A facile, protic ionic liquid route to *N*-substituted 5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamides and *N*-substituted 3-oxoisoindoline-4-carboxylic acids

Christopher P Gordon, Nolene Byrne and Adam McCluskey*

Received 25th November 2009, Accepted 15th April 2010
First published as an Advance Article on the web 5th May 2010
DOI: 10.1039/b924835h

Treatment of highly decorated bicyclo[2.2.1]heptadienes with the protic ionic liquid, TfOH:TEA effected quantitative conversion to the corresponding *N*-substituted 5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamides. This approach provides rapid access important chemical space for the rapid development of highly functionalised oxoisoindoline and is highly substrate tolerant.

Introduction

Over the past decade or so, our team has developed a keen interest in the rapid access to biologically active materials. Our efforts have ranged from protein phosphatase inhibitors as anticancer agents,[1–17] through to novel inhibitors of the large GTPase, dynamin.[18–23] Pivotal to our efforts is ease of access and rapid decoration of chemical scaffolds. In this regard we place synthetic elegance over complexity with highly focused library development the driver of each new therapeutic area. Here medicinal and synthetic chemistry diverge, with the former access to compounds addressing diverse chemical space being more important than the synthesis of complex molecules, which is more typically the remit of the synthetic chemist. These two areas, though, are not mutually exclusive.

Our use of scaffolds in chemistry is exemplified by the development of protein phosphatase inhibitors embodied by the cantharidin (**1**) and norcantharidin (**2**) scaffolds (Fig. 1). In this arena little skeletal modification that retains or improves on the biological activity of the parent compounds is possible.[8,11,24,25]

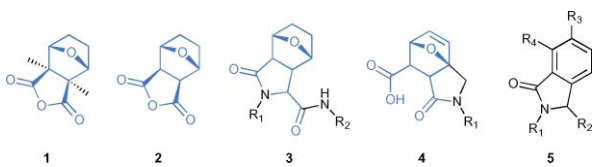


Fig. 1 Chemical structures of cantharidin (**1**), norcantharidin (**2**), tricyclic lactams (**3** and **4**) and substituted oxoisoindolenes (**5**).

More recently, increasing attention has been placed on the development of medicinal chemistry scaffolds in an environmentally benign manner, *i.e.* green medicinal chemistry. This and our on-going interest in the cantharidin and norcantharidin scaffolds led us to investigate the synthesis of the tricyclic lactams (**3** and **4**)[26,27] rationalising that there was sufficient structural similarity to suggest that either the protein phosphatase or the anticancer activity of **1** and **2** may be retained. We were more interested, however, in the possibility of developing an elegant entry to substituted oxoisoindolenes (**5**) which would permit rapid access to chemical space that we had previously not been able to access in any of our medicinal chemistry programs.[28–31]

An additional attraction for the synthesis of oxoisoindolenes (**5**) is that they, potentially, represent advanced intermediates in the synthesis of the biologically active natural products, lennoxamine (**6**), aristoyagonine (**7**), and neuvamine (**8**), amongst others (Fig. 2).[32–38]

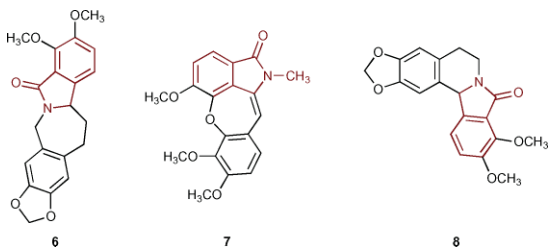


Fig. 2 Natural products containing an oxoisoindolene core.

The synthesis of functionalised oxoisoindolenes is not well described in the literature, as such we were keen to explore rapid access to illustrative examples of **5**.[28–31] Of the reports of oxoisoindolenes, the most expedient route commences with the Diels–Alder addition of furfurylamines (formed by the reductive amination of furfural with a variety of amines) followed by addition of maleic anhydride.[31] The resulting 3-substituted 4-oxo-10-oxa-3-azatricyclo[5.2.1.0]dec-8-ene-6-carboxylic acids are then subjected to treatment with cH_2SO_4/CH_3OH at reflux to afford the corresponding oxoisoindolenes. Similar ring opening aromatisation reactions have also been effected by the use of HCl and CF_3SO_3H.[39,40] As described, these processes have a number of major limitations including, but not limited to, the lack of substrate flexibility permitting rapid decoration of the oxoisoindolene scaffold, and the requirement for acid tolerant substituents.

In the development of novel **1** and **2** analogues, we have developed a rapid access to highly functionalised

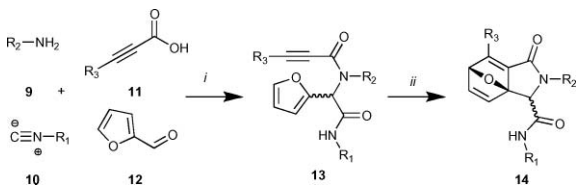
Chemistry, School of Environmental & Life Sciences, The University of Newcastle, University Drive, Callaghan, NSW 2308, Australia. E-mail: Adam.McCluskey@newcastle.edu.au; Fax: +61 2492 15472; Tel: + 61 2492 16486

4-oxo-10-oxa-3-azatricyclo[5.2.1.0]dec-8-enes,[25] and 4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (described herein) obviating our first limitation, and we believed that the replacement of cH_2SO_4/CH_3OH (or H_3PO_4 or HCl or CF_3SO_3H) with a protic ionic liquid may bypass the second limitation.

