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Prenylated sulfonyl amides from *Glycosmis* species

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Abstract

Nine new sulfur containing amides were isolated from the lipophilic leaf extracts of different varieties of *Glycosmis chlorosperma* and *G.* ex aff. *pseudoracemosa* mainly collected in Thailand. Their structures were elucidated by spectroscopic methods. All amides were shown to be characterized by a methylsulfonylpropenoic acid moiety linked to a *p*-geranyloxy- or *p*-prenyloxy-phenethylamide rest. The compounds differ by different states of oxidation (i) at the 2-position of the ethylamine unit, (ii) at the aromatic *m*-position of phenethylamine, or (iii) at the terminal methyl group of the geranyloxy side chain.

Keywords: Amides; Methylsulfonylpropenoic acid amides; Sulfones; *Glycosmis*; Rutaceae

1. Introduction

The genus *Glycosmis* (Rutaceae-Aurantioideae) was shown to be a rich source of different amides characterized by sulfur containing acid moieties derived from 3-(methylthio)-propenoic acid, 3-(methylsulfonyl)-propenoic acid, or thiocarbamic acid (Greger et al., 1993, 1994, 1996; Hofer et al., 1995, 1995, 1998; Vajrodaya et al., 1998). Several derivatives have already been synthesized in larger amounts for further biological testing and proof of structures (Hinterberger et al., 1994, 1998). In the leaf extracts of some species we also found non-sulfur containing amides, i.e. a series of novel anthranilic, isovaleric, and senecioic acid derived amides (Hofer et al., 1995; Greger et al., 1996). Based on bioassays with our test fungus *Cladosporium herbarum* and larvae of the cotton leaf worm *Spodoptera littoralis* (Lepidoptera, Noctuidae), some sulfur containing amides displayed high antifungal and/or insecticidal activity against *Cladosporium herbarum* and *Spodoptera littoralis*, respectively (Greger et al., 1993, 1996).

In order to get more information about the biogenetic capacity of *Glycosmis* we have now investigated the lipophilic leaf extracts of different collections of *G. chlorosperma* (Bl.) Sprengel (Stone, 1985) as well as an as yet unidentified variety of that species with simple leaves. In addition, a probably undescribed variety of *G. pseudoracemosa* (Guill.) Swingle was also analyzed which deviates from the unifoliolate type species by pinnate leaves. The leaf extracts of all three species were shown to be dominated by a variety of sulfonyl amides. As a result, nine novel amides, all derived from 3-(methylsulfonyl)-propenoic acid, were isolated and their structures determined by spectroscopic methods.

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2. Results and discussion

The $CHCl_3$ fractions of the methanolic leaf extracts

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were treated as described in Section 3 to afford the nine new compounds **2**–**5**, **7**–**9**, **11**, and **12**, together with several already known compounds of the same type, e.g. sakerine (**6**) (Hofer et al., 1995), dambullin (**10**) (Greger et al., 1994), and sakerol (Hofer et al., 1995). The corresponding UV spectra are characterized by maxima (or distinct shoulders) at 224–227 and 273–275 nm which are typical for this type of amides (Greger et al., 1994; Hofer et al., 1995). The methylsulfonylpropenoic amide moiety of all new compounds is characterized by IR bands at ~1650 cm^{-1} (KBr) or ~1675 cm^{-1} ($CHCl_3$) for the amide carbonyl group and a pair of strong lines at 1294–1300 and 1122–1126 cm^{-1} (KBr) or 1318 and 1136–1138 cm^{-1} ($CHCl_3$) for the SO_2 group. The identical 3-(methylsulfonyl)-propenoic acid moiety in all new compounds follows also from the ^1H and ^{13}C NMR data (compare the data for the olefinic protons 2-H and 3-H and for the S-CH_3 group in Tables 1 and 2 with corresponding data in Greger et al. (1994)).

The ^1H NMR spectra of compounds **2**–**5** show the typical aromatic resonance pattern for *para*-substituted benzenes (2 × 2H for 4′/8′ and 5′/7′, compare Table 1). The chemical shifts of $\delta = 7.08$ and 6.84 of compound **2** agree very well with the *para*-oxygenated phenethylamides previously isolated from *G. angustifolia* (Greger et al., 1996). The phenethyl resonances at $\delta = 3.61$ (*dt*, appearing as a *ps.q* due to the coupling with the amide proton) and 2.81 (*t*) together with the N–H resonance at 6.53 (*br.t*) are identical with the data of gerambullin (Greger et al., 1994) and confirm the phenethylamide partial structure. Compound **2** shows also all resonances of a C10 geranyl side chain (like the parent compound gerambullin), with the exception of one methyl resonance which is missing and substituted by a singlet of 2H at $\delta = 3.87$. One of the methyl groups is obviously oxidized to a primary alcohol. A strong NOE between 8″-H_2 and 6″-H proofs unambiguously the position of the CH_2OH group. All ^{13}C NMR data (e.g. $\delta = 69.3$ for C″-8 attached to an oxygen) and the molecular mass of $m/z = 421$ agree perfectly with the proposed structure of a 2-(8-hydroxygeranyloxy)-phenethylamide of methylsulfonyl-propenoic acid. As an oxygenated derivative of gerambullin, compound **2** was designated as gerambullol.

