

NATURAL PRODUCT COMMUNICATIONS

An International Journal for Communications and Reviews Covering all
Aspects of Natural Products Research



Volume 9. Issue 3. Pages 293-444. 2014
ISSN 1934-578X (printed); ISSN 1555-9475 (online)
www.naturalproduct.us

EDITOR-IN-CHIEF**DR. PAWAN K AGRAWAL**

Natural Product Inc.
7963, Anderson Park Lane,
Westerville, Ohio 43081, USA
agrawal@naturalproduct.us

EDITORS**PROFESSOR ALEJANDRO F. BARRERO**

Department of Organic Chemistry,
University of Granada,
Campus de Fuente Nueva, s/n, 18071, Granada, Spain
afbarre@ugr.es

PROFESSOR ALESSANDRA BRACA

Dipartimento di Chimica Bioorganica e Biofarmacia,
Università di Pisa,
via Bonanno 33, 56126 Pisa, Italy
braca@farm.unipi.it

PROFESSOR DEAN GUO

State Key Laboratory of Natural and Biomimetic Drugs,
School of Pharmaceutical Sciences,
Peking University,
Beijing 100083, China
gda5958@163.com

PROFESSOR YOSHIHIRO MIMAKI

School of Pharmacy,
Tokyo University of Pharmacy and Life Sciences,
Horinouchi 1432-1, Hachioji, Tokyo 192-0392, Japan
mimakiy@ps.toyaku.ac.jp

PROFESSOR STEPHEN G. PYNE

Department of Chemistry
University of Wollongong
Wollongong, New South Wales, 2522, Australia
spyne@uow.edu.au

PROFESSOR MANFRED G. REINECKE

Department of Chemistry,
Texas Christian University,
Forts Worth, TX 76129, USA
m.reinecke@tcu.edu

PROFESSOR WILLIAM N. SETZER

Department of Chemistry
The University of Alabama in Huntsville
Huntsville, AL 35809, USA
wsetzer@chemistry.uah.edu

PROFESSOR YASUHIRO TEZUKA

Institute of Natural Medicine
Institute of Natural Medicine, University of Toyama,
2630-Sugitani, Toyama 930-0194, Japan
tezuka@inm.u-toyama.ac.jp

PROFESSOR DAVID E. THURSTON

Department of Pharmaceutical and Biological Chemistry,
The School of Pharmacy,
University of London, 29-39 Brunswick Square,
London WC1N 1AX, UK
david.thurston@pharmacy.ac.uk

HONORARY EDITOR**PROFESSOR GERALD BLUNDEN**

The School of Pharmacy & Biomedical Sciences,
University of Portsmouth,
Portsmouth, PO1 2DT U.K.
axuf64@dsl.pipex.com

ADVISORY BOARD

Prof. Viqar Uddin Ahmad
Karachi, Pakistan

Prof. Giovanni Appendino
Novara, Italy

Prof. Yoshinori Asakawa
Tokushima, Japan

Prof. Roberto G. S. Berlinck
São Carlos, Brazil

Prof. Anna R. Bilia
Florence, Italy

Prof. Maurizio Bruno
Palermo, Italy

Prof. César A. N. Catalán
Tucumán, Argentina

Prof. Josep Coll
Barcelona, Spain

Prof. Geoffrey Cordell
Chicago, IL, USA

Prof. Fatih Demirci
Eskişehir, Turkey

Prof. Dominique Guillaume
Reims, France

Prof. Ana Cristina Figueiredo
Lisbon, Portugal

Prof. Cristina Gracia-Viguera
Murcia, Spain

Prof. Duvvuru Gunasekar
Tirupati, India

Prof. Hisahiro Hagiwara
Niigata, Japan

Prof. Kurt Hostettmann
Lausanne, Switzerland

Prof. Martin A. Iglesias Arteaga
Mexico, D. F., Mexico

Prof. Leopold Jirovetz
Vienna, Austria

Prof. Vladimir I Kalinin
Vladivostok, Russia

Prof. Niel A. Koorbanally
Durban, South Africa

Prof. Chiaki Kuroda
Tokyo, Japan

Prof. Hartmut Laatsch
Göttingen, Germany

Prof. Marie Laccaille-Dubois
Dijon, France

Prof. Shoen-Sheng Lee
Taipei, Taiwan

Prof. Imre Mathe
Szeged, Hungary

Prof. Ermino Murano
Trieste, Italy

Prof. M. Soledade C. Pedras
Saskatoon, Canada

Prof. Luc Pieters
Antwerp, Belgium

Prof. Peter Proksch
Düsseldorf, Germany

Prof. Phila Raharivelomanana
Tahiti, French Polynesia

Prof. Luca Rastrelli
Fisciano, Italy

Prof. Stefano Serra
Milano, Italy

Prof. Monique Simmonds
Richmond, UK

Dr. Bikram Singh
Palampur, India

Prof. John L. Sorensen
Manitoba, Canada

Prof. Johannes van Staden
Scottsville, South Africa

Prof. Valentin Stonik
Vladivostok, Russia

Prof. Winston F. Tinto
Barbados, West Indies

Prof. Sylvia Urban
Melbourne, Australia

Prof. Karen Valant-Vetschera
Vienna, Austria

INFORMATION FOR AUTHORS

Full details of how to submit a manuscript for publication in Natural Product Communications are given in Information for Authors on our Web site <http://www.naturalproduct.us>.

