-5 (δ_{C} 6.45)/ C-4 (δ_{C} 138.1), C-9; and by a
95 comparison with published data (Chen et al., 2004; Chen et al., 2007). A 1,1-dimethylallyl
96 fragment was indicated by two methyls [δ_{H} 1.48 (6H, s)] and three olefinic protons [δ_{H} 5.09
97 (1H, d, *J* = 12.0 Hz), 5.09 (1H, d, *J* = 17.4 Hz), and 6.18 (1H, dd, *J* = 10.2, 17.4 Hz)]. The 1,1-
98 dimethylallyl moiety was determined to bind to C-3 by an HMBC correlation from H-12 (δ_{H}
99 1.48), H-13 (δ_{H} 1.48) to C-3 (δ_{C} 132.8), while methoxylation at C-6 was indicated by an HMBC
100 correlation from OMe (δ_{H} 3.84) to C-6 (δ_{C} 145.7). An ABX-spin system, together with two
101 downfield aromatic carbons at δ_{C} 146.5 and 146.9, and an HMBC correlation of OMe (δ_{H} 3.87)/
102 C-3' (δ_{C} 146.9), was typical for the presence of a 3-methoxy-4-hydroxybenzene moiety. The
103 structure of the side chain was elucidated based on HMBC and COSY correlations, as shown
104 in Fig. 2. The two substructures were connected through 7-*O*-7' and 8-*O*-8' etheric bonds, which

105 were assured by key HMBC correlations of H-7' (δ_{H} 5.22)/C-7 (δ_{C} 135.7) and H-8' (δ_{H} 4.36)/C-
106 8 (δ_{C} 132.0). The coupling constant ($J= 5.4$ Hz) of the two vicinal protons H-7' and H-8'
107 indicated that they are *trans*-orientated (Bozzo et al., 2003; Chen et al., 2004). However,
108 NOESY correlations did not allow the determination of the relative configuration at C-10'.
109 Therefore, the planar structure of **1** was established as 2-(2-(2,2-dimethyl-1,3-dioxolan-4-
110 yl)propan-2-yl)-3-(4-hydroxy-3-methoxyphenyl)-5-methoxy-8-(2-methylbut-3-en-2-yl)-2,3-
111 dihydro-9H-[1,4]dioxino[2,3-h]chromen-9-one.

112 Compound **2** had the same molecular formula as **1**, which was indicated by a deprotonated
113 ion peak at m/z 565.2419 ($[\text{M}-\text{H}]^-$, calcd for $\text{C}_{32}\text{H}_{37}\text{O}_9$, 565.2443) in the HRESI mass spectrum.
114 NMR data of **2** were similar to **1**, except for C-7', 8', and 10' (Table 1). The coupling constants
115 of H-7' and H-8' were 6.6 Hz, which is typical for *trans*-conformation of the two protons (Bozzo
116 et al., 2003; Chen et al., 2004). Again, the relative configuration of position C-10' could not be
117 established by NOESY. Thus, the planar structure of **2** was determined as 2-(2-((2,2-dimethyl-
118 1,3-dioxolan-4-yl)propan-2-yl)-3-(4-hydroxy-3-methoxyphenyl)-5-methoxy-8-(2-methylbut-
119 3-en-2-yl)-2,3-dihydro-9H-[1,4]dioxino[2,3-h]chromen-9-one.

120 Considering the presence of a 2,2-dimethyl-1,3-dioxolane group in compounds **1** and **2**,
121 which can potentially be introduced while extraction/fractionation using acetone, an LC-MS
122 analysis of the crude methanolic extract of *A. bunius* was performed for further confirmation
123 (data not shown in detail). The obtained MS spectra in extracted ion chromatogram mode did
124 not indicate the presence of **1** (MW: 526.58) or **2** (MW: 526.58) in the extract. Thus, it was
125 concluded that these two compounds are artifacts. Nevertheless, also the original structures, i.e.
126 those without the dioxolane group, were found to be previously undescribed natural products.

127 Both compounds shared the same planar structure, and the relative configuration of C-7'
128 and 8' was determined to be *trans* (gauche), based on the previously mentioned coupling
129 constants (lower 3J coupling constants due to the gauche effect) and observed NOE from H-7'
130 to H-2' in **1** and **2**. Moreover, these two compounds displayed different retention times on an
131 achiral C-18 column, indicating diastereoisomers. Considering the observed mirror ECD
132 spectra (Figure 3A), it can be concluded that the stereochemistry of C-10' has to be the same in
133 **1** and **2**, and the rest are to be mirror images of each other. To establish the relative configuration
134 of C-10', NMR chemical shift calculation followed by DP4+ probability calculation was
135 implemented. Briefly, geometrical optimization and NMR calculation were performed at
136 CPCM/mPW1PW91/6-31+G(d,p)/B3LYP/6-31G(d) basis set and level of theory in chloroform
137 on two possible isomers: 1 (7'*R*,8'*R*,10'*R*) and 2 (7'*R*,8'*R*,10'*S*). Further DP4+ probability

138 calculation (Grimblat et al., 2015) using experimentally obtained chemical shifts of **1** indicated
139 the presence of isomer **1** with a probability of 100% (Fig. S1.8, Supplementary data).
140 Subsequent simulation of the ECD spectrum at CPCM/TD-DFT/cam-B3LYP/6-
141 31+G(d,p)/B3LYP/6-31+G(d,p)/CPCM basis set and level of theory in acetonitrile resulted in
142 a spectrum matching with that of compound **1**. Ultimately and based on the aforementioned
143 data, the absolute configurations of compounds **1** and **2** were established as 7'*R*,8'*R*,10'*R* and
144 7'*S*,8'*S*,10'*R*, respectively. Both compounds (including their unmodified structures) are
145 previously unreported natural products, and they were named buniusines A and B.

146 The molecular formula of **3** was evidenced by a dominant HRESIMS peak at *m/z*
147 589.2433 ([M+Na]⁺, calcd for C₃₂H₃₈O₉Na, 589.2408), and its 1D-NMR data resembled those
148 of **1** and **2**. However, a detailed analysis of the HMBC spectrum showed correlations of H-8'
149 (δ_{H} 4.36)/C-7 (δ_{C} 136.5) and H-7' (δ_{H} 5.22)/C-8 (δ_{H} 131.2), indicating that compound **3** is a
150 regional isomer of **1** and **2**. Moreover, LC-MS analysis again indicated that a 2,2-dimethyl-1,3-
151 dioxolane moiety was introduced during the extraction process (data not shown in detail). The
152 conformation of H-7' and H-8' was determined to be *trans*-type (*gauche*) by a coupling constant
153 of 4.8 Hz (Bozzo et al., 2003; Chen et al., 2004) and NOE correlations between H-8' and H-2'.
154 To establish the relative configuration of C-10' similar to **1** and **2**, the DP4+ probability
155 calculation for two possible isomers (1: 7'*S*,8'*S*,10'*R* and 2: 7'*S*,8'*S*,10'*S*) was applied. The
156 results confirmed isomer 2 with a probability of 99.83% to be the correct stereoisomer.
157 Furthermore, using ECD calculation, the absolute configuration of compound **3** was established
158 as 7'*S*,8'*S*,10'*S* (Fig. S3.8, Supplementary Data). Collectively, the structure of **3** was deduced as
159 (2*S*,3*S*)-3-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-2-yl)-2-(4-hydroxy-3-
160 methoxyphenyl)-5-methoxy-8-(2-methylbut-3-en-2-yl)-2,3-dihydro-9H-[1,4]dioxino[2,3-
161 h]chromen-9-one, a compound named buniusine C.

162 Buniusines A-C (**1-3**) belong to the class of coumarinolignans, which can be found in
163 other *Antidesma* species, such as antidesmanins A-D in *A. pentandrum* root (Chen et al., 2004).
164 The characteristic features of these natural products are a coumarin core connected with a
165 phenylpropanoid moiety via two ether bonds. In addition, an 1,1-dimethylallyl moiety is often
166 linked with C-3 of the coumarin core (Chen et al., 2007). Chen and colleagues (2004) reported
167 the isolation and identification of two racemic mixtures of similar structures, antidesmanins C
168 and D. However, due to small quantities of isolated compounds, their exact chemical structure
169 could not be confirmed (Chen et al., 2004). In our study, compounds **1-3** might have been
170 modified by acetone during the fractionation procedure. However, these changes permitted the

171 isolation of individual isomers on a conventional C-18 column, whose absolute configuration
172 was then determined on the basis of ECD and NMR calculations.

173 Compound **4** was isolated as a yellowish amorphous powder. Its molecular formula could
174 be established by a deprotonated ion peak at m/z 531.3018 ($[M-H]^-$, calcd for $C_{31}H_{39}N_4O_4$,
175 531.2977) in the HRESI mass spectrum. The 1H NMR spectrum showed multiple signals in the
176 aromatic range (δ_H 6.5-7.5 ppm), one N-methyl group [δ_H 2.22 (3H, s)], and four doublet methyl
177 groups [δ_H 0.68 (3H, d, $J=$ 6.6 Hz), 0.73 (3H, d, $J=$ 6.6 Hz), 0.86 (3H, d, $J=$ 6.6 Hz), and 1.14
178 (3H, d, $J=$ 7.2 Hz)]. Three carbon signals in the range of δ_C 165-175 ppm were found; knowing
179 that also four nitrogen atoms are present, this indicated three amide functionalities in the
180 molecule. 1D and 2D NMR data analysis along with a comparison to literature values
181 (Lomchoey et al., 2018) assigned these nitrogens to *p*-oxystyrylamine, 2-hydroxyleucine,
182 phenylalanine, and 4-benzyl-3-methyl-5-oxoimidazolidine moieties, which strongly suggested
183 the cyclopeptide alkaloid scaffold of **4**. *p*-Oxystyrylamine was identified by HMBC
184 correlations from H-1 (δ_H 6.40) to C-13/14/15 (δ_C 131.6, 132.0, and 130.6, respectively) and
185 from H-13 (δ_H 7.04) and H-15 (δ_H 7.03) to C-11. The presence of 2-hydroxyleucine and
186 phenylalanine was confirmed by spin system H-6/H-5/H-17/H-18(H-19)/H-20 and H-8/H-9/H-
187 21(H-22)/H-23, as well as HMBC correlations of H-5 (δ_H 4.04)/C-4 (δ_C 167.4), H-6 (δ_H 5.44)/C-
188 7 (δ_C 168.3), and H-9 (δ_H 4.85)/C-7. As for the 4-benzyl-3-methyl-5-oxoimidazolidine moiety,
189 COSY coupling networks of H-26/H-27 and H-31/H-32/H-33/H-34/H-35, along with a series
190 of HMBC correlations of H-28 (δ_H 3.25 and 4.07)/C-25 (δ_C 172.4), C-26 (δ_C 67.5); N-Me (δ_H
191 2.22)/ C-26, C-28 (δ_C 68.4); and H-29 (δ_H 2.94 and 3.11)/C-30, C-31 (δ_C 137.2 and 130.2)
192 confirmed its presence in **4**. The HMBC correlations of H-9 (δ_H 4.85)/C-11 (δ_C 156.1); H-5 (δ_H
193 4.04)/C-7 (δ_C 168.3); H-8 (δ_H 4.55)/C-25 (δ_C 172.4), C-28 (δ_C 68.4) indicated the connection of
194 the four substructures, resulting in the planar structure of **4** as shown. Conformation of the
195 double bond was *Z* because of the coupling constants of H-1 and H-2 ($J=$ 9.6 Hz). The relative
196 *erythro* configuration of C-8 and C-9 was deduced from a $^3J_{8,9}$ value of 7.8 Hz (Lomchoey et
197 al., 2018). The NOESY spectrum displayed correlations between H-6 (NH) and H-8; H-6 and
198 H-17 (but no correlations between H-6 and H-5); H-26 and H-18; a strong correlation between
199 H-9 and H-28b (δ_H 4.07) and a weak correlation with H-28a (δ_H 3.25); and H-28 and H-9,
200 conclusively resulting in deciphering the relative configuration of this structure as
201 5*S,8*S,9*S,26*S. Further calculation of the ECD spectrum indicated the absolute
202 configuration of **4** as 5*S*,8*S*,9*S*,26*S*. From all deductions shown above, the structure of **4** was
203 finally determined as (3*S*,4*S*,7*S*,*Z*)-4-((*S*)-4-benzyl-3-methyl-5-oxoimidazolidin-1-yl)-7-

204 isobutyl-3-isopropyl-2-oxa-6,9-diaza-1(1,4)-benzenacycloundecaphan-10-ene-5,8-dione, a
205 previously undescribed natural product named buniusamide A.

