Design, synthesis and spectroscopic characterisation of a focused library based on the polyandrocarpamine natural product scaffold

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Abstract

A focused library based on the marine natural products polyandrocarpamines A (**1**) and B (**2**) has been designed and synthesised using parallel solution-phase chemistry. *In silico* physicochemical property calculations were performed on synthetic candidates in order to optimise the library for drug discovery and chemical biology. A library of ten 2-aminoimidazolone products (**3–12**) were prepared by coupling glycohydrazide and a variety of aldehydes using a one-step stereoselective aldol condensation reaction under microwave conditions. All analogues were characterised by NMR, UV, IR and MS. The library was evaluated for cytotoxicity towards the prostate cancer cell lines, LNCaP, PC-3 and 22Rv1.

Keywords: focused library; natural product scaffold; polyandrocarpamine; microwave chemistry; physicochemical parameters; 2-aminoimidazolone

Introduction

Natural products are enjoying a renaissance in the quest to design and select molecules for screening libraries. Proponents of natural products contend that secondary metabolites produced on the surface of a protein can interact with biology space that includes, *inter alia*, the surfaces of other proteins, receptors, DNA and RNA. This makes them ideal candidates for inclusion into screening libraries for evaluation against a range of biological targets.^[1,2] Indeed, it has been reported that around one-third of current drugs can trace their genesis back to a natural product, making libraries based on this strategy indispensable for the discovery of new probe and lead molecules.^[3-6] Natural product templates are also structurally distinct from many synthetics and occupy different areas of chemical space.^[3,7] By way of example, Shoichet *et al.* have examined structural motifs in screening libraries and found that 83% (12,977) of core ring scaffolds present in natural products were absent from commercial collections.^[8] Additionally, their analysis suggests that collections containing molecules based on scaffolds present in natural products, but absent from commercial collections will improve hit rates.^[8] Importantly, screening libraries based on, or inspired by, natural products complement synthetic libraries and effectively increase the serendipitous value of high-throughput screening (HTS).^[7,9]

We have previously reported the stereoselective synthesis of the marine natural products, polyandrocarpamines A (**1**) and B (**2**), using a high-yielding one-step aldol condensation reaction under microwave conditions.^[10,11] Due to our interest in the use of natural products as templates for unique chemical library production,^[12-17] and the predicted amenability of the new stereoselective microwave chemistry for analogue generation, we herein describe the design, synthesis and spectroscopic characterisation of a focused library based on the polyandrocarpamine (2-aminoimidazolone) scaffold. The cytotoxicity of all library members towards three prostate cancer cell lines (LNCaP, PC-3 and 22Rv1) is also reported.

Results and Discussion.

In silico physicochemical property calculations were initially performed on a number of potential

polyandrocarpamine analogues before embarking on the synthesis. Only those analogues that adhered to the definitions of fragment or reduced complexity sets were ultimately synthesised^[18,19]. These design criteria helped guide the synthesis of library members that would contain desirable physicochemical properties which, in turn, can facilitate bioavailability and assist potential downstream medicinal chemistry optimisation.

Fragment libraries are defined by Astex's "rule of 3",^[18] i.e. MW < 300; clog P ≤ 3; the number hydrogen-bond donors (HBD, i.e. the count of NH + OH) ≤ 3; and the number of rotatable, non-terminal, bonds (RTB) ≤ 3. Reduced complexity sets^[19] are somewhat similar, i.e. MW < 350; clog P ≤ 2; HBD ≤ 3; the number of hydrogen-bond acceptors (HBA, the total count of N + O atoms) ≤ 8; (RTB) ≤ 6; and the number of heavy atoms ≤ 22.

