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Facile ring-opening of *N*-acylisatins for the development of novel peptidomimetics

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ABSTRACT

A range of novel mono- and bis-glyoxylamide peptidomimetics were prepared via the facile ring-opening of *N*-acylisatins with amino acids and peptide derivatives. The ring-opening of *N*-acylisatins with dipeptides and tripeptides was discovered to be the most efficient strategy for the synthesis of second and third generation glyoxylamides.

1. Introduction

Peptides are a major class of biological molecules that play critical roles at all levels of cellular and physiological regulation, and have thus attracted attention in the design of therapeutic agents. For example, novel peptides have been used to disrupt the regulatory systems in Gram-positive bacteria, which are typically mediated by auto-inducing peptides.[1] The heptapeptide RNAIII-inhibiting peptide has recently been reported to be an effective quorum sensing inhibitor of *Staphylococcus aureus* and *Staphylococcus epidermidis*.[2,3]

Peptides typically show higher bactericidal potency and lower propensity for generating resistance compared to conventional antibiotics, such as penicillin and sulfonamides, but also suffer from low metabolic stability and poor pharmacokinetic properties.[4–6] These characteristics have resulted in increasing interest in the development of peptide alternatives, such as peptidomimetics.

Peptidomimetics mimic the primary structure of peptides through use of amide bond isosteres and/or modification of the peptide backbone through the incorporation of an unnatural functionality. Examples include the use of (*Z*)-alkene isosteres and insertion of triazole moieties.[7] Peptide mimics typically show higher metabolic stability and improved bioavailability without compromising the selectivity and potency of the parent peptide sequence.[3,4,8] This approach has been successfully applied to the development of HIV protease inhibitors and glycoprotein IIa/IIIa antagonists.[3,6]

The C2 carbonyl moiety of *N*-acylisatins behaves as an imide carbonyl group as opposed to the conventional amide carbonyl functionality in isatin.[9] The result is that *N*-acylisatins are more susceptible to nucleophilic ring-opening addition reactions in the presence of hard nucleophiles, such as amines and alcohols. This facile ring-opening reaction, if performed using a peptide nucleophile, could readily facilitate the development of a novel range of peptide mimics, which possess a phenylglyoxylic acid functionality.[10] It was envisaged that the aromatic ring derived from the isatin core would increase the metabolic stability of the peptide sequence. Meanwhile, the introduction of the glyoxylamide moiety could prove potentially advantageous due to its prevalence in a range of natural and synthetic bioactive compounds.

We disclose herein the ring-opening reaction of *N*-acylisatins with amino acids and short peptide sequences, as well as the synthesis of new bis-glyoxylamides, in our efforts to develop novel peptidomimetics as potential therapeutic agents.

2. Results and discussion

2.1. Synthesis of first generation peptidomimetics

As a starting point to our investigation, the nucleophilic ring-opening of *N*-acetylisatin **1** with glycine was studied. As the free amino acid failed to react, the carboxylic acid was protected as the methyl ester. Treatment of *N*-acetylisatin **1** with glycine methyl ester hydrochloride and sodium hydroxide in a dichloromethane/

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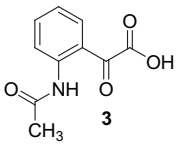
water (v/v 3:1) biphasic system for 24 h at room temperature afforded the target peptide mimic **2a** upon acidic workup in a low yield of 20%. Examination of the reaction conditions suggested that the low yield of product could be attributed to the sodium hydroxide catalyst acting as a nucleophile. The competing ring-opening reaction with hydroxide would produce the corresponding acid **3** as an insoluble by-product after washing the reaction mixture with dilute aqueous hydrochloric acid.

The effect of several different bases on the selectivity of the ring-opening reaction was subsequently investigated. The reactions were performed under the classic Schotten–Baumann conditions[11] described previously and the crude products were analysed by thin layer chromatography, ^{1}H NMR spectroscopy and IR spectroscopy. The use of potassium hydroxide as a base was found to produce a 20:80 mixture of the peptide mimic and carboxylic acid by-product. The formation of the by-product was confirmed through IR spectroscopy, which exhibited a strong adsorption at ν=3390 cm^{-1} indicative of the carboxylic acid functional group.



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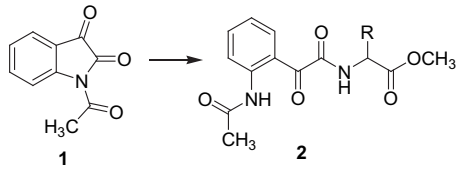
When potassium carbonate was used, unreacted starting material was predominately recovered together with a 15% yield of the peptide mimic **2a**. Gratifyingly, the use of sodium bicarbonate as a base provided a 65% yield of the desired product **2a**. After further optimization studies, it was found that the pre-neutralization of the glycine methyl ester hydrochloride salt with saturated sodium bicarbonate in chilled water before addition to a solution of *N*-acetylisatin in dichloromethane avoided the formation of the carboxylic side product **3**. Additionally, the use of 2.5 equiv of glycine methyl ester hydrochloride afforded the most efficient conversion.

In light of these results, *N*-acetylisatin **1** was reacted under these conditions with L-valine, L-phenylalanine, D-phenylalanine and L-methionine methyl ester hydrochlorides to produce the *N*-glyoxylamino acid esters **2a**–**e** in 85–97% yield (Scheme 1, Table 1). In addition, the ring-opening reaction of *N*-acetylisatin **1** upon treatment with sarcosine methyl ester hydrochloride gave the corresponding *N*-methylated glycine derivative **2f** in 60% yield. Interestingly, two rotational isomers of peptidomimetic **2f** were detected by ^{1}H NMR spectroscopy in $CDCl_3$, which was postulated to be due to the absence of a stabilizing hydrogen bond to the carbonyl group in the benzylic position and restricted rotation of the *N*-methylglyoxylamine group.



Scheme 1. Regents and conditions: amino acid methyl ester hydrochloride salt, $NaHCO_3$, CH_2Cl_2/H_2O (1:1 v/v), 0 °C to rt, 24 h.

Attention subsequently turned to the use of acidic and basic amino acids. The ring-opening reaction of *N*-acetylisatin with L-lysine methyl ester proved to be problematic with only the carboxylic acid **3** being produced. It was assumed that the reaction was inhibited by the presence of the additional amino group, which increased the solubility of the amino acid in the aqueous medium. It was envisaged that protection of the additional amino group would facilitate the desired reaction; however, this approach was not pursued due to difficulties in preparing the *tert*-butoxycarbonyl or carbobenzyloxyl mono-*N*-protected L-lysine methyl ester. On the other hand, the ring-opening reaction of *N*-acetylisatin with L-aspartic acid dimethyl ester hydrochloride successfully produced the target *N*-glyoxylamino acid ester **2g** as a sticky oil in 65% yield.

Table 1
First generation peptidomimetics

Entry	Amino acid[a]	Product[b]	Yield[c] (%)
1	Glycine	**2a**	65
2	L-Valine	**2b**	97
3	L-Phenylalanine	**2c**	98
4	D-Phenylalanine	**2d**	98
5	L-Methionine	**2e**	85
6	Sarcosine	**2f**	60
7	L-Aspartic acid	**2g**	65

[a] As the methyl ester hydrochloride salt.
[b] R=corresponding amino acid substituent.
[c] Isolated yield.

2.2. Synthesis of second and third generation peptidomimetics

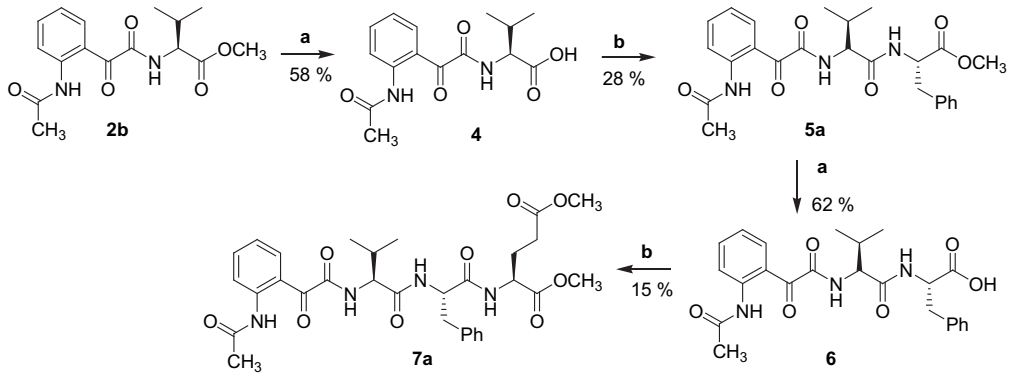
It was anticipated that second and third generation peptidomimetics could be generated by hydrolysis of the methyl ester moiety of the first generation analogues followed by amide coupling with another amino acid (Scheme 2).

The hydrolysis reaction of analogue **2b** was attempted by stirring with 1.0 M aqueous sodium hydroxide in a biphasic solvent system. However, this led to the presumed decomposition of the desired carboxylic acid **4**. Several base systems were consequently screened and it was found that the use of either 0.5 M aqueous potassium hydroxide in methanol or 0.8 M lithium hydroxide in an 8:2 mixture of methanol and water furnished the target carboxylic acid **4** in satisfactory yields. Overall, it was determined that the slow addition of base to an ice cold solution of the peptide mimic in methanol protected the desired product from decomposition. Amide coupling of carboxylic acid **4** and L-phenylalanine methyl ester hydrochloride was performed at room temperature for 48 h in a mixture of dichloromethane and dimethylformamide (v/v 3:2) in the presence of activating agent 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDAC), additive 1-hydroxybenzotriazole hydrate (HOBt), which stabilizes the active ester intermediate[12] thus reducing the possibility of racemisation and bases *N*-methylmorpholine and *N*,*N*-diisopropylethylamine. Purification of the crude product by column chromatography afforded the second generation peptidomimetic **5a** as a light yellow solid in 28% yield.