The field of ionic liquids has exploded over the past decade with considerable interest in the tunable nature of these solvents. Our current interest lies within a discrete subset of these ionic liquids, protic ionic liquids (pILs).[41–49] With pILs their properties are governed by the free energy of proton transfer from the Brønsted acid to the Brønsted base during pIL synthesis. The effective acidity of pILs depends on the values of the transfer energy, and this quantity controls many aspects of the behaviour of pILs. In many regards pILs offer a more subtle degree of tunability with the percentage conversion of the reaction being tuned by the choice of acid and base components altering the proton activity of the pIL solution. Thus, with retention of the base strength whilst varying the acid strength, the proton activity of the resulting pIL varies.[43,45] We rationalised that the use of pILs of varying degrees of proton activity would influence the outcomes of the acid catalysed rearrangements of our 4-oxo-10-oxa-3-azatricyclo[5.2.1.0]dec-8-enes and related azatricyclodec-8-ene-6-carboxylic acids.

Results and discussion

In order to conduct the proposed studies we applied in-house methodologies for the synthesis of the necessary oxabicyclo[2.2.1]heptadiene scaffold as shown in Scheme 1. Initially an acetylenic amide (**13**) was synthesised *via* an Ugi condensation of 2-furaldehyde (**12**), 2-butynoic acid (**11**), an isonitile (**10**), and an amine (**9**). Conversion to the oxabicyclo[2.2.1]heptadiene scaffold (**14**) *via* an intramolecular Diels–Alder (IMDA) reaction was effected smoothly under thermal conditions.

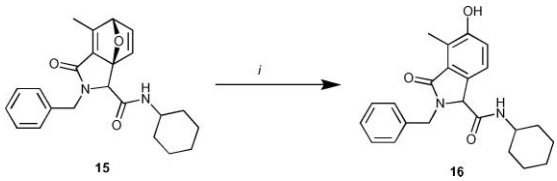


Scheme 1 Reagents and conditions: (i) **9**, **10**, **11**, **12**, CH_3OH, room temperature, 30 min; (ii) $PhCH_3$, sealed tube 200 °C, 36 h.

With a well defined route to the required highly substituted oxabicyclo[2.2.1]heptadiene (**14**) scaffold, we firstly examined an acid catalysed rearrangement. After a series of optimisation reactions we found that the transformation to the oxoisoindolene scaffold was smoothly effected under microwave heating at 120 °C for 20 min. We limited our initial examination to the conversion of (**15**) to (**16**) as shown in Scheme 2.

Having established that the desired transformation occurred under similar conditions to those reported for less decorated oxoisoindolenes we next turned our attention to the use of pILs to effect the same transformation.

Five pILs were surveyed for their ability to effect the desired transformation. These pILs display varying degrees of acidity with H_2SO_4:TEA the most acidic through to AcOH:TEA being



Scheme 2 Reagents and conditions: (i) 80% H_3PO_4, microwave, 120 °C, 20 min.

classified as basic. Each pIL in turn was used as both reaction solvent and transformation catalyst. The data in Table 1 clearly indicates an efficient transformation from **15** to **16** under acidic pIL treatment with both H_2SO_4:TEA and TfOH:TEA resulting in 100% conversion and 91 and 95% isolated yields respectively after workup following 20 min heating at 80 °C (microwave). This compares very favourably with our model reaction with 80% H_3PO_4 at 120 °C (microwave heating) for 20 min. It is also apparent that the proton activity has a significant impact on the efficiency of the conversion process with neutral AcOH:TFA only returning unreacted starting material, whilst the basic pILs H_3PO_4:TEA and TFA:TEA affording 56 and 30% isolated yields respectively. These conversion rates are in keeping with the known relative proton activities of the pILs examined herein.

As one of our drivers to develop these oxoisoindolene analogues was to examine their potential anticancer activity, we compared the effect of treating a panel of human carcinoma cell lines with **15** and **16**. These data are shown in Table 2.

Entry into the oxoisoindolene scaffold (**15** → **16**) resulted in a 10 to 20 fold reduction in cell death across the panel of cell lines examined. Hence we chose not to evaluate there potential as anticancer agents further, but rather chose to focus on examining

Table 1 Optimisation of oxo-bridgehead opening in the conversion of **15** to **16**, 2-benzyl-*N*-cyclohexyl-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide

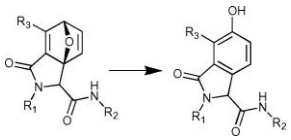
pIL	Temp (°C)	Time (min)	Yield (%)
H_2SO_4:TEA	80	20	91
TfOH:TEA	80	20	96
AcOH:TEA	80	20	0
H_3PO_4:TEA	80	20	56
TFA:TEA	80	20	30

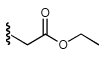
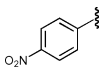
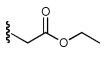
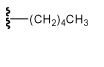
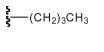
Table 2 Evaluation of the anticancer activity of **15** and **16** against a panel of human carcinoma cell lines

Human carcinoma cell line	**15** GI_{50} (μM)	**16** GI_{50} (μM)
HT29[a]	3.2 ± 0.1	23 ± 1
SW480[a]	3.2 ± 0.1	25 ± 1
MCF-7[b]	7.5 ± 0.4	26 ± 9
A2780[c]	4.4 ± 0.3	24 ± 2
H460[d]	3.3 ± 0.2	32 ± 0
A431[e]	2.9 ± 0.2	31 ± 1
DU145[f]	2.1 ± 0.3	52 ± 9
BE2-C[g]	3.7 ± 0.6	53 ± 2
SJ-G2[h]	1.7 ± 0.1	41 ± 11

[a] HT29 and SW480 (colon carcinoma). [b] MCF-7 (breast carcinoma). [c] A2780 (ovarian carcinoma). [d] H460 (lung carcinoma). [e] A431 (skin carcinoma). [f] DU145 (prostate carcinoma). [g] BEC-2 (neuroblastoma). [h] SJ-G2 (glioblastoma).

