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Full Paper

Synthesis, Structures, and Conformations of Linked Bis-Glyoxylamides Derived from Bis-Acylisatins

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A series of bis-glyoxylamides possessing hydrophobic alkyl chains was successfully synthesised by ring opening of bis-acylisatins with amines or amino acid alkyl esters. The crystal structures revealed the interplay of intra- and intermolecular interactions (NH···O and C=O···C=O interactions) and the conformations of these long molecules.

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Introduction

Various non-covalent interactions, such as hydrogen bonding, π–π stacking, and hydrophobic interactions, are involved in the formation and stabilisation of molecular self-assemblies.[1–8] Molecules containing more than one hydrogen bond donor/acceptor group and/or aromatic rings can form multiple types of such interactions simultaneously.[9] The synthesis of oligomers containing identical units in one molecule is a strategy that has been used to facilitate a greater number of non-covalent interactions between chains.[10–14] In particular, the self-assembly of polyamides and oligoamides has been extensively studied because of their structural similarity to proteins, where both intramolecular and intermolecular hydrogen bonding interactions play an important role in determining their secondary and tertiary structures.[15–20] However, there are no strict rules governing the rational design of these compounds and predicting the self-organisation processes for different molecules remains difficult.

We have previously demonstrated that mono-glyoxylamides can undergo different modes of assembly depending on the nature of cooperative effects between strong and weak non-covalent interactions. The parent glyoxylamide **1** exhibited dimeric association,[21] while *N*-acylglyoxylic amides **2** containing alkyl side chains formed supramolecular assemblies.[22,23] As part of our continued interest in glyoxylamides and their derivatives, we targeted bis-glyoxylamides **3** and **4** as interesting scaffolds for further investigation into the self-assembly of this class of molecules (Chart 1). We report herein the synthesis of novel bis-glyoxylamides derived from oxalyl-bis-isatins or bis-acylisatins linked through their carbonyl groups, and analyse the intra- and intermolecular interactions of these molecules in the solid state.

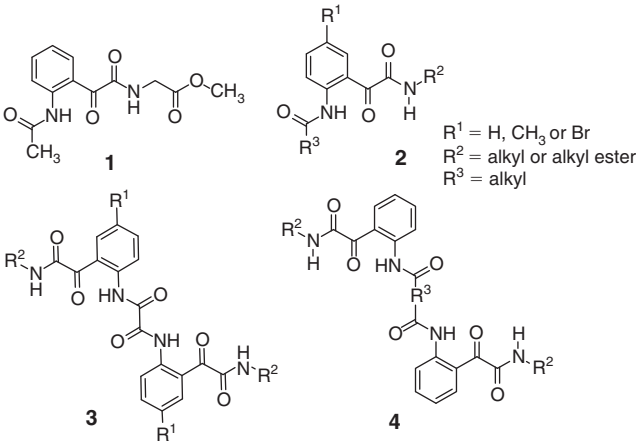
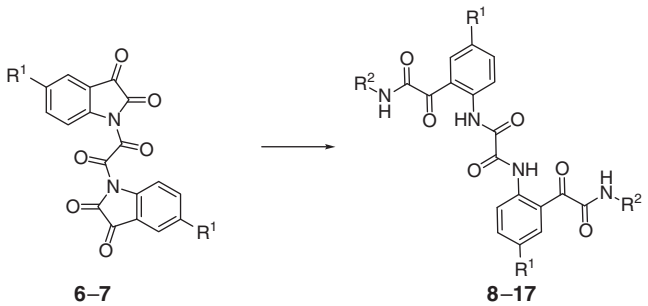


Chart 1.

Results and Discussion

Synthesis of Oxalyl-Bis-Glyoxylamides

The synthesis of some bis-glyoxylamides from *N*-oxalyl-bis-isatin has been previously reported by our group and some analogues showed potent quorum sensing (QS) inhibitor activity against Gram-positive bacteria.[21] In this study, novel bis-glyoxylamides were synthesised by nucleophilic ring-opening reactions of *N*-oxalyl-bis-isatin with alkyl amines or amino acid alkyl esters. The oxalyl isatins were in turn prepared using a modification of the procedure described by Black and Moss.[24] In the present work, oxalyl-bis-isatins were heated at reflux for 6 h in dichloromethane with hexylamine, dodecylamine, or



Scheme 1. Reagents and conditions: CH_2Cl_2, alkylamine, reflux, 4 h or mono alkyl ester hydrochloride salts, saturated $NaHCO_3$, CH_2Cl_2–H_2O (v/v, 6 : 2), 5°C to room temperature, 24 h.

Table 1. Synthesis of bis-glyoxylamides 8–17

Entry	Product	R^1	R^2	Yield[A] [%]
1	**8**	H	hexyl	54
2	**9**	CH_3	hexyl	50
3	**10**	H	dodecyl	59
4	**11**	CH_3	dodecyl	61
5	**12**	H	octadecyl	53
6	**13**	CH_3	octadecyl	56
7	**14**	H	glycine hexyl ester	42
8	**15**	CH_3	glycine hexyl ester	36
9	**16**	H	alanine hexyl ester	38
10	**17**	CH_3	alanine hexyl ester	43

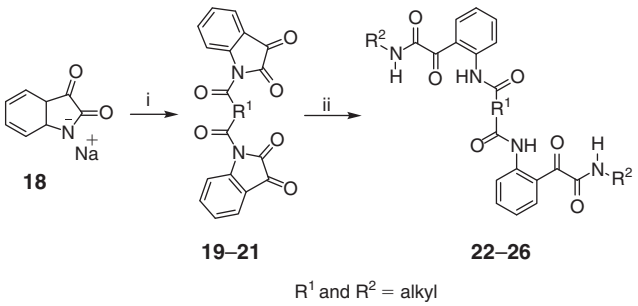
[A]Isolated yield (reaction was not optimised).

octadecylamine to give analogues **8**–**13** in 50–61 % yields (Scheme 1, Table 1). The bis-glyoxylamide peptidomimetics were synthesised using the methodology and reaction conditions previously described.[21] Hence, the oxalyl-bis-isatins were stirred in dichloromethane for 24 h with amino alkyl ester hydrochloride salts and sodium hydrogen carbonate at 5°C to room temperature to give the desired products **14**–**17** in 36–43 % yields (Scheme 1, Table 1).

Synthesis of Linked Bis-Glyoxylamides

Acyl chlorides, including isophthaloyl chloride, succinyl chloride, and adipoyl chloride, were reacted with sodium isatide in anhydrous benzene under reflux to give the corresponding bis-acylisatins **19**–**21** in 69–89 % yields. The targeted bis-acylisatins **19**–**21** were then reacted with various amines to give the corresponding bis-glyoxylamides **22**–**26** in moderate yields (Scheme 2, Table 2).

Isatin **27** was reacted with 2,3-*O*-iso-propylidene-L-tartaryl chloride (**28)** in the presence of pyridine in dichloromethane to generate the desired L-tartaryl bis-acylisatin **29** in 35 % yield (Scheme 3). The tartaryl chloride **28** was prepared according to the method of Choi et al.[25] from 2,3-*O*-iso-propylidene-L-tartrate, which was itself obtained from L-tartaric acid.[26] The presence of the tartaryl moiety in compound **29** was confirmed by ^{1}H NMR spectroscopy, where the methine and methyl protons of the tartaryl group appeared as singlets at 6.06 and 1.58 ppm. The L-tartaryl bis-acylisatin **29** was heated at reflux with *n*-butylamine in dichloromethane to afford the tartaryl-bis-glyoxylamide **30** in 40 % yield. The ^{1}H NMR spectrum of

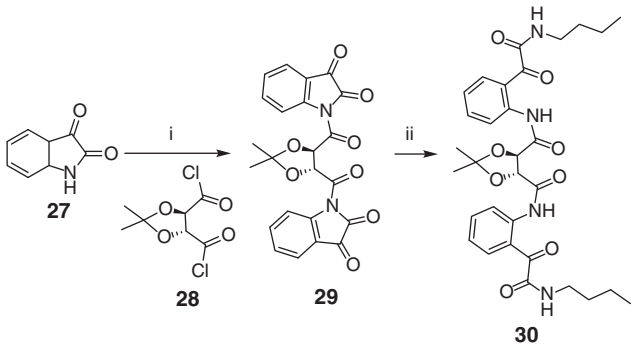


Scheme 2. Reagents and conditions: (i) acyl chlorides, anhydrous benzene, reflux; (ii) amines, CH_2Cl_2, reflux.

Table 2. Synthesis of bis-glyoxylamides 22–31

Entry	Product	R^1	R^2	Yield[A] [%]
1	**22**	1,3-phenylene	H	91
2	**23**	$-(CH_2)_2-$	H	62
3	**24**	$-(CH_2)_4-$	$-CH_3$	68
4	**25**	$-(CH_2)_4-$	*t*-butyl	47
5	**26**	$-(CH_2)_4-$	*n*-butyl	60
6	**30**	tartaryl	*n*-butyl	40

[A]Isolated yield (reaction was not optimised).