206 Based on an HRESIMS signal at m/z 619.2909, the molecular formula of **5** was
207 determined to be $C_{37}H_{40}N_4O_5$ ($[M-H]^-$, calcd for $C_{37}H_{39}N_4O_5$, 619.2926). 1H and ^{13}C NMR
208 spectra of this compound showed similarities to those of **4** (Table 2), indicating the same
209 cyclopeptide scaffold. However, the ^{13}C NMR spectrum revealed four carbon signals in the
210 range of δ_C 165-170 ppm, suggesting the molecule contains four amide groups. The presence
211 of a *p*-oxystyrylamine moiety was assured by COSY coupling chains of H-15/H16; H-12/H-13;
212 and H-1/H-2/H-3, as well as HMBC correlations from H-1/C-13, C-14, C-15 and from H-2/C-
213 4. A 2-hydroxyphenylalanine moiety was determined by characteristic COSY coupling
214 networks of H-21/H-22/H-23/H-24/H-25 and H-9/H-8/H-26, as well as key HMBC correlations
215 from H-9 (δ_H 5.93)/C-20 (δ_C 137.5), C-21 (δ_C 128.4), C-25 (δ_C 128.4); and H-8 (δ_H 4.74)/C-7
216 (δ_C 170.6). A proline moiety was indicated by a coupling chain H-17/H-18/H-19/H-5 in the
217 COSY spectrum and an HMBC correlation from H-5 (δ_H 3.85) to C-4 (δ_C 166.5). In addition to
218 that, phenylalanine was also identified by two COSY coupling networks of H-31/H-32/H-33/H-
219 34/H-35 and H-29/H-30/H-36, as well as an HMBC correlation of H-36 (δ_H 5.80)/C-27 (δ_C
220 170.9). These substructures could be connected by key HMBC correlations of H-2 (δ_H 6.74),
221 H-5 (δ_H 3.85)/C-4 (δ_C 166.5); H-5/C-7 (δ_C 170.6); H-9 (δ_H 5.93)/C-11 (δ_C 155.5); and H-8 (δ_H
222 4.74)/C-27 (δ_C 170.9). Furthermore, a pentanamide moiety was identified by a COSY
223 correlation chain [H-41/H-40(H-42)/H-39/H-38] and a typical HMBC crosspeak of H-38 (δ_H
224 5.64)/C-37 (δ_C 166.5). This moiety was linked to C-28, as evidenced by an HMBC crosspeak
225 of H-28 (δ_H 4.54)/C-37 (δ_C 166.5). The double bond at C-38/C-39 had *E* type conformation (J
226 = 15.0 Hz), whereas the relative configuration of 2-hydroxyphenylalanine was *trans* because of
227 a coupling constant of $J = 7.2$ Hz (Caro et al., 2012). The NOESY spectrum was not helpful to
228 deduce the relative configuration of other chiral centers at positions C-5 and C-28. Hence, DP4+
229 probability calculation was applied to reveal the relative configuration of **5**. The geometrical
230 optimization followed by NMR chemical shift calculation was performed at
231 CPCM/mPW1PW91/6-31+G(d,p)//B3LYP/6-31G(d) in chloroform for four possible
232 diastereoisomers (isomer 1: 5*R*,8*S*,9*S*,28*S*, isomer 2: 5*S*,8*S*,9*S*,28*R*, isomer 3: 5*R*,8*S*,9*S*,28*R*,
233 and isomer 4: 5*S*,8*S*,9*S*,28*S*), keeping in mind that the relative configuration of C-8 and C-9 is
234 fixed (8**S*,9**S*). Further computation of DP4+ probability concluded isomer 2 (5*S*,8*S*,9*S*,28*R*)
235 with a probability of 96.59% to be the correct stereoisomer (Fig. S5.8, Supplementary Data).
236 The calculated ECD spectrum revealed to be opposite of the experimental one obtained in
237 acetonitrile (Fig. 3E). Therefore, the structure of **5** was ultimately determined as (*E*)-*N*-((*S*)-1-

238 (((1²*R*,8*R*,9*R*,*Z*)-2,10-dioxo-8-phenyl-7-oxa-3-aza-1(2,1)-pyrrolidina-6(1,4)-
 239 benzenacyclodecaphan-4-en-9-yl)amino)-1-oxo-3-phenylpropan-2-yl)-4-methylpent-2-
 240 enamide, a novel compound named buniusamide B.

241 Compound **8** showed a dominant deprotonated ion peak [M-H]⁻ at *m/z* 334.2007 (cacl'd
 242 for C₁₉H₂₈NO₄, 334.2024) in the HRESI mass spectrum, which, together with the ¹³C NMR
 243 data, indicated the molecular formula C₁₉H₂₉NO₄. ¹H NMR and HSQC spectra displayed
 244 signals assignable to amine [δ_{H} 8.79 (1H, s)], hydroxy [δ_{H} 6.86 (1H, s)], methoxy [δ_{H} 3.95 (3H,
 245 s)], and terminal methyl [δ_{H} 0.87 (3H, t, *J*= 6.6 Hz)] groups, as well as a methylene chain [δ_{H}
 246 1.21-1.44 (m)]. The ¹³C NMR spectrum showed characteristic resonances of an aliphatic ketone
 247 (δ_{C} 193.6), a conjugated ketone (δ_{C} 175.2), four olefinic carbons (δ_{C} 148.5, 139.3, 137.3, and
 248 131.2), an oxygenated carbon (δ_{C} 72.7), a methoxy (δ_{C} 59.8), and an aliphatic chain (δ_{C} 14.2-
 249 38.1). Overall, 1D NMR data of **8** resembled that of antidesmone (**9**) (Bringmann et al., 2000a;
 250 Bringmann et al., 2000b), except for the presence of a carbon signal at δ_{C} 72.7. The position of
 251 this oxygenated carbon was located by HMBC correlations of H-11/C-5 (δ_{C} 72.7), C-6 (δ_{C}
 252 32.4), C-10 (δ_{C} 137.5). Other key HMBC correlations for an antidesmone backbone were also
 253 found, specifically OMe (δ_{H} 3.95)/C-3 (δ_{C} 148.5), and 2-Me (δ_{H} 2.38)/C-2 (δ_{C} 139.3), C-3 (δ_{C}
 254 148.5). NOESY crosspeaks of 2-Me (δ_{H} 2.38)/ OMe (δ_{H} 3.95) and NH (δ_{H} 8.79) supported the
 255 proposed planar structure. The absolute configuration at position C-5 was established to be *S*
 256 by ECD calculation with TD-DFT/cam-B3LYP/6-31G+(d,p)/CPCM (acetonitrile) functions
 257 (Fig. 3F). Collectively, the structure of **8** was elucidated as (*S*)-5-hydroxyantidesmone.

258 Compound **16** was isolated as white amorphous powder, its molecular formula C₄₁H₄₄O₁₄
 259 established due to an *m/z* signal at 759.2651 ([M-H]⁻, cacl'd for C₄₁H₄₃O₁₄, 759.2658). The ¹³C
 260 NMR spectrum displayed 37 resonances, including one ester carbon, eight oxygenated aromatic
 261 carbons, sixteen aromatic carbons, nine oxygenated carbons, and three methoxy groups. With
 262 the HSQC spectrum and molecular formula it can be deduced that there was a symmetrical
 263 aromatic ring in the molecule. The COSY spectrum showed six coupling networks, specifically
 264 H-7/H-8[H-8'(H-9')/H-7']/H-9; H-5'/H-6'; H-5''/H-6''; H-7''/H-8''/H-9''; H-7'''/H-8'''; and H-
 265 5'''/H-6'''. HMBC correlations from H-7 (δ_{H} 4.74) to C-1 (δ_{C} 137.9), C-2 (δ_{C} 103.0); and from
 266 H-7' (δ_{H} 4.76) to C-1' (δ_{C} 132.9), C-2' (δ_{C} 108.8), C-6' (δ_{C} 119.1), as well as a comparison with
 267 reported ¹³C NMR data from literature provided evidences for a medioresinol moiety (Xiong et
 268 al., 2011). A phenylpropanoid moiety was evidenced by a series of HMBC correlations of H-
 269 7'' (δ_{H} 4.89)/C-1'' (δ_{C} 130.9), C-2'' (δ_{C} 108.6), C-6'' (δ_{C} 119.0). In addition, couplings of H-7'''
 270 (δ_{H} 7.51)/ C-1''' (δ_{C} 127.2), C-2''' (δ_{C} 109.4), C-6''' (δ_{C} 123.2), and C-9''' (δ_{C} 167.2) indicated the

271 presence of ferulic acid. The connection of these substructures was determined by crosspeaks
 272 of H-8'' (δ_{H} 4.56)/C-4 (δ_{C} 134.1) and H-9'' (δ_{H} 4.33 and 4.46)/C-9''' (δ_{C} 167.2). HMBC
 273 correlations also facilitated location of the methoxyl groups as 3,5-OMe (δ_{H} 3.87)/C-3,5 (δ_{C}
 274 153.8); 3'-OMe (δ_{H} 3.91)/C-3' (δ_{C} 146.9); 3''-OMe (δ_{H} 3.92)/C-3'' (δ_{C} 146.9); and 3'''-OMe (δ_{H}
 275 3.89)/C-3''' (δ_{C} 146.8). Relative configuration of the medioresinol moiety was established by
 276 coupling constants of $^3J_{7,8}$ and $^3J_{7',8'}$ (4.8 Hz), as well as empirical rules of $\Delta\delta_{\text{H-9}, \text{H-9}'}$
 277 (experimental data: 0.35 and 0.39 ppm; reference data: $\Delta\delta_{\text{H-9}, \text{H-9}'}$ for H-7/H-8 *trans*, H-7'/H-8'
 278 *trans* 0.30-0.40 ppm; $\Delta\delta_{\text{H-9}, \text{H-9}'}$ for H-7/H-8 *cis*, H-7'/H-8' *cis* <0.20 ppm) (Shao et al., 2018).
 279 The relative configuration of positions C-7'' and C-8'' of the phenylpropanoid moiety was of
 280 *erythro* type as evidenced by a small coupling constant of 3.6 Hz (Xiong et al., 2011), whereas
 281 configuration of the double bond between C-7''' and C-8''' was of *E*-type ($J=$ 15.6 Hz). The
 282 medioresinol moiety was configured (*7R,7'R,8S,8'S*) due to a negative Cotton effect at 207 nm
 283 in the CD spectrum, which was comparable to that of (-)-acortatarinowin F and (-)-eudesmin
 284 (Lu et al., 2015). The 7''*R* configuration was evidenced by a negative Cotton effect at 345 nm
 285 (the E band) in the Rh₂(OCOCF₃)₄-induced CD spectrum of **16** (Fig. S7.7, Supplementary data)
 286 (Gerards and Snatzke, 1990; Xiong et al., 2011). Taking all observations together, the structure
 287 of **16** was established as (*7R,7'R,7''R,8S,8'S,8''S*)-9''-feruloyl-4',4''-dihydroxy-3,3',3'',5-
 288 tetramethoxy-7,9':7',9'-diepoxy-4,8''-oxy-8,8'-sesquieolignan-7''-ol.