Table 3 Conversion of highly decorated oxabicyclo[2.2.1]heptadienes to highly decorated oxoisoindolenes (**17–21**) upon treatment with TfOH:TEA



Entry (compound)	R_1	R_2	R_3	Yield (%)
1 (**17**)				91
2 (**18**)				96
3 (**19**)				87
4 (**20**)				85
5 (**21**)				95

the scope of the pIL mediated transformation. With this in mind we selected a small, but diverse subset of highly decorated oxabicyclo[2.2.1]heptadienes and treated them with TfOH:TEA (Table 3).

In all instances we observe rapid, clean and substituent tolerant conversion to the desired oxoisoindolene scaffold. The *N*-substituent is delivered *via* amines (**9**, Scheme 1), and all substituents are well tolerated from the electron-withdrawing aromatic moieties (Table 3 entries 1 (*p*-chloroaniline) and 2 (*p*-nitroaniline)), through to electron-donating, aliphatic and simple aromatic substituents (Table 3 entries 3 (*p*-hydroxyaniline), 4 (*N*,*N*-dimethylaminopropan-1-amine) and 5 (benzylamine)). Carboxamide, and ester (Table 3, entries 1–3) substituents are delivered *via* isocyanides (**10**, Scheme 1), and again are well tolerated, as are simple alkyl substituents on the phenyl ring. Products are initially accessed by either dichloromethane or ethylacetate extractive work up.[50]

While our IMDA approach affords rapid access to the required oxabicyclo[2.2.1]heptadiene scaffold, we have also developed a rapid flow and microwave chemistry based approach to a related series of azatricyclodec-8-ene-6-carboxylic acids (**22**). Though lacking the diene moiety that collapses to substituted 5-hydroxy-3-oxoisoindoline-1-carboxamides (**14**), we rationalized that end stage aromatization *via* extrusion of the –OH moiety might provide sufficient driving force to allow an expedient access to isoindoe-5-carboxylic acids (**23**) (Fig. 3).

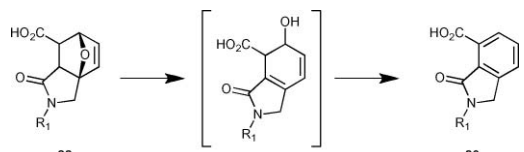
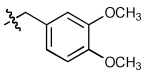
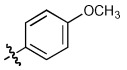
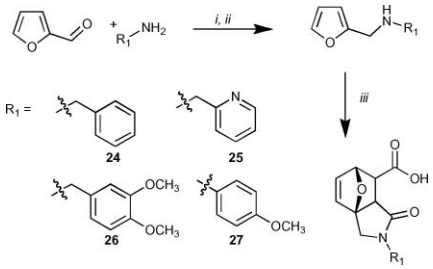


Fig. 3 Proposed route to synthetic route to 3-oxoisoindoline-4-carboxylic acids (**23**) from azatricyclo-8-ene-6-carboxylic acids (**22**).

Table 4 Conversion of azatricyclodec-8-ene-6-carboxylic acids (**24–27**) to 3-oxoisoindoline-4-carboxylic acid (**28–31**) upon treatment with TfOH:TEA

Entry (compound)	R_1	Yield (%)
1 (**28**)		92
2 (**29**)		95
3 (**30**)		88
4 (**31**)		85

Access to the precursor azatricyclodec-8-ene-6-carboxylic acids was readily effected by a simple sequence of imine formation (microwave heating), reduction using the ThalesNano H-cube and a microwave mediated Diels–Alder reaction with maleic anhydride as shown in Scheme 3.



Scheme 3 Reagents and conditions: (i) microwaves, 150 W, 100 °C, 5 mins; (ii) H-cube hydrogenation, 0.05 M imine in EtOH, 10% Pd/C, 50 °C, 50 bar H_2 pressure, 1 mL min^{-1}; (iii) toluene, microwaves, 250 W, 60 °C, 10 mins, 60–85%.

This three-step conversion proceeded smoothly and in excellent overall yield (60–85%) with the products collected by filtration. Subsequent treatment of **24–27**, in turn, with the pIL TfOH:TEA afforded smooth conversion to the corresponding 3-oxisoindoline carboxylic acids (**28–31**, Table 4) in excellent yields (85–92%). Products were isolated by extractive work up.

Our approach to substituted oxoisoindolenes is highly versatile with considerable breadth available *via* the individual components of the initial bicyclo[2.2.1]heptadiene and bicyclo[2.2.1]hept-5-ene scaffolds. Of these components, only the acetylenic dienophiles are poorly represented in the range of commercially available starting materials.

Conclusions

Herein we have effected, for the first time, an elegantly simple synthetic entry point to a series of highly decorated oxoisoindolenes. Our approach is highly efficient with excellent yields, atom economy, and with the use of pILs, microwave irradiation and flow chemistry approaches, avoids the use of harsh acidic conditions opening up the use of more acid labile substituents.

Experimental

General experimental

All starting materials were purchased from Aldrich Chemical Co. and Lancaster Synthesis. Solvents were bulk, and distilled from glass prior to use. Reaction progress was monitored by TLC on aluminium plates coated with silica gel with fluorescent indicator (Merck 60 F_{254}), and flash chromatography was conducted utilising SNAP Biotage KP-SIL columns. ^{1}H and ^{13}C spectra were recorded on a Bruker Advance AMX 300 MHz spectrometer at 300.13 and 75.48 MHz, respectively. Chemical shifts are relative to TMS as internal standard. All compounds returned satisfactory. Mass spectra were obtained using a micromass liquid chromatography Z-path (LCZ) platform spectrometer. Mass to charge ratios (*m*/*z*) are stated with their peak intensity as a percentage in parentheses. All mass spectra were obtained *via* the ES method thus fragmentation patterns were not observed. The University of Wollongong, Australia, Biomolecular Mass Spectrometry Laboratory, analyzed samples for HRMS. The spectra were run on a micromass QTof2 spectrometer using polyethylene glycol or polypropylene glycol as the internal standard.

