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Chirality of the molecular assembly determined by intra-/inter-N–H···O hydrogen bonding in doubly substituted *N*-octanoylglyoxylic amides

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ABSTRACT

N-Octanoylglyoxylic amides have been synthesized from *N*-octanoylisatins and their self-assembly analyzed in the solid state by X-ray crystallography. Of the seven compounds, only two utilize intramolecular N1–H1···O2 hydrogen bonds, whereas five of them forgo this intramolecular hydrogen bond to achieve two centrosymmetric N–H···O bonds possessing a non-planar conformation with intramolecular triple C=O···C=O dipolar contacts. These alternative conformations with resulting intermolecular interactions influence the self-assembly process distinctly; the former have molecules packed in chiral space groups whereas the latter associate in non-chiral space groups.

1. Introduction

Investigation of hydrogen bonding patterns and other forms of inter- and intramolecular interactions are of profound interest due to their potential applications in molecular recognition, crystal engineering and biological and material sciences.[1] In particular, the hydrogen bond motifs of carboxylic acids and amides have been particularly well studied and are well-known to form reliable supramolecular synthons.[2,3] Such self-assembled structures can be formed by a variety of building blocks, where peptides have drawn significant attention due to their structural diversity. The application of peptide building blocks in biosensors, tissue engineering and the development of antibacterial agents has also already been demonstrated.[4] However, designing synthetic self-assembled architectures formed by amphiphilic molecules to construct functional materials remains a big challenge.[5]

The structures of corresponding glyoxylamides possess remarkable molecular features, such as hydrogen bond acceptor/donor properties and a comparatively high molecular dipole moment. These properties allow glyoxylamides to establish highly variable tectons for the construction of supramolecular assemblies.[6–8] Despite this, these interesting molecules have been poorly studied to date.

In previous studies, we found methyl 2-(2-(2-acetamidophenyl)-2-oxoacetamido)acetate **1** self-assembles into a dimer via hydrogen bonding between the glyoxylamide NH proton and the acetamide oxygen atom.[9] Introduction of an alkyl chain on the glyoxylamide to give *N*-acetylglyoxylic amides **2a**–**c** and **3** was found to further enhance the self-assembly properties of these compounds, which no longer favoured the dimeric conformation displayed by the parent compound **1**. Different molecular conformations were observed for compounds **2a**–**c** and **3**, arising from different cooperative effects between strong and weak interactions.[10]

In order to better understand the self-assembly properties of amphiphilic glyoxylamides and to construct unique supramolecular assemblies, it was of interest to subsequently examine the self-assembly of a new series of *N*-acylglyoxylic amides, which bear a hydrophobic alkyl chain on the amide side of the molecule or long alkyl chains on both sides of the molecule. Herein, we report the supramolecular architectures as a result of intra/intermolecular interactions displayed by these new *N*-octanoylglyoxylic amides **4**.

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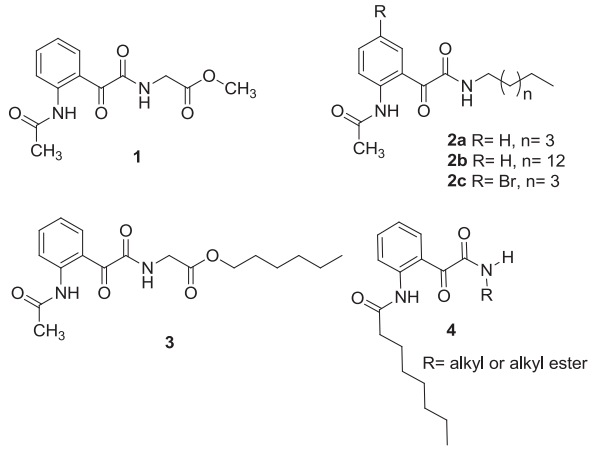
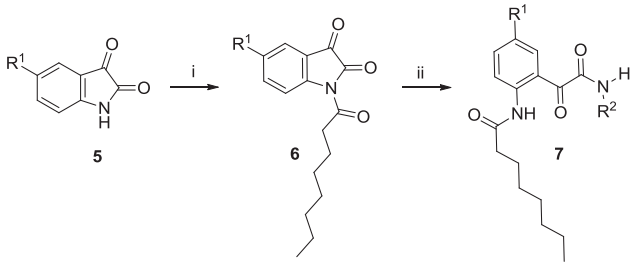


2. Results and discussion

2.1. Synthesis of *N*-octanoylglyoxylic amides

N-Octanoylisatins **6a**–**c** were prepared by addition of the isatin **5a**–**c** to a suspension of sodium hydride in dry THF, followed by dropwise addition of octanoyl chloride in dry THF to the purple mixtures at 5 °C. The reaction mixtures were subsequently warmed to room temperature and then quenched with ice water and extracted with ethyl acetate to give *N*-octanoylisatins **6** in 78–87% yields (Scheme 1).



Scheme 1. Reagents and conditions: (i) octanoyl chloride, NaH, THF, 0 °C to rt, 4 h, (ii) amine, CH_2Cl_2, reflux, 4 h.

N-Octanoylisatins **6** were then subjected to nucleophilic ring-opening with a range of amines and amino acid alkyl esters. Treatment of *N*-octanoylisatins **6** with ammonia or methylamine in dichloromethane under reflux for 1–2 h gave the corresponding *N*-octanoylglyoxylic amides **7a**–**f** in 56–72% yields. Similarly, reaction of *N*-octanoylisatins **6** with hexylamine, dodecylamine or octadecylamine under reflux in dichloromethane for 4–6 h generated the corresponding *N*-octanoylglyoxylic amides **7g**–**o** in moderate to good yields of 55–71% (Scheme 1, Table 1).

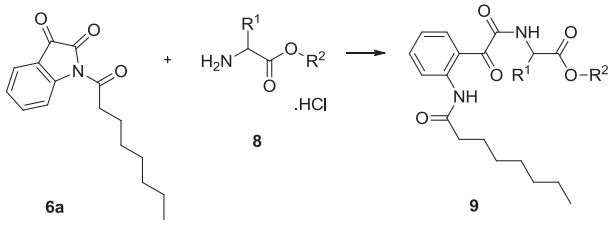
The corresponding *N*-octanoylglyoxylamide amino acid derivatives **9** were prepared via our previous described methods.[11] The *N*-octanoylisatin **6a** was stirred in dichloromethane for 24–28 h with an amino acid methyl ester hydrochloride salt **8** and sodium hydrogen carbonate, initially at 5 °C and then gradually warmed to room temperature to give the desired glyoxylamide peptidomimetics **9a**,**b** in 44–52% yields. In a similar fashion, treatment of *N*-octanoylisatin **6a** with a variety of amino acid alkyl ester hydrochloride salts **8** produced the corresponding glyoxylamide peptidomimetics **9c**–**f** in 42–56% yield (Scheme 2, Table 2).

Glyoxylamides **7** and **9** were subsequently recrystallized from a range of solvents including methanol, ethanol, dichloromethane/hexane and acetonitrile via slow evaporation of the solvent at room temperature. Crystals suitable for X-ray structure determination were successfully obtained for compounds **7a**, **7d**, **7i**, **7k**, **7l**, **9a** and **9d**, while the other compounds afforded only amorphous solids.

Table 1
Synthesis of *N*-octanoylglyoxylic amides **7**

Entry	Product	R_1	R_2	Yield[a] (%)
1	**7a**	H	H	63
5	**7b**	Br	H	72
3	**7c**	CH_3	H	60
4	**7d**	H	CH_3	67
5	**7e**	Br	CH_3	56
6	**7f**	CH_3	CH_3	71
7	**7g**	H	$(CH_2)_5CH_3$	71
8	**7h**	Br	$(CH_2)_5CH_3$	64
9	**7i**	CH_3	$(CH_2)_5CH_3$	73
10	**7j**	H	$(CH_2)_{11}CH_3$	60
11	**7k**	Br	$(CH_2)_{11}CH_3$	67
12	**7l**	CH_3	$(CH_2)_{11}CH_3$	66
13	**7m**	H	$(CH_2)_{17}CH_3$	59
14	**7n**	Br	$(CH_2)_{17}CH_3$	55
15	**7o**	CH_3	$(CH_2)_{17}CH_3$	56

[a] Isolated yield (reaction was not optimized).



Scheme 2. Reagents and conditions: amino acid alkyl ester hydrochloride salt, $NaHCO_3$, CH_2Cl_2/H_2O (1:1 v/v), 0 °C to rt, 24 h.

Table 2
Synthesis of *N*-octanoylglyoxylic amide peptidomimetics **9**

Entry	Amino acid[a]	Product	R_1	R_2	Yield[b] (%)
1	Glycine	**9a**	H	CH_3	46
2	L-Alanine	**9b**	CH_3	CH_3	52
3	Glycine	**9c**	H	$(CH_2)_3CH_3$	44
4	L-Alanine	**9e**	CH_3	$(CH_2)_3CH_3$	56
5	Glycine	**9d**	H	$(CH_2)_5CH_3$	42
6	L-Alanine	**9f**	CH_3	$(CH_2)_5CH_3$	55

[a] As the alkyl ester hydrochloric salt.
[b] Isolated yield (reaction was not optimized).

2.2. Crystal structures

Single crystal X-ray structure determinations were carried out on compounds **7a**, **7d**, **7i**, **7k**, **7l**, **9a** and **9d**. A summary of their crystallographic data is provided in Table 3. Crystal structures of these compounds have well ordered alkyl chains, but **7a** contained two crystallographically independent molecules, one with an ordered structure and one disordered with two alternate conformations. The bromo compound **7k** was isostructural with the methyl compound **7l**.

