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Synthesis of dendrimeric *N*-glyoxylamide peptide mimics

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ABSTRACT

A range of peptidomimetic dendrimers based on 1,3,5-benzenetricarbonyl trichloride and tris(2-aminoethyl)amine central cores has been synthesised through the facile ring-opening of *N*-acylisatins with amino acids, alcohols and other amines.

Inefficient drug delivery is a key factor that hinders the efficacy of many synthetic antibiotics for the treatment of infectious diseases.[1,2] The development of effective drug delivery systems is, therefore, required to enhance the performance of current antibiotics. Recently, the use of dendrimers as DNA carriers and drug delivery systems has gained considerable attention in pharmaceutical and medicinal chemistry. Dendrimers are well-defined macromolecules with highly branched architectures that can adopt a spherical three-dimensional structure. In addition, they possess a high density of functional groups which promote host–guest chemistry at both the interior and periphery of the dendrimer.[2–4] As an example, Kohle et al. have described a polyamidoamine dendrimer that can efficiently carry, on average, 78 molecules of ibuprofen into cells and then release the drug at an appreciably slower rate in vitro than pure ibuprofen.[5]

The step-wise, controlled construction of dendrimers frequently utilizes the formation of the stable amide bond, generating macromolecules with comparable numbers of amide bonds as those found in proteins.[6] As a logical extension of this concept, several amino acid or peptide-based dendrimers have been reported.[7–9] The pharmacological utility of peptides derived from natural amino acids is limited, however, due to their poor metabolic stability, low bioavailability, and toxicity.[10,11] Recent advances in peptide chemistry have focused on peptidomimetics. Peptidomimetics are small peptide-like molecules which utilize functional groups such as aromatic rings and pyrrole moieties to stabilize the molecular structure and enhance bioavailability, while maintaining the favorable biological properties of the natural peptides.[10]

We were interested in the development of novel peptidomimetics derived from *N*-acylisatins and have previously reported their facile ring-opening with various amino-ester hydrochloride salts to give glyoxylamide peptide mimics that possess significant anti-bacterial activity.[12] We report herein the synthesis of the dendrimer analogues of these compounds for potential use as an effective drug delivery system for anti-bacterial agents. Two commonly used central cores, 1,3,5-benzenetricarbonyl trichloride and tris(2-aminoethyl)amine,[13] were selected for this initial study. 1,3,5-Benzenetricarbonyl trichloride is a highly reactive achiral *C*3-symmetric rigid structure which has been found to possess a hydrogen-bonded columnar-type packing which can enhance the length of the dendrimer assembly. Tris(2-aminoethyl)amine is a tridentate ligand with three aminoethyl groups attached to the central nitrogen atom.

Dendrimers based on a 1,3,5-benzenetricarbonyl trichloride core unit were developed as shown in Scheme 1. Isatin (**1**) and 1,3,5-benzenetricarbonyl trichloride (**2**) were reacted with sodium hydride in 1,4-dioxane at 0 °C and the reaction mixture was allowed to warm to room temperature overnight. Tris-isatin **3** was isolated as a yellow solid in 75% yield after aqueous work-up and column chromatography. The ^{1}H NMR spectrum of tris-isatin **3** indicated the compound was threefold symmetric, displaying two doublets at 7.79 and 8.03 ppm, equating to H4 and H7, respectively, and two triplets at 7.39 and 7.81 ppm which corresponded to H5 and H6. The protons of the benzene moiety appeared as a singlet at 8.75 ppm.

The ring-opening of the tris-isatin **3** system was initially investigated using a range of alcohols and amines. Tris-isatin **3** was found to undergo tandem ring-opening in neat solutions of methanol, ethanol, and *n*-butanol to afford benzenetricarbonyl