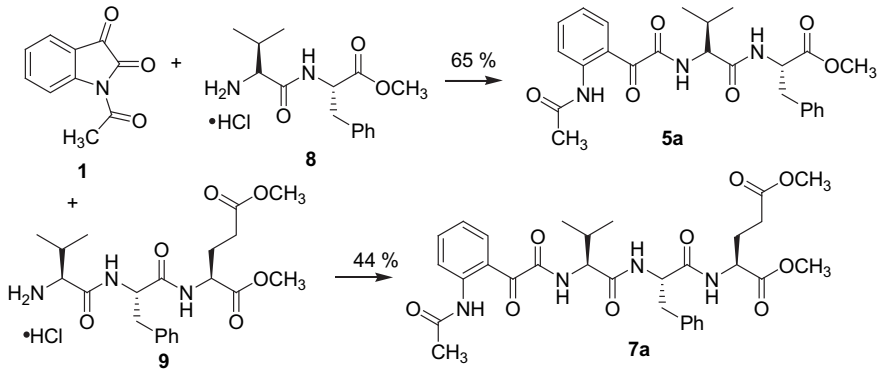
Subsequent hydrolysis of the second generation mimic **5a** followed by amide coupling with L-glutamic acid methyl ester hydrochloride gave the corresponding third generation peptidomimetic **7a** in only 15% yield. The poor yield was attributed to difficulties during the purification of this compound, a common problem when performing multiple amide coupling reactions.

Due to the limited versatility of the initial strategy, the ring-opening reaction of *N*-acetylisatin with dipeptides and tripeptides was examined. Coupling of the selected amino acids was conducted under mild conditions in the presence of EDAC and HOBt, with Boc groups being used to protect the free amine. The dipeptides were furnished in 72–86% yield while the tripeptides were obtained in slightly lower yields of 50–72%.

The nucleophilic ring-opening of *N*-acylisatin **1** with the dipeptide hydrochloride salt **8** was achieved using the standard conditions to give the dipeptidomimetic **5a** in 65% yield. In a similar fashion the ring-opening of *N*-acylisatin **1** with tripeptide hydrochloride salt **9** produced the third generation peptide mimic **7a** in 44% yield (Scheme 3).



Scheme 2. Reagents and conditions: (a) KOH (0.5 M), MeOH, 0 °C to rt, 1.5 h (b) amino acid methyl ester hydrochloride salt, EDAC, HOBt, pyridine, 0 °C to rt, 52 h.



Scheme 3. Reagents and conditions: $NaHCO_3$, CH_2Cl_2/H_2O (2:1 v/v), 0 °C to rt, 24 h.

Overall, the second strategy produced the model dipeptide **5a** and tripeptide **7a** in significantly higher yields and purity. This methodology was therefore extended to a range of second and third generation *N*-glyoxylamine peptidomimetics (Table 2).

Table 2
Second and third generation peptidomimetics

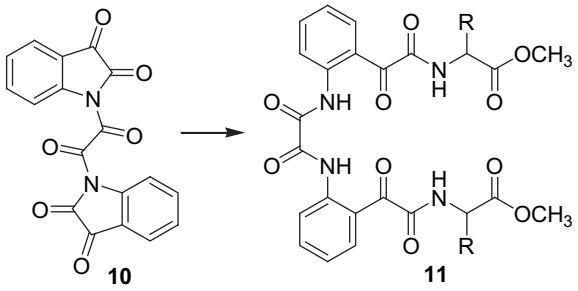
Entry	Dipeptides and tripeptides[a]	Product	Yield[b] (%)
1	L-Valine-L-phenylalanine	**5a**	65
2	L-Valine-D-phenylalanine	**5b**	65
3	L-Valine-L-methionine	**5c**	55
4	L-Valine-L-phenylalanine-L-glutamic acid	**7a**	44
5	L-Alanine-L-valine-D-phenylalanine	**7b**	30

[a] As the methyl ester hydrochloride salt.
[b] Isolated yield.

2.3. Synthesis of bis-glyoxylamides

The versatility of the established methodology was thought to lend itself towards the tandem ring-opening of two isatin units to provide convenient access to both *C*,*C*′ and *N*,*N*′-linked bis-glyoxylamides.

It was envisaged that *C*,*C*′ linked bis-glyoxylamides could be prepared by the duel ring-opening reaction of oxalyl bisisatin **10**. Treatment of oxalyl bisisatin **10** with 4 equiv of glycine methyl ester hydrochloride was found to produce polymeric products. When the number of equivalents was increased to ten, however, the anticipated bis-glyoxylamide **11a** was successfully isolated but in a very low yield of 3%. The reaction efficiency was improved by the use of a bulkier amino acid, with the ring-opening of oxalyl bisisatin **10** with 4 equiv of L-valine methyl ester hydrochloride affording a 42% yield of bis-glyoxylamide **11b**. In a similar fashion, 30–35% yields of first generation *C*,*C*′-linked bis-glyoxylamides **11c**–**e** were prepared (Scheme 4, Table 3, entries 1–5).



Scheme 4. Regents and conditions: amino acid methyl ester hydrochloride salt, $NaHCO_3$, CH_2Cl_2/H_2O (4:1 v/v), 0 °C to rt, 24 h.

Table 3
First and second generation *C*,*C*′-linked bis-glyoxylamides

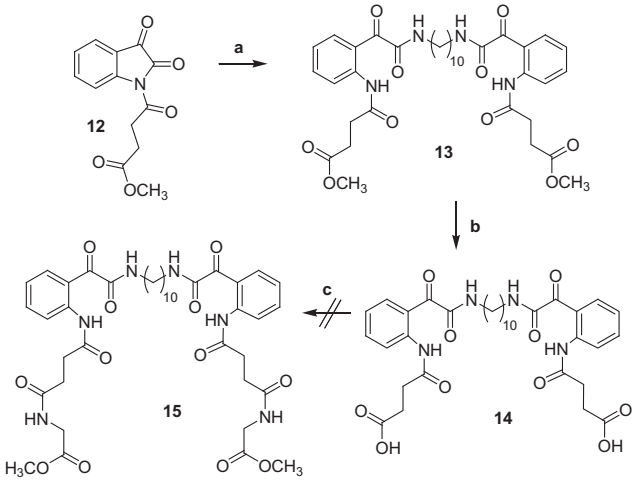
Entry	Amino acid[a]	Product[b]	Yield[c] (%)
1	Glycine	**11a**	3
2	L-Valine	**11b**	42
3	L-Phenylalanine	**11c**	35
4	D-Phenylalanine	**11d**	33
5	L-Methionine	**11e**	30
6	L-Valine-L-phenylalanine	**11f**	20
7	L-Valine-D-phenylalanine	**11g**	20
8	L-Valine-L-methionine	**11h**	20

[a] As the methyl ester hydrochloride salts.
[b] R=corresponding amino acid substituent.
[c] Isolated yield.

In accordance with the preparation of second generation peptidomimetics described previously, ring-opening of oxalyl bisisatin **10** with dipeptides proved to be an efficient strategy in the synthesis of second generation bis-glyoxylamides **11f**–**h** (Table 3, entries 6–8).

Preparation of third generation *C,C′*-linked bis-glyoxylamides proved to be problematic. Ring-opening of oxalyl bisisatin **10** with a tripeptide afforded a mixture of products. The ^{1}H NMR spectrum of the crude product indicated the desired bis-glyoxylamide was formed; however, it could not be isolated due to the poor solubility of the crude material and apparent decomposition upon loading onto silica or alumina columns.

It was envisaged that *N,N′*-linked bis-glyoxylamides could be prepared by the ring-opening of *N*-acylisatins with a diamines followed by amide coupling with a peptide (Scheme 5).



Scheme 5. Reagents and conditions: (a) *i*-Pr$_2$NEt, CH_2Cl_2, rt, 28 h; (b) aq KOH (0.5 M), MeOH, 0 °C to rt, 1.5 h; (c) glycine methyl ester hydrochloride salt, *i*-Pr$_2$NEt, EDAC, HOBt, NMM, CH_2Cl_2/DMF (v/v 8:2), 0 °C to rt, 72 h.

Acylation of isatin with succinyl chloride afforded methyl 4-oxo-4-(2,3-dioxoindolin-1-yl)butanoate **12** in 60% yield. Subsequent reaction with 1,10-diaminodecane in the presence of Hünig's base in dichloromethane yielded the *N,N′*-linked bis-glyoxylamide **13** in 35% yield after column purification. Hydrolysis of the methyl ester moieties was achieved by stirring in methanolic potassium hydroxide at room temperature for 90 min. Acidic workup gave dibutanoic acid **14** as an off-white solid in 40% yield.

Coupling of intermediate **14** with glycine methyl ester hydrochloride was performed in the presence of EDAC and HOBt but the reaction was found to produce a complex mixture of products, which possessed similar R_f values and could not be separated. The use of pentafluorophenyl diphenylphosphinate as an alternate coupling reagent also furnished a complex mixture of products. It was postulated that the presence of many hydrogen bonding sites in the intermediate **14** was interfering with the desired amide coupling reaction.

3. Conclusion

The facile ring-opening of *N*-acylisatins with amino acid and peptide derivatives was found to be a versatile synthetic route to a range of novel glyoxylamide peptidomimetics.

The ring-opening of *N*-acylisatins with dipeptides and tripeptides was found to be a more efficient strategy for the synthesis of second and third generation glyoxylamides than the extension of the peptide chain through hydrolysis and amide coupling of the first generation analogues.

