Prenylated Flavonoids from the Root of Egyptian *Tephrosia apollinea* – Crystal Structure Analysis

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Three complex 7-oxygenated-8-prenylflavones, (-)-semiglabrin and (-)-pseudosemiglabrin, which are diastereoisomers, and lanceolatin A have been isolated from the root of *Tephrosia apollinea* (Del.) Link (Leguminosae) growing in Southern Egypt, together with two phytosterols, stigmasterol and sitosterol. The structures of the isolated compounds have been elucidated by means of physical and several spectroscopic methods including UV, IR, ^{1}H, ^{13}C NMR, DEPT, 2D ^{1}H-^{1}H COSY, HSQC, HMBC experiments, and high resolution mass spectrometry (HR-MS), as well as some chemical transformations. The stereochemistry of the structures of (-)-semiglabrin and lanceolatin A have been confirmed by X-ray crystal structure analysis. The anticarcinogenic properties of the isolated compounds showed no inhibitory mechanisms concerning the initiation, promotion, and progression stage of carcinogenesis. Moreover, the *in vitro* antimicrobial activities of the root ethanolic extract are discussed.

Key words: Tephrosia apollinea, Leguminosae, 7-Oxygenated-8-prenyl-flavones, Lanceolatin A, Antimicrobial Activity

Introduction

Tephrosia Pres. (Leguminosae, Papilionoideae) is a large tropical and subtropical genus of about 300 species [1]. Several reports have indicated that the extract of some species of the genus have piscicidal, insecticidal, repellent [2] and anti-cancer properties [3]. Earlier phytochemical screening [2] of a number of species revealed the presence of rotenoids, isoflavones, flavanones, chalcones, flavonols and flavones. Within the group of flavones, 5,7-oxygenated and 7-oxygenated compounds, which are characterized by the presence of a prenyl unit at C-8, are well known. In many cases, these prenylated flavones have undergone further substitution and cyclization leading to complex molecules. *Tephrosia apollinea* (Del.) Link is a perennial shrublet distributed in Africa. In Egypt, it is abundant in the Nile Valley, along the coast of the Red Sea and in all Egyptian deserts [4]. We have undertaken a study of the constituents of the root of this species. Prenylated flavonoids from hop (*Humulus lupulus* L.) were shown to modulate drug metabolism *in vitro* by inhibition of various cytochrome (Cyp) enzymes and by induction of quinone reductase (QR) activity in murine hepatoma cells. In addition, antioxidant and cytotoxic effects and 8-prenylnaringenin (8-PN) isolated from hops has been identified as a potent phytoestrogen [5]. Therefore, anticarcinogenic properties of the isolated prenylated flavonoids of the plant underinvestigation at the initiation, promotion, and progression stage of tumor development to identify novel potential chemopreventive agents are reported. Moreover, the *in vitro* antimicrobial activities of the root ethanolic extract are discussed.

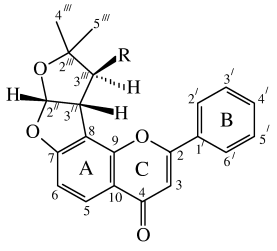
Results and Discussion

Roots of *T. apollinea* were collected, air dried, and extracted with petroleum ether (60 – 80 °C) and CH_2Cl_2. The CH_2C1_2 extract was concentrated and subjected to preliminary separation by column chromatography over silica gel, eluting with *n*-hexane-EtOAc of increasing polarity. Individual fractions

Table 1. ^{1}H NMR spectral data for compounds **1 – 5** (500 MHz, $CDCl_3$, TMS as internal standard)*.

Proton No.	**1**[a]	**2**	**3**[a]	**4**	**5**[a]
H-3	6.76 (1H, *s*)	6.78 (1H, *s*)	6.74 (1H, *s*)	6.80 (1H, *s*)	6.76 (1H, *s*)
H-5	8.15 (1H, *d*, $J = 8.5$)	8.11 (1H, *d*, $J = 8.5$)	8.16 (1H, *d*, $J = 8.5$)	8.17 (1H, *d*, $J = 8.5$)	8.12 (1H, *d*, $J = 8.8$)
H-6	6.93 (1H, *d*, $J = 8.5$)	6.91 (1H, *d*, $J = 8.5$)	6.92 (1H, *d*, $J = 8.5$)	6.89 (1H, *d*, $J = 8.5$)	7.02 (1H, *d*, $J = 8.8$)
H-2′/-6′	7.90 (2H, *m*)	7.92 (2H, *m*)	7.80 (2H, *dd*, $J = 8.0, 2.0$)	7.80 (2H, *m*)	7.90 – 7.92 (2H, *m*)
H-3′/-5′	7.52 (2H, *m*)	7.52 (2H, *m*)	7.52 (2H, *dd*, $J = 8.0, 2.0$)	{ 7.40 – 7.60 (3H, *m*)	{ 7.50 – 7.51 (3H, *m*)
H-4′	7.51 (1H, *m*)	7.51 (1H, *m*)	7.51 (1H, *m*)		
H-1″	–	–	–	–	6.97 (1H, *d*, $J = 16.5$)
H-2″	6.62 (1H, *d*, $J = 6.5$)	6.61 (1H, *d*, $J = 6.6$)	6.49 (1H, *d*, $J = 6.5$)	6.45 (1H, *dd*, $J = 4.6, 1.8$)	6.82 (H, *d*, $J = 16.5$)
H-3″	4.30 (1H, *d*, $J = 6.5$)	4.30 (1H, *d*, $J = 6.6$)	4.60(1H, *dd*, $J = 8.8, 6.5$)	4.46 (1H, *m*)	–
H-4″, H-5″	–	–	–		1.55 (3H, *s*), 1.50 (3H, *s*)
H-3‴	5.63 (1H, *s*)	4.35 (1H, *d*, $J = 6.0$)**	5.55 (1H, *d*, $J = 8.8$)	4.46 (1H, *m*)#	–
H-4‴	1.08 (3H, *s*)[b]	1.04 (3H, *s*)	1.37 (3H, *s*)[b]	1.41 (3H, *s*)	–
H-5‴	1.30 (3H, *s*)[b]	1.40 (3H, *s*)	1.12 (3H, *s*)[b]	1.22 (3H, *s*)	–
OAc-2‴′	2.22 (3H, *s*)	–	1.46 (3H, *s*)	–	–
OH	–	2.24 (1H, *d*, $J = 6.0$)	–	3.60 (1H, *brs*)	1.65 (1H, *brs*)##
OMe-1‴	–	–	–	–	3.98 (3H, *s*)

[a,b] Assignments confirmed by 1D and 2D experiments; * values are in δ (ppm) Coupling constants (J) in parentheses are given in Hz; ** singlet after D_2O exchange; # broad doublet after D_2O exchange; ## exchangeable D_2O.



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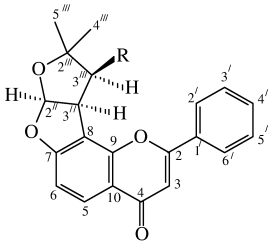
2 R = OH



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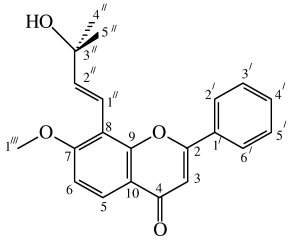
4 R = OH



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were subsequently separated and purified by LH–20 Sephadex chromatography and prep. TLC. This procedure yielded, in order of elution, three compounds **1, 3** and **5**. The isolated compounds were characterized mainly by physical (m. p., $[\alpha]_D$) and several spectroscopic methods including UV, IR, ^{1}H, ^{13}C NMR, DEPT, 2D ^{1}H-^{1}H COSY, HSQC, HMBC experiments, and high resolution mass spectrometry (HR-MS), as well as some chemical transformations. Moreover, the stereochemistry of the isolated compounds **1** and **5** was confirmed by X-ray crystallographic analysis.

Compound **1** was obtained as colourless needles, m. p. 258 – 260 °C, $[\alpha]_D^{25} - 275°$ (c 0.35, $CHCl_3$). The molecular formula $C_{23}H_{20}O_6$ was determined by high resolution mass spectrometry (HR-MS) and showed the exact mass at m/z 392.1260. This was then confirmed by Electron impact (EI)-MS which showed a molecular ion at *m/z* 392. The ultraviolet (UV) spectrum showed absorption at λ_{max} 307, 254, 247 (sh) and 215 nm indicating its flavone character. The UV spectrum remained unchanged on addition of alkali indicating the absence of a phenolic hydroxyl group. The infrared (IR) spectrum showed features characteristic of the flavone system with a band at 1735 cm^{-1}, as expected for CO group of an acetate moiety. The band at 1640 cm^{-1} was attributed to the γ-pyrone moiety [6].

