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Convolutamines I and J, antitrypanosomal alkaloids from the bryozoan *Amathia tortusa*

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ABSTRACT

Mass-directed isolation of the CH_2Cl_2/CH_3OH extract from the marine bryozoan *Amathia tortusa* resulted in the purification of two new brominated alkaloids, convolutamines I (**1**) and J (**2**). The structures of **1** and **2** were determined following spectroscopic data analysis. Both compounds were isolated during a drug discovery program aimed at identifying new antitrypanosomal leads from a prefractionated natural product library. Compounds **1** and **2** were shown to be active toward the parasite *Trypanosoma brucei brucei* with IC_{50} values of 1.1 and 13.7 μM, respectively. Preliminary toxicity profiling was also performed on both **1** and **2** using the human embryonic kidney cell line, HEK293. Compound **1** was shown to exhibit cytotoxicity against HEK293 with an IC_{50} of 22.0 μM whilst **2** was inactive at 41.0 μM.

1. Introduction

Over the past three decades natural product research on marine bryozoans has resulted in the identification of a number of secondary metabolites,[1] many of which have displayed antibacterial,[2,3] nematocidal,[4] and anticancer activity.[5–9] The most well-known bryozoan-derived compounds are the bryostatins, which are potent antineoplastic macrocyclic polyketides that have made clinical trials.[5–9] The majority of bryozoan metabolites isolated to date have been alkaloids,[1] such as the convolutamines,[4,10,11] euthyroideones,[12] amathaspiramides,[13] flustramines,[14–18] and lutamides.[19] We have incorporated these sessile invertebrates into our biota collection on account of them being a proven source of bioactive small molecules. The extracts from 95 marine bryozoans, from either Queensland (tropical) or Tasmanian (temperate) waters, were part of a larger prefractionated natural product library that was screened using a 384-well Alamar Blue™ based HTS assay to estimate *Trypanosoma brucei brucei* viability.[20] *T. b. brucei* has been utilized to initially identify active compounds for prospective development against Human African Trypanosomiasis (HAT).[21] HAT is a disease affecting many areas of Africa, which is caused by two subspecies of trypanosomes, *Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense*. *T. b. gambiense* causes the chronic form of the disease in Western and Central Africa whilst *T. b. rhodesiense* causes the acute form of the disease in Eastern and Southern Africa. Analysis of the HTS data identified one fraction derived from an *Amathia tortusa* sample that was active in the *T. b. brucei* viability assay and also displayed some selectivity (>10 times) against the HEK293 human embryonic kidney cell line. (+)-LRESIMS analysis of the active fraction identified a complex cluster of ions between *m*/*z* 467 and 477 that were believed to correspond to compound(s) responsible for the observed bioactivity. Subsequent mass-directed fractionation of the large-scale crude extract derived from *A. tortusa* afforded the new alkaloids, convolutamines I (**1**) and J (**2**) (Fig. 1). This Letter reports the isolation and structure elucidation of the new β-phenylethylamine-based alkaloids **1** and **2**. The antitrypanosomal activity of convolutamines I and J against *T. b. brucei* and their cytotoxicity towards HEK293 is also reported.

2. Results and discussion

The freeze-dried and ground bryozoan *A. tortusa*, was initially extracted with *n*-hexane, followed by CH_2Cl_2/CH_3OH (4:1), and finally CH_3OH. All CH_2Cl_2/CH_3OH extracts were combined and chromatographed using C_{18}-bonded silica HPLC (MeOH/H_2O/0.1% TFA) to yield convolutamines I (**1**, 2.3 mg, 0.046% dry wt) and J (**2**, 3.8 mg, 0.076% dry wt) (Fig. 1).