289 Compound **17** had the same molecular formula as **16** (m/z 759.2636, [M-H]⁻, calcd for
 290 C₄₁H₄₃O₁₄, 759.2658). Also, 1D and 2D NMR data were in good agreement, suggesting that
 291 both compounds share the same lignan scaffold (Table 3). However, the coupling constant $^3J_{7'',8''}$
 292 (8.4 Hz) indicated that compound **17** was the *threo* isomer of **16**. The relative configuration of
 293 the medioresinol moiety was established by coupling constants of $^3J_{7,8}$ and $^3J_{7',8'}$ (4.8 Hz), as
 294 well as by empirical rules of $\Delta\delta_{\text{H-9}, \text{H-9}'}$ data (experimental data: 0.36 and 0.37 ppm; reference
 295 data: $\Delta\delta_{\text{H-9}, \text{H-9}'}$ for H-7/H-8 *trans*, H-7'/H-8' *trans* 0.30-0.40 ppm; $\Delta\delta_{\text{H-9}, \text{H-9}'}$ for H-7/H-8 *cis*, H-
 296 7'/H-8' *cis* < 0.20 ppm) (Shao et al., 2018). A positive Cotton effect at 209 nm indicated the
 297 (*7S,7'S,8R,8'R*) configuration of the medioresinol moiety, which was opposite to that of **16**. The
 298 Rh₂(OCOCF₃)₄-induced CD spectrum method was applied to determine absolute configuration
 299 at position C-7''. The observed positive Cotton effect at 351 nm (E band), which again was
 300 opposite to **16**, indicated 7''*S* configuration (Fig. S8.7, Supplementary data). Collectively, the
 301 structure of **17** was (*7S,7'S,7''S,8R,8'R,8''S*)-9''-feruloyl-4',4''-dihydroxy-3,3',3'',5-
 302 tetramethoxy-7,9':7',9'-diepoxy-4,8''-oxy-8,8'-sesquieolignan-7''-ol.

303 The molecular formula of **20** was established as C₂₈H₂₆O₁₈ by a HRESIMS signal at *m/z*
304 649.1051 ([M-H]⁻, cacl'd for C₂₈H₂₅O₁₈, 649.1046). ¹H and ¹³C NMR spectra of this compound
305 displayed characteristic signals for a sugar moiety [δ_{H} 5.92 (1H, d, *J*= 8.4 Hz), 5.22 (1H, dd, *J*=
306 8.4, 9.6 Hz), 3.82 (1H, m), 3.62 (1H, t, *J*= 9.6 Hz), 3.86 (1H, m, H-5), 4.41 (1H, dd, *J*= 5.4,
307 12.0 Hz), 4.67 (1H, dd, *J*= 1.8, 12.0 Hz); δ_{C} 94.1, 74.2, 76.1, 71.7, 76.6, 64.6] and galloyl
308 residues [δ_{H} 7.01 (2H, s), 7.05 (2H, s), 7.22 (1H, d, *J*= 1.8 Hz), 7.23 (1H, d, *J*= 1.8 Hz); δ_{C}
309 168.1, 167.6, 166.5]. Overall, shift values were very similar to 1,2,6-tri-*O*-galloyl- β -D-
310 glucopyranose (Owen et al., 2003), except for split proton signals [δ_{H} 7.22 (1H, d, *J*= 1.8 Hz),
311 7.23 (1H, d, *J*= 1.8 Hz)] and an additional methoxy group [δ_{H} 3.89 (3H, s)]. Position of the
312 latter was located by a HMBC cross-peak to C-3^{'''}. The sugar was determined to be β -D-
313 glucopyranose by a large coupling constant of the anomeric proton [δ_{H} 5.92 (1H, d, *J*= 8.4 Hz)],
314 by NOESY correlations, and by comparing NMR data with the literature (Owen et al., 2003).
315 GC-MS analysis of the hydrolysis product in comparison to authentic sugars also supported this
316 conclusion. Therefore, the structure of **20** was determined as 1,2-di-*O*-galloyl-6-(3-
317 methoxygalloyl)-*O*- β -D-glucopyranose.

318 The known compounds were identified as frangufoline (**6**) (Han et al., 1990), sanjoinine
319 (**7**) (Han et al., 1990), antidesmone (**9**) (Bringmann et al., 2000b), 17-*O*-(β -D-
320 glucopyranosyl)antidesmone (**10**) (Buske et al., 2001), waltherione F (**11**) (Cretton et al., 2014),
321 aristolochic acid A (**12**) (Cai and Cai, 2010), α -linolenic acid (**13**) (Lee et al., 2016), linoleic
322 acid (**14**) (Lee et al., 2016), *p*-hydroxyphenylethyl *trans*-ferulate (**15**) (Darwish and Reinecke,
323 2003), 5'-demethoxycarolignan Z (**18**) (Bouzeroune et al., 2016), syringaresinol (**19**) (An et
324 al., 2016), 1,3,6-tri-*O*-galloyl- β -D-glucopyranose (**21**) (Yoshida et al., 1984), 1,2,4,6-tetra-*O*-
325 galloyl- β -D-glucopyranose (**22**) (Tanaka et al., 1985), acetonylgranatin B (**23**) (Tanaka et al.,
326 1992), acetonylheliocopin A (**24**) (Tanaka et al., 1992), acetonylterchebin (**25**) (Tanaka et
327 al., 1992), acetonylcarpinusin (**26**) (Tanaka et al., 1992), 1-*O*- β -D-(2,4-dihydroxy-6-
328 methoxyphenyl)-6-*O*-(4-hydroxy-3,5-dimethoxybenzoyl)-glucopyranose (**27**) (Bicker et al.,
329 2009), 4-hydroxy-2-methoxyphenyl-6-*O*-syringoyl- β -D-glucopyranoside (**28**) (Hiltunen et al.,
330 2006), mangiferin (**29**) (Martin et al., 2008), quercitrin (**30**) (Abdullaeva et al., 2016), rutin (**31**)
331 (Kiyekbayeva et al., 2018), pectolinarin (**32**) (Peng, 2011), and vitexin (**33**) (Torres-Tapia et
332 al., 2013) by comparing their NMR spectroscopic data with those reported in literature.

333 2.2. The anti-advanced glycation endproducts (AGE) activity of isolated compounds

334 As they were available in sufficient amount, fourteen of the isolated natural products were
335 investigated for their anti-AGEs activity. The substances were evaluated in a concentration

336 range of 1 μM to 3 mM in comparison with the positive control (aminoguanidine: IC_{50} 1.4 mM).
337 Among them, ellagitannins **23-26**, the phenylpropanoid **15**, and the quercetin glycosides **30-31**
338 exhibited moderate inhibition of AGEs formation (Table 4). Rutin (**31**, IC_{50} 100 μM) has
339 already been described as an AGEs inhibitor (Séro et al., 2013). Among the now tested
340 compounds, *p*-hydroxyphenylethyl *trans*-ferulate (**15**), with two additional phenolic groups,
341 was the second most potent inhibitor (IC_{50} 150 μM), still being ten times more active than the
342 positive control. Also, the ellagitannins with IC_{50} values of 200 μM emerged as potential anti-
343 AGEs, possibly due to many reducing phenolic groups in their structure. Indeed, using the same
344 assay, many antioxidant polyphenols inhibited AGEs formation, most likely through their
345 antioxidant potential (Rouger et al., 2015). As AGE formation is involved in many ailments,
346 including joint diseases (Séro et al., 2013), this bioactivity might contribute to the traditional
347 use of *A. bunius* against rheumatoid arthritis.

348

349 **3. Conclusions**

350 Phytochemical investigations on the aerial parts of *Antidesma bunius* led to the isolation
351 and identification of 33 compounds, including nine previously undescribed compounds. Their
352 planar chemical structures and absolute configurations were determined by a combination of
353 ECD simulation, NMR calculation, and other chemical modification methods. The results
354 revealed that *A. bunius* aerial parts contain unusual natural compound classes, such as
355 cyclopeptides and coumarinolignans. The advanced glycation endproducts (AGE) inhibition
356 bioassay was employed to evaluate bioactivity of some of the isolated compounds, in which
357 rutin and *p*-hydroxyphenethyl *trans*-ferulate were the most active compounds with IC_{50} below
358 0.2 mM.

359 *A. bunius* is a popular medicinal plant in Asia, and the present study indicated that it is
360 a source of structurally uncommon compounds, so that it definitely deserves more scientific
361 attention in the future.

362

363 **4. Experimental**

364 *4.1. General experimental procedures*

365 Optical rotations were measured on a J-715 spectropolarimeter (Jasco, Japan) in a 10.0
366 cm tube, using the suitable solvent for each compound (MeOH or CHCl_3). IR spectra were

367 recorded on an Alpha FTIR spectrometer (Bruker), and ECD spectra on a J-1500
368 spectropolarimeter (JASCO, Japan). NMR experiments were carried out on an Avance II (600
369 MHz, Bruker, USA) using tetramethylsilane (TMS) as internal standard (Euriso-Top, France).
370 HRESIMS spectra were recorded on a micrOTOF-Q II (Bruker) operated by Hystar software.
371 For fractionation a Reveleris[®] system (Buchi, Switzerland) with detection wavelengths always
372 set to 205, 254, and 280 nm, or open columns filled with silica-gel, RP-18 material or Sephadex
373 LH-20 (Sigma-Aldrich, USA) were used. Final purifications were sometimes conducted on a
374 semi-preparative Dionex HPLC system, equipped with a P580 pump, ASI 100 automated
375 sample injector, UVD 170 U detector, and Gilson Ambimed 206 fraction collector, using a
376 Phenomenex Synergi 4u MAX-RP 80A column (250 × 10 mm, 4 μm particle size). The flow
377 rate was always set at 2.00 mL/min. All solvents required for extraction and isolation were
378 purchased from VWR (Austria). Ultrapure water was produced by a Sartorius arium 611 UV
379 system (Germany).

380 4.2. Plant material

381 *Antidesma bunius* (L.) Spreng. (Euphorbiaceae) aerial parts were collected in Ba Vi,
382 Hanoi, Vietnam (GPS: 21°03'60.0"N, 105°20'3.0"E) in January 2018. The sample was
383 authenticated by M.Sc. Duc Trong Nghiem from the Department of Botany, Hanoi University
384 of Pharmacy, Hanoi, Vietnam. A voucher specimen (2018/01-AB) is deposited at the Institute
385 of Pharmacy/ Pharmacognosy, University of Innsbruck, Innsbruck, Austria.

