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Dihydrochalcones and Flavonolignans from *Iryanthera lancifolia*†

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An extract from the pericarps of *I. lancifolia* afforded two dihydrochalcones (**1** and **2**) and two flavonolignans (**3** and **4**), with compounds **2**−**4** being of novel structure. The antioxidant activities of compounds **1**−**4** were evaluated through the measurement of malondialdehyde production, and $Q_{1/2}$ (concentration necessary for 50% inhibition of autoxidation) data were calculated. The $Q_{1/2}$ values obtained for **1**−**4** and the standard compounds α-tocopherol and quercetin were 6.9, 4.7, 5.5, 4.8, 12.1, and 7.6 μg/mL, respectively.

Flavonolignans are considered to be biosynthesized through oxidative coupling between a flavonoid and a lignan unit. Biologically active compounds of this type have been found already in *Silybum marianum* (L.) Gaertn. (Asteraceae), such as the antihepatotoxic silybin, silycristin, and silymarin,[1] and also in *Hydnocarpus wightiana* Blume (Flacourtiaceae), which is used traditionally in the treatment of leprosy and has afforded hydnowightin and neohydnowightin.[2] Chemical studies carried out on Myristicaceae species have shown that flavonolignans are restricted to the genus *Iryanthera* and have been found so far in the fruits of *I. laevis*[3,4] and *I. grandis*[5] and in the bark of *I. ulei*[4] and *I. paraensis*.[4] In these compounds, the flavonoid part is based on a dihydrochalcone unit, while the lignan unit is, in most cases, of the diarylbutane type. The crushed leaves of *Iryanthera* species are used by the Amazonian Indians for healing seriously infected wounds and cuts, and the latex from the bark of *Iryanthera* species is mixed with warm water for treating gastric infections.[6] Myristicaceous fruits are rich in easily oxidizable fatty acids and triglycerides, and this suggests the necessity of producing antioxidant substances in these tissues in order to maintain the integrity of the seeds and thereby increase the prospects of germination. This work describes the isolation from the pericarps of *Iryanthera lancifolia* Ducke and the structure determination of the novel dihydrochalcone **2** and the novel flavonolignans **3** and **4** (designated, respectively, as iryantherins K and L), as well as the antioxidant evaluation of compounds **1**−**4**.

Results and Discussion

Dihydrochalcone **1** has been isolated previously from *I. grandis* fruits;[7] *I. laevis* fruits[3] and trunk wood;[8] *I. ulei* bark and trunk wood;[9] and *I. sagotiana* leaves, inflorescences,[10] and bark.[11] The compound was identified as 2′,4′-dihydroxy-4,6′-dimethoxydihydrochalcone by analysis of its spectral data and comparison with literature values.[7,8]

The ^{1}H NMR spectrum of dihydrochalcone **2** was slightly different from that of **1** in that it showed two doublets at δ 6.82 (J = 8.6 Hz) and 7.15 (J = 8.6 Hz) due to the protons of a *p*-disubstituted B ring and two broad singlets at δ 5.97 and 6.01 for the protons of a tetrasubstituted A ring. This spectrum also showed two triplets at δ 2.91 (J = 7.5 Hz) and 3.27 (J = 7.5 Hz), typical of a dihydrochalcone moiety, and signals due to two aromatic methoxyl groups (δ 3.77

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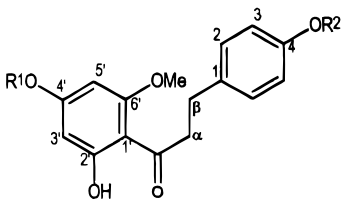
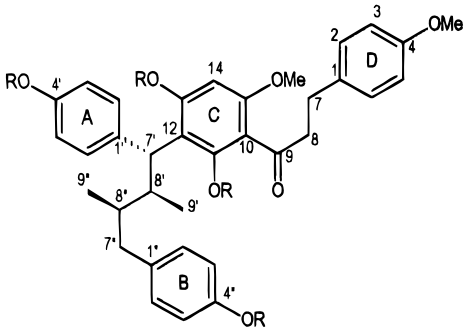