It is intriguing to note that only two of the molecules (**7a** and **9d**) utilize intramolecular N1–H1···O2 hydrogen bonding, whereas the remaining five (**7d**, **7i**, **7k**, **7l** and **9a**) adopt different conformations to achieve stabilization through C=O···C=O dipolar contacts involving three C=O groups (the two carbonyls of the glyoxylamide and the amide carbonyl group). However, the reasons that influence these alternatives are not obvious. Fig. 1 shows the crystal structures of **9a** and **9b** depicting the significant intramolecular interactions. Crystal structures of **7a**, **7d**, **7i**, **7k** and **7l** are shown in Fig. S1, Supplementary data. These two choices of conformations, either to form N–H···O or C=O···C=O contacts, are achieved by

Table 3
Crystal data collection and structure refinement parameters of **7a**, **7d**, **7i**, **7k**, **7l**, **9a** and **9d**

Compound	**7a**	**7d**	**7i**	**7k**	**7l**	**9a**	**9d**
Chemical formula	$C_{16}H_{22}N_2O_3$	$C_{17}H_{24}N_2O_3$	$C_{23}H_{36}N_2O_3$	$C_{28}H_{45}BrN_2O_3$	$C_{29}H_{48}N_2O_3$	$C_{19}H_{26}N_2O_5$	$C_{30}H_{20}N_4O_6$
M_r	580.71	304.38	388.54	537.57	472.69	362.42	532.50
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic	Orthorhombic	Orthorhombic	Triclinic	Monoclinic
Space group	$P2_12_12_1$	*Pbca*	*Pbca*	$Pca2_1$	$Pca2_1$	$P-1$	$P2_1$
Temperature (K)	152	100	100	154	154	155	100
a, b, c (Å)	7.8980 (7), 9.8793 (9), 39.517 (4)	9.906 (2), 17.958 (4), 19.396 (4)	14.005 (3), 9.4400 (19), 35.398 (7)	13.7253 (17), 22.889 (3), 9.3591 (11)	13.7253 (17), 22.889 (3), 9.3591 (11)	8.8866 (7), 9.9456 (11), 12.5215 (15)	5.096 (1), 42.589 (9), 5.4520 (11)
α, β, γ (°)	—	—	—	—	—	76.528 (5), 85.606 (5), 63.657 (3)	90, 98.40 (3), 90
V (Å^3)	3083.4 (5)	3450.4 (12)	4679.9 (16)	2940.2 (6)	2940.2 (6)	964.01 (17)	1170.6 (4)
Z	4	8	8	4	4	2	2
μ (mm^{-1})	0.09	0.08	0.07	1.43	0.07	0.09	0.07
Crystal size (mm)	0.60×0.33×0.05	0.03×0.02×0.01	0.10×0.02×0.01	0.50×0.10×0.02	0.51×0.32×0.04	0.34×0.11×0.08	0.10×0.02×0.01
T_{min}, T_{max}	0.950, 0.996	Absorption corrections are not applied	Absorption corrections are not applied	0.538, 0.967	0.966, 0.997	0.970, 0.993	Absorption corrections are not applied
No. of measured, independent and observed [$I>2\sigma(I)$] reflections	18,504, 5294, 3459	36,556, 2543, 2388	41,308, 3863, 2892	17,744, 4661, 2079	17,993, 4926, 3325	12,366, 3335, 2381	14,483, 3773, 3655
R_{int}	0.098	0.024	0.099	0.139	0.086	0.037	0.233
$R[F^2>2\sigma(F^2)]$, $wR(F^2)$, S	0.147, 0.347, 1.20	0.042, 0.112, 1.09	0.081, 0.185, 1.12	0.075, 0.233, 1.06	0.065, 0.192, 1.07	0.038, 0.128, 1.03	0.075, 0.168, 0.90
No. of reflections	5294	2543	3863	4661	4926	3335	3773
No. of parameters	376	201	260	309	320	241	282
No. of restraints	414	0	0	53	79	0	1
$\Delta\rangle_{max}$, $\Delta\rangle_{min}$ (e Å^{-3})	0.58, −0.75	0.29, −0.24	0.25, −0.33	0.43, −0.80	0.42, −0.36	0.29, −0.37	0.54, −0.44
CCDC number	915508	915509	915510	915511	915512	915513	915514

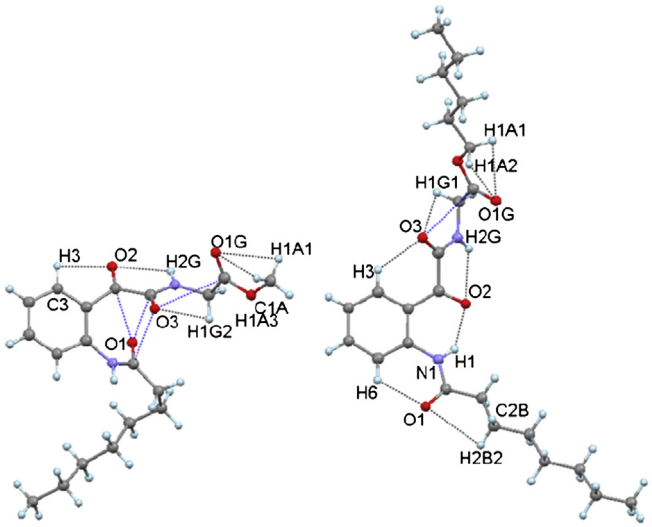


Fig. 1. Intramolecular interactions present in molecules **9a** (left) and **9d** (right). Black dotted lines represent the hydrogen bonding interactions, whereas the blue dotted lines represent the dipolar C═O···C═O interactions.

rotating both the side chains about the C1–N1 and C2–C8 bonds by approximately 180°, respectively. The N–H···O hydrogen bonding keeps the aromatic 'head' part co-planar with the amide group at C2 and the glyoxylamide at C3, whereas in making the dipolar contacts these groups deviate out of plane. The resulting effects on their supramolecular organization are discussed later. The geometric parameters of the intramolecular interactions are given in Table S1, Supplementary data.

The amide and glyoxylamide chains interact with each other in the five crystal structures (**7d**, **7i**, **7k**, **7l** and **9a**) for which the N1–H1···O2═C intramolecular hydrogen bond is absent. The two carbonyls of the glyoxylamide functionality adopt their normal *transoid* conformation[12] and both participate in dipolar C═O···C═O interactions with the amide carbonyl group. This triple carbonyl interaction was observed in two crystal structures formed by **2c** and reported in our earlier paper.[10] The intercarbonyl distances (2.52–3.15 Å) and angles (74–123°) for these structures appear in Table S1, Supplementary data. Allen et al. have described both the antiparallel and orthogonal C═O···C═O dipolar interactions.[13] The orthogonal motif is encountered more frequently, especially in crystal structures of proteins and other amide-containing compounds,[14,15] because it is less subjected to steric effects.[16] However, the intramolecular orthogonal triple carbonyl dipolar association is the variant observed here. Although the distances observed are conventional, several of the angles are slightly compromised by the molecular geometry and deviate from ideal orthogonality. Nonetheless, this packing motif occurs consistently and it is clearly effective for molecules of this general type. Although Allen et al. demonstrated that these dipolar interactions can compete effectively with strong hydrogen bonds in crystal packing,[13] the situation is rather different here since the carbonyl dipoles operate together with strong and weak hydrogen bonding interactions (N–H···O and C–H···O).

2.3. Supramolecular organization

Interesting correlations were observed between intramolecular contacts and their effect on the overall molecular organization. When the molecule makes intramolecular C═O···C═O contacts, both N–H groups form intermolecular N–H···O hydrogen bonds, which are always across a centre of symmetry. However, when N1 makes an intramolecular N1–H1···O2 hydrogen bond, this leaves only N2 available for the intermolecular N–H···O contact, which is repeated by translation along the shortest unit cell axis. The intermolecular interaction distances and angles of all seven structures are summarized in Table S2, Supplementary data.

The five crystal structures (**7d**, **7i**, **7k**, **7l** and **9a**) that feature the intramolecular triple carbonyl interaction motif also contain significant intermolecular N–H···O═C hydrogen bonded associations.

Molecules of **9a** (Fig. 2) are arranged along the *b* direction and their interaction results in the formation of tape assemblies.[17,18] Two cyclic centrosymmetric hydrogen bonded motifs are present, involving –CO–CO–NH···O=C–NH– interaction on one side of the molecule, and –CO–(NH)C=O···HN–CO– interaction on the other. Similar arrangements are present in the other four crystal structures, and all five form non-chiral space groups.

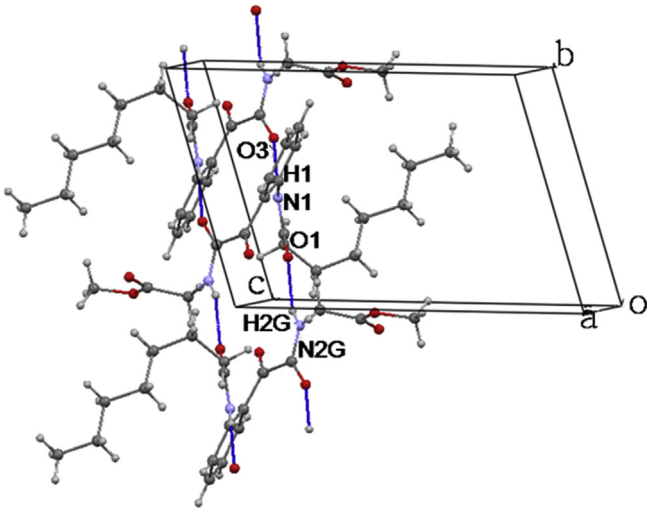


Fig. 2. Crystal structure of **9a**, highlighting the intermolecular amide hydrogen bonding along *b*.

The remaining crystals (**7a** and **9d**) contain intramolecular H1–N1···O2 hydrogen bonding, but also utilize intermolecular amide hydrogen bonding. These crystals are more complex, in the sense that their achiral molecules assemble to produce helices and these cause formation of the chiral space groups $P2_12_12_1$ and $P2_1$, respectively. In the case of **9d**, the molecules are simply translated along *a* and are linked into a hydrogen bonded chain by means of –CO–(NH)C=O···HN–CO–CO– interactions (Fig. 3).

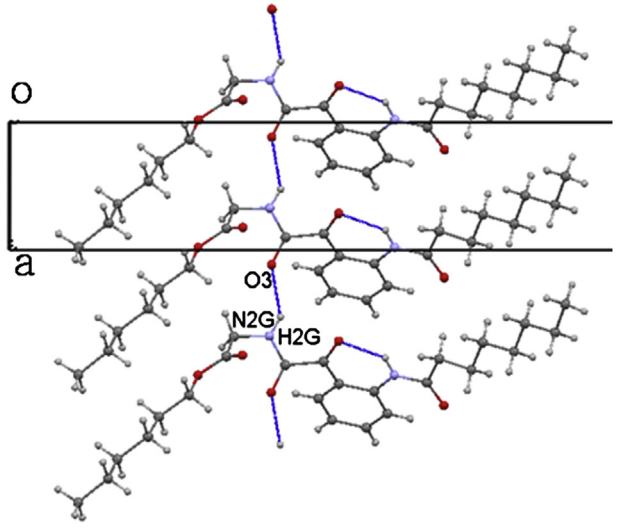


Fig. 3. Crystal structure of **9d** showing the intermolecular hydrogen bonded chain. The 2_1 screw axis (not shown) runs along the (horizontal) long axis *b*.

Crystals of **7a** contain two crystallographically independent molecules (coloured green and blue in Fig. 4). These form a dimeric assembly around a pseudo-inversion centre by using intermolecular N–H···O=C hydrogen bonds. Further association of these dimers looks at first like a ladder assembly,[19] but closer inspection reveals a tape running along the direction of the *ab* diagonal.[19,20] This is created by two molecules of **7a** in adjacent dimers interacting by means of ···H–N–C=O··· hydrogen bonding to produce an eight-membered cycle around a second pseudo-inversion centre.

