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Article

Indoquinoline Alkaloids from *Sida rhombifolia* (L.) (Malvaceae) and Antimicrobial Evaluation of Cryptolepinone Derivatives

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Considering the relevance of natural products to the development of new drugs, this study focuses on the species *Sida rhombifolia* (L.), Malvaceae, widely used as a traditional remedy in several countries. The species is used to treat several diseases such as fevers, skin diseases, stomach pain, diarrhea, gum infection, conjunctivitis, urinary infections and inflammation. Many researchers around the word have investigated its pharmacological potential, and many uses have been confirmed. In spite of that, the phytochemical composition of its extracts is still poorly investigated. This research aims to make advances on the understanding of the constituents of *S. rhombifolia* identifying its alkaloidal compounds using ultra-high performance liquid chromatography coupled to mass spectrometry (UPLC-QTOF-MS/MS). By analyzing its alkaloidal fraction, it was possible to identify: 11-cryptolepine carboxylic acid (**1**), cryptolepine (**2**), quindoline (**3**), 11-methoxyquidoline (**4**), quindolinone (**5**), cryptolepinone (**6**), and 11-quindoline methyl ester (**7**). The alkaloids **1** and **7** are being reported for the first time from *Sida* genus. Based on the antimicrobial potential of cryptolepinone-type alkaloids, we prepared by semi-synthesis two cryptolepinone derivatives: 10-methylcryptolepinone (**8**) and the unreported compound 10-ethylcryptolepinone (**9**). Both derivatives were tested against fungal and bacterial strains and 10-methylcryptolepinone (**8**) showed strong activity against *Cryptococcus neoformans*, *Candida albicans*, *Candida tropicalis*, *Aspergillus fumigatus* and *Aspergillus flavus.*

Keywords: *Sida rhombifolia*, alkaloids, cryptolepinone derivatives, *Cryptococcus neoformans*

Introduction

The historical use of natural products to treat diseases is considered one of the most relevant contribution of nature to the modern civilization.[1] Many plant extracts, compounds and its derivatives have been used against several human health problems such as cancer, malaria and other infections, cardiovascular and mental diseases, among others.[2]

Phytochemical and biological studies granted to the society most of the modern drugs available. Nowadays, the research on medicinal plants has been reinforced by instruments such as ultra-high-performance liquid chromatography and hyphenations with mass spectrometers which may achieve identification by fragmentation and

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perform highly sensitive quantification of metabolites in many complex samples.[3-5]

Aiming to contribute to the development of new drugs from natural products, in this study, we focused on the species *Sida rhombifolia* (L.), from Malvaceae family, widely used as traditional remedy in several countries. The plant is popularly known as '*mata-pasto*', '*granxuma*' and '*relógio*' in Brazil, as '*bala*' in India, and '*sidaguri*' in Indonesia.[6,7]

The literature cites the folk uses of the species, mainly its leaves and roots, to treat fevers, skin diseases, stomach pain, diarrhea, gum infection, conjunctivitis, cough, urinary infections, inflammation, hypertension and diabetes.[6-10] Pharmacological investigations have supported many of its popular uses.[7,11-15]

In spite of the relevance of the species, the phytochemical composition of its extracts is still poorly investigated. Regarding its chemical composition, the occurrence of steroids, alkaloids, flavonoids, coumarins and phaeophytins have been reported.[6,9,14,16,17]

The occurrence of alkaloids on *Sida* species has chemotaxonomic relevance to Malvaceae family, since it occurs almost exclusively in *Sida* genus.[18] Alkaloids have been reported from *Sida cordifolia*, *S. acuta*, *S. glutinosa*, *S. szechuensis*, *S. humilis*, *S. pilosa* and *S. rhombifolia*.[6,19-21] According to the current literature, indoquinoline alkaloids are predominant in the *Sida* genus and only six alkaloids have been identified from *S. rhombifolia*.[21]

Indoquinoline alkaloids and alkaloid-rich fractions of *Sida* species, such as *S. rhombifolia* and *S. cordifolia* have been previously associated with antimicrobial activity against bacteria and fungae.[22-25]

Based on the pharmacological relevance of *S. rhombifolia*, this work aimed to identify the compounds present in total alkaloids fraction (TAF) extracted from *S. rhombifolia* aerial parts. Considering that antimicrobial activity of extracts and compounds from *S. rhombifolia* have been investigated,[12,22,23,26-28] in the study we obtained and tested cryptolepinone derivatives in order to evaluate their antimicrobial activity.