The ^{1}H NMR spectrum of compound **1** integrated for 20 protons. The two up field singlets at $\delta = 1.08$ (3H) and $\delta = 1.30$ (3H) were assigned to H-4‴ and H-5‴ (*gem*-dimethyl), respectively, adjacent to an oxygen function. A singlet at $\delta = 6.76$ (H-3) was attributed to the flavone nucleus [7]. The proton nuclear magnetic resonance (^{1}H NMR) spectral data are in agreement with that of (-)-Semiglarin [2] except for remarkable differences in the B-ring protons, where H-2′/-6′ appear as a multiplet centered at $\delta = 7.90$ (2H). Also, H-3′/-5′ appear as a multiplet centered at $\delta = 7.52$ (2H), and the H-4′ appears as a multiplet centered at $\delta = 7.51$ (1H). Moreover, the examination of the ^{1}H-^{1}H connectivities in the homonuclear COSY spectrum of **1** showed the correlations between the H-2′/-6′ and H-3′/-5′. The ^{1}H assignments were unambiguously confirmed by ^{1}H-^{1}H correlation spectroscopy (COSY)

Carbon No.	**1**[a]	**2**	**3**[a]	**4**	**5**[a]
C-2	162.85 *s*	162.32 *s*	162.66 *s*	162.17 *s*	163.34 *s*
C-3	107.75 *d*	107.49 *d*	107.63 *d*	106.91 *d*	107.10 *d*
C-4	177.43 *s*	177.57 *s*	177.54 *s*	177.52 *s*	178.28 *s*
C-5	128.88 *d*	128.25 *d*	128.71 *d*	128.59 *d*	125.49 *d*
C-6	109.02 *d*	108.95 *d*	108.92 *d*	108.91 *d*	108.96 *d*
C-7	163.70 *s*	163.70 *s*	164.55 *s*	165.20 *s*	162.65 *s*
C-8	112.39 *s*	113.55 *s*	111.44 *s*	111.52 *s*	114.27 *s*
C-9	153.25 *s*	153.12 *s*	153.82 *s*	154.00 *s*	154.56 *s*
C-10	118.74 *s*	118.44 *s*	118.42 *s*	118.02 *s*	118.14 *s*
C-1′	131.55 *s*	131.55 *s*	131.39 *s*	131.39 *s*	132.19 *s*
C-2′/-6′	126.35 *d*	126.00 *d*	126.19 *d*	126.09 *d*	126.44 *d*
C-3′/-5′	129.03 *d*	129.18 *d*	129.13 *d*	129.03 *d*	129.04 *d*
C-4′	131.63 *d*	131.63 *d*	131.73 *d*	131.73 *d*	131.47 *d*
C-1″	–	–	–	–	144.05 *d*
C-2″	112.36 *d*	112.18 *d*	111.73 *d*	112.05 *d*	115.23 *d*
C-3″	52.82 *d*	54.82 *d*	47.95 *d*	49.65 *d*	71.57 *d*
C-4″/-5″	–	–	–	–	30.02 *q*
C-2‴	87.81 *s*	88.21 *s*	84.62 *s*	85.42 *s*	–
C-3‴	80.19 *d*	81.00 *d*	76.75 *d*	79.15 *d*	–
C-4‴	27.45 *q*	27.37 *q*	27.59 *q*	27.90 *q*	–
C-5‴	23.11 *q*	22.90 *q*	23.19 *q*	22.89 *q*	–
C-1⁗(-COMe)	169.59*s*	–	169.81 *s*	–	–
C-2⁗(-COMe)	20.78 *q*	–	20.29 *q*	–	–
C-1⁗(-OMe)	–	–	–	–	56.20 *q*

Table 2. ^{13}C NMR spectral data for compounds **1**–**5** (125 MHz, $CDCl_3$, TMS as internal standard)*.

[a] Assignments confirmed by 2D NMR HSQC and HMBC; * multiplicites deduced from DEPT experiments.

Carbon No.	**1** HMBC with H	**3** HMBC with H	**5** HMBC with H
C-2	2′/6′,3	2′/6′,3	2′/6′,3
C-4	5,3	5,3	5,3
C-7	5,2″,3″	5,2″,3″	5,1″,1‴(-OMe)
C-8	6,3‴,3″	6,3‴,3″	6,2″
C-9	5	5,3″	5,1″
C-10	6,3	6,3	6,3
C-1′	3′/5′,3	3′/5′,3	3′/5′,3
C-2′/-6′	3′/5′	3′/5′,4′	3′/5′,4′
C-3′/-5′	4′	4′	2′/6′,4′
C-4′	3′/5′	2′/6′	2′/6′
C-2″	3‴,3″	–	–
C-3″	2″	–	1″,2″,5″
C-4″	–	–	2″,5″
C-5″	–	–	2″,4″
C-2‴	2″,3‴,3″,5‴(Me_2), 4‴(Me_1)	2″,3″,4‴(Me_1),5‴(Me_2)	–
C-3‴	3″,5‴(Me_2), 4‴(Me_1)	2″,4‴(Me_1),5‴(Me_2)	–
C-4‴(Me_1)	3‴,5‴(Me_2)	3‴,5‴(Me_2)	–
C-5‴(Me_2)	4‴(Me_1)	3‴,4‴(Me_1)	–
C-1⁗(COO)	3‴,2⁗-Me	3‴,2⁗-Me	–

Table 3. HMBC spectral data for compounds **1**, **3** and **5**.

and ^{1}H-^{13}C correlation experiments (HSQC), and are summarized in Table 1.

The ^{13}C NMR spectrum of compound **1** showed the presence of 21 signals, 13 of which can be accounted for by the flavone nucleus. Two of these signals are related to C-4‴ and C-5‴ at $\delta = 27.45$ and $\delta = 23.11$ (*gem*-dimethyl), respectively, indicating the presence of only one aliphatic quaternary carbon atom at $\delta = 87.81$ assignable for C-2‴. Also, the acetate moiety is indicated by the presence of a methyl group or C-2⁗ at $\delta = 20.78$ and carbonyl group or C-1⁗ at $\delta = 169.59$. Signals for the remaining carbons could be assigned by comparison with those reported for (-)-semiglabrin [8]. However, the carbon assignment of (-)-semiglabrin by Whaterman and Khalid [2] for C-8 was farther up field (2.39 ppm) than the observed data. The ^{13}C assignments of **1** were established by ^{1}H-detected heteronuclear single quantum coherence

Table 4. Crystal data and structure refinement for compounds **1** and **5**.

	Compound **1**	Compound **5**
Identification code	CARD2	CARD1
Project title	Card2	Card1
Empirical formula	C_{23} H_{20} O_6	C_{21} H_{20} O_4
Formula weight	392.39	336.37
Temperature [K]	293(2)	293(2)
Wavelength [Å]	0.71073	1.54178
Crystal system	orthorhombic	monoclinic
Space group	$P2_12_12_1$	$P2_1$/c
Unit cell dimensions	$a = 6.719(2)$ Å	$a = 7.3441(3)$ Å
	$b = 12.725(3)$ Å	$b = 11.310(1)$ Å
	$c = 21.789(6)$ Å	$c = 20.573(2)$ Å
		$\beta = 90.377(5)^\circ$
Volume [Å^3]	1862.9(9)	1708.8(2)
Z	4	4
Density (calcd.) [Mg/m^3]	1.399	1.307
Absorption coeff. [mm^{-1}]	0.101	0.730
$F(000)$	824	712
Crystal size [mm]	0.72 × 0.12 × 0.06	0.56 × 0.18 × 0.18
Colour / shape	colorless / needle	colorless / prism
θ Range for data collection [°]	1.85 to 24.99	4.30 to 56.74
Index ranges	$-7 \le h \le 7$,	$-7 \le h \le 7$,
	$-15 \le k \le 15$,	$-12 \le k \le 12$,
	$-25 \le l \le 25$	$-22 \le l \le 22$
Reflections collected	3795	4946
Independent reflections	3261	2275
R(int)	0.1692	0.0280
θ_{max}	24.99°	56.74°
Completeness	99.9%	100.0%
Measurement device	— SiemensP4/PC diffractometer —	
Refinement method	— Full-matrix least-squares on F^2 —	
Data / restraints / params	3261 / 0 / 262	2275 / 0 / 230
Goodness-of-fit on F^2	0.962	1.047
Final R indices	$R1 = 0.1049$,	$R1 = 0.0385$,
$[I > 2\sigma(I)]$	$wR2 = 0.1265$	$wR2 = 0.1002$
R Indices (all data)	$R1 = 0.3509$,	$R1 = 0.0462$,
	$wR2 = 0.1957$	$wR2 = 0.1068$
Absolute structure param.	−4(5)	
Extinction coefficient		0.0112(7)
Largest diff. peak and hole [e·Å^{-3}]	0.273 and −0.287	0.158 and −0.143

(HSQC) and ^{1}H-detected heteronuclear multiple bond connectivity (HMBC) spectroscopies, as shown in Tables 2 and 3.

The distortionless enhancement by polarization transfer (DEPT) experiments (performed at 90° and 135°) were carried out to ascertain the nature of the carbon atoms. They showed fourteen positive peaks for three methyl and eleven methine carbons. The negative peaks for methylene carbons were absent. The other nine resonances were due to the quaternary carbons.

The electron impact (EI) mass spectrum of compound **1** showed a molecular ion peak at *m/z* 392 [M$^+$] together with the loss of acetic acid to give *m/z* 332,

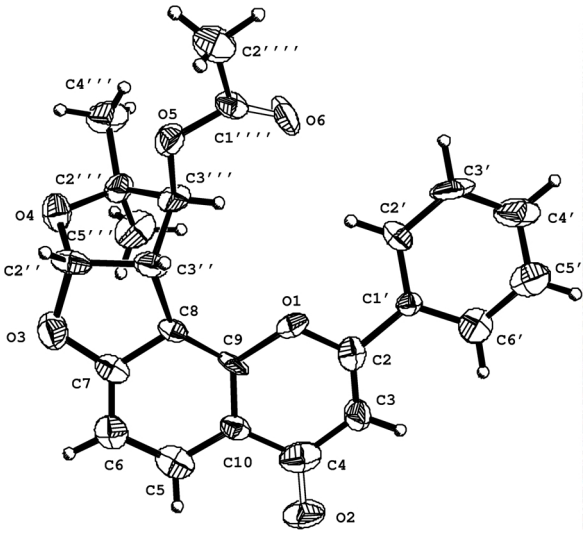

Fig. 1. ORTEP view of compound **1**, thermal ellipsoid at 50% probability level.

which is the base peak of the spectrum. There was also a significant peak at *m/z* 102 corresponding to Ph-CH=CH$^+$, the fragment commonly observed in the MS of flavones with an unsubstituted B-ring [9].