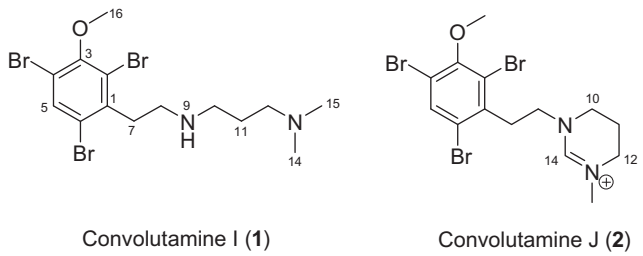

Figure 1. Chemical structures for convolutamines I (**1**) and J (**2**).

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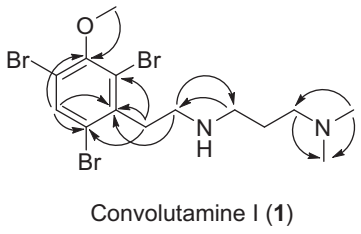
The TFA salt of convolutamine I (**1**) was isolated as a clear gum. The (+)-LRESIMS spectrum of **1** revealed a 1:3:3:1 cluster of ions at *m*/*z* 471/473/475/477 $[M\text{-}TFA+H]^+$, indicative of three bromine atoms. The molecular formula of the free base of **1** was determined to be $C_{14}H_{21}Br_3N_2O$ on the basis of the (+)-HRESIMS and NMR data (Table 1). The ^1H NMR spectra of **1** displayed an isolated aromatic proton at δ_H 8.05 (1H, s), a methoxyl signal at δ_H 3.79 (3H, s), five methylene resonances [δ_H 3.28 (2H, m); 3.11 (2H, m); 3.05 (2H, m); 3.00 (2H, m) and; 1.97 (2H, tt, J = 7.8, 7.8 Hz)] and a six-proton N-methyl signal at δ_H 2.78 (6H, s). The ^{13}C NMR spectrum of **1** showed 13 signals that resonated between δ_C 20.9 and 153.8. HSQC data analysis allowed all nonexchangeable protons to be assigned to their directly attached carbons; this permitted the identification of five quaternary carbons in **1**. Analysis of the gCOSY spectrum readily allowed the five methylene resonances to be assigned to $-CH_2CH_2-$[δ_H 3.28/3.11] and $-CH_2CH_2CH_2-$ [δ_H 3.05/1.97/3.11] substructures. The latter 1,3-disubstituted propane system was capped at one end with an N,N-dimethyl substituent based on strong ($^3J_{CH}$) HMBC correlations from the methylene at δ_H 3.11 to the N-methyl carbons at δ_C 42.4 (Fig. 2).

Additional support for the structure of **1** was provided by HMBC correlations from the N-CH_3 protons at δ_H 2.78 to the propane substructure carbons at δ_C 53.8 and 20.9. Linking of the 1,2-disubstituted ethane unit to the $-CH_2CH_2CH_2N(CH_3)_2$ chain through an N atom was also achieved through interpretation of HMBC correlations and NMR chemical shifts. Strong three-bond HMBC correlations were observed between the propane protons resonating at δ_H 3.05 to the ethane carbon at δ_C 48.3 and also from the ethane protons at δ_H 3.11 to the propane carbon at δ_C 48.3. The ^1H and ^{13}C chemical shifts for the methylene directly attached to the central N atom were consistent with literature NMR data for similar alkylated N bridged systems.[11,19] The remaining unassigned protons at δ_H 8.05 and 3.79 were associated with a 1,2,3,4,6-pentasubstituted benzene system. Both proton signals showed strong $^3J_{CH}$ correlations to the oxygenated aromatic carbon at δ_C 153.8 suggesting a *meta* orientation between the isolated aromatic methine proton (δ_H 8.05) and the methoxyl group (δ_H 3.79, δ_C 60.4). A further $^3J_{CH}$ correlation from δ_H 8.05 to the aromatic quaternary carbon at δ_C 136.6, which also exhibited HMBC correlations to both ethylene signals at δ_H 3.28 and 3.00 meant the diamine aliphatic chain was connected to the pentasubstituted benzenoid system. The three bromine atoms were attached to the remaining quaternary aromatic carbons resonating at δ_C 119.7, 117.0 and 121.6. This 2,4,6-tribromo-3-methoxy-benzene system assignment was further supported by comparison with NMR data reported for the previously isolated and related brominated bryozoan alkaloids.[11,19] With the substitution pattern of the aromatic ring determined, convolutamine I was assigned to structure **1**.



