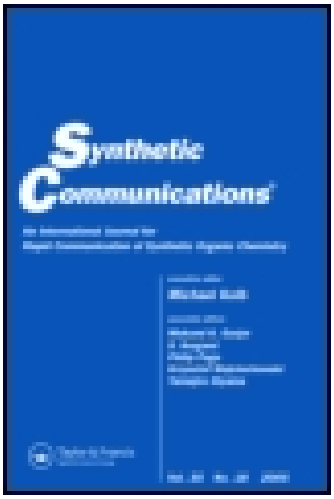

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Indolizine Studies, Part 5: Indolizine-2-carboxamides as Potential HIV-1 Protease Inhibitors[ ]

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INDOLIZINE STUDIES, PART 5: INDOLIZINE-2-CARBOXAMIDES AS POTENTIAL HIV-1 PROTEASE INHIBITORS[1]

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1,1-Carbonyldiimidazole-promoted coupling of Baylis–Hillman-derived indolizine-2-carboxylic acids with a range of amine and amino acid derivatives has provided access to the corresponding carboxamides in moderate to excellent yield.

Keywords: Baylis–Hillman reaction; HIV-1 protease inhibitors; indolizine-2-carboxamides

The HIV/AIDS pandemic has already been responsible for the death of millions of people worldwide, and it is estimated that there are 5 million new infections every year.[2] The development of inhibitors that target key enzymes in the HIV-1 life cycle, namely, reverse transcriptase (HIV-RT),[3] integrase (HIV-IN),[4] and protease (HIV-PR),[5] has improved life expectancy. However, the efficacy of these drugs has been mitigated by the development of resistance and the unpleasant side effects, which, in turn, may lead to patient non-compliance. Although the problem of drug resistance has been addressed, at least temporarily, by the implementation of highly active antiretroviral therapy (HAART), which involves the combination of HIV-PR and HIV-RT inhibitors,[6] there is an urgent need for new, improved, and cost-effective anti-HIV drugs.

In an earlier study, we reported the preparation of analogs of the HIV-1 protease inhibitor ritonavir.[7] In this approach, Baylis–Hillman-derived chromene, coumarin, and thiochromene heterocyclic systems were attached to the amino termini of the hydroxyethylene dipeptide isostere, present in ritonavir **1**. We have, subsequently, been exploring the construction of novel, and more synthetically accessible, truncated analogs in which various heterocyclic moieties are linked to a peptido-mimetic chain as illustrated in Fig. 1.

Indolizine derivatives have been reported to exhibit valuable biological activity as potential calcium entry blockers,[8] cardiovascular agents,[8,9] anti-5-hydroxytryptamine,[10] antihistamine,[10] antitumor,[11] anti-*Mycobacterium tuberculosis* (TB),[12] anticancer,[8,13] and anti-HIV[8,14] agents. Various approaches have been developed

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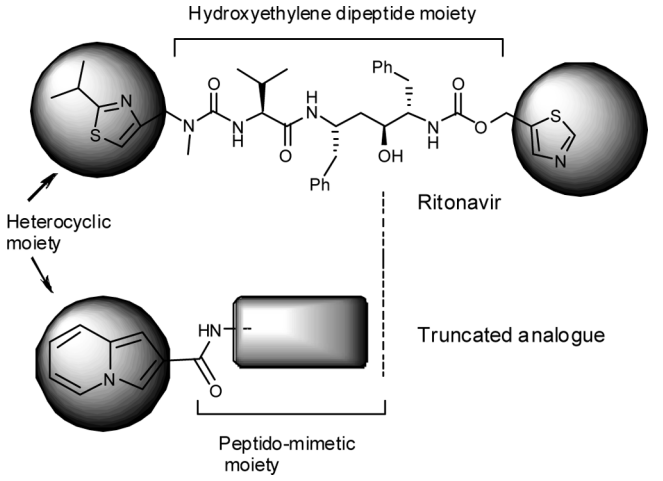
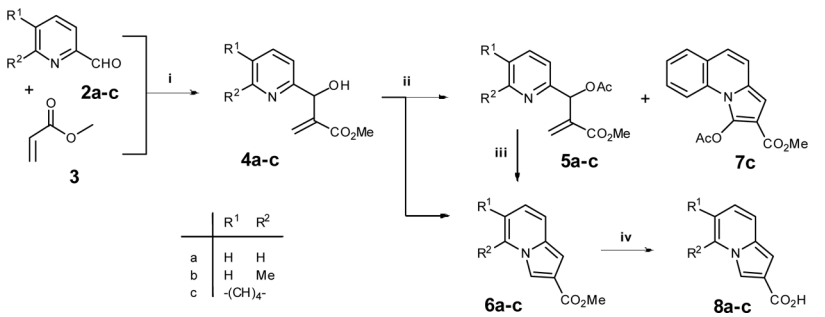