Microwave heating was conducted using a CEM Discover Microwave and flow hydrogenation conducted using a ThalesNano H-Cube flow hydrogenator. Specific conditions are given below.

Protic Ionic Liquid preparation

Anhydrous trifluoromethanesulfonic acid (> 98%), triethylamine (> 99.5%), phosphoric acid (H_3PO_4, 85%, ACS grade), glacial acetic acid (CH_3COOH 99%), and sulfuric acid (H_2SO_4, 95–98%, ACS grade) were obtained from Sigma Aldrich.

Protic Ionic Liquids (PILs) are formed by proton transfer between a Brønsted acid and a Brønsted base. The addition of acid, by drop-wise addition to the amine, was carried out by cooling the amine solution to −78 °C using an acetone/dry-ice bath. The mixture was stirred at room temperature for several hours. The mixture was then placed in a rotorvap for several hours at 60 °C and vacuum dried at 0.01 mmHg for 24 h at 60 °C.

(3*R*,3a*S*,6*R*)-2-(benzyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-*N*-(cyclohexyl)-3a,6-epoxy-3a*H*-isoindole-3-carboxamide (15). A solution of benzylamine (0.13 mL, 1.2 mmol), 2-furaldehyde (0.10 mL, 1.2 mmol), 2-butynoic acid (0.12 g, 1.4 mmol), cyclohexyl isocyanide (0.15 mL, 1.2 mmol) and anhydrous MeOH (10.0 mL) was stirred at room temperature for 0.5 h. 2-Butynoic acid (1.2 eq, 1.4 mmol) was added and the resulting mixture was stirred for 0.5 h prior to the addition of an isocyanide (1 eq, 1.2 mmol). The mixture was stirred at room temperature for 2 h, quenched with 1 M NaOH (100 mL), extracted with CH_2Cl_2 (2 × 50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. A sealed tube was charged with the crude mixture, toluene (80 mL), degassed, and heated (250 °C) for 36 h. The resulting mixture concentrated *in vacuo* and subjected to flash silica gel column chromatography.

The crude material was subjected to flash silica gel column chromatography (3 : 2 EtOAc : hexanes) to ***S*-15** followed by further elution (2 : 1 EtOAc : hexanes) afforded ***R*-15** (0.74 g, 33%) as an brown solid (m.p. 209–211 °C); ^{1}H NMR (300 MHz) (DMSO-d_6): δ 7.98 (1H, d, J = 7.7 Hz), 7.34 (3H, m), 7.20 (3H, d, J = 7.0 Hz), 7.08 (1H, d, J = 5.2 Hz), 5.43 (1H, d, J = 5.5 Hz), 5.01 (1H, d, J = 15.3 Hz), 4.55 (1H, s), 3.72 (1H, d, J = 15.3 Hz) 3.61–3.41 (1H, m), 2.07 (3H, s), 1.84–1.41 (6H, m), 1.15 (4H, m); ^{13}C NMR (300 MHz) (DMSO-d_6): δ 163.3, 156.7, 145.3, 142.6, 142.5, 136.4, 128.7, 127.5, 127.4, 91.4, 90.7, 60.5, 47.8, 44.8, 32.24, 32.19, 25.0, 24.3, 24.2, 13.8; MS (ESI$^+$) *m*/*z* 379 (M + 1, 100%); HRMS (ESI$^+$) calculated for $C_{23}H_{27}N_2O_3$ 379.1943.

General procedure 1

(*R*)-2-Benzyl-*N*-cyclohexyl-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (16). A suspension of (3*S*,3a*S*,6*R*)-2-(benzyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-*N*-(cyclohexyl)-3a,6-epoxy-3a*H*-isoindole-3-carboxamide (**15**) (0.19 g, 0.50 mmol) in 3.0 mL of H_3PO_4 (80%) was irradiated with microwaves (100 °C, 200 W) for 40 min. The resulting solution was diluted with 2 M NaOH, extracted with CH_2Cl_2 (2 × 25 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude reaction mixture was subjected to flash silica gel chromatography (2 : 3 EtOAc : hexanes) to afford (*R*)-2-benzyl-*N*-cyclohexyl-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (0.14 g, 72%) as an off-white semi-solid.

General procedure 2

(*R*)-2-Benzyl-*N*-cyclohexyl-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (16). A suspension of (3*S*,3a*S*,6*R*)-2-(benzyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-*N*-(cyclohexyl)-3a,6-epoxy-3a*H*-isoindole-3-carboxamide (**15**) (0.2 g, 0.52 mmol) in 2.0 mL of specified pIL was irradiated with microwaves (80 °C, 200 W) for 20 min. The resulting solution was diluted with 2 M HCl, extracted with CH_2Cl_2 (2 × 25 mL), dried ($MgSO_4$), and concentrated *in vacuo* to afford (*R*)-2-benzyl-*N*-cyclohexyl-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (0.18 g, 91%) as an off-white semi-solid. Yields as per Table 1.