Three other molecular descriptors not specifically identified in the above two sets, i.e. water solubility,^[20] as measured by log S_w; the number of rings; and polar surface area (PSA) were also included as part of the design process. Increasing aqueous solubility (where log S_w ≥ -5) can improve oral bioavailability. The number of rings are part of the descriptor set for "lead-like" molecules^[19] (where the number of rings ≤ 4) and embodies starting points that can be optimised into lead- or probe-like molecules with better pharmacokinetic profiles, selectivity and/or activity. PSA is an important measure of cell permeability and ideally is ≤ 140 Å² or ≤ 100 Å² in the case of the central nervous system (CNS) where drugs are required to cross the blood-brain barrier.^[21,22] The results of our *in silico* physicochemical property studies and our targeted structures are detailed in Table 1 and Figure 1, respectively.

The 10 target molecules (**3–12**) that met our design criteria were subsequently synthesised by coupling glycyamidine (**13**) with 10 different commercially available aldehydes in the presence of NaOAc and AcOH under microwave conditions (Scheme 1).^[10]

Work-up of each separate reaction mixture, followed by semi-preparative C₁₈-bonded HPLC (H₂O/CH₃OH/0.1% TFA) yielded the TFA salts of the desired 2-aminoimidazolones (**3–12**) in yields

ranging from 6 to 58% (Figure 1).

The purity of the polyandrocarpamine-based library (**1–12**) was determined using microfluidics C_{18} μ PLC and ranged from 80 to 98%. Compounds **3–12** were spectroscopically characterised using 1D and 2D NMR (1H , ^{13}C , gCOSY, HSQC, gHMBC, ROESY), UV and MS data. All compounds were obtained as only one geometric isomer, as shown by the 1H and ^{13}C NMR data (Tables 2 and 3). This was initially assumed to be the *Z* isomer as previously reported for polyandrocarpamines A (**1**) and B (**2**),^[10,11] based on $^{13}C/^1H$ long-range coupling constants.^[23–25] Confirmation that the new polyandrocarpamine analogues also had *Z* stereochemistry was achieved by analysis of two analogues (**3** and **8**) via gHSQMBC NMR experiments. The gHSQMBC data for **3** and **8** indicated that the coupling constants between the exocyclic protons [δ_H 6.86 (H-4) for **3**; δ_H 7.00 (H-4) for **8**] and the imidazolone carbonyl [δ_C 164.8 (C-2) for **3**; δ_C 164.9 (C-2) for **8**] were 4.9 and 4.8 Hz, respectively, which is consistent for *Z* geometry.^[10,11,24,25]

In our previous synthesis of polyandrocarpamines A (**1**) and B (**2**) we reported the cytotoxicity of both these marine alkaloids against three tumour cell lines (H460, MCF-7 and SF268) and showed that both **1** and **2** displayed selective toxicity towards the SF268 cancer cells with GI_{50} values of 65 and >80 μ M, respectively.^[10] In order to further expand the cytotoxicity studies for both **1** and **2**, as well as evaluate the new polyandrocarpamine-based library for potential toxicity towards several prostate cancer cell lines (LNCaP, PC-3 and 22Rv1), compounds **1–12** were all screened at 125 μ M for 48 h (Table 2). Compound **3** was the most active against the LNCaP cell line with 61% growth recorded at 125 μ M. None of the library members showed any significant effect towards the PC-3 cell line.

In summary, a focused library based on the marine natural products polyandrocarpamines A and B has been synthesised using parallel solution-phase microwave chemistry. The design of the library has specifically taken into account many of the physicochemical parameters considered desirable for drug discovery and chemical biology. This library is currently available for screening by academia and industry, in an effort to foster collaborations between chemists and biologists.