Amide **3** is characterized by a simple geranyloxy side chain attached to a *para* substituted aromatic system with the same geranyl NMR data as in gerambullin (**1**,

Table 1
^1H NMR data for amides **2**–**5**, **7**–**9**, **11**, and **12**[a]

	2	**3**	**4**	**5**	**7**	**8**	**9**	**11**	**12**
2	6.81 *d*	6.89 *d*	6.89 *d*	6.97 *d*	6.82 *d*	6.84 *d*	6.81 *d*	6.78 *d*	6.82 *d*
3	7.36 *d*	7.39 *d*	7.38 *d*	7.40 *d*	7.34 *d*	7.36 *d*	7.35 *d*	7.36 *d*	7.36 *d*
SCH_3	2.99 *s*	3.01 *s*	3.00 *s*	3.01 *s*	2.99 *s*	2.99 *s*	2.99 *s*	3.00 *s*	2.99 *s*
NH	6.53 *br.t*	6.30 *br.dd*	6.69 *br.dd*	6.90 *br.dd*	6.46 *br.t*	6.65 *br.t*	6.10 *br.t*	5.79 *br.t*	6.06 *br.t*
1′	3.61 *dt*	a: 3.81 *ddd*	a: 3.80 *ddd*	a: 3.80 *ddd*	3.60 *dt*	3.63 *dt*	3.60 *dt*	3.63 *dt*	3.62 *dt*
		b: 3.42 *ddd*	b: 3.47 *ddd*	b: 3.46 *ddd*					
2′	2.81 *t*	4.83 *dd*	4.82 *dd*	4.81 *br.m*	2.76 *t*	2.80 *t*	2.76 *t*	2.77 *t*	2.81 *t*
4′	7.08 *d*	7.28 *d*	7.27 *d*	7.23 *d*	6.76 *s*	6.70 *s*	6.76 *s*	6.76 *d*	6.70 *d*
5′	6.84 *d*	6.92 *d*	6.89 *d*	6.83 *d*	OH: 5.88 *br.s*	OMe: 3.86 *s*	OH: 6.60 *br.s*	OH: 5.69 *br.s*	OMe: 3.85 *s*
7′	6.84 *d*	6.92 *d*	6.89 *d*	6.83 *d*	6.77 *d*	6.77 *d*	6.79 *d*	6.81 *d*	6.83 *d*
8′	7.08 *d*	7.28 *d*	7.27 *d*	7.23 *d*	6.62 *d*	6.69 *d*	6.61 *d*	6.63 *dd*	6.69 *dd*
1″	4.57 *d*	4.54 *d*	4.58 *d*	4.58 *d*	4.62 *d*	4.65 *d*	4.53 *d*	4.56 *d*	4.56 *d*
2″	5.42 *tm*	5.48 *tm*	5.42 *tm*	5.45 *tm*	5.42 *t*	5.43 *t*	5.48 *t*	5.48 *tm*	5.51 *tm*
4″	2.14 *t*	2.10 *m*	2.14 *t*	2.28 *t*	2.14 *t*	2.13 *t*	2.12 *t*	1.81 *br.s*	1.77 *br.s*
5″	2.18 *td*	2.10 *m*	2.18 *td*	2.50 *q*(*td*)	2.18 *q*(*td*)	2.18 *q*(*td*)	2.22 *q*(*td*)	1.75 *br.s*	1.73 *br.s*
6″	5.26 *tm*	5.09 *tm*	5.25 *tm*	6.32 *tm*	5.27 *t*	5.26 *t*	5.26 *t*		
8″	3.87 *br.s*	1.68 *br.s*	3.86 *br.s*	9.02 *s*	3.90 *s*	3.88 *s*	1.80 *d*		
9″	1.62 *br.s*	1.61 *br.s*	1.62 *br.s*	1.66 *br.s*	1.63 *br.s*	1.62 *br.s*	4.03 *br.s*		
10″	1.76 *br.s*	1.74 *br.s*	1.76 *br.s*	1.77 *br.s*	1.75 *br.s*	1.76 *br.s*	1.76 *d*		