Scheme 3. Reagents and conditions: (i) pyridine, CH_2Cl_2, reflux, 3.5 h; (ii) *n*-butylamine, CH_2Cl_2, reflux, 1.5 h.

tartaryl-bis-glyoxylamide **30** included two NH signals, with a downfield singlet at 11.80 ppm corresponding to the amide NH protons and a triplet at 7.34 ppm corresponding to the glyoxylamide NH protons.

The targeted bis-glyoxylamides **8**–**17**, **22**–**26**, and **30** were recrystallised from various solvents by slow evaporation of the solvent at room temperature. Crystals suitable for X-ray structure determination were successfully obtained for compounds **9** and **24**–**26**[27–30] from methanol, while the other compounds yielded only amorphous solids. Single crystal X-ray structure determinations were carried out on compounds **9** and **24**–**26**.

Crystal Structures

The crystal structure of **9** (Fig. 1a) contains two crystallographically independent molecules, one with an ordered structure and one with a disordered structure with two alternate conformations because of the flexibility of the alkyl side chains (the disordered structure is not shown). The two alkyl side chains in the ordered structure of **9** are in a *trans* relationship. Both molecules have a planar core and form intramolecular

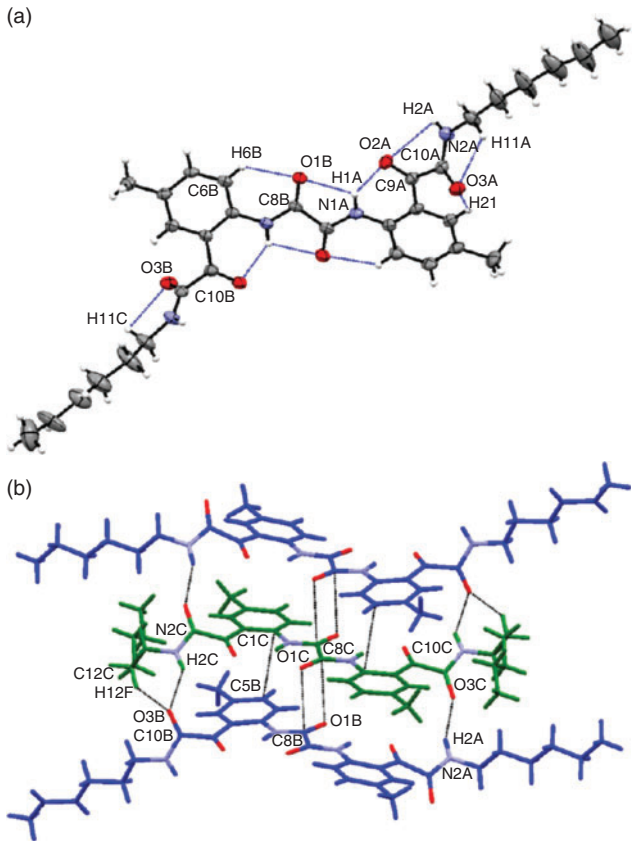


Fig. 1. *ORTEP* diagrams showing the (a) intramolecular interactions (blue dotted lines) and (b) the intermolecular interactions (black dotted lines) of compound **9**. The disordered alkyl chains are not shown for clarity.

N–H···O hydrogen bonding interactions. In addition, the oxygen atoms of the oxalyl group act as acceptors for intramolecular hydrogen bonding interactions with the aromatic C6–H6 and the amide N1–H1 protons. These interactions increase the ridigidity of the molecule and induce planarity of the aromatic head groups with the amide and the glyoxylamide groups.

In terms of intermolecular interactions, two identical strong N2–H2···O3 hydrogen bonds are formed between the glyoxylamide N–H protons and oxalyl groups of separate molecules of **9**, while the planar cores participate in π···π stacking interactions (Fig. 1b). Additionally, the carbonyl groups of the oxalyl moiety form C=O···C=O intermolecular interactions, in addition to the intramolecular N–H···O hydrogen bonding interactions described above (Fig. 1a, b). Interestingly, these interactions are very different from those of compounds **24–26** (see below). Details of the intra- and intermolecular interactions of **9** and a three-dimensional representation of the extended molecular assembly of the compound are shown in the Supplementary Material (Tables S1 and S2, Fig. S1).

Perspective views of molecules of **24–26** are shown in Fig. 2. In the two bis-glyoxylamides **25** and **26**, each molecule occupies a crystallographic centre of symmetry coinciding with the midpoint of the bond C9–C9′ (centrosymmetrically related C9). Meanwhile, compound **24**, although similar to the other two structures, has a pseudo centre of symmetry. Interestingly, this molecule of **24** crystallises in a chiral space group $P2_1$.

Significant conformational differences were observed in the crystal structures of bis-glyoxylamides **25** and **26**, with molecule **26** being more similar in conformation to molecule **24**.

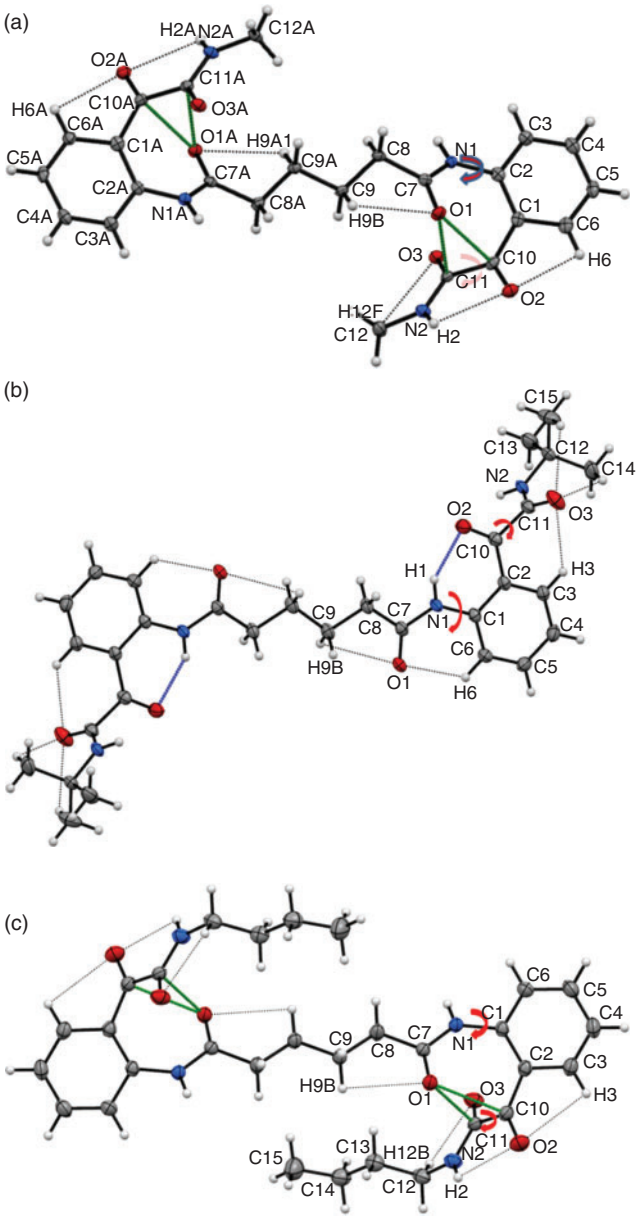


Fig. 2. *ORTEP* figures of (a) **24**, (b) **25** and (c) **26** showing the intramolecular interactions (dotted lines).

The intramolecular N1–H1···O2 hydrogen bond found in bis-glyoxylamide **25** is absent in bis-glyoxylamide **26** because of rotation of the aromatic ring around the N1–C1 bond of the latter molecule by ~180°. As a result, molecule **25** is almost planar (except for the protruding *t*-butyl substituent), whereas molecule **26** is twisted at both ends.

Weak intermolecular C–H···O interactions on both sides of the molecule **25** provide additional support to stabilise the assembly (Fig. 2).