4. Experimental

4.1. General

Melting points were measured using a Reichert microscope (Gallenkamp hot stage apparatus) and are uncorrected. Optical rotations were measured using an Autopol 1 Automatic Polarimeter. Optical rotations were measured at a wavelength of 589 nm and at a temperature of 26 °C. Infrared spectra were recorded with a Thermo Nicolet 370 FTIR spectrometer. UV–vis spectra were recorded using a Varian Cary 100 Scan spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in the designated solvents on a Bruker Avance DPX300 (300 MHz) or a Bruker DMX600 (600 MHz) spectrometer and were internally referenced relative to the solvent nuclei. Acid-free deuterated chloroform was obtained by passing the solvent through a short column of anhydrous K_2CO_3 prior to use. Low resolution mass spectrometric analysis was carried out at the Biomedical Mass Spectrometry Facility, UNSW, and the spectra was recorded on Q-TOF Ultima API (Micromass). High resolution mass spectra were performed at the Campbell Microanalytical Laboratory, University of Otago, New Zealand. Microanalyses were performed on a Carlo Erba Elemental Analyzer EA 1108 at the Campbell Microanalytical Laboratory, University of Otago, New Zealand. Gravity column chromatography was carried out using Merck 230–400 mesh ASTM silica gel.

*4.1.1. Methyl 2-(2-(2-acetamidophenyl)-2-oxoacetamido)acetate (**2a**).* To a stirred solution of the *N*-acetylisatin (0.50 g, 2.6 mmol) in dichloromethane (10 mL) was added a mixture of glycine methyl ester hydrochloride (1.10 g, 8.9 mmol) and saturated sodium hydrogen carbonate solution (3 mL) in water (7 mL) at 5 °C. The reaction mixture was warmed to room temperature and stirred for 24 h. The organic layer was diluted with dichloromethane (20 mL) and extracted with aqueous hydrochloric acid (0.5 M, 15 mL) and water (20 mL). The organic extract was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by gravity column chromatography over silica with dichloromethane to give the title compound **2a** as an off-white solid (0.45 g, 62%). Mp 142–145 °C; R_f 0.29 (EtOAc/CH_2Cl_2, v/v 2:8). Found: C, 56.27; H, 5.16; N, 10.10%. $C_{13}H_{14}N_2O_5$ requires: C, 56.11; H, 5.07; N, 10.07%. ^{1}H NMR (300 MHz; $CDCl_3$): δ 10.9 (1H, br s, NHCO), 8.66 (1H, dd, *J* 1.1, 8.6 Hz, H7), 8.36 (1H, dd, *J* 1.1, 8.1 Hz, H4), 7.60 (1H, dt, *J* 1.5, 8.0 Hz, H6), 7.36 (1H, br s, CONH), 7.12 (1H,dt, *J* 1.5, 7.7 Hz, H5), 4.19 (2H, d, *J* 5.6 Hz, CONHCH_2CO), 3.81 (3H, s, $COOCH_3$), 2.22 (3H, s, $COCH_3$). ^{13}C NMR (75 MHz; $CDCl_3$) δ 190.9, 169.2, 169.1, 162.8, 142.1, 136.6, 134.3, 122.5, 120.6, 118.4, 52.5, 41.1, 25.3. IR (KBr): ν_{max} 3319, 3264, 3077, 2958, 1748, 1673, 1655, 1605, 1582, 1564, 1530, 1451, 1417, 1371, 1333, 1297, 1211, 1166, 1094, 1033, 1004, 979, 966, 941, 764, 708, 681, 598, 524, 490 cm^{-1}. UV (MeOH): λ_{max} 339 (ε 3040 cm^{-1} M^{-1}), 267 (7350), 234 (20,076), 205 (10,940). HRMS (ESI) *m/z* 301.0800 (M+Na)$^+$, $C_{13}H_{14}N_2O_5Na$ requires: 301.0795.

*4.1.2. (S)-Methyl 2-(2-(2-acetamidophenyl)-2-oxoacetamido)-3-methyl butanoate (**2b**).* This compound was prepared by the same method as compound **2a**, from *N*-acetylisatin (0.30 g, 1.6 mmol) and L-valine methyl ester hydrochloride (0.41 g, 2.4 mmol). The title compound **2b** was obtained as a fine yellow solid (0.50 g, 97%). Mp 69–71 °C. R_f 0.47 (EtOAc/CH_2Cl_2, v/v 1:9); $[\alpha]_D^{26}$ +2.2 (*c* 0.009, MeOH). Found: C, 60.08; H, 6.28; N, 8.76%. $C_{16}H_{20}N_2O_5$ requires: C, 59.99; H, 6.29; N, 8.74%. ^{1}H NMR (600 MHz; $CDCl_3$): δ 10.9 (1H, br s, NHCO), 8.69 (1H, dd, *J* 1.2, 8.4 Hz, H7), 8.36 (1H, dd, *J* 1.2, 8.1 Hz, H4), 7.63 (1H, dt, *J* 1.2, 7.8 Hz, H6), 7.29 (1H, d, *J* 9.0 Hz, CONH), 7.14 (1H, dt, *J* 1.2, 7.8 Hz, H5), 4.65 (1H, dd, *J* 2.4, 4.5 Hz, α-CH val), 3.81 (1H, s, $COOCH_3$), 2.31 (1H, m, $CHCH(CH_3)_2$), 2.25 (3H, s, $COCH_3$), 1.01 (3H, d, *J* 7.2 Hz, CH_3), 0.98 (3H, d, *J* 7.2 Hz, CH_3). ^{13}C NMR (150 MHz; $CDCl_3$) δ 207.4, 191.7, 171.9, 169.7, 163.0, 137.2, 134.8, 122.9, 121.1, 118.8, 57.75, 52.9, 31.8, 25.9, 19.5, 18.1. IR (KBr): ν_{max} 3261, 3066, 2963, 2934, 2882, 1740, 1672, 1655, 1607, 1588, 1533, 1452, 1372, 1333, 1298, 1253, 1209, 1168, 1152, 1042, 1018, 878, 821, 756, 705, 683, 597, 552, 522, 484 cm^{-1}. UV (MeOH): λ_{max} 345 (ε 1740 cm^{-1} M^{-1}), 238 (13,450),

205 (10,500). HRMS (ESI) *m*/*z* 343.1264 $(M+Na)^+$, $C_{16}H_{20}N_2O_5Na$ requires: 343.1270.

*4.1.3. (S)-Methyl 2-(2-(2-acetamidophenyl)-2-oxoacetamido)-3-phenyl propanoate (**2c**).* This compound was prepared by the same method as compound **2a**, from *N*-acetylisatin (0.10 g, 0.53 mmol) and L-phenylalanine methyl ester hydrochloride (0.29 g, 1.3 mmol). The title compound **2c** was obtained as an off-white solid (0.18 g, 98%). Mp 116–118 °C. R_f 0.45 (EtOAc/CH_2Cl_2, v/v 1:9); $[\alpha]_D^{26}$ −7.4 (*c* 0.02, MeOH). Found: C, 64.89; H, 5.34; N, 7.54%. $C_{20}H_{20}N_2O_5$ requires: C, 65.21; H, 5.47; N, 7.60%. ^{1}H NMR (300 MHz; $CDCl_3$): δ 10.9 (1H, br s, NHCO), 8.68 (1H, dd, *J* 1.5, 8.7 Hz, H7), 8.17 (1H, dd, *J* 1.5, 8.3 Hz, H4), 7.60 (1H, dt, *J* 1.5, 7.4 Hz, H6), 7.32–7.15 (5H, m, ArH), 7.08 (1H, dt, *J* 1.1, 7.5 Hz, H5), 5.32 (1H, br s, CONH), 4.99 (1H, m, α-CH phe), 3.75 (3H, s, $COOCH_3$), 3.31–3.08 (2H, m, $CHCH_2Ar$), 2.14 (3H, s, $COCH_3$). ^{13}C NMR (75 MHz; $CDCl_3$) δ 191.7, 171.0, 169.4, 162.8, 141.9, 136.4, 135.4, 134.2, 129.2, 128.6, 127.2, 122.4, 120.3, 118.1, 53.2, 52.5, 37.8, 25.3. IR (KBr): ν_{max} 3336, 3284, 3059, 3030, 2955, 1743, 1678, 1664, 1604, 1577, 1515, 1446, 1374, 1309, 1294, 1281, 1245, 1209, 1178, 1164, 1126, 1103, 1031, 1004, 932, 908, 829, 798, 765, 701, 680, 658, 597, 549, 522, 501 cm^{-1}. UV (MeOH): λ_{max} 337 (ε 6260 cm^{-1} M^{-1}), 267 (14,410), 234 (34,790), 205 (33,320). HRMS (ESI) *m*/*z* 391.1264 $(M+Na)^+$; $C_{20}H_{20}N_2O_5Na$ requires 391.1270.

*4.1.4. (R)-Methyl 2-(2-(2-acetamidophenyl)-2-oxoacetamido)-3-phenyl propanoate (**2d**).* This compound was prepared by the same method as compound **2a**, from *N*-acetylisatin (0.10 g, 0.53 mmol) and D-phenylalanine methyl ester hydrochloride (0.29 g, 1.3 mmol). The title compound **2d** was obtained as an off-white solid (0.18 g 98%). Mp 116–118 °C; R_f 0.45 (EtOAc/CH_2Cl_2, v/v 1:9); $[\alpha]_D^{26}$ +6.3 (*c* 0.02, MeOH). Found: C, 64.89; H, 5.34; N, 7.54%, $C_{20}H_{20}N_2O_5$ requires: C, 65.21; H, 5.47; N, 7.60. ^{1}H NMR (300 MHz; $CDCl_3$): δ 10.9 (1H, br s, NHCO), 8.49 (1H, dd, *J* 1.5, 8.7 Hz, H7), 7.84 (1H, dd, *J* 1.5, 8.3 Hz, H4), 7.61 (1H, d, *J* 8.3 Hz, CONH), 7.44 (1H, dt, *J* 1.1, 8.1 Hz, H6), 7.31–7.16 (5H, m, ArH), 6.96 (1H, dt, *J* 1.1, 7.8 Hz, H5), 4.99–4.95 (1H, m, α-CH phe), 3.74 (3H, s, $COOCH_3$), 3.29–3.06 (2H, m, $CHCH_2Ar$), 2.09 (3H, s, $COCH_3$). ^{13}C NMR (75 MHz; $CDCl_3$) δ 192.0, 171.1, 169.4, 163.1, 141.9, 136.3, 135.6, 134.2, 129.2, 128.6, 127.2, 122.4, 120.2, 118.0, 53.2, 52.5, 37.7, 25.2. IR (KBr): ν_{max} 3336, 3284, 3059, 3030, 2955, 1743, 1678, 1664, 1604, 1577, 1515, 1446, 1374, 1309, 1294, 1281, 1245, 1209, 1178, 1164, 1126, 1103, 1031, 1004, 932, 908, 829, 798, 765, 701, 680, 658, 597, 549, 522, 501 cm^{-1}. UV (MeOH): λ_{max} 339 (ε 3740 cm^{-1} M^{-1}), 268 (8470), 234 (20,720), 205 (18,790). HRMS (ESI) *m*/*z* 391.1264 $(M+Na)^+$; $C_{20}H_{20}N_2O_5Na$ requires 391.1270.