Convolutamine I (**1**)

Figure 2. Key HMBC correlations for convolutamine I (**1**).

The TFA salt of the minor metabolite, convolutamine J (**2**), was isolated as a clear gum. In a similar manner to **1** the (+)-LRESIMS spectrum of **2** revealed a 1:3:3:1 cluster of ions suggesting that this molecule also contained three bromine atoms. The molecular formula of the quaternary ammonium cation of **2** was determined to be $C_{14}H_{18}Br_3N_2O^+$ on the basis of the (+)-HRESIMS and NMR data (Table 1). The NMR data of **2** displayed a high degree of homology with **1**, and readily allowed a 2,4,6-tribromo-3-methoxy-phenethylamine substructure to be assigned for **2**. COSY and HSQC data analysis established that **2** also contained a $-CH_2CH_2CH_2-$ moiety, however, the ^1H [δ_H 3.40/2.01/3.30] and ^{13}C [δ_H 42.5/18.2/44.0] chemical shifts for this system suggested that the structural differences between **1** and **2** were associated with this portion of the molecule. The remaining unassigned ^1H chemical shifts included a downfield methine resonance at δ_H 8.27 and an N-methyl signal at δ_H 3.13, which were assigned to carbons at δ_H 153.2 and 41.2, respectively from the HSQC data. The HMBC spectrum revealed four correlations (δ_C 51.9, 44.0, 42.5, and 41.2) associated with the proton at δ_H 8.27, and two correlations (δ_C 153.2, 44.0) from the N-methyl signal at δ_H 3.13 (Fig. 3). The combined NMR data permitted the saturated *N*-methyl pyrimidine system to be assigned.

Strong ROESY correlations between δ_H 8.27/3.56, δ_H 8.27/3.13 and δ_H 3.13/3.30 confirmed the assignment of the six-membered ring (see Fig. 3). Hence convolutamine J was assigned to structure **2**.

Compounds **1** and **2** were evaluated for their ability to inhibit *T. b. brucei*. This sub species is related to *T. b. rhodesiense* and *T. b.*

Table 1
NMR data for convolutamines I (**1**) and J (**2**)[a]

	1			**2**		
Position	δ_C	δ_H mult. (J in Hz)	gHMBC	δ_C	δ_H mult. (J in Hz)	gHMBC
1	136.6			137.1		
2	121.6			121.6		
3	153.8			153.7		
4	117.0			116.7		
5	135.5	8.05 s	1, 2,[b] 3, 4, 6	135.3	8.06 s	1, 2,[b] 3, 4, 6
6	119.7			119.8		
7	33.5	3.28 m	1, 2, 6, 8	35.3	3.24 t (7.8)	1, 2, 6, 8
8	43.8	3.00 m	1, 7, 8	51.9	3.56 t (7.8)	1, 7, 10, 14
9						
10	43.8	3.05 m	10,[b] 11, 12	42.5	3.40 t (6.0)	11, 12, 14
11	20.9	1.97 tt (7.8, 7.8)	10, 12	18.2	2.01 tt (6.0, 6.0)	10, 12
12	53.8	3.11 m	10, 11, 14, 15	44.0	3.30 t (6.0)	10, 11, 14, 15
13						
14	42.4	2.78 s	11, 12, 15	153.2	8.27 br s	8, 10, 12, 15
15	42.4	2.78 s	11, 12, 14	41.2	3.13 s	12, 14
16	60.4	3.79 s	3	60.3	3.80 s	3

[a] Recorded in DMSO-d_6 at 30 °C.
[b] Weak correlation.