In molecule **26**, weak C–H···O and N2–H2···O2 intermolecular interactions are observed, complementing C=O···C=O dipolar interactions in a cluster of three carbonyl groups (Fig. 2). These dipolar associations[22,23,31] might influence the orientation of O2 and O3, as seen in the torsion angles for O2–C10–C11–O3 (95.2(4) in molecule **25** and −152.12(13) in molecule **26**) and C7–N1–C1–C6 (−7.3(5) in molecule **25** and −141.99(13) in molecule **26**). The geometric parameters of the

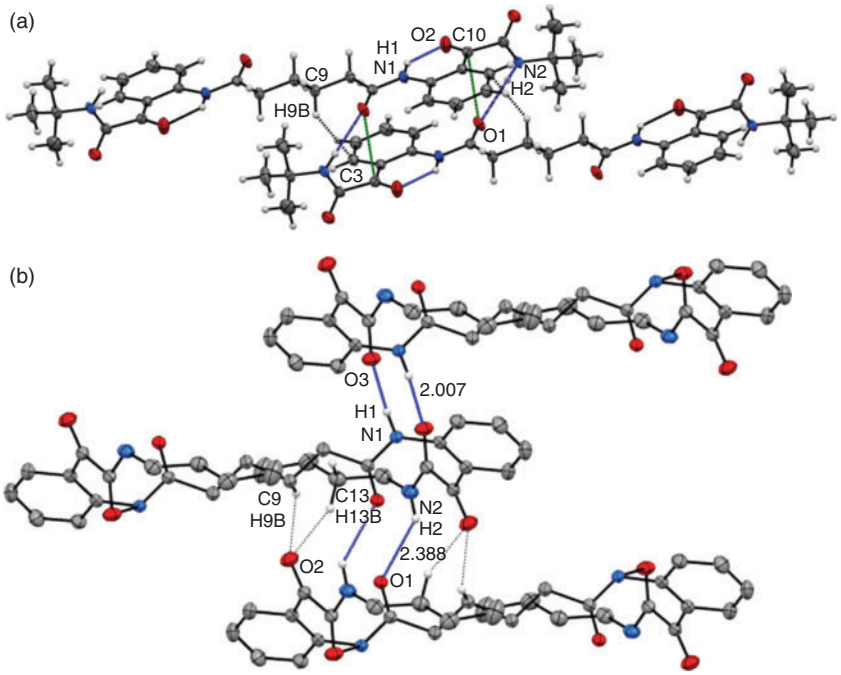


Fig. 3. Intermolecular interactions (blue dotted lines) present in molecules (a) **25** and (b) **26**.

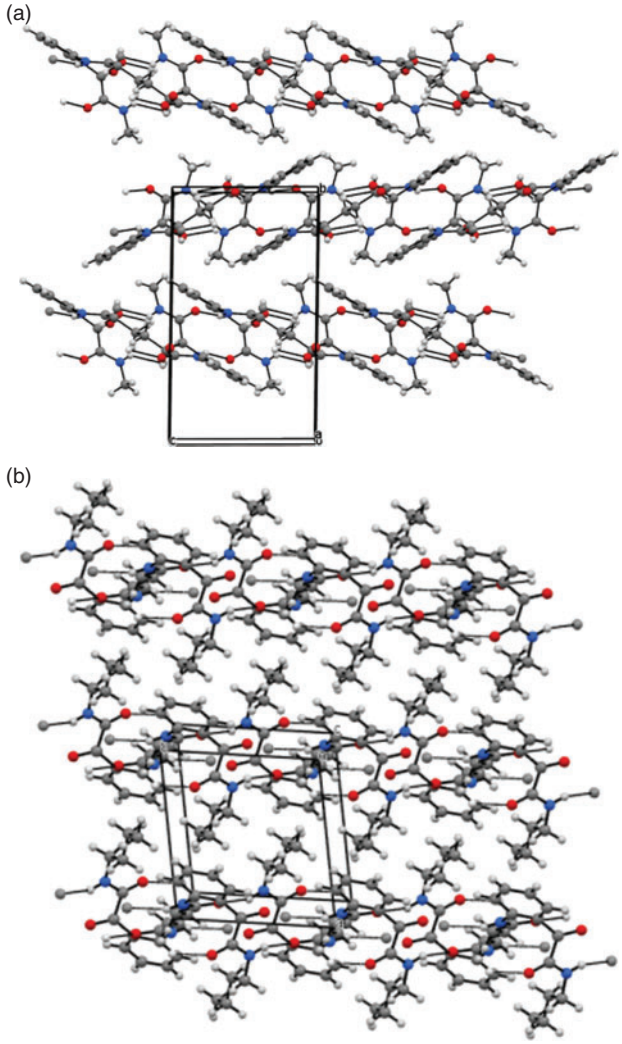


Fig. 4. Packing of (a) **24** and (b) **26**.

intramolecular interactions of **24–26** are provided as Supplementary Material (Tables S1 and S2). The formation of intramolecular N–H···O interactions, either with overall planarity in the molecule or alternately with a twisted conformation, has been previously observed in the mono-glyoxylamides.[22,23] It is significant that the linked bis-glyoxylamides synthesised in this work are also able to adopt these two conformations.

Once the amide N1–H1 proton is engaged in a strong intramolecular hydrogen bond, the glyoxylamide N2–H2 proton makes centrosymmetrically related intermolecular hydrogen bonds with O1. In molecule **26**, both N1–H1 and N2–H2 protons make centrosymmetric intermolecular interactions with O3 and O1 respectively from neighbouring molecules on either side (Fig. 3). In molecule **25**, the intermolecular dipolar interaction (C7=O1···C10=O2) exists supporting the N2–H2···O1 bond; whereas weaker N2–H2···O1 is supported by two centrosymmetric bifurcated C–H···O contacts (C9–H9B···O2 and C13–H13B···O2) in molecule **26**. Complementarity of the intra- and intermolecular interactions present in molecules **25** and **26** (and **24**) should hold the key to the nucleation process which produces the two different conformations observed in the solid state. Pictures of the extended molecular assemblies in three dimensions are shown in the Supplementary Material.

Molecules of **24** and **26** pack together to form layers held together by N–H···O hydrogen bonding (Fig. 4). However, the packing structures differ with respect to the orientation of layers in the three dimensions. In molecule **24**, the next layer has a 2_1 screw relationship with the first layer, whereas in molecule **26**, the third layer is merely a translation of the preceding layers. The centre of symmetry in molecule **26** coincides with the crystallographic centre (in $\bar{P}1$), while molecule **24** has a non-crystallographic centre and crystallises in the non-centrosymmetric space group $P2_1$.

Conclusion

A series of bis-glyoxylamides possessing hydrophobic alkyl chains was successfully synthesised by ring opening of

oxalyl-bis-isatins or bis-acylisatins with amines or amino acid alkyl esters. The crystal structure of oxalyl-bis-glyoxylamide **9** has a planar core, and the carbonyl groups of the oxalyl moiety participate in both intramolecular N–H···O hydrogen bonding and intermolecular C=O···C=O (carbonyl–carbonyl) dipolar interactions.

Crystal structures of bis-glyoxylamides **24–26** with an *n*-butyl linker reveal that molecules **24** and **26** have similar conformations in the solid state that were significantly different from that of molecule **25**, as a result of the complementarity of the intra- and intermolecular interactions present in the molecules. Molecules **25** and **26** possess a crystallographic centre of symmetry, while molecule **24** exhibits a pseudo centre of symmetry. Additionally, compound **24** crystallises in the chiral space group $P2_1$.

Experimental

General

Melting points were measured using a Reichert microscope (Gallenkamp hot stage apparatus) and are uncorrected. Infrared spectra were recorded with a Thermo Nicolet 370 FTIR spectrometer with the sample prepared as a KBr pellet. UV-Vis spectra were recorded using a Varian Cary 100 Scan spectrometer. NMR data were recorded using a Bruker DPX300 instrument (^{1}H at 300 MHz, ^{13}C at 75.4 MHz) at 25°C and reported as chemical shift (δ) relative to $SiMe_4$. Low and high 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). 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.

N,N′-*Bis-(2-(2-(hexylamino)-2-oxoacetyl)phenyl) oxalamide (**8**)*

A mixture of oxalyl-bis-isatin **6** (0.20 g, 0.57 mmol) and hexylamine (0.12 g, 1.14 mmol) in dichloromethane (30 mL) was heated at reflux for 6 h. The cooled reaction mixture was concentrated under vacuum. The crude product was purified by column chromatography using silica gel and a mixture of dichloromethane and hexane as eluent. The title compound was obtained as an off-white solid (0.17 g, 54 %), mp 264–265°C. ν_{max} (KBr)/cm^{-1} 3330, 3248, 2929, 2856, 1714, 1645, 1600, 1579, 1526, 1452, 1377, 1324, 1257, 1209, 1121, 837, 764. λ_{max} (THF)/nm (ε/M^{-1} cm^{-1}) 246 (51 100), 342 (28 300). δ_H (300 MHz, pyridine-d_5) 0.75 (t, *J* 7.0, 6H, 2 × $CH_2(CH_2)_4CH_3$), 1.12–1.36 (m, 12H, 2 × $CH_2CH_2(CH_2)_3CH_3$), 1.58–1.69 (m, 4H, 2 × $NHCH_2CH_2(CH_2)_3CH_3$), 3.53–3.59 (m, 4H, 2 × $NHCH_2CH_2(CH_2)_3CH_3$), 7.17–7.22 (m, 2H, ArH), 7.53–7.58 (m, 2H, ArH), 8.47 (dd, *J* 7.9, 1.4, 2H, ArH), 8.84 (d, *J* 8.3, 2H, ArH), 9.98 (t, *J* 5.6, 2H, 2 × $CONHCH_2$), 12.92 (s, 2H, 2 × NHCO). δ_C (75 MHz, pyridine-d_5) 13.9 (2 × $CH_2(CH_2)_4CH_3$), 26.6, 29.4, 31.3 (2 × $CH_2(CH_2)_4CH_3$), 39.3 (2 × $NHCH_2$), 120.8, 149.8 (4 × ArC), 122.5, 123.9, 124.0, 136.4 (8 × ArCH), 158.6, 165.1, 194.6 (6 × C=O). *m/z* 551.26. TOF-ESI Anal. Calc. for $C_{30}H_{39}N_4O_6$ $[M+H]^+$: 551.28. Anal. Calc. for $C_{30}H_{38}N_4O_6$: C 65.44, H 6.96, N 10.17. Found: C 65.51, H 6.92, N 10.13 %.