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Experimental

General experimental section

UV spectra were recorded on a JASCO V-650 spectrophotometer. The ^1H , gCOSY, HSQC, gHMBC, gHSQMBC and ROESY NMR spectra were recorded at 30 °C on a Varian 600 MHz Unity INOVA spectrometer equipped with a triple resonance cold probe. The ^{13}C NMR spectra were recorded at 30 °C on a Varian 500 MHz Unity INOVA spectrometer. The ^1H and ^{13}C chemical shifts were referenced to the proto-deutero solvent peaks for CD_3OD at δ_{H} 3.31 and δ_{C} 49.00, respectively. Coupling constants (J) are given in Hz. Compounds **4**, **5**, **8–12** had one drop of TFA added to the CD_3OD solution in order to improve solubility. ^1H NMR spectra acquisition details included: spectrometer frequency = 599.721 MHz, acquisition time = 2.049 s, relaxation delay = 1.000 s, 90° pulse = 7.34 μs , spectral width = 7225 Hz, FT data size = 32K and digital resolution = 0.221 Hz. ^{13}C NMR spectra acquisition details included: spectrometer frequency = 125.718 MHz, acquisition time = 1.242 s, relaxation delay = 1.000 s, 90° pulse = 7.600 μs , spectral width = 26393 Hz, FT data size = 32K and digital resolution = 0.806 Hz. The gradient COSY was acquired with 128 F1 increments using 4 transients per increment, and the ^1H spectral width was set at 7225 Hz. Sinebell weighting was applied to each dimension and zero filled to 2K points. The HSQC was acquired with 128 F1 increments using 8 transients per increment, and the ^1H and ^{13}C spectral widths were set at 7225 and 25632 Hz, respectively. Gaussian weighting was applied to both ^1H and ^{13}C dimensions, which were then zero filled to 2K and 1K, respectively. A one-bond coupling constant delay was set using 140 Hz, and WURST decoupling was applied during acquisition.

The gradient HMBC was acquired with 128 F1 increments using 32 transients per increment, and the ^1H and ^{13}C spectral widths were set at 7225 and 36199 Hz, respectively. A one-bond coupling constant of 140 Hz and long-range coupling constant of 8 Hz were used to set the delays in the pulse sequence. Sinebell weighting was applied to both ^1H and ^{13}C dimensions, which were then zero filled to 4K and 1K, respectively. The gradient HSQMBC was acquired with 128 F1 increments using 32 transients per increment, and the ^1H and ^{13}C spectral widths were set at 7225 and 33181 Hz, respectively. A one-bond coupling constant of 140 Hz and long-range coupling constant of 8 Hz were used to set the delays in the pulse sequence. Gaussian weighting was applied to both ^1H and ^{13}C dimensions, which were then zero filled to 4K and 1K, respectively. The ROESY was acquired with 256 F1 increments using 16 transients per increment, and the ^1H spectral width was set at 7225 Hz. A mixing time of 500 ms was used. Gaussian weighting was applied to both dimensions, which were then zero filled to 2K. 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 Biotage Initiator was used for microwave reactions. A Waters 600 pump equipped with a Waters 996 PDA detector and a Waters 717 autosampler were used for HPLC. A ThermoElectron C_{18} Betasil 5 μm 143 Å column (21.2 mm $\times$ 150 mm) and a YMC diol 5 μm 120 Å column (20 mm $\times$ 150 mm) were used for semi-preparative HPLC separations. All solvents used for chromatography, UV, and MS were Lab-Scan HPLC grade, and the H_2O was Millipore Milli-Q PF filtered. All synthetic reagents were purchased from Sigma-Aldrich.

Molecular property descriptor calculations

Structures of compounds **1–12** were drawn using Cambridge Soft[®] ChemDraw[®] and converted to SMILES code. Scitegic Pipeline Pilot v 6.1 was then employed to calculate the molecular property descriptors shown in Table 1 using a protocol that incorporated a SMILES reader; bad valence and Lipinski filters; and molecular formula, molecular property counts, surface area and volume, and solubility calculators.