[a] Coupling constants. **2**: $J(2, 3) = 14.6$ Hz, $J(1', 2') = 6.8$ Hz, $J(1', NH) = 6.0$ Hz, $J(4', 5') = J(7', 8') = 8.5$ Hz, $J(1'', 2'') = 6.4$ Hz, $J(4'', 5'') = 6.2$ Hz, $J(5'', 6'') = 6.6$ Hz; **3**: $J(2, 3) = 14.7$ Hz, $J(1'a, 1'b) = 13.8$ Hz, $J(1'a, 2') = 3.6$ Hz, $J(1'a, NH) = 7.2$ Hz, $J(1'b, 2') = 8.1$ Hz, $J(1'b, NH) = 4.5$ Hz, $J(4', 5') = J(7', 8') = 8.7$ Hz, $J(1'', 2'') = J(5'', 6'') = 6.5$ Hz; **4**: $J(2, 3) = 14.7$ Hz, $J(1'a, 1'b) = 13.8$ Hz, $J(1'a, 2') = 4.3$ Hz, $J(1'a, NH) = 6.9$ Hz, $J(1'b, 2') = 7.2$ Hz, $J(1'b, NH) = 5.2$ Hz, $J(4', 5') = J(7', 8') = 8.7$ Hz, $J(1'', 2'') = 6.5$ Hz, $J(4'', 5'') = 6.2$ Hz, $J(5'', 6'') = 6.7$ Hz; **5**: $J(2, 3) = 14.8$ Hz, $J(1'a, 1'b) = 13.6$ Hz, $J(1'a, 2') = 4.0$ Hz, $J(1'a, NH) = 6.7$ Hz, $J(1'b, 2') = 7.8$ Hz, $J(1'b, NH) = 5.1$ Hz, $J(4', 5') = J(7', 8') = 8.5$ Hz, $J(1'', 2'') = 6.5$ Hz, $J(4'', 5'') = J(5'', 6'') = 7.1$ Hz; **7**: $J(2, 3) = 14.7$ Hz, $J(1', 2') = J(1', NH) = 6.3$ Hz, $J(7', 8') = 8.0$ Hz, $J(1'', 2'') = J(4'', 5'') = J(5'', 6'') = 6.5$ Hz; **8**: $J(2, 3) = 15.0$ Hz, $J(1', 2') = J(1', NH) = 6.3$ Hz, $J(7', 8') = 7.8$ Hz, $J(1'', 2'') = J(4'', 5'') = J(5'', 6'') = 6.5$ Hz; **9**: $J(2, 3) = 14.6$ Hz, $J(1', 2') = J(1', NH) = 6.5$ Hz, $J(7', 8') = 8.5$ Hz, $J(1'', 2'') = J(4'', 5'') = J(5'', 6'') = 6.8$ Hz, $J(2'', 10'') \sim J(6'', 8'') \sim 1.5$ Hz; **11**: $J(2, 3) = 14.7$ Hz, $J(1', 2') = 6.6$ Hz, $J(1', NH) = 6.0$ Hz, $J(4', 8') = 2.0$ Hz, $J(7', 8') = 8.2$ Hz, $J(1'', 2'') = 6.9$ Hz; **12**: $J(2, 3) = 14.6$ Hz, $J(1', 2') = 6.6$ Hz, $J(1', NH) = 6.0$ Hz, $J(4', 8') = 2.0$ Hz, $J(7', 8') = 8.4$ Hz, $J(1'', 2'') = 6.5$ Hz. Other resonances. **5**: 2′-OH 3.14 *br.s*.

Greger et al., 1994), however, the ^{1}H NMR pattern of the phenethylamide part has changed significantly. The CH_2 resonance next to the amide nitrogen (α position, 1′ in the formula scheme) has changed to two clearly separated diastereotopic methylene signals at $\delta = 3.81$ (*ddd*, J = 13.8, 7.2, and 3.6 Hz) and 3.42 (*ddd*, J = 13.8, 8.1, and 4.5 Hz). The benzylic CH_2 group has changed to a low field *dd* of 1H at $\delta = 4.83$ with J = 8.1 and 3.6 Hz (β position, 2′ in the formula scheme). The NH group appears as broad *dd* with J = 7.2 and 4.5 Hz. These data are only compatible with the sequence –NH–CH_2–CH(OH)–Ar. The benzylic β-hydroxyl group is also reflected in the chemical shift of the aromatic protons 4′-H/8′-H ($\delta = 7.28$) which show a downfield shift of 0.2 ppm compared to the corresponding simple phenethylamides (e.g. **2**, compare Table 1). The observed resonance pattern for the β-hydroxyphenethylamide unit agrees also very well with a previously synthesized methylthiopropenoic acid analogue (Hinterberger et al., 1998). Amide **3** was named β-hydroxygerambullin since it differs from gerambullin (**1**, Greger et al., 1994) only by an additional oxygenation at position β of the phenethylamine moiety.

β-Hydroxy derivatives of phenethylamides were shown to be new for *Glycosmis*. They may be considered as possible precursors of other, previously isolated derivatives of phenethylamides, e.g. the α,β-unsaturated illukumbins from Sri Lankan *G. mauritiana* (Greger et al., 1993, corr. structures in Hinterberger et al., 1994). Generally, β-hydroxyphenethylamides are already known from other Rutaceae, e.g. aegeline (β-hydroxy-*p*-methoxyphenethylamide of cinnamic acid) from *Aegle marmelos* Correa (Chatterjee et al., 1959).

In comparison with amide **3**, the ^{1}H NMR data of compounds **4** and **5** show an identical resonance pattern for the β-hydroxyphenethyl amide part of the molecule. Concerning the terpenoid side chain of compound **4**, one of the methyl groups is substituted by a CH_2OH group (8″-H_2 as a singlet at $\delta = 3.86$; compare with compound **2**, Table 1). In compound **5**, C-8″ is further oxidized to an aldehyde function (8″-H as a singlet at $\delta = 9.02$, C-8″ as a dublet at $\delta = 196.2$). The trivial names β-hydroxygerambullol (**4**) and β-hydroxygerambullal (**5**) indicate these characteristic functional groups. The positions of the CH_2OH and the CHO groups in **4** and **5**, respectively, were confirmed by differential NOE measurements (strong NOEs 6″ ↔ 8″). The optical activities of the β-hydroxy compounds **3**–**5** are characterized by their optical rotations (see Section 3), however, no absolute configurations have been determined.