N,N′-*Bis-(2-(2-(hexylamino)-2-oxoacetyl)-4-methylphenyl) oxalamide (**9**)*

This compound was prepared by the same method as compound **8** from oxalyl bis-isatin **7** (0.21 g, 0.57 mmol) and hexylamine (0.12 g, 1.14 mmol) as an off-white solid (0.16 g, 50 %). The solid, recrystallised from pyridine by slow evaporation of the solvent at room temperature, yielded crystals suitable for X-ray crystal structure determination, mp 260–262°C. ν_{max} (KBr)/cm^{-1} 3265, 3095, 2927, 2855, 1696, 1644, 1580, 1517, 1459, 1408, 1378, 1302, 1248, 1137, 1041, 979, 864, 803, 757. λ_{max} (THF)/nm (ε/M^{-1} cm^{-1}) 248 (14 700), 252 (30 100). δ_H (300 MHz, $CDCl_3$) 0.85 (t, *J* 7.0, 6H, 2 × $NHCH_2(CH_2)_4CH_3$), 1.23–1.35 (m, 12H, 2 × $CH_2CH_2(CH_2)_3CH_3$), 1.45–1.51 (m, 4H, 2 × $NHCH_2CH_2(CH_2)_3CH_3$), 2.34 (s, 6H, 2 × $ArCH_3$), 3.47–3.49 (m, 4H, 2 × $NHCH_2CH_2(CH_2)_3CH_3$), 7.59 (d, *J* 8.6, 2H, ArH), 7.63 (s, 2H, 2 × CONH), 8.51 (d, *J* 8.5, 2H, ArH), 8.53 (d, *J* 8.6, 2H, ArH), 12.36 (s, 2H, 2 × NHCO). δ_C (75 MHz, $CDCl_3$) 14.3 (2 × $CH_2(CH_2)_4CH_3$), 21.0 (2 × $ArCH_3$), 22.8, 26.8, 29.5, 31.7 (2 × $CH_2(CH_2)_4CH_3$), 39.9 (2 × $NHCH_2$), 118.7, 126.2, 140.0 (6 × ArC), 121.1, 132.5, 137.6 (6 × ArCH), 163.2, 169.3, 192.6 (6 × C=O). *m/z* 579.3170. HR-ESI Anal. Calc. for $C_{32}H_{43}N_4O_6$ $[M+H]^+$: 579.3177. Anal. Calc. for $C_{32}H_{42}N_4O_6$: C 66.41, H 7.32, N 9.68. Found: C 66.42, H 7.28, N 9.61 %.

N,N′-*Bis-(2-(2-(dodecylamino)-2-oxoacetyl)phenyl) oxalamide (**10**)*

This compound was prepared by the same method as compound **8** from oxalyl bis-isatin **6** (0.15 g, 0.43 mmol) and dodecylamine (0.16 g, 0.86 mmol) as an off-white solid (0.18 g, 59 %), mp 244–246°C. ν_{max} (KBr)/cm^{-1} 3315, 3085, 2918, 2850, 1716, 1645, 1600, 1579, 1529, 1452, 1377, 1312, 1277, 1210, 1121, 853, 764. λ_{max} (THF)/nm (ε/M^{-1} cm^{-1}) 246 (32 800), 343 (17 050). δ_H (300 MHz, pyridine-d_5) 0.82 (t, *J* 6.5, 6H, 2 × $CH_2CH_2(CH_2)_9CH_3$), 1.18–1.39 (m, 36H, 2 × $CH_2CH_2(CH_2)_9CH_3$), 1.64–1.74 (m, 4H, 2 × $NHCH_2CH_2(CH_2)_9CH_3$), 3.56–3.63 (m, 4H, 2 × $NHCH_2(CH_2)_9CH_3$), 7.16–7.22 (m, 2H, ArH), 7.53–7.57 (m, 2H, ArH), 8.49 (dd, *J* 7.9, 1.6, 2H, ArH), 8.89 (d, *J* 8.2, 2H, ArH), 9.99 (t, *J* 5.7, 2H, 2 × CONH), 12.91 (s, 2H, 2 × NHCO). δ_C (75 MHz, pyridine-d_5) 14.0 (2 × $CH_2(CH_2)_{10}CH_3$), 22.6, 26.6, 29.1, 29.2, 29.2, 29.4, 29.5, 29.5, 29.5, 31.3 (2 × $CH_2(CH_2)_{10}CH_3$), 39.6 (2 × $NHCH_2$), 118.7, 141.9 (6 × ArC), 120.6, 122.5, 134.3, 136.4 (8 × ArCH), 162.8, 169.2, 192.1 (6 × C=O). *m/z* 719.43. TOF-ESI Anal. Calc. for $C_{42}H_{63}N_4O_6$ $[M+H]^+$: 719.47. Anal. Calc. for $C_{42}H_{62}N_4O_6$: C 70.16, H 8.69, N 7.79. Found: C 70.27, H 8.78, N 7.77 %.

N,N′-*Bis-(2-(2-(dodecylamino)-2-oxoacetyl)-4-methylphenyl)oxalamide (**11**)*

This compound was prepared by the same method as compound **8** from oxalyl bis-isatin **7** (0.16 g, 0.43 mmol) and dodecylamine (0.16 g, 0.86 mmol) as a yellow solid (0.20 g, 61 %), mp 224–226°C. ν_{max} (KBr)/cm^{-1} 3280, 3081, 2919, 2850, 2359, 2340, 1701, 1642, 1578, 1512, 1454, 1406, 1376, 1330, 1300, 1244, 1135, 866, 753. λ_{max} (THF)/nm (ε/M^{-1} cm^{-1}) 250 (33 800), 347 (13 700). δ_H (300 MHz, $CDCl_3$) 0.88 (t, *J* 6.9, 6H, 2 × $CH_2(CH_2)_{10}CH_3$), 1.23–1.35 (m, 36H, 2 × $CH_2CH_2(CH_2)_9CH_3$), 1.55–1.66 (m, 4H, 2 × $NHCH_2CH_2(CH_2)_9CH_3$), 2.39 (s, 6H, 2 × $ArCH_3$), 3.47–3.49 (m, 4H, 2 × $NHCH_2CH_2(CH_2)_9CH_3$), 7.06 (t, *J* 5.6, 2H, 2 × CONH), 7.49 (dd, *J* 8.6, 2.1, 2H, ArH), 8.48 (d, *J* 1.6, 2H, ArH), 8.71 (d, *J* 8.5, 2H, ArH), 12.63 (s, 2H, 2 × NHCO). δ_C (75 MHz, $CDCl_3$) 14.0 (2 × $CH_2(CH_2)_{10}CH_3$), 20.8 (2 × $ArCH_3$), 22.6, 26.8, 29.2, 29.3, 29.4, 29.5, 29.5, 31.8 (2 × $CH_2(CH_2)_{10}CH_3$), 39.6 (2 × $NHCH_2$), 120.1, 133.8, 137.5 (6 × ArC), 120.6, 134.9, 137.0 (6 × ArCH), 158.3, 161.8, 190.8 (6 × C=O). *m/z* 769.4861. HR-ESI Anal. Calc. for $C_{44}H_{67}N_4O_6$ $[M+Na]^+$: 769.4875. Anal. Calc. for

$C_{44}H_{66}N_4O_6$: C 70.74, H 8.91, N 7.50. Found: C 70.80, H 9.07, N 7.51 %.

N,N′-Bis-2-(2-(octadecylamino)-2-oxoacetyl)phenyl) oxalamide (**12**)

This compound was prepared by the same method as compound **8** from oxalyl bis-isatin **6** (0.10 g, 0.29 mmol) and octadecylamine (0.16 g, 0.58 mmol) as an off-white solid after purification by column chromatography (0.14 g, 53 %), mp 220–222°C. ν_{max} (KBr)/cm^{-1} 3314, 3252, 2918, 2850, 1717, 1646, 1600, 1579, 1529, 1452, 1376, 1313, 1276, 1212, 1167, 839, 763. λ_{max} (THF)/nm (ε/M^{-1} cm^{-1}) 246 (26 800), 343 (13 200). δ_H (300 MHz, pyridine-d_5) 0.82 (t, *J* 6.8, 6H, 2 × $CH_2CH_2(CH_2)_9CH_3$), 1.18–1.39 (m, 60H, 2 × $CH_2CH_2(CH_2)_{15}CH_3$), 1.65–1.78 (m, 4H, 2 × $NHCH_2CH_2(CH_2)_{15}CH_3$), 3.53–3.66 (m, 4H, 2 × $NHCH_2(CH_2)_{15}CH_3$), 7.15–7.21 (m, 2H, ArH), 7.54–7.52 (m, 2H, ArH), 8.47 (dd, *J* 7.9, 1.5, 2H, ArH), 8.89 (d, *J* 8.2, 2H, ArH), 9.98 (t, *J* 5.6, 2H, 2 × CONH), 12.94 (s, 2H, 2 × NHCO). δ_C (75 MHz, pyridine-d_5) 14.0 (2 × $CH_2(CH_2)_{16}CH_3$), 22.6, 26.6, 29.1, 29.2, 29.2, 29.4, 29.5, 29.5, 29.5, 31.2 (2 × $CH_2(CH_2)_{16}CH_3$), 39.6 (2 × $NHCH_2$), 118.6, 141.9 (4 × ArC), 120.6, 122.5, 134.3, 136.4 (8 × ArCH), 161.8, 167.2, 190.1 (6 × C=O). *m/z* 887.6620. HRMS (ESI) Anal. Calc. for $C_{54}H_{87}N_4O_6$ $[M+H]^+$: 887.6603.