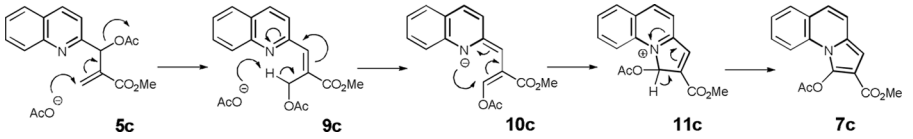
Figure 1. Design rationale for truncated analogs.

for the synthesis of indolizine derivatives.[15] These include condensation reactions (i.e., the Scholtz[15] and Chichibabin reactions[16]), 1,3-dipolar cycloaddition,[17] and an approach pioneered in our own group involving the use of Baylis–Hillman methodology.[18] Attention has also been given to the preparation and rotational isomerism of a series of indolizine-2-carboxamides.[19] In an extension of these earlier studies, we now report the synthesis and characterization of a series of indolizine-based truncated analogs of the hydroxyethylene dipeptide isosteres, typified by ritonavir.

The indolizine-2-carboxylate esters **6a–c** were prepared using the methodology developed previously[18] (Scheme 1). Thus, the pyridine-2-carbaldehydes **2a–c** were treated with methyl acrylate **3** and 1,4-diazabicyclo[2.2.2]octane (DABCO) (or 3-hydroxyquinuclidine) in chloroform to afford the Baylis–Hillman adducts **4a–c**. Cyclization to the corresponding indolizine-2-carboxylate esters **6a–c** was effected by heating the acetates **5a–c** in acetic anhydride at 120 °C for 30 min. Acetylation



Scheme 1. Synthesis of indolizine scaffolds. Reagents and conditions: (i) DABCO or 3-hydroxyquinuclidine, $CHCl_3$; (ii) Ac_2O, 100 °C, 30 min; (iii) 120 °C, 1 h; and (iv) KOH, EtOH, reflux, 16 h, then dil. HCl.

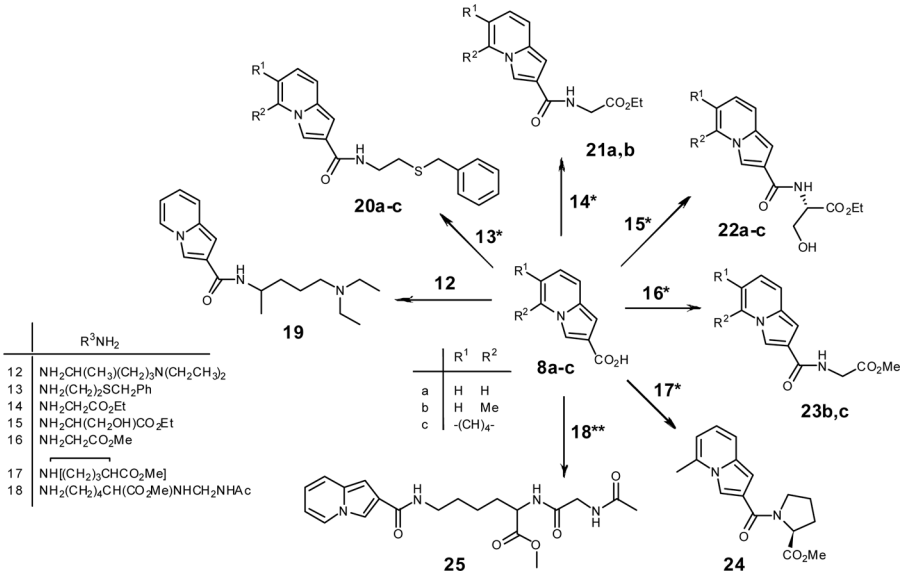


Scheme 2. Proposed mechanism for the formation of methyl 1-acetoxypyrrolo[1,2-*a*]quinoline-2-carboxylate **7c**.

of the alcohol precursors **4a–c** (at 100 °C for 30 min) has been found to facilitate cyclization,[18] but, not surprisingly under these conditions, the acetylated products may be accompanied by some of the corresponding cyclized derivatives. In the case of the quinoline derivative **4c**, the acetylated product **5c** was accompanied not only by the corresponding indolizine **6c** but also by the unexpected 1-acetoxyindolizine **7c** as a minor product (ca. 6%). Both the presence of the acetoxy moiety (a good leaving group) and its location at C-1 rather than C-3 were surprising, and the formation of this minor product is attributed to allylic displacement of the 3-acetoxy group, followed by an aza-Nazarov cyclization as illustrated in Scheme 2. A kinetic–mechanistic study of the cyclization step (**5** → **6**) has already been published.[1] The indolizine-2-carboxylate esters were saponified using ethanolic potassium hydroxide; neutralization then afforded the carboxylic acids **8a–c**, required as precursors for the title carboxamides, in moderate yield (57–65%).

