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Germination and Growth of the Invasive Weeds *Bidens pilosa* and *Digitaria insularis* Regulated by Novel Kaurane Diterpene Amides

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MADB and RGP designed the research and performed the experiments. Author RGP conducted the data analysis. Authors QSG and BCV performed some experiments. All the authors contributed to improving the paper and approved the final manuscript.

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ABSTRACT

Novel kaurane ditepene monoamides were synthesized with good yields, directly from unprotected symmetrical aliphatic and aromatic diamines, hydroxylamines, dichlorophenylamines and *ent*-kaurenoic acid (**1**), using a modified protocol for monoacylation. These amides were tested against seed germination and growth of radicle and shoot of the weeds *Bidens pilosa* (Asteraceae), and *Digitaria insularis* (Poaceae). The concentrations used were 1.0 mM, 100.0, 10.0, and 1.0 μM. Propanil, the commercial herbicide, was used as internal reference. Monoamides from symmetrical aliphatic diamines were the most actives. Their log *P* (3.66-4.20) were closer to the value of 4.15, appropriate for herbicides. They were, in some cases, at the lower concentrations, more active

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than propanil. Generally, inhibitory effects were more significant on *B. pilosa* than on *D. insularis*. Monomide from ethylenediamine gave the best dose / response for inhibition growth of radicle and shoot of *B. pilosa*, with I_{50} 3.25 and 16.3 μM, respectively.

Keywords: Kaurane diterpenes amides; phytotoxicity; Bidens pilosa; Digitaria insularis.

1. INTRODUCTION

Global demand for food due to the increase of the world population has encouraged the maximization of agricultural production, which include principally the use of herbicides and pesticides. However, harmful effect of these chemicals to the environment and health is a major limitation on their use.

Natural products offer an unparalleled source of structural diversity and, with little overlap with modified synthetic compounds, are enable to provide substances with many biological activities [1]. Among them, phytotoxicity is of major importance, since these derivatives can be a source of potential herbicides. The continued utilization of commercial herbicides, generally not biodegradable, has led to the development of serious environmental pollution problems. Also, resistance is reported to almost all of them. Therefore, there is a growing need for new herbicides with safer toxicological and environmental profiles and new modes of action [2]. Natural products derivatives can provide new potential herbicides with broad structural diversity, with novel modes of action, with activity at low doses, selective, biodegradable, and have low environmental impact [3].

Kaurane diterpenoids are a very important class of natural products, widespread in the plant kingdom. They are intermediates in the biosynthesis of a number of plant and fungal metabolites, including gibberellins, well known plant growth hormones used in agriculture [1]. *Ent*-kaurenoic acid (**1**) (Fig. 1) present many biological activities and can be isolated with a very good yield (5.0-10.0%) from extracts of several species, such as *Annona squamosa* [4] and *Annona glabra* [5], edible fruits of Annonaceae, from essencial oil of *Copaifera langsdorffii*, Fabaceae [6], and *Sphagneticola trilobata*, Asteraceae [7]. Its ready availability from natural sources, as well the phytotoxicity showed by some derivatives on *Lactuca sativa* L. (lettuce) [8,9], has encouraged us to evaluate the effect of monoamides **2**-**14** (Fig. 1) on dicotyledonous *Bidens pilosa* (Asteraceae) (and monocotyledonous *Digitaria insularis* (Poaceae) weeds, present in both annual and perennial crops all over the world (Fig. 2). The commercial herbicide propanil [*N*-(3,4-dichlorophenyl) propanamide (**15**)], which contains an amide group (Fig. 1), was used as internal reference.

2. MATERIALS AND METHODS

2.1 General Experimental Instruments, Chromatographic Materials and Chemicals

Infrared (IR) spectra were recorded on a FT-IR, model MB102 from ABB Bomem (Quebec, Canada). Nuclear Magnetic Resonance (NMR) spectra (1D and 2D) were recorded in CD_3OD or $CDCl_3$, at room temperature, on a Bruker Avance DPX 200 MHz spectrometer (^{1}H-NMR, 200 MHz; ^{13}C-NMR, 50 MHz), from Bruker Analytic (Ettlingen, Germany). Electrospay Ionization Mass Spectrometry (ESI-MS) of amides **2**-**14** were performed using a IT-TOF (Shimadzu Corporation, Kyoto, Japan). Direct infusion analyses were conducted by simultaneously operating the electrospray source in the positive and negative modes and adjusting the nebulizer gas (N_2) to a flow rate of 1.5 L min^{-1}. The collision energy was 10 eV and cone voltage 5 kV. The capillary temperature was constant, at 200℃. An m/z range of 50–1000 was recorded. The samples were directly introduced into the ESI source by injecting 4 μL of sample via the LC autosampler. Water and methanol were employed as the mobile phases at a flow rate of 0.2 mL min^{-1}.