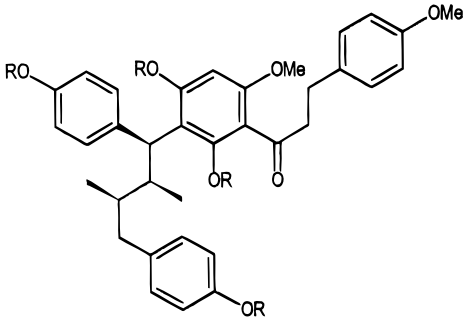
1 $R^1 = H; R^2 = Me$

2 $R^1 = Me; R^2 = H$



3 R = H

3a R = Ac



4 R = H

4a R = Ac

and 3.84) in **2**. Comparative differential NOE experiments for **1** and **2** defined the position of the methoxyl groups. Dihydrochalcone **1** had the signals for H-3 and H-5 enhanced when MeO-4 (δ 3.72) was irradiated, while dihydrochalcone **2** had the signals for H-3′ and H-5′ enhanced upon irradiation of MeO-4′ (δ 3.77). Irradiation of HO-4′ (δ 9.71) of dihydrochalcone **1** enhanced the signal for H-3′ and H-5′, but the signals due to the B ring aromatic protons of dihydrochalcone **2** were not increased when either methoxyl group of this compound was irradiated. The positions of the methoxyl groups were confirmed through observation of mass spectral prominent fragment peaks at *m*/*z* 167 (11) and 121 (100) for dihydrochalcone **1** and at *m*/*z* 181 (14) and 107 (100) for dihydrochalcone **2**.[8,10]

Flavonolignans **3** and **4** had their structures determined through analysis of their ^{1}H and ^{13}C NMR spectra (Tables 1 and 2) and by comparison with the model compounds iryantherins G and H, isolated from *I. grandis* fruits.[5] The ^{1}H NMR data (Table 1) for **3** showed absorptions of a dihydrochalcone, with two triplets at δ 2.86 (J = 7.5 Hz) and 3.16 (J = 7.5 Hz) and two doublets at ca. δ 7 due to aromatic protons. Also apparent were signals for a diarylbutane-type lignan, constituted by two doublets at δ 0.63 (J = 6.9 Hz) and 0.68 (J = 6.9 Hz) for the methyl groups at C-8″ and C-8′, two double doublets at δ 2.35 (J = 8.2, 13.4 Hz) and 2.50 (J = 6.6, 13.4 Hz), which were assigned to the H-7″ benzylic protons, and signals around δ 1.8 and 3.0 assigned to the H-8′ and H-8″ protons, respectively. The doublet at δ 4.15 (J = 11.6 Hz) was assigned to H-7′, where the flavonoid and lignan parts of the molecule are attached to each other. All assignments for the aliphatic protons in **3** were confirmed by ^{1}H−^{1}H shift-correlated NMR spectroscopy (Table 3). The structure determination of **4** was based on comparison of its ^{1}H and ^{13}C NMR spectral data with those of **3**. Significant differences were observed only for the chemical shifts of the chiral carbons C-7′, C-8′, and C-8″ as well as for protons and carbons attached to or near these chiral centers, indicating that **3** and **4** form a pair of diastereoisomers. Chemical shift assignments for the aliphatic protons of the lignan unit in **4** were based on ^{1}H−^{1}H COSY (Table 3), as well as the HMQC and HMBC data (Figure 1).

The differential NOE spectra of **3** and **4** (Figure 2) showed enhancement of signals for Me-9″ and Me-9′ when H-7′ and H-7″ were irradiated, respectively. Conversely, the H-7′ and H-7″ signals were enhanced, in turn, upon irradiation of Me-9″ and Me-9′. These observations indicated the spatial vicinity of H-7″ and Me-9′ and of a *syn*-periplanar relationship between H-7′ and Me-9″. These prerequisites, allied to the *anti*-periplanar relationship between H-7′ and H-8′, evidenced by application of the Karplus equation to their coupling constant (J = 11.0 Hz), gives the molecules of **3** and **4** a relative rigidity. This excludes stereochemical arrangements where the configurations of C-8′ and C-8″ are both *R* or both *S* and leads to only two possible alternatives, *rel*-7′*R*,8′*S*,8″*R* (I) and *rel*-7′*S*,8′*S*,8″*R* (II). Localization in the shielding cones of the A and B rings provides relative protection to Me-9′ in I and to Me-9″ in II. Hence, the ^{1}H and ^{13}C NMR chemical shifts at relatively highfield for Me-9′ in the spectra of **3**, and for Me-9″ in the spectra of **4**, enabled the configurations I and II, respectively, to be established for these compounds.

