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neo-Clerodane diterpenoids from *Ajuga*: structural elucidation and biological activity

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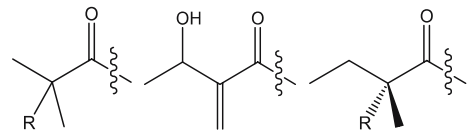
Abstract The presence of several types of allelochemicals has been reported from *Ajuga*, a Labiatae genus comprising more than 40 species of wide distribution in extratropical regions of both hemispheres. The genus is of great medicinal and economic importance and among the biological properties of the secondary metabolites, the antifeedant activity against pest insects appears to be related to the presence of *neo*-clerodane type diterpenes. This review focuses on the isolation and structural elucidation of this type of compounds from *Ajuga* species and the hemisynthetic compounds of closely related structure obtained. The reported biological activity of crude extracts and isolated diterpenes will be briefly commented.

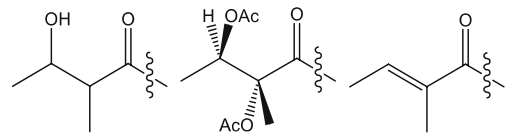
Keywords Labiatae · *Ajuga* · Diterpene · *neo*-Clerodane · Biological activity

Abbreviations The abbreviations used for substituents, other than the common acetyl, ethyl, hydroxyl, methyl, propionyl (Ac, Et, HO, Me, Pr), will be:



1a, R=H **2** **3a, R=H**

1b, R=OAc **3b, R=OAc**



4 **5** **6**

iBu (**1a**) isobutyryl (2-methylpropionyl).

iBu2A (**1b**) 2-acetoxyisobutyryl (2-acetoxy-2-methylpropionyl).

HMB (**2**) 3-hydroxy-2-methylenebutyryl (sometimes quoted as 2-hydroxy-3-methylenebutyryl either by use of a wrong numbering or by an unfortunate typing error).

MB (**3a**) 2-methylbutyryl (sometimes quoted as dihydrotigloyl), the *S* configuration (shown) has been established in some reports by X-ray analysis.

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MB2A (**3b**) 2-acetoxy-2-methylbutyryl (*R* configuration shown).
MB3A (**4**) 3-acetoxy-2-methylbutyryl.
MBdAe (**5**) *erythro*-2,3-diacetoxy-2-methylbutyryl (2*S*,3*R* or 2*R*,3*S* absolute configuration remains to be clarified; 2*R* shown as relative configuration).
Tig (**6**) tigloyl ((*E*)-2-methyl-2-butenoyl).

Introductory remarks

The presence of secondary metabolites in *Ajuga* has been reviewed a number of times, usually as part of a wider coverage. A general reference to be first considered is ''Advances in Labiate Science'' (Haley and Reynolds 1992).

Early contributions from our group were focused on allelochemicals such as phytoecdysteroids and clerodane diterpenoids (Camps et al. 1981a; Camps and Coll 1993) and specific and comprehensive coverage of such diterpenes appeared during the 90's (Merritt and Ley 1992; Rodríguez-Hahn et al. 1994; Arfan et al. 1996; Piozzi 1997). As for insect antifeedant activity, the best-known and most extensively studied biological property of these diterpenes, the test results of the clerodane diterpenoids have been compiled (Klein Gebbinck et al. 2002), and several general reviews have been published recently (Isman 2002; Koul 2005).

General introduction: the *Ajuga* genus of the Labiatae

The Labiatae is a widespread family of about 220 genera comprising almost 4000 species distributed throughout most of the world (Hedge, 1992). The increasing number of commonly known crops in this family (1959: 38, 1986: 129, 1999: 174) reflects the intensification of taxonomical and ethnobotanical research in this field (Pistrick 2002). The chemistry of the Labiatae is very extensive and dominated by reports concerning the essential oils (mainly mono- and sesquiterpenes) found in genera of economic importance, but chemical constituents such as diterpenes and higher terpenes, iridoids, sugars, phenolics and others, may offer a great significance as taxonomic characters (Richardson 1992) and biologically active compounds with a potential ecological role (Cole 1992). The isolation of **ajugarins** (I-III) from *Ajuga remota* (Kubo et al. 1976), as moderately strong antifeedants, attracted the attention not only towards the genus *Ajuga*, but also to the related *Teucrium* and *Scutellaria* genera, amongst others (Simmonds and Blaney 1992; Merritt and Ley 1992). *Ajuga* is (described as) a genus with about 40 annuals and perennials from the mint family, occurring in the cooler parts of Europe, Asia, Africa and Australia (http-1) or (*Ajuga*) plants are annual, biennial or perennial, herbaceous, rarely shrubs with about 40–50 species: (distributed over) Asia, Europe, especially in the Near East; 18 species in China, namely *pygmaea, sciaphila, nubigena, lupulina, ovalifolia, linearifolia, ciliata, campylanthoides, forrestii, campylantha, multiflora, bracteosa, pantantha, dictyocarpa, macrosperma, decumbens, nipponensis* (Flora of China 1994). In Europe the genus is represented by 10 species (*orientalis, genevensis, pyramidalis, reptans, tenorii, salicifolia, laxmannii, piskoi, iva, chamaepitys*) and four subspecies (*A. chamaepitys* (L.) Schreber subsp. *chamaepitys* and subsp. *chia*, and *A. salicifolia* subsp. *salicifolia* and subsp. *bassarabica*) (Ball 1972). A range of intermediates can be found for *Ajuga chamaepitys* subspecies, with names such as *A. suffrutescens* Lange, or *A. pseudochia* Schost. for various combinations of characters. The geographical distribution of the 10 species, along with synonyms, subspecies, varieties, provisional names etc., may be obtained on-line (http-2).

However, a survey based on the Index Kewensis (1885–1991) listed more than 100 species distributed worldwide (Darvas 1991) and well over 200 records are returned when searching *Ajuga* in comprehensive plant databases (http-3). The presence of clerodane diterpenes has been reported in less than 20% of the above mentioned number of species.

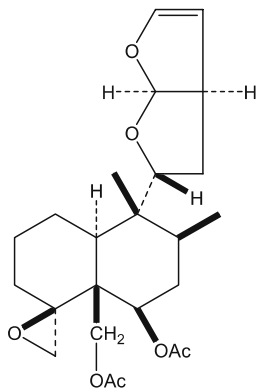
The clerodane historical background: The 60's and 70's

The structure and stereochemistry (apart from absolute configuration) of clerodin, a diterpenoid

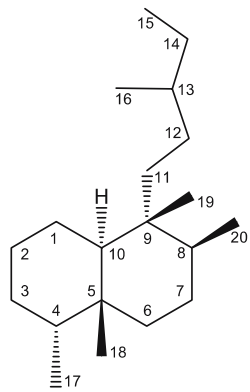
bitter principle isolated from the Indian bhat tree *Clerodendron infortunatum* (Verbenaceae), were established using X-ray analysis of a bromolactone derivative (Sim et al. 1961; Barton et al. 1961a, b). The parent hydrocarbon skeleton has been known as **clerodane** ever since. In Chemical Abstracts the term *clerodane* is defined as: Naphthalene, decahydro-1,2,4a,5-tetramethyl-1-(3-methylpentyl)-, [1R-[1α(R*),2β,4aβ,5β,8aα]]-.

tion later confirmed by X-ray crystallographic studies of a *p*-bromobenzoate chlorohydrin derivative (Kato et al. 1973b).

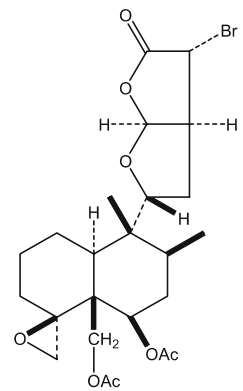
As already mentioned, **ajugarins I-III** were isolated from *Ajuga remota* (Kubo et al. 1976) as moderately strong antifeedants [although according to a later review "The diterpenoid ajugarin I... attracted a great deal of attention as a potent antifeedant" (Simmonds 1998)]. The ajugarins



clerodin-1961



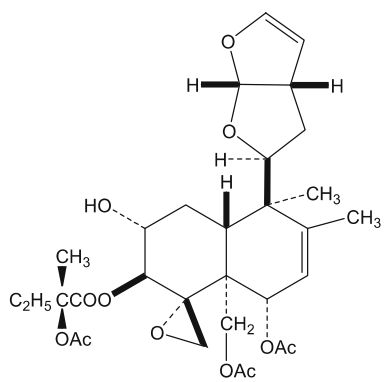
clerodane skeleton
(first numbering system)



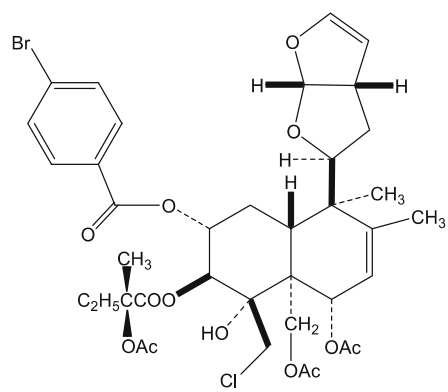
clerodin bromolactone

More than ten years later, clerodendrin A and B were isolated from *Clerodendron tricotomum* Thunb. (Verbenaceae) as the antifeeding active principles, and their structures displayed the same clerodane carbon skeleton (Kato et al. 1972). However, the absolute configuration of clerodendrin A was considered to be the antipode of clerodin from c.d. and o.r.d. considerations (Kato et al. 1973a), thus as ***ent*-clerodane**, a configuration later confirmed by X-ray crystallographic studies of a *p*-bromobenzoate chlorohydrin derivative (Kato et al. 1973b).

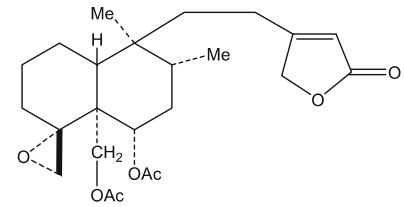
displayed a new type of side chain functionality, and their structure was described as *ent*-clerodane, hence as antipodal to that of clerodin, on the basis of the c.d. sign of a 6-oxo-derivative (15,16,19-triacetoxy-4-hydroxyclerodan-6-one) [c.d. (MeOH) Δε (298 nm) – 3.41, compared to a positive c.d (EtOH) Δε (302 nm) +3.51 for the clerodin-derived 6-ketone].