Experimental

Plant material

Aerial parts of *Sida rhombifolia* L. were collected at Santa Rita City, Northeast of Brazil (SisGen AE1E834). The plant identification was carried out by Profa Dra Maria de Fátima Agra. A sample of the species has been kept at Herbário Prof Lauro Pires Xavier, Federal University of Paraiba, under the code Agra 7045.

Extraction procedure

The solvents and reagents were obtained from Merck (São Paulo, Brazil) and used without further purification. The plant material was oven dried (40 ºC) for 72 h. The material was ground yielding 5.5 kg of powder. The powder was solvent-extracted by maceration with ethanol 95% (EtOH) for 72 h. The obtained solution was evaporated under reduced pressure, resulting in the crude ethanol extract, coded as CEE (370.0 g). A sample of CEE (170.0 g) was used to obtain the total alkaloid fraction (TAF).

The protocol used for extraction and obtention of the TAF (1.8 g) was based on acid-base partitioning in separation funnel, following the method applied by Chaves *et al.*[6] The resulting TAF was analyzed by ultra-high performance liquid chromatography coupled to mass spectrometry (UPLC-QTOF-MS/MS) to identify the compounds in the sample.

Ultra-high performance liquid chromatography coupled to mass spectrometry (UPLC-QTOF-MS/MS)

The chromatography used for separation of the substances was carried out on the ACQUITY UPLC (Waters, Milford, MA, USA) system containing an autosampler (4 °C), injection volume of 5-10 µL and the Waters Acquity UPLC BEH C18 (2.1 mm × 50 mm, 1.7 µm). The eluents used were water with 0.1% formic acid (solvent A) and acetonitrile with 0.1% formic acid (solvent B) (Sigma, St. Louis, USA). The mobile phase flow rate was 0.4 mL min^{-1}. The elution was performed in the following gradient mode: from 0 to 5 min increasing from 5 to 10% of solvent B; and then from 5 to 9 min, increasing from 10 to 95% of solvent B.

The UPLC was connected to a XEVO-G2XSQTOF (Waters, Manchester, United Kingdom) mass spectrometer by an electrospray ionization interface (ESI). The mass analysis was carried out in positive mode on mass spectrometer (MS) coupled with an electrospray ionization source. It has been used a quadrupole time-of-flight tandem MS. The data was obtained from 50 to 1200 *m/z*. Additionally, MS^E analysis were performed, allowing the precursor and product ion to be detected and acquired in the same injection. A standard solution of leucine-enkephalin (0.2 ng mL^{-1}) was used for calibration. The general conditions of the experiment followed the method described by Silva *et al.*[29]

The TAF was analyzed on positive mode. The software Waters MassLynx v 4.1 was used for processing the data.

Preparation and purification of *S. rhombifolia* alkaloid derivatives

General procedures

Chromatographic columns were used to purify the compounds obtained by semi-synthesis. Neutral alumina (Sigma, St. Louis, USA) was used as stationary phase. For qualitative monitoring of the reaction progress, analytical thin-layer chromatography (TLC) was carried out with silica gel plates (Merck, São Paulo, Brazil, TLC silica gel 60 F254) and the spots were revealed using *p*-anisaldehyde or under UV light (254 and 366 nm) (Sigma-Aldrich, São Paulo, Brazil). The derivative compounds were identified by nuclear magnetic resonance (NMR) (Bruker BioSpin GmbH, using the frequency of 400 MHz for ^{1}H and 100 MHz for ^{13}C) in deutered chloroform ($CDCl_3$) (Cambridge Isotope Laboratories, Massachusetts, USA).