The differential NOE spectra of **3** and **4** showed additionally spatial proximity between the signals assigned to MeO-15 and H-14, to H-7′ and H-2′/H-6′, to H-7″ and H-2″/H-6″, and also to MeO-4 and H-3/H-5. These observations together with the correlations concerning aromatic protons shown in the ^{1}H−^{1}H shift-correlated spectra allowed complete assignments of the ^{1}H NMR data of compounds **3** and **4** (Table 1).

Either compound **3** or **4** has been isolated previously from *I. ulei* bark,[4] but no conclusions regarding its sterochemistry were made at the time. Comparison of the ^{13}C NMR data of its acetylated derivative with those obtained for the acetylated flavonolignans **3** and **4**, especially the signals at or near the chiral centers C-7′, C-8′, and C-8″ suggests that the flavonolignan isolated from *I. ulei* bark has the same relative stereochemistry as **4**.

The evaluation of the antioxidant activity through malondialdehyde (MDA) production[12,13] for compounds **1**−**4** indicated potent inhibitory activities ($Q_{1/2}$ 6.9, 4.7, 5.5, and 4.8 μg/mL, respectively), as compared to α-tocopherol and quercetin ($Q_{1/2}$ 12.1 and 7.6 μg/mL, respectively) in this bioassay.

Experimental Section

General Experimental Procedures. Uncorrected melting points were obtained on an electrothermal apparatus. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. The UV and IR spectra were recorded on a Perkin−Elmer Lambda 3B and a Perkin−Elmer FT−IR 1750 spectrophotometer, respectively. The ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded on a Bruker AC-

Table 1. ^{1}H NMR Data for Compounds **3**, **4**, **3a**, and **4a** (200 MHz)

proton	**3**[a]	*J* (Hz)	**4**[a]	*J* (Hz)	**3a**[b]	*J* (Hz)	**4a**[b]	*J* (Hz)
2, 6	7.09 d	8.5	7.08 d	8.1	7.07 d	7.5	7.16 d	8.0
3, 5	6.77 d	8.5	6.77 d	8.1	6.88 d	7.7	7.03 d	8.4
7	2.86 t	7.5	2.83 t	6.6	2.86 t	7.6	2.89 t	7.0
8	3.16 t	7.5	3.15 t	6.6	3.24 t	7.6	3.09 t	7.0
14	5.81 s		5.64 s		6.03 s		6.43 s	
2′, 6′	7.30 d	8.3	7.08 d	8.1	7.29 d	8.5	7.16 d	8.0
3′, 5′	6.61 d	8.3	6.59 d	8.1	6.77 d	8.5	6.83 bs	
7′	4.15 d	11.6	4.39 d	11.0	3.96 d	11.4	4.08 d	10.0
8′	2.98 ddq	2.8, 6.8, 11.7	2.8−2.9 m		2.9−3.0 m		2.9−3.0 m	
9′	0.68 d	6.9	0.65 d	6.6	0.83 d	7.4	0.64 d	6.8
2″, 6″	6.88 d	8.1	6.88 d	8.1	7.02 d	7.7	7.16 d	8.0
3″, 5″	6.67 d	8.1	6.71 d	8.8	6.83 d	7.5	7.03 d	8.4
7″	α: 2.35 dd	8.2, 13.4	α: 2.41 d	6.6	2.2−2.4 m		2.2−2.6 m	
	β: 2.50 dd	6.6, 13.4	*β*: 2.42 d	6.6				
8″	1.7−1.9 m		1.7−1.9 m		1.6−1.8 m		1.9−2.1 m	
9″	0.63 d	6.9	0.74 d	5.9	0.64 d	6.6	0.85 d	6.5
MeO-4	3.68 s		3.58 s		3.67 s		3.77 s	
MeO-15	3.73 s		3.73 s		3.71 s		3.86 s	
HO-11	14.34 s		14.48 s					

[a] Measured in $CDCl_3$ + DMSO-d_6. [b] Measured in $CDCl_3$.