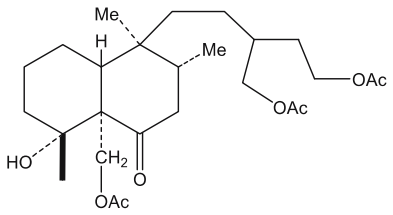
clerodendrin A (CDDA)



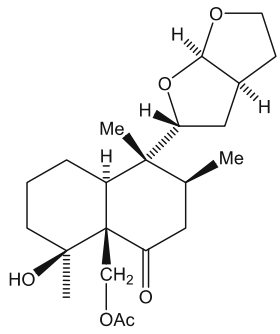
CDDA *p*-bromobenzoate chlorohydrin



ajugarin I (AJG-I)



6-oxo-derivative from AJG-I

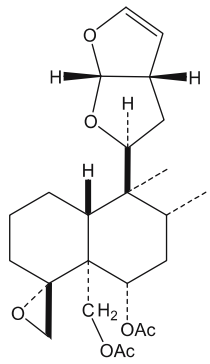


clerodin-derived 6-ketone
(clerodane skeleton)

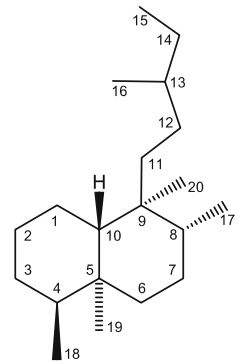
During the seventies, further isolation of a growing number of compounds with clerodane structures, brought up conflicting results for absolute stereochemistries. Whereas being considered antipodal to that published for clerodin, a common chirality was adduced from c.d. exciton chirality studies and physico-chemical correlation. These contradictions prompted a fresh X-ray study of clerodin bromolactone that verified the earlier X-ray work, but revealed that an unfortunate error occurred in the preparation of the diagrams and stereoformulae, and led to the reversal of the currently accepted absolute configuration of clerodin (Rogers et al. 1979) to *ent*-clerodane.

As a consequence of the reversal of clerodin absolute configuration, that of other *trans*-fused clerodanes had to be reversed also, unless assigned on the basis of well established general chiroptical rules. The configuration of ajugarins was accordingly immediately revised as *ent-neo*-clerodane (Trivedi et al. 1979) but, shortly after, direct evidence for the *neo*-clerodane (*ent*-clerodane) absolute configuration considered in the first instance, was provided by the X-ray assignment of 12-bromoajugarin I (Kubo et al. 1980).

At the same time and to avoid confusion in all future work, but to indicate the reversal being



clerodin: revised structure
(*ent*-clerodane; *neo*-clerodane)



***neo*-clerodane skeleton**
(*ent*-clerodane)

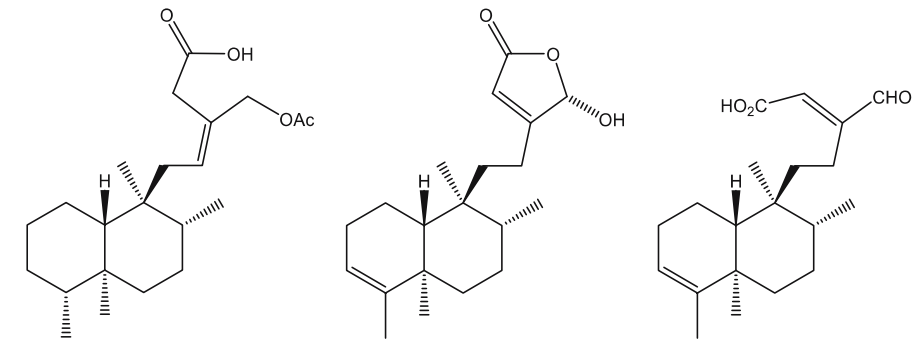
considered, the names *neo*-clerodane and *ent-neo*-clerodane were proposed to substitute the previous *ent*-clerodane and clerodane structures, respectively. This proposal has been universally accepted, despite the risk of confusion pointed out (Piozzi 1997), derived from the biogenetic relationship of *neo*-clerodanes and the *ent*-labdane precursors. The clerodane numbering in the widely circulated proposal known as the Rowe nomenclature (Rowe 1968/1969), as shown, has been widely adopted also, but occasional use of the old one may lead to minor correlation problems and different semi-systematic names.

Dihydrocompounds were indicated in the early literature as series I when the vinyl ether grouping was reduced and as series II when the 1,2-epoxide system had been reductively opened (Barton et al. 1961a). Throughout this review *dihydro* will be used as a short notation meaning 14,15-dihydro, whereas the non-oxiranic clerodanes or derivatives will be dealt with as 4,18-disubstituted compounds. The C-15 derived hemiacetals (or acetals) have been reported either as 14,15-dihydro-15-hydroxy (or alkoxy/acyloxy) or as 14-hydro-15-hydroxy (or alkoxy/acyloxy) compounds.

The *neo*-clerodane diterpenes reported from *Ajuga*

With only one exception recorded so far, all the *neo*-clerodane diterpenes isolated from *Ajuga* fall into any one of the two major structural groups, according to the side chain type (involving the C(11)-C(16) fragment of the clerodane skeleton). The ethylbutenolide substructure (13-en-15, 16-lactone) was first reported for the ajugarins I-III isolated from *Ajuga remota* (Kubo et al. 1976) (ajugarin-like group), and this group has received the code **A** accordingly. On the other hand, ajugareptansin was isolated from *Ajuga reptans* (Camps et al. 1979) and it was the first example of a clerodin-like (either tetrahydro or hexahydro) furo[2,3-b]furan system (or 11,16:15,16-diepoxy), the code selected for this group being **C**. The very special side-chain of *ajugalaevigatic acid* (Topçu et al. 2004) is somehow related to the first group, by opening of the lactone ring and deconjugation of the double bond. Furthermore, the structure of this compound is remarkable also by showing no substitution in usually oxygenated positions (C-4, C-6, C-18, C-19): it is the one and only example for C-6, and it is also unique in bearing an unsubstituted C-18 in an open (non-oxiranic) C-4;C-18 structure. As for C-19, this feature has been reported already in a few instances (ajugarins IV, V, deacetylajugarin IV, and ajugalide D). Ajugalaevigatic acid may also be structurally related to the clerodane diterpenoids isolated from *Polyalthia longifolia* Thw (Annonaceae) (Phadnis et al. 1988).

In Table 1 are presented the reported occurrences from the isolation sources and a bold character indicates the first structural elucidation (‘‘new’’ compounds), whereas in Table 2 are summarised the hemisynthetic compounds prepared from the isolated diterpenes. Plant names



Ajugalaevigatic acid ***Polyalthia longifolia*** **diterpenoids**

Table 1 Reports on *neo*-clerodane diterpene isolation from *Ajuga* species

Species	Reference	Diterpenes	Group
A. australis R. Br. Prod.	de la Torre (1997)	ajugapitin	CA
		14,15-dihydro-15-hydroxyajugapitin[m]	CC
A. bracteosa (A. remota)	Kubo (1976)	**ajugarin I-III**	**A2, A5, A43**
	Kubo (1980)	***clerodin***	***CAa1***
		12-bromoajugarin I (X-ray)	
	Kubo (1982)	**ajugarin IV**	**A49**
	Kubo (1983)	**ajugarin V**	**A1**
A. bracteosa (*A. remota* Benth.)	Odek-Ogunde (1993)	ajugarin I-III	A
	Cantrell (1999)	ajugarin I-II	A
		clerodin	CA
A. bracteosa Wall. Ex Benth.	Verma (2002)	**bracteonin A**	**CS2**
		(mixture of *R/S* C-15 epimers)	
		14,15-dihydroajugapitin[a]	CB
		14-hydro-15-hydroxyajugapitin[am]	CC
A. bracteosa (*A. remota* Benth.)	Kuria (2002)	ajugarin I	A
A. bracteosa Benth	Riaz (2004)	clerodinin A[ab]	CA
		lupulin A[ab]	CA
		dihydroajugapitin	CB
		dihydroclerodin[a]	CB
A. bracteosa (*A. remota* Benth)	Coll (2005)	ajugarin I, II, IV, V	A
		deacetylajugarin IV[a]	A
		ajugapitin[a]	CA
		clerodin	CA
		dihydroajugapitin	CB
		dihydroclerodin	CB
		14-hydro-15-hydroxyajugapitin[m]	CC
		14-hydro-15-hydroxyclerodin[am]	***CCa1***
A. chamaepitys (L.) Schreber	Hernández (1982)	**ajugapitin**	**CAb10**
		14,15-dihydroajugapitin	**CBb10**
A. chamaepitys (L.)	Camps (1984b)	**15-ethoxy-14-hydroajugapitin**[c]	**CFb4**
		14-hydro-15-hydroxyajugapitin[m]	**CCb10**
	Camps (1987)	**chamaepitin**[m]	**CCb12**
		15-ethoxy-14-hydroajugapitin	C
		14-hydro-15-hydroxyajugapitin[m]	CC
A chamaepitys var. *chia*[d]	Boneva (1990)	**ajugachin A, B**	**CAb8, CAb12**
		ajugapitin	CA
		14,15-dihydroajugapitin	CB
A chamaepitys ssp.*laevigata*	Topçu (2004)	**ajugalaevigatic acid**	**AS1**
A. ciliata Bunge var. *villosior* A. Gray	Shimomura (1989a)	**ajugamarin B4, B5**	**A41, A40**
		ajugamarin E1-E3	**A38, A39, A26**
		ajugamarin F1-F3	**A11, A9, A10**
		deacetylajugarin IV	**A48**
		ajugarin IV	A
A. decumbens Thunb.	Shimomura (1989b)	**ajugamarin A2, F4, G1, H1**, B2[a]	**A35, A8, A36, A33**, A
	Min (1989)	**ajugacumbin A, B, D**[e]	**A4, A6, A7.1**
		ajugacumbin C[e]	A38.1
	Min (1990)	**ajugacumbin E**[e]**, F**	**A26.1, A44**
		ajugamarin[a](AJM A1)	A
	Chen (1995)	**ajugacumbin G**, A, B	**A3**, A
	Amano (1997)	**ajugatakasin A, B**	**A37, A32**
		ajugamarin A1, B1[a], G1, H1	A
		clerodendrin D[a] (= ajugapitin)	CA
	Takasaki (1999)[f]	ajugamarin A1,A2	A
		ajugapantin A	A
		ajugatakasin A	A
	Nishida (2004)	ajugatakasin A, B	A