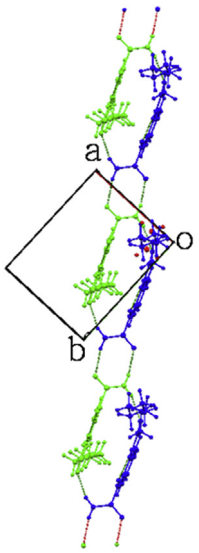


Fig. 4. Crystal structure of **7a** showing how the two crystallographically independent molecules (green or blue) form a hydrogen bonded tape assembly.

The chloro–methyl interchange rule is an unusual phenomenon encountered in crystal engineering. If only molecular close packing is significant, then the similar spherical shape and size of chloro (20 Å^3) and methyl (24 Å^3) groups can allow two isosteric molecules to adopt the same crystal packing.[20–22] On the other hand, since chlorine has a rich interaction chemistry that differs considerably from methyl, entirely different crystal structures will result in other cases. If the chlorine atom is involved in significant interactions within its crystal, e.g., a structure containing Cl···Cl associations of less than 4 Å, then it is unlikely that crystals of its methyl analogue will pack in the same manner. The occurrence of chloro–methyl isostructurality has been estimated to be around 26%.[23] Here, bromo compound **7k** and methyl compound **7l** crystallize in the same manner, making this an example of the less commonly reported bromo-methyl interchange. The bromine atom (26 Å^3) of **7k** does not participate in any major intermolecular attractions, its closest contact being with two hydrogen atoms of a neighbouring methyl group (d=3.281 Å and 3.355 Å; D=3.615 Å). The isostructural methyl compound **7l** has a corresponding C···C value of D=3.685 Å.

The van der Waals interactions between alkyl chains (alkyl···alkyl chains at ~4 Å) was observed predominantly in structures **7a** and **9d** (Fig. 5), containing intra N–H···O hydrogen bonding. Similar packing motifs were also noted in structures containing longer alkyl chains (**2a**, **2b** and **3**).[10] The remaining five structures (**7d**, **7i**, **7k**, **7l** and **9a**) lacking the intramolecular N–H···O hydrogen bond contained packing modes that lacked this alkyl···alkyl chain interaction. Crystal packings of **9a** and **9b** are shown in Fig. 4 and crystal packings of **7a**, **7d**, **7i** and **7l** are shown in Fig. S2, Supplementary data.

The intermolecular hydrogen bonding behaviour of the glyoxylamides in the solid state were also obtained from FT-IR spectroscopy by focussing on the three amide vibrations, N–H stretching (νN–H), C=O stretching (amide I) and N–H bending (amide II). Characteristic intermolecular hydrogen bonding IR bands[24–26] were observed for **7a**–**o** and **9a**–**f** at 3406–3172 cm^{-1} (νN–H), 1658–1597 cm^{-1} (amide I) and 1544–1512 cm^{-1} (amide

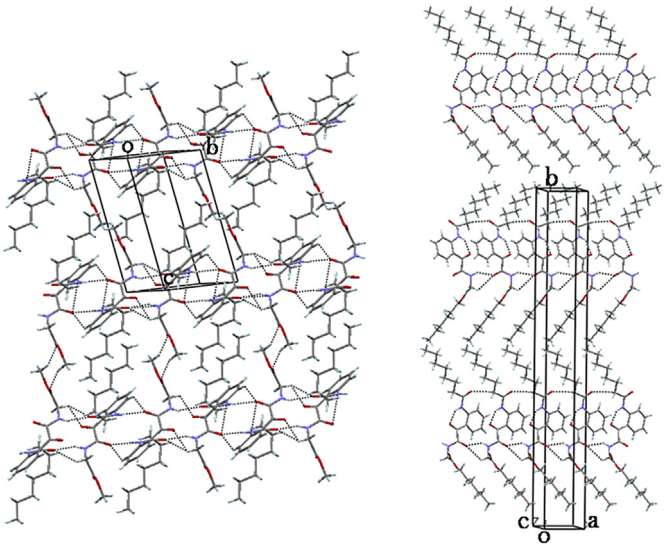


Fig. 5. Crystal packings of **9a** (left) and **9d** (right).

II), indicating that these glyoxylamide series were highly packed with hydrogen-bonded amides.

The concentration-dependent ^{1}H NMR spectroscopy measurements of NH groups-containing compounds show the presence of intermolecular NH hydrogen bonding interactions for their aggregation in solution.[27–31] Intermolecular π–π stacking interactions also have been demonstrated to play a fundamental role in stabilizing the self-assembled supramolecular structures of aromatic ring-containing compounds.[32–35] In these glyoxylamide series having NH groups and aromatic ring, the intermolecular NH hydrogen bondings and π–π stacking interactions are expected to be the driving forces for aggregation to persist in the solution phase.

3. Conclusion

A series of *N*-octanoylglyoxylic amides were synthesized by ring-opening of *N*-octanoylisatins with a range of amines and amino acid alkyl esters. There are two types of molecular conformations, which had a fundamental effect on the intermolecular interactions used in the self-assembly process and the formation of well-defined supramolecular architectures.

The five crystal structures (**7d**, **7i**, **7k**, **7l** and **9a**) that feature triple C═O···C═O dipolar contacts have strong amide hydrogen bonding along the *b* direction. Their molecular interactions resulted in the formation of tape assemblies, which formed in non-chiral space groups, e.g., *Pbca*, $Pca2_1$ and *P*–1.

The crystals of **7a** and **9d** made both intra- and inter N–H···O hydrogen bonds (only with translated molecules) interactions. The planar head groups assembled to generate helices forming the chiral space groups $P2_12_12_1$ and $P2_1$, respectively. It is interesting that a smaller amide exhibits dimorphic behaviour, one containing intra N–H···O and the other one lacking it.[36,37] Here, the synthesized molecules with longer alkyl substituents have not shown any polymorphic behaviour despite our thorough crystal screening. Studies of the substituted glyoxylamides are still ongoing in order to fully elucidate the factors, which control their self-assembly process in the solid state.

4. Experimental

4.1. 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 300 MHz, ^{13}C 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.

4.1.1. 1-Octanoylindoline-2,3-dione ***6a****.* A mixture of octanoic acid (10.88 g, 61.5 mmol) and excess thionyl chloride was heated at reflux for 2 h, and then N_2 gas was introduced to remove the remaining thionyl chloride to give the octanoyl chloride. To a suspension of sodium hydride (1.30 g, 54 mmol) in dry THF (80 mL) was added isatin (6.02 g, 41 mmol) in small portions over 15 min under nitrogen. Octanoyl chloride in dry THF (20 mL) was then added dropwise to the chilled purple mixture over 5–10 min. The reaction mixture was warmed to room temperature for 4 h. The reaction mixture was then carefully quenched with ice water and extracted with ethyl acetate. The combined organic extracts were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude material was recrystallized from hexane to give the compound as a brownish yellow solid (9.29 g, 83%). Mp 82–84 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, *J*=6.5 Hz, 3H, $CH_2(CH_2)_5CH_3$), 1.25–1.46 (m, 8H, $CH_2CH_2(CH_2)_4CH_3$), 1.70–1.79 (m, 2H, $CH_2CH_2(CH_2)_4CH_3$), 3.10 (t, *J*=7.3 Hz, 2H, $CH_2CH_2(CH_2)_4CH_3$), 7.33 (dt, *J*=7.5, 0.9 Hz, 1H, ArH), 7.69–7.79 (m, 2H, ArH), 7.89 (dd, *J*=8.2, 0.5 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 ($CH_2(CH_2)_5CH_3$), 22.5, 24.0, 28.9, 31.6 ($CH_2(CH_2)_5CH_3$), 38.3 ($COCH_2(CH_2)_5CH_3$), 118.3, 119.2, 125.2, 126.0 (ArCH), 138.8, 148.8 (ArC), 157.7, 173.1, 180.3 (C═O); IR (KBr): ν_{max} 2955, 2918, 2852, 1749, 1656, 1592, 1579, 1335, 1465, 1384, 1356, 1330, 1277, 1259, 1204, 1131, 1087, 955, 886, 816, 759 cm^{-1}; UV (DMF): λ_{max} 238 (ε 2250 cm^{-1} M^{-1}), 241 (2350), 261 (2850), 269 (3750); HRMS (ESI) *m*/*z* calculated for $C_{16}H_{20}NO_3$ $(M+H)^+$ 274.1365. Found 274.1429.

4.1.2. 5-Bromo-1-octanoylindoline-2,3-dione ***6b****.* This compound was prepared by the same method as compound **6a** from 5-bromoisatin (6.01 g, 27 mmol) and octanoyl chloride (6.59 g, 40.51 mmol) as a brownish yellow solid (7.39 g, 78%). Mp 142–144 °C; UV (DMF): λ_{max} 238 (ε 5550 cm^{-1} M^{-1}), 252 (5700), 276 (7150); IR (KBr): ν_{max} 2950, 2921, 2867, 1781, 1703, 1604, 1518, 1460, 1431, 1394, 1383, 1328, 1307, 1283, 1253, 1220, 1197, 1059, 972, 847, 770 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, *J*=6.6 Hz, 3H, $CH_2(CH_2)_5CH_3$), 1.24–1.48 (m, 8H, $CH_2CH_2(CH_2)_4CH_3$), 1.69–1.77 (m, 2H, $CH_2CH_2(CH_2)_4CH_3$), 3.09 (t, *J*=6.6 Hz, 2H, $CH_2CH_2(CH_2)_4CH_3$), 7.82 (dd, *J*=8.8, 2.2 Hz, 1H, ArH), 7.89 (dd, *J*=2.2, 0.4 Hz, 1H, ArH), 8.37 (dd, *J*=8.8, 0.4 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 ($CH_2(CH_2)_5CH_3$), 22.6, 24.1, 29.0, 29.0, 31.7 ($CH_2(CH_2)_5CH_3$), 38.3 ($COCH_2(CH_2)_5CH_3$), 119.5, 127.9, 136.1 (ArCH), 120.1, 141.3, 147.6 (ArC), 158.0, 173.1, 180.4 (C═O); HRMS (ESI) *m*/*z* calculated for $C_{16}H_{19}BrNO_3$ $(M+H)^+$ 352.0543 (^{79}Br). Found 352.0538 (^{79}Br).