Single crystal X-ray analysis established the complete structure and relative stereochemistry of compound **1**. The data are summarized in Tables 4–9. A view of the solid-state conformation is illustrated in Fig. 1. The remarkable feature of the stereochemistry of **1** is the *syn* beta-oriented disposition of the protons attached to C-2″ and C-3″ and the pseudo-axial acetoxy substituent at C-3‴. Cremer and Pople [10] parameters indicated that the five-membered rings in the bisfurano moiety adopt twisted ($q^2 = 0.110$ Å, $\phi = 95^\circ$ and $q^2 = 0.322$ Å, $\phi = 123^\circ$) conformations, with pseudo C_2 symmetry axis passing throughout O-3 and C-2″, respectively. The flavone moiety is essentially planar (angle between the γ-pyrone moiety and phenyl ring is 9.6°) with the H-2′, displaying intermolecular short contacts with the O-l (2.331 Å) and the $O_{carbonyl}$ (2.457 Å) of the acetoxy group. In the light of the above data compound **1**, was named as (-)-semiglabrin and has been established to be 2‴,2‴-dimethyl-3‴-acetoxy-tetrahydrofurano-[3″,2″-b]-dihydrofurano-[5″,4″-h]-flavone.

Compound **3** was obtained as colourless prisms, m. p. 169–171 °C, $[\alpha]_D^{25} - 379^\circ$ (c 0.90, $CHCI_3$). The molecular formula $C_{23}H_{20}O_6$ was determined by high resolution mass spectrometery (HR-MS) and showed the exact mass at *m/z* 392.1258. This was then con-

Table 5. Non-hydrogen atoms fractional coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\times 10^3$ Å^2) for compounds **1** and **5**.

Atom	*x*	*y*	*z*	U_{eq}*
Compound **1**				
O(1)	6933(13)	5300(6)	2677(3)	33(2)
O(2)	4336(14)	7324(7)	1442(4)	56(3)
O(3)	2310(14)	6038(7)	4195(4)	49(3)
O(4)	4793(14)	5677(7)	4917(4)	42(3)
O(5)	7453(14)	3993(6)	4516(3)	43(3)
O(6)	10141(14)	3626(7)	3941(4)	54(3)
C(2)	7740(20)	5500(9)	2118(5)	32(3)
C(3)	6970(20)	6159(10)	1705(5)	40(4)
C(4)	5160(30)	6726(11)	1825(6)	50(4)
C(5)	2600(20)	7087(9)	2637(6)	42(4)
C(6)	1850(20)	6951(10)	3238(5)	40(4)
C(7)	2840(20)	6248(11)	3597(6)	40(4)
C(8)	4580(20)	5686(10)	3424(5)	35(4)
C(9)	5227(19)	5857(10)	2839(5)	31(3)
C(10)	4304(19)	6547(10)	2443(6)	32(4)
C(1′)	9683(18)	4937(10)	2041(5)	24(3)
C(2′)	10527(19)	4403(9)	2526(6)	35(3)
C(3′)	12310(20)	3849(11)	2447(6)	57(5)
C(4′)	13160(20)	3822(11)	1883(6)	60(5)
C(5′)	12390(20)	4338(10)	1386(6)	54(4)
C(6′)	10580(20)	4881(10)	1466(6)	43(4)
C(2″)	3664(18)	5255(10)	4447(5)	38(4)
C(3″)	5020(20)	4923(10)	3920(5)	39(4)
C(2‴)	6840(20)	5846(11)	4722(5)	36(4)
C(3‴)	7090(20)	5006(9)	4216(5)	37(4)
C(4‴)	8169(19)	5700(10)	5268(5)	54(4)
C(5‴)	7120(20)	6971(18)	4450(5)	57(5)
C(1⁗)	8970(20)	3373(10)	4305(6)	31(4)
C(2⁗)	8950(20)	2362(10)	4668(5)	67(5)
Compound **5**				
O(1)	2664(2)	4362(1)	4798(1)	42(1)
O(2)	3869(2)	3567(2)	6680(1)	64(1)
O(3)	1293(2)	8323(1)	5280(1)	56(1)
O(4)	3223(2)	8007(1)	2989(1)	57(1)
C(2)	3199(2)	3257(2)	4968(1)	41(1)
C(3)	3570(3)	2965(2)	5590(1)	48(1)
C(4)	3460(3)	3811(2)	6107(1)	47(1)
C(5)	2627(3)	5900(2)	6362(1)	49(1)
C(6)	2093(3)	6999(2)	6161(1)	50(1)
C(7)	1773(3)	7232(2)	5501(1)	44(1)
C(8)	1946(2)	6341(2)	5030(1)	40(1)
C(9)	2471(2)	5227(2)	5264(1)	38(1)
C(10)	2838(3)	4981(2)	5918(1)	42(1)
C(1′)	3343(2)	2476(2)	4394(1)	42(1)
C(2′)	3074(3)	2912(2)	3770(1)	52(1)
C(3′)	3281(3)	2189(2)	3233(1)	59(1)
C(4′)	3744(3)	1023(2)	3307(1)	60(1)
C(5′)	3995(3)	571(2)	3922(1)	61(1)
C(6′)	3806(3)	1291(2)	4464(1)	53(1)
C(1″)	1652(3)	6481(2)	4324(1)	43(1)
C(2″)	1717(3)	7442(2)	3965(1)	48(1)
C(3″)	1555(3)	7508(2)	3233(1)	47(1)
C(4″)	97(3)	8403(2)	3049(1)	61(1)
C(5″)	1193(4)	6326(2)	2908(1)	62(1)
C(1‴)	1014(3)	9235(2)	5751(1)	60(1)

* U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 6. Hydrogen atoms fractional coordinates ($\times 10^4$) and isotropic displacement parameters ($\times 10^3$ Å^2) for compounds **1** and **5**.

Atom	*x*	*y*	*z*	U_{eq}
Compound **1**				
H(3)	7632	6254	1318	48
H(5)	1925	7535	2350	50
H(6)	718	7334	3391	48
H(2′)	9881	4426	2919	42
H(3′)	12885	3472	2785	69
H(4′)	14386	3443	1829	73
H(5′)	13058	4339	996	64
H(6′)	9972	5235	1126	52
H(2″)	2926	4663	4598	46
H(3″)	4765	4217	3787	47
H(3‴)	8113	5175	3923	45
H(4‴ A)	9324	6143	5252	65
H(4‴ B)	8608	4982	5271	65
H(4‴ C)	7422	5845	5634	65
H(5‴ A)	7487	7464	4764	68
H(5‴ B)	5908	7202	4262	68
H(5‴ C)	8154	6952	4145	68
H(2⁗ A)	10086	1950	4552	80
H(2⁗ B)	7774	1975	4560	80
H(2⁗ C)	8971	2491	5102	80
Compound **5**				
H(3)	3916	2167	5690	58
H(5)	2861	5759	6815	58
H(6)	1934	7617	6475	60
H(2′ A)	2752	3727	3709	63
H(3′)	3093	2508	2805	71
H(4′)	3890	526	2932	71
H(5′)	4305	−248	3977	73
H(6′)	3996	967	4891	63
H(1‴)	1372	5766	4093	52
H(2″)	1885	8177	4191	58
H(4 A)	4080(40)	7530(20)	3106(12)	69
H(4″ A)	−2	8455	2584	74
H(4″ B)	415	9162	3225	74
H(4″ C)	−1053	8171	3228	74
H(5″ A)	2211	5810	2981	74
H(5″ B)	1049	6435	2448	74
H(5″ C)	111	5978	3084	74
H(1‴ A)	2122	9360	5991	72
H(1‴ B)	52	9019	6041	72
H(1‴ C)	712	9958	5531	72

firmed by Electron impact (EI)-MS which showed molecular ion at *m/z* 392. The ultraviolet (UV) and infrared (IR) spectra were similar to that of compound **1**.

Table 7. Bond lengths [Å] and bond angles [°], with standard deviations in parentheses for compounds **1** and **5**.

