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Extremely Potent Antifeedant *neo*-Clerodane Derivatives of Scutecyprol A

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Two known *neo*-clerodane diterpenoids, scutecyprol A (**1**) and scutalbin C (**2**), have been isolated from the acetone extract of the aerial parts of *Scutellaria sieberi*. The antifeedant activity of scutecyprol A (**1**), of its 15-oxo derivative (**3**), and of several halohydrins (**4**−**9**), synthesized starting from compounds **1** and **3**, against *Spodoptera littoralis* have been determined and structure-antifeedant relationships are discussed.

KEYWORDS: ***Scutellaria sieberi*; scutecyprol A; halohydrins; antifeedant activity; *Spodoptera littoralis***

INTRODUCTION

Clerodane diterpenoids have been found in hundreds of species of plants from various families (*1*, *2*). Several genera from the Verbenaceae and Lamiaceae families have been identified as rich sources of *neo*-clerodane diterpenoids. These metabolites have attracted considerable attention for their biological activities, which include piscicidal (*3*), trypanocidal (*4*)), and antibacterial (*5*−*7*) properties. Furthermore, antiinflammatory (*8*−*10*), hepatotoxic (*11*), hypoglycemic (*12*), antileukemia (*13*), and antitumor or cytotoxic activities (*14*−*16*) have been reported from in vitro experiments using mammalian organism or tissue cultures. *neo*-Clerodane diterpenoids are best-known for their antifeeding properties against insects, and recently a review was published on the antifeedant activity of natural and semisynthetic *neo*-clerodanes (*17*). *Scutellaria* is a unique cosmopolitan genus of the subfamily Scutellariodeae belonging to the Lamiaceae family. Species of this genus are distributed throughout the world, although the majority grow in Asia. The genus contains a rich diversity of *neo*-clerodane diterpenoids including compounds with epoxides, lactones, and hydrofurofuran groups (*18*). The chemistry and antifeedant activity of the *neo*-clerodanes of *Scutellaria* were recently reviewed (*18*).

The presence of a C-4/C-18 α-epoxy ring has been considered to play an important role in the antifeedant activity of *neo*-clerodanes; in fact, the most active *neo*-clerodanes such as jodrellins A and B (*19*) and ajugapitin (*20*) have this structural moiety. On the other hand, tafricanin B, with a chlorohydrin function at C-4/C-18, is a potent antifeedant against *Locusta migratoria* (*21*), and the halohydrin derivative of ajugacumbin A is more active against *Ostrinia furnacalis* than ajugacumbin A, whereas the bromhydrin and iodohydrin derivatives are less active (*22*).

In the present study we report on the isolation of two known *neo*-clerodane diterpenoids from *Scutellaria sieberi* Benth., a species not studied before, and on the antifeedant activity of its metabolites against *Spodoptera littoralis*.

Several semisynthetic derivatives, in which the C-4/C-18 oxirane ring is opened, have also prepared and tested to study their influence on the bioactivity.

MATERIALS AND METHODS

Instruments. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. IR spectra were determined with a Perkin-Elmer 257 instrument. ^{1}H and ^{13}C NMR spectra were obtained on Bruker AC-250 operating at 250 and 62.7 MHz for proton and carbon, respectively. DEPT experiments were acquired on the same apparatus. Measurements were made in $CDCl_3$, chemical shifts were referred to TMS set at 0 ppm, and coupling constants are given in hertz. Mass spectra were recorded on a Finnigan TSQ70 instrument (70 eV, direct inlet). Elemental analysis was carried out with a Perkin-Elmer 240 apparatus. Flash chromatography was performed by using silica gel (article 7754, 0.040−0.063 mesh).

Plant Material. *S. sieberi* Benth., growing wild in Crete (Greece), was cultivated in the Orto Botanico "G. E. Ghirardi" University of Milan, at Toscolano (Garda Lake, Brescia), Italy. Plant material was collected in June 2002.