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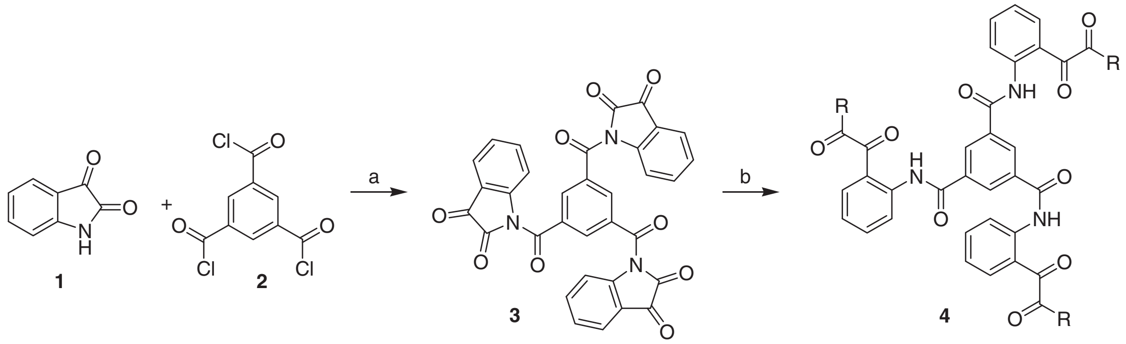


Scheme 1. Reagents and conditions: (a) NaH, anhydrous 1,4-dioxane, 0 °C to rt, 24 h; (b) alcohol or amine, CH_2Cl_2, reflux, 6 h.

tris-glyoxylesters **4a–c** in 62–76% yield. Similar treatment of tris-isatin **3** with 3.5 equiv of amines in dichloromethane afforded the tris-gloxylamides **4d–f**. In general, the yield of the tris-gloxylamides **4** was found to decrease as the length of the alkyl chain increased (Table 1).

With the successful formation of tris-gloxylamides from alcohols and amines, attention turned to the use of amino acids for the preparation of dendrimeric peptidomimetics. The ring-opening of tris-isatin **3** with glycine methyl ester hydrochloride was conducted under the previously reported conditions[13] in a dichloromethane–water (v/v = 3:1) biphasic solvent system in the presence of sodium hydrogen carbonate. Dendrimer **5a** was isolated as off-white flakes in 20% yield after purification by column chromatography.[14] The ^{1}H NMR spectrum showed the presence of a doublet at 3.96 ppm and a singlet at 3.62 ppm, which were assigned as the methylene and methyl ester protons, respectively. High resolution mass spectrometric analysis showed a peak at 863.2166 which was consistent with $(M-H)^+$ for compound **5a**.

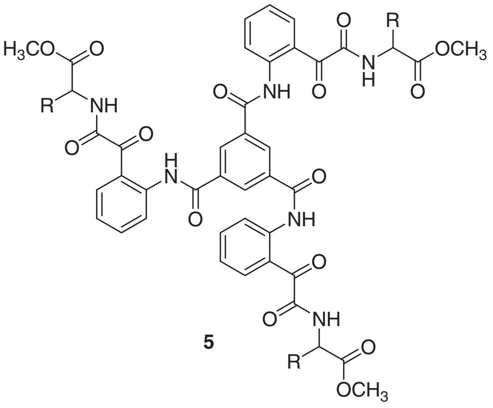
The reaction yield was subsequently increased upon use of a mono-phasic solution of dichloromethane and triethylamine employed as the base. Tris-isatin **3** was ring-opened at room temperature over 48 h with a range of amino acid methyl ester hydrochlorides to generate peptidomimetics **5b–d** in 25–43% yields (Table 2). Unfortunately, attempts to crystallise compounds **5a–d** from a range of solvents in order to perform X-ray diffraction studies proved unsuccessful.

With the successful preparation of the first generation of tris-glyoxylamide peptidomimetics, efforts were directed toward the synthesis of second generation mimics using dipeptides. Ring-opening of tris-isatin **3** with L-valine-L-phenylalanine methyl ester hydrochloride was conducted under the optimized reaction conditions. However, the desired *N*-1,3,5-tris-glyoxylamide peptide mimic was not produced and only polymeric by-products were observed by ^{1}H NMR spectroscopy. Further reaction optimization was performed by varying the number of equivalents of the dipeptide hydrochloric salt and examining the use of a biphasic solvent system, but in all cases none of the desired compound was produced. It was, therefore, reasoned that the sterically bulky nature of the two substrates hindered the reaction.

