Humulane and Germacrane Sesquiterpenes from *Ferula lycia*

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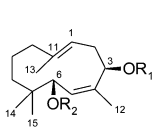
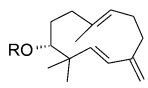
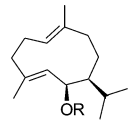
Five new juniferol esters (**1**−**5**), along with six known humulane derivatives (**6**−**11**), were isolated from the roots of *Ferula lycia*, an endemic Turkish species. The fruits of the same species were also investigated and led to the isolation of these same compounds, as well as two known germacrane esters (**12** and **13**). All isolated sesquiterpenes were assayed for cytotoxicity against two tyrosine kinase inhibitor-resistant cell lines, K562R and DA1-3b/M2$^{BCR\text{-}ABL}$. The two most active compounds, juniferinin (**7**) and 6-*β*-*p*-hydroxybenzoyloxygermacra-1(10),4-diene (**12**), were moderately active against Raji lymphoma cells but also displayed some toxicity against healthy bone marrow cells.

Ferula lycia Boiss. (Apiaceae) is an indigenous species of the Lycia mountains in Turkey.[1] The genus *Ferula* is known to be a good source of sesquiterpene derivatives.[2,3] Several of these compounds were shown to have antiproliferative, cytotoxic, and potential cancer chemopreventive properties for several cancer cell lines.[3−9] In particular, some sesquiterpene esters isolated from *Ferula elaeochytris* Korovin showed an inhibitory effect against two chronic myeloid leukemia (CML) cell lines,[10] K562R and DA1-3b/M2$^{BCR\text{-}ABL}$, which provide different mechanisms of resistance resembling those observed in CML patients treated with tyrosine kinase inhibitors (imatinib and dasatinib).[11,12] As a part of a continuing search for bioactive compounds, the roots and the fruits of *F. lycia* have been investigated. The isolation of 13 compounds (**1**−**13**), of which five are new (**1**−**5**), is reported herein, together with the cytotoxic activities of all isolated compounds.

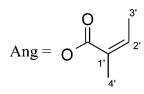
Successive chromatographic fractionation of a light petroleum extract from the roots of *F. lycia* yielded five new sesquiterpene esters, namely, lyciferins A−E (**1**−**5**), along with six known compounds, which were identified by NMR, MS, and comparison of their data with those already published: juniferdin (**6**),[13] juniferinin (**7**),[14] juniferin (**8**),[14] benzoylfervanol (**9**),[15] *p*-hydroxybenzoylfervanol (**10**),[15] and vanilloylfervanol (**11**).[15]



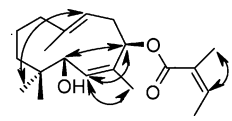




1	R_1 = Ang, R_2 = H	**9**	R = Bnz	**12**	R = *p*-OHBz
2	R_1 = Ang, R_2 = Ac	**10**	R = *p*-OHBz	**13**	R = Van
3	R_1 = Bnz, R_2 = H	**11**	R = Van		
4	R_1 = Bnz, R_2 = Ac				
5	R_1 = Van, R_2 = Ac				
6	R_1 = *p*-OHBz, R_2 = H				
7	R_1 = *p*-OHBz, R_2 = Ac				
8	R_1 = Van, R_2 = H				



Compound **1** was isolated as a colorless oil. The HRESIMS of **1** showed a $[M + Na]^+$ ion peak at *m*/*z* 343.2239, which indicated a molecular formula of $C_{20}H_{32}O_3$. The ^{13}C NMR spectrum displayed 20 signals, of which 15 could be assigned to a sesquiterpene substructure. Analysis of the ^1H, ^{13}C (JMOD), and HSQC NMR spectra revealed signals indicative of two tertiary oxygenated



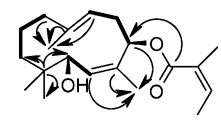


Figure 1. Selected COSY (—), HMBC (C→H), and NOESY (H↔H) correlations for compound **1**.

