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Benzoxazinoids and iridoid glucosides from four *Lamium* species

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Abstract

A new class of compounds for the plant family Lamiaceae, benzoxazinoids, was found in *Lamium galeobdolon*. From the aerial parts of the species were isolated the new 2-*O*-β-D-glucopyranosyl-6-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (6-hydroxy blepharin) together with four known benzoxazinoids, DHBOA-Glc, blepharin, DIBOA, DIBOA-Glc, as well as harpagide, 8-*O*-acetyl-harpagide and salidroside. Eight known iridoid glucosides, 24-*epi*-pterosterone and verbascoside were isolated from *Lamium amplexicaule*, *L. purpureum* and *L. garganicum*. The iridoids, 5-deoxylamiol and sesamoside, as well as the phytoecdysone, 24-*epi*-pterosterone, were found for the first time for the genus *Lamium*. The phytochemical data are discussed from a systematic and evolutionary point of view.

Keywords: *Lamium*; Lamiaceae; Benzoxazinoids; Iridoid glucosides; Chemotaxonomy

1. Introduction

The genus *Lamium* L. (Lamiaceae) comprises about 40 species (Willis, 1973), distributed in Europe, Asia and Africa. The separation of *Lamium galeobdolon* L. in the monotypic genus *Galeobdolon* Adens (*Lamiastrum* Heist ex Fabr.) still remains disputable. Some *Lamium* plants have been used in official and folk medicine. The most popular is *L. album* L. with uterytonic, astringent, antispasmodic and anti-inflammatory activities (Bremness, 1995; Scygan et al., 1989). Previous phytochemical investigations of the genus *Lamium* resulted in the isolation of iridoid glucosides, flavonoids, phenolics, phenylpropanoids, polysaccarides, triterpene saponins, tannins and phytoecdysteroids (Berezina et al., 2000; Savchenko et al., 2001 and references cited therein). Three *Lamium* species have been studied extensively for their iridoid composition, *L. album* (Brieskorn and Ahlborn, 1973; Eigtved et al., 1974; Damtoft, 1992), *L. amplexicaule* (Scarpati and Guiso, 1967, 1969; Inouye et al., 1977; Bianco et al., 1980; Guiso and Martino, 1983; Kobayashi et al., 1986) and *L. galeobdolon* (Wieffering and Fickensher, 1974; Bianco et al., 1986). Another seven *Lamium* species were screened by paper chromatography more than 30 years ago (Adema, 1968; Kooiman, 1972).

In the present paper, a phytochemical study of *Lamium galeobdolon* (*Lamiastrum galeobdolon*, *Galeobdolon luteum*), *L. amplexicaule*, *L. garganicum* and *L. purpureum* is presented. The isolation of benzoxazinoids (**1**–**5**), iridoid glucosides (**6**–**7**, **9**–**16**), phenylpropanoids (**8**, **18**) and a phytoecdysteroid (**17**) is reported, and the chemosystematic implications of the results are discussed.

2. Results and discussion

2.1. *Lamium galeobdolon L. ssp. galeobdolon*

The water-soluble part of the ethanolic extract from aerial parts, after separation by different chromatographic techniques, afforded the new benzoxazinoid glucoside **1** together with seven known compounds. Compounds **2**–**5** were identified as the benzoxazinones 2-*O*-β-D-glucopyranosyl-7-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (**2**) (Nagao et al., 1985), blepharin (**3**) (Tietze

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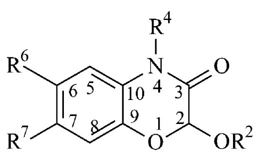
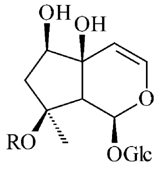
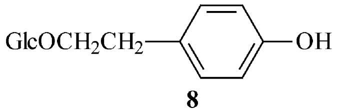


	R^2	R^4	R^6	R^7
1	Glc	H	OH	H
2	Glc	H	H	OH
3	Glc	H	H	H
4	H	OH	H	H
5	Glc	OH	H	H



	R
6	H
7	Ac



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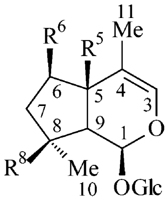
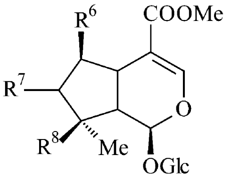
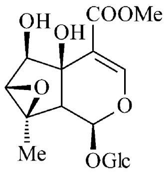


	R^5	R^6	R^8
9	OH	OH	OH
10	OH	OH	OAc
11	H	OH	OH



	R^6	R^7	R^8
12	OH	β-OH	OH
13	OH	H	OH
14	OH	H	OAc



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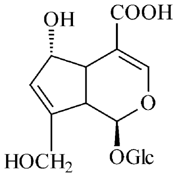