Extraction and Isolation. Dried and finely powdered aerial parts of *S. sieberi* (550 g) were extracted for 1 week with Me_2CO (3 × 5 L) at room temperature. The residue (25 g) obtained by removal of the solvent at reduced pressure was chromatographed on a silica gel (article 7754, deactivated with 15% H_2O, 500 g) column, packed in petroleum ether, using a petroleum ether−EtOAc gradient solvent system (0 → 80% EtOAc in petroleum ether, total 6 L) followed by EtOAc (1 L) and a mixture of EtOAc and MeOH (9:1, 1 L). The fraction eluted with petroleum ether−EtOAc 70% was purified by column chroma-

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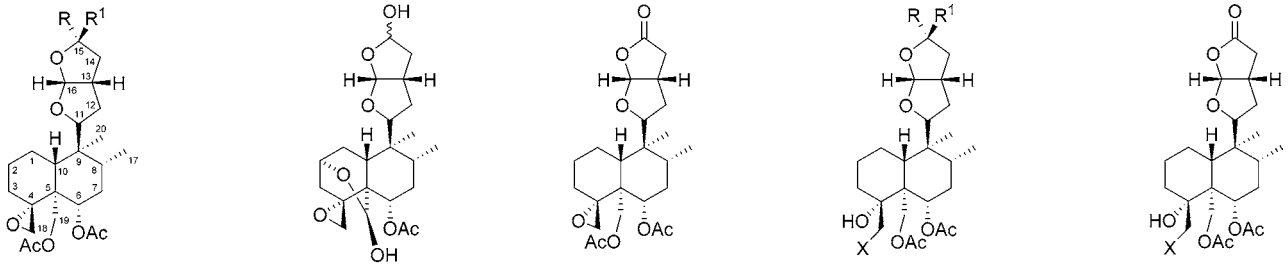

1a R = H R^1 = OH 15*R*
1b R = OH R^1 = H 15*S*

2

3

4a X = Cl R = H R^1 = OH 15*R*
4b X = Cl R = OH R^1 = H 15*S*
5a X = Br R = H R^1 = OH 15*R*
5b X = Br R = OH R^1 = H 15*S*
6a X = I R = H R^1 = OH 15*R*
6b X = I R = OH R^1 = H 15*S*

7 X = Cl
8 X = Br
9 X = I

Figure 1. Structures of compounds **1**–**9**.

Table 1. ^{1}H NMR Data for Compounds **1** and **3**–**9** (250 MHz in $CDCl_3$)