(oxymethine) carbons ($\delta_{H/C}$ 5.46/72.2, C-3; $\delta_{H/C}$ 4.08/70.1, C-6) and two tertiary ($\delta_{H/C}$ 5.09/119.0, CH-1; $\delta_{H/C}$ 5.54/129.9, CH-5) and two quaternary (δ_C 134.8, C-4; δ_C 140.0, C-11) olefinic carbons, as well as two corresponding vinylic methyls ($\delta_{H/C}$ 1.69/18.5, CH_3-13; $\delta_{H/C}$ 1.70/17.4, CH_3-12) and two methyl singlets ($\delta_{H/C}$ 0.98/23.0, CH_3-14; $\delta_{H/C}$ 0.92/23.1, CH_3-15). The $^1H-^1H$ COSY spectrum enabled three structural fragments to be established, (**a**) =CH−CH_2−CHOR−, (**b**) =CH−CHOR−, and (**c**) −CH_2−CH_2−CH_2−, which could be connected by observing the correlations in the HMBC experiment (Figure 1). The correlations of the methyl singlet CH_3-12 (δ_H 1.70) to C-3 (δ_C 72.2), C-4 (δ_C 134.8), and C-5 (δ_C 129.9) helped to establish the connectivity between the fragments **a** and **b**, while the correlation of CH_3-13 (δ_H 1.69) to C-1 (δ_C 119.0), C-10 (δ_C 37.7), and C-11 (δ_C 140.0) was used to link **a** with **c**. The linkage of fragments **b** and **c** was confirmed by the peak correlations of both methyl groups at CH_3-14 (δ_H 0.98) and CH_3-15 (δ_H 0.92) with H-6 (δ_H 4.08) and the two geminal protons, H_2-8 (δ_H 1.19 and 1.29), with C-7 (δ_C 36.9). The relative configuration of **1** was determined by NOESY experiments (Figure 1).[15] The *cis* configuration of C-4,C-5 was established by observing the cross-peak of H-5 and CH_3-12, while the absence of any correlation between H-1 and CH_3-13 supported the hypothesis of a *trans* configuration of the C-1,C-11 double bond. Furthermore, H-3 (δ_H 5.46) was correlated with both H-5 (δ_H 5.54) and H-6 (δ_H 4.08), so the orientation of the C-3 and C-6 hydroxy groups was determined as being on the same side of the molecule. Thus, the sesquiterpene moiety of **1** was established as the known dihydroxylated α-humulene derivative, juniferol.[13,14] The remaining ^1H NMR signals of **1** were characteristic of a 2-methylbutenoyl moiety, with two methyl groups at δ_H 1.90 (q, J = 7.5 Hz) and δ_H 1.99 (dq, J = 7.5, 1.4 Hz) and a tertiary olefinic proton at δ_H 6.10 (qq, J = 7.5, 1.4 Hz). A *cis* configuration (corresponding to an angeloyl moiety) was established by observing the cross-peak of H-2′ and CH_3-4′ in the NOESY experiment. Other significant correlations in the HMBC spectrum of **1** were observed from the deshielded proton H-3 (δ_H 5.46) to the carboxylic carbon (δ_C 168.3) and suggested the position of the angeloyl group at C-3. The structure of compound **1** was closely related to the juniferol esters previously

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Table 1. NMR Spectroscopic Data (300 MHz, $CDCl_3$) for Lyciferins A-E (**1**−**5**)