Seeds were incubated at 25℃ in a Fanem 347 CDG controlled-environment chamber (São Paulo, Brazil).

Silica gel Merck (Darmstadt, Germany) 100-200 and 200-425 mesh and Sephadex LH-20 was purchased from Sigma Chemicals Co (St. Louis, USA) and were used for column chromatography; silica gel Merck 60G (from Sigma) was used for thin-layer chromatography. Solvents of PA and HPLC grade were purchased from Vetec (Brazil) and Sigma, respectively, and reagents were purchased from Sigma-Aldrich (USA). Propanil was supplied by Dr. Karam, from

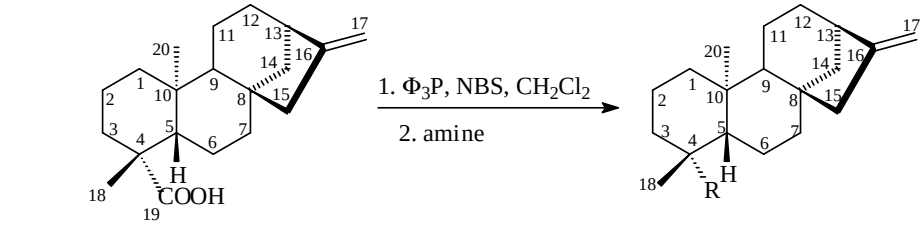
Embrapa Milho e Soja / Sete Lagoas, MG (Brazil).

2.2 Plant Specimen

Aerial parts of *S. trilobata*, Asteraceae (collected in Usiminas garden, Belo Horizonte, Minas Gerais, Brazil), were dryed at room temperature, grinded, and the powder was extracted with commercial ethanol for 15 days, also at room temperature. After removal of the solvent under reduced pressure, the ethanol extract was submitted to chromatography on a silica gel column with ascending polarities of hexane/ dichloromethane. *Ent*-kaur-16-en-19-oic acid (**1**) was isolated as a white solid with 9.6% yield from dichloromethane fractions.

2.3 General Synthetic Procedure for Amides 2-14

This methodology was adapted from [10]. A mixture of triphenylphosphine (527.0 mg, 2.0 mmol) and *ent*-kaurenoic acid (**1**, 302.0 mg, 1.0 mmol), in dichloromethane (10.0 mL) was cooled to 0-5℃. *N*-Bromosuccinimide (410.0 mg, 2.5 mmol) was added, the mixture was stirred for 15 min, and then the amine (1.0-7.0 mmol) was directly introduced. The temperature was kept during and after the amine addition at 0-5℃, for monoamines and aminoalcohols, and at ~ -20℃ (this temperature was obtained with dry ice in ethyl acetate), for diamines. The reaction times were 30 min for monoamines and aminoalcohols and 10 min for diamines. After removal of excess of amine and solvent, the residue was submitted to chromatography on a silica gel column, with ascending polarities of hexane / ethyl acetate/ methanol (for amides from monoamines) and to flash chromatography on silica gel (200-425 mesh) column with ethyl acetate / methanol 7:3 (for monoamides from diamines). Column chromatography on a Sephadex LH-20 (chloroform / methanol 6:4) column was used in final purification.



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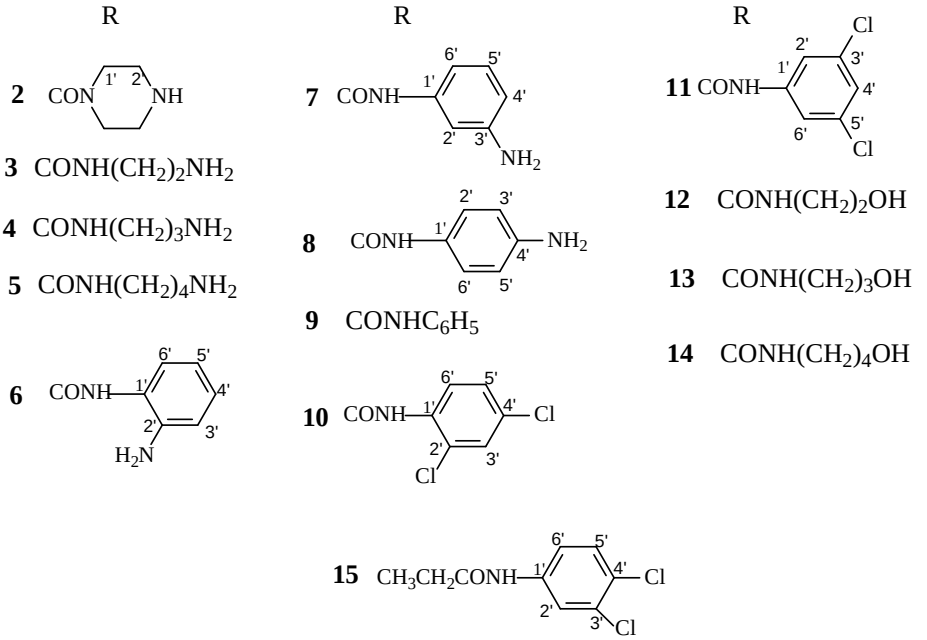