Authors may reproduce/republish portions of their published contribution without seeking permission from NPC, provided that any such republication is accompanied by an acknowledgment (original citation)-Reproduced by permission of Natural Product Communications. Any unauthorized reproduction, transmission or storage may result in either civil or criminal liability.

The publication of each of the articles contained herein is protected by copyright. Except as allowed under national "fair use" laws, copying is not permitted by any means or for any purpose, such as for distribution to any third party (whether by sale, loan, gift, or otherwise); as agent (express or implied) of any third party; for purposes of advertising or promotion; or to create collective or derivative works. Such permission requests, or other inquiries, should be addressed to the Natural Product Inc. (NPI). A photocopy license is available from the NPI for institutional subscribers that need to make multiple copies of single articles for internal study or research purposes.

To Subscribe: Natural Product Communications is a journal published monthly. 2013 subscription price: US\$2,395 (Print, ISSN# 1934-578X); US\$2,395 (Web edition, ISSN# 1555-9475); US\$2,795 (Print + single site online); US\$595 (Personal online). Orders should be addressed to Subscription Department, Natural Product Communications, Natural Product Inc., 7963 Anderson Park Lane, Westerville, Ohio 43081, USA. Subscriptions are renewed on an annual basis. Claims for nonreceipt of issues will be honored if made within three months of publication of the issue. All issues are dispatched by airmail throughout the world, excluding the USA and Canada.

neo-Clerodane Diterpenoids from *Scutellaria galericulata*Petko I. Bozov^a, Plamen N. Penchev^b and Josep Coll^{c,*}^aDepartment of Biochemistry and Microbiology, Plovdiv University, 24 Tzar Asen Str., 4000-Plovdiv, Bulgaria^bDepartment of Analytical Chemistry, Plovdiv University, 24 Tzar Asen Str., 4000-Plovdiv, Bulgaria^cDepartment of Biological Chemistry and Molecular Modeling, Institut de Química Avançada de Catalunya, CSIC, J. Girona 18-26, 08034-Barcelona, Spain

josep.coll@iqac.csic.es

Received: October 17th, 2013; Accepted: November 26th, 2013

Four *neo*-clerodane diterpenoids, neoajugapyrin A, scutegalerins A and B and scutecolumnin C have been isolated from the acetone extract of the aerial parts of *Scutellaria galericulata*. Neoajugapyrin A and scutecolumnin C are reported in this species for the first time, whereas scutegalerins A and B are new compounds. NMR data of neoajugapyrin A are discussed in detail to support the proposed revised structure of ajugapyrin A.

Keywords: *Scutellaria galericulata*, *Ajuga pyramidalis*, Labiatae, *neo*-Clerodane diterpenes.

Scutellaria (Labiatae) species provide a rich source of *neo*-clerodane diterpenes [1] with potent insect antifeedant and antifungal activities [2,3]. Plant material of *S. galericulata* L. growing in the UK (Royal Botanic Gardens, Kew), Spain (Madrid province) and Bulgaria has been studied previously, and seven novel *neo*-clerodanes were reported: jodrellin T, 14,15-dihydrojodrellin T, galericulin [4], scutegalin A, scutegalin B [5], scutegalin C and scutegalin D [6], whereas jodrellin B was isolated previously from *S. woronowii* Juz. [2]. 14,15-Dihydrojodrellin T, scutegalin A, and scutegalin D were present in the Bulgarian plant [7]. All compounds, except galericulin, displayed a 2 α ,19-hemiacetal functionality. In continuation of our systematic studies on *Scutellaria* species [8-10], we have reinvestigated *S. galericulata* from a different geographical area. Here we report on the isolation of neoajugapyrin A (1), scutegalerin A (2), scutegalerin B (3) and scutecolumnin C (4), with full structural elucidation of 1 and 2. Neoajugapyrin A (which turned out to be 3 β -hydroxyscutecyprin) was isolated previously and named ajugapyrin A, but reported as 1 β -hydroxyscutecyprin from *Ajuga pyramidalis* [11]. The previously proposed structure has now been found to be wrong and the name neoajugapyrin A is proposed to indicate the new revised structure (with improved NMR data). The trivial name scutegalerin A is given to the real, now isolated, 1 β -hydroxyscutecyprin.

Two TLC homogeneous fractions and a mixture were obtained after chromatography of the acetone extract of the aerial parts of the Bulgarian plant. Compound 1 was isolated from the most polar fraction and the IR spectrum revealed the presence of hydroxyl and acetyl groups and, in addition, bands for (*E*)-2-methyl-2-butenyl ester, but the absence of those for either a lactone or furan moiety. The ¹H NMR spectrum of 1 (250 MHz) was identical (direct comparison) with that previously reported for ajugapyrin A [11]. Owing to the limited NMR data available we completed a comprehensive NMR study (600 MHz) to improve the structural elucidation and facilitate identification in subsequent isolations. The ¹H-broadband-decoupled ¹³C NMR and the DEPT spectra of 1 (Table 1) displayed 27 and 21 (5x CH₃, 6x CH₂, 10x CH) signals, respectively. Data of hexahydrofurofuran, tiglyl and acetyl moieties, as well as for C-6 to C-10 in ring B, were in close agreement with those for the scutecyprin parent system [12; Bozov and Penchev,