	lyciferin A (**1**)		lyciferin B (**2**)		lyciferin C (**3**)		lyciferin D (**4**)		lyciferin E (**5**)	
position	δ_C (mult.)	δ_H (*J* in Hz)	δ_C (mult.)	δ_H (*J* in Hz)	δ_C (mult.)	δ_H (*J* in Hz)	δ_C (mult.)	δ_H (*J* in Hz)	δ_C (mult.)	δ_H (*J* in Hz)
1	119.0, qC	5.09, t (8.0)	119.0, qC	5.17, t (8.0)	118.8, qC	5.12, t (8.0)	118.9, qC	5.23, t (8.0)	118.9, qC	5.21, t (8.0)
2	29.8, CH_2	2.47, m	30.3, CH_2	2.54, 2.39 m	29.8, CH_2	2.56 m	30.4, CH_2	2.63, 2.47, m	30.4, CH_2	2.63, 2.47, m
3	72.2, CH	5.46, dd (11.0, 4.5)	72.6, CH	5.60, dd (11.0, 4.5)	73.0, CH	5.61[a]	73.1, CH	5.80, dd (12.0; 4.5)	73.1, CH	5.78, dd (12.0; 4.5)
4	134.8, qC		139.8, qC		134.7, qC		139.4, qC		139.4, qC	
5	129.9, CH	5.54, d (10.2)	124.2, CH	5.49, d (10.2)	130.2, CH	5.62[a]	124.7, CH	5.50, d (10.5)	124.7, CH	5.49, d (10.5)
6	70.1, CH	4.08, d (10.2)	71.5, CH	5.41, d (10.2)	70.1, CH	4.23, d (10.5)	71.6, CH	5.47, d (10.5)	71.6, CH	5.46, d (10.5)
7	36.9, qC		36.7, qC		36.5, qC		36.9, qC		36.9, qC	
8	36.4, CH_2	1.19, 1.29, m	36.4, CH_2	1.19, 1.29, m	36.8, CH_2	1.29, 1.09, m	36.8, CH_2	1.27, 1.10, m	36.8, CH_2	1.27, 1.10, m
9	23.1, CH_2	1.67, 1.31, m	22.1, CH_2	1.67, 1.31, m	23.1, CH_2	1.65, 1.28, m	22.9, CH_2	1.65, 1.31, m	22.9, CH_2	1.65, 1.31, m
10	37.7, CH_2	2.17, 1.59, m	37.4, CH_2	2.17, 1.59, m	37.7, CH_2	2.16, 1.58, m	37.9, CH_2	2.19, 1.55, m	37.9, CH_2	2.19, 1.55, m
11	140.0, qC		139.4, qC		140.2, qC		140.0, qC		140.0, qC	
12	17.4, CH_3	1.70, d (1.9)	18.1, CH_3	1.74, d (1.9)	17.4, CH_3	1.75, d (1.3)	18.6, CH_3	1.83, d (1.3)	18.6, CH_3	1.89, d (1.3)
13	18.5, CH_3	1.69, s	18.5, CH_3	1.77 s	18.5, CH_3	1.72, s	18.3, CH_3	1.82, s	18.3, CH_3	1.81, s
14	23.0, CH_3	0.98, s	24.2, CH_3	0.96, s	23.0 CH_3	1.0, s	24.3, CH_3	0.99, s	24.3, CH_3	0.98, s
15	23.1, CH_3	0.92, s	22.7, CH_3	0.83, s	22.9, CH_3	0.94, s	22.8, CH_3	0.86, s	22.8, CH_3	0.84, s
CO	168.3, qC		167.5, qC		166.3 qC		165.9 qC		165.9 qC	
1′	128.4, qC		128.1, qC		130.3, qC		130.0, qC		122.8, qC	
2′	138.7, CH	6.10, qq (7.5, 1.4)	137.3, CH	6.03, qq (7.5, 1.4)	129.6, CH	8.04, d (7.5)	129.7, CH	8.00, d (7.5)	111.9, CH	7.58, d (2.2)
3′	15.8, CH_3	1.99, dq (7.5, 1.4)	15.7, CH_3	1.97, dq (7.5, 1.4)	128.4, CH	7.45, t (7.5)	128.4, CH	7.44, t (7.5)	113.9, CH	6.92, d (8.3)
4′	20.6, CH_3	1.90, q (7.5)	20.7, CH_3	1.87, q (7.5)	133.1, CH	7.57, t (7.5)	132.6, CH	7.55, t (7.5)	146.0, qC	
5′					128.4, CH	7.45, t (7.5)	128.4, CH	7.44, t (7.5)	149.8, qC	
6′					129.6, CH	8.04, d (7.5)	129.7, CH	8.00, d (7.5)	124.4, CH	7.63, dd (8.3; 2.2)
OCH_3									56.04, CH_3	3.94 s
$\underline{C}OCH_3$			171.0, qC				170.7, qC		170.7, qC	
$CO\underline{CH_3}$			21.1, CH_3	2.06 s			21.2, CH_3	2.09 s	21.2, CH_3	2.10 s

[a] Signal partially obscured.

reported in *Ferula juniperina* Korovin and was thus identified as 3-angeloyljuniferol (lyciferin A).[13,14]

The ^1H and ^{13}C NMR spectroscopic data of the four other new compounds (**2**−**5**) were very similar to those of **1** (Table 1), except for the ester units.

Compound **2** was isolated as a colorless oil. The molecular formula was determined by HRMS as $C_{22}H_{34}O_4$ (*m/z* 385.2469 $[M + Na]^+$). Compound **2** showed the presence of two ester moieties: angeloyl, with spectroscopic data close to those of the ester moiety in compound **1** (see Table 1), and an acetyl (one methyl singlet at δ_H 2.06 in the ^1H NMR spectrum; the corresponding primary carbon was observed at δ_C 21.1 and the carboxyl signal at δ_C 171.0 in the ^{13}C NMR spectrum). The other NMR spectroscopic data of **2** were closely comparable to those of **1**. The acetyl group was concluded to be at C-6 from the downfield shifts of the C-6 (δ_C 71.5) and H-6 (δ_H 5.41) signals as compared with those of **1**, as well as the correlation between H-6 and the carboxylic carbon at δ_C 171.0 in the HMBC experiment.