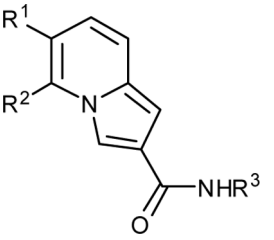
With the indolizine-2-carboxylic acids **8a–c** in hand, attention could be turned to the formation of the series of amide derivatives. Earlier studies had indicated that the best general method for accessing indolizine-2-carboxamides involved direct reaction of the carboxylic acid with the amine in the presence of the coupling agent, carbonyl diimidazole (CDI) in dry dimethylformamide (DMF).[19] In the present study, the amino compounds chosen for reaction were 1-methyl-5-(diethylamino)butylamine **12**, *S*-benzylcysteamine **13**, glycine ethyl ester **14**, L-serine ethyl ester **15**, glycine methyl ester **16**, L-proline methyl ester **17**, and the dipeptide, *N*-acetyl-glycine-lysine methyl ester **18**. Compounds **12–17** were used as the hydrochloride salts and compound **18** was used as the acetate salt; in these cases, pyridine was added as a base to release the free amino compound. The indolizine-2-carboxylic acids **8a–c** and CDI were each dissolved in dry DMF (with pyridine for reactions involving salts), and the resulting mixtures were heated at 40 °C for 5 min. After cooling to room temperature, the amino compound (**12–18** or their hydrochloride salts) was added, and the mixture was stirred overnight at room temperature (Scheme 3). Purification of the crude products was achieved using preparative layer chromatography to afford the corresponding indolizine-2-carboxamide derivatives **19–25** in 64–97% yield (Table 1). The products were all characterized by spectroscopic [infrared (IR), one- and two-dimensional NMR] and elemental [high-resolution mass spectrometry (HRMS)] analysis.

Baylis–Hillman methodology has thus been successfully used to access a range of 13 novel *N*-substituted indolizine-2-carboxamides as truncated ritonavir analogs. Enzyme-binding, enzyme-inhibition, and in silico enzyme receptor-site docking studies of these compounds are planned to explore their potential as readily accessible HIV-1 protease inhibitors.



Scheme 3. Formation of carboxamide derivatives **19–25**. Reagents and conditions: CDI, DMF, 40 °C then amino compounds **12–18** (as *hydrochloride or **acetate salt with pyridine), rt, overnight.

Table 1. Isolated yields of the indolizine-2-carboxamides **19–25** (Scheme 3)



Compound	R^1	R^2	R^3	Yield (%)
19	H	H	$-CH(CH_3)(CH_2)_3N(CH_2CH_3)_2$	69
20a	H	H	$-(CH_2)_2SCH_2Ph$	64
20b	H	Me	$-(CH_2)_2SCH_2Ph$	79
20c		$-(CH)_4-$	$-(CH_2)_2SCH_2Ph$	97
21a	H	H	$-CH_2CO_2Et$	66
21b	H	Me	$-CH_2CO_2Et$	40
22a	H	H	$-CH(CH_2OH)CO_2Et$	47
22b	H	Me	$-CH(CH_2OH)CO_2Et$	44
22c		$-(CH)_4-$	$-CH(CH_2OH)CO_2Et$	34
23b	H	Me	$-CH_2CO_2Me$	82
23c		$-(CH)_4-$	$-CH_2CO_2Me$	70
24	H	Me	$-CH_2(CH_2)_2CH(CO_2Me)-$	50
25	H	H	$-CH_2(CH_2)_3CH(CO_2Me)NHCH_2NHAc-$	60

EXPERIMENTAL

Low-resolution mass spectra were obtained on a Finnegan Mat GCQ spectrometer, whereas HRMS were recorded on Micromass 70-70E (University of the North-West) and Waters API-Q-TOF Ultima spectrometers (University of Stellenbosch). NMR spectra were recorded on a Bruker 400 MHz AVANCE spectrometer and were referenced using solvent signals (δ_H: 7.26 ppm for residual $CHCl_3$ and δ_C: 77.0 ppm for $CDCl_3$). IR spectra were recorded on a Perkin-Elmer Fourier transform (FT)–IR Spectrum 2000 spectrometer using nujol mulls or thin films. Melting points were determined using a Reichert hot-stage apparatus and are uncorrected. Reagents used in this project were supplied by Aldrich and used without further purification. The indolizine-2-carboxylate esters **6a–c** and the corresponding acids **8a–c** are known and were obtained following reported procedures.[18,19] The novel carboxamides **19–25** were prepared as follows.