N-(4-Methyl-2-(2-(octadecylamino)-2-oxoacetyl)phenyl)-N′-(4-methyl-6-(2-(octadecylamino)-2-oxoacetyl) cyclohexa-1,5-dien-1-yl)oxalamide (**13**)

This compound was prepared by the same method as compound **8** from oxalyl bis-isatin **7** (0.11 g, 0.29 mmol) and octadecylamine (0.16 g, 0.58 mmol) as an off-white solid (0.13 g, 46 %), mp 228–230°C. ν_{max} (KBr)/cm^{-1} 3302, 2918, 2850, 1712, 1647, 1583, 1523, 1459, 1374, 1303, 1248, 1188, 1160, 819, 788. λ_{max} (THF)/nm (ε/M^{-1} cm^{-1}) 250 (24 900), 348 (11 750). δ_H (300 MHz, $CDCl_3$) 0.88 (t, *J* 7.1, 6H, 2 × $CH_2(CH_2)_{16}CH_3$), 1.23–1.34 (m, 60H, 2 × $CH_2CH_2(CH_2)_{15}CH_3$), 1.54–1.65 (m, 4H, 2 × $NHCH_2CH_2(CH_2)_{15}CH_3$), 2.39 (s, 6H, 2 × $ArCH_3$), 3.36–3.45 (m, 4H, 2 × $NHCH_2CH_2(CH_2)_{15}CH_3$), 7.08 (s, 2H, 2 × CONH), 7.49 (d, *J* 8.4, 2H, ArH), 8.47 (s, 2H, ArH), 8.71 (d, *J* 8.4, 2H, ArH), 12.62 (s, 2H, 2 × NHCO). δ_C (75 MHz, $CDCl_3$) 14.0 (2 × $CH_2(CH_2)_{16}CH_3$), 20.8 (2 × $ArCH_3$), 22.6, 26.8, 29.2, 29.3, 29.4, 29.5, 29.6, 31.8 (2 × $CH_2(CH_2)_{16}CH_3$), 39.6 (2 × $NHCH_2$), 120.1, 133.8, 137.5 (6 × ArC), 120.6, 134.9, 137.0 (6 × ArCH), 158.3, 161.9, 190.8 (6 × C=O). *m/z* 939.5958. HRMS (ESI) Anal. Calc. for $C_{56}H_{92}N_4O_6Na$ $[M+Na]^+$: 939.7017. Anal. Calc. for $C_{56}H_{92}N_4O_6$: C 73.48, H 9.91, N, 6.12. Found: C 73.35, H 10.03, N 6.51 %.

Dihexyl 2,2′-((2,2′-((Oxalylbis(azanediyl))bis(2,1-phenylene))bis(2-oxoacetyl))bis(azanediyl))diacetate (**14**)

A solution of glycine hexyl ester hydrochloride (0.21 g, 1.08 mmol) containing saturated $NaHCO_3$ was added to a stirred solution of the oxalyl bis-isatin **6** (0.15 g, 0.43 mmol) in dichloromethane (25 mL) at 5°C. The reaction mixture was warmed to room temperature and stirred for 24–28 h. The organic layer was diluted with CH_2Cl_2 (25 mL) and washed with aqueous HCl (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 column chromatography using silica gel and a mixture of dichloromethane and hexane as eluent. The title compound was obtained as an off-white solid (0.12 g, 42 %), mp 164–166°C. ν_{max} (KBr)/cm^{-1} 3282, 3078, 2955, 2931, 2858, 1733, 1714, 1646, 1600, 1578, 1452, 1372, 1310, 1273, 1200, 1169, 1065, 992, 868, 765. λ_{max} (THF)/nm (ε/M^{-1} cm^{-1}) 234 (15 350), 262 (18 700), 342 (12 700). δ_H (300 MHz, $CDCl_3$) 0.88 (t, *J* 6.9, 6H, 2 × $CH_2(CH_2)_4CH_3$), 1.28–1.46 (m, 12H, 2 × $CH_2CH_2(CH_2)_3CH_3$), 1.66–1.74 (m, 4H, 2 × $CH_2CH_2(CH_2)_3CH_3$), 4.21–4.26 (m, 8H, 2 × $NHCH_2COOCH_2(CH_2)CH_3$), 7.28–7.34 (m, 2H, ArH), 7.57 (t, *J* 5.3, 2H, 2 × $NHCH_2COO$), 7.71–7.77 (m, 2H, ArH), 8.41 (dd, *J* 8.1, 1.5, 2H, ArH), 8.67 (dd, *J* 8.5, 1.0, 2H, ArH), 12.70 (s, 2H, 2 × NHCO). δ_C (75 MHz, $CDCl_3$) 14.0 (2 × $CH_2(CH_2)_4CH_3$), 22.5, 25.5, 28.5, 31.4 (2 × $CH_2(CH_2)_4CH_3$), 41.5 (2 × $NHCH_2COO$), 66.1 (2 × $COOCH_2(CH_2)_4CH_3$), 120.0, 140.1 (4 × ArC), 120.9, 124.2, 134.9, 136.6 (8 × ArCH), 158.4, 162.0, 168.8, 189.9 (8 × C=O). *m/z* 667.2908. HRMS (ESI) Anal. Calc. for $C_{34}H_{43}N_4O_{10}$ $[M+H]^+$: 667.2901.

Dihexyl 2,2′-((2,2′-((Oxalylbis(azanediyl))bis(3-methyl-6,1-phenylene))bis(2-oxoacetyl))bis(azanediyl))diacetate (**15**)

This compound was prepared by the same method as compound **14** from oxalyl bis-isatin **7** (0.15 g, 0.39 mmol) and glycine hexyl ester hydrochloride (0.19 g, 0.98 mmol) as a yellow solid (0.11 g, 38 %), mp 184–186°C. ν_{max} (KBr)/cm^{-1} 3347, 3202, 2927, 2870, 1742, 1682, 1584, 1518, 1460, 1413, 1363, 1310, 1263, 1182, 1135, 1079, 1037, 969, 863, 754. λ_{max} (THF)/nm (ε/M^{-1} cm^{-1}) 237 (37 350), 249 (43 150), 348 (21 450). δ_H (300 MHz, $CDCl_3$) 0.93 (t, *J* 6.8, 6H, 2 × $CH_2(CH_2)_4CH_3$), 1.29–1.45 (m, 12H, 2 × $CH_2CH_2(CH_2)_3CH_3$), 1.66–1.74 (m, 4H, 2 × $CH_2CH_2(CH_2)_3CH_3$), 2.42 (s, 6H, 2 × $ArCH_3$), 4.22–4.26 (m, 8H, 2 × $NHCH_2COOCH_2(CH_2)_4CH_3$), 7.51–7.59 (m, 4H, 2 × ArH and 2 × $NHCH_2COO$), 8.40 (d, *J* 1.4, 2H, ArH), 8.74 (d, *J* 8.6, 2H, ArH), 12.58 (s, 2H, 2 × NHCO). δ_C (75 MHz, $CDCl_3$) 14.0 (2 × $CH_2(CH_2)_4CH_3$), 20.9 (2 × $ArCH_3$), 22.5, 25.5, 28.5, 31.4 (2 × $CH_2(CH_2)_4CH_3$), 41.6 (2 × $NHCH_2COO$), 66.1 (2 × $COOCH_2(CH_2)_4CH_3$), 120.0, 133.9, 137.7 (6 × ArC), 120.8, 134.9, 137.3 (6 × ArCH), 158.3, 162.2, 168.8, 190.0 (8 × C=O). *m/z* 717.3113. HRMS (ESI) Anal. Calc. for $C_{36}H_{47}N_4O_{10}$ $[M+H]^+$: 717.3106.