Compound **3** was isolated as a colorless oil. The molecular formula was determined by HRMS as $C_{22}H_{30}O_3$ (*m/z* 365.2089 $[M + Na]^+$). The ^1H and ^{13}C NMR spectra of **3** displayed the presence of a benzoyl [δ_H 7.45 (2H, t, $J = 7.5$ Hz, H-3′,5′), 7.57 (1H, t, $J = 7.5$ Hz, H-4′), 8.04 (2H, d, $J = 7.5$ Hz, H-2′,6′); δ_C 128.4 (C-3′,5′), 129.6 (C-2′,6′), 130.3 (C-1′), 133.1 (C-4′), 166.3 (COO)]. In the HMBC spectrum, a correlation of H-3 (δ_H 5.61) with the carboxylic carbon (δ_C 166.3) confirmed the attachment of the acyl to C-3. Compound **4** ($C_{24}H_{32}O_4$, determined by HRMS, *m/z* 407.2198 $[M + Na]^+$) also contained both a benzoyl and an acetyl moiety (see data in Table 1), which were located at C-3 and C-6, respectively, from the HMBC experiment.

The molecular formula of compound **5** was determined by HRMS as $C_{25}H_{34}O_6$ (*m/z* 453.2003 $[M + Na]^+$). NMR data showed the presence of 4-hydroxy-3-methoxybenzoyl (= vanilloyl) [δ_H 6.92 (1H, d, $J = 8.3$ Hz, H-3′), 7.58 (1H, d, $J = 2.2$ Hz, H-2′), 7.63 (1H, dd, $J = 8.3$, 2.2 Hz, H-6′); δ_C 111.9 (C-2′), 113.9 (C-3′), 122.8 (C-1′), 124.4 (C-6′), 146.0 (C-4′), 149.8 (C-5′), 165.9 (COO)] and acetyl moieties. The respective locations of these ester moieties at C-3 and C-6 were deduced from the HMBC spectrum.

General NMR data and NOESY experiments indicated the sesquiterpene moiety and relative configuration of compounds **2**−**5** to be identical to those of **1**. Hence, compounds **2**−**5** were established as 3-angeloyl-6-acetyljuniferol (lyciferin B), 3-benzoyljuniferol (lyciferin C), 3-benzoyl-6-acetyljuniferol (lyciferin D), and 3-vanilloyl-6-acetyljuniferol (lyciferin E), respectively. This was in agreement with MS and HRMS data for these compounds (see Experimental Section). To the best of our knowledge, compounds **1**−**5** are all new combinations of known sesquiterpene and acyl moieties. The determination of their relative configuration was justified by NOESY experiments, as explained above and reported in Figure 1 for compound **1**. Although the lack of any NOE effect between H-1 and CH_3-13 can be considered as an insufficient justification for the *trans* configuration assignment of the C-1,C-11 double bond, the present findings correspond to the relative configuration of juniferol and juniferdin as previously determined by X-ray crystallography.[16,17]

The CH_2Cl_2-soluble fraction of a methanolic fruit extract of *F. lycia* (see Experimental Section) was separated and purified by silica gel column chromatography to afford compounds **1**−**11**, together with two known compounds, 6-β-*p*-hydroxybenzoyloxygermacra-1(10),4-diene (**12**) and 6-β-vanilloyloxygermacra-1(10),4-diene (**13**), the structures of which were identified by literature comparison of their observed and reported physical and spectroscopic data.[18] The co-occurrence of humulane and germacrane esters in a *Ferula* species is rare. In addition to the fruits of *F. lycia*, the association of similar compounds has been reported from the roots of *F. lapidosa* Korovin and *F. tenuisecta* Korovin.[19]

All isolated compounds were tested in vitro for their cytotoxic activity against resistant chronic myeloid leukemia (CML) cell lines,

Table 2. Cytotoxicity (IC_{50} in μM, mean ± SE from three experiments) of Compounds **1**−**13** against Two Leukemia Cell Lines in Vitro[a,b]

	cell line	
compound	DA1-3b/M2$^{BCR-ABL}$	K562R
2	45.0 ± 0.9	>50
4	45.0 ± 1.9	>50
5	20.1 ± 1.1	41.5 ± 1.2
6	23.7 ± 1.1	>50
7	18.6 ± 1.2	33.0 ± 1.1
8	29.0 ± 0.9	>50
12	24.7 ± 0.8	25.3 ± 1.0
camptothecin[c]	30.0 ± 0.5	2.0 ± 0.2