Table 1 continued

Species	Reference	Diterpenes	Group
		ajugamarin A1, B1, G1, H1	A
		clerodendrin D (= ajugapitin)	CA
A. genevensis L.	Malakov (1991)	**ajugavensin A-C**	**CBa7, CBa8, CBa6**
	Malakov (1992)	ajugavensin A,B (X-ray)	
A. iva	Camps (1982)	**ivain I-IV**	**CBb2, CBa5, CEorFb1, CBb3**
A. iva (A. pseudoiva (L.) Schreber)	Camps (1984a)	**2-acetylivain I**	**CBb1**
		14,15-dihydroajugapitin[a]	CB
A. iva (A. pseudoiva)	Ben Jannet (1999)	**hativene A-C**	**CFb3, CEb3, CEb2**
		lupulin A[ab]	CA
		14,15-dihydroajugapitin	CB
	Ben Jannet (2000)	hativene A-C	CF, CE, CE
		lupulin A	CA
		14,15-dihydroajugapitin	CB
A. iva (L.) Schreber	Bondí (2000)	ivain IV	CB
		14,15-dihydroajugapitin	CB
A. lupulina (Maxim.)	Chen (1996a)[g],b	***lupulin D***[a] ***(= clerodinin-A)***[b]	***CE***
	Chen (1996b)	**lupulin A-C**[b]	**CEb5, CEa10, CS3**
		lupulin D	CE
	Chen (1997)[h]	lupulin A	
A. macrosperma Wall	Shen (1993a)	**ajugamacrin A, B**	**A22, A23**
	Shen (1993b)	**ajugamacrin C-E**	**A27, A28, A31**
A. nipponensis Makino	Shimomura (1981)	**ajugamarin** (prelim. account) (X-ray pBB)	**A34**
	Shimomura (1983)	ajugamarin(AJM A1) (X-ray pBB)	A
		ajugamarin B1 (= dihydroajugamarin)	**A30**
		ajugamarin-clorohydrin	**A47**
	Shimomura (1989c)	**ajugamarin B2, B3, C1, D1**	**A29, A42, A25, A46**
		ajugamarin A1, B1	A
		ajugarin-I[a]	A
A. nipponensis	Liu (1995)	ajugamarin L2[i](= AJC B)	=A6
A. orientalis L.	de la Torre (1997)	**ajugaorientin**	**CBa11**
A. pantantha Hand-Mazz	Shen (1993b)	**ajugapantin A** (= AJM C1 diAc)	**A20**
		ajugamarin C1 and/or ajugacumbin B[j]	A
A. pseudoiva, see *A. iva (A. pseudoiva)*			
A. pyramidalis	Boneva (1998)	**ajugapyrin A**	**CS1**
A. remota, see A. *bracteosa (A. remota)*			
A. reptans	Camps (1979)	**ajugareptansin** (X-ray pBB)	**CBa9**
	Solans (1979)	ajugareptansin pBB X-ray	
	Camps (1981b)	**ajugareptansone A, B**	**A18, A19**
	Miravitlles (1982)	ajugareptansone A (X-ray)	A
	Solans (1983)	ajugareptansone B (X-ray)	A
	Miravitlles (1985)	2-oxoivain I (X-ray)	
	Malakov (1998)	**areptin A, B**	**CBc1, CAa11**
		ajugareptansin	CB
		ajugaorientin	CB
		ajugachin A[a]	CA
A reptans cv Catlins Giant	Bremner (1998)	**14,15-dehydroajugareptansin**	**CAa9**
		ajugareptansin	CB
		3β-hydroxyajugavensin B (= ajugaorientin)[a]	CB
		3α-hydroxyajugamarin F4[k]	***revised*** (as A12)
A. reptans	Carbonell (2001)	**ajugatansin A1, B1, D1**	**A17, A12, CBc2**
		ajugavensin A[a]	CB
		ajugareptansone A	A
	Nishida (2004)	**ajugareptone**	**A13**

Table 1 continued

Species	Reference	Diterpenes	Group
		ajugareptansone A	A
		ajugatansin B1	A
A. salicifolia L.	Bozov (1993)	**14,15-dihydro-15-hydroxyajugachin A**[m]	**CCb8**
A. taiwanensis Nakai *ex* Murata	Chan (2005)	**ajugalide A-D**	**A24, A21, A7, A50**
		ajugamacrin B	A
		ajugapantin A	A
		ajugamarin C1	A

1. bold = new compound; bold italics = first report in *Ajuga* of known compound

2. references identified by means of only first author's name

3. papers on X-ray analysis of derivatives are included

[a] Previously reported compounds, first isolation in this species (only if two or more entries)

[b] C-15 structural assignment revised (Ben Jannet 1999)

[c] The compound (C-15α stereochemistry; single; erroneously quoted as an epimeric mixture (Beauchamp 1996)) was reported with no stereochemical assignment for C-15. α-Assignment based on the NMR data matching those of 15β-ethoxy-14-hydroajugapitin (Beauchamp 1996), prior to stereochemistry revision (cf. Ben Jannet 1999)

[d] Described as a subspecies (http-2)

[e] Structural reassignment proposed (Coll 2002)

[f] This paper provides for isolated diterpenes the corresponding original reference only for ajugamarin-A2

[g] The formula shows a *neo*-clerodane skeleton, but the paper displays an *ent-neo*-clerodane structure from the view with ellipsoids, with a 15α-methoxy in both

[h] The formula shows a 15β-methoxy *ent-neo*-clerodane skeleton but from the view with ellipsoids a 15α-methoxy *neo*-clerodane is displayed

[i] The compound was previously described, but it was reported as new

[j] One name appears in the abstract, the other in the experimental part

[k] Structural assignment revised (Carbonell 2001)

[m] Mixture of C-15 epimers

used by the authors are maintained, but *A. remota* and *A. pseudoiva* have been treated as synonyms of *A. bracteosa* and *A. iva* respectively (http-3, http-2). In Table 3 the new isolated compounds are listed in alphabetical order. Table 4 shows the structures of ajugarin-like natural and hemisynthetic compounds (A coded) including only compounds with the intact ethylbutenolide substructure. The structures are numbered in sequence and two major features, substitution or not of ring A (C-1 and C-3) or/and C-12, lead to different subgroups. Hemisynthetic compounds are included and numbered following the closest natural diterpene. Conversely, in Table 5, closely related diterpenes isolated from other sources have been included along with the clerodin-like ones (C coded). A second capital letter is introduced to point out the side chain function type: A, tetrahydrofurofuran; B, hexahydrofurofuran; C, hemiacetal; D, 15, 16-olide; E, 15α-acetal; F, 15β-acetal; a low case letter follows next to indicate the ring A substitution subgroup, and finally the numbering sequence. A few special structures are indicated by the code Cd (most as CBd due to the hexahydrofurofuran group in the side chain).

Discussion

Unfortunate errors, apparently, occurred again in the X-ray analysis reports for the isolates from *Ajuga lupulina*, in the preparation of the diagrams and stereoformulae. On a semisystematic bases, the structures of lupulin A, B and D (Chen et al. 1996b) could be described as 15β-methoxydihydroajugapitin, 15α-methoxydihydrocaryoptinyl 2-methylbutanoate and 15α-methoxydihydroclerodin respectively. However, in the corresponding X-ray report for lupulin

Table 2 Hemisynthetic compounds prepared from *Ajuga neo*-clerodane diterpenes

Ajuga species	Reference	N[a]	L[b]	Compound
A. bracteosa (A. remota)	Kubo (1976)	–		dihydroajugarin I
		4		clerodanepentaol (4,6,15,16,19)
		5		4-hydroxy-6-clerodanone triacetate (15,16,19)
		6		6-oxoajugarin-III/6-oxoajugarin-II-diol (4,18)[c]
		7		6-oxoajugarin-III-acetate (18)[c]
	Kubo (1980)	5	A9.1	12(*R*)-bromoajugarin I (X-ray)
	Kubo (1982)	2		6-oxoclerodane triacetate (15,16,18)
	Kubo (1983)	2		4-hydroxy-6-oxoclerodane diacetate (15,16)
A. chamaepitys (L.)	Camps (1984b)	5	CDb16	2,15-dioxo-dihydroajugapitin
	Camps (1987)	6	CDb17	2,15-dioxo-chamaepitin
A. ciliata Bunge var. *villosior* A. Gray	Shimomura (1989a)	6a	A23	ajugamarin E1 1,19-diAc = **ajugamacrin B**
		6a	A23	ajugamarin E2 1,6-diAc = **ajugamacrin B**
		9a	A8	ajugamarin F1 6,19-diAc = **ajugamarin F4**
A. decumbens Thunb	Shimomura (1989c)		A47.1	ajugamarin G1 chlorohydrin (from AJM A1)
			A46.4	ajugamarin H1 chlorohydrin (from AJM B1)
	Chen (1995)	4,5,6	A45.1,4,6	ajugacumbin A-HCl, HBr, HI
		7	A43.1	ajugacumbin A 4,18-diol
		8	A45.5	ajugacumbin B-HBr (from AJC A)[d]
		9	A51.5	ajugacumbin A-al
		10	A51.8	ajugacumbin dione
	Chen (1996c)	3,4,5		*ajugacumbin A-HCl, HBr, HI*
		6		*ajugacumbin A-diol*
		7		*ajugacumbin B-HBr (from AJC A)*
		8	A51.4	ajugacumbin A 4β-Br,18-hydroxy[e]
		9		*ajugacumbin A-al*
		10		*ajugacumbin dione*
		11	AS3	ajugacumbin A hydroxyacid
	Xu (1998)	6,5,3		*ajugacumbin A-HCl, HBr, HI*
		2	A45.3	ajugarin I HBr
		7,4	A51.3	*ajugacumbin B-HBr* and 4-epimer
		11,12	A51.6	*ajugacumbin A-al*, ajugacumbin B-al
		9		*ajugacumbin A hydroxyacid*
		8	A6.2	ajugacumbin G 6-propionyl analog
A. iva (A. pseudoiva)	Camps (1982)	7	CBb15	2-oxoivain I
		6	CS4	2,18-epoxyivain I
	Miravitlles (1985)	II		*2-oxoivain I (X-ray)*
(*A. pseudoiva* (L.) Schreber)	Bellés (1985)	17	CBb5	2-acetyl-14,15-dihydroajugapitin
A. lupulina (Maxim.)	Chen (1996b)	5		*14-hydro-15-hydroxyclerodin (C-15 mixture)*
A. nipponensis Makino	Shimomura (1981)	–		ajugamarin *p*-bromobenzoate
	Shimomura (1983)	4	A37.1	12-oxoajugamarin
		–	A46.5	ajugamarin-acetate chlorohydrin
		5		*ajugamarin p-bromobenzoate*
	Shimomura (1989c)	3a	A20	ajugamarin C1 1,12-diAc = **ajugapantin A**
		–	A46.1	ajugamarin C1-chlorohydrin
		2a	A46.3	ajugamarin B1-chlorohydrin
		2b	A45.8	ajugamarin B1-acetoxyhydrin (or AJM D1 6-acetate)
		2c	A45.7	ajugamarin D1 6,12-diAc
A. pyramidalis	Boneva (1998)	3	CS1A	ajugapyrin A Ac
A. reptans	Camps (1979) Solans (1979)			ajugareptansin *p*-bromobenzoate
	Bellés (1985)	8		ajugareptansin pentaol
	Malakov (1998)	3	CBc3	oxoareptin A
		4	CAa10	areptin B Ac
A. salicifolia L.	Bozov (1993)	3	CDb8	14,15-dihydro-15-oxoajugachin A