N-[4-(Diethylamino)-1-methylbutyl]indolizine-2-carboxamide 19

Indolizine-2-carboxylic acid **8a** (0.100 g, 0.63 mmol) was dissolved in dry DMF (3 ml) in a round-bottomed flask fitted with a reflux condenser and a drying tube. 1,1′-Carbonyldiimidazole (CDI) (0.160 g, 0.954 mmol) was added to the mixture, which was heated at 40 °C for 5 min. The mixture was allowed to cool to room temperature, 1-methyl-5-(diethylamino)butylamine **12** (0.245 g, 1.55 mmol) was added, and the resulting mixture was stirred overnight. The reaction was then quenched with water (1 ml), and the solvent was removed under reduced pressure. Aqueous Na_2CO_3 (1 M, 15 ml) was added to the residue, and the mixture was extracted with EtOAc (2×24 ml) and then washed sequentially with water (24 ml) and saturated brine (24 ml). The extract was dried over $MgSO_4$, and the solvent removed in vacuo to afford a yellow oil (0.241 g), which was purified by flash chromatography [on silica; elution with CH_2Cl_2–aqueous ammonia–methanol (20:4:1)] to afford *N*-[4-(diethylamino)-1-methylbutyl]indolizine-2-carboxamide **19** as a yellow oil (0.132 g, 69.4%). Found M^+: 301.216652; $C_{18}H_{27}N_3O$ requires M, 301.215413. ν_{max}(KBr)/cm^{-1} 1609 (NHC=O); δ_H (400 MHz; $CDCl_3$) 1.00 (6H, t, *J* 7.2 Hz, $2 \times CH_3CH_2$), 1.25 (3H, d, *J* 6.8 Hz, $CHCH_3$), 1.55 (4H, m, $CH_2CH_2CH_2N$), 2.44 (2H, t, *J* 3.2 Hz, CH_2CH_2N), 2.52 (4H, q, *J* 7.2 Hz, CH_3CH_2N), 4.21 (1H, m, $CHCH_3$), 6.02 (1H, d, *J* 9.6 Hz, NH), 6.51 (1H, m, Ar-H), 6.56 (1H, s, Ar-H), 6.68 (1H, m, Ar-H), 7.34 (1H, d, *J* 9.2 Hz, Ar-H), 7.74 (1H, d, *J* 0.8 Hz, Ar-H) and 7.86 (1H, dd, *J* 7.0 and 0.6 Hz, Ar-H); δ_C (100 MHz; $CDCl_3$) 11.5 (q), 21.1 (q), 23.6 (t), 35.0 (t), 45.1 (d), 46.8 (t), 52.7 (t), 96.9 (d), 111.8 (d), 113.9 (d), 118.2 (d), 119.8 (d), 124.2 (s), 125.4 (d), 132.8 (s) and 164.1 (s).

N-[2-(Benzylthio)ethyl]indolizine-2-carboxamide 20a

Indolizine-2-carboxylic acid **8a** (0.100 g, 0.63 mmol) in dry DMF (5 ml) and dry pyridine (3 ml) was reacted with *S*-benzylcysteamine hydrochloride **13** (0.200 g, 0.960 mmol), following the procedure described for the preparation of *N*-[4-(diethylamino)-1-methylbutyl]indolizine-2-carboxamide **19**, to afford a crude product, which was purified by preparative layer chromatography [on silica; elution

with CH_2Cl_2–methanol (20:4)] to afford *N*-[2-(benzylthio)ethyl]indolizine-2-carboxamide **20a** as a yellow solid (0.12 g, 65%), mp 104–106 °C. Found M^+: 310.113786; $C_{18}H_{18}N_2OS$ requires M, 310.113985. ν_{max}(KBr)/cm^{-1} 1652 (C=O); δ_H (400 MHz; $CDCl_3$) 2.69 (2H, t, *J* 6.4 Hz, CH_2CH_2S), 3.61 (2H, m, CH_2CH_2S), 3.76 (2H, s, CH_2Ar), 6.38 (1H, br s, NH), 6.52 (1H, m, Ar-H), 6.57 (1H, s, Ar-H), 6.70 (1H, dd, *J* 8.4 and 6.8 Hz, 6-H), 7.24 (1H, m, Ar-H), 7.33 (5H, m, Ar-H), 7.74 (1H, d, *J* 1.2 Hz, Ar-H) and 7.88 (1H, d, *J* 6.4 Hz, Ar-H); δ_C (100 MHz; $CDCl_3$) 31.3 (t), 35.8 (t), 37.9 (t), 97.1 (d), 111.9 (d), 114.0 (s), 118.3 (d), 120.0 (d), 123.5 (s), 125.4 (d), 127.1 (d), 128.6 (d), 128.8 (d), 132.9 (s), 138.1 (s) and 164.7 (s).

N-[2-(Benzylthio)ethyl]-5-methylindolizine-2-carboxamide 20b

Following the procedure described for the synthesis of *N*-[2-(benzylthio)-ethyl]indolizine-2-carboxamide **20a**, *S*-benzylcysteamine hydrochloride **13** (0.200 g, 0.960 mmol) was reacted with 5-methylindolizine-2-carboxylic acid **8b** (0.100 g, 0.571 mmol) to afford *N*-[2-(benzylthio)ethyl]-5-methylindolizine-2-carboxamide **20b** as a green oil (0.147 g, 78.9%). Found M + 1: 325.1376; $C_{19}HN_{21}OS$ requires MH^+, 325.1376. ν_{max}(KBr)/cm^{-1} 1642 (C=O); δ_H (400 MHz; $CDCl_3$) 2.46 (3H, s, 5-CH_3), 2.69 (2H, t, *J* 6.8 Hz, 11-CH_2), 3.61 (2H, q, *J* 6.8 and 7.2 Hz, 10-CH_2), 3.74 (2H, s, $ArCH_2$), 6.40 (1H, d, *J* 6.8 Hz, Ar-H), 6.68 (3H, m, Ar-H and NH), 7.23–7.34 (6H, overlapping signals, Ar-H) and 7.70 (1H, s, Ar-H); δ_C (100 MHz; $CDCl_3$) 18.5 (q), 31.1 (t), 35.7 (t), 38.0 (t), 97.5 (d), 110.9 (d), 111.3 (d), 117.4 (d), 118.6 (d), 123.3 (s), 127.0 (d), 128.5 (d), 128.7 (d), 133.1 (s), 133.5 (s), 138.0 (s) and 165.0 (s).