^{1}H NMR (300 MHz) (DMSO-d_6): δ 9.67 (1 H, bs), 8.34 (1 H, d, J = 7.8 Hz), 7.44–7.22 (3 H, m), 7.18 (2 H, d, J = 7.6 Hz), 7.05 (1 H, d, J = 8.1 Hz), 6.95 (1 H, d, J = 8.1 Hz), 5.14 (1 H, d, J = 15.1 Hz), 4.66 (1 H, s), 3.88 (1 H, d, J = 15.1 Hz), 3.51 (1 H, m), 2.46 (3 H, s), 1.84–1.43 (5 H, m), 1.16 (5 H, m); ^{13}C NMR (300 MHz) (DMSO-d_6): δ 168.9, 166.0, 155.9, 137.0, 132.3, 129.1, 128.6, 127.8, 127.3, 122.4, 119.7, 177.7, 60.7, 47.7, 44.0, 32.2, 32.1, 25.0, 24.3, 9.2; MS (ESI$^+$) *m*/*z* 379 (M + 1, 100%); HRMS (ESI$^+$) calculated for $C_{23}H_{27}N_2O_3$; 379.1943.

(*R*)-Ethyl 2-(5-hydroxy-4-methyl-2-(4-chlorophenyl)-3-oxoisoindoline-1-carboxamido)acetate (17). Synthesised as described in general procedure 2 from (3*S*,3a*S*,6*R*)-2-(4-chlorophenyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-*N*-(2-ethoxy-2-oxoethyl)-3a,6-epoxy-3a*H*-isoindole-3-carboxamide (0.2 g, 0.50 mmol), and 2.0 mL TE:TfOH affording *R*)-ethyl 2-(5-hydroxy-4-methyl-2-(4-chlorophenyl)-3-oxoisoindoline-1-carboxamido)acetate as a pale brown solid in a 91% yield.

^{1}H NMR (300 MHz) (DMSO-d_6): δ 9.62 (1 H, bs), 9.03 (1H, t, J = 5.6 Hz), 7.58 (2H, d, J = 9.0 Hz), 7.42 (2H, d, J = 8.9 Hz), 7.08 (1 H, d, J = 8.0 Hz), 6.95 (1 H, d, J = 8.0 Hz), 5.03 (1 H, s), 4.07 (2H, q, J = 7.1 Hz) 3.86 (2H, qd,

$J = 17.4, 5.7$ Hz), 2.19 (3H, s), 1.14 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (75 MHz) (DMSO-d_6): δ 169.1, 167.5, 162.7, 161.8, 142.9, 142.4, 141.8, 137.2, 129.0, 128.4, 122.9, 119.7, 117.8, 62.9, 60.5, 40.8, 14.0, 13.9; MS (ESI+) m/z 403 (M + 1, 100%); HRMS (ESI$^+$) calculated for $C_{20}H_{20}ClN_2O_5$ 403.0982.

(*R*)-Ethyl-2-(5-hydroxy-4-methyl-2-(4-nitrophenyl)-3-oxoisoindoline-1-carboxamido)acetate (18). Synthesised as described in general procedure 2 from (3*S*,3a*S*,6*R*)-2-(4-nitrophenyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-*N*-(2-ethoxy-2-oxoethyl)-3a,6-epoxy-3a*H*-isoindole-3-carboxamide (0.2 g, 0.48 mmol), and 2.0 mL TE:TfOH affording (*R*)-ethyl-2-(5-hydroxy-4-methyl-2-(4-nitrophenyl)-3-oxoisoindoline-1-carboxamido)acetate as a pale brown in a 96% yield.

^{1}H NMR (300 MHz) (DMSO-d_6): δ 9.61 (1 H, bs), 9.18 (1H, t, $J = 5.7$ Hz), 8.24 (2H, d, $J = 9.1$ Hz), 7.83 (2H, d, $J = 9.1$ Hz), 7.08 (1 H, d, $J = 7.9$ Hz), 6.95 (1 H, d, $J = 7.9$ Hz), 4.94 (1 H, s), 4.05 (2H, q, $J = 7.0$ Hz), 3.87 (2H, qd, $J = 17.6, 5.7$ Hz), 2.22 (3H, s), 1.13 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (75 MHz) (DMSO-d_6): δ 169.2, 167.3, 165.2, 162.1, 144.3, 143.1, 142.8, 141.9, 141.8, 124.3, 120.3, 120.2, 118.3, 62.8, 60.6, 40.8, 14.2, 13.9; MS (ESI$^+$) *m/z* 414 (M + 1, 100%); HRMS (ESI$^+$) calculated for $C_{20}H_{20}N_2O_7$ 414.1223.

(*R*)-Methyl 2-(5-hydroxy-2-(4-hydroxyphenyl)-4-methyl-3-oxoisoindoline-1-carboxamido)acetate (19). Synthesised as described in general procedure 2 from (3*S*,3a*S*,6*R*)-2-(4-hydroxyphenyl)-1,2,3,6-tetrahydro-7-propyl-1-oxo-*N*-(2-methoxy-2-oxoethyl)-3a,6-epoxy-3a*H*-isoindole-3-carboxamide (0.2 g, 0.54 mmol), and 2.0 mL TE:TfOH, affording (*R*)-methyl 2-(5-hydroxy-2-(4-hydroxyphenyl)-4-methyl-3-oxoisoindoline-1-carboxamido)acetate as a pale yellow solid in a 87% yield.

^{1}H NMR (300 MHz) (DMSO-d_6): δ 9.61 (1 H, bs), 9.32 (1H, bs) 9.03 (1H, t, $J = 5.6$ Hz), 7.58 (2H, d, $J = 8.9$ Hz), 7.42 (2H, d, $J = 8.9$ Hz), 7.11 (1 H, d, $J = 8.1$ Hz), 6.98 (1 H, d, $J = 8.1$ Hz), 4.97 (1 H, s), 3.75 (2H, qd, $J = 17.4, 5.7$ Hz), 3.51 (3H, s), 3.35 (3H, s); ^{13}C NMR (75 MHz) (DMSO-d_6): δ 169.1, 167.5, 162.7, 161.8, 142.9, 141.8, 137.2, 129.0, 128.4, 122.9, 118.2, 117.8, 62.9, 60.5, 40.8, 14.0, 13.9; MS (ESI$^+$) m/z 371 (M + 1, 100%); HRMS (ESI$^+$) calculated for $C_{19}H_{19}N_2O_6$ 371.1165.