	1a (15*R*)	**1b** (15*S*)	**3**	**4a** (15*R*)	**4b** (15*S*)	**5a** (15*R*)	**5b** (15*S*)	**6a** (15*R*)	**6b** (15*S*)	**7**	**8**	**9**
6β	4.68 br dd	4.68 br dd	4.69 br dd	5.00 dd	5.00 dd	5.06 dd	5.06 dd	5.15 dd	5.15 dd	4.97 dd	5.05 dd	5.11 dd
11α	4.00 dd	4.59 dd	4.13 dd	3.99 dd	4.59 dd	3.96 dd	4.56 dd	3.95 dd	4.58 dd	4.10 dd	4.12 dd	4.08 dd
13β	3.09 m	2.82 m	3.19 m	3.07 m	2.87 m	3.06 m	2.92 m	3.04 m	2.85 m	3.19 m	3.16 m	3.19 m
14A	*a*	*a*	2.91 dd	*a*	*a*	*a*	*a*	*a*	*a*	2.91 dd	2.89 dd	2.90 dd
14B	*a*	*a*	2.41 dd	*a*	*a*	*a*	*a*	*a*	*a*	2.41 dd	2.39 dd	2.41 dd
15α	5.64 d			5.64 d		5.64 d		5.64 d				
15β		5.53 d			5.54 d		5.54 d		5.54 d			
16β	5.80 d	5.78 d	6.06 d	5.79 d	5.77 d	5.78 d	5.76 d	5.78 d	5.76 d	6.05 d	6.05 d	6.05 d
Me-17	0.86 d	0.88 d	0.88 d	0.89 d	0.91 d	0.89 d	0.91 d	0.89 d	0.91 d	0.91 d	0.90 d	0.91 d
18A	2.98 dd	2.98 dd	2.99 d	4.01 d	4.03 d	3.95 d	3.97 d	3.79 s	3.81 s	4.00 d	3.92 d	3.78 s
18B	2.21 d	2.21 d	2.22 d	3.91 d	3.89 d	3.88 d	3.86 d	3.79 s	3.81 s	3.90 d	3.87 d	3.78 s
19A	4.89 d	4.89 d	4.89 dd	5.01 d	5.01 d	5.02 d	5.02 d	5.05 d	5.05 d	4.99 d	5.00 d	5.04 d
19B	4.37 br d	4.37 br d	3.38 br dd	4.65 d	4.65 d	4.64 d	4.64 d	4.62 d	4.62 d	4.65 d	4.63 d	4.63 d
Me-20	0.95 s	0.94 s	0.96 s	1.01 s	1.02 s	1.00 s	1.01 s	1.00 s	1.01 s	1.03 s	1.02 s	1.02 s
Ac	2.10 s	2.10 s	2.12 s	2.11 s	2.11 s	2.11 s	2.11 s	2.10 s	2.10 s	2.12 s	2.11 s	2.12 s
Ac	1.95 s	1.95 s	2.03 s	2.02 s	2.02 s	2.02 s	2.02 s	2.01 s	2.01 s	2.03 s	2.02 s	2.03 s
OH	2.78 br s	2.78 br s		2.85 br s	2.85 br s	2.90 br s	2.90 br s	3.04 br s	3.04 br s			
J (Hz)												
3α,18A	2.4	2.4	2.4	0	0	0	0	0	0	0	0	0
6β,7α	11.5	11.5	11.7	11.5	11.5	11.5	11.5	11.5	11.5	11.7	12.0	11.8
6β,7β	4.9	4.9	4.1	4.9	4.9	4.9	4.9	4.9	4.9	4.1	4.3	4.2
6β,19B	<0.5	<0.5	<0.5	0	0	0	0	0	0	0	0	0
8β,17	6.4	6.4	6.3	6.2	6.2	6.1	6.1	6.1	6.1	6.3	6.2	6.2
11α,12A	11.8	11.2	11.4	11.8	11.2	11.8	11.2	11.8	11.2	11.4	11.4	11.4
11α,12B	4.5	6.5	5.0	4.5	6.5	4.5	6.5	4.5	4.5	5.0	5.0	5.0
13β,14A	n.o.[b]	n.o.	10.6	n.o.	n.o.	n.o.	n.o.	n.o.	n.o.	10.6	10.6	10.6
13β,14B	n.o.	n.o.	3.9	n.o.	n.o.	n.o.	n.o.	n.o.	n.o.	3.9	3.9	3.9
13β,16β	5.3	5.3	5.6	5.7	5.7	5.7	5.7	5.6	5.6	5.7	5.7	5.7
14A,14B	n.o.	n.o.	18.7	n.o.	n.o.	n.o.	n.o.	n.o.	n.o.	18.8	18.8	18.8
14A,15α	4.0			4.6		4.8		4.4				
14A,15β		0			0		0		0			
14B,15α	0			0		0		0				
14B,15β		5.3			5.2		5.5		5.8			
18A,18B	4.0	4.0	4.0	11.2	11.2	10.7	10.7			11.3	10.7	
19A,19B	12.2	12.2	12.1	13.2	13.2	13.2	13.2	13.0	13.0	13.1	13.0	13.0

[a] Overlapped signals. [b] n.o., not observed.

tography (petroleum ether−EtOAc 50%) to afford a subfraction that was dissolved in EtOAc and allowed to crystallize (−20 °C) to give 1.2 g of scutecyprol A (**1**). The fraction eluted with petroleum ether−EtOAc 70% was purified by column chromatography (CH_2Cl_2/MeOH 49:1) to give 10 mg of scutalbin C (**2**).

15-Oxoscutecyprol A (3). Scutecyprol A (**1**; 150 mg) was dissolved in CH_2Cl_2 (20 mL) and oxidized with a solution of pyridinium dichromate (870 mg) in CH_2Cl_2 (20 mL) at room temperature for 24 h. After dilution with H_2O (50 mL) and extraction with Et_2O (6 × 50 mL), the extract was washed with H_2O and dried, and the solvent was evaporated to give 145 mg of 15-oxoscutecyprol A (**3**): mp 191−193 °C (from petroleum ether−EtOAc); $[\alpha]_D^{25}$ −22.3 ($CHCl_3$; *c* 0.20); IR ν_{max} (film) 3012, 2950, 2880, 1758, 1734, 1720, 1374, 1230, 1112; EIMS, 450 (8) $[M]^+$, 390 (15), 331 (10), 286 (15), 264 (20), 204 (62), 126 (100); ^{1}H NMR, see **Table 1**; ^{13}C NMR, see **Table 2**.