Synthesis of the HCl salt of glycoxyamidine

Our modified microwave method for the synthesis of glycoxyaminde has been previously reported.^[10]

General method for the 2-aminoimidazolone synthesis

The relevant aldehyde (0.74 mmol) was added to a slurry of the HCl salt of glycoxyamidine (100 mg, 0.74 mmol), NaOAc (91 mg, 1.11 mmol) and AcOH 414 μ L, 7.20 mmol) then heated under microwave conditions at 160 °C for 20 min. Ice cold water (1 mL) was added to the reaction mixture and the solid collected by filtration under vacuum. The solid was pre-adsorbed on C₁₈-bonded silica, then packed into a stainless steel cartridge (10 $\times$ 30 mm) that was subsequently attached to a C₁₈ Betasil HPLC column. Isocratic HPLC conditions of 95% H₂O (1.0% TFA)/5% CH₃OH (1.0% TFA) were initially employed for the first 10 min, then a linear gradient to CH₃OH (1.0% TFA) was run over 40 min, followed by isocratic conditions of CH₃OH (1.0% TFA) for a further 10 min, all at a flow rate of 9 ml/min. Sixty fractions (60 $\times$ 1 min) were collected from the start of the HPLC run then analysed by (+)-LRESIMS in order to identify which fractions contained the compound of interest. Subsequent lyophilization of the relevant fraction(s) yielded the TFA salt of the product in high-purity. If purity criteria (>90%) was not initially satisfied, repeat C₁₈ HPLC purification using identical conditions to those described above was typically undertaken.

Compound 3: White amorphous solid (31 mg, 8% yield); UV (CH₃OH)/nm (log ϵ) 237 (3.96), 255 (3.77), 280 (3.81), 329 (4.07), 340 (4.08); ¹H and ¹³C NMR (CD₃OD) data see Tables 2 and 3, respectively; (+)-LRESIMS *m/z* 266 (100%), 268 (100%); (+)-HRESIMS *m/z* 265.9921 (C₁₀H₉⁷⁹BrN₃O [M+H]⁺ requires 265.9924).

Compound 4: Pale yellow amorphous solid (13 mg, 6% yield); UV (CH₃OH)/nm (log ϵ) 237

(3.94), 349 (4.16); ^1H and ^{13}C NMR (CD_3OD) data see Tables 2 and 3, respectively; (+)-LRESIMS m/z 236 (100%); (+)-HRESIMS m/z 236.0832 ($\text{C}_{11}\text{H}_{11}\text{FN}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ requires 236.0830).

Compound 5: Pale yellow amorphous solid (39 mg, 22% yield); UV (CH_3OH)/nm ($\log \epsilon$) 237 (3.89), 281 (3.64), 339 (4.01); ^1H and ^{13}C NMR (CD_3OD) data see Tables 2 and 3, respectively; (+)-LRESIMS m/z 236 (100%); (+)-HRESIMS m/z 236.0832 ($\text{C}_{11}\text{H}_{11}\text{FN}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ requires 236.0830).

Compound 6: White amorphous solid (215 mg, 58% yield); UV (CH_3OH)/nm ($\log \epsilon$) 237 (3.79), 340 (4.05); ^1H and ^{13}C NMR (CD_3OD) data see Tables 2 and 3, respectively; (+)-LRESIMS m/z 138 (45%), 275 (100%); (+)-HRESIMS m/z 275.1501 ($\text{C}_{14}\text{H}_{19}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$ requires 275.1502).

Compound 7: Light brown amorphous solid (27 mg, 9% yield); UV (CH_3OH)/nm ($\log \epsilon$) 237 (3.91), 259 (3.91), 327 (3.88), 345 (3.87); ^1H and ^{13}C NMR (CD_3OD) data see Tables 2 and 3, respectively; (+)-LRESIMS m/z 273 (100%); (+)-HRESIMS m/z 273.1345 ($\text{C}_{14}\text{H}_{17}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$ requires 273.1346).

Compound 8: White amorphous solid (19 mg, 7% yield); UV (MeOH)/nm ($\log \epsilon$) 238 (3.72), 280 (3.68), 348 (3.99); ^1H and ^{13}C NMR (CD_3OD) data see Tables 2 and 3, respectively; (+)-LRESIMS m/z 254 (100%); (+)-HRESIMS m/z 254.1029 ($\text{C}_{13}\text{H}_{12}\text{N}_5\text{O}$ $[\text{M}+\text{H}]^+$ requires 254.1036).