Table 2. ^{13}C NMR Spectral Data for Compounds **3**, **4**, **3a**, and **4a** (50.3 MHz)

carbon	**3**[a]	**4**[a]	**3a**[b]	**4a**[b]
1	137.4 s[c]	135.3 s[c]	133.5 s[c]	132.9 s[c]
2, 6	129.9 d	130.1 d	129.3 s	129.3 s
3, 5	114.4 d	113.6 d	120.9 d	120.8 d
4	158.4 s	157.5 s	157.9 s	157.0 s
7	31.0 t	30.1 t	29.1 t	29.4 t
8	46.8 t	45.9 t	46.6 t	45.3 t
9	205.3 s	204.3 s	201.0 s	206.2 s
10	105.0 s	104.6 s	121.3 s	121.4 s
11	161.7 s	160.8 s	*d*	*d*
12	111.5 s	111.5 s	113.7 s	113.9 s
13	161.7 s	162.3 s	*d*	*d*
14	91.2 d	90.8 d	108.8 d	105.0 d
15	161.7 s	164.8 s	159.9 s	158.0 s
1′	134.1 s	133.0 s	139.0 s	138.8 s
2′, 6′	130.5 d	130.0 d	129.5 s	130.2 s
3′, 5′	115.0 d	114.4 d	121.1 d	121.1 d
4′	154.9 s	153.9 s	148.7 s	148.8 s
7′	45.4 d	41.8 d	42.1 d	42.0 d
8′	37.1 d	35.0 d	36.3 d	35.3 d
9′	12.6 q	11.0 q	12.3 q	11.0 q
1″	134.6 s	133.8 s	140.8 s	138.8 s
2″, 6″	130.6 d	130.1 d	130.1 d	130.2 d
3″, 5″	115.3 d	114.9 d	121.1 d	121.1 d
4″	154.9 s	154.2 s	148.8 s	148.2 s
7″	42.7 t	41.3 t	41.8 t	41.0 t
8″	37.1 d	32.6 d	36.3 d	35.3 d
9″	12.65 q	13.1 q	12.3 q	14.0 q
MeO-4	55.6 q	55.0 q	55.2 q	55.2 q
MeO-15	55.7 q	55.1 q	55.6 q	55.2 q
*C*H$_3$CO			21.0 q	20.6 q
*C*H$_3$CO			21.4 q	21.2 q
CH$_3$*C*O			169.2 s	169.5 s

[a] Measured in $CDCl_3$ + DMSO-d_6. [b] Measured in $CDCl_3$. [c] Multiplicities were established from HMQC and DEPT spectra (s = singlet, d = doublet, t = triplet, and q = quartet). [d] Signal not observed.

200 spectrometer, in $CDCl_3$ + DMSO-d_6 or $CDCl_3$ with TMS as internal reference. HMQC and HMBC (125 MHz) experiments were performed on a Bruker DRX-500 instrument, in $CDCl_3$ + DMSO-d_6. EIMS data were obtained at 70 eV on a HP 5988-A mass spectrometer. Elemental analysis data were obtained on a Perkin−Elmer 2400 CHN elemental analyzer. Flash chromatography was carried out on Si gel 60 (Merck 40−63 μm), and HPLC separations were performed on a Perkin−Elmer Series 4 chromatograph with a Hewlett−Packard HP 1050 UV/vis detector.

Plant Material. *I. lancifolia* fruits were collected at Reserva Gavião (WWF−INPA), near Manaus, Amazon, Brazil, in 1989. A voucher specimen (141860 MG) has been deposited at Herbarium João Murça Pires, Museu Paraense Emílio Goeldi, Belém, PA, Brazil.

Table 3. ^{1}H−^{1}H Correlations for Compounds 3 and 4 and HMQC Correlations for Compound 4

	^{1}H−^{1}H COSY[a]		HMQC[b]
position	**3**	**4**	**4**
7	3.18	3.15	30.1
8	2.86	2.83	45.9
14			90.8
7′	2.98	2.8−2.9	41.8
8″	0.68, 4.24	0.65, 1.7−1.9, 4.39	32.6
9′	2.98	2.8−2.9	11.0
7″α	1.7−1.9	1.7−1.9	41.3
8″	0.63, 2.35	0.74, 2.41, 2.8−2.9	35.0
9″	1.7−1.9	1.7−1.9	13.1

[a] ^{1}H−^{1}H measurements at 200 MHz for compound **3** and at 500 MHz for compound **4**. [b] HMQC measurements at 125 MHz for compound **4**.