Dihexyl 2,2′-((2,2′-((Oxalylbis(azanediyl))bis(2,1-phenylene))bis(2-oxoacetyl))bis(azanediyl)) dipropanoate (**16**)

This compound was prepared by the same method as compound **14** from oxalyl bis-isatin **6** (0.15 g, 0.43 mmol) and L-alanine hexyl ester hydrochloride (0.23 g, 1.08 mmol) as a white solid (0.11 g, 36 %), mp 170–172°C. ν_{max} (KBr)/cm^{-1} 3365, 3250, 2931, 2856, 1755, 1717, 1649, 1601, 1579, 1529, 1453, 1412, 1324, 1299, 1237, 1167, 1052, 937, 769. λ_{max} (THF)/nm (ε/M^{-1} cm^{-1}) 236 (22 900), 259 (28 550), 346 (18 900). δ_H (300 MHz, $CDCl_3$) 0.92 (t, *J* 6.6, 6H, 2 × $CH_2(CH_2)_4CH_3$), 1.31–1.42 (m, 12H, 2 × $(CH_2)_2(CH_2)_3CH_3$), 1.57 (d, *J* 7.2, 6H, 2 × $NHCHCH_3COO$), 1.66–1.73 (m, 4H, 2 × $CH_2CH_2(CH_2)_3CH_3$), 4.20–4.25 (m, 4H, 2 × $COOCH_2(CH_2)_4CH_3$), 4.65–4.75 (m, 2H, 2 × $NHCHCH_2COO$), 7.28–7.32 (m, 2H, 2 × ArH), 7.60 (d, *J* 7.6, 2H, 2 × $NHCHCH_2COO$), 7.69–7.75 (m, 2H, ArH), 8.64 (dd, *J* 8.1, 1.5, 2H, ArH), 8.86 (dd, *J* 8.1, 0.9, 2H, ArH), 12.71 (s, 2H, 2 × NHCO). δ_C (75 MHz, $CDCl_3$) 14.0 (2 × $CH_2(CH_2)_4CH_3$), 18.2 (2 × $NHCHCH_3COO$), 20.2 (2 × $ArCH_3$), 22.5, 25.5, 28.5, 31.4 (2 × $CH_2(CH_2)_4CH_3$), 48.6 (2 × $NHCHCH_3COO$), 66.0 (2 × $COOCH_2(CH_2)_4CH_3$), 120.0, 137.7 (4 × ArC), 120.8, 133.9, 134.9, 137.2 (8 × ArCH), 158.4, 161.5, 171.9, 190.1 (8 × C=O). *m/z* 695.3206. HRMS (ESI) Anal. Calc. for $C_{36}H_{47}N_4O_{10}$ $[M+H]^+$: 695.3214.

*Dihexyl 2,2′-((2,2′-((Oxalylbis(azanediyl))bis(3-methyl-6,1-phenylene))bis(2-oxoacetyl))bis(azanediyl)) dipropanoate (**17**)*

This compound was prepared by the same method as compound **14** from oxalyl bis-isatin **7** (0.15 g, 0.39 mmol) and L-alanine hexyl ester hydrochloride (0.21 g, 0.98 mmol) as a yellow solid (0.18 g, 43 %), mp 178–180°C. ν_{max} (KBr)/cm^{-1} 3286, 2929, 2859, 1742, 1698, 1649, 1578, 1515, 1547, 1407, 1389, 1303, 1276, 1249, 1233, 1115, 988, 865, 788. λ_{max} (THF)/nm (ε/M^{-1} cm^{-1}) 237 (16 550), 249 (22 050), 347 (9700). δ_H (300 MHz, $CDCl_3$) 0.92 (t, *J* 6.0, 6H, 2 × $CH_2(CH_2)_4CH_3$), 1.28–1.45 (m, 12H, 2 × $(CH_2)_2(CH_2)_3CH_3$), 1.57 (d, *J* 7.2, 6H, 2 × NHCHCH_3COO), 1.66–1.76 (m, 4H, 2 × $CH_2CH_2(CH_2)_3CH_3$), 2.43 (s, 6H, 2 × $ArCH_3$), 4.20–4.25 (m, 4H, 2 × $COOCH_2(CH_2)_4CH_3$), 4.65–4.75 (m, 2H, 2 × NHCHCH$_3$COO), 7.28–7.32 (dd, *J* 8.7, 2.2, 2H, ArH), 7.58 (d, *J* 7.7, 2H, 2 × NHCHCH_2COO), 8.41 (d, *J* 1.9, 2H, ArH), 8.75 (d, *J* 8.2, 2H, ArH), 12.62 (s, 2H, 2 × NHCO). δ_C (75 MHz, $CDCl_3$) 14.0 (2 × $CH_2(CH_2)_4CH_3$), 18.1 (2 × NHCHCH_3COO), 20.9 (2 × $ArCH_3$), 22.5, 25.5, 28.5, 31.4 (2 × $CH_2(CH_2)_4CH_3$), 48.6 (2 × NHCHCH$_3$COO), 66.0 (2 × $COOCH_2(CH_2)_4CH_3$), 120.1, 133.9, 137.7 (6 × ArC), 120.8, 134.9, 137.2 (6 × ArCH), 158.4, 161.5, 171.9, 190.1 (8 × C=O). *m/z* 745.3405. HRMS (ESI) Anal. Calc. for $C_{38}H_{50}N_4O_{10}Na$ $[M+Na]^+$: 745.3419. Anal. Calc. for $C_{38}H_{50}N_4O_{10}$: C 63.14, H 6.97, N 7.75. Found: C 63.40, H 7.09, N 7.58 %.

*1-(3-(2,3-Dioxo-1*H*-indole-1-carbonyl)benzoyl)-1*H*-indole-2,3-dione (**19**)*

A solution of isophthaloyl chloride (3.03 g, 15 mmol) in anhydrous benzene was added dropwise to a stirred suspension of sodium isatide (5.00 g, 30 mmol) in anhydrous benzene. The reaction mixture was warmed for 10 min to complete the reaction and then heated under reflux for 5 min and quickly filtered to remove the salt. The solvent was evaporated under vacuum to give the title compound as a yellow solid (5.69 g, 89 %), mp 186–187°C. ν_{max} (KBr)/cm^{-1} 1775, 1745, 1725, 1690, 1650, 1600, 1585, 1535, 1340, 1300, 1210, 1165, 1000, 760, 750, 715. λ_{max} (THF)/nm (ε/M^{-1} cm^{-1}) 237 (38 100), 267 (15 250), 341 (8550). δ_H (300 MHz, DMSO-d_6) 7.27–8.56 (m, 12H, 12 × ArH). This compound was too insoluble for ^{13}C NMR spectrum to be recorded. *m/z* Found 427.05. TOF-ESI Anal. Calc. for $C_{24}H_{15}N_2O_6$ $[M+H]^+$: 427.09. Anal. Calc. For $C_{24}H_{14}N_2O_6.H_2O$: C 64.87, H 3.63, N 6.30. Found: C 65.04, H 3.60, N 6.21 %.

*1-(4-(2,3-Dioxo-1*H*-indol-1-yl)-4-oxobutanoyl)-1*H*-indole-2,3-dione (**20**)*

This compound was prepared by the same method as compound **19** from sodium isatide (5.00 g, 30 mmol) and succinyl chloride 2.08 g, 13.4 mmol) as a yellow powder (3.49 g, 69 %), mp 255–257°C. ν_{max} (KBr)/cm^{-1} 1770, 1740, 1715, 1600, 1590, 1400, 1340, 1300, 1255, 1215, 1175, 1155, 1085, 920, 890, 800, 770, 700. λ_{max} (THF)/nm (ε/M^{-1} cm^{-1}) 238 (37 750), 270 (15 640), 341 (8600). δ_H (300 MHz, DMSO-d_6) 3.45 (s, 4H, 2 × $NCOCH_2$), 7.37–8.32 (m, 8H, 8 × ArH). This compound was too insoluble for a ^{13}C NMR spectrum to be recorded. *m/z* 379.13. TOF-ESI Anal. Calc. for $C_{20}H_{15}N_2O_6$ $[M+H]^+$: 379.09. Anal. Calc. For $C_{20}H_{14}N_2O_6$: C 63.49, H 3.73, N 7.40. Found: C 63.40, H 3.50, N 7.40 %.

*1-(6-(2,3-Dioxo-1*H*-indol-1-yl)-6-oxohexanoyl)-1*H*-indole-2,3-dione (**21**)*

A solution of adipoyl chloride (2.44 g, 13.4 mmol) in anhydrous benzene (30 mL) was added dropwise over 10 min to a stirred suspension of sodium isatide (5.00 g, 30 mmol) in anhydrous benzene (150 mL). The reaction mixture was heated at reflux for 2 h. The hot mixture was then filtered, washed with water, and dried to give a yellow solid (3.91 g, 72 %), mp >200°C (dec.). ν_{max} (KBr)/cm^{-1} 1775, 1740, 1700, 1605. λ_{max} (THF)/nm (ε/M^{-1} cm^{-1}) 237 (38 000), 269 (15 450), 342 (8800). δ_H (300 MHz, DMSO-d_6) 1.76 (s, 4H, $NHCH_2(CH_2)_2CH_2NH$), 3.07 (s, 4H, $NHCH_2(CH_2)_2CH_2NH$), 7.36 (t, *J* 7.2, 2H, 2 × ArH), 7.76–7.99 (m, 4H, 4 × ArH), 8.28 (d, *J* 8.2, 2H, 2 × ArH). This compound was too insoluble for a ^{13}C NMR spectrum to be recorded. *m/z* 719.33. TOF-ESI Anal. Calc. for $C_{22}H_{19}N_2O_6$ $[M+H]^+$: 407.12. Anal. Calc. for $C_{22}H_{16}N_2O_6$: C 65.38, H 4.00, N 6.91. Found: C 65.00, H 4.21, N 6.72 %.

