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Short Report

Caavuranamide, a Novel Steroidal Alkaloid from the Ripe Fruits of *Solanum caavurana* Vell. (Solanaceae)

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A investigação fitoquímica dos frutos maduros de *Solanum caavurana* Vell. (Solanaceae) forneceu um novo alcaloide esteroidal do tipo espirosolano, caavuranamida, juntamente com os alcaloides 4-tomatiden-3-ona e 5α-tomatidan-3-ona. Suas estruturas foram elucidadas através de métodos espectroscópicos. As atividades antiproliferativa e antimicrobiana para o extrato etanólico e subfrações provenientes de partição e de extração ácido-base foram investigadas. A caavuranamida apresentou atividade antibacteriana similar ao controle positivo cloranfenicol contra *Rhodococcus equi.*

Phytochemical investigation of the ripe fruits of *Solanum caavurana* Vell. (Solanaceae) afforded a novel steroidal alkaloid with spirosolane-type skeleton, named as caavuranamide, together with the alkaloids 4-tomatiden-3-one and 5α-tomatidan-3-one. Their structures were elucidated on the basis of spectroscopic methods. The antiproliferative and antimicrobial activities for the ethanolic extract, sub-fractions obtained from partition and acid-base treatment were also evaluated. Caavuranamide showed antibacterial activity similar to the chloramphenicol positive control against *Rhodococcus equi.*

Keywords: *Solanum caavurana,* Solanaceae, caavuranamide, steroidal alkaloids, spirosolane

Introduction

The genus *Solanum* is the most representative of Solanaceae family, comprising about 1400 species[1] mainly distributed in tropical and subtropical regions of Americas, Africa and Australia.[2] In Brazil, about 350 *Solanum* species have been identified, many of them endemic.[3]

Solanum caavurana Vell. grows as a bush or a small tree with *ca.* 5 m high, and is widely distributed in Brazil (in Ceará, Bahia, Mato Grosso do Sul, Paraná and Santa Catarina States), occurring in Paraguay and Argentina as well. It is popularly known as 'laranjinha do mato', 'jurubebarana'[2] or 'jurubeba-branca', being used in folk medicine to treat anemia, liver disorders and as digestive as well.[1] Although phytochemical studies on *Solanum* species resulted in the isolation of a great variety of steroidal alkaloids and glycoalkaloids,[4,5] to the best of our knowledge, the only report found for this species was an unsuccessful search for solasodine in its unripe fruits.[6]

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Here, we report the identification of a novel steroidal alkaloid, named as caavuranamide (**1**), along with the known 4-tomatiden-3-one (**2**) and 5α-tomatidan-3-one (**3**), isolated from the ethanolic extracts of the ripe fruits of *Solanum caavurana* Vell.

Experimental

General experimental procedures

Melting point (mp) was determined on a Quimis Q-340S23 micromelting point apparatus. IR spectra were acquired on a BIORAD FTS-3500, Fourier transform infrared (FTIR) equipment. Optical rotation was measured by using a Rudolph Research (Flanders, New Jersey) Autopol III automatic spectropolarimeter. Nuclear magnetic resonance (NMR) data were recorded at 293 K in $CDCl_3$ on a Varian Inova 500 operating at 11.7 T, observing ^1H at 500 MHz and ^{13}C at 125 MHz. Chemical shifts (δ) are given in ppm relative to TMS (tetramethylsilane) (δ 0.00) as the internal standard. The electron spray ionization mass spectra (HRESIMS and HRESIMS/MS) were acquired in positive ion mode and recorded on a quadrupole-time of flight instrument (UltrOTOF-Q, Bruker Daltonics, Billerica, MA). The conditions were: capillary voltage of 3400 V, dry gas temperature of 180 °C, dry gas flow of 4 L h^{-1}, nitrogen as nebulizer gas and 10 mmol L^{-1} NaTFA (sodium trifluoroacetate) was used as the standard for internal and external calibration. For tandem mass spectrometry analysis (ESIMS/MS), nitrogen was used as the collision gas. Silica gel 60 (70-230 mesh) was used for column chromatography, aluminum precoated silica-gel plates (60 F_{254} Merck, 0.25 mm) were used for analytical thin layer chromatography (TLC), and glass precoated silica-gel plates (60 PF_{254} Merck, 1 mm) were used for preparative TLC. The spots were detected by spraying with Dragendorff's or *p*-anisaldehyde reagents, followed by heating.