N-[2-(Benzylthio)ethyl]pyrrolo[1,2-*a*]quinoline-2-carboxamide 20c

Following the procedure described for the synthesis of *N*-[2-(benzylthio)-ethyl]indolizine-2-carboxamide **20a**, *S*-benzylcysteamine hydrochloride **13** (0.200 g, 0.960 mmol) was reacted with pyrrolo[1,2-*a*]quinoline-2-carboxylic acid **8c** (0.100 g, 0.47 mmol) to afford *N*-[2-(benzylthio)ethyl]pyrrolo[1,2-*a*]quinoline-2-carboxamide **20c** as a yellow oil (0.162 g, 96.7%). Found M + 1: 361.1389; $C_{22}H_{21}N_2OS$ requires MH^+, 361.1375. ν_{max}(KBr)/cm^{-1} 1732 (C=O); δ_H (400 MHz; $CDCl_3$) 2.71 (2H, t, *J* 6.4 Hz, NCH_2CH_2), 3.63 (2H, m, NCH_2), 3.76 (2H, s, $ArCH_2$), 6.68 (2H, m, Ar-H and NH), 6.99 (1H, d, *J* 9.2 Hz, Ar-H), 7.20–7.34 (7H, overlapping signals, Ar-H), 7.46 (1H, m, Ar-H), 7.59 (1H, d, *J* 7.6 Hz, Ar-H), 7.81 (1H, d, *J* 8.0 Hz, Ar-H) and 8.34 (1H, s, Ar-H); δ_C (100 MHz; $CDCl_3$) 31.2 (t), 35.8 (t), 38.1 (t), 100.5 (d), 114.0 (d), 114.3 (d), 118.7 (d), 120.3 (d), 122.6 (s), 123.9 (s), 124.5 (d), 127.0 (d), 128.1 (d), 128.5 (d), 128.6 (d), 128.8 (d), 131.2 (s), 132.8 (s), 138.0 (s) and 164.6 (s).

N-Carbethoxymethylindolizine-2-carboxamide 21a

Following the procedure described for the synthesis of *N*-[2-(benzylthio)-ethyl]indolizine-2-carboxamide **20a**, glycine ethyl ester hydrochloride **14** (0.200 g, 1.40 mmol) was reacted with indolizine-2-carboxylic acid **8a** to afford *N*-[(carbethoxy)methyl]indolizine-2-carboxamide **21a** as a green oil (0.097 g, 66%).

Found M^+: 246.099889; $C_{13}H_{14}N_2O_3$ requires M, 246.100442. ν_{max}(KBr)/cm^{-1} 1637 (NHC=O) and 1705 (C=O); δ_H (400 MHz; $CDCl_3$) 1.31 (3H, t, *J* 7.2 Hz, CH_3), 4.24 (2H, s, NCH_2), 4.27 (2H, q, *J* 7.2 Hz, CH_3CH_2), 6.50–6.54 (2H, overlapping signals, Ar-H), 6.64 (1H, s, NH), 6.69 (1H, m, Ar-H), 7.36 (1H, d, *J* 9.2 Hz, Ar-H), 7.77 (1H, s, Ar-H) and 7.88 (1H, d, *J* 6.8 Hz, Ar-H); δ_C (100 MHz; $CDCl_3$) 14.2 (q), 41.5 (t), 61.6 (t), 97.3 (d), 112.0 (d), 114.1 (d), 118.3 (d), 120.0 (d), 122.9 (s), 125.4 (d), 132.9 (s), 164.7 (s) and 170.3 (s).