Obtention of 10-methylcryptolepinone (**8**)

To obtain the first derivative (compound **8**) it has been used 30 mg of TAF, 18 mg of crushed KOH and ethanol (10 mL). The mixture was kept under agitation up to completed dissolution of reagents (20 min). Then, it was added 1.0 mL of iodomethane (CH_3I). The reaction was monitored by TLC under UV light (254 nm) for 3 h. After that, the ethanol was evaporated and the obtained material was solubilized in ethyl acetate and partitioned with water.[30] Then, the organic layer was dehydrated with anhydrous Na_2SO_4, followed by filtration and evaporation in rotatory evaporator. The obtained sample was chromatographed packed with neutral alumina and solutions composed by hexane, ethyl acetate and methanol, increasing polarity, as mobile phase. From this procedure, it was possible to purify the compound **8** (13.4 mg). The compound was identified by ^{1}H and ^{13}C NMR (Table 1).

Obtention of 10-ethylcryptolepinone (**9**)

The reaction was carried out by adding 30 mg of TAF, 18 mg of KOH and ethanol (10 mL). The dissolution of reagents was similar to described for compound **8**. After that, it has been added to the reaction 1.0 mL of bromoethane (CH_3CH_2Br). The occurrence of the reaction was analyzed by TLC for 3 h and the subsequent procedures to dry and purify the compound **9** were similar to those described for compound **8**. After chromatographic column it was possible to purify the compound **9** (9.3 mg) that was identified by ^{1}H and ^{13}C NMR (Table 1).

Table 1. NMR data (^{1}H and ^{13}C) of compounds **6**, **8** and **9** (δ, 400 and 100 MHz, $CDCl_3$)

C	Cryptolepinone (**6**)		10-Methylcryptolepinone (**8**)		10-Ethylcryptolepinone (**9**)	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	8.44 (1H, dd, *J* 8.1 and 1.4 Hz)	149.90	8.67 (1H, dd, *J* 8.1 and 1.6 Hz)	126.82	8.67 (1H, dd, *J* 8.1 and 1.7 Hz)	126.89
2	7.35 (1H, dtd, *J* 8.1 Hz)	120.00	7.35 (1H, dtd, *J* 8.1 Hz)	121.11	7.35 (1H, dtd, *J* 8.1 Hz)	121.14
3	7.77 (1H, dtd, *J* 8.7 and 1.4 Hz)	130.70	7.70 (1H, dtd, *J* 8.4 and 1.6 Hz)	131.46	7.70 (1H, dtd, *J* 8.0 and 1.7 Hz)	131.47
4	7.95 (1H, dl, *J* 8.7 Hz)	115.10	7.55 (1H, dd, *J* 8.4 Hz)	114.35	7.55 (1H, d, *J* 8.0 Hz)	114.36
4a	–	139.10	–	140.38	–	140.40
N-5(CH_3)	4.36 (3H, s)	35.40	4.34 (3H, s)	36.19	4.35 (3H, s)	36.25
5a	-	129.80	–	131.43	–	131.73
6	8.38 (1H, dl, *J* 8.4 and 1.0 Hz)	115.70	8.23 (1H, dl, *J* 8.0 and 1.0 Hz)	122.81	8.23 (1H, d, *J* 8.0 and 1.0 Hz)	122.98
6a	–	122.40	–	115.90	–	116.13
7	7.20 (1H, dtd, *J* 8.4 Hz)	118.60	7.18 (1H, dtd, *J* 8.0 Hz)	119.40	7.22 (1H, dt, *J* 8.0 Hz)	119.32
8	7.47 (1H, dtd, *J* 8.3 and 1.0 Hz)	126.50	7.55 (1H, dt, *J* 8.6 and 1.0 Hz)	127.47	7.54 (1H, dt, *J* 8.3 and 1.0 Hz)	127.44
9	7.57 (1H, dl, *J* 8.3 Hz)	112.30	7.63 (1H, dl, *J* 8.6 Hz)	110.43	7.63 (1H, dl, *J* 8.3 Hz)	110.51
9a	–	138.20	–	140.34	–	139.33
N-10(CH_3)	–	–	4.41 (3H, s)	31.59	–	–
10a	–	123.00	–	123.10	–	122.54
11	–	166.40	–	169.90	–	169.30
11a	–	122.90	–	125.12	–	125.10
12	–	–	–	–	4.98 (2H, q, *J* 7.12)	39.68
13	–	–	–	–	1.46 (3H, t, *J* 7.12)	15.87
NH-10	11.89 (1H, s)	–	11.89 (1H, s)	–	–	–