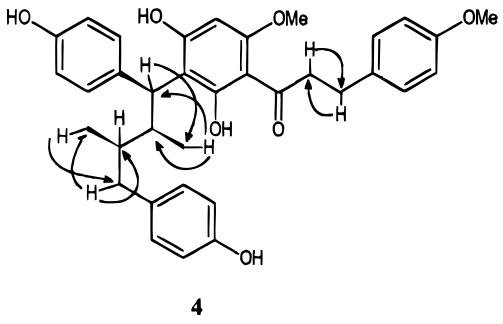


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Figure 1. HMBC carbon−proton correlations for compound **4** (indicated by arrows from ^{1}H to ^{13}C). Measurements made at 125 MHz.

Extraction and Isolation. Dried pericarps of *I. lancifolia* (7.0 g) were powdered and extracted with $CHCl_3$−MeOH (2:1) at room temperature. The dried extract (1.1 g) was submitted to Si gel flash column (hexane−EtOAc gradient), which afforded eight pooled fractions, A−H. Fractions A−D afforded several butanolides, a tocotrienol, and a lignan, as described elsewhere.[14] Fraction E was recrystallized from $CHCl_3$−hexane to yield **1** (11 mg, 0.157% w/w dry material)[7,8] and **1** plus **2** (18 mg). The latter fraction was submitted to HPLC [RP_{18} column, 250 × 22 mm, 5 μm Merck; MeOH−H_2O (86:14)] and afforded **1** (8 mg, 0.114% w/w dry material) and **2** (3 mg, 0.043% w/w dry material). Fractions F and G were shown to contain a mixture of dihydrochalcones and flavonolignans through analysis of their ^{1}H NMR spectra. The constituents of fraction H were separated by HPLC (RP_{18} column, 250 ×

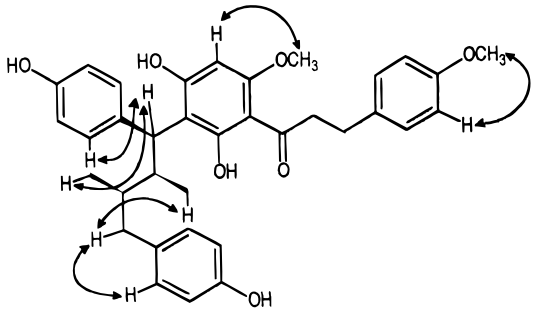

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Figure 2. Selected NOESY interactions for compound **4**.

22 mm, 5 μm Merck; MeOH−H_2O 78:22) and gave **3** (16 mg, 0.228% w/w dry material) and **4** (75 mg, 1.071% w/w dry material).

2′,4-Dihydroxy-4′,6′-dimethoxydihydrochalcone (**2**): obtained as white needles (hexane); mp 182−184 °C; UV (MeOH) λ_{max} (log ϵ) 232 (4.45), 285 (4.39) nm; IR (KBr) ν_{max} 3257, 1648, 1633, 1567, 1511, 1297, 1196, 1164, 1110, 1030, 800; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.15 (2H, d, J = 8.6 Hz, H-2, H-6), 6.82 (2H, d, J = 8.6 Hz, H-3, H-5), 6.01 (1H, s, H-3′), 5.97 (1H, s, H-5′), 3.84 (3H, s, CH_3O-6′), 3.77 (3H, s, CH_3O-4′), 3.27 (2H, t, J = 7.5 Hz, H-α), 2.91 (2H, t, J = 7.5 Hz, H-β); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 204.7 (s, C=O), 167.2 (s, C-4′), 163.4 (s, C-6′), 163.2 (s, C-2′), 157.8 (s, C-4), 96.5 (d, C-3′), 90.9 (d, C-5′), 55.6, 55.2 (q, MeO-4′, MeO-6′), 45.9 (t, C-α), 29.0 (t, C-β); EIMS m/z 302 $[M]^+$ (9), 181 (14), 149 (5), 120 (46), 107 (100); anal. C 67.32%, H 6.15%, calcd for $C_{17}H_{18}O_5$, C 67.55%, H 5.96%.