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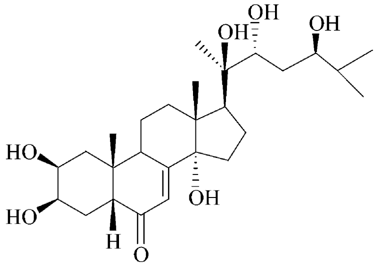

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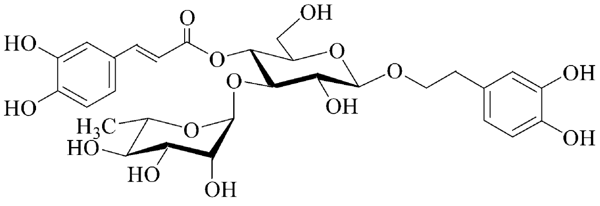

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et al., 1991), 4-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (**4**) and 2-*O*-β-D-glucopyranosyl-4-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (**5**) (Baumeler et al., 2000). Two C_9 iridoid glucosides, harpagide (**6**) and 8-*O*-acetyl-harpagide (**7**), as well as the phenylpropanoid salidroside (**8**) were identified by comparison with reported data (Boros and Stermitz, 1990; Li et al., 1999; Jensen, 2000).

The molecular formula of compound **1** was determined as $C_{14}H_{17}O_9N$ by HR-FAB mass spectrometry. It showed similar ^1H NMR spectral data to those of (2*R*)-2-*O*-β-D-glucopyranosyl-7-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (**2**) and the same molecular mass according to the EI MS (molecular ion peak at *m*/*z* 343). The fragment at *m*/*z* 181 $[M-162]^+$ in the mass spectrum indicated the presence of a hexose unit. The ^1H NMR spectrum showed the presence of an ABX system at δ 7.05 (1H, *d*, $J=9.3$ Hz), 6.50 (1H, *dd*, $J=2.5$, 9.3 Hz) and 6.51 (1H, *d*, $J=2.5$ Hz) indicating that the hydroxyl group was attached to the aromatic ring and excluding positions at C-5 and C-8. The differences in the ^1H NMR data of **1** and **2** (α 6.71 *d*, $J=8.5$ Hz, H-5; δ 6.47 *d*, $J=2.5$ Hz, H-8; δ 6.41 *dd*, $J=2.5$, 8.5 Hz, H-6) assigned a C-6 position of the hydroxyl group in **1**, e.g. a 6-hydroxy derivative of blepharin. The ^{13}C NMR data are summarized in Table 1. Moreover, all carbon signals are established using COSY and HMQC. On the basis

Table 1
^{13}C NMR spectral data of compounds **1**–**2** (DMSO-d_6, 100 MHz)[a]

C	1	2
2	97.6 *d*	94.6
3	163.8 *s*	159.7
5	104.7 *d*	115.9
6	154.2 *s*	109.5
7	109.3 *d*	153.5
8	113.7 *d*	104.8
9	141.1 *s*	141.0
10	120.4 *s*	118.2
Glucose		
1′	102.6 *s*	102.5
2′	73.3 *d*	73.3
3′	77.4 *d*	77.3
4′	69.6 *d*	69.7
5′	76.7 *d*	76.6
6′	61.0 *t*	60.9

[a] Assignments were established by DEPT and HMQC spectra.

of these data, the structure of compound **1** was elucidated to be 2-*O*-β-D-glucopyranosyl-6-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one.

The appearance of benzoxazinoids for the first time in the Lamiaceae is of significant interest. These secondary metabolites are the only group of arylhydroxamic acid derivatives so far detected in plants and exhibit a variety of biological activities. Intensive studies on their distribution and biological activities in monocotyledonous plants in the family Gramineae were reported. They were proved to be important allelochemicals and play role in the protection of plants towards bacteria, fungi and insects in many crop plants (Niemayer, 1988). Until now, their occurrence in only three dicotyledonous families were reported: Acanthaceae (Wolf et al., 1985; Pratt et al., 1995; Kanchanapoom et al., 2001), Ranunculaceae (Ozden et al., 1992) and Scrophulariaceae (Pratt et al., 1995).

2.2. Lamium amplexicaule L., L. garganicum L. and L. purpureum L.

The water-soluble parts of the ethanolic extracts of the studied species were separated by a combination of chromatographic methods. Ten known compounds, of which eight iridoids (**9**–**16**), one phytoecdysone (**17**) and one phenylpropanoid (**18**) were isolated and identified by ^{1}H and ^{13}C NMR spectral data and compared with published information. All isolated iridoids belong to the C_{10} iridoid type.