Compound **1**			
O(1)-C(2)	1.358(12)	O(1)-C(9)	1.393(13)
C(2)-C(3)	1.334(15)	C(2)-C(1′)	1.449(16)
C(3)-C(4)	1.436(18)	C(4)-O(2)	1.259(14)
C(4)-C(10)	1.482(17)	C(5)-C(10)	1.402(16)
C(5)-C(6)	1.414(15)	C(6)-C(7)	1.361(16)
C(7)-O(3)	1.377(13)	C(7)-C(8)	1.424(17)
C(8)-C(9)	1.363(14)	C(8)-C(3″)	1.482(14)
C(9)-C(10)	1.379(15)	C(1′)-C(2′)	1.379(14)
C(1′)-C(6′)	1.392(14)	C(2′)-C(3′)	1.399(17)
C(3′)-C(4′)	1.357(17)	C(4′)-C(5′)	1.370(15)
C(5′)-C(6′)	1.407(16)	O(3)-C(2″)	1.456(13)
C(2″)-O(4)	1.383(12)	C(2″)-C(3″)	1.524(15)
C(3″)-C(3‴)	1.538(17)	O(4)-C(2‴)	1.457(14)
C(2‴)-C(4‴)	1.498(14)	C(2‴)-C(3‴)	1.545(14)
C(2‴)-C(5‴)	1.561(14)	C(3‴)-O(5)	1.466(12)
O(5)-C(1⁗)	1.366(13)	O(6)-C(1⁗)	1.165(13)
C(1⁗)-C(2⁗)	1.511(16)		
C(2)-O(1)-C(9)	117.4(10)	C(3)-C(2)-O(1)	124.7(13)
C(3)-C(2)-C(1′)	124.3(12)	O(1)-C(2)-C(1′)	111.0(11)
C(2)-C(3)-C(4)	121.3(13)	O(2)-C(4)-C(3)	123.7(14)
O(2)-C(4)-C(10)	121.6(15)	C(3)-C(4)-C(10)	114.7(13)
C(10)-C(5)-C(6)	120.8(13)	C(7)-C(6)-C(5)	115.9(13)
C(6)-C(7)-O(3)	123.1(13)	C(6)-C(7)-C(8)	125.5(13)
O(3)-C(7)-C(8)	111.4(12)	C(9)-C(8)-C(7)	115.4(12)
C(9)-C(8)-C(3″)	136.3(13)	C(7)-C(8)-C(3″)	107.4(11)
C(8)-C(9)-C(10)	122.9(13)	C(8)-C(9)-O(1)	114.7(11)
C(10)-C(9)-O(1)	122.4(11)	C(9)-C(10)-C(5)	119.4(13)
C(9)-C(10)-C(4)	119.4(13)	C(5)-C(10)-C(4)	121.2(13)
C(2′)-C(1′)-C(6′)	119.0(12)	C(2′)-C(1′)-C(2)	120.6(11)
C(6′)-C(1′)-C(2)	120.2(11)	C(1′)-C(2′)-C(3′)	120.4(12)
C(4′)-C(3′)-C(2′)	119.1(14)	C(3′)-C(4′)-C(5′)	122.9(15)
C(4′)-C(5′)-C(6′)	117.6(14)	C(1′)-C(6′)-C(5′)	120.8(13)
C(7)-O(3)-C(2″)	109.2(10)	O(4)-C(2″)-O(3)	110.8(11)
O(4)-C(2″)-C(3″)	109.7(10)	O(3)-C(2″)-C(3″)	106.2(9)
C(8)-C(3″)-C(2″)	104.4(11)	C(8)-C(3″)-C(3‴)	116.1(12)
C(2″)-C(3″)-C(3‴)	101.9(9)	C(2″)-O(4)-C(2‴)	111.1(9)
O(4)-C(2‴)-C(4‴)	108.2(10)	O(4)-C(2‴)-C(3‴)	102.1(11)
C(4‴)-C(2‴)-C(3‴)	114.6(11)	O(4)-C(2‴)-C(5‴)	111.2(11)
C(4‴)-C(2‴)-C(5‴)	110.1(12)	C(3‴)-C(2‴)-C(5‴)	110.4(10)
O(5)-C(3‴)-C(3″)	106.0(11)	O(5)-C(3‴)-C(2‴)	107.9(8)
C(3″)-C(3‴)-C(2‴)	104.4(11)	C(1⁗)-O(5)-C(3‴)	118.8(10)
O(5)-C(1⁗)-C(2⁗)	108.1(11)	O(6)-C(1⁗)-O(5)	125.0(13)
O(6)-C(1⁗)-C(2⁗)	126.7(13)		

Table 7 (continued).

Compound **5**			
O(1)-C(2)	1.355(2)	O(1)-C(9)	1.377(2)
C(2)-C(3)	1.347(3)	C(2)-C(1′)	1.479(3)
C(3)-C(4)	1.435(3)	C(4)-O(2)	1.245(2)
C(4)-C(10)	1.452(3)	C(5)-C(6)	1.367(3)
C(5)-C(10)	1.393(3)	C(6)-C(7)	1.401(3)
C(7)-O(3)	1.361(2)	C(7)-C(8)	1.404(3)
O(3)-C(1‴)	1.430(2)	C(8)-C(9)	1.403(3)
C(8)-C(1″)	1.474(3)	C(9)-C(10)	1.397(3)
C(1′)-C(2′)	1.389(3)	C(1′)-C(6′)	1.391(3)
C(2′)-C(3′)	1.383(3)	C(3′)-C(4′)	1.371(3)
C(4′)-C(5′)	1.377(3)	C(5′)-C(6′)	1.389(3)
C(1″)-C(2″)	1.316(3)	C(2″)-C(3″)	1.511(3)
C(3″)-O(4)	1.442(3)	C(3″)-C(4″)	1.520(3)
C(3″)-C(5″)	1.517(3)		
C(2)-O(1)-C(9)	120.45(14)	C(3)-C(2)-O(1)	121.82(17)
C(3)-C(2)-C(1′)	126.63(18)	O(1)-C(2)-C(1′)	111.53(15)
C(2)-C(3)-C(4)	121.93(18)	O(2)-C(4)-C(3)	122.67(19)
O(2)-C(4)-C(10)	122.01(18)	C(3)-C(4)-C(10)	115.32(16)
C(6)-C(5)-C(10)	120.87(17)	C(5)-C(6)-C(7)	120.67(18)
O(3)-C(7)-C(6)	122.37(17)	O(3)-C(7)-C(8)	116.41(16)
C(6)-C(7)-C(8)	121.22(18)	C(7)-O(3)-C(1‴)	117.81(16)
C(9)-C(8)-C(7)	115.67(16)	C(9)-C(8)-C(1″)	118.22(16)
C(7)-C(8)-C(1″)	126.10(17)	O(1)-C(9)-C(10)	120.53(17)
O(1)-C(9)-C(8)	115.37(15)	C(10)-C(9)-C(8)	124.07(17)
C(5)-C(10)-C(9)	117.46(18)	C(5)-C(10)-C(4)	122.64(17)
C(9)-C(10)-C(4)	119.88(17)	C(2′)-C(1′)-C(6′)	118.09(18)
C(2′)-C(1′)-C(2)	121.10(18)	C(6′)-C(1′)-C(2)	120.78(17)
C(3′)-C(2′)-C(1′)	120.9(2)	C(4′)-C(3′)-C(2′)	120.6(2)
C(3′)-C(4′)-C(5′)	119.4(2)	C(4′)-C(5′)-C(6′)	120.5(2)
C(5′)-C(6′)-C(1′)	120.5(2)	C(2″)-C(1″)-C(8)	129.53(18)
C(1″)-C(2″)-C(3″)	126.73(18)	O(4)-C(3″)-C(2″)	107.76(16)
O(4)-C(3″)-C(4″)	104.56(16)	O(4)-C(3″)-C(5″)	109.72(17)
C(2″)-C(3″)-C(4″)	109.45(17)	C(2″)-C(3″)-C(5″)	114.07(16)
C(5″)-C(3″)-C(4″)	110.81(19)		

The ^{1}H NMR spectrum of compound **3** resembled that of the previously reported spectrum for (-)-pseudosemiglabrin [2] except for remarkable differences in the B-ring protons, where H-2′/-6′ appear as double of doublets centered at $\delta = 7.80$ (2H, $J =$ 8.0, 2.0). Also, H-3′/-5′ appear as double of doublets at $\delta = 7.52$ (2H, $J = 8.0, 2.0$), while the H-4′ appears as a multiplet centered at $\delta = 7.51$ (1H). The two-dimensional (2D) ^{1}H-^{1}H and ^{1}H-^{13}C correlation spectroscopies (COSY) showed that the stereochemistry of *gem*-dimethyl of compound **3** are in the opposite direction to the *gem*-diemethyl of compound **1**. In compound **3**, the two up field singlets of *gem*-dimethyl centered at $\delta = 1.12$ (3H) and $\delta = 1.37$ (3H) which were assigned to H-5‴ and H-4‴, respectively, whereas the two up field singlets of *gem*-dimethyl of compound **1** appear at $\delta = 1.08$ (3H) and $\delta = 1.30$ (3H) which were assigned to H-4‴ and H-5‴, respectively. The ^{1}H assignments were unambiguously confirmed by ^{1}H-^{1}H correlation spectroscopy (COSY) and ^{1}H-^{13}C correlation experiments (HSQC), and are summarized in Table 1.

The ^{13}C NMR of compound **3** showed the presence of 21 signals. The data are in agreement with that of (-)-pseudosemiglabrin [11] except for remarkable differences, where the data of C-2″ and C-6 were reversible, as well as the data of C-2‴ and C-3‴ were also reversible. The assignment of C-2″ appears at $\delta = 111.73$, whereas C-6 appears at $\delta = 108.92$. Also, the assignment of C-2‴ appears at $\delta = 84.62$, whereas

Table 8. Torsion angles [°] for compounds **1** and **5**.