The ^{1}H NMR spectra of the new compounds **7**–**9** show different aromatic resonance patterns in comparison with the *p*-substituted derivatives **1**–**5**. In the case of **7**, a singlet at $\delta = 6.76$ and two doublets (AB system) at $\delta = 6.77$ and 6.62 together with a broad phenolic OH resonance at $\delta = 5.88$ are clearly in favour

Table 2
^{13}C NMR data for amides **2**, **5**, **7**–**9**, **11**, and **12**[a]

	2	**5**	**7**	**8**	**9**	**11**	**12**
1	162.1 *s*	162.7 *s*	162.0 *s*	162.0 *s*	161.9 *s*	161.9 *s*	161.9 *s*
2	136.1 *d*	135.9 *d*	136.1 *d*	136.0 *d*	135.9 *d*	135.9 *d*	135.8 *d*
3	139.0 *d*	139.5 *d*	139.2 *d*	139.1 *d*	139.3 *d*	139.2 *d*	139.4 *d*
SCH_3	42.9 *q*	42.9 *q*	43.0 *q*	42.9 *q*	43.0 *q*	42.9 *q*	42.9 *q*
1′	41.6 *t*	47.5 *t*	41.4 *t*	41.4 *t*	41.5 *t*	41.6 *t*	41.6 *t*
2′	34.7 *t*	72.8 *d*	34.9 *t*	35.1 *t*	34.9 *t*	34.9 *t*	35.2 *t*
3′	130.6 *s*	133.8 *s*	131.9 *s*	131.2 *s*	131.8 *s*	139.3 *s*	138.1 *s*
4′	130.1 *d*	127.6 *d*	115.4 *d*	113.2 *d*[b]	115.9 *d*	115.1 *d*	113.8 *d*
5′	115.3 *d*	115.3 *d*	146.7 *s*	150.0 *s*	146.7 *s*	146.6 *s*[b]	150.1 *s*[b]
6′	157.8 *s*	158.6	144.9 *s*	147.3 *s*	145.3 *s*	145.2 *s*[b]	147.6 *s*[b]
7′	115.3 *d*	115.3 *d*	112.5 *d*	112.6 *d*[b]	112.7 *d*	112.8 *d*	112.4 *d*
8′	130.1 *d*	127.6 *d*	120.4 *d*	120.8 *d*[c]	120.2 *d*[b]	120.5 *d*	121.0 *d*
1″	64.9 *t*	64.6 *t*	65.9 *t*	65.8 *t*	65.5 *t*	66.3 *t*	66.3 *t*
2″	120.6 *d*	121.7 *d*	120.2 *d*	121.0 *d*[c]	120.3 *d*[b]	119.6 *d*	120.3 *d*
3″	140.9 *s*	139.8 *s*[b]	141.8 *s*	140.2 *s*	143.8 *s*	131.6 *s*	130.9 *s*
4″	39.2 *t*	38.1 *t*	39.2 *t*	39.2 *t*	39.3 *t*	26.2 *q*	26.2 *q*
5″	25.5 *t*	26.9 *t*	25.4 *t*	25.4 *t*	26.4 *t*	18.6 *q*	18.6 *q*
6″	125.9 *d*	154.9 *d*	125.7 *d*	125.9 *d*	128.0 *d*		
7″	135.4 *s*	139.9 *s*[b]	135.7 *s*	135.4 *s*	135.9 *s*		
8″	69.3 *t*	196.2 *d*	69.3 *t*	69.3 *t*	21.9 *q*		
9″	14.1 *q*	9.5 *q*	14.2 *q*	14.1 *q*	61.7 *t*		
10″	17.0 *q*	16.9 *q*	17.0 *q*	17.0 *q*	17.5 *q*		

[a] Other resonances. **8**: 5′-OMe 56.3 *q*; **11**: 5′-OMe 56.3 *q*.
[b,c] Interchangeable within the columns.

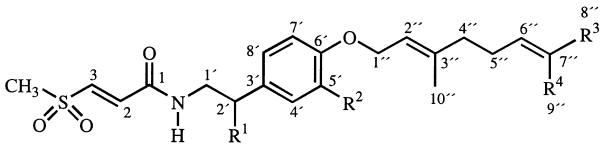
of a dopamide structure which can be derived from simple phenethylamides by an additional oxygenation at position 5′. We have already isolated a series of similar dopamides from several *Glycosmis* species (Hofer et al., 1995). The parent compound of this series is the *p*-geranyloxy-*m*-hydroxyphenethylamide of methylsulfonylpropenoic acid (sakerine, **6**). In the case of compound **8**, the aromatic resonances are very similar to **6** (Hofer et al., 1995) and **7**, however, the phenolic OH resonance is missing. Obviously it has been methylated to an aromatic methoxy group ($\delta = 3.86$, *s*, 3H, see Table 1). In the ^{13}C NMR spectrum, the 5′-C resonance shows the expected downfield shift of about 3.5 ppm due to the change from 5′-OH to 5′-OCH_3 (Table 2). The ^{1}H and ^{13}C NMR resonances of the terpenoid moiety of molecules **7** and **8** are almost identical and differ from the corresponding data of the side chain of sakerine only by transformation of the 8″ methyl group to the primary alcohol function CH_2OH (compare the NMR data of the 8″-hydroxylated derivatives **2**, **4**, **7**, and **8**). In the case of compound **9** all ^{13}C resonances are comparable with the ones of **7** and **8**, however, in the ^{1}H NMR spectra there are some significant differences concerning the CH_2OH or the CH_3 groups at positions 8″ and 9″. Measurement of differential NOEs proved unambiguously an *E* configuration for the C-6″–C-7″ double bond in compound **7** and a *Z* configuration in compound **9**. Strong NOE relationships $CH_2(OH) \rightarrow 6''$-H and $CH_3 \rightarrow 5''$-H_2 were observed for the 6-*E* isomer **7**, but $CH_2(OH) \rightarrow 5''$-H_2 and 6″-H $\rightarrow CH_3$ for the 6-*Z* isomer **9** (see Section 3). The isomeric compounds **7** and **9** were designated as sakerinol A and sakerinol B, the phenolic methylation product of the former, compound **8**, as *O*-methylsakerinol A. The structures were confirmed by FD–MS giving the proper molecular ions (see Section 3).