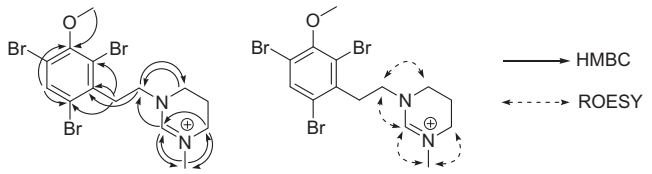


Figure 3. Key HMBC and ROESY correlations for convolutamine J (**2**).

gambiense, which cause the disease HAT. Convolutamine I (**1**) was shown to be the more active alkaloid towards *T. b. brucei,* with an IC_{50} value of 1.1 μM (Table 2). Convolutamine J (**2**) was shown to display an IC_{50} value of 13.7 μM. Preliminary toxicity profiling was also performed on both **1** and **2** using the human embryonic kidney cell line, HEK293. Compound **1** was shown to exhibit cytotoxicity against these cells with an IC_{50} of 22.0 μM whilst **2** was inactive at 41.0 μM.

The previously reported convolutamines A–H (**3**–**10**) (see Fig. 4) were all isolated from the bryozoan *Amathia convoluta,* and limited biological evaluations have been undertaken.[4,10,11] From what has been reported, convolutamines A (**3**), B (**4**) and D (**6**) exhibit moderate cytotoxicity against murine P388 lymphocytic leukemia cells with IC_{50} values ranging from 1.4 to 17.5 μg/mL,[10,11] while convolutamine F (**8**) weakly prevents cell division of fertilized sea urchin eggs with an IC_{50} of 81 μg/mL.[10,11] Convolutamine H (**10**) has been identified as an inhibitor (LD_{99} = 0.20 μg/mL) of the free-living larval stages of the parasitic nematode *Haemonchus contortus*, which is a pathogen of sheep and other ruminants.[4]

The in silico physicochemical profiling for compounds **1** and **2** is summarized in Table 2. Definitive structures of hits from natural product extract screening are not generally known until final structural elucidation. To hone in on more lead-like and drug-like molecules that could potentially progress to lead identification, the extracts from our biota samples were triaged through a process that includes an initial log *P* filter (the so-called 'Lord of the Rules')[22] followed by fractionation and, finally, MW determination of the components in the HTS hit fractions. While compounds **1** and **2** are too large to be considered leads, they are never-the-less well positioned in terms of log *P*, hydrogen bond acceptor count (HBA), hydrogen bond donor count (HBD),[23,24] polar surface area (PSA)[25] and rotatable bonds (RTB).[26] Interestingly, Leeson's analysis of the physicochemical properties considered essential for drug development found that antiinfectives had the most extreme property profiles of any therapy area.[27]

3. Conclusion

Mass-directed isolation of the CH_2Cl_2/CH_3OH extract from the Australian marine bryozoan, *A. tortusa*, resulted in the identification of two new brominated alkaloids, convolutamines I (**1**) and J (**2**), both of which exhibited antitrypanosomal activity. Compound **1** was shown to be most active towards the *T. b. brucei* parasite with an IC_{50} value of 1.1 μM. Low toxicity against the HEK293 cell line suggests that this structure class may be suitable for lead identification. The physiochemical properties for the convolutamines reported here suggests a medicinal chemistry effort that lowers MW and log *P* with a concomitant increase in binding and selectivity will improve the ligand efficiency[28] and contribute to the potential development of a new class of antitrypanosomal compounds. The data reported here, in conjunction with our previous publications on antitrypanosomal natural products,[29–32] provides further support for continued research into the discovery of new antiHAT lead molecules from nature.