Fig. 1. Structures of *ent*-kaurenoic acid (1), amides 2-14 and propanil (15)

A

B

Fig. 2. A) *Bidens pilosa* plant and plantule; B) *Digitaria insularis* plant and plantule

2.4 Bioassay

This methodology was based on [9]. Seeds of *B. pilosa* and *D. insularis* were gently furnished by Dr. D. Karam, from Embrapa Milho e Soja, Sete Lagoas, MG, Brazil. Germination and growth were conducted with twenty seeds per 100 mm Petri dishes containing two 9.0 cm sheet of Whatman no. 1 filter paper as suport. Four replicates were used for each concentration (1.0 mM, 100.0, 10.0, and 1.0 μM). Dishes were covered with Parafilm to reduce evaporation and incubated in a Fanem 347 CDG controlled-environment chamber, with control of light (12 hours), at 25℃, during 7 days for *B. pilosa* and 14 days for *D. insularis*. After this time, the number of germinated seeds were counted (a seed was considered to be germinated when the radicle was at least 0.2 mm long), the radicle and shoots were streched out, photographed and their lengh were measured by using Image J software. The commercial herbicide propanyl was used as the internal reference.

2.5 Data Analysis

The effects on germination and growth are given in bar charts as percent differences from control, and consist of the differences (in cm) between mean values of seeds with tested compounds and mean values for control (seeds grown without addition of tested compounds) / mean values for control x 100. Thus, nul value represents control, positive values represent stimulation of the studied parameter and negative values represent inhibition. Data were evaluated using Student's *t*-tests and the differences between the experiment and control were significant at a value of $P \leq 0.05$.

2.6 Determination of I_{50} and Log *P* for Compounds 2-14

The concentrations required by compounds **2**-**14** for 50% growth inhibition (I_{50}) of radicle and shoot of the two weeds were determined by a logistic regression analysis. For I_{50} calculations, inhibition data versus concentrations were plotted into dose response curves, the concentrations expressed in logarithmic scale and inhibition data in percentages. From these curves, linear regressions were achieved and *R* values (regression determination coefficient) was near 1 (> 0.95). Log *P* for compounds **2**-**14** were calculated using the program Molinspiration [12].

Table 1. Spectroscopic data of compounds 2-14

Compound name (number). Yield %	Spectroscopic data
N-Piperazine-*ent*-caur-16-en-19-amide (**2**). 69%.	^{1}H NMR and ^{13}C NMR: Ref [9]. ESI-MS: m/z 371.3024 ([M+1]$^{+}$) (calc. for $C_{24}H_{39}N_2O$ 371.3062).
N-(Ethyl-2-amino)-*ent*-caur-16-en-19-amide (**3**). 71%.	^{1}H NMR and ^{13}C NMR: Ref [9]. ESI-MS: m/z 345.2865 ([M+1]$^{+}$) (calc. for $C_{22}H_{37}$ N_2O 345.2906).
N-(Propyl-3-amino)-*ent*-caur-16-en-19-amide (**4**). 76%.	^{1}H NMR and ^{13}C NMR: Ref [9]. ESI-MS: m/z 359.3039 ([M+1]$^{+}$) (calc. for $C_{23}H_{39}$ N_2O 359.3062).
N-(Butyl-4-amino)-*ent*-caur-16-en-19-amide (**5**). 78%.	^{1}H NMR and ^{13}C NMR: Ref [9]. ESI-MS: m/z 373.3197 ([M+1]$^{+}$) (calc. for $C_{24}H_{41}$ N_2O 373.3219).
N-*o*-Aminophenyl-*ent*-caur-16-en-19-amide (**6**). 65%.	^{1}H NMR : Table 2. ^{13}C NMR: Table 3. ESI-MS: m/z 393.2881 ([M+1]$^{+}$) (calc. for $C_{26}H_{37}N_2O$ 393.2906).
N-*m*-Aminophenyl-*ent*-caur-16-en-19-amide (**7**). 61%.	^{1}H NMR : Table 2. ^{13}C NMR: Table 3. ESI-MS: m/z 393.2905 ([M+1]$^{+}$) (calc. for $C_{26}H_{37}N_2O$ 393.2906).
N-*p*-Aminophenyl-*ent*-caur-16-en-19-amide (**8**). 71%.	^{1}H NMR : Table 2. ^{13}C NMR: Table 3. ESI-MS: m/z 393.2887 ([M+1]$^{+}$) (calc. for $C_{26}H_{37}N_2O$ 393.2906).
N-Aminophenyl-*ent*-caur-16-en-19-amide (**9**). 75%.	^{1}H NMR and ^{13}C NMR: Ref [9]. ESI-MS: m/z 378.2754 ([M+1]$^{+}$) (calc. for $C_{26}H_{36}$ NO 378.2797).
N-(2,4-Dichlorophenyl)-*ent*-caur-16-en-19-amide (**10**). 60%.	^{1}H NMR : Table 2. ^{13}C NMR: Table 3. ESI-MS: m/z 446.1953 ([M+1]$^{+}$) (calc. for $C_{26}H_{34}NOCl_2$ 446.2017).
N-(3,5-Dichlorophenyl)-*ent*-caur-16-en-19-amide (**11**). 62%.	^{1}H NMR : Table 2. ^{13}C NMR: Table 3. ESI-MS: m/z 446.2015 ([M+1]$^{+}$) (calc. for $C_{26}H_{34}NOCl_2$ 446.2017).
N-(Ethyl-2-hydroxy)-*ent*-caur-16-en-19-amide *N*-(Ethyl-2-hydroxy)-*ent*-caur-16-en-19-amide (**12**). 78%.	^{1}H NMR : Table 2. ^{13}C NMR: Table 3. ESI-MS: m/z 346.2705 ([M+1]$^{+}$) (calc. for $C_{22}H_{36}NO_2$ 346.2746).
N-(Propyl-2-hydroxy)-*ent*-caur-16-en-19-amide (**13**). 77%.	^{1}H NMR : Table 2. ^{13}C NMR: Table 3. ESI-MS: m/z 360.2889 ([M+1]$^{+}$) (calc. for $C_{23}H_{38}NO_2$ 360.2903).
N-(Butyl-2-hydroxy)-*ent*-caur-16-en-19-amide (**14**). 70%.	^{1}H NMR : Table 2. ^{13}C NMR: Table 3. ESI-MS: m/z 374.3017 ([M+1]$^{+}$) (calc. for $C_{24}H_{40}NO_2$ 374.3059).