4.1.3. 5-Methyl-1-octanoylindoline-2,3-dione ***6c****.* This compound was prepared by the same method as compound **6a** from 5-methylisatin (6.02 g, 37 mmol) and octanoyl chloride (9.82 g, 55.5 mmol) as a brownish yellow solid (9.24 g, 87%). Mp 94–96 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, *J*=7.0 Hz, 3H, $CH_2(CH_2)_5CH_3$), 1.24–1.46 (m, 8H, $CH_2CH_2(CH_2)_4CH_3$), 1.68–1.78 (m, 2H, $CH_2CH_2(CH_2)_4CH_3$), 2.39 (s, 3H, $ArCH_3$), 3.08 (t, *J*=7.5 Hz, 2H, $CH_2CH_2(CH_2)_4CH_3$), 7.49–7.57 (m, 2H, ArH), 7.89 (d, *J*=8.4 Hz, 1H,

ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 ($CH_2(CH_2)_5CH_3$), 22.3 ($ArCH_3$), 22.5, 24.0, 28.9, 31.6 ($CH_2(CH_2)_5CH_3$), 38.2 ($COCH_2(CH_2)_5CH_3$), 118.1, 125.2, 136.1 (ArCH), 119.2, 139.5, 146.8 (ArC), 158.0, 173.0, 180.4 (C=O); IR (KBr): ν_{max} 2955, 2919, 2855, 1780, 1709, 1655, 1620, 1588, 1486, 1462, 1394, 1385, 1331, 1295, 1261, 1230, 1170, 1043, 993, 845 cm^{-1}; UV (DMF): λ_{max} 260 (ε 2900 cm^{-1} M^{-1}), 272 (3700); HRMS (ESI) *m*/*z* calculated for $C_{17}H_{22}NO_3$ $(M+H)^+$ 288.1521. Found 288.1589.

4.1.4. N-(2-(2-Amino-2-oxoacetyl)phenyl)octanamide ***7a***. A mixture of *N*-octanoylisatin **6a** (0.35 g, 1.28 mmol) and ammonia (0.08 g, 5 mmol) in dichloromethane (30 mL) was heated at reflux for 1–2 h. The cooled reaction mixture was concentrated in vacuo. 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 (0.23 g, 63%). The solid, recrystallized from methanol via slow evaporation of the solvent at room temperature, yielded crystals suitable for X-ray crystal structure determination. Mp 152–154 °C; found: C, 66.26; H, 7.60; N, 9.59%, $C_{16}H_{22}N_2O_3$ requires C, 66.18; H, 7.64; N, 9.65%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, *J*=6.6 Hz, 3H, $COCH_2CH_2(CH_2)_4CH_3$), 1.18–1.36 (m, 8H, $COCH_2CH_2(CH_2)_4CH_3$), 1.61–1.71 (m, 2H, $COCH_2CH_2(CH_2)_4CH_3$), 2.42 (t, *J*=7.7 Hz, 2H, $COCH_2(CH_2)_5CH_3$), 6.19 (s, 1H, CONH*H*), 6.78 (s, 1H, CON*H*H), 7.03–7.08 (m, 1H, ArH), 7.50–7.56 (m, 1H, ArH), 8.22 (dd, *J*=8.1, 1.4 Hz, 1H, ArH), 8.60 (dd, *J*=8.6, 0.9 Hz, 1H, ArH), 10.86 (s, 1H, NHCO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 ($COCH_2(CH_2)_5CH_3$), 22.6, 25.5, 29.0, 29.2, 31.7 ($COCH_2(CH_2)_5CH_3$), 38.7 ($COCH_2$), 118.2, 142.3 (ArC), 120.8, 122.5, 134.3, 136.8 (ArCH), 165.1, 172.7, 191.6 (C=O); IR (KBr): ν_{max} 3340, 3190, 2954, 2925, 2855, 1677, 1608, 1581, 1529, 1453, 1412, 1295, 1219, 1164, 1100, 979, 874, 808, 751 cm^{-1}; UV (DMF): λ_{max} 261 (ε 4500 cm^{-1} M^{-1}), 272 (7150), 338 (4100); HRMS (ESI) *m*/*z* calculated for $C_{16}H_{23}N_2O_3$ $(M+H)^+$ 291.1703. Found 291.1703.

4.1.5. N-(2-(2-Amino-2-oxoacetyl)-4-bromophenyl)octanamide ***7b***. This compound was prepared by the same method as compound **7a** from *N*-octanoylisatin **6b** (0.35 g, 1 mmol) and ammonia (0.08 g, 5 mmol) as an off-white solid (0.28 g, 72%). Mp 169–170 °C; found: C, 52.14; H, 5.56; N, 7.65%, $C_{16}H_{21}BrN_2O_3$ requires C, 52.04; H, 5.73; N, 7.56%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, *J*=7.0 Hz, 3H, $COCH_2CH_2(CH_2)_4CH_3$), 1.23–1.37 (m, 8H, $COCH_2CH_2(CH_2)_4CH_3$), 1.67–1.77 (m, 2H, $COCH_2CH_2(CH_2)_4CH_3$), 2.41 (t, *J*=7.8 Hz, 2H, $COCH_2(CH_2)_5CH_3$), 5.67 (s, 1H, CONH*H*), 6.70 (s, 1H, CON*H*H), 7.69 (dd, *J*=9.1, 2.5 Hz, 1H, ArH), 8.54 (d, *J*=2.3 Hz, 1H, ArH), 8.63 (d, *J*=9.1 Hz, 1H, ArH), 10.80 (s, 1H, NHCO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 ($COCH_2(CH_2)_5CH_3$), 22.6, 25.4, 29.0, 29.1, 31.7 ($COCH_2(CH_2)_5CH_3$), 38.7 ($COCH_2$), 118.3, 132.2, 134.1 (ArC), 122.5, 136.4, 139.4 (ArCH), 161.9, 169.1, 190.7 (C=O); IR (KBr): ν_{max} 3341, 3249, 2928, 2852, 1696, 1678, 1658, 1603, 1577, 1518, 1460, 1394, 1290, 1242, 1205, 1095, 988, 837, 792 cm^{-1}; UV (DMF): λ_{max} 236 (ε 3050 cm^{-1} M^{-1}), 261 (4750), 272 (8350), 345 (3050); HRMS (ESI) *m*/*z* calculated for $C_{16}H_{21}BrN_2O_3Na$ $(M+Na)^+$ 391.0629 (^{79}Br). Found 391.0629 (^{79}Br).

4.1.6. N-(2-(2-Amino-2-oxoacetyl)-4-methylphenyl)octanamide ***7c***. This compound was prepared by the same method as compound **7a** from *N*-octanoylisatin **6c** (0.37 g, 1.28 mmol) and ammonia (0.08 g, 5 mmol) as an off-white solid (0.23 g, 60%). Mp 133–135 °C; found: C, 67.27; H, 7.75; N, 9.11%, $C_{17}H_{24}N_2O_3$ requires C, 67.08; H, 7.95; N, 9.20%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, *J*=6.8 Hz, 3H, $COCH_2CH_2(CH_2)_4CH_3$), 1.23–1.35 (m, 8H, $COCH_2CH_2(CH_2)_4CH_3$), 1.61–1.75 (m, 2H, $COCH_2CH_2(CH_2)_4CH_3$), 2.33 (s, 3H, $ArCH_3$), 2.41 (t, *J*=7.8 Hz, 2H, $COCH_2(CH_2)_5CH_3$), 5.67 (s, 1H, CONH*H*), 6.62 (s, 1H, CON*H*H), 7.43 (dd, *J*=9.0, 1.6 Hz, 1H, ArH), 8.09 (d, *J*=1.7 Hz, 1H, ArH), 8.59 (d, *J*=8.6 Hz, 1H, ArH), 10.79 (s, 1H, NHCO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 ($COCH_2(CH_2)_5CH_3$), 20.7 (Ar–CH_3), 22.6, 25.5, 29.0, 29.2, 31.7 ($COCH_2(CH_2)_5CH_3$), 38.6 ($COCH_2$), 118.3, 132.2, 140.0 (ArC), 120.8, 134.1, 137.7 (ArCH), 164.9, 172.5, 191.5 (C=O); IR (KBr): ν_{max} 3342, 3177, 2928, 2853, 1677, 1656, 1594, 1525, 1460, 1405, 1296, 1255, 1238, 1034, 936, 839, 795 cm^{-1}; UV (DMF): λ_{max} 272 (ε 25,750 cm^{-1} M^{-1}), 348 (13,100); HRMS (ESI) *m*/*z* calculated for $C_{17}H_{24}N_2O_3Na$ $(M+Na)^+$ 327.1787. Found 327.1676.

4.1.7. N-(2-(2-(Methylamino)-2-oxoacetyl)phenyl)octanamide ***7d***. This compound was prepared by the same method as compound **7a** from *N*-octanoylisatin **6a** (0.35 g, 1.28 mmol) and methylamine (0.06 g, 2 mmol) as an off-white solid (0.26 g, 67%). The solid, recrystallized from methanol via slow evaporation of the solvent at room temperature, yielded crystals suitable for X-ray crystal structure determination. Mp 80–82 °C; found: C, 67.24; H, 8.16; N, 9.27%, $C_{17}H_{24}N_2O_3$ requires C, 67.08; H, 7.95; N, 9.20%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, *J*=7.0 Hz, 3H, $COCH_2CH_2(CH_2)_4CH_3$), 1.22–1.36 (m, 8H, $COCH_2CH_2(CH_2)_4CH_3$), 1.57–1.78 (m, 2H, $COCH_2CH_2(CH_2)_4CH_3$), 2.38 (t, *J*=7.7 Hz, 2H, $COCH_2(CH_2)_5CH_3$), 2.96 (d, *J*=5.1 Hz, 3H, $NHCH_3$), 6.93 (s, 1H, CONH), 7.06–7.12 (m, 1H, ArH), 7.53–7.59 (m, 1H, ArH), 8.41 (dd, *J*=8.1, 1.6 Hz, 1H, ArH), 8.64 (dd, *J*=8.5, 0.6 Hz, 1H, ArH), 10.93 (s, 1H, NHCO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 ($COCH_2(CH_2)_5CH_3$), 22.6, 25.5, 29.0, 29.2, 31.7 ($COCH_2(CH_2)_5CH_3$), 26.2 ($NHCH_3$), 38.7 ($COCH_2$), 118.7, 142.2 (ArC), 120.7, 122.4, 134.4, 136.6 (ArCH), 163.6, 172.6, 193.0 (C=O); IR (KBr): ν_{max} 3284, 3252, 2926, 2853, 1698, 1665, 1608, 1533, 1485, 1406, 1337, 1301, 1248, 1212, 1080, 939, 867, 763 cm^{-1}; UV (DMF): λ_{max} 231 (ε 4450 cm^{-1} M^{-1}), 261 (6800), 272 (8900), 338 (5000); HRMS (ESI) *m*/*z* calculated for $C_{17}H_{24}N_2O_3Na$ $(M+Na)^+$ 327.1679. Found 327.1673.