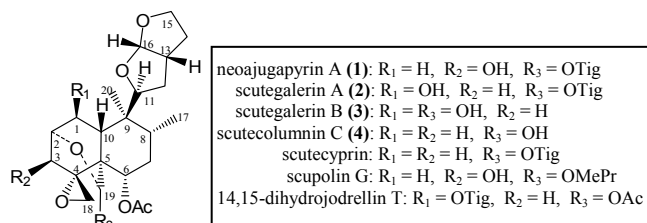


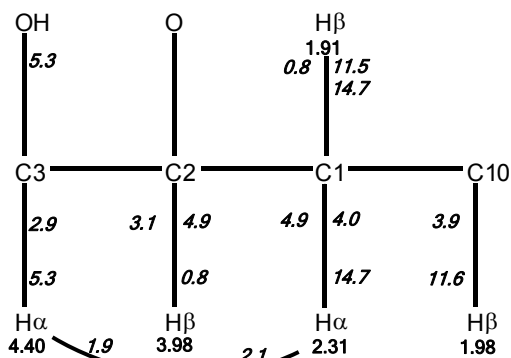
Figure 1: Structures of isolated *neo*-clerodanes and compounds used in the discussion

unpublished data]. Some signal assignments and *J* constants are corrected owing to improved resolution of the ¹H NMR spectrum. Thus, spectral data of the tiglic acid moiety were in agreement with published values [5,12,13], but the clear multiplicities now observed for Me-4' and Me-5' pointed out the interchange of assignment of these signals (as appearing in [11]). Furthermore, the 4.40 *m* was reported as collapsing "into a *t* after addition of D₂O" pointing out a likely reversal of 1 α /2 β assignments. Moreover, since the δ_{H} 2.55 brd assigned to H-3 α in scutecyprin [12] was not present, O-substitution at C-3 rather than at C-1 was considered a likely possibility requiring an unambiguous rationale. Furthermore, the two O functions at C-2 and C-3 may be accounted for in two different ways depending on the carbon involved in the bridge to C-19 and the one with the free hydroxyl function, forming either the common 2.2.2 or a 3.2.1 bi-cyclic system. Detailed analysis of the HSQC/HMBC spectra for C-1 to C-5 established the C(2)-O-C(19) bridge unambiguously: δ_{H} 3.98 as H-2 [HMBC correlations with C-19, C-10 and the reciprocal H-19 to C-2], whereas H-3 α (δ_{H} 4.40/ δ_{C} 70.1) displayed only the reciprocal H-18 to C-3 correlation. The spin system in ring A (H-10—[H-1 α —H-1 β]—H-2 β —H-3 α) was finally elucidated from strong ¹H-¹H COSY cross signals and has been summarized in Figure 2. It is worth mentioning the strong ¹H-¹H COSY correlation and the relatively large ⁴*J* constant between H-3 α and H-1 α signals, a likely consequence of flat zig-zag (W) arrangement in the compound skeleton. This arrangement would not be present if the hydroxyl group were at the 3 α position, whereas 1 β ,3 β NOE interaction could be expected. Moreover, as reported, the δ_{H} 4.40 band width is reduced after shaking with D₂O (at 250 MHz the HO signal overlaps/exchanges with the "water" band at ca. δ_{H} 1.6).

Table 1: Neoajugapyrin A (**1**)^a and scutegalerins A (**2**)^b and B (**3**)^b NMR data.