(*R*)-2-(3-(Dimethylamino)propyl)-5-hydroxy-3-oxo-*N*,4-dipentylisoindoline-1-carboxamide (20). Synthesised as described in general procedure 2 from (3*S*,3a*S*,6*R*)-2-(4-*N*,*N*-dimethylaminopropyl)-1,2,3,6-tetrahydro-7-pentyl-1-oxo-*N*-(pentyl)-3a,6-epoxy-3a*H*-isoindole-3-carboxamide (0.2 g, 0.48 mmol), and 2.0 mL TE:TfOH affording (*R*)-2-(3-(dimethylamino)-propyl)-5-hydroxy-3-oxo-*N*,4-dipentylisoindoline-1-carboxamide as a yellow solid in a 85% yield.

^{1}H NMR (300 MHz) (DMSO-d_6): δ 9.61 (1 H, bs), 8.47 (1 H, t, $J = 5.5$ Hz), 7.08 (1 H, d, $J = 7.9$ Hz), 6.95 (1 H, d, $J = 7.9$ Hz), 4.94 (1 H, s), 3.89–3.62 (2 H, m), 3.19-2.81 (4 H, m), 2.10 (6 H, s), 1.78-1.53 (2 H, m), 1.53-1.34 (10 H, m), 1.24 (4 H, m), 0.83 (6 H, m); ^{13}C NMR (300 MHz) (DMSO-d_6): δ 168.6, 167.4, 155.5, 132.4, 129.3, 127.2, 119.7, 117.8, 61.6, 56.5, 44.9, 38.9, 38.6, 31.4, 29.3, 28.5, 28.4, 25.4, 22.9, 21.9, 21.7, 13.9, 13.8; MS (ESI$^+$) *m/z* 418 (M + 1, 100%); HRMS (ESI$^+$) calculated for $C_{24}H_{40}N_3O_3$; 418.2991.

(*R*)-2-Benzyl-*N*-butyl-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide (21). Synthesised as described in general procedure 2 from (3*S*,3a*S*,6*R*)-2-(benzyl)-1,2,3,6-tetrahydro-7-methyl-1-oxo-*N*-(butyl)-3a,6-epoxy-3a*H*-isoindole-3-carboxamide (0.2 g, 0.57 mmol), and 2.0 mL TE:TfOH affording (*R*)-2-benzyl-*N*-butyl-5-hydroxy-4-methyl-3-oxoisoindoline-1-carboxamide as a white solid in a 95% yield.

^{1}H NMR (300 MHz) (DMSO-d_6): δ 9.67 (1 H, s), 8.57 (1H, t, $J = 5.6$ Hz), 7.44–7.22 (3 H, m), 7.18 (2 H, d, $J = 7.6$ Hz), 7.05 (1 H, d, $J = 8.1$ Hz), 6.95 (1 H, d, $J = 8.1$ Hz), 5.06 (1H, d, $J = 15.1$ Hz), 4.16 (1H, s), 3.74 (1H, d, $J = 15.1$ Hz), 3.17 (2H, qd, $J = 13.0, 6.5$ Hz), 2.13 (3H, s), 1.50–1.16 (4H, m), 0.88 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz) (DMSO-d_6): δ 166.5, 162.7, 159.0, 142.5, 142.4, 135.9, 132.4, 128.7, 127.9, 127.5, 118.8, 117.3, 61.1, 44.6, 38.3, 30.8, 19.3, 13.8, 13.5; MS (ESI$^+$) m/z 353 (M + 1, 100%); HRMS (ESI$^+$) calculated for $C_{21}H_{25}N_2O_3$ 353.1787.

General procedure 3

3-Benzyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (24). A neat solution of benzylamine (0.20 mL, 1.8 mmol) and 2-furaldehyde (0.17 mL, 1.8 mmol) was irradiated with microwaves (150 W, 100 °C) for 5 min. The resulting mixture was diluted with EtOH (36 mL) to afford a ~0.05 M solution which was subsequently hydrogenated with a H-cube system loaded with 10% Pd/C CatCart, at 50 °C, under 50 bar of H_2 pressure, and a flow rate of 1 mL min^{-1}. The eluate was concentrated *in vacuo* and to the crude mixture was added toluene (3.0 mL) and maleic anhydride (0.26 g, 2.7 mmol). The resulting solution was irradiated with microwaves (250 W, 60 °C) for 10 min, cooled (0 °C), and the resulting precipitate was collected and washed with cold diethyl ether to afford 3-benzyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (0.39 g, 76%) as a white solid (m.p. 151–152 °C).

^{1}H NMR (300 MHz) (MeOH): δ 7.57–7.07 (5 H, m), 6.55 (1 H, d, $J = 5.8$ Hz), 6.44 (1 H, dd, $J = 5.8, 1.7$ Hz), 5.09 (1 H, d, $J = 1.7$ Hz), 4.81 (1 H, bs), 4.54 (1 H, d, $J = 15.2$ Hz), 4.44 (1 H, d, $J = 15.2$ Hz), 3.94 (1 H, d, $J = 11.8$ Hz), 3.55 (1 H, d, $J = 11.8$ Hz), 2.92 (1 H, d, $J = 9.1$ Hz), 2.73 (1 H, d, $J = 9.1$ Hz); ^{13}C NMR (75 MHz) (MeOH): δ 173.6, 171.6, 135.8, 135.3, 134.8, 127.8, 126.9, 126.6, 88.1, 81.3, 50.5, 47.3, 45.4, 44.1; MS (ESI$^+$) m/z 286 (M+1, 100%); HRMS (ESI$^+$) for $C_{16}H_{16}NO_4$, calculated 286.2946, found 286.2947.