4. Experimental

4.1. General methods

UV and IR spectra were recorded on a Jasco V650 UV/Vis spectrophotometer and a Bruker Tensor 27 spectrometer, respectively. NMR spectra were recorded at 30 °C on either a Varian 500 MHz Unity INOVA or 600 MHz NMR system spectrometer. The latter spectrometer was equipped with a triple resonance cold probe. The ^1H and ^{13}C chemical shifts were referenced to the proto-deutero solvent peaks for DMSO-d_6 at δ_H 2.49 and δ_C 39.5. LRESIMS were recorded on a Waters ZQ mass spectrometer. HRESIMS were recorded on a Bruker Daltonics Apex III 4.7e Fourier-transform mass spectrometer. A Waters 600 pump equipped with a Waters 996 PDA detector and a Waters 717 autosampler were used for HPLC. A ThermoElectron C_{18}-bonded silica Betasil 5 μm 143 Å column (21.2 × 150 mm) was used for semi-preparative HPLC separations. An Alltech stainless steel guard cartridge (10 × 30 mm) and end-capped Sepra C_{18}-bonded silica (Phenomenex) was used for preadsorption work. All solvents used for chromatography, UV, MS were Lab-Scan HPLC grade, and the H_2O was Millipore Milli-Q PF filtered. *T. b. brucei* BS427 cells were kindly supplied by Dr Achim Schnaufer (University of Edinburgh), whilst at the Seattle Biomedical Research Institute, USA. HEK293 cell lines were purchased from the American Tissue Culture Collection. The 384-well Falcon sterile tissue culture treated plates were obtained from Becton Dickinson (BD). Dulbecco's Modified Eagles Medium (DMEM), Roswell Park Memorial Institute 1640 (RPMI 1640) medium, DMEM:HAMS F12, sodium pyruvate, nonessential amino acids (NEAA), Alamar Blue, penicillin, streptomycin and Foetal Bovine Serum (FBS) were purchased from Invitrogen.

4.2. Biological material

The bryozoan, *A. tortusa*, was collected by trawling at a depth of 63 m in Bass Strait, Tasmania, Australia, on the 9th of February 2005. A voucher specimen (TAS00962) has been deposited with Aquenal Pty Ltd, Tasmania, Australia.

4.3. Extraction and isolation

The freeze-dried and ground bryozoan (5 g) was poured into a conical flask (1 L), *n*-hexane (125 mL) was added and the flask was shaken at 200 rpm for 2 h. The *n*-hexane extract was filtered under gravity then discarded. CH_2Cl_2/CH_3OH (4:1, 125 mL) was added to the de-fatted bryozoan in the conical flask and shaken at 200 rpm for 2 h. The resulting extract was filtered under gravity, and set aside. CH_3OH (125 mL) was added and the CH_3OH/bryozoan mixture was shaken for a further 2 h at 200 rpm. Following gravity

Table 2
Physicochemical and biological activity for compounds **1** and **2**

Compound	Physicochemical parameters[a]						IC_{50} ± SD (μM)		SI
	MW	Log *P*	HBA	HBD	PSA	RTB	*T. b. brucei*	HEK293	
1	473	4.1	3	1	24.5	8	1.1 ± 0.2	22.0 ± 0.2	18.3
2	470	3.9	2	0	15.5	4	13.7 ± 2.5	Inactive at 41.0 μM	NA

[a] In silico calculations performed on the free bases of **1** and quaternary ammonium cation of **2** using Pipeline Pilot version 6.1.5 software, MW = molecular weight (Da), HBA = H-bond acceptors, HBD = H-bond donors, PSA = polar surface area, RTB = No. rotatable bonds. SI = selectivity index NA = not applicable.