Table 2. ^{1}H-NMR (200 MHz) chemical shift values (δ) for diterpenes amides from kaurenoic acid (1)

H	6*	7*	8*	10**	11**	12**	13**	14**
H-13	2.64 (bs, 1H)	2.63 (bs, 1H)	2.63 (bs, 1H)	2.63 (bs, 1H)	2.63 (bs, 1H)	2.64 (bs, 1H)	2.64 (bs, 1H)	2.63 (bs, 1H)
H-17$_a$	4.75 (bs, 1H)	4.74 (bs, 1H)	4.74 (bs, 1H)	4.74 (bs, 1H)	4.74 (bs, 1H)	4.74 (bs, 1H)	4.74 (bs, 1H)	4.74 (bs, 1H)
H-17$_b$	4.80 (bs, 1H)	4.80 (bs, 1H)	4.80 (bs, 1H)	4.80 (bs, 1H)	4.80 (bs, 1H)	4.79 (bs, 1H)	4.80 (bs, 1H)	4.79 (bs, 1H)
H-18	1.29 (s, 3H)	1.29 (s, 3H)	1.29 (s, 3H)	1.30 (s, 3H)	1.30 (s, 3H)	1.18 (s, 3H)	1.18 (s, 3H)	1.15 (s, 3H)
H-20	0.95 (s, 3H)	0.95 (s, 3H)	0.97 (s, 3H)	0.94(s, 3H)	0.94 (s, 3H)	0.93 (s, 3H)	0.93(s, 3H)	0.91(s, 3H)
H-1'	#	#	#	#	#	3.42 (bs, 2H)	3.41 (q, *J* = 5.6, 2H)	3.26 (bs, 2H)
H-2'	#	7.20-7.26 (m, 1H)	7.20-7.26 (m, 2H)	#	7.47 (s, 1H)	3.73 (bs, 2H)	1.80 (m, 2H)	1.45-1.69 (m, 2H)
H-3'	6.77-6.82 (m, 1H)	#	6.65 (bd, *J* = 8.6, 2H)	7.39 (s, 1H)	#	#	3.63 (bt, *J* = 5.4, 2H)	1.45-1.69 (m, 2H)
H-4'	7.06 (bt, *J* = 7.6, 1H)	6.64 (d, *J* = 7.8, 1H)	#	#	1H)	#	#	3.39 (bs, 2H)
H-5'	6.77-6.82 (m, 1H)	7.08 (t, *J* = 7.8, 1H)	#	7.24 (d, *J* = 9.2, 1H)	#	#	#	#
H-6'	7.16 (bd, *J* = 7.4, 1H)	6.45 (d, *J* = 7.6, 1H)	#	8.34 (d, *J* = 8.8, 1H)	7.47 (s,1H)	#	#	#
NH	7.32 (bs, 1H)	superimposed to H-2'	#	7.87 (s, 1H)	7.29(bs,1H)	6.14 (m, 1H)	6.04 (m, 1H)	5.8 (m, 1H)