Compound **1**		Compound **5**		Compound **1**		Compound **5**	
C(9)-O(1)-C(2)-C(3)	−2.6(17)	C(9)-O(1)-C(2)- C(3)	−0.4(3)	C(2′)-C(3′)-C(4′)-C(5′)	2(2)	C(2)-C(1′)-C(2′)-C(3′)	177.4(2)
C(9)-O(1)-C(2)-C(1′)	173.5(10)	C(9)-O(1)-C(2)-C(1′)	−179.20(15)	C(3′)-C(4′)-C(5′)-C(6′)	−3(2)	C(1′)-C(2′)-C(3′)-C(4′)	0.5(4)
O(1)-C(2)-C(3)-C(4)	0(2)	O(1)-C(2)-C(3)-C(4)	−1.5(3)	C(2′)-C(1′)-C(6′)-C(5′)	−4(2)	C(2′)-C(3′)-C(4′)-C(5′)	0.3(4)
C(1′)-C(2)-C(3)-C(4)	−175.8(12)	C(1′)-C(2)-C(3)-C(4)	177.17(18)	C(2)-C(1′)-C(6′)C(5′)	−178.8(12)	C(3′)-C(4′)-C(5′)-C(6′)	−0.8(4)
C(2)-C(3)-C(4)-O(2)	−177.0(13)	C(2)-C(3)-C(4)-O(2)	−177.0(2)	C(4′)-C(5′)-C(6′)-C(1′)	4(2)	C(4′)-C(5′)-C(6′)-C(1′)	0.6(4)
C(2)-C(3)-C(4)-C(10)	2.3(19)	C(2)-C(3)-C(4)-C(10)	2.9(3)	C(6)-C(7)-O(3)-C(2″)	−179.9(12)	C(2′)-C(1′)-C(6′)-C(5′)	0.2(3)
C(10)-C(5)-C(6)-C(7)	−2.2(18)	C(10)-C(5)-C(6)-C(7)	−1.1(3)	C(8)-C(7)-O(3)-C(2″)	−3.2(15)	C(2)-C(1′)-C(6′)-C(5′)	−177.94(19)
C(5)-C(6)-C(7)-O(3)	179.1(12)	C(5)-C(6)-C(7)-O(3)	−177.97(19)	C(7)-O(3)-C(2′)-O(4)	114.7(11)	C(9)-C(8)-C(1″)-C(2″)	−156.6(2)
C(5)-C(6)-C(7)-C(8)	2.8(19)	C(5)-C(6)-C(7)-C(8)	1.6(3)	C(7)-O(3)-C(2′)-C(3″)	−4.5(14)	C(7)-C(8)-C(1″)-C(2″)	22.5(3)
C(6)-C(7)-C(8)-C(9)	−3(2)	C(6)-C(7)-O(3)-C(1‴)	−3.5(3)	C(9)-C(8)-C(3″)-C(2″)	180.0(16)	C(8)-C(1″)-C(2″)-C(3″)	174.50(19)
O(3)-C(7)-C(8)-C(9)	−179.2(12)	C(8)-C(7)-O(3)-C(1‴)	176.87(18)	C(7)-C(8)-C(3″)-C(2″)	−11.8(15)	C(1″)-C(2″)-C(3″)-O(4)	−119.0(2)
C(6)-C(7)-C(8)-C(3″)	−173.6(13)	O(3)-C(7)-C(8)-C(9)	178.99(16)	C(9)-C(8)-C(3″)-C(3‴)	69(2)	C(1″)-C(2″)-C(3″)-C(4″)	127.8(2)
O(3)-C(7)-C(8)-C(3″)	9.7(15)	C(6)-C(7)-C(8)-C(9)	−0.6(3)	C(7)-C(8)-C(3″)-C(3‴)	−123.1(13)	C(1″)-C(2″)-C(3″)-C(5″)	3.1(3)
C(7)-C(8)-C(9)-C(10)	2(2)	O(3)-C(7)-C(8)-C(1″)	−0.2(3)	O(4)-C(2″)-C(3″)-C(8)	−110.0(12)		
C(3″)-C(8)-C(9)-C(10)	169.4(15)	C(6)-C(7)-C(8)-C(1″)	−179.80(18)	O(3)-C(2″)-C(3″)-C(8)	9.9(14)		
C(7)-C(8)-C(9)-O(1)	−180.0(11)	C(2)O(1)-C(9)-C(10)	0.5(2)	O(4)-C(2″)-C(3″)-C(3‴)	11.3(14)		
C(3″)-C(8)-C(9)-O(1)	−12(2)	C(2)-O(1)-C(9)-C(8)	178.78(15)	O(3)-C(2″)-C(3″)-C(3‴)	131.2(10)		
C(2)-O(1)-C(9)-C(8)	−175.0(11)	C(7)-C(8)-C(9)-O(1)	−179.09(15)	O(3)-C(2′)-O(4)-C(2‴)	−106.8(11)		
C(2)-O(1)-C(9)-C(10)	3.3(16)	C(1″)-C(8)-C(9)-O(1)	0.1(2)	C(3″)-C(2″)-O(4)-C(2‴)	10.2(15)		
C(8)-C(9)-C(10)-C(5)	−1.4(19)	C(7)-C(8)-C(9)-C(10)	−0.9(3)	C(2′)-O(4)-C(2‴)-C(4‴)	−148.3(11)		
O(1)-C(9)-C(10)-C(5)	−179.6(11)	C(1″)-C(8)-C(9)-C(10)	178.32(17)	C(2″)-O(4)-C(2‴)-C(3‴)	−27.0(13)		
C(8)-C(9)-C(10)-C(4)	176.9(14)	C(6)-C(5)-C(10)-C(9)	−0.4(3)	C(2′)-O(4)-C(2‴)-C(5‴)	90.7(12)		
O(1)-C(9)-C(10)-C(4)	−1.2(18)	C(6)-C(5)-C(10)-C(4)	177.94(19)	C(8)-C(3′)-C(3‴)-O(5)	−160.3(10)		
C(6)-C(5)-C(10)-C(9)	1.6(18)	O(1)-C(9)-C(10)-C(5)	179.53(16)	C(2′)-C(3″)-C(3‴)-O(5)	86.9(12)		
C(6)-C(5)-C(10)-C(4)	−176.7(12)	C(8)-C(9)-C(10)-C(5)	1.4(3)	C(8)-C(3′)-C(3‴)-C(2‴)	85.9(12)		
O(2)-C(4)-C(10)-C(9)	177.7(12)	O(1)-C(9)-C(10)-C(4)	1.1(3)	C(2′)-C(3″)-C(3‴)-C(2‴)	−26.9(12)		
C(3)-C(4)-C(10)-C(9)	−1.5(18)	C(8)-C(9)-C(10)-C(4)	−176.96(17)	O(4)-C(2″)-C(3‴)-O(5)	−79.6(13)		
O(2)-C(4)-C(10)-C(5)	−4(2)	O(2)-C(4)-C(10)-C(5)	−1.1(3)	C(4‴)-C(2‴)-C(3‴)-O(5)	37.1(16)		
C(3)-C(4)-C(10)-C(5)	176.8(12)	C(3)-C(4)-C(10)-C(5)	178.94(18)	C(5‴)-C(2‴)-C(3‴)-O(5)	162.1(11)		
C(3)-C(2)-C(1′)-C(2′)	169.5(12)	O(2)-C(4)-C(10)-C(9)	177.21(19)	O(4)-C(2″)-C(3‴)-C(3″)	32.9(11)		
O(1)-C(2)-C(1′)-C(2′)	−6.6(15)	C(3)-C(4)-C(10)-C(9)	−2.7(3)	C(4‴)-C(2‴)-C(3‴)-C(3″)	149.6(11)		
C(3)-C(2)-C(1′)-C(6′)	−15.3(19)	C(3)-C(2)-C(1′)-C(2′)	−174.3(2)	C(5‴)-C(2‴)-C(3‴)-C(3″)	−85.4(13)		
O(1)-C(2)-C(1′)-C(6′)	168.6(11)	O(1)-C(2)-C(1′)-C(2′)	4.4(3)	C(3″)-C(3‴)-O(5)-C(1⁗)	115.3(11)		
C(6′)-C(1′)-C(2′)-C(3′)	2.6(19)	C(3)-C(2)-C(1′)-C(6′)	3.7(3)	C(2‴)-C(3‴)-O(5)-C(1⁗)	−133.3(11)		
C(2)-C(1′)-C(2′)-C(3′)	177.8(12)	O(1)-C(2)-C(1′)-C(6′)	−177.52(17)	C(3‴)-O(5)-C(1⁗)-O(6)	8.0(19)		
C(1′)-C(2′)-C(3′)-C(4′)	−2(2)	C(6′)-C(1′)-C(2′)-C(3′)	−0.8(3)	C(3‴)-O(5)-C(1⁗)-C(2⁗)	−177.2(11)		

Table 9. Anisotropic displacement parameters ($\times 10^3$ Å^2) for compounds **1** and **5**[#].