position	1			2			3	
	$\delta^{13}\text{C}$, nH	$\delta^1\text{H}$	<i>m, J</i> (in Hz)	$\delta^{13}\text{C}$, nH	$\delta^1\text{H}$	<i>m, J</i> (in Hz)	$\delta^1\text{H}$	<i>m, J</i> (in Hz)
1	22.6, CH ₂	2.30	dddd, 14.7; 4.9; 4.0; 2.1	67.1, CH	4.38	ddd ^e , 3.9; 3.0; 1.2	4.33	ddd, 4.6; 3.2; 1.1
2	71.0, CH	3.98	ddd, 14.6; 11.5; 0.9	69.3, CH	4.11	dt, 5.1; 2.7	4.10	dt, 4.9; 2.6
3	70.1, CH	4.40	ddd, 4.9; 3.1; 0.8	30.9, CH ₂	2.46	br d, 14.4	2.49	br dd, 14.3; 2.5
4	65.9, C		ddd, 5.1; 2.9; 1.9 (2.1)		2.25	m ^h	ca. 2.22	m ^h
5	42.5, C			60.1, C				
6	68.2, CH	4.63	dd, 11.9; 4.7	43.4, C				
7	33.3, CH ₂	1.65 ^e		67.8, CH	4.62	dd, 11.7; 4.5	4.68	dd, 11.3; 4.6
8	35.4, CH	1.39	ddd, 13.1; 4.6; 3.0	32.5, CH ₂	1.63	m ^h	ov ⁱ	-
9	41.2, C	1.53	ddd, 13.1; 4.6; 3.0	1.37	ddd, 13.0; 4.5; 2.9		ca. 1.45	m ^h
10	40.7, CH	1.98	dq, 12.8; 6.6; 3.1	35.6, CH	1.53	m ^h	ov ⁱ	-
11	86.4, CH	4.09	dd, 11.6; 3.9	40.5, C				
12	33.3, CH ₂	1.92 ^e	dd, 11.0; 5.7	51.8, CH	1.76	d, 2.9	1.71	d, 3.2
13	41.8, CH	2.84	br ddd, 5.1; 3.0; 1.2	87.2, CH	4.09	dd, 11.3; 5.0	4.07	dd, 11.8; 5.1
14	32.6, CH ₂	2.15	ddt, 12.7; 9.2; 8.3	33.6, CH ₂	1.97	td, 12.5; 9.3	1.97	td, 12.0; 9.4
15B ^c	68.3, CH ₂	3.8765	ddd, 8.8; 8.7; 6.6	41.6, CH	2.92	br tt ^f , 9.2; 4.6	2.92	br tt ^f , 9.4; 4.7
15A ^c	3.8617	ddd, 8.7; 8.1; 4.5	32.7, CH ₂	32.7, CH ₂	2.22	m ^h	ca. 2.22	m ^h
16	108.1, CH	5.63	d, 5.1	174 ^e	1.74	m ^h	ca. 1.74	m ^h
17	16.4, CH ₃	0.89	d, 6.1	68.9, CH ₂	3.9414	ddd, 8.8; 8.2; 6.7	3.94	-
18B ^d	44.1, CH ₂	3.09	d, 4.3	3.8755	ddd, 8.8; 7.9; 4.5	3.88	-	-
18A	2.88	d, 4.3	108.4, CH	5.69	d, 5.2	5.69	d, 5.2	d, 5.2
19	91.0, CH	6.76	s	16.0, CH ₃	0.89	d, 6.6	0.90	d, 6.3
20	14.3, CH ₃	1.19	s	50.4, CH ₂	3.00	d, 4.3	2.96	d, 4.0
1' (C=O)	166.0, C			18A	2.51	d, 4.3	2.51	d, 4.0
2'	128.7, C			19	6.68	s	5.61	s
3'	138.7, CH	7.06	qq, 7.1; 1.4	20	1.22	s	1.16	s
4'	14.5, CH ₃	1.80	dq, 7.1; 1.2	166.4, C				
5'	11.9, CH ₃	1.87	quint ^g , 1.3	128.8, C				
6' (C=O)	170.0, C			3'	138.7, CH	7.11	qq, 7.0; 1.5	
6 ² (Me)	21.0, CH ₃			4'	14.6, CH ₃	1.81	dq, 7.1; 1.1	
(HO)	2.05	d, 5.3		5'	11.9, CH ₃	1.90	dq ⁱ , 1.2	
(HO)	2.39			6' (C=O)	169.9, C			
				6 ² (Me)	21.0, CH ₃	1.80	s	2.06
				(HO)	3.51			s

^a CDCl₃, ¹H 600.13 MHz, δ_{ref} 7.26; ¹³C 150.9 MHz, δ_{ref} 77.0 ppm; ^b CDCl₃, ¹H 400 MHz, δ_{ref} 7.26; ¹³C 101 MHz, δ_{ref} 77.0 ppm; ^c $\delta^1\text{H}$ adjusted by spin simulation; ^d endo hydrogen; ^e data from COSY; ^f apparent multiplicity; ^g after D₂O addition; ^h multiplicity and coupling constants could not be estimated; ⁱ overlapped with the "water" band at ca. δ_{H} 1.6.

**Figure 2:** Ring A spin system of **1** (H-10—[H-1 α —H-1 β —H-2 β —H-3 α]; *J* in italics)

Therefore, the structure was elucidated as 3 β -hydroxyscutecyprin (and named as neoajugapyrin A to indicate the change to a new revised structure supported by NMR data, as discussed). Additional inferences could be drawn by comparison of selected NMR spectral data for H-1 α and H-3 α in neoajugapyrin A with those of some *neo*-clerodanes with 2 α ,19 and 4 α ,18 epoxy rings [4,5,12,14], as given in Table 2. As a whole, the ¹H NMR spectrum of **1** is very close to that of scutecyprin and scupolin G and similar to that of 14,15-dihydrojodrellin T.

Table 2: C-1/C-3 substitution effects in *neo*-clerodanes with 2 α ,19 and 4 α ,18 epoxy rings.

compound	substitution		δ_{H}	δ_{H}	δ_{C}
	C-1	C-3	H-1 α	H-2 β /H-3 α	C-4/C-18
neoajugapyrin A, 1	H ₂	H,OH	2.31	3.98 ddd 4.9,3.1,0.8/ 4.40 ddd 5.3,2.9,1.9	65.9/44.1
scupolin G	H ₂	H,OH	n.r. ^a	4.32 m w ^{1/2} 4.5/ 3.95 dd 4.1,3.2 ^b	65.8/44.0 ^b
scutecyprin	H ₂	H ₂	n.r. ^a	4.18 m w ^{1/2} 6/ 2.55 br d 14.3 ^c 2.36 dtd ^d	60.6/50.2 ^c 60.6/50.2 ^d
14,15-dihydrojodrellin T	H,OTig	H ₂	5.51 m ^e	4.42 dt 5.3,2.6/ 2.48 br d 14.8 ^e	59.6/50.2 ^f

^a data not reported; ^b data from [14]; ^c data from [12]; ^d Bozov PI, Penchev PN, unpublished NMR spectral data; ^e data from [4]; ^f data from [5].