386 4.3. Extraction and isolation

387 The dried and powdered aerial parts of *A. bunius* (0.9 kg) were extracted with MeOH (2
388 L × 3 times × 2h) in an ultrasonic bath, and the combined extracts were evaporated under
389 reduced pressure to obtain 80.3 g of green residue. The crude extract was suspended in distilled
390 water (1 L), and then partitioned with EtOAc and *n*-BuOH (each 1 L × 3 times). The organic
391 solvent layers were evaporated *in vacuo* to obtain respective portions.

392 The EtOAc-soluble extract (22.3 g) was fractionated on a silica gel column (8 × 15 cm,
393 40-63 μm), eluting with a gradient of petroleum ether (PE) and acetone (from 20:1 to 0:1),
394 which resulted in 16 fractions (ABE 1-16). Fraction ABE 4 (1.5 g) was further purified on a
395 normal-phase silica gel flash column (40 g NP cartridge, 0-50 min: 0-10% acetone in PE, 50-
396 90 min: 10-20% acetone in PE, flow rate 8 mL/min), to obtain subfractions ABE 4.1-3. Fraction
397 ABE 4.1 was subjected to a C₁₈ flash column (12 g RP cartridge, 0-50 min: 60-85% MeOH,
398 50-85 min: 85-90% MeOH, flow rate 10 mL/min) to yield compounds **13** (11.0 mg) and **14**
399 (41.6 mg). Fraction ABE 10 (0.3 g) was also further fractionated using a 12g C₁₈ cartridge (0-

400 40 min: 80-100% MeOH, 40-65 min: 100% MeOH, flow rate 7 mL/min) to obtain subfractions
401 ABE 10.1-4. Preparative HPLC was employed to purify subfractions ABE 10.3 (52 mg, 0-30
402 min: 55-70% CH₃CN) and 10.4 (44 mg, 0-35 min: 65-80% CH₃CN) to yield in compounds **8**
403 (1.4 mg) and **11** (4.0 mg), respectively. Fraction ABE 11 (0.5 g) was separated by flash
404 chromatography (12g C₁₈ cartridge, 0-40 min: 30-60% MeOH, 40-85 min: 60-85% MeOH, 85-
405 105 min: 85-90% MeOH, flow rate 8 mL/min) to afford subfractions ABE 11.1-4. Fraction
406 ABE 11.3 (75 mg), which revealed four major peaks in the HPLC chromatogram, was purified
407 by preparative HPLC, using 65% CH₃CN as eluent, to obtain compounds **1** (2.1 mg), **2** (1.5
408 mg), **3** (1.2 mg), and **9** (1.5 mg). Fraction ABE 12 (0.6 g) was first fractionated on a flash
409 column (12 g RP cartridge, 0-40 min: 40-70% MeOH, 40-80 min: 70-100% MeOH, flow rate
410 8 mL/min). Fraction ABE 12.3 (0.3 g) was selected for further purification using size-exclusion
411 chromatography (Sephadex LH-20, MeOH as eluent, 1 × 35 cm), resulting in subfractions ABE
412 12.3.1-6. By preparative HPLC, compounds **4** (1.5 mg), **5** (1.6 mg), and **7** (2.4 mg) from ABE
413 12.3.3 (63 mg, 0-40 min: 55-85% CH₃CN), as well as compound **12** (2.3 mg) from ABE 12.3.6
414 (32 mg, 0-30 min: 45-56% CH₃CN) could be obtained. Another fraction, ABE 14 (1.2 g), was
415 separated on a RP-C₁₈ flash column (12 g RP cartridge, 0-40 min: 30-65% MeOH, 40-60 min:
416 65-80% MeOH, flow rate 8 mL/min) to obtain seven subfractions (ABE 14.1-7). Subfraction
417 ABE 14.4 (85 mg) was purified by preparative HPLC (0-24 min: 30-40% CH₃CN) to yield
418 compounds **15** (24.7 mg) and **19** (2.8 mg). In the acetone solution of ABE 14.7 a white
419 precipitate appeared. It was removed by centrifugation and washed with cold acetone to obtain
420 compound **6** (5.0 mg); the remaining solution was subjected to a Sephadex LH-20 column (1 ×
421 35 cm, CH₂Cl₂ : acetone = 85:15 as eluent). Out of the seven subfractions collected, compounds
422 **16** (2.1 mg) and **17** (1.6 mg) were isolated by prep. HPLC (0-40 min: isocratic 40% CH₃CN)
423 from ABE 14.7.5 (48 mg); subfraction ABE14.7.7 (55 mg) yielded compound **18** (0-30 min:
424 47-56% CH₃CN). Next, ABE 16 (4.2 g) was fractionated by Reveleris flash chromatography
425 (80 g RP cartridge, 0-30 min: 5-30% MeOH, 30-110 min: 30-80% MeOH, flow rate 15 mL/min)
426 into subfractions ABE 16.1-8. ABE 16.3 (1.3 g) was further separated on a Sephadex LH-20
427 column (1 × 35 cm, MeOH) into seven subfractions (ABE 16.3.1-7). Based on HPLC analysis,
428 ABE 16.3.5 and ABE 16.3.7 were chosen for further purification. Subfraction ABE 16.3.5 (0.3
429 g) was subjected to a smaller RP-C₁₈ flash column (12 g RP cartridge, 0-50 min: 10-20% ACN,
430 50-70 min: 20-25% MeOH, flow rate 7 mL/min) to obtain compound **21** (6.7 mg), and fraction
431 ABE 16.3.5.4 (60 mg) was purified by preparative HPLC (0-35 min: 15-24% CH₃CN) to yield
432 compounds **20** (3.1 mg) and **24** (3.1 mg). Subfraction ABE 16.3.7 (0.3 g) was first resolved by
433 flash chromatography (12 g RP cartridge, 0-50 min: 10-20% CH₃CN, 50-70 min: 20-22%

434 CH₃CN, flow rate 7 mL/min), before being subjected to preparative HPLC (0-35 min: 18-23 %
435 CH₃CN), to afford compounds **22** (2.1 mg), **23** (3.8 mg), and **26** (5.0 mg). Additionally,
436 fractions ABE 16.4 (0.3 g) and ABE 16.5 (0.4 g) were purified by Sephadex LH-20 (1 × 35 cm,
437 MeOH as eluent) to obtain compounds **25** (29.7 mg) and **27** (14.5 mg), as well as compound **30**
438 (6.1 mg).

439 The *n*-BuOH soluble part (19.6 g) was initially fractionated on an open silica gel column
440 (8 × 15 cm, 40-63 μm), using stepwise gradient elution with EtOAc and MeOH (ratio from 20:1
441 to 0:1) to obtain 10 fractions (ABB 1-10). Fraction ABB 3 (1.2 g) was separated by flash
442 chromatography (12 g RP cartridge, 0-50 min: 10-50% MeOH, 50-90 min: 50-75% MeOH,
443 flow rate 10 mL/min), and then compound **28** (2.9 mg) purified using Sephadex LH-20 material
444 (1 × 35 cm column, MeOH). Fraction ABB 5 (1.5 g) was first divided into 11 subfractions
445 (ABB 5.1-11) on a C₁₈ Reveleris column (12 g RP cartridge, 0-50 min: 10-50% MeOH, 50-85
446 min: 50-80% MeOH, flow rate 10 mL/min). Subfraction ABB 5.7 (0.5 g) was submitted to a
447 Sephadex LH-20 column (1 × 35 cm, MeOH) to obtain five further fractions (ABB 5.7.1-5). In
448 the methanolic solution of ABB 5.7.4, white crystals formed at the bottom of vial. They were
449 filtered and washed with cold MeOH to yield compound **29** (2.1 mg). Subfraction ABB 5.8 was
450 purified by Sephadex LH-20 column chromatography (1 × 35 cm, MeOH), before compound
451 **33** (1.6 mg) could be isolated by preparative HPLC (0-30 min: 15-24 % CH₃CN). Subfraction
452 ABB 5.11 (0.1 g) was also purified using preparative HPLC (0-30 min: 25-34 % CH₃CN) to
453 obtain compound **32** (1.6 mg). Another fraction, ABB 7 (1.2 g), was initially fractionated by
454 flash chromatography (12 g RP cartridge, 0-50 min: 10-50% MeOH, 50-90 min: 50-80%
455 MeOH, flow rate 10 mL/min), then on Sephadex LH-20 material (1 × 35 cm, MeOH), and
456 finally subjected to preparative HPLC (0-31 min: 13-22 % CH₃CN), resulting in the isolation
457 of compound **31** (2.3 mg). The same approach was utilised to isolate compound **10** (6.2 mg)
458 from fraction ABB 8 (1.3 g), however using a slightly modified HPLC gradient (0-35 min: 20-
459 30 % CH₃CN).

460 4.3.1. *Buniusine A (1)*

461 White amorphous powder; $[\alpha]_D^{20} +81.0$ (*c* 0.05, CHCl₃); UV (CH₂Cl₂) λ_{\max} (log ϵ) 228
462 (4.42), 321 (4.05) nm; ECD (CH₃CN) λ_{\max} ($\Delta\epsilon$) 192 (+6.21), 210 (-2.11), 221 (-4.82), 249
463 (+3.88), 279 (-2.71), 326 (+6.66); IR ν_{\max} 3414, 2927, 1712, 1397, 1121, 1033, 734 cm⁻¹; ¹H
464 and ¹³C NMR data, see Table 1; HRESIMS *m/z* 565.2424 [M-H]⁻ (calcd for C₃₂H₃₇O₉,
465 565.2443).

466 4.3.2. *Buniusine B (2)*

467 White amorphous powder; $[\alpha]_D^{20}$ -11.3 (*c* 0.08, CHCl₃); UV (CH₂Cl₂) λ_{\max} (log ϵ) 228
 468 (4.21), 323 (3.82) nm; ECD (CH₃CN) λ_{\max} ($\Delta\epsilon$) 206 (+3.76), 215 (+1.90), 246 (-3.59), 281
 469 (+3.28), 325 (-3.83); IR ν_{\max} 3434, 3393, 2927, 2822, 1397, 1139, 1064, 734 cm⁻¹; ¹H and ¹³C
 470 NMR data, see Table 1; HRESIMS *m/z* 565.2419 [M-H]⁻ (calcd for C₃₂H₃₇O₉, 565.2443).

471 4.3.3. *Buniusine C (3)*

472 White amorphous powder; $[\alpha]_D^{20}$ -19.5 (*c* 0.06, CHCl₃); UV (CH₂Cl₂) λ_{\max} (log ϵ) 227
 473 (4.21), 323 (3.81) nm; ECD (CH₃CN) λ_{\max} ($\Delta\epsilon$) 206 (+4.04), 214 (+6.67), 238 (-3.61), 309 (-
 474 5.20); IR ν_{\max} 3393, 2925, 1710, 1397, 1137, 1065, 735 cm⁻¹; ¹H and ¹³C NMR data, see Table
 475 1; HRESIMS *m/z* 589.2433 [M+Na]⁺ (calcd for C₃₂H₃₈O₉Na, 589.2408).