*Solvent: *$CDCl_3$; **CD_3OD; s=singlet; d=duplet; t=triplet; q=quartet; m=multiplet; bs=broad singlet; bd=broad duplet; bt=broad triplet*

Table 3. ^{13}C-NMR (50 MHz) chemical shift values (δ) for diterpenes amides from kaurenoic acid (1)

C	6*	7*	8*	10**	11**	12**	13**	14**
1	41.10	41.10	41.10	41.00	41.00	41.00	41.00	41.10
2	19.40	19.30	19.40	19.20	19.20	19.30	19.30	19.40
3	38.50	38.40	38.50	38.40	38.30	38.20	38.30	38.30
4	44.30	44.30	44.30	44.20	44.20	44.20	43.80	43.70
5	57.40	57.50	57.50	57.30	57.30	57.30	57.30	57.30
6	22.60	22.50	22.60	21.40	21.50	22.40	22.40	22.40
7	41.50	41.50	41.50	41.40	41.40	41.40	41.40	41.50
8	44.50	44.70	44.40	45.40	45.00	44.20	44.20	44.20
9	55.10	55.10	55.10	55.00	55.00	55.00	55.00	55.00
10	39.60	39.70	39.60	39.90	39.80	39.60	39.60	39.60
11	18.50	18.50	18.50	18.40	18.40	18.40	18.40	18.40
12	33.00	33.00	33.00	33.00	33.00	33.00	33.00	33.00
13	43.80	43.70	43.80	43.70	43.70	43.70	43.70	43.70
14	39.70	39.60	39.70	39.70	39.60	39.60	39.50	39.20
15	48.90	48.80	48.90	49.20	49.20	48.80	48.80	49.90
16	155.70	155.70	155.80	155.60	155.50	155.80	155.80	155.80
17	103.10	103.10	103.10	103.10	103.30	103.00	103.00	103.00
18	30.90	29.80	29.90	29.80	29.60	30.00	30.40	30.10
19	176.00	175.30	175.00	175.50	175.60	178.70	178.50	177.10
20	16.20	15.80	15.80	15.40	15.40	15.60	15.80	15.80
1'	124.90	139.00	129.30	133.80	133.80	42.60	36.20	48.10
2'	140.80	107.20	122.50	128.60	118.20	62.70	32.30	26.00
3'	118.40	146.80	115.50	127.80	135.20	#	59.50	29.90
4'	127.0	110.2	143.25	134.70	123.90	#	#	62.30
5'	119.7	129.7	115.45	127.80	135.20	#	#	#
2	19.40	19.30	19.40	19.20	19.20	19.30	19.30	19.40

*Solvent: *$CDCl_3$; **CD_3OD*

3. RESULTS AND DISCUSSION

3.1 Synthesis of Monoamides

Monoamides **2**-**14** (Fig. 1) were obtained from reaction of *ent*-kaurenoic acid (**1**) with aliphatic symmetrical diamines, *o*-, *m*-, and *p*-aromatic diamines, dichlorophenylamines, and hydroxylamines. The intermediate acid halide was prepared using triphenylphosphine and N-bromosuccinimide. The neutral medium is important in order to avoid acid addition on exocyclic double bond of kaurene skeleton. Yields of monoamides were in the range of 61-78%, by careful control of reaction conditions, principally temperature and time. This result is an important achievement, since synthesis of monoamides from diamines (without previous protection of one of the two amine groups) and carboxylic acid derivatives has been very problematic, due to the competition with bis-amidation.

Monoamides **2**-**5**, and **9** were previously synthesized and were evaluated on germination, radicle and shoot growth of lettuce [9]. Amides **6**-**8** and **10**-**11**, **13**-**14** (Fig. 1) are described here for the first time, to the best of our knowledge. Synthesis of amide **12** is reported [11]; however, the phytotoxic activity described here is inedit for all compounds. These amides were tested against germination, radicle and shoot growth of *B. pilosa* and *D. insularis*. Both species are the most infesting weeds in orchards, pastures and cultures of rice, soybeen, and cotton. Propanil (**15**, Fig. 1), the internal reference, is one of the world's most widely used contact herbicides. ^{1}H-MNR and ^{13}C-MNR data for novel amides **6**-**8** and **10**-**14** are listed in Table 2 and Table 3, respectively.