Compound 9: White amorphous solid (50 mg, 14% yield); UV (CH_3OH)/nm ($\log \epsilon$) 236 (3.78), 265 (3.86), 337 (4.10); ^1H and ^{13}C NMR (CD_3OD) data see Tables 2 and 3, respectively; (+)-LRESIMS m/z 254 (100%); (+)-HRESIMS m/z 254.1029 ($\text{C}_{13}\text{H}_{12}\text{N}_5\text{O}$ $[\text{M}+\text{H}]^+$ requires 254.1036).

Compound 10: Pale yellow amorphous solid (39 mg, 16% yield); UV (MeOH)/nm (log ϵ) 237 (3.73), 267 (3.57), 366 (4.18); ^1H and ^{13}C NMR (CD_3OD) data see Tables 2 and 3, respectively; (+)-LRESIMS m/z 208 (100%); (+)-HRESIMS m/z 208.0544 ($\text{C}_9\text{H}_{10}\text{N}_3\text{OS}$ $[\text{M}+\text{H}]^+$ requires 208.0539).

Compound 11: White amorphous solid (60 mg, 25% yield); UV (MeOH)/nm (log ϵ) 237 (3.65), 282 (3.37), 364 (3.99); ^1H and ^{13}C NMR (CD_3OD) data see Tables 2 and 3, respectively; (+)-LRESIMS m/z 208 (100%); (+)-HRESIMS m/z 208.0535 ($\text{C}_9\text{H}_{10}\text{N}_3\text{OS}$ $[\text{M}+\text{H}]^+$ requires 208.0539).

Compound 12: Pale yellow amorphous solid (54 mg, 19% yield); UV (MeOH)/nm (log ϵ) 237 (3.78), 273 (3.69), 362 (4.18); ^1H and ^{13}C NMR (CD_3OD) data see Tables 2 and 3, respectively; (+)-HRESIMS m/z 271.9487 ($\text{C}_8\text{H}_7^{79}\text{BrN}_3\text{OS}$ $[\text{M}+\text{H}]^+$ requires 271.9487).

Compound purity analysis

Compounds **1–12** were all analysed for purity by C_{18} μPLC . A 30 mM solution in DMSO was made for each compound, diluted 1:30 using DMSO (30 μL final volume) then dispensed into a Greiner flat bottomed 384-well microtitre plate (Cat. # 781201). All samples were analyzed on a Nanostream CX microfluidics system using a Brio 24-column μPLC C_{18} cartridge (Grace Vydac GENESIS C_{18} 7 μm , 120 $\text{\AA}$, 1.0 $\times$ 8.0 mm, Cat. # 4207002). Each sample was injected (0.5 μL) onto one of the 24 Brio cartridge columns. Isocratic μPLC conditions of 10% CH_3CN (0.01% TFA) / 90 % H_2O (0.01% TFA) were employed for the first 5 min, then a linear gradient to CH_3CN (0.01% TFA) was run over 15 min, followed by isocratic conditions of CH_3CN (0.01% TFA) for a further 10 min, all at a flow rate of 400 $\mu\text{L}/\text{min}$. All UV active peaks at 254 nm were integrated and area % calculated, thus allowing a purity % for each compound to be determined. Retention time / purity % for each compound were as follows: 11.36 min / 98% (compound **1**); 11.22 min / 98% (compound

2); 12.43 min / 91% (compound 3); 11.83 min / 93% (compound 4); 11.94 min / 97% (compound 5); 10.62 min / 87% (compound 6); 11.85 min / 98% (compound 7); 10.65 min / 94% (compound 8); 11.98 min / 81% (compound 9); 11.74 min / 92% (compound 10); 11.54 min / 89% (compound 11); 12.29 min / 97% (compound 12).