*N,N′-Bis(2-(2-amino-2-oxoacetyl)phenyl)isophthalamide Hydrate (**22**)*

The title compound was prepared by bubbling gaseous ammonia through a solution of isophthaloyl bis-isatin **19** (0.51 g, 1.2 mmol) in dimethylformamide. The title compound was obtained as a colourless powder (0.50 g, 91 %), mp 208–209°C. ν_{max} (KBr)/cm^{-1} 3410, 3290, 1727, 1690, 1678, 1650, 1611, 1587, 1535, 1315, 1220, 1168, 982, 792, 702. λ_{max} (THF)/nm (ε/M^{-1} cm^{-1}) 238 (38 500), 270 (1600), 341 (9000). δ_H (300 MHz, DMSO-d_6) 7.30–8.57 (m, 16H, 12 × ArH and 2 × $-CONH_2$), 11.64 (s, 2H, 2 × ArNHCO). δ_C (75 MHz, DMSO-d_6) 121.78, 122.69, 123.99, 126.85, 129.52, 130.56, 132.51, 134.72, 134.91, 139.40 (ArC and ArCH), 164.56, 165.99, 193.43 (6 × C=O). *m/z* 459.20. TOF-ESI Anal. Calc. for $C_{24}H_{19}N_2O_6$ $[M+H]^+$: 459.13. Anal. Calc. for $C_{24}H_{18}N_4O_6.H_2O$: C 60.50, H 4.23, N 11.76. Found: C 60.41, H 4.51, N 12.02 %.

*N,N′-Bis(2-(2-amino-2-oxoacetyl)phenyl)succinamide (**23**)*

The title compound was prepared by treating a suspension of succinyl bis-isatin **20** (0.57 g, 1.5 mmol) in absolute ethanol with a solution of aqueous ammonia (30 mL, 2 M). The title compound was collected by filtration, recrystallised from ethanol–DMF, and obtained as a pale yellow powder (0.38 g, 62 %), mp 223–224°C. ν_{max} (KBr)/cm^{-1} 3410, 3220, 1700, 1670, 1642, 1605, 1584, 1530, 1450, 1318, 1220, 1175, 1160, 1150, 1127, 980, 774. λ_{max} (THF)/nm (ε/M^{-1} cm^{-1}) 237 (38 050), 267 (15 600), 341 (8900). δ_H (300 MHz, DMSO-d_6) 2.74 (s, 4H, -$COCH_2CH_2CO$), 7.15–8.17 (m, 12H, 8 × ArH and 2 × $–CONH_2$), 10.81 (s, 2H, 2 × ArNHCO). δ_C (75 MHz, DMSO-d_6) 121.20, 122.30, 123.28, 132.12, 134.52, 139.21 (ArC and ArCH), 166.19, 170.67, 192.91 (6 × C=O). *m/z* 411.19. TOF-ESI Anal. Calc. for $C_{20}H_{19}N_4O_6$ $[M+H]^+$: 411.13. Anal. Calc. for $C_{20}H_{18}N_4O_6$: C 58.53, H 4.42, N 13.65. Found: C 58.41, H 4.22, N 13.42 %.

*N,N′-Bis(2-(2-(methylamino)-2-oxoacetyl)phenyl) adipamide (**24**)*

A solution of 1,1′-(adipoyl) bis-isatin **21** (0.50 g, 1.24 mmol) and methylamine (25 % aqueous, 0.8 mL, 6 mmol) in dichloromethane (30 mL) was heated at reflux for 3 h. The cooled solution was washed with dilute hydrochloric acid, dried over anhydrous magnesium sulfate, and concentrated under vacuum.

The crude product was purified by suction column chromatography using dichloromethane as eluent to give the title compound as a white solid (0.40 g, 68 %), mp 194–196°C. ν_{max} (KBr)/cm^{-1} 3354, 3279, 3254, 1699, 1668, 1608, 1531, 1482, 1407, 1302, 1275, 1212, 940, 757. λ_{max} (THF)/nm (ε/M^{-1} cm^{-1}) 239 (36 900), 270 (14 600), 345 (8400). δ_H (300 MHz, DMSO-d_6) 1.63 (s, 4H, $COCH_2CH_2CH_2CH_2CO$), 2.37–2.43 (m, 4H, $COCH_2CH_2CH_2CH_2CO$), 2.73 (d, *J* 4.9, 6H, 2 × $NHCH_3$), 7.22 (d, *J* 7.9, 2H, ArH), 7.66–7.58 (m, 4H, ArH), 7.88 (d, *J* 7.9, 2H, ArH), 8.61 (d, *J* 4.9, 2H, 2 × $NHCH_3$), 10.56 (s, 2 H, 2 × NHCO). δ_C (75 MHz, DMSO-d_6) 25.8 (2 × $NHCH_3$), 24.7 ($COCH_2CH_2CH_2CH_2CO$), 36.7 ($COCH_2CH_2CH_2CH_2CO$), 121.8, 123.7, 132.0, 132.4 (8 × ArCH), 124.1, 138.9 (4 × ArC), 164.4, 171.7, 191.9 (6 × C=O). *m/z* 467.14. TOF-ESI Anal. Calc. for $C_{24}H_{27}N_4O_6$ $[M+H]^+$: 467.19. Anal. Calc. for $C_{24}H_{26}N_4O_6$: C 61.79, H 5.62, N 12.01. Found: C 61.51, H 5.61, N 11.77 %.

N,N′-*Bis*(2-(2-(tert-*butylamino*)-2-oxoacetyl)phenyl) *adipamide* (***25***)

A solution containing 1,1′-(adipoyl)bis-isatin **21** (0.50 g, 1.24 mmol) and *tert*-butylamine (1.3 mL, 3 mmol) in dichloromethane (30 mL) was heated at reflux for 5 h. The cooled solution was diluted with dichloromethane, washed with dilute hydrochloric acid, and then washed with brine and dried over magnesium sulfate. The solvent was evaporated under vacuum to give the title compound (0.32 g, 47 %) as a light yellow solid, mp 193–195°C. ν_{max} (KBr)/cm^{-1} 3312, 1687, 1662, 1609, 1586, 1532, 1449, 1297, 1206, 1161, 759. λ_{max} (THF)/nm (ε/M^{-1} cm^{-1}) 238 (33 000), 267 (16 000), 344 (8600). δ_H (300 MHz, $CDCl_3$) 1.44 (s, 18H, 2 × $C(CH_3)_4$), 1.63–1.86 (m, 4H, $COCH_2CH_2CH_2CH_2CO$), 2.37–2.48 (m, 4H, $COCH_2CH_2CH_2CH_2CO$), 6.73 (s, 2H, 2 × COCONH), 7.10 (t, *J* 8.3, 2H, ArH), 7.56 (t, *J* 8.3, 2H, ArH), 8.24 (d, *J* 8.3, 2H, ArH), 8.63 (d, *J* 8.3, 2H, ArH), 10.97 (s, 2H, 2 × NHCO). δ_C (75 MHz, $CDCl_3$) 28.8 (2 × $C(CH_3)_4$), 25.2 (2 × $COCH_2CH_2$), 38.5 (2 × $COCH_2$), 52.5 (2 × $C(CH_3)_4$), 119.1, 142.3 (4 × ArC), 121.1, 122.8, 134.7, 136.6 (8 × ArCH), 162.8, 172.1, 193.1 (6 × C=O). *m/z* 551.22. TOF-ESI Anal. Calc. for $C_{30}H_{39}N_4O_6$ $[M+H]^+$: 551.28. Anal. Calc. for $C_{30}H_{38}N_4O_6 \cdot 0.25H_2O$: C 64.91, H 6.99, N 10.09. Found: C 65.24, H 7.21, N 9.68 %.