*4.1.5. (S)-Methyl 2-(2-(2-acetamidophenyl)-2-oxoacetamido)-4-(methylthio)-butanoate (**2e**).* This compound was prepared by the same method as compound **2a**, from *N*-acetylisatin (0.10 g, 0.53 mmol) and L-methionine methyl ester hydrochloride (0.27 g, 1.3 mmol). The title compound **2e** was obtained as a yellow liquid (0.17 g, 85%). R_f 0.36 (EtOAc/CH_2Cl_2, v/v 1:9); $[\alpha]_D^{26}$ −6.9 (*c* 0.07, MeOH). Found: C, 54.20; H, 5.70; N, 7.76%, $C_{16}H_{20}N_2O_5S$ requires: C, 54.53; H, 5.72; N, 7.95%. ^{1}H NMR (300 MHz; $CDCl_3$): δ 10.9 (1H, br s, NHCO), 8.66 (1H, dd, *J* 1.1, 8.3 Hz, H7), 8.35 (1H, dd, *J* 1.5, 8.3 Hz, H4), 7.61 (1H, dt, *J* 1.5, 7.9 Hz, H6), 7.51 (1H, d, *J* 7.9 Hz, CONH), 7.12 (1H, dt, *J* 1.1, 7.7 Hz, H5), 4.82 (1H, m, α-CH Met), 3.81 (3H, s, $COOCH_3$), 2.59 (2H, t, *J* 7.1 Hz, γ-CH Met), 2.34–2.22 (1H, m, β-CH_aH_b Met), 2.23 (3H, s, SCH_3), 2.18–2.09 (1H, m, β-CH_aH_b Met), 2.12 (3H, s, $COCH_3$). ^{13}C NMR (75 MHz; $CDCl_3$) δ 190.9, 171.3, 169.2, 162.4, 142.2, 136.7, 134.3, 122.5, 120.6, 118.3, 52.74, 51.63, 31.20, 29.88, 25.38, 15.4. IR (KBr): ν_{max} 3293, 3072, 2953, 2918, 2847, 1745, 1647, 1607, 1548, 1528, 1450, 1368, 1299, 1209, 1165, 1130, 1004, 877, 758, 682, 600, 551, 521 cm^{-1}. UV (MeOH): λ_{max} 338 (ε 2520 cm^{-1} M^{-1}), 234 (15,019), 207 (7680). HRMS (ESI) *m*/*z* 375.0985 $(M+Na)^+$; $C_{16}H_{20}N_2O_5SNa$ requires 375.0991.

*4.1.6. Methyl 2-(2-(2-acetamidophenyl)-N-methyl-2-oxoacetamido) acetate (**2f**).* This compound was prepared by the same method as compound **2a**, from *N*-acetylisatin (0.10 g, 0.53 mmol) and sarcosine methyl ester hydrochloride (0.20 g, 1.5 mmol). The title compound **2f** was obtained as a yellow liquid (80 mg, 52%). R_f 0.26 (EtOAc/CH_2Cl_2, v/v 1:9); Found: C, 57.45; H, 5.60; N, 9.57%. $C_{14}H_{16}N_2O_5$ requires: C, 57.53; H, 5.52; N, 9.58%. ^{1}H NMR (300 MHz; $CDCl_3$): δ 11.2 (1H, br s, NHCO), 11.1 (1H, br s, NHCO), 8.72 (1H, dd, *J* 0.8, 8.7 Hz, H7), 8.68 (1H, dd, *J* 0.50, 8.6 Hz, H7′), 7.86 (1H, dd, *J* 1.5, 7.9 Hz, H4), 7.68 (1H, dd, *J* 1.5, 8.1 Hz, H4′), 7.57 (1H, dt, *J* 1.1, 8.7 Hz, H6), 7.54 (1H, dt, *J* 1.5, 7.9 Hz, H6′), 7.13 (1H, dt, *J* 0.75, 7.6 Hz, H5), 7.07 (1H, dt, *J* 1.1, 7.4 Hz, H5′), 4.21 (2H, s, CH_2), 4.02 (2H, s, CH_2'), 3.76 (3H, s, OCH_3), 3.62 (3H, s, OCH_3'), 3.10 (3H, s, NCH_3'), 2.96 (3H, s, NCH_3), 2.20 (3H, s, $COCH_3$), 2.18 (3H, s, $COCH_3'$). ^{13}C NMR (75 MHz; $CDCl_3$) δ 195.2, 194.7, 169.4, 169.3, 168.5, 168.3, 166.8, 166.3, 142.4, 142.3, 136.9, 136.8, 134.1, 133.9, 122.9, 122.5, 120.4, 120.3, 117.6, 52.41, 50.81, 47.8, 36.14, 33.51, 25.39. IR (KBr): ν_{max} 3304, 3028, 2955, 1749, 1701, 1654, 1605, 1584, 1529, 1450, 1433, 1367, 1321, 1296, 1239, 1205, 1162, 1134, 1108, 1058, 1031, 976, 959, 947, 899, 756, 713, 691 cm^{-1}. UV (MeOH): λ_{max} 341 (ε 12,010 cm^{-1} M^{-1}), 268 (25,690), 236 (68,840), 204 (41,760). HRMS (ESI) *m*/*z* 315.0959 $(M+Na)^+$; $C_{14}H_{16}N_2O_5Na$ requires: 315.0957.

*4.1.7. (S)-Dimethyl 2-(2-(2-acetamidophenyl)-2-oxoacetamido) succinate (**2g**).* This compound was prepared by the same method as compound **2a**, from *N*-acetylisatin (0.20 g, 1.1 mmol) and L-aspartic acid dimethyl ester hydrochloride (0.50 g, 2.6 mmol). The title compound **2g** was obtained as a yellow liquid (0.20 g, 54%). R_f 0.20 (EtOAc/CH_2Cl_2, v/v 1:9); $[\alpha]_D^{26}$ −6.3 (*c* 0.01, MeOH). Found: C, 54.83; H, 5.17; N, 8.00%, $C_{16}H_{18}N_2O_7$ requires: C, 54.86; H, 5.18; N, 8.00%. ^{1}H NMR (300 MHz; $CDCl_3$): δ 10.9 (1H, br s, NHCO), 8.69 (1H, dd, *J* 1.5, 8.7 Hz, H7), 8.35 (1H, dd, *J* 1.5, 7.9 Hz, H4), 7.76 (1H, d, *J* 8.3 Hz, CONH), 7.62 (1H, dt, *J* 1.1, 7.9 Hz, H6), 7.14 (1H, dt, *J* 1.1, 7.5 Hz, H5), 4.98–4.92 (1H, m, α-CH Asp), 3.81 (3H, s, $COOCH_3$), 3.73 (3H, s, $COOCH_3$), 3.16 (1H, dd, *J* 4.5, 17.5 Hz, β-CH_aH_b Asp), 2.94 (1H, dd, *J* 4.5, 17.5 Hz, β-CH_aH_b Asp), 2.24 (3H, s, $COCH_3$). ^{13}C NMR (75 MHz; $CDCl_3$) δ 190.8, 171.1, 170.1, 169.2, 162.4, 142.3, 136.8, 134.3, 122.4, 120.6, 118.2, 53.07, 52.21, 48.49, 35.60, 25.43. UV (MeOH): λ_{max} 337 (ε 2890 cm^{-1} M^{-1}), 289 (2520). HRMS (ESI) *m*/*z* 373.1012 $(M+Na)^+$, $C_{16}H_{18}N_2O_7Na$ requires 373.1012.

*4.1.8. (S)-Methyl 2-((S)-2-(2-(2-acetamidophenyl)-2-oxoacetamido)-3-methylbutanamido)-3-phenylpropanoate (**5a**).* This compound was prepared by the same method as compound **2a**, from *N*-acetylisatin (0.50 g, 2.6 mmol) and L-valine-L-phenylalanine methyl ester hydrochloride (1.1 g, 8.9 mmol). The title compound **5a** was obtained as a pale yellow solid (0.50 g, 40%). Mp 178–180 °C; R_f 0.10 (EtOAc/CH_2Cl_2, v/v 1:9); $[\alpha]_D^{26}$ +4.3 (*c* 0.01, MeOH); Found: C, 64.31; H, 6.39; N, 8.96%, $C_{25}H_{29}N_3O_6$ requires: C, 64.23; H, 6.25; N, 8.99%. ^{1}H NMR (300 MHz; $CDCl_3$): δ 10.9 (1H, br s, NHCO), 8.62 (1H, dd, *J* 1.1, 8.3 Hz, H7), 8.25 (1H, dd, *J* 1.1, 8.1 Hz, H4), 7.59 (1H, dt, *J* 1.1, 7.9 Hz, H6), 7.46 (1H, d, *J* 8.7 Hz, CONH), 7.24–7.15 (5H, m, ArH), 7.12 (1H, dt, *J* 1.1, 7.7 Hz, H5), 6.41 (1H, d, *J* 7.9 Hz, CONH), 4.92–4.83 (1H, m, α-CH Phe), 4.34 (1H, dd, *J* 6.8, 8.9 Hz, α-CH Val), 3.73 (3H, s, $COOCH_3$), 3.20–3.05 (2H, m, $CHCH_2Ar$), 2.22 (3H, s, $COCH_3$), 1.99 (1H, m, $CHCH(CH_3)_2$), 0.99 (3H, d, *J* 6.8 Hz, CH_3), 0.95 (3H, d, *J* 6.8 Hz, CH_3). ^{13}C NMR (75 MHz; $CDCl_3$) δ 191.3, 171.5, 169.7, 169.3, 162.8, 142.1, 136.5, 135.4, 134.1, 129.1, 128.6, 127.2, 122.4, 120.6, 118.4, 58.5, 53.1, 52.3, 37.7, 31.2, 25.3, 19.0, 17.8. IR (KBr): ν_{max} 3301, 3066, 2963, 2869, 1744, 1650, 1585, 1530, 1451, 1370, 1297, 1212, 1164, 1032, 990, 875, 753, 700, 678, 599, 551 cm^{-1}. UV (MeOH/TFA v/v 9.5:0.5): λ_{max}

336 (ε 3470 $cm^{-1}\,M^{-1}$), 267 (8340), 238 (7290). HRMS (ESI) *m/z* 490.1949 $(M+Na)^+$, $C_{25}H_{29}N_3O_6Na$ requires 490.1954.