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Compound **1**						
O(1)	40(6)	36(6)	24(5)	8(4)	−5(5)	−2(5)
O(2)	63(8)	56(7)	48(6)	24(6)	−14(6)	0(6)
O(3)	48(7)	46(6)	52(6)	6(5)	15(6)	11(6)
O(4)	40(7)	41(6)	45(6)	−12(5)	8(5)	−5(6)
O(5)	55(7)	40(6)	33(5)	9(5)	11(6)	11(6)
O(6)	38(7)	52(7)	71(7)	15(6)	28(6)	22(6)
C(2)	38(10)	20(7)	38(8)	−13(7)	3(8)	−5(8)
C(3)	35(10)	48(10)	38(8)	9(8)	11(8)	3(9)
C(4)	63(12)	35(10)	50(10)	−4(8)	−21(10)	−5(10)
C(5)	40(10)	21(8)	65(9)	8(7)	−5(9)	−5(8)
C(6)	32(9)	40(10)	48(9)	−10(8)	−4(8)	−15(8)
C(7)	28(9)	42(9)	50(9)	0(8)	−7(8)	2(8)
C(8)	32(9)	37(9)	36(8)	6(7)	−3(7)	18(8)
C(9)	20(8)	23(8)	50(9)	14(7)	−2(7)	13(7)
C(10)	26(9)	32(9)	37(8)	−4(7)	−8(7)	2(7)
C(1′)	29(8)	20(7)	22(6)	−2(6)	−4(6)	1(7)
C(2′)	28(9)	29(8)	47(8)	2(8)	2(7)	5(7)
C(3′)	88(14)	47(10)	36(9)	8(8)	−33(11)	19(11)
C(4′)	76(13)	46(12)	60(10)	−16(8)	−42(11)	11(11)
C(5′)	45(10)	69(12)	47(9)	12(9)	−4(9)	−14(10)
C(6′)	61(11)	23(8)	46(8)	3(7)	3(9)	1(9)
C(2″)	28(8)	34(9)	52(9)	7(8)	−19(7)	−5(7)
C(3″)	38(9)	40(9)	40(8)	−1(7)	−11(8)	13(8)
C(2‴)	43(9)	39(9)	26(7)	−7(7)	−2(7)	4(8)
C(3‴)	60(11)	19(7)	32(7)	14(6)	3(8)	12(8)
C(4‴)	62(11)	57(11)	43(8)	−15(8)	−25(8)	−3(9)
C(5‴)	85(13)	26(8)	59(9)	10(8)	0(10)	−11(10)
C(1⁗)	33(9)	21(8)	39(9)	−6(8)	−8(7)	6(7)
C(2⁗)	78(13)	52(11)	71(11)	12(9)	5(10)	32(10)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Compound **5**						
O(1)	54(1)	44(1)	29(1)	−1(1)	0(1)	2(1)
O(2)	82(1)	78(1)	31(1)	9(1)	1(1)	20(1)
O(3)	77(1)	49(1)	42(1)	−6(1)	2(1)	11(1)
O(4)	65(1)	55(1)	52(1)	15(1)	10(1)	3(1)
C(2)	39(1)	45(1)	37(1)	4(1)	2(1)	0(1)
C(3)	56(1)	51(1)	38(1)	6(1)	2(1)	7(1)
C(4)	48(1)	63(1)	29(1)	7(1)	2(1)	4(1)
C(5)	55(1)	64(1)	27(1)	−2(1)	4(1)	−1(1)
C(6)	58(1)	59(1)	34(1)	−9(1)	5(1)	1(1)
C(7)	45(1)	49(1)	38(1)	0(1)	5(1)	0(1)
C(8)	40(1)	48(1)	31(1)	−1(1)	3(1)	−3(1)
C(9)	37(1)	49(1)	29(1)	−2(1)	5(1)	−3(1)
C(10)	41(1)	56(1)	30(1)	4(1)	3(1)	−1(1)
C(1′)	40(1)	47(1)	37(1)	−1(1)	0(1)	−1(1)
C(2′)	65(1)	52(1)	40(1)	0(1)	0(1)	6(1)
C(3′)	73(2)	69(2)	37(1)	−7(1)	−3(1)	5(1)
C(4′)	64(1)	64(1)	50(1)	−18(1)	−2(1)	3(1)
C(5′)	66(1)	47(1)	68(2)	−11(1)	−5(1)	4(1)
C(6′)	62(1)	50(1)	46(1)	2(1)	−3(1)	2(1)
C(1″)	50(1)	45(1)	35(1)	−1(1)	−1(1)	−1(1)
C(2″)	62(1)	46(1)	37(1)	−2(1)	1(1)	−3(1)
C(3″)	62(1)	45(1)	34(1)	5(1)	5(1)	−2(1)
C(4″)	66(1)	66(1)	52(1)	6(1)	−1(1)	7(1)
C(5″)	98(2)	54(1)	34(1)	1(1)	0(1)	−6(1)
C(1‴)	69(1)	55(1)	55(1)	−13(1)	−1(1)	8(1)

[#] The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2\boldsymbol{a}^{*2}\boldsymbol{U}_{11}+\ldots+2hk\boldsymbol{a}^*\boldsymbol{b}^*\boldsymbol{U}_{12}]$.

C-3‴ appears at $\delta = 76.75$. The ^{13}C assignments of **3** were unambiguously confirmed by two-dimensional (2D) ^{1}H-^{13}C correlation spectroscopies (HSQC and HMBC), as shown in Tables 2 and 3.

The DEPT experiments (performed at 90° and 135°) were carried out to ascertain the nature of the carbon atoms. They showed results that were similar to that of compound **1**.

The electron impact (EI) mass spectrum of compound **3** showed a fragmentation pattern similar to that of compound **1** leading to the speculation that the two compounds are also isomers.

It is worth noting that, (-)-pseudosemiglabrin **3** is a diastereoisomer of (-)-semiglabrin **1** because the $[\alpha]_D$ of the former −379° has the same sign but higher value than in the latter. Furthermore, (-)-pseudosemiglabrin **3** has 3 chiral centers at C-2″, C-3″ and C-3‴ where the splitting of the protons on the two latter carbons differ from (-)-semiglabrin **1**, as shown in Table 1.

Our attempts to effect deacetylation of compounds **1** and **3** under mild alkaline hydrolysis (see Experimental Section) to give alcohols **2** and **4** were successful. These alcohols were identical in all respects (m. p., UV, IR, NMR, and EI-MS) with natural (-)-semiglabrinol and (-)-pseudosemiglabrinol, respectively. In this work, we present the total assignments of the ^{1}H and ^{13}C NMR spectra of the compounds **2** and **4**, and are recorded in Tables 1 and 2. Hence, their structures have been established as 2‴,2‴-dimethyl-3‴-hydroxy-tetrahyrofurano-[3″,2″-b]-dihydrofurano-[5″,4″-h]-flavone.

Compound **5** was obtained as colourless prismatic needles, m. p. 186 – 188 °C. The molecular formula $C_{21}H_{20}O_4$ was determined by high resolution mass spectrometry (HR-MS) and showed the exact mass at *m/z* 336.1362. This was then confirmed by Electron impact (EI)-MS which showed a molecular ion at *m/z* 336. The ultraviolet (UV) spectrum showed absorptions at λ_{max} 318, 262 and 224 nm, unaffected by the addition of alkali precluding the presence of phenolic OH groups. The infrared (IR) spectrum showed characteristic absorption bands of a flavone system

Table 10. Hydrogen bonds [Å and °] for compound **5**.

D-H…A	d(D-H)	d(H…A)	d(D…A)	∠ (DHA)
O(4)-H(4A)…O(2)$^{\#1}$	0.86(3)	2.00(3)	2.859(2)	176(2)

Symmetry transformations used to generate equivalent atoms:
$^{\#1}$ $-x+1, -y+1, -z+1$.

with bands at 1635 and 1590 cm^{-1}, which were attributed to γ-pyrone CO and styryl, respectively. The bands at 3500, 1384 and 1149 cm^{-1}, as expected for the tertiary OH group [12].

The ^{1}H NMR spectrum of compound **5** integrated for 20 protons. In the aromatic region, a singlet at $\delta =$ 6.76 (H-3) indicative for a flavone nucleus [7]. Multiplets at $\delta = 7.90-7.92$ (2H) and $\delta = 7.50-7.51$ (3H), and the two *ortho* coupled doublets at $\delta = 8.12$ (1H, $J = 8.8$) and $\delta = 7.02$ (1H, $J = 8.8$) showed lack of substitution in ring B and at C-5 and C-6, respectively. The presence of a methoxyl group was also evident by a singlet at $\delta = 3.98$ (3H). The relative positions of the methoxyl group and the side chain at C-7 and C-8, respectively, were determined by benzene induced solvent shift which resulted in the up field shift of the methoxy proton signal (0.23 ppm) [13]. The remaining nine protons were typically those of the rarely encountered 3″-hydroxy-3″-methyl-trans-isobut-1″-enyl side chain, and observed as follows: i) the two singlets centered at $\delta = 1.55$ (3H) and at $\delta = 1.50$ (3H) were assigned to H-4″ and H-5″ (*gem*-dimethyl), respectively, ii) a broad singlet at $\delta = 1.65$ (1H, exchangeable D_2O) was assigned to a hydroxyl (OH) proton, and iii) the two doublets centered at $\delta = 6.97$ (1H, $J = 16.5$) and at $\delta = 6.82$ (1H, $J = 16.5$) were assigned to coupled H-1″ and H-2″, respectively [14]. The J value indicated a *trans*-configuration [15]. The ^{1}H assignments were unambiguously confirmed by ^{1}H-^{1}H correlation spectroscopy (COSY) and ^{1}H-^{13}C correlation experiments (HSQC), and are summarized in Table 1.

The ^{13}C NMR spectra of pure **5** showed the presence of 18 signals and had not been previously recorded. The ^{13}C assignments of **5** were unambiguously established by two-dimensional (2D) ^{1}H-^{13}C correlation spectroscopies (HSQC and HMBC), as shown in Tables 2 and 3.

The DEPT experiments (performed at 90° and 135°) were carried out to ascertain the nature of the carbon atoms. They showed thirteen positive peaks for three methyl and ten methine carbons. The negative peaks for methylene carbons were absent. The other eight resonances were due to the quaternary carbons.

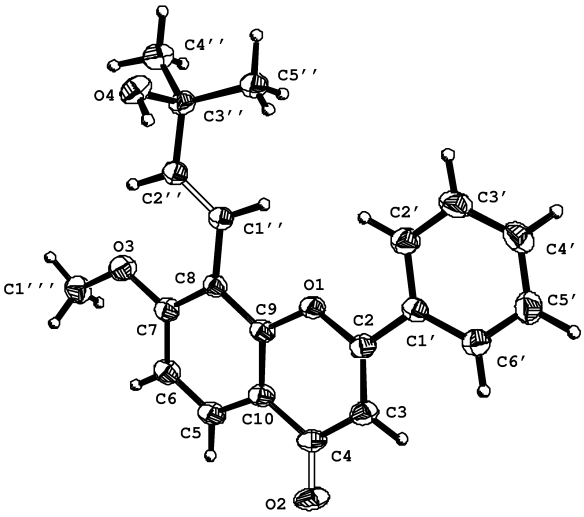

Fig. 2. ORTEP view of compound **5**, thermal ellipsoid at 30% probability level.