N-Carbethoxymethyl-5-methylindolizine-2-carboxamide 21b

Following the procedure described for the synthesis of *N*-[2-(benzylthio)-ethyl]indolizine-2-carboxamide **20a**, 5-methylindolizine-2-carboxylic acid **8b** (0.100 g, 0.571 mmol), and glycine ethyl ester hydrochloride **14** (0.200 g, 1.40 mmol) were reacted to afford *N*-carbethoxymethyl-5-methylindolizine-2-carboxamide **21b** as a yellow oil (0.059 g, 39.9%). Found M + 1: 261.1250; $C_{14}H_{17}N_2O_3$ requires MH^+, 261.1239. ν_{max}(KBr)/cm^{-1} 1647 (NHC=O) and 1693 (C=O); δ_H (400 MHz; $CDCl_3$) 1.29 (3H, t, *J* 7.2 Hz, CH_3CH_2), 2.45 (3H, s, Ar-CH_3), 4.24 [4H, overlapping s and q (*J* 7.2 Hz), NCH_2 and CH_3CH_2], 6.38 (1H, d, *J* 6.8 Hz, Ar-H), 6.66–6.70 (2H, overlapping signals, Ar-H), 6.80 (1H, br s, NH), 7.26 (1H, t, *J* 4.6 Hz, Ar-H) and 7.68 (1H, s, Ar-H); δ_C (100 MHz; $CDCl_3$) 14.1 (q), 18.5 (q), 41.5 (d), 61.5 (d), 97.9 (d), 111.0 (d), 111.3 (d), 117.5 (d), 118.6 (d), 122.6 (s), 133.1 (s), 133.5 (s), 165.1 (s) and 170.4 (s).

Ethyl (2*S*)-3-Hydroxy-2-(indolizine-2-carboxamido)propanoate 22a

Following the procedure described for the synthesis of *N*-[2-(benzylthio)ethyl]-indolizine-2-carboxamide **20a**, L-serine ethyl ester hydrochloride **15** (0.200 g, 1.18 mmol) was reacted with indolizine-2-carboxylic acid **8a** to afford ethyl (2*S*)-3-hydroxy-2-(indolizine-2-carboxamido)propanoate **22a** as a yellow oil (0.080 g, 47%). Found M^+: 276.109981; $C_{14}H_{16}N_2O_4$ requires M, 276.111007. ν_{max}(KBr)/cm^{-1} 1633 (NHC=O) and 1700 (C=O); δ_H (400 MHz; $CDCl_3$) 1.27 (4H, t, *J* 6.8 Hz, CH_3CH_2 and overlapping OH signal), 4.04 (2H, d, *J* 3.6 Hz, $CHCH_2$), 4.24 (2H, q, *J* 6.0 Hz, CH_3CH_2), 4.83 (1H, m, $CHCH_3$), 6.45 (1H, m, Ar-H), 6.63 (2H, m, Ar-H), 7.18 (1H, d, *J* 7.2 Hz, NH), 7.24 (1H, s, Ar-H), 7.71 (1H, d, *J* 1.2 Hz, Ar-H) and 7.76 (1H, dd, *J* 7.0 and 1.0 Hz, Ar-H); δ_C (100 MHz; $CDCl_3$) 14.4 (q), 55.4 (d), 62.2 (t), 63.8 (t), 98.0 (d), 112.2 (d), 114.5 (d), 118.6 (d), 120.2 (d), 122.8 (s), 125.7 (d), 133.1 (s), 165.6 (s) and 171.1 (s).

Ethyl (2*S*)-3-Hydroxy-2-(5-methylindolizine-2-carboxamido)-propanoate 22b

Following the procedure described for the synthesis of *N*-[2-(benzylthio)-ethyl]indolizine-2-carboxamide **20a**, L-serine ethyl ester hydrochloride **15** (0.200 g, 1.18 mmol) was reacted with 5-methylindolizine-2-carboxylic acid **8b** (0.100 g, 0.571 mmol) to afford ethyl (2*S*)-3-hydroxy-2-(5-methylindolizine-2-carboxamido)-propanoate **22b** as a yellow oil (0.072 g, 44%). Found M + 1: 291.1374; $C_{15}H_{19}N_2O_4$ requires MH^+, 291.1395. ν_{max}(KBr)/cm^{-1} 1649 (NHC=O) and 1732

(C=O); δ_H (400 MHz; $CDCl_3$) 1.27 (3H, t, *J* 7.2 Hz, CH_2CH_3), 2.39 (3H, s, Ar-CH_3), 4.05 (2H, d, *J* 3.2 Hz, OCH_2), 4.24 (2H, q, *J* 7.2 Hz, CH_2CH_3), 4.85 (1H, m, NCH), 6.34 (1H, d, *J* 6.4 Hz, Ar-H), 6.65 (1H, m, Ar-H), 6.71 (1H, s, NH), 7.21 (1H, d, *J* 9.2 Hz, Ar-H), 7.24 (1H, s, Ar-H) and 7.64 (1H, s, Ar-H); δ_C (100 MHz; $CDCl_3$) 14.0 (q), 18.4 (q), 55.2 (d), 61.9 (t), 63.5 (t), 98.2 (d), 111.0 (s), 111.3 (d), 117.5 (d), 118.6 (d), 122.3 (s), 133.1 (s), 133.5 (s), 165.5 (s) and 170.8 (s).