[a] Compounds with IC_{50} < 50 μM on at least one cell line are shown. [b] Compounds **1**, **3**, **11**, and **13** were not active against both cell lines. [c] IC_{50} nM.

including an imatinib- and dasatinib-resistant murine cell line (DA1-3b/M2$^{BCR-ABL}$) and an imatinib-resistant human cell line (K562R). The IC_{50} values of compounds active against at least one cell line at a concentration < 50 μM are given in Table 2. Compound **12** was the most active on K562R (IC_{50} = 25.3 μM), while the most potent compounds against DA1-3b/M2$^{BCR-ABL}$ were **5** and **7** (IC_{50} = 20.1 and 18.6 μM, respectively). The cytotoxic effects of compounds **7** and **12** were also evaluated against other leukemic and normal cell lines. For Raji cells (a lymphoma cell line), their IC_{50} values were 13.0 ± 2.1 and 20.9 ± 1.2 μM, respectively, with that of the positive control, camptothecin, being 1.0 ± 0.3 μM. For bone marrow cells from healthy volunteers, compound **12** exhibited IC_{50} >50 μM, and **7** IC_{50} 30.7 ± 2.3 μM. Germacranolides (sesquiterpene lactones) and α-humulene have been reported to exhibit cytotoxic activities against several tumor cell lines.[20−22]

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Perkin-Elmer 343 polarimeter. UV spectra were recorded on a Biochrom WPA Lightwave II UV−visible spectrometer. IR spectra were recorded on a Thermo Nicolet Avatar 320 FT-IR spectrometer. NMR spectra were recorded on a Bruker Avance 300 spectrometer in the Laboratoire d'Application de RMN (LARMN), Université Lille 2, and analyzed with Topspin 1.3. Mass spectra (ESIMS), including HRMS, were obtained on 55Q710 Finnigan MAT, API3000 (Perkin-Elmer Sciex), and Thermo Scientific Orbitrap Exactive (Bremen, Germany) mass spectrometers, using heated electrospray (HESI-II), at the Centre de Mesures et d'Analyses (CMA), Université de Lille 2. HPLC analyses were performed with a Shimadzu apparatus (LC-10AS pumps, SCD-10A detector, SCL-10Avp controller, LC solution software). The column was an Interchim RP-18 (250 × 4.6 mm, 5 μm). The solvent system was H_2O in ACN, with a linear gradient from 80% to 100% in 20 min, flow rate 1 mL/min. Semipreparative HPLC was carried out using an Interchim RP-18 (250 × 10 mm, 5 μm) column with a CH_3OH−H_2O gradient. Silica gel 60 was provided by Merck and Sephadex LH-20 by Pharmacia. TLC was performed on Merck F254 silica gel plates (10 × 10 cm).

Plant Material. The roots and fruits of *Ferula lycia* were collected and authentified by Y. G at Koya, Bozkir, between Karabayir and Kovalik villages (Turkey), in August 2008. A voucher specimen (MKUF-101) is deposited in the herbarium of the Department of Botany, Mustafa Kemal University, Turkey.

Extraction and Isolation. Dried and powdered roots of *F. lycia* (200 g) were extracted with light petroleum (3 × 1.5 L, each) at room temperature for 24 h, to give 20 g of a dark brown, viscous mass. A 9 g aliquot was fractionated by silica gel column chromatography eluted with a light petroleum−EtOAc gradient (100% light petroleum to 100% EtOAc, v/v) to give fractions A−N. Fractions B (27 mg), D (78 mg), E (162 mg), and H (300 mg) were compounds **9**−**11** and **6**, respectively. Fraction C (1098 mg) was submitted to silica gel column chromatography, eluted with a cyclohexane−EtOAc gradient (100% to 90% cyclohexane), yielding compounds **1** (27 mg), **2** (40 mg), **3** (25 mg), and **4** (30 mg). Fraction I (83 mg) was purified by semipreparative HPLC using an 80% to 100% CH_3OH gradient in H_2O to yield compounds **7** (14 mg), **8** (30 mg), and **5** (16 mg).