In *L. amplexicaule* were found four known iridoids, lamioside (**10**) (Scarpati and Guiso, 1967), lamalbide (**12**) (Eigtved et al., 1974), shanzhiside methyl ester (**13**) and deacetyl asperulosidic acid (**16**) (Boros and Stermitz, 1990). Many authors have been investigated the iridoid composition of *L. amplexicaule* (Scarpati and Guiso, 1967, 1969; Inouye et al., 1977; Bianco et al., 1980; Guiso et al., 1983; Kobayashi et al., 1986). However, the obtained results varied to a great extent. Our data are similar to those of Kobayashi et al. (1986).

From *L. garganicum* were isolated the known iridoid glucosides lamalbide (**12**), shanzhiside methyl ester (**13**), barlerin (**14**) and sesamoside (**15**) (Boros and Stermitz, 1990), as well as the phenylpropanoid, verbascoside (**18**) (Andary et al., 1982). Sesamoside was found for the first time for the genus *Lamium*. The report of lamiol and lamioside in *L. garganicum* was based on paper chromatography (Adema, 1968), which makes their presence in the species uncertain.

From *L. purpureum* were isolated three iridoids, lamiol (**9**) lamioside (**10**) (Scarpati and Guiso, 1967), and 5-deoxylamiol, (**11**) (Boros and Stermitz, 1990) together with the phytoecdysone, 24-*epi*-pterosterone (**17**) (Ohta et al., 1996) and verbascoside (**18**). Both, 5-deoxylamiol and 24-*epi*-pterosterone were found for the first time for the genus *Lamium*. Recently, another phytoecdyson, 20-hydroxyecdysone, was found in *L. purpureum* (Savchenko et al., 2001). The presence of these compounds in the *Lamium* is of interest because of their role in plant–insect interactions and potential contribution to the crop protection strategies (Dinan, 1998).

2.3. Chemosystematic significance

The chemical profile of *Lamium galeobdolon* differs significantly to the other studied *Lamium* species and supports its segregation as a genus. *L. galeobdolon* contains iridoids of the C_9 type and benzoxazinoids, whereas in *L. purpureum, L. amplexicaule* and *L. garganicum* C_{10} iridoid glycosides and no benzoxazinoids were found. According to Zoz and Litvinenko (1979) the genus *Lamiastrum* (*Galeobdolon*) contains flavonols, while *Lamium*, both flavones and flavonols. The sculpturing of the pollen in *L. galeobdolon* is different from the other *Lamium* species (Abu-Asab and Cantino, 1994) but the authors do not support its genus status. Inclusion of *Galeobdolon* within *Lamium* was supported also by a molecular study, where *Lamium* appeared in two clades (Wink and Kaufmann, 1996). *L. amplexicaule* and *L. garganicum* are members of Clade I together with *L. album* (a species containing secoiridoids) and the genus *Marrubium*. Clade II includes *L. galeobdolon, L. maculatum* and *L. purpureum*. Apparently, more morphological, chemical and molecular studies are needed to assess the phylogenetic relationships within the genus.

Some evolutionary implications could be based on the knowledge of the iridoid biosynthesis.The presence of C_9 iridoids corresponds to a higher biogenetic stage after decarboxylation of C_{10} iridoids and determines an evolutionary more advanced position of *L. galeobdolon* than the other *Lamium* species. This is supported also by the appearance of defensive compounds (benzoxazinoids) to increase the plant defense. On the other hand, *L. purpureum* contains C_{10} iridoids with 4-CH_3 substituent produced at an earliear biogenetic stage than those with 11-COOR substituents in the probably more advanced *L. amplexicaule* and *L. garganicum*.

3. Experimental

3.1. General

^1H (250 MHz) NMR spectrum was recorded on Bruker DRX 250 MHz spectrometer and ^{13}C NMR (100 MHz) spectrum on Bruker AMX 400 MHz with TMS as internal standard. HR-FAB-MS were obtained with JEOL JMS-AX 500. EI MS were obtained with Hewlett Packard 5972 mass spectrometer. LPLC was carried out with Merck Lobar RP-18 columns.

3.2. Plant material

L. galeobdolon was collected in May 1997 at Losen Mt.; *L. amplexicaule* in May 1997 at the Urvich region near Sofia; *L. garganicum* in May 2001 at the Urvich region and *L. purpureum* in May 1999 at the Vitosha Mt., Bulgaria. The species were identified by Dr. L. Evstatieva and vouchers deposited in the Herbarium of the Institute of Botany, Bulgarian Academy of Sciences (SOM).

3.3. Extraction and isolation

Dried ground aerial parts of the plants were extracted with EtOH. The concentrated extracts were suspended in H_2O, extracted with $(CH_2Cl)_2$ and the H_2O-soluble part further separated by combination of chromatographic techniques.