Table 2 continued

Ajuga species	Reference	N[a]	L[b]	Compound
Teucrium massiliense [deacetylajugarin II (3)]	Caballero (2001)	4	A2.1	19-deacetylajugarin I
		7	A4.1	19-oxoajugarin I
		5	A6.1	19-oxoajugarin II
		6	A6.3	6-oxo-ajugarin II
		8	A45.2	6-oxo-ajugarin II · HCl
		9	AS2	1α,19-epoxy-ajugarin II
		10	A51.7	ajugarin-4,6-dione
Miscellaneous source	Blaney (1988)	17	CS5	tetrahydroclerodin

1. Highlighted by bold character, natural diterpenes first reported as hemisynthetic compounds

2. Some hemisynthetic compounds are reported without preparation procedure to be used in biological activity tests)

[a] Number of the compound in the reference

[b] Location in Tables 4 (A) and 5 (C)

[c] The formula depicted (clerodane numbering) does not conform to the text [R_{18} OR (not OH); R_{19} OAc (not OR)]

[d] R_1 should be (obviously) H rather than OH for compound 8

[e] R^2 = OH, R^3 = β-Br (Chen 1996c) or R^2 = Br, R^3 = 4β-OH (as in Xu 1998)

D, named not as a clerodin derivative but as a deoxy-caryoptinol (3-deoxy-14,15-dihydro-15-methoxycaryoptinol) (Chen et al. 1996a), whereas the formula (with a few stereochemistries undisclosed) shows the corresponding *neo*-clerodane skeleton as expected and 15α-methoxy substitution (referred as C 17), the view with displacement ellipsoids depicts an *ent-neo*-clerodane structure and yet a 15α-methoxy substitution. Conversely, in the X-ray report for lupulin A (although this name is not used in the paper, and the used ones are of questionable accuracy) the formula shown now is 15β-methoxydihydroajugapitin as *ent-neo*-clerodane, but in the corresponding view with displacement ellipsoids the structure appears as the enantiomeric *neo*-clerodane 15α-methoxy compound (Chen et al. 1997). Later on, lupulin A was isolated once more and reported as the *neo*-clerodane 15β-methoxydihydroajugapitin on the basis of the NMR relationship with hativene A (Ben Jannet et al. 1999). This compound displays H-11 NOE with H-15, H_3-19 and H_3-20, whereas hativene B (15α-methoxy) the NOE of H-11 is with OMe, H_3-19 and H_3-20.

Although the statement ''Lupulin B (C-15 epimer of Lupulin A)...'' (Ben Jannet et al. 1999) should be changed to ''Lupulin B (displaying at the C-15 stereogenic centre the opposite configuration of Lupulin A...''), the paper results brought up a second conflicting issue in the literature, namely the reported (or unreported) stereochemistry at the C-15 position of hemiacetal derivatives, and prompted a proposal for reversal of the previously assigned stereochemistries at that position for lupulin A (change from β to α) and B (change from α to β) as well as for clerodinins A and B. Thus, H-11 appearing at ca. δ 3.99 points out the 15β-methoxy stereochemistry, whereas H-11 would appear at ca. δ 4.37 for the α isomer.

On the other hand, the structural assignments for clerodinins C and D were based on the ''old'' thermodynamic stability rational because there was no observed NOE between H-11 and the CH_2 of OEt (Beauchamp et al. 1996), as well as for 3β-acetoxyclerodinin C and the 15-ethoxydihydroajugapitin analogues. The NMR data reported for 15α-assignments (δ 3.99 and 3.98) point out the corresponding β orientation and vice versa, and thus, the structural assignments require again the corresponding reversal (clerodinin C and 3β-acetoxyclerodinin C change from β to α; clerodinin D change from α to β; and the 15-ethoxydihydroajugapitin analogues exchange assignment).

Ivain III (Camps et al. 1982) and 15-ethoxydihydroajugapitin (Camps et al. 1984b) were isolated as single enantiomers but no C-15 stereochemistry was assigned [15-ethoxydihydro ajugapitin was quoted as a C-15 epimeric mixture (Beauchamp et al. 1996)]. The reported NMR data for H-11 (δ 4.48 in both), provides the evidence for C-15 α configuration of the isolated isomer.

Table 3 Alphabetical list of *neo*-clerodane diterpenes isolated from *Ajuga*

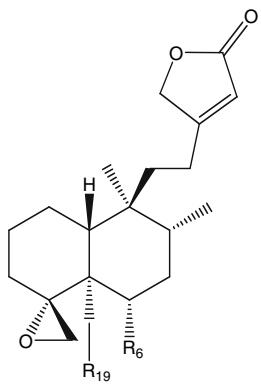
Ajugarin-like	**A**	**Ajugarin-like**	**A**
Ajugacumbin A	4	Ajugamarin E1	38
Ajugacumbin B	6	Ajugamarin E2	39
Ajugacumbin C[a]	35.1	Ajugamarin E3	26
Ajugacumbin D	7.1	Ajugamarin F1	11
Ajugacumbin E	26.1	Ajugamarin F2	9
Ajugacumbin F	44	Ajugamarin F3	10
Ajugacumbin G	3	Ajugamarin F4	8
Ajugalide A	24	Ajugamarin G1	36
Ajugalide B	21	Ajugamarin H1	33
Ajugalide C	7	Ajugamarin L2	= 6
Ajugalide D	50	Ajugapantin A	20
Ajugamacrin A	22	Ajugareptansone A	18
Ajugamacrin B	23	Ajugareptansone B	19
Ajugamacrin C	27	Ajugareptone	13
Ajugamacrin D	28	Ajugarin I	2
Ajugamacrin E	31	Ajugarin I chlorohydrin	45
Ajugamarin A1	34	Ajugarin II	5
Ajugamarin (A1) chlorohydrin	47	Ajugarin III	43
Ajugamarin A2	35	Ajugarin IV	49
Ajugamarin B1	30	Ajugarin V	1
Ajugamarin B2	29	Ajugatakasin A	37
Ajugamarin B3	42	Ajugatakasin B	32
Ajugamarin B4	41	Ajugatansin A1	17
Ajugamarin B5	40	Ajugatansin B1	12
Ajugamarin C1	25	Deacetylajugarin IV	48
Ajugamarin D1	46	Deoxyajugarin I	51
Clerodin-like	**C**	**Clerodin-like**	**C**
3β-Acetoxyclerodinin C	Fa6	14,15-Dehydroajugareptansin	Aa9
2-Acetylivain I	Bb1	14,15-Dihydroajugapitin	Bb10
Ajugachin A	Ab8	14,15-Dihydroclerodin	Ba1
Ajugachin B	Ab12	15α-Ethoxy-14-hydroajugapitin	Eb4
Ajugaorientin	Ba11	15β-Ethoxy-14-hydroajugapitin	Fb4
Ajugapitin	Ab10	Hativene A	Fb3
Ajugareptansin	Ba9	Hativene B	Eb3
Ajugatansin D1	Bc2	Hativene C	Eb2
Ajugavensin A	Ba7	14-Hydro-15-hydroxyajugachin A	Cb8
Ajugavensin B	Ba8	14-Hydro-15-hydroxyajugapitin	Cb10
Ajugavensin C	Ba6	14-Hydro-15-hydroxyclerodin	Ca1
Areptin A	Bc1	3β-Hydroxyajugavensin B	= Ba11
Areptin B	Aa11	Ivain I	Bb2
Chamaepitin	Cb12	Ivain II	Ba5
Clerodin	Aa1	Ivain III	EF?b1
Clerodinin A	Ea3	Ivain IV	Bb3
Clerodinin C	Fa2	Lupulin A	Eb5
Clerodinin D	Ea2	Lupulin B	Ea10
		Lupulin D	= Ea3
Special Structures			
Ajugalaevigatic acid	AS1	Ajugapyrin A	CS1
		Bracteonin A	CS2
		Lupulin C	CS3

[a] Ajugacumbin C structure was revised to Ajugamarin A2 (A35.1 = A35) (Coll 2002)

Table 6 summarises the occurrences of clerodane diterpenes in *Ajuga* species and compares data derived from the present report with those of a previous one (Vestri Alvarenga et al. 2001) based on data published until December 1997 in widespread journals indexed in Chemical Abstracts.