General Procedure for Halohydrin Formation. Scutecyprol A (**1**) or 15-oxoscutecyprol A (**3**) (30 mg) was dissolved in 4 mL of THF, and 3 equiv of AcOH and 40 equiv of LiX (LiCl, LiBr, LiI) were added to the solution. The reaction was allowed to stand for 24 h and then diluted with H_2O (10 mL) and extracted with AcOEt (4 × 20 mL); the extract was washed with H_2O and dried, and the solvent was evaporated. The residue was purified by colum chromatography to give halohydrins (**4**−**9**).

18-Chloro-4α*-hydroxyscutecyprol A (4):* 27 mg; yield, 88%; amorphous solid; IR ν_{max} (film) 3440, 3012, 2945, 2874, 1732, 1690, 1210,

Table 2. ^{13}C NMR Data for Compounds **1**, **3**, and **7**–**9** (62.7 MHz in $CDCl_3$)

	1a (15*R*)	**1b** (15*S*)	**3**	**7**	**8**	**9**
1	22.17 t	22.20 t	22.23 t	22.00 t[a]	21.94 t[a]	21.84 t[a]
2	24.95 t	25.01 t	24.94 t	22.31 t[a]	22.27 t[a]	22.23 t[a]
3	32.70 t	32.74 t	32.57 t	31.68 t	33.05 t	35.99 t
4	65.01 s	65.05 s	64.94 s	76.69 s	76.27 s	75.59 s
5	45.55 s	45.55 s	45.47 s	48.37 s	48.33 s	47.24 s
6	71.95 d	72.10 d	71.69 d	74.10 d	74.08 d	74.47 d
7	33.40 t	33.40 t	33.37 t	33.46 t	33.55 t	33.59 t
8	36.06 d	36.16 d	35.79 t	35.44 d	35.46 d	35.49 d
9	40.13 s	40.18 s	40.32 s	40.87 s	40.67 s	40.89 s
10	48.48 d	48.30 d	48.19 d	49.87 d	45.33 d	45.53 s
11	83.61 d	83.55 d	84.25 d	84.44 d	84.44 d	84.48 d
12	32.08 t	32.47 t	32.57 t	32.69 t	32.69 t	32.75 t
13	40.01 d	41.03 d	37.97 d	37.99 d	37.97 d	38.00 d
14	38.83 t	39.86 t	35.17 t	35.08 t	35.07 t	35.08 t
15	98.67 d	98.41 d	175.79 s	175.52 s	175.18 s	175.15 s
16	107.46 d	109.50 d	106.67 d	106.62 d	106.62 d	106.61 d
17	16.47 q	16.40 q	16.63 q	17.08 q	17.06 q	17.08 q
18	48.32 t	48.44 t	48.42 t	45.22 t	40.67 t	17.91 t
19	61.71 t	61.81 t	61.55 t	63.39 t	63.52 t	63.73 t
20	13.98 q	14.01 q	13.87 q	14.58 q	14.58 q	14.70 q
Ac	170.11 s	171.00 s	170.86 s	170.85 s	170.07 s	170.00 s
Ac	170.11 s	171.00 s	170.10 s	170.85 s	170.07 s	170.00 s
Ac	21.18 q	21.14 q	21.16 q	21.38 q	21.37 q	21.36 q
Ac	21.18 q	21.14 q	21.16 q	21.58 q	21.57 q	21.57 q

[a] These assignments may be reversed.

1182; EIMS, 452 (1) $[M - HCl]^+$, 434 (6) $[M - HCl - H_2O]^+$, 392 (10), 332 (12), 284 (13), 264 (20), 204 (100); ^1H NMR, see **Table 1**.

18-Bromo-4α-hydroxyscutecyprol A (5): 35 mg; yield, 98%; amorphous solid; IR ν_{max} (film) 3398, 3000, 2986, 1736, 1692, 1210, 1180; EIMS, 452 (1) $[M - HBr]^+$, 434 (5) $[M - HBr - H_2O]^+$, 386 (16), 330 (18), 284 (20), 264 (25), 204 (100); ^1H NMR, see **Table 1**.

18-Iodo-4α-hydroxyscutecyprol A (6): 36 mg; yield, 95%; amorphous solid; IR ν_{max} (film) 3400, 3015, 2945, 2880, 1747, 1697, 1204, 1184; EIMS, 452 (5) $[M - HI]^+$, 434 (8) $[M - HI - H_2O]^+$, 323 (25), 286 (18), 264 (26), 204 (100); ^1H NMR, see **Table 1**.