Plant material

The ripe fruits of *S. caavurana* were collected in the Parque Estadual de Vila Rica do Espírito SAnto (PEVR: 23°55' S, 51°57' W), in the municipal district of Fênix (Paraná State, Brazil), in January 2004. A voucher specimen (No. 28280) was deposited at the Herbarium of the Botany Department from Universidade Federal do Paraná (UPCB-UFPR).

Extraction and isolation

The ripe fruits of *S. caavurana* were dried at 40 °C, crushed, pulverized (180.5 g) and successively extracted at room temperature with petrol (30-60 °C) (5 days) and ethanol (5 days), with the solvent removed every 24 h. The ethanolic extract was submitted to liquid-liquid partition with CH_2Cl_2 followed by *n*-butanol (*n*-but). Removal of the solvents under reduced pressure furnished 2.6 and 3.0 g of CH_2Cl_2 and *n*-but fractions, respectively, both revealing positive TLC Dragendorff's test. CH_2Cl_2 fraction was dissolved in 3% aqueous HCl and the acid liquid phase then extracted with $CHCl_3$ (3 × 20 mL). The organic fractions were combined, dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the neutral $CHCl_3$ fraction (947.0 mg). The remaining aqueous acid solution was adjusted to pH 10-12 with 37% aqueous NH_4OH followed by extraction with $CHCl_3$ (3 × 20 mL). The resulting organic fractions were treated as previously described to yield an alkaloid residue (122.5 mg), which was purified by preparative TLC eluted with EtOAc-MeOH 90:10 to yield **1** (6.6 mg). The neutral $CHCl_3$ fraction (947.0 mg) was subjected to silica-gel column chromatography, with gradient elution of CH_2Cl_2/EtOAc from 100:0 to 25:75, EtOAc/MeOH from 100:0 to 90:10 and MeOH, affording a total of 184 fractions (20 mL each), which were assembled in 18 subfractions according to their composition on TLC. Subfractions 10 (34.2 mg) and 9 (50.7 mg) were purified by preparative TLC eluted with CH_2Cl_2/MeOH 90:10 and CH_2Cl_2/MeOH 95:5, respectively, to yield **2** (5.0 mg) and **3** (2.5 mg).

Caavuranamide (**1**)

Yellowish powder; ^1H and ^{13}C NMR data given in Table 1; mp 115-117 ºC; $[\alpha]_D^{25}$ + 6.3 ($CHCl_3$; *c* 0.0027); IR (KBr) ν_{max}/cm^{-1} 3429, 2930, 2852, 2362, 2341, 1656, 1543, 1456, 1383, 1264, 1037, 973, 872, 750 and 668; HRESIMS *m/z* 443.3705 $[M + H]^+$ (calcd. for $C_{28}H_{46}N_2O_2 + H^+$, 443.6770).

4-Tomatiden-3-one (**2**)

Light-yellow amorphous powder; ^1H and ^{13}C NMR data given in Table 1; HRESIMS *m/z* 412.3320 $[M + H]^+$ (calcd. for $C_{27}H_{41}NO_2 + H^+$, 412.6338).

5α-Tomatidan-3-one (**3**)

Yellow amorphous powder; ^1H and ^{13}C NMR data given in Table 1; HRESIMS *m/z* 414.3443 $[M + H]^+$ (calcd. for $C_{27}H_{43}NO_2 + H^+$, 414.6496).

In vitro antimicrobial activity

The antimicrobial activity of the crude extracts and fractions were tested against nine microorganisms

(*Bacillus subtilis* ATCC 6051, *Escherichia coli* ATCC 11775, *Enterococcus faecium* CCT 5079, *Micrococcus luteus* ATCC 4698, *Pseudomonas aeruginosa* ATCC 13388, *Rhodococcus equi* ATCC 25729, *Staphylococcus aureus* ATCC 6538, *Salmonella choleraesuis* ATCC 10708 and *Staphylococcus epidermides* ATCC 12228). Compound **1** was tested against *E. coli, R. equi, S. aureus, S. epidermides* and *S. choleraesuis.*