As can be seen, the reported H-2 β /H-3 α assignment for scupolin G [14] may also be reversed (the rationale for the irradiation result changes ⁴*J*_{H-3,H-1} to ³*J*_{H-2,H-1} = 3.2 Hz). Therefore, the HO-substitution effect must be an up-field rather than downfield shift at the vicinal proton: $\delta_{\text{H-2}\beta}$ 4.18 (in scutecyprin) to 3.95 instead of to 4.32 (in scupolin G). From Table 2, the δ_{H} for H-1 α are very close in neoajugapyrin A and scutecyprin, as well as the δ_{H} for H-2 β /H-3 α in neoajugapyrin A/scupolin G and scutecyprin/14,15-dihydrojodrellin T, thus reflecting the methylene group at the corresponding position. Also, the hydroxyl group at C-3 (as in neoajugapyrin A and scupolin G) leads to either a high- or low-frequency shift of about 5-6 ppm for C-4 or C-18 carbon signals (last column of Table 2).

To our surprise, spectral data for **2** pointed to the true 1 β -hydroxyscutecyprin structure. Again, two H-C-O signals were part of ring A, but now, one was located at δ_{H} 4.38 and coupled to a δ_{H} 1.77 doublet ($J = 2.9$ Hz), pointing out the HC(1)-HC(10) relationship. Furthermore, this presumed HC(1)-O signal was coupled to the second H-C-O multiplet (δ_{H} 4.11, dqcosy) partly overlapping with HC(11)-O (δ_{H} 4.09). The four cross peaks displayed at δ_{H} 4.09/4.11 (δ_{H} 2.44, 2.22, 1.97 and 1.65) were sorted out as each pair in the HSQC spectrum by correlation with δ_{C} 30.8 (the first two) and δ_{C} 33.5 (the last two). Therefore, they could be assigned as C-3 and C-12, respectively. Thus, after a detailed study of the multiplicities, the spin system of ring A could be completed as shown in Figure 3.

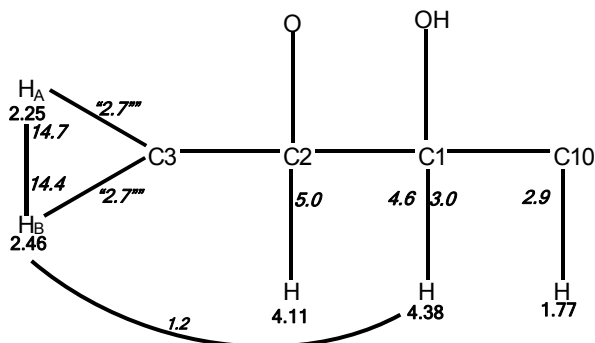


Figure 3: Ring A spin system of **2** (H-10—H-1 α —H-2 β —[H-3A—H-3B]); J in *italics*).

Further evidence supporting the stereochemistry was derived from NOESY results: H-C(6) interaction with H_B-C(18), H-C(8) and H-C(10) places all of them on the same β -side, and H-C(1) with H-C(20) on the same α -side. The pattern recognition (both as ddd) of the H₂C(15) spin subsystem (AB part of an AB-XY-M-xy-a spin system) is worthy of mention, owing to the anisotropic effect upon hydroxyl substitution at C-1. Chemical shifts and coupling constants reported in Table 1 were adjusted by spin simulation (and in turn those of **1**). The now isolated 1 β -hydroxyscutecyprin was named scutegalerin A (**2**).

A third (minor) isolated compound displayed most of the ¹H NMR structural features as **2** (Table 1). However, the tigloyl substituent signals were not present, while the expected change for a hydroxyl group as a C-19 substituent was observed [HC(19): δ_{H} 5.61 vs. δ_{H} 6.68 ppm]. The compound (1 β -hydroxyscutecolumnin C) was named scutegalerin B (**3**).

Scutecolumnin C (**4**) was identified (based on ¹H NMR data) as the fourth isolated neo-clerodane and is reported for the first time in this species. It has been found previously in extracts of *S. columnae* [15,16], *S. alpina* [17] and *S. alpina* subsp. *javallambrensis* [18].

Experimental

Structural data: ¹H NMR spectra were recorded on either Bruker DRX-250, Varian Mercury-400 or Bruker Avance II+ spectrometers, operating at 250.13 MHz, 400.13 or 600.130 MHz, respectively. ¹³C NMR spectra were recorded at 100.61 and 150.903 MHz, respectively on the corresponding spectrometers. TMS was used as internal standard and CDCl₃ as solvent. Chemical shifts (δ) are expressed in ppm and coupling constants (J) in Hertz. The IR spectra of **1** and **4** were registered in KBr pellets on a Perkin-Elmer 1750 FT-IR spectrometer from 4000 cm⁻¹ to 450 cm⁻¹ at resolution 4 cm⁻¹ with 9 scans.

Plant material: The stems of *Scutellaria galericulata* were collected in June 2012 near Pleven, Bulgaria, and voucher specimens (no. 11927) were deposited in the Herbarium of the Higher Institute of Agriculture at Plovdiv, Bulgaria.