The new compounds **11** and **12** show again all NMR resonances of methylsulfonylpropenoic amides of a dopamine derived amine moieties. However, in the case of **11** and **12** a simple prenyloxy side chain is attached to the aromatic system. The prenyloxyphenethylamine derived parent compound, dambullin (**10**), was isolated previously from a Sri Lankan *G. angustifolia* (Greger et al., 1994). The resonances 1–3, 1′, 2′, and 1″–4″ of compounds **11** and **12** are almost identical with the corresponding data of dambullin (**10**, Greger et al., 1994). The aromatic ^{1}H and ^{13}C NMR resonances 3′–8′ of compound **11** resemble very much those of **7**, and the product of phenolic methylation **12** compares very well with compound **8** (Tables 1 and 2). The names sakambullin for **11** and *O*-methylsakambullin for **12** should indicate the relationship to dambullin (**10**), but also to the related dopamide derived sakerines **6**–**8**. The mass spectral data (HR–MS for **11** and FD–MS for **12**, see Section 3) are in full agreement with the proposed structures.

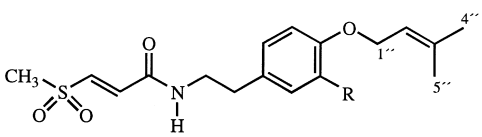
The lipophilic leaf extracts of three different provenances of *G. chlorosperma* were investigated: collection (a) from south Thailand (Koh Tarutao), (b) from Singapore, and (c) from Malaysia (Pulau Penang). All were characterized by varying amounts of different methylsulfonylpropenoic acid amides and several flavanons which will be described elsewhere. The amides **7**, **8**, **11**, and **12** were isolated from collection (a), amide **5** was obtained from (b), and amide **4** from (c). In addition to these new compounds collections (b) and (c) contained also dambullin (**10**) (Greger et al., 1994) which was identified by HPLC-UV with an authentic sample.

The unidentified variety of *G. chlorosperma* collected in Thale Ban (south Thailand) was characterized by six amides all derived from 3-(methylsulfonyl)-propenoic acid. Two were the already known dambullin (**10**, Greger et al., 1994) and sakerol (5″-hydroxydambullin, Hofer et al., 1995), whereas four were shown to be new (**2**–**4** and **11**).

Compound **9** was isolated from *G.* ex aff. *pseudoracemosa* collected in south Thailand (Khao Pu Khao Ya). The extract contained also sakerine (**6**) (Hofer et al., 1995) identified by HPLC-UV together with four



	R^1	R^2	R^3	R^4	
1	H	H	CH_3	CH_3	Gerambullin
2	H	H	CH_2OH	CH_3	Gerambullol
3	OH	H	CH_3	CH_3	β-Hydroxygerambullin
4	OH	H	CH_2OH	CH_3	β-Hydroxygerambullol
5	OH	H	CHO	CH_3	β-Hydroxygerambullal
6	H	OH	CH_3	CH_3	Sakerine
7	H	OH	CH_2OH	CH_3	Sakerinol A
8	H	OCH_3	CH_2OH	CH_3	*O*-Methylsakerinol A
9	H	OH	CH_3	CH_2OH	Sakerinol B



10	R = H	Dambullin
11	R = OH	Sakambullin
12	R = OCH_3	*O*-Methylsakambullin

different flavanons which are presently under investigation.

3. Experimental

3.1. General

Melting points: Kofler hot stage microscope, Reichert (Vienna); NMR: Bruker AM 400 WB (TMS, δ/ppm, J in Hz); MS: Finnigan MAT 900 S; IR: Perkin-Elmer 398; Optical rotation: Perkin-Elmer 241 polarimeter; UV: Perkin-Elmer Lambda 5; HPLC: Hewlett-Packard HP 1090 II, UV diode array detection at 230 nm, column 290 × 4 mm (Spherisorb ODS, 5 μm), mobile phase MeOH (gradient 60–100%) in aqueous buffer (0.015 M phosphoric acid, 0.0015 M tetrabutylammonium hydroxide, pH 3), flow rate 1 ml/min; all steps of the isolation procedure and the purity of the final products were examined by HPLC.