18-Chloro-4α-hydroxy-15-oxoscutecyprol A (7): 24 mg; yield, 75%; amorphous solid; $[\alpha]^{25}_D$ −16.4 ($CHCl_3$; *c* 0.10); IR ν_{max} (film) 3430, 3005, 2950, 2880, 1760, 1734, 1720, 1422, 1230, 1082; EIMS, 450 (5) $[M - HCl]^+$, 390 (20), 331 (12), 288 (15), 264 (20), 204 (70), 127 (100); ^1H NMR, see **Table 1**; ^{13}C NMR, see **Table 2**.

18-Bromo-4α-hydroxy-15-oxoscutecyprol A (8): 36 mg; yield, 98%; amorphous solid; $[\alpha]^{25}_D$ −18.2 ($CHCl_3$; *c* 0.20); IR ν_{max} (film) 3428, 3010, 2980, 2880, 1760, 1732, 1724, 1418, 1230, 1084; EIMS, 450 (5) $[M - HBr]^+$, 390 (16), 331 (8), 288 (10), 264 (18), 204 (62), 127 (100); ^1H NMR, see **Table 1**; ^{13}C NMR, see **Table 2**.

18-Iodo-4α-hydroxy-15-oxoscutecyprol A (9): 38 mg; yield, 98%; amorphous solid; $[\alpha]^{25}_D$ −12.0 ($CHCl_3$; *c* 0.10); IR ν_{max} (film) 3424, 3014, 2980, 2876, 1770, 1730, 1720, 1420, 1230, 1082; EIMS, 450 (4) $[M - HI]^+$, 390 (20), 331 (10), 288 (12), 264 (16), 204 (60), 127 (100); ^1H NMR, see **Table 1**; ^{13}C NMR, see **Table 2**.

Insects. Larvae of the Lepidopteran *S. littoralis* (Boisd.) were from cultures reared on a wheat-based diet (*23*).

Antifeedant Bioassay. A binary choice feeding bioassay using glass-fiber disks (Whatman GF/A, 2.1 cm diameter) was used to evaluate the activity of the compounds against the final stadium larvae of *S. littoralis* (*24*). The compounds were applied to glass-fiber disks made palatable by the addition of 100 μL of a sucrose solution (50 mM). Control disks carried only sucrose, whereas the treatment disks carried in addition 100 μL of a solution of one of the test compounds at a concentration of 0.1−500 ppm. The disks were left to dry and then weighed. Larvae (24−36 h into the final stadium) were placed individually in Petri dishes (8.5 cm diameter) with a control and treatment disk. The bioassay was terminated after 50% of either disk was eaten (to avoid the situation when the test changes from a choice test to a no-choice test when 100% is eaten) or after 18 h if the insect had not eaten 50% of either disk. Most of these experiments lasted for 15−18 h. The larvae were removed, and the disks were dried and reweighed. The feeding index, $FI = [(C - T)/(C + T)] \times 100$, was calculated, where *C* and *T* represent the mass eaten of control and treatment disks, respectively. Regression analysis was used to establish the concentration required to obtain a feeding index of 50% (FI_{50}). The *F* test was used to evaluate whether the responses of the insects differed. Each concentration of each compound was tested against batches of five individual larvae taken from one to three generations of insects. Thus, each concentration was tested against 5−15 insects. The results from the feeding index at 100 ppm are presented under Results and Discussion as this is a standard concentration used to compare activity across all compounds tested against the insects at the Royal Botanic Gardesn in Kew. The Wilcoxon test was used to compare the amount of the control and treatment disks eaten at 100 ppm.

Table 3. Effect of Compounds **1**–**9** on the Feeding Behavior of Final Stadium Larvae of *S. littoralis*[a]

compound	FI_{50}[b]	95% confidence limits
1	21.5a	8–24
3	22.5a	7–25
4	48c	32–75
5	43c	31–58
6	47c	37–63
7	33b	24–26
8	47c	20–124
9	46c	22–84

[a] $P < 0.01$, Wilcoxon matched pairs test, $n = 10$–15. [b] Concentration (ppm) estimated to give a feeding index of 50% and the 95% confidence limits associated with this value. Values followed by different letters differ significantly ($P < 0.01$) (*F* values; see text for details).