3.2 Bioactive Profiles

The results observed for amides **2**-**14** on radical and shoot growth and germination of *B. pilosa* and *D. insularis* are showed in Fig. 3 and Fig. 4,

respectively. The inhibition increased with increasing concentrations for all compounds. At 1 mM, amides **2**-**14** inhibited almost 100% of radicle and shoot growth of both weeds, principally *B. pilosa* (Fig. 3). The most active compounds on both weeds, in a general way, were the monoamides from ethylenediamine (**3**) and and propylenediamine (**4**), and radicle growth was most affected than shoot growth. The first compound inhibited ~30% of radicle growth of *B. pilosa* at 1 μM and shoot growth of about 80%, 60%, and 40% at the concentrations of 100, 10 and 1 μM, respectively. In both cases **3** showed more activity than propanil. Monoamides **6**-**8**, from aromatic symmetrical diamines, affected less shoot than radicle growth of *D. insularis* in all concentrations (Fig. 4). Compound **8** presented ~50% inhibition of shoot growth of *B. pilosa* at 1 μM, more active than propanil (Fig. 3). The presence of chlorine atoms on aromatic ring of amides **10** and **11** increased their inhibitory effect, compared to amide **9**, from aniline. On radicle growth of *B. pilosa*, the inhibition of amide from 3,5-dichloroaniline (**11**) reached ~80%, at 100 μM. Interestingly, amide **10**, with the same chlorine substitution pattern as propanil (**15**) and the herbicide 2,4-D, was slightly less inhibitory than amide **11**, in concentrations lower than 1 mM (Fig. 3). Monoamides **12**-**13** were good radicle growth inhibitors of both weeds, principally *B. pilosa*, at 1 mM and 100 μM (Fig. 3). Germination of *B. pilosa* (Fig. 3) was almost completely inhibited for all compounds at 1 mM, which was not the case for *D. insularis* (Fig. 4): only compounds **2**-**5** and propanil inhibited 100% germination of *D. insularis*, at this concentration. On germination of *B. pilosa*, **3** and **12** showed better inhibitory results than propanil at 10 and 1 μM, respectively.

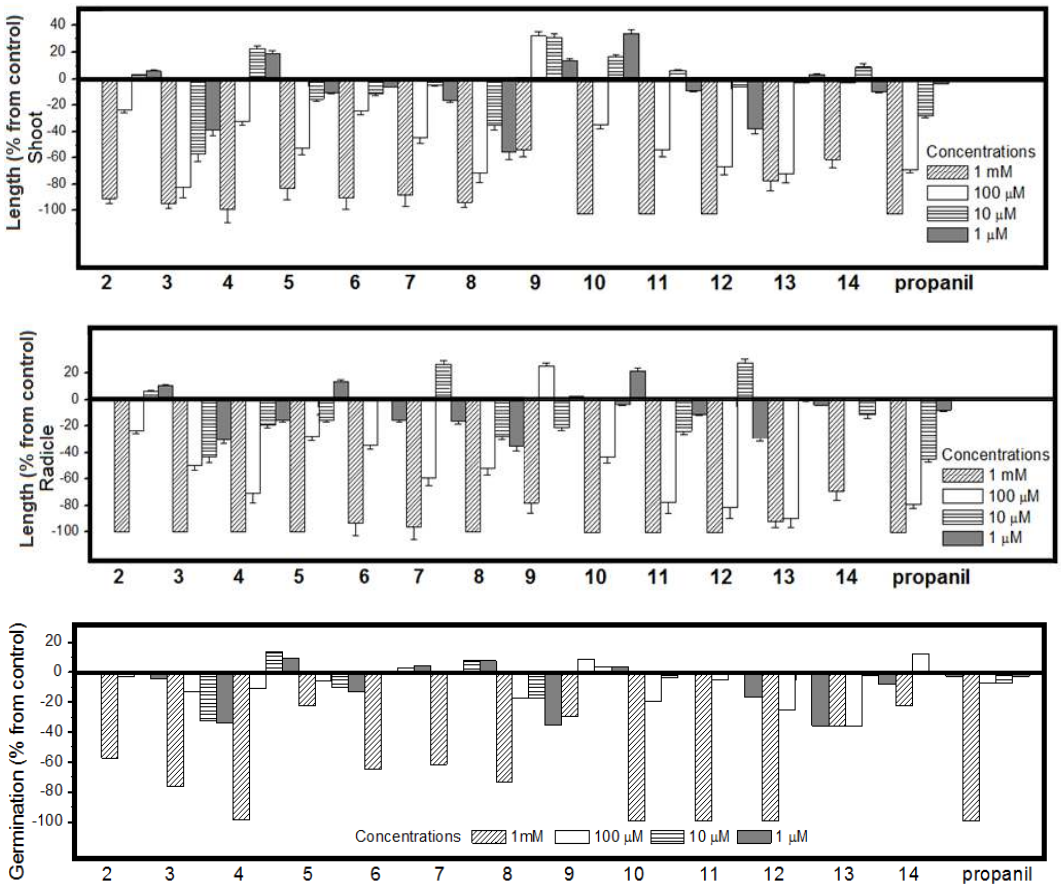

Fig. 3. Effect of amides 2-14 and propanil on shoot and radicle length, and germination of *B. pilosa*. Values are presented as percentage differences from the control, zero representing an observed value identical to the control, a positive value representing stimulation and a negative value representing inhibition