Table 1
Benzenetricarbonyl tris-gloxylamides

Entry	R	Product	Yield (%)
1	OCH_3	**4a**	76
2	OCH_2CH_3	**4b**	67
3	$O(CH_2)_3CH_3$	**4c**	62
4	$NH(CH_2)_3CH_3$	**4d**	74
5	$NH(CH_2)_5CH_3$	**4e**	59
6	$NH(CH_2)_7CH_3$	**4f**	48

Table 2
Benzenetricarbonyl tris-gloxylamide peptidomimetics

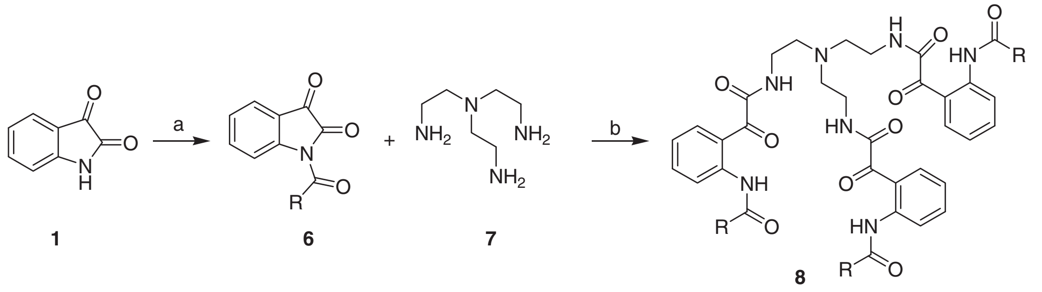


Entry	R	Amino acid[a]	Product	Yield (%)
1	H	Glycine	**5a**	20
2	$CH(CH_3)_2$	L-Valine	**5b**	25
3	$CH_2CH(CH_3)_2$	L-Leucine	**5c**	35
4	$CH(CH_2)_2SCH_3$	L-Methionine	**5d**	43

[a] As the methyl ester hydrochloride salt.

The development of dendrimers based on the second core unit, tris(2-aminoethyl)amine (**7**), was subsequently investigated as a potentially less sterically demanding starting substrate (Scheme 2). In this case, the ring-opening of *N*-acylisatin would be achieved by the dendritic central unit **6** itself, instead of by peptides as in the previous series. Thus, isatin (**1**) was reacted with methyl chloroformate in the presence of sodium hydride to give methyl carbamate **6a** in 72% yield. Subsequent ring-opening with tris(2-aminoethyl)amine (**7**) using a modification of the procedure reported by Orvig et al.[15] afforded tris-peptide mimic **8a** in 30% yield as yellow flakes after column chromatography (Table 3). After some optimization, we found that the formation of by-products was reduced through use of a high dilution reaction mixture (10^{-3} M).

The successful formation of trimer **8a** was confirmed using X-ray crystallography (Fig. 1). The X-ray crystal structure revealed that the three arms of the trimer were orientated downward to form a cage structure. As such, these structures may potentially possess interesting metal binding capabilities.



Scheme 2. Reagents and conditions: (a) acid chloride, NaH, 1,4-dioxane, 0 °C to rt, 45 min; (b) DIPEA, CH_2Cl_2, 0 °C to rt, 24 h.

Table 3
Tris(aminoethyl)amine gloxylamide peptidomimetics

Entry	R	Product	Yield[a] (%)
1	OCH_3	**8a**	30
2	$CH_2CH_2COOCH_3$	**8b**	28

[a] Isolated yields.