Antimicrobial evaluation of compounds **8** and **9**

Test microorganisms

The used strains were granted by the MICOTECA (Mycology Laboratory of the Pharmaceutical Sciences Department, UFPB, João Pessoa, Brazil). It has been used the bacterial strains: *Staphylococcus aureus* ATCC-25923, *Pseudomonas aeruginosa* ATCC-25853, and *Escherichia coli* ATCC-18739; and the fungal strains: *Candida albicans* ATCC-60193, *Candida tropicalis* ATCC-13803, *Cryptococcus neoformans* LM-49, *Aspergillus fumigatus* ATCC-40640, and *Aspergillus flavus* ATCC-13013.

Determination of minimum inhibitory concentration (MIC)

The compounds **8** and **9** were solubilized in a solution of dimethyl sulfoxide (DMSO) at 5% (250 µL) and Tween 80 at 2% (100 µL*)*, with final volume completed with sterile distilled water up to 5 mL. The antimicrobial activity was determined by microdilution in a 96-well plate using liquid medium for cell culture (Techno Plastic Products, Switzerland), the positive controls were made with gentamicin (64 µg mL^{-1}) for inhibition of bacteria and amphotericin B (32 µg mL^{-1}) for antifungal activity.

For the inoculum preparation, the samples were collected from bacterial strains cultures in brain heart infusion medium (BHI) and for fungi sample from the Sabouraud agar dextrose medium (ASD) (Difco Laboratories, France).

For the assessment of biological activity, it has been used BHI broth and Roswell Park Memorial Institute (RPMI) 1640 medium with L-glutamine and no bicarbonate. The microorganism inoculums were prepared with sterile physiological solution (0.9%) and adjusted according to the Mc Farland scale to obtain 10^6 colony-forming units *per* mL (CFU mL^{-1}).[31,32]

To start the experiment, 100 µL of twice-concentrated RPMI/BHI broth was placed in the wells, then 100 µL of the test compound emulsions was transferred into the wells on the first line of the plate. From that, the concentrations of 1024 to 16 µg mL^{-1} were prepared by dilution.[33] Finally, 10 µL of strains suspensions were added and placed in bacterial stove at 35 ± 2 °C for 24-48 h (bacteria and yeast) or 28 ± 2 °C for 7 days for filamentous fungi.

After 24 h, for experiments with bacteria, 20 µL of 0.01% resazurin dye (INLAB, São Paulo, Brazil) was added as an indicator of bacterial growth.[34] The MIC for each tested compound is determined as the lowest concentration able to inhibiting the growth of the microorganism. The antimicrobial activities were interpreted according to the MIC, following the literature criteria: to values smaller than 500 µg mL^{-1} = strong activity; 500 to 1500 µg mL^{-1} = moderate activity and greater than 1500 µg mL^{-1} = weak activity or inactive substance.[35-38]

Results and Discussion

The base peak chromatograms are presented in Figure S1a (Supplementary Information (SI) section). The chromatogram showing the TAF alkaloidal profile was recorded at 290 nm (Figure S1b). The showed peaks were identified as indoquinoline-type alkaloids, based on their characteristic UV absorbances and accurate masses for both precursor compounds and their ions.[39,40] Indoquinoline alkaloids are an uncommon group of alkaloids, composed by two different fused ring systems, an indole and a quinoline.[41]

Two groups of compounds were identified: cryptolepine-like and quindoline-like compounds (Figure 1). The UV-Vis spectra showed commonly three maximum absorbances: 270-280, 311-367 and 406-429 nm, compatible with indoquinoline alkaloids.[39] The mass spectrometry data of the identified compounds are shown in Table 2.