3.2. Plant material

The provenances of *G. chlorosperma* (Bl.) Sprengel are (a) Ao Son, Kho Tarutao, Tarutao National Park, Satun province, south Thailand (four individuals, HG334, HG336-338), (b) Bukit Timah Nature Reserve, Singapore (two individuals, HG436 HG437), and (c) Muka Head, Pulau Penang, north Malaysia (HG31). The unifoliate variety of *G. chlorosperma* (HG218) was collected in Thale Ban National Park, Satun province, south Thailand. The relative of *G. pseudoracemosa* was collected in Khao Pu Khao Ya, Phattalung, south Thailand (HG712). Voucher specimens are deposited at the Herbarium of the Institute of Botany, University of Vienna (WU).

3.3. Extraction and isolation

Generally, the air dried leaves were extracted with MeOH at room temperature for 7 days, filtered and concentrated. The remaining aqueous phase was extracted with $CHCl_3$. The resulting extract was evaporated to dryness and roughly separated by CC on a silica gel column (Merck silica gel 60, 35–70 mesh) by elution with petroleum ether/ether mixtures with ether increasing from 0% to 100% and finally with 0% to 100% methanol in ether. The combined fractions eluted with 25–50% MeOH in Et_2O contained the sulfones which were further separated by preparative MPLC with 30–50% EtOAc in hexane (400 × 40 mm column, Merck LiChroprep silica 60, 25–40 μm, UV detection at 254 nm). Compounds **2**–**4** and **11**: 12 g of dried leaves of the unifoliolate variety of *G. chlorosperma* gave after partition in $CHCl_3$ 600 mg of extract and after crude separation by CC ca. 130 mg of raw material containing the sulfones. The final separation by MPLC yielded 4 mg of compound **3**, followed by 15 mg of **2**, 45 mg of **4**, and 6 mg of **11**. Compounds **7**, **8**, **11**, and **12**: 53 g of dried leaves of *G. chlorosperma* (collection a) gave a $CHCl_3$ extract of ca. 1.5 g and after CC 350 mg of combined sulfones. The final separation by MPLC gave 103 mg of compound **11**, 84 mg of **12**, 47 mg of **7**, and 45 mg of **8**. Compound **5** was isolated from *G. chlorosperma* (collection b): 20 g dry leaves, 410 mg $CHCl_3$ extract, 137 mg crude material after CC and finally 7.8 mg pure product after prep. MPLC followed by an additional prep. DC. A further sample of *G. chlorosperma* (collection c, 54 g of dry leaves, 920 mg extract) yielded after analoguous workup 23 mg of pure **4**. Compound **9** was isolated from *G.* ex aff. *pseudoracemosa* (80 g of dry leaves, 2.4 g extract in the $CHCl_3$ phase), giving a yield of 7 mg after final MPLC (50% EtOAc).

3.4. Gerambullol {(*E*)-3-(methylsulfonyl)-propenoic acid (2*E*,6*E*)-4-(8-hydroxy-3,7-dimethyl-2,6-octadienyloxy)-phenethyl amide} (**2**)

Colourless crystals from Et_2O, mp 128–129°C. UV λ^{MeOH} nm 275 *sh*, 224 *sh*. IR ν^{KBr} cm^{-1} 3422 *m*, 3294 *m*, 3060 *w*, 2924 *w*, 1654 *s*, 1636 *m*, 1546 *m*, 1512 *m*, 1466 *w*, 1388 *w*, 1320 *w*, 1300 *s*, 1242 *m*, 1176 *w*, 1144 *w*, 1126 *s*, 1008 *w*, 962 *w*, 820 *w*, 778 *w*, 518 *m*. ^1H and ^{13}C NMR see Tables 1 and 2. MS (70 eV, 200°C) *m*/*z* (rel. int.): 421 (9, M^+), 270 (64), 269 (55, $CH_3SO_2CH{=}CH{-}CONH{-}CH_2CH_2{-}C_6H_4{-}p{-}OH^+$), 187 (10), 152 (52), 134 (71), 121 (77), 107 (77), 93 (65), 84 (44), 80 (56), 71 (73), 63 (37), 57 (64), 55 (69), 53 (68), 43 (100); HR–MS: $M_{exp} = 421.1924$, $M_{calc} = 421.1923$ for $C_{22}H_{31}NO_5S$.

3.5. β-Hydroxygerambullin {(*E*)-3-(methylsulfonyl)-propenoic acid (*E*)-2-[4-(3,7-dimethyl-2,6-octadienyloxy)-phenyl]-2-hydroxyethyl amide} (**3**)

Colourless crystals from Et_2O, mp 126–128°C; $[\alpha]_D^{20} = +25$ ($CHCl_3$, $c = 0.2$). UV λ^{MeOH} nm 273 *sh*, 224. IR ν^{KBr} cm^{-1} 3396 *s*, 3256 *m*, 2966 *w*, 2922 *m*, 1670 *m*, 1646 *s*, 1636 *m*, 1628 *m*, 1560 *w*, 1540 *w*, 1512 *m*, 1294 *s*, 1238 *m*, 1174 *w*, 1122 *s*, 1006 *w*, 978 *w*, 828 *w*, 668 *w*, 514 *m*. ^1H NMR see Table 1. MS (70 eV, 200°C) *m*/*z* (rel. int.): 403 (4, M^+-H_2O), 267 (70, $CH_3SO_2CH{=}CH{-}CONH{-}CH{=}CH{-}C_6H_4$-*p*-$OH^+$), 188 (10), 163 (13), 153 (21), 145 (20). 134 (60), 123 (83), 117 (19), 107 (36), 93 (67), 81 (80), 69 (100), 65 (63), 55 (50), 53 (33), 43 (66).