The electron impact (EI) mass spectrum of compound **5** showed a molecular ion peak at *m/z* 336 [M$^+$], together with other fragment peaks at *m/z* 321 [M$^+$-Me], 319[M$^+$-OH], 318 [M$^+$-H_2O], 303 [M$^+$-Me-H_2O], 287 [M$^+$-H_2O-OMe] and base peak at *m/z* 265 [12]. All these above assignments were confirmed by the single crystal X-ray analysis, Fig. 2 and Tables 4–10. As found in compound **1**, the flavone moiety is essentially planar and in the crystal the molecules stack along the ***a*** axis forming centrosymmetric dimers by hydrogen bonding between the hydroxyl group and the carbonyl group of the γ-pyrone, [H…O: 2.00 (3) Å; O…O: 2.859(2) Å; O-H…O: 176(2)°]. In the light of the above data compound **5** was named lanceolatin A and has been formulated to be 7-methoxy-8-(3″-hydroxy-3″- methyl-trans-isobut-1″-enyl)-flavone.

The petroleum ether (60–80 °C) extract of *T. apollinea* root was subjected to silica gel G CC eluting with *n*-hexane-EtOAc mixtures with increasing polarities which afforded two phytosterols, stigmasterol **6** and sitosterol **7**, which were characterized by comparison of their physical (m. p., $[\alpha]_D$) and spectroscopic (IR, ^{1}H and ^{13}C NMR, and EI-MS) data with those of authentic samples or spectroscopic data described in the literature [16–18].

Anticarcinogenic properties

The anticarcinogenic properties of the isolated prenylated flavonoids **1**, **3** and **5** showed no significant

Table 11. *In vitro* antimicrobial activity of the root ethanolic extract, chloramphenicol, and trosyed® (diameter of inhibited zone, mm)*.

Microorganisms	I	II	III
Bacterial species			
Bacillus cereus	22.0	25.0	NT
Escherichia coli	13.0	22.0	NT
Serratia marcescens	12.0	18.0	NT
Fungal species			
Aspergillus fumigatus	00.0	NT	19.0
Aspergillus flavus	00.0	NT	22.0
Penicillium chrysogenum	00.0	NT	24.0

I = The root ethanolic extract (2 mg/ml); II = chloramphenicol (2 mg/ml); III = trosyed® (2 mg/ml); * 18 – 25 mm = high inhibition activity; 12 – 17 mm = medium inhibition activity; 00.0 = no inhibition; NT = not tested.

inhibitory mechanisms at the initiation, promotion, and progression stage of carcinogenesis (see Experimental Section).

To our knowledge, compound **1** was shown to display antimalarial activity [19]. Compounds **1** and **3** have inhibitory effect against human platelet aggregation [20, 21].

Antimicrobial activity

The root ethanolic extract of *T. apollinea* was tested by the cup-plate method [22] against six species of microorganisms (three bacteria and three fungi). Bacterial species comprised *Bacillus cereus* (Gram-positive), and *Escherichia coil* and *Serratia marcescens* (Gram-negative) *versus* Chloramphenicol as a positive control. The selected fungal species included *Aspergillus flavus* (aflatoxigenic species), *A. fumigatus* (human pathogenic species) and *Penicillium chrysogenum versus* Trosyd® as a positive control. Data are recorded in Table 11.

In antibacterial testing, the root ethanolic extract was found to have high antibacterial activity towards *Bacillus cereus*, whereas, it exhibited moderate inhibitory effect against *Escherichia coli* and *Serratia marcescens*. The inhibitory action was always lower than that of the reference sample Chloramphenicol. On the contrary, the root extract was generally inactive against the tested fungi.

Experimental Section

General

All melting points were measured on a Kofler's hot stage microscope and are uncorr. Ultraviolet (UV) spectra were recorded on a Shimadzu UV-160A spectrometer in MeOH and infrared (IR) spectra on a Shimadzu IR-450 spectrometer. ^{1}H, ^{13}C NMR, DEPT, 2D ^{1}H-^{1}H COSY, HSQC and HMBC were measured on a JEOL GSX-500 and a Bruker DRX-500 spectrometers in $CDCl_3$, unless otherwise stated. Chemical shifts are shown in δ values (ppm) with tetramethylsilane (TMS) as an internal reference. All mass spectra (MS) and HR-MS were taken under electron impact (EI) conditions using an M-80 (Hitachi) or a JMS-HX-110 (JEOL) spectrometer having a direct inlet system. Optical rotations were measured on a Perkin Elmer 192 Polarimeter, with a 10 cm microcell in $CHCl_3$· CC: Silica gel (Merck, 60 – 120 mesh) and Sephadex LH-20 (Pharmacia). TLC and prep. TLC: Silica ge1 60 GF_{254} (Merck). TLC zones were visualized either by spraying with vanillin-sulphuric acid or under UV light. All evaporation were done *in vacuo* on a rotary evaporator. Ether refers to diethyl ether throughout.

Plant material

The root of *T. apollinea* (Del.) Link were collected in August 1999 from Wadi Kubbaniya, Northwest of Aswan, Southern Egypt. Identification was kindly verified by Professor Dr. Loutfy Boulos, Department of Botany, Faculty of Science, Cairo University, Cairo, Egypt. A voucher specimen (No. 529) has been deposited at the Botany Department Herbarium, Faculty of Science, South Valley University, Aswan, Egypt.

Extraction and isolation

Air-dried and powdered root (1.5 kg) of *T. apollinea* were defatted with petroleum ether (60 – 80 °C) at room temp. for 48 h. The defatted root were further extracted with CH_2Cl_2 at root temp. for 48 h.

Chromatography of the CH_2 Cl_2 extract

The CH_2Cl_2 extract (*ca.* 15 g) was subjected to silica gel CC. Successive elution with *n*-hexane-EtOAc (10:1, 4:1, 2:1, l:l), EtOAc and MeOH afforded 12 fractions. Each fraction was further separated by Sephadex LH-20 followed by prep. TLC [solvent: *n*-hexane-ether (1:1,1:3), *n*-hexane-EtOAc (9:1, 8:2, 7:3), *n*-hexane-Me_2CO(8:2), CH_2Cl_2-Me_2CO(9:1)] to give (-)-semiglabrin **1** (50 mg), (-)- pseudosemiglabrin **3** (45 mg), and lanceolatin A **5** (30 mg).

*(-)-Semiglabrin; 2‴,2‴-dimethyl-3‴-acetoxy-tetrahydrofurano-[3″,2″-b]-dihydrofurano-[5″,4″-h]-flavone (**1**)*

$C_{23}H_{20}O_6$; crystallized from CH_2Cl_2-MeOH as colourless needles, m.p. 258 – 260 °C, $[\alpha]_D^{25}$ – 275° (*c* 0.35, $CHCl_3$). – UV (MeOH): $\lambda_{max} = 307$, 254, 247 (sh) and 215 nm. – IR (KBr): $\tilde{\nu} = 1735$ (acetate CO), 1640 cm^{-1} (γ-pyrone CO) [6]. -^{1}H NMR: The ^{1}H assignments were achieved by ^{1}H–^{1}H correlation spectroscopy (COSY) and

HSQC experiments, see Table 1. -^{13}C NMR: The ^{13}C attributions were achieved by HSQC and HMBC experiments, see Tables 2 and 3. – HR-MS: *m/z* 392.1260 [M^+] ($C_{23}H_{20}O_6$ requires 392.1258). – MS (EI, 70 eV): *m/z* (%) = 392(16) [M^+], 332(100), 317(38), 303(19), 289(31), 263 (26), 230 (15), 160 (18), 102 (9) and 43 (65) [9].

*(-)-Semiglabrinol; 2‴,2‴-dimethyl-3‴-hydroxy-tetrahydrofurano-[3″,2″-b]-dihydrofurano [5″,4″-h]-flavone (**2**)*

Compound **1** (20 mg) was dissolved in the minimum amount of 0.1% KOH and allowed to stand for 24 h. The mixture was diluted with H_2O and exited with CH_2Cl_2 to give a colourless oil. Crystallization from Me_2CO gave **2** as a white needles (15 mg), m.p. 247 – 249 °C, $[\alpha]_D^{25} - 266°$ (c0.10, $CHCl_3$). – UV (MeOH): λ_{max} = 308, 255, 243 (sh) and 211 nm . – IR (KBr): $\tilde{\nu}$ = 3350 (OH), 1635 (γ-pyrone CO) and 1600 cm^{-1} (C=C). -^{1}H and -^{13}C NMR spectra of this compound were in agreement with the data reported for natural (-)-semiglabrinol [23], see Tables 1 and 2. – MS (EI, 70 eV): *m/z* (%) = 350 (33) [M^+], 332 (100), 317 (46), 289 (30), 263 (35), 230 (19), 160 (25), 149 (34), 103 (16) and 43 (30).

*(-)-Pseudosemiglabrin (**3**)*

$C_{23}H_{20}O_6$; crystallized from MeOH as colourless prisms, m. p. 169 – 171 °C, $[\alpha]_D^{25} - 379°$ (c0.90, $CHCl_3$). -UV and -IR were identical to **1**. – ^{1}H NMR: The ^{1}H assignments were achieved by ^{1}H–^{1}H correlation spectroscopy (COSY) and HSQC experiments, see Table 1. – ^{13}C NMR: The ^{13}C attributions were achieved by HSQC and HMBC experiments, see Tables 2 and 3. – HR-MS: *m/z* 392.1258 [M^+] ($C_{23}H_{20}O_6$ requires 392.1256). – MS (EI, 70 eV): The data were similar to that of compound **1**.