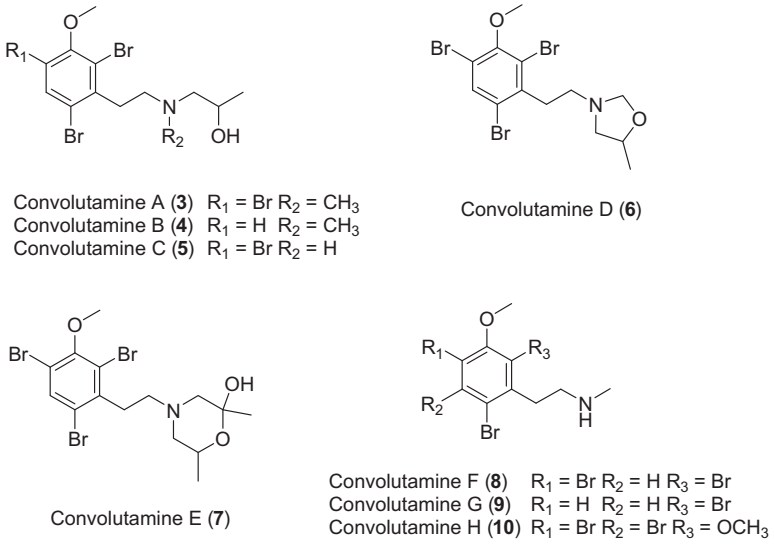


Figure 4. Chemical structures for convolutamines A–H (**3**–**10**).

filtration the biota was extracted with another volume of CH_3OH (125 mL), while being shaken at 200 rpm for 16 h. The CH_2Cl_2/CH_3OH (4:1) and CH_3OH extracts were all combined and dried down under reduced pressure to yield a brown solid (0.48 g). This extract was subsequently preadsorbed onto C_{18} bonded silica (1.0 g), then packed into a stainless steel cartridge (10 × 30 mm) and attached to a C_{18} semi-preparative HPLC column. Isocratic HPLC conditions of 90% H_2O (0.1% TFA)/10% CH_3OH (0.1% TFA) were initially employed for the first 10 min, then a linear gradient to CH_3OH (0.1% TFA) was run over 40 min, followed by isocratic conditions of CH_3OH (0.1% TFA) for a further 10 min, all at a flow rate of 9 mL/min with the Betasil C_{18} 5 μm column. Sixty fractions (60 × 1 min) were collected from time = 0 min then analyzed by (+)-LRESIMS. Fractions 37 and 39 contained the desired ion clusters at *m*/*z* 471/473/475/477 and 467/469/471/473, respectively. Subsequent lyophilization of each of these fractions yielded convolutamines I (**1**, 2.3 mg, 0.046% dry wt) and J (**2**, 3.8 mg, 0.076% dry wt).

4.3.1. TFA salt of convolutamine I (1)

Stable clear gum; UV (MeOH) λ_{max} (log ε) 214 (4.71), 227 sh (4.34), 291 (3.40) nm; IR ν_{max} (KBr) 1683, 1558, 1542, 1456, 1417, 1361, 1205, 1135 cm^{-1}; ^1H and ^{13}C NMR data [$(CH_3)_2SO$-d_6], see Table 1; (+)-LRESIMS *m*/*z* (rel. int.) 471 (33), 473 (100), 475 (100), 477 (33); (+)-HRESIMS *m*/*z* 470.9263 ($C_{14}H_{22}{}^{79}Br_3N_2O$ [M-TFA+H]$^+$ requires 470.9277).

4.3.2. TFA salt of convolutamine J (2)

Stable clear gum; UV (MeOH) λ_{max} (log ε) 214 (4.76), 227 sh (4.43), 287 (3.48) nm; IR ν_{max} (KBr) 1636, 1455, 1412, 1359, 1204, 1143 cm^{-1}; ^1H and ^{13}C NMR data [$(CH_3)_2SO$-d_6], see Table 1; (+)-LRESIMS *m*/*z* (rel. int.) 467 (33), 469 (100), 471 (100), 473 (33); (+)-HRESIMS *m*/*z* 466.8980 ($C_{14}H_{18}{}^{79}Br_3N_2O$ [M-TFA]$^+$ requires 466.8964).