Ethyl (2*S*)-3-Hydroxy-2-{pyrrolo[1,2-*a*]quinoline-2-carboxamido}-propanoate 22c

Following the procedure described for the synthesis of *N*-[2-(benzylthio)ethyl]-indolizine-2-carboxamide **20a**, L-serine ethyl ester hydrochloride **15** (0.200 g, 1.18 mmol) was reacted with pyrrolo[1,2-*a*]quinoline-2-carboxylic acid **8c** (0.100 g, 0.47 mmol) to afford ethyl (2*S*)-3-hydroxy-2-{pyrrolo[1,2-*a*]quinoline-2-carboxamido}propanoate **22c** as a brown oil (0.0524 g, 34.2%). Found M + 1: 327.1348; $C_{18}H_{19}N_2O_4$ requires MH^+, 327.1345. ν_{max}(KBr)/cm^{-1} 1638 (NHC=O) and 1732 (C=O); δ_H (400 MHz; $CDCl_3$) 1.31 (3H, t, *J* 7.0 Hz, CH_2CH_3), 3.08 (1H, br s, OH), 4.09 (2H, m, CH_2OH), 4.27 (2H, q, *J* 7.0 Hz, CH_2CH_3), 4.87 (1H, m, NCH), 6.71 (2H, s, Ar-H), 6.91 (1H, d, *J* 9.6 Hz, Ar-H), 7.12 (1H, d, *J* 9.2 Hz, 5Ar-H), 7.17 (1H, d, *J* 7.2 Hz, NH), 7.26 (1H, s, OH), 7.30 (1H, t, *J* 7.6 Hz, Ar-H), 7.44 (1H, t, *J* 7.4 Hz, Ar-H), 7.54 (1H, d, *J* 7.6 Hz, Ar-H), 7.78 (1H, d, *J* 8.0 Hz, Ar-H) and 8.30 (1H, s, Ar-H); δ_C (100 MHz; $CDCl_3$) 14.1 (q), 55.2 (d), 62.0 (t), 63.7 (t), 101.0 (d), 114.2 (d), 114.4 (d), 118.7 (d), 120.4 (d), 121.8 (s), 124.0 (s), 124.6 (d), 128.2 (d), 128.6 (d), 131.3 (s), 132.8 (s), 165.1 (s) and 170.8 (s).

N-Carbomethoxymethyl-5-methylindolizine-2-carboxamide 23b

Following the procedure described for the synthesis of *N*-[2-(benzylthio)-ethyl]indolizine-2-carboxamide **20a**, glycine methyl ester hydrochloride **16** (0.200 g, 1.59 mmol) was reacted with 5-methyindolizine-2-carboxylic acid **8b** (0.100 g, 0.571 mmol) to afford *N*-carbomethoxymethyl-5-methylindolizine-2-carboxamide **23b** as a brown oil (0.115 g, 81.9%). Found M + 1: 247.1091; $C_{13}H_{15}N_2O_3$ requires MH^+, 247.1083. ν_{max}(KBr)/cm^{-1} 1649 (NHC=O) and 1730 (C=O); δ_H (400 MHz; $CDCl_3$) 2.46 (3H, s, OCH_3), 3.78 (3H, s, Ar-CH_3), 4.25 (2H, d, *J* 5.2 Hz, CH_2), 6.39 (1H, d, *J* 6.4 Hz, Ar-H), 6.68–6.72 (2H, overlapping signals, Ar-H), 6.76 (1H, br s, NH), 7.27 (1H, d, *J* 9.6 Hz, Ar-H) and 7.69 (1H, s, Ar-H); δ_C (100 MHz; $CDCl_3$) 18.5 (q), 41.3 (t), 52.3 (q), 97.8 (d), 111.0 (d), 111.4 (d), 117.6 (d), 118.7 (d), 122.6 (s), 133.2 (s), 133.6 (s), 165.1 (s) and 170.8 (s).

N-(Carbomethoxymethyl)pyrrolo[1,2-*a*]quinoline-2-carboxamide 23c

Following the procedure described for the synthesis of *N*-[2-(benzylthio)-ethyl]indolizine-2-carboxamide **20a**, glycine methyl ester hydrochloride **16** (0.200 g, 1.59 mmol) was reacted with pyrrolo[1,2-*a*]quinoline-2-carboxylic acid **8c** (0.100 g, 0.47 mmol) to afford *N*-(carbomethoxymethyl)pyrrolo[1,2-*a*]quinoline-2-carboxamide **23c** as a brownish-yellow oil (0.094 g, 70%). Found M + 1: 283.1083; $C_{16}H_{15}N_2O_3$ requires MH^+, 283.1083. ν_{max}(KBr)/cm^{-1} 1659 (NHC=O) and 1733

(C=O); δ_H (400 MHz; $CDCl_3$) 3.80 (3H, s, CH_3), 4.27 (2H, d, *J* 5.2 Hz, CH_2), 6.71 (1H, d, *J* 0.8 Hz, Ar-H), 6.75 (1H, br s, NH), 6.98 (1H, d, *J* 9.2 Hz, Ar-H), 7.20 (1H, d, *J* 9.6 Hz, Ar-H), 7.33 (1H, t, *J* 7.6 Hz, Ar-H), 7.48 (1H, t, *J* 7.6 Hz, Ar-H), 7.59 (1H, d, *J* 7.6 Hz, Ar-H), 7.82 (1H, d, *J* 8.4 Hz, Ar-H) and 8.33 (1H, s, Ar-H); δ_C (100 MHz; $CDCl_3$) 41.3 (t), 52.3 (q), 100.7 (d), 114.2 (d), 114.4 (d), 118.7 (d), 120.4 (d), 122.0 (s), 124.0 (s), 124.6 (d), 128.2 (d), 128.7 (d), 131.3 (s), 132.9 (s), 164.7 (s) and 170.9 (s).