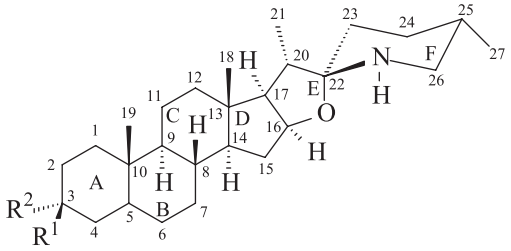
The bacteria strains were subcultured overnight at 36 °C in Nutrient Agar (Merck). Inoculum for the assays were prepared by diluting a scraped cell mass in 0.85% NaCl solution, adjusted to McFarland scale 0.5 and confirmed by spectrophotometer reading at 580 nm. Cell suspensions were finally diluted to 10^4 cfu mL^{-1} for use in the activity assays. Minimal inhibitory concentration (MIC) tests were carried out according to Eloff,[7] using Müller-Hinton broth on a tissue-culture test plate (96 wells). The stock solutions of crude extracts and fractions were diluted and transferred into the first well, and serial dilutions were made, so that concentrations in the range of 1.000-0.015 mg mL^{-1} were obtained. Chloramphenicol (Merck) was used as the reference antibiotic control in the range of 0.250-0.002 mg mL^{-1}. The inoculum was added to all wells, and the plates were incubated at 36 °C for 48 h. Each concentration was screened in triplicate. Antimicrobial activity was detected by adding 20 µL of 0.5% TTC (triphenyltetrazolium chloride, Merck) aqueous solution. MIC was defined as the lowest concentration of the sample that inhibited visible growth, as indicated by TTC staining (dead cells are not stained by TTC).

In vitro antiproliferative activity assay

Human tumor cell lines U251 (glioma, CNS), UACC-62 (melanoma), MCF-7 (breast), NCI-H460 (lung, non-small cells), OVCAR-03 (ovarian), HT-29 (colon), 786-0 (renal), NCI-ADR/RES (ovarian expressing phenotype multiple drugs resistance) and K562 (leukemia) were kindly provided by National Cancer Institute (NCI, U. S. Department of Health and Human Services). Stock cultures were grown in medium containing 5 mL RPMI 1640 (Gibco-BRL) supplemented with 5% fetal bovine serum. Peniciline:streptomicine (1000 µg mL^{-1}:1000 UI mL^{-1}, 1 mL L^{-1}) was added to experimental cultures. Cells in 96 well plates (100 µL cells *per* well) were exposed to sample concentrations in DMSO/RPMI (0.25, 2.5, 25 and 250 µg mL^{-1}) at 37 °C, 5% of CO_2 in air for 48 h. Final DMSO concentration did not affect cell viability. Afterwards, cells were fixed with 50% trichloroacetic acid and cell proliferation determined by spectrophotometric quantification (540 nm) of cellular protein content using sulforhodamine B assay. Using the concentration-response curve for each cell line, TGI (concentration that produces total growth inhibition or cytostatic effect) was determined through non-linear regression analysis using software ORIGIN 7.5 (OriginLab Corporation).[8]

Results and Discussion

The ethanolic extract from the ripe fruits of *Solanum caavurana* afforded steroidal alkaloids **1**-**3** (Figure 1).



1 R^1 = NHCHO; R^2 = H
2 R^1 = R^2 = O; $\Delta^{4,5}$
3 R^1 = R^2 = O

Figure 1. Chemical constituents isolated from the ripe fruits of *Solanum caavurana*.

Caavuranamide (**1**) was isolated as a yellowish powder and gave a positive Dragendorff reagent test. Its molecular formula $C_{28}H_{46}N_2O_2$ was calculated from the HRESIMS quasi-molecular ion peak $[H + H]^+$ at *m/z* 443.3705. The HRESIMS/MS revealed two fragments at *m/z* 255.2139 and 300.2349 corresponding to a difference of 45.0210 Da, suggesting the loss of a formamide group (H_2N-CHO, calcd. 45.041 Da).

The decoupled ^{13}C NMR spectrum of **1** (Table 1) displayed 28 carbon signals, mainly in the sp^3 C field characteristic of steroidal alkaloids,[9] whereas DEPT-135 (distortionless enhancement by polarization transfer) analysis aided to attribute the presence of four methyl groups, one carbonyl (δ_C 160.3), eleven methylenes, nine methines (including one oximethine) and three quaternary carbons.