*4.1.9. (R)-Methyl 2-((S)-2-(2-(2-acetamidophenyl)-2-oxoacetamido)-3-methylbutanamido)-3-phenylpropanoate (**5b**).* This compound was prepared by the same method as compound **2a**, from *N*-acetylisatin (0.50 g, 2.6 mmol) and L-valine-D-phenylalanine methyl ester hydrochloride (1.1 g, 8.9 mmol). The title compound **5b** was obtained as an off-white solid (0.50 g, 40%). Mp 197–199 °C; R_f 0.11 (EtOAc/CH_2Cl_2, v/v 1:9); $[\alpha]_D^{26}$ +1.9 (*c* 0.01, MeOH/DMSO v/v 9.5:0.5). Found: 63.94; H, 6.25; N, 8.99%, $C_{25}H_{29}N_3O_6$ requires: C, 64.23; H, 6.25; N, 8.99%. ^{1}H NMR (300 MHz; $CDCl_3$): δ 10.9 (1H, br s, NHCO), 8.67 (1H, dd, *J* 1.1, 8.7 Hz, H7), 8.29 (1H, dd, *J* 1.1, 8.1 Hz, H4), 7.60 (1H, dt, *J* 1.5, 7.9 Hz, H6), 7.46 (1H, d, *J* 8.7 Hz, CONH), 7.25 (5H, m, ArH), 7.09 (1H, dt, *J* 1.1, 7.7 Hz, H5), 6.29 (1H, d, *J* 7.9 Hz, CONH), 4.92 (1H, m, α-CH Phe), 4.36 (1H, dd, *J* 5.6, 8.9 Hz, α-CH Val), 3.74 (3H, s, $COOCH_3$), 3.21–3.04 (2H, m, $CHCH_2Ar$), 2.23 (3H, s, $COCH_3$), 2.14 (1H, m, $CHCH(CH_3)_2$), 0.91 (3H, d, *J* 6.8 Hz, CH_3), 0.87 (3H, d, *J* 6.8 Hz, CH_3). ^{13}C NMR (75 MHz; $CDCl_3$) δ 191.0, 172.7, 171.6, 169.6, 162.7, 142.1, 136.6, 135.5, 134.2, 129.1, 128.6, 127.2, 122.5, 120.6, 118.4, 58.3, 53.1, 52.4, 37.9, 31.2, 25.3, 19.1, 17.4. IR (KBr): ν_{max} 3313, 3243, 3079, 2967, 2879, 1727, 1635, 1585, 1527, 1450, 1368, 1296, 1212, 1164, 998, 755, 698, 551 cm^{-1}. UV (MeOH/TFA, v/v 9.5:0.5): λ_{max} 335 (ε 2130 $cm^{-1}\,M^{-1}$), 266 (5250), 235 (9450), 207 (6390). HRMS (ESI) *m/z* 490.1932 $(M+Na)^+$, $C_{25}H_{29}N_3O_6Na$ requires 490.1954.

*4.1.10. (S)-Methyl 2-((S)-2-(2-(2-acetamidophenyl)-2-oxoacetamido)-3-methylbutanamido)-4-(methylthio)butanoate (**5c**).* This compound was prepared by the same method as compound **2a**, from *N*-acetylisatin (0.10 g, 0.53 mmol) and L-valine-L-methionine methyl ester hydrochloride (0.41 g, 1.37 mmol). The title compound **5c** was obtained as a yellow solid (85 mg, 36%). Mp 150–152 °C; R_f 0.14 (EtOAc/CH_2Cl_2, v/v 1:9); $[\alpha]_D^{26}$ −5.3 (*c* 0.01, MeOH/DMSO v/v 9.5:0.5). Found: C, 55.56; H, 6.64; N, 9.26%, $C_{21}H_{29}N_3O_6S$ requires: 55.86; H, 6.47; N, 9.31%. ^{1}H NMR (300 MHz; $CDCl_3$): δ 10.9 (1H, br s, NHCO), 8.64 (1H, dd, *J* 1.1, 8.7 Hz, H7), 8.24 (1H, dd, *J* 1.5, 7.9 Hz, H4), 7.59 (1H, dt, *J* 1.5, 7.9 Hz, H6), 7.50 (1H, d, *J* 8.7 Hz, CONH), 7.11 (1H, dt, *J* 1.1, 7.5 Hz, H5), 6.79 (1H, d, *J* 7.9 Hz, CONH), 4.73 (1H, m, α-CH Met), 4.40 (1H, dd, *J* 6.8, 8.8 Hz, α-CH Val), 3.76 (3H, s, $COOCH_3$), 2.52 (2H, t, *J* 7.2 Hz, γ-CH_2 Met), 2.27–2.21 (1H, m, β-CH_aH_b Met), 2.22 (3H, s, $COCH_3$), 2.16 (1H, m, $CHCH(CH_3)_2$), 2.07 (3H, s, SCH_3), 2.04–1.97 (1H, m, β-CH_aH_b Met), 1.04 (3H, d, *J* 4.6 Hz, CH_3), 1.02 (3H, d, *J* 4.7 Hz, CH_3). ^{13}C NMR (75 MHz; $CDCl_3$) δ 191.3, 171.9, 169.9, 169.3, 162.9, 142.1, 136.6, 134.1, 122.5, 120.6, 118.4, 58.6, 52.5, 51.6, 31.3, 31.1, 29.8, 25.4, 19.1, 17.9, 15.4. IR (KBr): ν_{max} 3281, 3074, 2963, 1745, 1637, 1585, 1529, 1450, 1370, 1298, 1213, 1165, 1006, 754, 677 cm^{-1}. UV (MeOH/TFA, v/v: 9.5:0.5): λ_{max} 338 (ε 2020 $cm^{-1}\,M^{-1}$), 267 (4650), 230 (16,950), 214 (15,270). HRMS (ESI) *m/z* 474.1669 $(M+Na)^+$, $C_{21}H_{29}N_3O_6SNa$ requires 474.1675.

*4.1.11. (S)-Dimethyl 2-((S)-2-((S)-2-(2-(2-acetamidophenyl)-2-oxoacetamido)-3-methylbutanamido)-3-phenylpropanamido) pentanedioate (**7a**).* This compound was prepared by the same method as compound **2a**, from *N*-acetylisatin (0.10 g, 0.49 mmol) and L-valine-L-phenylalanine-L-glutamic acid dimethyl ester hydrochloride (0.49 g, 1.3 mmol). The title compound **7a** was obtained as a light yellow solid (0.12 g, 44%). Mp 236–238 °C; R_f 0.34 (EtOAc/CH_2Cl_2, v/v 1:9); $[\alpha]_D^{26}$ −0.9 (*c* 0.01, MeOH/DMSO v/v 9.5:0.5); Found: C, 60.80; H, 6.27; N, 8.98%, $C_{31}H_{38}N_4O_9$ requires C, 60.97; H, 6.57; N, 9.17%. ^{1}H NMR (300 MHz; DMSO-d_6): δ 10.6 (1H, br s, NHCO), 8.50 (1H, d, *J* 9.1 Hz, CONH), 8.41 (1H, d, *J* 7.9 Hz, CONH), 8.30 (1H, d, *J* 7.9 Hz, CONH), 8.02 (1H, d, *J* 8.3 Hz, H7), 7.61 (1H, t, *J* 7.5 Hz, H6), 7.55 (1H, d, *J* 7.9 Hz, H4), 7.25–7.19 (6H, m, ArH), 7.17 (1H, t, *J* 7.1 Hz, H5), 4.60–4.57 (1H, m, α-CH Phe), 4.28–4.22 (2H, m, α-CH Val, α-CH Glu), 3.58 (3H, s, $COOCH_3$), 3.55 (3H, s, $COOCH_3$), 3.02–2.71 (2H, m, $CHCH_2Ar$), 2.33–2.30 (2H, m, γ-CH_2 Glu), 2.04 (3H, s, $COCH_3$), 1.99–1.95 (2H, m, β-CH_2 Glu), 1.83–1.76 (1H, m, $CHCH(CH_3)_2$), 0.81 (3H, d, *J* 5.6 Hz, CH_3), 0.79 (3H, d, *J* 6.0 Hz, CH_3). ^{13}C NMR (75 MHz; DMSO-d_6) δ 192.1, 172.6, 172.0, 171.3, 170.1, 169.1, 164.1, 139.8, 135.3, 134.8, 132.4, 129.5, 128.4, 126.7, 123.5, 121.2, 119.8, 57.8, 53.9, 52.3, 51.7, 51.5, 37.8, 31.3, 29.8, 26.3, 24.6, 19.5, 18.2. IR (KBr): ν_{max} 3285, 2958, 2918, 1739, 1639, 1583, 1531, 1450, 1385, 1298, 1210, 1163, 1025, 626 cm^{-1}. UV (MeOH/TFA, v/v 9.5:0.5): λ_{max} 336 (ε 6200 $cm^{-1}\,M^{-1}$), 268 (44,000). HRMS (ESI) *m/z* 633.2531 $(M+Na)^+$, $C_{31}H_{38}N_4O_9Na$ requires: 633.2536.