4.4. *T. b. brucei* alamar blue viability assay

T. b. brucei cells were maintained in a log phase of growth in HMI-9 media,[33] by splitting cells at 24 or 48 h intervals. Cells were grown overnight to 1 × 10^6 cells/mL in three 25 cm^3 tissue culture flasks. Cells from a flask were diluted for the assay and inoculated into black clear bottom 384 well plates (BD, Franklin Lakes, NJ). The plates were then incubated for 24 h at 37 °C and 5% CO_2. Following incubation, the compounds dissolved in DMSO along with DMSO only for control wells, were prediluted 1:21 in HMI-9 medium without FCS using a Minitrack™ robotic liquid handler (Perkin Elmer, Meriden CT, USA). DMSO solution was added to cells as positive growth control while 2 mg/mL pentamidine (Sigma, St. Louis, Missouri) in DMSO was employed as a negative growth control. Five μL of the diluted compounds/controls were added to each plate. Plates were incubated for a further 48 h at 37 °C and 5% CO_2. Alamar Blue diluted in HMI-9 media + 10% FBS was added to each well to give a final assay concentration of 10%. The plates were then incubated for 2 h at 37 °C and 5% CO_2 then transferred to room temperature, protected from light, and incubated for a further 22 h. Wells were read at excitation 535 nm, emission 590 nm on a Victor II™ Wallac plate reader (Perkin Elmer, Meriden CT, USA). Compounds were screened in triplicate dose response *n* = 3. A separate control plate with serial dilutions of the reference compounds pentamidine, diminazene (Sigma) and puromycin (Calbiochem) in DMSO were included in each experimental replicate. The IC_{50} of each compound was calculated by plotting% inhibition (100% inhibition was equal to 2.3 μM final pentamidine) against log [compound] in the software package PRISM 4 graph pad (denoted IC_{50} by PRISM). The IC_{50} was the concentration of compound that was estimated to lead to 50% of growth; with the minimum and maximum of 0% growth (cells co-incubated with 2.3 μM pentamidine) and 100% growth (no compound addition). All experiments were performed in triplicate. IC_{50} values for known drug controls were 15.1 ± 2.1 μM for pentamidine and 70.1 ± 2.0 μM for diminazene. Pentamidine is a HAT registered drug and diminazene is a veterinary registered drug against *T. b. brucei*.

4.5. HEK293 cytotoxicity assay

HEK293 cells were maintained in log phase growth in 75 cm^2 tissue culture flasks in DMEM high glucose, 1% sodium pyruvate, 1% NEAA and 10% FBS. Cells were harvested and inoculated into black clear bottom 384-well plates at a cell density of 7.27 × 10^4 cells/mL and a volume of 55 μL per well, in DMEM high glucose, 1% sodium pyruvate, 1% NEAA and 10% FBS. The compounds dissolved in DMSO or DMSO only for control wells were pre-diluted 1:21 in DMEM high glucose, 1% sodium pyruvate, 1% NEAA without FBS using a Minitrack robotic liquid handler. Five microliters of the diluted samples were added to each plate to give a final DMSO concentration of 0.42% in the assay. Plates were incubated for 48 h at 37 °C and 5% CO_2. An Alamar Blue solution, diluted in DMEM high glucose, 1% sodium pyruvate,1% NEAA and

10% FBS was added to each well to give a final assay concentration of 10%. The plates were then incubated for 4 h at 37 °C, 5% CO_2 and incubated at room temperature protected from light for 20 h. Wells were read at excitation 535 nm, emission 590 nm on a Victor II™ Wallac plate reader (PerkinElmer, Waltham, USA). Compounds were screened in triplicate dose response, $n = 3$. A separate control plate with serial dilutions of the reference compounds pentamidine, diminazene (Sigma) and puromycin (Calbiochem) were included in each experimental replicate. The IC_{50} of each compound was calculated in the graph pad program PRISM as per the *T. b. brucei* assay. IC_{50} values for the known drug controls were 50% activity at 71 μM for pentamidine and no activity detected at 70 μM for diminazene.

Acknowledgments

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Supplementary data

Supplementary data (^1H and ^{13}C NMR spectra for convolutamines I (**1**) and J (**2**)) associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2011.06.006.

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