Extraction and isolation: Dried and finely powdered aerial parts of *S. galericulata* (2.8 kg) were extracted with Me₂CO (3 x 8 L) at room temperature for a week. After filtration, the solvent was evaporated to dryness under reduced pressure and low temperature (<40°C) yielding a gum (35.2 g), which was dissolved in aq. Me₂CO (40% H₂O, v/v, 100 mL). This solution was cooled to 4°C for 24 h and filtered. The filtrate was extracted with CHCl₃ (3 x 200 mL) and the organic layer was dried (Na₂SO₄) and evaporated in vacuum to afford a residue (3.9 g, bitter fraction). This was subjected to CC (45 g silica gel Merck n. 7734, deactivated with 10% H₂O, w/w). Pure light petroleum (5 L), followed by a gradient of light petroleum - EtOAc mixtures (10:1 to 4:1) and dichloromethane were used first as eluting solvents. The diterpene fractions (100 mL each) were eluted with 2% methanol in DCM yielding scutecolumnin C (**4**, 6 mg, 3 flasks) followed by 39.5 mg of a mixture (4 flasks, two TLC spots upon EtOAc elution) and 53 mg of **1** (10 flasks). Repeated prep TLC of the mixture (2% methanol in DCM) afforded further amounts of **4** (1.3 + 2.3 mg) and 19.9 mg of a diterpene mixture. Prep TLC separation of this mixture (*n*-hexane-EtOAc, 1:4, x 3) further yielded **2** (1.6 mg), **3** (0.9 mg) and a minor amount of **4**.

Neoajugapyrin A (**1**)

Colorless needles from acetone.

MP: 200-202°C (lit. [11]) MP: 198-200° from Et₂O-petrol).

TLC: R_f 0.67 (EtOAc).

IR (KBr): 3403, 2967, 2939, 2901, 2873, 1723, 1698, 1654, 1464, 1386, 1336, 1295, 1261, 1250, 1158, 1092, 1082, 1066, 1052, 1018, 986, 966, 942, 918, 899, 875, 835, 777, 732, 679, 628, 603, 568, 527, 485, 469 cm⁻¹.

¹H and ¹³C NMR: Table 1 (Supplementary data Table 1A).

calcd for C₂₇H₃₈O₉: 506.251585 (lit. [11]: m/z (rel. int.) 506 [M]⁺

(0.12); C₁₇H₃₈O₄ (wrong formula) requires: C, 64.01, H 7.56%;

Found: C, 62.19; H, 7.41)

Scutegalerin A (**2**)

Colorless oil

TLC: R_f 0.49 (EtOAc)

¹H and ¹³C NMR: Table 1 (Supplementary data Table 1B).

Scutegalerin B (**3**)

Colorless oil

TLC: R_f 0.49 (EtOAc).

¹H NMR: Table 1.

Scutecolumnin C (**4**)

TLC: R_f 0.81 (EtOAc).

IR (KBr): 3444, 2960, 2877, 1729, 1648, 1456, 1374, 1249, 1093, 1021, 970, 921, 878, 732, 601 cm⁻¹.

¹H and ¹³C NMR: as in [17] with minor differences

Supplementary data: Tables of complete spectral data and the ¹H NMR, ¹³C NMR and 2D NMR spectra (with enlarged detailed sections for multiplets and cross peaks) are included in a "Supplementary Data" section.

Acknowledgments - We gratefully acknowledge the Bulgarian National Science Fund, Contract DDWU02/37 and the Spanish MICYT (project AGL2004/05252) for financial support.

References

- [1] Bruno M, Piozzi F, Rosselli S. (2002) Natural and hemisynthetic neoclerodane diterpenoids from *Scutellaria* and their antifeedant activity. *Natural Product Reports*, **19**, 357-378.
- [2] Anderson JC, Blaney WM, Cole MD, Fellows LL, Ley SV, Sheppard RN, Simmonds MSJ. (1989) The structure of two new clerodane diterpenoid potent insect antifeedants from *Scutellaria woronowii* (Juz); jodrellin A & B. *Tetrahedron Letters*, **30**, 4737-4740.
- [3] Cole MD, Bridge PD, Dellar JE, Fellows LE, Clare Cornish M, Anderson JC. (1991) Antifungal activity of neo-clerodane diterpenoids from *Scutellaria*. *Phytochemistry*, **30**, 1125-1127.
- [4] Cole MD, Anderson JC, Blaney WM, Fellows LE, Ley SV, Sheppard RN, Simmonds MSJ. (1990) Neo-clerodane insect antifeedants from *Scutellaria galericulata*. *Phytochemistry*, **29**, 1793-1796.
- [5] Rodríguez B, de la Torre MC, Rodríguez B, Bruno M, Piozzi F, Savona G, Simmonds MSJ, Blaney WM, Perales A. (1993) neo-Clerodane insect antifeedants from *Scutellaria galericulata*. *Phytochemistry*, **33**, 309-315.
- [6] Rodríguez B, de la Torre MC, Rodríguez B, Gómez-Serranillos P. (1996) neo-Clerodane diterpenoids from *Scutellaria galericulata*. *Phytochemistry*, **41**, 247-253.
- [7] Boneva IM, Malakov PY, Papanov GY, Tomova K. (1999) Diterpenoids and sterols from *Scutellaria galericulata*. *Bulgarian Chemical Communications*, **31**, 269-275.
- [8] Bozov PI, Malakov PY, Papanov GY, de la Torre MC, Rodríguez B, Perales A. (1993) Scutalpin A, a neo-clerodane diterpene from *Scutellaria alpina*. *Phytochemistry*, **34**, 453-456.
- [9] Bozov PI, Papanov GY, Malakov PY. (1994) neo-Clerodane diterpenoids from *Scutellaria alpina*. *Phytochemistry*, **35**, 1285-1288.
- [10] Malakov PY, Bozov PI, Papanov GY. (1997) A neo-clerodane diterpenoid from *Scutellaria orientalis* subs. *pinnatifida*. *Phytochemistry*, **46**, 587-589.
- [11] Boneva IM, Malakov PY, Papanov GY. (1998) Ajugapyrin A, a neo-clerodane diterpene from *Ajuga pyramidalis*. *Phytochemistry*, **47**, 303-305.
- [12] Bruno M, de la Torre MC, Piozzi F, Rodríguez B, Savona G, Arnold NA. (1993) A neo-clerodane diterpenoid from *Scutellaria cypria* var. *elatior*. *Phytochemistry*, **33**, 931-932.
- [13] Fraser RR. (1960) Long-range coupling constants in the NMR spectra of olefins. *Canadian Journal of Chemistry*, **38**, 549-553.
- [14] de la Torre MC, Rodríguez B, Bruno M, Vassallo N, Bondi ML, Piozzi F, Servettaz O. (1997) Neoclerodane diterpenoids from *Scutellaria polyodon*. *Journal of Natural Products*, **60**, 1229-1235.
- [15] de la Torre MC, Bruno M, Piozzi F, Rodríguez B, Savona G, Servettaz O. (1992) neo-Clerodane diterpenoids from *Scutellaria columnae*. *Phytochemistry*, **31**, 3639-3641.
- [16] Malakov PY, Papanov GY, Deltchev VB. (1998) II-Episcutecolummin C, a neo-clerodane diterpenoid from *Scutellaria columnae*. *Phytochemistry*, **49**, 811-815.
- [17] de la Torre MC, Rodríguez B, Bruno M, Piozzi F, Savona G, Vassallo N, Servettaz O. (1995) neo-Clerodane diterpenoids from *Scutellaria alpina*. *Phytochemistry*, **38**, 181-187.
- [18] Muñoz DM, de la Torre MC, Rodríguez B, Simmonds MSJ, Blaney WM. (1997) Neo-clerodane insect antifeedants from *Scutellaria alpina* subsp. *javalambrensis*. *Phytochemistry*, **44**, 593-597.