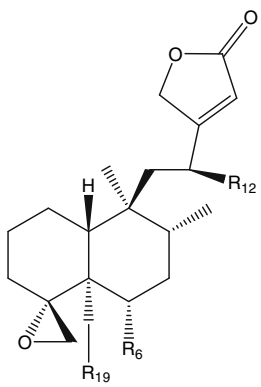
Table 4 Structures of natural and hemisynthetic *neo*-clerod-13-en-15,16-olides from *Ajuga*

oxiranic C4-C18 structures



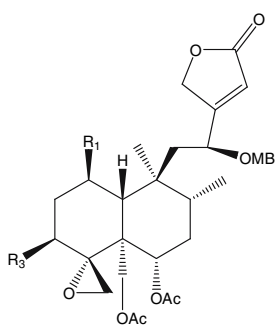
A	Rn	compound	R_6	R_{19}
1		Ajugarin V	OAc	H
2		Ajugarin I	OAc	OAc
2.1	(C4)	19-Deacetylajugarin I	OAc	OH
3		Ajugacumbin G	OAc	OHMB
4		Ajugacumbin A	OAc	OTig
4.1	(C7)	19-Oxoajugarin I	OAc	(C_{19})=O
5		Ajugarin II	OH	OAc
5.1	(C3)	Deacetylajugarin II	OH	OH
6		Ajugacumbin B_1	OH	OTig
6.1	(C5)	19-Oxoajugarin II	OH	(C_{19})=O
6.2	(X8)	Ajugacumbin G-Pr	OPr	OHMB
6.3	(C6)	6-Oxoajugarin II	(C_6)=O	OAc

[1]Liu 1995: the same compound was isolated (ajugamarin L2)
C: Caballero 2001; X: Xu 1998



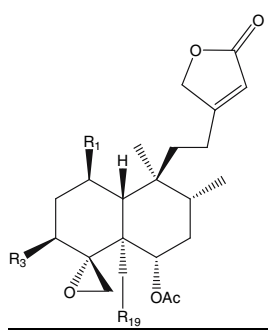
A	Rn	compound	R_6	R_{12}	R_{19}
7		Ajugalide C	OAc	OH	OAc
7.1		**Ajugacumbin D**	**OAc**	**OH**	**OTig**
8		Ajugamarin F4	OAc	OMB	OAc
9		Ajugamarin F2	OAc	OMB	OH
9.1	(K5)	12-Bromoajugarin I	OAc	Br	OAc
10		Ajugamarin F3	OH	OMB	OAc
11		Ajugamarin F1	OH	OMB	OH

K: Kubo1980



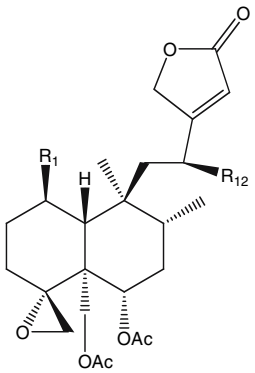
A	Rn	compounad	R_1	R_3
12		Ajugatansin B1	H	OH
12.1		***3α-Hydroxyajugamarin F4†***	***H***	***(α)OH***
13		Ajugareptone	(C_1)=O	OH

† revised to 3β= Ajugatansin B1



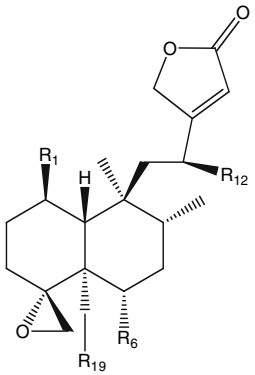
A	Rn	compound	R_1	R_3	R_{19}
14	***7.1***	***AjugacumbinD***	***H***	***OH***	***OTig***
15	***35.1***	***AjugacumbinC***	***(α)OAc***	***OAc***	***OTig***
16	***26.1***	***AjugacumbinE***	***(α)OAc***	***(α)OAc***	***OHMB***
17		Ajugatansin A1	OH	OMB	OAc
18		Ajugareptansone A	(C_1)=O	OMB	OAc
19		Ajugareptansone B	(C_1)=O	(C_2)=CH	OAc

Table 4 continued



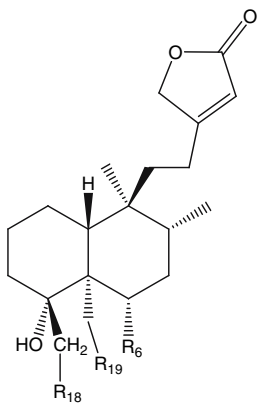
A	Rn	compound	R_1	R_{12}
20		AjugapantinA	OAc	OAc
21		Ajugalide B	OAc	OH
22		Ajugamacrin A	OAc	OiBu
23		Ajugamacrin B	OAc	OMB
24		Ajugalide A	OH	OAc
25		Ajugamarin C1	OH	OH
26		Ajugamarin E3	OH	OMB
26.1		**Ajugacumbin E?**	**OHMB**	**OAc**
27		Ajugamacrin C	OiBu	OiBu
28		Ajugamacrin D	OiBu	OMB
29		Ajugamarin B2	OMB	OAc
30		Ajugamarin B1	OMB	OH
31		Ajugamacrin E	OMB	OiBu
32		Ajugatakasin B	OMB	OMB
33		Ajugamarin H1	OMB	OTig
34		Ajugamarin A1	OTig	OH
35		Ajugamarin A2	OTig	OAc
35.1		**ajugacumbin C?**		
36		Ajugamarin G1	OTig	OMB
37		Ajugatakasin A	OTig	OTig
37.1	(S4)	12-Oxoajugamarin A	OTig	(C_{12})=O

S: Shimomura 1983



A	Rn	compound	R_1	R_6	R_{12}	R_{19}
38		Ajugamarin E1	OH	OAc	OMB	OH
39		Ajugamarin E2	OH	OH	OMB	OAc
40		Ajugamarin B5	OMB	OAc	OAc	OH
41		Ajugamarin B4	OMB	OAc	OH	OH
42		Ajugamarin B3	OMB	OH	OH	OAc

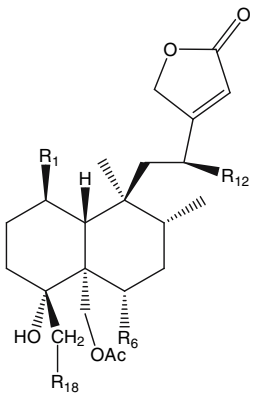
open C4-C18 structures



A	Rn	compound	R_{18}	R_6	R_{19}
43		Ajugarin III	OH	OAc	OAc
43.1	(Ch7)	Ajugacumbin A 4,18-diol	OH	OAc	OTig
44		Ajugacumbin F	OH	OH	OH
45		Ajugarin I-chlorohydrin	Cl	OAc	OAc
45.1	(Ch4)	Ajugacumbin A-chlorohydrin	Cl	OAc	OTig
45.2	(Ca8)	6-Oxoajugarin II-chlorohydrin	Cl	(C_6)=O	OAc
45.3	(X2)	Ajugarin I-bromohydrin	Br	OAc	OAc
45.4	(Ch5)	Ajugacumbin A- bromohydrin	Br	OAc	OTig
45.5	(Ch8)	Ajugacumbin B- bromohydrin	Br	OH	OH
45.6	(Ch6)	Ajugacumbin A- iodohydrin	I	OAc	OTig

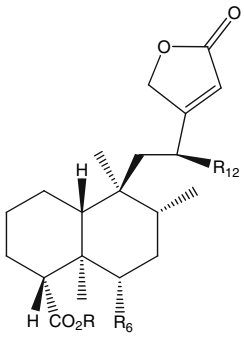
Ca: Caballero 2001; Ch: Chen 1995; X: Xu 1998

Table 4 continued



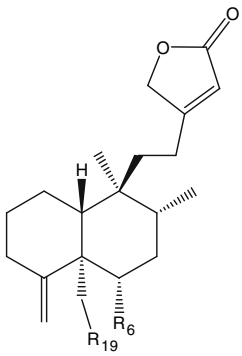
A	Rn	compound	R_{18}	R_1	R_6	R_{12}
45.7	(Sc2c)	Ajugamarin D1-diacetate	OAc	OMB	OAc	OAc
45.8	(Sc2b)	Ajugamarin B1-acetoxyhydrin[1]	OAc	OMB	OAc	OH
46		Ajugamarin D1	OAc	OMB	OH	OH
46.1	(Sc[2])	Ajugamarin C1-chlorohydrin	Cl	OH	OAc	OH
46.2	(Sc[3])	Ajugamarin C1 12-MB HCl	Cl	OH	OAc	OMB
46.3	(Sc2a)	Ajugamarin B1-chlorohydrin	Cl	OMB	OAc	OH
46.4	(Sb[4])	Ajugamarin H1-chlorohydrin	Cl	OMB	OAc	OTig
46.5	(S[5])	Ajugamarin A1 12-Ac HCl	Cl	OTig	OAc	OAc
47		Ajugamarin A1-chlorohydrin	Cl	OTig	OAc	OH
47.1	(Sb[6])	Ajugamarin G1 chlorohydrin	Cl	OTig	OAc	OMB

[1] or ajugamarin D1 acetate
[2] prepared from ajugamarin C1 (Sc3)
[3] prepared from ajugamarin C1 (Sc3)
[4] prepared from ajugamarin B1 (AJM-B1 12Tig HCl)
[5] prepared from ajugamarin A1 HCl (3)
[6] prepared from ajugamarin A1 (AJM-A1 12MB HCl)
S: Shimomura 1983; Sb: Shimomura 1989b; Sc: Shimomura 1989 c



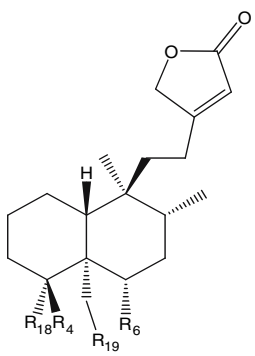
A	Rn	compound	R_6	R_{12}	R
48		Deacetylajugarin IV	OH	H	Me
48.1	(C4)	Deacetylajugarin IV acid	OH	H	H
49		Ajugarin IV	OAc	H	Me
49.1	(C3)	Ajugarin IV acid	OAc	H	H
50		Ajugalide D	OH	OH	Me