*3.6. β-Hydroxygerambullol {(E)-3-(methylsulfonyl)-propenoic acid (2E,6E)-2-[4-(8-hydroxy-3,7-dimethyl-2,6-octadienyloxy)-phenyl]-2-hydroxyethyl amide} (**4**)*

Colourless crystals from Et_2O, mp 131–133°C; $[\alpha]_D^{20} = +38$ ($CHCl_3$, $c = 0.2$). UV λ^{MeOH} nm 273 *sh*, 224 *sh*. IR ν^{KBr} cm^{-1} 3362 *m*, 3256 *m*, 2926 *m*, 2866 *w*, 1670 *m*, 1648 *s*, 1626 *m*, 1612 *m*, 1534 *m*, 1512 *m*, 1450 *w*, 1294 *s*, 1240 *m*, 1174 *w*, 1140 *m*, 1122 *s*, 1086 *w*, 1006 *m*, 978 *m*, 952 *w*, 854 *w*, 828 *m*, 772 *w*, 676 *w*, 518 *m*. ^1H NMR see Table 1. MS (70 eV, 260°C) *m/z* (rel. int.): 268 (4), 267 (4, $CH_3SO_2CH{=}CH{-}CONH{-}CH{=}CH{-}C_6H_4{-}p{-}OH^+$), 137 (14), 123 (12), 93 (14), 85 (17), 80 (42), 69 (24), 65 (100), 63 (34), 57 (32), 55 (32), 43 (48).

*3.7. β-Hydroxygerambullal {(E)-3-(methylsulfonyl)-propenoic acid (2E,6E)-2-[4-(3,7-dimethyl-8-oxo-2,6-octadienyloxy)-phenyl]-2-hydroxyethyl amide} (**5**)*

Colourless oil; $[\alpha]_D^{20} = +21$ ($CHCl_3$, $c = 0.4$). UV λ^{MeOH} nm 275 *sh*, 227. IR ν^{CHCl_3} cm^{-1} 3428 *m*, 3060 *w*, 2926 *m*, 2854 *w*, 1678 *s*, 1610 *m*, 1510 *s*, 1408 *w*, 1318 *s*, 1248 *m*, 1174 *m*, 1138 *s*, 1080 *w*, 1000 *m*, 966 *m*, 832 *w*, 548 *m*, 538 *w*, 526 *m*, 516 *s*, 510 *m*, 506 *s*. ^1H and ^{13}C NMR see Tables 1 and 2. MS (70 eV, 210°C) *m/z* (rel. int.): 417 (6, $M^+ - H_2O$), 273 (21), 267 (39, $CH_3SO_2CH{=}CH{-}CONH{-}CH{=}CH{-}C_6H_4{-}p{-}OH^+$), 145 (29), 134 (24), 123 (100), 117 (18), 107 (16), 95 (17), 93 (53), 81 (35), 71 (23), 65 (20), 55 (52).

*3.8. Sakerinol A {(E)-3-(methylsulfonyl)-propenoic acid (2E,6E)-3-hydroxy-4-(8-hydroxy-3,7-dimethyl-2,6-octadienyloxy)-phenethyl amide} (**7**)*

Colourless crystals from Et_2O, mp 133–135°C. UV λ^{MeOH} nm 275, 225 *sh*. IR ν^{CHCl_3} cm^{-1} 4210 *m*, 3540 *w*, 3300 *w*, 2924 *w*, 1676 *s*, 1600 *m*, 1506 *s*, 1456 *w*, 1318 *s*, 1272 *m*, 1182 *w*, 1136 *s*, 994 *m*, 960 *m*, 850 *w*, 628 *w*, 556 *w*, 534 *w*. ^1H and ^{13}C NMR see Tables 1 and 2; differential NOE's: 1″-H_2 → (7′-H, 2″-H_2, and 10″-H_3), 8″-H_2 → (6″-H), 9″-H_3 → (5″-H_2 and 8″-H_2), 10″-H_3 → (1″-H_2 and 5″-H_2); assignments supported by C,H-COSY and C/H long range correlations. MS (70 eV, 200°C) *m/z* (rel. int.): 285 (5, $CH_3SO_2CH{=}CH{-}CONH{-}CH_2CH_2{-}C_6H_3$-*m*-OH-*p*-$OH^+$), 256 (6), 136 (33), 123 (16), 80 (39), 71 (25), 69 (41), 65 (100), 57 (53), 44 (93); FD–MS: 437 (M^+) for $C_{22}H_{31}NO_6S$.