Mammalian cell toxicity assays

All cell lines were cultured in RPMI 1640 medium supplemented with 10% foetal calf serum (CSL, Australia) at 5% CO₂, 99% humidity and 37 °C. Routine mycoplasma tests were always negative for each cell line using the Takara PCR Mycoplasma Detection Set (Scientifix, Cheltenham, Australia). Cytotoxicities of compounds were determined by clonogenic survival of LNCaP, PC-3 and 22Rv1 prostate cancer cells. Cells were plated into 96-well microtitre plates at 5×10^3 cells/well (PC-3) or 1.0×10^4 cells/well (LNCaP and 22Rv1), and allowed to adhere overnight. Compounds were added to the culture medium at 125 μ M, and plates were incubated in the above conditions for 48 h. Cell survival was then assayed using the WST-1 cell proliferation reagent (Roche, Castle Hill, Australia). Briefly, 10 μ L of the WST-1 reagent was added directly to each well at a final concentration of 10% WST-1, and the cells were then maintained for an additional 2 h. Plates were then read at 450 nm and 650 nm (reference) on a Fisher Scientific Multiskan MCC/340 microplate reader (Pathtech, Preston, Australia). Background absorbance of WST-1 and the specific compound was factored into the calculation. Data was taken from triplicate wells for each compound, and each experiment was performed in triplicate. Data (mean $\pm$ standard error) is represented as the percentage growth of cells treated with each compound relative to non-treated cells.

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Table 1. *In silico* physicochemical property data for compounds **1–12**.^a

Compound	MW	cLogP	HBD	HBA	RTB	LogSw	No. rings	PSA
1	233	0.533	3	6	2	-2.099	2	96.94
2	219	0.307	4	6	1	-1.588	2	107.9
3	266	1.539	2	4	1	-3.534	2	67.47
4	235	0.98	2	5	2	-2.844	2	76.71
5	235	0.98	2	5	2	-2.834	2	76.71
6	274	0.913	2	6	5	-2.713	2	79.94
7	272	0.641	2	6	2	-2.241	3	79.95
8	253	0.461	2	6	2	-3.343	3	85.3
9	253	1.182	3	6	2	-3.142	3	96.16
10	207	0.89	2	4	1	-2.895	2	95.71
11	207	1.231	2	4	1	-2.867	2	95.72
12	272	1.493	2	4	1	-3.51	2	95.72

^aScitegic Pipeline Pilot v 6.1 was employed to calculate the molecular property descriptors.

Table 2. ¹H NMR (600 MHz) data for compounds **3–12**.^a

Position	¹ H (mult., <i>J</i> in Hz)									
	3	4	5	6	7	8	9	10	11	12
4	6.86 (s)	6.87 (s)	6.92 (s)	6.88 (s)	7.18 (s)	7.00 (s)	6.88 (s)	7.06 (s)	7.21 (s)	7.01 (s)
6	7.79 (s)	7.43 (d, 12.0)	7.31 (d, 7.8)	7.64 (d, 8.4)		7.91 (d, 8.4)		7.38 (d, 3.6)		7.56 (s)
7				7.12 (d, 8.4)	7.19 (d, 7.2)	7.86 (d, 8.4)	8.29 (s)	6.92 (d, 3.6)	7.07 (d, 5.4)	
8	7.59 (d, 7.8)				7.44 (dd, 7.2, 7.2)				7.70 (d, 5.4)	7.71 (s)
9	7.39 (dd, 7.8, 7.8)	7.19 (dd, 9.0, 8.4)	7.19 (d, 8.4)	7.12 (d, 8.4)	7.17 (dd, 7.8, 7.2)	7.86 (d, 8.4)	7.57 (d, 7.2)	2.57 (s)	2.41 (s)	
10	7.58 (d, 7.8)	7.39 (d, 8.4)	7.19 (d, 8.4)	7.64 (d, 8.4)	7.56 (d, 7.8)	7.91 (d, 8.4)	7.54 (d, 7.2)			
11		3.93 (s)	3.94 (s)	4.42 (t, 4.8)	2.97 (t, 4.8)	9.54 (s)	7.50 (t, 7.2)			
12				3.62 (t, 4.8)	3.84 (t, 4.8)	7.80 (s)	7.54 (d, 7.2)			
13				2.99 (s)	3.84 (t, 4.8)	8.13 (s)	7.57 (d, 7.2)			
14				2.99 (s)	2.97 (t, 4.8)					

^aSpectra were recorded in CD₃OD at 30 °C.