The carbinolic hydrogen H-16 (δ_H 4.14) was correlated with C-16 (δ_C 78.5) in the HSQC (heteronuclear single quantum correlation) spectrum, that also showed four methyl hydrogens at δ_H 0.82 (s), 0.83 (s), 0.86 (d, *J* 6.5 Hz) and 0.96 (d, *J* 6.5 Hz) correlated to carbons at δ_C 16.9 (C-18), 11.4 (C-19), 19.3 (C-27) and 15.8 (C-21), respectively, possessing characteristic chemical shifts for steroidal alkaloid methyl groups. The signals at δ_C 78.5 (C-16), 99.3 (C-22) and 50.2 (C-26) supported a spirosolane-type structure.[9] Through 2D NMR spectral data [HSQC, HMBC (heteronuclear multiple bond correlation) and NOESY (nuclear Overhauser effect spectroscopy)], the chemical

Table 1. ^{1}H and ^{13}C NMR spectral data[a] for compounds **1**-**3**

Position	**1**		**2**		**3**	
	δ_C	δ_H (J in Hz)[b]	δ_C	δ_H (J in Hz)[b]	δ_C	δ_H (J in Hz)[b]
1	32.7	1.02 (m), 1.72 (m)	35.7	1.72 (m), 2.02 (m)	38.5	2.08 (m), 1.38 (m)
2	32.1	1.68 (m), 1.25 (m)	33.9	2.41 (m), 2.44 (m)	38.1	2.11 (m), 2.10 (m)
3	47.6	3.86 (m)	199.6		212.0	
4	34.9	1.54 (m)	123.9	5.74 (s)	44.7	2.32 (m), 2.29 (m)
5	45.3	1.18 (m)	171.2		46.7	1.55 (m)
6	28.2	1.21 (m)	32.8	2.36 (m), 2.07 (m)	28.8	1.36 (m), 1.21 (m)
7	32.0	1.68 (m), 0.89 (m)	32.2	1.83 (m), 1.22 (m)	32.7	2.07 (m), 1.30 (m)
8	35.0	1.54 (m)	35.1	1.73 (m)	34.9	1.62 (m)
9	54.7	0.69 (m)	53.8	1.05 (m)	53.9	0.82 (m)
10	36.2		38.7		35.7	
11	20.9	1.28 (m), 1.54 (m)	20.8	1.46 (m), 1.54 (m)	21.2	2.11 (m), 1.57 (m)
12	40.2	1.13 (m), 1.71 (m)	39.8	1.16 (m), 1.75 (m)	40.1	1.17 (m), 1.21 (m)
13	40.9		40.7		40.9	
14	55.9	1.07 (m)	55.1	1.09 (m)	55.6	1.08 (m)
15	32.6	1.24 (m), 2.00 (m)	32.6	2.40 (m), 2.43 (m)	31.9	1.68 (m), 1.21 (m)
16	78.5	4.14 (m)	78.3	4.16 (q, 7.5)	78.4	4.14 (q, 7.5)
17	62.0	1.60 (m)	61.8	1.68 (m)	61.9	1.55 (m)
18	16.9	0.82 (s)	16.8	0.89 (s)	16.9	0.86 (s)
19	11.4	0.83 (s)	17.4	1.21 (s)	11.5	1.04 (s)
20	42.9	1.66 (m)	43.0	1.66 (m)	43.0	1.74 (m)
21	15.8	0.96 (d, 6.5)	15.9	0.98 (d, 6.5)	15.9	0.98 (d, 6.5)
22	99.3		99.4		99.1	
23	26.6	1.66 (m), 1.34 (m)	26.6	1.67 (m), 1.36 (m)	26.6	1.66 (m), 1.37 (m)
24	28.4	1.56 (m), 1.37 (m)	28.5	1.62 (m), 1.33 (m)	28.5	1.64 (m), 1.34 (m)
25	30.9	1.60 (m)	31.0	1.60 (m)	31.0	1.61 (m)
26	50.2	2.74 (m)	50.2	2.71 (m), 2.75 (m)	50.2	2.73 (m), 2.76 (m)
27	19.3	0.86 (d, 6.5)	19.3	0.88 (d, 6.5)	19.3	0.87 (d, 6.5)
C<u>H</u>O	160.3	8.12 (m)				
N<u>H</u>CHO		5.36 (d, 7.5)				

[a]Experiments were carried out at 500 MHz for ^{1}H and 125 MHz for ^{13}C in $CDCl_3$ and TMS as internal reference (δ 0.00 ppm); [b]assignments confirmed by DEPT-135, HSQC, HMBC and NOESY experiments.

shifts of all hydrogens, as well as its correlations, were fully established (Table 1).