C: Chen 1992



A	Rn	compound	R_6	R_{19}
51		DeoxyajugarinI[1]	OAc	OAc
51.1	(L15)	Deacetyldeoxyajugarin II	OH	OH

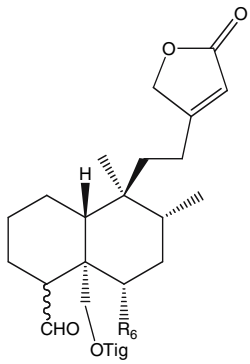
[1] Luteijn 1982: Prepared by synthesis (compound 14)
L: Ley 1983



A	Rn	compound	R_{18}	R_4	R_6	R_{19}
51.2	(J33)	4-Epiajugarin I	CH_2	-O	OAc	OAc
51.3	(X4)	4-Epiajugacumbin B HBr	CH_2Br	OH	OH	OTig
51.4	(C8)	4-Bromo-18-hydroxyajugacumbin A	CH_2OH	Br	OAc	OTig

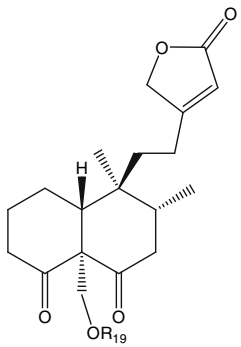
J: Jones 1986; C: Chen 1996; X: Xu 1998

Table 4 continued



A	Rn	compound[1]	R_6
51.5	(C9)	Ajugacumbin-A18-al	OAc
51.6	(X12)	Ajugacumbin-B18-al	OH

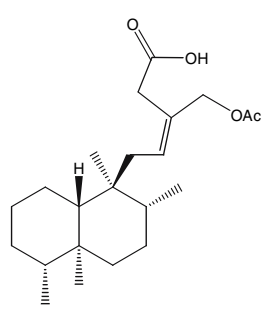
C: Chen 1995; X: Xu 1998



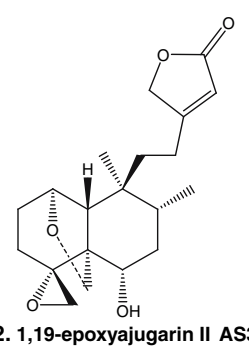
A	Rn	compound	R_{19}
51.7	(Ca10)	Ajugarin 4,6-dione	Ac
51.8	(Ch10)	Ajugacumbin A 4,6-dione	Tig

Ca: Caballero 2001; Ch: Chen 1995

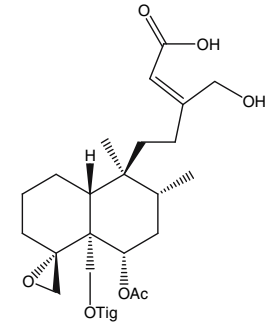
AJUGARIN-RELATED SPECIAL STRUCTURES



AS1. Ajugalaevigatic acid



AS2. 1,19-epoxyajugarin II
Caballero 2001(C9)



AS3. Ajugacumbin hydroxyacid
Chen1996c (11)

1. Rn: Reference and reference numbering for hemisynthetic compounds; revised structure location

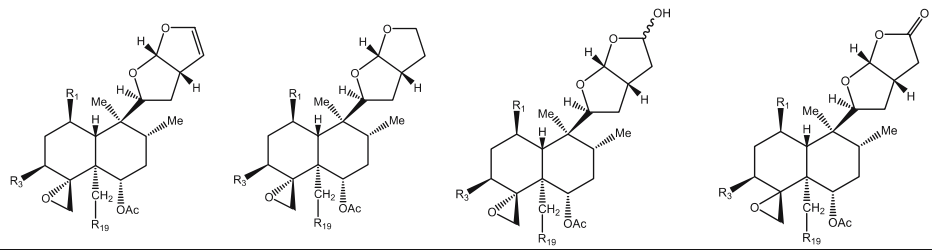
2. Substitution order: H (no substituent); O-substituents in alphabetical order; =O; other substituents (halogen order: Cl, Br, I.)

3. *p*-Bromobenzoates are not included

For better convenience, data for *A. iva* and *A. pseudoiva* are kept separate as in that report. In summary, the number of occurrences reported (Vestri Alvarenga et al. 2001) was 82, and has increased to 108 and to 179 according to the references collected in the present report [up to December 1997 (to compare with the aforementioned reference) and 2005, respectively]. The number of isolated new *neo*-clerodane diterpenes was 74 (Vestri Alvarenga et al. 2001) but according

Table 5 Natural and hemisynthetic furofuran *neo*-clerodanes from *Ajuga* (closely related compounds from another source in italics; low case is used for hemisynthetic compounds)

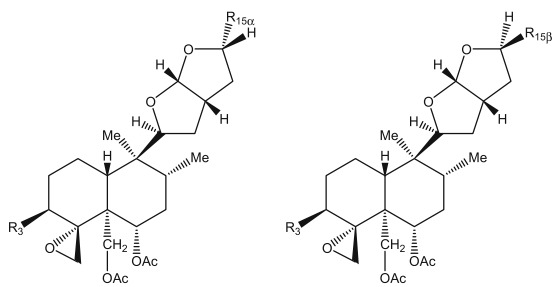
a. C-2 unsubstituted *neo*-clerodanes (C-3 α-stereochemistry highlighted by **bold** character)



A.- tetrahydro	B.- hexahydro	C.- hemiacetal	D.- lactone	a	R_1	R_3	R_{19}
Clerodin[1a]	14,15-Dihydroclerodin[1b]	14-Hydro-15-hydroxyclerodin[1c,2]	clerodin lactone[1d]	1	H	H	OAc
		Scutalpin O[3b]		2	H	H	OiBu
Caryoptin[4a]	***Dihydrocaryoptin***[4b]	***Caryoptin hemiacetal***[4c]	***caryoptin lactone***[4d]	3	**H**	**OAc**	**OAc**
3-epi-Caryoptin[5a]	*14,15-dihydro-3-epi-caryoptin*[5b]	*14-Hydro-15-hydroxy-3-epi-caryoptin*[6]		4	H	OAc	OAc
	Ivain II			5	H	OiBu	OAc
	Ajugavensin C			6	OH	H	OTig
	Ajugavensin A (rev)			7	OMB	H	OAc
	Ajugavensin B (rev)			8	OTig	H	OAc
14,15-Dehydroajugareptansin	Ajugareptansin			9	OMB	OH	OAc
areptin B acetate				10	OTig	OAc	OAc
Areptin B	Ajugorientin (3β-hydroxy-AJV B)			11	OTig	OH	OAc

[1] [a] (**I**; R=Ac); [b] (**II**; R=Ac, R'=R''=H); [c] (**II**; R=Ac, R'=OH, R''=H); [d] (V; R=H) in Barton 1961
[2] Named also as: clerodin hemiacetal[1c] and scutecyprol A [3a]
[3] [a] compound 40; [b] compound 41 in Bruno 2002:
[4] [a] (**I**); [b] (**II**); [c] (**III**); [d] (**VII**) in Hosozawa 1973
[5] [a] compound 3; [b] compound 4 in Hosozawa 1974b
[6] Pandey 2005

a. C-2 unsubstituted *neo*-clerodanes (C-3 α-stereochemistry highlighted by **bold** character)

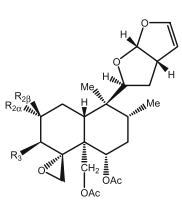
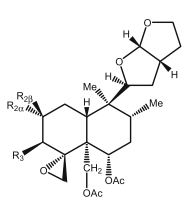
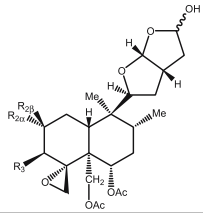
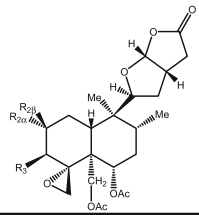


E.- α acetal	F.- β acetal	a	R_3	R_{15}
	clerodin hemiacetal acetate[1a]	1	H	OAc
Clerodinin C rev[2,3]	Clerodinin D rev[2,3]	2	H	OEt
Clerodinin A rev[4] (Lupulin D)	*Clerodinin B rev*[4]	3	H	OMe
	clerodin hemiacetal propionate[1b]	4	H	OPr
	clerodin hemiacetal anhydride[1c]	5	H	-O-
3β-Acetoxyclerodinin C[5]		6	OAc	OEt
	15-Methoxy-dihydro-3-epicaryoptin[6]	7	OAc	OMe
	Inermes A[7a]	8	OAc	-O-
	Inermes B[7b]	9	OAc	-O-R
	Lupulin B rev[8]	10	OMB	OMe

[1] [a] (II; R=Ac, R'=OAc, R''=H); [b] (II; R=Ac, R'=OPr, R''=H); [c] (VI) in Barton 1961
[2] compound III (mentioned as clerodin ethanol adduct without data or stereochemistry) in Hosozawa 1974a
[3] C-15 stereochemistry revised here, according to Ben Jannet 1999
[4] Lin 1989 (clerodinin A was originally reported as β acetal and B as α; revised by Ben Jannet 1999)
[5] compound IV (mentioned as caryoptin ethanol adduct without data or stereochemistry) in Hosozawa 1974a
[6] compound 1 (may be named 3β-acetoxyclerodinin B) in Achari 1992
[7] [a] one residue linking α, the other β; [b] one of the two residues contains a 1-OMe substituent in Pandey 2005
[8] stereochemistry revised (formerly as α acetal) by Ben Jannet 1999

Table 5 continued

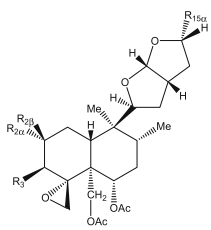
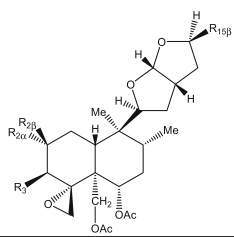
b. C2,C3 disubstituted *neo*-clerodanes