Seven alkaloids have been identified and the particular fragmentation patterns are described as follows: tree peaks **1**, **2** and **6** showed the characteristic fragmentation of cryptolepine-type alkaloids. The compounds **2** and **6**, was identified as cryptolepine (*m/z* 233.1073, $[M + H]^+$) and cryptolepinone (*m/z* 249.1021, $[M + H]^+$) respectively, with fragmentation in accordance with literature.[41] The compounds **2** and **6** were compared to the standard samples.[6] Compound **1** exhibited a protonated ion $[M + H]^+$ at *m/z* 277.0970. Its product ion at *m/z* 259.0959 $[M + H - H_2O]^+$ and 231.0910 $[M + H - H_2O - CO]^+$, indicated a carboxylic acid functional group in the structure of cryptolepine. A fragment ion at *m/z* 204.0808 $[M + H - CO_2 - CH_3N]^+$ corroborated that, and compound **1** was identified as 11-cryptolepine carboxylic acid.[42,43]

Compound **3** was identified as the alkaloid quindoline and the substances **4**, **5**, and **7** were characterized as its derivatives.[40] The protonated ions $[M + H]^+$ at *m/z* 249.1027, 235.0865, and 277.0979 indicated the presence of the groups methoxy, ketone, and methyl ester attached to the quindoline structure, respectively. Therefore, the compounds were identified as 11-methoxyquindoline (**4**), quindolinone (**5**), and 11-quindoline methyl ester (**7**). The product ions at *m/z* 234.0790 $[M + H - CH_3]^+$, 218.0850 $[M + H - OCH_3]^+$ to 11-methoxyquindoline, *m/z* 206.0841 $[M + H - CO]^+$ to quindolinone, and *m/z* 245.0724 $[M + H - CH_3OH]^+$, 217.0772 $[M + H - CH_3OH - CO]^+$ to 11-quindoline methyl ester, supported the structural identification of these alkaloids.[6]

Table 2. Mass spectrometry data of alkaloidal fraction from of *Sida rhombifolia*

Compound	t_R / min	λ_{max} / nm	$[M + H]^+$	$[M + H]^+$ calculated	Error / ppm	MS[2] (*m/z*)	Identification
1	1.49	275, 367, 434	277.0970	277.0971	−0.36	259.0959 $[M + H - H_2O]^+$, 231.0910 $[M + H - H_2O - CO]^+$, 204.0808 $[M + H - CO_2 - CH_3N]^+$	cryptolepine carboxylic acid
2	2.31	280, 367, 429	233.1073	233.1073	0.00	218.0834 $[M + H - CH_3]^+$, 190.0644 $[M + H - N_2]^+$	cryptolepine[a]
3	2.69	277, 366, 422	219.0912	219.0916	−1.83	190.0647 $[M + H - HN_2]^+$	quindoline
4	3.38	279, 345	249.1027	249.1022	−2.00	234.0790 $[M + H - CH_3]^+$, 218.0850 $[M + H - OCH_3]^+$	methoxy-quindoline
5	4.24	269, 323, 396	235.0865	235.0865	0.00	206.0841 $[M + H - CO]^+$	quindolinone
6	5.56	272, 311, 406	249.1021	249.1021	0.00	234.0781 $[M + H - CH_3]^+$, 206.0824 $[M + H - CH_3 - CO]^+$	cryptolepinone[a]
7	8.03	273, 311	277.0979	277.0971	2.89	245.0724 $[M + H - CH_3OH]^+$, 217.0772 $[M + H - CH_3OH - CO]^+$	11-quindoline methyl ester

[a]Compared to standard sample previous isolated (Chaves *et al.*[6]); t_R: retention time.