3-(2-Pyridinylmethyl)-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]-dec-8-ene-6-carboxylic acid (25). Synthesised as described in general procedure 3 from 2-pyridinylmethanamine (1.30 mL, 12.0 mmol), 2-furaldehyde (1.2 mL, 12 mmol), and maleic anhydride (1.76 g, 18 mmol) to afford 3-(2-pyridinylmethyl)-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (3.05 g, 60%) as a light brown solid (m.p. 92–94 °C). ^{1}H NMR (300 MHz) (DMSO-d_6): δ 12.30 (1 H, s), 8.50 (1 H, d, $J = 4.5$ Hz), 7.74 (1 H, dt, $J = 7.8, 1.7$ Hz), 7.26 (2 H, m), 6.58 (1 H, d, $J = 5.7$ Hz), 6.42 (1 H, dd, $J = 5.7, 1.7$ Hz), 5.02 (1 H, d, $J = 1.5$ Hz), 4.54 (1 H, d, $J = 15.2$ Hz), 4.44 (1 H, d, $J = 15.2$ Hz), 4.05 (1 H, d, $J = 11.6$ Hz), 3.57 (1 H, d, $J = 11.6$ Hz), 2.88 (1 H, d, $J = 9.2$ Hz), 2.51 (1 H, d, $J = 9.2$ Hz); ^{13}C NMR (75 MHz) (DMSO-d_6): δ 172.8, 170.7, 156.4, 149.0, 136.8, 136.5, 135.5, 122.2, 120.8, 88.4, 81.0, 49.9, 48.2, 47.3, 44.4; MS (ESI$^+$) *m/z* 287 (M + 1, 100%); HRMS (ESI$^+$) for $C_{15}H_{15}N_2O_4$, calculated 287.0954, found 287.0954.

3-[2-(3,4-Dimethoxyphenyl)ethyl]-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (26). Synthesised as described in general procedure 3 from 2-furaldehyde (0.30 mL, 3.66 mmol), (3,4-dimethoxyphenyl)methanamine (0.61 g, 3.66 mmol), and maleic anhydride (0.54 g, 5.49 mmol) to afford 3-[2-(3,4-dimethoxyphenyl)ethyl]-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (1.07 g, 85%) as an off-white solid (m.p. 134–135 °C).

^{1}H NMR (300 MHz) (DMSO-d_6): δ 12.31 (1 H, s), 6.86 (1 H, d, $J = 8.2$ Hz), 6.80 (1 H, s), 6.75 (1 H, d, $J = 8.2$ Hz), 6.54 (1 H, d, $J = 5.7$ Hz), 6.40 (1 H, dd, $J = 5.7$, 1.4 Hz), 4.99 (1 H, d, $J = 1.2$ Hz), 4.49 (1 H, d, $J = 15.1$ Hz), 4.15 (1 H, d, $J = 15.1$ Hz), 3.88 (1 H, d, $J = 11.6$ Hz), 3.70 (6 H, bs), 3.40 (1 H, d, $J = 11.6$ Hz), 2.85 (1 H, d, $J = 9.2$ Hz), 2.49 (1 H, d, $J = 9.2$ Hz); ^{13}C NMR (75 MHz) (DMSO-d_6): δ 172.9, 170.3, 148.8, 147.7, 136.5, 135.5, 128.7, 119.3, 111.5, 110.6, 88.3, 81.0, 55.3, 55.2, 50.1, 47.1, 44.6, 44.4; MS (ESI$^+$) m/z 346 (M + 1, 100%); HRMS (ESI$^+$) for $C_{18}H_{20}NO_6$, calculated 346.1212, found 346.1212.

3-(4-Methoxyphenyl)-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]-dec-8-ene-6-carboxylic acid (27). Synthesised as described in general procedure 3 from 4-methoxyaniline (0.40 g, 1.9 mmol), 2-furaldehyde (0.60 mL, 1.9 mmol), and maleic anhydride (0.27 g, 2.8 mmol) to afford 3-(4-methoxyphenyl)-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (0.39 g, 68%) as an off-white solid (m.p. 134–135 °C).

^{1}H NMR (300 MHz) (DMSO-d_6): δ ppm 12.31 (1 H, s), 7.54 (2 H, d, $J = 8.6$ Hz), 6.92 (2 H, d, $J = 8.6$ Hz), 6.61 (1 H, d, $J = 5.5$ Hz), 6.46 (1 H, d, $J = 4.7$ Hz), 5.02 (1 H, s), 4.48 (1 H, d, $J = 11.5$ Hz), 3.98 (1 H, d, $J = 11.5$ Hz), 3.72 (3 H, s), 3.01 (1 H, d, $J = 8.9$ Hz), 2.55 (1 H, d, $J = 8.9$ Hz); ^{13}C NMR (75 MHz) (DMSO-d_6): 172.8, 169.7, 155.6, 136.8, 135.3, 132.6, 121.0, 113.7, 87.3, 81.2, 55.1, 51.2, 49.3, 45.1; MS (ESI$^+$) m/z 302 (M + 1, 100%); HRMS (ESI$^+$) for $C_{16}H_{15}NO_5$, calculated 301.0950, found 301.0948.