4.1.8. N-(4-Bromo-2-(2-(methylamino)-2-oxoacetyl)phenyl)octanamide ***7e***. This compound was prepared by the same method as compound **7a** from *N*-octanoylisatin **6b** (0.35 g, 1 mmol) and methylamine (0.06 g, 2 mmol) as an off-white solid (0.23 g, 56%). Mp 136–138 °C; found: C, 53.17; H, 5.94; N, 7.45%, $C_{17}H_{23}BrN_2O_3$ requires C, 53.27; H, 6.05; N, 7.31%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, *J*=7.0 Hz, 3H, $COCH_2CH_2(CH_2)_4CH_3$), 1.23–1.34 (m, 8H, $COCH_2CH_2(CH_2)_4CH_3$), 1.66–1.76 (m, 2H, $COCH_2CH_2(CH_2)_4CH_3$), 2.40 (t, *J*=7.9 Hz, 2H, $COCH_2(CH_2)_5CH_3$), 2.98 (d, *J*=5.1 Hz, 3H, $NHCH_3$), 6.87 (s, 1H, CON*H*CH_3), 7.67 (dd, *J*=9.2, 2.4 Hz, 1H, ArH), 8.58 (d, *J*=0.6 Hz, 1H, ArH), 8.60 (d, *J*=5.8 Hz, 1H, ArH), 10.83 (s, 1H, NHCO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 ($COCH_2(CH_2)_5CH_3$), 22.6, 25.4, 29.0, 29.1, 31.7 ($COCH_2(CH_2)_5CH_3$), 26.3 ($NHCH_3$), 38.7 ($COCH_2$), 118.3, 132.2, 139.2 (ArC), 122.5, 134.3, 136.6 (ArCH), 161.9, 172.4, 190.6 (C=O); IR (KBr): ν_{max} 3358, 3281, 2928, 2854, 1702, 1665, 1602, 1525, 1482, 1407, 1382, 1337, 1282, 1244, 1202, 1074, 956, 870, 741 cm^{-1}; UV (DMF): λ_{max} 261 (ε 3750 cm^{-1} M^{-1}), 272 (5800), 344 (2050); HRMS (ESI) *m*/*z* calculated for $C_{17}H_{23}BrN_2O_3Na$ $(M+Na)^+$ 405.0784 (^{79}Br). Found 405.0778 (^{79}Br).

4.1.9. N-(4-Methyl-2-(2-(methylamino)-2-oxoacetyl)phenyl)octanamide ***7f***. This compound was prepared by the same method as compound **7a** from *N*-octanoylisatin **6c** (0.37 g, 1.28 mmol) and methylamine (0.06 g, 2 mmol) as an off-white solid (0.29 g, 71%). Mp 110–112 °C; found: C, 68.22; H, 8.51; N, 8.52%, $C_{18}H_{26}N_2O_3$ requires C, 67.90; H, 8.23; N, 8.80%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, *J*=7.0 Hz, 3H, $COCH_2CH_2(CH_2)_4CH_3$), 1.23–1.34 (m, 8H, $COCH_2CH_2(CH_2)_4CH_3$), 1.66–1.76 (m, 2H, $COCH_2CH_2(CH_2)_4CH_3$), 2.40 (t, *J*=7.8 Hz, 2H, $COCH_2(CH_2)_5CH_3$), 2.98 (d, *J*=5.1 Hz, 3H, $NHCH_3$), 6.87 (s, 1H, CON*H*CH_3), 7.67 (dd, *J*=9.2, 2.4 Hz, 1H, ArH), 8.58 (d, *J*=0.6 Hz, 1H, ArH), 8.60 (d, *J*=5.8 Hz, 1H, ArH), 10.83 (s, 1H, NHCO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 ($COCH_2(CH_2)_5CH_3$), 20.8 ($ArCH_3$), 22.6, 25.5, 29.0, 29.2, 31.7 ($COCH_2(CH_2)_5CH_3$), 26.22 ($NHCH_3$), 38.6 ($COCH_2$), 118.3, 132.2, 140.0 (ArC), 120.8, 134.3, 137.4 (ArCH), 164.5, 172.5, 191.4 (C=O); IR (KBr): ν_{max} 3289, 3255, 2926,

2849, 1697, 1663, 1611, 1532, 1497, 1464, 1406, 1388, 1336, 1293, 1249, 1200, 1081, 976, 821, 741 cm^{-1}; UV (DMF): λ_{max} 236 (ε 2850 cm^{-1} M^{-1}), 261 (4150), 274 (6500), 342 (3450); HRMS (ESI) *m*/*z* calculated for $C_{18}H_{27}N_2O_3$ $(M+H)^+$ 319.2016. Found 319.2011.

4.1.10. N-(2-(2-(Hexylamino)-2-oxoacetyl)phenyl)octanamide ***7g***. A mixture of *N*-octanoylisatin **6a** (0.35 g, 1.28 mmol) and hexylamine (0.13 g, 1.28 mmol) in dichloromethane (30 mL) was heated at reflux for 4–6 h. The cooled reaction mixture was concentrated in vacuo. 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 (0.33 g, 71%). Mp 96–98 °C; found: C, 70.26; H, 9.23; N, 7.45%, $C_{22}H_{34}N_2O_3$ requires C, 70.55; H, 9.15; N, 7.48%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (m, 6H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_3CH_3$), 1.24–1.43 (m, 14H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_3CH_3$), 1.57–1.78 (m, 4H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_3CH_3$), 2.42 (t, *J*=7.6 Hz, 2H, $COCH_2(CH_2)_5CH_3$), 3.37–3.44 (m, 2H, $NHCH_2CH_2(CH_2)_3CH_3$), 6.83 (s, 1H, CONH), 7.09–7.14 (m, 1H, ArH), 7.56–7.62 (m, 1H, ArH), 8.41 (dd, *J*=8.1, 1.6 Hz, 1H, ArH), 8.68 (dd, *J*=8.5, 0.8 Hz, 1H, ArH), 10.96 (s, 1H, NHCO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 14.0 ($COCH_2(CH_2)_5CH_3$ and $NHCH_2(CH_2)_4CH_3$), 22.4, 22.5, 25.4, 26.5, 28.9, 29.1, 29.2, 31.3, 31.6 ($COCH_2(CH_2)_5CH_3$ and $NHCH_2(CH_2)_4CH_3$), 38.6 ($COCH_2$), 39.6 ($NHCH_2$), 118.5, 142.2 (ArC), 120.6, 122.3, 134.4, 136.5 (ArCH), 162.8, 172.4, 192.1 (C=O); IR (KBr): ν_{max} 3289, 3176, 3113, 927, 2855, 1689, 1666, 1605, 1527, 1483, 1468, 1411, 1377, 1316, 1255, 1214, 1078, 946, 823, 757 cm^{-1}; UV (DMF): λ_{max} 261 (ε 9100 cm^{-1} M^{-1}), 270 (13,250), 348 (5100); MS (TOF-ESI) *m*/*z* calculated for $C_{22}H_{35}N_2O_3$ $(M+H)^+$ 375.25. Found 375.26.

4.1.11. N-(4-Bromo-2-(2-(hexylamino)-2-oxoacetyl)phenyl)octanamide ***7h***. This compound was prepared by the same method as compound **7g** from *N*-octanoylisatin **6b** (0.35 g, 1 mmol) and hexylamine (0.10 g, 1 mmol) as an off-white solid (0.29 g, 64%). Mp 150–152 °C; found: C, 58.47; H, 7.37; N, 6.30%, $C_{22}H_{33}BrN_2O_3$ requires C, 58.28; H, 7.34; N, 6.18%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (m, 6H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_4CH_3$), 1.24–1.43 (m, 14H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_3CH_3$), 1.57–1.78 (m, 4H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_3CH_3$), 2.41 (t, *J*=7.7 Hz, 2H, $COCH_2(CH_2)_5CH_3$), 3.37–3.44 (m, 2H, $NHCH_2CH_2(CH_2)_3CH_3$), 6.86 (s, 1H, CONH), 7.68 (dd, *J*=9.1, 2.4 Hz, 1H, ArH), 8.59–8.63 (m, 2H, ArH), 10.86 (s, 1H, NHCO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 14.0 ($COCH_2(CH_2)_5CH_3$ and $NHCH_2(CH_2)_4CH_3$), 22.4, 22.5, 25.3, 26.5, 28.9, 29.0, 29.1, 31.3, 31.6 ($COCH_2(CH_2)_5CH_3$ and $NHCH_2(CH_2)_4CH_3$), 38.6 ($COCH_2$), 39.7 ($NHCH_2$), 114.7, 122.4, 141.1 (ArC), 120.2, 136.5, 139.0 (ArCH), 161.8, 172.4, 190.6 (C=O); IR (KBr): ν_{max} 3280, 3172, 2927, 2872, 2853, 1666, 1596, 1544, 1515, 1482, 1412, 1380, 1294, 1260, 1244, 1207, 1131, 895, 828 cm^{-1}; UV (DMF): λ_{max} 230 (ε 300 cm^{-1} M^{-1}), 337 (450); HRMS (ESI) *m*/*z* calculated for $C_{22}H_{34}BrN_2O_3$ $(M+H)^+$ 453.1675 (^{79}Br). Found 453.1736 (^{79}Br).

4.1.12. N-(2-(2-(Hexylamino)-2-oxoacetyl)-4-methylphenyl)octanamide ***7i***. This compound was prepared by the same method as compound **7g** from *N*-octanoylisatin **6c** (0.37 g, 1.28 mmol) and hexylamine (0.13 g, 1.28 mmol) as a white solid (0.36 g, 73%). The solid, recrystallized from methanol via slow evaporation of the solvent at room temperature, yielded crystals suitable for X-ray crystal structure determination. Mp 125–127 °C; found: C, 71.17; H, 9.34; N, 7.36%, $C_{23}H_{36}N_2O_3$ requires C, 71.10; H, 9.34; N, 7.21%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85–0.92 (m, 6H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_3CH_3$), 1.24–1.36 (m, 14H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_3CH_3$), 1.57–1.78 (m, 4H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_3CH_3$), 2.34 (s, 3H, Ar–CH_3), 2.40 (t, *J*=7.8 Hz, 2H, $COCH_2(CH_2)_5CH_3$), 3.37–3.44 (m, 2H, $NHCH_2CH_2(CH_2)_3CH_3$), 6.75 (s, 1H, CONH), 7.42 (dd, *J*=8.6, 2.2 Hz, 1H, ArH), 8.16 (d, *J*=1.7 Hz, 1H, ArH), 8.58 (d, *J*=8.6 Hz, 1H, ArH), 10.86 (s, 1H, NHCO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7, 14.1 ($COCH_2(CH_2)_5CH_3$ and $NHCH_2(CH_2)_4CH_3$), 20.7 ($ArCH_3$), 22.6, 22.6, 25.5, 26.6, 29.0, 29.2, 29.3, 31.4, 31.7 ($COCH_2(CH_2)_5CH_3$ and $NHCH_2(CH_2)_4CH_3$), 38.7 ($COCH_2$), 39.7 ($NHCH_2$), 118.8, 132.0, 139.9 (ArC), 121.3, 134.8, 37.9 (ArCH), 162.8, 172.4, 192.2 (C=O); IR (KBr): ν_{max} 3281, 2917, 2854, 1666, 1613, 1522, 1499, 1467, 1413, 1309, 1269, 1236, 1195, 1169, 821 cm^{-1}; UV (DMF): λ_{max} 260 (ε 6750 cm^{-1} M^{-1}), 275 (9350), 347 (5700); HRMS (ESI) *m*/*z* calculated for $C_{23}H_{37}N_2O_3$ $(M+H)^+$ 389.2726. Found 389.2787.