*4.1.12. (R)-Methyl 2-((S)-2-((S)-2-(2-(2-acetamidophenyl)-2-oxoacetamido)propanamido)-3-methylbutanamido)-3-phenylpropanoate (**7b**).* This compound was prepared by the same method as compound **16a**, from *N*-acetylisatin (0.50 g, 2.6 mmol) and L-alanine-L-valine-D-phenylalanine methyl ester hydrochloride (0.53 g, 1.4 mmol). The title compound **7b** was obtained as an off-white solid (0.12 g, 42%). Mp 228–230 °C; R_f 0.26 (EtOAc/CH_2Cl_2, v/v 0.5:9.5); $[\alpha]_D^{26}$ −1.8 (*c* 0.01, MeOH/DMSO v/v 9.5:0.5). ^{1}H NMR (300 MHz; DMSO-d_6): δ 10.63 (1H, br s, NHCO), 8.79 (1H, d, *J* 7.5 Hz, CONH), 8.44 (1H, d, *J* 7.9 Hz, CONH), 7.99 (1H, d, *J* 8.3 Hz, H7), 7.87 (1H, d, *J* 9.1 Hz, CONH), 7.70 (1H, d, *J* 7.9 Hz, H4), 7.60 (1H, t, *J* 7.5 Hz, H6), 7.26–7.15 (5H, m, ArH), 7.14 (1H, t, *J* 7.6 Hz, H5), 4.89–4.82 (1H, m, α-CH Phe), 4.63–4.54 (1H, m, α-CH Ala), 4.21 (1H, dd, *J* 6.4, 9.1 Hz, α-CH Val), 3.61 (3H, s, $COOCH_3$), 3.09–2.80 (2H, m, $CHCH_2Ar$), 2.06 (6H, s, $COCH_3$), 1.85–1.76 (1H, m, $CHCH(CH_3)_2$), 1.26 (3H, d, *J* 7.2 Hz, $CHCH_3$), 0.64 (3H, d, *J* 6.4 Hz, CH_3), 0.59 (3H, d, *J* 6.8 Hz, CH_3). ^{13}C NMR (75 MHz; DMSO-d_6): δ 192.4, 172.4, 171.8, 171.2, 169.4, 164.2, 139.5, 137.7, 135.4, 134.9, 129.6, 128.7, 126.7, 123.6, 121.6, 120.3, 58.3, 53.0, 52.4, 49.0, 37.0, 31.3, 24.7, 19.4, 18.5, 17.9. IR (KBr): ν_{max} 3295, 3067, 2958, 1732, 1640, 1585, 1530, 1451, 1371, 1299, 1212, 1165, 1033, 750, 698 cm^{-1}. UV (MeOH/Ac2O, v/v 9.5:0.5): λ_{max} 339 (ε 2320 $cm^{-1}\,M^{-1}$), 269 (5460), 237 (6960). HRMS (ESI) *m/z* 561.2320 $(M+Na)^+$, $C_{28}H_{34}N_4O_7Na$ requires 561.2325.

*4.1.13. Dimethyl 2-(2-(oxamidophenyl)-2-oxoacetamido)diacetate (**11a**).* To a stirred solution of *N*-oxalyl bisisatin (0.20 g, 0.57 mmol) in dichloromethane (60 mL) was added a mixture of glycine methyl ester hydrochloride (0.58 g, 4.6 mmol) and saturated sodium hydrogen carbonate (3 mL) in water (7 mL) at 5 °C. The reaction mixture was warmed to room temperature and stirred for 24 h. The organic layer was diluted with dichloromethane (30 mL) and extracted with aqueous hydrochloric acid (0.5 M, 25 mL) and water (20 mL). The organic extract was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by column chromatography with a solvent gradient system from dichloromethane/triethylamine (v/v 9.5:0.5) to dichloromethane/ethyl acetate/triethylamine (v/v 8:1.5:0.5) to give the title compound **11a** as a yellow solid (10 mg, 3%). Mp 234–246 °C; R_f 0.71 (ethyl acetate/CH_2Cl_2, v/v 0.5:9.5). Found: C, 54.60; H, 4.18; N, 10.54%; $C_{24}H_{22}N_4O_{10}$ requires: C, 54.75; H, 4.21; N, 10.64%. ^{1}H NMR (300 MHz; DMSO-d_6): δ 12.5 (2H, br s, NHCO), 9.49 (2H, t, *J* 5.6 Hz, CONH), 8.67 (2H, d, *J* 1.1, 8.7 Hz, H7, H7′), 8.03 (2H, dd, *J* 1.5, 7.9 Hz, H4, H4′), 7.83 (2H, dt, *J* 1.1, 8.7 Hz, H6, H6′), 7.40 (2H, dt, *J* 1.1, 7.5, H5, H5′), 4.08 (2H, d, *J* 6.0 Hz, $CONHCH_2$), 3.69 (6H, s, OCH_3). ^{13}C NMR (75 MHz; DMSO-d_6) δ 194.2, 170.1, 165.8, 158.7, 139.5, 136.8, 134.6, 124.9, 120.9, 120.5, 52.5, 40.7. IR (KBr): ν_{max} 3333, 2966, 2935, 2873, 1755, 1703, 1652, 1600, 1578, 1526, 1453, 1279, 1224, 1166, 1032, 1014, 958, 762 cm^{-1}. UV (MeOH/TFA, v/v 9.5:0.5): λ_{max} 342 (ε 14,840 $cm^{-1}\,M^{-1}$), 213 (66,100). HRMS (ESI) *m/z* 549.1227 $(M+Na)^+$, $C_{24}H_{22}N_4O_{10}Na$ requires 549.1234.

*4.1.14. (S)-Dimethyl 2-(2-(oxamidophenyl)-2-oxoacetamido)-di-3-methylbutanoate (**11b**).* This compound was prepared by the same method as compound **11a**, from *N*-oxalyl bisisatin (0.12 g, 0.34 mmol) and L-valine methyl ester hydrochloride (0.28 g,

1.7 mmol). The title compound **11b** was obtained as an off-white solid (0.10 g, 48%). Mp 270–272 °C; R_f 0.65 (EtOAc/light petroleum, v/v 2:8); $[\alpha]_D^{26}$ +57.2 (*c* 0.005, MeOH/DMSO v/v 9.5:0.5). Found: C, 59.11; H, 5.66; N, 9.10%. $C_{30}H_{34}N_4O_{10}$ requires: C, 59.01; H, 5.61; N, 9.18. ^{1}H NMR (300 MHz; $CDCl_3$): δ 12.7 (2H, br s, NHCO), 8.85 (2H, dd, *J* 0.75, 8.7 Hz, H7, H7′), 8.62 (2H, dd, *J* 1.5, 7.9 Hz, H4, H4′), 7.70 (2H, dt, *J* 1.5, 7.9 Hz, H6, H6′), 7.46 (2H, d, *J* 9.0 Hz, CONH), 7.28 (2H, dt, *J* 0.75, 7.5 Hz, H5, H5′), 4.63 (2H, dd, *J* 4.9 Hz, 9.0 Hz, α-CH Val), 3.79 (6H, s, $COOCH_3$), 2.35–2.25 (2H, m, $CHCH(CH_3)_2$), 1.02 (6H, d, *J* 6.8 Hz, CH_3), 0.99 (6H, d, *J* 6.8 Hz, CH_3). ^{13}C NMR (75 MHz; $CDCl_3$) δ 190.6, 171.6, 162.2, 158.8, 140.5, 136.3, 135.0, 135.3, 124.6, 120.3, 57.98, 52.9, 31.8, 19.5, 18.2. IR (KBr): ν_{max} 3297, 2968, 2932, 2875, 1740, 1651, 1576, 1510, 1450, 1373, 1302, 1262, 1207, 1168, 1118, 1025, 865, 757, 670, 558 cm^{-1}. UV (MeOH/TFA, v/v 9.5:0.5): λ_{max} 341 (ε 12,420 cm^{-1} M^{-1}), 213 (62,550). HRMS (ESI) *m*/*z* 633.2167 $(M+Na)^+$, $C_{30}H_{34}N_4O_{10}Na$ requires 633.2173.

*4.1.15. (S)-Dimethyl 2-(2-(oxamidophenyl)-2-oxoacetamido)-di-3-phenyl propanoate (**11c**).* This compound was prepared by the same method as compound **11a**, from *N*-oxalyl bisisatin (0.20 g, 0.57 mmol) and L-phenylalanine methyl ester hydrochloride (0.49 g, 2.3 mmol). The title compound **11c** was obtained as an off-white solid (0.11 g, 27%). Mp 219–221 °C; R_f 0.76 (CH_2Cl_2); $[\alpha]_D^{26}$ −67.1 (*c* 0.007, MeOH/DMSO v/v 9.5:0.5). Found: C, 64.34; H, 4.80; N, 7.80%. $C_{38}H_{34}N_4O_{10}$ requires: C, 64.58; H, 4.85; N, 7.93. ^{1}H NMR (300 MHz; $CDCl_3$): δ 12.6 (2H, br s, NHCO), 8.80 (2H, dd, *J* 1.1, 8.6 Hz, H7, H7′), 8.39 (2H, dd, *J* 1.5, 8.1 Hz, H4, H4′), 7.67 (2H, dt, *J* 1.5, 7.3 Hz, H6, H6′), 7.39 (2H, d, *J* 8.3 Hz, CONH), 7.30 (2H, td, *J* 1.5, 7.5 Hz, H5, H5′), 7.35–7.15 (12H, m, ArH), 5.01–4.94 (2H, m, α-CH Phe), 3.76 (6H, s, $COOCH_3$), 3.30–3.11 (4H, m, $CHCH_2Ar$). ^{13}C NMR (75 MHz; $CDCl_3$) δ 190.0, 170.8, 161.5, 158.3, 139.9, 136.4, 135.2, 134.7, 129.2, 128.7, 127.3, 124.0, 120.7, 119.8, 53.4, 52.5, 38.0. IR (KBr): ν_{max} 3393, 3300, 3028, 2948, 1748, 1735, 1698, 1672, 1650, 1576, 1512, 1448, 1301, 1274, 1212, 1167, 1122, 1026, 867, 756, 704, 674 cm^{-1}. UV (MeOH/TFA, v/v 9.5:0.5): λ_{max} 342 (ε 10,760 cm^{-1} M^{-1}), 267 (16,610). HRMS (ESI) *m*/*z* 729.2167 $(M+Na)^+$, $C_{38}H_{34}N_4O_{10}Na$ requires 729.2173.