2-Benzyl-3-oxo-2,3-dihydro-1*H*-isoindole-5-carboxylic acid (28). Synthesised as described in general procedure 2 from **24** (0.20 g, 0.70 mmol), and 2.0 mL TEA:TfOH to afford 2-benzyl-3-oxo-2,3-dihydro-1*H*-isoindole-5-carboxylic acid (0.18 g, 96%) as an off-white solid (m.p. 164–165 °C).

^{1}H NMR (300 MHz) (DMSO-d_6): δ 8.13 (1 H, d, $J = 6.7$ Hz), 7.85 (1 H, d, $J = 6.7$ Hz), 7.78 (1 H, t, $J = 6.7$ Hz), 7.37–7.30 (5 H, m), 4.84 (2 H, s), 4.60 (2 H, s); ^{13}C NMR (75 MHz) (DMSO-d_6): δ 168.9, 164.8, 143.1, 135.9, 132.3, 131.7, 128.7, 128.3, 127.9, 127.8, 127.7, 50.8, 46.3; MS (ESI$^+$) m/z 268 (M + 1, 100%); HRMS (ESI$^+$) for $C_{16}H_{14}NO_3$, calculated 268.0895, found 268.0891.

2-[2-(3,4-Dimethoxyphenyl)ethyl]-3-oxo-2,3-dihydro-1*H*-isoindole-5-carboxylic acid (29). Synthesised as described in general procedure 2 from **25** (0.20 g, 0.58 mmol), and 2.0 mL TEA:TfOH to afford 2-[2-(3,4-dimethoxyphenyl)ethyl]-3-oxo-2,3-dihydro-1*H*-isoindole-5-carboxylic acid (0.17 g, 90%) as an off-white solid (m.p. 179–180 °C).

^{1}H NMR (300 MHz) (DMSO-d_6): δ 8.13 (1 H, d, $J = 6.7$ Hz), 7.85 (1 H, d, $J = 6.7$ Hz), 7.78 (1 H, t, $J = 6.7$ Hz), 6.86 (1 H, d, $J = 8.2$ Hz), 6.80 (1 H, s), 6.75 (1 H, d, $J = 8.2$ Hz), 4.84 (2 H, s), 4.60 (2 H, s); 3.70 (6 H, bs); ^{13}C NMR (75 MHz) (DMSO-d_6): δ 168.9, 164.8, 149.9, 148.8, 147.7, 143.1, 138.7, 136.5, 135.9, 135.5, 128.8, 119.3, 111.52, 110.5, 55.4, 55.2, 50.5, 47.1; MS (ESI$^+$) m/z 328 (M + 1, 100%); HRMS (ESI$^+$) for $C_{18}H_{18}NO_5$, calculated 328.3313 found 328.3313.

2-(2-Pyridinylmethyl)-3-oxo-2,3-dihydro-1*H*-isoindole-5-carboxylic acid (30). Synthesised as described in general procedure 2 from **26** (0.20 g, 0.70 mmol), and 2.0 mL TEA:TfOH to afford 2-(2-pyridinylmethyl)-3-oxo-2,3-dihydro-1*H*-isoindole-5-carboxylic acid (0.18 g, 96%) as an off-white solid (m.p. 139–140 °C).

^{1}H NMR (300 MHz) (DMSO-d_6): δ 8.50 (1 H, d, $J = 4.5$ Hz), 8.13 (1 H, d, $J = 6.7$ Hz), 7.85 (1 H, d, $J = 6.7$ Hz), 7.78 (1 H, t, $J = 6.7$ Hz), 7.74 (1 H, dt, $J = 7.8$, 1.7 Hz), 7.26 (2 H, m), 4.84 (2 H, s), 4.60 (2 H, s); ^{13}C NMR (75 MHz) (DMSO-d_6): δ 172.8, 170.7, 156.4, 149.9, 149.0, 138.7, 136.8, 136.5, 135.5, 128.8, 127.3, 122.2, 120.8, 50.8, 46.3; MS (ESI$^+$) m/z 269 (M + 1, 100%); HRMS (ESI$^+$) for $C_{15}H_{13}N_2O_3$, calculated 269.2674, found 269.2673.

2-(4-Methoxyphenyl)-3-oxo-2,3-dihydro-1*H*-isoindole-5-carboxylic acid (31). Synthesised as described in general procedure 2 from **27** (0.20 g, 0.67 mmol), and 2.0 mL TEA:TfOH to afford 2-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1*H*-isoindole-5-carboxylic acid (0.17 g, 90%) as an off-white solid (m.p. 169–170 °C).

^{1}H NMR (300 MHz) (DMSO-d_6): δ ppm 8.13 (1 H, d, $J = 6.7$ Hz), 7.85 (1 H, d, $J = 6.7$ Hz), 7.78 (1 H, t, $J = 6.7$ Hz), 7.54 (2 H, d, $J = 8.6$ Hz), 6.92 (2 H, d, $J = 8.6$ Hz), 4.60 (2 H, s); 3.72 (3 H, s); ^{13}C NMR (75 MHz) (DMSO-d_6): 172.8, 169.7, 155.7, 147.9, 144.2, 136.8, 135.3, 135.2, 131.8, 121.3, 114.4, 113.7, 56.5, 55.1; MS (ESI$^+$) m/z 284 (M + 1, 100%); HRMS (ESI$^+$) for $C_{16}H_{14}NO_4$, calculated 284.0845 found 284.0842.

Acknowledgements

This work was supported by the Australian Research Council. We thank Drs Jennette A Sakoff and Jayne Gilbert for growth inhibition studies on compounds **15** and **16**.

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50 Standard laboratory practice involves rotary evaporation and solvent collection for recycling. Rotary evaporation is conducted using a Heidolph coupled to a Vacuubrand PC 3001 vario vacuum pump cooled with reticulated chilled water (8 °C). Typically >85% recover is achieved and the solvent recycled.