New Schiartane-type Triterpene from <i>Kadsura heteroclita</i> and their Cytotoxic Activities Pham Thi Hong Minh, Do Tien Lam, Nguyen Quyet Tien, Nguyen Ngoc Tuan, Vu Phuong Nhung, Nong Van Hai, Phan Van Kiem, Nguyen Xuan Nhiem, Chau Van Minh, Park Seon Ju and Kim Seung Hyun	373
C-Lactam Derivatives of Oleanolic Acid. Hydrolysis and Further Acylation of Methyl Acetyloleanolate C-Lactam and C-Thiolactam Barbara Bednarczyk – Cwynar and Lucjusz Zaprutko	375
New Acylated Triterpene Glycosides from the Roots of <i>Polygala tenuifolia</i> Minpei Kuroda, Takaaki Shizume and Yoshihiro Mimaki	379
Cucurbitane-type Triterpene Glycosides from the Fruits of <i>Momordica charantia</i> Pham Hai Yen, Duong Thi Dung, Nguyen Xuan Nhiem, Hoang Le Tuan Anh, Dan Thi Thuy Hang, Duong Thi Hai Yen, Nguyen Thi Cuc, Ninh Khac Ban, Chau Van Minh and Phan Van Kiem	383
Cytotoxic Effects of Four Aescin Types on Human Colon Adenocarcinoma Cell Lines Ewa Seweryn, Michał Gleńsk, Kamila Środa-Pomianek, Ireneusz Ceremuga, Maciej Włodarczyk and Andrzej Gamian	387
Structures of Violaceosides C, D, E and G, Sulfated Triterpene Glycosides from the Sea Cucumber <i>Pseudocolochirus violaceus</i> (Cucumariidae, Dendrochirotida) Alexandra S. Silchenko, Anatoly I. Kalinovsky, Sergey A. Avilov, Pelageya V. Andryjaschenko, Pavel S. Dmitrenok, Vladimir I. Kalinin, Ekaterina A. Yurchenko and Salim S. Dautov	391
<u>Review/Account</u>	
Phytotoxic Terpenes Produced by Phytopathogenic Fungi and Allelopathic Plants Alessio Cimmino, Anna Andolfi and Antonio Evidente	401
Pungent and Bitter, Cytotoxic and Antiviral Terpenoids from Some Bryophytes and Inedible Fungi Yoshinori Asakawa, Fumihiro Nagashima, Toshihiro Hashimoto, Masao Toyota, Agnieszka Ludwiczuk, Ismiarni Komala, Takuya Ito and Yasuyuki Yagi	409
Terpenoids and Sterols from Some Japanese Mushrooms Yasunori Yaoita, Masao Kikuchi and Koichi Machida	419
Phytochemicals and Biological Activities of Poisonous Genera of Ericaceae in China Xiaohong Wang, Rui Jiang, Zizhen Liu, Weirui Liu, Meng Xie, Shengli Wei and Gaimei She	427