Powdered fruits of *F. lycia* (400 g) were extracted with CH_3OH (3 × 2 L) at room temperature for 24 h. The CH_3OH extract (40 g) was dissolved in H_2O and submitted to liquid−liquid extraction with CH_2Cl_2 to yield 23 g of extract. An aliquot (8 g) was submitted to silica gel column chromatography, eluted with a light petroleum−EtOAc gradient (100% light petroleum to 100% EtOAc), to give fractions A′−L′. Fraction G′ (1.5 g) was compound **6**. Fraction C′ (200 mg) was submitted to a silica gel column chromatography eluted with a cyclohexane−EtOAc gradient (100% cyclohexane to 90:10), yielding compounds **9** (10 mg), **1** (5 mg), **2** (40 mg), **3** (5 mg), and **4** (10 mg). Fraction E′ (2.1 g) gave compounds **10** (200 mg) and **11** (82 mg) after being chromatographed over silica gel eluted with a light petroleum−EtOAc gradient (100% light petroleum to 70:30). Fraction F′ (2.5 g) was also purified in the same conditions to yield compounds **12** (315 mg) and **13** (50 mg). Fraction I′ (60 mg) was purified by semipreparative RP-HPLC using an 80% to 100% CH_3OH gradient in H_2O to yield compounds **7** (5 mg), **8** (10 mg), and **5** (6 mg).

Lyciferin A (1): amorphous oil; $[\alpha]^{21}_D$ −24.0 (*c* 0.5, EtOH); IR (KBr) ν_{max} 3457, 2925, 1716, 1632, 1384, 1239, 1159, 1041, 1016, 963 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; HRESIMS *m/z* 343.2239 [M + Na]$^+$ (calcd for $C_{20}H_{32}O_3Na$, 343.2249).

Lyciferin B (2): amorphous oil; $[\alpha]^{21}_D$ −39.4 (*c* 0.5, EtOH); IR (KBr) ν_{max} 2928, 1736, 1716, 1456, 1383, 1236, 1159, 1041, 1016, 963 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; HRESIMS *m/z* 385.2340 [M + Na]$^+$ (calcd for $C_{22}H_{34}O_4Na$, 385.2349).

Lyciferin C (3): amorphous oil; $[\alpha]^{21}_D$ −3.2 (*c* 0.2, EtOH); UV (CH_3OH) λ_{max} (log ε) 227 (3.92) nm; IR (KBr) ν_{max} 3457, 2924, 2853, 1717, 1709, 1642, 1462, 1384, 1239, 1159, 1041, 1016, 963 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; HRESIMS *m/z* 365.2081 [M + Na]$^+$ (calcd for $C_{22}H_{30}O_3Na$, 365.2093).

Lyciferin D (4): amorphous oil; $[\alpha]^{21}_D$ +1.3 (*c* 0.2, EtOH); UV (CH_3OH) λ_{max} (log ε) 227 (3.93) nm; IR (KBr) ν_{max} 2924, 2853, 1717, 1709, 1642, 1462, 1384, 1239, 1159, 1041, 1016, 963 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; HRESIMS *m/z* 407.2185 [M + Na]$^+$ (calcd for $C_{24}H_{32}O_4Na$, 407.2193).

Lyciferin E (5): amorphous oil; $[\alpha]^{21}_D$ +24.6 (*c* 0.5, EtOH); UV (CH_3OH) λ_{max} (log ε) 262 (4.29), 292 (3.83) nm; IR (KBr) ν_{max} 2938, 2853, 1719, 1683, 1610, 1444, 1277, 1234, 1100, 975, 961 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; HRESIMS *m/z* 453.2236 [M + Na]$^+$ (calcd for $C_{25}H_{34}O_6Na$, 453.2248).

Cytotoxicity Assays. The imatinib-resistant human chronic myeloid leukemia K562 cell line (K562R) and dasatinib-resistant leukemic mouse DA1-3b p210$^{BCR-ABL}$ cell line (DA1-3b/M2) have been described previously.[11,12,23] Bone marrow cells were obtained from three healthy volunteers.[24] Donors gave informed consent in accordance with the Declaration of Helsinki. Raji cells (derived from Burkitt lymphoma) were purchased from the American Type Culture Collection (ATCC, Manassas, VA).[25] All cells were cultured in RPMI 1640 medium supplemented with 1% glutamine, 1% penicillin/streptomycin, and 10% fetal calf serum (all from Gibco/BRL, Eggenstein, Germany). Toxicity was analyzed using the MTT method, as described previously.[10]

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of lyciferins A−E (**1**−**5**). This material is available free of charge via the Internet at http://pubs.acs.org.

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