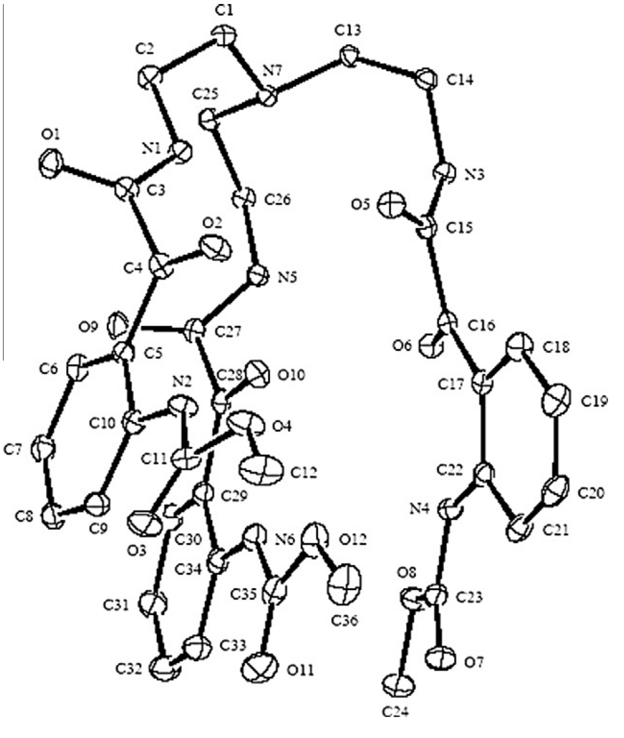


Figure 1. ORTEP diagram of **8a**.[16]

Isatin (**1**) was then reacted with methyl 4-chloro-4-oxobutyrate to give the longer chain *N*-oxobutanoate **6b** in 60% yield. Reaction of **6b** with tris(2-aminoethyl)amine (**7**) produced peptidomimetic **8b** in 28% yield. Saponification of the methyl ester groups was subsequently investigated on the basis that the peptide chain could then be extended through amide coupling with the free acids. Saponification of **8b** with aqueous potassium hydroxide in methanol proved to be problematic, however, producing polymeric by-products in preference to the desired tris-carboxylic acid. It was postulated that polymerization was favoured due to the presence of so many labile groups.

In summary, the facile ring-opening of *N*-acylisatins with alcohols, amines, and amino acids has been successfully applied to the synthesis of peptidomimetic dendrimers. 1,3,5-Benzenetricarbonyl trichloride and tris(2-aminoethyl)amine were investigated as the central core unit and several examples of both types of dendrimers were produced.

Acknowledgments

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14. *Representative procedure for* **5a**: Glycine methyl ester hydrochloride (6.0 mmol) was added to a stirred solution of 1,3,5-triacylisatin **3** (1.0 mmol) in CH_2Cl_2 (60 ml) and saturated $NaHCO_3$ in H_2O (3 ml) at 5 °C. The reaction was warmed to room temperature and stirred for 24 h. The organic layer was washed with aqueous HCl (0.5 M, 25 ml) and H_2O (20 ml) before being concentrated under vacuum. Trituration with CH_2Cl_2 gave **5a** as fine off-white flakes (20%). Mp 178–180 °C, ^1H NMR (300 MHz, DMSO-d_6): 11.6 (3H, br s, NHCO), 9.24 (3H, t, *J* 5.6 Hz, CONH), 8.75 (3H, s, H13, H15, H17), 8.16 (3H, dd, *J* 1.5, 7.9 Hz, H7, H7′, H7″), 7.85 (3H, dd, *J* 1.5, 7.9 Hz, H4, H4′, H4″), 7.75 (3H, *J* 1.5, 7.5 Hz, H6, H6′, H6″), 7.37 (3H, dt, *J* 1.5, 7.5 Hz, H5, H5′, H5″), 3.96 (6H, d, *J* 6.0 Hz, CH_2), 3.62 (9H, s, $COOCH_3$). ^{13}C NMR (75 MHz, DMSO-d_6): 191.9, 169.9, 164.5, 164.4, 138.9, 135.6, 135.1, 132.6, 130.0, 124.7, 124.3, 122.8, 52.3, 40.9. HRMS (ESI) *m/z* calcd for $C_{42}H_{35}N_6O_{15}$ $(M-H)^+$ 863.2166; found 863.2166. Anal. Calcd for $C_{42}H_{36}N_6O_{15}$: C, 58.33; H, 4.20; N, 9.72. Found: C, 58.30; H, 4.44; N, 9.44.
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16. Crystallographic data for the structure in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 806995 (**8a**). X-ray crystal structures were obtained by Mohan Bhadbhade, Crystallography Laboratory, UNSW Analytical Centre, Sydney, Australia.