A.- tetrahydro	B.- hexahydro	C.- hemiacetal	D.- lactone	b	$R_{2\alpha}$	$R_{2\beta}$	R_3
	2-Acetylivain I[1]			1	H	OAc	OiBu
	Ivain I			2	H	OH	OiBu
	Ivain IV			3	H	OH	OMB
clerodendrin C acetate[2a]				4	OAc	H	OiBu2A
	2-acetyl-14,15-dihydroajugapitin[3]			5	OAc	H	OMB
clerodendrin B acetate[2b]				6	OAc	H	OMB2A
Athaliadiol[4]				7	OH	H	OH
Ajugachin A		14-Hydro-15-hydroxyajugachin A	15-oxodihydroajugachin A	8	OH	H	OiBu
Clerodendrin C[2a]				9	OH	H	OiBu2A
Ajugapitin (Clerodendrin D)	14,15-Dihydroajugapitin	14-Hydro-15-hydroxyajugapitin		10	OH	H	OMB
Clerodendrin B[2c,5]				11	OH	H	OMB2A
Ajugachin B		Chamaepitin		12	OH	H	OMB3A
Clerodendrin H[6]				13	OH	H	OMBdAe
Galericulin[7]				14	OH	H	OTig
	2-oxoivain I			15	= O		OiBu
			2,15-dioxodihydroajugapitin	16	= O		OMB
			2,15-dioxochamaepitin	17	= O		OMB3A

[1] More precise name: 2-*O*-Acetylivain I or Ivain I acetate
[2] [a] compound 3a; [b] compound 2a; [c] compound 3a;[d] compound 2a in Jagan Mohan Rao 1993
[3] More precise name: 2-*O*-Acetyl-14,15-dihydroajugapitin or 14,15-dihydroajugapitin acetate
[4] compound 10 in Nishida 2004
[5] compound II in Kato 1972
[6] compound IIc in Kawai 1998
[7] compound 8 in Bruno 2002

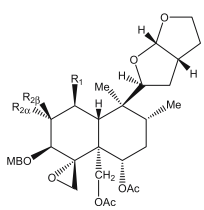
b. C2,C3 disubstituted *neo*-clerodanes

E.- α acetal	F.- β acetal	b	$R_{2\alpha}$	$R_{2\beta}$	R_3	R_{15}
Ivain III[1]		1	H	OH	OiBu	OEt
Hativene C		2	H	OH	OiBu	OMe
Hativene B	Hativene A	3	OH	H	OiBu	OMe
15α-Ethoxy-14-hydroajugapitin[2]	15β-Ethoxy-14-hydroajugapitin[2]	4	OH	H	OMB	OEt
Lupulin A rev[3]		5	OH	H	OMB	OMe

[1]: Stereochemistry not established in the original paper, the NMR data match a 15α epimer
[2]: The NMR data match the opposite stereochemistry
[3]: Stereochemistry revised (formerly as β acetal)
Ben Jannet 1999: Stereochemistry revisions proposed on NOE results

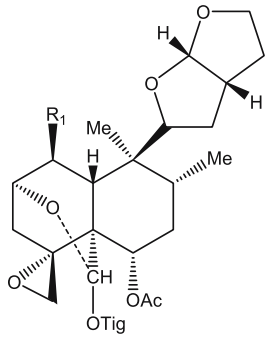
c. Ring A trisubstituted *neo*-clerodanes



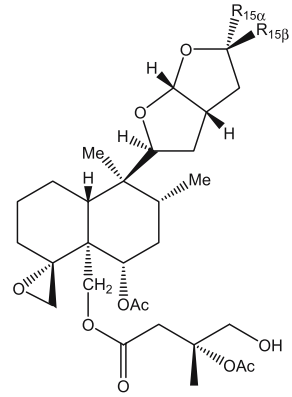
B.- hexahydro	c	R_1	$R_{2\alpha}$	$R_{2\beta}$
Areptin A	1	OH	H	OAc
Ajugatansin D1	2	OTig	OH	H
1-oxoareptin A	3	=O	H	OAc

Table 5 continued

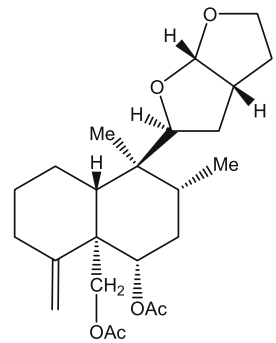
CLERODIN -RELATED SPECIAL STRUCTURES



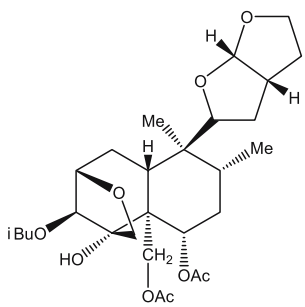
CS1. Ajugapyrin A (R_1=OH)
CS1A. Ajugapyrin A acetate(R_1=OAc)



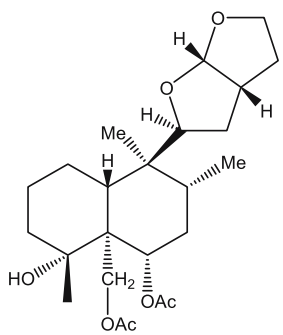
CS2. Bracteonin A (R_{15}=H,MeO)
(mixture of both epimers)



CS3. Lupulin C[1]



CS4. 2,18-epoxyivain I



CS5. tetrahydroclerodin[3]

[1] Hexahydrofurofuran stereochemistry as in Lupulin D X-ray analysis[2]
[2] Chen 1996
[3] compound 17 in Blaney 1988

to this review only 73 are accounted for and 84 by the end of 2005, whereas newly found in *Ajuga* but previously isolated from other sources are 4 and 5 more, respectively. Those figures were provided by studies on 18 species, 1 subspecies, and 1 variety of *Ajuga* reported by 37 and 54 papers respectively. Three more papers dealing with X-ray analysis of derivatives have not been included.

The clerodane diterpenes isolated from *Ajuga* displayed a few remarkable features. The original skeleton was preserved in C-5, C-7, C-8, C-9, C-10, C-17, and C-20: C-5 and C-9 were always tetra-substituted; C-6, C-8 and C-10 were always CH; C-7 always CH_2; and C-17 and C-20 always CH_3. These features are maintained with the only exception of ajugalaevigatic acid which displays a CH_2 at C-6. Different oxidation patterns were found in ring A, but in ring B only C-6 appeared oxygenated (always AcO in the furofuran series). In the butenolide series (40 out of 74 records), C-13 and C-15 displayed a double bond and no attached H, whereas C-11 and C-16 are CH_2. C-12 appeared as CH_2 or CH (13:27). In the furofuran series, C-11 and C-13 were obviously a CH (34 out of 74 records), and C-12 a CH_2 (for a total of 47 out of 74). Other main features were: C-19 (CH_3/CH_2 2/72), C-4 (C/C = /CH 70/2/2) and C-18 (CH_2/CH_2 = /C = 70/2/2). No

example of single C-2 substitution in ring A has been found in *Ajuga* (a common feature in *Scutellaria*, bridging often to C-19) (Bruno et al. 2002).

The statement ''Compound 6, a naturally occurring diterpene, was previously isolated from this plant'' (Chen et al. 1996c; cf. Min et al. 1989), the plant being *Ajuga decumbens*, has not been supported by the reference provided. However, the structure of compound 6 may be described actually as 6-*O*-acetylajugacumbin F (cf. Min et al. 1990) and remains to be confirmed whether it is a true naturally occurring compound with no structural elucidation report, or an unfortunate printing error for ajugacumbin F (R^1 = H rather than Ac).

Biological activities of *neo*-clerodane diterpenes isolated from *Ajuga* species

Insect antifeedant activity of *neo*-clerodane diterpenes is by far the most extensively studied biological property and has been recently reviewed as already mentioned in the *Introductory Remarks* section. However, a wider spectrum of biological as well as pharmacological activities of these compounds has been reported.

The genus *Ajuga* has been reported as of great medicinal importance, and plant use in folk medicine is usually quoted in the introductory sections of the papers. Use as astringent in swollen wounds, as a febrifuge in stomachache, diarrhoea, rheumatic fevers, bites from insects, eye trouble, as well as diseases of the bladder has been described (Muhammad et al. 1999). *A. remota* is used as a remedy for fever, toothache, dysentery, high blood pressure, skin diseases, stomachache, malaria, oedema, pneumonia and liver problems (Kokwaro 1993; Odek-Ogunde et al. 1993) and *A. decumbens* has been used for its antiinflammatory, antitussive, and expectorant effects (Takasaki et al. 1999). In the Moroccan pharmacopeia *A. iva* is known as a panacea (cure-all) and specifically for gastrointestinal disorders, hypertension, diabetes and as an anthelmintic (El Hilaly et al. 2004) and in Algeria to treat diabetes, and is known to have antiinflammatory, antifungal, antimicrobial, antifebrile, anthelmintic activity (Bondí et al. 2000), etc.

The folk uses of this array of properties have attracted the phytochemical investigation on these plants searching the support of experimental evidence. The secondary metabolites isolated are of a wide range, but only a reduced number of *neo*-clerodane diterpenes isolated from *Ajuga* plants have been evaluated for an activity other than antifeedancy.

In this section, we would like to compile the information regarding the bioactivities other than insect-antifeedant/insecticidal or insect-feeding-stimulant of *neo*-clerodane diterpenes isolated from *Ajuga* species which is summarized in Table 7.

Antibacterial

Some *neo*-clerodane diterpenes isolated from *Ajuga lupulina* were tested for antibacterial activity (Chen et al. 1996b). The activity of compounds lupulin A, B, D and clerodin hemiacetal (the acid hydrolysate of lupulin D) was tested by using a paper-diffusion method. In vitro antibacterial evaluation of lupulin A showed strong activity against *Pseudomonas aeruginosa* and *Escherichia coli* (inhibitory zone 3–5 mm), and weak activity against *Staphylococcus aureus* (1.5 mm). Lupulin B and clerodin hemiacetal exhibited weak antibacterial activity against *S. aureus* and *E. coli* (1.2 mm), with no activity against *P. aeruginosa*. Lupulin D showed no activity against any of the list organisms at the concentrations used (0.02 mg/mL). The structure of a new diterpene with antibacterial activity against *P. aeruginosa* and *E. coli* isolated from *A. lupulina* was established by means of X-ray crystallographic analysis (Chen et al. 1997). The compound should be lupulin A, but neither this name was used, nor bioassay results were reported. Preliminary biological tests for hativenes A-C showed high anti-bacterial activities towards *P. aeruginosa, E. coli* and *Salmonella typhimurium* according to the introduction of the paper on the structural elucidation (Ben Jannet et al. 1999).