N,N′-*Bis*(2-(2-(butylamino)-2-oxoacetyl)phenyl) *adipamide* (***26***)

A solution of 1,1′-(adipoyl)bis-isatin **21** (0.50 g, 1.24 mmol) and *n*-butylamine (0.3 mL, 3 mmol) in dichloromethane (150 mL) was heated at reflux for 3 h. The cooled solution was washed with dilute hydrochloric acid three times, and then twice with saturated sodium bicarbonate and dried over magnesium sulfate. The solvent was evaporated under vacuum. Recrystallisation from dichloromethane/hexane gave the title compound as a light apricot coloured solid (0.41 g, 60 %), mp 170–173°C, ν_{max} (KBr)/cm^{-1} 3360, 3291, 3257, 1693, 1674, 1655, 1607, 1531, 1482, 1290, 1270, 1226, 1175, 1152, 951, 761. λ_{max} (THF)/nm (ε/M^{-1} cm^{-1}) 239 (37 900), 269 (15 400), 343 (8500). δ_H (300 MHz, $CDCl_3$) 0.95 (t, *J* 7.1, 6H, 2 × CH_2CH_3), 1.31–1.39 (m, 4H, 2 × CH_2CH_3), 1.52–1.58 (m, 4H, 2 × $CH_2CH_2CH_3$), 1.63–1.86 (m, 4H, $COCH_2CH_2CH_2CH_2CO$), 2.37–2.48 (m, 4H, $COCH_2CH_2CH_2CH_2CO$), 3.18–3.38 (m, 4H, 2 × $NHCH_2$), 6.93 (s, 2H, 2 × COCONH), 7.12 (t, *J* 8.3, 2H, ArH), 7.58 (t, *J* 8.3, 2H, ArH), 8.35 (d, *J* 8.3, 2H, ArH) 8.64 (d, *J* 8.3, 2H, ArH), 11.01 (s, 2H, 2 × NHCO). δ_C (75 MHz, $CDCl_3$) 17.0 ($NHCH_3$), 20.4, 25.2, 31.7 (6 × CH_2), 38.5 (2 × $NHCOCH_2$), 39.7 (2 × $NHCH_2$), 119.3, 142.4 (4 × ArC), 121.2, 122.9, 134.8, 136.8 (8 × ArCH), 163.3, 172.1, 192.6 (6 × C=O). *m/z* 573.28. TOF-ESI Anal. Calc. for $C_{30}H_{38}N_4O_6$ $[M+Na]^+$: 573.26. Anal. Calc. for $C_{30}H_{38}N_4O_6 \cdot 0.25H_2O$ C 64.91, H 6.99, N 10.09. Found: C 64.94, H 7.03, N 10.01 %.

1,1′-((4R,5R)-2,2-Dimethyl-1,3-dioxolane-4,5-dicarbonyl) bis(indoline-2,3-dione) (***29***)

A solution of 2,3-*O*-iso-propylidene-L-tartaryl chloride (11.97 g, 52.7 mmol) in dichloromethane (50 mL) was added dropwise to a stirred suspension of isatin (14.73, 100 mmol) and pyridine (10.3 mL) in dichloromethane (150 mL). The reaction mixture was heated at reflux for 3.5 h and allowed to cool. The mixture was washed three times with dilute HCl, twice with saturated $NaHCO_3$, dried over magnesium sulfate, and the solvent was evaporated under vacuum. Purification by suction coloumn chromatography (dichloromethane) gave the title compound (7.830 g, 35 %). δ_H (300 MHz, $CDCl_3$) 1.58 (s, 6H, $C(CH_3)_2$), 6.06 (s, 2H, CH), 7.40 (t, 2H, *J* 7.2, 8.2, ArH), 7.83–776 (m, 4H, ArH), 8.48 (d, 2H, *J* 8.2, ArH).

(4R,5R)-N,N′-*Bis*(2-(2-(butylamino)-2-oxoacetyl)phenyl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxamide (***30***)

A solution of **29** (1.00 g, 2.23 mmol) and *n*-butylamine (0.36 g, 4.9 mmol) in dichloromethane (20 mL) was heated at reflux for 1.5 h. After cooling to room temperature, the solution was washed twice with dilute HCl, twice with saturated $NaHCO_3$, dried over magnesium sulfate, and the solvent was evaporated under vacuum. Purification by gravity coloumn chromatography (5 % MeOH/CH_2Cl_2) gave the title compound (0.54 g, 40 %) as yellow crystals, mp 150–154°C. ν_{max} (KBr)/cm^{-1} 3283, 1703, 1649, 1583, 1520, 1450, 1297, 1213, 756. λ_{max} (THF)/nm (ε/M^{-1} cm^{-1}) 239 (40 900), 267 (17 900), 340 (9690). δ_H (300 MHz, $CDCl_3$) 0.92 (t, 6H, *J* 6.8, 2 × CH_2CH_3), 1.53 (s, 6H, $C(CH_3)_2$), 1.38, 1.59, 3.37 (m, each 4H, 2 × CH_2), 4.84 (s, 2H, CHCH), 7.34 (t, 2H, *J* 6.2, COCONH), 7.07 and 7.42 (t, each 2H, *J* 7.2, 8.2, ArH), 8.21 and 8.51 (d, each 2H, *J* 9.2, 8.2, ArH), 11.80 (s, 2H, NHCO). δ_C (75 MHz, $CDCl_3$) 13.74 (CH_3), 26.51 ($C(CH_3)_2$), 20.12, 31.31, 39.39 ($(CH_2)_3CH_3$), 78.49 (CHCH), 113.93 ($C(CH_3)_2$), 120.43, 123.21, 134.40, 136.10 (ArCH), 119.28, 140.59 (ArC), 163.54, 169.70 (CONH), 192.62 (CO). *m/z* 595.29. TOF-ESI Anal. Calc. for $C_{31}H_{38}N_4O_8$ $[M+H]^+$: 595.27. Anal. Calc. for $C_{31}H_{38}N_4O_8$: C 62.61, H 6.44, N 9.42. Found: C 62.66, H 6.42, N 9.24 %.

Structure Determination

Suitable single crystals of **9**, **25**, and **26** selected under a polarising microscope (Leica M165Z) were picked up on a MicroMount (MiTeGen, USA) consisting of a thin polymer tip with a wicking aperture. The X-ray diffraction measurements were carried out on a Bruker KAPPA APEX II CCD diffractometer at 150 K by using graphite-monochromated $Mo_{K\alpha}$ radiation (λ 0.710723 Å). The single crystals, mounted on the goniometer using cryo loops for intensity measurements, were coated with paraffin oil and then quickly transferred to the cold stream using an Oxford Cryo stream attachment. Symmetry related absorption corrections using the program *SADABS*[32] were applied and the data were corrected for Lorentz and polarisation effects using Bruker *APEX2* software.[33] All structures were solved by direct methods and the full-matrix least-squares refinements were carried out using *SHELXL*.[34] The non-hydrogen atoms

were refined anisotropically. The molecular graphics were generated using *Mercury*.[35]

The X-ray diffraction measurements for **9** and **24** were carried out at MX1 and MX2 beamlines at the Australian Synchrotron Facility, Melbourne. The procedure for diffraction intensity measurements on both beamlines was similar. The crystal was mounted on the goniometer using a cryo loop for diffraction measurements, was coated with paraffin oil, and then quickly transferred to the cold stream using a Cryo stream attachment. Data were collected using Si <111> monochromated synchrotron X-ray radiation (λ 0.71023 Å) at 100(2) K and were corrected for Lorentz and polarisation effects using the *XDS* software.[36] The structure was solved by direct methods and the full-matrix least-squares refinements were carried out using *SHELXL*.[34]

Supplementary Material

The geometric parameters of the intramolecular interactions, intermolecular interaction distances and angles, and molecular assemblies of **9**, **24**–**26** as well as the ^{1}H and ^{13}C NMR spectra of compounds **13**–**17** are available on the Journal's website.

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[27] Crystals of **9** were obtained from methanol. Crystal data: $C_{32}H_{40.67}N_4O_6$, MW 577.35, Monoclinic, $P2_1/c$. Cell dimensions: a 9.1920 (18), b 23.833 (5), c 21.695 (4) Å and β 98.59 (3)°, Z 6, T 100 K. D_{calcd} 1.224 Mg m^{-3}. Data/restraints/parameters 8258:48:612. Final R indices, $R[F^2 > 2s(F^2)] = 0.090$, $wR(F^2) = 0.252$. CCDC 958544.

[28] Crystals of **24** were obtained from methanol. Crystal data: $C_{24}H_{26}N_4O_6$, MW 466.49, Monoclinic, $P2_1$. Cell dimensions: a 9.1500 (18), b 14.679 (3), c 9.3670 (19) Å and β 114.43 (3)°, Z 2, T 100 K. D_{calcd} 1.353 Mg m^{-3}. Data/restraints/parameters 3311:1:310. Final R indices, $R[F^2 > 2s(F^2)] = 0.042$, $wR(F^2) = 0.113$. CCDC 957127.

[29] Crystals of **25** were obtained from methanol. Crystal data: $C_{30}H_{38}N_4O_6$, MW 550.64, Monoclinic, $P2_1/c$. Cell dimensions: a 8.9927 (18), b 9.941 (2), c 16.474 (3) Å and β 102.128 (11)°, Z 4, T 150 K. D_{calcd} 1.270 Mg m^{-3}. Data/restraints/parameters 2522:0:184. Final R indices, $R[F^2 > 2s(F^2)] = 0.058$, $wR(F^2) = 0.164$. CCDC 957125.

[30] Crystals of **26** were obtained from methanol. Crystal data: $C_{30}H_{38}N_4O_6$, MW 550.64, Triclinic, $P\bar{1}$. Cell dimensions: a 8.9717 (4), b 9.1948 (4), c 9.6574 (4) Å and α 64.779 (2)°, β 81.225 (2)°, γ 89.513 (2)°, Z = 1, T = 150 K. D_{calcd} 1.286 Mg m^{-3}. Data/restraints/parameters 2462:0:182. Final R indices, $R[F^2 > 2s(F^2)] = 0.035$, $wR(F^2) = 0.096$. Crystallographic data excluding structure factors have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 957126. A copy of the data can be obtained free of charge from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK or e-mail: deposit@ccdc.cam.ac.uk.

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