476 4.3.4. *Buniusamide A (4)*

477 Yellowish amorphous powder; $[\alpha]_D^{20}$ -188.9 (*c* 0.08, CHCl₃); UV (CH₂Cl₂) λ_{\max} (log ϵ)
 478 228 (4.52); ECD (CH₃CN) λ_{\max} ($\Delta\epsilon$) 200 (-16.62), 212 (+9.06), 243 (-26.38); IR ν_{\max} 3391,
 479 3292, 3052, 3032, 1673, 1451, 1183, 732, 697 cm⁻¹; ¹H and ¹³C NMR data, see Table 2;
 480 HRESIMS *m/z* 531.3018 [M-H]⁻ (calcd for C₃₁H₃₉N₄O₄, 531.2977).

481 4.3.5. *Buniusamide B (5)*

482 White amorphous powder; $[\alpha]_D^{20}$ -61.0 (*c* 0.08, CHCl₃); UV (CH₂Cl₂) λ_{\max} (log ϵ) 227
 483 (4.42); ECD (CH₃CN) λ_{\max} ($\Delta\epsilon$) 203 (-5.44), 217 (+7.09), 239 (-45.73); IR ν_{\max} 3391, 3291,
 484 2958, 2926, 1656, 1621, 1599, 1417, 1227, 732, 697 cm⁻¹; ¹H and ¹³C NMR data, see Table 2;
 485 HRESIMS *m/z* 619.2909 [M-H]⁻ (calcd for C₃₇H₃₉N₄O₅, 619.2926).

486 4.3.6. *5S-hydroxyantidesmone (8)*

487 White amorphous powder; $[\alpha]_D^{20}$ +8.1 (*c* 0.07, CHCl₃); UV (CH₂Cl₂) λ_{\max} (log ϵ) 247
 488 (4.16), 336 (3.47) nm; ECD (CH₃CN) λ_{\max} ($\Delta\epsilon$) 211 (+12.50), 232 (-23.93), 316 (-10.71), 353
 489 (+24.53), 367 (+24.80); IR ν_{\max} 3217, 2923, 2853, 1698, 1611, 1548, 1271, 1165 cm⁻¹; ¹H NMR
 490 (CDCl₃, 600 MHz) δ_{H} 2.16 (1H, m, H-6a), 2.37 (1H, m, H-6b), 2.59 (1H, ddd, *J*= 4.2, 15.0,
 491 18.6 Hz, H-7a), 2.76 (1H, ddd, *J*= 3.0, 4.2, 18.6 Hz, H-7b), 1.71 (1H, m, H-11a), 2.12 (1H, m,
 492 H-11b), 1.41 (1H, m, H-12a), 1.68 (1H, m, H-12b), 1.31 (2H, m, H-13), 1.28 (2H, m, H-14),
 493 1.29 (2H, m, H-15), 1.25 (2H, m, H-16), 1.28 (2H, m, H-17), 0.87 (3H, t, *J*= 6.6 Hz, H-18),
 494 3.95 (3H, s, OMe), 6.86 (1H, s, OH), 8.79 (1H, s, NH); ¹³C NMR (CDCl₃, 150 MHz) δ_{C} 139.3
 495 (C-2), 148.5 (C-3), 175.2 (C-4), 72.7 (C-5), 32.4 (C-6), 34.3 (C-7), 193.6 (C-8), 131.2 (C-9),

496 137.5 (C-10), 38.1 (C-11), 23.9 (C-12), 30.2 (C-13), 29.7 (C-14), 29.4 (C-15), 32.0 (C-16), 22.8
 497 (C-17), 14.2 (C-18), 14.9 (2-Me), 59.8 (3-OMe); HRESIMS m/z $[M-H]^-$ 334.2007 (calcd for
 498 $C_{19}H_{28}NO_4$, 334.2024).

499 4.3.7. (7*R*,7'*R*,7''*R*,8*S*,8'*S*,8''*S*)-9''-feruloyl-4',4''-dihydroxy-3,3',3'',5-tetramethoxy-7,9':7',9'-
 500 diepoxy-4,8''-oxy-8,8'-sesquieolignan-7''-ol (**16**)

501 White amorphous powder; $[\alpha]_D^{20}$ +1.2 (*c* 0.05, $CHCl_3$); UV (CH_2Cl_2) λ_{max} (log ϵ) 228
 502 (4.56), 286 (4.27), 320 (4.28) nm; IR ν_{max} 3444, 2926, 2853, 1700, 1634, 1514, 1267 cm^{-1} ; ECD
 503 (CH_3CN) λ_{max} ($\Delta\epsilon$) 208 (-1.44), 220 (+1.19), 230 (-1.23), 245 (+4.50), 292 (+2.74), 324
 504 (+2.50); 1H and ^{13}C NMR data, see Table 3; HRESIMS m/z 759.2651 $[M-H]^-$ (calcd for
 505 $C_{41}H_{43}O_{14}$, 759.2658).

506 4.3.8. (7*S*,7'*S*,7''*S*,8*R*,8'*R*,8''*S*)-9''-feruloyl-4',4''-dihydroxy-3,3',3'',5-tetramethoxy-7,9':7',9'-
 507 diepoxy-4,8''-oxy-8,8'-sesquieolignan-7''-ol (**17**)

508 White amorphous powder; $[\alpha]_D^{20}$ +2.5 (*c* 0.08, $CHCl_3$); UV (CH_2Cl_2) λ_{max} (log ϵ) 228
 509 (4.56), 285 (4.29), 320 (4.31) nm; IR ν_{max} 3445, 2929, 2853, 1702, 1633, 1592, 1265, 1123,
 510 1055, 733, 701 cm^{-1} ; ECD (CH_3CN) λ_{max} ($\Delta\epsilon$) 209 (+3.83), 231 (+0.36); 1H and ^{13}C NMR
 511 data, see Table 3; HRESIMS m/z 759.2636 $[M-H]^-$ (calcd for $C_{41}H_{43}O_{14}$, 759.2658).

512 4.3.9. 1,2-di-*O*-galloyl-6-(3-methoxygalloyl)-*O*- β -*D*-glucopyranose (**20**)

513 Brownish gum; $[\alpha]_D^{20}$ -52.4 (*c* 0.05, MeOH); UV (MeOH) λ_{max} (log ϵ) 218 (4.61), 277
 514 (4.24) nm; IR ν_{max} 3252 (br), 2947, 2840, 1700, 1606, 1317, 1194, 1005, 760 cm^{-1} ; 1H NMR
 515 (MeOH-*d*₄, 600 MHz) δ_H 5.92 (1H, d, *J* = 8.4 Hz, H-1), 5.22 (1H, dd, *J* = 8.4, 9.6 Hz, H-2), 3.82
 516 (1H, m, H-3), 3.62 (1H, t, *J* = 9.6 Hz, H-4), 3.86 (1H, m, H-5), 4.41 (1H, dd, *J* = 5.4, 12.0 Hz,
 517 H-6a), 4.67 (1H, dd, *J* = 1.8, 12.0 Hz, H-6b), 7.01 (2H, s, H-2', 6'), 7.05 (2H, s, H-2'', 6''), 7.22
 518 (1H, d, *J* = 1.8 Hz, H-2'''), 7.23 (1H, d, *J* = 1.8 Hz, H-6'''), 3.89 (3H, s, OMe); ^{13}C NMR (MeOH-
 519 *d*₄, 150 MHz) δ_C 94.1 (C-1), 74.2 (C-2), 76.1 (C-3), 71.7 (C-4), 76.6 (C-5), 64.6 (C-6), 120.0
 520 (C-1'), 110.5 (C-2', 6'), 146.5 (C-3', 5'), 140.6 (C-4'), 166.5 (C-7'), 121.1 (C-1''), 110.4 (C-2'',
 521 6''), 146.4 (C-3'', 5''), 140.0 (C-4''), 167.6 (C-7''), 121.3 (C-1'''), 106.3 (C-2'''), 149.2 (C-3'''),
 522 140.7 (C-4'''), 146.3 (C-5'''), 112.0 (C-6'''), 168.1 (C-7'''), 56.7 (OMe); HRESIMS m/z 649.1051
 523 $[M-H]^-$ (calcd for $C_{28}H_{25}O_{18}$, 649.1046).

524 4.4. Acid hydrolysis and GC/MS

525 Compound **20** (2.0 mg) and 1 mL HCl 1N in MeOH were stirred for 3 h at 60 °C in a
 526 sand bath. The reaction mixture was neutralized with sodium bicarbonate and partitioned with

527 EtOAc (3 times \times 1 mL); the water layer was dried to obtain 0.7 mg of sugar fraction for
528 analysis.

529 The sugar fraction was derivatized with L-cysteine methyl ester hydrochloride (1.5 mg in
530 200 μ L pyridine, 60°C, 1 h), subsequently silylated with BSTFA and TMCS (99:1, v/v)
531 (200 μ L, 60°C, 1 h), and then analyzed by GC-MS. Reference compounds D-glucose (t_R =
532 77.31 min) and L-glucose (t_R = 77.59 min) were derivatized and analyzed using the same
533 protocol. D-glucose was detected in **20**. GC-MS analyses were carried out on an Agilent 5975C
534 Series GC/MSD System comprising a 7693 autosampler, a Triple AxisDetector (MS), and a
535 7890A GC. An Agilent HP-5MS column (30 m \times 250 μ m \times 0.25 μ m) was used for analysis, the
536 other settings were as follows: temperature gradient: 70°C for 2 min, then 2°C/min to 150°C
537 (hold 150°C for 2 min), then 5°C/min to 220°C (hold 220°C for 15 min), then 15°C/min to
538 300°C (hold 300°C for 10 min); total run time: 88 min; injection volume: 1 μ L; split ratio 10: 1;
539 carrier gas: helium; flow rate: 7.5 mL/min.

540 4.5. Calculation of ECD spectra

541 The 3D structure of selected compounds was subjected to MacroModel 9.1 (Schrödinger.
542 LLC, USA) to perform conformational analysis (parameters: MMFF force field; gas phase;
543 maximum iterations: 10,000; maximum number of steps: 10,000; energy window: 5 kcal/mol).
544 Conformers occurring in an energy window of 5 kcal/mol were subjected to geometry
545 optimization and energy calculation using first DFT/B3LYP/6-31G (d) in the gas phase and
546 then DFT/B3LYP/6-31G+(d,p)/CPCM in acetonitrile with Gaussian 16 (M. J. Frisch et al.,
547 2016). No imaginary frequencies were observed for the optimized structures. Calculation of
548 excitation energy (nm), rotatory strength, dipole velocity (R_{vel}) and dipole length (R_{len}) were
549 performed by TD-DFT/cam-B3LYP/6-31G+(d,p)/CPCM (acetonitrile) for **1-3** and **8**, and TD-
550 DFT/B3LYP/6-31G+(d,p)/CPCM (acetonitrile) for **4** and **5**. ECD curves were extracted by
551 SpecDis v.1.7 software with a half-band of 0.2-0.3 eV (Bruhn et al., 2017). The Boltzmann-
552 averaged ECD spectra were shifted \pm 25 nm in the UV range, and then compared with the
553 experimental results.