Table 3. ^{13}C NMR (125 MHz) data for compounds **3–12**.^a

Position	^{13}C									
	3	4	5	6	7	8	9	10	11	12
1	158.5	158.1	158.3	159.1	157.8	158.6	157.3	157.5	157.6	158.1
2	164.8	165.1	165.0	166.8	165.5	164.9	164.8	164.8	164.8	164.6
3	127.6	125.5	119.5	126.1	127.0	128.1	124.6	122.9	123.2	125.4
4	116.3	117.5	117.8	117.5	116.1	115.5	110.2	112.2	110.6	109.5
5	135.5	126.1	130.1	127.3	127.1	135.4	112.0	134.3	145.2	137.5
6	133.2	117.7	116.3	132.9	153.9	132.7	150.1	134.4	130.2	134.1
7	124.1	153.7	149.7	116.4	120.1	124.1	136.5	128.7	132.4	112.9
8	133.9	150.9	154.7	160.4	132.4	136.9	131.2	148.2	130.5	128.7
9	131.9	115.0	117.7	116.4	124.5	124.1	129.8	15.9	14.2	
10	129.5	128.5	124.0	132.9	131.2	132.7	130.2			
11		56.9	57.0	63.3	54.3	135.8	130.3			
12				57.7	68.2	122.2	130.2			
13				44.0	68.2	122.5	129.8			
14				44.0	54.3					

^aSpectra were recorded in CD_3OD at 30 °C.

Table 4. *In vitro* activity of compounds **1–12** against prostate cancer cells.

Compound	% growth ($\pm$ SE) relative to non-treated cells at 125 μ M ^a		
	LNCaP	PC-3	22Rv1
1	106 ($\pm$ 5.0)	87 ($\pm$ 3.0)	36 ($\pm$ 1.6)
2	108 ($\pm$ 12.7)	94 ($\pm$ 12.9)	80 ($\pm$ 12.6)
3	61 ($\pm$ 14.0)	129 ($\pm$ 12.0)	67 ($\pm$ 3.3)
4	89 ($\pm$ 5.6)	116 ($\pm$ 9.0)	56 ($\pm$ 8.0)
5	86 ($\pm$ 12.0)	107 ($\pm$ 7.6)	74 ($\pm$ 6.0)
6	101 ($\pm$ 7.2)	108 ($\pm$ 1.8)	85 ($\pm$ 7.0)
7	123 ($\pm$ 22.7)	121 ($\pm$ 15.4)	105 ($\pm$ 12.0)
8	101 ($\pm$ 10.8)	108 ($\pm$ 2.3)	90 ($\pm$ 7.0)
9	93 ($\pm$ 5.0)	102 ($\pm$ 11.5)	78 ($\pm$ 3.0)
10	101 ($\pm$ 10.1)	102 ($\pm$ 5.8)	74 ($\pm$ 3.4)
11	103 ($\pm$ 4.7)	113 ($\pm$ 6.0)	99 ($\pm$ 0.2)
12	93 ($\pm$ 6.6)	91 ($\pm$ 7.0)	61 ($\pm$ 1.5)
DMSO^b	93 ($\pm$ 6.6)	112 ($\pm$ 8.0)	98 ($\pm$ 2.7)

^anon-treated cells = 100. ^bDMSO = vehicle control.

Figure 1. Chemical structures of library members **1–12**

Scheme 1. Reagents/conditions: (i) NaOAc/AcOH, μ w, 160 °C, 20 min.

Graphical Abstract

Design, synthesis and spectroscopic characterisation of a focused library based on the polyandrocarpamine natural product scaffold

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