L. galeobdolon (97 g dry wt); EtOH extract (7.7 g); $(CH_2Cl)_2$ fraction (2.1 g). The H_2O-soluble part (5.5 g) was separated on a charcoal column with H_2O–MeOH mixtures (5, 30, 50 and 100% MeOH), MeOH–Me_2CO (1:1) and MeOH–$(CH_2Cl)_2$ (1:1). The latter two fractions were combined and separated on a silica gel column with MeOH–$CHCl_3$–H_2O (60:15:4 lower layer and 60:22:4) to yield pure **4** (frs. 3–6, 43 mg). Frs. 28–42 (86 mg) were further separated on a RP-18 silica gel Lobar column with H_2O–MeOH (20–60% MeOH) to afford pure **8** (4 mg), **6** (3.5 mg), **3** (4.8 mg) and **7** (5.2 mg). Frs. 43–65 (110 mg) were separated by RP-18 silica gel Lobar column with 0–45% MeOH to obtain pure **1** (2 mg), **2** (8 mg) and **5** (32 mg).

L. amplexicaule (155 g dry wt); EtOH extract (9.2 g); $(CH_2Cl)_2$ fr. (2.9 g). The H_2O-soluble part (6.3 g) was filtered through charcoal and separated by DCCC (Büchi) with $CHCl_3$–MeOH–H_2O–PrOH (9:12:8:2) by ascending mode to yield pure **13** (frs. 18-23, 100 mg) and **10** (frs. 32–46, 286 mg). Frs. 6–9 (100 mg) were further separated on a silica gel column with *iso*-PrOH–$C_6H_5CH_3$–EtOAc–H_2O (50:10:25:12.5) to yield **16** (14 mg). Frs. 10–17 (280 mg) were purified on a silica gel column with MeOH–$CHCl_3$–H_2O (60:22:4) to obtain **12** (73 mg).

L. garganicum (25 g dry wt); EtOH extract (4.1 g); $(CH_2Cl)_2$ fr. (0.4 g). The H_2O-soluble part (3.4 g) was separated by DCCC with $CHCl_3$–MeOH–H_2O–PrOH (9:12:8:2) by ascending mode to yield pure **15** (frs. 16–19, 27 mg) and **14** (frs. 31–43, 91 mg). Frs. 7–9 (163 mg) and 13–15 (45 mg) were further subjected to Lobar RP–18 column eluted with MeOH–H_2O (0–50% MeOH) to afford pure **18** (23 mg), **12** (29 mg) and **15** (13 mg), **13** (10 mg), respectively.

L. purpureum (300 g dry wt); EtOH extract (9.8 g); $(CH_2Cl)_2$ fr. (3.1 g). The H_2O-soluble part (6.5 g) was separated on a charcoal column as it was described for *L. garganicum*. The 30 and 50% MeOH frs. were combined (230 mg) and separated by silica gel chromatography with $CHCl_3$–MeOH–H_2O (60:15:4 lower layer and 60:22:4) to afford a mixture of **9** and **11** (41 mg), which was further separated by RP-18 Lobar chromatography with 30–75% MeOH to pure **9** (14 mg) and **11** (13 mg). The combined MeOH (110 mg) and MeOH–Me_2CO (297 mg) frs. were separated on a silica gel column with $CHCl_3$–MeOH–H_2O (60:15:4 lower layer and 60:22:4) to afford **10** (60 mg) and a mixture of **9** and **11** (113 mg). Pure **17** (9 mg) and **18** (16 mg) were obtained after DCCC separation of the MeOH–$(CH_2Cl)_2$ fr. (960 mg) at the conditions mentioned above.

3.3.1. 2-O-β-D-Glucopyranosyl-6-hydroxy-2H-1,4-benzoxazin-3(4H)-one (*1*)

White solid. ^1H NMR (DMSO-d_6): δ 10.70 (1H, *s*, NH), 9.48 (1H, *s*, OH), 7.05 (1H, *d*, $J = 9.3$ Hz, H-8), 6.51 (1H, *d*, $J = 2.5$ Hz, H-5), 6.50 (1H, *dd*, $J = 2.5$ and 9.3 Hz, H-7), 5.84 (1H, *s*, H-2), 4.56 (1H, *d*, $J = 7.9$ Hz, H-1′), 3.69 (1H, *brd*, $J = 11.5$ Hz, H-6′), 3.47 (1H, *dd*, $J = 11.5$ and 5.7 Hz, H-6′); ^{13}C NMR (DMSO-d_6): Table 1; Positive FAB-MS 366 $[M+Na]^+$. HR-MS: *m*/*z* 343.0903 ($C_{14}H_{17}O_9N$, expected 343.2861). EI MS *m*/*z* (rel. int.): 343 (5) $[M]^+$, 181 (23) $[M-162]^+$, 165 (12) $[M-178]^+$, 152 (33) $[181-CHO]^+$, 136 (20) $[165-CHO]^+$, 73 (36), 57 (35), 44 (100).

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