554 4.6. Calculation of NMR chemical shifts and DP4+ probability analysis

555 Diastereomers of **1**, **2** and **5** were subjected to conformational analysis in the gas phase
556 (as mentioned in section 4.5). The conformers occurring in the energy window of 5 kcal/mol
557 were subjected to geometry optimization using DFT/B3LYP/6-31G(d) in the gas phase with
558 Gaussian 16. NMR chemical shift calculations were performed using GIAO/mPW1PW91/6-

559 31G+(d,p)/CPCM/chloroform, shielding tensors of all conformers were Boltzmann averaged
560 and used for DP4+ probability calculation using the excel file provided by Grimblat's group
561 (Grimblat et al., 2015).

562 4.7. AGEs inhibition assay

563 Inhibition of pentosidine-like AGEs formation was measured according to a previously
564 published protocol (Séro et al., 2013). In short, depending on available sample material, stock
565 solutions (SS) were prepared in DMSO at concentrations of 10 or 30 mM, respectively. These
566 SS were then diluted with 50 mM phosphate buffer (pH: 7.4) yielding working solutions (WS)
567 at a concentration range of 10^{-5} to $3 \cdot 10^{-2}$ mol/L. Ten microliter of each WS were deposited in
568 96 black well bottom plates (Fisher Scientific, Illkirch, France) and mixed with 90 μ L of a
569 solution containing BSA (11 mg/L), D-ribose (0.55 M), and phosphate buffer (50 mM, NaN_3
570 0.02%, pH 7.4). Plates were then incubated for 24 h at 37°C before measuring their fluorescence
571 (λ_{exc} : 335 nm, λ_{em} : 385 nm) using an Infinite M200 plate reader (Tecan, Lyon, France).
572 Fluorescence resulting from the incubation, under the same BSA (final concentration: 10
573 mg/mL) and tested compound (10^{-6} to $3 \cdot 10^{-3}$ mol/L) concentrations, was subtracted for each
574 measurement. The control, *i.e.* no inhibition of AGEs formation, consisted of BSA (10 mg/mL)
575 and D-ribose (0.5 M). Results (table 1) are expressed as IC_{50} (mM) and compared with
576 aminoguanidine (positive control). Samples exhibiting an IC_{50} of more than 1 mM were
577 considered inactive. Dimethyl sulfoxide served as negative control and was processed the same
578 way as the WS.

579

580 Declaration of competing interest

581 The authors declare no competing financial interest.

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586 Appendix A. Supplementary data

587 Supplementary data (including 1D and 2D-NMR spectra, HRESIMS, and DP4+
588 probability analyses of previously undescribed compounds) to this article can be found online.

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- 749
- 750

751 **Figure and Table legends**

752

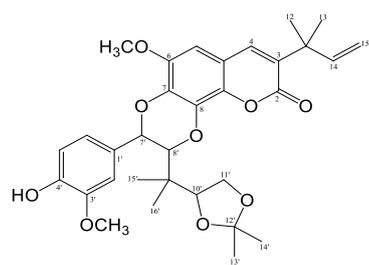
753 Fig. 1. Chemical structures of isolated compounds from *A. bunius* aerial parts.754 Fig. 2. Key HMBC (H→C) and ^1H - ^1H COSY correlations of compounds **1-5**, **8**, **16**, **17**, and **20**.755 Fig. 3. Experimental CD spectra of **1** and **2**; (B-F) Calculated and experimental ECD spectra
756 of **2**, **3**, **4**, **5**, and **8**.

757

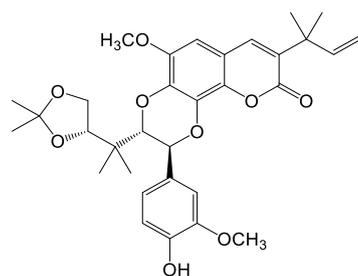
758 Table 1. NMR spectroscopic data (600 MHz, CDCl_3) for compounds **1-3**.759 Table 2. NMR spectroscopic data (600 MHz, CDCl_3) for compounds **4** and **5**.760 Table 3. NMR spectroscopic data (600 MHz, CDCl_3) for compounds **16** and **17**.761 Table 4. Anti-AGEs activity of selected natural products isolated from *A. bunius* aerial parts.

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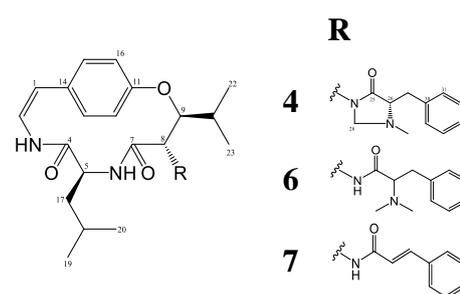
763 Fig.1



1 7'R, 8'R, 10'R
2 7'S, 8'S, 10'R



3

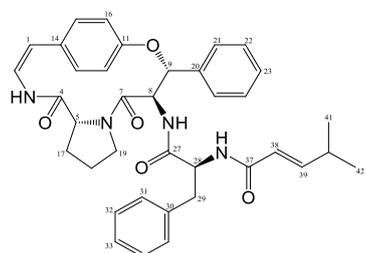
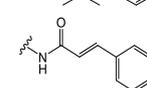
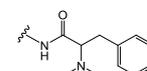
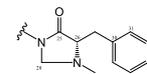


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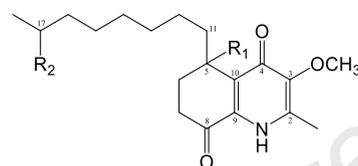
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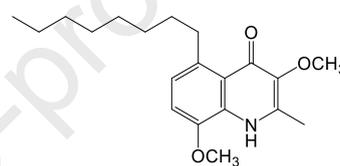
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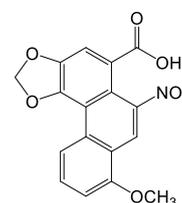
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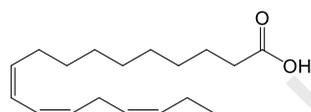
| | R₁ | R₂ |
|-----------|----------------------|----------------------|
| 8 | α -OH | H |
| 9 | β -H | H |
| 10 | β -H | O-glc |



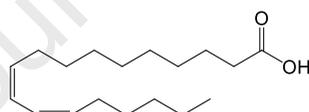
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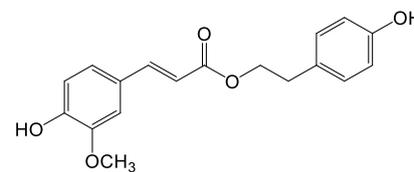
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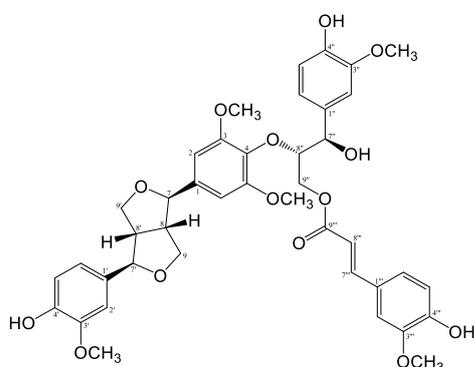
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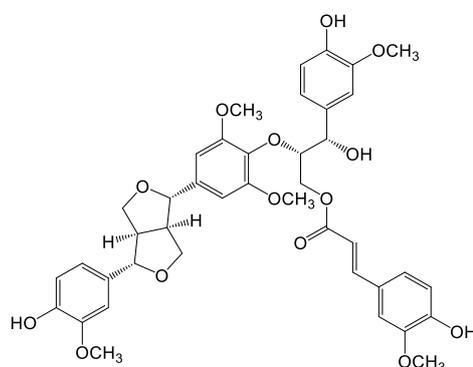
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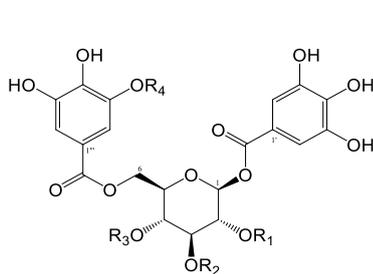
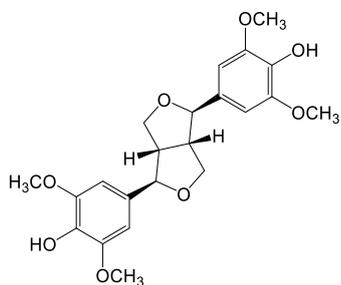
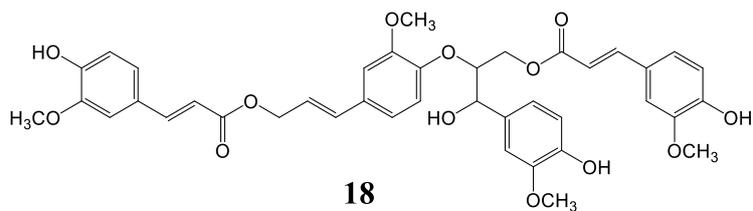
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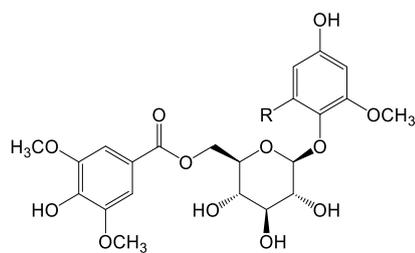
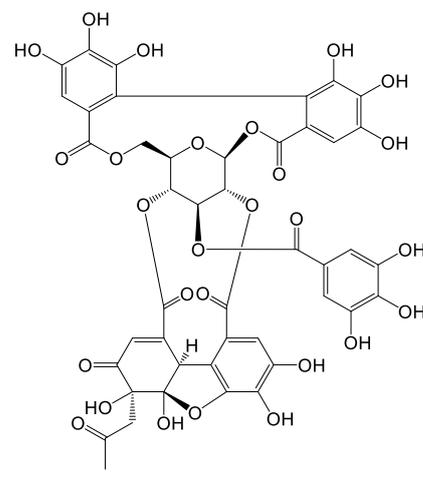
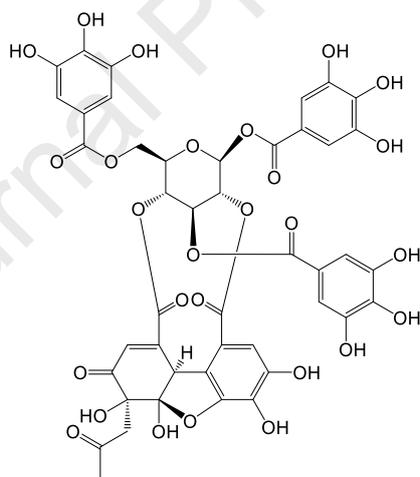
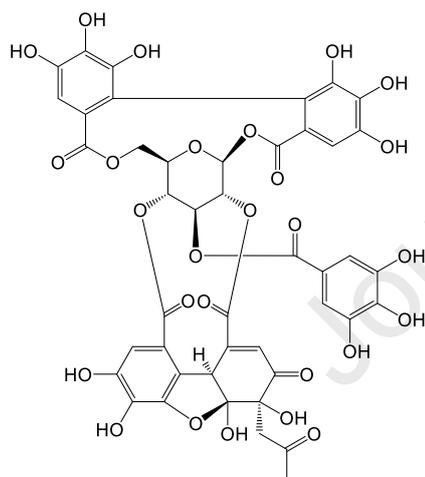
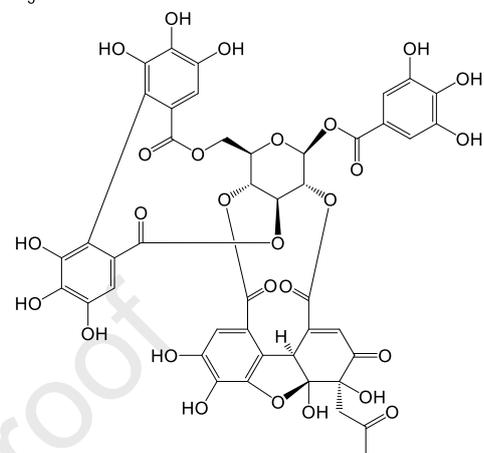
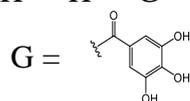
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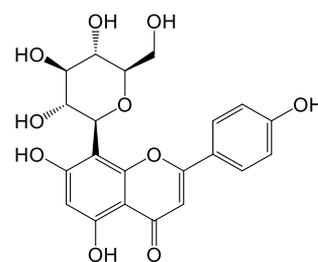
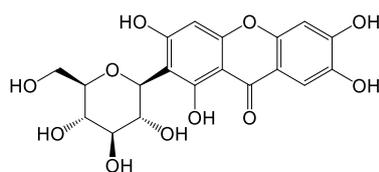
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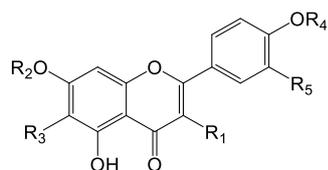