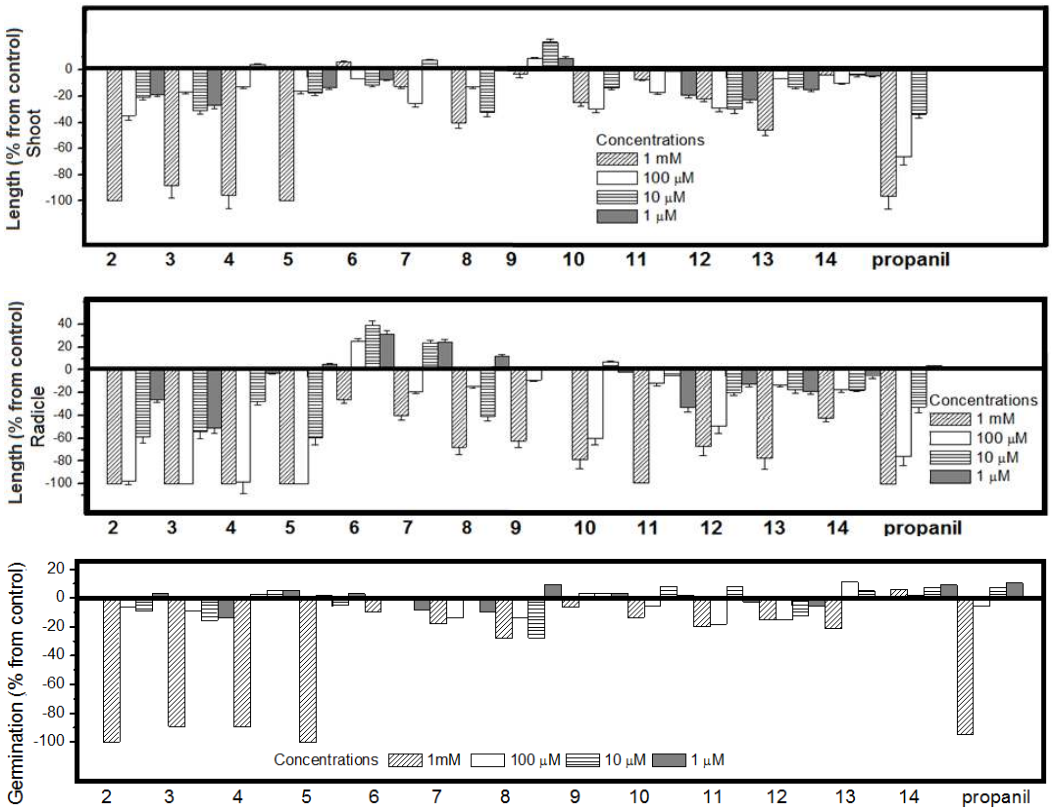

Fig. 4. Effect of amides 2-14 and propanil on shoot and radicle length, and germination of *D. insularis*. Values are presented as percentage differences from the control, zero representing an observed value identical to the control, a positive value representing stimulation and a negative value representing inhibition

The concentrations required by compounds **2**-**14** for 50% growth inhibition (I_{50}) of radicle and shoot of the two weeds were determined by a logistic regression analysis. The best relations dose/response were observed for compound **2**, from piperazine, which showed I_{50} values of 8.71 and 22.5 µM for radicle and shoot growth of *D. insularis*, respectively, and I_{50} values of 91.4 and 72.4 µM for radicle and shoot growth of *B. pilosa*, respectively. Compound **3**, from ethylenediamine, also gave a good dose/response for inhibition growth of radicle and shoot of *B. pilosa*, with I_{50} 3.25 and 16.3 µM, respectively (Fig. 5).

Lipinski's Rule of five (Ro5) [13] is considered to be the reference in defining physicochemical and structural properties profiles for optimal bioavailability of drug and agrochemical candidates. In this study, the structures of over 2000 pharmaceuticals were analyzed in terms of molecular mass, calculated log *P* (the logarithm of the octanol/water partition coefficient), number of hydrogen-bond donors and number of hydrogen-bond acceptors. Molecules that would obey these Rules should exert acceptable solubility and cell permeability properties. According to [13], log *P* limit 4.15 is appropriate for herbicides. As showed in Table 4, mlog *P* values (calculated from the program Molinspiration [12]) for monoamides from symmetrical aliphatic diamines **2**-**5** (log *P* 3.66-4.20) were closer to this value above and thus presented the best inhibitory effect, in a general way. Amides **6**-**8**, from symmetrical aromatic diamines were more lipophilic than the former ones (log *P* 5.28-5.30), probably due to the aromatic ring. The presence of chlorine in the aromatic ring increases lipophilicity since amides **10** and **11** presented log *P* (7.51 for both) higher than that of amide **9** (log *P* 6.22), from aniline. Monoamides **12**-**14** showed log *P* values slightly above those observed for amides **2**-**5** (log *P* 4.22-4.77), this result being probably related with the number of hydrogen-donor sites. It was also observed that the lipophilicity enhanced with the carbon chain length.