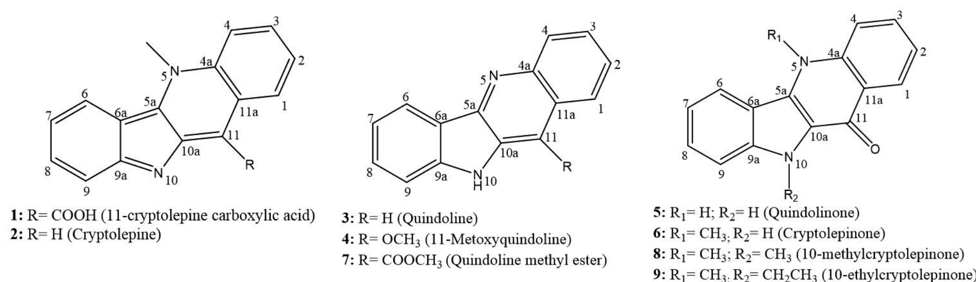

Figure 1. Structure of alkaloids from *S. rhombifolia* and cryptolepinone derivates.

This is the first report of 11-cryptolepine carboxylic acid (**1**) and 11-quindoline methyl ester (**7**) from species of *Sida* genus. The compounds cryptolepine and cryptolepinone, previously reported from *S. rhombifolia* were found to be the major alkaloids in TAF. Previous studies[22,23] have shown the antimicrobial activity of criptolepinone and other alkaloids from *S. rhombifolia*. The production of antimicrobial compounds may justify the use of *S. rhombifolia* against fever and infectious diseases.

In this study we produced cryptolepinone *N*-methy and *N*-ethyl derivatives in order to evaluate their antimicrobial activity. Alkaloidal tertiary amines, for example piperine, nicotine, and codeine, possess important functionalities and are present in several natural products and synthetically derivative pharmaceuticals, including antimicrobials, analgesics, antihistamines, local anesthetics, tricyclic antidepressants, among others.[44,45] Alkylation of indoquinoline alkaloids increases the electron density in the ring system due to the electron-donating effect of the alkyl group. This effect may potentialize the hydrophobic interactions that are relevant to many drugs to interact with their targets.[46]

The obtained derivatives, compounds **8** and **9** (Figure 1), were prepared by semi-synthesis from TAF and purified by chromatography column, as described in Experimental section. Based on the fact that cryptolepine and cryptolepinone were the major compounds in the TAF, we used the TAF itself as starting material for the semi-synthesis by alkylation under basic conditions. At this condition only the cryptolepinone structure reacted due to the presence of an acid proton in the N-10 of cryptolepinone.[47] The obtained derivatives were identified by ^1H and ^{13}C NMR. When compared to cryptolepinone NMR data, the spectra of compound **8** showed one additional methyl at δ_H 4.4 (3H, s) and δ_C 31.6 ppm. The mentioned data along with the absence of the singlet at δ_H 11.9 (1H, s), attributed to the N-10 proton of cryptolepinone,[14] led to identify the compound **8** as 10-methyl cryptolepinone. Its spectral data are supported by the literature.[30]

The NMR spectra of compound **9** showed a triplet at δ_H 1.5 (3H, t, J 7.11 Hz) coupling to a quartet at δ_H 4.9 (2H, q, J 1.0 Hz). Its ^{13}C NMR showed carbons at δ_C 15.9 and δ_C 39.7 ppm indicating the occurrence of an ethyl radical in the molecule. The NMR analysis led to identify the compound **9** as the unreported compound 10-ethylcryptolepinone.

Table 3. Minimum inhibitory concentration (MIC) of compounds **8** and **9** against bacterial and fungal strains

Compounds/control	MIC / (μg mL^{-1})							
	S. aureus ATCC-25923	*E. coli* ATCC-18739	*P. aeruginosa* ATCC-25853	*C. albicans* ATCC-60193	*C. tropicalis* ATCC-13803	*C. neoformans* LM-49	*A. fumigatus* ATCC-40640	*A. flavus* ATCC-13013
10-Methylcryptolepinone (**8**)	+	+	+	256	256	64	256	512
10-Ethylcryptolepinone (**9**)	+	+	+	512	512	64	512	1024
Control: medium	–	–	–	–	–	–	–	–
Control: microorganism	+	+	+	+	+	+	+	+
Control: anfotericin B	×	×	×	32	32	32	32	32
Control: gentamicin	–	–	–	×	×	×	×	×

(+): microorganism growth, (–): no microorganism growth, (×): not applicable.