| | R₁ | R₂ | R₃ | R₄ |
|-----------|----------------------|----------------------|----------------------|----------------------|
| 20 | G | H | H | CH ₃ |
| 21 | H | G | H | H |
| 22 | H | H | G | H |



| | R |
|-----------|----------|
| 27 | OH |
| 28 | H |





| | R₁ | R₂ | R₃ | R₄ | R₅ |
|-----------|-----------------------|-----------------------|----------------------|----------------------|----------------------|
| 30 | <i>O</i> -rha | H | H | H | OH |
| 31 | <i>O</i> -glc(6→1)rha | H | H | H | OH |
| 32 | H | <i>O</i> -glc(6→1)rha | OCH ₃ | CH ₃ | H |

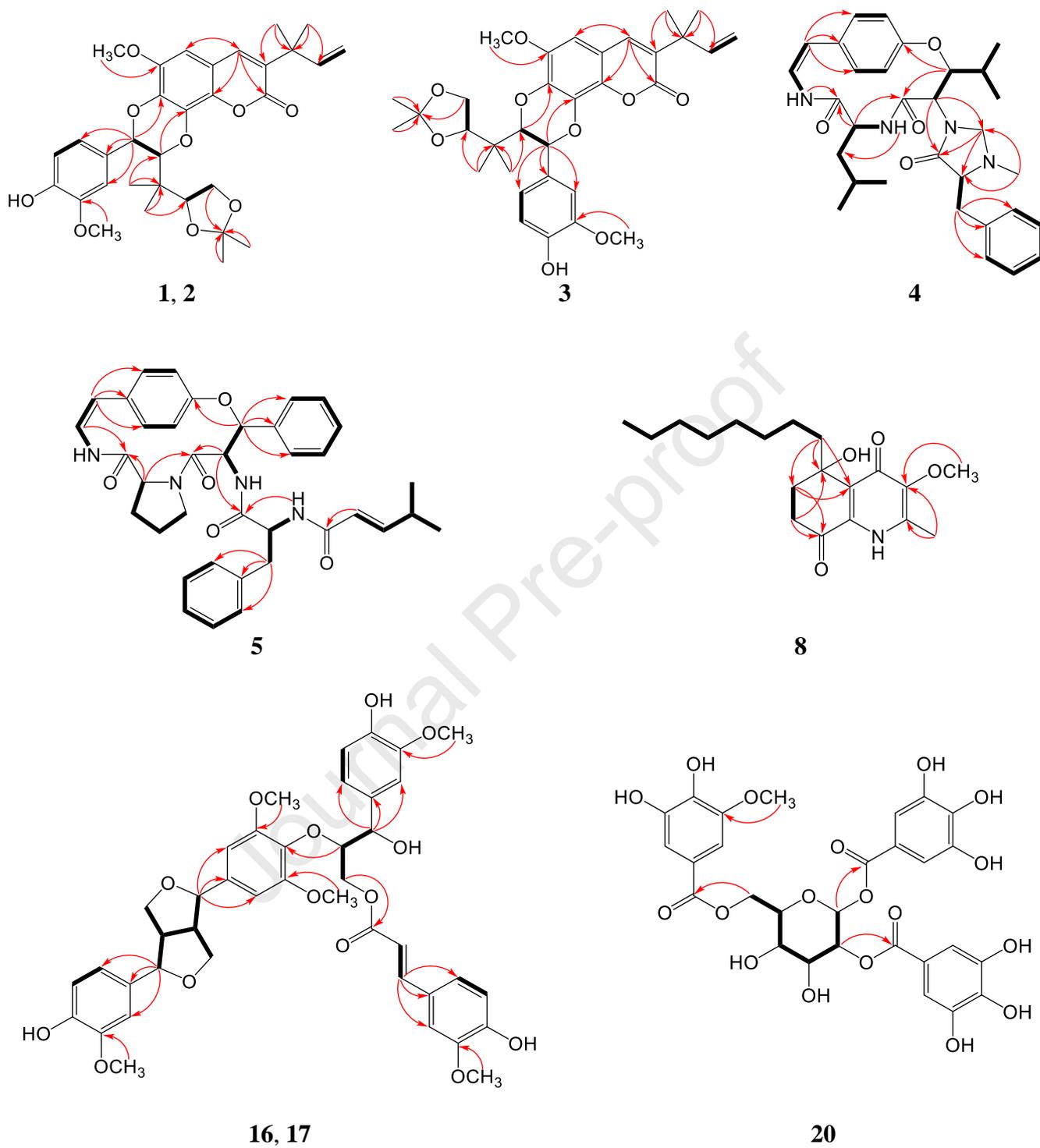
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Journal Pre-proof