The ^{1}H NMR spectrum revealed a signal at δ_H 8.12 (m, 1H) that was assigned to the formyl hydrogen of the formamide group, which existence was previously evidenced by HRESIMS analysis, in association with the presence of a downfield carbonyl group at δ_C 160.3. The existence of a hydrogen at δ_H 3.86 and the remaining broad low field signal at δ_H 5.36 (d, 1H, J 7.5 Hz) were assigned to H-3 and the formamide *N*-hydrogen, respectively, by analogy with solanopubamide A.[10]

The NOESY spectrum was used to confirm the proposed stereochemistry assignments made for caavuranamide **1** (Figure 2), as the *trans* junction of A/B ring and *cis* junction of D/E ring, as well as (25*S*)-22β*N*-spirosolane configuration (as observed for tomatidine)[9] and the orientation of 3β-*N*-formylamino group. A strong NOE (nuclear Overhauser effect) was observed between the

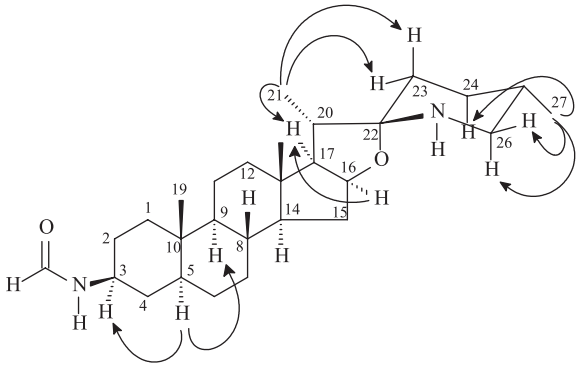


Figure 2. Relevant NOESY correlations observed for caavuranamide (**1**).

signal of C<u>H</u>$_3$-27 (δ_H 0.86) with the signal of H-26 (δ_H 2.74) and H-24$_{ax}$ (δ_H 1.37), indicating that CH_3-27 is in equatorial position. Strong correlations could also be observed among C<u>H</u>$_3$-21 (δ_H 0.96) with H-17 (δ_H 1.60), H-23 (δ_H 1.66 and 1.34) and H-16 (δ_H 4.14), suggesting

a *S* configuration for C-22 and the *cis* junction of the D/E ring. The axial orientation of H-5 (δ_H 1.18) was sustained by intense correlations with H-9$_{ax}$ (δ_H 0.69) and H-3$_{ax}$ (δ_H 3.86). This later information denotes that the substituent *N*-formylamino located in C-3 is found in 3β arrangement. The above findings supported the configuration (25*S*,22*S*)-3β-*N*-formylamino-5α-spirostane which is in agreement with solanopubamide A[10] and with data reported for (22*S*,25*S*)-3β-amino-5α-spirosolane.[11]

It is known that steroidal alkaloids isolated from the Solanaceae possess almost exclusively a 3-hydroxyl substituent or its glycosylated derivatives. The only report of a *N*-formyl steroidal alkaloid in the *Solanum*[10] genus indicated a solanidane-type skeleton. Caavuranamide [(22*S*,25*S*)-3β-*N*-formylamino-5α-spirosolane] (**1**) is the second report of a *N*-formyl steroidal alkaloid in this genus, and the first with a spirosolane-type skeleton.

Compounds **2** and **3** were identified on the basis of ^{1}H and ^{13}C NMR spectral data (Table 1) as 4-tomatiden-3-one and 5α-tomatidan-3-one, respectively. Although substance **2** has been obtained before by microbial[12] conversion of tomatidine, this is the first report of its isolation directly from plants. Compound **3** was previously isolated[13] from the roots of a hybrid plant between *Lycopersicon esculentum* Mill. and *L. hirsutum* Humb. et Bonpl. (Solanaceae). The ^{1}H and ^{13}C NMR data, as well as the assignments of chemical shifts for both compounds, were incomplete in the literature, and are now supported by DEPT-135 and HSQC experiments.