The cryptolepinone derivatives were tested against bacterial and fungal strains. Both tested compounds showed strong antifungal activity against *C. neoformans* LM-49 (MIC = 64 μg mL^{-1}), presenting a MIC value close to the drug control amphotericin B (Table 3).

The compound 10-methylcryptolepinone (**8**) showed strong active against *Candida albicans* ATCC-60193 (MIC = 256 μg mL^{-1}), *Candida tropicalis* ATCC-13803 (MIC = 256 μg mL^{-1}), *Aspergillus fumigatus* ATCC-40640 (MIC = 256 μg mL^{-1}) and *Aspergillus flavus* ATCC-13013 (MIC = 512 μg mL^{-1}). The compound **9** was active against the same strains, but it has presented greater MIC than compound **8**. It has been previously suggested that the *N*-alkyl groups are relevant for antimicrobial activity.[48,49]

Better solubility can be an important task for the presented MIC differences.[50] The alkylation of cryptolepinone (log P 2.51) increased its liposolubility. The calculated log P for compound **8** was found to be 2.74, and the longer chain of ethyl radical on compound **9** increased its log P to 3.08. Many studies[23,42,43,51,52] have showed that the antimicrobial action of cryptolepine type alkaloids is developed by inhibiting the topoisomerase II causing lysis of susceptible cells. Other possible action mechanism mentioned to cryptolepine type alkaloids is its ability to intercalate into deoxyribonucleic acid (DNA) strucutre.[47,53] In any case, due the likely intracelular activity of the compounds some hydrosolubility may be determinant to pass through cell wall, avoid inespecific membrane retention and reach intracelullar targets to develop the antifungal activity.[54]

The demonstrated antifungal activity of cryptolepinone derivatives, along with the identification of previously showed antimicrobial compounds such as cryptolepin, quindoline and other *S. rhombifolia* metabolites indicates that the species is a prolific source of potentially active antimicrobial substances.[22,23]

Conclusions

This research led to identify indoquinoline alkaloids from *S. rhombifolia* aerial parts: 11-cryptolepine carboxylic acid, cryptolepine, quindoline, 11-methoxyquinoline, quindolinone, cryptolepinone and 11-quindoline methyl ester. The compounds 11-cryptolepine carboxylic acid and 11-quindoline methyl ester are being reported from the first time on *Sida* genus. *N*-Methyl and *N*-alkyl cryptolepinone derivatives showed strong antifungal activity against *Cryptococcus neoformans*, being potential candidates for drug development. Our findings along with previous studies contributed to demonstrate that *S. rhombifolia* is a prolific source of potentially active antimicrobial substances.[55,56]

Supplementary Information

Supplementary information (UV spectra, NMR spectra, and chromatograms) is available free of charge at http://jbcs.sbq.org.br as PDF file.

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Author Contributions

Oliveira, Fernandes, Teles, Chaves, Gomes, Silva, Freire, Cordeiro, Lima, Agra and Vanderlei de Souza were responsible for conceptualization, data curation, formal analysis, investigation and supervision; Silva, Freire, Lima, Agra and Vanderlei de Souza for funding acquisition and resources; Oliveira, Fernandes, Teles, Chaves, Gomes, Silva, Freire,

Cordeiro, Lima, Agra and Vanderlei de Souza for methodology; Oliveira and Vanderlei de Souza for project administration; Silva and Lima for software; Oliveira, Fernandes, Teles, Chaves, Gomes, Silva, Freire, Cordeiro, Lima, Agra and Vanderlei de Souza for validation; Oliveira, Fernandes, Teles, Chaves, Gomes, Silva, Freire, Cordeiro, Lima, Agra and Vanderlei de Souza for visualization; Oliveira, Fernandes, Teles, Chaves, Silva, Freire, Cordeiro, Lima, Agra and Vanderlei de Souza for writing - original draft; Oliveira, Fernandes, Teles, Chaves, Gomes, Silva, Freire, Cordeiro, Lima, Agra and Vanderlei de Souza for writing - review and editing.

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