*3.9. O-Methylsakerinol A {(E)-3-(methylsulfonyl)-propenoic acid (2E,6E)-4-(8-hydroxy-3,7-dimethyl-2,6-octadienyloxy)-3-methoxyphenethyl amide} (**8**)*

Colourless crystals from Et_2O, mp 125–127°C. UV λ^{MeOH} nm 275, 227 *sh*. IR ν^{CHCl_3} cm^{-1} 3546 *w*, 3432 *w*, 3300 *w*, 2924 *m*, 2856 *w*, 1674 *s*, 1588 *m*, 1512 *s*, 1464 *m*, 1418 *w*, 1318 *s*, 1260 *m*, 1186 *w*, 1158 *m*, 1138 *s*, 996 *m*, 968 *m*, 854 *w*, 632 *w*, 558 *w*, 544 *w*. ^1H and ^{13}C NMR see Tables 1 and 2. MS (70 eV, 200°C) *m/z* (rel. int.): 299 (6, $CH_3SO_2CH{=}CH{-}CONH{-}CH_2CH_2{-}C_6H_3{-}m{-}OCH_3{-}p{-}OH^+$), 193 (4), 150 (100), 137 (36), 93 (12), 69 (15), 65 (27), 57 (17); FD–MS: 451 (M^+) for $C_{23}H_{33}NO_6S$.

*3.10. Sakerinol B {(E)-3-(methylsulfonyl)-propenoic acid (2E,6Z)-3-hydroxy-4-(8-hydroxy-3,7-dimethyl-2,6-octadienyloxy)-phenethyl amide} (**9**)*

Colourless crystals from Et_2O, mp 98–100°C. UV λ^{MeOH} nm 275, 225 *sh*. IR ν^{CHCl_3} cm^{-1} 4210 *m*, 3540 *w*, 3300 *w*, 2924 *w*, 1676 *s*, 1600 *m*, 1506 *s*, 1456 *w*, 1318 *s*, 1272 *m*, 1182 *w*, 1136 *s*, 994 *m*, 960 *m*, 850 *w*, 628 *w*, 556 *w*, 534 *w*. ^1H and ^{13}C NMR see Tables 1 and 2; differential NOE's: 1″-H_2 → (7′-H, 2″-H, and 10″-H_3), 2″-H → (1″-H_2 and 4″-H_2), 6″-H → (4″-H_2, 5″-H_2 and 8″-H_3), 9″-H_2 → (5″-H_2 and 8″-H_3); assignments supported by C,H-COSY and C/H long range correlations. MS (70 eV, 200°C) *m/z* (rel. int.): 285 (19, $CH_3SO_2CH{=}CH{-}CONH{-}CH_2CH_2{-}C_6H_3{-}m{-}OH{-}p{-}OH^+$), 175 (20), 136 (100), 123 (35), 107 (39), 93 (44), 81 (36), 69 (42), 65 (18), 55 (45); FD–MS: 437 (M^+) for $C_{22}H_{31}NO_6S$.

*3.11. Sakambullin {(E)-3-(methylsulfonyl)-propenoic acid 3-hydroxy-4-(3-methyl-2-butenyloxy)-phenethyl amide} (**11**)*

Colourless crystals from Et_2O, mp 111–113°C (Et_2O). UV λ^{MeOH} nm 275, 224 *sh*. IR ν^{CHCl_3} cm^{-1} 3534 *m*, 3430 *w*, 3050 *w*, 3042 *w*, 3038 *m*, 3030 *s*, 3008 *s*, 1678 *s*, 1630 *w*, 1590 *m*, 1512 *s*, 1458 *m*, 1438 *w*, 1318 *s*, 1272 *s*, 1250 *w*, 1244 *m*, 1184 *m*, 1176 *m*, 1138 *s*, 994 *m*, 958 *s*, 850 *m*, 628 *m*, 600 *w*, 566 *w*. ^1H and ^{13}C NMR see Tables 1 and 2. MS (70 eV, 150°C) *m/z* (rel. int.): 353 (26, M^+), 285 (23, $CH_3SO_2CH{=}CH{-}CONH{-}CH_2CH_2{-}C_6H_3{-}m{-}OH{-}p{-}OH^+$), 204 (94), 191 (59), 148 (54), 136 (100), 123 (98), 107 (26), 91 (28), 77 (61), 69 (88), 63 (46), 55 (44), 43 (59); HR–MS: $M_{exp} = 353.1295$, $M_{calc} = 353.1297$ for $C_{17}H_{23}NO_5S$.

*3.12. O-Methylsakambullin {(E)-3-(methylsulfonyl)-propenoic acid 4-(3-methyl-2-butenyloxy)-3-methoxyphenethyl amide} (**12**)*

Colourless crystals from Et_2O, mp 136–138°C. UV λ^{MeOH} nm 275, 227 *sh*. IR ν^{CHCl_3} cm^{-1} 3430 *w*, 3050 *w*, 3044 *w*, 2934 *m*, 1676 *s*, 1632 *w*, 1590 *m*, 1514 *s*, 1464 *m*, 1418 *w*, 1318 *s*, 1258 *s*, 1148 *m*, 1138 *s*, 996 *m*, 968 *s*, 958 *m*, 850 *m*, 626 *w*, 558 *w*. ^1H and ^{13}C NMR see Tables 1 and 2. MS (70 eV, 200°C) *m/z* (rel. int.): 367 (2, M^+), 299 (16, $CH_3SO_2CH{=}CH{-}CONH{-}CH_2CH_2{-}$

C_6H_3–*m*–OCH_3–*p*–OH^+), 218 (7), 150 (100), 137 (76), 71 (15), 69 (73), 53 (16); FD–MS: 367 (M^+) for $C_{18}H_{25}NO_5S$.

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