(1″*R,2″*S**,3″*R**)-3′-(1″,4″-Di-*p*-hydroxyphenyl-2″,3″-dimethylbutyl)-2′,4′-dihydroxy-4,6′-dimethoxydihydrochalcone (iryantherin K)** (**3**) $[\alpha]^{25}_D$ −36.0° (*c* 1.6, MeOH); UV (MeOH) λ_{max} (log ϵ) 245 (4.81), 288 (4.31) nm; IR (KBr) ν_{max} 3354, 1701, 1611, 1511, 1433, 1244, 1209, 1100, 1030, 825, 807; ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 200 MHz), see Table 1; ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 50 MHz), see Table 2; EIMS m/z 570 $[M]^+$ (1), 407 (100), 302 (14), 287 (1), 268 (6), 245 (3), 167 (56), 163 (4), 162 (20), 161 (18), 147 (18), 134 (57), 121 (92), 107 (50), 91 (14), 77 (16); anal. C 73.43%, H 6.84%, calcd for $C_{35}H_{38}O_7$, C 73.68%, H 6.67%.

Iryantherin K Tetraacetate (**3a**): ^{1}H NMR ($CDCl_3$, 200 MHz), see Table 1 and δ 2.17, 2.22 (4 AcO); ^{13}C NMR ($CDCl_3$, 50 MHz), see Table 2 and δ 21.0, 21.4 (4 Me), 169.2 (4 CO).

(1″*S,2″*S**,3″*R**)-3′-(1″,4″-Di-*p*-hydroxyphenyl-2″,3″-dimethylbutyl)-2′,4′-dihydroxy-4,6′-dimethoxydihydrochalcone (iryantherin L)** (**4**) $[\alpha]^{25}_D$ +45.6° (*c* 1.9, MeOH); UV (MeOH) λ_{max} (log ϵ) 248 (4.22), 285 (4.17); IR (KBr) ν_{max} 3360, 1699, 1612, 1511, 1454, 1441, 1242, 1210, 1096, 1030, 825, 806, 668; ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 200 MHz), see Table 1; ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 50 MHz), see Table 2; EIMS m/z 570 $[M]^+$ (1), 407 (100), 302 (12), 287 (1), 268 (4), 245 (4), 167 (25), 163 (2), 162 (10), 161 (10), 147 (10), 134 (22), 121 (58), 107 (23), 91 (5), 77 (7); anal. C 73.31%, H 6.92%, calcd for $C_{35}H_{38}O_7$, C 73.68%, H 6.67%.

Iryantherin L tetraacetate (**4a**): ^{1}H NMR ($CDCl_3$, 200 MHz), see Table 1 and δ 2.25, 2.31 (4 AcO); ^{13}C NMR ($CDCl_3$, 50 MHz), see Table 2 and δ 20.6, 21.2 (4 Me), 169.5 (4 CO).

Acetylation of Flavonolignans. To each flavonolignan (5 mg), Ac_2O (1.0 mL) and C_5H_5N (1.0 mL) were added and left overnight. Cold H_2O was added to each reaction mixture, and the organic phase was extracted with $CHCl_3$ and then washed successively with aqueous HCl (2%) and cold H_2O. Each acetylated flavonolignan was then purified by HPLC (RP_{18} column, 250 × 22 mm, 5 μm Merck; MeOH−H_2O 78:22).

Bioassay. Antioxidant activity was evaluated through measurement of the ability of test compounds to inhibit spontaneous lipid peroxidation of brain homogenates, as has been described in more detail elsewhere.[12,13] MDA production was measured after its reaction with thiobarbituric acid TBA, and the calculated antioxidant capacities (AOC) of the percentage of thiobarbituric acid reactant substance measurements were obtained for several dilutions and plotted graphically (1/AOC × 1/[extract]). The $Q_{1/2}$ (concentration necessary to inhibit 50% of the spontaneous autoxidation of brain homogenate) was then determined for compounds **1**−**4** and reference compounds (α-tocopherol and quercetin), in comparison with the extent of oxidation in the absence of drug (100% of oxidation).

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