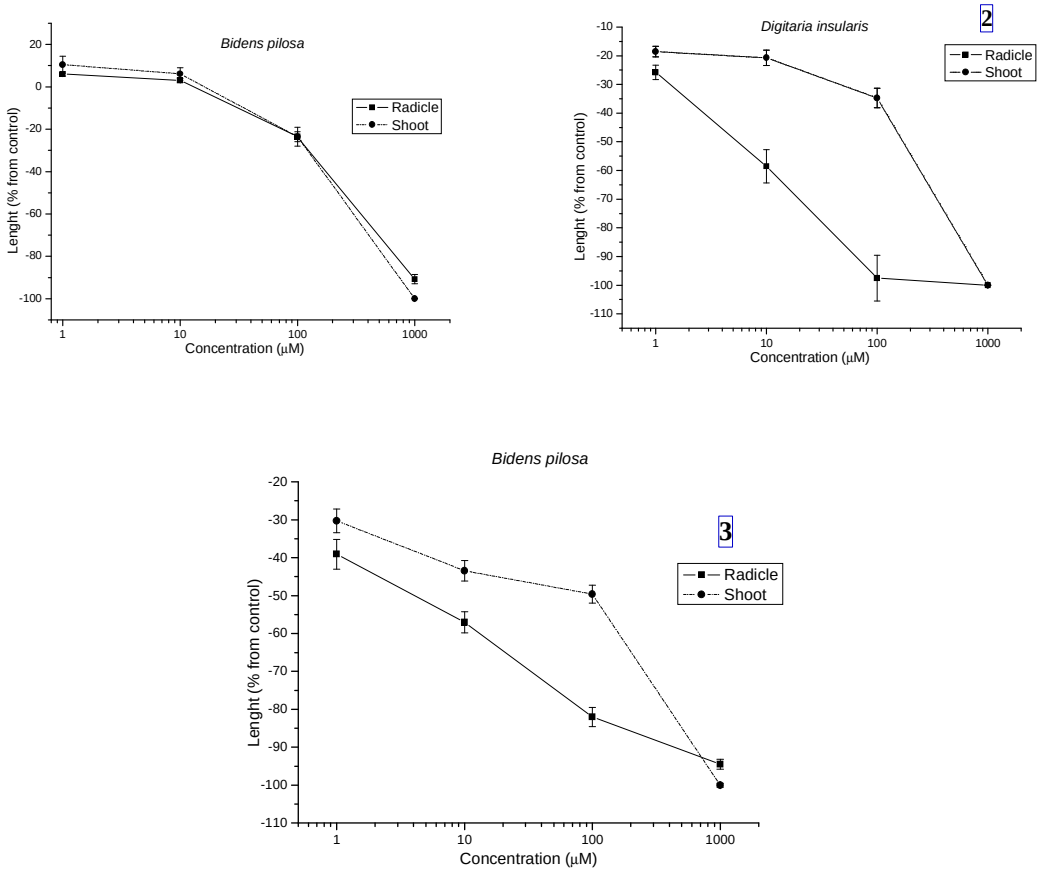

Fig. 5. Effects of compounds 2 and 3 on the shoot and radicle growth of *B. pilosa* and *D. insularis*. Means ±SE from four independent experiments with 20 plants for each dtermination are shown

Table 4. The log *P* values of amides 2-14

Compound	Log *P*	Compound	Log *P*
2	4.07	9	6.22
3	3.66	10	7.51
4	3.93	11	7.51
5	4.20	12	4.22
6	5.66	13	4.50
7	5.28	14	4.77
8	5.30	-	-

Values are the means of, at least, two independent determinations; errors are within ±20%

4. CONCLUSION

At 1 mM, the inhibitory activity of monoamides **2**-**14** and propanil (**15**) was generally analogous, approaching 100% in most cases. In a general way, the best inhibitory results were observed on *B. pilosa* and amides **3**, **4**, **8**, **12** and **13** were more active than propanil at concentrations lower than 1 mM. Also, the inhibitory activity of amides **2**-**14** was much more intense on radicle than on shoot growth of *D. insularis*.

Calculated log *P* for these amides confirmed the Lipinski's Rule of 5, and amides **2**-**5**, the most active on both weeds, presented log *P* values closer than the value establish in [13] for herbicides.

The concentrations required for 50% growth inhibition (I_{50}) for radicle and shoot growth of *B. pilosa* presented the best results (3.25 and 16.3 µM, respectively)

In conclusion, the high levels of inhibitory activity showed by these monoamides (more active than the commercially herbicide amide propanil at the lower concentrations) on germination and growth

control of two important economical weeds, suggest that they might be leading compounds for new herbicides.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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