*4.1.16. (R)-Dimethyl 2-(2-(oxamidophenyl)-2-oxoacetamido)-di-3-phenyl propanoate (**11d**).* This compound was prepared by the same method as compound **11a**, from *N*-oxalyl bisisatin (0.20 g, 0.57 mmol) and D-phenylalanine methyl ester hydrochloride (0.49 g, 2.3 mmol). The title compound **11d** was obtained as an off-white solid (0.11 g, 27%). Mp 220–222 °C; R_f 0.78 (CH_2Cl_2); $[\alpha]_D^{26}$ +45.1 (*c* 0.008, MeOH/DMSO v/v 9.5:0.5). Found: C, 64.55; H, 4.89; N, 7.86%. $C_{38}H_{34}N_4O_{10}$ requires: C, 64.58; H, 4.85; N, 7.93%. ^{1}H NMR (300 MHz; $CDCl_3$): δ 10.6 (2H, br s, NHCO), 8.80 (2H, dd, *J* 1.1, 8.6 Hz, H7, H7′), 8.39 (2H, dd, *J* 1.1, 8.1 Hz, H4, H4′), 7.67 (2H, dt, *J* 1.5, 7.3 Hz, H6, H6′), 7.39 (2H, d, *J* 8.3 Hz, CONH), 7.35 (2H, dt, *J* 1.5, 7.5 Hz, H5, H5′) 7.33–7.15 (12H, m, ArH), 5.01–4.94 (2H, m, α-CH Phe), 3.76 (6H, s, $COOCH_3$), 3.30–3.11 (4H, m, $CHCH_2Ar$). ^{13}C NMR (75 MHz; $CDCl_3$) δ 190.0, 170.8, 161.5, 158.3, 139.9, 136.4, 135.2, 134.7, 129.2, 128.7, 127.3, 124.0, 120.7, 119.8, 53.4, 52.5, 38.0. IR (KBr): ν_{max} 393, 3300, 3024, 2945, 1748, 1736, 1672, 1650, 1575, 1510, 1448, 1274, 1211, 1167, 1121, 1026, 756, 704 cm^{-1}. UV (MeOH/TFA, v/v 9.5:0.5): λ_{max} 341 (ε 8480 cm^{-1} M^{-1}), 267 (13,610). HRMS (ESI) *m*/*z* 729.2167 $(M+Na)^+$, $C_{38}H_{34}N_4O_{10}Na$ requries 729.2173.

*4.1.17. (S)-Dimethyl 2-(2-(oxamidophenyl)-2-oxoacetamido)-di-4-(methylthio)butanoate (**11e**).* This compound was prepared by the same method as compound **11a**, from *N*-oxalyl bisisatin (0.20 g, 0.57 mmol) and L-methionine methyl ester hydrochloride (0.46 g, 2.3 mmol). The title compound **11e** was obtained as an off-white solid (0.10 g, 26%). Mp 208–210 °C; R_f 0.78 (CH_2Cl_2); $[\alpha]_D^{26}$ −7.0 (*c* 0.009, MeOH/DMSO v/v 9.5:0.5) Found: C, 53.63; H, 5.12; N, 8.22%. $C_{30}H_{34}N_4O_{10}S_2$ requires: C, 53.40; H, 5.08; N, 8.30%. ^{1}H NMR (300 MHz; $CDCl_3$): δ 12.7 (1H, br s, NHCO), 8.83 (2H, d, *J* 8.3 Hz, H7, H7′), 8.62 (2H, d, *J* 8.3 Hz, H4, H4′), 7.69 (2H, dt, *J* 0.9, 8.3 Hz, H6, H6′), 7.67 (2H, d, *J* 7.5 Hz, CONH), 7.27 (2H, dt, *J* 0.9, 8.3 Hz, H5, H5′), 4.85–4.80 (2H, m, α-CH Met), 3.81 (6H, s, OCH_3), 2.59 (4H, t, *J* 7.1 Hz, γ-CH_2 Met), 2.34–2.10 (2H, m, β-CH_2 Met), 2.12 (6H, s, SCH_3). ^{13}C NMR (75 MHz; $CDCl_3$) δ 189.8, 171.1, 161.6, 158.3, 139.9, 136.5, 134.8, 124.1, 120.8, 119.9, 52.7, 51.7, 31.4, 29.8, 15.4. IR (KBr): ν_{max} 3266, 3079, 2952, 2917, 2842, 1746, 1651, 1602, 1576, 1507, 1451, 1301, 1269, 1211, 1168, 1121, 991, 865, 759, 671, 559, 489 cm^{-1}. UV (MeOH/TFA, v/v 9.5:0.5): λ_{max} 342 (ε 8620 cm^{-1} M^{-1}), 267 (13,900), 247 (8150). HRMS (ESI) *m*/*z* 697.1609 $(M+Na)^+$, $C_{30}H_{34}N_4O_{10}S_2Na$ 697.1614.

*4.1.18. (S)-Dimethyl 2-((S)-2-(2-(oxamidophenyl)-2-oxoacetamido)-di-3-methylbutanamido)-3-phenylpropanoate (**11f**).* This compound was prepared by the same method as compound **11a**, from *N*-oxalyl bisisatin (0.20 g, 0.57 mmol) and L-valine-L-phenylalanine methyl ester hydrochloride (0.90 g, 2.9 mmol). The title compound **11f** was obtained as a pale yellow solid (0.12 g, 23%). Mp 267–268 °C; R_f 0.79 (MeOH/EtOAc/lightpetroleum, v/v 1:1:8); $[\alpha]_D^{26}$ −7.1 (*c* 0.08, MeOH/DMSO v/v 9.5:0.5) Found: C, 63.50; H, 5.67; N, 9.10%. $C_{48}H_{52}N_6O_{12}$ requires: C, 63.71; H, 5.79; N, 9.29%. ^{1}H NMR (300 MHz; DMSO-d_6): δ 12.6 (2H, br s, NHCO), 9.04 (2H, d, *J* 8.6 Hz, CONH), 8.64 (2H, d *J* 7.9 Hz, NHCO), 8.58 (2H, d, *J* 7.9 Hz, H7, H7′), 7.80 (2H, dt, *J* 0.5, 8.3 Hz, H6, H6′), 7.72 (2H, d, *J* 7.1 Hz, H4, H4′), 7.30 (2H, dt, *J* 0.5, 7.7 Hz, H5, H5′), 7.26–7.19 (10H, m, ArH), 4.55–4.51 (2H, m, α-CH Phe), 4.37 (2H, dd, *J* 6.4, 7.8 Hz, α-CH Val), 3.56 (6H, s, $COOCH_3$), 3.08–2.92 (4H, m, $CHCH_2Ar$), 2.03–2.00 (2H, m, $CHCH(CH_3)_2$), 0.91 (6H, d, *J* 6.4 Hz, CH_3), 0.85 (6H, d, *J* 6.4 Hz, CH_3). ^{13}C NMR (75 MHz; DMSO-d_6) δ 194.7, 172.1, 170.6, 165.4, 158.5, 139.4, 137.4, 136.4, 134.7, 129.4, 128.6, 126.9, 124.8, 120.3, 57.6, 53.9, 52.2, 36.9, 31.1, 19.4, 18.2. IR (KBr): ν_{max} 3281, 3064, 2961, 2873, 1742, 1643, 1576, 1508, 1449, 1373, 1300, 1211, 1168, 1031, 985, 867, 756, 700, 668, 558, 49 0 cm^{-1}. UV (MeOH/TFA, v/v 9.5:0.5): λ_{max} 340 (ε 12,000 cm^{-1} M^{-1}), 211 (56,170). HRMS (ESI) *m*/*z* 927.3535 $(M+Na)^+$, $C_{48}H_{52}N_6O_{12}Na$ requires 927.3541.