Natural Product Communications

2014

Volume 9, Number 3

Contents

Bioactive Terpenes – From Isolation to Chemical Synthesis

<u>Original Paper</u>	<u>Page</u>
An Expedient Synthesis of Linden Ether Stefano Serra and Alessandra A. Cominetti	293
Simple and Short Synthesis of <i>Trans</i>-(<i>R</i>)-Nerolidol, a Pheromone Component of Fruit Spotting Bug Thanh C. Le and Kamlesh R. Chauhan	297
Monoterpene Citral Derivatives as Potential Antimalarials Soni Singh, Reena P. Khandare, Manish Sharma, Virendra K. Bhasin and Sujata V. Bhat	299
A General Synthetic Approach to Hydroquinone Meroterpenoids: Stereoselective Synthesis of (+)-(<i>S</i>)-Metachromin V and Alliodorol Stefano Serra, Alessandra A. Cominetti and Veronica Lissoni	303
Synthetic Approach to the Psoracorylifols George A. Kraus and Pengfei Dong,	309
Chemotaxonomic Value of Magastigmane Glucosides of <i>Cichorium calvum</i> Klaudia Michalska, Alex Beharav and Wanda Kisiel	311
Cyclonerol Derivatives from <i>Trichoderma longibrachiatum</i> YM311505 Qi-Cun Xuan, Rong Huang, You-Wei Chen, Cui-Ping Miao, Kai-Xia Ma, Tang Wang and Shao-Hua Wu	313
Anti-influenza Sesquiterpene from the Roots of <i>Reynoutria japonica</i> Nguyen Xuan Nhiem, Phan Van Kiem, Chau Van Minh, Nguyen Thi Hoai, Ho Viet Duc, Bui Huu Tai, Tran Hong Quang, Hoang Le Tuan Anh, Sang-Gu Yeo, Jae-Hyoung Song, Doo-Sung Cheon, Moon Ho Park, Hyun-Jeong Ko and Seung Hyun Kim	315
Lactarane Sesquiterpenes from the European Mushrooms <i>Lactarius aurantiacus</i>, <i>L. subdulcis</i>, and <i>Russula sanguinaria</i> Gianluca Gilardoni, Omar Malagòn, Solveig Tosi, Marco Clericuzio and Giovanni Vidari	319
Laurane-, Cyclolaurane-, and Cuparane-type Sesquiterpenes from the Marine Red Alga <i>Laurencia okamurai</i> Yi Liang, Xiao-Ming Li, Chun-Shun Li, Hong Sun and Bin-Gui Wang	323
The First Isolation of Furanoterpenophilane from <i>Ligularia nelumbifolia</i> Hiroshi Hirota, Yurie Horiguchi, Satoru Kawaii, Ryo Hanai, Xun Gong and Chiaki Kuroda	325
Use of (<i>S</i>)-<i>trans</i>-γ-Monocyclofarnesol as a Useful Chiral Building Block for the Stereoselective Synthesis of Diterpenic Natural Products Stefano Serra, Alessandra A. Cominetti and Veronica Lissoni	329
Bioactivity-guided Isolation of Antiproliferative Compounds from the Roots of <i>Onopordum acanthium</i> Boglárka Csupor-Löffler, István Zupkó, Judit Molnár, Peter Forgo and Judit Hohmann	337
Distribution of (-)-Hamanasic Acid A in South American Species of <i>Flourensia</i> and Phytotoxic Effects of Leaf Aqueous Extracts Daniela López, Leonardo A. Piazza, Mariana P. Silva, Marisa J. López Rivilli, Juan J. Cantero, Graciela M. Tourn and Ana L. Scopel	341
neo-Clerodane Diterpenoids from <i>Scutellaria galericulata</i> Petko I. Bozov, Plamen N. Penchev and Josep Coll	347
Seed Dormancy Breaking Diterpenoids, Including Novel Brassicenes J and K, from Fungus <i>Alternaria brassicicola</i>, and their Necrotic/Apoptotic Activities in HL-60 Cells Hiromichi Kenmoku, Sayaka Takeue, Megumi Oogushi, Yasuyuki Yagi, Takeshi Sassa, Masao Toyota and Yoshinori Asakawa	351
Facile Access to Optically Active Ring C Aromatic Diterpene Derivatives from (+)-Manool. First Synthesis of 13,14-Dihydroxy-8,11,13-podocarpatrien-7-one Mária L. Nóvoa, Franklin J. Salazar, Carlos Gámez, Ana Y. Angarita, Eleonora Tropper, Nieves Canudas and José E. Villamizar	355
Antiproliferative Effects of 12-Oxoheteronemin vs Heteronemin Siriporn Kittiwisut, Cristina C. Rohena, Supreeya Yuenyongsawad, Susan L. Mooberry and Anuchit Plubrukarn	359
New Cembranoids from the Soft Coral <i>Sinularia arborea</i> Li-Hsueh Wang, Kuan-Hua Chen, Chang-Feng Dai, Tsong-Long Hwang, Wei-Hsien Wang, Zhi-Hong Wen, Yang-Chang Wu and Ping-Jyun Sung	361
T-DNA Insertion Alters the Terpenoid Content Composition and Bioactivity of Transgenic <i>Artemisia annua</i> Netiya Karaket, Suthep Wiyakrutta, Marie-Aleth Lacaille-Dubois and Kanyaratt Supaibulwatana	363
A New Cytotoxic Tirucallane from the Twigs of <i>Walsura trichostemon</i> Jirapast Sichaem, Pongpun Siripong, Santi Tip-pyang and Jatuporn Phaopongthai	367
A New Ergostane Triterpenoid from Cultures of the Basidiomycete <i>Inocybe lilacina</i> Dong-Ze Liu, Qi Liu, Ping Yang, and Wen-Xia Jiang	369
New Ursane Triterpene from the Fruits of <i>Terminalia arjuna</i> Rashadul Hossain, Rajia Sultana, Aychout Adhikari, Muhammad Iqbal Choudhary, Yusuff Ali and Shahed Zaman	371

Continued inside backcover