Table 6 Clerodane diterpene occurrences in *Ajuga* species

Species	Reference	ON/R	ON/F	ON/A	new/R	new
A. australis	de la Torre (1997)	1+1[2]	**2**	2	0	0
A. bracteosa/remota	Kubo (1976)	3			3	
	Kubo (1980)	1			***1***	
	Kubo (1982)	1			1	
	Kubo (1983)	1			1	
	Odek-Ogunde (1993)	3	9	3	0	5+***1***
	Cantrell (1999)	3			0	
	Verma (2002)	1+2[2]			1	
	Kuria (2002)	1			0	
	Riaz (2004)	4			0	
	Coll (2005)	9+2[2]	**31**		***1***[2]	6+***2***
A. chamaepitys	Hernández (1982)	2			2	
	Camps (1984b)	1+1[2]			2	
	Camps (1987)	1+2[2]	**7**	8	12	5
A. chamaepitys var.*chia*	Boneva (1990)	4	**4**	3	2	2
A. chamaepitys ssp. *laevigata*	Topçu (2004)	1	**1**	–	1	1
A. ciliata var.*villosior*	Shimomura (1989a)	10	**10**	10	9	9
A. decumbens	Shimomura (1989b)	5			4	
	Min (1989)	4			3[a]	
	Min (1990)	3			2[b]	
	Chen (1995)	3			1	
	Amano (1997)	7	22	10	2	12
	Takasaki (1999)	4			0	
	Nishida (2004)	7	**33**		0	12
A. genevensis	Malakov (1991)	3			1[c]	
	Malakov (1992)	2	**5**	3	2	3
A. iva	Camps (1982)	4	4	4	4	4
	Bondí (2000)	2	**6**		0	4
A. iva (A. pseudoiva)	Camps (1984a)	2	2	2	1	1
	Ben Jannet (1999)	5			3	
	Ben Jannet (2000)	5	**12**		0	4
A. lupulina	Chen (1996b)	4			3	
	Chen (1996a)	1			***1***	
	Chen (1997)	1	**6**	4	0	3+***1***
A. macrosperma	Shen (1993a)	2			2	
	Shen (1993b)	3	**5**	5	3	5
A. nipponensis	Shimomura (1981)	1			1	
	Shimomura (1983)	3			2	
	Shimomura (1989c)	7			4	
	Liu (1995)	1	**12**	10	0	7
A. orientalis	de la Torre (1997)	1	**1**	1	1	1
A. pantantha	Shen (1993b)	2[d]	**2**[d]	2	1	1
A. parviflora	Beauchamp (1996)	11	**11**	11	5+***2***	5+**2**
A. pyramidalis	Boneva (1998)	1	**1**	–	1	1
A. reptans	Camps (1979)	1			1	
	Camps (1981a)	2			2	
	Miravitlles (1982)	1			0	
	Solans (1983)	1	5	2	0	3
	Malakov (1998)	5			2	
	Carbonell (2001)	5			3	
	Nishida (2004)	3	**18**		1	9
A. reptans cv. Catlins Giant	Bremner (1998)	4	**4**	–	1[e]	1[e]
A. salicifolia	Bozov (1993)	1[2]	1[2]	2	1[2]	1[2]
A. taiwanensis	Chan (2005)	7	**7**	–	4	4
Total (end of 1997)	**37**		**108**	**82**		**73+4**
(end of 2005)	**54**		**179**			**84+5**

Table 6 continued

ON/R: occurrence number in each reference

ON/F: cumulative occurrence number from data published until December 1997 and 2005 as found in references cited in this review

ON/A: occurrence number from data published until December 1997 as quoted in Vestri Alvarenga 2001

new/R: compounds reported for the first time (bold italics when only newly found in *Ajuga*)

new: total number of compounds reported for the first time in each *Ajuga* species

n^2 number of C-15 epimeric mixtures

[a] The reported structure for AJC-C has been questioned and apparently it is not a new compound. A revision of the reported structure for AJC-D has been proposed (Coll 2002)

[b] A more plausible structure for AJC-E has been proposed (Coll 2002)

[c] The structure of ajugavensins A and B was revised (Malakov 1992)

[d] Not clear if there is one or two known compounds (just one is more likely)

[e] The reported structure of a second new compound reported was revised later (Carbonell 2001)

Table 7 Assayed bioactivities of *neo*-clerodane diterpenes isolated from *Ajuga* species

Ajuga species	Assayed bioactivity	Microorganism/cell line used	Compounds	Reference
A. lupulina	Antibacterial	*Pseudomonas aeruginosa, Escherichia coli*	lupulins A, B, D, clerodin hemiacetal	Chen et al. (1996)
		P. aeruginosa	lupulin A?	Chen et al. (1997)
A. pseudoiva	Antibacterial	*P. aeruginosa, E. coli, Salmonella typhimurium*	hativenes A-C	Ben Jannet et al. (1999)
A. decumbens	Cancer chemopreventive	–	ajugapantin A, ajugamarins A1, A2 ajugatakasin A	Takasaki et al. (1999)
A. remota	Antimycobacterial	*Mycobacterium tuberculosis*	ajugarin I, II, clerodin	Cantrell et al. (1999)
	Antimalarial Cytotoxicity	*Plasmodium falciparum* A431 (skin carcinoma)	ajugarin I	Kuria et al. (2001)
A. chamaepitys ssp. *laevigata*	Antifungal Cytotoxicity	Yeast KB, LU1, Col2, LNCaP, hTERT RPE1, A2780	ajugalaevigatic acid	Topçu et al. (2004)

Antimycobacterial

The compounds ajugarin I, II and clerodin isolated from *Ajuga remota* were inactive (minimum inhibitory concentrations >128 μg/mL) against *Mycobacterium tuberculosis* in a radiorespirometric bioassay (Cantrell et al. 1999).

Antifungal

Consecutive petroleum ether, dichloromethane, and methanol extracts of *Ajuga remota* aerial parts were tested for their antifungal activity in a disc diffusion assay. The microorganisms used were *Trichophyton mentagrophytes, Microsporum gypseum, Candida albicans* and *Cladosporium cucumerinum*. The petroleum ether fraction was found to be the most effective against the tested pathogens (Kariba 2001). It was a preliminary study with no discussion on the compounds responsible for the bioactivity.

Antiplasmodial

Ajuga remota Benth is the most frequently used medicinal herb for malaria treatment in Kenya. In a preliminary study to confirm this ethnobotanical use, the antimalarial activity of this plant extracts were assayed (Kuria et al. 2001a). The IC_{50} of the ethanol macerate (the most active one) was 55 and 57 μg/mL against chloroquine sensitive strains of *Plasmodium falciparum* FCA/20GHA and W2 respectively. In 2001 the culture in Europe of the African variety of *A. remota* was introduced, specifically in Belgium, and although the initial attempt of in vitro propagation was not

successful, the culture in greenhouse was. The extracts of the plant grown in Belgium had an antimalarial activity similar to the one obtained with African plants (Kuria et al. 2001b). In a further evaluation of the in vivo antiplasmodial activity, ajugarin I resulted moderately active, with an IC_{50} of 23 ± 30 μM against FCA 20/GHA. It was suggested to consider ajugarin I as a lead compound to synthesize new pharmaceutically important derivatives with possibly higher antimalarial activity (Kuria et al. 2002).

Citotoxicity

Ajugarin I did not exhibit cytotoxicity against A431 (skin carcinoma) cell line. Ajugalaevigatic acid isolated from *Ajuga chamepitys* ssp. *laevigata* was tested in a yeast based microtiter assay for antifungal and cytotoxic potential but it showed neither selective DNA damaging nor antifungal activity. Cytotoxicity against a panel of cell lines was also investigated and it was found to be weakly active (17.7 μg/mL) against the A2780 human ovarian cancer cell line (Topçu et al. 2004).

Cancer chemoprevention

Ajugapantin A, ajugamarins A1 and A2 and ajugatakasin A, isolated from *Ajuga decumbens*, were tested for their inhibitory effects on Epstein-Barr virus early antigen (EBV-EA) induction by the tumor promoter, 12-*O*-tetradecanoylphorbol-13-acetate (TPA), in Raji cells, as a primary screening test for antitumor-promoters (potential cancer chemopreventive agents). The remarkable inhibitory effects of the extracts was traced to compounds of different chemical nature, whereas none of the diterpenes showed potent inhibition on EBV-EA induction (Takasaki et al. 1999).

Hypoglycaemic effects

The lyophilised aqueous extract of the whole plant of *Ajuga iva* (L.) Schreber was examined for its hypoglycaemic effect in normal and streptozotocin-induced diabetic rats (El Hilaly and Lyoussi 2002). Hypoglycaemic activity was experimentally demonstrated and toxicological studies did show that the aqueous extract could be considered as free of toxic effects at hypoglycaemic doses.

Hypotensive effects

Treatment with an *Ajuga remota* extract can arrest and reverse the progression of an induced hypertensive cardiovascular disease in experimentally hypertensive rats and cause a significant reduction in the systolic blood pressure from hypertensive levels (BP ≥ 140 mmHg) to normotensive levels (BP ≤ 140 mmHg). Chemical characterization of the crude extract led to the isolation of the known clerodane diterpenes ajugarins I-III as the major components (Odek Ogunde et al. 1993).

The in vivo effect of a lyophilised aqueous extract of the whole plant of *Ajuga iva* (L.) Schreber on the systolic blood pressure was examined and also the ex vivo and in vitro effects on the vasomotor tone of aortic rings isolated from normotensive rats. The study showed that the extracts elicited different vasodilatory properties and two modes of action could be distinguished, in view of the sensitivity to NO synthase inhibitor L-NNA. It possesses NO-mediated and NO-independent vasorelaxing properties in vitro, while only the endothelium-independent effect was observed ex vivo (El Hilaly et al. 2004).

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