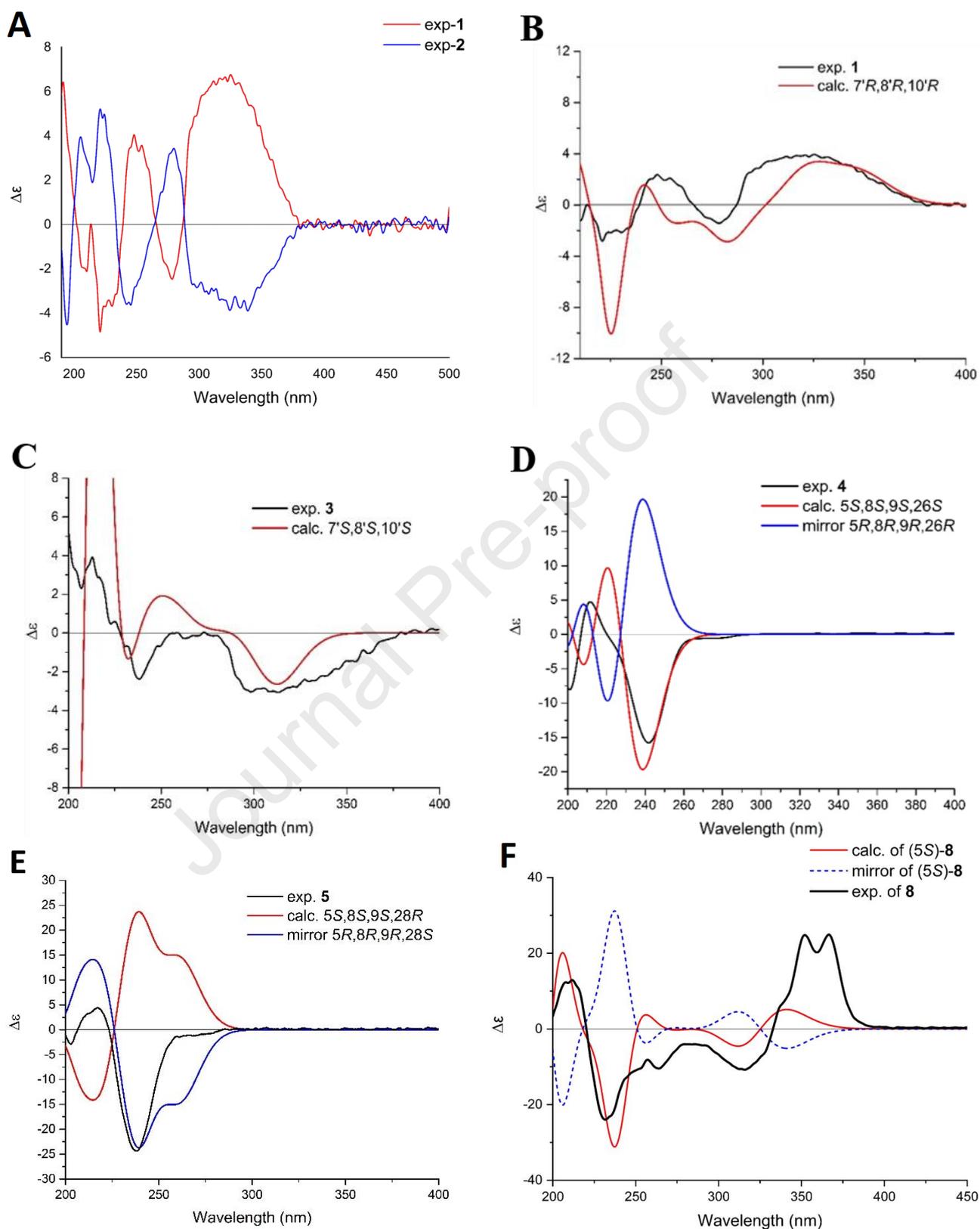
767 Fig. 2



768

769

770 Fig. 3



771

772

773 Table 1

| position | 1 | | 2 | | 3 | |
|-----------------|----------|--|----------|----------------------------------|----------|--------------------------------------|
| 2 | 159.9 | | 159.9 | | 160.1 | |
| 3 | 132.8 | | 132.8 | | 132.6 | |
| 4 | 138.1 | 7.46, s | 138.2 | 7.48, s | 138.2 | 7.45, s |
| 5 | 100.0 | 6.45, s | 100.0 | 6.47, s | 100.7 | 6.47, s |
| 6 | 145.7 | | 145.6 | | 145.8 | |
| 7 | 135.7 | | 136.5 | | 136.5 | |
| 8 | 132.0 | | 132.0 | | 131.2 | |
| 9 | 137.9 | | 138.2 | | 138.2 | |
| 10 | 112.3 | | 112.0 | | 111.8 | |
| 11 | 40.7 | | 40.7 | | 40.6 | |
| 12 ^a | 26.2 | 1.48, s | 26.2 | 1.49, s | 26.2 | 1.45, s |
| 13 ^a | 26.2 | 1.48, s | 26.2 | 1.49, s | 26.2 | 1.45, s |
| 14 | 145.8 | 6.18, dd (10.2, 17.4) | 145.8 | 6.19, dd (10.2, 17.4) | 145.8 | 6.15, dd (10.2, 17.4) |
| 15 | 112.1 | 5.09, d (12.0) 5.09, d (17.4) | 112.3 | 5.09, d (12.0) 5.09, d (17.4) | 112.3 | 5.06, d (10.2) 5.07, d (17.4) |
| 1' | 129.6 | | 129.3 | | 129.5 | |
| 2' | 110.6 | 6.91, d (1.8) | 111.2 | 6.93, d (1.8) | 110.6 | 6.92, m |
| 3' | 146.9 | | 146.7 | | 146.9 | |
| 4' | 146.5 | | 146.5 | | 146.5 | |
| 5' | 114.7 | 6.89, d (8.4) | 114.4 | 6.89, d (8.4) | 114.5 | 6.87, d (8.4) |
| 6' | 121.6 | 6.94, dd (1.8, 8.4) | 122.4 | 6.96, dd (1.8, 8.4) | 121.3 | 6.92, m |
| 7' | 76.4 | 5.22, d (5.4) | 77.8 | 5.15, d (6.6) | 75.4 | 5.22, d (4.8) |
| 8' | 80.3 | 4.36, d (5.4) | 82.2 | 4.16, d (6.6) | 80.7 | 4.36, d (4.8) |
| 9' | 40.7 | | 40.3 | | 40.9 | |
| 10' | 79.5 | 4.44, t (7.2) | 77.9 | 4.14, t (7.2) | 80.1 | 4.29, t (7.2) |
| 11' | 65.4 | 3.79, dd (7.2, 8.4) 4.09, dd (7.2, 8.4) | 65.2 | 3.70, t (8.4) 3.90, m | 65.8 | 3.78, t (8.4) 4.11, dd (6.6, 8.4) |
| 12' | 108.9 | | 108.9 | | 108.3 | |
| 13 ^b | 25.1 | 1.35, s | 25.4 | 1.27, s | 25.2 | 1.34, s |
| 14 ^b | 26.4 | 1.38, s | 26.5 | 1.37, s | 26.5 | 1.38, s |
| 15 ^c | 17.5 | 0.97, s | 19.4 | 0.87, s | 17.0 | 0.97, s |
| 16 ^c | 19.3 | 0.72, s | 21.2 | 0.95, s | 20.0 | 0.76, s |
| 6-OMe | 56.5 | 3.84, s | 56.4 | 3.84, s | 56.6 | 3.87, s |
| 3'-OMe | 56.2 | 3.87, s | 56.1 | 3.89, s | 56.2 | 3.87, s |

774 ^{a,b,c} interchangeable signals

775

776 Table 2

| position | 4 | | 5 | |
|----------|-------|-----------------------------|-------|-----------------------|
| 1 | 116.7 | 6.40, d (9.6) | 116.1 | 6.40, d (7.8) |
| 2 | 125.9 | 6.65, dd (8.4, 9.6) | 125.7 | 6.74, d (7.8) |
| 3 | | 6.38 (d, 8.4) | | 6.57, d (8.4) |
| 4 | 167.4 | | 166.5 | |
| 5 | 52.8 | 4.04, m | 59.2 | 3.85, d (7.2) |
| 6 | | 5.44, d (7.8) | | |
| 7 | 168.3 | | 170.6 | |
| 8 | 57.0 | 4.55, d (7.8) | 56.0 | 4.74, dd (7.2, 10.2) |
| 9 | 80.6 | 4.85, dd (1.8, 7.8) | 82.1 | 5.93, d (7.2) |
| 11 | 156.1 | | 155.5 | |
| 12 | 122.5 | 7.15, dd (2.4, 8.4) | 123.7 | 7.36, m |
| 13 | 131.6 | 7.04, m | 132.1 | 7.12, m |
| 14 | 132.0 | | 132.8 | |
| 15 | 130.6 | 7.03, m | 130.5 | 7.07, m |
| 16 | 123.0 | 7.11, dd (2.4, 8.4) | 123.7 | 7.24, m |
| 17 | 39.2 | 1.31, ddd (3.0, 12.0, 15.0) | 26.1 | 1.39, m |
| | | 1.78, ddd (3.0, 10.2, 15.0) | | 2.17, m |
| 18 | 24.5 | 1.21, m | 24.6 | 1.45, m |
| | | | | 1.77, m |
| 19 | 21.2 | 0.73, d (6.6) | 46.9 | 2.90, t (8.4) |
| | | | | 3.10, dt (6.6, 12.0) |
| 20 | 23.5 | 0.86, d (6.6) | 137.5 | |
| 21 | 28.9 | 1.50, m | 128.4 | 7.35, m |
| 22 | 14.7 | 0.68, d (6.6) | 128.5 | 7.24, m |
| 23 | 20.7 | 1.14, d (7.2) | 128.4 | 7.24, m |
| 24 | | | 128.5 | 7.24, m |
| 25 | 172.4 | | 128.4 | 7.35, m |
| 26 | 67.5 | 2.85, m | | 7.41, d, 9.6 |
| 27 | | | 170.9 | |
| 28 | 68.4 | 3.25, dd (1.8, 5.4) | 54.3 | 4.54, m |
| | | 4.07, d (5.4) | | |
| 29 | 35.9 | 2.94, dd (5.4, 14.4) | 36.2 | 2.81, dd (10.2, 15.0) |
| | | 3.11, dd (4.2, 14.4) | | 3.32, dd (1.8, 15.0) |
| 30 | 137.2 | | 136.4 | |
| 31,35 | 130.2 | 7.24, m | 128.8 | 7.06, m |
| 32,34 | 128.3 | 7.27, m | 128.9 | 7.21, m |
| 33 | 126.7 | 7.22, m | 126.9 | 7.11, m |
| 36 | | | | 5.80, d (7.8) |
| 37 | | | 166.5 | |
| 38 | | | 117.9 | 5.64, d (15.0) |
| 39 | | | 153.9 | 6.76, dd (6.6, 15.0) |
| 40 | | | 31.3 | 2.49, m |
| 41 | | | 21.6 | 1.14, d (6.6) |
| 42 | | | 21.6 | 1.11, d (7.2) |
| N-Me | 39.3 | 2.22, s | | |

777

778

779 Table 3

| position | 16 | | 17 | |
|----------|-----------|----------------------|-----------|-----------------------|
| 1 | 137.9 | | 137.8 | |
| 2, 6 | 103.0 | 6.61, s | 102.7 | 6.58, s |
| 3, 5 | 153.8 | | 153.0 | |
| 4 | 134.1 | | 135.9 | |
| 7 | 86.2 | 4.74, d (5.4) | 86.1 | 4.73, t (4.8) |
| 8 | 54.7 | 3.08, m | 54.7 | 3.06, m |
| 9 | 71.7 | 3.91, m | 71.7 | 3.90, m |
| | | 4.26, dd (6.6, 9.0) | | 4.26, dd (7.2, 9.0) |
| 3, 5-OMe | 56.4 | 3.87, s | 56.2 | 3.87, s |
| 1' | 132.9 | | 132.9 | |
| 2' | 108.8 | 6.89, m | 108.7 | 6.89, m |
| 3' | 146.9 | | 146.6 | |
| 4' | 145.5 | | 145.4 | |
| 5' | 114.4 | 6.89, m | 114.4 | 6.89, m |
| 6' | 119.1 | 6.82, d (7.8) | 119.1 | 6.82, dd (1.8, 7.8) |
| 7' | 85.9 | 4.76, d (5.4) | 85.9 | 4.75, d (4.8) |
| 8' | 54.2 | 3.12, m | 54.2 | 3.10, m |
| 9' | 72.3 | 3.91, m | 72.2 | 3.91, m |
| | | 4.30, m | | 4.28, dd (7.2, 9.0) |
| 3'-OMe | 56.1 | 3.91, s | 56.0 | 3.83, s |
| 4'-OH | | 5.59, s | | 5.59, s |
| 1'' | 130.9 | | 131.7 | |
| 2'' | 108.6 | 7.02, m | 109.5 | 6.88, m |
| 3'' | 146.9 | | 146.6 | |
| 4'' | 145.0 | | 145.6 | |
| 5'' | 114.2 | 6.87, m | 114.4 | 6.84, d (8.4) |
| 6'' | 119.0 | 6.76, d (7.8) | 120.3 | 6.89, m |
| 7'' | 71.7 | 4.89, d (3.6) | 74.4 | 5.10, d (8.4) |
| 8'' | 83.4 | 4.56, dt (3.6, 7.2) | 87.1 | 4.07, m |
| 9'' | 62.6 | 4.33, m | 63.8 | 4.01, m |
| | | 4.46, dd (8.4, 12.0) | | 4.53, dt (3.0, 12.6) |
| 3''-OMe | 56.1 | 3.92, s | 56.1 | 3.95, s |
| 4''-OH | | 5.53, s | | 5.53, s |
| 7''-OH | | 4.21, dd (2.4, 7.8) | | 4.67, dd (1.8, 9.6) |
| 1''' | 127.2 | | 127.2 | |
| 2''' | 109.4 | 7.00, m | 109.3 | 7.06, m |
| 3''' | 146.8 | | 146.9 | |
| 4''' | 148.1 | | 148.2 | |
| 5''' | 114.8 | 6.90, m | 114.9 | 6.93, dd (1.8, 7.8) |
| 6''' | 123.2 | 7.03, m | 123.4 | 7.07, m |
| 7''' | 144.9 | 7.51, dd (4.2, 15.6) | 145.2 | 7.56, dd (12.0, 15.6) |
| 8''' | 115.7 | 6.24, dd (1.2, 15.6) | 115.2 | 6.35, dd (3.0, 15.6) |
| 9''' | 167.2 | | 167.1 | |
| 3'''-OMe | 56.1 | 3.89, s | 56.1 | 3.91, s |
| 4'''-OH | | 5.83, s | | 5.87, s |

780

781

782 Table 4

| compound | IC₅₀ (mM) |
|--|-----------------------------|
| Frangufoline (6) | NA |
| Sanjoinenine (7) | NA |
| Antidesmone (9) | 0.7 |
| 17- <i>O</i> -(β -D-glucopyranosyl)antidesmone acid (10) | 1.0 |
| Waltherione F (11) | ^b |
| <i>p</i> -hydroxyphenylethyl <i>trans</i> -ferulate (15) | 0.15 |
| 1,3,6-tri- <i>O</i> -galloyl- β -D-glucopyranose (21) | NA |
| Acetylgranatin B (23) | 0.2 |
| Acetylhelioscopinin A (24) | 0.2 |
| Acetylterchebin (25) | 0.2 |
| Acetylcarpinusin (26) | 0.2 |
| 1- <i>O</i> - β -D-(2,4-dihydroxy-6-methoxyphenyl)-6- <i>O</i> -(4-hydroxy-3,5-dimethoxybenzoyl)-glucopyranose (27) | 0.5 |
| Quercitrin (30) | 0.2 |
| Rutin (31) | 0.10 |
| Aminoguanidine ^a | 1.4 |

783 ^areference ^bstrong fluorescence interferences, NA = not active but no fluorescence

784 interferences

785

Highlights

- A comprehensive phytochemical characterization of *Antidesma bunius* is presented.
- Nine undescribed natural products were among the 33 isolated compounds.
- They represent coumarinolignans, cyclopeptides and furofuran-type lignans.
- Their configuration was established by ECD experiments and NMR calculations.
- Some compounds indicated inhibition of advanced glycation endproducts formation.

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Conflict of interest

- none

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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