4.1.13. N-(2-(2-(Dodecylamino)-2-oxoacetyl)phenyl)octanamide ***7j***. This compound was prepared by the same method as compound **7g** from *N*-octanoylisatin **6a** (0.27 g, 1 mmol) and dodecylamine (0.18 g, 1 mmol) as an off-white solid (0.28 g, 60%). Mp 78–80 °C; found: C, 73.10; H, 10.27; N, 6.15%, $C_{28}H_{46}N_2O_3$requires C, 73.32; H, 10.11; N, 6.11%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (m, 6H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_9CH_3$), 1.21–1.43 (m, 26H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_9CH_3$), 1.56–1.78 (m, 4H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_9CH_3$), 2.41 (t, *J*=7.8 Hz, 2H, $COCH_2(CH_2)_5CH_3$), 3.37–3.44 (m, 2H, $NHCH_2CH_2(CH_2)_9CH_3$), 6.83 (t, *J*=5.4 Hz, 1H, CONH), 7.08–7.14 (m, 1H, ArH), 7.6–7.6 (m, 1H, ArH), 8.36 (dd, *J*=8.0, 1.4 Hz, 1H, ArH), 8.68 (dd, *J*=8.5, 0.9 Hz, 1H, ArH), 10.99 (s, 1H, NHCO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 14.0 ($COCH_2(CH_2)_5CH_3$ and $NHCH_2(CH_2)_{10}CH_3$), 22.5, 22.6, 25.4, 26.8, 28.9, 29.6, 29.1, 29.2, 29.4, 29.5, 29.5, 31.6, 31.8 ($COCH_2(CH_2)_5CH_3$ and $NHCH_2(CH_2)_{10}CH_3$), 38.6 ($COCH_2$), 39.6 ($NHCH_2$), 118.6, 142.2 (ArC), 120.6, 122.3, 134.4, 136.5 (ArCH), 162.8, 172.4, 192.1 (C=O); IR (KBr): ν_{max} 3281, 2919, 2852, 1665, 1605, 1526, 1485, 1467, 1412, 1377, 1320, 1267, 1248, 1158, 1112, 1077, 966, 948, 757 cm^{-1}; UV (DMF): λ_{max} 260 (ε 5550 cm^{-1} M^{-1}), 274 (7750), 340 (4850); HRMS (ESI) *m*/*z* calculated for $C_{28}H_{47}N_2O_3$ $(M+H)^+$ 459.3508. Found 459.3571.

4.1.14. N-(4-Bromo-2-(2-(dodecylamino)-2-oxoacetyl)phenyl)octanamide ***7k***. This compound was prepared by the same method as compound **7g** from *N*-octanoylisatin **6b** (0.35 g, 1 mmol) and dodecylamine (0.18 g, 1 mmol) as an off-white solid (0.36 g, 67%). The solid, recrystallized from methanol via slow evaporation of the solvent at room temperature, yielded crystals suitable for X-ray crystal structure determination. Mp 142–144 °C; found: C, 62.72; H, 8.47; N, 5.27%, $C_{28}H_{45}BrN_2O_3$ requires C, 62.56; H, 8.44; N, 5.21%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (m, 6H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_9CH_3$), 1.21–1.43 (m, 26H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_9CH_3$), 1.56–1.78 (m, 4H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_9CH_3$), 2.41 (t, *J*=7.7 Hz, 2H, $COCH_2(CH_2)_5CH_3$), 3.37–3.44 (m, 2H, $NHCH_2CH_2(CH_2)_9CH_3$), 6.87 (s, 1H, CONH), 7.68 (dd, *J*=9.0, 2.5 Hz, 1H, ArH), 8.59–8.63 (m, 2H, ArH), 10.87 (s, 1H, NHCO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 14.0 ($COCH_2(CH_2)_5CH_3$ and $NHCH_2(CH_2)_{10}CH_3$), 22.5, 22.6, 25.3, 26.8, 28.9, 29.0, 29.1, 29.2, 29.3, 29.4, 29.5, 29.5, 31.6, 31.8 ($COCH_2(CH_2)_5CH_3$ and $NHCH_2(CH_2)_{10}CH_3$), 38.6 ($COCH_2$), 39.7 ($NHCH_2$), 114.7, 122.3, 141.1 (ArC), 120.1, 136.5, 139.0 (ArCH), 161.9, 172.4, 190.6 (C=O); IR (KBr): ν_{max} 3276, 2921, 2851, 1667, 1596, 1514, 1481, 1412, 1379, 1294, 1245, 1207, 1130, 952, 826, 755 cm^{-1}; UV (DMF): λ_{max} 259 (ε 3900 cm^{-1} M^{-1}), 269 (16,100), 344 (5750); HRMS (ESI) *m*/*z* calculated for $C_{28}H_{46}BrN_2O_3$ $(M+H)^+$ 537.2614 (^{79}Br). Found 537.2673 (^{79}Br).

4.1.15. N-(2-(2-(Dodecylamino)-2-oxoacetyl)-4-methylphenyl)octanamide ***7l***. This compound was prepared by the same method as compound **7g** from *N*-octanoylisatin **6c** (0.29 g, 1 mmol) and dodecylamine (0.18 g, 1 mmol) as an off-white solid (0.31 g, 66%). The solid, recrystallized from methanol via slow evaporation of the solvent at room temperature, yielded crystals suitable for X-ray crystal structure determination. Mp 92–94 °C; found: C, 73.74; H, 10.43; N, 6.04%,

$C_{29}H_{48}N_2O_3$ requires C, 73.68; H, 10.23; N, 5.93%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, J=6.92 Hz, 6H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_9CH_3$), 1.23–1.38 (m, 26H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_9CH_3$), 1.61–1.78 (m, 4H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_9CH_3$), 2.34 (s, 3H, $ArCH_3$), 2.41 (t, J=7.8 Hz, 2H, $COCH_2(CH_2)_5CH_3$), 3.37–3.44 (m, 2H, $NHCH_2CH_2(CH_2)_9CH_3$), 6.87 (t, J=5.4 Hz, 1H, CONH), 7.42 (dd, J=8.6, 2.0 Hz, 1H, ArH), 8.16 (d, J=1.8 Hz, 1H, ArH), 8.58 (d, J=8.6 Hz, 1H, ArH), 10.86 (s, 1H, NHCO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 14.1 ($COCH_2(CH_2)_5CH_3$ and $NHCH_2(CH_2)_{10}CH_3$), 20.7 ($ArCH_3$), 22.6, 22.7, 25.5, 26.9, 29.0, 29.2, 29.3, 29.3, 29.4, 29.6, 29.6, 29.6, 31.7, 31.9 ($COCH_2(CH_2)_5CH_3$ and $NHCH_2(CH_2)_{10}CH_3$), 38.7 ($COCH_2$), 39.7 ($NHCH_2$), 118.7, 132.0, 139.9 (ArC), 121.3, 134.8, 137.8 (ArCH), 163.1, 172.4, 192.3 (C=O); IR (KBr): ν_{max} 3276, 3086, 2919, 2852, 1665, 1612, 1521, 1500, 1467, 1413, 1378, 1301, 1271, 1248, 1169, 950, 822, 712 cm^{-1}; UV (DMF): λ_{max} 264 (ε 9250 cm^{-1} M^{-1}), 271 (12,900), 348 (6850); HRMS (ESI) m/z calculated for $C_{29}H_{49}N_2O_3$ $(M+H)^+$ 473.3665. Found 473.3725.

4.1.16. N-(2-(2-(Octadecylamino)-2-oxoacetyl)phenyl)octanamide ***7m***. This compound was prepared by the same method as compound **7g** from *N*-octanoylisatin **6a** (0.27 g, 1 mmol) and octadecylamine (0.27 g, 1 mmol) as an off-white solid (0.32 g, 59%). Mp 68–70 °C; found: C, 75.30; H, 11.00; N, 5.33%, $C_{34}H_{58}N_2O_3$ requires C, 75.23; H, 10.77; N, 5.16%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (m, 6H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_{15}CH_3$), 1.21–1.43 (m, 38H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_{15}CH_3$), 1.56–1.79 (m, 4H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_{15}CH_3$), 2.42 (t, J=7.8 Hz, 2H, $COCH_2(CH_2)_4CH_3$), 3.37–3.44 (m, 2H, $NHCH_2CH_2(CH_2)_{15}CH_3$), 6.81 (t, J=5.7 Hz, 1H, CONH), 7.08–7.14 (m, 1H, ArH), 7.56–7.62 (m, 1H, ArH), 8.36 (dd, J=8.1, 1.42 Hz, 1H, ArH), 8.69 (dd, J=8.6, 0.9 Hz, 1H, ArH), 10.99 (s, 1H, NHCO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 14.0 ($COCH_2(CH_2)_5CH_3$ and $NHCH_2(CH_2)_{16}CH_3$), 22.5, 22.6, 25.4, 26.8, 28.8, 29.0, 29.1, 29.2, 29.3, 29.4, 29.5, 29.6, 31.6, 31.8 ($COCH_2(CH_2)_5CH_3$ and $NHCH_2(CH_2)_{16}CH_3$), 38.6 ($COCH_2$), 39.6 ($NHCH_2$), 118.6, 142.2 (ArC), 120.6, 122.3, 134.4, 136.5 (ArCH), 162.7, 172.4, 192.0 (C=O); IR (KBr): ν_{max} 3321, 2918, 2850, 1710, 1641, 1604, 1585, 1529, 1468, 1376, 1312, 1295, 1213, 1160, 921, 862, 760, 721 cm^{-1}; UV (DMF): λ_{max} 258 (ε 8650 cm^{-1} M^{-1}), 272 (12,200), 337 (7250); HRMS (ESI) m/z calculated for $C_{34}H_{59}N_2O_3$ $(M+H)^+$ 543.4447. Found 543.4517.