Methyl (2*S*)-1-[(5-Methylindolizin-2-yl)carbonyl]pyrrolidine-2-carboxylate 24

Following the procedure described for the synthesis of *N*-[2-(benzylthio)-ethyl]indolizine-2-carboxamide **20a**, L-proline methyl ester hydrochloride **17** (0.200 g, 1.20 mmol) was reacted with 5-methylindolizine-2-carboxylic acid **8b** (0.100 g, 0.571 mmol) to afford methyl (2*S*)-1-[(5-methylindolizin-2-yl)carbonyl]-pyrrolidine-2-carboxylate **24** as a brown oil (0.080 g, 50%). Found M + 1: 287.1383; $C_{16}H_{19}N_2O_3$ requires MH^+, 287.1396. ν_{max}(KBr)/cm^{-1} 1603 (NC=O) and 1736 (C=O); δ_H (400 MHz; $CDCl_3$) 2.00 (2H, m, $CH_2CH_2CH_2$), 2.13 and 2.30 (2H, 2 × m, $CHCH_2$), 2.48 (3H, s, Ar-CH_3), 3.75 (3H, s, OCH_3), 3.96 (2H, m, NCH_2), 4.69 (1H, dd, *J* 8.2 and 5.0 Hz, $CHCH_2$), 6.40 (1H, d, *J* 6.8 Hz, Ar-H), 6.68 (1H, m, Ar-H), 6.78 (1H, s, Ar-H), 7.29 (1H, t, *J* 9.0 Hz, Ar-H) and 7.68 (1H, s, Ar-H); δ_C (100 MHz; $CDCl_3$) 18.5 (q), 25.4 (t), 28.9 (t), 49.1 (t), 52.1 (q), 59.8 (d), 99.7 (d), 110.9 (d), 112.7 (d), 117.5 (d), 118.3 (d), 122.8 (s), 132.9 (s), 165.2 (s) and 173.0 (s).

1-(Indolizin-2-yl)-7-carbomethoxy-1,9,12-trioxo-2,8,11-triazatridecane 25

Indolizine-2-carboxylic acid **8a** (0.100 g, 0.63 mmol) in dry DMF (5 ml) was reacted with *N*-acetyl-glycine-lysine methyl ester acetate salt **18** (0.150 g, 0.578 mmol) following the procedure described for the preparation of *N*-[4-(diethylamino)-1-methylbutyl]indolizine-2-carboxamide **19**. The crude product was purified using preparative layer chromatography [on silica; elution with CH_2Cl_2–methanol (20:4)] to afford 1-(indolizine-2-yl)-7-carbomethoxy-1,9,12-trioxo-2,8,11-triazatridecane **25** as a brown solid (0.150 g, 60.1%), mp 114–116 °C. Found M^+: 402.1880; $C_{20}H_{26}N_4O_5$ requires M, 402.1903. ν_{max}(nujol)/cm^{-1} 1741 (C=O), 1664, 1638, 1630 (3 × NHC=O); δ_H (400 MHz; $CDCl_3$) 1.40 and 1.56 (4H, 2 × m, $NCH_2CH_2CH_2$), 1.76 and 1.88 (2H, 2 × m, CH_2CH), 1.99 (3H, s, CH_3CO), 3.36 and 3.50 (2H, 2 × m, NCH_2), 3.70 (3H, s, OCH_3), 3.94 (1H, dd, *J* 16.8 and 4.8 Hz, NCH_aCO) and 4.05 (1H, dd, *J* 16.8 and 5.6 Hz, NCH_bCO), 4.47 (1H, m, CH_2CH), 6.50 (1H, t, *J* 6.8 Hz, Ar-H), 6.16 (1H, br s, NH), 6.64–6.69 (2H, overlapping signals, Ar-H), 6.89 (1H, m, NH), 7.30 (1H, d, *J* 8.8 Hz, Ar-H), 7.41 (1H, d, *J* 7.2 Hz, NH), 7.85 (1H, s, Ar-H) and 7.90 (1H, d, *J* 6.8 Hz, Ar-H); δ_C (100 MHz; $CDCl_3$) 22.0 (t), 22.9 (q), 29.1 (t), 30.8 (t), 38.3 (t), 43.1 (t), 52.2 (q), 52.4 (d), 97.1 (d), 111.9 (d), 114.3 (d), 118.4 (d), 119.7 (d), 123.3 (s), 125.6 (d), 132.9 (s), 165.6 (s), 169.2 (s), 170.8 (s) and 172.5 (s).

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