*(-)-Pseudosemiglabrinol (**4**)*

Mild alkaline hydrolysis of compound **3**, 15 mg as mentioned above gave **4** as white needles from Me_2CO (12 mg), m.p. 268 – 269 °C, $[\alpha]_D^{25} - 255°$ (c0.50, $CHCl_3$). -UV and -IR were identical to **2**. -^{1}H and -^{13}C NMR spectra of this compound were in agreement with the data reported for natural (-)-pseudosemiglabrinol [23], see Tables 1 and 2. – MS (EI, 70 eV): The data were similar to those of compound **2**.

*Lanceolatin A; 7-methoxy-8-(3″-hydroxy-3″-methyl-trans-isobut-1″-enyl)-flavone (**5**)*

$C_{21}H_{20}O_4$; crystallized from MeOH as colourless prismatic needles, m. p. 186 – 188 °C. – UV (MeOH): λ_{max} = 318, 262, 224 nm. – IR (KBr): $\tilde{\nu}$ = 3500, 1384, 1149 (ter. OH), 1635,1590 (γ-pyrone CO and styryl), 1410, 1265, 970, 815, 780 and 710 cm^{-1}. -^{1}H NMR: The ^{1}H assignments were achieved by ^{1}H–^{1}H correlation spectroscopy (COSY) and HSQC experiments, see Table 1. -^{13}C NMR: The ^{13}C attributions were achieved by HSQC and HMBC experiments, see Tables 2 and 3. – HR-MS: *m/z* 336.1362 [M^+] ($C_{21}H_{20}O_4$ requires 336.1360). – MS (EI, 70 eV): The data are in agreement with those reported in the literature [12].

*X-ray crystallographic analysis for compounds **1** and **5** [24]*

*Crystal data for compound **1***

$C_{23}H_{20}O_6$; MW 392.39, orthorhombic, space group $P2_12_12_1$ ($\mathbf{D}_2^4$) no. 19 from Laue symmetry and systematic absences: $h00$ when $h \neq 2n$, $0k0$ when $k \neq 2n$, $00l$ when $l \neq 2n$; a = 6.719 (2) Å, b = 12.725 (3) Å, c = 21.789 (6) Å, V = 1862.9 (9) Å^3 , Z = 4, D_c = 1.399 g cm^{-3}, μ(Mo-K$_\alpha$ radiation) = 0.101 mm^{-1}; crystal dimensions: 0.72 × 0.12 × 0.06 mm, see Table 4.

*Crystal data for compound **5***

$C_{21}H_{20}O_4$; MW 336.37, monoclinic, space group $P2_1/c$ ($\mathbf{C}_{2h}^5$) no. 14 from Laue symmetry and systematic absences: $h0l$ when $l \neq 2n$, $0k0$ when $k \neq 2n$, $00l$ when $l \neq 2n$, a = 7.3441 (3) Å, b = 11.310 (1) Å, c = 20.573 (2) Å, β = 90.377 (5)°, V = 1708.8 (2) Å^3, Z = 4, D_c = 1.307 g cm^{-3}, μ(Cu-K$_\alpha$ radiation) = 0.730 mm^{-1}; crystal dimensions: 0.56 × 0.18 × 0.18 mm, see Table 4.

Unit cell parameters were obtained by least-squares fit of 35 ($20 < \theta < 25°$ for compound **1**, $50 < \theta < 56°$ for compound **5**) accurately centered reflections. Intensity data ($3261 + h$, $+k$, $+l$ plus Friedel pairs reflections for **1**, $2275 + h$, $+k$, $\pm l$ reflections for **5**) were recorded at 25 °C on a Siemens P4/PC diffractometer [Mo-K$_\alpha$ radiation for **1**, Cu-K$_\alpha$ for **5**, graphite monochromator, ω-2θ scans, $\theta_{max} = 25°$ for **1**, $\theta_{max} = 56.75°$ for **5**]. The intensities of three reference reflections, monitored every 97 measurements during data collection, showed no significant variation ($< 3\%$) throughout. The usual Lorentz and polarization corrections were applied to intensity data and all the data were used for the structure refinement.

Both crystal structures were solved by direct methods (SIR 92) [25]. Initial coordinates for all nonhydrogen atoms were obtained from E-maps. The enantiomer in case of structure of (-)-semiglabrin was chosen to yield the same stereochemistry at C-2″ and C-3″ as in **1**. Positional and thermal parameters of these atoms (first isotropic and then anisotropic) were adjusted by means of several rounds of full-matrix least-squares calculations [26] during which $\Sigma(w|F_o^2 - F_c^2|)^2$, with $w = 1/[\sigma^2(F_o^2) + (0.0269P)^2]$ for **1** and, $w = 1/[\sigma^2(F_o^2) + (0.0574P)^2 + 0.2638P]$ for **5**. All the hydrogen atoms were included as fixed contributions and not refined. Their idealized positions were generated from the geometries about the attached carbon atoms, and forced to ride on it with a fixed isotropic temperature factor, $\boldsymbol{U}$ =

1.2 times the $\boldsymbol{U}_{eq}$ of the parent C–atom. The refinements converged at

$$R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.1049,$$
$$wR^2 = \left\{\Sigma\left[w\left(F_o^2 - F_c^2\right)^2\right]/\Sigma w\left(F_o^2\right)^2\right\}^{1/2} = 0.1265,$$
$$\boldsymbol{S} = \left\{\Sigma\left[\boldsymbol{w}\left(\boldsymbol{F}_o^2 - \boldsymbol{F}_c^2\right)^2\right]/(\boldsymbol{n}-\boldsymbol{p})\right\}^{1/2} = 0.962$$

for **1**, and $R = 0.0385$, $wR^2 = 0.1002$, $S = 1.047$ for **5**. Final difference Fourier syntheses contained no unusual features [$\Delta\rho$(e/Å^3) max: min = 0.273: −0.287 for **1**, 0.158: −0.143 for **5**]. The crystallographic data of the compounds **1** and **5** are summarized in Tables 4 – 10.

Chromatography of the petrolelum ether (60 – 80 °C) extract

Evaporation of the petroleum ether (60 – 80 °C) extract gave a dark brown residue (*ca.* 100 g). 20 g was chromatographed over silica gel CC (one kg) and the column was eluted with *n*-hexane-EtOAc (4:1, 2:1, 1:1), EtOAc and MeOH afforded two phytosterols, stigmasterol **6** (50 mg) and sitosterol **7** (70 mg).

*Stigmasterol (**6**)*

$C_{29}H_{48}O$; crystallized from Me_2O as colourless crystal, m.p. 170 – 172 °C, $[\alpha]_D^{25} - 51°$ (c 0.90, $CHCl_3$). The spectroscopic data including IR, ^{1}H and ^{13}C NMR, and EI-MS are in agreement with those published in the literature [16, 17].

*β-Stiosterol (**7**)*

$C_{29}H_{50}O$; crystallized from Me_2CO as white needles, m.p. 135 – 137 °C, $[\alpha]_D^{25} - 36°$(c 0.90, $CHCl_3$). The spectroscopic data including IR, ^{1}H NMR, and EI-MS are in agreement with those reported in the literature [18].

Cancer chemopreventive activity

For the identification of novel cancer chemopreventive agents, we have set up a broad spectrum of cell- and enzyme-based *in vitro* assays with markers relevant for measuring inhibition of carcinogenesis during the initiation, promotion, and progression stage. The bioassay systems offer fast (within days), sensitive, and cost-effective identification and evalution of isolated compounds **1**, **3** and **5** for the development of effective chemopreventive agents and the elucidation of their mechanism of action. As a measure to detect anti-initiating properties, we focused on the modulation of carcinogen metabolism, *i.e.*, carcinogen activation by phase 1 cytochrome (Cyp) 1A enzymes and detoxification by phase 2 enzyme quinone reductase (QR) and on the prevention of oxidative damage by scavenging of reactive oxygen species (ROS) and inhibition of nitric oxide (NO) production. With respect to antitumor promoting activity, we have established models to measure the influence of potential chemopreventive agents on generation or effects of endogenous tumor promoters, *i.e.*, prostaglandins (PGs) and 17β-estradiol (E2). Finally, for the inhibition of carcinogenesis in the progression phase, we investigated a series of complementary antiproliferative mechanisms, *i.e.*, inhibition of DNA synthesis and cell cycle progression and induction of apoptosis and terminal cell differentiation (for experimental detail see [5]). The isolated prenylated flavonoids **1**, **3** and **5** showed no significant cancer chemopreventive activity.

Biological investigations

The preliminary screening test was performed according to the cup-plate method [22]. Bacteria were allowed to grow on nutrient agar medium, whereas fungi were cultured on Sabourand's dextrose agar [27]. At the time of inoculation, cups (5 mm diameter) were made in the agar media (3 cups per plate). The root ethanolic extract of *T. apollinea*, and the reference samples of Chloramphenicol and Trosyd® were disolved in dimethyl sulphoxide (DMSO) to prepare 2 mg/ml solutions. Aliquots (10 μl of each) of the above solutions were pipetted into these cups. Cultures were incubated at 28 °C for 24 h for bacteria and 3 – 7 days in the case of the fungi. The diameters of the inhibition zones around the cups were measured in mm. The results of antimicrobial activity of the root ethanolic extract are given in Table 11. The results of Chloramphenicol and Trosyd® as positive controls are also included.

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