4.1.17. N-(4-Bromo-2-(2-(octadecylamino)-2-oxoacetyl)phenyl)octanamide ***7n***. This compound was prepared by the same method as compound **7g** from *N*-octanoylisatin **6b** (0.35 g, 1 mmol) and octadecylamine (0.27 g, 1 mmol) as an off-white solid (0.34 g, 55%). Mp 298–300 °C; found: C, 65.86; H, 9.24; N, 4.50%, $C_{34}H_{57}BrN_2O_3$ requires C, 65.68; H, 9.24; N, 4.51%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (m, 6H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_{15}CH_3$), 1.21–1.43 (m, 38H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_{15}CH_3$), 1.56–1.78 (m, 4H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_{15}CH_3$), 2.43 (t, J=7.8 Hz, 2H, $COCH_2(CH_2)_4CH_3$), 3.37–3.44 (m, 2H, $NHCH_2CH_2(CH_2)_{15}CH_3$), 6.88 (t, J=5.3 Hz, 1H, CONH), 7.68 (dd, J=9.1, 2.4 Hz, 1H, ArH), 8.58–8.63 (m, 2H, ArH), 10.87 (s, 1H, NHCO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 14.0 ($COCH_2(CH_2)_5CH_3$ and $NHCH_2(CH_2)_{16}CH_3$), 22.5, 22.6, 25.3, 26.8, 28.9, 29.0, 29.1, 29.2, 29.3, 29.4, 29.5, 29.6, 31.6, 31.8 ($COCH_2(CH_2)_5CH_3$ and $NHCH_2(CH_2)_{16}CH_3$), 38.6 ($COCH_2$), 39.7 ($NHCH_2$), 114.7, 122.3, 141.1 (ArC), 120.1, 136.5, 139.0 (ArCH), 161.9, 172.4, 190.6 (C=O); IR (KBr): ν_{max} 3406, 3282, 2920, 2850, 2358, 2342, 1667, 1646, 1597, 1518, 1469, 1412, 1393, 1288, 1248, 1159, 1099, 966, 826, 720 cm^{-1}; UV (DMF): λ_{max} 261 (ε 32,050 cm^{-1} M^{-1}), 271 (48,600), 347 (20,700); HRMS (ESI) m/z calculated for $C_{34}H_{58}BrN_2O_3$ $(M+H)^+$ 621.3553 (^{79}Br). Found 621.3622 (^{79}Br).

4.1.18. N-(4-Methyl-2-(2-(octadecylamino)-2-oxoacetyl)phenyl)octanamide ***7o***. This compound was prepared by the same method as compound **7g** from *N*-octanoylisatin **6c** (0.29 g, 1 mmol) and octadecylamine (0.27 g, 1 mmol) as an off-white solid (0.31 g, 56%). Mp 78–80 °C; found: C, 75.55; H, 11.04; N, 5.15%, $C_{35}H_{60}N_2O_3$ requires C, 75.49; H, 10.86; N, 5.03%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, J=6.67 Hz, 6H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_{15}CH_3$), 1.23–1.36 (m, 38H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_{15}CH_3$), 1.57–1.77 (m, 4H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_{15}CH_3$), 2.33 (s, 3H, $ArCH_3$), 2.39 (t, J=7.8 Hz, 2H, $COCH_2(CH_2)_5CH_3$), 3.37–3.44 (m, 2H, $NHCH_2CH_2(CH_2)_{15}CH_3$), 6.84 (t, J=5.3 Hz, 1H, CONH), 7.39 (dd, J=8.5, 2.1 Hz, 1H, Ar–H), 8.11 (d, J=1.7 Hz, 1H, ArH), 8.55 (d, J=8.7 Hz, 1H, ArH), 10.86 (s, 1H, NHCO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 14.1 ($COCH_2(CH_2)_5CH_3$ and $NHCH_2(CH_2)_{16}CH_3$), 22.6, 22.7, 25.5, 26.9, 29.0, 29.1, 29.2, 29.3, 29.4, 29.6, 29.7, 31.7, 31.9 ($COCH_2(CH_2)_5CH_3$ and $NHCH_2(CH_2)_{16}CH_3$), 20.7 ($ArCH_3$), 38.7 ($COCH_2$), 39.7 ($NHCH_2$), 118.8, 132.0, 139.9 (ArC), 121.3, 134.8, 137.4 (ArCH), 163.0, 172.3, 192.2 (C=O); IR (KBr): ν_{max} 3323, 2916, 2849, 1701, 1663, 1642, 1589, 1523, 1469, 1418, 1376, 1327, 1295, 1231, 1162, 846, 781 cm^{-1}; UV (DMF): λ_{max} 275 (ε 9800 cm^{-1} M^{-1}), 346 (5700); HRMS (ESI) m/z calculated for $C_{35}H_{61}N_2O_3$ $(M+H)^+$ 557.4604. Found 557.4660.

4.1.19. Methyl 2-(2-(2-octanamidophenyl)-2-oxoacetamido)acetate ***9a***. A solution of glycine methyl ester hydrochloride (0.40 g, 3.2 mmol) containing saturated $NaHCO_3$ was added to a stirred solution of the *N*-octanoylisatin **6a** (0.35 g, 1.28 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 compounds was obtained as an off-white solid (0.21 g, 46%). The solid, recrystallized from methanol via slow evaporation of the solvent at room temperature, yielded crystals suitable for X-ray crystal structure determination. Mp 82–84 °C; found: C, 63.09; H, 7.24; N, 7.79%, $C_{19}H_{26}N_2O_5$ requires C, 62.97; H, 7.23; N, 7.73%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, J=7.0 Hz, 3H, $COCH_2CH_2(CH_2)_4CH_3$), 1.23–1.35 (m, 8H, $COCH_2CH_2(CH_2)_4CH_3$), 1.66–1.79 (m, 2H, $COCH_2CH_2(CH_2)_4CH_3$), 2.42 (t, J=7.7 Hz, 2H, $COCH_2(CH_2)_5CH_3$), 3.80 (s, 3H, $COCH_3$), 4.18 (d, J=5.4 Hz, 2H, $NHCH_2COO$), 7.08–7.14 (m, 1H, ArH), 7.23 (s, 1H, CONH), 7.57–7.63 (m, 1H, ArH), 8.36 (dd, J=8.1, 1.5 Hz, 1H, ArH), 8.71 (dd, J=8.3, 1.5 Hz, 1H, ArH), 10.96 (s, 1H, NHCO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 ($COCH_2(CH_2)_5CH_3$), 22.6, 25.5, 29.0, 29.2, 31.7 ($COCH_2(CH_2)_5CH_3$), 38.7 (CH_2CONH), 41.2 ($NHCH_2COO$), 52.7 ($COOCH_3$), 118.3, 142.5 (ArC), 120.7, 122.4, 134.5, 136.9 (ArCH), 162.9, 169.4, 172.6, 190.9 (C=O); IR (KBr): ν_{max} 3284, 2919, 2856, 1763, 1697, 1664, 1606, 1527, 1481, 1437, 1407, 1369, 1313, 1267, 1201, 1180, 1030, 940, 806, 771 cm^{-1}; UV (MeOH): λ_{max} 235 (ε 17,400 cm^{-1} M^{-1}), 272 (7700), 344 (4500); HRMS (ESI) m/z calculated for $C_{19}H_{27}N_2O_5$ $(M+H)^+$ 363.1842. Found 363.1910.

4.1.20. Methyl 2-(2-(2-octanamidophenyl)-2-oxoacetamido)propanoate ***9b***. This compound was prepared by the same method as compound **9a** from *N*-octanoylisatin **6a** (0.35 g, 1.28 mmol) and L-alanine methyl ester hydrochloride (0.45 g, 3.2 mmol) as an off-white solid (0.19 g, 52%). Mp 48–50 °C; found: C, 63.99; H, 7.64; N, 7.53%, $C_{20}H_{28}N_2O_5$ requires C, 63.81; H, 7.50; N, 7.44%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, J=6.66 Hz, 3H, $COCH_2CH_2(CH_2)_4CH_3$), 1.23–1.40 (m, 8H, $COCH_2CH_2(CH_2)_4CH_3$), 1.52 (d, J=5.4 Hz, 3H, $NHCHCH_3COO$), 1.68–1.78 (m, 2H, $COCH_2CH_2(CH_2)_4CH_3$), 2.42 (t, J=7.7 Hz, 2H, $COCH_2(CH_2)_5CH_3$), 3.79 (s, 3H, $COCH_3$), 4.62–4.71 (m, 1H, $NHCHCH_3COO$), 7.08–7.14 (m, 1H, ArH), 7.23 (d, J=7.2 Hz, 1H, CONH), 7.57–7.63 (m, 1H, ArH), 8.36 (dd, J=8.3, 1.6 Hz, 1H, ArH), 8.71 (dd, J=8.5, 0.7 Hz, 1H, ArH), 10.97 (s, 1H, NHCO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 ($COCH_2(CH_2)_5CH_3$), 18.1 ($NHCHCH_3COO$),

22.6, 25.5, 29.0, 29.2, 31.7 ($COCH_2(CH_2)_5CH_3$), 38.8 (CH_2CONH), 48.3 ($NHCHCH_3COO$), 52.8 ($COOCH_3$), 118.3, 142.5 (ArC), 120.7, 122.4, 134.5, 136.8 (ArCH), 162.2, 172.5, 172.6, 191.1 (C=O); IR (KBr): ν_{max} 3283, 2923, 2852, 1738, 1709, 1650, 1604, 1582, 1526, 1448, 1347, 1277, 1214, 1067, 977, 873, 760 cm^{-1}; UV (MeOH): λ_{max} 234 (ε 14,700 cm^{-1} M^{-1}), 271 (6900), 343 (4100); HRMS (ESI) *m/z* calculated for $C_{20}H_{29}N_2O_5$ $(M+H)^+$ 377.1998. Found 377.2059.