RESULTS AND DISCUSSION

An acetone extract of the aerial parts of *S. sieberi* was fractioned by column chromatography. Repeated column chomatographies and crystallization led to the isolation of two *neo*-clerodane diterpenoids. The first one was identified as scutecyprol A (**1**), a metabolite with a 15-hydroxyhexahydrofurofuran system, previously found in *Scutellaria cypria* (*25*) as a 1:1 mixture of the two C-15 epimers. In this case its NMR spectra gave only one signal for each proton and carbon, different from the previously examined mixture (*25*) in which several signals for protons appeared as double signals. Consequently, in *S. sieberi* only an epimer was present, and its 15*R* configuration has been recently determined (*26*). When the pure 15*R* epimer of scutecyprol A was dissolved in $CHCl_3$, after 1 h, a complete isomerization was observed as clearly indicated by its ^1H and ^{13}C NMR spectra.

The second diterpenoid was identified as the 1:1 mixture of the two C-15 epimers of scutalbin C (**2**), previously isolated from *S. albida* (*27*).

Treatment of scutecyprol A (**1**) with pyridinium dichromate in CH_2Cl_2 allowed the 15-oxo derivative (**3**) to be synthesized. Its NMR spectra showed the absence of the hemiacetalic group and the presence of a γ-lactone ($\delta_{C-15} = 175.79$; $\delta_{C-14} = 35.17$; $\delta_{H\text{-}14A} = 2.91$ dd; $\delta_{H-14B} = 2.41$ dd).

Both scutecyprol A (**1**) and its 15-oxo derivative (**3**) were treated in turn with LiCl, LiBr, and LiI to give six different halo derivatives (**4**−**9**) in which the 4−18 epoxide was converted in chlorohydrin, bromohydrin, and iodohydrin groups, respectively. Their ^1H and ^{13}C NMR spectra are reported in **Tables 1** and **2**.

The results from the feeding assay are presented in **Table 3**. All compounds gave a 100% feeding index at 100 ppm. In a previous study (*28*), the activity of scutecyprol A (**1**) was lower (69 ± 13) than recorded in this study. This could be because the previously tested scutecyprol A (**1**) was a mixture of the

two C-15 epimers, whereas in this study the more active 15*R* isomer (**1a**) has been tested. Scutalbin C (**2**) activity, reported previously (*29*), was quite low, despite its having the C-4/C-18 epoxy ring, but it is the only one of the nine compounds to have an acetal bridge between C-2 and C-19. Thus, the activity of this compound can be compared with that of other *neo*-clerodanes that have this bridge, such as the active jodrellins A and B (*18*). Scutalbin C (**2**) is reported here because it was found to be in *S. sieberi* with scutecyprol A (**1**) and thus indicates that *S. sieberi* contains *neo*-clerodanes with and without the acetal bridge. However, because it was not active, no further work was undertaken on it in this study.

Other results from the feeding assay showed that all of the other compounds tested were active antifeedants. As shown, the potency did vary when tested for FI_{50} (**Table 3**). Scutecyprol A (**1a**) and its 15-oxo derivative (**3**) were more active than the halogenated derivatives (**4**−**9**). Thus, opening of the epoxy ring does result in a decrease in activity. A comparison of the halogenated derivatives (**4**−**6**) of **1** versus the derivatives (**7**−**9**) of **3** shows that the chlorohydrin derivative of **3** is more active than the chlorohydrin derivative of **1** and that this compound is also more active than the other halogenated derivatives. Although opening of the C-4/C-18 epoxy ring had resulted in a decrease in activity, the compounds remain potent antifeedants against *S. littoralis*. Other *neo*-clerodanes with FI_{50} values similar to those of the derivatives (**4**−**9**) were isolated from species of *Salvia* and include compounds such as 6-β-hydroxysalviarin (FI_{50} = 24) or 1(10)-dehydrosalviarin (FI_{50} = 32) (*30*). However, these *Salvia neo*-clerodanes differ from the *Scutellaria neo*-clerodanes as they had different functional groups at C-9 and do not have the C-4/C-18 epoxy ring. These results show there is scope for further modification to be made to the *neo*-clerodane molecule to establish which moieties are essential for the molecule to retain its potency as an antifeedant.

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