*4.1.19. (R)-Dimethyl 2-((S)-2-(2-(oxamidophenyl)-2-oxoacetamido)-di-3-methylbutanamido)-3-phenylpropanoate (**11g**).* This compound was prepared by the same method as compound **11a**, from *N*-oxalyl bisisatin (0.20 g, 0.57 mmol) and L-valine-D-phenylalanine methyl ester hydrochloride (0.90 g, 2.9 mmol). The title compound **11g** was obtained as a pale yellow solid (0.12 g, 23%). Mp 254–256 °C; R_f 0.80 (CH_3OH/EtOAc/light petroleum, v/v 1:1:8); $[\alpha]_D^{26}$ +115.0 (*c* 0.06, MeOH/DMSO v/v 9.5:0.5). Found: C, 63.50; H, 5.67; N, 9.10%. $C_{48}H_{52}N_6O_{12}$: C, 63.71; H, 5.79; N, 9.29. ^{1}H NMR (300 MHz; DMSO-d_6): δ 12.6 (2H, br s, NHCO), 9.04 (2H, d, *J* 8.6 Hz, CONH), 8.64 (2H, dd *J* 1.1, 7.9 Hz, H7, H7′), 8.58 (2H, d, *J* 7.9 Hz, CONH), 7.80 (2H, dt, *J* 1.1, 8.3 Hz, H6, H6′), 7.72 (2H, dd, *J* 1.1, 7.1 Hz, H4, H4′), 7.30 (2H, dt, *J* 1.1, 8.3 Hz, H5, H5′), 7.22 (10H, m, ArH), 4.52 (2H, m, α-CH Phe), 4.37 (2H, dd, *J* 6.4, 7.8 Hz, α-CH Val), 3.56 (6H, s, $COOCH_3$), 3.00 (4H, m, $CHCH_2Ar$), 2.03–2.00 (2H, m, $CHCH(CH_3)_2$), 0.99 (6H, d, *J* 6.0 Hz, CH_3), 0.85 (6H, d, *J* 6.0 Hz, CH_3). ^{13}C NMR (75 MHz; DMSO-d_6) δ 194.7, 172.1, 170.6, 165.4, 158.5, 139.4, 137.4, 136.4, 134.7, 129.4, 128.6, 126.9, 124.8, 120.3, 57.6, 53.9, 52.2, 36.9, 31.1, 19.4, 18.2. IR (KBr): ν_{max} 3284, 3084, 2957, 2873, 1742, 1639, 1576, 1508, 1449, 1350, 1209, 1211, 1168, 1031, 985, 867, 757, 701, 668, 558, 490 cm^{-1}. UV (MeOH/TFA, v/v 9.5:0.5): λ_{max} 338 (ε 8710 cm^{-1} M^{-1}), 211 (60,190). HRMS (ESI) *m*/*z* 927.3535 $(M+Na)^+$, $C_{48}H_{52}N_6O_{12}Na$ requires 927.3541.

*4.1.20. (S)-Dimethyl 2-((S)-2-(2-(oxamidophenyl)-2-oxoacetamido)-di-3-methylbutanamido)-4-(methylthio)butanoate (**11h**).* This compound was prepared by the same method as compound **11a**, from *N*-oxalyl bisisatin (0.20 g, 0.57 mmol) and L-valine-L-methionine methyl ester hydrochloride (0.95 g, 3.1 mmol). The title compound

11h was obtained as a light yellow solid (0.10 g, 20%). Mp 258–260 °C; R_f 0.82 (CH_3OH/EtOAc/light petroleum, v/v 1:1:8); $[\alpha]_D^{26}$ +8.7 (*c* 0.06, MeOH/DMSO v/v 9.5:0.5). Found: C, 54.73; H, 6.12; N, 9.63%. $C_{40}H_{52}N_6O_{12}S_2$ requires: C, 55.03; H, 6.00; N, 9.63%. ^{1}H NMR (300 MHz; DMSO-d_6): δ 12.6 (2H, br s, NHCO), 9.14 (2H, d, *J* 8.3 Hz, H7 H7′), 8.69 (2H, d, *J* 8.7 Hz, H4, H4′), 8.59 (2H, d, *J* 7.2 Hz, CONH), 7.81 (2H, dt, *J* 0.5, 5.3 Hz, H6, H6′), 7.36 (2H, dt, *J* 0.5, 7.5 Hz, H5, H5′), 4.50–4.43 (2H, m, α-CH Met), 4.32 (2H, d, *J* 4.0 Hz, α-CH Val), 3.62 (6H, s, $COOCH_3$), 2.52 (4H, t, *J* 6.0 Hz, γ-CH_2 Met), 2.09–2.07 (2H, m, CH*CH*$(CH_3)_2$), 2.03 (3H, s, SCH3), 2.00–1.83 (4H, m, β-CH_2 Met), 0.95 (6H, d, *J* 6.8 Hz, CH_3), 0.90 (6H, d, *J* 6.8 Hz, CH_3). ^{13}C NMR (75 MHz; DMSO-d_6) δ 194.7, 172.4, 170.9, 162.7, 158.5, 140.3, 139.4, 137.5, 136.5, 124.8, 120.3, 57.9, 52.3, 51.2, 31.1, 30.8, 29.8, 19.5, 18.4, 14.9. IR (KBr): ν_{max} 3281, 3075, 2962, 2873, 1740, 1639, 1577, 1508, 1449, 1376, 1301, 1211, 1167, 1117, 985, 874, 754, 669, 559 cm^{-1}. UV (MeOH/TFA, v/v 9.5:0.5): λ_{max} 341 (ε 10,710 cm^{-1} M^{-1}), 213 (68,110). HRMS (ESI) *m*/*z* 871.3012 (M+Na)$^+$, $C_{40}H_{51}N_6O_{12}S_2$ requires 871.3012.

*4.1.21. Dimethyl N,N′-(decane-1,10-diyl)bis(4-(2-(2-amino-2-oxoacetyl) phenylamino)-4-oxo-dibutanoate) (**13**).* To a stirred solution of methyl 4-(2,3-dioxoindolin-1-yl)-4-oxo-butanoate **12** (0.50 g, 1.9 mmol) in dichloromethane (25 mL) was added dimethylaminopyridine (0.5 mmol) via a cannula. 1,10-Diaminodecane (0.16 g, 0.95 mmol) was then added in small portions over 10 min and the resulting reaction mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with dichloromethane (30 mL) and extracted with aqueous potassium hydroxide (0.5 M, 20 mL). The solvent was evaporated under reduced pressure and the crude residue obtained was purified by column chromatography with a solvent gradient system from dichloromethane/triethylamine (v/v 9.5:0.5) to dichloromethane/ethyl acetate/triethylamine (v/v 8.5:0.5:0.5) to afford the title compound **13** as a light yellow solid (0.45 g, 35%). Mp 136–138 °C; R_f 0.80 (CH_2Cl_2). ^{1}H NMR (300 MHz; $CDCl_3$): δ 11.0 (2H, br s, NHCO), 8.63 (2H, dd, *J* 1.1, 8.5 Hz, H7, H7′), 8.38 (2H, dd, *J* 1.5, 8.1 Hz, H4, H4′), 7.58 (2H, dt, *J* 1.5, 8.7 Hz, H6, H6′), 7.11 (2H, dt, *J* 1.1, 7.7 Hz, H5, H5′), 6.88 (2H, t, *J* 5.3 Hz, CONH), 3.69 (6H, s, $COCH_3$), 3.39 (4H, q, *J* 7.2 Hz, CH_2), 2.75 (8H, s, CH_2), 1.60 (4H, m, CH_2), 1.32 (10H, m, CH_2). ^{13}C NMR (75 MHz; $CDCl_3$) δ 191.9, 172.9, 170.4, 162.7, 141.8, 136.4, 134.3, 122.5, 120.7, 118.8, 51.8, 39.5, 32.6, 29.2, 29.1, 28.9, 28.8, 26.7. IR (KBr): ν_{max} 3318, 2923, 2852, 1741, 1710, 1639, 1606, 1585, 1533, 1450, 1375, 1321, 1211, 1155, 995, 895, 803, 763, 715, 678, 633 cm^{-1}. UV (MeOH/TFA, v/v 9.5:0.5): λ_{max} 338 (ε 4830 cm^{-1} M^{-1}), 267 (11,010), 227 (49,030). HRMS (ESI) *m*/*z* 717.3114 (M+Na)$^+$, $C_{36}H_{46}N_4O_{10}Na$ requires 717.3112.

*4.1.22. N,N′-(Decane-1,10-diyl)bis(4-(2-(2-amino-2-oxoacetyl)phenyl amino)-4-oxo-dibutanoic acid) (**14**).* To a stirred solution of compound **13** (0.50 g, 0.73 mmol) in methanol (30 mL) at 5 °C was added a solution of aqueous potassium hydroxide (0.50 M, 5 mL) in methanol (5 mL). The resulting yellow-orange solution was warmed to room temperature and stirred for 1.5 h. The excess methanol was then removed under reduced pressure and the dark yellow-orange residue obtained was partitioned between ethyl acetate (60 mL) and aqueous hydrochloric acid (0.50 M, 30 mL). The organic phase was separated and the aqueous layer was extracted with ethyl acetate (2×40 mL). The combined organic extracts were washed with water, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The yellow residue obtained was triturated with dichloromethane to afford the title compound **14** as an off-white solid (0.30 g, 63%). Mp 166–168 °C; R_f 0.53 ($MeOH/CH_2Cl_2$, v/v 1:9); Found: C, 61.03; H, 6.47; N, 8.37%. $C_{34}H_{42}N_4O_{10}$ requires: C, 61.25; H, 6.35; N, 8.40%. ^{1}H NMR (300 MHz; DMSO-d_6): δ 12.2 (2H, br s, OH), 10.7 (2H, s, NHCO), 8.72 (2H, t, *J* 5.6 Hz, CONH), 8.00 (2H, d, *J* 7.9 Hz, H7, H7′), 7.63 (2H, d, *J* 7.5 Hz, H4, H4′), 7.61 (2H, t, *J* 7.5 Hz, H6, H6′), 7.21 (2H, t, *J* 7.5 Hz, H5, H5′), 3.17 (4H, dd, *J* 6.4, 13.0 Hz, NH*CH*$_2$$CH_2$), 2.54 (8H, m, CH_2), 1.46 (4H, m, CH_2), 1.26 (10H, br s, CH_2). ^{13}C NMR (75 MHz; DMSO-d_6) δ 197.8, 173.9, 171.0, 164.3, 139.5, 134.9, 132.4, 123.6, 122.9, 121.5, 38.8, 31.8, 29.3, 29.1, 29.0, 28.9, 26.7. IR (KBr): ν_{max} 3330, 2923, 2851, 1698, 645, 1603, 1582, 1526, 1447, 1374, 1323, 1295, 1235, 1211, 1157, 907, 762, 677 cm^{-1}. UV (MeOH/TFA, v/v 9.5:0.5): λ_{max} 337 (ε 4520 cm^{-1} M^{-1}), 267 (10,030), 220 (54,990). HRMS (ESI) *m*/*z* 689.2788 (M+Na)$^+$, $C_{34}H_{42}N_4O_{10}Na$ requires 689.2799.

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