4.1.21. Butyl 2-(2-(2-octanamidophenyl)-2-oxoacetamido)acetate ***9c***. This compound was prepared by the same method as compound **9a** from *N*-octanoylisatin **6a** (0.35 g, 1.28 mmol) and glycine butyl ester hydrochloride **112** (0.59 g, 3.2 mmol) as an off-white solid (0.23 g, 44%). Mp 88–90 °C; found: C, 65.59; H, 8.23; N, 6.88%, $C_{22}H_{32}N_2O_5$ requires C, 65.32; H, 7.97; N, 6.93%; ^1H NMR (300 MHz, $CDCl_3$): δ 0.89–1.01 (m, 6H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2(CH_2)_2CH_3$), 1.28–1.50 (m, 10H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2CH_2CH_3$), 1.66–1.81 (m, 4H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2CH_2CH_3$), 2.42 (t, *J*=7.8 Hz, 2H, $COCH_2(CH_2)_5CH_3$), 4.21–4.28 (m, 4H, $NHCH_2COO$ and $NHCH_2CH_2CH_2CH_3$), 7.14–7.19 (m, 1H, ArH), 7.31 (s, 1H, CONH), 7.63–7.69 (m, 1H, ArH), 8.36 (dd, *J*=8.1, 1.6 Hz, 1H, ArH), 8.71 (dd, *J*=8.6, 1.0 Hz, 1H, ArH), 11.02 (s, 1H, NHCO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7, 14.1 ($COCH_2(CH_2)_5CH_3$ and $NHCH_2(CH_2)_2CH_3$), 19.1, 22.6, 25.5, 29.0, 29.2, 30.6, 31.7 ($COCH_2(CH_2)_5CH_3$ and $NHCH_2(CH_2)_2CH_3$), 39.4 (CH_2CONH), 41.9 ($NHCH_2COO$), 66.2 ($COOCH_2$), 118.6, 142.8 (ArC), 120.4, 122.8, 134.7, 137.2 (ArCH), 163.2, 169.2, 172.7, 191.4 (C=O); IR (KBr): ν_{max} 3282, 2921, 2858, 1760, 1695, 1663, 1605, 1526, 1481, 1466, 1409, 1364, 1312, 1243, 1029, 941, 772 cm^{-1}; UV (MeOH): λ_{max} 234 (ε 20,050 cm^{-1} M^{-1}), 273 (8850), 343 (5200); HRMS (ESI) *m/z* calculated for $C_{22}H_{33}N_2O_5$ $(M+H)^+$ 405.2311. Found 405.2382.

4.1.22. Hexyl 2-(2-(2-octanamidophenyl)-2-oxoacetamido)acetate ***9e***. This compound was prepared by the same method as compound **9a** from *N*-octanoylisatin **6a** (0.35 g, 1.28 mmol) and glycine hexyl ester hydrochloride (0.63 g, 3.2 mmol) as a yellowish solid (0.23 g, 42%). The solid, recrystallized from methanol via slow evaporation of the solvent at room temperature, yielded crystals suitable for X-ray crystal structure determination. Mp 56–58 °C; found: C, 66.46; H, 8.35; N, 6.46%, $C_{24}H_{36}N_2O_5$ requires C, 66.64; H, 8.39; N, 6.48%; ^1H NMR (300 MHz, $CDCl_3$): δ 0.85–0.92 (m, 6H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2(CH_2)_4CH_3$), 1.26–1.40 (m, 14H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_3CH_3$), 1.61–1.78 (m, 4H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_3CH_3$), 2.41 (t, *J*=7.8 Hz, 2H, $COCH_2(CH_2)_5CH_3$), 4.21–4.28 (m, 4H, $NHCH_2COO$ and $NHCH_2CH_2(CH_2)_3CH_3$), 7.07–7.13 (m, 1H, ArH), 7.31 (t, *J*=5.1 Hz, 1H, CONH), 7.55–7.61 (m, 1H, ArH), 8.34 (dd, *J*=8.1, 1.6 Hz, 1H, ArH), 8.69 (dd, *J*=8.6, 0.9 Hz, 1H, ArH), 10.97 (s, 1H, NHCO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 14.1 ($COCH_2(CH_2)_5CH_3$ and $NHCH_2(CH_2)_4CH_3$), 22.5, 22.6, 25.5, 28.5, 29.0, 29.2, 31.4, 31.7 ($COCH_2(CH_2)_5CH_3$ and $NHCH_2(CH_2)_4CH_3$), 38.7 (CH_2CONH), 41.0 ($NHCH_2COO$), 66.1 ($COOCH_2$), 118.3, 142.4 (ArC), 120.6, 122.4, 134.5, 136.8 (ArCH), 163.1, 169.0, 172.6, 191.2 (C=O); IR (KBr): ν_{max} 3337, 2923, 2855, 1757, 1706, 1663, 1643, 1606, 1586, 1532, 1468, 1451, 1417, 1359, 1259, 1194, 1130, 958, 815, 753 cm^{-1}; UV (MeOH): λ_{max} 235(ε 24,400 cm^{-1} M^{-1}), 273 (11,400), 344 (6850); MS (TOF-ESI) *m/z* calculated for $C_{24}H_{37}N_2O_5$ $(M+H)^+$ 433.26. Found 433.29.

4.1.23. Butyl 2-(2-(2-octanamidophenyl)-2-oxoacetamido)propanoate ***9e***. This compound was prepared by the same method as compound **9a** from *N*-octanoylisatin **6a** (0.35 g, 1.28 mmol) and L-alanine butyl ester hydrochloride (0.58 g, 3.2 mmol) as an off-white solid (0.30 g, 56%). Mp 42–44 °C; found: C, 66.05; H, 8.38; N, 6.63%, $C_{23}H_{34}N_2O_5$ requires C, 66.00; H, 8.19; N, 6.69%; ^1H NMR (300 MHz, $CDCl_3$): δ 0.84–0.96 (m, 6H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2(CH_2)_2CH_3$), 1.24–1.45 (m, 10H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2CH_2CH_3$), 1.52 (d, *J*=7.2 Hz, 3H, $NHCHCH_3COO$), 1.60–1.78 (m, 4H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2CH_2CH_3$), 2.42 (t, *J*=7.9 Hz, 2H, $COCH_2(CH_2)_5CH_3$), 4.14–4.22 (m, 2H, $NHCH_2CH_2CH_2CH_3$), 4.60–4.70 (m, 1H, $NHCHCH_3COO$), 7.06–7.11 (m, 1H, ArH), 7.43 (d, *J*=7.4 Hz, 1H, CONH), 7.54–7.59 (m, 1H, ArH), 8.30 (dd, *J*=8.1, 1.5 Hz, 1H, ArH), 8.68 (dd, *J*=8.6, 0.9 Hz, 1H, ArH), 10.98 (s, 1H, NHCO); ^{13}C NMR (75 MHz, $CDCl_3$): 13.7, 14.1 ($COCH_2(CH_2)_5CH_3$ and $NHCH_2(CH_2)_2CH_3$), 18.1 ($NHCHCH_3COO$), 19.3, 22.6, 25.5, 29.0, 29.2, 30.6, 31.7 ($COCH_2(CH_2)_5CH_3$ and $NHCH_2(CH_2)_2CH_3$), 38.7 (CH_2CONH), 48.4 ($NHCHCH_3COO$), 65.7 ($COOCH_2$), 118.3, 142.4 (ArC), 120.6, 122.4, 134.4, 136.7 (ArCH), 162.6, 172.1, 172.6, 191.5 (C=O); IR (KBr): ν_{max} 3288, 2922, 2868, 1753, 1706, 1661, 1640, 1587, 1533, 1451, 1376, 1312, 1276, 1205, 1162, 1067, 878, 764 cm^{-1}; UV (MeOH): λ_{max} 234 (ε 25,900 cm^{-1} M^{-1}), 272 (10,500), 344 (5900); MS (TOF-ESI) *m/z* calculated for $C_{23}H_{35}N_2O_5$ $(M+H)^+$ 419.25. Found 419.21.

4.1.24. Hexyl 2-(2-(2-octanamidophenyl)-2-oxoacetamido)propanoate ***9f***. This compound was prepared by the same method as compound **9a** from *N*-octanoylisatin **6a** (0.35 g, 1.28 mmol) and L-alanine hexyl ester hydrochloride (0.67 g, 3.2 mmol) as an off-white solid (0.31 g, 55%). Mp 32–34 °C; found: C, 67.30; H, 8.79; N, 6.42%, $C_{25}H_{38}N_2O_5$ requires C, 67.24; H, 8.58; N, 6.27%; ^1H NMR (300 MHz, $CDCl_3$): δ 0.85–0.93 (m, 6H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2(CH_2)_4CH_3$), 1.24–1.41 (m, 14H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_3CH_3$), 1.54 (d, *J*=7.2 Hz, 3H, $NHCHCH_3COO$), 1.63–1.79 (m, 4H, $COCH_2CH_2(CH_2)_4CH_3$ and $NHCH_2CH_2(CH_2)_3CH_3$), 2.42 (t, *J*=7.9 Hz, 2H, $COCH_2(CH_2)_5CH_3$), 4.13–4.25 (m, 2H, $NHCH_2CH_2(CH_2)_3CH_3$), 4.61–4.72 (m, 1H, $NHCHCH_3COO$), 7.09–7.16 (m, 1H, ArH), 7.32 (d, *J*=7.6 Hz, 1H, CONH), 7.58–7.64 (m, 1H, ArH), 8.30 (dd, *J*=8.1, 1.6 Hz, 1H, ArH), 8.73 (dd, *J*=8.6, 0.9 Hz, 1H, ArH), 10.99 (s, 1H, NHCO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7, 14.1 ($COCH_2(CH_2)_5CH_3$ and $NHCH_2(CH_2)_4CH_3$), 18.2 ($NHCHCH_3COO$), 22.5, 22.6, 25.5, 25.5, 28.5, 29.0, 29.2, 31.4, 31.7 ($COCH_2(CH_2)_5CH_3$ and $NHCH_2(CH_2)_4CH_3$), 48.5 ($NHCHCH_3COO$), 38.8 (CH_2CONH); IR (KBr): ν_{max} 3301, 2927, 2856, 2359, 1752, 1707, 1661, 1642, 1586, 1531, 1451, 1377, 1274, 1205, 1066, 876, 763 cm^{-1}; 66.1 ($COOCH_2$), 118.3, 142.5 (ArC), 120.7, 122.4, 134.5, 136.8 (ArCH), 162.3, 172.1, 172.6, 191.3 (C=O); UV (MeOH): λ_{max} 234 (ε 24,950 cm^{-1} M^{-1}), 273 (10,900), 342 (6300); MS (TOF-ESI) *m/z* calculated for $C_{25}H_{39}N_2O_5$ $(M+H)^+$ 447.28. Found 447.23.

4.2. Structure determination

Suitable single crystals of **7a**, **7k**, **7l** and **9a** selected under the polarizing 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-Kα 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[38] were applied and the data were corrected for Lorentz and polarization effects using Bruker APEX2 software.[39] All structures were solved by direct methods and the full-matrix least-squares refinements were carried out using SHELXL.[40] The non-hydrogen atoms were refined anisotropically. The molecular graphics were generated using mercury.[41]

The X-ray diffraction measurements for **7d**, **7i** and **9d** 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 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 polarization effects using the XDS software.[42] The structure was solved by direct methods and the full-matrix least-squares refinements were carried out using SHELXL.[40]

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Supplementary data

Fig. S1 shows the crystal structures of **7a**, **7d**, **7i**, **7k** and **7l**. Fig. S2 shows the crystal packings of **7a**, **7d**, **7i** and **7l**. The geometric parameters of the intramolecular interactions are summarized given in Table S1. The intermolecular interaction distances and angles of **7a**, **7d**, **7i**, **7k**, **7l**, **9a** and **9d** are listed in Table S2. X-ray crystallographic information files (CIF) for the structures are CCDC 915508–915514 (Table 3). 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 are available. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.07.052.

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