The crude extracts and fractions obtained from acid-base treatment were evaluated for antimicrobial (Table 2) and *in vitro* antiproliferative activities (Table 3). According to Table 2, the ethanolic extracts do not show significant activity for neither of tested microorganisms, whereas CH_2Cl_2 and *n*-but extracts, as well as those subfractions obtained from acid-base treatment, showed potent activity for *E. coli, M. luteus, R. equi, B. subtilis* and *E. faecium*, being similar and even in some cases, stronger than positive control chloramphenicol. Compound **1** (6.6 mg) exhibited activity (MIC 135 μmol L^{-1}) similar to chloramphenicol

Table 2. Antibacterial activity of extracts, fractions and compound **1** of ripe fruits of *S. caavurana*

Extract and fractions	MIC / (μg mL^{-1})								
	Microorganisms								
	B. subtilis	*E. coli*	*E. faecium*	*M. luteus*	*P. aeruginosa*	*R. equi*	*S. aureus*	*S. choleraesuis*	*S. epidermides*
EtOH extract	[b]	[b]	[b]	[b]	[b]	500	[b]	700	[b]
CH_2Cl_2 fraction	125	125	125	60	[b]	60	700	600	300
n-But fraction	125	60	125	60	[b]	60	500	400	250
Neutral $CHCl_3$ fraction	30	60	60	60	[b]	60	600	400	300
Alkaloid residue	60	60	60	60	[b]	30	600	200	250
Compounds	MIC / (μmol L^{-1})								
Caavuranamide (**1**)	[a]	[b]	[a]	[a]	[a]	135	1580	[b]	[b]
Chloramphenicol[c]	62	124	217	155	2630	124	62	186	0.124

[a]Not tested; [b]concentration > 1000 μg mL^{-1}; [c]positive control for bacteria.

Table 3. Antiproliferative activity of extracts and fractions of ripe fruits of *S. caavurana* against cancer cell lines

Extracts and fractions	TGI / (μg mL^{-1})									
	Tumor cell lines									
	U251	UACC-62	MCF-7	NCI-H460	OVCAR-3	HT-29	786-0	K562	NCI-ADR/RES	VERO
EtOH extract	[b]	2.11	93.06	[b]	84.49	60.90	60.62	[b]	102.13	[b]
CH_2Cl_2 fraction	75.53	[b]	142.48	[b]	139.66	115.39	94.97	[b]	*b*	[b]
n-But fraction	82.45	[b]	100.40	[b]	117.84	62.13	46.04	[b]	243.35	[b]
Neutral $CHCl_3$ fraction	90.47	8.09	57.17	100.27	100.27	73.67	80.63	[b]	82.37	[b]
Alkaloid residue	65.59	37.14	98.21	[b]	51.77	228.07	74.64	[b]	61.20	[b]
Doxorubicin[a]	3.24	0.15	10.49	> 25	5.62	> 25	3.73	> 25	> 25	> 25

[a]Positive control; [b]concentration > 250 mg mL^{-1}; U251 (glioma CNS), UACC-62 (melanoma), MCF-7 (breast), NCI-H460 (lung, non-small cells), OVCAR-3 (ovarian), HT-29 (colon), 786-0 (renal), K562 (leukemia), NCI-ADR/RES (ovarian expressing phenotype multiple drugs resistance) and VERO (renal, normal cells, green monkey); TGI: concentration (μg mL^{-1}) total growth inhibition.

(MIC 124 μmol L^{-1}) for *R. equi*, but it is less active than the alkaloid residue that furnished **1**.

For *in vitro* antiproliferative activity, the extracts and respective subfractions showed to be active for a wide range of human tumor cell lines, with the ethanolic extract and neutral $CHCl_3$ fraction presenting the strongest antiproliferative results for melanoma (UACC-62) with TGI values of 2.11 and 8.09 μg mL^{-1}, respectively.

Conclusions

The present phytochemical investigation of the ripe fruits of *S. caavurana* Vell. afforded a novel steroidal alkaloid with spirosolane-type skeleton, named as caavuranamide (**1**), together with the alkaloids 4-tomatiden-3-one (**2**) and 5-α-tomatidan-3-one (**3**). Compound (**1**) showed significant antibacterial activity (MIC 135 mol L^{-1}) for *R. equi*, similar to chloramphenicol (MIC 124 mol L^{-1}).

Supplementary Information

Supplementary information (Figure S1-S20) is available free of charge at http://jbcs.sbq.org.br as PDF file.

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